RESEARCH REPORT
2006
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Our mission is to be a Centre of Excellence in biomedical research.

We are dedicated to the advancement of science and the translation of research findings into better health care.

We strive to provide an environment that enhances individual growth, collaboration, achievement, and recognition.
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The King Faisal Specialist Hospital and Research Centre holds the distinction of being one of the most advanced medical facility in the region, consistently elevating the bar in the quality of services it offers to the general population. This would not be possible without the contributions of our researchers and the advanced methodologies and techniques they are introducing consistently through the years.

Our success is attributable to the intellectual range and depth of our scientific and technical staff. Their ability to recognize the potentials of pioneering research work blurs the line between research and reality. The diversity of our research activities and our interdisciplinary approach help link discoveries in one specialty to advance in another discipline.

This publication celebrates our research activities in 2006, detailing our achievements and progress. But at a time when stem cell research brings excitement and hope, and while some promises made by gene therapy have been fulfilled, much work is yet to be done considering the sobering reality that some debilitating diseases such as cancer and diabetes still continue to plague society.

Qasim Al-Qasabi, MD, FRCSI, FACS
Chief Executive Director
King Faisal Specialist Hospital and Research Centre
Join us in our fight to improve the quality of healthcare logically and globally. The road we take will not be easy, but together, the challenges we face and the journey along the way should be manageable.
Three interrelated activities have enabled the King Faisal Specialist Hospital and Research Centre to provide essential services to its patient population: specialized medical services, academic and training activities, and research. Without a sound research program and a dedicated academic and training curriculum, the ability to deliver quality healthcare becomes a monumental task.

We have witnessed in 2006 the emergence of a number of new and exciting research programs that will define our role in the search to curb some of the most prevalent diseases in the region, with our hopes to elucidate the detailed mechanism of disease formation as well as to cultivate innovative methodologies to eradicate the consequences of these diseases. To illustrate, the steady rise in the number of Saudi nationals afflicted with diabetes is alarming and warrants a renewed enthusiasm to once and for all contain this disease; the issue concerning some common genetic diseases in the Kingdom is not about to go away anytime soon; and of course, the threat and devastation brought by cancer, cardiovascular diseases, infections, and metabolic disorders are just too wide-ranging and must be addressed, expeditiously. Today, our researchers have joined hands with our partners from around the world to embark on research platforms that will address these concerns.
This annual report will underscore some of the notable achievements we have so far made in our effort to become a center of excellence in research. We will present some of the diversified approach we employ that makes King Faisal Specialist Hospital and Research Centre a melting pot for collaboration and teamwork, innovation, and idea exploration.

On behalf of all the clinical researchers and scientists of the King Faisal Specialist Hospital and Research Centre, I invite you to celebrate with us a year’s worth of invigorating research.
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The
Research Centre
Annual Research Report
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The
Office of Research Affairs
The Office of Research Affairs

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

The goals of the ORA are:

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

THE RESEARCH ADVISORY COUNCIL

Mission and Membership

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

Sultan T Al Sedairy, PhD (Chairman)
Futwan A Al Mohanna, PhD (Vice-Chairman)
Maha Mishari Al Saud, MD (Coordinator)
Mohamed Al Turki, CCRP (Coordinator)
Adnan Ezzat, MD
Abdulrazaq Al-Jazairi, PharmD
Moahmmed Hijazi, MD
Brian Meyer, PhD
Ghazi Al-Sbeih, MD, PhD
Khalid Abu-Amero, PhD

Co-Director
Maha Al-Saud, MD
Co-Director
Mohamed Al-Turki, CCRP

Members
Ibrahim Awad Ali (Transferred to RC-Admin 26 November 2006)
Grace B. Dela Torre
Daisy Herrero
Ghada Al Hawsawi, HRA
Nisar Ahmed Mohamed
Imran (Transferred to RC-Admin 26 November 2006)
Weaam Al Jassim, RPh
Farid El Khazen (Up to July 2006)
Ma. Pilarcita C. Miranda
(From 05 August 2006)
Mercedita Sahi, RN
Abeer Hassan Al Sayed, MD
Maqbool Ahmed Sharifi, MD
Melvin Z. Velasco (Transferred to RC-Admin 26 November 2006)
Ainul Yaqiin Mabaning (Up to 19 September 2006)
Supporting Committees

The Research Advisory Council is supported by five standing committees:

The Animal Care and Use Committee (ACUC)

- Ghazi Al-Sbeih, MD, PhD (Chairman)
- Jalal Saour, MD
- Aaron Kwaasi, PhD (till Feb 2007)
- Nisreen Al-Moghrabi, PhD
- Mohammad Jamal Arif, PhD (till November 2006)
- Saad Al-Garni, MD, FRCS
- Khalid Abu-Khabar, PhD
- Ahmed Al-Jedai, PharmD
- Azhar Chishti, DVM, PhD (till 06 June 2006)
- Crisologo Caliao (till 30 March 2005)

The Basic Research Committee (BRC)

- Brian Meyer, PhD (Chairman)
- Said Dermime, PhD
- Shahab Uddin Khan, PhD
- Sayed Akhtar, MD (till 01 March 2006)
- Serdar Coskun, DVM, PhD, HCLD
- Mohamed Shoukri, PhD
- Ali Hellani, PhD (till 31 August 2005)
- George Roberts, MD (till 26 November 2006)
- Katherine Collison, PhD
- Osama Alsmadi, PhD

The Clinical Research Committee (CRC)

- Abdulrazzaq Al-Jazairi, PharmD (Chairman)
- Majid Al-Fayyadh, MD
- Ali Al-Zahrani, MD
- Ahmed Bahatheq, PharmD (till 04 December 2005)
- Wälid Mourad MD, FCAP, FRCPC (till Dec 06)
- Asim Belgaumi, MD
- Abdullah Al-Khenizan, MD
- Kristian Thesstrup Pedersen, MD, PhD (till 31 Aug 05)
- Michael Nester, PhD
- Suzanne Robertson, PhD

The Research Ethics Committee (REC)

- Moahmmed Hijazi, MD (Chairman)
- Edward DeVol, PhD (till June 2006)
- Nasser Al-Rajhi, MD (till 01 March 2005)
- Abdellatif Rejjal, MD
- Bent Stigsby, MD, PhD
- Mehmet Inan, PhD
- Mohammed Ashour, Ms, Dip Clinical Pharm
- Noora Al-Malhooq (till 01 March 2005)
- Wafaa Khallaf
- Abdul Hamid El-Bushra
- Heather Byrne, RN (till 07 April 2006)

The Recombinant DNA Committee (RDC)

- Khalid Abu Amero, PhD (Chairman) (till 12 Dec 2006)
- Zuhair Al-Hassnan, MD
- Sahar Al-Thawadi, MD
- Faiqa Imtiaz, PhD
- Syed Hussain, PhD (till 01 March 2006)
- Namik Kaya, PhD
- Hazem, Ghebeh, PhD
- Taher Uz Zaman, PhD
- Azadali Moorji
Proposal and Publication Processing

1. Processed 121 research proposals, that were submitted from the following departments:

<table>
<thead>
<tr>
<th>Department</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>King Faisal Heart Institute</td>
<td>16</td>
</tr>
<tr>
<td>Biological &amp; Medical Research</td>
<td>16</td>
</tr>
<tr>
<td>King Faisal Cancer Centre</td>
<td>9</td>
</tr>
<tr>
<td>Neurosciences</td>
<td>9</td>
</tr>
<tr>
<td>Obstetric &amp; Gynecology</td>
<td>9</td>
</tr>
<tr>
<td>Medicine</td>
<td>7</td>
</tr>
<tr>
<td>Centre for Clinical Studies &amp; Empirical Ethics</td>
<td>7</td>
</tr>
<tr>
<td>Pathology &amp; Laboratory Medicine</td>
<td>6</td>
</tr>
<tr>
<td>Genetics</td>
<td>5</td>
</tr>
<tr>
<td>Biomedical Physics</td>
<td>5</td>
</tr>
<tr>
<td>Biostatistics, Epidemiology &amp; Scientific Computing</td>
<td>4</td>
</tr>
<tr>
<td>Pediatric Hematology/Oncology</td>
<td>4</td>
</tr>
<tr>
<td>Comparative Medicine</td>
<td>4</td>
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</table>

2. Processed 106 applications for publication that were submitted from the following departments:

<table>
<thead>
<tr>
<th>Department</th>
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<tbody>
<tr>
<td>Biological &amp; Medical Research</td>
<td>31</td>
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<tr>
<td>Pathology</td>
<td>8</td>
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<tr>
<td>Medical Genetics</td>
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<tr>
<td>Medicine</td>
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</tr>
<tr>
<td>Biomedical Physics</td>
<td>6</td>
</tr>
<tr>
<td>Centre for Clinical Studies &amp; Empirical Ethics</td>
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<tr>
<td>Genetics</td>
<td>6</td>
</tr>
<tr>
<td>King Faisal Cancer Centre</td>
<td>5</td>
</tr>
<tr>
<td>King Faisal National Centre for Children’s Cancer &amp; Research</td>
<td>5</td>
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<table>
<thead>
<tr>
<th>Department</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arabian Diagnostic Laboratory</td>
<td>5</td>
</tr>
<tr>
<td>Biostatistics, Epidemiology &amp; Scientific Computing</td>
<td>3</td>
</tr>
<tr>
<td>Cycotron &amp; Radiopharmaceuticals</td>
<td>3</td>
</tr>
<tr>
<td>Outside Institution</td>
<td>2</td>
</tr>
<tr>
<td>Neuroscience</td>
<td>3</td>
</tr>
<tr>
<td>Biological Repository Centre</td>
<td>1</td>
</tr>
<tr>
<td>Dentistry</td>
<td>1</td>
</tr>
<tr>
<td>Urology</td>
<td>1</td>
</tr>
</tbody>
</table>
3. The table above summarizes the activities of the five standing Committees of the RAC, namely, REC, RDC, CRC, BRC, and ACUC.


**Sponsored Research & Intellectual Property**

1. The estimated research cost, proposed for Basic and Clinical research proposals, were SR 23,782,530.00 and SR 6,863,775.00 respectively, for a grand total of SR 30,646,305.00. The detailed budgets (in Saudi Riyals), proposed for Clinical and Basic research proposals is as follows:

<table>
<thead>
<tr>
<th>Committee</th>
<th>Pathology</th>
<th>Radiology</th>
<th>Special Lab</th>
<th>Personnel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>500,987.00</td>
<td>123,750.00</td>
<td>175,700.00</td>
<td>4,165,794.00</td>
</tr>
<tr>
<td>Basic</td>
<td>40,000.00</td>
<td>0.00</td>
<td>130,000.00</td>
<td>9,092,100.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Committee</th>
<th>Inpatient</th>
<th>Outpatient</th>
<th>Equipment</th>
<th>Supplies</th>
<th>Pharmacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>63,000.00</td>
<td>277,100.00</td>
<td>0.00</td>
<td>1,096,582.00</td>
<td>81,452.00</td>
</tr>
<tr>
<td>Basic</td>
<td>0.00</td>
<td>0.00</td>
<td>5,345,695.00</td>
<td>5,378,789.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Committee</th>
<th>Animal</th>
<th>Statistics</th>
<th>Publications</th>
<th>Travel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical</td>
<td>0.00</td>
<td>84,660.00</td>
<td>113,000.00</td>
<td>181,750.00</td>
</tr>
<tr>
<td>Basic</td>
<td>269,630.00</td>
<td>79,628.00</td>
<td>161,850.00</td>
<td>748,000.00</td>
</tr>
</tbody>
</table>

2. 28 Research proposals required research agreements with external sponsors and collaborators, which included 11 KACST*, 05 Clinical Trials, 06 Bioequivalence Studies, and 06 Collaborative research agreements.

* KACST - King Abdulaziz City for Science and Technology

3. A total of 13 Research Agreements were signed with sponsors and/or collaborators which included 11 funded projects with total external funds to KFSH&RC of SR 4,136,253.00.

4. Total value of external funds received for Sponsored Projects was SR 2,678,920.27.

5. 20 Research Grant opportunities identified and information distributed

**Assurance & Compliance**

1. Surveyed 68 research projects (997 medical records, MR). (Compared to 2005 the section surveyed 62 research projects involving reviewing 697 medical records) A summary of the findings comparing 2005 & 2006 are given in the following table:
### Consent documentation compliance

<table>
<thead>
<tr>
<th></th>
<th>2005</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent forms filed in Medical Records</td>
<td>92%</td>
<td>*96%</td>
</tr>
<tr>
<td>Consent process documented in Medical Records</td>
<td>51%</td>
<td>*65%</td>
</tr>
</tbody>
</table>

### Adherence to protocol

<table>
<thead>
<tr>
<th></th>
<th>2005</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion/exclusion criteria met</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Protocol specific procedures completed</td>
<td>100%</td>
<td>*99%</td>
</tr>
</tbody>
</table>

### Safety Issues

<table>
<thead>
<tr>
<th></th>
<th>2005</th>
<th>2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Adverse Events reported to RAC</td>
<td>59%</td>
<td>*86%</td>
</tr>
<tr>
<td>Serious Unexpected Adverse Events appropriately reported to RAC</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>

* Overall the filing of consent forms and the documentation of the study process in medical records (charts) improved compared from last year.

- The filing of consent forms in medical records (charts) increased by 4% compared to last year.
- The documentation of the study process in medical records (charts) increased by 14% compared from last year.

* The completion of protocol specific procedures decreased by 1% compared from last year.

* The adverse events reported to RAC (PR&FR) increased by 27% compared from last year.

* For ACUC project the Assurance & Compliance Section surveyed a total of 16 research projects.

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### Scientific Information Office

The Scientific Information Office (SIO) provides the Research Centre with graphical materials used for international and local presentations, workshops, symposia, and publications. In 2006, the section has designed, produced and performed the following:

<table>
<thead>
<tr>
<th>Service</th>
<th>Qty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Banners</td>
<td>20</td>
</tr>
<tr>
<td>Web updates</td>
<td>165</td>
</tr>
<tr>
<td>Image scanning and editing</td>
<td>516</td>
</tr>
<tr>
<td>Posters</td>
<td>56</td>
</tr>
<tr>
<td>Book</td>
<td>1</td>
</tr>
<tr>
<td>Brochures, flyers, programs</td>
<td>43</td>
</tr>
<tr>
<td>Folders, letter heads, logos, forms, signs, Power point presentation slides &amp; backgrounds, book markers, etc.</td>
<td>Multiple</td>
</tr>
</tbody>
</table>
The
Arabian Diagnostics Laboratory
In 2006 Arabian Diagnostics Laboratories (ADL) has consolidated research programs in hereditary hearing loss and hereditary vision impairment and initiated a new program on the molecular basis of immune deficiency. The main focus remained on the development of research programs with substantial translational potential by keeping with the laboratory’s commitment to the provision of diagnostic services. ADL was re-accredited by the College of American Pathologists and has positioned itself for inclusion into ICIS through which its services will be made available in 2007. ADL has also made additional progress in understanding the molecular basis of several inborn errors of metabolism and continues to identify Arab specific mutations in a range of hereditary diseases. In addition, we have adopted SNP based genotyping for linkage analysis that has substantially increased its capacity for the mapping and identification of genes underlying novel Mendelian diseases, an area that remains a high priority. The best examples over 2006 are the mapping of novel loci underlying hereditary deafness, juvenile rheumatoid arthritis, blepharophimosis and other rare Mendelian traits. We have also continued to establish the role of several genes in type 2 diabetes within Arab populations programs to investigate the genetics of nephropathies and that of long QT (cardiovascular) syndromes in the Saudi population. They were initiated in 2006 and have already identified the molecular basis of these in some instances.

RESEARCH PROJECTS

Hereditary Deafness Study
Autosomal recessive genes are responsible for about 80% of hereditary nonsyndromic deafness of pre-lingual onset. DFNB1 is caused primarily by mutations in the GJB2 gene that are responsible for approximately 50% of pre-lingual, recessive deafness in various populations. To date, 738 patients/family members and 80 families are enrolled, and analysis of 500 individuals strongly suggests that DFNB1 does not play a dominant role (~2-5%) in non-syndromic hereditary deafness in the Saudi population. This has accelerated our efforts to conduct prioritized linkage analysis on 11 families (with 3 or more affected members) using Affymetrix 10K Array SNP technology. Typical results (high LOD score) allow identification of a particular region on a specific chromosome, which contains the gene causing the underlying molecular defect in a particular family. Currently, using a candidate gene approach, we have identified the disease-causing mutations in 2 families and have identified strong candidates in...
remaining families that provided high LOD scores on various chromosomes. Identification of the most common forms of hereditary deafness, their incidence and distribution in the Saudi population and application of this knowledge to newborn and pre-marital screening will have a major impact upon early management of hereditary deafness.

**Hereditary Vision Impairment**

This program has been investigating the molecular basis of primarily recessively inherited vision impairment. During 2006, as a result of ongoing research projects or samples submitted for diagnostic purposes, we identified the molecular basis of disease in several of these disorders. In 2005, more than 10 novel mutations covering six disorders resulting in vision impairment were identified. This year similar progress has been made in other disorders such as congenital cataract, Ehler-Danlos and other syndromes. Collaborative research with a Division of the Harvard Medical school is currently being developed on the basis of lens abnormalities. Several rare and apparently novel ocular abnormalities are currently being mapped and the program is expanding to include areas such as retinoblastoma and xeroderma pigmentosa.

**Inborn Errors of Metabolism**

Seven inborn errors of metabolism, argininosuccinic acid lyase deficiency (ASL), propionicacidemia (PPA), HMG CoA lyase deficiency, methylmalonic aciduria (MMA), very long chain acyl-CoA dehydrogenase deficiency (VLCAD), medium chain acyl-CoA dehydrogenase (MCAD) and tyrosinemia are currently under study to identify the underlying molecular basis of these diseases in the Saudi population. In 2006, we have identified between >75% of the disease-causing mutations (novel and previously published) that are specifically responsible for the occurrence of MCAD and tyrosinemia. Our previous findings in ASL, HMG CoA lyase deficiency and PPA have been introduced as diagnostic tests and have facilitated counseling and prevention activities, including prenatal diagnosis and PGD.

**DNA Diagnostics**

In 2006, ADL provided diagnostic tests for inherited disorders such as cystic fibrosis, fragile X syndrome, myotonic dystrophy, hereditary hemochromatosis, coagulopathies, MELAS, sickle cell anemia and huntington disease among others. During this past year, the ADL laboratory was inspected and re-accredited by the College of American Pathologists. The ADL test repertoire has been approved for inclusion into ICIS and will facilitate electronic requesting and reporting of its test repertoire within the KFSHRC system. ADL has also developed parentage testing for thoroughbred and Arab horses. This is the first time that this has been available in the Kingdom and contracts for the provision of this service have been negotiated with the Ministry of Agriculture. Collectively the number of samples processed by ADL is now approaching 1000.

**Other Research Projects**

ADL has continued in mapping and cloning genes underlying several Mendelian diseases as part of approved research projects. These include congenital cataract, severe combined immune deficiency, ataxia with oculomotor apraxia, parkinsonism, hereditary spastic paraplegia, familial juvenile rheumatoid arthritis, a novel myopathy, LQT syndrome, microcephaly and several nephropathies. In the latter two cases, the introduction of high density genotyping using the Affymetrix 10K chip and subsequent linkage analysis has facilitated the identification of novel loci and resolved constraints present using lower density microsatellite based genome scans. The adoption of this technology has been invaluable in pursuing the mapping of Mendelian traits in several of the programs discussed above.
FUTURE RESEARCH DIRECTION

Integration of Arabian Diagnostic Laboratories (ADL) with the Department of Genetics and Restructuring of Research and Service Units of the Department of Genetics and ADL.

Provision of Molecular Diagnostics for Inherited Diseases to KFSHRC via ICIS, measured expansion of such service on a National/Regional basis via an E-commerce interface and provision of Genomic Services on a National/Regional basis.

Expansion of Laboratory Information Management System and staged implementation throughout the Department of Genetics/Research Centre.

Establishment of a Collaborative Program with Research Units of the Harvard Medical School and the Broad Institute of MIT.

PUBLICATIONS

Full length articles

The Department of
Biological and Medical Research
The Department of

Biological and Medical Research

Vision

Quality research from laboratory bench to patient bed.

Mission

The department supports original research that should make a significant contribution to knowledge in medical and biological sciences, with attention to and emphasis on cellular, molecular, immunological, chemical and microbiological experimental investigations.

Over the past few years, there was an increased emphasis on attempts to contribute to the understanding of disease mechanisms at the cellular- and molecular-levels. Our programs support the conduction of biological and medical research for promoting more effective patient care. We have an unprecedented opportunity to investigate and train at the interface of biology and medicine, and thus to explore and build the next generation of information for understanding biological mysteries and improving human health.

During the year 2006 the Biological and Medical Research Department continued its programs to further the development of scientific achievements in research in a diversity of fields, including but not limited to allergy and aerobiology, breast cancer, carcinogenesis, cell biology, coagulation, DNA repair and apoptosis, environmental health, histocompatibility and immunogenetics, laser medicine, biomedical chemistry, molecular virology and infectious diseases, proteomics, and tumor immunology. In addition to equipment in each area, communal equipment and core facilities are available for use, including but not limited to flow cytometry, confocal microscopy, ultracentrifugation, beta and gamma scintillation counting, film processing, and autoclaving. Our scientists continued to obtain external research funding, both nationally and internationally, and train nationals at the pre- and post-doctoral levels. Major achievements for the year include:

- Setting up the Diabetes Research Program in 2006, consisting of seven main projects
- Successful execution of the clinical trial of indigenous allergens
- Collection of freshly-resected breast cancer and tumor adjacent tissues from Saudi patients
- Establishment of fibroblast cell lines from breast tissues
- Generation of gene expression profiles in breast tumor cells
- Modulation of DNA adducts by natural plant-derived chemicals and marine compounds
Modulation of various tumor suppressor and apoptosis-related genes by plant and marine-derived chemical compounds in both normal and cancer cells.

Differential induction of programmed cell death in breast cancer cell lines.

Tumor suppressor p16 protein controls the shuttling of the RNA binding protein HuR from the nucleus to cytoplasm.

Genotyping of methicillin-resistant Staphylococcus aureus.

Molecular identification of strains of several pathogenic viruses in intravenous drug users’ sera.

Microarray analysis of THP-1 macrophage-like cells after infection with leishmania major.

Shown that the p53/p21 DNA damage response pathway is defective in most tumor associated fibroblasts derived from breast cancer Saudi patients.

Comprehensive study of lasers and LED in wound and burn healing in normal and diabetic rats.

Extrapolation of animal laser and LED dosimetry for clinical trials.

Demonstration of the expression of the B7-H1 (a T cells inhibitory molecule) as an immune escape mechanism in breast cancer patients.

Providing direct evidence to the association between B7-H1 expression and proliferation and direct relation to breast cancer patients prognosis.

Discovery of T regulatory cell clones specific to the leukemia-associated antigen WT1 in patients with leukemia.

The Department consists of 13 Sections and 2 core facilities, each contributing to the achievement of our goals and missions. Our staff consists of 29 scientists, 39 technical support staff, 13 administrative staff, 6 joint/adjunct scientists and 19 collaborators. In 2006, a total of 13 students pursued postgraduate education in the Department. We continue to foster the education of future scientists. Throughout the year, many graduates from national universities have received training in our laboratories. As well, a number of high school students from the Riyadh area and student sponsored by the Establishment of King Abdulaziz and His Companions for the Gifted have visited the Department and toured the laboratories so that they might gain an insight into various fields of research.

We strive to be an internationally recognized department emphasizing an integrative approach to biological and chemical questions from the molecular to the global level. Our scientists are working to expand collaborations that will increase the image of the Department and enhance its influence nationally and internationally. In conclusion, the advances made in the science of biology and medicine and the number of future projects already planned lead the way to another productive year in 2007. More information concerning each Section of the Department follows.
Our scientific and clinical activities during the year 2006 were mainly focused on two approved projects viz: (A) Clinical Trial of Indigenous Allergens in Saudi Arabia (Efficacy of Diagnostic Kits (RAC approved # 2060 006) and (B) Isolation, Purification and Immunochemical Characterization of Allergenic Protein(s) from *Amaranthus viridis* Pollen Grains (RAC approved # 2050 029).

The clinical trials of our indigenous kits were conducted at different clinics and hospitals in Saudi Arabia as well as in Dubai, Al-Ain and in Sudan. The results are being collected and analyzed. At the moment, a battery of 30 allergens plus positive and negative controls were produced and tested. The initial data indicate that, majority of indigenous allergens were reactive in both adult & pediatric patients. The results further indicate that some indoor allergens (cat & cockroach included) and weeds allergen were important factors in most patients. The findings will have a far-reaching significance for the diagnoses of allergies and asthma in the kingdom and the Gulf countries.

The purification and immunochemical characterization of *Amaranthus viridis* was approved by the Research Advisory Council. However, the funding has been requested from KACST. This is most prevalent pollen in the air of many regions of the country. Some clinics are using a species of *Amaranthus* which is rare in the country. This appears to be the reason behind mainly mild reactivity with commercial SPT extracts. Our findings will provide a clue to this variation in the reactivity pattern with commercial and indigenous species.

**RESEARCH PROJECTS**

**Project Title:** RAC approved # 2060 006: Indigenous Allergens in Saudi Arabia: Efficacy of Diagnostic Kits

**Investigators:** Syed M. Hasnain, PhD, FACAIAI, FAAAAI, Abdulrahman Al-Frayh, MD, FACAIAI, FAAAAI

**Project Description**

This RAC approved project deals with efficacy of allergy diagnostic kits prepared in collaboration with M/S Immunotek, Madrid, Spain. The selection of allergens was based on our research findings in different areas in the kingdom and the production was completed using indigenous raw materials. The project is aimed at providing clinically relevant and quality diagnostic products for the diagnosis of respiratory allergies including bronchial asthma and allergic rhinitis. The kits will be used for routine *in vivo* Skin Prick Testing (SPT).
The data to be collected in this project will reveal valuable information including the efficacy of our products (indigenous materials) and the clinical (IgE mediated) sensitivity of the local population to these allergens. The ultimate result will not only benefit the Saudi population but may also provide a basis of commercial venture for production of such diagnostic kits. The kits, though primarily aimed for the people of Saudi Arabia, may be used in other parts of the world particularly in adjoining Arab countries.

The purpose of the research is to evaluate the efficacy of indigenous allergens diagnostic kits on patients having symptoms of inhalant allergies particularly asthma and allergic rhinitis.

A panel of 30 different allergens, having indigenous origins and selected on the basis of aerobiological studies conducted over the years at 10 locations of the country will be tested in allergic subjects by Skin Prick Test (SPT).

**Progress**

In Progress.

**Project Title: RAC# 2050029: Isolation, Purification and Immunochemical Characterization of Allergenic Protein(s) from Amaranthus viridis Pollen Grains**

**Investigators:** Syed M. Hasnain, PhD, FACAAI, FAAAAI, Abdulkareem Ayodele Alaiya, MB.BS, MPH, PhD, Mai Al-Mohanna, PhD

**Project Description**

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

In this project we intend to conduct a series of bio- and immunological experiments to characterize A. viridis allergens and their epitope determinants. Attempts will be made to purify western blot-specified allergens by conventional as well as advanced proteins purification methodologies. As it is well established that pollen proteins allergenicity is partly encoded by their glycan chains, glycoprotein-staining tests (PAS staining) for A. viridis SDS-PAGE separated proteins will indicate glycoproteins in the crude extract. ELISA and periodic acid oxidation of allergens will provide information on allergens epitope determinant, while ELISA-inhibition tests using known glycan structures will help to throw light on nature of epitope determinant(s).

It is expected that the findings of this project will be beneficial for many allergy sufferers by inclusion of A. viridis in the diagnostic profile of the country for *in vitro* and *in vivo* diagnostic tests. These data will also be useful in future studies on indigenous weeds allergens in general and A. viridis in particular.

**Progress**

In progress.

**FUTURE RESEARCH DIRECTION**

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


Presentations


The main target of this unit is dealing with applied Enzymology or Biocatalysis in chiral drug developments. Chiral drug discovery is an emerging area of research. Nowadays, it becomes a central issue in medicinal and pharmaceutical industry especially in the development of new drugs. The market value for chiral platform technologies will reach 2.7 billion US$ by 2007 with an average annual growth rate of 10.8%.

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

We are also working with physicians on studying the effect of alpha-blockers on the canine ureter (Cooperation with the department of Urology, RAC project Nr 2050032).
Project Title: From enzymes to chiral metal catalysts: asymmetric access to enantiomerically pure/enriched pharmaceuticals and related biologically active compounds. KACST Project Nr (AT-08/25), RAC Nr 2010 044

Budget: 476,600.00 SR

Status
Ongoing.

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

Project Title: Studying the effect of alpha-blockers on the canine ureter. A cooperation with the department of Urology. RAC project No: 2050032

Status
Ongoing.

FUTURE RESEARCH DIRECTION

1. Production of highly thermostable lipase enzymes from thermophilic bacterium isolated from Saudi soil for industrial clinical and pharmaceutical applications.
2. The development of tailor-made biocatalysts suitable for industrial production of pharmaceutical compounds.
3. Extensive use of chirality in drug discovery and clinical applications.
4. Provide chromatographic services for the Medical Department.

PUBLICATIONS


22. Muller, P; Allenbach, Y; Chappellet, S; Ghanem, A “Asymmetric cyclopropanations and cycloadditions of dioxocarbenes”. *Synthesis* 2006, 10, 1689-1696.


Breast Cancer

Breast cancer accounts for 21 percent of all female cancers in Saudi Arabia and 22 percent in the world. It ranks at the top among cancers in females in GCC countries. Based on existing clinicopathological parameters, it is difficult to differentiate the disease into different subgroups and to predict the response to a particular chemotherapy regimen. Recent studies have shown that breast tumors can be classified into different molecular subtypes associated with distinct clinical outcomes by their global expression profiles that are not evident by conventional methodologies. Thus, demonstrating the clinical utility of gene expression data.

Our aim is to do the molecular profiling of breast tumors for our population by using the powerful microarray technology. This will help in uncovering the molecular heterogeneity of breast tumors and will offer novel insight into breast tumorigenesis and therapy management. We are also interested to know what type of differences exists between our population and Caucasian populations at gene expression level and whether these differences are important in therapy selection. Moreover we intend to examine the gene-expression profile of stroma tissue surrounding tumor to detect any differences and similarities in expression patterns, which may aid in understanding the role of stroma in tumor generation and maintenance.
RESEARCH PROJECTS

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

Investigators: Suad M. Bin Amer, PhD (Principal Investigator), Abdelillah Aboussekhra, PhD, Said Dermime PhD, Naser ElKum, PhD, Dahees Ajarim, MD, Tahir Al-Tweigeri, Osama Al- Malik, MD, Asma Tulbah, MD, Manal Al- Zaid, MD, Yasser Khafaga, MD

Project Description

Breast Cancer has a major impact on the health of women worldwide including Saudi Arabia, where it is considered the most frequently diagnosed cancer and the leading cause of cancer deaths. We anticipate to conduct a multidisciplinary research program aiming at understanding the causes of breast cancer in relatively young population and hence to investigate novel therapeutic approaches.

Progress

- We have analyzed expression profiles of 38 invasive carcinomas and 8 tumor adjacent tissues using BD atlas cDNA Expression Arrays. Gene expression profiling in women with breast cancer in a Saudi Population. (Breast Cancer Research, Submitted)
- We have now progressed to Affymetrix Gene Chip Technology and so far we have done 50 samples, which show promising results.
- Fibroblast cell lines were developed from surgically resected breast tissue and the tissue surrounding the tumor and gene expression profiles were generated. Gene expression profiles of the fibroblasts from breast tumors and normal tissue compared with the tumor expression profiles. Saudi Medical Journal, Volume 27 Number 4 April 2006, 463-469
- Different genes were analyzed to be used as molecular markers for the progression of breast cancer. Evaluation of BP1 as an indicator of disease progression and its correlation with clinicopathological parameters in breast cancer patients. (In preparation)

FUTURE RESEARCH DIRECTION

The natural continuation of our project involves analysis of the gene expression profile of fine needle aspiration (FNA), and blood samples of patients with breast cancer before and after preoperative chemotherapy to identify different molecular subtypes of breast cancer, which will eventually lead to therapy management.
Identification and characterization of various environmental and dietary factors in cancer development continues to be an important and strategic goal of our Research Unit in order to develop effective measures for prevention and control of cancers. Our major priorities are to understand the etiology of various human cancers in the Kingdom and subsequently design and implement the strategies for their prevention and therapies.

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

RESEARCH PROJECTS

Project Title: Role of Novel Compounds from Plant, Marine, and Microbial Sources in the Breast Cancer Prevention. RAC# 2030041

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

Project Description

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

Progress

As we mentioned in the previous progress report, the modulation of benzo[a]pyrene (BP)-DNA adducts in the MCF-7 cells treated with dozens of natural compounds. The selected compounds were further tested for their
anticancer potentials using cellular viability and apoptosis in various human breast cancer and normal epithelial cell lines obtained from ATCC (USA). The apoptosis has been used as a novel target for screening the new compounds for their anticancer potential. We found differential response depending on the type of cell lines and compounds. Solanine and erysolin showed potent apoptotic activities against both the normal and cancer cell lines. In fact, the apoptotic effect was more pronounced in the normal cells which may make them unsuitable for chemopreventive aspect.

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

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

Project Title: Etiology and Prevention of HRT (Hormone Replacement Therapy)-Induced Gynecological Cancers: An In-Vitro Study. RAC # 2040 033 (KACST MS 10-5)


Project Description

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

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

Progress

Preliminary testing of 17-beta estradiol,equilin and equilinin were tested on Mcf-7,Mda and endometrial cancer (Hec 1) were done. As well as standardization of dose time points also done.

Project Title: Identification of Environmental and Genetic Factors that Influence Breast Cancer Development and Therapy in Saudi Females. RAC # 2031 091 (KACST AT 24-32)
**Investigators:** Suad Al-Amer, Jamal M. Arif, Naser Elkum, Abdelilah Aboussekhra, Said Dermime and others

**Project Description**

The program project with five multidisciplinary projects namely, epidemiology, etiology, immunotherapy, cancer markers and genetic factors to understand the etiology and prevention and/or therapy of breast cancer in Saudi Arabia.

**Progress**

The program project was funded in 2005 for ~SR1.27 million. Our project "Role of DNA damage in the breast cancer etiology and prevention" (~SR 230,000) has started in the beginning of 2006, but we withdrew from the project because of Dr. Jamal's departure who is one of the co-principal investigators.

**FUTURE RESEARCH DIRECTION**

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

**PUBLICATIONS**

**Full length**


Abstracts:


Book Chapters

Figure 1: Effect of High Fructose Corn Syrup (HFCS) on hepatic triglyceride production and mitochondrial function.

Figure 2: On-line Food Frequency Questionnaire of Saudi School Children. Food frequency data will be correlated with Body Mass Index (BMI), waist-to-hip measurements (WHR) and Total Body Fat.
RESEARCH PROJECTS

Project Title: RAC#2060 007 Metabolic Syndrome, Diabetes and Cognitive Decline: effect of dietary components on Insulin Resistance, hyperlipidemia, Inflammation and cognition in a rodent model.

Investigators: Collison, K; Saleh, S; Inglis, A; Bakheet, R; Al-Johi, M; Shoukri, M and Al-Mohanna, F

Project Description

Metabolic syndrome, Diabetes and Cognitive Decline: effect of dietary components on Insulin Resistance, hyperlipidemia, Inflammation and cognition in a rodent model.

Progress

The pilot study has been completed. Phase 1: 50% completed.


Investigators: Collison, K; Subhani SN; Shoukri, M and Al-Mohanna, F.

Project Description

Food frequency survey of dietary habits in the Saudi population: correlation of diet with body mass index, waist-to-hip ratio and total body fat as indices for risk factors for the development of the Metabolic Syndrome.

Progress

90% complete and manuscript is in progress.

Project Title: In vitro metabolic studies into the etiology of Nonalcoholic Fatty Liver Disease (NAFLD) and Nonalcoholic Hepatic Steatosis (NASH) in hepatocytes.

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

Project Description

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

Progress

90% complete and manuscript is in progress.

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

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

Project Description

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

Progress

Phases 0 and I are completed. Phases 2-5 are ongoing.

Project Title: Whole Genome Scanning for Diabetes Associated Genes.

Investigator: Al-Mohanna, F.

Project Description

Whole genome scanning for diabetes-associated genes.

Progress

Ongoing.

Project Title: RAC# 2050 046 Vaccinia Virus Complement Control Protein (VCP) : Potential to Prevent Damage to Xenoreactive Cells.

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

Project Description

VCP is a potent anti-inflammatory molecule. We will use the lentiviral gene delivery system to ascertain its anti-inflammatory effects in a small-animal model.

Progress

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

Project Title: LAF237 Drug trial in Type 2 Saudi Diabetic Patients

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

Project Description

Current pharma begins to fail the average diabetic patient between 10 and 20 years into the disease. Better and more effective drugs are urgently required in order to avoid some of the more devastating and costly consequences of poorly controlled Type 2 diabetes, namely nephropathy, neuropathy and amputation of necrotic tissue. LAF237 (Vildagliptin, Novartis) is an oral DPP-IV inhibitor which has completed Phase III clinical trials and is due for FDA filling in 2006. In trials, LAF237 demonstrated a strong efficacy in lowering HbA1c levels, improving pancreatic islet cell function and insulin sensitivity, whilst maintaining neutral effect on body weight.

Progress

Recruiting patients.

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

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

Project Description

Use of aortic banding to induce gene expression of proteins involved in Myocyte renmodelling.
Biopsy specimens were taken at all stages in addition to full work-up and ECG monitoring. Banding progressively loosened to reverse procedure and further biopsy material taken. RNA, DNA and protein samples stored for analysis.

**Project Title: Serial Analysis of Gene Expression (SAGE) of Genes Involved in Xenorecognition of Foreign Antigens**

**Investigators:** Al-Mohanna F & Saleh, S

**Project Description**

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

**Progress**

These genes are now in the process of being analysed.

**FUTURE RESEARCH DIRECTION**

All of the above seven diabetes projects will continue to be pursued. We aim to build our program from this established research basis using as many resources and staff as we can accommodate.

**PUBLICATIONS**

(only those appeared on 2003-2006)

Eight (8) publications for the period 2004 – 2006 (see below).


Thrombosis both arterial and venous is the most common cause of morbidity and mortality in many countries. The causes of venous thrombosis (VT) in Saudi Arabia is believed to be similar to those in other countries, however the degree that each contributes to VT in the Saudi population is not known. The incidence and prevalence of VT and venous thromboembolism (VTE) and their trend in Saudi Arabia is not known. There is good reason to suspect that this will increase as it did in other populations as they move from developing to becoming developed. The increase may be mitigated if preventive measures are used for patients both in hospitals and in communities.

Acute rheumatic fever and rheumatic heart disease are the most common cardiovascular diseases in children and young adults. Medical and surgical treatments are not curative and have to be continued indefinitely with increasing cost. Primary and secondary prevention programs have decreased the incidence and recurrence of new cases but require extensive and continued effort. The development of a safe and effective vaccine remains the best hope for controlling or even eradicating the problem.

The thrust of the CRU is to study issues related to causes, incidence, prevalence and trend of VT and VTE in Saudi Arabia. Two projects are ongoing for the sixth year.

The CRU is also actively involved in testing the efficacy of a prototype vaccine against rheumatic heart disease.

**CURRENT APPROVED AND ONGOING PROJECTS**

**I. Thrombosis and Familial Thrombophilia (TAFT) Registry RAC 2001 017.**

**Investigators PI(s):** Jalal Saour FRCPI, Layla Mammo PhD  
**Co Investigators:** The Thromboembolic Service; Mohammed Shoukri PhD

**Project title:** The Saudi Thrombosis and Familial Thrombophilia (S-TAFT) Registry (KACST AT 23-35)

**Investigators PI:** Jalal Saour FRCPI  
**Co Investigator:** Layla Mammo PhD

**Statistics Consultant:** Mohammed Shoukri PhD
Project Description

S-TAFT registry is housed at King Faisal Specialist Hospital and Research Centre. This Registry, which is for Saudi nationals only, has evolved to The Saudi Thrombosis and Familial Thrombophilia (S-TAFT) registry. This registry is funded by KACST for three years.

Saudi subjects with venous or arterial thrombosis attending the Anticoagulation Clinic, Neurology, Obstetric and Gynaecology, and Gastroenterology are identified. After obtaining their written informed consent the DNA is tested for polymorphisms in prothrombotic gene(s). Patients testing positive for the mutation(s) are counseled by their attending physician and asked to have their families tested.

The Thrombotic Blood Bank stores all collected DNA's for future testing of new hereditary factors and to discover novel factors.

Progress

1. The S-TAFT registry active and ongoing for the 7th continuous year and it is in the last year of funding by KACST.
2. Two abstracts were generated both were podium presentations.
   a. The 8th Research Day, Department of Medicine KFSHRC.
   b. 18th International Symposium on Proteolysis and Fibrinolysis, San Diego, USA, August 26-31, 2006,
3. Results of testing 903 healthy Saudi subjects were collated and was published in the Journal Thrombosis and Haemostasis.

II. Study – in Saudi Arabia- to test the efficacy of a prototype vaccine against rheumatic heart disease (KACST AT 22 77).

Investigators (PI): Layla Mammo PhD
Co-Investigators: Shaheen Nakeeb, MVP, PhD, Maie Shahid, FRCP, Jalal Saour FRCP

Project Description

The effectiveness of a prototype vaccine- developed and tested in mice by the founder at Queensland Institute for Medical Research (QIMR), Brisbane - Australia, is to be evaluated in baboons. An initial pilot study will determine whether it is possible to infect baboons with Streptococcal pyogenes, a bacteria, by challenging them with a virulent strain. This phase has been successfully completed. It is followed by the active phase where four groups of baboons are studied. Three groups will be protected with different doses of a prototype vaccine and will later be challenged with the virulent bacteria; and then compared to the fourth untreated group.

Progress

Due to an outbreak of TB infection in the Animal Facility, baboons used for this study were euthanized on November 22, 2005. Clearance from all concerned to repeat the final phase of this project was obtained during January 2007.

The Active Phase was restarted on January 15, 2007.

One abstract entitled “Successful Challenging Of The Papio Hamadryas Baboon With Group A Streptococci Isolates From Human” was presented as a Poster. During The 8th Research Day, Department of Medicine. May 16, 2006.

This poster was selected for the Third Best Research Award.
III. Inferior Vena Caval (IVC) Filters, KFSH&RC Experience. RAC 2051059

Investigators (PI): Jalal Saour, MD, FRCP, Abdulaziz Al Harthi, MD, Layla Mammo, PhD
Co-Investigators: Mona El Sharif, MD, Ebtisam Bakhsh, MD, Taugir Rana, MD

Objectives

This project will look at the KFSHRC experience in managing patients with IVC FILTERS. Part of the project is to assess these patients for hereditary thrombophilia. The results will influence future management of those patients.

Status

Final report submitted, manuscript in preparation.

IV. The Registry for Thromboembolic Diseases (TED) RAC 2001 045

Investigators PI(s): Habib Bassil MD, Jalal Saour FRCPI, Layla Mammo PhD
Co-Investigators: The Thromboembolic Service Team

Project Description

All patients attending the KFSHRC - Anticoagulation Clinic with thromboembolic diseases are entered into the registry database and followed to assess safety, efficacy and other management issues.

Progress

Developed into a KFSHRC based registry, the TED registry.

TRAINING AND EDUCATION

During 2006, the CRU accepted two Saudi and one non Saudi Trainees.

OTHER ACTIVITIES

Members of CRU

- Travel to peripheral Ministry of Health Hospitals in the Kingdom as part of the Hospital Outreach Program and to promote the S-TAFT registry.
- Contributed to the design and implementation of “VTE Prevention Workshop” September 2006.

FUTURE PLANS

Due to operational changes all above projects shall be terminated.

PUBLICATIONS

Manuscripts

Abstracts and Presentations - 2006


   - The Syndrome of Venous Thrombosis- Toward a National Registry. Riyadh.
   - Venous Thrombosis In Pregnancy. Abha.

Abstracts and Presentations 2005


Biological and Medical Research


Presentations and Abstracts - 2004


Awards

1. Third Best Research Award from the Department of Medicine, KFSHRC. The 8th Research Day, May, 2006.

2. Top (Best) Award from the Department of Medicine, KFSHRC. The 7th Research Day, May 17, 2005

3. Second Best Award from the Department of Medicine, KFSHRC. The 7th Research Day, May 17, 2005.
Cancer is a complex and heterogeneous genetic disease that results from the accumulation over age of a plethora of genetic and epigenetic alterations in various genes, which leads to uncontrolled cell proliferation and resistance to cell death. The major goal of this research section is to participate in understanding the fundamental processes that regulate the equilibrium between cell proliferation and cell death and to identify and characterize molecular biomarkers for cancer staging/grading. We are also interested in discovering novel and efficient drugs that can be used for prevention and/or treatment of cancer.

The major findings of this year are the following:

- The \( \gamma \)-synuclein oncogene is demethylated in different stages of ovarian carcinomas, and also in normal tissues from ovarian cancer patients.
- *Piperidone-curcumine* is more effective than curcumin in triggering apoptosis, arresting cell proliferation and modulating the expression of cancer related proteins.
- Most of the medulloblastoma cells are defective in the cell cycle arrest at the post-replicative stages in response to the chemotherapeutic agents lomustine and vincristine.
- The majority of breast cancer Stromal fibroblasts are defective in the induction of p53 and p21 in response to \( \gamma \)-rays and express low levels of these tumor suppressor proteins.

**RESEARCH PROJECTS**

**Project Title:** Expression of \( \gamma \)-Synuclein and Its Role in Ovarian Cancer in Saudi’s Female Patients. RAC # 2050041

**Investigators:** Nisreen Al Moghrabi (PI), Hany Salem, Wafa Ajoor, Nada Al-Sahan and Asma Tulbah

**Project Description**

\( \gamma \)-synuclein, known initially as breast cancer specific gene (BCSG1), is a new candidate oncogene that is found to be highly expressed in late stage breast and ovarian cancer. The oncogenic activation of \( \gamma \)-synuclein, which is due to the loss of its epigenetic control, results in compromised mitotic checkpoint, significant increase in cell motility and invasiveness *in vitro*, profound augmentation of metastasis *in vivo* and resistance to drugs that cause apoptosis through the JNK pathway such as taxol and vinblastine. Our main objective is to study...
the methylation status, together with the level of the expressed message and protein of \(\gamma\)-synuclein gene, in the different stages of ovarian carcinomas: (a) benign cyst adenoma, (b) borderline tumor, (c) noninvasive micro papillary carcinoma (MPC), (d) invasive low-grade carcinoma (invasive MPC) and late stages ovarian cancer, in Saudi female patients in an attempt to use it as, (I) an early predictor marker for malignant progression, (II) as a predictive factor for chemotherapy resistance, and (III) as a molecular indicator of tumor metastasis.

**Progress**

So far, 13 fresh and 24 archived ovarian cancer tissues (11 ovarian cancer tissues and 10 non-neoplastic non-ovarian tissues obtained from the same patients) of different stages have been tested for the methylation status of the \(\gamma\)-synuclein gene using the MS-PCR technique. All fresh cancer tissues showed demethylated status of the gene, but at different levels. For the Archived tissues: all Mucinous type (3 out of 11) showed total demethylation, all Endometrioid type (4 out of 11) showed partial demethylation. Importantly, all non-neoplastic non-ovarian tissues obtained from 11 patients showed partial demethylation, indicating the occurrence of ongoing epigenetic changes in other non-neoplastic tissues.

![Figure 1. Ethidium bromide stained agarose gel showing MS-PCR products relative to the \(\gamma\)-synuclein gene.](image)

**Project Description**

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

**Progress**

10 primary medulloblastoma primary cells were established and characterized: In response to the chemotherapeutic drugs lomustine and vicristine, they are relatively resistant and most of them are defective in delaying the cell cycle at the G2/M phase. RNA and protein levels of various important tumor suppressor and onco-genes are presented in Figure 2.

It is noteworthy that for all the genes that have been studied the RNA levels do not always reflect the levels of the corresponding protein.

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

**Project Title:** Cellular and Molecular Characterization of Medulloblastoma in Saudi Patients: Correlation with Prognosis and Therapy. RAC # 2050016
Figure 2. RT-PCR and western blots showing the expression levels of different genes in medulloblastoma primary cells developed from Saudi patients.

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

Completed.

We have shown this year that the tumor suppressor p16 protein controls UV-dependent activation of the tumor suppressor/oncogene p21 protein through the control of the sub-cellular distribution of the RNA binding HuR protein.

Project Title: Functional identification of breast cancer genetic predisposing factors. KACST/RAC# 2031 091

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

Project Description

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

Progress

About 30% of the project has been achieved.

We have characterized 10 primary tumor-associated fibroblasts and have shown that most of them are defective in the γ-ray signaling pathway, which is under the control of the protein kinase ATM. Furthermore, the expression levels of p53 and its downstream effector p21 are reduced in these cells. These results indicate that tumor associated fibroblasts have an active role in the development and progression of breast cancer and that the treatment of these neoplasms should take in account the presence of these “premalignant” cells, especially in preventing cancer recurrence.

Project Title: Effect of Curcumin Analogues on Breast Cancer Cell Lines. RAC # 2050 039

Investigators: A. Aboussekhra (PI), A. Al-Hazzaa, K. Youssef, E. Al-Hejaily

Project Description

Pilot study aiming at investigating the effects of curcumin and two of its analogues on breast cancer cell lines. Our main objectives are to study
the cytotoxic effect of these agents, their effects on the cell cycle and cell cycle proteins as well as their ability to trigger cell death. The current study is designed as an attempt to identify a potential new drug with efficient and selective cytotoxic effect.

Progress

About 70% of this research project has been achieved.

We have studied the effect of curcumin and two analogues on two "normal" and three neoplastic epithelial cells and have shown that piperidone-curcumine triggers apoptosis in epithelial cells more efficiently and selectively than curcumin and ethyl-curcumine (Fig. 3). Furthermore, piperidone-curcumine is more effective in up-regulating tumor suppressor genes and down regulating oncogenes, which suggests that this agent is potentially a potent anti-cancer agent.

FUTURE RESEARCH DIRECTION

Further characterize the piperidone-curcumine as potential potent anti-cancer drug. Elucidate the role of breast fibroblasts in the development of breast carcinoma and search for molecules/drugs able to suppress this carcinogenic effect. Continue to study the role of the γ-synuclein gene in the development and progression of ovarian cancer. Concerning medulloblastoma, the most common childhood malignant brain tumor, we would like to investigate the link between the expression of some important genes and the response of these neoplasms to various anti-cancer agents.

PUBLICATIONS


![Figure 3. AnnexinV-Propidium Iodide/Flow cytometry. Effect of curcumin and analogues on the MDA-MB231 breast cancer cell line.](image-url)
The immune response plays a critical role in various diseases and therapeutic approaches, including organ transplantation, autoimmune diseases, and cancer and infectious diseases. This response is under the control of different important molecules such as human leukocyte antigens (HLA), NK cells receptors (KIR) and cytokines molecules. These molecules are of great interest because of their importance due to high polymorphism, predominant expression and predisposition ability to mount an immune response. The competence of these molecules to recognize different (self and non-self) antigens explains: why organs transplanted between individuals are rejected (unless immunosuppressive drugs are administered to transplant recipients), their critical roles in the development of autoimmune diseases, as well as cancer and infectious diseases. The mission of the Histocompatibility and Immunogenetics Research Unit (H&I) is to elucidate fundamental molecular mechanisms and cellular processes that control immune responses in order to increase understanding how these genes function and to apply this knowledge to improve the therapy by tailoring the treatment based on individual genetic background.

In close collaboration with clinicians and scientists of the KFSH&RC and with the IHWG and SBT team from University of Utrecht, Netherlands, the section is focusing on:

- Initial determination of the frequencies of HLA class I and II alleles in the Saudi Arabian population, in order to define novel alleles to explore their genetic polymorphisms for Anthropological studies.
- Understanding the immunobiology and genetics of HLA polymorphisms, cytokine and KIR molecules, and their role in the immunogenetics of hematopoietic stem cell transplantation and renal allograft rejection that leads to engraftment and organ rejection.
- Genetic alteration of HLA molecules and assessing their abnormalities in malignant cells.
- Investigating of HLA-associated diseases such as autoimmune diseases (RA, BD and IDDM) and infectious diseases.
- Establishment of Saudi HLA genome database.
RESEARCH PROJECTS

Project Title: Identification of HLA Alleles in Normal Saudi Individuals by Sequence Based Typing. RAC # 2010002

Principal Investigators: Khaled Al-Hussein, PhD  
Co-Investigator: Abdelghani Tbakh, MD

Project Description

Human leukocytes antigens (HLA) might play a role in the causation and the development of most autoimmune diseases, cancer, susceptibility to infectious agents and most importantly allografts 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 would not detect all allelic variations with precision without information on their DNA sequences. In this KACST approved project, 1000 healthy Saudi individuals from various regions of the Kingdom of Saudi Arabia will be HLA typed using a valuable method known as sequence based typing (SBT) where a spectrum of HLA class I and II alleles will be identified. This will allow us in establishing a Saudi HLA allele database in the Kingdom.

Progress

During the course of this project, twenty-one HLA-A alleles were detected. HLA-A*0231 and HLA-A*3102/3104-5 were found to be the most frequent. The most diversified region in the HLA-Class I loci is the HLA-C Twenty-eight HLA-C alleles were detected. This is a preliminary data from normal Saudi individuals. Results will still vary as the data are still accumulated and were not obtained from the entire subjects (1000 samples).

Project Title: HLA Gene Associations in Behcets Disease and Rheumatoid Arthritis Patients in Saudi Arabia. RAC # 2000030

Principal Investigator: Abdullah Al-Dalaan, MD  
Co-Investigators: Ahmed Al-Shaikh, MD, Salman Al-Saleh, MD, Khaled Al-Hussein, PhD

Project Description

Behcets disease (BD) and rheumatoid arthritis (RA) are common rheumatoid ailment in the Kingdom of Saudi Arabia. It is established that these are autoimmune diseases, which result from destruction of self-tissue via false immune recognition of targets through the HLA molecules. Genes of the HLA region are therefore, very important for BD and RA. The widely reported risk genes for BD is the class I (HLA-B and –C), while a strong association has been found between RA and HLA Class II (HLA-DRB1 and –DQB1). This KACST approved project aims to define the possible genetic factors underlying susceptibility to BD and RA in Saudi Arabian population by identifying HLA Class I (-A, -B and –C) and class II (-DRB and -DQB) genes using sequence based typing (SBT) has advantage over other techniques specially serology and may result in the identification of novel markers for BD and RA and lead to new methods in the diagnosis and treatment of the disease susceptible individuals.

Progress

Molecular typing of HLA-Class I and Class II was performed by sequence based typing (SBT). Allele frequencies were compared between 100 BD patients and ethnically matched healthy
controls. Positive association was demonstrated by HLA-B*51011/5108/5103-04/5106 and HLA-Cw*0602-04 and negative association was exhibited by HLA-B*3501/-06/3508/35091-92 and HLA-Cw*04011-12/0403/0405/0407. HLA-Class II alleles (DQB and DRB) do not show any association with BD. The study revealed that the HLA-B51 and HLA-Cw*06 alleles are pathogenic factors in behcets disease.

**Project Title**: HLA Gene Association in Patients with Type 1 Diabetes in Saudi Arabia. RAC # 2000029

**Principal Investigators**: Khaled Al-Hussein, PhD  
**Co-Investigators**: Mohammed Al-Ahmed, MD, Ameera Gaafar PhD

**Project Description**

Type 1 diabetes is an autoimmune illness that can result from interaction of genetic, immunological and environmental factors that lead to the destruction of beta cells of the islets of langerhans in the pancreas of both human and animals, mediated by both CD4+ and CD8+ T cells. Genetic predisposition to the disease through HLA-Class II genes (DRB, DQA and DQB) has been dealt with extensively for the past three decades. Since T cells see the antigen in the context of MHC antigen, immunogenetical studies are also imperative to decipher the causation of beta cell autodestruction through the interaction of both humoral and cell mediated interaction. We attempt to study the correlation of these factors in a cohort of Saudi population consisting of 100 newly diagnosed type 1 diabetic patients and 100 age and sex matched Saudi controls.

**Progress**

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 addition, this project will focus on the Immunogenetics of this disease and the role of CD4+, CD8+ T cells on the destruction of beta cells of the islets of Langehans in the pancreas. So far we collected samples and analysed the frequency of HI CD4+ and CD8+ T cells from IDDM and normal subjects.

**Project Title**: Evaluation of Anti-Tumor Activity of γδ T Cell. RAC # 2030022

**Principal Investigators**: Mahmoud Al-Jurf MD and Khaled Al-Hussein, PhD  
**Co-Investigators**: Ameera Gaafar PhD, Abdelghani Tbakhi MD, Hamad Al-Omar MD, Ahder Al Sayed MD

**Project Description**

The task of innate effector cells such as macrophages, NK cells, NKT cells, and γδ T cells in tumor immuno-surveillance and tumor immunotherapy has recently been revisited. T cells bearing the TCR γδ represent a minor subset of human peripheral T cells (1-10%), differing from αβ T cells in cell surface phenotype. Their distribution and function in humans is less well characterized, though some evidence has been gathered indicating that γδ T cells have been shown to exhibit major histocompatibility complex (MHC)-unrestricted cytotoxicity against some tumors. In addition, it has been recognized that donor-derived γδ T-cell may serve as facilitating cells, promoting the engraftment of donor hematopoietic stem cells across varying degrees of MHC disparity. Yet, the in-depth position of γδ T cells in the immune response of tumor patients remains largely elusive and controversial. Thus, the aim of this study is to characterize γδ T-cells and to investigate its antitumor effect in cancer patients.
Progress
As a spin off the above listed project, we conducted the following investigation: γδ-T cells were screened for the known granzyme B and perforin gene polymorphisms in the breast cancer and normal controls.

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 # 990029

Principal Investigators: Hamad Al-Omar, MD and Khaled Al-Hussein, PhD
Co-Investigators: Ameera Gaafar PhD, Mahmoud Al-Jurf MD, Anwar Iqbal MD, Abdelghani Tbakhi, MD

Project Description
Dendritic cells (DC) are potent and professional antigen presenting (APC) cells, and activate naive T cells e.g antileukemia activity. This cellular interaction and activation provides a model for immunotherapy and circumvent the side effects, which may arise from adoptive transfer of donor leukocytes infusions such as graft versus host disease (GVHD) and bone marrow aplasia. DC from patients with CML demonstrated a lower capacity of T cell stimulation when compared to DC from normal subjects. Also, DC from these patients was shown to be heterogeneous in their origin (i.e. some are driven form a CML clone carrying the bcr/abl translocation and others are driven form a normal clone without the translocation). It is believed that CD34-/lineage-cells, which are capable of multi-lineage hematopoietic generation, could represent earlier stem cells as compared to CD34+/lineage-cells. These cells may have higher proportions of bcr/abl-negative cells that might have a better antigen presentation capacity. It is the aim of this study to find out if the DC from CD34-/lineage-compartment carry the bcr/abl translocation and to assess their antigen presentation capacity.

Progress
DC generated and differentiated from CD34-lineage obtained from CML, express higher levels of antigen presentation costimulatory molecules and mixed lymphocytes reaction than DC from CD34+Lineage.

Project Title: Study of the Association Between HLA-DRB1 Alleles and Vogt-Koyanagi-Harada’s Disease in Saudi Patients. RAC # 2050034.

Principal Investigators: Khalid Tabbara, MD, Khaled Al Hussein, PhD

Vogt-yanagi-Harada disease is a potentially blinding disorder that afflicts the uvea in the eye leading to chronic inflammation. The disease is characterized by an acute onset followed by chronic progressive bilateral panuveitis associated with exudative retinal detachment. In Saudi Arabia, VKH has been found to be a common cause of uveitis as previously reported by Islam and Tabbara. Increased risk among those with a certain HLA genotypes showing strong association with DRB1 *0405 and DRB1 *0410 and VKH disease were previously reported. It has been suggested that HLA DRB1 gene is one of the candidate genes of VKH. This association has been shown among patients in Japan and Brazil. In Saudi Arabia, there has been no study on the genetic predisposition among patients with VKH disease.

Progress
Genomic DNA was extracted from 20 blood samples obtained from VKH patients. The project is progressing well and we anticipated that the project would be completed within the coming 12 months.
Project Title: Determination of polymorphism(s) in genes controlling the immune responses in Saudi renal transplant patients experiencing graft rejection. RAC # 2041081.

Principal Investigators: Khalid Abdulmohsen Al Meshari, MD
Co-Investigators: Abdelghani Tabakhi, MD, Khaled Al Hussein, PhD

Project Description

Despite major advancement in the field of organ transplantation, acute and chronic rejection remains the primary cause of short and long-term allograft failure. Optimal matching and negative serological cross-match (confrontation with allogenic organ transplantation) still lead to both humoral and cellular alloimmune responses resulting in graft rejection. Although current immunosuppressive agents are effective in inhibiting alloreactive T lymphocytes, they are not able to counteract the detrimental effect of preformed HLA antibodies, hence leading to hyperacute rejection. The immune system and its genes are of crucial importance and key elements to facilitate the comprehensive logistics of the microenvironment needed for graft acceptance. Key elements such as MHC and KIR genes, which regulate surface molecules, expressed on target cells (HLA molecules expressed at the graft) and natural killer cells (killer cell immunoglobulin-like receptors) respectively, create an innate alloreactive capacity causing cytolytic activity leading to the destruction of the graft. As the frequencies of HLA and KIR alleles vary considerably among different ethnic groups, an increasing amount of evidence suggests that some ethnic groups such as native Africans possess greater genetic diversity than found in the Americans or the Europeans affecting the outcome of organ transplantation. The possibility that genetic/ethnic differences may determine the clinical outcome among Saudi Arabian transplant patients has not been investigated to-date. In this research study, we propose to examine the features of some of the immune genes that reflect the demands imposed by intense selection such as MHC, cytokines and KIR genes, particularly the polymorphic states of these genes in relation to renal transplant outcome. Hopefully intensive monitoring of Saudi transplant patients with more sophisticated new tools will lead to an identification of some optimal parameters to predict the presence or absence of detrimental factors underlying alloimmune responses in clinical transplantation. It would be clinically rewarding to utilize validated molecular markers enabling an identification beforehand of those donor/recipients combinations, that do or do not lead to a destructive alloimmune response, and selectively exclude transplantation with donors that are likely to induce a strong alloimmune reaction.

Progress

Genomic DNA was extracted from blood samples collected from 25 donors and 25 recipients. Amplification of KIR was carried out by PCR reaction mixture

Project Title: Clinical Significance of Natural Killer Cells Receptors (KIR) Genes Polymorphisms in the Outcome of Bone Marrow Transplantation in Hematological Malignancies. RAC # 2051001

Principal Investigators: Mahmoud Al-Jurf MD
Co-Investigators: Abdelghani Tabakhi, MD, Khaled Al Hussein, PhD

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 cell 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 and therefore involved in the control of NK cell tolerance to self, as well as in the elimination of cells that have down regulation of MHC class I molecules.

Progress

Research has been approved by KACST to be commenced on April 2007.

PUBLICATIONS

2. Al-Hussein KA, Rama NR, Abdullah MA, Rozemuller E and Tilanus MG. Influence of the HLA-DRB1*04 and HLA-Cw*07 alleles on the susceptibility of Rheumatoid Arthritis in Saudi patients. The BSR Annual Meeting and the BHPR Spring Meeting, a joint meeting with the The German Society for Rheumatology Annual Meeting, Germany, April 19-22, 2005.
Low Power Laser Therapy (LPLT) is recognized worldwide for its importance in Dentistry, Dermatology, Immunology, Neuroscience, Oncology, Rheumatology and Physical Therapy.

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

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

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

Figure 1. BioMechanical and Biochemical Analysis of scars after Low Power Laser Therapy (LPLT)
Figure 2. Photodynamic Therapy (PDT) of Human Undifferentiated Thyroid Carcinoma Using 5-Amino-Levulinic Acid.

RESEARCH PROJECTS

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

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

Project description

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

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

- Determine the effects of several Low Power Laser (LPL) GaAs diode-lasers 532nm, 633nm, 670nm, 785nm, 810nm and 980nm on wound/burn healing in the non-diabetic and diabetic rats.
- Explore the use of low power from the widely used high power (HPL) surgical lasers, e.g. Nd: YAG (1060nm), Er: YAG (2940nm), CO2 (10600nm), and excimer lasers for biomodulation.
- Use polychromatic light emitting diode (LED) as new light source in wound healing.
- Determine the efficiency of laser biostimulation using IR and UV then compare it with wound healing drugs solcoseryl (SS), regranex (RG) and polygen (PG).
- Determine whether a synergistic or additive effect exists in varying the drug dose and laser dose combinations.
- Biomechanical and biochemical testing of scars after various Laser/LED and drug treatments.

Progress

This project is currently in its final year. Seventeen (17) Abstracts and Seven (7) manuscripts have been published.

Project Title: Laser Biostimulation: Wound Healing. (# 960002).

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

Project Description

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

FUTURE RESEARCH DIRECTION

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

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

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

Papers


Abstracts


3. Al-Watban FAH, Gonzaga VD. Medical Lasers for Photodynamic Therapy and Wound Healing Acceleration, Conference of King Abdulaziz City for Science and Technology (KACST)”, King Faisal Hall Intercontinental Hotel, Riyadh, KSA, 11-14 November.


International Congresses Organized by Laser Medicine Research Section

- Laser Therapy International Symposium 2006, King Faisal Specialist Hospital and Research Centre, 14-15 March 2006/14-15 Safar 1427, Riyadh, KSA.
Commendable Achievement

Dr. Farouk A.H. Al-Watban, MSc, PhD, FASLMS, President of World Association for Laser Therapy (WALT) from 2006-2008.
Infectious diseases continue to pose serious health problems worldwide and Saudi Arabia is no exception. Our unit concentrates on studying the distribution and prevalence of infectious agents in the Kingdom. Molecular techniques are employed to study viral and bacterial genomic variations and genotypes. Our major effort in this direction was on human diarrhea viruses, and bacteria that cause nosocomial infections including *Acinetobacter sp.*, *vancomycin*-resistant *enterococci*, and methicillin-resistant *Staphylococcus aureus*. Other projects include the development of computational tools for the analysis of DNA sequences to study phylogenetic relationship between infectious organisms and the relationship between disease status and infectious organisms. Also, the Section is also collaborating with other scholars on various projects on detection and pathogenesis of infectious diseases.

**SPECIAL ACCOMPLISHMENTS**

- Continue to use molecular methods for tracing nosocomial pathogens in our hospital and other hospitals inside and outside Riyadh.
- Standardization of molecular diagnostic methods for detection of pathogens in various clinical samples.
- Studying host-pathogen interaction and pathogenesis at the molecular level. This was done by studying Epstein-Bar virus (EBV) and *Leishmania major* and some of the mechanisms involved in their interactions with host cells.
- Collaborate with various Saudi universities in the supervision of graduate students.
- Training of students on molecular techniques in microbiology.

**RESEARCH PROJECTS**

**Project Title:** Genotyping of Hepatitis B (HBV)

**Investigators:** Mohammed N. Al-Ahdal, M. Rezeig, A. Hassan, Damian dela Cruz, Ahmed Al-Qahtani
Project Description

This project was carried out to identify HBV genotypes prevalent in Saudi Arabia. As genotyping plays an important role in HBV treatment, PCR and DNA sequencing were used to study HBV genotypes. Our results show that genotyping can identify the seven HBV genotypes; even two or more genotypes exist in one clinical sample (Fig. 1). Previous studies report that HBV infected patients belong to genotype D, however there was no extensive study conducted for the presence of recombinant genotypes present in one sample. These results reveal that recombination of genotypes could exist in one sample, however, these results are preliminary and we are conducting further studies to validate this finding.

Figure 1. Distribution of genotypes of HBV infection.

Progress

Continuing.

Project Title: Detection of transmissible virus infection among intravenous Drug users

Investigators: Mohammed N. Al-Ahdal, Damian Dela Cruz, A. Al-Zahrani

Project Description

Serum samples were collected from intravenous drug users and were examined for the presence of a panel of transmissible pathogenic viruses. The following viruses were studied: HCV, CMV, HBV, Parvovirus B-19, TTV, HHV-6, HDV and EBV. One hundred sixty eight samples were tested and our results show that the following viruses were detected in these samples as follows: HBV in 7.14% (12), HCV in 22% (37), TTV in 67.85% (114) and HHV-4 in 0.6% (1). HDV, HHV-5, HHV-6 and parovirus B-19 were not detected in any of these samples.

Project Title: Epidemiology of Diarrheal Virus Infection in Pediatric Patients in Three Major Cities in Saudi Arabia

Investigators: Hamsa T. Tayeb, Mohammed N. Al-Ahdal, Micheal J. Cartear, Ahmed A. Al-Qahtani, Damian M. Dela Cruz

Project Description

This project is continuing from previous years to study the epidemiology of diarrheal viruses in the Kingdom. Firstly, genotyping of adenovirus was accomplished using PCR-RFLP technique. Of all ELISA-positive, 50% were EAdV-41, 42.9% were EAdV- 40 and 7.1% were untypable by this technique. A representative gel of the analysis is shown in Fig. 2.

Non-denaturing polyacrylamide gel electrophoresis (PAGE) was used to study the genotypes of rotavirus. RNA molecules were purified from stool samples positive for rotavirus and were fractionated on PAGE. Figure 3 is a representative of the results obtained. Short profiles of RNA were evident in 90% of the samples analyzed and 10% showed long electropherotype.
Figure 2. RFLP pattern of the PCR product of the hexon gene of adenovirus using HhaI restriction enzyme (Panel A) and Rsal (Panel B). M is the PUC18/ MspI molecular weight marker.

Progress

Continuing.

Project Title: Characterization of Molecular Interaction Between Epstein-Barr Virus (EBV) and Mammalian Cells

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

Project Description

1. Detailed mapping of the CpG methylation status of the BART region.

C666.1 tumor cells that harbor EBV were used for the methylation status. EBV DNAs from these cells were analyzed by restriction fragment technique and Southern hybridization. Eleven probes were used and the analysis yielded a candidate region of 870 bases that was hypomethylated and this region extends from upstream of the transcription start to a region that is downstream of exon I. The summary of the detailed methylation analysis is shown in Fig. 4.

2. Cellular proteins that bind sequences within the unmethylated regions of the BART promoter.

To identify transcription factors that could bind to the BART promoter sequence, extracts from both HEK293 and C666.1 cells were tested with nine different double stranded oligonucleotides (designated 1 to 9) spanning the whole unmethylated region of the promoter. Only two probes 5 and 9 yielded a mobility shift suggesting the existence of factors that could bind to these sequences (Fig. 5). Computer analysis has shown that it is likely that several known transcription factors could interact with this promoter including RUNX1, GATA, HSF and STATs. Revealing the exact mechanisms in this possible interaction could lead to how EBV induces pathogenesis.
Project Title: Clonal Distribution of Methicillin-Resistant Staphylococcus aureus in Saudi Arabia

Investigators: Alwaleed Alaidan, Marie Bohol, Ahmed Al-Qahtani, Mohammed N. Al-Ahdal

Project Description

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of hospital-acquired infections that are becoming increasingly difficult to combat because of emerging resistance to all current antibiotic classes. The evolutionary origins of MRSA are poorly understood, no rational nomenclature exists, and there is no consensus on the number of major MRSA clones or the relatedness of clones described from different countries. The present study was designed to detect the presence of MRSA strains, to perform comparative chromosomal DNA analysis of MRSA strains using Pulsed-field gel electrophoresis and to identify major MRSA clones in Saudi Arabia. A total of 300 isolates of MRSA were procured from 5 regions in Saudi Arabia. Isolates were identified as MRSA strains according to the National committee for Clinical Laboratory Standards (NCCLS) guidelines and fingerprinted by PFGE. Data were stored and analyzed with BioNumeric software (Applied Maths, BVBA, Sint-Martens-Latem, Belgium). Primary results show as previous studies have suggested that MRSA strains are highly clonal. Analysis of *Sma*I macrorestriction profiles of the 297 MRSA clinical isolates revealed 127 unique patterns that clustered above 85% similarity into 10 PFGE types (M1-M10) by computer analysis. Figures 6 is a representative for the data obtained.

Figure 4. Sequence of the unmethylated CpG islands analyzed in the BART region. Black box indicate where unmethylated sequences are located.

Figure 5. Unmethylated region of BART promoter that show sites with possible binding sites for some known transcription factors.

Progress

Continuing.
Progress

Continuing.

Project Title: Comparative performance of the COBAS Amplicor assay and in-house real-time PCR assay for diagnosis of Chlamydia trachomatis infection

Investigators: Hamid Jalal, Abdulrahman Al-Suwaine, Hannah Stephen, Christopher Cane and Christopher Sonnex

Project Description

Four different assays were investigated, the COBAS Amplicor CT test (Amplicor PCR), in-house real-time PCR (IHRT-PCR), in-house nested cryptic plasmid PCR and in-house nested major outer membrane protein PCR. These assays were performed on genital swabs from 1000 consecutive patients. The samples were designated true positive if Chlamydia trachomatis DNA was detected by at least two of the four mentioned assays while a sample was defined as true negative if C. trachomatis DNA was detected in only one or none of the assays. By this criterion, amplicor PCR designated 144 samples positive: 128 (89%) of 144 were true positive and 16 (11%) were false positive (Table 1). IHRT-PCR detected 126 of 129 true positive samples and did not generate any false positive results. We conclude that the sensitivity of IHRT-PCR was comparable with, and specificity was higher than amplicor PCR for the diagnosis of genital chlamydial infection.
Table 1. Performance of molecular assays for the diagnosis of *C. trachomatis* infection.

<table>
<thead>
<tr>
<th>Assay</th>
<th>No. of true positives</th>
<th>No. of false positives</th>
<th>No. of true negatives</th>
<th>No. of false negatives</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predictive value (%)</th>
<th>Negative predictive value (%)</th>
<th>Efficiency (%)</th>
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<td>485</td>
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<td>IHRT-PCR</td>
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<td>50</td>
<td>9</td>
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<td>475</td>
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</table>

Progress

Completed.

FUTURE RESEARCH DIRECTION

- Studying host genetic polymorphisms that contribute to disease progression in HBV and HCV infected patients.
- Studying viral mutations that contribute to emergence of nucleoside analogs-resistant HBV strains.
- Continue standardization of molecular methods for the detection and quantification of nucleic acids from emerging and re-emerging pathogens.
- Continue identification of strains responsible for nosocomial pathogenesis and community spread of resistant pathogen.
- Studying host molecules essential for host-pathogen interaction.

SERVICES

In addition to consultations requested by internal departments, universities, and government agencies, services offered by our section include:

- Plasmid DNA purification/characterization
- Genomic DNA and RNA isolation
- Genomic DNA and cDNA cloning

- PCR diagnostics
- Pathogen genotyping by PCR, RFLP, RAPD and PFGE
- Recombinant virus construction
- Transformation/transduction protocols
- Southern, Northern, Western blot analysis

EDUCATION AND TRAINING

In 2006, two full-time PhD students were advised by our Section (Ms Maha Al Mozaini and Ms Hamsa Tayeb). One MSc student (Quweet Qabbani) from KSU is being advised by Dr. Ahmed Al-Qahtani who serves as a co-advisor. One MSc student (Bothaina Al-Shahrani) from KSU is being advised by Dr. Al-Waleed Al-Aidan who serves as a co-advisor for her Masters thesis. One MSc student (Maha Al-Amer) from KSU is currently using our facilities to perform different techniques required for her Master’s work. The following individuals have been trained in our section for various periods of times throughout the year 2006: Nada al-Harbi, Reem Al-Mashaabi, Saad Al-Qahtani and Tahani Al-Hazani.

PUBLICATIONS — (2004-2006)

1. Al-Mozaini M, Al-Ahdal M, Kessie G, Dela Cruz D, Rezeig M, Al-Shammary F. 2006. Molecular epidemiology and genotyping of TT virus isolated from Saudi blood donors and


Our research interest is directed at translational clinical cancer proteomics (from lab bench to bedside). We study the molecular alterations involved in different human solid epithelial tumors as well as hematological malignancies. We use state of the art proteomics technologies including protein separation by 2-D gel electrophoresis and MALDI-TOF mass spectrometry for automated protein identification (Figure1). Currently, we study the complex protein expression patterns that may be decisive for the biological behavior and treatment sensitivity of specific human tumors.

Goals and Objectives

- Our goal is to conduct proteomics research of clinical relevance to patient care.
- To discover potential biomarkers for routine diagnostics/ novel way of artificial tumor classification using multivariate data analysis of differentially expressed proteins.
- Encourage national and international collaborative proteomics projects and provide educational/training supports.

Progress

We have succeeded in setting up a functional clinical proteomics laboratory. Six research projects were approved by ORA within 2 years of establishment. Because of some obvious limitations of working with fresh clinical materials, we have managed to present two posters at international meetings. Two manuscripts are in preparation and it is anticipated that we will soon start to publish some of our findings during this current year.
Figure 1

Biomarker Discovery Strategies

Clinical Samples

Tumor Tissue

WCL/Total Proteins

>2000 spots

Image Analysis

Protein Identification
MALDI-TOF-MS/ LC/MS/MS

Discovery of potential biomarkers present in both tissue and serum

Validation of biomarkers in large archival materials

Blood/BM Serum/Plasma

Crude/Total Proteins

>1000 spots

Figure 2

Novel way of artificial tumor classification using multivariate data analysis of differentially expressed proteins

Sample Types

Blood

Tumor biopsy

Protein Fingerprints

Multivariate analysis
(Artificial intelligence algorithms)

Matching with 2-DIE dbs-
of different tumors

Ubiquitin

C12

C15

C16

V1

V2

V3

V4

Artificial diagnosis

Biological and Medical Research Dept – King Faisal Specialist Hospital and Research Centre – Annual Report 2006 (5-7 March 2007)
RESEARCH PROJECTS

Proposal # 2050 040

Chronic myeloid leukemia: Development and validation of therapeutic hematoproteomic biomarkers.

Running Title: Protein Expression Profiling in Chronic Myeloid Leukemia

Principal Investigator: Ayodele Abdulkareem Alaiya, MB.BS, MPH, PhD
Co-Principal Investigators: Mahmoud Al-Jurf, MD and Naeem Chaudhri, MD
Co-Investigators: Mai Al-Mohanna, PhD, Entezam Sahovic, MD, Fahad Al Mohareb, MD, Fahad Al Sharif, MD, Hamad Al Omar, MD, Hazzaa Al Zahrani, MD, Ali Al Shanqeeti, MD, Abdelghani Tbakhi, MD

Project Description

This project will focus on the analysis of global protein expression profiles for patients with CML in the chronic phase (CP CML). We will analyze peripheral blood (plasma/serum) and bone marrow samples from the same patients using 2-D gel electrophoresis and computer-assisted image analysis. Proteins of interest will be identified by peptide mass fingerprinting and sequencing.

The goal is to identify novel protein biomarkers that predict response to therapy or disease resistance. This information will help clinicians develop a customized treatment plan for each individual patient.

Progress

1. Sample collection has commenced since August 2006. (Nine samples collected so far)

Proposal # 2060 021

Proteomics approach to biomarker discovery in aplastic anemia

Principal Investigator: Ayodele Abdulkareem Alaiya, MB.BS, MPH, PhD
Co-Investigators: Mahmoud Al-Jurf, MD, Naeem Chaudhri, MD, Mai Al-Mohanna, PhD, Entezam Sahovic, MD, Fahad Al Mohareb, MD, Fahad Al Sharif, MD, Hamad Al Omar, MD, Hazzaa Al Zahrani, MD, Ali Al Shanqeeti, MD and Abdelghani Tbakhi, MD

Project Description

This study will focus on the analysis of global protein expression profiles in patients with aplastic anemia (AA), paroxysmal nocturnal hemoglobinuria (PNH) and hypoplastic myelodysplastic syndrome (MDS). We will analyze peripheral blood (Plasma/serum) and bone marrow samples from the same patients using 2-D gel electrophoresis and computer-assisted image analysis.

Proteins of interest will be identified by peptide mass fingerprinting and sequencing. The goal is to identify novel protein biomarkers that can differentially diagnose various bone marrow failure syndromes and provide accurate patient stratification. This will help clinicians to reach an accurate diagnosis and consequently provide appropriate and rational therapeutic approach based on the individual patient’s protein expression profile.
Progress

1. RAC approved in principle (October 2006)
2. Sample collection has commenced since Nov 2006. (Three samples collected so far)

Proposal # 2050 043

Clinical proteomics: Development of novel biomarkers for diagnosis of ovarian cancer: Funded by King Abdulaziz City for Science and Technology (KACST) under the Limited Grants Program.

Principal Investigator: Ayodele Abdulkareem Alaiya, MB.BS, MPH, PhD
Co-Investigators: Mai Al-Mohanna, PhD, Hany Al-Salem, MD, Ismail Al-Badawi, MD, Jamal Al-Subhi, MD, Nada Al-Sahan, MD and Asma Tulba MD

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

The main goal of our work is to develop tools for accurate classification of borderline tumors. For this purpose in mind, we will use the mini-2-DE gels for the proteome analysis. This technology is rapid, simple and sensitive, thus making it especially applicable for routine tumor diagnostic purposes.

Protein spots that differed significantly in their expression between benign and malignant tumors will be identified and then will be used for objective and accurate molecular classification of borderline ovarian tumors particularly in the differential diagnosis of borderline tumors and carcinomas.

Progress

1. KACST Funding was granted late 2006.
2. Sample collection has just started in Jan 2007

OTHER ON GOING PROJECTS

Proposal # 2050 014

Protein profiling: Understanding the mechanisms of tumor response to therapy in a mouse model.

Principal Investigator: Ayodele Abdulkareem Alaiya, MBBS, MPH, PhD
Co-Investigators: Mai Al-Mohanna, PhD, Raafat El-Sayed, DVM & Falah Al-Mohanna, DVM

Project Description

This pilot study will be based on a mouse 4T1 breast tumor model. The 4T1 mammary carcinoma cell line is transplantable and the tumor grows both in nude mice BALB/c and in tissue culture. In addition, the cells give rise to tumor that is invasive and can easily metastasize to distance sites, thus mimicking human mammary cancer. These characteristics of 4T1 make it suitable for in vivo experimental animal model for human breast cancer.

We will analyze complex protein mixtures from tissue and serum samples from the same individual animal using 2D gel electrophoresis and computer assisted image analysis. Proteins of interest will be identified by peptide mass fingerprinting and sequencing. The rationale is to be able to identify groups of proteins whose functional roles are involved in the mechanism of tumor response to therapy.
Progress

1. First-year progress report has been approved by ORA. Since this is a prospective study involving fresh clinical tissue specimens, new cases are being added and the analysis is on going.
2. An abstract was accepted during 5th HUPO world congress at Long Beach California, 28th Oct - 1st Nov 2006.
3. A poster was presented during the above mentioned meeting.
4. A manuscript is in preparation.
5. Analysis of serum samples will commence shortly.

Proposal # 2050 011

Clinical proteomics: Development of novel biomarkers for translational ovarian cancer research.

Principal Investigator: Ayodele Abdulkareem Alaiya, MB,BS, MPH, PhD
Co-Investigators: Mai Al-Mohanna, PhD, Adnan Munkarah, MD, Hany Al-Salem, MD, Ismail Al-Badawi, MD, Jamal Al-Suhbi, MD, Nada Al-Sahan, MD, Asma Tulba MD & Nayyer Cheema, MD

Project Description

This project will focus 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.

We will analyze normal and tumor tissue as well as serum samples from the same patients using 2-D gel electrophoresis and computer assisted image analysis. Proteins of interest will be identified by peptide mass fingerprinting and sequencing. The goal is to identify novel protein biomarkers that can predict subset of patients who will develop total, incomplete or no response to therapy. This information will help clinicians to choose the right treatment for a particular individual patient.

Proposal # 2050 026

Clinical cancer proteomics: Understanding the cellular and molecular biology of prostate tumors

Principal Investigator: Ayodele Abdulkareem Alaiya, MB,BS, MPH, PhD
Co-Principal Investigator: Ali Bin Mahfooz, MD
Co-Investigators: Mai Al-Mohanna, PhD, Mohammad Aslam, MD, Irfan Ahmed, MD, and Kamal Hanash, MD

Project Description

We will study gene expression of prostate tumors at the protein level by means of 2-D gel electrophoresis and computerized image analysis. The main interest is focused on the complex protein expression pattern of human prostate tumors of varying malignancy potential in order 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 which could complement the diagnostic markers already in use, and to start a wider scan of the prostate proteome for carcinoma specific markers. Novel proteins will be characterized by means of highly sensitive mass spectrometry and if necessary sequence analysis.
Progress

1. First-year progress report has been approved by ORA. Since this is a prospective study involving fresh clinical tissue specimens, new cases are being added and the analysis is on going.
2. Preliminary data is planned for presentation shortly during the Urology Department Clinical grand rounds.
3. Detailed computer assisted image analysis is on going.

FUTURE RESEARCH DIRECTION

Recent progress in the proteomic field facilitates the search for markers defining different diseases including malignant transformation, malignancy potential and tumor treatment sensitivity. These markers can rapidly become of utmost importance for early cancer detection and individualized therapy.

A number of potential biomarkers have been identified by proteome studies. Our goal is to validate some of the potential biomarkers in different disease conditions using other methods such as immunohistochemistry. This is important because clinicians can only be convinced to use markers that have been shown to have prognostic or treatment predictive value in consecutive patient’s materials.

The generated proteome data will also be translated into artificial learning models; which can be used for diagnosis, prognosis and treatment prediction. Our preliminary data indicates that analysis of proteome data have an enormous potential to be further developed into a “proteome scanner”, i.e., an artificial intelligence tool capable of assisting clinical decisions in establishing a more accurate diagnosis and prognosis (Figure 2).

PUBLICATIONS

The Tumor Immunology Section is a research facility established in 2003, to carry out research in the areas of cancer immunology and immunomodulation.

The Tumor Immunology Major Interests are:

1. Vaccination: To apply recent molecular and immunological techniques to discover novel tumor antigens overexpressed in Saudi patients with leukemia and breast cancer.

2. Immunomodulation: To design immunological tools that can result in the enhancement of immune responses to tumor cells.

3. Clinical trial design and implementation.


RESEARCH PROJECTS

1. Project Title: Use of Human Dendritic Cells as Potential Adjuvant for Generation of Specific Immune Responses to the Tumor-Associated Antigen Wilms Tumor (WT1) in the Saudi and Middle East populations. RAC# 2030 006

Investigators: Said Dermime (PI), Mahmoud Al-Jurf, Khaled Al-Hussein, Abdelghani Tbakhli

Duration of Study

Three (3) years.

2. Project Title: Investigation of the B7-H1 Molecule Expression by Breast Cancer and Myeloid Dendritic Cells of Saudi Breast Cancer Patients and Blockade of the Molecule as an Approach for Cancer Immunotherapy. RAC# 2030 034

Investigators: Said Dermime (PI), Taher Twegiery, Suad Bin Amer, Asma Tulbah, Amal Qattan, Cynthia Lehe

Duration of Study

Three (3) years.
3. Project Title: Investigation of M-Phase Phosphoprotein (MPP11) as a Novel Target for Leukaemia T Cell Immunotherapy. RAC# 2040 010

Investigators: Said Dermime (PI), Mahmoud Al-Jurf, Hazem Ghebeh, Ghofran Al-Qudaihi

Duration of Study
Two (2) years.

4. Project Title: The Use of ELISpot Assay as a Novel Technique for a More Accurate and Rapid Diagnosis of Mycobacterium Tuberculosis. RAC# 2040 005

Investigators: Said Dermime (PI), Fatin Al Zamel, Abdulrahman Al Rajhi, Volkmar Schoellhorn

Duration of Study
Two (2) years.

5. Project Title: The use of tumor-derived RNA transfected in human DC to generate breast cancer specific T cells in the Saudi women. KACST

Investigators: Said Dermime (PI), Suad Bin Amer, Taher Twegiery

Duration of Study
Three (3) years.

6. Project Title: Enhancing the Immunogenicity of Low-Affinity HLA-A2 Wilms Tumor-Restricted CTL Epitopes by Selective Amino Acid Replacements: Implication in the Generation of Effective Cancer Vaccines and Adoptive T Lymphocyte Therapy in Population. KACST

Investigators: Said Dermime (PI), Mahmoud Al-Jurf, Abdelghani Tbakhi

Duration of Study
Two (2) years.

PROGRESS AND RECENT FINDINGS

1. We were the first group to show the expression of the B7-H1 (a T cells inhibitory molecule) in breast cancer patients. Interestingly our findings indicate that B7-H1 correlates with important prognostic factors, which are associated with high-risk patients. B7-H1 may represent an important additional risk factor in breast cancer patients with advanced disease and suggests its involvement in the tumor immune escape in breast cancer (a manuscript entitled “The B7-H1 (PD-L1) T lymphocyte-inhibitory molecule is expressed in breast cancer patients with infiltrating ductal carcinoma: Correlation with important high-risk prognostic factors” has been published in Neoplasia; 2006; 8:190). A poster was presented at the 20th Anniversary Annual Meeting of the International Society for Biological Therapy of Cancer (ISBTC) held in November 11-13, 2005 in Alexandria, Virginia, USA and published in the Journal of Immunotherapy, 2005; 8(6): 630 (see attached abstract).

2. Furthermore, we were the first group to provide direct evidence to the association between B7-H1 expression and proliferation. (A manuscript entitled “Expression of B7-H1 in breast cancer patients is strongly associated with high proliferative Ki-67-expressing tumor cells” has been accepted for publication in the International Journal of Cancer). A poster was presented at the 25th Congress of the
International Association for Breast Cancer Research held in September 15-18, 2006 in Montreal, Quebec, Canada and published in the journal Breast Disease, 2006; 25: 67. See Figure 1.

Figure 1. (A) Correlation of B7-H1 expression with the Ki-67 marker in 69 breast cancer patients. Patients were grouped into three main categories, low (0 to 19%), moderate (20 to 39%), and high (≥ 40%) based on Ki-67 expression. *p*< 0.001 represent a highly significant correlation between B7-H1 and Ki-67 as analyzed by linear regression and ANOVA multivariate analysis. (B) Representative immunocytochemical double staining of cytoplasmic B7-H1 (pinkish color) and nuclear Ki-67 (blackish brown color) staining of invasive ductal carcinoma of 3 patients with different levels of expression. Cells were counterstained with hematoxylin. Photomicrographs are at x540 magnification.

3. In collaboration with Peter Stern Lab in Manchester, UK, we have demonstrated the immunogenicity of the 5T4 tumor antigen as an oncofoetal protein expressed in many types of solid tumors. This work was started in Manchester before I left to Riyadh. A manuscript entitled “CD8 T cell recognition of human 5T4 oncofoetal antigen” by L Smyth, E Elkord, T Taher, HR Jiang, DJ Burt, A Clayton, PA van Veelen, A de Ru, F Ossendorp, CJM Melief, JW Drijfhout, Dermime S, RE Hawkins and PL Stern was published in the Int J Cancer, 2006; 119:1638-47.

4. Another project investigates the immunogenicity of WT1 antigen as a potential target for leukemia T cell immunotherapy. In this, we used a pool of 110 synthetic overlapping 15 mer peptides (WT1-PepMix) across the entire WT1 protein to generate WT1-specific T cell clones, which proliferated and produced T regulatory cells specific cytokines in response to stimulation with one of these peptides. We were the first to show a T regulatory cell against the leukemia-associated antigen WT1. A manuscript is being prepared to be submitted to Blood and a poster was presented at the 1st Joint Meeting of European National Societies of Immunology Congress, Palais des Congress, Paris, France, (6-9 September 2006). See Figure 2.

Figure 2. Generation of anti-WT1 immune regulatory responses: The proliferative activity of the TCC-42 regulatory T cell clone is WT1-84 peptide specific.

5. Development of reliable and sensitive assays to monitor immune responses in patients after infection was another goal of the Tumor Immunology Lab. We have recently validated a rapid serological test for MTB infection in the Tumor Immunology Section. Another complementary test known as TB-ELISPOT was also standardized locally at the Tumor Immunology section. These two tests provide accurate and, at least in the first test, rapid
diagnosis of MTB infection. Others and we have found in the first test (serological test) that is a population dependent (may be a strain dependent). Positive results from the first test method would enable physicians to initiate therapy immediately. The second test method, when positive, would allow physicians to reduce the period of treatment to 2-3 months, thereby ensuring cost-effectiveness and avoiding unnecessary long-term treatment with possible side effects. This rapid TB tests may be useful tools for first-line testing of suspected cases, epidemiological studies and in designing a quality health system to reduce health hazards in developing and resource-poor countries. We expect to generate revenues from this service, which will help in providing more funds for research and developing more advanced technologies. A request for establishment of an advanced immunodiagnostic laboratory for *Mycobacterium tuberculosis* has been submitted to the Research Centre business office for evaluation.

6. The TB-ELISPOT technique is now being used routinely at the tumor immunology lab to solve very complicated TB diagnostic cases at the KFSH&RC (3 cases this year) in which decision-making was dependent on our results.

7. We have adapted the ELISPOT assay to screen for anti-EBV T cell frequencies in 2 healthy donors to select for best candidate with high T cell frequencies to be used as a donor for BMT patient with pharyngeal carcinoma (first BMT for this type of disease in the world to be carried out by Dr. Hamed Al-Omar). The decision for selection was made based on our data. Interestingly, the patient is doing very well after BMT (tumor shrinks dramatically).

**FUTURE RESEARCH DIRECTION**

The Tumor Immunology Lab is carrying out research in the areas of cancer vaccination and immunomodulation.

1. For the cancer vaccination program: we are applying current molecular and immunological techniques to discover novel tumor antigens over-expressed in Saudi patients with leukemia and breast cancer. In this, 4 projects (2 supported internally [projects 1 & 3 above] and the other 2 supported by KACST [projects 5 & 6 above) are being carried out. Significant progress has been made. For example, we have identified a novel anti-WT1 T cell clone. We have investigated some epitopes, which are now being used to develop a cancer vaccine. More investigations are needed to finalize this study and a clinical trial to vaccinate leukemia patients will be designed and implemented based on such epitopes in the near future.

2. For the immunomodulation program: we aim at designing immunological tools that can result in the inhibition of signals generated by over-expressed molecules on tumor cells. An example is to investigate the over-expression of B7-H1 in Saudi breast cancer patients and designing specific antibodies to specifically target this molecule. We have shown for the first time the expression of the B7-H1 in 53% breast cancer patients and its expression was tumor specific as evidenced by its association with tumor tissues but not with adjacent tissues from the same patients’ breast. We were also the first group to provide direct evidence to the association between B7-H1 expression and proliferation. We are planning to continue studying the relation of this molecule to other inhibitory factors such as regulatory T cells. In collaboration with Prof. Otto Majdic (Institute of Immunology, University of Wien, Austria) we have obtained an anti-B7-H1 monoclonal antibody, which works on paraffin-embedded archived samples. We will use this antibody to analyze the expression of this molecule in a large number of breast cancer patients and correlate its expression with a 5-year patient survival to determine if such a molecule will prove to be an important diagnostic/prognostic factor in breast cancer patients.
3. Development of reliable and sensitive assays to monitor immune responses in cancer patients after treatments is an important goal of the Tumor Immunology Lab. In this, we are introducing a sensitive and a reliable technique (ELISPOT) to measure the natural immune responses of leukemia patients in remission to 2 important tumor antigens (Proteinase 3 and WT1).

PUBLICATIONS (2004-2006)

Peer reviewed articles


4. EK Meziane, T Bhattacharyya, AC. Armstrong, C Qian, RE. Hawkins, PL. Stern & S Dermime. The Use of adenoviruses encoding CD40L and/ or IL-2 against B cell lymphoma. *Int J Cancer*; 2004; 111:910.


Abstracts


Flow Cytometry is a very effective tool for researchers to characterize and enumerate cells of interest by size, shape, surface, intracellular expression of molecules of interest, and function. Flow cytometry provides data on large numbers of individual cells and it is very fast. Thousands of cells per second can be analyzed and sorted. The applications to which it can be applied have expanded rapidly from cell sorting, to measurement of cell surface protein and intracellular antigens, and the analysis of DNA. The Flow Cytometry and Cell Sorting Core Facility at the Research Centre offers wide range of instrumentation and flow cytometric applications using the state-of-the-art instrument available in the facility. The facility offer full support and guidance to the investigators needing assistance with experimental design, data analysis and data interpretation. With the future plan of acquiring the state-of-the-art instruments BD FACSAria™ cell sorter and BD-LSR II, will certainly facilitate our goal to render best server to wide range users at Research Centre.
Flow cytometry is extremely powerful and can lend itself to a wide range of applications including, but not limited to:

- FACS cell sorting
- DNA cell cycle analysis
- DNA ploidy analysis
- Apoptosis
- Immunophenotyping
- Calcium kinetics
- Bacterial measurements
- GFP measurements

- Intracellular antigen measurement
- Cytokine detection
- Platelet analysis
- Cell proliferation assays
- Cellular viability
- Data analysis and data interpretation

The following statistics illustrate the nature and volume of samples handled by the facility as an average in a period of one month.

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<tr>
<th>TYPE OF SERVICE PROVIDED</th>
<th>SERVICE RECIPIENT (Department/University)</th>
<th>VOLUME (i.e., number of samples processed)</th>
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</thead>
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<td>Cell Separation</td>
<td>KFSH&amp;RC</td>
<td>20 samples/mo</td>
</tr>
<tr>
<td>DNA Cell cycle Analysis</td>
<td>KFSH&amp;RC</td>
<td>280 samples/mo</td>
</tr>
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<td>Immunophenotyping</td>
<td>KFSH&amp;RC</td>
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<td>Cell Viability</td>
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<td>Apoptosis</td>
<td>KFSH&amp;RC</td>
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<tr>
<td>Intracellular Staining</td>
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<td>25 samples/mo</td>
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**CORE RESEARCH ACTIVITIES**

**Project Title:** Minimum Residual Disease (MRD) in Acute lymphoblastic leukemia (ALL) in children

**Investigators:** Dr. Abdallah Al Nassar, Dr. Tariq Al Asaad, Dr. Khaled Al Hussein, Dr. Hassan El Solh, Dr. Hassan El Bushra

**Project Description**

Almost all children who are treated for acute lymphocytic leukemia (ALL) enter complete
remission. However, nearly one fourth of these patients subsequently experience relapse and have a poor prognosis. Many relapses may be preventable if at-risk patients can be identified early and given more intensive therapy. The study of minimal residual disease (MRD) is an attempt to detect and define the significance of leukemia invisible to normal morphologic examination. MRD is closely related to the risk of relapse during all the course of chemotherapy and can be used as a prognostic factor as soon as induction therapy is completed. The risk of relapse rises steeply with the amount of residual blasts, and the extent of MRD predict the outcome more precisely than simple presence or absence. Using rapid flow-cytometric techniques capable of detecting one leukemic cell in 10000 normal cells, we are studying MRD in children with ALL in first clinical remission after 28 or 43 days of treatment.

Progress

On going.

**Project Title: Multi Drug Resistance (MDR) in ALL in Children**

**Investigator:** Dr. Abdallah Al Nassar, Dr. Khaled Al Hussein, Dr. Abdullah Baothman, Dr. Hassan El Solh, Dr. Hassan El Bushra

**Project Description**

One of the mechanisms leading to relapse in childhood acute leukemias is thought to be emergence of multi drug resistance. The expression of multi-drug resistance phenotype is a key determinant in the development of therapeutic and chemotherapeutic drugs. For many novel compounds the accessibility, solubility, clearance rate and drug-drug interactions can mean the difference between a wonder drug and a lethal drug. The classical form of multi-drug resistance hinges on the presence of P-glycoprotein (Pgp) structure at the cell membrane. Pgp acts as a drug efflux pump, thus providing a system to rid cells of both toxic and therapeutic compounds. Flow cytometry is particularly useful to monitor MDR level not only in leukemic patients with resistant or relapsed disease but also in some patient at diagnosis and in complete remission.

**Progress**

On going.

**Project Title: Study of the Tumor Suppressor Genes in DNA Repair and Cell Cycle Checkpoints.**

**Investigators:** Dr. Abdelilah Aboussekhra, Dr. Mai Al Mohanna, Dr. Khaled Al Hussein

**Project Description**

Alteration in the genes that encode DNA cell cycle regulation and DNA repair leads to neoplasms. Therefore understanding the genes that play role in DNA repair and cell cycle check points helps in the prevention of cancer. Flow cytometry plays an important role to study the genes which control the DNA cell cycle.

**Progress**

On going.

**Project Title: Screening of Selected Herbal Medicines for Cytotoxicity in Human Cells In Vitro**

**Investigators:** Dr. Fahad Al Khodairy, Dr. Khaled Al Hussein
Project Description

Plant extracts have been used for ages to cure various ailments. Drugs such as vinblastine, purified from plant extract (*Vinca rosea linn*) found to be useful as anti cancer drug. Flow cytometry is utilised for monitoring cell cycle, apoptosis and cytotoxicity of plant extracts in various cell lines as well as cells isolated from fresh tissues.

Progress

On going.

Project Title: Towards the Understanding of Sperm Role in Fertilization and Early Embryonic Development: A pilot study

Investigators: Namik Kaya, PhD Ali Hellani, PhD

Project Description

Male factor infertility is common in patients undergoing infertility treatment in our hospital. Many of such cases have unexplained in nature and patients were treated without knowing the reason why they are infertile. A recent study suggested that sperm delivers not only DNA but also RNA to the oocytes. In this pilot study, spermatozoa from a total of 100 patients will be screened for the level of 6mRNAs that have been pointed out to have role on fertilization and early embryonic development. Their level will be correlated to the outcomes of the treatment. Flow Cytometry will play an important role to detect apoptotic sperm.

Progress

On going.
Project Title: Evaluation of anti-tumor activity of $\gamma\delta$T cells in cancer patients

Investigators: Dr. Khaled Al-Hussein, Dr. Mahmoud Al Jurf, Dr. Shoukri Bazarbashi, Dr. Abdelghani Tbakhi, Dr. Ahmed Al Omar

Project Description

$\gamma\delta$ T cells play important role in immunological control against malignancies. In recent review, reports have shown that preferential expansion of $\gamma\delta$ T cells in certain malignancies supports a possible role of this cells in immunological surveillance against cancer. In vitro studies have demonstrated that peripheral $\gamma\delta$ T cells of healthy donors similarly have several fold greater cytolytic activity in various tumor cell lines. In this project, Flow cytometry will be used to study the direct role of $\gamma\delta$ T cells in tumor elimination by studying their cytotoxic effect and the intracellular cytokines they produce in cancer patients. Also to evaluate the $\gamma\delta$ T cells functions whether they are deficient in different cancer patients in comparison with healthy donors.

Progress

On going.

FUTURE RESEARCH DIRECTION

In 2007 under the new section head, Dr. Chaker Adra, the facility will play a very important role supporting the stem cell research projects that he is going to establish at the Research Centre.

The department has a comprehensive plan to modernize its facility with the acquisition of the state-of-the art instruments BD FACS-Aria™ cell sorter and BD-LSR II. The BD FACS-Aria™ cell sorter sets a new standard for high performance flow cytometry. Based on a revolutionary new design in instrumentation, this easy-to-use benchtop system delivers high-speed sorting and multicolor analysis. A customized 355nm UV laser option for the BD FACS-Aria™ allows for precise sorting of side population of stem cells labeled with Hoechst 33342. This is the ideal candidate for stem cell research. This will facilitate our goals to render advanced service to the cutting edge research programs in stem cell research.

BD-LSR II would support wide range research applications with the possibility of acquiring information up to 20 different set parameters on a single cell. This will be a great asset to any flow cytometry core facility.

PUBLICATIONS


Modern daily life is exposed to a wide range of environmental pollutants, which may have a great impact on our environment and public health. In the Environmental Health Section (EHS), our current focus is to assess the impact of some of the pollutants such as heavy metals, pesticides, and polycyclic aromatic hydrocarbons. We completed two RAC projects and two manuscripts have already been submitted to peer review journals for publication. Part of our mission is to offer training to high school students, university undergraduates, and graduates. Last year, we were happy to offer three gifted students from King Abdulaziz Foundation Program a training program for one month which helped them learn the conduct of scientific research and to assist them in their career planning. This report describes the progress of our ongoing projects, identifying 2005-2006 significant accomplishments as well as future directions.

**RESEARCH PROJECTS**

A. Completed Research Projects

**Project Title: Exposure to Environmental Pollutants and its Effects on the Outcome of *In Vitro* Fertilization Treatment. RAC # 2010 006**

This project is in collaboration with the IVF clinic and the Biostatistics, Epidemiology & Scientific Computing Department. The duration of the project was three years, which started on 14th of January 2002.

**Primary Investigator:** Iman Al-Saleh  
**Co-Investigators:** Kamal Jaroudi, Coskin Serdar, Abdulaziz Al-Sharhani, and Mohammad Ashraf Chaudhry

**Summary of the results**

Between 2002 and 2003, a prospective study was conducted to look for the influence of exposure to lead, cadmium, and mercury among 619 Saudi women undergoing IVF program age 19-50 years old on pregnancy outcome and fertilization rate. Lead, cadmium, and mercury concentrations were measured in both blood and follicular fluid. After adjusting for relevant confounding variables, the association between blood lead levels and fertilization rate remained significant (OR=0.377, 95% CI 0.143–0.989). Conversely, pregnancy outcome was significantly associated with an increased coffee intake, living in...
former province and women's working status. Our data revealed that lead, cadmium and mercury were detected in 86.5%, 85.2% and 84.6% respectively of the tested IVF women. Of the heavy metals measured in blood and follicular fluid, mercury ≥ 5.8 µg/L (EPA reference dose) found in the blood and follicular fluid of 18.7% and 8.3% of the women respectively. Though, the binary logistic regression model failed to correlate mercury exposure to pregnancy or fertilization rate outcomes, its presence in blood and follicular fluid could provide a warning of its possible adverse effects on the physiology of reproductive system or have consequence fetal development. A number of risk factors; which were suspected to influence blood or follicular heavy metals levels, were also investigated. Use of skin-lightening creams and dental amalgam fillings were the main predictors of mercury exposure.

One manuscript has already been submitted to peer-reviewed journal for publication.

**Project Title:** The role of *Nigella sativa* and a number of its antioxidant constituents towards azoxymethane-induced genotoxic effects and colon cancer in rats. RAC # 2030 027

This project is in collaboration with the Carcinogenesis Research Unit, Biological & Medical Research Department, the Colorectal Section and Department of Biochemistry, King Saud University. The duration of the project was 24 months, which started on 30th June 2003.

**Primary Investigators:** Iman Al-Saleh  
**Co-Investigators:** Jamal Arif, Nasser Al-Sanea, Alaa Abdul-Jabber

**Summary of the results**

The aim of this study was to examine the chemopreventive effect of *Nigella sativa* and some of its antioxidants constituents such as selenium, thymoquinone, vitamins E and A by assessing a number of biomarkers of colon cancer in male rats treated with a colon carcinogen, azoxymethane (AOM). Sixty male sprague-dawley rats were randomly assigned to two groups: vehicle control (1 to 5 subgroups) and experimental (6 to 10 subgroups). Rats in each group were fed one of the following diet: basal diet, 200 mg/kg *Nigella sativa*, 0.2 mg/kg selenium, 1.2 mg/kg all-trans-retinol plus 100 mg/kg dl-α-tocopherol and 10 mg/kg thymoquinone respectively. Only rats in subgroups 6 to 10 were then administered AOM (15 mg/kg, given two times, 1 wk apart) and fed their respective diets until 5 weeks. All rats were then scarified. Colons were examined for the presence of colonic aberrant crypt foci (ACF) as an indicator of preneoplastic lesions. Levels of malonaldehyde (MDA) in the serum and liver were measured as an indicator of oxidative stress, while tail moment in whole blood and 8-Hydroxy-2’-deoxyguanosine (8-OH-dG) in the colon were considered as a measure of DNA damage. Time course changes in the levels of selenium, vitamin A and E in serum were also tested. The result of this study showed that supplementation with vitamins was effective on ACF whereas *Nigella sativa* and thymoquinone did not seem to have any effect. When biomarkers of DNA damage and oxidative stress were utilized to evaluate the protective effect of supplements, *Nigella sativa* showed inhibitory effects using the comet assay on day 34 in the AOM-treated rat group but not on MDA in both serum and liver. Alternatively, selenium, thymoquinone and vitamins showed inhibitory effect only on MDA contents in the liver. Oxidative damage to colon DNA was not affected with *Nigella sativa* and its constituents. Although the exact mechanisms involved in the protective effects of *Nigella sativa* against the initiation of colon carcinogenesis are not clearly understood at present, the results of this study suggest that its inhibitory effects might depend on the combined
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competitive inhibition of a number of antioxidant constituents of this plant. However, the usefulness of *Nigella sativa* for colon cancer chemoprevention needs further research.

One manuscript has already been submitted to peer-reviewed journal for publication.

**Project Title:** DNA Damage Due to Polycyclic Aromatic Hydrocarbons Exposure Among Colon Cancer Patients and its Possible Role in Inducing Carcinogenesis. RAC # 2020 014

This project is in collaboration with the Carcinogenesis Research Unit, Biological & Medical Research Department, the Colorectal Section, Department of Surgery and the Biostatistics, Epidemiology & Scientific Computing Department. The project was for 24 months which started on 9th September 2002.

**Primary Investigators:** Iman Al-Saleh
**Co-Investigators:** Jamal Arif, Nasser Al-Sanea, Alaa Abdul-Jabber and Mohamed Hassan Gamal El Din

**Summary of the results**

**Preliminary findings:** Colon cancer represents 4.9% of all tumors at King Faisal Specialist Hospital & Research Centre. Environmental and dietary carcinogens such as polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines (HCAs) have long been suspected to play a prominent role in colon cancer etiology. We designed a case control study to test the hypothesis whether the presence of DNA adducts can play role in the etiology of colon cancer. DNA adducts were measured in 22 cancerous and 19 non-cancerous tissues of newly diagnosed colon cancer patients by 32p-postlabeling technique. Normal colon tissues from 19 hospital patients served as controls. The mean level of adducts per $10^{10}$ nucleotides in cancerous and non-cancerous tissues were $165.18 \pm 222.52$ and $120.86 \pm 189.17$ respectively and were significantly higher than controls ($32.83 \pm 57.54$ per $10^{10}$ nucleotides). Histogram of DNA adducts in cancerous, non-cancerous and normal tissues are shown in Figure 1. No BPDE-DNA adducts were found. No relationship was found between urinary cotinine as marker of tobacco smoke and 1-hydroxypyrene as an indicator of individual’s internal dose of PAHs and DNA adducts. In a logistic regression model, only adducts in cancerous tissues were associated with the subsequent risk of colon cancer, with an OR of $7.295$ [95% CI: 0.695-76.621] after adjustment for age and the duration of living in the current region, but of a borderline significance ($P=0.098$). Although it is difficult to make a definite conclusion from a small data set, our preliminary results suggest the potential role of DNA adducts in the colon carcinogenesis process. Additional study with larger sample size is needed to confirm our preliminary finding. It is also important to identify the structural characterization of these unknown DNA adducts in order to have a better understanding whether environmental carcinogens play a role in the etiology of colon cancer.

One manuscript has already been submitted to peer-reviewed journal for publication.

**Figure 1.** Comparison of DNA adducts levels in tissues of controls and colon cancer patients. Cancerous and non-cancerous tissues were taken from the same patient.
B. Ongoing Research Projects

Project Title: Longitudinal Study of Prenatal and Postnatal Lead Exposure And Early Cognitive Development in Al-Kharj, Saudi Arabia. RAC # 2031 050

This project is funded by Prince Salman Centre for Disability Research (PSCDR # 02-R-0028-NE-02-EP-1) with a total fund of SR 535,352. This project is in collaboration with King Khalid Hospital, Al-Kharj. The duration of the project is for 36 months. We have started the project on 23rd June 2003.

Primary Investigators: Iman Al-Saleh
Co-Investigators: Michael Nester, Lina Minchari, Mohamed Hassan Gamal El Din, Abdulla Rabah and Carolyn Schroeder

Project Description

Extensive data show a direct link between low-level lead exposure during early development and deficits in neurobehavioral-cognitive performance evident late in childhood through adolescence. These consistent studies have demonstrated the presence of a constellation of neurotoxic and other adverse effects of lead on blood lead levels, which may be as low as 10 µg/dl. Risk factors for prenatal exposure to lead involve maternal exposure and body burden of lead. There are both exogenous and endogenous factors contributing to maternal blood lead levels and in utero exposure to the fetus. Our previous study, which investigated 124 pregnant women living in Riyadh, found out that there is a strong correlation between the maternal and cord blood lead levels confirming the transfer of lead from the mother to the fetus. This longitudinal study is designed to assess the effect of exposure to lead prenatally and postnatally on early cognitive development of infants living in a rural area such as Al-Kharj area where the use of traditional cosmetics and remedies is still common. Lead was measured in 664 umbilical cord blood samples collected from healthy pregnant women. Based on the results of blood lead levels in the collected cord blood samples, a total of 198 infants were classified into three groups for neuropsychological assessments as follows: Low lead risk group: ≤1.045 µg/dl; mid lead risk group: >1.045-<3.458 µg/dl; and upper lead risk group: ≥ 3.458 µg/dl. Development was assessed semiannually, beginning at the age of 6, 12, 18 and 24 months, with the use of the mental development index of the Bayley Scales of Infant Development. Venous blood samples were obtained at the same time to provide a measure of postnatal lead exposure. A detailed questionnaire was completed to gather basic socioeconomic, demographic, health and other risk factors that may affect exposure to lead.

Progress

During this year, we have managed to accomplish the following steps:
- Completed the Bayley Scales of Infant Development assessment, blood withdrawal and filled up the questionnaires for 56 infants aged 18 months (Stage IV) on 2nd January 2006 as well as blood lead analyses and data entry;
- Completed the Bayley Scales of Infant Development of the remaining 42 infants at the age of 24 months (Stage V) on 19th June 2006 as well as blood lead analyses and data entry; &
- The Data Management Group has started entering the newly collected data using SIR computer database application.

Preliminary Results

The mean lead levels in blood from the umbilical cord were 2.731 µg/dl. The mean values in infants: at the age of 6 months, 12 months and 18 months, were 3.360, 3.244 and 3.982 µg/dl respectively. When we looked at the distribution of children developmental index (MDI and PDI scores) according to age. At
6, 12 and 18 months, the mean MDI scores were 99.26, 108.74 and 97.05 respectively while the mean PDI scores were 98.13, 104.26 and 94.34 respectively. The distribution of blood lead levels, MDI scores and PDI scores according to the stage of the study are indicated in Table 1. ANOVA test showed significant evidence of variation in blood lead levels ($F=15.954, P=0$), MDI scores ($F=22.959, P=0$) and PDI scores ($F=14.048, P=0$). As shown in Figure 1, blood-lead levels increased with age. The maximum blood lead levels were observed at the age of 18 months. Age groups were compared by Scheffe’s post hoc test. It was found that blood lead levels in 18-months infants were significantly higher than those in other categories ($P=0.035$). Blood lead levels ≥ 10 µg/dl (the United States Center for Disease Control (CDC) allowable threshold limit) found in 2.5% of newborn, 2.8% of 6-months old infants and 2.6% of 12-months old infants while none were found at the 18-months infants. On the other hand, both MDI and PDI scores at 12 months group were significantly higher than 6 and 18-month groups with p-value <0.001. Looking at the score profile of infants, we found MDI scores of ≤ 80 in 3 infants (6-months stage), 2 (12-months stage) and 1 (18-months stage). While PDI scores of ≤ 80 were identified in 3 infants (6-months stage), 2 infants (12-months stage) and 5 infants (18-months stage). These infants had blood lead levels < 5.0 µg/dl. Spearman ranks correlation coefficients between cord blood levels and postnatal lead levels in infants were 0.352 ($P = 0$) for 6-months old, 0.204 ($P = 0.073$) and 0.310 ($P = 0.02$) for 18-months old.

### Table 1. The results of blood lead levels and Developmental Index during the four stages of the study.

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood lead levels (µg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cord blood</td>
<td>119</td>
<td>2.731 ± 2.517</td>
<td>0.296-17.233</td>
</tr>
<tr>
<td>6-months</td>
<td>107</td>
<td>3.360 ± 2.383</td>
<td>0.379-16.184</td>
</tr>
<tr>
<td>12-months</td>
<td>78</td>
<td>3.360 ± 2.383</td>
<td>0.577-14.116</td>
</tr>
<tr>
<td>18-months</td>
<td>56</td>
<td>3.982 ± 1.063</td>
<td>2.516-7.141</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Standardized Mental Development Index scores</th>
<th>N</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-months</td>
<td>106</td>
<td>99.26 ± 11.084</td>
<td>71-143</td>
</tr>
<tr>
<td>12-months</td>
<td>80</td>
<td>108.74 ± 11.875</td>
<td>74-131</td>
</tr>
<tr>
<td>18-months</td>
<td>56</td>
<td>97.05 ± 8.984</td>
<td>64-151</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Standardized psychomotor Development Index scores</th>
<th>N</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-months</td>
<td>105</td>
<td>98.13 ± 11.151</td>
<td>78-150</td>
</tr>
<tr>
<td>12-months</td>
<td>80</td>
<td>104.26 ± 12.081</td>
<td>67-124</td>
</tr>
<tr>
<td>18-months</td>
<td>56</td>
<td>94.34 ± 8.300</td>
<td>68-108</td>
</tr>
</tbody>
</table>

![Figure 2. The distribution of blood lead levels, MDI Scores & PDI Scores in the studied infants according to the stage of the study.](image)
Univariate regression analysis was performed in order to look at the association of the infant’s cord or postnatal blood lead levels and their neuropsychological scores. There were statistically no significant relations between cord blood levels or postnatal blood lead levels and test scores ($P>0.05$) as indicated in Table 2.

<table>
<thead>
<tr>
<th>Variable outcome</th>
<th>Cord blood lead levels</th>
<th>Postnatal blood lead levels (18 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
<td>$P$</td>
</tr>
<tr>
<td>MDI scores</td>
<td>0.158</td>
<td>0.244</td>
</tr>
<tr>
<td>PDI scores</td>
<td>0.218</td>
<td>0.106</td>
</tr>
</tbody>
</table>

We have also tried to classify our infants by the quartiles of blood lead levels with the lowest group as a reference category as shown in Table 2. The results showed that the second quartile of cord blood lead levels showed negative significant relationship with PDI scores of infants at the age of 18 months ($P=0.005$). Though, all the three quartiles of postnatal blood lead levels were inversely associated with MDI and PDI at 18 months, only the third quartile was significant with MDI scores ($P=0.012$). However, these results are not conclusive because we did not adjust for confounding variables effect because the study has not been yet completed.

**Project Title:** Effects of environmental pollutants exposure on the pregnancy outcome of women in Al-Kharj area. RAC # 2040 017

This project is funded by King Abdulaziz City for Science and Technology (KACST # AT 23-7) with a total fund of SR 393,600. This project is in collaboration with King Khalid Hospital, Al-Kharj. The duration of the project is 36 months. We have started the project on 7th July 2005.

**Primary Investigators:** Iman Al-Saleh
**Co-Investigators:** Mohamed Hassan Gamal El Din and Abdulla Raba

**Project Description**

*In utero* exposures to environmental contaminants can occur through maternal-placental transfer. High level maternal exposures to environmental pollutants, such as lead, mercury, cadmium, DDT, polycyclic aromatic hydrocarbons and tobacco smoke have been associated with congenital anomalies, severe developmental and cognitive impairment, and growth retardation in offspring. Evidence shows that fetuses and infants are more affected than adults by a variety of environmental pollutants because of differential exposure, physiologic immaturity and a longer lifetime over which diseases initiated in early life can develop. It is clear that the Saudi population, like any other populations, is susceptible to environmental pollutants in spite of the difference in the sources of exposure. Moreover, there have a number of hospital-based studies in different cities in Saudi Arabia, which noted a high prevalence of birth defects, infant mortality and congenital malformations with regional variations in the pattern. This cross-sectional study will examine the potential links between environmental pollutants and the pregnancy outcome of Saudi women living in Al-Kharj district. Prenatal exposure to lead, cadmium, mercury, DDT, polycyclic aromatic hydrocarbons and tobacco smoke will be measured in 1522 umbilical cord, venous blood samples and placental tissues collected at the time of delivery. Furthermore, urinary cotinine and 1-hydroxypyrene (as a major pyrene metabolite), will be determined in mothers as an indicator of tobacco smoke and individual’s internal dose of PAHs respectively. A detailed questionnaire will be administered at birth, which assesses risk of exposure to these pollutants. Pregnancy outcomes evaluation such as incidence of small for gestation (less than tenth percentile of weight for each completed gestational week between
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22 and 44 weeks), low birth weight (<2500 g), gestational duration (from the last menstrual period to the termination of pregnancy), fetal death (fetus born ≥500 g or ≥22 weeks' gestation with no signs of life), neonatal death (death <28 days of life) and other congenital malformations. A number of studies have emphasized the important role that oxidative DNA damage is playing in various diseases including cancer due to carcinogenic compounds. Peroxidative lipid damage will be determined as malondialdehyde production in the presence of thiobarbituric acid in serum samples. The genotoxic effects of environmental pollutants on the fetus will be evaluated by using comet assay, where the migration of DNA from the center of cells will be measured. It is hoped that findings of this study will help to understand the source of exposure among the studied population and to develop interventions to minimize its impact.

Progress

During the last year, the following steps were accomplished:

- The completion of sample collection, with a total of 1578 women who agreed to participate in the study. The sample reached 6312 consisting of cord blood, maternal venous blood, placental tissue and urine samples (approximately 1578 each);
- Laboratory analysis of lead in 1573 cord and in 1577 maternal venous blood samples; a total of 3150 samples;
- Laboratory analysis of DNA damage in a total of 715 cord blood and 710 venous blood samples. We were not able to measure DNA damage in all samples due to shortage of technical staff and the inability to analyze the blood received within the same day;
- Laboratory analysis of cotinine in a total of 1572 urine samples;
- Laboratory analysis of creatinine in a total of 1573 urine samples;
- Laboratory analysis of cadmium in 1376 cord blood samples;
- Laboratory analysis of DDT, DDE and DDD in 240 cord blood and 240 maternal venous blood;
- Laboratory analysis of malonaldehyde (MDA) in 1182 cord blood and 101 maternal venous blood samples; &
- The completion of data entry for 1578 women using SIR computer database application. Our data manager is currently in the process of cleaning and validating the data.

FUTURE RESEARCH DIRECTION

- Develop a fee-for-service program utilizing the existing human and technical expertise and resources.
- 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.

PUBLICATIONS

Abstract

Full-length papers


The Department of Biomedical Physics
The Biomedical Physics Department has a diversity of responsibilities which can be divided into (1) services (2) research and (3) education. It constitutes four sections namely, the Radiation Physics; Imaging Physics; Health Physics; and Biomedical Physics Research. Majority of its resources are directed towards patient care in the form of clinical physics support services to Radiation Oncology and Radiation Therapy for treatment of cancer patients, and other hospital-based operations for diagnostic procedures. It also ensures implementation of quality assurance program on all radiation-producing equipment and a comprehensive radiation safety program for the safe use of ionizing radiation. Our staff is involved in radiation and biology research aiming to improve the treatment of cancer patients. Various approved research projects resulted in 8 papers published in 2006.

The Department also encompasses two major core facilities, i.e., the Secondary Standards Dosimetry Laboratory and Gamma Irradiation Facility. The Gamma Irradiation Facility provides high-dose rate irradiation for research experiments and sterilization of materials for the Hospital, as well as, to outside institutions for a fee. The Secondary Standards Dosimetry Laboratory (accredited by IAEA and WHO) serves as a regional information source offering a variety of dosimetric services which range from instrument calibrations to acceptance testing of fully configured systems. The dosimetric services are also performed on a fee-for-service basis. The Department has generated considerable amount of income over the past year through its medical physics consulting services, calibration of equipment, TLD personnel radiation monitoring services and gamma sterilization services.

In addition to the aforementioned, we have maintained active participation in various education and training program activities. We hosted and organized the Radiological Physics Refresher Course for residents in Radiology in August 2006, which is accredited by the Saudi Board of Radiology. We trained a number of university students and provide support for their research projects. We also extended training to other professionals from collaborating institutions outside the Kingdom including IAEA fellows. Approximately 70 lectures were given to the Radiology residents and other requesting departments in the Hospital. The in-service departmental education program continued in the form of Journal Club presentations on topics relevant to the Department functions. The Department had developed a residency training program in medical physics and medical dosimetry to resolve the problem of recruiting qualified medical physics professionals.
More details of sectional activities are shown in each section/core facility report.

RESEARCH PROJECTS

The Department has been involved in various research projects. Details of which are found in each section/core facility report.

FUTURE RESEARCH DIRECTION

The Department will continue to conduct radiation biology research in support of quality patient care. The future research direction for all sections and core facilities of the Biomedical Physics Department is indicated in their respective reports.

PUBLICATIONS

The Department had published 8 papers, from approved research projects, in international journals. All publications of the Biomedical Physics Department staff for the year 2006 are listed in each section/core facility report.
Biomedical Physics Research

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

The research laboratory continued its close collaboration with the Oncology Department. Radiation therapy is a major arm of cancer treatment and management. The radiosensitivity of tumors and normal tissues varies considerably between patients. Although many factors could contribute to this variability (Figure 1), it is mainly governed by genetic factors. Research focuses on studying the genetic determinants of radiosensitivity in Saudi cancer patients. In 2006, we demonstrated an association between single nucleotide polymorphisms (SNPs) in certain genes and the severity of complications following radiotherapy. A large study is ongoing to confirm these results. These SNPs could be used as a predictive test for radiosensitivity that when implemented in clinic, will allow tailoring the cancer treatment to each individual patient. The objective is to improve treatment outcome by increasing tumor control while reducing complications in normal tissues (Figure 1).
RESEARCH PROJECTS

Project Title: Study Comparing Radiosensitivity, DNA Repair, Misrepair and Alterations in Protein Expression Between Fibroblasts Derived from Patients Having Different Normal Tissue Reactions to Radiotherapy: Potential for a Predictive Assay. RAC# 2000 031

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

Project Description

Most cancer patients (50-70%) receive radiation treatment during the management of their disease. Recent advances in imaging and optimization of radiation delivery and tumor targeting will improve patient outcome and allow for dose escalation. However, the tolerance of normal tissues constitutes the limiting factor for dose escalation in radiotherapy. Patients vary considerably in their normal tissue response to radiotherapy even after similar treatment. The causes of this variability are not well understood but have been linked to
cellular radiosensitivity, which is largely attributed to putative genetic factors. The aim of this project is to identify these factors that influence and control radiosensitivity. The endpoints include clonogenic survival, DNA repair, proteins and genes expression, cell aging and senescence, and polymorphic genetic variations that have been more recently investigated as cause of differences between patients.

Progress

We have previously showed a correlation between p53 or p21 proteins (encoded by TP53 and CDKN1A genes, respectively) induction following irradiation and inherent radiation sensitivity. To shed light on the genetic factors involved, we hypothesized that amino acid substitution variants in these two highly radiation responsive proteins are associated with, and could explain individual variations in radiosensitivity. The two non-synonymous single nucleotide polymorphisms TP53 codon 72 Arg/Pro G>C and CDKN1A codon 31 Ser/Arg C>A were genotyped in 92 normal fibroblast cell strains of different radiosensitivity. The clonogenic survival fraction at 2 Gy (SF2) ranged between 0.15 and 0.50 (mean = 0.34, SD = 0.08) (Figure 2). The mean SF2 divided the cell strains into radiosensitive (45) and normal control (47). Significant association was observed between SF2 and TP53 codon 72 haplotype (C vs. G, P = 0.01); however, no association was observed between CDKN1A codon 31 haplotype and radiosensitivity (P = 0.86) despite the apparent trend (Figure 3). The variant TP53 Arg72 allele was associated with relative decrease in radiosensitivity presumably due to sub-optimum function leading to less stringent control on cell division. We conclude that certain SNPs in susceptible genes can influence cellular radiation response. The identification of the risk alleles could ultimately be used as predictive markers for radiosensitivity to help stratifying individuals to risk assessment of radiation exposure.
Based on these results we set out to identify genetic predictive markers of radiosensitivity, which are being sought for stratifying radiotherapy treatment of cancer patients and risk assessment of radiation-exposure. We hypothesized that single nucleotide polymorphisms (SNPs) in susceptible genes are associated with, and the number of risk alleles has incremental effect on individual radiosensitivity. The study included 4 additional amino acid substitution variants in candidate genes (ATM 1853 Asp/Asn G>A, XRCC1 399 Arg/Gln G>A, XRCC3 241 Thr/Met C>T and TGFβ1 10 Leu/Pro T>C). These were genotyped by direct sequencing in 54 fibroblast strains of different radiosensitivity (26 radiosensitive cases and 28 normal controls). The genotype distribution in function of radiosensitivity is illustrated in figure 4. Significant association was observed between SF2 and ATM 1853 Asn, XRCC3 241 Met and TGFβ1 10 Leu alleles (P = 0.05, 0.02 and 0.02, respectively). The number of risk alleles increased with increasing radiosensitivity and groups’ comparison showed statistically significant difference between the radiosensitive and the control groups (P ≤ 0.001). We conclude that SNPs in susceptible genes influence cellular radiation response and that the number of risk alleles has combined effect on radiosensitivity. Individuals with multiple risk alleles could be more susceptible to radiation effects than those with less risk alleles. These results may have implications in predicting normal tissue reactions to radiotherapy and risk assessment of radiation exposure.

Figure 4. The relationship between radiosensitivity (SF2) and genotype distribution of 6 assessed polymorphisms in 54 fibroblast cell strains (solid circles). The open circles represent the mean SF2 by genotype. The error bars = 1SD.
To check for a possible involvement of SNPs in clinical radiosensitivity, we tested the hypothesis that individual variations in normal tissue reactions to radiotherapy are associated with polymorphic variations in these candidate genes. This pilot study involved 50 Head and Neck cancer patients. The grade of fibrosis (G), a late complication to radiotherapy, was scored. The above-mentioned SNPs were genotyped in all patients and the frequency was determined as related to the grade of fibrosis (Figure 6). Allelic distribution in the normally sensitive (control, G0-1) and radiosensitive (cases, G2-3) groups of patients is given in figure 7. Results showed that the XRCC1 399 G allele \(P = 0.05\) and the XRCC3 241 T allele \(P = 0.04\) were significantly associated with higher clinical radiosensitivity. The TGF\(\beta\)1 10 T showed a borderline association \(P = 0.07\). There was a clear trend toward increased sensitivity with increasing the number of risk alleles (Figure 8). We conclude that this preliminary study confirms the association between certain SNPs and risk of radiation-induced normal tissue complications and supports the assumption that clinical radiosensitivity depends on the combined effects of variations in several genes.

**FUTURE RESEARCH DIRECTION**

Based on the encouraging results associating the presence of certain genetic variations, radiosensitivity and late reactions to radiotherapy, we are extending this work to a larger cohort of patients and including more polymorphisms in radiation responsive genes. Another project is to check for a possible
link between mitochondrial DNA mutations and polymorphisms as related to radiosensitivity of cancer patients. Related to an earlier project using the p53 knockout mice, since we found an increased radioresistance when p53 is inactivated, we would like to further confirm this observation by using drugs that block or rescue p53 functions to ascertain that the radioresistant phenotype is related to p53 inactivation and not to the production of a mutant form of p53.

PUBLICATIONS

Manuscripts


Abstracts/Congress Proceedings

The Health Physics Section is committed to its mission of limiting the risks of exposures to patients, staff and members of the public. It is recognized by the International Atomic Energy Agency (IAEA) as a center for training in radiation protection and measurement. Its personnel radiation dose monitoring service is accredited by IAEA, thus meeting the international high standards for radiation protection. The Section obtained the King Abdulaziz City for Science & Technology (KACST) as the only reference laboratory for personnel radiation dose monitoring and instrument calibration and therefore the number of clientele increased by about 15-20% from last year. It obtained recognition from the International Atomic Energy Agency (IAEA) as the center for developing experts on radiation protection in interventional radiology with the continuing technical support for the research project on radiation protection. One staff was granted an international scientific visit and Research Centre was made a recipient of equipment and supplies for the research project. It was selected by the IAEA as the only institution in the Kingdom to orally present the research project on optimization of radiation protection in pediatric cardiac catheterization during the International Conference on Quality Assurance and New Techniques in Radiation Medicine held in Vienna, Austria on 13-15 November 2006. The Section takes pride in the establishment of technical and research collaboration with Italy and member countries of the European Commission on radiation protection in interventional radiology.

Section

Health Physics

Head of Section
Abdalla N. Al-Haj, PhD, CSRP

Members
Ibrahim Al-Gain, BS
Heba Al-Humaidan, BS
Celestino S. Lagarde, BS
Charlie S. Lagarde, MS, CHP, NRRPT
Aida M. Lobriguito, MS
<table>
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<tr>
<th>TASKS</th>
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<td>Patients rooms surveyed for radiation level</td>
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<tr>
<td>Patients rooms decontaminated</td>
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<tr>
<td>Electron microscopes evaluated for scatter radiation</td>
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<td>Rooms evaluated for shielding adequacy</td>
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<td>Patient dose assessment performed</td>
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<td>Consultative advice provided</td>
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<td>a) In-house lectures</td>
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<td>d) Three month on-the-job training on radiation protection and measurements</td>
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<td>e) Lectures conducted for personnel from outside facilities</td>
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<td>b) Manuscripts accepted for publication</td>
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<tr>
<td>c) Research in progress</td>
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| Table 1. Activities accomplished by the Health Physics Section for year 2006 in providing services to KFSH&RC and other facilities in the Kingdom of Saudi Arabia and the countries in the Gulf region. |

![Figure 1. Graph showing the number of instruments and institutions that are being served for instrument calibration in year 2006.](image1)

![Figure 2. Graph showing the number of institutions served for TLD personnel radiation dose monitoring service for year 2006.](image2)
RESEARCH PROJECT

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

Project Description

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

Principal Investigator: Abdalla N. Al-Haj, PhD

Progress

In Progress.

FUTURE RESEARCH DIRECTION

The research project focuses on radiation dose assessment in interventional procedures and intends to include different equipment modalities, more complex procedures and additional institutions. The project aims to develop a national training program on radiation safety in interventional radiology.

PUBLICATIONS

Abstracts accepted for presentation


Manuscripts Approved for Publication


Most of the activities in the Imaging Physics section are concentrated in providing clinical imaging physics services to the departments of Radiology, OR, Dentistry, Cath Lab and Radiotherapy of the KFSH&RC (Riyadh); the Department of Radiology of the King Fahad National Children’s Cancer Centre & Research (KFNCCC&R), and to surrounding Royal Palace satellite clinics. The imaging modalities assisted are: dentistry, general (digital) radiography, portable radiography, bone densitometry, computed radiography, conventional and digital fluoroscopy, angiography, conventional and digital mammography, computed tomography (CT), ultrasound, positron emission tomography (PET), PET/CT, nuclear medicine, 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 medical imaging 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.

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

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

**Project Description**

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

**Progress**

KACST grant received and project will commence.

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

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

**Project Description**

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

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

Project Title: Performance Test Data Analysis of Scintillation Cameras

Investigators: O. Demirkaya and R. Al Mazrou

Project Description

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

Progress

We have developed a set of image analysis tools to calculate the performance parameters of scintillation cameras and SPECT systems from test data acquired according to the National Electrical Manufacturers Association NU 1-2001 guidelines. The calculation methods are either completely automated or require minimal user interaction; minimizing potential human errors. The developed methods are robust with respect to varying conditions under which these tests may be performed. The core algorithms have been validated for accuracy. They have been extensively tested on images acquired by the gamma cameras from different vendors. All the algorithms are incorporated into a graphical user interface that provides a convenient way to process the data and report the results. The entire application has been developed in MATLAB programming environment and is compiled to run as a stand-alone program. The developed image analysis tools provide an automated, convenient and accurate means to calculate the performance parameters of gamma cameras and SPECT systems. The application has also proved to be a very useful tool in our workshops and trainings. A manuscript describing the methods has been submitted.
Project Title: Survey of Quality Control and Clinical Practice in Nuclear Medicine Departments in the Kingdom of Saudi Arabia for the year 2006

Investigators: R. Al Mazrou, A. Arafah, O. Demirkaya and T. Albaghdadi

Project Description

Nuclear Medicine is a clinical diagnostic and therapeutic specialty, which uses non-sealed radionuclides to image internal body organs, evaluate their various physiological functions with gross morphology and treat selected diseases. Nuclear medicine imaging procedures often identify abnormalities very early in the progression of a disease—long before some medical problems are apparent with other diagnostic tests. This early detection allows a disease to be treated early in its course when there may be a more successful prognosis.

This study will be a repeat of a similar previous one conducted seven years ago through a grant from KACST. In this project, data will be collected from all nuclear medicine departments existing in the Kingdom of Saudi Arabia. A survey will be conducted asking certain questions about these departments quality control procedures, clinical procedures performed (including imaging, non-imaging and therapeutic procedures), existing equipment and radioactive isotopes used.

Progress

Project proposal has been submitted and awaiting KACST approval.

FUTURE RESEARCH DIRECTION

The primary activity of the clinical research being performed is directed to PET/CT application in medicine where imaging applications are being developed to assist Radiologists in improving their clinical protocols to improve diagnostic detection of malignant disease. This research will also assist the institution in optimizing modality utilization (PET/CT versus just CT or MRI) thus minimizing the time of diagnosis and reducing radiation exposure to patients, many of which are pediatric.

PUBLICATIONS

Book

Image Processing with MATLAB: Applications in Medicine and Biology, Omer Demirkaya, Musa H. Asyali, Prasanna Sahoo, M. Shoukri (a contract has been signed with CRC Press and the work is in progress).

Articles

1. Al-zoghaibi, Fahad; Abuleef, Hana; Demirkaya, Omer; Khabar, Khalid Bioinformatics and experimental derivation of an efficient 3’ untranslated region and use in translationally active linear DNA with minimum Poly(A) region (accepted to Gene Journal).

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

Our Section supports the treatment of 1646 cancer patients, providing 2781 medical physics procedures for the year.

Our Radiation Physics Section, in collaboration with the King Faisal Cancer Center, has launched the state-of-the-art Intensity Modulated Radiation Therapy (IMRT) technique, which increases conformal dose planning and delivery enabling superior normal tissue sparing for cancer patients undergoing radiation therapy treatment. In fact, on July 25, 2006, the first cancer patient was treated with fully dynamic IMRT. It is the first IMRT case in the whole Kingdom.

Priority for next year is the development and implementation of innovative radiotherapy techniques such as IGRT and IORT as well as engineering of affiliation contracts with major radiotherapy vendors to turn our Radiation Therapy service into a reference site for Saudi and Middle East customers. Our Section's aim is to help turn our services into a centre of excellence in clinical medical physics and radiation oncology.
RESEARCH PROJECTS

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

Principal Investigator: Belal Moftah

Project Description

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

Progress

The grant proposal was submitted to and approved by the General Directorate of Research, Annual Grants Program of the King AbdulAziz City of Science and Technology (KACST). The project is to start at the beginning of 2007. (KACST Project No. AT-25-85, approved funding, SR 652,000)

Project Title: Investigation of the Accuracy of the Photon Dose Calculation Algorithm for a Treatment Planning System (Eclipse). (Project # 2040015)

Investigators: Belal Moftah (KFSH&RC Co-Supervisor), Magdi Ghannam (KSU Co-Supervisor), Mariam Hashim (M.Sc. Student)

Project Description

This project has been assigned to the student for her research project as part of her master thesis completion. An extensive set of measured data was developed for the purpose of verifying the accuracy of a photon dose-calculation algorithm for the treatment planning system (Eclipse) and its application in cancer patients. This data set was applied to a commonly used photon-beam dose-calculation algorithm with the following goals of: (1) Validating the assumed parameters used in the beam model; and (2) Evaluating the accuracy of the dose calculation in various clinically relevant situations.

Progress

Proposal has been written and was approved by the Office of Research Affairs. Dose measurements as well as treatment planning calculations have been completed. Analysis of data was completed, Thesis was approved and published and the M.Sc. degree was conferred on the student, July 2006.

FUTURE CLINICAL RESEARCH DIRECTION

Project Title: Image Guided Radiation Therapy (IGRT) and Adaptive Gated Radiotherapy

Project Description

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

Progress

Research in preparation. The World leading provider of IGRT system has agreed to partner with KFSH&RC to provide the state-of-the-art ExacTrac X-Ray 6D system free of charge (quoted cost is
about SR 3.5 Million). KFSH&RC will be the first center to provide IGRT technique outside Europe and North America. An affiliation proposal has been drafted and submitted for senior management approval. Once approved, a research project will be written and submitted.

Project Title: Incorporation of PET/CT into Radiation Treatment Planning

Project Description

PET/CT is a new hybrid imaging modality combining the advantages of both PET (metabolic imaging) and CT (anatomic imaging) to better localize the metabolically active cancerous tissue. This project is to investigate the usefulness of hardware coregistered PET/CT images for target volume definition for three dimensional conformal radiation therapy treatment planning.

Progress

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

PUBLICATIONS

Books


Publications in Peer-Reviewed Journals:


Conference Proceedings

Presentations at Scientific meetings

2. Belal Moftah, Physics Applications in Cancer Treatment, Department of Physics, King Saud University, Riyadh, Saudi Arabia, February 26, 2006.
The role of the Clinical Dosimetry and Treatment Planning Unit is to provide all calculation and planning for our cancer patients undergoing radiation therapy in order to maximize the prescribed dose to the tumor and minimize the dose to surrounding normal and critical structures such as the spinal cord, brain stem, optic chiasm, kidneys, etc. Very sophisticated computer algorithms are used to achieve this goal. The algorithms utilize imaging information from CT, MR and PET and enable 3-D rendering to provide accurate and spatial images to aid in the process of tumor and normal and critical structures definition.

2006 was a very hectic year due to increase in workload (12%) while at the same time, a senior staff member (Dr. Jayaraman) resigned leaving the Unit even shorter of staff. In addition to this, new junior staff members were hired who required time-consuming training and supervision.

In July 2006, IMRT was introduced. IMRT requires much more time for volume localization by the Radiation Oncologists, planning and QA by Medical Dosimetrists/ Medical Physicists. This was the first IMRT patient treated in the Kingdom of Saudi Arabia. Since the first patient was treated, two other patients were planned using IMRT but the final clinical decision was to change them to 3-D conformal planning.

In order to keep up with the constant increase in workload, train new staff members and progress into new treatment and planning modalities such as IMRT, IGRT and IMRS, more experienced senior staff are needed in the Unit.
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**TRAINING AND EDUCATION ACTIVITIES**

We have continued to provide training in clinical dosimetry and treatment planning to BSc students in Medical Physics from different universities within the kingdom.

**PUBLICATIONS**

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

Figure 1
CORE SERVICE ACTIVITIES

The activities of the Gamma Irradiation Facility in 2006 are as follows:

1. Continued to provide sterilization for hospital needs (Cyclotron kits and supplies of ART laboratory.
2. Contacted King Faisal Foundation to provide sterilization services to preserve ancient documents and very old books using Gamma rays. Research concerning the different types of papers and its compatibility to gamma sterilization has to be done, using some requested equipment. Research will start as soon as these equipment are received.
3. Started to provide training for physicists from KACST with a one week Dosimetry workshop.
4. Provided gamma irradiation services for Master Degree student from King Saud University, College of pharmaceutical science.
5. Conducted Inter-comparison study with RISO National Laboratory, DENMARK resulting in very accurate Dosimetry (less than 3% difference in routine Dosimetry).
6. Obtained Quality Management System ISO 9001: 2000 certification on 01 January 2006. The new quality management system of the Facility is equipped to fulfill the requirements of the customers and to provide high quality irradiation services.

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. The quantity of sterilized materials in the Gamma Facility has doubled compared to previous year's activity. The Facility will pursue its income generating opportunities through sterilization of medical products/materials using gamma irradiation.
The Secondary Standard Dosimetry Laboratory (SSDL) of the Biomedical Physics Department ensures high accuracy in radiation measurements and dosimetry for all applications of ionizing radiation. The high accuracy in measurement is maintained by successfully meeting the high standards set by the International Atomic Energy Agency (IAEA) and the World Health Organization (WHO) for radiation protection and radiotherapy levels of calibration. It gained the IAEA recognition as the first SSDL in the Kingdom to obtain the IAEA and WHO accreditation thus making it a recognized calibration laboratory in the whole world. It is also recognized by the King Abdulaziz City for Science & Technology (KACST) as the only reference laboratory for instrument calibration in the Kingdom that meets national regulatory requirements and international standards. The SSDL continues to provide services to the different Departments of King Faisal Specialist Hospital and Research Centre (KFSH & RC) and to other institutions in the Kingdom of Saudi Arabia and the Gulf region.

ACTIVITIES

For the year 2006 the SSDL provided calibration services to 5 Departments of KFSH&RC, 3 government agencies, 6 government hospitals, 8 private hospitals and 22 private companies. It has also extended the provision of calibration services to 1 country in the Gulf region. A total of 354 radiation-measuring instruments were calibrated, intercompared and acceptance tested. These instruments include 316 survey meters, 32 pocket dosimeters, 4 radiotherapy dosimeters and 2 diagnostic dosimeters. A total of 38 quality control tests of counting systems were performed. It has also provided irradiation services for the quality control test of TLD readers of service providers in the Kingdom where a total of 678 TLD badges were irradiated. To ensure accuracy in its calibration, the SSDL participated in the IAEA and WHO annual postal dose audit for radiotherapy energy level of calibration where it obtained a very satisfactory result.
Figure 1. Graph showing the number of external facilities served by the SSDL in year 2006.

Figure 2. Graph showing the type and number of instruments calibrated in years 2005 & 2006.
The Department of Biostatistics and Epidemiology
The year 2006 has been a year of accomplishments for the Department of Biostatistics and Epidemiology. The most significant contributions are the expansion of several web-based registries to multi-centers, and serious planning to become regional. The completion of the Puberty Project, spearheaded by our epidemiologists and the production of the 5-year cumulative report for the GCCR. It is clear to the department that its role is recognized by higher administration as important to the institution’s pursuit of its overall mission – the provision of core quantitative support in the areas of biostatistics and epidemiology, the research into epidemiological issues that affect the health of the institution’s patients as well as the population of the Kingdom at large, and the development of new methodologies into analysis of biomedical data.

RESEARCH PROJECTS

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

This report presents the accomplishments of the various groups in terms of the research projects on which the respective participated. Some research projects are internally driven by the department’s staff, and some are directed by investigators outside the department. Project-based research is the fundamental process through which we function as a department. During the year, over 50 projects were registered by the Department. The work resulted in books, publications, presentations, and workshops. Associated with each project listed in this report is a statement as to the product resulting from the efforts of departmental staff working on the project.

In comparison to 2005, our productivity has been at par with the past. The number of staff has decreased in the past year. However, despite that, the publication rate has maintained its level. We continue to aim for higher impact publications, and to that end believe that we have been particularly successful. Also, despite the decrease in the number of staff, the core facilities have continued to maintain their support of important projects, e.g. the provision of high quality computing services, the accurate collection of patient data on nine disease registries and the expansion of both the congenital heart disease and neural tube defects registries, the development and enhancements to technical services.
databases, the management of gigabytes of research
data for ever increasingly complex research projects,
the often-customized analysis of genetic data, and
the efficient provision of administrative support to
a research department.

We look forward to the year 2007 as a transitional
year when new initiatives will be pursued and other
initiatives suspended – of special note are increased
sophistication into epidemiological studies, the
focus on the registries and developing strategies for
long-term support thereof and the applications of
computational statistics and its application in the
analysis of micro-array gene expressions data. The
department plans to establish the national birth
defect registry with support from Prince Salman
Centre for Disability Research. Our base of support
provided to Hospital administration is now wider
and we expect to be an important partner in the
Data Warehouse Project.
The Biostatistics Research Unit (BRU) enjoys a special status in the department. We are motivated by the curiosity of clinicians and scientists to pursue knowledge for its own sake and for what it may yield. Knowledge - whether newly discovered or interpreted by our researchers, or newly acquired, is a powerful agent of change in the lives of our staff and the hospital community in general. The most interesting feature of the BRU is its ability to transform itself to serve the Hospital and the Research Centre well and effectively. Our commitment to fulfill the mission of the Research Centre and the Hospital is distilled in our mission:

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

Our principles are summarized in:

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

**RESEARCH PROJECTS**

**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. To illustrate the issue we focus on continuously and normally distributed responses. Let $X_T$ and $X_R$ designate the normally distributed variable of interest for the test and the reference drugs, respectively with means and it is of interest to test:

$$H_0: \frac{\mu_T}{\mu_R} \leq \theta_1 \text{ or } \frac{\mu_T}{\mu_R} \geq \theta_2 \text{ versus } H_1: \frac{\mu_T}{\mu_R} \leq \theta_2$$

Here, $\theta_1$ and $\theta_2$ are preset limits. If the observations follow a lognormal distribution with the general assumption that the means are positive, there is international consensus that the equivalence should be assessed on the log-scale (see, Schuirmann 1987, Liu & Weng 1994). One should realize that the ratio of means is an adequate parameter to assess equivalence for continuous data.

For categorical data the situation is different, since the means are replaced by rates hence the ratio of means becomes a risk ratio.

There are two competing designs under which BE can be investigated; the first being the parallel-group 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 $C(\alpha)$” testing procedure. It possesses an interesting property in that it is locally most powerful against alternatives in the neighborhood of the null.

**Progress**

The $C(\alpha)$ 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. The information matrix under the null hypothesis has been approximated by the Psi function and its derivatives have shown to possess closed form. This will make the problem of inference feasible by the practicing statistician.

**Project Title:** Comparing the Reliability of Measurements of Two Laboratories. RAC# 2040028

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

**Project Description**

The need for error-free diagnoses has been the subject of intense discussion among medical decision makers. The discussion has been fueled by both economical and ethical considerations. Countries
where medical care is a publicly provided good are suffering from the increase in the cost of health care, and the steady reduction of government spending in this area. It is clear then, that unnecessary repeated and costly testing should be avoided in order to ensure efficient delivery of care. Likewise, under a free enterprise health care system, prudent fiscal policies of Health Maintenance Organizations (HMO) mandate physicians to require only few reliable tests, so that decision regarding treatment modality is correctly made.

In view of this, all laboratory tests must be validated before being introduced for patient testing to ensure that the reported measurements (e.g., blood glucose levels) meet a desired degree of reliability. Validating a new technique begins with the consideration for, and selection of a new test method for patient’s use. Evaluating the analytic performance of medical tests is required to assess the degree of error expected due to inaccuracy and imprecision and to confirm that the level of errors is bounded primarily by clinical requirements.

There are inherent statistical issues that must be dealt with in our attempt to understand sources of errors in clinical measurements. One needs to understand the types of errors (random or systematic) and how to measure their magnitude, and if the degree of error affects the interpretation and possibly patient’s care. Clearly, if the potential error is large enough to lead to misdiagnosis, then the measuring instrument is not acceptable. The accuracy of a measuring technique is defined by the international Federation of Clinical Chemists (IFCC) as the closeness of the agreement between the measured value and the “true” value measured by a non-faulty device. Definitive methods, such as mass spectrometry, are used to develop primary reference materials, which can then be used for development of reference methods by manufacturers. Comparative methods means, to a great extent, are obtained from the measurements generated by multiple laboratories using a variety of instruments and techniques. On the other hand, precision of a measuring technique means its ability to reproduce its own results. It is therefore very important to assess the magnitude of such errors by calculating a measurement reliability index. The intra-class correlation coefficient (ICC) has emerged as a universally acceptable index to assess reliability, and its properties have been investigated by many researchers (Shoukri et al., 2003).

In this proposal we shall establish a model by which one can evaluate the ICC for each of two laboratories measuring the same set of subjects.

Progress

During the elapsed period a good progress has been achieved:

1. We derived the likelihood function and the likelihood estimators for the intra-class correlations (ICC), and the inter-class correlation.
2. Under the present model, it has been reported that the within subject coefficient of variation (WSCV) can be a good competitor to the ICC. We developed the likelihood ratio test, the Wald test and the score tests on the equality of correlated WSCV.
3. Extensive Monte-Carlo simulations have been designed to evaluate the asymptotic power and empirical levels of tests of significances of the differences between measures of reliability based on the above tests. We report that the score test was, to our surprise, quite inferior, and the Wald test is excellent. This is a useful finding, because the Wald test is very simple to calculate by the non-experts, and does not require numerical algorithms as the likelihood ratio test does.
4. A per has been published and a final report has been submitted and accepted by RAC.
Project Title: Hierarchical Modeling of Correlated Binary Traits with Applications to Asthma and Hay Fever Twins Data. RAC# 2030 010

Investigator: M. M. Shoukri

Project Description

Many common diseases have a genetic contribution, evidence for this being that close relatives of an affected person are more likely to be affected themselves. Many genes are likely to be involved in the susceptibility to such diseases, perhaps interacting with environmental risk factors. We are working to develop statistical models to analyze data for traits or diseases that cluster in families to gauge the contribution of the genetic factors to the variability of disease distribution. When the main issue is whether two diseases share common genetic and environmental factors, then one needs to select an appropriate design. For this project we chose “twins” as they are uniquely matched for age and many other factors. The main objectives of the this project are:

- Estimating the degree of clustering of two diseases among twins
- Estimating the level of associations between two diseases
- Comparing the levels of clustering in monozygotic twins to that in dizygotic twins.

Progress

A multivariate probability distribution for binary traits has been constructed. We estimated the model parameters using the method of moments and illustrated the methodologies on the asthma and hay fever data collected from the “Australian Twins Registry”. A paper has been accepted by Statistics in Medicine.

Project Title: Estimating Incremental Cost-effectiveness Ratios from Cluster Randomized Intervention Trials. RAC# 2030039

Investigators: M. M. Shoukri (PI), M. A. Chaudhary

Project Description

The statistic of interest in most health economic evaluations is the incremental cost-effectiveness ratio. Since the distribution of the statistic is usually positively skewed and far from normal and since the variance of the ratio estimator is intractable, the health economics literature has suggested a number of alternative approaches to estimating confidence intervals for cost-effectiveness ratios. These approaches are restricted to individual level data. The extension of cost effectiveness analysis methods to cluster randomized data still remains to be a challenge. This study aims to fill this gap by extending the methods for the interval estimation of incremental cost-effectiveness ratios for individual data to cluster randomization intervention trials and make some empirical comparisons.

Progress

The proposal was developed and approved. Literature review and some initial research work have been accomplished last year. Preliminary results are presented at the American Public Health Association (APHA) meeting. The project has been concluded and a final report has been submitted to TAC.

Project Title: The Power of Detecting Heterogeneity in Meta-Analysis. RAC# 2060032

Investigators: M. M. Shoukri, G. El-Din Mohamed
Project Description

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

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

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

This proposal deals with the problem of between and within studies heterogeneity. Although the within study heterogeneity is always reported with each study, one can reduce its level by employing an appropriate transformation. The issue of reducing the within study heterogeneity and proper estimation of the between studies variance and their joint effect on the power of detecting heterogeneity will be explored in this proposal.

Study Objectives

This proposal has several objectives:

1. Instead of using the LODR as an effect size, we shall use the risk difference (RD). The reason being, there is only one traditionally transformation to normality when the odds ratio is used as an effect size. Therefore, we have no other competing transformation. However, if the RD is used, several competing alternatives exist to stabilize the variance of the RD: the logit, the inverse sign, and the Wald are examples of such transformations.

2. The chi square distribution has been used to test for heterogeneity in MA, by approximating the test of homogeneity Q using its first two moments (see Jackson 2006). We propose an alternative model other than the chi square approximation. The proposed approximation should account for the possible skewness in the reported effect sizes, and is expected to improve the power of the test. To be specific, instead of using a two-moment approximation, we propose the three parameters Johnson’s family of distribution (1970).

3. It is noted that most MA studies focus on the
randomized controlled clinical trials (RCCT). However, there are situations when the number of RCCT may not be sufficient, and one would be tempted to mix RCCT with other studies. This mixture is likely to increase the heterogeneity. However, through meta-regression one should be able to account for differences in these study designs and increase the power of detecting significant over all effect size.

4. The proposed methodology will be illustrated on studies that investigate the effect of folic acid taken by pregnant women on neural tube defects among new born.

This project has just been accepted by RAC. Some work based on preliminary meta-analysis of folic acid and neural tube defect has been presented to the Neural Tube Defects Work Shop on January 16-17, 2007.

Project Title: Signal to Noise Estimation as a Measure of Reproducibility: Design, Estimation and Applications. RAC# 2030028

Primary Investigators: M. Shoukri, N. Elkum

Project Description

Inter-observer reliability studies are conducted to investigate the reproducibility and level of agreement on assessments made by diagnostic procedures. Typically several assessments on each of a series of subjects and their scores are evaluated. A widely recognized index of reliability is the intra-class correlation coefficient (ICC). One of the most important criticisms that can be directed at the ICC is that its value depends heavily on the between-subject variation. An alternative measure of reliability that will be considered in this project is the signal-to-noise ratio (SNR). This project considers the use of SNR for assessing the reproducibility or reliability of measurement. It also derives the optimal allocation for the number of subjects and the number of repeated measurements that minimizes the variance of the estimated SNR. Cost constraints are discussed for both normally and non-normally distributed responses.

Progress

The project has been completed and final report has been submitted to RAC. A paper has been published.

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

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

Co-Investigators: M. Shoukri

Project Description

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

Progress

The project has been successfully completed and a paper has been accepted for publication.
Project Title: Modeling Circadian Rhythms in Failure Time Data. RAC# 2060011

Primary Investigator: N. Elkum

Project Description

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

Progress

The project approved by RAC, a paper has been published.

Project Title: Flow Cytometric Analysis of Minimal Residual Disease in Pediatric Acute Lymphoblastic Leukemia at KFSH&RC. RAC# 2001 007

Primary Investigators: A. Al-Nasser (Pediatric Hematology/Oncology), T. Al-Asaad
Co Investigators: H. El-Solh, A. Al-Omari, K. Al-Hussien, N. Elkum, A. Silo

Project Description

In the treatment of acute lymphoblastic leukemia (ALL), risk factors present at diagnosis are used to assign treatment protocols of varying intensity. However, significant numbers of patients without these high risk factors perform poorly on standard risk protocols. Other prognostic indicators are required to identify patients who are likely to relapse, and therefore may benefit from more intensive treatment.

This is a prospective study that investigates the prognostic value of monitoring minimum residual disease (MRD) in pediatric patients with ALL. The ultimate goal of this study is to use MRD as a marker to reassign patients with ALL to appropriate treatment protocols. An established technique based on immunological detection of residual leukemic cells by flow-cytometry will be used to check MRD in newly diagnosed ALL cases at KFSH&RC. The information gained from this study will related directly to ALL as it presents in Saudi Arabia, without any geographical or genetic bias, which may be present in the international experience. The application of this information may ultimately result in an increased overall survival of children presenting with ALL in Saudi Arabia

Progress

Data collection is in progress but due to the nature of the study the accrual of patients is very slow. Continue to accrue patients to achieve the target sample of 250 patients

Project Title: P-glycoprotein in Childhood Acute Leukemias in the Kingdom of Saudi Arabia: A Prospective Study of Expression and Function and Correlation with Outcome. RAC# 2001004

Primary Investigator: A. Al-Nasser
Co-Investigators: S. Al-Daama, H. El-Solh, K. Al-Hussien, N. Elkum, A. Silo
Project Description

P-glycoprotein (PGp), an ATP-dependent transmembranous protein, detected in malignant cells by flow-cytometry, actively extrudes a variety of lipophilic compounds of the cell including anti-neoplastic agents such as anthracyclines, vinca alkaloids and epipodophylo toxins, thus leading to lower intracellular drug accumulations and reduced cell toxicity. This is a five-year prospective study that follows up newly diagnosed cases of acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) patients at KFSH&RC among children aged less than 14 years of age.

Progress

Data collection is in progress but due to the nature of the study the accrual of patients is very slow. Ninety six patients enrolled between April 2002 and 12 October 2005; 21 patients dropped-out of the study.

Project Title: Optimal Sampling Time Designs in Pharmacokinetic Studies. RAC# 2021025

Investigators: N. Elkum, M. Asyali
Co-Investigators: M. Shoukri

Project Description

This project provides an optimal selection procedure that substantially improves the accuracy of area under the curve (AUC) estimation in bioavialability studies.

Progress

A paper is submitted for publication.

Project Title: Acute Biphenotypic: Review of the Diagnostic Criteria and Laboratory Presentation, Single Center Experience. RAC# 2041007

Primary Investigator: T. M. Owaidah
Co-Investigators: G. Roberts, A. Iqbal, N. Elkum

Project Description

Biphenotypic acute leukemia (BAL) is a rare disease, which is identified in 5-20% of acute leukemia. Knowledge about BAL is limited, both in terms of clinical and biological presentation and also with regard to treatment outcome. Due to a lack of objective criteria, there have been difficulties in establishing whether BAL represents a distinct clinicobiological entity. The clinical significance of BAL has not been determined and there has been a lack of uniformity in treatment. This retrospective study aims to review the King Faisal Specialist Hospital and Research Centre experience with BAL patients who presented during the last four-year period. Clinical and biological data at presentation and during induction phase, treatment result and patient outcome will be studied. We will review and evaluate the diagnostic criteria including confirmation of the diagnosis using the EGIL scoring system and ultra structural study of myeloperoxidase as a new marker that could help in defining the cell lineage involved in biphenotypic leukemia. We believe that this review could contribute to the knowledge about BAL and might provide new criteria for its diagnosis.

Progress

Study has been completed. An abstract was presented in ASH and a paper published in Leukemia.
Project Title: Using Support Vector Machines for Prognosis and Survival Prediction in Breast Cancer. RAC# 2040 006

Primary Investigators: N. Elkum, T. Twegery (Oncology)
Co-Investigator: W. Greer

Project Description

The support vector machine (SVM) is a new machine-learning approach to decision-making, which offers certain advantages over more traditional neural network algorithms. It has already been successfully applied to a number of research areas in medicine and biology, including various studies in breast cancer. The purpose of the research project is to apply these methods to breast cancer patients at KFSH&RC, with a view to developing a clinical tool that can be used to make predictions based on information available at patient presentation.

Progress

Data collection has been completed; data management and cleaning are completed. A draft paper under preparation.

Project Title: Identification of Environmental and Genetic Factors that Influence Breast Cancer Development and Therapy in Saudi Females. RAC# 2031091

Primary Investigator: S. B. Amer
Co-Primary Investigator: N. Elkum

Project Description

A major grant proposal submitted to the King Abdulaziz City of Science and Technology, Riyadh, Kingdom of Saudi Arabia and approved for funding, SR 1,272,080.00. The cancer data of the Kingdom of Saudi Arabia show that breast cancer is hitting the largest proportion of the female population of the cancer patients. Because of the lack of any original data on this subject in the Kingdom of Saudi Arabia, a case control study is planned to be conducted at national level. This research study will describe the risk factors of breast cancer and relationship among these factors for the Saudi population thus giving a better understanding of this disease in this part of the world. Based on this research, attempts can be made to lower down both the incidence and mortality rates.

Project Title: Proposal for Evaluation of the Expression of CD66C Monoclonal Antibody in Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia: An Early Predictor of Outcome and a Marker for Detection of Minimal Residual Disease. RAC# 2041 058

Primary Investigator: T. M. Owaidah
Co-Investigators: G. Roberts, N. Elkum

Project Description

We are analyzing the expression of KOR-SA 3544 antigen on Philadelphia (Ph) positive acute lymphoblastic leukemia (ALL) as a possible prognostic marker that can be used in detection of minimal residual disease. In this study we are planning to do retrospective analysis of the data for expression of CD66c in cases of acute leukemia who presented to KFSH&RC, and for whom the full immunophenotypic analysis for different surface antigens performed at the time of presentation for diagnostic purposes and correlate findings with cytogenetics and molecular results.
Progress

Data collection was completed. It is in data cleaning stage.

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

**Primary Investigator:** A. Abousekhra  
**Co-Investigator:** N. Elkum

**Project Description**

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

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

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

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

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

**Progress**

RAC approved the project and tissue collections are in progress.

**Project Title: Gene-Environment Interaction: TP53 Gene Mutation Spectrum in Breast Cancer in Saudi Arabia. RAC# 2040037**

**Primary Investigator:** A. Abousekhra  
**Co-Investigator:** N. Elkum

**Project Description**

Breast cancer remains a worldwide public health concern. The incidence and mortality from breast cancer varies significantly in ethnically and geographically distinct populations, which suggests that the causes of this disease are both genetic and
environmental. While the environmental causing factors are still largely unknown, several genetic related ones have been identified and some of them turned out to be valuable for diagnostic and therapeutic practices. Among these, the TP53 gene has been shown to be of great importance and has been also used as mutagen test. Indeed, the pattern of TP53 mutations varies among geographically and ethnically diverse populations.

In order to determine the frequency and the nature of TP53 mutations among the breast cancer Saudi females the TP53 gene will be sequenced from 100 paraffin-embedded tissue sections derived from patients treated in the KFSH&RC. Subsequently, we will study the potential correlation between these mutations and the age and the geographical origin of these patients.

The resulting information will allow the identification of potential breast cancer-related carcinogens in Saudi Arabia and will be instrumental in developing health and regulatory policies that will help in increasing the protection of the more susceptible groups from risks of environmental carcinogens.

**Progress**

Funded by King AbdulAziz City of Science and Technology, Riyadh, Kingdom of Saudi Arabia (SR 49,000.00). Tissue collections are in progress.

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

**Primary Investigator:** H. Al-Ashgar  
**Co-Investigators:** K. Alsawat, N. Elkum

**Project Description**

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

**Progress**

The data has been collected respectively from patient’s charts. It is in cleaning stage.

**Project Title:** Efficacy of Peginterferon Alpha-2a in Hbe Ag Negative Chronic Hepatitis B: Naïve versus Lamivudine Resistance Patients. RAC# 2051045

**Primary Investigator:** H. Al-Ashgar  
**Co-Investigators:** K. Alsawat, N. Elkum

**Project Description**

This is a prospective, randomized, open label, multicenter study comparing the efficacy and safety of peg interferon Alpha-2a (40 kDa), in HbeAg negative chronic hepatitis B naïve and lamivudine resistance Saudi patients who fulfilled all the inclusion and exclusion criteria. The study will be conducted at 6 different major hospitals in Riyadh: KFSH & RC, Security Force Hospital, National Guard Hospital, Military Hospital, Riyadh Central Hospital, and King Khalid University hospital. Sixty-five patients, who met all the inclusion and exclusion criteria, will be included in the study for the next 1-year and the study will be completed after 96 weeks of last patient enrollment.
Progress

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

Project Title: Knowledge and Awareness About Cancer and Its Prevention: Attitude Towards Cancer Preventive Health Behaviour. RAC# 2051041. KACST# MS 11-1

Principal Investigator: K. Ravichandran
Co-investigators: G. E. Mohamed, N. Al Hamdan, A. Al Rowais

Project Description

Worldwide, there were over 10 million new cases of cancer and more than 6 million deaths from cancer by 2000. Although the disease has often been regarded as a problem principally of the developed world, in fact, of the 10 million new cancer cases annually, 4.7 million were in the more developed countries and nearly 5.4 million were in the less developed countries. Although much remains to be learned about the etiology of cancer, at least one-third of the cases are preventable by such means as controlling tobacco and alcohol use, moderating diet, and immunizing against viral hepatitis B. Further one-third of cases can be controlled by early detection, and therefore prompt treatment, where resources allow.

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

Progress

This project was approved by KACST. Preparation to start data collection is underway.

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

Principal Investigator: I. Al-Saleh (BMR)
Co-investigators: G. Mohamed, A. A. Hogah (Primary Health Care Unites, Al Karj, MOH)

Project Description

Selenium is an essential element, cofactor for glutathione peroxidase activity whose deficiency may induce modification in the cellular antioxidative status and induce the appearance of different diseases. Studies suggest that a serum selenium concentration of 0.045 µg/ml may correlate with an increased risk of coronary heart diseases, coronary atherosclerosis and cancer. The selenium content of the soil determines its concentration in the food chain, which in turn determines the regional nutritional selenium status. Previous studies by the principal investigator in Al-Kharj province reported low selenium levels in the soil of 3 dairy farms and the milk of lactating mothers living in that region. This could be a public health problem and research is needed to determine the magnitude of the problem in specific areas in Saudi Arabia and to identify the
factors that should be taken into consideration for prevention. Generally, selenium functions as an antioxidant that works in conjunction with vitamin E. A cross-sectional study will be conducted among Saudi children and adults attending the Primary Health Care Units in Al-Kharj province. In order to assess the selenium and vitamin E status and its association between DNA damage and antioxidant status. Serum and fingernail samples will be collected for this study.

Progress

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

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

**Primary Investigator:** I. Al-Saleh (BMR)  
**Co-investigators:** G. E. Mohamed, J. Arif (BMR), N. Al Sanea (Surgery), A. Abdul Jabbar (Surgery)

**Project Description**

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

Progress

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

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

**Primary Investigators:** K. Al Maghrabi (Medicine)  
**Co-Principal Investigator:** R. Al-Hubail (Medicine)  
**Co-investigators:** G. Mohammed, M. Hijazi (Medicine), N. Abouchala (Medicine), T. Wetterberg (Medicine)

**Project Description**

Anemia is common in the critically ill patients. By day 3 of intensive care units (ICU) admission, ~95% of the patients have hemoglobin concentration below normal. Blood transfusion and blood conservation are complementary activities that constitute the clinical arena of transfusion medicine. Recent improvement in the safety of the blood supply and the increasing costs associated with transfusion therapies have led to a re-evaluation of the clinical practices of blood transfusion and blood conservation. The transfusion practice in the ICU patients is variable and the current transfusion
Biostatistics and Epidemiology guidelines may not be suitable for critically ill patients. The rate of transfusion in ICU ranges from 4% to 66% with average transfusion rate of 44%. The rate of transfusion will increase with increasing length of stay in ICU. Hebert PC et al. in the TRICC trial demonstrated that using transfusion trigger of 7 gm and maintaining hemoglobin concentration between 7.0-9.0 gm/dl in normovolemic patients is at least as effective as and possibly superior to a liberal transfusion strategy, in which a transfusion trigger of 10.0 gm/dl and hemoglobin concentration were maintained at 10.0-12.0 gm/dl were used. With the exception of patients acute myocardial infarction and unstable angina. Using a restrictive strategy of red blood cell transfusion demonstrated a reduction in the total transfusion and decreased the chance for exposure to blood product, which carry a great importance in the presence of donor shortage and variable multiple risks associated with transfusion.

Progress

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

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

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

Project Description

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

Progress

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

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

Primary Investigator: A. Alzahrani
Co-investigators: G. Mohamed, S. Bakheet (Medicine), S. Al Sobhi (Surgery), S. Salam (Medicine)

Project Description

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

Project Description

Extensive data shows a direct link between low-level lead exposure during early development and deficits in neurobehavioral-cognitive performance evident late in childhood through adolescence. These consistent studies have demonstrated the presence of a constellation of neurotoxic and other adverse effects of lead at blood lead levels as low as 10 g/dl. Risk factors for prenatal exposure to lead involve maternal exposure and body burden of lead. There are both exogenous and endogenous factors contributing to maternal blood lead levels and in utero exposure to the fetus. Our previous study which investigated 124 pregnant women living in Riyadh revealed a strong correlation between the maternal and cord blood lead levels confirming the transfer of lead from the mother to the fetus. This longitudinal study is designed to assess the effect of exposure to lead prenatally and postnatally on early cognitive development of infants living in a rural area such as Al-Kharj area where the use of traditional cosmetics and remedies is still common. Lead will be measured in 1000 umbilical cord blood samples collected from healthy pregnant women by means of zeeman atomic absorption spectrophotometer, coupled to graphite tube atomizer. Based on their cord blood lead levels, infants will be classified into three groups for neuropsychological assessments: low lead exposure risk group (below the 10th percentile), medium lead exposure risk group (at approximately 50th percentile) and high lead exposure risk group (above the 90th percentile). Development will be assessed semiannually, beginning at the age of 6, 12, 18 and 24 months, with the use of the mental development index of the Bayley Scales of Infant Development. Venous blood samples will be obtained at the same times to provide a measure of postnatal lead exposure. We shall use a detailed questionnaire to gather basic socioeconomic, demographic, health and other risk factors for exposure to lead.
Progress

Data collection and entry completed. Statistical analysis is underway.

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

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

Project Description

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

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

Progress

Approved by RAC.

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

Primary Investigators: I. Al-Saleh (BMR)
Co-investigators: G. Mohamed, S. Coskun (Pathology), K. Jaroudi (Obstetrics and Gynecology)

Project Description

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

Progress

Data collection in the final stage.
Project Title: A Prospective Study of Invasive Fungal Infections Among Paediatric Patients 0-14 Years of Age with Haematological Malignancies at King Faisal Specialist Hospital & Research Centre and KFNCCC&R. RAC# 2041006


Project Description

Invasive fungal infections (IFI) are more prevalent than ever, presenting an enormous challenge to healthcare professionals. This prevalence is directly related to the growing population of immunocompromised individuals resulting from changes in medical practice such as the use of intensive chemotherapy and immunosuppressive drugs. In the hospital, complicated surgical procedures, widespread use of implanted devices, and the administration of a broad spectrum of antibiotics have dramatically increased the incidence of nosocomial fungal infections. Candida species are now the fourth most common cause of nosocomial bloodstream infection. Systemic fungal infections are a main cause of morbidity and mortality in patients with haematological malignancies. The aim of this study is to determine the incidence of IFI in pediatrics patients with haematologic malignancies and to assess the rate and risk factors related to fungal colonization and relationship to IFI.

Progress

Data collection completed.

Project Title: Hunting for One of the Autism Genes that Might Be Linked to Osteopetrosis with Renal Tubular Acidosis. Rac# 2030046, PSCDR 02-R-0029-NE-02-AU-1

Primary Investigators: N. Kaya, A. Al-Odaib
Co-investigators: B. Meyer, N. Sakati, M. Nester, M. S. Inan, D. Colak

Project Description

The main goal of this project is to identify an autism gene at chromosome 8q22 region in patients with osteopetrosis with renal tubular acidosis (OPRTA). The disease, which is almost only encountered in Saudi Arabia, is caused by a truncation mutation in the carbonic anhydrase II (CA2) gene. The OPRTA patients (in total 31 patients) are subdivided into three groups: 1) with normal mentality, 2) with mild/moderate mental retardation and 3) with pervasive developmental disorder/autism. The genetic gene signatures in these three groups are studied.

Progress

Gene expression studies were performed on total RNA extracted from the blood of the 31 consented patients. We utilized Affymetrix GeneChip System and used “GeneChip Human Genome U133 Plus 2.0” gene expression arrays. The mutation analysis on CA2 gene is preformed and confirmed the presence of mutation in the patients. The gene signature and pathway analysis on some of the patients are performed and identified significantly expressed genes in these patients. We are in the process of identifying the gross changes and performing mapping studies on OPRTA patients.

Project Title: Molecular Genetic Studies in Chromosome Disorders. RAC# 2040042

Primary Investigator: N. Kaya
Co-investigators: P. Ozand, M. Owain, N. Sakati, D. Colak, A. Al-Odaib, M. Inan, N. Al-Dosari, C. Walter, Z. Hasnen
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 24 samples and recently tested agilent microarray system and affymetrix’s genechip technology to work on these patients. Our initial evaluation of these systems shows that we may be able to detect genomic gross changes with high resolution (5-50 kb). This will greatly improve the identification of abnormalities that were not detected by standard karyotyping techniques.

Project Title: Molecular Characterization of Autism Spectrum Diseases: A Pilot Study for Three Distinct Disorders. RAC# 2040024

Primary Investigator: N. Kaya
Co-investigators: A. Al-Odaib, O. Demirkaya, N. Sakati, D. Colak, M. S. Inan

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 three disorders within the autism spectrum diseases phenotypically different but all of which manifest autism have been selected. These are Fragile-X with autism, Rett syndrome, osteopetrosis with autism, and very early and severe infantile autism. The aforementioned hypothesis will try to determine the gene signatures related to autistic derangements within each autistic disorder by detecting changes in genetic pathways. It is done 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 a few genes that are common among the autism spectrum diseases. One of these genes is involved in chromosome inactivation and imprinting and severely down-regulated among all the autistic patients (regardless of having fragile-X or retd or osteopetrosis).

Project Title: Pathogenesis of Early Infantile Primary Lactic Acidosis. RAC# 2050009

Primary Investigators: N. Kaya, M. Al-Owain

Project Description

This study aims to establish the sequence of pathological events in early infantile lactic acidosis patients. This will be achieved by serially studying the apoptosis and the derangement of the nuclear/mitochondrial oxidative phosphorylation (OXPHOS) genes and their transcription profiling in such infants. For the microarray analysis, we will be using ABI 1700 system to determine the gene signatures in whole blood and identify key genes unknown to participate in the nuclear / mitochondrial dialogue for this disease.
Progress

We are in the phase of collecting clinical samples.

Project Title: Applications of Copulas in Analyzing Clinical Data. RAC# 2060022

Investigators: P. Kumar, M. Shoukri

Project Description

Most biomedical/clinical data are multivariate/multifactor types. To analyze such data, methodologies currently in practice are based on the Pearson’s correlation as the measure of dependence among the variables. However, researchers have recently noticed that the correlation and hence the methods based on this measure do not possess the desired statistical properties of a good dependence measure. In particular, correlation fails to describe the tail-end behavior of data and extreme endpoints which is the case in most survival and clinical studies. What are needed therefore are the alternative measures of dependence. This project primarily aims to introduce the applications of the copula functions and copula based methodologies as an alternative to the currently used correlation based methodologies for the analysis of repeated/multifactor measurement data from the biomedical/clinical studies.

Further, A copula based simulation methodology is illustrated by considering the data from the “Aortic Stenosis: Simultaneous Doppler – Catheter Correlative Study” to assess the accuracy of the Doppler echocardiography in determining aortic valve area. This new methodological approach is a useful alternative for modeling dependence and a more appropriate statistical methodology for the clinicians/medical researchers engaged in bio-informatics and decision making research. A manuscript based on this analysis has been submitted for publication to the BMC Medical Informatics and Decision Making Journal.

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

Investigator: M. Fawzi, A. Eldali

Project Description

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

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

Progress

Data analysis phase. Several publications and presentations resulted from this project.
Project Title: Study, Using a Baboon Model, of the Coagulation Response Patterns to Severe Heat Stress and its Relation to Inflammation and Cell Injury. RAC# 2002067

Investigators: A. Bouchama, A. Eldali

Project Description

Heatstroke is associated with massive activation of coagulation leading to microvascular thrombosis in various organs, and death. Knowledge of the molecular mechanisms responsible for this activation of coagulation in heatstroke is important for the development of new modalities of treatment. Using a baboon model of heatstroke, we propose to test the hypothesis that (1) cellular injury and death in heatstroke are the result of disseminated intravascular coagulation initiated by the expression of tissue factor, and (2) that blocking the activation of coagulation either by a tissue factor pathway inhibitor (TFPI) or recombinant activated protein C reduce significantly the coagulopathic and lethal effects of heat. Four baboons are heat stressed to a rectal temperature of 43.5 C (LD100 heat at 48 hours) in a modified neonatal incubator where the environmental temperature is maintained at 47 C. The animals are monitored for vital signs, and the concentrations of coagulation (thrombin-antithrombin complexes, soluble fibrin monomers, D-Dimers, tissue factor) and fibrinolysis components (plasmin-antiplasmin complexes, tissue plasminogen activator and plasminogen activator inhibitor) and inflammatory mediators (TNF, IL-1, IL-6, IL-10) at T=15 minutes during heat stress and T=1, 6, 24, 48 hours during recovery/progression of injury. Four sham-heated baboons will serve as a control group. Survival at 3 days will be compared between each group.

Progress

Data analysis completed for phase I & II. Phase III of the project is now in the data analysis phase. Several publications and presentations resulted from this project.

Project Title: Leptin Level, Leptin Receptor Gene Polymorphism and Reproductive Hormones in Saudi Females with Polycystic Ovary Syndrome. RAC# 2020030

Investigators: M. Daghestani, M. A. Chaudhary, S. Bhatia, A. Eldali

Project Description

Polycystic ovary syndrome (PCOS) is often associated with obesity and insulin resistance, both of which are features that are linked to the leptin and leptin receptor (LEPR) genes. Genes in several metabolic pathways, including those regulating insulin metabolism and insulin action, have been proposed as contributing to the development of PCOS.

Leptin, the small peptide hormone coded by the ob gene, is an adipocyte-derived hormone which plays a central role in the regulation of body and energy homeostasis, and in signaling to the brain that adequate energy stores are available for reproduction by regulating the hypothalamic-pituitary-gonadal axis, recent in-vitro observations indicate that leptin may also have direct intra-ovarian actions. The role, however, of leptin in PCOS is not clear. Some studies have reported increased levels of leptin in PCOS, while others report that they are normal. In this study, we will test the hypothesis that part of the metabolic disturbances in PCOS is due to an inherited defect in the leptin receptor gene.

In Saudi Arabia, no studies have investigated the correlation between plasma leptin levels and reproductive hormones levels in normal Saudi
females and Saudi females with polycystic ovarian syndrome, and no studies have been done on the leptin receptor gene of Saudi females with polycystic ovary syndrome. Hence this project is designed to investigate these parameters.

Progress

Data analysis completed.

Project Title: Gulf Center for Cancer Registration. RC Admin Approved. BESC# 032/2001

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

Project Description

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

Project Title: Thromboembolic Disorders Registry. RAC# 2001045, BESC# 004/2001


Project Description

Venous thromboembolism (VTE) comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE is a significant cause of morbidity and mortality all over the world. Deep vein thrombosis (DVT) affects primarily the veins of the lower leg and thigh. A thrombus forms in a proximal vein, blocking the flow of blood and often (but not always) causing swelling and inflammation. While deep vein thrombosis is not life threatening, the thrombus can break free and travel to the pulmonary artery or one of its branches and block pulmonary blood flow, leading to pulmonary embolism (PE), the most serious sequela of DVT. The Thromboembolic Disorders Registry of King Faisal Specialist Hospital and Research Centre was established in February 2001 as collaboration between Registries Core Facility of Biostatistics, Epidemiology and Scientific Computing Department and King Faisal Internal Medicine Department. All patients presenting to the
Thromboembolic Service in the section of Internal Medicine are registered. However only those who understand, accept and sign the informed consent forms are included in the registry. Objectives: 1. Data resource that could assist the health care to evaluate the results of their therapeutic effort and analyze reasons for complication like the thromboembolic episodes or bleeding disorders occurring during anticoagulation therapy. 2. To provide leadership in establishing and maintaining comprehensive TED registry in collaboration with other national organizations. 3. Serve as database for future research. 4. Data resource could enable us to improve some methods of prophylaxis of DVT and standardize the recommended regimens for prophylaxis, which could lead to improvement of the approaches to prevention. 5. Enable stratification of patients into different risk groups.

Progress

Data analysis and presentation for this project has been done in SAS for the purpose of generating the TEDR Annual/Cumulative Report 2006.

Project Title: Venous Thrombosis and Familial Thrombophilia Registry. RAC# 2001017. BESC# 006/2000


Project Description

Thrombosis, both arterial and venous, and thromboembolism remain a major cause of mortality and morbidity. Venous thrombosis (VT) and venous thromboembolism (VTE) are related to venous stasis, abnormalities in blood vessels and a hypercoagulable state. Hypercoagulable state can be acquired. The incidence and prevalence of VT and VTE and their trend in Saudi Arabia is not known.

However, there is good reason to suspect that they will increase as the population ages, patients undergo and survive more major surgeries and, survive chemotherapy for malignancies, myocardial infarctions and CVA. The registry will serve as a surveillance tool to collect data on occurrence at KFSH&RC and the nine MOH affiliate hospitals, trends and outcome and risk factors of patients with VT, VTE and FT. It also has clinical, research, and educational objectives. It is possible that once this registry is well established it could evolve into a national registry. Preliminary unofficial discussions with staff of National Guard Hospital showed a significant interest. One can see including several of the university hospitals at a later stage.

Progress

Data analysis and presentation for this project has been done in SAS for the purpose of generating the S_TAFT final report for KACST.

Project Title: Cleft Lip/Palate and Craniofacial Anomalies Registry. RAC# 991030. BESC# 007/1999

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

Project Description

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

SAS' programs have been written for data analysis and presentation for the CLPR Annual/ Cumulative Report 2006. Additional reports have been produced for publication purposes. Technical support is provided when needed.

Project Title: Epilepsy Registry. RAC# 2011059. BESC# 009/1997


Project Description

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

Progress

Data analysis and presentation for this project has been done in SAS for the purpose of generating the Epilepsy Registry Annual/Cumulative Report 2006.

Project Title: Neuromuscular Disease Registry. RAC# 2031053. BESC# 010/1997

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

Project Description

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

Progress

Data analysis and presentation for this project has been done in SAS for the purpose of generating the NMDR Annual/Cumulative Report 2006. Technical support is provided when needed.

Project Title: Congenital Heart Disease Registry. RAC# 991026. BESC# 011/96

**Project Description**

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

**Progress**

Data analysis and presentation for this project has been done in SAS® for the purpose of generating the CHDR Annual/Cumulative Report 2006.

**Project Title:** Evaluation of Inpatient and Outpatient Satisfaction. RC Admin Approved. BESC# 013/2006

**Investigators:** M. Hijazi, M. Sinno, A. Brown, M. Shoukri, G. Mohamed, S. Al Ageel, W. Ventura, A. Eldali, S. Hashim

**Project Description**

Clinical outcome is strongly influenced by patients’ satisfaction with the manner is which healthcare is provided. Inpatient and outpatient satisfaction surveys are used by KFSH&RC to identify opportunities for improvement, and compare data before and after interventions. They measure such service attributes as availability (for example, access to services and wait times), respect and caring (including courtesy, confidentiality, empathy, effective listening and communication), and the physical infrastructure within which healthcare is delivered (for instance, cleanliness, comfort and privacy). The scale and scoring system were developed by Quality Resource Management Department (QRM) in collaboration with the Biostatistics, Epidemiology and Scientific Computing and Patient Relations Departments. A five-point Likert scale is used for most questions, which are divided into domains, such as Admission Staff, Nursing Staff, etc. The questionnaires are revised annually after feedback from hospital departments, and then pilot studies undertaken to establish their validity and test-retest reliability. Trained interviewers from Patient Relations Department administer the questionnaires to representative samples of inpatients and outpatients. They may be completed by either the patient themselves, a family member or the interviewer. Staff enter the data into web-based forms developed by QRM, who perform the statistical analysis and disseminate the results on a quarterly basis.

**Progress**

Sample reports were produced in SAS® for test purposes. The project is ongoing at present.
Project Title: Neural Tube Defects Registry.  
RAC# 991029, BESC# 018/1999

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

Project Description

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

Progress

Data analysis and presentation for this project has been done in SAS for the purpose of generating the NTDR Annual/Cumulative Report 2006. Technical support is provided when needed.

Project Title: National Diabetes Registry. RC Admin Approved. BESC# 028/2001

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

Project Description

Diabetes mellitus (DM) is a major and growing problem in the Kingdom of Saudi Arabia causing prolonged ill health, disability, early death and high health cost. Diabetes being a chronic disease causes chronic complications with high morbidity and mortality rate. To monitor this disease in the Kingdom of Saudi Arabia, a National Diabetes Registry (NDR) was established in 1996. The DM registry will help in having better knowledge on the geographic distribution, the demographic characteristics and the clustering of DM in families. The DM registry will serve as an easily accessible source for data on Saudi diabetics. This will encourage researchers to study the problem of DM in the Kingdom. The aggregation, analysis and presentation of information about DM is expected to significantly contribute to the medical understanding, demonstrating trends in management, improving the quality of care for DM patients and supporting planning and development.

Progress

Tables, graphs and charts under production in SAS for the purpose of generating the Diabetes Registry Cumulative Report.

Project Title: National Cancer Registry Research and Control, RC Admin Approved. BESC# 032/2001

Investigators: H. Eid, E. De Vol, R. Kandasamy, S. Hashim

Project Description

The National Cancer Registry (NCR) of Saudi Arabia is a population-based registry developed in 1992. It was established under the jurisdiction
of the Ministry of Health (MOH) by the Order of His Excellency, the Minister of Health. The NCR commenced reporting cancer cases from 01 January 1994. The primary goal of the NCR is to define the population-based incidence of cancer in Saudi Arabia. Programs for early detection and cancer screening, as well as cancer research projects, are planned for future consideration.

**Progress**

Graphs, charts, tables, etc., for this project are being reproduced in SAS® to be used in the NCR Annual/Cumulative Report 2006.

**Project Title:** Is Myomectomy Justifiable in Preventing Recurrence of Discrete Subaortic Obstruction?. RAC# 2031072. BESC 036 / 2003

**Investigators:** T. Pasha, A. Sallehuddin, Z. Al Halees, M. Al Joufan, S. Hashim

**Project Description**

Discrete sub-aortic stenosis is commonly treated by simple surgical enucleation of the obstructing membrane. Septal myotomy or myectomy may be added to further relieve the obstruction and avert recurrence at the expense of possible damage to the aortic valve, interventricular septum, mitral valve and atrio-ventricular conduction tissue. In this study 390 patients will be reviewed. These patients had surgery for discrete sub-aortic stenosis at King Faisal Specialist Hospital and Research Centre from 1985 to 2002. Our main objective is to compare the rate of recurrence and incidence of complications between the two surgical methods. Our aim is to also define the preoperative indicators that could guide us in our decision whether to carry out the more aggressive muscle resection or not. This will be a retrospective review using information from medical records. A pediatric cardiologist will review the echocardiographic images to ascertain the presence or otherwise of specific features that may be important in the development of recurrent obstruction. The types of data to be collected are dichotomous, categorical as well as continuous and will be analyzed using appropriate statistical tools. Both univariate and multivariate analyses will be carried out to evaluate the pre-operative indicators. The event-free survival will be analyzed using the Kaplan-Meyer method.

**Progress**

The project is in the data collection phase at present.

**FUTURE RESEARCH DIRECTION**

The BRU has focused on a number of important problems in basic methodological research, alongside collaboration in some major retrospective clinical investigations and genetic studies. It has addressed five main areas: clustering in trials, meta-analysis, and research initiated by clinicians from the King Faisal Heart Institute. We have collaborated in major mitochondrial studies from the Department of Genetics. Computational Biostatistics is becoming in high demand, particularly the development of methodology for the analysis of large micro-array gene expressions data. Other collaborations have included major trials in urology, cancer, cardiovascular disease, and diabetes.

With the diverse interests and the skills of the BRU staff we continue to meet the increasing demands by scientists and clinicians for statistical support. We shall continue to support the mission of the research centre in advancing biomedical research.
PUBLICATIONS

Refereed Papers


**Conference Proceedings**


**Invited Presentation**


**Abstracts**

In an era of extraordinary advances in scientific knowledge and methods, epidemiology provides essential tools for understanding disease etiology and for identifying effective and efficient approaches to prevention and treatment. The Epidemiology Research Unit (ERU) within the department of Biostatistics, Epidemiology, and Scientific Computing (BESC) at the King Faisal Specialist Hospital and Research Centre (KFSH&RC) is an interdisciplinary section which encompasses a broad range of research areas, including cancer, cardiovascular disease, diabetes, child and adolescent health, obesity, nutrition, genetic diseases, and women’s health. The Epidemiology Research Unit 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 unit maintains close collaborative ties with other units in the department as well as with a number of other departments in KFSH&RC. In addition, the scientists within the Epidemiology Research Unit have strong links to other institutions and programs, serving as advisors, committee members or collaborating coinvestigators at the Ministry of Health, King Abdulaziz Medical City, Prince Salman Center for Disability Research, the Executive Board for the GCC States, and Saudi Commission for Health Specialties. Teaching activities of the ERU scientists and staff, either as invited speakers, lectures, or through training of summer students, has contributed to the local public health knowledge infrastructure.

Currently, the unit has 4 scientists, 3 research associates and 1 administrative staff. The Epidemiology Research Unit scientists practice epidemiology as a broad scientific discipline, addressing the occurrence of disease and the distribution of health status in the population. By integrating causal concepts at the molecular, cellular, clinical, and social-environmental levels, our diverse unit works to maintain an intellectual environment that facilitates the integration of biological, social, and analytic approaches. The diverse activities of the Epidemiology Research Unit during the past year ranged from school-based, cross-sectional studies, validation studies, clinical studies, cancer surveillance, to randomized trials for clinical interventions. The unit was involved in as much as 15 active studies during 2006. Results of these studies have provided the basis for significant national public health policy concerns. In addition, the staff of the Epidemiology Research Unit strives to provide service to the community by giving technical advice and assistance to other academic institutions, to local, national and international health agencies, to other individuals or groups in the community, and by carrying out research, which is relevant to community needs.
RESEARCH PROJECT

Project Title: Gulf Center for Cancer Registration (GCCR). RAC# 2061022

Investigators: A. Al-Zahrani, R. Kandasamy, A. Al-Madouj

Project Description

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

Progress

The total number of incidence cancer cases registered among GCC nationals from January 1998 to December 2002, were 41,475 (Male 20,928; Female 20,547).

Almost half of the cancer cases had either regional or distant metastasis at the time of diagnosis. Only 22.6% of patients presented with localized tumors and less than 2% with in situ. The Age Standardized Rate (ASR) per 100,000 for males in the GCC States was highest in Bahrain and Qatar (158.7 and 157 respectively) followed by Kuwait (132.6), Oman (99.1), UAE (70.1) and Saudi Arabia (66.1). In females it was high in Qatar (165.2) followed by Bahrain (142.3), Kuwait (136.7), Oman (85.4), UAE (81.9) and Saudi Arabia (62.9). In general, age specific incidence rates for all cancers increase with age in both genders.

Breast cancer is the most common cancer in the GCC States accounted to 10.8% from all cancers and 21.8% from cancers among females. NHL (7.4%) and leukemia (7.3%) are the second and third most common cancer in the GCC States followed by colorectal (6.7%) and thyroid cancers (5.8). Liver cancer ranked second most common cancer in men next to NHL, whereas thyroid cancer ranked second in women next to breast cancer. In children, leukemia (33.2%) appeared to be the leading cancer followed by cancer of the brain and nervous system (13.2%), Hodgkin disease (10.0%), and non-Hodgkin’s lymphoma (8.3%).

- Published the first five year cancer incidence cumulative report, ‘Cancer Incidence in Gulf Cooperation Council States, 1998-2002’.
- Organized a two-day workshop for tumor registrars from all the GCC States on “Concepts in Cancer Data Management”, held in November 25-26, 2006, in Riyadh.
- Made poster presentation in the KFCC International Cancer Symposium 2006 held at KFSHRC, Riyadh.
- An original article entitled “Association of Reproductive Factors with the Incidence of Female Breast Cancer in the GCC Countries” was accepted for publication by EMHJ.

Project Title: Riyadh Puberty Study. BESC# 011/2005

Research Coordination and Technical Support: A. Bin Muammar, W. Al-Obaid

Project Description

Background: Age of onset of pubertal characteristics are influenced by genetic, geographic, dietary and socioeconomic factors, however local clinicians
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. A previous study by Altwajri, et al., in a non-Saudi children population, found plasma levels of total cholesterol to be influenced predominantly by pubertal stage, unlike adults, where diet is a major controller. The association between plasma cholesterol and sex hormones is not well established, and has been explored by only a few studies.

**Aims:** (1) To determine the average age of onset of pubertal characteristics, and the factors associated with it, among school children aged 6 - 14 years old living in Riyadh, (2) To examine the role of puberty and sex hormones on the control of plasma cholesterol and lipid concentrations among these children.

**Study Design:** Cross-sectional study among female and male school children in Riyadh. One thousand children, aged 6 - 14 years old, will be selected into the sample using a cluster sample design.

**Data collection:** BMI, Tanner stage, gynecomastia, axillary hair, plasma concentration of total cholesterol, LDL, HDL, LH, FSH, estradiol, testosterone. Parental questionnaire, dietary assessment.

**Progress**

Grant proposal was approved by funding institution, the National Guard Health Affairs. Ministry of Education granted approval for the study, and provided permission to visit any boys or girls school in Riyadh area for data collection. A stratified random sample was used. Schools were stratified according to 4 geographic areas in Riyadh. Two boys and two girls schools were randomly selected from each area, totaling 16 schools altogether. Within each school, a random selection of classrooms ranging from grade 1 to 10 were chosen. Separate data collection teams were set up for the boys and girls schools, where each team consisted of pediatric endocrinology consultants for the pubertal assessment, nurses for anthropometric measurements, phlebotomists for collecting blood samples, in addition to several assistants and a research coordinator. Questionnaires and data collection forms were designed. Informational brochures detailing all aspects of the study and data collection were developed for the parents. School visits were conducted initially by the investigators to meet with the school administrators and students, and to distribute the informational brochure and the consent forms. Data collection was conducted several days after initial visit. Data collection was completed in May 2006. Data was entered into the database and is currently undergoing validation and cleaning. Lab results data has been received and is ready to be merged with the cleaned dataset.

**Project Title:** Sodium Bicarbonate & Acetylcysteine in Decreasing Contrast Induced Nephropathy (SADCIN). BESC# 004/2007

**Investigators:** F. Al Turki, M. Sunaid, S. Shah, M. Nawaz, J. Al Buraiki, W. Hassan, H. Al Sergani, A. Al-Zahrani

**Project Description**

In SADCIN trial, we will select ‘high risk’ patients (with estimated Glomerular Filtration Rate of less than 60ml/min, assessed through Modification of Diet in Renal Disease study group formula – MDRD) with or without Diabetes Mellitus (DM), who account for 20% - 25% incidence of CIN. These patients inevitably would have the worse outcome in terms of CIN had they not received any of the four modalities (arms) of treatment. We will randomize these patients into 4 groups. Of these, 3 groups with 100 patients in each will receive the most common
therapy that is being used and found potentially appealing. The fourth group will be used to examine a new strategy for prevention of CIN which consists of 2 proven agents that will be used to obtain synergistic properties. Since DM is a common disease and affects ~20% to 25% of our population, is also a major co-morbidity in patients with CIN. Each arm of our study will have 50% of DM patients to eliminate the component of bias that might have been encountered in a non-stratified study.

We will conduct a randomized prospective study to assess the efficacy of different methods that are commonly used in our institution to reduce contrast induced nephropathy (CIN) following cardiac catheterization.

**Progress**

This project was submitted to RAC for approval. The CRF was designed and developed.

**Project Title:** Validation of the Arabic Symptom Assessment Tool. BESC# 018/2006

**Investigators:** M. Al Shehri, A. Al-Zahrani, M. Shoukri, S. Al-Sairafy, A. Al-Madouj

**Project Description**

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

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

**Progress**

This project was submitted to RAC for approval. The CRF was designed and developed.

**Project Title:** Prospective Evaluation of Risk-Adapted Therapy for Pediatric Patients with Non-Lymphoblastic Non-Hodgkin Lymphoma (PEDNHL04-1). RAC# 2051018

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

**Project Description**

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

Over three decades ago, it was realized that pediatric NHL as a group was a highly chemosensitive entity. Chemotherapeutic regimes have since been developed that have resulted in an extremely good outcome for children with this malignant disorder. Currently, with intensive, multi-agent chemotherapy protocols, over 90% of patients with limited stage disease, and between 65-85% patients with advanced disease, can expect to be cured. The wider range of cure rates seen for the advanced stage disease is a reflection of the differing response of the different histologic subtypes, and the overall poorer prognosis of patients with CNS disease. Objective of this study is to determine if treatment intensity for pediatric patients with non-lymphoblastic hodgkin lymphoma can be stratified based on the relative risk for relapse to reduce treatment related toxicity, while maintaining the high cure rates.

**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. An interviewer, using a structured questionnaire, will obtain the required information from randomly selected individuals and an informed oral consent will be obtained before the interview. Descriptive statistics will be used to compute frequency of response to socio-demographic characteristic, awareness on cancer and attitude towards early detection methods. Chi square test and logistic regression will be used to analyze the data, as appropriate.

**Progress**

The project was approved both by RAC and KACST and will be funded by KACST. Data collection will start from 2007.

**Project Title:** Cleft Lip/Palate (CL/P) and Craniofacial Anomalies Registry. RAC# 991030

**Investigators:** A. Al-Johar, K. Ravichandran, S. Shazia, E. Shail, Al Rubiya
Project Description

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

Progress

With a part time Patient Translator provided by Department of Dentistry, and borrowed help from Biostatistics, Epidemiology and Scientific Computing Department the registry was able to publish a report. During the six and half year period (June 1999 - 2005) this registry registered a total of 886 cases. Out of the 886 cases 597 (67.4%) cases had only cleft of lip and/or palate, 79 (8.9%) cases had only cranial/facial anomalies and 210 (23.7%) cases had both CL/P and CF anomalies. There were 451 males and 356 females with CL/P; the male to female ratio is 1.3:1. As an overall accumulation, the Cleft of hard palate was common followed by bilateral cleft lip and palate. Out of the 289 craniofacial anomalies 153 were male and 136 were female; the male to female ratio is 1.1:1. Among craniofacial anomalies more than 50% of the cases had only facial, 15.2% had only cranial and 32.5% had both the anomalies.

There were 841 Saudi (M=472; F=369) and 45 Non Saudi (M=19; F=26). Most of the cases (874; 98.6%) are from Saudi Arabia. Within the Kingdom, Riyadh region had more number of cases (272; 31.3%) followed by Eastern (135; 15.6%) and Asir (131; 15.1%) region. More than one quarter of the cases (236; 26.6%) had family history of deformities.

The primary surgeries like Initial lip & nose repair, Initial palate repair accounts to 5.6% and 6.1%, respectively, of the total procedures (8,533) done. About 91% of these surgeries were done initially at KFSH&RC and less than 9% were done outside KFSH&RC.

- Published a report, ‘Cleft Lip/Palate and Craniofacial Anomalies 1999-2005’.
- A manuscript has been submitted to the peer reviewed The Cleft Palate-Craniofacial Journal.

Project Title: Survey of Dietary Habits in the Saudi Population: Correlation of Diet with BMI and H/W Ratio as Indices of Risk Factors for Development of the Metabolic Syndrome. BESC# 009/2006

Investigators: K. Collison (BMR), Y. Al-Twaijri, A. Alzahrani, M. Shoukri
Technical Support: S. Subhani

Project Description

Metabolic Syndrome, the fore-runner of Type-2 Diabetes (T2D), is a cluster of disorders which combine to increase dramatically the risk of premature mortality due to cardiovascular disease and/or arteriosclerosis. These disorders include dyslipidemia (hypertriglyceridemia and hypercholesterolemia), hyperglycemia, hypertension and excessive weight gain. The incidence of this syndrome in the Saudi population is sky-rocketing at an alarming rate and will require aggressive medical intervention in the near future. One recent study indicates that the incidence of metabolic syndrome in Saudi is currently in the region of 37% of the adult male population and 42% of adult females between the ages of 30 and 70.
Excessive weight gain is strongly associated with metabolic syndrome (MS), however it is unclear as to whether this is a cause of MS or a consequence of metabolic dysbalance. Fat distribution is important: adiposity associated with the internal organs and viscera (termed visceral adiposity) is associated with a state of low-grade inflammation which is now believed to be the cause of increased risk of coronary heart disease and atherosclerosis. Peripheral fat mass associated with subcutaneous deposits, confers insulin-sensitizing and anti-atherogenic effects. Body mass index (BMI) measurements correlate well with degree of obesity and development of the metabolic syndrome. Waist-to-hip ratio measurements provide the easiest obtainable indices of the extent of visceral adiposity without resorting to expensive imaging techniques. Both measurements provide valuable information as to extent of risk of developing metabolic syndrome.

Despite an increase in population wealth, little is known about the daily dietary intake amongst the Saudi population. Information gathered from an epidemiological study of dietary intake versus BMI and waist-to-hip measurements and presented as a queryable database, will provide clinicians and researchers with much-needed information. 3 age-groups will be surveyed: 11-13 yr old boys and girls; 19-23 yr old male and female university students, and 30-50 yr old male and female consumers. Height, weight, waist, and hip circumference measurements will be recorded for each participant, and a simple but informative dietary habit survey will be completed. Information will be entered onto a database. Correlations between overweight individuals and distinct non-overlapping dietary patterns will be ascertained. Preventive nutrition intervention strategies might be derived as a consequence of these studies, which will have a direct translational health benefit to the Saudi population at risk.

Progress

Proposal submitted to RAC for approval. Database created.

Project Title: The Effect of Sexual Maturation on the Association Between Plasma Total Cholesterol Concentration and Dietary Intake in Children Participating in Project Heartbeat. BESC# 022/2004

Investigators: Y. Al-Twaijri, R. S. Day, R. Harrist (University of Texas), J. Dwyer, L. Ausman (Tufts University), D. Labarthe (CDC)

Project Description

Purpose: To determine if the Keys and Hegsted equations predict change in plasma total cholesterol in pubertal children aged 8-18 years old enrolled in project heartbeat, and the associations of the Keys and Hegsted dietary scores with total cholesterol in these children.

Methods: 679 children aged 8, 11 and 14 at baseline were followed for four (4) years, forming a synthetic cohort which permitted the longitudinal assessment of dietary data, plasma total cholesterol, Tanner stage, age, and body mass index (BMI) from ages 8-18 years old.

Results: Neither the Keys nor Hegsted scores were significantly associated with plasma total cholesterol levels after controlling for sex, age, BMI and sexual maturation. Change in total cholesterol levels from baseline to follow-up 4 years later was not associated with change in the Keys or Hegsted scores, nor with intakes of saturated fatty acids, polyunsaturated fatty acids, cholesterol, or total fat. However, changes in total cholesterol levels, using either the equation of Keys or that of Hegsted were significantly different from the observed changes 4 years later (p=0.00).

Conclusion: The Keys and Hegsted predictive equations were derived from studies on adult
males, and are not sufficiently precise to be used for protecting change in plasma total cholesterol in healthy children and adolescents of pubertal age. Although the Keys and Hegsted predictive equations were not associated with plasma total cholesterol in these children, the scores continue to be useful tools for screening and dietary assessment.

**Progress**

Two manuscripts resulting from the research of the principal investigator have been approved by the Centers for Disease Control Publications Clearance Committee. Negotiations are currently underway to publish all research papers from this landmark study as a supplement to one of the leading peer reviewed public health journals.

**Project Title: Prevalence of Anemia and the Transfusion Practice in Critically III Patients.**

**BESC# 006/2003**

**Investigators:** K. Maghrabi, R. Al Hubail, G. Mohammed  
**Technical Support:** W. Al-Obaid

**Project Description**

Despite the safety of restrictive strategy of red blood cell transfusion in volume resuscitated patients was demonstrated, we believe that the transfusion practice in ICU still variable and non-compliant with the best evidence available in the literature, which could lead to improper utilization of resources and expose the patients to the risk of transfusion’s adverse effects. We would like to study the prevalence of anemia and red blood cell transfusion practice in our unit. In addition the practice of other blood product transfusion, (platelets and fresh frozen plasma) will be evaluated.

**Progress**

Data collection and data entry have been completed.

**Project Title: Preimplantation genetic Diagnosis in Saudi Arabia. RAC# 2041078**

**Investigators:** A. AlSulaiman, A. AlOdaib  
**Technical Support:** W. Al-Obaid

**Project Description**

At the present time prenatal diagnosis is available for severe genetic abnormalities in Saudi Arabia. However no intervention if a serious abnormality is detected except abortion. Recently, King Faisal Hospital and research Center offers the Preimplantation Genetic Diagnosis (PGD) for this purpose, which is in compliance with the sharia regulations. The extent to which PGD is acceptable to the individuals for whom it is intended is relatively unexplored, and remains a crucial issue that may ultimately determine the value of PGD as an alternative to prenatal diagnosis in high risk couples.

**Progress**

During the approved period of this project, more than 173 subjects were interviewed. A questionnaire (30 questions) was administered by study subjects recruited from PGD, IVF, ENT and oncology clinics.

**Project Title: Evaluating the Knowledge, Attitude and Psychosocial Impact of Premarital Screening for Hemoglobinopathy in the Saudi Population. RAC# 2061056**
Investigators: A. AlSulaiman, J. Hewison, A. AlSulaiman, A. AlSwayyed, T. Owaidah
Technical Support: W. Al-Obaid

Project Description

Premarital screening has begun to play a very important role in early detection and prevention of genetic disorders and other non-genetic transmitted diseases. The inauguration of the premarital screening program in Saudi Arabia 2 years ago was to detect and prevent hemoglobinopathy was a milestone in the management of these groups of inherited genetic disorders.

Progress

The study is in the data collection phase.

Project Title: A Randomized, Open-label, Comparative Evaluation of Conversion from Calcineurin Inhibitors to Sirolimus Versus Continued Use of Calcineurin Inhibitors in Renal Allograft Recipients. BESC# 023/2003

Investigators: K. Hamawi, A. Bin-Muammar

Project Description

This is a two-year study. Randomization is expected to be closed at the end of September 2003, depending whether the goal total of 750 is reached.

Primary Efficacy: To determine the effect of conversion from calcineurin inhibitor (CI) to Sirolimus (SRL) - based therapy on renal function 52 weeks after randomization, as indicated by the change from baseline calculated glomerular filtration rate (GFR, Nankivell method) and to demonstrate superiority of the SRL conversion versus CI continuation regimens in patients with baseline Nankivell GFRs > 40 mL/min or non inferiority

Progress

- All required data was extracted.
- Forms were completed, validated by the monitor and sent to the Central Data Office in Paris.
- Final Report was submitted to RAC.
- All the auditing visits were successfully done.


Investigators: A. Al Hokail, A. Bin-Muammar

Project Description

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

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

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

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

**Progress**

- The study initial base was established
- All the necessary documents were collected
- The study was submitted to the RAC for approval.

**Project Title:** Effects of Environmental Pollutants Exposure on the Pregnancy Outcome of Women in Al-Kharj Area. BESC# 008/2005

**Investigators:** I. Al-Saleh, G. El-Din Mohamed
**Technical Support:** A. Bin-Muammar

**Project Description**

In utero exposures to environmental contaminants can occur through maternal-placental transfer. High level maternal exposures to environmental pollutants, such as lead, mercury, cadmium, DDT, polycyclic aromatic hydrocarbons and tobacco smoke have been associated with congenital anomalies, severe developmental and cognitive impairment, and growth retardation in offspring. Evidence shows that fetuses and infants are more affected than adults by a variety of environmental pollutants because of differential exposure, physiologic immaturity and a longer lifetime over which diseases initiated in early life can develop. Our previous studies have shown that Saudi population, like other countries, is susceptible to environmental pollutants in spite of the difference in the sources of exposure. Moreover, there have a number of hospital-based studies in different cities in Saudi Arabia reporting the high prevalence of birth defects, infant mortality and congenital malformations with regional variations in the pattern. This cross-sectional study will be conducted to examine potential links between environmental pollutants and the pregnancy outcome of Saudi women living in Al-Kharj region. Prenatal exposure to lead, cadmium, mercury, DDT, polycyclic aromatic hydrocarbons and tobacco smoke will be measured in 1522 umbilical cord, venous blood samples and placental tissues collected at the time of delivery. Furthermore, urinary cotinine and 1-hydroxypyrene (as a major pyrene metabolite), will be determined in mothers as an indicator of tobacco smoke and individual’s internal dose of PAHs respectively. Within this study, we will conduct a nested control case-control study to assess the relation between exposure to these pollutants and miscarriages before 22 weeks of gestation. A detailed questionnaire will also be administered at birth which assesses risk of exposure to these pollutants. Pregnancy outcomes evaluation such as incidence of small for gestation (less than tenth percentile of weight for each completed gestational week between 22 and 44 weeks), low birth weight (<2500 g), gestational duration (from the last menstrual period to the termination of pregnancy), fetal death (fetus born 500 g or 22 weeks’ gestation with no signs of life), neonatal death (death <28 days of life) and other continental malformations. A number of studies have emphasized the important role that oxidative DNA damage due to carcinogenic compounds is playing in various diseases including cancer. Peroxidative lipid damage will be determined as malondialdehyde production in the presence of thiobarbituric acid in serum samples. The genotoxic effects of environmental pollutants on the fetus will be evaluated by using comet assay, where the migration of DNA from the
center of cells will be measured. Findings of this study will offer advantages of understanding source of exposure among the studied population and to develop interventions to minimize its impact.

Progress

- All data was entered.
- All necessary database programs were written and successfully executed.
- 50% of the lab data was merged to with the database. Other 50% is under process in RC Environmental Lab.

PUBLICATIONS

Core Facility

Registries

The Biostatistics, Epidemiology and Scientific Computing Department (BESC) has gained extensive experience in disease registration through its support to four hospital-based, two regional and one national registry. The BESC department has the expertise to design, develop, and to maintain registry databases as well as proper utilization of collected health data that are usually produced in the form of annual reports and presented in scientific meetings locally and internationally.

RESEARCH PROJECTS

Current Research Projects

Currently, the Registries Core Facility (RCF) is administering four hospital-based and two regional registries. We are providing technical and user support to Saudi National Diabetes registry and several other research projects. Data requests for the spin-off projects, after necessary documentation, were furnished to researchers from the CHD, Epilepsy and CLCP registries. Extensive data auditing for all the hospital-based registries took place. All the registries’ annual/cumulative reports were submitted for year 2005. A successful implementation of the cross-mapping project of ICD-9 (International Classification of Disease, 9th edition) coding to EPCC (European Pediatric Cardiac Code) coding manual was completed on the CHD registry database.

Project Title: Congenital Heart Defects Registry (CHDR). RAC# 991026

Investigators: C. Canver, M. Al Jufan, F. Al Mohanna, M. Shoukri, A. Omrani, S. N. Subhani, A. Al-Firm

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 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. The data abstraction and collection effort began on January 3, 1998. It is noteworthy to mention that the registry is now internet-based, facilitating...
expansion efforts to other institutions in the Kingdom. In this regard Military Hospital joined the CHD registry in the year 2003.

Progress

- Data audited prior to cumulative report data tabulation.
- Cross-mapping project of (International Classification of Disease, 9th edition) ICD-9 coding to (European Pediatric Cardiac Code) EPCC coding manual completed and implemented on the registry database.
- Meetings for possible collaborations with King Khalid Hospital and King Fahad Medical City.
- Statistics for all year cases as of December 31, 2006 is:

<table>
<thead>
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<th>Collaborating Hospitals</th>
<th>New cases</th>
<th>Follow up cases</th>
<th>Diagnosis coding</th>
<th>Treatment coding</th>
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- Statistics for year 2006 is:

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<tr>
<th>Collaborating Hospitals</th>
<th>New cases</th>
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<tr>
<td>Prince Sultan Cardiac Centre</td>
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<td>440</td>
<td>1185</td>
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</tbody>
</table>

- Disease coder from King Faisal Specialist Hospital & Research Centre is visiting Prince Sultan Cardiac Centre twice a week to complete the backlog of disease coding from year 2003. So far 1185 cases from year 2003 and 2004 have been coded.

Project Title: Neural Tube Defects Registry (NTDR). RAC# 991029E

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

Project Description

Neural Tube Defects refer to a group of lesions that occur at various positions along the spinal cord, which are ultimately due to a defect in the closure of the neural groove to form an intact neural tube. Anencephaly, spina bifida and encephalocele account for almost all NTD’s. Both genetic and environmental risk factors are known to be involved in the etiology of NTD’s. Available evidence indicates that supplements of folic acid can reduce NTD’s 50% - 70%. 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.

This registry is a prospective collection of all patients diagnosed with neural tube defects who present to the hospital from January 1, 2000. The internet-based registry software has been designed in-house with the features of a national registry.

Progress

There had been tremendous efforts in terms of further collaborations for the Neural Tube Defects Registry.
- Data audited prior to annual report data tabulation.
- On-going collaboration with Disable Children Association.
- Riyadh Medical Centre (RMC) also known as Shemaisy Hospital has signed a memorandum of agreement with KFSH&RC for collaboration.
- A retrospective data collection of new variables introduced in the registry took place in year 2006 as followed up cases.
- Statistics for all year as of December 31, 2006 is:

<table>
<thead>
<tr>
<th>Collaborating Hospitals</th>
<th>New cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>King Faisal Specialist Hospital</td>
<td>444</td>
</tr>
<tr>
<td>Disable Children Association</td>
<td>39</td>
</tr>
</tbody>
</table>

- Statistics for year 2006 is:

<table>
<thead>
<tr>
<th>Collaborating Hospitals</th>
<th>New cases</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>King Faisal Specialist Hospital</td>
<td>46</td>
<td>51</td>
</tr>
<tr>
<td>Disable Children Association</td>
<td>39</td>
<td>16</td>
</tr>
</tbody>
</table>

**Project Title: Epilepsy Registry, RAC # 2011059**

**Investigators:** A. Al-Semari, D. McLean, S. Al-Yamani, D. McDonald, Z. Patay, A. Rifai, A. Ghomraoui, S. N. Subhani, N. Siddiqui

**Project Description**

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

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

**Progress**

- Data audited prior to cumulative report data tabulation.
- Telecommunication presentation of Epilepsy Registry to hospitals in Jeddah, Dammam, Riyadh, and Madina took place in June 2006.
- Secured collaborations from Riyadh Military Hospital, King Abdulaziz Medical City/King Fahad National Guards Hospital, Riyadh and KFSH&RC, Jeddah.
- Memorandum of agreements from these hospitals has been signed and now personal trainings are in progress before actual data acquisition can take place.
- Statistics for all year as of December 31, 2006 is:

<table>
<thead>
<tr>
<th>New cases</th>
<th>Diagnosis</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>King Faisal Specialist Hospital</td>
<td>1801</td>
<td>1132</td>
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- Statistics for year 2006 is:

<table>
<thead>
<tr>
<th>New cases</th>
<th>Diagnosis</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>King Faisal Specialist Hospital</td>
<td>573</td>
<td>575</td>
</tr>
</tbody>
</table>
Project Title: Cleft Lip / Palate and Craniofacial Anomalies Registry (CLCPR). RAC# 991030

Investigators: A. Al Johar, E. Al-Shail, A. Al Rubaiya, R. Kandasamy, S. N. Subhani, E. Al Jarba

Project Description

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

Over the past couple of years the registry underwent major software modifications to include the craniofacial anomalies along with the usual cleft lip and palate patients’ registration. The first annual report (cumulative from 1999 until 2005) is in process of revision and finalization.

Progress

- Registry data was audited and was completed with diagnosis for reporting.
- Registry first cumulative report was published.
- Paper titled “Prevalence of cleft lip and palate in hospital based population in Saudi Arabia: retrospective study”, has been submitted to “The Cleft Palate-Craniofacial Journal” Pittsburgh, US.
- Statistics for all year as of December 31, 2006 is:

<table>
<thead>
<tr>
<th></th>
<th>New cases</th>
<th>Treatment Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>King Faisal Specialist Hospital</td>
<td>979</td>
<td>2900</td>
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</table>

- Statistics for year 2006 is:

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<thead>
<tr>
<th></th>
<th>New cases</th>
<th>Diagnosis Coding</th>
<th>Treatment Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>King Faisal Specialist Hospital</td>
<td>95</td>
<td>960</td>
<td>273</td>
</tr>
</tbody>
</table>

Project Title: Thromboembolic Disorders Registry (TEDR). RAC# 2001045


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.

Thromboembolic disorders comprise all conditions, which may lead to thromboses with or without embolism whether on the arterial or the venous side of the circulation. It is clear that TED represent an important public health problem. The Thromboembolic Disorders (TED) Registry of King Faisal Specialist Hospital and Research Centre was 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

- Additional functionalities e.g. new charts, reports and search engine incorporated within the software.
- Data audited prior to cumulative report data tabulation.
- Hospital level collaboration started in terms of new case and follow up reporting on TED cases.
- Statistics for all year as of December 31, 2006 is:

<table>
<thead>
<tr>
<th>Hospital</th>
<th>New Cases</th>
<th>Follow Up Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>King Faisal Specialist</td>
<td>2108</td>
<td>1612</td>
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</tbody>
</table>

- Statistics for year 2006 is:

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<thead>
<tr>
<th>Hospital</th>
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<th>Follow Up Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>King Faisal Specialist</td>
<td>290</td>
<td>13</td>
</tr>
</tbody>
</table>

Project Title: Neuromuscular Disease Registry (NMDR). RAC# 991029E

Investigators: S. Bohlega, B. Stigsby, H. Al-Dhalan, S. N. Subhani, A. Yassen

Project Description

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

Progress

- Data audited prior to cumulative report data tabulation.
- Hospital level collaboration started in terms of new and treatment cases reporting on NMD.
- Statistics for all year as of December 31, 2006 is:

<table>
<thead>
<tr>
<th>Hospital</th>
<th>New Cases</th>
<th>Diagnosis Coding</th>
<th>Treatment Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>King Faisal Specialist</td>
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<td>1349</td>
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- Statistics for year 2006 is:

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<th>Hospital</th>
<th>New Cases</th>
<th>Diagnosis Coding</th>
<th>Treatment Coding</th>
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</thead>
<tbody>
<tr>
<td>King Faisal Specialist</td>
<td>399</td>
<td>399</td>
<td>484</td>
</tr>
</tbody>
</table>

Project Title: National Diabetes Registry (Research Centre Administration approved)


Project Description

Diabetes mellitus is a major and growing problem in the kingdom of Saudi Arabia causing prolonged ill health, disability, early death and high health cost. Diabetes being a chronic disease causes chronic complications with high morbidity and mortality rate. To monitor this disease in the Kingdom of
Saudi Arabia, a Saudi Diabetes Registry (SDR) was established in 1996. The SDR main office is located at the Diabetes Center, King Abdulaziz University Hospital, King Saud University. The registry committee consists of members coming from King Saud University, King Faisal Specialist Hospital and Prince Salman Bin Abdulaziz Hospital. The plan is to gradually include hospitals and to require them to file a Diabetes Registry form for every patient where diabetes mellitus have been diagnosed.

As a collaborative contribution from King Faisal Specialist Hospital, a web-based software with a centralized source of data was designed in-house in the BESC department which is activated since the year 2000, registering patients from various hospitals (currently 18 hospitals) from all over Riyadh region.

**Progress**

- During the year 2006, three more hospitals joined the registry. Currently there are 18 participating hospitals registering patients using the web-based on-line software.
- As of December 31, 2006 a total of 33344 patients registered in the centralized database.
- Several registry presentations were provided to doctors in King Khalid Eye Specialist Hospital and King Abdul Aziz University Hospital.
- Registry presentation given in the “National Diabetes Day” hosted by King Abdulaziz University Hospital in the city of Taif.
- Lectures on various diabetes related technical topics were given in the “Doctors Training Programs” and “Diabetes Educators Courses”
- Usage of Geographical Information System enhanced and more maps added to the GIS query engine of the registry.

**Project Title:** WCST-64 (A Study for Arabic Speaking Individuals). RAC# 2041048

Investigators: A. Hassan, N. Siddiqui

**Project Description**

The Wisconsin Card Sorting Test-64 (WCST-64), a shortened version of the WCST-64, and the Word Fluency Test (WFT) are known neuropsychological tools for assessing frontal lobe functioning. In this study, 100 Arabic-speaking male and female normal adults, 20 male and female adult patients with chronic schizophrenia, and 80 male and female adult patients with various focal brain lesions, are evaluated with the WCST-64 and the WFT. The study proposes that the WCST-64 can differentiate adult patients with focal frontal lobe lesions from both normal adult individuals and patients with non-frontal lesions. The aims and objectives of this study are:

1. To obtain local WCST-64 normative data for Arabic-speaking normal individuals (denoted control sample).
2. To empirically validate the WCST-64 in clinical samples comprising Arabic-speaking patients with a specific brain dysfunction or a diagnosis of schizophrenia (denoted clinical samples).

**Progress**

This project started in the 1st Quarter of 2005 by Dr. Ahmed Hassan from the Department of Neurosciences. The collaboration with the Department of Biostatistics, Epidemiology and Scientific Computing began by the end of 2nd Quarter of 2005. Till the end of the year 2005, some cases fulfilling the criteria were identified and almost 25 cases have been completed.

**Project Title:** Maternal Obesity and Neonatal Congenital Cardiovascular Defects. RAC# 2051046
Investigators: H. Khalil, A. Saleh, F. Al-Mohanna, S. N. Subhani

Project Description

In this case-control study all newborn infants with isolated congenital cardiovascular defects diagnosed and treated at our center from 1998-2005 were reviewed. Neonates with chromosomal anomalies or mothers with pre-existing diabetes were excluded. Maternal data includes; age, height, pre-pregnancy weight, peri conceptional multivitamin use, gestational age, pre-pregnancy medical condition, drug ingested during pregnancy and viral infection during pregnancy were recorded and analyzed. Women were categorized into three groups based on their BMI; Group 1: average weight 19-25 kg/m² (n = 130), Group 2: obese 30-35 kg/m² (n = 44) and Group 3: morbid obese > 35 kg/m² (n = 30). All congenital cardiovascular defect babies were matched with normal babies who were delivered during the same study period.

Progress

Out of collected 11,079 babies data, 206 infants had isolated congenital cardiovascular defects and were matched with 146 normal infants who delivered during the same study period. The distribution of maternal and neonatal characteristics among cases and control were similar. The most frequent cardiac lesion was multiple defects 123/206 (59.7%) (more than one valve anomaly or defect, e.g. ventricular septal defect + arterial septal defect etc.). The most frequent single lesion was arterial septal defect 27/206 (13.1%), followed by ventricular septal defect 16/206 (7.8%). There were no significant differences in the cardiac defects between the three groups. However, patent ducts arteriosis was significantly higher in group 3 versus group 1 (OR= 1.8 95% CI: 1.33-2.1).

Project Title: Survey of Dietary Habits in the Saudi Population. BESC# 009/2006

Investigators: K. S. Collison, Y. Al-Twaijri, M. Shoukri, S. N. Subhani, A. Al-Zahrani

Project Description

In this study, intelligent questions will be asked about the types of foods consumed in light of previous research, and to get a clear idea as to dietary patterns amongst the 3 age groups. Dietary patterns will be compared to BMI and waist-to-hip ratio measurements. Participants will receive a short explanation as to how their involvement will benefit the Saudi population as a whole once the study has been completed. A brief consent form will be completed. Data will be acquired in an un-biased and non-judgmental way, and upon completion of each survey, participants will be offered standard KFSH&RC dietary information leaflets with the aim of improving health awareness.

Progress

- Web-based software for the project has been designed by RCF, tested and is in use.
- Extensive search engine with complete dietary analysis incorporated within the database software.
- So far a total of 223 test cases collected from various schools, entered into the web-based database for Phase-I analysis.

FUTURE RESEARCH DIRECTION

Plans of collaboration with King Fahad Medical City and King Khalid Hospital, Riyadh for the CHDR. On-going collaboration with the Disabled Children Association, Riyadh and new collaboration with King Khalid Hospital, Riyadh for the NTDR. On-going collaboration with Riyadh Military Hospital,
King Abdulaziz Medical City/King Fahad National Guard Hospital, Riyadh and KFSH&RC, Jeddah for the Epilepsy Registry. Collaborations for the CLCP, TEDR, NMDR and the National Diabetes Registry. To complete the project WCST-64 by the end of 2007, after testing 100 samples and 100 controls. To be able to complete and submit the project report for the Maternal Obesity project. To be able to achieve the following goals for the Survey of Dietary Habits project:

- Identify staff to conduct the survey and acquaint them with correct measurement techniques and survey data acquisition method.
- Contact schools and Universities to ensure willing participation.
- Conduct surveys
- Enter survey results in database
- Analyze data.

**PUBLICATIONS**

2. Poster Presentation on “Maternal obesity and neonatal congenital cardiovascular defects”. Hala Khalil, MSc, Ahmed Saleh, MD, Futwan Al-Mohanna, PhD, Shazia Naz Subhani, MSc.
8. Various spin off research papers and abstracts for the National Diabetes Registry.
9. Poster Presentation on “Maternal obesity and neonatal congenital cardiovascular defects” in 5th International Conference of Medical Sciences of National Research Centre (NRC), 19 to 21.
Technical Databases

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 computer applications those could be used to support research activities or clinical research registries. The facility provides training to the use of in-house developed databases and is committed to design and develop databases and registries applications on request.

RESEARCH PROJECTS

1 - New Applications (Under Development)

1.1 Middle East Childhood Cancer Alliance (MECCA)

Pediatric oncologists from sixteen countries of the 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.

1.2 Neuro-psychology Database

Neuropsychology is a clinical discipline with assessment, diagnostic, and treatment/rehabilitative roles. A vast volume of data, obtained from patients undergoing comprehensive neuropsychological evaluation as part of the routine multidisciplinary clinical practice of diagnosing neurological conditions, is available in paper format. An electronic database for such clinical data is believed to be more appropriate format than the traditional paper format, for the following reasons:

- More effective storage with easy accessibility.
- Data can be reviewed and analyzed against similar data obtained using other modalities, such as MRI, EEG, and PET, hence allowing for further improvements in the sensitivity and specificity of tools used to produce the data.
- Research and academic activities are made possible.
The neuropsychological database currently being developed will contribute significantly to the active Comprehensive Epilepsy Surgery Program in this hospital. It will allow for reviewing the sensitivity of the neuropsychological tools used to obtain clinical data for patients being considered suitable for epilepsy surgery. Such a review will help in establishing local clinical tools and tests with higher degree of accuracy for neuropsychological evaluation of Saudi and other citizens with neurological conditions.

1.3 Congenital Heart Defects Registry (New version). RAC# 991026

The Congenital Heart Defects registry application maintains a database of all patients with CHD. It is a hospital based patient registry that is designed by the TDBCF using the classic ASP technology. Currently CHD is a regional registry with Prince Sultan Cardiac Centre, Riyadh working in collaboration with King Faisal Specialists Hospital & Research Centre. To maintain more powerful and up to date application, a new CHD web-based application is being re-developed using ASP DotNET technology. The new application contains all enhanced features of the old registry application.

1.4 Epilepsy Registry (New version). RAC# 2011059

It is a hospital-based registry, with national registry features, to register patients with epilepsy. It is the first of its kind in the Kingdom, and can be used as a good resource in the treatment and management of the disease. New version is being developed using latest available advanced technologies to further facilitate the registry application users. Due to collaborations with different organizations in the Kingdom, several changes are being made to the new and old application versions.

2 - Under Test Applications (Phase-I)

2.1 Thermo Luminescent Dosimetry (TLD)

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

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

2.2 National Cancer Registry (NCR)

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.

2.3 Gulf Center for Cancer Registration. RAC# 2061022

The Gulf Center for Cancer Registration (GCCR) was established to create incidence database and
Biostatistics and Epidemiology

gather other epidemiological data on cancer for the Gulf Cooperation Council (GCC) countries. Under the ministerial approval of the GCC Health Ministers, GCCR collates population-based incidences from GCC and other epidemiological data of cancer. A Web-based application developed by TDBCF to encourage the centralized cancer registry data management across the GCC countries. 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.

3 On-going Application (Users Support & Maintenance)

3.1 Congenital Heart Defects Registry. RAC# 991026

This is a hospital based patient registry. TDBCF are collaborating with the Registries Core Facility in maintaining the web based clinical registry for congenital heart disease patients. The features designed within the registry allow it to be used on the national level for the patient’s registration as well.

3.2 National Diabetes Registry, RC Administration Approved. BESC# 028/2001

The National Diabetes Registry is a joint project between King Saud University Hospital and King Faisal Specialist Hospital & Research Centre. This registry is planned for kingdom wide use for the online registration of diabetic patients. Currently over 10,000 patients from different hospitals within Riyadh Region has been entered and validated in the registry.

3.3 National Neural Tube Defects Registry. RAC# 991029

Neural Tube Defects (NTDs) are a group of serious birth defects that occur in pregnancy. The purpose of this registry is to be a reliable, valid, and timely information source for NTDs in KSA. The registry aims to provide statistics to public health programs and health care professionals for use in planning and evaluation.

3.4 Epilepsy Registry. RAC# 2011059

It is a hospital-based registry, with national registry features, to register patients with epilepsy. It is the first of its kind in the Kingdom, and can be used as a good resource in the treatment and management of the disease.

3.5 Cleft Lip Cleft Palate & Craniofacial Disorders Registry. RAC# 991030

This is a hospital-based registry designed with the national registry features. It registers patients with CLCP and craniofacial disorders.

3.6 National Genetic and Birth Defects Registry. RAC# 2031017

Saudi Arabia has an inordinately large number of birth and genetic diseases; particularly autosomal recessive diseases are encountered more frequently than in the west. This probably is due to consanguineous marriages that have been the custom for many years and to a founder effect. No reliable data is available for their prevalence. A web-based registry application was developed to manage valuable related data for public health and genetic disease prevention programs of the Kingdom.

3.7 Thromboembolic Disorders Registry. RAC# 2001045

This is a hospital-based registry with national registry features. We are collaborating with Registries Core
3.8 Saudi Thrombosis and Familial Thrombophilia Registry. RAC# 2001017

The web implementation for Saudi Thrombosis and Familial Thrombophilia Registry (S-TAFTR) is designed by TDBCF in 2003. The application is designed to be used nation-wide, providing real-time reports, charts, and data export facilities.

3.9 Neuromuscular Diseases Registry. RAC# 2031053

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.

3.10 National Premarital Screening Application

The National Premarital Screening Application is a cooperative work between the Research Centre and The Ministry of Health for hereditary blood diseases. A web-based application is developed in order to facilitate the quest to identify couples at risk and to serve as a future central information reserve to provide better understanding and treatment of the disease.

3.11 New Born Screening Lab Database

We have developed & designed a database, which comprises of web-based forms & reports connected to an SQL database running on a dedicated central server with extensive security and database features. Soon this web database will be extended to a national level web-based, database system.

3.12 Allergy and Aerobiology Lab Database Application

Allergy and Aerobiology Lab receives samples to be tested from various organizations and companies. The web-based application makes it easier for the lab to manage samples and their test result by merging the information in a relational database, accessible from the intranet. Samples and their results can be added, viewed, and updated through the application.

3.13 Research Centre Annual Statistical Report Application

The RC Annual Statistical Report Application is aimed at documenting the activities of the Research Centre along with budgeting information of each unit on a yearly basis. A quarterly or annual report based on the activities, employees and budget information of units is generated.

3.14 GCC Drug-Abuse Application

This is a joint project between different collaborating hospitals and King Faisal Specialist Hospital & Research Centre. The users of the GCC countries have designed this project in English as well as in Arabic versions for data entry purposes.

3.15 Application for Oligonucleotide Synthesis

King Faisal Specialist Hospital and Research Centre provides processed primers to researchers working in the hospital or out of the hospital. Aragene Laboratory receives requests from and prepares primers for several KFSHRC researchers and non-KFSHRC researcher on daily basis. The web-based application offers requester his/her registration. A user can start on-line ordering once the authorized
personnel of Aragene Laboratory accept his/her registration request.

3.16 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.

3.17 Research Centre Inventory Management System

The Research Centre Inventory Management System is established to help users to monitor, control and follow up their unit’s inventory. The user can add, and edit items in their inventory and also issue several reports on the inventory items.

3.18 Search Engine Database for Interferon and Cytokine Research Unit

The web implementation of ARE Database Search Engine has been redesigned with improvements in the speed and appearance. This search engine is one of its kind in all the GCC countries. The application allows the users to perform a search on ARE database based on criteria like Gene Symbol, Unigene ID, Unigene Definition, Locus, Human Mouse, Refreq ID, Refreq Definition and ARE Cluster Group.

3.19 Internet Mapping for Clinical Registries

Using ESRI ArcGIS 9.0 and ARCIMS 4.0 mapping software, TDBCF has successfully implemented internet GIS for National Diabetes Registry and is now exploring ways to incorporate the same to all the other clinical registries as well. Admin users of the Diabetes Registry can query the database using this sophisticated query tool, which shows the data to be displayed as maps using geographic and spatial data along with the registry data for a better more clear insight of the data.

4 Users’ Training

TDBCF Section is committed to provide users training sessions at the completion of each application. TDBCF has provided training sessions for users of Thermo Luminescent Dosimetry (TLD), Neuromuscular Diseases Registry (NMDR), Saudi Thrombosis and Familial Thrombophilia (S-TAFT) Registry and Epilepsy Registry applications.

5 Professional Training

5.1 Saudi Students (Summer Training)

TDBCF participates in the training of the students to enhance their abilities by introducing the latest technologies and providing them professional training. Two students from them were given training for 3 months. The students were introduced classic and latest technologies being used in the section. The students were given small tasks to build their confidence. Later, they put on real projects so they could gain the professional experience.

6 Other Activities

6.1 Gulf Centre for Cancer Registration (GCCR) Workshop

Members of TDBCF participated in the GCCR workshop organized by GCCR coordinators in Riyadh. Presented the Cancer Registry Web application for Gulf Countries developed by TDBCF.
6.2 Attended/participated in the “Digital Health Workshop”

6.3 Attended “Project Management Professional (PMP)” training

6.4 Attended training sessions on “Management Skills Development”

6.5 Attended training on “Securing Networks with PIX and ASA”
### Core Facility

#### Computing Services

The Computing Services Core Facility (CSCF) provides server-based computing services for 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.

The CSCF contributes to the provision of a computational infrastructure, consultancy services and maintains a collection of scientific and biological programming software and computing resources.

During the year 2006, CSCF setup new PCs, workstations, printers, servers and other major computer peripherals. The CSCF was successful in setting-up and configuring two (2) servers (HP and IBM) at KFNCCC&R with Windows Server 2003 operating system.

The configuration of many PCs with laboratory instruments and the installation of software based on the requirements of the particular users were also successful.

CSCF successfully carried out preventative maintenance (PM) in the BESC and the National Laboratory for Newborn Screening (NLNBS) PCs in the Research Centre. The preventative maintenance will be extended to KFNCCC&R and RC-KFSH when we have adequate staff members to support the requirement. Preventive maintenance is being carried out on a quarterly basis.

Preventive maintenance consists of 31+ tasks that would boost the performance of the machines, stabilize platforms, and increase the productivity and efficiency and will reduce the support costs. These tasks are related but not limited to:

- Operating systems updates
- Disk defragmentation,
- Software updates,
- Service packs for Windows and MS Office 2000/2003,
- Cleaning internet browser temporary internet and offline files
- Updates of the anti-virus software.

---

**Head of Facility**
Parver A. Siddiqi

**Members**
- Mashnouf Al-Rowaily
- Arnie Tayco
- Yousef Hussain
- Michael Edquiban
- Bander Al-Khudairi
- Mohamed Al-Malki
CSCF staff attended following courses during the year 2006.

**Course Name**
1. Supporting Users Running Windows XP Operating System
2. Supporting Users Running Applications on Windows XP
5. Implementing, Managing, Maintaining Windows Server 2003
6. Network Infrastructure: Network Services
7. Strategy and strategic management (2 hours lecture)

CSCF successfully upgraded as well as installed/replaced PCs in the Research Centre. The group also successfully replaced department's desktops with laptops.

**CORE FACILITY ACTIVITIES**

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

CSCF Help Desk is a big boost to support the RC-KFSH & KFNCCC-R users.

The core facility activities are:
- To keep the servers (Windows 2000, Windows 2003, LINUX, UNIX) running with minimum down time.
- To administer the network users and services.
- To maintain network infrastructure within the Department.
- To troubleshoot and solve hardware, software or network related problems, for users in the department and the Research Centre (RC-KFSH & KFNCCC-R), focusing on PCs connected to laboratory instruments.
- To setup and configure workstations and servers.
- To install and upgrade Windows OS and Windows applications software.
- To support the requirements of visitors in conjunction with their presentations in the Research Centre.
- To continue to upgrade software to meet the needs of users.

**BMR Administration:** Setup, configured and installed new PCs, troubleshoot hardware and software problems.

**BMR Environment:** Setup and configured new PCs to be used at the laboratory. Replaced old computer connected to the instrument.

**BMR DNS Repair and Apoptosis:** Setup, configured, installed and hooked up PCs with the instruments.

**BMR Cell Biology:** Reconfigured and upgraded workstations used in the Confocal Laboratory. Also assisted vendor's engineers in troubleshooting laboratory instruments.

**BMR Coagulation:** Setup new PCs and printers for the senior scientist and technicians that included software needed for research projects.

**BMR Allergy & Aerobiology:** Setup and configured PCs for laboratory use as well as for the technicians.

**BMR Biomedicine Chemistry:** Setup and configured PCs.

**BMR Breast Cancer:** Setup, configured and upgraded PCs as well as printers in the new offices/laboratory.
BMR Carcinogenesis: Setup and configured PCs and printer.

BMR Flow Cytometry: Setup and configured PCs and MACs to be used with laboratory instruments.

BMR Laser Medicine: Setup and configured PCs and printers.

BMR Molecular Virology & Infectious Diseases: Setup PCs and troubleshoot hardware and software problem related to the laboratory instruments. Helped Saudi trainees in setting up laptops for their work in the laboratory.

BMR Tumor Immunology: Set and configured PCs and troubleshoot hardware and software problems.

RC Administration: Setup and configured new PCs and Laptops for meetings and presentations. Setup wireless connection in the Office of the Deputy Executive Director.

Department of Cyclotron and Radiopharmaceuticals: Setup new PCs and upgraded existing operating system to meet the requirements for the new billing system.

Department of Biomedical Physics: Setup, configured, and installed new PCs and printers.

Department of Comparative Medicine: Setup, configured, installed new PCs and printers (both at RC-KFSH and KFNCCC&R). Also attended a seminar on how to handle and troubleshoot new laboratory applications.

Department of Genetics: Setup and configured PCs and laptops for new laboratory technicians. Also setup printers (B/W and Colored).

Department of National Laboratory for Newborn Screening (NLNBS): Setup and configured PCs for the users, which will be used with instruments. Setup a backup procedure for backing up laboratory data on a daily basis.

KFNCCC&R: Setup, configured, installed and hooked up PCs to the laboratory instruments. Setup new server for the group as a file and web server. Laboratory data is being backed up on the server on a daily basis.

Arabian Diagnostics Laboratory (ADL): Setup and configured new PCs and printer. CSCF staff member assigned at CCC is maintaining four laboratory servers.

Oncology Data Unit (ODU), Department of Oncology: Setup and configured new HP server as a file and web server. Setup and reconfigured the existing PC-based server for backup purposes. HP server is being maintained by one of the CSCF staff member assigned at CCC.

Biomolecular Research Program (BRP): Setup and configured PCs and printers. Setup and hooked up PCs with the instruments. Helped vendor to do remote link in order to install and check the instrument.

Centre of Innovative Technology (CIT): Setup and configured new PCs and printer. Configured laptop to access user data from the desktop. Helped in installing the software on the laptop as well as on the desktop.

PET: Supported SUN Solaris console and all workstation located through out the Hospital. Troubleshoot PACS network related problem on SUN workstation located in the Radiology Department.
### Number of Calls REGISTERED at BESC Help-Desk per Department

<table>
<thead>
<tr>
<th>Department</th>
<th>Number of Calls</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC-Admin</td>
<td>13</td>
</tr>
<tr>
<td>BESC</td>
<td>163</td>
</tr>
<tr>
<td>BMR</td>
<td>112</td>
</tr>
<tr>
<td>BRC</td>
<td>8</td>
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<tr>
<td>BMP</td>
<td>20</td>
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<td>BRP</td>
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<tr>
<td>C&amp;R</td>
<td>27</td>
</tr>
<tr>
<td>CIT</td>
<td>2</td>
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<tr>
<td>CPPEO</td>
<td>19</td>
</tr>
<tr>
<td>CMD</td>
<td>57</td>
</tr>
<tr>
<td>Genetics</td>
<td>35</td>
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<tr>
<td>NLNBS</td>
<td>82</td>
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<tr>
<td>ORA</td>
<td>26</td>
</tr>
<tr>
<td>T&amp;E</td>
<td>10</td>
</tr>
<tr>
<td>ADL-CCC</td>
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<tr>
<td>RC-CCC</td>
<td>49</td>
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<tr>
<td><strong>Total</strong></td>
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</table>

### Number of Calls NOT REGISTERED at BESC Help-Desk per Department

<table>
<thead>
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</tr>
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<td>BRP</td>
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<td>C&amp;R</td>
<td>21</td>
</tr>
<tr>
<td>CIT</td>
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<tr>
<td>CPPEO</td>
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<tr>
<td>CMD</td>
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<td>NLNBS</td>
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<tr>
<td>T&amp;E</td>
<td>8</td>
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<td>ADL-CCC</td>
<td>10</td>
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<tr>
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<td>12</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>441</strong></td>
</tr>
</tbody>
</table>

### ITA Help Desk

**Incident Log:**
- 436 (requests such as: network ports, PC and printer hardware replacement, etc.)

**Change Order:**
- 126 (requests such as: new internet and email accounts, installation of ITA software, etc.)
The
Centre for Clinical Studies and Empirical Ethics
The Centre for Clinical Studies and Empirical Ethics

The Centre for Clinical Studies and Empirical Ethics (CCSEE) has established itself as a national/regional centre of excellence for conducting bioequivalence studies and for training clinical research professionals. The activities of the CCSEE are strategically chosen to: 1) build an appropriate, self-sustaining infrastructure, and 2) concentrate on projects of direct translateral values. The CCSEE is currently expanding in the empirical ethics and applied clinical research fields.

In preparation for accreditation by the College of American Pathologists (CAP), the CCSEE focused on the reorganization of the Bioanalysis laboratory and completion of the requirements for accreditation. A custom-made Internal Policies and Procedures covering the laboratory routines were finalized. A searchable, updatable, and user-friendly laboratory inventory database of over 2800 items was established.

The total gross income of the CCSEE in 2006 was SR 453,750.

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

Members
Syed Alvi, PhD
Sameer Al-Rawithi, PhD (on extended leave)
Haneah Al-Mosuly, MD (from December 2006)
Eman Al-Gaai, RPh, CCRP,
MHHA (Flexible Employment Program)
Marilyn Lockyer, RN, CCRP,
BSc (Until November 2006)
Ahmed Yusuf
Saleh Al-Dgither
Rajaa Hussein, RPh
Samar El-Hawai, RPh (Flexible Employment Program)
Hubertus Hoenen (Until November 2006)
Mohammad Alqaderi, RN,
MSN (From October 2006)
Abdel Raheem Ahmed
Maria Lourdes Bautista
RESEARCH PROJECTS

Project Title: Randomized, Single-Dose, Two-Treatment (Generic and Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Pioglitazone 45 mg Under Fasting Conditions (RAC # 2051 025)

Project Description
The aim of this study is to compare the bioavailability of two oral formulations containing pioglitazone: Actos® 45 milligram tablet, an innovator and registered drug, and Pioglitazone JPTM 45 milligram tablet, a generic drug that has not yet been registered in Saudi Arabia.

Progress
Completed.

Project Title: Randomized, Single-Dose, Two-Treatment (Generic and Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Rosiglitazone 8 mg Under Fasting Conditions (RAC # 2051 026)

Project Description
The aim of the study is to compare the bioavailability of two oral formulations containing rosiglitazone: Avandia® 8 milligram tablet, an innovator and registered drug and Rosiglitazone TM 8 milligram tablet, a generic drug that has not yet been registered in Saudi Arabia.

Progress
Completed.

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

Project Description
Much attention has recently been devoted to strengthening the safeguards for research subjects. This study will provide information essential in evaluating the ethical quality of research done in Saudi Arabia.

Progress
Ongoing. About 75% of the planned data collection has been completed.

Project Title: Does King Faisal Specialist Hospital and Research Centre Have a Chaperone Problem? (RAC # 2051 037)

The aims of the study are

1. To determine the proportion of out-patients at KFSHRC who are interviewed/examined by a physician of the opposite sex in the absence of a chaperone and whether this differ among the different clinics.
2. To determine if the chaperone, when present, was provided by the hospital or was a patient’s companion.
3. To determine the degree of patients acceptance/preference to be interviewed/examined by a physician of the opposite sex without a chaperone.

Progress
Completed. A manuscript was provisionally accepted for publication in the Annals of Saudi Medicine.
Project Title: Randomized, Single-Dose, Two-Treatment, (Generic and Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Rabeprazole 20 mg Tablet Under Fasting Conditions (RAC # 2051 068)

Project Description

The aim of this study is to compare the bioavailability of two oral formulations containing rabeprazole: Pariet® 20 milligram tablet, an innovator and registered drug and RabeprazoleTM 20 milligram tablet that has not yet been registered in Saudi Arabia.

Progress

Closed. A quantitative assay to measure rabeprazole has been developed and fully validated.

Project Title: Measuring Placebo Effect by Elimination and Investigating Its Mechanism of Action (RAC # 2051 072)

Project Description

Placebos have been in use for centuries in medical practice. However, there is continued controversy regarding their effectiveness and mechanisms of action. We propose to measure the effect of placebo by a novel design, determine its interaction with the effect of active drug, and explore whether placebo exerts part of its effect at the pharmacokinetics level.

Progress

Ongoing. The project is KACST funded for the year 1427 (KACST # AT-26-45) and is currently recruiting.

Project Title: Modeling Ethical Resolution: Mapping Points of Ethical Equilibrium (RAC # 2060 004)

Project Description

Making decision on ethical issues is based on beliefs and on balancing several ethical values/principles. The different ways individuals of different backgrounds use and balance ethical principles have not been well defined. We propose to use Q methodology to identify models of ethical decision-making and points of ethical equilibrium in regards to three controversial bioethical topics. The extent people use ethical principles other than those described in the four-principles-plus-scope approach (i.e., respect for autonomy, beneficence, non-maleficence, and justice) will be examined. The association of various demographic factors with the identified models and the effect of formal ethical education will be studied. We will also explore the stability of the identified models/points of equilibrium over time, within demographic groups, and across topics. The results are expected to have important contributions to empirical studies of ethical resolution and to evidence-based ethics regarding current bioethical issues. It may show that beliefs aside, ethical resolution models/points of equilibrium may not be different across nations or segments of society. It will also provide empirical evidence for or against the adequacy of the simplified four-principles-plus-scope approach in biomedicine.

Progress

Ongoing. Resubmitted to KACST for funding (KACST # AT-27-1).
Project Title: Randomized, Single-Dose, Two-Treatment (Generic and Innovator), Two Period, Two-Sequence, Crossover, Bioequivalence Study of Ramipril 10 mg Tablet Under Fasting Conditions (RAC # 2061 053)

Project Description

The aim of this study is to compare the bioavailability of two tablet formulations containing 10 mg ramipril: an innovator registered formulation and a generic formulation that has not yet been registered in Saudi Arabia.

Progress

Ongoing. A quantitative assay to measure ramipril has been developed and fully validated. An agreement with the sponsor is pending.

Project Title: Randomized, Single-Dose, Two-Treatment (Generic and Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Simvastatin 40 mg and Ezetimibe 10 mg Combination Tablets Under Fasting Conditions (RAC # 2061 059)

Project Description

The aim of the study is to compare the bioavailability of two combination tablet formulations containing simvastatin 20 mg and ezetimibe 10 mg: an innovator registered formulation and a generic formulation that has not yet been registered in Saudi Arabia.

Progress

Ongoing. An agreement with the sponsor is pending.

Project Title: Randomized, Single-Dose, Two-Treatment (Generic and Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Moxifloxacin 200 mg Tablet Under Fasting Conditions (RAC # 2061 062)

Project Description

The aim of the study is to compare the bioavailability of two formulations of moxifloxacin 200 mg tablet: an innovator registered formulation (reference) and a generic formulation that has not yet been registered in Saudi Arabia.

Progress

Ongoing. An agreement with the sponsor is pending.
Project Title: Randomized, Single-Dose, Two-Treatment, (Generic and Innovator) Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Irbesartan 150 mg and Hydrochlorothiazide 12.5 mg Combination Tablets (RAC # 2061 063)

Project Description

The aim of this study is to compare the bioavailability of two formulations of a combination tablet containing irbesartan 150 mg and hydrochlorothiazide 12.5 mg: an innovator registered formulation and a generic formulation that has not yet been registered in Saudi Arabia.

Progress

Ongoing. An agreement with the sponsor is pending.

Project Title: Placebos at KFSHRC: Types, Extent of Use, and Physicians (RAC # 2061 066)

The aims of this study are

1. To determine the extent and types of, and reasons for, placebo prescribing by physicians at the KFSHRC
2. To compare the results of this study with similar studies conducted in other settings.

Progress

Completed. A manuscript has been submitted for publication.

Project Title: Randomized, Single-Dose, Two-Treatment, (Generic and Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Diclofenac 50 mg Tablet under Fasting Conditions (RAC # 2061 067)

Project Description

The aim of the study is to compare the bioavailability of one tablet formulation containing 50 mg diclofenac: an innovator registered formulation and a generic formulation that has not yet been registered in Saudi Arabia.

Progress

Ongoing. An agreement with the sponsor is pending.

Project Title: Randomized, Single-Dose, Two-Treatment, (Generic and Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Meloxicam 15 mg Tablet Under Fasting Conditions (RAC # 2061 070)
Project Description

The aim of this study is to compare the bioavailability of two formulations of meloxicam 15 mg tablet: an innovator registered formulation and a generic formulation that has not yet been registered in Saudi Arabia.

Progress

Ongoing. An agreement with the sponsor is pending.

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

Project Description

Generic formulations of prescription drugs can, through their relatively lower cost, improve healthcare as long as they maintain their registration-quality and public trust. On the other hand, the market availability of several generic formulations raises a concern regarding their interchangeability, despite being proven to be individually therapeutically interchangeable with their corresponding innovator formulation. We propose to assess the quality and therapeutic interchangeability of generic formulations in the drug market of Saudi Arabia, using fifteen, commonly-used, oral, solid, immediate-release, and non-combinational drugs.

Progress

Submitted to KACST for funding (KACST # AT-27-40).

Project Title: Randomized, Single-Dose, Two-Treatment (Generic and Innovator), Two-Period, Two-Sequence, Crossover, Bioequivalence Study of Ibuprofen 400 mg Tablet under Fasting Conditions (RAC # 2071 002)

Project Description

The aim of this study is to compare the bioavailability of two formulations of ibuprofen 400 mg tablet: an innovator registered formulation and a generic formulation that has not yet been registered in Saudi Arabia.

Progress

Ongoing. A quantitative assay has been developed. An agreement with the sponsor is pending.

Project Title: Sodium Bicarbonate in Preventing Contrast Induced Nephropathy (SIPCIN): A Randomized Controlled Study (RAC # 2071 003)

Project Description

Contrast-induced-nephropathy (CIN) is a not uncommon disease that is associated with important morbidity and mortality, particularly in high risk patients. The strategy of choice to prevent CIN has not been established. We plan to conduct an open-label, randomized, stratified, parallel-group study to compare normal saline infusion to sodium bicarbonate infusion. 220 adult patients scheduled for routine cardiac catherization will be enrolled. They will be stratified according to the presence or absence of DM, or an estimated GER of less than 60 ml/hr before being block-randomized to the two groups. The incidence of the CIN will be determined based on the average of two measurements of
creatinine level before and 48 hours after the procedure, and an increase of 25% or 0.5 mg/dL (44.2 umol/L) or more. The data will be analyzed by the chi square test.

Progress
Submitted to RAC for approval.

Project Title: Randomized, Single-Dose, Two-Treatment, (Generic and Innovator), Two-Sequence, Crossover, Bioequivalence Study of Ketoprofen 25 mg Tablet Under Fasting Conditions (RAC # 2071 007)

Project Description
The aim of this study is to compare the bioavailability of two formulations of ketoprofen 25 mg tablet: an innovator registered formulation and a generic formulation that has not been registered in Saudi Arabia.

Progress
Ongoing. A quantitative assay has been developed and fully validated. An agreement with the sponsor is pending.

Project Title: Medical Chaperoning at KFSH&RC: Physicians’ Views (RAC # 2071 011)

Project Description
We plan to study KFSH&RC physicians’ practice regarding medical chaperoning, identify factors that influence the use of chaperones, examine physicians’ perception of chaperoning in general, and examine reasons for use of chaperones. We will use a survey tool consisting of 18 questions.

Progress
Submitted to RAC for approval.

Project Title: Randomized, Single-Dose, Two-Treatment, (Generic and Innovator), Two-Sequence, Crossover, Bioequivalence Study of Glibenclamide 5 mg Tablet Under Fasting Conditions (RAC # 2071 017)

Project Description
The aim of this study is to compare the bioavailability of two formulations of glibenclamide 5 mg tablet: an innovator registered formulation and a generic formulation that has not been registered in Saudi Arabia.

Progress
Ongoing. A quantitative assay has been developed and fully validated. An agreement with the sponsor is pending.

Project Title: Pain among King Faisal Specialist Hospital and Research Centre Cancer In-Patients: Prevalence, Severity, Impact on Quality of Life, and Adequacy of Management

Project Description
The purpose of this study is to systematically explore pain prevalence, severity, impact on quality of life, and adequacy of management among King Faisal Specialist Hospital and Research Centre (KFSH&RC) cancer patients during hospitalization. 200 consecutive patients will be studied and data will be collected through semi-structured interview and the following instruments: (a) Demographic data sheet (DDS), (b) Brief Pain Inventory (BPI), (c) The World Health Organization Quality of Life –brief (WHOQOL), (d) Memorial Symptom Assessment Scale (MSAS), and (e) Pain Management Index (PMI).
Progress

Submitted to RAC for approval.

Project Title: Lansoprazole in Human Plasma: HPLC Assay and Stability

Project Description

A High Performance Liquid Chromatography (HPLC) assay for the measurement of lansoprazole level in human plasma was developed and fully validated.

Progress

Completed.

FUTURE DIRECTIONS

With the vision of expanding its research activities and enriching its expertise, the CCSEE has recently welcomed the joint appointment of Dr. Fawaz Abdullah Alturki, Consultant Adult Cardiologist, King Faisal Heart Institute (KFHI), and Dr. Mohammed Alsunaid, Consultant Nephrologist, Department of Medicine, KFSH&RC.

A two-week HPLC hands-on course is planned with the aim of providing basic understanding of pharmaceutical analysis and bioequivalence studies. A course on Biomedical Ethics and laws is being developed. The bi-annual Clinical Research Professionals’ Course is being updated. A new webpage for CCSEE is being finalized.

PUBLICATIONS

The Department of Comparative Medicine
The Department of
Comparative Medicine

The Department of Comparative Medicine (DCM) assists the research activities of scientists and physicians at the King Faisal Specialist Hospital & Research Centre (KFSH&RC) by providing animals, veterinary care, an array of technical services and expertise to all investigators. Most animal species, from rodents to primates are available. Our staff is made up of veterinarians, scientists, technicians and nurses. Current research activities conducted by our staff include investigations in heatstroke, infectious diseases, cardiovascular and neurodegenerative disorders. In conjunction with other departments, DCM offers courses and workshops in minimal invasive laparoscopy and micro-surgical techniques. In conjunction with the Training and Education section, DCM offers extensive training programs in biochemistry, molecular biology and microbiology to graduate and undergraduate students.

Chairman
Abderrezak Bouchama, MD

Members
Perlie F. Bohol
Ma. Cecilia Badajos (part of the year)
EXPERTISE

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

SIGNIFICANT ACHIEVEMENTS

- Two pre-clinical trials were successfully conducted using our unique baboon model of heatstroke.
- Full membership with the advisory board of WHO on global warming and effect on public health.
- Set-up of a new laboratory to investigate new aspects of heatstroke and sepsis.
- Development and validation of new tools to diagnose brucellosis (PCR & recombinant DNA technology) and Mycobacterium tuberculosis (Spoligotyping).
- Successful acquisition of 3 grants from KACST.
- 5 Workshops were conducted
- 4 Educational training sections were provided
- 4 Manuscripts were published and 3 are in press.
- 1 Eminent visiting scientist was housed by the DCM (2 high quality seminars + collaborations).
- 2 New international collaborations were established.

ACADEMIC TRAINING and WORKSHOPS

During the last year, the Dept. actively participated in various workshops and educational trainings.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Number of participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training of graduate and undergraduate students</td>
<td>7 High School students</td>
</tr>
<tr>
<td>Microsurgery workshop</td>
<td>4 B.Sc. students</td>
</tr>
<tr>
<td>Laparoscopy &amp; Workshop</td>
<td>8 Participants</td>
</tr>
<tr>
<td>Bowel Anastomosis workshop</td>
<td>121 Participants</td>
</tr>
<tr>
<td></td>
<td>40 Participants</td>
</tr>
</tbody>
</table>

COLLABORATIONS

National

- KFSHRC, Riyadh
- National Guard Hospital, Riyadh
- Military Hospital, Riyadh
- National Commission for Wildlife Conservation and Development, Taif

International

- Eli Lilly & Company, Indianapolis, USA
- Centre for Disease Control (CDC), Atlanta, USA
- Ontario Cancer Institute/University of Toronto, Toronto, Canada
- Center for Research in Neurodegenerative Diseases, University of Toronto, Toronto, Canada
- INSERM, University of Paris VII, Paris, France
- Hopital Louis Mourrier, Paris, France
- Universite Louis Pasteur, Strasbourg, France
• Institut Pasteur de Lille, Lille, France
• Royal Free University College Medical School, London, England
• University of Paisley, Scotland, England
• World Health Organization, European Centre for Environment and Health, Rome, Italy
• Ministry of Health, Rome, Italy
• Lofarma S.P.A, Milan, Italy
• National Institute of Public Health and the Environment, The Netherlands
• University of Salzburg, Salzburg, Austria
• Institut Pasteur de Guadeloupe, Guadeloupe

PROJECTS IN PROGRESS

• Heatstroke
• 6 projects
• Tuberculosis
• 3 projects
• Date palm allergen characterization 1 project

DATA

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<th>Category</th>
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<td>Administrative Staff</td>
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<td>Animals in the inventory</td>
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<tr>
<td>Publications</td>
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<td>Meetings</td>
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<tr>
<td>Seminars/presentations</td>
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</tr>
<tr>
<td>Total funding</td>
<td>SAR 2.75 Million</td>
</tr>
</tbody>
</table>
The Experimental Surgery program is designed to help the enhancement of surgical skills of surgeons in various disciplines. The section supports research by helping investigators to devise the appropriate animal models that closely resemble human diseases. The programme provides training and workshops in all areas of surgical disciplines.

The Animal Experimental Surgery Staff maintain and operate surgical theatre, which is suitable for major operative procedures on both small and large laboratory animals. The surgical theatre is equipped with state of the art anaesthesia and monitoring equipment to ensure the success of all surgical procedures, heart-lung machine, echocardiogram, blood gas machine haematology analyser as well as a full line of surgical instruments. Dental X-ray, fluroscopy facilities, Laparscopy and Endoscopy equipments and facilities are also available. Equipment and expertise are available to support routine and specialized surgical procedures including cardiovascular, neurosurgical, and others. The professional staffs of LAF are available to perform surgical and aesthetic procedures in support of research protocols, in collaborative efforts.

Head of Unit
Ra‘afat M. El-Sayed, DVM, MVSc

Members
Falah H. Al-Mohanna, DVM (part of the year)
Farraj A. Al-Samer
Ludivina A. Apilado
Sahar I. Salem
Crisologo J. Caliao (part of the year)
Merfat A. Elyan
TRAINING & WORKSHOPS

The Laboratory Animal Facility & Experimental Surgery Staff collaborate with staff from various departments of the hospital and Research Centre to offer training and workshops that were attended by participants from Saudi Arabia and overseas in the following disciplines:

- Microsurgery
- Laparoscopy
- Endoscopy
- Bowel Anastomosis

Training in Animal Microsurgery

The Microsurgery Laboratory at CMD, KFSH&RC in collaboration with the departments of Neuroscience offer two types of courses:

1. A continuous course held on Sunday and/or Wednesday mornings for hospital staff and candidates who live in the Riyadh area.
2. The Intensive courses are given 4 times a year and each section runs for five consecutive days for a total of 40 hours. Participants who achieve the required level of competence after satisfactory completion of at least 30 hours of hands-on practice in the relevant microsurgery procedures are issued with certificates.

The following departments use the Microsurgery Animal Laboratory:

- Department of Neurosurgery
- Department of Urology
- Department of Plastic surgery
- Cardiovascular Department

Animal Training & Laparoscopy

Minimal invasive surgical training programmes are offered in Laparoscopic and Thoracoscopic procedures. The duration of the program, which is offered 4 times a year, is between 1 & 3 days for a total 10 to 30 hours. Training includes the following:

1. Intra-abdominal orientation is carried out from diaphragm to the pelvis, learning tactile and feedback and depth perception.
2. Once the candidate is comfortable with that aspect of training (orientation), they will proceed with some actual procedures, which will involve:
   a. Appendectomy; removal of appendix
   b. Cholecystectomy; removal of gall bladder
   c. Splenectomy; removal of spleen
   d. Nissen fundoplication
   e. Gynecology: Tubal Ligation, Ovarian Cystectomy, Oopherectomy, Vaginal Hysterecctomy Pelvic Lymphadenectomy
   f. Bowel Anastomosis: stapling techniques (side to side, end to end and combined techniques), Tracheostomy, Laparotomy, Gastrectomy, Aortotomy with vein patch, Knot (basic knot, square knot two-hand and one-hand technique) and Robotic bench work: set-up, scopes and robotic suturing
## FACTS AND FIGURES

Workshops conducted in Year 2006

<table>
<thead>
<tr>
<th>Workshops/ Principal Investigator(s)</th>
<th>Date</th>
<th>Participants</th>
<th>Animals Used</th>
</tr>
</thead>
</table>
| **Minimally Invasive Surgery & Laparoscopy**  
Dr. I. Al Badawi  
(Department of Obstetrics & Gynecology) | April 24-26, 2006 | 81           | 9 dogs       |
|                                         | September 18, 2006 | 40           | 3 dogs       |
| **Bowel Anastomosis and Laparoscopy**  
Drs. Abdul Jabbar & O’ Regan  
(Department of Surgery) | May 25, 2006     | 40           | 8 dogs       |
| **Intensive Microsurgery Course**  
Dr. E. Al Shail  
(Department of Neurosciences) | January 21-25, 2006 | 4            | 25 rats      |
|                                         | March 4-8, 2006  | 4            | 25 rats      |
Heatstroke is a public health problem in Saudi Arabia, during the pilgrimage to Makkah, especially when it falls into the hot cycle of the year. For example in August 1985, there were 2,000 cases of heatstroke of which 1,000 died in temperate climates. Severe heat waves have recently led to an unprecedented 70,000 in Europe, of which a third was due to heatstroke. As sophisticated climate model predicts an increasing frequency and severity of heat-waves, the incidence of heatstroke with an outcome of mortality or neurologic morbidity is expected to rise if in addition to preventive measures, novel therapy are not developed. Heatstroke unit has been performing clinical and experimental research on the molecular and cellular mechanisms of tissue injury in heatstroke for almost 20 years with the perspective of discovering novel therapies. This accumulated experience has earned the unit a worldwide recognition underlined by our designation as a full member of the advisory board of the WHO environment and health, Europe. We have also been asked to draft, a working document on the effect of heat on health and the protection of the population to this emerging environmental threat. When these recommendations will be officially endorsed by the WHO, this will be a major accomplishment for the Research Centre.
RESEARCH PROJECTS

Project Title: Treatment of Heatstroke With Anti-Inflammatory Glucocorticoids: A Study In Baboons. RAC# 2020 017 – Phase 2


Project Description

Severe heatstroke induces excessive inflammation and coagulation activation suggesting that their immunomodulation may be beneficial. Here, we tested the hypothesis that blocking the inflammatory pathways using a steroidal anti-inflammatory drug reduces the lethal effects of heat and improve outcome.

The project was carried out on ten juvenile baboons that received dexamethasone before and during the course of severe heatstroke or placebo. We examined the effect of Dexamethasone on markers of organ injury/dysfunction, inflammatory response (IL-6 and C5a b) and animal outcome (survival versus mortality).

Progress

Project completed and one manuscript was accepted in Shock journal (In press). In addition, one abstract was presented at the annual meeting of the American Society of Critical Care Medicine in San Francisco, USA (Jan. 11-17, 2006).

Project Title: Effect of Xigris “Recombinant Activated Protein C” on Inflammatory and Haemostatic Responses in Primates Suffering from Lethal Heatstroke: Relation to Outcome. RAC# 2020 017 – Phase 3

Investigators: Abderrezak Bouchama, Mohammed Dehbi, Aaron Kwaasi, George Roberts, Corinne Kunzelmann

Project Description

This project is supported in part by a Grant from Eli-Lilly, Indianapolis, USA. We aim to assess the effect of recombinant activated protein C (Xigris), an inhibitor of the coagulation system on the inflammatory response, organ functions and survival in baboons suffering from lethal heatstroke.

Fourteen animals were randomized to Xigris (n=7) given at 24 µg/kg/hr continuous infusion at the onset of heatstroke and compared with animals (n=7) treated with placebo. We examined the effect of Xigris on markers of organ injury/dysfunction, inflammatory and coagulation responses and animal outcome (survival versus mortality).

Progress

The in vivo aspects of this project were completed. Other in vitro “confirmatory” aspects are in progress.

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

Investigators: Abderrezak Bouchama, Mohammed Dehbi, Aaron Kwaasi, Ahmed Maqbool, Arslan Loualich, Mohammed Chishti, George Roberts

Project Description

Heat shock proteins (referred to as molecular chaperones) represent a growing family of stress-inducible proteins. They act by helping in the refolding of misfolded proteins in response to various stresses including heat stress, and thus, they play key roles in maintaining cellular homeostasis.
and integrity during the exposure to a given stress. In this project, we investigated the expression profile of 3 major heat shock proteins (Hsp-60, Hsp-70 and Hsp-72) in a baboon model of heatstroke and the possible relationships with outcome.

Animals were randomly divided into 3 groups: sham-heated group, moderate heatstroke group and severe heatstroke group. Tissue samples were obtained at immediate autopsy (non-survivors) and euthanasia at 72-h (survivors) and homogenized. Expression of Hsps was monitored by western blot on lysates prepared from various organs.

**Progress**

Project was completed and one manuscript is in preparation. In addition, two abstracts were accepted as posters. Society of Critical Care Medicine in San Francisco, USA (Feb. 17-21, 2007) and the 2007 meeting on Trauma, Shock, Inflammation and Sepsis “TSIS 2007”, Munich, Germany (Mar. 13-17, 2007).

**Project Title:** Proteomic profiling of an experimental baboon model of heatstroke

**Investigators:** Abderrezak Bouchama, Mohammed Dehbi, Aaron Kwaasi Ayodele Alaiya, Mai Al-Mohanna

**Project Description**

The completion of human genome sequence and the recent development of numerous profiling technologies are providing the opportunity of discovering key proteins as biomarkers for a wide range of diseases including heat injury. In this project, we applied the proteomic profiling technology to identify targets that are deregulated during severe heatstroke using our baboon model. Animals were randomly divided into 3 groups: sham-heated group, moderate heatstroke group and severe heatstroke group. Tissue samples were obtained at immediate autopsy (non-survivors) and euthanasia at 72-h (survivors). Liver tissues were homogenized, proteins were separated on 2D-gel electrophoresis and stained. Data were processed with the appropriate software (Bio-Rad).

**Progress**

Our preliminary analysis indicated a total of 38 polypeptides that are differentially expressed between sham and severe heatstroke groups. The identity of these polypeptides and the validation of the data will be the next step. This work was presented as a poster during the Joint 3rd AOHUPO & 4th Structural Biology & Functional Genomics Conference, Singapore (Dec. 4-7, 2006).

**FUTURE RESEARCH DIRECTIONS**

1. **Evaluating novel therapies using the primate models of heatstroke (KACST approved grant; 340,000 SAR for 2 years).** This project is a direct extension of our strategic goals to unravel the mechanisms of tissue injury, organ failure and death in heatstroke. This project consists of a preclinical trial using novel inhibitors of tissue factor/Factor VII, 2 key targets involved in the coagulation cascade. We anticipate that successful molecules will form the basis for human trial. The project was postponed due to outbreak of Mycobacterium bovis.

2. **Brain injury in heatstroke: Study using diffusion MRI, MR-spectroscopy & PET in baboons (KACST approved grant; 1,500,000 SAR for 3 years).** This project will emphasize on the early heatstroke-induced brain alterations in a real time. The project is expected to start soon as baboons become available.
3. Development of an in-house mouse model of heatstroke (RAC approved project). In this project, we will be focusing on the molecular mechanisms governing the inflammatory, tissue injury and death responses in response to severe heatstroke. It will also open avenues to use knockout and transgenic mice technologies. Such information will be extrapolated from rodent to understand the mechanisms in the primate counterpart.

4. Investigating the molecular basis of resistance/sensitivity to heat stress in human volunteers using both genomic and proteomic profiling approaches (This project was approved by the Basic Research Committee but pending for ethical approval). We hypothesize that the application of functional genomics using gene expression profiling, both at the level of transcriptomics and proteomics, will help to identify the molecular basis that underlie the loss of tolerance to heat based on age and gender (i.e. the young, elderly male and female subjects).

PUBLICATIONS


According to estimated given by the World Health Organization (WHO), *Mycobacterium tuberculosis* (MTB) kills 3 million people per annum and there are 8 million new cases each year. One third of the world’s population is infected with MTB and a new person is infected each second. Tuberculosis (TB) is a major health problem in Saudi Arabia and humans as well as animals are infected. The incidence of TB in animals is not known and no efforts have been made in this area to date. In humans the incidence varies from one region to another and reports on incidence rate of TB in Saudi Arabia give a contradictory picture. In Jeddah for instance reports show that the incidence rate is 64 per 100,000. On the other hand in Riyadh the incidence rate is 32 per 100,000. 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: Molecular Epidemiology of Tuberculosis in Saudi Arabia

Investigators: Sahal Al-Hajoj, PhD; Fahad Al-Rabiah, MD, Abdullah Al-Dress, BSc

Project Description

The identification of strains of *Mycobacterium tuberculosis* gives a clearer picture as to which strain is more prevalent in various regions. Detection of the resistance traits to the first or second line of antibiotics will enable the workers in the field to manage and control the infection. Restriction fragment length polymorphism analysis (RFLP) using IS6110 and spoligotyping are specific and sensitive techniques in use to type strains of mycobacterium tuberculosis in Saudi Arabia.

Progress

The project has been completed and one manuscript was submitted to *Journal of Clinical Microbiology*. A final report has been submitted to KACST as well.

Project Title: Fingerprinting of Mono and Multi-drug Resistant TB

Investigators: Sahal Al-Hajoj, PhD, Fahad Al-Rabiah, MD, Sahar Al-Thawadi, MD

Project Description

This project is a direct extension of the work that was started in 2003. In this project, we emphasized on the mechanisms leading to the spread of multi-drug resistant TB. More specifically, we examined whether there are certain strains that are causing the drug resistance, and if so, what is their prevalence, their location across the country, their antibiotic resistance profile and finally, the proportion of imported strains.

Project Title: Molecular Basis of Drug Resistant Tuberculosis in Saudi Arabia

Investigators: Fahal Al-Rabiah, MD, Sahal Al-Hajoj, PhD, Sahar Al-Thawadi, MD

Project Description

The main goal of this project is to extensively evaluate the efficacy of the recently implemented Direct Observed Therapy (DOTS) control program of tuberculosis in Saudi Arabia, and its relationship to other developed countries. This will be accomplished through (a) the molecular analysis of the emergent patterns of drug resistance and, (b) the determination of the rate of transmission versus acquisition of drug resistance, by combining genotyping data with clinical data. To achieve this goal, we propose to identify in Saudi Arabia the frequencies of gene mutations associated with drug-resistance and the distribution of multi-locus Variable Number Tandem Repeat (VNTR) genotypes of drug-resistant strains, based on a national collection of mycobacterium tuberculosis. Obtained results will facilitate the development of a national database in a generalized standard format as a new tool for the adaptation of strategies for controlling the dissemination of Multi-drug resistant TB (MDR-TB) strains in the country. This project will be a cornerstone, and serve as the basis for the institution of a National Reference Center.
Progress

More than 300 isolates have been collected from all over the country. Our preliminary analysis indicated that these strains are mono and multi-drug resistant. Work is still ongoing.

Preparations are underway to start this project.

FUTURE RESEARCH DIRECTION

Epidemiology of drug resistance TB in Saudi Arabia (KACST approved grant). The purpose of this project is to study the drug resistance level in the country.

International Collaborations

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 Guadalupe, Institut of Pasteur de Guadeloupe.
4. Dr. Timothy McHugh, UK, Department of Medical Microbiology, Royal Free University College Medical School, London.

PUBLICATIONS

One of the main activities of the Laboratory Animal Facility (LAF), is to maintain and provide purebred animal species for the research needs of scientists and physicians. The section keeps colonies of mice, rats, hamsters, guinea pigs, rabbits, dogs and baboons. The staff of the section ensures that newly procured animals are taken through strict quarantine procedures and remain healthy.

Apart from satisfying the needs of KFSH&RC, the facility offers services to researchers in other institutions of the Kingdom. Our veterinarians advise animal users on the selection and procurement of animals that are suitable for their respective studies and our staff makes sure that animals are cared for and used in accordance with international guidelines.

The LAF trains scientists, technicians and students in the proper handling, care and use of animals in scientific research. In addition to providing the facilities mentioned above, the facility has laboratories and surgical rooms in which research programs, training courses and international workshops are conducted.

Core Facility

Laboratory Animal Facility

Head of Unit
Ra‘afat M. El Sayed, DVM, MVSc

Members
Falak H. Al-Mohanna, DVM
(on scholarship leave)
Catalino L. Santos
Crisologo J. Caliao (part of the year)
Merfat A. Elyan
Julius D. Mabborang
Wilfredo B. Antiquerra
Rolando G. Monzaga
Pio O. Oliveras
Romy O. Oliveras (part of the year)
Ruben C. Delos Santos
Mona A. Saleh (RC Grant)
CORE SERVICE ACTIVITIES

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

1. Advising on the selection and procurement of the appropriate animals for experiments.
2. Maintaining and providing appropriate animals to various investigators.
3. Training animal users with emphasis on proper handling and care of laboratory animals.
4. Pre and post-surgical cares
5. Housing animals in accordance with the Standard Operating Procedures (SOPs).
6. Veterinary care such as disease prevention, treatment and vaccination.
7. Liaise with the Pest Control section for the euthanasia of harmful and trapped animals.

RESEARCH PROJECTS

The LAF is actively involved in providing and/or collaborating with several investigators at KFSHR as summarized in the following table.

<table>
<thead>
<tr>
<th>Projects</th>
<th>Approved in 2006</th>
<th>Active before 2006</th>
<th>Completed in 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluation of a modified technique of heterotopic heart transplantation in dog &amp; rat (RAC# 2060 019)</td>
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<tr>
<td>Dr. C. Canver (King Faisal Heart Institute)</td>
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<tr>
<td>Metabolic syndrome, diabetes &amp; cognitive decline: effect of dietary components on insulin resistance, hyperlipidemia, Inflammation and cognition in a rodent model (RAC#2060 007)</td>
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<tr>
<td>Dr. K. Collison (Department of Biological &amp; Medical Research)</td>
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<tr>
<td>Synthesis of different radiofluorinated precursors for rapid Production of new PET radiopharmaceuticals (RAC# 2040 027)</td>
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<tr>
<td>Dr. I. Al Jammaz (Department of Biological &amp; Medical Research)</td>
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<tr>
<td>Signaling pathways involved in heatstroke pathogenesis (RAC#2063 013)</td>
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<tr>
<td>Dr. M. Dehbi (Department of Comparative Medicine)</td>
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<tr>
<td>The effect of α adrenergic blockers on the ureter: an in vivo study in the dogs (RAC# 2050 032)</td>
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<tr>
<td>Dr. R. Seyam (Department of Urology)</td>
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<tr>
<td>Coagulation &amp; fibrinolysis response patterns to severe heatstroke &amp; its relation to inflammation &amp; cell injury in baboon model: effect of tissue factors neutralization on outcome (RAC# 2050 012)</td>
<td>√</td>
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<td>Int</td>
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<tr>
<td>Dr. A. Bouchama (Department of Comparative Medicine)</td>
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<tr>
<td>Brain injury in heatstroke: study using diffusion MRI, MR-spectroscopy &amp; PET in experimental baboon (RAC# 2060 003)</td>
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<tr>
<td>Dr. A. Bouchama (Department of Comparative Medicine)</td>
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<tr>
<td>Testing the effectiveness of a prototype vaccine against rheumatic heart disease in baboon (RAC# 2011 036)</td>
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<tr>
<td>Dr. L. Mammo (Department of Biological &amp; Medical Research)</td>
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<tr>
<td>Study Title</td>
<td>Sponsor</td>
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<tr>
<td>Application of technetium-99m (I)-tricarbonyl precursor to label a “mini-peptide” with potential for cancer targeting (RAC# 2040 022)</td>
<td>√ Pro (Department of Biological &amp; Medical Research)</td>
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<tr>
<td>Production of ‘cold kits’ for technetium-99m radiopharmaceuticals (RAC# 2042 001)</td>
<td>√ Pro (Department of Biological &amp; Medical Research)</td>
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<tr>
<td>Photo bio-stimulation: laser effect in wound healing of diabetic &amp; non diabetic rats (RAC# 2020 002)</td>
<td>√ Pro (Department of Biological &amp; Medical Research)</td>
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<tr>
<td>Identification of genes involved in thyroid cancer metastasis by microsurgery analysis of thyroid carcinoma cell line with high metastasis potential (RAC# 2040 012)</td>
<td>√ Pro (Department of Biological &amp; Medical Research)</td>
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<tr>
<td>Study of photodynamic therapy with laser wounds for determination of efficiency in optimum dosimetry &amp; its limitations (RAC# 2020 001)</td>
<td>√ Pro (Department of Biological &amp; Medical Research)</td>
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<tr>
<td>Establishing atrioventricular synchrony in dogs with surgically created complete atrioventricular block (RAC# 2031 019)</td>
<td>√ Col (Department of Cardiovascular)</td>
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<tr>
<td>Maximum tissue temperature &amp; propagation of heat in knee joint &amp; soft tissue after application of ultrasound therapy versus low level laser in dogs (RAC# 2050 020)</td>
<td>√ Col (Department of Physical Therapy)</td>
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<td>Optimization of tunica albuginea free graft for coproplasty: an experimental animal study (RAC# 2031 086)</td>
<td>√ Col (Department of Urology)</td>
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<tr>
<td>Effect of recombinant activated protein C on inflammatory &amp; hemostatic responses in primates from lethal heatstroke: Relation to outcome (RAC# 2020 017 Phase III)</td>
<td>√ Int (Department of Comparative Medicine)</td>
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<tr>
<td>Cellular &amp; molecular mechanisms in cardiac failure using a reversible ovine model (RAC# 2020 025)</td>
<td>√ Col (Drs. M. Qutainah &amp; F. Al-Mohanna)</td>
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<tr>
<td>Early and sustained inflammatory response in experimental heatstroke in baboons: effects of cooling and relation to outcome (RAC# 2020 017 Phase I)</td>
<td>√ Int (Department of Comparative Medicine)</td>
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<tr>
<td>Treatment of heatstroke with glucocorticoids: a study in baboons (RAC# 2020 017 Phase II)</td>
<td>√ Int (Department of Comparative Medicine)</td>
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<tr>
<td>Protein Profiling: understanding the mechanisms of tumor response to therapy in a mouse model (RAC# 2050 014)</td>
<td>√ Col (Department of Biological &amp; Medical Research)</td>
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</table>

Col - collaboration project  Pro - providing animals  Int - internal projects
The Department of Cyclotron and Radiopharmaceuticals
Cyclotron and Radiopharmaceuticals Department performs two distinct functions in the Research Centre. Radiopharmaceuticals manufacturing and radiotracer research.

Radiopharmaceutical manufacturing: Radiopharmaceuticals are the pharmaceutical products that are labeled with radioactive isotopes, and are the key ingredients in practice of nuclear medicine, either for diagnostic imaging or for therapy. C&R Department is the only facility of this kind within the geographical region manufacturing these specialty products. Moreover, C&R Department within the Research Center has been manufacturing several different cyclotron-based radiopharmaceuticals (diagnostics) for over two decades, and has recently added therapeutic products derived from reactor-based isotopes. Of special interest are the radiopharmaceuticals labeled with positron emitting radionuclides as integral components of the most contemporary imaging modality of positron emission tomography (PET). Research Centre was the first in the Middle East to establish a clinical PET center (1995).

Working towards the ultimate goal of comprehensive manufacturing facility, several new products are added at regular intervals. As a result, some 40 nuclear medicine centers in the Kingdom and abroad rely upon products manufactured in the C&R production facility. An obvious requirement for pharmaceutical manufacturing is the adherence to the national and international guidelines of Good Manufacturing Practices (GMP). C&R Department manufacturing protocols are not only designed to adhere to the regulatory requirements, but also follow the ISO 9001:2000 Quality Management System for further quality enhancement.

Radiotracer Research: Radiotracers are the tools for probing at molecular level the biochemical and physiological processes. A well designed molecule labeled with an appropriate radioisotope has the potential to probe specific biological systems in vivo with minimum perturbation of the whole organism. Research Section staff in the C&R Department engages in research and development with an aim to develop radiotracers through hypothesis driven research that entails developing radiolabeling procedures culminating into bioactive molecules tagged with radioisotopes. Active research projects culminates into several publications and presentations at international conferences.
ACCOMPLISHMENTS YEAR 2006

Radiopharmaceutical manufacturing: In the Year 2006, manufacturing activity lived up to its mandate of manufacturing pharmaceutical products conforming to international standard of purity, efficacy and safety. C&R Department measured up to this requirement through adherence to international guidelines of Good Manufacturing Practices (GMP) and the ISO 9001:2000 Quality Management System. Volume of production remained relatively unsatisfactory owing to technical problems with the aging cyclotron. Consequently, products distribution to the user centers remained at less than the traditional level, with considerable decrease in both, volume of production and the revenues. However, installation of the new cyclotron (RDS, 11 MeV) dedicated to production of positron labeled radiopharmaceuticals, along with construction of phase I of the Cyclotron expansion building resulted in reliable and high volume production of PET radiopharmaceuticals.

Expertise and experience in radioisotopes and radiopharmaceuticals manufacturing in the C&R Department continued to be recognized by the International Atomic Energy Agency (IAEA, Vienna). Several expert and consultation missions were assigned to the senior staff in the C&R Department to share their experience with developing countries in the Western Asia region and beyond. Also, a senior scientist has been appointed to co-author a number of manuals in book format for benefit of the cyclotron isotope manufacturers.

Radiotracer Research: The small research group continued to perform radiotracer development, generate new research proposal and the extramural research funds and to publish research results in peer reviewed journals. Specific attention was focused on establishing a Molecular Imaging facility to take advantage of KFSH&RC’s commending position in resources availability and PET imaging.

Highlights of the accomplishments for the year 2006:

Radiopharmaceuticals Production Related:

- 10502 units of radiopharmaceuticals distribution to 40 nuclear imaging centers in the Kingdom and abroad
- SR 5.67 Million in revenues from distribution of radiopharmaceuticals
- 99% process success rate in manufacturing radiopharmaceutical products
- Achieved objectives of the ISO 9001:2000 Quality Management System, including customer satisfaction rate of 95%
- Sodium Fluoride (F-18), a new radiopharmaceutical for bone imaging
- International Atomic Energy Agency (IAEA) activities:
  - A senior scientist appointed as Editor for Proceedings of the International Symposium on Trends in Radiopharmaceuticals.
  - A senior scientist appointed as a Consultant for Establishing Quality Assurance and Good Manufacturing Practices of Medical Radioisotopes and Radiopharmaceuticals in Western Asia Region.
  - A senior scientist appointed as Expert to advise a national laboratory in South Africa on Production and QA/QC of FDG (PET radiopharmaceutical).
  - Participation in a research project to improve isotopes production rate in a cyclotron.
  - A senior scientist appointed to co-author three manuals in book format pertaining to manufacturing cyclotron isotopes and radiopharmaceuticals.
  - Regional training course hosted at the Research Center, attended by 40 national and international delegates.
Cyclotron and Radiopharmaceuticals

Radiotracer Research Related:

- Six active research projects
- SR1.65 Million Grant funds (KACST funded, over 3-4 years)
- Six publications in peer-reviewed journals
- Twelve abstracts and presentations

FUTURE DIRECTIONS

With an ultimate aim of becoming a single source of all radiopharmaceutical needs of the Kingdom, an ambitious project entailing physical expansion of the C&R Department has been initiated. Upon completion of this project, perhaps in year 2008, we expect to achieve our ultimate objective of self-reliance and capacity building for the Nation. Project entails:

- Replacement of the aging cyclotron with a 30 MeV medium energy medical cyclotron
- Installation of Technetium-99m Generators manufacturing plant
- Installation of Cold Kits manufacturing plant
- Construction of Phase II of the Cyclotron Expansion building

In summary, in the Year 2006, C&R Department continued to experience considerable decline in radiopharmaceuticals production activity due to equipment trouble. On the brighter side, research accomplishments remained strong, most notably the seed project for establishing a molecular imaging program and installation and commissioning of the small cyclotron for PET radiopharmaceuticals production.
The utilization of nuclear molecular imaging will be sustained by developing novel, selective and sensitive radiotracers based on sound physiological, biochemical and pharmacological concepts. For this reason our research has focused on radiolabeling bioactive molecules such as peptides, peptidomimetics and drugs and to explore their potential application as diagnostic or therapeutic radiopharmaceuticals. Ideally these target molecules must be labeled with isotopes of natural elements such as C-11, N-13 or O-15. However, the short half-lives of these isotopes place limitations on their application. Nonetheless F-18 has been an excellent substitute for these elements. The replacement of a hydrogen or hydroxyl by F-18 in some cases has resulted in a better radiotracer. These investigations require the development of efficient, fast and simple chemical reactions, optimizing analytical methods and techniques for the product and finally performing the requisite in vitro and in vivo tests including imaging to prove their eventual utility in humans.

Radiohalogenated peptides and drug molecules are potential radiotracers for targeting a gamut of diseases including cancer, infection and inflammation, apoptosis, tissue and organ rejection, diabetes, etc. We have developed several radiohalogenated prosthetic groups based on aromatic, heterocyclic and aliphatic molecules. We have labeled by this method bioactive peptides including bombesin analogs, mimics of somatostatin, “mini” peptides, folate derivatives and drug molecules. These are being evaluated in the appropriate in vitro and in vivo systems.

Additionally, the kinetics of most ligand-receptor interactions favors their radiolabeling with Tc-99m and other short-lived radionuclides such as Cu-64. Radiometal chelates of bioactive peptide conjugates have been synthesized applying various chelation strategies. In vitro and in vivo tests on these complexes are ongoing.

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

Project Project Title: Imaging Pancreatic β-Cell Mass with Radiohalogenated Synthetic Non-Peptide Somatostatin Agonist. KACST (#AT-20-04) Grant, 2001-2004, Extended

Primary Investigator: Amartey JK; Co-Is: Al-Jammaz I, and Parhar RS

Aims

- To synthesize and characterize radiohalogenated ligands based on a pharmacophore selective for the SSTR1.
- To perform radioligand-binding assay on isolated pancreatic islets.
- To perform biodistribution studies in normal and non-obese diabetic (NOD) mice to establish the in vivo distribution profile of the tracer especially the extent of accumulation in the pancreas.
- To perform autoradiographic and histochemical experiments in diabetic animal model to attempt to correlate the number of labeled beta cells per region of interest (ROI) to the accumulated radioactivity.

Progress

- Final report submitted and manuscripts in process.

Figure 1. Confocal laser scanning fluorescent micrographs of isolated mouse islet indirectly labeled for insulin (red) and AL3-FITC (green). The superimposed images are shown in the lower micrograph. Images were acquired using UltraView LCI confocal system (PerkinElmer, USA). Images were processed using Volocity improv® software (Improvision Inc. Coventry, UK).

Project Title: Application of Technetium-99m (I)-Tricarbonyl Precursor to Label a “Mini-Peptide” With Potential for Cancer Targeting. RAC# 2040-022, (2004-2006).

Primary Investigator: Amartey JK; Co-I: Al-Qahtani M

Aims

- Synthesize a peptide-bifunctional conjugate based on the di-imidazole-chelating moiety.
- Prepare a Tc-99m complex of the conjugate using the [Tc(CO)3] core.
- Evaluate the [Tc(CO)3] peptide radiotracer in radioligand receptor binding studies on SSTR using AR42J cell line or rat pancreatic islets.
Progress

- The synthesis and characterization of the Tc(CO)$_3$X$_3$ core was completed.
- Several precursor molecules leading to the chelation group have been prepared.
- Complexation and chromatographic analysis of model complexes was completed.
- The complexation with conjugated peptide and testing completed.

Project Title: Synthesis of Radiofluorinated Precursors for Rapid Production of New PET Radiopharmaceuticals. (RAC # 2040-0027, 2004-2006).

Primary Investigator: Al Jammaz, I; CoI: Amartey JK

Aims

- To develop variety of benzene (hydrophobic) and pyridine (hydrophilic) fluorinated substrates in a fast way.
- To radiofluorinate bioactive molecules and perform in-vitro and in-vivo characterization to determine their potentiality as imaging agents.

Progress

- The cold and radioactive N-succinimidyl-4-fluoronicotinate, isonicotinate (SFP) and fluorobenzoyl hydrazide (FBH) were prepared and characterized.
- SFP and FBH were successfully coupled to folate hydrazide and N-succinimidyl activated folate respectively.

Project Title: Preparation and Characterization of Radiolabeled Bombesin Peptide Analogs for Targeting Human Cancers: A Foundation Stone for Molecular Imaging Program (KACST #AT 25-06, RAC# 2030-058).

Primary Investigators: Al-Jammaz I and Okarvi SM

Co-Investigators: Bin Amer S; Amartey JK

Aims

- To synthesize analogs of bombesin (BBN) peptide containing critical receptor binding sequence but different spacer group between the peptide and the chelating sequence
- To radiolabel these peptides with Tc-99m (SPECT) and F-18 (PET)
- To study in vitro and in vivo characteristics of the radiolabeled peptides using BBN receptor-positive cell lines (e.g. PC-3 and MCF-7).

Progress

- A number of BBN peptide analogs have been synthesized containing different spacer groups.
- Initial experiments of radiolabeling BBN peptide analogs with Tc-99m was achieved by the ligand exchange method in the presence of stannous tartrate.
- Coupling of prosthetic groups with BBN peptides is partially completed.
- Radiolabeling of BBN peptides with F-18 is in progress.
- After radiolabeling, purification and isolation of the desired radiolabeled peptides, in vitro cell-binding characteristics and internalization into breast cancer cells and in vivo experiments of Tc-99m/F-18-labeled BBN conjugates will be performed.
Project Title: Standardized High Current Liquid and Gas Targets for Cyclotron Production of Diagnostic and Therapeutic Radiopharmaceuticals (IAEA# SAU13483, RAC# 2050 027, 2006-2008).

Primary Investigator: Al-Jammaz I
Co-Investigators: Miliebari S, AlYanbawi S, Rahma S, Van-Heerden W

Aims

To increase production yields, specific activity, chemical purity and availability of F-18, N-13, Kr-81 and I-123 radiopharmaceuticals that are used in nuclear medicine by improving the following:

- beam current irradiation
- diagnostic tool for target monitoring during irradiation
- more understanding of in-target chemistry and recovery and characterization of a very expensive enriched material.

Progress

- Different degraders (aluminum and graphite) were fabricated and tested on F-18 targets.
- Beam current was elevated to 38µA without blowing off or damaging degraders. This resulted in better F-18 yield, higher specific activity, less radiation exposure and reliability of FDG production.

Project Title: Brain Injury in Heat Stroke: Study Using Diffusion MRI, MR-Spectroscopy and PET in Experimental Baboon (RAC # 206003, KACST AT-26-42).

Primary Investigator: Abderrezak Bouchama
Co-Investigators: Mohammed Al-Qahtani

Aims

On an experimental non-human primate model of moderate and severe heatstroke that closely replicates human heatstroke, particularly the brain injury. The use of new neuron-imaging techniques such as Diffusion-Weighted Magnetic Resonance Imaging (DWMRI), Magnetic Resonance Spectroscopy (MRS), and (PET) to experimental baboon as follows:

- Test the hypothesis that neurologic injury of heat stroke is due to cerebral ischemia.
- If so, identify susceptible brain regions to ischemia and their time-course until recovery or infraction.
- Investigate whether cellular energy metabolism, cell membranes and neuronal integrity, and inflammation are associated with heatstroke related brain damage.
- And finally correlate the findings with neurologic outcome and mortality.
- Answering these basic questions may add to our understanding, and thereby might help formulate future neuroprotective strategies in heat stroke.

Progress

To commence in 2007.

Project Title: Synthesis and biodistribution of 2-[123I] Iodomelatonin in normal mice (RAC 2050-025, 2005-2006).

Primary Investigator: I. Al-Jammaz

Aim

- To radioiodinate synthetic melatonin by electrophilic method and study the biodistribution in mice.
Progress

- Final report in progress.

FUTURE RESEARCH DIRECTION

The results obtained so far on these projects are encouraging. In the development of the prosthetic groups for radiohalogenation we have successfully prepared compounds labeled with either $^{18}$F or $^{123/125}$I. These have been attached to selected molecules with moderate to high labeling efficiencies. With this technique in hand we are in a position to radiohalogenate specific biomolecules targeting cancer, infection and inflammation, etc. Biological evaluations of some of the promising radiotracers are ongoing to fully establish their utility. Additionally, we continue to explore methods which reduce the radiohalogenation reaction times.

Bifunctional derived radiometal chelating experiments with Tc-99m and other radiometals shall be pursued. In the field of nuclear and radiochemistry the next area of investigation to increase yield would be target re-design and better electroplating to improve cooling during irradiation. Therefore we intend to continue to intensify our efforts in these areas and to develop and produce other short-lived radionuclides to further our overall goals.

PUBLICATIONS


Abstracts and Presentations

2. Expanding the $^{18}$F-fluorination of biomolecules with $^{18}$F-fluoroalkylating agents. M.H. Al-Qahtani, C. Esguerra, J.K. Amartey, 13th European Symposium on Radiopharmacy and Radiopharmaceuticals, March 30-April 2, 2006, Italy.
8. I. Al-Jammaz, Production and Quality Control of radiopharmaceuticals in Saudi Arabia, IAEA Regional Meeting, Dubai, UAE, (March 2006).
The Department of Genetics
The Department of Genetics

The Department of Genetics consists of several research and service units including, Biochemical Genetics, Cardiovascular and Pharmacogenomics, Functional Genomics, Gene Therapy, Mitochondrial Research, Neurogenetics, Population Genetics and Sequencing/Genotyping core facilities. In addition, the Department works closely with Arabian Diagnostic Laboratories, an independent unit to be integrated into the Department in 2007. The Department is also involved in basic/translational research and the provision of molecular genetic services including diagnostic testing for inherited diseases. Central to these functions are the establishment of collaborative programs, technology transfer, education/training, and academic participation through publication and presentation. Some of our achievements in 2006 are highlighted below and are detailed elsewhere in reports from individual research units.

- Externally funded research program in Hereditary Impairment of Hearing – Common genetic cause excluded. Genes identified in several families. Novel genetic basis demonstrated in several families.

- Identification of common mutations underlying disease in 80-95% of patients for 5 metabolic diseases in the Saudi population. Paves the way for prevention rather than early detection and intervention.

- Collaborative program with KKESH in mitochondrial and nuclear gene alterations underlying hereditary vision impairment. Novel genes, mutations and mechanisms identified.

- Re-accreditation of the Arabian Diagnostics Laboratory by the College of American Pathologists.

- Identification of the molecular basis of Severe Combined Immune Deficiency in a large cohort of patients from KFSHRC.

- Original research contributions to aetiology and genetic intervention of thyroid cancer. High impact publications in journals such as Oncogene.

- Mapping of loci underlying more than 5 novel Mendelian diseases.

- Initiation of collaborative research with the Harvard Medical School and the Broad Institute of MIT.

- Over 30 publications in well recognized international journals covering the fields of ophthalmology, oncology, nephrology, neurology, endocrinology, medical genetics and rheumatology.
- Membership of the International Society for Animal Genetics. Recognition of ADL as an accredited laboratory for parentage testing in Arabian and thoroughbred horses

FUTURE DIRECTIONS

A summary of the major objectives for the Department of Genetics in 2007 is presented below:

1. Development/continuation of program based research in hereditary hearing loss, hereditary vision impairment, inherited errors of metabolism, inherited neurodevelopmental disorders, genetic basis of hereditary impairment of immunity, genetics of type 2 diabetes, genetics of autism, genetics of the neuronal ceroid lipofuscinoses, genetics of recessive end stage renal disease, and genetics of neuromuscular disorders.

2. Integration of Arabian Diagnostic Laboratories (ADL) with the Department of Genetics and restructuring of research and service units of the Department of Genetics and ADL.

3. Provision of molecular diagnostics for inherited diseases to KFSHRC via ICIS, measured expansion of such service on a national/regional basis via an E-commerce interface and provision of genomic services on a national/regional basis.

4. Establishment of a polygenic diseases research unit.

5. Expansion of laboratory information management system and staged implementation throughout the Department of Genetics/Research Centre.

6. Establishment of a collaborative program with research units of the Harvard Medical School and the Broad Institute of MIT.
The Biochemical Genetics is a clinical research unit with major interest in the molecular and biochemical characterization of inherited disorders. The favorable standing of the research unit results in the referral of metabolic diseases that enable service to collaborate with a number of extramural institutions. The goals of the Unit are to:

1. Identify patients whom have rare or unusual IEM. and establish useful correlation among the aforementioned parameters.
2. Collaborating with other members in the Department of Genetics to localize genes and establish mutations in those patients with IEM.
3. Collaborates with *In Vitro* Fertilization Unit in performing preimplantation diagnosis.
4. Hosting graduate students in the field of biochemical and molecular genetics.
5. In collaboration with several national institutions, we are investigating the involvement of genetic factors in obesity in Saudi Arabia.

**RESEARCH PROJECTS**

The Biochemical Genetics unit is contributing to the following projects:

- Pre-implantation Genetic Diagnosis for the Most Prevalent Metabolic Disorders in Saudi Arabia.
- Karyotyping for Chromosome Abnormalities in Patients with Autistic Spectrum Disorders.
- Relationship 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.
- Preimplantation Genetics Diagnosis in Saudi Arabia: Parents’ Attitudes
- Molecular Genetic Studies in Chromosome Disorders
- Molecular Characterization of Autism Spectrum Diseases: A Pilot Study for Three Distinct Disorders
- The National Genetic & Birth Defects Registry
- Hunting for One of the Autism Genes that Might be Linked to Osteoporosis with Renal Tubular Acidosis
- Molecular Genetic Analysis of Five Inherited Metabolic Disorders Frequently Encountered in the Metabolic Clinic
- A Molecular Look on Early Infantile Primary Lactic Acidosis: Pilot Study.
Project Title: Pre-implantation Genetic Diagnosis for the Most Prevalent Metabolic Disorders in Saudi Arabia. RAC Project # 2021023

Investigators: Ali Al-Odaib, PhD, Aida Al Aqeel MD, Serdar Coskun PhD, Pinar Ozand, MD PhD, Nadia Sakati MD

Project Description

In the last two decades a large number of genetic diseases have been diagnosed. For some of these disorders effective and non-costly treatment procedures are available. While for most of the others either the treatment is ineffective or very costly. Some diseases in the latter category are encountered frequently. Therefore this project attempts to prevent the occurrence of such disorders by applying the Preimplantation Genetic Diagnosis (PGD) to selected genetic disorders. The following diseases are common in the Kingdom and each pose a major difficulty in its management either due to unrewarding results or due to the cost involved. These diseases are: Propionic Acedimia, Nieman-Pick disease B, Gaucher Disease, Biopterin Dependent Phenylketonuria, Canavan Disease.

Although any neurometabolic disease with a known gene structure and mutations particular to the Kingdom can be selected for preimplantation genetic diagnosis, certain priorities should take precedence to include the disease in the PGD program. These are:

1. It must be a disease that is encountered frequently.
2. It must be a disease that causes significant morbidity requiring life-long intensive treatment.
3. It must be a disease that precludes successful management, leading to eventual neurologic crippling and death.
4. It must be a disease the present treatment modalities are prohibitively expensive.
5. It must be a disease with an identified gene structure and its prevalent mutation known.

Progress

In our previous report we gave in detail the results of the mutation analysis of genes responsible for nieman-pick disease –B, propionic aciduria, and biopterin dependent phenylketonuria.

In this report we are presenting the results of the molecular studies for Gaucher disease and Canavan disease.

Gaucher Disease: Gaucher disease is inherited as an autosomal recessive trait. it is caused mainly by mutations in the GBA Gene. The GBA gene (beta-glucocerebrosidase, glucosylceramidase, acid beta-glucosidase, D-glucosyl-N-acylsphingosine glucohydrolase) is ~7.2–7.4 Kb in size, consists of 11 exons located on the human 1 q21chromosome. Its protein precursor contains 536 amino acids and its mature protein is 497 amino acids long. There are three cases we screened for the mutations. In one of them we found a compound heterozygote mutation on Exon 9 and Exon 10. The other two cases have the same mutation on Exon 10. Followings are the mutations we detected:

1. F397S (cDNA: 1307 T → C) on Exon 9 and L444P ( 6433 T → C) on Exon 10 (COMPOUND HETEROZYGOTE) F397S/L444P
2. L444P ( 6433 T → C) on Exon 10 (L444P/L444P)

Canavan Disease: Canavan-Von Bogaert-Bertrand disease (OMIM 271900) is a progressive neurodegenerative disease. In its typical phenotypic presentation it appears within first few months of
life with hypotonia, later increased reflexes and spasticity, severe developmental delay, macrocephaly, and later on with seizures and optic atrophy. To date there have been more 53 mutations including gross deletions, the largest one with around 92 kb, have been reported. In 2006, we identified a large deletion (~7 Kb) of ASPA gene associated with the mild clinical onset. Our detailed analysis includes the scanning of the all exons and 50-100 bp of exon-intron junctions in the ASPA gene for mutation analysis, RT-PCR, real-time RT-PCR, mtDNA screening for known mutations, whole-genome transcription profiling in fibroblasts using ABI 1700 microarray system, and pathway analysis of microarray data utilizing PANTHER, Pubgene, Pathart, and Pathway Architect.

Results

Long PCR results showed a deletion pattern in the family. Patient has the deletion whereas father, mother and brother are carriers. These finding were confirmed by RT-PCR experiments. In addition, the investigation of the mitochondrial DNA showed no point mutations and deletions associated with the following mitochondria diseases: MELAS, MERRF, NARP, cardiomyopathies, LHON, Kearns-Sayre, CPEO, Pearson Marrow/Pancreas Syndrome.

Our microarrays results indicates that ASPA gene and as well as some of the lysosomal genes were significantly down-regulated in the patient’s fibroblasts. Some of these genes may involve in the cause of brain edema. We recently work on the confirmation of our microarray results, performing enzyme assay on the fibroblasts and determining the exact location of the mutation on genomic DNA using long inverse-PCR technique.

Project Title: Leptin Level, Leptin Receptor Gene Polymorphism and Reproductive Hormones in Saudi Females with Polycystic Syndrome

Investigators: Maha Daghestani, PhD, Ali Al-Odaib PhD, Pinar Ozand MD, PhD, Ahmed Al-Himadi PhD

Project Description

This study was designed to investigate changes in leptin levels and its relationship to some hormonal changes (neuropeptide Y, insulin, FSH, LH, E2, progesterone, testosterone, androstenedione and SHBG), metabolic and anthropometric parameters associated with PCOS in lean, overweight and obese patients when compared to lean, overweight and obese normal controls.

Progress

Overall, leptin levels among lean, overweight and obese patients with PCOS did not differ significantly from those in the control groups (13.650±3.15, 23.794±6.401, 41.06±14.157 vs. 13.650±3.150, 22.60±6.004, 46.044±20.580 ng/ml respectively). Leptin level was remarkably increasing with increased body weight. Leptin is correlated with many variables in the study groups, the strongest correlation was found between leptin and BMI in lean, overweight, obese control groups (r = 0.81, P<.0001 r = 0.78, P<.0001 and r = 0.48, P<.0001 respectively) as well as overweight and obese patients with PCOS(r = 0.5, P= 0.0003 and r = 0.6, P= 0.01 respectively ).

Women with PCOS and obese normal women have an increased risk of cardiovascular disease. They exhibit an abnormal lipid profiles characterized by significantly raised serum concentrations of triglyceride, cholesterol and LDL and reduced serum level of HDL.

Comparing the PCOS patients group with BMI-matched groups revealed significantly higher circulating fasting insulin, glucose, LH, E2,
testosterone and serum androstenedione. The levels of insulin, \( E_2 \), testosterone and serum androstenedione show increased trend toward greater weights whether they were PCOS patients or they were normal subjects.

The progesterone and SHBG levels were generally lower among the PCOS patients. Also, it was noted that there were apparent gradient decline of the progesterone and SHBG levels among the normal females with increased body weight.

The control that was exerted by leptin on hypothalamic NPY cannot be seen in peripheral blood and no difference in serum NPY concentrations was detected between the lean, overweight, obese patients with PCOS and the control groups.

Analyzing the leptin receptor gene by sequencing samples from 90 well-characterized patients with PCOS revealed previously identified amino acid variants in exons 4 (Lys109Arg), 6 (Gln223Arg) and 14 (Lys656Asn), a silent mutation T→C at position 1029 (Ser343 Ser) of exon 9, a silent mutation (A→C) at position 3057 (Pro 1019 Pro) of exon 20, variants at position 31 (C→T) and at position 70 (T→C) of exon 1, intronic variants at position 120 (C→T) of intron 1, at position 1546 (A→G) of intron 3 and at position 37 (A→C) of intron 19, as well as the pentanucleotide insertion in the 3′-untranslated region (3′-UTR). The allele frequencies of these polymorphisms did not all differ from those in the general population, as assessed in 122 female controls. Though, the reduction was occurred in allele frequency of exon 6, intron 19 and 3′-UTR of obese patients with PCOS as well as exon 14 and intron 3 of lean patients with PCOS.

Our study revealed some differences in allele and genotype frequencies of different polymorphism which were obtained in different BMI of control groups. The allele frequency of the insertion allele (+) of 3′UTR was significantly higher in overweight (0.353) and obese females (0.322) compared to the frequency in lean females (15.6). The results of this study show that the insertion allele was associated with elevated insulin level in obese group. For the Q223R polymorphism in exon 6, the result shows that the highest frequency of Arg/Arg homozygotes and Arg/Gln heterozygotes were recorded among obese subjects (22.11%, 52.63% respectively), also the obese subjects had the highest Arg allele frequency among lean and overweight groups. Furthermore, the genotype (C/C, C/A) and the allele (C) frequencies of intron 19 polymorphism increased significantly in obese control group.

Several anthropometric measurements, metabolic and hormone variables associated with polymorphisms in LEPR gene. The LEPR gene polymorphisms were found to be associated with LH level in PCOS patients. Thus, the present study may indicate that LEPR polymorphism might alter the LH levels and result in reproductive disorders.

**Project Title:** Relationships between serum resistin and leptin levels, body mass index, lipid profile, polymorphisms in the resistin gene promoter and leptin receptor gene in obese Saudi children

**Investigators:** Maha Dagestani Maha PhD, Ali Al-Odaib Ali PhD, Namig Kaya PhD, Abdullh Al-Herbish MD, Ali Al-Zahrani MD, Rawdah Sunbul MD

**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 beings. C/G polymorphism in the promoter of resistin gene is associated with BMI in obese subjects; also Variations in the leptin receptor gene locus could be involved in the regulation of body weight. We aim to explore the relationship between serum resistin and leptin levels 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.

In Saudi Arabia, no studies have investigated the correlation between serum leptin levels and resistin hormone levels in lean overweight and obese children and no studies have been done on the leptin receptor gene or resistin gene of Saudi children. Hence this project is designed to investigate these parameters. The main goals of this project are:

1. To evaluate interactions among leptin and resistin hormones in lean overweight and obese children.
2. To investigate the association between Resistin, leptin levels and certain parameters associated with metabolic syndrome and anthropometry.
3. To evaluate the associations between body composition variables and four common leptin receptor polymorphisms (K109R, Q223R, and K656N) and C/G in promoter of RETN gene.
4. To investigate the possible carbohydrate and lipid profile abnormalities in obese children.
5. To study the variable of Anthropometric measurements in obese children.

**FUTURE RESEARCH DIRECTION**

We are completing the pre-implantation genetic diagnosis for the most prevalent metabolic disorders in saudi arabia projects. We are expecting a significant progress on the fine characterization of the deletion mutation in Canavan disease. We will focus on conducting the biochemical determination of the concentration of ghrelin hormone in lean and obese Saudi females with polycystic ovary in comparison to normal lean and obese females. As well, we are planning to complete the screening of all 21 exons, the 5'UTR and 3'UTR of INSR gene and 300bp of β2-Adrenergic Receptor. In collaboration with the Department of Neurosciences, we are submitting a new project titled: Clinical, Histopathological, Biochemical and Molecular characteristics of Neuronal Ceroid Lipofuscinosis (NCL) in Saudi Arabia. The main goal of this project is to Retrospective and prospective clinical, Epidemiological, Biochemical, and Molecular in-depth study of cases diagnosed with NCL since 1997 and new cases presenting with the major or minor form of NCL with positive inclusion material.

**Recent Articles**


**Progress**

We are in process of recruiting subjects for this project. Concurrently, we are optimizing the biochemical analysis of insulin, glucose, lipid profile, resistin, and leptin hormones in the selected cases and controls.
The Cardiovascular and Pharmacogenetics Unit endeavours to understand the role genetic variations in the manifestation of cardiovascular diseases and in the intraindividual differences in patient responses to drug therapy of these disorders. Currently, we are focusing on two areas of interest (a) employing whole genome approach to discover genes associated with cardiovascular syndromes and disorders including familial hypertrophic cardiomyopathy, Long QT syndrome, Brugada and Sinus sick syndrome and (b) association of single nucleotide polymorphisms (SNPs)/haplotypes with manifestation and/or patient responses to drug treatment of hyperlipidaemia and hypertension.

For the current report period, we partially determined the prevalence of SNPs and evaluated possible association of intra-individual patient responses to antihyperlipidaemia therapy with simvastatin (20 mg/day) with some SNPs in 5 genes, the 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), cholesteryl ester transfer protein, sterol-regulatory element binding protein (SREBP-2), cleavage-activating protein (SCAP) and cytochrome P450 subtype 3A4 (CYP3A4). Thus far, we found 5 novel and 3 familiar SNPs in the studied regions of the HMGCR gene in the Saudi population. Among these, the rs3846663 was significantly associated with lack of decrease in triglycerides (TG) (p<0.025), and the rs17238540 with the manifestation of hypercholesterolaemia (p<0.001) and possibly differential responses to simvastatin therapy. In another study investigating the role of CYP3A4 gene variants, carriers of the wild type A/A allele of the rs2740574 exhibited greater reduction in total cholesterol (Chol) (5.3±0.11 vs 4.7±0.11; p<0.001) and in low density lipoprotein (LDL) (3.3±0.10 vs 2.9±0.08; p<0.001), compared to heterozygous A/G carriers. Homozygote C/C carriers of the rs12721620 showed significant reduction in Chol (5.2±0.10 vs 4.6±0.10; p<0.001) and in LDL (3.3±0.09 vs 2.8±0.08, p<0.001) compared to the heterozygote C/T. However, linear regression analysis suggested an association of the heterozygote with reduction in triglycerides (TG) (P≤0.041) and Chol (P≤0.032), pointing to this SNP as a potential predictor of TG and Chol responses to simvastatin treatment. In the studies involving the SREBF-2 C/G (rs4822063) and SCAP C/T (rs12487736), an increase in HDL was observed which was greater in subjects homozygous for the C or T alleles when compared with C/T heterozygotes (10.8±5.8 and 8.0±6.4 respectively vs −2.2±9.3, P=0.030), indicating that the SCAP C/T polymorphism is a significant predictor of the HDL response to simvastatin treatment (P=0.014). In conclusion, the association studies so far suggest potential relevance for some SNPs in candidate genes, which promise to be of clinical value when validated in larger population studies.
RESEARCH PROJECTS

Project 2010020: Evaluation of the Relevance of Single Nucleotide Polymorphism for Coronary Artery Disease in the Saudi population

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

Project Description

This study aims at identifying SNPs and haplotypes in candidate genes for the risk of CAD using the Saudi population as a study model. The study consists of two parts (a) identification of SNPs and/or haplotypes in the general population (b) establishment of the relevance of haplotypes for the manifestation of coronary artery disease and its risk factors such as hyperlipidaemia and hypertension in the Saudi population.

Progress

Identification of novel SNPs has been partially accomplished in a number of candidate genes including the β2-adrenergic receptor, cholesteryl ester transfer protein, lipoprotein lipase, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, and association studies of the discovered SNPs with disease manifestation are currently underway.

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

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

Project Description

This study aims at identifying mutations in candidate genes for intra-individual differences in patient responses to drug therapy of hypercholesterolemia and hypertension using the Saudi population as a study model. We will first identify SNPs and/or haplotypes in the selected genes and then establish their role in patient responses to antihypercholesterolemia treatment with statins (lipid lowering agents) and hypertension therapy with losartan in a population of about 3,000 Saudi patients.

Progress

We have already identified some SNPs in several candidate genes and performed association studies of statin therapy for the 3-hydroxy-3-methylglutaryl-coenzyme A reductase, sterol-regulatory element binding protein, cleavage-activating protein and cytochrome P 450 subtype 3A4 genes and losartan therapy for angiotensin receptor subtype II. This process is ongoing in larger numbers, and efforts are underway to identify possibly haplotypes of interest for further studies.

Project # 2050035: Clinical and Molecular Characterization of Patients with Inherited Arrhythmogenic Disorders

Investigators: Zohair Al-Hasnain, Nduna Dzimiri, Salma Majid and Brian Meyer

Project Description

This study aims at identifying genes responsible for inherited arrhythmogenic disorders in the Saudi population. This information should serve a number of clinical objectives including confirmation of diagnosis stratification of patients...
and prophylactically purposes in the management of patients with arrhythmogenic disorders.

**Progress**

Patient data collection and target gene identification procedures are underway for the LQT syndrome, Brugada and Sinus sick syndrome.

**FUTURE RESEARCH DIRECTION**

We hope to discover new genes that can be utilized for diagnostic purposes and haplotypes that may be useful toward individualization of medication in the treatment of various cardiac disorders.

**PUBLICATIONS**

**Full-length papers**


**Abstracts**


Gene Therapy Unit is currently conducting experimental gene therapy research of thyroid cancer, elucidating molecular defects leading to thyroid tumorigenesis, microarray analysis of gene expression profiles to identify molecular markers involved in thyroid cancer progression and metastasis for future diagnosis and gene therapy. Significant progress has been made on every front. We demonstrated that IL-12 induced cannabinoid receptor 2 (CB2) expression, which could be used as a target for future therapeutic intervention. We have successfully completed the project of microarray analysis of genes involving thyroid cancer metastasis, and identified S100A4 as a marker for tumor metastasis and provided the proof of concept in its therapeutic potential by knock-down of its expression via RNA interference. Furthermore, we investigated BRAF mutation in thyroid carcinoma from Saudi population. BRAF V600E mutation was detected in 17 of 41 papillary thyroid carcinomas (41.46%), and all 3 anaplastic thyroid carcinomas. The mutation was associated with lymph node metastasis and poor prognosis.
RESEARCH PROJECTS

Project Title: IL-12 Gene Therapy of Anaplastic Thyroid Carcinoma (RAC #2030057)

Investigators: Yufei Shi, Ali Al-Zahrani , Ranjit S. Parhar, Minjing Zou

Project Description

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

Progress

Previously, we demonstrated that tumorigenicity of anaplastic thyroid carcinoma cell line ARO was significantly reduced following interleukin 12 (IL-12) gene transfer in nude mice. We suspected that tumor target structure in ARO/IL-12 cells might be changed as a result of IL-12 expression and such a change may make them more susceptible to be killed through mechanisms apart from NK-dependent pathway (Human Gene Therapy, 14, 1741, 2003). To identify genes involved in the change of tumor target structure in ARO/IL-12 cells, we examined gene expression profile of ARO and ARO/IL-12 by microarray analysis of 3757 genes using Atlas Glass Human 3.8 II microarray. The most highly expressed gene is cannabinoid receptor 2 (CB2), which is expressed 8 fold higher in ARO/IL-12 cells than ARO cells. CB2 agonists such as JWH-133 and JWH-015, and mixed CB1/CB2 agonist WIN-55,212-2 can induce significantly higher rate of apoptosis in ARO/IL-12 cells than ARO cells. Similar results were obtained when ARO cells were transfected with CB2 transgene (ARO/CB2). A considerable regression of thyroid tumors generated by inoculation of ARO/CB2 cells was observed in nude mice following local administration of JWH-133 at 50 µg/day. We also demonstrated significant increase in the induction of apoptosis in ARO/IL12 and ARO/CB2 cells following incubation with 15 nM paclitaxel, indicating that tumor cells were sensitized to chemotherapy following CB2 overexpression. These data suggest that CB2 overexpression may contribute to the regression of anaplastic thyroid tumor in nude mice following IL-12 gene transfer. Given that cannabinoids have shown antitumor effects in many types of cancer models, CB2 may be a viable therapeutic target for the treatment of anaplastic thyroid carcinoma.

The project is currently funded by a grant from KACST (AT 24-11) for three years (2005-2008).

Project Title: Microarray Analysis of Metastasis-Associated Gene Expression Profiling in a Murine model of Thyroid Carcinoma Pulmonary Metastasis (RAC #2040012)

Investigators: Yufei Shi and Minjing Zou
Project Description

Tumor cell invasion and metastasis are the hallmark of malignant neoplasm. Despite advances in the management of thyroid carcinoma and other solid tumors, the development of metastasis continues to be the most significant cause in cancer mortality. In order to gain new insights into this complex process in thyroid carcinoma, we established a thyroid carcinoma cell line with high metastatic capacity. Global patterns of gene expression were analyzed in cell lines with high and low metastatic capacity. We hope to identify genes involved in thyroid metastasis and the information could be used as biomarker to predict the prognosis and potential target for gene therapy.

Progress

We previously identified S100A4 as a significant contributor in thyroid cancer metastasis by microarray analysis (J Clin Endocrinol Metab.89: 6146-6154, 2004) and immunohistochemistry (British J Cancer 93:1277-1284, 2005). To evaluate whether S100A4 gene can be targeted for therapeutic purpose, we examined the effects of S100A4 gene expression knockdown by RNA interference on the growth and metastasis of human anaplastic thyroid carcinoma cells in BALB/c nude mice (nu/nu). A plasmid construct was made that expressed small hairpin RNA (shRNA) specific for S100A4 (targeting exon 2 of S100A4 mRNA). The construct was stable transfected into the human anaplastic thyroid carcinoma cell line ARO (ARO/S100A4-shRNA). Quantitative real-time RT-PCR analysis showed that the S100A4 expression was reduced by 71.3% ± 4.7 in ARO/S100A4-shRNA cells as compared to control cells expressing shRNA specific for green fluorescent protein (ARO/GFP-shRNA). The growth rate of ARO/S100A4-shRNA cells was reduced by 46% ± 7.6 compared to the ARO/GFP-shRNA control in a cell proliferation assay. Moreover, cell cycle analysis showed increased G2/M accumulation in ARO/S100A4-shRNA cells. Tumor formation and growth induced by subcutaneous injection of 5 x 10⁶ ARO/S100A4-shRNA cells into the nude mice were significantly reduced and no tumor metastasis was found in any of the mice. The in vitro invasive potential of ARO/S100A4-shRNA cells was reduced by 90% when compared to ARO/GFP-shRNA cells. These data suggest that reduction of S100A4 by RNA interference is a viable approach to inhibit tumor growth and metastasis. Given that S100A4 is overexpressed in many kinds of tumors, the current study provides the proof of concept in its therapeutic potential and warrants further development.

Project Title: Investigation of Mitochondrial DNA Mutations in Human Thyroid Carcinomas (RAC #2040019).

Investigators: Khaled K Abu-Amero, Ali Al-zahrani, Minjing Zou, Yufei Shi

Project Description

Although thyroid carcinoma represents 1% of all malignant diseases it is the most common malignancy of the endocrine system, accounts for the majority of deaths from endocrine cancers. As in most solid tumors, the malignant transformation of thyroid epithelial cells is thought to arise through multiple genetic changes involving the activation of proto-oncogenes and the loss of tumor suppressor genes by point mutation, deletion, and gene rearrangement. Significant progress has been made to elucidate the molecular mechanisms that determine thyroid tumor development and progression. However, most investigations have mainly focused on the alterations of nuclear DNA. The alterations of mitochondrial DNA (mtDNA) has received much less attention, even though higher copy numbers of mitochondria have been found in thyroid carcinoma and the
mutational rate of mtDNA is at least 10 times higher than nuclear DNA due to its continuous exposure to high levels of reactive oxygen species generated during oxidative phosphorylation and lack of efficient DNA repair mechanisms. In the present study, we plan to investigate thyroid tumors and tumor cell lines for mtDNA mutation.

**Progress**

We previously detected high frequency of somatic mitochondrial gene mutations in both benign and malignant thyroid follicular tumor specimens (Oncogene, 24:1455-1460, 2005) and germline mutations in medullary thyroid carcinoma (Oncogene, 25:677-684, 2006). To gain a full spectrum of mtDNA mutation in this group of patients, we are currently screening the same tumor DNA for mtDNA common deletion. Preliminary data showed that the common deletion was present in both normal and tumor specimens, although it appears more frequent in tumor tissues as compared to normal controls.

**Project Title: Investigation of BRAF Mutation in Thyroid Carcinoma from Saudi Population (RAC #2050 048).**

**Investigators:** Minjing Zou, Essa Y Baitei, and Yufei Shi

**Project Description**

*BRAF* is a serine/threonine kinase that serves as an immediate downstream effector of RAS in the RAS-RAF-MEK-ERK-MAP kinase-signaling cascade. Oncogenic mutations in *BRAF* are common in human cancers and nearly all of which are the T1799A transversion in exon 15 of the gene, resulting in V600E mutation (previously named V599E) in the protein. This mutation is believed to produce a constitutively active kinase by disrupting hydrophobic interactions between residues in the activation loop and residues in the ATP binding site. Activating *BRAF* mutation in papillary thyroid carcinoma (PTC) has recently been reported in many studies ranging from 28% to 83%. The *BRAF* mutation has not been studied in the Arab population. We plan to investigate *BRAF* mutation in thyroid cancer from Saudi population.

**Progress**

We investigated *BRAF* mutation from 63 thyroid tumors from Saudi Arabia: 10 multinodular goiters, 41 papillary thyroid carcinomas (PTC), 5 follicular variants of PTC (FVPTC), 2 follicular thyroid carcinomas (FTC), 2 Hürthle cell carcinomas, and 3 anaplastic thyroid carcinomas (ATC). *BRAF*V600E mutation was detected in 17 out of 41 PTC (41.46%), and all the 3 ATC (100%). No mutation was found in 10 multinodular goiters, 5 FVPTC, 2 FTC, and 2 Hürthle cell carcinomas. There is higher frequency of *BRAF* mutation in classic PTC patients with stages III and IV tumors (9/14, 64.29%) as compared to those with stages I and II tumors (8/27, 29.63%) (*P*<0.05, Fisher’s exact test). Among 8 stages I and II patients with *BRAF*V600E mutation, 6 had local lymph note metastasis (75%), whereas in those 24 stages I and II tumors without *BRAF* mutation, 10 had local lymph note metastasis (41.67%). In total 31 patients with lymph note metastasis, 15 had *BRAF* mutations in their tumors (48.39%), whereas in the remaining 15 patients without lymph note metastasis, only 2 were found to have *BRAF* mutations (13.33%). The difference was statistically significant (*P*<0.05). *BRAF* mutation was also found to be associated with older age (*P*<0.05). Interestingly, *BRAF* pseudogene transcripts were detected in 3 of 10 (30%) multinodular goiters, 17 of 41 (41.46%) PTCs, and 1 of 5 (25%) FVPTCs. There was higher detection frequency of pseudogene transcripts in tumors without *BRAF* mutation (14/21, 66.67%) than those with *BRAF* mutation (7/21, 33.33%) (*P*<...
These data suggest that \textit{BRAF} mutations are specific to classic PTC and contribute to the disease progression to poorly differentiated and anaplastic carcinoma. It remains to be determined whether \textit{BRAF} pseudogene transcripts play a role in thyroid tumor development.

**FUTURE RESEARCH DIRECTION**

We plan to start \textit{in vivo} experimental IL-12 gene therapy for thyroid cancer using recombinant IL-12 adenovirus as soon as we receive nude mice. We will try to complete the mitochondrial project and continue the newly initiated \textit{BRAF} project.

**PUBLICATIONS**

In the past few years, mitochondrial defects have been implicated in a wide variety of degenerative diseases, aging and cancer. Most mitochondrial diseases occur in tissues that have high-energy requirements such as heart, muscle, the renal and the endocrine system. These diseases display wide variety of phenotypes. Studies on patients with these diseases have revealed much about the complexities of mitochondrial genetics, which involves an interaction between mutations in the mitochondrial and nuclear genomes. The essential role of mitochondrial oxidative phosphorylation in cellular energy production, the generation of reactive oxygen species, and the initiation of apoptosis have suggested a number of novel mechanisms for mitochondrial pathology. However, the exact pathophysiology of mitochondrial diseases remains to be elucidated. Mitochondrial diseases never been investigated in Arab population before and the pattern of mitochondrial DNA (mtDNA) mutations or nuclear mutations influencing the mitochondrial functions are largely unknown. The main objective of this unit is to research into the pathology of mitochondrial disorders common in Saudi population.
RESEARCH PROJECTS

1. Investigation of the Role of Mitochondrial DNA Variations in the Expression of Late Normal Tissue Complications Following Radiotherapy (RAC # 2040 025).
4. Molecular Genotyping of Arab Patients with Various Optic Neuropathies (RAC # 2040 008).
5. Clinical, Molecular and Biochemical Characterization of Various Mitochondrial Disorders in Saudi Patients (RAC # 2050 028).
6. Investigation of Mitochondrial DNA Mutation in Human Thyroid Carcinoma (RAC # 2040 019).

FUTURE RESEARCH DIRECTION

The Mitochondrial Research Laboratory will continue investigating mutation of the mitochondrial genome as a marker or cause of optic neuropathies, myopathies and other disorders. In addition familial studies will be performed to identify mutations in nuclear encoded mitochondrial proteins that result in dysfunction and disease. Particular attention will be given to recessive disease likely to be more prominent in consanguineous populations such as that present in Saudi Arabia.

PUBLICATIONS

Research Articles

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

Altogether neurogenetic, physiatric 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 Peninsula. Our long-term goal is to translate this genetic work into biological research directed towards the understanding the pathophysiology of neurogenetic diseases.

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

Project Title: Positional Cloning of Genes Underlying Genetic Disorders with Prominent Neurodevelopmental Manifestations in Several Extended Families. RAC 2060 035

Investigators: Namik Kaya, PhD (PI)
Moeen Al-Sayed, MD

Project Description

The specific aim of this project is to determine gene/s or regions that are critical and likely to play role on the manifestations of genetic disorders with prominent neurodevelopmental features. We will be utilizing high density 500K Affymetrix SNP genechips to perform genotyping, aCGH, and mapping studies on the patients.

Progress

The project is recently submitted to RAC and we are waiting for the approval.

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

Investigators: Namik Kaya, PhD (PI), Pinar Ozand, MD, PhD, Nadia Sakati MD, Mehmet Inan, PhD, Dilek Colak, PhD, Ali Al-Odaib, PhD, Naji Al-Dosari, PhD, Claudia Walter, PhD

Project Description

The specific aim of this project is to identify chromosomal abnormalities of patients clinically suspected to have a chromosome disorder.

Project Title: Hunting for an Autism Gene in Patients with Osteopetrosis and Renal Tubular Acidosis. PSCDR 02-R-0029-NE-02-AU-1

Investigators: Namik Kaya, PhD (PI), Pinar Ozand, MD, PhD, Brian Meyer, PhD, Nadia Sakati, MD, Dilek Colak, PhD, Ali Al-Odaib, PhD, Mehmet Inan, PhD, Michael Nester, PhD

Project Description

The specific aim of this project is to identify autism related gene/s or regions in patients who osteopetrosis with renal tubular acidosis (OPRTA) and autism. This is a disease almost only encountered in Saudi Arabia and shows only one mutation regardless the ethnic origin indicating a forefather effect. Using the Affymetrix genechip technology we will be able to identify the genomic gross changes at the DNA level and identify regions likely to involve in autism. The OPRTA patients are subdivided into three groups: 1) with normal mentality, 2) with mild/moderate mental retardation and 3) with pervasive developmental disorder/autism. The genetic signatures in these three groups are studied by ABI 1700 and Affymetrix system. Appropriate age and sex matching controls are subjected to the same studies.
**Project Title: Molecular Characterization of Autism Spectrum Diseases: A Pilot Study for Three Distinct Disorders. RAC Project # 2040-024**

**Investigators:** Namik Kaya, PhD (PI), Mehmet Sait Inan, PhD, Pinar Ozand, MD PhD, Nadia Sakati MD, Dilek Colak, PhD, Ali Al-Odaib, PhD, Omer Demirkaya, PhD

**Project Description**

This is a pilot study to test the hypothesis that the individual disorders existing in the autism spectrum might share disturbed molecular and physiological pathways. For this purpose we have selected several disorders within the autism spectrum diseases phenotypically different but all of which manifest autism. These are Fragile-X with autism, rett syndrome, osteopetrosis with autism, and very early and severe infantile autism. The aforementioned hypothesis will try to determine common gene/s among these four types of the diseases.

**Progress**

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 a few genes that are common among the autism spectrum diseases. One of these genes is involved in chromosome inactivation and imprinting and severely down-regulated among all the autistic patients (regardless of having fragile-X or rett or osteopetrosis).

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

**Primary Investigators:** Mohammad Al-Owain, MD, Namik Kaya, PhD

**Co-Investigators:** Pinar Ozand, Khaled Abu-Amero, Ali Al-Odaib, Mehmet S. Inan, Abdulghani Tbakhi, Dilek Colak, Zuhair Al-Hasnan

**Project Description**

This study aims to establish the sequence of pathological events in early infantile lactic acidosis patients. This will be achieved by serially studying the apoptosis and the derangement of the nuclear/mitochondrial oxidative phosphorylation (OXPHOS) genes and their transcription profiling in such infants. For the microarray analysis we will be using ABI 1700 system to determine the gene signatures in whole blood and identify key genes unknown to participate in the nuclear / mitochondrial dialogue for this disease.

**Progress**

We are in the phase of collecting clinical samples.

**Project Titles (Collaborations)**

- Molecular and biochemical characterization of mitochondrial encephalomyopathy among Saudi patients (Dr. Namik Kaya, Co-I)
- Mitochondrial defects in Arab patients with various optic neuropathies (Dr. Namik Kaya, Co-I)
- Relationship between serum resistin and leptin levels, body mass index, lipid profile, polymorphism in the resistin gene promoter and leptin receptor gene in obese Saudi children. (Dr. Namik Kaya, Co-I)
- Towards the understanding of sperm role in fertilization and early embryonic development: A Pilot Study (Dr. Namik Kaya, PI)

FUTURE RESEARCH DIRECTION

We have made a significant progress on the determination of the gene signatures in some of autism spectrum disorders. We are in the process of finalizing our project and working on manuscripts. We have established a cutting-edge NeuroGenetics Lab and recently submitted a new project focusing on the positional cloning of genes underlying genetic disorders with prominent neurodevelopmental manifestations. We put a special emphasize on the identification of chromosomal abnormalities that have implications in dysmophia, mental retardation, and some other diseases and disorders likely to involve nervous system. Our main goals for the establishment of this unit is a) to create basic and clinically applicable basic research projects that will focus on the determination of genes, their expression profiles, identifying the critical SNPs and disease related markers b) to train graduate students and postdoctoral students, and create opportunities to pursue their degrees c) to establish a comprehensive database for these diseases. We also would like to focus on the recently approved projects, collect data according to our proposals, and finally publish our results well-known journals in our field.

PUBLICATIONS

Recent Articles

3. Shen T, Kaya N, Zhao F, Cao Y, and Heress H. Co-expression patterns of the neuropeptides vasoactive intestinal peptide and cholecystokinin with the transduction molecules alpha-gustducin and T1R2 in rat taste receptor cells. Neuroscience. 130(1): 229-238. 2005
**Recent Abstracts and Presentations**


Our mission is to elevate the quality of genetics and genomics studies in research and clinical medicine.

Human Genetics and Genomics studies have improved significantly during the past several years. This enabled us to obtain the genetic maps, genetic signature, array based chromosomal analysis, SNP analysis and DNA sequence of many genetic disorders in the Kingdom. Unfortunately, Saudi Arabia has an inordinately large number of genetic diseases; particularly autosomal recessive diseases are encountered more frequently than in the west. This probably is due to consanguineous marriages that have been the custom for many years and to a founder effect.

In order to achieve our goal, we designed several projects that will help us to understand and explore the impact of genetics on public health, education, and disease prevention. These projects will help us to appreciate the role of genetic diversity within the Saudi population.
RESEARCH PROJECTS

Project Title: The National Genetic and Birth Defect Registry

Project Description

The Arabian Peninsula, particularly Saudi Arabia, holds a special place in the world as far as inherited diseases are concerned. No reliable data are available for their prevalence. However in some instances it may be 40-80 times higher than any other country in the west. This project was established to register dysmorphic patients, chromosome abnormalities, patients with inherited metabolic diseases as well as children with diverse inherited neuro-metabolic diseases.

It is coordinated by collaboration between the Department of Genetics and the Department of Biomedical Statistics and Scientific Computing. This proposal was a one year pilot project since eventually the registry will be performed on a long-term basis. Eventually all the existing patients in the genetic and metabolic clinics will be entered into the database retrospectively as well as all new patients identified will be tabulated prospectively. As other hospitals start participating into the programs, and as the neonatal screening program is initiated, the all new patient data will be tabulated at the end of an extension of this proposal.

All patients encountered in the clinics of genetics/metabolic diseases and neuro-degenerative diseases were entered into a database starting the approval of this project in middle June 2003.

First, all patients with genetic diseases encountered within the system of KFSH & RC were entered. The patients were classified as Saudis and non-Saudi Arab patients. Other ethnic groups such as, Pakistanis, Indians, etc. were not entered into the registry.

After these efforts are initiated, it is anticipated that the patients with inherited diseases from the pediatric endocrinology and gastro-enterology clinics will also be registered. The KFSH & RC receives only a minor fraction of inherited pediatric hematology cases. Therefore, no attempt will be made to register them. There are twelve genetic disease clinics per week and thirteen pediatric neurology clinics at KFSHRC. Initially, six clinical interviewers were attended the clinics in KFSH&RC. Most genetic cases were seen in the clinics, and the registry activity was confined there. Those patients that are admitted were sick children and were usually also followed up in the clinics. If an admitted patient expires without a clinical follow up, the clerk is notified and the information is tabulated in the registry sheet.

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Project Title: Preimplantation Genetic Diagnosis in Saudi Arabia: Parents’ Experiences and Attitudes King Faisal Specialist Hospital and Research Center. Project# 2041078

Investigator: Dr. Ayman Al-Sulaiman, Dr. Ali Al-Odaib

Project Description

At the present time prenatal diagnosis is available for severe genetic abnormalities in Saudi Arabia. However no intervention if a serious abnormality is detected except abortion. Recently, King Faisal Hospital and Research Centre offers the Preimplantation Genetic Diagnosis (PGD) for this purpose, which is in compliance with the Sharia regulations. The extent to which PGD is acceptable to the individuals for whom it is intended is relatively unexplored, and remains a crucial issue that may ultimately determine the value of PGD as an alternative to prenatal diagnosis in high-risk couples.

The study’s primary aim is to assess parents’ attitudes toward different reproductive technology. Hence, the research questions examined in this study are designed to fulfill the following aims:

1. Seeks to compare the possible acceptance of prenatal and preimplantation genetic diagnosis by parents at genetic risk in Saudi Arabia.
2. Seeks to report the experiences and attitudes of parents who have undergone preimplantation genetic diagnosis.

The study aims required Saudi parents (fathers and mothers) to be recruited which had:

1. Child with a genetic disorder from the clinical genetic (50 Families)
2. Experience with PGD (50 Families)
3. Experience with IVF clinic from the KFSHRC (50 Families)
4. Experience with non syndromic deafness (50 Families)

Progress

During the approved period of this project, more than 173 subjects were interviewed.

We used a questioner (30 questions) with each case. Those individuals were recruited from the following clinics:

- PGD clinic, 36 subjects have been interviewed.
- IVF clinic, 43 subjects have been interviewed.
- ENT clinic, 44 subjects have been interviewed.
- Oncology clinic, 50 subjects have been interviewed.

These data have been entered into the SPSS program. There are more patients need to be recruited. The collected data will be analyzed and manuscripts will be prepared.

Project Title: Evaluating the Knowledge, Attitudes and Psychosocial Impact of Premarital Screening for Hemoglobinopathy in the Saudi Population

Investigator: Ayman Al-Sulaiman, PhD, Jenny Hewison, Ph.D, Ahmad Alsulaiman, MD, Aziza Alswayyed, MD, Tarek M. Owaidah, MD, FRCPA
Project Description

Premarital screening has begun to play a very important role in early detection and prevention of genetic disorders and other non-genetic transmitted diseases. The inauguration of the premarital screening program in Saudi Arabia 2 years ago to detect and prevent hemoglobinopathies was a milestone in the management of these groups of inherited genetic disorders.

In the proposed study, we will investigate the level of knowledge about the program, attitudes towards the program among the Saudi couples planning marriage, and the psychological and social impact of the program in the general population.

Objectives of the Study

1. To assess the knowledge of the Saudi public about the premarital screening program (PMS) and the attitude of the community towards it.
2. To assess community attitudes towards premarital screening for other conditions and diseases that might be included in the program in the future.
3. To assess levels of knowledge in couples coming forward for testing.
4. To compare attitudes in screening programme participants who have and have not received their own test results, and to assess:
   a. Psychological effects
   b. Social effects
5. To assess the benefit of the program in terms of the proportion of couples with unfavourable results who proceed with their marriage

Participants in the study

The study aims require three different groups of participants (each group including males and females). The first group will be drawn from the general population at King Faisal Hospital and Research Center outpatient clinics, the second group from couples presenting for premarital screening, and the third group from couples who have received their results. The second and third groups will be recruited at King Fahad Medical City in Riyadh and King Fahad hospital Alhfouf. A total of 900 people will be interviewed, (450 males and 450 females), spread evenly across the three study groups.

Proposed application of findings

The results of the study should inform the implementation of the premarital screening programme, which will be most successful if its presentation to the public addresses:

1. The knowledge and attitudes of the Saudi population to PMS.
2. The concerns that members of the Saudi population might have regarding the psychological and social impact of the PMS program

PUBLICATIONS


Published booklets

1. Preventive Ways for Hereditary Diseases.
2. Premarital Screening
Published educational pamphlets

1. Citrullinemia
2. HMG-COA-Lyase Deficiency
3. Isovaleric Acidemia
4. Methylmalonic Acidemia
5. Beta-ketothiolase Deficiency
6. Medium chain acyl-CoA hydrogenase
7. Galactosemia
8. Biotinidase Deficiency (BTD)
9. Congenital Hypothyroidism
10. Congenital Adrenal Hyperplasia
11. Argininosuccinate Lyase Deficiency

Manuscripts

1. Similarity and different views towards prenatal diagnosis and termination of the pregnancy for a range of different genetic conditions. Ayman Alsulaiman, J. Hewison. Department of Genetics, Research Center King Faisal Hospital and RC, Riyadh, School of Medicine, University of Leeds, UK

2. Attitudes to prenatal diagnosis and termination of pregnancy for thirty genetic conditions among women with different cultural and religious backgrounds. Ayman Alsulaiman, J. Hewison. K. Aboamro. Department of Genetics, Research Center King Faisal Hospital and RC, Riyadh, School of Medicine, University of Leeds, UK

3. Attitudes toward abortion among parents of children with thalassaemia or sick cell anemia. Ayman Alsulaiman, J. Hewison. Department of Genetics, Research Center King Faisal Hospital and RC, Riyadh, School of Medicine, University of Leeds, UK
The mission of the genomics core laboratory is to provide access to a wide variety of state of art as well as high throughput molecular biology technologies. This facility is organized to be operated by a team of dynamic scientists to facilitate sequencing, genotyping, cell culturing, gene expression and more for basic and clinical applications.

Up to date services include

- DNA sequencing and mutation detection/genotyping
- Single Nucleotide Polymorphisms screening
- Quantitative Real Time-PCR
- DNA chip Karyotyping
- Expression array system
- Ciphergen Chip System

Genomics Core Facility

Head
Ali Al-Odaib, PhD

Members
Walid El-Sherif
Fatma Al-Zahrani
DNA sequencing and mutation detection/genotyping

Sequencing is the process of reading the nucleotides in a fragment of DNA. The DNA sequence provides information for molecular biologists to elucidate the genetics of their system of study, and evaluate the progress of their genetic research projects. The facility offers DNA sequencing service based on an Amersham Biosciences MegaBACE DNA Analysis System providing sequences for researchers from single-stranded, double-stranded and PCR-derived DNA templates. MegaBACE system is a 96 capillary sequencer, which provides high throughput fragment sequencing; approximately 96 fragment analysis in less than 3 hours. Besides the MegaBACE, the facility includes the ABI Prism 3100 Avant genetic analyzer which was upgraded from 4 capillaries to 16 capillaries.

Single Nucleotide Polymorphisms Screening

The Genomics Core Laboratory provides the NanoChip system to the Department of Genetics. This is a high throughput SNP/mutation analysis system that permits the analysis of 100 fragments in 90 minutes. As such at present the system will be used for pharmacogenomic studies for adult diseases as tendency for coronary heart disease, hypercholesterolemia, sensitivity to cholesterol reducing drugs and even in certain cases of adult type 2 diabetes. Future expansion will be large-scale application of mtDNA mutations / polymorphisms and the study of SNP associated with certain types of autism.

Quantitative Real Time-PCR

Real-time PCR is a specific, sensitive, and reproducible approach to quantitatively measure the initial amount of the template. Real-Time PCR can be applied to several applications such as quantitation of gene expression, array verification, drug therapy efficacy, DNA damage measurement, mitochondrial DNA studies, methylation detection, and more. In principle, real-time PCR monitors the fluorescence emitted during the reaction as an indicator of amplicon production during each PCR cycle. The real-time progress of the reaction can be viewed by a sensitive camera that monitors the fluorescence in each sample at frequent intervals during the PCR Reaction. There are two real-time system at the core facility, the first is the capillary based Light Cycler by Roche; and the other is a 96-well plate the Opticon 2 system from MJ Research.

Expression Array System

In order to improve the research quality, the Genomic Core Unit offers the 1700 Chemiluminescence Microarray Analyzer from ABI. This system is a recently developed microarray system which utilizes the power of chemiluminescence enabling scientists to detect as little as a femtomole of expressed mRNA. The ABI 1700 uses Celera's private database which comprises more than 8000 extra genes that are very well accurate and annotated and also publicly available genes.

Ciphergen Chip System

The Series 4000 with the Pattern Track process is the most recent addition to the Genomic Core Unit. This system enables biomarker discovery, purification, identification, and quantitative assays at the bench-top. The system provides high sensitivity, resolving power, and reproducibility for biomarker discovery; pattern recognition software to select optimal combinations of biomarkers; automated single- or multi-marker assay optimization; and validation of high-throughput assays.
The mission of the Department of Human Cancer Genomic Research (DHCGR) is to conduct translational research on cancers that are more prevalent in the Kingdom of Saudi Arabia. The main focus of the Research Centre is to perform high quality translational research using state of the art technology including affymetrix, tissue micro array and high throughput sequencing analyzer. The main mission of this department is also to design better strategies to diagnose, prognosticate and treat neoplasm that are specifically relevant to Saudi Arabia as compared to the Western population.

The primary focus of DHCGR at the KFNCCandR is to perform high quality research according to international standards. Its centerpiece is a unique bio-repository center consisting of archival frozen tumor tissue samples and ATCC as well as in house established cell lines that allow large scale and high throughput research. Our long-term goal is towards developing diagnostic or therapeutic strategies to improve the management of cancer in the Kingdom of Saudi Arabia and provide unprecedented tools for translational research in the region.

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

1. Section of Experimental Pathology
2. Section of Molecular Oncology
3. Biological Repository Center

Chairman
Khawla Al-Kuraya, MD, FCAP
Scientific Staff
Shahab Uddin Khan, PhD
Jehad Abubaker, PhD
Magbool Ahmed, PhD
Hassan Al-Dosari
Naif Al-Jommah, BSc
Valerie Atizado, BSMT
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Prashant Bavi MD
Sayer Al Habib, MScc
Azhar R Hussain, MBBS
Muna Ibrahim, DVM
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Azadali Moorji BSc
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Shakail U Siddiqui MBBS
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Meher Sultana, MSc
Administrative Staff
Saad Al Odaib
Maria Victoria Concepcion
Myra Maningas

National Collaboration
Department of Pathology, KFSHandRC
Department of Oncology, KFSHandRC
Department of Colo-Rectal Surgery, KFSHandRC
Department of Obstetrics and Gynecology, KFSHandRC
Department of Paediatric Hematology/Oncology, KFNCCandR, KFSHandRC
Pathology Services Division, Saudi Aramco, Saudi Arabia

International Collaboration
Department of Pathology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.
Section of Experimental Pathology

The section of Experimental Pathology has undertaken major projects aimed at identifying the different genetic lesions that can be utilized as either diagnostic markers, or therapeutic targets aimed at improving the overall survival of cancer patients in this region. These projects have been established because dependence on western data is not sufficient to treat these tumors as the genetic signature of cancers arising from this region is different from the western population. We are utilizing the latest technology to study these cancers. We are actively collaborating nationally and internationally with other scientific groups to achieve our objectives.

Section of Molecular Oncology

This section 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.

There are multiple ongoing projects that form the structure of the translational research program. Additionally, we have established functional assays using cell lines of different cancer entities and challenging them with various small natural or synthetic inhibitor molecules and studying the signaling, survival and apoptotic pathways following their treatment. Finally, the functional results are validated by real-time PCR and immunohistochemistry.

Biological Repository Center

The main stay of the biorepository center is the proper preservation and storage of archival frozen tumor tissue samples. In addition, we are performing extraction of DNA and RNA from these frozen samples as well as formalin fixed paraffin embedded tissues. These DNA and RNA samples are being utilized to perform gene profiling studies for RNA differential expression analysis and DNA for comparative genomic hybridization.

i. Biorepository Unit

Tasks

Collect and maintain archive of frozen tissues (normal and neoplastic), serum, urine, paraffin blocks from (clinical studies, outside collaborators, TMA projects), and cell lines (commercial cell lines and own cell lines made from fresh tumor tissue).

Activities

BRC is handling a number of different projects for samples and effectively serve, provide optimal storage and processing of specimens and when required by the researchers.

1. Processing biomaterial (DNA and/or RNA extraction from blood, tissues-frozen tissues and from paraffin blocks) for various research projects - total of 2600 specimens processed in the year 2006.

DNA Extraction from TMA samples
Human Cancer Genomic Research

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2. Cell blocks prepared from cell-lines used for immunohistochemistry (Colon, Lymphoma, Breast and Ovary) 40.


5. Processing tissue, fresh and frozen sections for histopathology, histochemistry and immunohistochemistry blanks. This may include fixation, paraffin embedding, tissue cutting and section staining. Sections may be cut and stained for all routine histochemical staining including hematoxylin and eosin, trichome, reticulin, as well as other. Immunoblanks also generated for various antibodies staining.

Number of sample processed:

- Paraffin blocks - 2000
- HandE stain - 2000
- Immunohistochemistry - 2000
- Frozen sections - 700

6. Storing biomaterial under controlled temperature:

- Liquid nitrogen facility - 409
- 80°C facility  - 84

- Maintaining supply of Liquid N₂ for 2 CryoMed Freezers for Dept. of Genetics, Research Centre
- Storage of Heart Valves and Bone Paste (Liquid N₂ vapour Phase storage), Dept. of cardiovascular Disease

7. Maintaining and distributing commercially available cell lines (ATCC) to the research investigator/clinicians with RAC approved projects.

ii. Tissue Microarrays (TMA) Unit

Cancer genomics has firmly established TMA technology and is now a leading source resource with a extensive archival of tumor specimens in a TMA format. A total of 1927 tumor and normal tissue specimens were arrayed in a TMA format in 2006. In addition we have a cell line block TMA.

The following pie diagram shows the percentage distribution of arrays established for different sites during the year 2006:
RESEARCH PROJECTS

Molecular signatures of cancer

The main goal of this project is to characterize cancer of different lineages in the Saudi Arabian population. Characterization of these cancers is very important to understand the underlying pathophysiology. In addition, it is also important to know as to how these cancers would respond to different chemotherapeutic drugs.

These goals shall be achieved by developing individual project within a program that focuses on tumors from different organ sites. We intend to investigate clinically relevant molecular signatures or individual gene alterations in a variety of lymphomas and epithelial carcinomas such as colon, thyroid and ovary using a combined DNA, RNA, protein and tissue microarray approach. This is a novel approach where gene expression profiling is being validated on tissue samples by tissue microarray. In addition, validation of gene expression is also done by RT-PCR and functional studies are performed on protein samples.

The program comprises of four (4) organ sites:

1. Hematological Malignancies
2. Thyroid
3. Colon
4. Ovary

1. HEMATOLOGICAL MALIGNANCIES

A: Diffuse Large B-Cell Lymphoma (DLBCL)


Project Title: Role of Phosphatidylinositol 3’-Kinase/AKT Pathway in Diffuse Large B-cell Lymphoma Survival

Project Description

Phosphatidylinositol 3-kinase (PI3'-kinase) is a key player in cell growth signaling in a number of lymphoid malignancies, but its role in diffuse large B-cell lymphoma (DLBCL) has not been fully elucidated. Therefore, we investigated the role of the PI3'-kinase/AKT pathway in a panel of 5 DLBCL cell lines and 100 clinical samples. AKT was phosphorylated in 5/5 DLBCL cell lines. Inhibition of PI3'-kinase/AKT pathway reduced phosphorylation of AKT, FOXO transcription factor and GSK3 and lead to apoptosis in 3/5 DLBCL cell lines (SUDHL4, SUDHL5 and SUDHL10 (inhibitor sensitive), while 2 DLBCL cell lines, SUDHL8 AND OCYLY19 (inhibitor resistant) were refractory to PI3'-kinase/AKT inhibitor induced apoptosis. Furthermore, we also noted a decrease in the expression level of X-linked inhibitor of apoptosis protein (XIAP) in the DLBCL cell lines sensitive to PI3'-kinase/AKT inhibitor after treatment. However, no effect was observed in XIAP protein levels in the resistant DLBCL cell lines. Finally, using immunohistochemistry, p-AKT was detected in 52% of DLBCL tumors tested. Furthermore, patients with high p-AKT expression were associated with poor prognosis and a trend was seen with higher IPI scores. We also investigated the relationship between PTEN and PIK3CA, a highly significant association between PIK3CA mutations and retention of PTEN protein expression was observed (P = 0.0146). PIK3CA mutations and PTEN loss are nearly mutually exclusive and combining these two groups was found to be significantly associated with poor overall survival (P = 0.0146). This implies that deregulated phosphatidylinositol 3,4,5 triphosphate (PIP3) is critical for tumorigenesis in a significant fraction
of DLBCL and that loss of PIP3 homeostasis by deregulation of either PIK3CA or PTEN relieves selective pressure for targeting of the other gene. Furthermore, activation of the AKT was observed in most of the DLBCL harboring PIK3CA mutations. Altogether, these results suggest that PI3'-kinase/AKT pathway may be a potential target for therapeutic intervention in diffuse large B-cell lymphoma.

**Progress**


Paper submitted to Human Mutations on PI3-kinase mutations titled "PIK3CA mutations are mutually exclusive with PTEN loss in diffuse large B-cell lymphoma" (Submitted December 2006).

Abstract accepted in AACR titled "PIK3CA mutations are mutually exclusive with PTEN loss in diffuse large B-cell lymphoma" (98th Annual meeting of American association of Cancer Research (AACR), Los-Angeles, April 14-18, 2007).

Abstract accepted in AACR titled "Inhibition of Phosphatidylinositol 3-kinase/AKT pathway Induces Apoptosis in Diffuse Large B-cell lymphoma". 97th Annual meeting of American association of Cancer Research (AACR), Washington DC, USA, April 1-5, 2006.

Project Title: Distinct Gene Expression Profiles Characterize the Nodal Versus Extranodal Diffuse Large B-Cell Lymphoma

Project Description

**Purpose:** Approximately one third of diffuse large B cell lymphoma (DLBCL) arises from tissues different from the lymph node. Perceived differences in outcome between extranodal and nodal DLBCL raise the possibility that these subgroups may represent different biological and clinical entities.

**Patients and Methods:** To examine possible differences between these DLBCL subgroups, Microarray Gene Chip technology was used for global gene expression profiles from nodal (n=19) and extranodal (n = 8) DLBCL. Quantitative RT-PCR was employed for validation of microarray data. Differential expression levels of p16 was confirmed by means of immunohistochemistry on a tissue microarray comprising more than 200 lymphoma samples.

**Results:** A total of 218, over expressed(124) and under expressed(94) genes were found to be differentially expressed in extra nodal DLBCL as compared with nodal DLBCL including cytokines/chemokines like CCL19, CCL2, CD6, CX3CR1, CXCR3, FYB, HLA-E, IGSF6, IL1R2, IL2RG, IL32, TLR5, TNFRSF25, TNFSF12, TNFSF13, TNFSF4, and XCL1/2, chromosome replication related genes (FOXM1, AuroraB, TOPBP1, CHK1, and CHK2), and DNA repair gene (RAD51, RAD54 and BRCA1). Q-PCR data confirmed with microarray data. Higher rate of p16 positivity was found in extranodal lymphomas. However prognostic importance of p16 was associated with nodal rather than extranodal lymphomas.

**Conclusion:** Downregulation of cytokines in extranodal DLBCL suggests loss of lymphocyte homing factors as one mechanism contributing to their development. Our data suggest that a better distinction of these subgroups based on molecular classifiers is feasible and may greatly facilitate determination of specific relevant clinical features and therapeutical implication of DLBCL with primary extranodal or nodal location.
Progress

Paper submitted to Clinical Cancer Research (Submitted December 2006).

Project Title: Lack of Cyclin H Expression is Independent Prognostic Marker for Poor Outcome in Diffuse Large B Cell Lymphoma

Project Description

Diffuse large-B-cell lymphoma (DLBCL) is the most common lymphoid malignancy in adults, accounting nearly 40% of all non-Hodgkin's lymphomas. Since combination chemotherapy cures only 40-50% of the patients, the identification of prognostic markers could help to develop risk-adapted treatment strategies. As proliferation of cells is essential for tumour growth, analysis of the cell cycle and its individual phases might give additional information on tumour progression and clinical behavior. Cyclin H is a substrate of protein kinase 2, a ubiquitously expressed serine/threonine protein kinase required for cell viability and cell cycle progression. Cyclin H occurs as a component of the cyclin H/Cdk 7/Mat 1 complex. Cdk 7 regulates cyclin H and this complex phosphorylates Cdk 1, 2, 4 and 6 leading to upregulation of kinase activity. Cyclin A, B, D3 and E have been studied in DLBCL and have shown to have a prognostic value. We evaluated for the first time the expression of cyclin H (1:300, Catalogue # 2927, Cell Signaling Technology, USA) by immunohistochemistry in 301 diffuse large B cell lymphomas in a tissue micro array format. We also studied expression of the cell cycle regulatory molecules p27 (1:100, clone IB4, Dako, Glostrup, Denmark) and p21 (1:200, clone SX-118, Dako, Glostrup, Denmark) by immunohistochemistry. Cyclin H expression was seen in 85.7% of the DLBCL and was correlated with p27 expression ($p<0.0001$) and p21 expression ($p=0.0253$). Our results show that nuclear expression of cyclin H expression in $>30\%$ of tumor cells were significantly associated with better overall survival, both in the univariate ($p=0.0008$) and multivariate analysis ($p=0.0220$). Furthermore its prognostic significance was independent of International Prognostic Index ($<0.0001$). Cyclin H expression by IHC is easy to evaluate on paraffin sections and the high prognostic value of cyclin H may be basis for future prospective trials. In addition, high prevalence of cyclin H expression suggests a possible target for individualized therapy.

Progress

Manuscript submitted to Clinical Cancer Research (December 2006).

B. Dissection of survival and apoptotic pathways in Lymphoma

Investigators: Khawla S. Al-Kuraya, Shahab Uddin, Azhar R. Hussain, Naif A. Al-Jomah

Project Title: Sanguinarine - Dependent Induction of Apoptosis in Primary Effusion Lymphoma Cells

Project Description

Primary Effusion Lymphoma (PEL) is an incurable, aggressive B-cell malignancy that develops rapid resistance to conventional chemotherapy. In efforts to identify novel approaches to block proliferation of PEL cells, we found that sanguinarine, a natural compound isolated from the root plant *Sanguinaria canadensis*, inhibits cell proliferation and induces apoptosis in a dose dependent manner in several PEL cell lines. Our data demonstrate that sanguinarine-treatment of PEL cells results in up-regulation of death receptor 5 (DR5) expression via generation of reactive oxygen species (ROS) and causes activation of caspase-8 and truncation of Bid. Subsequently,
tBid translocates to the mitochondria causing conformational changes in Bax, leading to loss of mitochondrial membrane potential and release of cytochrome c to the cytosol. Sanguinarine induced release of cytochrome c results in activation of caspase-9, -3, and polyadenosin-5’-diphosphate-ribose polymerase (PARP) cleavage leading to induction of caspase-dependent apoptosis. In addition, we demonstrate that pre-treatment of PEL cells with z-VAD-fmk, a universal inhibitor of caspases abrogates caspase and PARP activation and prevents cell death induced by sanguinarine. Moreover, treatment of PEL cells with sanguinarine down-regulates expression of inhibitor of apoptosis proteins (IAPs). Finally, NAC, an inhibitor of ROS, inhibits sanguinarine-induced generation of ROS, up-regulation of DR5, Bax conformational changes, activation of caspase-3 and down-regulation of IAPs. Taken together, our findings suggest that sanguinarine is a potent inducer of apoptosis of PEL cells via up-regulation of DR5 and raise the possibility that this agent may be of value in the development of novel therapeutic approaches for the treatment of PEL.

**Progress**


Abstract accepted in AACR titled “Sanguinarine induces apoptosis via up-regulation of Death Receptor 5 in Primary Effusion Lymphoma”. (98th Annual meeting of American association of Cancer Research (AACR), Los-Angeles, April 14-18, 2007).

**Project Title: Role of Proteosome Inhibitors on Cell Cycle and Apoptosis in Lymphoma**

**Project Description**

Proteosome inhibition is a novel approach for treating malignancy and has been approved for clinical use. The proteosome is the primary proteolytic mechanism in eukaryotic cells and inhibition of its catalytic activity initiates a cascade of events affecting cell cycle and apoptotic activities. These activities ultimately lead to cell cycle arrest and apoptosis in malignant cells however, the normal counterpart of these cells are spared. In this study, we used a panel of primary effusion lymphoma cell lines as well as Diffuse Large B-Cell Lymphoma cell lines to study the effects of proteosome inhibitor, MG132 on cell proliferation and apoptosis. Our data showed that proteosome inhibitor MG132 decreased cell viability as well as induced apoptosis in a dose dependent manner as detected by annexinV/PI dual staining. S-phase kinase-associated protein 2 (skp-2) is a proto-oncogene and over expressed in various types of tumors. We sought to determine the role of Skp-2 following proteosome inhibition in these cell lines. MG132 treatment of cell lines resulted in down-regulation of SKP-2 protein in a dose dependent manner, whereas the expression of p-27 was up regulated demonstrating an inverse relationship between these two proteins. Furthermore, MG132 treatment led to conformational changes in Bax protein and translocation to the mitochondria leading to the loss of mitochondrial membrane potential with subsequent release of cytochrome c from mitochondria into cytosol. Cytochrome c release caused activation of caspase-3 followed by polyadenosin-5' -diphosphate-ribose polymerase (PARP) cleavage. In addition, proteosome inhibitor treatment also caused down-regulation of inhibitor of apoptosis protein, XIAP. Taken together, our findings show that proteosome inhibition causes down-regulation of skp-2, up-regulation of p-27, inhibition of proliferation as well as caspase-dependent apoptosis in lymphoma cells suggesting a role of proteosome inhibitors in the treatment of these aggressive cancers.
Progress


Abstract accepted in AACR titled “Proteosome Inhibitor induces apoptosis in Primary Effusion Lymphomas”. (98th Annual meeting of American association of Cancer Research (AACR), Los Angeles, April 14-18, 2007).

C: Gene expression profiling in Childhood Acute Lymphoblastic Leukemia in the Kingdom of Saudi Arabia


Project Title: Molecular signatures in childhood Acute Lymphoblastic Leukemia in the Kingdom of Saudi Arabia

Project Description

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in childhood population. ALL is a heterogeneous group of disease that consists of various subtypes that allows to risk stratify the patients into favorable and unfavorable groups. Risk stratification of patients has definitely played an important role in the improvement of overall survival in childhood ALL. With the introduction of microarray technology, it has become increasingly clear that leukemia with different risk factors display distinct gene-expression profiles. The aim of this study was to investigate the gene expression profile on pediatric patients diagnosed with ALL using microarray analysis and study the common genetic subtypes in ALL samples using multiplex real-time RT-PCR. We studied 77 patients of newly diagnosed ALL at the King Faisal Specialist Hospital and Research center, Riyadh, Saudi Arabia. Using multiple parameters including age, sex and WBC count; we analyzed samples for differential expression of genes using the GeneChip® human genome U133 plus 2.0 microarray from Affymetrix. Based on the age of the patient, we compared samples between 1-9 years (favorable prognosis) to more than 10 years (unfavorable prognosis) of age. Using Avadis software from Strand genomics, we were able to identify 156 genes that were differentially expressed using a cutoff p value of 0.05. Out of this list, three genes were of interest to us as they were involved in either, cell cycle and/or apoptosis. They include the pro-apoptotic genes; TGF-beta induced apoptosis protein 2 (TAIP2) and Caspase Recruitment Domain member 14 (CARD14) that were 10.16 and 4.12 folds over-expressed in the favorable prognosis group respectively. In addition, another gene, cyclin A1 (CCNA1) that is involved in cell cycle was found to be down-regulated 4.84 folds in the favorable group. These genes have important clinical implications and can be used as prognostic markers in this age group. Interestingly, CyclinA1 is being currently targeted using siRNA to inhibit tumor growth and induce apoptosis in certain cancers. In addition to gene expression profiling, we also studied the four common genetic translocations detected in ALL by multiplex real-time RT-PCR. They include the t(12;21) TEL/AML1 fusion gene, t(9;22) BCR/ ABL fusion gene, t(4;11) MLL1/AF4 fusion gene and t(1;19) E2A/PBX1 fusion gene. We found that the genetic translocation detected in our samples varied from the published data on western population. We detected 15% of TEL/AML1 translocation which was less than that found in the western population (22%), 4% of BCR/ABL that was higher than the western population (2.2%) and 6.5% of E2A/PBX1, that was higher than the western population (3.8%). These data have important clinical significance as they allow us to better understand the underlying biology of ALL as well as risk stratifies ALL patients
according to their gene expression profiles and their genetic subtypes.

Progress

Abstract accepted in AACR titled "Molecular signatures in childhood Acute Lymphoblastic Leukemia in the Kingdom of Saudi Arabia". (98th Annual meeting of American association of Cancer Research (AACR), Los-Angeles, April 14-18, 2007).

THYROID


Project Title: Genome-Wide Expression Analysis of Middle Eastern Papillary Thyroid Cancer Reveals c-MET as A Novel Target for Cancer Therapy

Project Description

Objectives: To screen and validate the global gene expression in the Middle Eastern papillary thyroid carcinoma (PTC) using cDNA expression arrays and immunohistochemistry (IHC) on tumor tissue microarrays (TMA) in an attempt to find genes may be of importance in malignant progression of PTC in the Middle East which therefore can be targeted in cancer therapy.

Experimental Design: 29 PTC tissue specimens were compared with 7 morphologically normal thyroid specimens by use of HUG133-Plus2.0 gene cDNA microarray. Results for selected genes were confirmed by reverse transcription-PCR (RT-PCR). Protein expression of selected genes was further studied using tissue microarray consisting of 500 PTC and compared with histological normal thyroid tissue samples.

Results: 194 genes were over-expressed in PTC tissue relative to normal thyroid tissue. The genes that were up regulated in PTC were involved in cell cycle regulation, cell signaling and oncogenesis. Among these genes, c-MET was identified by immunohistochemical methods as protein that is over expressed in 40% of PTC and was significantly associated with more aggressive behavior e.g. higher stage, extensive nodal involvement and tall cell variant.

Conclusion: Our data suggests that c-MET dysregulation is associated with aggressive behavior and may serve as molecular biomarker and potential therapeutic target in this disease.

Progress

Manuscript being submitted to Journal of Clinical Endocrinology and Metabolism.

Project Title: Genetic Polymorphisms of Selected DNA Repair Genes and Papillary Thyroid Cancer Susceptibility in Middle Eastern Population

Project Description

Genetic polymorphisms of DNA repair genes seem to determine the DNA repair capacity, which in turn may affect the risk of thyroid cancer. We hypothesized that polymorphisms of genes responsible for DNA repair may be associated with risk of thyroid cancer. To evaluate the role of genetic polymorphisms of DNA repair genes in thyroid cancer, we conducted a hospital-based case-control study in Saudi population. 223 incident papillary thyroid cancer cases and 229 controls recruited from Saudi Arabian population were analyzed for 21 loci in eight selected DNA repair genes by PCR-RFLP including non-homologous end joining pathway genes LIGIV (LIGIV Asp62His, Pro231Ser, Trp46Ter), XRCC4 Splice G33243301A and
XRCC7 Ile3434Thr; homologous recombination pathway genes XRCC3 Arg94His and Thr241Met, RAD51 UTR T15452658C, A15455419G, RAD52 UTR C876074T and Glu221Gln, conserved DNA damage response gene Tp53 Pro47Ser, Pro72Arg, Tp53 UTR A7178189C and base excision repair gene XRCC1 Arg194Trp, Arg280His, Arg399Gln, Arg559Gln. We found that the RAD52 221 genotypes GC and variants carrying C allele, showed statistical significance and very high risk of developing thyroid cancer compared to wild type (p<0.001; OR=15.57 and 17.58 respectively). Similarly, RAD52 2259 genotypes CT and variant allele T showed a significant difference in terms of risk estimation (p<0.05), OR= 1.53; and p(<0.001) OR=1.922 respectively), comparing to control group. Remaining loci demonstrated no significance with risk. Of the 21 loci screened, we identified RAD52 2259 and RAD 52 221 may be of importance to disease process and may be associated with papillary thyroid cancer risk in Saudi Arabian population.

Progress

Manuscript submitted to Journal of Clinical Endocrinology and Metabolism (December 2006).

COLON


Project Title: Genomic Instability Pathways in Sporadic Colorectal Carcinomas of Saudi Arabia, Molecular and Tissue Microarray Analysis

Project Description

Objective: To study the genomic instability pathways in colorectal carcinomas of Saudi Arabia.

Summary background data: Genomic instability pathway is the major pathway for development of colorectal carcinoma. Identifying the microsatellite instable group of colorectal carcinomas and hereditary non polyposis cancer syndrome (HNPPC) has diagnostic, prognostic and evolving therapeutic significance.

Methods: We studied microsatellite instability pathway (MSI) in Saudi colorectal carcinomas (CRC) from 179 unselected patients by two methods: microsatellite analysis by PCR and immunohistochemistry (IHC) detection of MLH1 and MSH2 proteins. Loss of heterozygosity (LOH) of the adenomatous polyposis coli (APC) and TP53 genes were also done by PCR to identify the chromosomal instability pathway (CIN). TP53 mutations were studied by sequencing exons 5, 6, 7 and 8.

Results: Sixteen percent of the tumors showed high level instability (MSI-H), 19.3 % had low level instability (MSI-L) and the remaining 64.0 % tumors were stable. Survival of the MSI-H group was better as compared to the MSI-L or MSS group (p=0.0217). In the MSI-H group, 48 % were familial MSI tumors that could be attributable to the high incidence of consanguinity in the Saudi population. Loss of heterozygosity was seen in 41.17 % and TP53 mutations were found in 23.9 % of the cases studied.

Conclusions: A high proportion of familial MSI cases, a lower incidence of TP53 mutations and a subset of MSI-L/MSS tumors with no LOH events are some of the hallmarks of the Saudi colorectal carcinomas which need to be explored further.”

Progress

Abstract accepted for the13th Congress Of The European Society For Surgical Oncology, Venice, Italy 30th Nov-2nd Dec 2006.
Project Title: Correlation of \textit{PIK3} Mutations with Microsatellite Instability in Colorectal Carcinomas from the Middle East

Project Description

A wide variety of tumors show PIK3CA mutations leading to increased phosphatidylinositol-3 kinase (\textit{PI3K}) activity. We have determined the frequency of PIK3CA mutations in exons 9 and 20 that has previously been reported as mutational hotspot regions in distinct tumor models. One hundred and fifty colorectal carcinomas that were characterized previously for MSI status (125 MSS and 25 MSI) by PCR sequencing were evaluated.

PIK3CA mutations in exons 9 and 20 were present in 14.37\% (23 of 160) of the colorectal carcinomas tested. A \textit{PI3K} mutation was seen in 4 colon cell lines tested: DLD1, HCT15, HCT 116 and SW 948. Three of these cell lines were showing microsatellite instability status. Further more, we observed a strong association of \textit{PI3K} mutations with microsatellite instability status, which was statistically significant ($p=0.0046$).

Our data suggested that \textit{PI3K} mutations in colorectal cancer might be a consequence of mismatch repair deficiency.

Progress


OVARY


Project Title: Aspirin Induces Apoptosis in Ovarian Cancer Cells Via Inhibition of AKT and Down-Regulation of COX-2 expression

Project Description

Background: Previous studies have shown that treatment of epithelial ovarian cancer (EOC) cells with aspirin or non-steroidal anti-inflammatory drugs may induce apoptosis. The mechanism of this action is not known. We investigated the effect of aspirin treatment on one of the apoptotic pathways in ovarian cancer cells.

Methods: Three EOC cell lines (2774, and SKOV3) were treated with ASA at increasing concentrations. Treatment effect on cell apoptosis was assessed by flow cytometry and annexin V/PI dual staining. Expression of Cox-2, XIAP and activation of caspases were determined by western blotting using specific antibodies.

Results: Our data indicate that aspirin treatment induced apoptosis in the three EOC cell lines tested in a dose dependent manner. Aspirin suppressed the constitutively active AKT as well as down regulated the expression of COX2. Furthermore, aspirin induces truncation of BID, loss of mitochondrial membrane potential, as determined by JC1 staining and with subsequent activation of caspase-3 followed by polyadenosin-5'-diphosphate-ribose polymerase (PARP) cleavage. Finally, aspirin also inhibited the expression of XIAP, an anti-apoptotic protein that has been shown to be regulated by AKT.

Conclusion: Our findings suggest that aspirin suppresses constitutively active AKT and COX-2 expression, leading to inhibition of proliferation and induction of caspase-dependent apoptosis. These results provide the molecular basis and preliminary data for new treatment strategies that may incorporate aspirin and other NSAID drugs in treatment regimens for epithelial ovarian cancer.
Progress

Abstract accepted in International Gynecologic Cancer Society, October 14-18, 2006, Santa Monica, CA, USA.

FUTURE RESEARCH DIRECTION

The Department of Human Cancer Genomic Research will continue on our main focus "human cancer genomic research". With this broad agenda in mind, we have initiated several complimentary programs that will lead to identification; analysis and characterization of genetic alterations associated with cancer in Saudi Arabia and the success of this endeavor will be through a combination of basic, translational and clinical research.

Within our research laboratory, we will continue using state-of-the-art approaches to study fundamental questions regarding cancer in Saudi Arabia and the Middle East. In addition to Basic research, there is also a strong emphasis on translating basic science advances into more effective and highly reliable diagnostic and therapies.

PUBLICATIONS


### Abstracts


Factor Related Genes (IGF2R, IGFBP3) and Mucin 1 Transmembrane (MUC1) as Prognostic Markers for Papillary Thyroid Carcinoma in Saudi Arabia. Endo 2006, June 24-27, 2006, Boston, USA.


The
National Laboratory for Newborn Screening
The National Laboratory for Newborn Screening

The National Laboratory for Newborn Screening (NLNBS) is both a service and research unit and is currently in contract with Prince Salman Center for Disability Research (PSCDR), and the Saudi Ministry of Health to execute Phase I of the Saudi Newborn Screening Program. The number of participating Ministry of Health hospitals reached 22 and two more expected soon. Accordingly, this year saw a significant expansion in the newborn screening program where we received 60,000 blood spots from newborns (a 100% increase over year 2005) and 16,000 specimens of blood, plasma, urine and CSF for follow-up of treatment or from new patients from over 200 different hospitals. The total number of tests carried out on these samples exceeded 300,000 tests.

Our personnel increased by 30% financed from our fee-for-service funds. The new technical staff were trained and on line with our routine procedures in relatively short time. We also acquired two major pieces of equipment, an amino acid analyzer and a new tandem mass spectrometer.

NLNBS maintains an active research profile either independently or in collaboration with other KFSH&RC clinical departments. The product this year was several important publications in international journals. We also submitted two new projects for approval to the Research Advisory Council.
RESEARCH PROJECTS

Project Title: Phase-I of the Saudi Newborn Screening Program (SNBS).

Investigators: Mohamed Rashed, Amal Saadallah, Osama Al-Dirbashi, Mohamed Al-Amoudi, and Fahd El-Badaoui

Project Description

Phase I of the program targets 120,000 newborns from 24 major birth centers from different regions of KSA. The program includes screening dried blood spots from newborns at 24-72 hours after birth for 16 inherited metabolic and endocrine disorders (see list below).

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

The first 12 of these diseases are screened for by tandem mass spectrometry, the last 4 disorders will be screened for by four different fluoroimmuno assays.
Progress

The program has started on August 20, 2005 and currently we have 22 birth centers from 5 regions of the kingdom are onboard with two more to join in the next few weeks. The program is administered by Prince Salman Center for Disability Research (PSCDR) and financed and supervised by the Ministry of Health. We also have two major private hospitals onboard as well as KFSH&RC-Riyadh and Jeddah. In 2006 we screened 60,000 babies and the outcome is excellent where we found a large number of affected newborns yielding an incidence of 1:750. We are facing some logistical difficulties but this is improving gradually and significant difficulties convincing some families to bring their baby back for confirmation of screening results. This would require major effort from the Ministry of Health in campaigning for the program in the media.

Project Description

The project aims at the underlying molecular causes of five relatively common metabolic diseases. There are: argininosuccinic acid lyase deficiency, methylmalonic acidemia, propionic acidemia, HMG-CoA lyase deficiency, and glycogen storage disease type 4.

Progress

Several mutations were identified for each of the diseases, three publications were accepted and several other manuscripts are in preparation. The project is ongoing.

Project Title: L-2-Hydroxyglutaric Aciduria: Clinical, Biochemical and Molecular Analysis in a Large Saudi Family

Investigators: Moeen Al-Sayed, Mohamed Rashed, Eissa Faqeih, Osama Al-Dirbashi and Mohammed Faiyaz Ul-Haque

Project Description

L-2-Hydroxyglutaric Aciduria is a rare neurometabolic condition. The tentative defect has only been recognized recently. Performing this study will allow us to better characterize the disease in this family and at large in Saudi Arabia from clinical, biochemical and molecular perspectives. The detection of carrier status to enable reproductive or lifestyle decisions is important. This will have direct beneficial impact on this family and other families that are likely to be identified in the future.

Progress

Molecular investigation of family members revealed several mutations. The determination of the level of 2-hydroxyglutaric acid in affected and unaffected

Project Title: Molecular Genetic Analysis of Five Inherited Frequently Encountered in the Metabolic Clinic

Investigators: Moeen Al-Sayed, Faiqa Ahmed, Osama Al Smadi, Mohamed Rashed and Brian Meyer

Project Description

The project aims at the underlying molecular causes of five relatively common metabolic diseases. There are: argininosuccinic acid lyase deficiency, methylmalonic acidemia, propionic acidemia, HMG-CoA lyase deficiency, and glycogen storage disease type 4.

Progress

Several mutations were identified for each of the diseases, three publications were accepted and several other manuscripts are in preparation. The project is ongoing.
family members is still pending development of a specific assay. We are expecting one publication in 2007.

**Project Title:** Clinical, Biochemical and Molecular Profiles of Saudi Patients with Medium Chain Acyl CoA Dehydrogenase (MCAD) Deficiency

**Investigators:** Zuhair Al-Hassnan, Mohamed Rashed, Faiqa Ahmed, Zuhair Rahbeeni, Moeen Al-Sayed, Mohamed Al-Owain and Mohamed Al-Amoudi

**Project Description**

This project aims at better biochemical and clinical characterization of the MCAD phenotype in the Saudi population. It aims also at the identification of the disease-causing mutations in Saudi patients with MCAD.

Improvement of the biochemical characterization of the MCAD phenotype will be extremely useful for the Saudi newborn screening program to reduce false-positive results and thus reduce recall rate. The biochemical and clinical characterization of the phenotype will be also useful for selective screening of patients suspected with fatty acid oxidation defects. It may also lead to detection of other MCAD cases in siblings from affected families.

Detecting the causative mutations in affected families will serve several clinical purposes in such potentially fatal disease. It will enable clinicians to confirm the diagnosis, apply preventive measures such as pre-implantation genetic diagnosis, and screen at-risk family members for carrier status. Targeted premartial screening could then be implemented on individual families. Identification of carries by DNA testing will be followed by screening children of carrier parents for MCAD deficiency so prompt medical intervention could be implemented on positive cases.

**Progress**

Great progress was achieved in 2006 where we found several new cases through the newborn screening program and we managed to identify two novel mutations from the Saudi population. This is significant findings as no mutations were previously described in Arabs and the disease was sought to be mainly of Northern European origin. A manuscript is under preparation to describe our findings.

**Project Title:** Hereditary Tyrosinemia Type 1: Clinical, Biochemical and Molecular Characterization With Emphasis on Response to NTBC

**Investigators:** Moeen Al-Sayed, Faiqa Ahmed, Mohamed Rashed, Brian Meyer

**Project Description**

HT1 is a metabolic disorder of autosomal recessive inheritance and is the most serious and common of the genetic defects in tyrosine (tyr) catabolic pathway and results in extensive clinical and pathological manifestations involving mainly the liver, kidney, and peripheral nerves, and could be fatal. With the introduction of the drug NTBC, HT1 is now considered a treatable metabolic disease if detected early in life. The majority of patients treated with NTBC do well. Most abnormalities associated with the disorder improve upon treatment. However, there are several drawbacks of the treatment and primary prevention remains the best option available to combat this disease.

For the above reasons, prevention remains the most effective way of combating this disease. The disease exists in Saudi Arabia but has neither been well
characterized or well reported previously. This study will include two major elements; a) clinical and biochemical characterization of the disease in all patients with HT1 that are followed at KFSH&RC before and after treatment with NTBC, b) analysis of the defective gene to identify the underlying mutation/mutations each patient and his/her family. The purpose of the study is to have a better insight in the clinical, biochemical and molecular spectrum of this disorder in Saudi Arabia and the response to treatment with NTBC. In addition, by knowing the underlying molecular defect, we can help the families included in this study and their relatives with future pregnancies by prenatal and pre-implantation diagnosis. Carrier testing can also be offered. Finally, this study shall provide scientific data to establish the molecular diagnostic tests specifically suitable for Saudi population.

Progress

Significant achievements were made in this project this year. We identified biochemically a significant number of affected children from Saudi Arabia and Egypt who went into treatment, which is life-saving. From some of these several novel mutations were identified and the work is ongoing for some other patients. Two publications are expected in 2007.

Project Title: Clinical, Biochemical, and Molecular Profiles of Saudi Patients with Dihydropyrimidine Dehydrogenase Deficiency

Investigators: Zuhair Al-Hassnan, Mohammed Faiyaz Ul-Haque, Mohamed Rashed, and Amal Saadallah, Osama Al-Dirbashi, Zuhair Rahbeeni, Moeen Al-Sayed and Abdelgani Tbakhi

Project Description

This project aims to characterize the clinical phenotype, describe the biochemical profiles, and identify the disease-causing mutations in Saudi patients with DPD deficiency. Illustrating the clinical and biochemical profiles will further clarify such a highly variable disease. Detecting the causative mutations in affected families will serve several clinical purposes in such incurable disease. It will enable clinicians to confirm the diagnosis, apply preventive measures such as pre-implantation genetic diagnosis, and screen at-risk family members for carrier status, and then targeted premarital screening could be implemented on individual families.

Progress

Little progress was made here but efforts are underway to improve on the biochemical assay for this disease as it remains a frequently ordered test.

FUTURE RESEARCH DIRECTION

1. The development of high-throughput approaches to the diagnosis of a multitude of inherited metabolic and endocrine disorders. A project was submitted and under review to establish a second-tier testing for hepatorenal tyrosinemia (tyrosinemia type-1).
2. Further biochemical and molecular studies on purine and pyrimidine degradation disorders.
3. Further biochemical and molecular studies on fatty acid oxidation defects.
4. Pre-natal diagnosis for metabolic and endocrine disorders. One project was submitted and is under review.
5. The application of tandem mass spectrometry to screening and diagnosis of lysosomal storage diseases.
PUBLICATIONS


Program in Biomolecular Research
The ultimate goal of the research program is to focus on discovery and target validation of molecular pathways that are perturbed as a result of disease and can be targeted by therapeutics. The research program employs the fields of functional genomics, functional proteomics, and molecular therapeutics to achieve this purpose by narrowing the human transcriptome and proteome to early and transient response players. Thus, the program is focused on the important decision making players in innate immunity, cellular growth control, and 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 disease, and applying this knowledge for therapeutic purposes.

Using the unique tools developed in our program, we emphasized on the regulation of mRNA stability-mediated pathways by a number of RNA binding proteins, and the relationship of these interaction, to disease mechanisms.

Director
Khalid S. Abu Khabar, PhD

Members
Anas Al-Halees, PhD, Post Doctoral Fellow
Peer Mohideen, PhD, Post Doctoral Fellow
Hana Abulleef, MSc, Bioinformatics Assistant
Rashad el-Badrawi, M.Sc, Bioinformatics Assistant
Tala Bakheet, M.Sc, (on scholarship leave)
Maha Al-Ghamdi, MSc, Research Assistant
Wijdan, Al-Ahmadi, BSc, Research Technician
Latifa Al-Haj, BSc, Research Assistant
Nora Al-Suhaibani, PhD, Student
Fahad Al-Zoghaibi, BSc, (on scholarship leave)
Maher Al-Saif, BSc, Grant Employee
Mustafa Sheikh, BSc, Grant Employee

Functional Sections
Bioinformatics
Interferons and Cytokines (Mechanisms of Disease)
Molecular Biotechnology
Molecular Therapeutics (future)
RESEARCH PROJECTS

Project Title: Ribonuclease L Regulation of Cellular mrRNAs in Health and Disease

Principal Investigator: Khalid S. Abu Khabar

Aim

The aim of this project is to understand the mechanism of the cellular growth suppression by RNase L and how RNase L mutations associated with cancer can affect this regulation.

Progress

Having concluded the first part of this project which is modulation of the RNA binding protein, HuR, which is involved in tumorigenesis, we now focus on the effect of natural and laboratory mutants of RNase L on this pathway and other cellular mRNA targets.

Project Title: Functional Genomics of Early Response Transcriptome (KACST project)

Principal Investigator: Khalid S. Abu Khabar

Aim

The overall aim of the project is to develop structural and functional genomics tools specific to AU-rich elements, found in many unstable mrRNAs, in order to perform genome-wide analysis of ARE-gene expression.

Progress

More than 4000 probes were synthesized as PCR products for use with in-house made glass microarrays for use in profiling gene expression in different cellular models. Different optimizations and protocols were used in order to achieve best printing and hybridization qualities.

Project Title: Role of AU-Rich RNA Binding Protein, Tristetraprolin in Inflammation and Cancer

Principal Investigator: Khalid S. Abu Khabar

Others: Peer Mohideen, Ph.D. and Nora Al-Suhaibani, M.Sc.

Collaborators: John Hesketh (U.K) and Perry Blackshear (U.S.)

Aim

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

Progress

The role of the RNA binding proteins, tristetraprolin (TTP) and HuR are studied in relationship to response to innate immunity and cellular growth. Specifically, TTP expression and knockdown models are being studied. Several gene target candidates important in modulation of inflammation and cancer are identified and being extensively studied.

Project Title: Role of mRNA Stabilization in Innate Immunity to Viruses (NIH Sub-Contract)

Consortium (KFSH) Investigator: Khalid S. Abu Khabar

University of Washington Principal Investigator: Stephen J. Polyak, Ph.D.

Aim

The aim of the consortium work is to delineate the IFN response to viruses, particularly, hepatitis
C virus, and effect of chemokines and other modulators.

**Progress**

As a collaborative research with Dr. Steve Polyak (University of Washington, Seattle), we have focused on the role of RIG pathway, which is important in viral and double stranded RNA response, in AU-rich mRNA stability

**Project Title: Cloning of Non-Inducible Constitutively Active Promoter (Ad Hoc Project)**

**Principal Investigator:** Khalid S. Abu Khabar

**Aim and Progress**

Several housekeeping cellular promoters were cloned in order to find optimal promoter that constitutively expressed but not inducible. This ad hoc project was necessary in order pinpoint the effects that are solely due to post-transcriptional and not transcriptional effect in gene regulation in cellular disease models. Truncations and sequence optimization such as addition of introns were also performed.

**Project Title: Computational Biology and Bioinformatics of AU-Rich Elements**

**Principal Investigator:** Khalid S. Abu Khabar

**Aim and Progress**

Most of the activities were focused on mapping AU-rich elements, themselves, as 70 nucleotide regions, in the mRNA. This project is for use with laboratory investigations dealing with reporter constructs fused with sequences found by the bioinformatics approach. In addition, a number of collaborative studies to support bioinformatics needs were also executed.

**Project Title: Sequence Optimization for Hybrid 3’ Untranslated Regions for Production of Therapeutic Proteins (Technology Transfer Project)**

**Principal Investigator:** Khalid S. Abu Khabar

**Aim and Progress**

In order to apply the “patent-pending” technology of hybrid 3’UTR, we have initiated a technology transfer project for use in the production of therapeutic proteins. More than 25 variants were cloned and they are in the process of evaluation for boosting therapeutic protein production.

**OTHER RESEARCH PROJECTS**

Various collaborative research on modulation of gene expression by RNA binding proteins (Robert Gherzi, Italy; Dominique Morello; France).

**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 the various tools that were developed in the past two years. We will continue exploring the role of RNAse L in regulating cellular growth and as perturbed during cancer. Large-scale development of GFP reporter libraries for use with cell-based assays will be applied for studying RNA binding activities in cellular models of disease.

**PUBLICATIONS**


Training and Education
Training & Education

The Research Centre Training and Education Committee (RCTEC) was formed to provide and organize training and education activities in the Research Centre. It is designed to develop, promote, administer and implement education guidelines and procedures and to organize in-house training in progressive fields of science and technology. Special courses and workshops are offered throughout the year.

Expertise

The RCTEC facilitates external training and education for Saudi Arabians who wish to pursue MSc and PhD degrees and Postdoctoral Fellowship. Networks of partnerships with reputable scientific and educational local and international institutions have been established to ensure that the latest technology is acquired and career development is advanced.

Activities

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

Chairman
Mohammed N. Al-Ahdal, PhD

Members
Ayodele Alaiya, MD, PhD
Khaled Abu-Amero, PhD
Anas Alazami, DPhil
Abdalla Al-Haj, PhD
Ibrahim Al-Jammaz, PhD
Aaron Kwaasi, PhD
Ahmed Al-Qahtani, PhD
Yasmin Al-Twaijri, PhD

Administrative Staff
Huda Al-Mosallam
Marilyn Gabriel
Lama Sultan
Abdulrahman Al-Lahoo
1.1 Graduate Assistantship (GA)

The Research Centre offers eligible non-employee candidates the opportunity to pursue MSc or PhD in biomedical sciences in collaboration with scientific and educational institutions. Under this program the Research Center has received a scholarship funds from the King Khalid Foundation. The fund was directed towards higher education for Saudi women. The fund began in 2003 and aims to provide Saudi women who are holding a bachelor, master and/or PhD degree/s in biomedical sciences with the opportunity to develop their scientific skills through various scholarship programs. Eligible candidates can pursue their research studies abroad or at the KFSH&RC in collaboration with recognized international universities and institutes, in the following programs:

1.1.1 Graduate Study (MSc and PhD)
1.1.2 Scientific Training
1.1.3 Postdoctoral Fellowship

<table>
<thead>
<tr>
<th>Program</th>
<th>On-Board</th>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhD</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>MSc</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

1.2 In-House Training (I-HT)

The Research Centre provides training opportunities for eligible candidates from other institutions. These include:

1.2.1 Undergraduate students who are seeking training related to their university degree.
1.2.2 Individuals who are seeking training to enhance their qualifications.
1.2.3 Saudi Arabian employees in public and private sectors who want to develop an aptitude for research.

1.2.4 Recipients of fellowship sponsored by international institution such as the Institute of Atomic Energy Research (IAEA) seeking on-the-job training.
1.2.5 Medical fellows/residents for training in research methodology.
1.2.6 High school students interested in a career in biomedical sciences will be given a short orientation.

<table>
<thead>
<tr>
<th>Program</th>
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<th>Completed</th>
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</thead>
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<tr>
<td>In-House Training</td>
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<td>101</td>
</tr>
<tr>
<td>Summer Training</td>
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</tr>
</tbody>
</table>

1.3 Postdoctoral Fellowship (PDF)

This is a program of study and research training at an institution abroad for employees of the Research Centre. The Fellowship, of maximum duration of two years, should be relevant to the employees’ work and the future directions of the Research Centre. The program is under the hospital scholarship guidelines.

<table>
<thead>
<tr>
<th>Program</th>
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<th>Completed</th>
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</thead>
<tbody>
<tr>
<td>Postdoctoral Fellowship</td>
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</tbody>
</table>

1.4 In-House Graduate Research for Non-RC Employees (I-HGR)

This program is for MSc and PhD students from local or international universities who are interested in conducting their research project in the Research Centre under joint supervision with their university.

<table>
<thead>
<tr>
<th>Program</th>
<th>On-Board</th>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhD</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>MSc</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>
1.5 Saudi Career Development Program (SCDP)

The Program is designed to identify the unique skills and special knowledge necessary to effectively perform the target job. The Program aims to develop the individual’s scientific skill and knowledge based on his/her background to help meet the qualifications required for the target job after one year of training. The Research Centre offers career development to well-qualified Saudi graduates who wish to enhance their scientific and technical development.

<table>
<thead>
<tr>
<th>Program</th>
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<th>Completed</th>
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</thead>
<tbody>
<tr>
<td>SCDP</td>
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<td>0</td>
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</tbody>
</table>

1.6 Volunteer (Volu)

This program is for those qualified candidates who have hands-on experience in a specific field of science and interested to expand their skills through volunteering.

<table>
<thead>
<tr>
<th>Program</th>
<th>On-Board</th>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volunteer</td>
<td>11</td>
<td>8</td>
</tr>
</tbody>
</table>

1.7 Future Scientists (FS)

The aims of this program are to assist talented young 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.

<table>
<thead>
<tr>
<th>Program</th>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Future Scientists</td>
<td>13</td>
</tr>
</tbody>
</table>

1.8 Research Centre Seminar (RCS)

RCTEC represented by its office do organize a weekly seminar to be given by Research Center scientists. Invited seminars also take place from time to time in the Research Center through the close collaboration between the office and the concerned department.

<table>
<thead>
<tr>
<th>Program</th>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC Seminar</td>
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</tr>
</tbody>
</table>

1.9 Workshops and Conferences (WS&Conf)

The Research Centre Training and Education Office assists in organizing a number of annual workshops, conferences and special courses in specific field of science.

<table>
<thead>
<tr>
<th>Program</th>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Workshop/Courses</td>
<td>4</td>
</tr>
</tbody>
</table>

1.10 Other Responsibilities

RCTEC processes and ensures that all necessary guidelines are applied to the following leave categories:

- 1.10.1 Business Leave (BL)
- 1.10.2 Professional Leave (PL)
- 1.10.3 Sabbatical Leave (SL)

1.11 Ibn-Sena Research Program

The Ibn-Sena Research Program's aim is to provide a continuing education and training in the society and to promote collaborative programs between the Research Centre and other institutions. The Program is supported by King Abdulaziz and His Companions Foundation for the Gifted.
Radiation Safety Office
The main key target of the Radiation Safety Office (RSO) is to implement the radiation safety program at King Faisal Specialist Hospital and Research Centre. Its goal is to provide radiation safe working conditions for all KFSH&RC personnel and patients, as well as the general public. This goal is achieved by ensuring compliance with national regulatory requirements and recognized international standards.

The RSO coordinates and liaises with King Abdulaziz City for Science and Technology (KACST) and other national authorities on the purchase, use, transport and disposal of radioactive materials and radiation emitting equipment. It reviews and recommends to the Radiation Safety Committee (RSC) approval of authorizations for use of radioactive materials. The implementation of the KFSH&RC policies on radioactive waste management is the responsibility of the RSO. It provides technical consultation and services in the event of radiation incidents and emergencies. The RSO has a substantial commitment to training on radiation safety and it runs on-site lectures, presentations, and verbal instructions for users of radiation. The Office keeps and maintains documents and records pertaining to inventory of radioactive materials, radiation incidents, authorizations and other documents on radiation safety. The RSO collaboratively works with Health Physics Section of the Biomedical Physics Department. It maintains linkages with other KFSH&RC safety committees, national agencies and with international bodies such as IAEA.
Figure 1. Graph showing the monthly out-going sources for year 2006.

Figure 2. Graph showing the number of imported sources of radioactive isotopes in year 2006.
RSO ACTIVITIES

For the year 2006, the RSO applied for amendment of the KFSH&RC license from KACST for the radiation facility of Nuclear Medicine and the application has been successfully approved. It has renewed the KACST license to import radioactive materials and has submitted the application for the issuance of a license for the Cyclotron and Radiopharmaceuticals facility. It has also renewed the license of TLD Personal Monitoring and Secondary Standard Dosimetry Laboratory facilities for another two years. One application for authorization to use radioactive materials was evaluated and obtained the RSC approval and 7 certifications were issued for importation of radioactive materials. In radiation measurements, there were 636 incoming and 3731 outgoing sources of radioactive materials surveyed. In the principle of “As Low as Reasonably Achievable” (ALARA), 85 investigations were carried out on staff whose occupational doses exceeded the ALARA levels; 128 thyroid bioassays were performed. Five work areas and 2 equipments were surveyed for radiation and contamination levels. A total of 55 radioactive sealed sources were checked for inventory and 30 leak tests were undertaken. The RSO responded to 4 radiation incidents and provided 7 technical consultations. In the area of radioactive waste management, the generated radioactive wastes were managed by the decay-in storage method where 92 drums were surveyed and stored in Warehouse No. 6 and 45 drums of wastes were disposed. In education and training the RSO conducted 4 in-house lectures and provided a one-week on-the-job training on radiation safety to 3 university students. The RSO has maintained its linkage within the Hospital and with national and international bodies. Four RSC meetings were coordinated and the Office continued to have linkages and collaboration with other Hospital committees.

SPECIAL PROJECT-NEW RADIOACTIVE WASTE BUILDING

The construction phase of the new radioactive waste building has started in 2006. The RSO was given the lead role in preparation for its construction. The RSO has completed its review and evaluated the equipment needed for the new facility which is expected to be opened and fully operated before the end of the first quarter of 2007. The interlock system and the security alarm and access system designs were all evaluated to ensure compliance with national regulatory requirements for radiation protection during emergencies. All licensing requirements are submitted to KACST and its construction was favorably approved.

PUBLICATION

To keep abreast with the current national and international standards, the RSO has published the fourth edition of the Radiation Safety Manual. Information, procedures and requirements contained in this edition were derived from publications of international Commission on Radiological Protection (ICRP), and from local regulations of KACST. The new edition was distributed to all user departments after it was approved by the RSC, the Executive Director of Research Centre, and the Chief Executive Director.
The Medical and Clinical Operations Annual Research Report
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The Department of Anesthesiology

Chairman
Hossam Al Oufi

Deputy Chairman
Riaz Ahmad
Project Title: The feasibility of spinal anesthesia for laparoscopic general abdominal procedures in moderate risk patients.

Investigators: Yasser Ali, M Nagui Elmasry, Negmi Hisham, Bamehriz Fahad, Salem Abdel Rahman

Project Description

Background and knowledge

One of the major advantages of laparoscopic surgery is minimizing postoperative morbidity. Other patient’s benefits include reduction in postoperative pain, better cosmetic result and quicker return to normal activities. The previous limitations to the use of spinal anesthesia in laparoscopic surgery were the limited work space, high failure rate, more intra-operative morbidity and significant arterial blood gas alterations. The addition of a small-dose Ketamine infusion to propofol might provide a suitable sedative combination to be used with high spinal anesthesia, producing titratable sedation, increased hemodynamic stability, and minimal respiratory depression, without psychomimetic effects.

Patients and Methods

The presented study was done at KFSH&RC hospital, after patient consenting, where 8 ASA 3 patients undergoing various laparoscopic abdominal procedures were enrolled in the study. The exclusion criteria were ejection fraction below 45% and or peak expiratory flow rate and forced vital capacity of less than 65% of predicted values. After oral premeditation with midazolam 7.5-10 mg 30 min preoperatively, spinal anesthesia was conducted by bupivacaine 0.75% 3 ml at L3-4, in the lateral position to reach a sensory level at T4. Sedation was started by injecting the patients with a bolus of 0.4 mg/kg propofol and 0.1 mg/kg Ketamine prior to spinal anesthesia followed by infusion of 1.2 mg/kg/h and 0.3 mg/kg/h, respectively. The sedation requirements were adjusted to keep the patient sleepy with conservation of airway reflexes at level 3 on a 5 point sedation score. Oxygen was administered using face mask with a flow of 4-6 l/min to maintain 95% or more oxygen saturation. Heart rate, respiratory rate and SpO2 were monitored, together with direct arterial blood pressure monitoring and arterial blood gas analysis through arterial cannulation. Postoperative first time call for analgesia, total morphine consumption during 1st hour and incidence of complications were recorded. 24 hours later, surgeons’ and patients’ satisfaction were obtained and recorded.
Results

Heart rate and mean arterial blood pressure were significantly decreased after spinal anesthesia and intra-peritoneal insufflations of CO₂, with significant increase in arterial carbon dioxide tension accompanied by increase in the respiratory rate. The increase in respiratory rate led to gradual decrease of CO₂ level down to near the pre-operative PaCO₂ values. There was insignificant decrease in oxygen saturation throughout the intra-operative time. Postoperatively there were excellent surgeon and patient’s satisfaction. Only one patient regained sensation before completion of surgery and sedation was deepened to level 5 sedation score. The mean surgical time was 98.5 ±21.4 min while the mean anesthesia time was177.7 ± 20.1 min. First mean time call for analgesia was 50 ± 8 min. 7/18 patients required single dose of morphine of 4 mg during the 1st hour postoperatively.

Conclusions

The technique used is found to be safe and efficient from either the anesthetic and surgical point of view especially for sick patients with intermediate clinical predictors.

Progress


Project Title: Early Graft Function and Carboxyhemoglobin Level in Liver Transplanted Patients

Investigators: Yasser Ali, Hisham Negmi, Nagui Elmasry, Riaz Ahmad, Hossam Al Oufi, Hatem Khalaf

Project Description

Introduction

Heme-oxygenase-1 catalyzes hemoglobin into bilirubin, iron, and carbon monoxide, known vasodilator. Heme-oxygenase expression and carbon monoxide production as measured by blood carboxyhemoglobin levels increase in end stage liver disease patients. We hypothesized that there may be a correlation between carboxyhemoglobin level and early graft function in patients undergoing liver transplant surgeries.

Methods

In descriptive retrospective study, 39 patients scheduled for liver transplant between the year 2005 and 2006 in KFSH&RC are included in the study. All patients received general anesthesia with isoflurane in O₂ 50%. Levels of oxyhemoglobin, carboxyhemoglobin and methemoglobin concentration in percentage were recorded. Also the level of lactic acid, prothrombin time (PT), partial thromboplastin time (PTT), serum total bilirubin and ammonia were recorded. The numbers of blood units transfused were recorded. Measurements were taken as preoperative, anhepatic phase, end of surgery, post-operative on ICU admission and 24 hrs post-operatively.

Results

39 patients were included in the study with 13/39 for living donor liver transplant (LDLT) compared to 26/39 patients scheduled for deceased donor liver transplant (DDLT). The mean age was 35.9±16.9 years while the mean body weight was 60.3±20.9 Kg. Female to male ratio were 21/18. The median Packed red blood cell (PRBC) units was 4 (Rang 0-40). There was significant increase in carboxyhemoglobin level...
during the anhepatic phase, end of surgery and on ICU admission compared with preoperative value \((p<0.005)\). Although there was insignificant changes in methemoglobin level, there was significant decrease in oxyhemoglobin levels throughout the study period compared to the preoperative value \((p<0.005)\). The changes in carboxyhemoglobin level on ICU admission and 24 hrs postoperatively were positively correlated with the changes in serum total bilirubin and prothrombin time \((R = 0.35, 0.58, 0.3\) and 0.3 respectively \(p<0.05)\) but not with changes in serum lactic acid. The same strong correlation was found when analysing LDLT and DDLT patients separately between carboxyhemoglobin concentration and PT and total bilirubin while still the correlation with lactic acid was weak. There was no correlation between average perioperative carboxyhemoglobin concentration during different timing of measurements and average units of transfused blood \((R = -0.02)\) \(p> 0.05\).

**Conclusions**

The changes in carboxyhemoglobin level correlate with the changes in graft functions particularly prothrombin time and serum total bilirubin and may be used as an early, rapid and simple test for early evaluation of graft function.

**Progress**

Presented in the 2\textsuperscript{nd} International Pan Arab Conference for Liver Transplant Surgery held in KFSH&RC, March, 2007.

**Project Project Title: Intra-Peritoneal Bupivacaine Alone or in Combination With Morphine in Patients Undergoing Vertical Bypass Gastroplasty.**

**Investigators:** Yasser Ali, Hisham Negmi, M. Nagui Elmasry, Mohamed Rabie, Monzer Sadek, Fahd Bamehriz and Abdelrahman Salem

**Background and Knowledge**

Intra-peritoneal instillation of local anesthesia and morphine has been used to alleviate post-operative pain in laparoscopic surgery. Controversy exists about the efficacy of this technique.

**Methods**

We studied 48 patients scheduled for Vertical Bypass Gastroplasty (VBG). All of them received the same technique of general anesthesia (GA). Patients were randomly allocated into four equal groups. They received equal volumes of the test drug instilled in the peritoneal cavity at the end of laparoscopy, 50 ml of normal saline (Group S); 50 ml of bupivacaine 0.25% (Group B), 50 ml of bupivacaine 0.25%, plus morphine 40 mcg.kg\textsuperscript{-1} (maximum of 5 mg) Group M or (Group D) patients received the same regimen as Group M in addition, they received 75 mg intramuscular diclophenac after induction of general anesthesia. Wound edges were infiltrated with 10 ml bupivacaine 0.25% in all patients. Morphine 25-50 mcg.kg\textsuperscript{-1} was given intravenously every 10 min as a rescue analgesic to control postoperative pain in Post Anesthesia Care Unit (PACU). Post operative pain was evaluated using Visual Analogue Scale (VAS), vital signs, and morphine consumption, and time to receive rescue analgesia were measured at different intervals. The incidence of post-operative complications (respiratory depression, oxygen desaturation, and nausea and vomiting) was recorded as well as hospital stay.

**Results**

There was significant decrease in VAS, HR, MBP and morphine consumption in Groups M &D when compared to Groups S & B on admission and on discharge from PACU. There were significant decrease in time to receive rescue analgesia as well as significant reduction in hospital study in Groups M and D when compared to Groups S and B. However,
there was no significant difference between group S & B regarding the same parameters.

Conclusions

The presented technique is safe and easy to use with good postoperative morphine sparing analgesia, excellent patient satisfaction and short hospital stay.

Progress


Project Title: Comparative Study Between Two Different Anesthetic Techniques in Living Donor Hepatectomy (LDH)

Investigators: Mohamed Rabie MD, Hisham Negmi MD, Yasser Hammad MD, Hossam Al Oufi, FRCPC, Hatem Khalaf MD

Project Description

Background

Living donor hepatectomy (LDH) is now widely used to meet the need for liver grafts due to the shortage of cadaveric livers. Donor safety and perioperative anesthetic management are our major concern; the aim of our study was to compare two anesthetic techniques for management of living donor hepatectomy.

Patients and Methods

After ethical committee approval and informed written consent, 20 donors ASA I physical status undergoing hepatectomy for living related liver transplant were allocated randomly to one of two groups. Group A where anesthesia was induced with fentanyl 2ug/kg and propofol 2-3 mg.kg\(^{-1}\), and maintained with isoflurane 0.8-1.2% and fentanyl infusion 1-2 mcg.kg\(^{-1}\).h\(^{-1}\). In group B anesthesia was induced with sufentanil 0.2 mcg.kg\(^{-1}\), and propofol 2-3 mg.kg\(^{-1}\), and maintained with propofol infusion 6-12 mg.kg\(^{-1}\).h\(^{-1}\) and sufentanyl infusion 0.2-0.4 mcg.kg\(^{-1}\).h\(^{-1}\). Atracurium was the muscle relaxant for intubation and maintenance in both groups.

Results

There were no perioperative mortality in both groups, no significant statistical differences between both groups as regard demographic data, duration of surgery, duration of anesthesia, hospital stay, intraoperative hemodynamics, blood loss, liver function tests (PT, AST, ALT) measured in the first, third, and seventh days postoperative.

Conclusion

In conclusion, our study demonstrated that both anesthetic techniques were well tolerated for living donor hepatectomy, with no blood transfusion required, with short and safe discharge from PACU and short hospital stay, but with significant laboratory changes reflecting transient impairment in metabolic liver function. These procedures have proven useful as an important alternative to the cadaveric liver transplantation. Both techniques can be used as fast tract technique for living donor hepatectomy.

Progress

Published in the Middle East Journal in August 2006.

Project Title: Bilateral Thoracic Paravertebral Block For CABG
Investigators: Abdullah Al-Ghamdi, MD, Eatimad Bantan, MD, Fatma Al-Dammas, MD, Abdullah Al Halawani, MD, Riaz Ahmad, MD, Faridah Foula, RN

**Project Description**

During coronary artery bypass graft (CABG) with low or high-dose opioid anesthesia, patients may have a sympathetic activation to surgical stress (1). This sympathetic activation causes an increase in arterial blood pressure, tachycardia, and an increase in myocardial oxygen demand which will increase the myocardial oxygen extraction during surgical stimulation in these patients and may lead to myocardial ischemia.

High thoracic epidural anesthesia (TEA) offers a good adjunct to general anesthesia for CABG to haemodynamic stability (2) but carries the risk of neuroaxial heamatoma (3), and many studies have been done in this field (1,2,3).

Bilateral thoracic paravertebral block (BTPVB) may provide similar advantages to TEA in association with a lower risk of neuroaxial heamatoma. An observational study which was done on different cardiac surgeries and shows that continuous BTPVB technique is a feasible and provides good haemodynamic stability and allows early tracheal extubation (4), while a pilot study shows that BTPVB in conjunction with (intravenous patient controlled anesthesia) IVPCA provides effective analgesia after CABG surgery (5).

However, single shot BTPVB effect on intraoperative haemodynamic stability, postoperative pain control and early extubation has not been published or studied.

**Project Title:** Incidence and Major Adverse Events of Difficult Intubation in 25,040 Anaesthetics

**Investigators:** Siham Elrouby, MBBS, DA, Hossam Al Oufi, FRCPC, Mahmoud Aburimsh, MD, FRCA, Mohamed Shoukri, PhD

**Project Description**

**Background**

Difficult intubations carry a higher risk of morbidity and mortality.

**Aim**

To determine the incidence and major adverse anaesthetic events of difficult intubation, and, to study its relationship to age in a tertiary hospital.

**Method**

Data was collected prospectively from 25,040 non-cardiac general anaesthetics (1994-1999). Demographic characteristics of patients and Cormack and Lehane laryngoscopic view classification, methods of management, cardiac arrests, dental trauma, aspirations and death were encoded using a customised database program and analysed with SAS software.

**Results**

The incidence of difficult intubations was (0.96%). (14.8%) were grade 2, (59.9%) grade 3, and (25.2) grade 4. The incidence of difficult intubations in patients age group <1 year (1%) from (1 to < 5 years) (0.95%), from (5 to <10 years) (0.59%) and from (10 to <15 years) (0.3%) indicating decreased incidence with age in pediatric group. The Pearson correlation = 0.94 and the p value (<0.34). In the adult age groups
(15 to <20 years) was (0.65%), (20 to <40 years) was (0.47%), (40 <50 years) was (1.38%), (50 to <60 years) was 1.85%, (>60 years) was 1.9%. Pearsons correlation was positive r=0.85 (p value = 0.023) The incidence of failed intubations and ventilations was .004%.

Cardiac arrest and dental trauma incidences were increased indifficult intubation. Reversiable cardiac arrest (0.8% compared with0.004% in easy intubations; p<0.001) and dental injury (2%, compared with 0.07% in easy intubations (p<0.00001). There was no death or aspiration.

Conclusions

Difficult intubations are infrequent (0.96%) but are associated with a higher incidence of major anaesthetic adverse outcomes. There is a negative correlations with age in pediatric group and a positive one in adults group predictions of difficult intubations in high risk graoups would help to improve its adverse outcome.

Progress

Published in *ASA Anesthesiology Journal*, 2006; 105: A531.

**Project Title: Comparative Study between two Different Anesthetic Techniques in Living Donor Hepatectomy (LDH)**

**Investigators:** Hisham Negmi MD, Mohamed Rabie, MD, Yasser Hammad MD, Hossam Al-Oufi, FRCPC, Siham Elrouby, MD, Hatem Khalaf, MD

**Project Description**

**Aim of the work**

The aim of the present study was to compare two different anesthetic techniques of anesthesia during living donor hepatectomy (LDH) and its implications on the intraoperative hemodynamic, postoperative liver and coagulation function; PACU discharge time and hospital stay duration.

**Patients and Methods**

After ethical committee approval and informed written consent, 20 donors ASA physical status I undergoing hepatectomy for living related liver transplant were enrolled in our study. All donors underwent a full preoperative evaluation .CT was used for preoperative volumetric calculation of the estimated residual hepatic volume of the donors. GVBW ratio >0.8 was intended for recipients. In addition to the standard monitors, intraoperative monitoring included intra-arterial and central venous pressures monitoring and electrocardiogram, urine output, and central temperatures. Hypothermia was prevented during surgery by using warming blanket, Bair Hugger and perfusion warming. The surgical technique was also similar for all patients. Patients were randomly allocated into two groups. Group A where anesthesia was induced with fentanyl 2ug. kg⁻¹ and propofol 2-3 mg. Kg⁻¹, and maintained with isoflurane 0.8-1.2% in air /oxygen (FiO₂ = 0.4-0.5) and fentanyl infusion 1-2 mcg.kg⁻¹.h⁻¹. In group B anesthesia was induced with sufentanyl 0.2 mcg kg⁻¹, and propofol 2-3 mg.kg⁻¹, and maintained with propofol infusion 6-12 mg.kg⁻¹.h⁻¹ and sufentanyl
Anesthesia infusion 0.2-0.4 mcg.kg⁻¹.h⁻¹. Atracurium was the muscle relaxant for intubation and maintenance in both groups. For all patients, hemodynamic measurements (MABP, HR, and CVP) as well as arterial blood gas analysis, hematocrit, serum electrolytes, blood glucose and liver function test with coagulation data were obtained as a base line after establishing of monitoring, after removal of the graft, first, third and seventh days postoperative.

Results

There were no perioperative mortality in both groups, no significant statistical differences between both groups as regard demographic data, duration of operation, hospital stay, intraoperative hemodynamics, blood loss, and liver function tests (PT, AST, ALT) measured in the first, third, and seventh days postoperative. The mean duration of surgery was 394.3 ± 60.8, 398.9 ± 70.3 minutes and duration of anesthesia was 428 ± 52.5, 442 ± 77.4 minutes, the mean age group was 26.8 ± 5.3, 24.6 ± 4.5 in groups A & B respectively. No transfusion was needed for all patients in both groups, there was insignificant difference in the blood loss between both groups, the mean blood loss was 768 ± 225.1 ml and 829 ± 17.4 ml in groups A & B respectively. The Donors in both groups were successfully extubated in the operating room and transferred to PACU for overnight postoperative care and monitoring. The mean discharge time from PACU was 739.2 ± 48.2 and 753.6 ± 55.4 minutes in group A & B respectively with insignificant statistical difference between both groups. PT and INR were significantly elevated from the preoperative values 12.4 ± 0.4 , 0.9 ± 0.07 and 12.3 ± 0.6, 0.97 ± 0.06 in both groups A & B respectively with a maximal increase on (day 3 ) 19.6 ± 2.8 ,1.52 ± 0.16 and 18.9 ± 1.9, 1.53 ± 0.14, but latter showed a gradual decrease during the first week.

No blood products were required in both groups to achieve an INR < 1.4. Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) increased significantly in both groups in the immediate postoperative period as shown in figures 2 & 3, but with insignificant statistical difference between the two groups. Patients were discharged home after 6.8 ± 0.78 days in group A & 7.2 ± 0.63 days in group B with insignificant statistical difference between both groups.

Conclusion

Our study demonstrated that both anesthetic techniques were comparable and well tolerated for living donor hepatectomy for living related liver transplantation, with no blood transfusion required, with short discharge time from PACU and short hospital stay. There were significant laboratory changes reflecting transient impairment in metabolic liver function postoperative which gradually returned to normal. Both techniques can be used as fast tract technique for living donor hepatectomy.

Progress

Published in the Middle East Journal, 2006.
The Department of Dentistry

Chairman
Abdulrahman Al Dawood, BDS, MDSc
The Section of

Pediatric Dentistry

RESEARCH PROJECTS

Project Title: Validity and Reliability of the Arabic Translation of the Child Oral-Health Related Quality of Life Questionnaire (CPQ11-14) in Saudi Arabia. RAC # 2051009

Investigators: Zikra Alkhayal and Alison Brown, QRM

Aim

The purpose of this study was to test the validity and reliability of an Arabic translation and adaptation of the child oral-health-related quality of life questionnaire (CPQ11-14) in Saudi Arabia.

Design

The modified questionnaire included two global ratings (oral health and oral-health-related well-being), and a battery of 36 questions in four domains (oral symptoms, functional limitation, emotional well-being and social well-being). The study population consisted of 174, 11-14 year old children (65% health and 35% medically compromised). Clinical data on caries status and malocclusion were collected for 138 of the children, and 47 completed the questionnaire a second time.

Results

There was a significant difference in mean total scale scores between children with and without malocclusions (P<0.05). Significant relationships were identified between caries status and oral symptoms subscale scores, and between malocclusion and total scale and social well-being subscale scores (P<0.05). Correlation was highly significant between scale scores and global ratings (P<0.01). Cronbach’s alpha was 0.81 and the test-retest reliability was substantial (r=0.65, P>0.001). However, problems were encountered in Saudi Arabia regarding self-reporting of age, and the questionnaire was too long for many of the medically compromised patients.

Conclusions

The questionnaire is valid and reliable for use in Saudi Arabia, although development of a shorter version is recommended.
Project Title: Prevalence of Cleft Lip and Palate in Hospital Based Population KFSHRC – Retrospective Study. RAC # 991030

Investigator: Aziza Al Johar

Objectives

To report the patterns of cleft lip and/or cleft palate (CL/P) in Saudi Arabia from the data collected at a tertiary care hospital.

Design and Setting

A descriptive study based on the Cleft lip/palate and Craniofacial Anomalies Registry functioning at King Faisal Specialist Hospital & Research Center (KFSH&RC), Riyadh.

Patients

All the CL/P patients registered by the registry since June 1999 till December 2005. Results: During the six-and-half-year period a total of 807 cases of CL/P were retrospectively registered. There were 451 males and 356 females with a male to female ratio of 1.3:1. Cleft lip and palate (CLP) was more common (387) than isolated cleft of palate (CP) (294) and isolated cleft lip (CL) (122). Male predominated in CLP and CL while female in CP with male to female ratio of 1.6:1, 1.22:1 and 0.9:1 for CLP, CL and CP, respectively. Riyadh region had more numbers of cases (32.0%), followed by Asir (15.6%) and Eastern (14.6%) regions. Parents of 439 cases had consanguineous marriages; positive family history of cleft was seen in 224 cases. There was a significant association between consanguineous marriage of parents and positive family history of CL/P (p=0.02). Ninety one cases had congenital heart disease out of the 238 cases with associated anomalies. 40.5% of the children with CP had associated anomalies while 23.0% of the children with CL and CP had associated malformations.

Conclusion

The pattern of cleft observed in this study does not differ significantly from those reported in literature for the Arab populations.

PUBLICATIONS

Project Title: The Effects of Periodontal Tissue Health and Treatment on Glycemic Control within Diabetics - A Multi-Center Study.
KACST ARP 21-3, RAC # 2021024

Investigators: K Al Zoman, S Al Mubarak, A. Al Zaid, A. Al Suwayed, A. Al Ghofaili, S. Sobki, M. Tariq and M Abu-Ras

Project Description

The objective of this study was to evaluate whether diabetic patients with chronic periodontitis would experience improvement in periodontal health and glycemic control after scaling and root planning (SRP) with and without adjunctive therapy (doxycycline hyclate 20 mg, twice/day). Subjects were divided into four test groups: (A) one session of SRP at baseline visit, and placebo tablets twice/day starting at baseline visit and continuing for 3 months only, (B) one session of SRP at baseline visit, and doxycycline hyclate (20 mg, twice/day) starting at baseline visit and continuing for 3 months only, (C) two session of SRP, first at baseline visit and the second at 6-month visit, and placebo tablets twice/day at baseline visit and 6-month visit continuing for 3 months at each visit, and (D) two session of SRP, first at baseline visit and the second at 6-month visit, and doxycycline hyclate 20 mg, twice/day at baseline visit and 6-month visit continuing for 3 months at each visit. The study procedures at day 0, included preliminary oral examination, blood drawing, collection of gingival fluid for bacterial analysis, and dental x-ray. Periodontal parameters include recording of Probing Pocket Depth (PPD), Clinical Attachment Level (CAL), Plaque Index (PI), Modified Gingival Index (MGI) and Bleeding on Probing (BOP). Bacterial analysis for pathogenic anaerobes in gingival crevicular fluid including Porphyromonas gingivalis (pg), Bacteroids forsythus (Bf) Actinobacillus actinomycetemcomitans (Aa), and Prevotella intermedia (Pi) was performed by PCR method. The over all bacterial loads (Pg, Bf, Aa and Pi) showed a decrease towards the end of study as compared to base line. The results of clinical assessment showed significant improvement in oral hygiene parameters at 3, 6, 9 and 12 months visits when compared to base line values for all groups. No significant difference was found between the different groups at the follow up visits. The results of biochemical analysis showed no significant change in diabetes markers including blood glucose, HbA1c (DCCT), as
compared to the base line. However, when we reanalyzed subjects according to the baseline level of HbA1c, we noticed a statistically significant reduction for those patients whom had their HbA1c ranging from 7-9 for all groups separately and when combined together (p<0.05) Table (1&2). The results suggest that mechanical scaling and root planning has positive effect in terms of overall bacterial load and periodontal indices. The improvement in metabolic condition is clinically and significantly noticeable when the HbA1c value is <9. Therefore, it is important for diabetic patients to control their periodontal condition, as there is a tendency to have a better improvement of the glycated hemoglobin value for those patients with good to fair metabolic control measured with HbA1c.

**Progress**

Completed.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment Type</th>
<th>Baseline</th>
<th>3 Months</th>
<th>6 Months</th>
<th>9 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (n = 43)</td>
<td>SRP + Placebo</td>
<td>8.82 ± 0.27</td>
<td>8.41 ± 0.38**</td>
<td>8.45 ± 0.41*</td>
<td>8.77 ± 0.39</td>
<td>9.08 ± 0.48</td>
</tr>
<tr>
<td>B (n = 32)</td>
<td>SRP + LDD</td>
<td>8.77 ± 0.29</td>
<td>8.39 ± 0.32**</td>
<td>8.36 ± 0.38*</td>
<td>8.43 ± 0.23*</td>
<td>8.70 ± 0.47</td>
</tr>
<tr>
<td>C (n = 29)</td>
<td>SRP + Placebo</td>
<td>8.91 ± 0.317</td>
<td>8.55 ± 0.54**</td>
<td>8.48 ± 0.26*</td>
<td>8.38 ± 0.39**</td>
<td>8.79 ± 0.44</td>
</tr>
<tr>
<td>D (n = 28)</td>
<td>SRP + LDD</td>
<td>8.89 ± 0.29</td>
<td>8.34 ± 0.22**</td>
<td>8.30 ± 0.27**</td>
<td>8.23 ± 0.41**</td>
<td>8.44 ± 0.52*</td>
</tr>
</tbody>
</table>

**Table 1.** Effect of Periodontal Treatment on HbA1c (%) (7-9).

Values are Mean±SEM *P-Values versus base line, t-test *P<0.05, **P<0.01, ***P<0.001

**Groups compared:**
# A vs B,
$ A vs C,
† A vs D,
‡ B vs C,
f B vs D,
¶ C vs D.

<table>
<thead>
<tr>
<th>All Groups</th>
<th>Baseline</th>
<th>3 Months</th>
<th>6 Months</th>
<th>9 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 132)</td>
<td>8.81 ± 0.26</td>
<td>8.41 ± 0.30*</td>
<td>8.25 ± 0.29**</td>
<td>8.12 ± 0.37*</td>
<td>7.79 ± 0.48**</td>
</tr>
</tbody>
</table>

**Table 2.** Effect of Periodontal Treatment on HbA1c (DCCT) for all groups (%) (7-9).

Values are Mean±SEM *P-Values versus base line, t-test *P<0.05, **P<0.01, ***P<0.001

Values are Mean±SEM *P-Values versus base line, t-test *P<0.05, **P<0.01, ***P<0.001
Project Title: The Prevalence of Periodontal diseases in Saudi Arabia. KACST AT-26/50

Investigators: S. Al Mubarak, K. AlZoman, A. Al Suwayed, A. AlGhamdi, I. Zainalabdeen, A. Jamil Choudhry, A. Al Nowaiser and M. Al Hawawi

Project Description

The purposes of this cross-sectional study are to:

- Evaluate the pertinence of early periodontal diagnosis within medical services for Saudi patients in the private and public sectors.
- Evaluate periodontal disease prevention methods within the private and public sectors.
- Determine the epidemiology and different causes of periodontal diseases in Saudi patients.
- Suggest the methods to reduce the incidence of periodontal diseases.

Progress

Grant Approval from KACST.

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Project Title: Evaluation of Dental Extraction Suturing INR on Post Operative Bleeding Patients Maintained on Oral Anti-Coagulant Therapy. KACST LGP-10-2

Investigators: S. Al Mubarak, K. Al Zoman, M. A. Rass, A. AlSuwyed, A. Alabdulaaly and S. Ciancio

Project Description

The purpose of this study is to evaluate if dental extractions can be safely performed in patients on warfarin therapy without altering the dose of anticoagulant

Progress

On going.

PUBLICATION

The Dermatology Unit

Medical Director
Adullah Al-Fadley
RESEARCH PROJECTS

Project Title: Skin-Homing DC8 + T-lymphocytes Show Preferential Growth In Vitro and Suppress CD4 + T-cell Proliferation in Patients with Early Stages of Cutaneous T-cell Lymphoma

A total of 27 T-lymphocyte cell strains were established from skin biopsies of 24 patients with various stages of cutaneous T-cell lymphoma (CTCL) by addition of the T-cell growth factors interleukin (IL)-2 and IL-4. Cellular proliferation and phenotypic changes were measured over 3 months in culture, and T-cell clones were studied using T-cell receptor-γ re-arrangement techniques. An average outgrowth of 134 million T-lymphocytes from a 4-mm skin biopsy was observed over 2 months. Initially, most T-cells expressed the CD4+ phenotype. In 17 cell strains from patients with early CTCL, a statistically significant predominance of CD8+ T-lymphocytes developed over 8-weeks' culture, indicating that CD8+ T-cells were predominant in cell strains from advanced CTCL (p<0.05). TCR-γ re-arrangement studies revealed, on average, 12 T-cell clones per cell strain, which was reduced over time to 6 T-cell clones per cell strain. Lymphocytes from peripheral blood could kill lymphocytes from an autologous cell strain, suggesting the presence of autoreactive cytotoxic T-cells. Our study suggests how skin-homing CD8+ T-lymphocytes from patients with early stage CTCL can suppress the in vitro growth of skin-homing CD4+ T-lymphocytes, indicating immune surveillance.

Project Title: Leiomyosarcoma of the Chest Wall with Cutaneous Metastases to the Scalp in a Patient with Systemic Sclerosis

Leiomyosarcoma (LMS) is a rare malignant neoplasm. Cutaneous metastases of LMS is very rare. It has been reported from uterus, retroperitoneum deep soft tissue of lower extremity and from the mesentery. We described a patient with systemic sclerosis who developed cutaneous metastatic LMS after 20 months of therapy with cyclophosphamide of 50 mg/day. Cyclophosphamide is known to cause LMS of bladder; can it cause LMS elsewhere again remains to be answered. Since cyclophosphamide is commonly used as an immunosuppressant as well as an antineoplastic agent, we would like to stress that clinicians using this drug be aware of it potential risks.
PUBLICATIONS


The Department of Family Medicine and Polyclinics

Chairman
Abdulaziz Al Nasser

Deputy Chairman
Ahmed Hassan

Deputy Chairman
Abdulaziz Al Saif
RESEARCH PROJECTS

Project Title: The Outcome of Hematopoietic Stem Cell Transplant for Wiskott-Aldrich Syndrome Patients: A Single Center Study

Principal Investigator: Rand Arnaout
Co-Principal Investigators: Abdalaziz Al-Ghonaium and Amal Al-Seraihy
Other Investigators (Peds): Hassan Al-Rayes, Saleh Al-Muhsen, Hamoud Al-Mousa and Hasan Al-Dhekri
Pathology & Lab Med: Abdelghani Tbakhi and Tarek Owaidah
Pediatric Hematology/Oncology: Mouhab Ayas, Abdullah Al-Jefri, Samira Rifai and Ashraf Radwan

Project Description

Wiskott-Aldrich Syndrome (WAS), an X-linked recessive disorder, consists of the triad of eczema, microplatelet thrombocytopenia and recurrent infections due to immune deficiency. They also have an increased risk of autoimmune disorders and lymphoreticular neoplasia.

In 1994, the WASP gene responsible for the disorder was cloned and has provided an effective tool to confirm the diagnosis of WAS and its milder form X-linked thrombocytopenia (XLT). It is also helpful to identify the carrier females and facilitate prenatal diagnosis.

Bone marrow transplantation (BMT) for WAS patients was first performed in 1968, by Bach et al and now it is the treatment of choice for WAS patients.

Without stem cell transplantation, patient might die from bleeding, infection or malignancy. Both cellular and humeral immunity is affected in WAS patient. In addition to the correction of thrombocytopenia and immunodeficiency, hematopoietic stem cell transplant (HSCT), is assumed to decrease the possibility of malignancy.

In a recent report from the International Bone Marrow Transplant Registry, 170 WAS patients had been transplanted, with a 70% 5-year probability of survival. The available survival data emphasize the importance of early transplantation. WAS patients usually fail the T-cell depleted bone marrow transplantation.
Progress

This project is approved by The Research Advisory Council, numbered RAC (#2051051). The project is currently ongoing and the final report is due in April 2007.
The
King Faisal Cancer Centre

Director
Dahish Ajarim

Deputy Director
Mahmoud Al Jurf
The King Faisal Cancer Centre

The King Faisal Cancer Centre (KFCC) is a newly established structure for cancer care of adult patients with a mission of providing excellent cancer treatment, education and research by means of integrated team work and the vision to become the best international centre for cancer research, prevention, and treatment. Accredited by the World Health Organization (WHO) as a collaborating centre for cancer prevention and control, KFCC patients are assessed in multidisciplinary clinics and treated in accordance with disease specific internationally accepted management guidelines. The Research Unit provides support for research projects and serves as a hospital base for cancer and bone marrow transplantation registries. KFCC continues to be actively involved in institutional, national, and international research protocols with priority given to those addressing national oncology problems. KFCC houses the National Cancer Registry and the Gulf Council Countries (GCC) Cancer Registry which defines population-based incidence of cancer in the Kingdom. The goal of KFCC is to establish an internationally renowned Cancer Institute to meet the ever growing needs of patients with cancer and hematological disorders.

The following is a summary of the department’s activities during 2006.

- First Academic and Research Day was held on 31st May 2006 and was heavily attended by the Oncologists from all the Cancer Centers in Riyadh.
- Accomplished very successful International Symposium on Cancer from 7-9 November, 2006, which was attended by world renowned speakers from the Gulf region, Europe and North America.
- Initiated steps for Radiation Oncology department to join the Radiation Therapy Oncology Group (RTOG).
- Letters of interest to join South West Oncology Group (SWOG) and Cancer and Leukemia Group B (CALGB) were submitted.
- STEMSoft (BMT Data Management Software) was upgraded to increase productivity.
- Designed several new CRF’s for new Principal Investigators.
- New HLA-DR1 & 2 protocol initiated in collaboration with the Histopathology.
- Spearheaded collaboration with several pharmaceutical companies to initiate myriad of international and multicenter clinical trials at the KFCC. Several new projects were submitted to RAC for approval to enhance overall, median and diseases free survival of our cancer patients as well as augment the quality of life.
- Prepared new protocol using Alemtuzumab treatment for steroid-refractory acute graft vs. host disease for patients undergoing Bone Marrow Transplantation.
- One new Saudi Assistant Tumor Registrar was hired in the Research Unit, and now comprises 50% of the Tumor Registry Staff.
- Future plans include Clinical Research Coordinator Course and CCRP Review Course and examination at the KFSH&RC for the clinical research professionals, not only for the hospitals in Riyadh, but the whole Kingdom.
- Dr. Mohareb did a presentation at the Bone Marrow Transplant Symposium in USA on 12 February and talked about Saudi Experience of Clinical Research.
- Collaborated with American Society of Therapeutic Radiology & Oncology (ASTRO) to translate Breast Cancer and other patient educational brochures in Arabic.
RESEARCH PROJECTS

The research projects of the KFCC are categorized into:

- Database
- Protocol
- Research Study
- Registries

DATABASE

Project Title: Prospective and Retrospective Data Collection of Breast Cancer Cases from 2000 to Present. (RAC#2051-029)

Investigators: D Ajarim, T Twegieri, S Akhtar, A Al Sayed

Project Description
Breast cancer database.

Progress
Active, continuous plus follow-up; rapid accrual.

Project Title: Prospective Data Collection of Newly Diagnosed Hodgkin’s Disease and Non-Hodgkin’s Lymphoma Cases. (RAC# 2002-010)

Investigators: D Ajarim, M Al-Shabanah, M El-Foudch

Project Description
Lymphoma database

Progress
Active; slow accrual; complicated CRF.

Project Title: Prospective Data Collection of Newly Diagnosed Nasopharyngeal CA Cases (RAC#2051 017).

Investigators: N Al Rajhi, A Al-Amro, M Memon

Project Description
Nasopharyngeal Cancer.

Progress
Active; accrue approx. 4-5 per week and follow-up.

Project Title: Prospective Data Collection of Multiple Myeloma Cases. (RAC#2031-048).

Investigators: F Al-Sharif, M Aljurf, N Chaudhri
**Project Description**

Myeloma database.

**Progress**

Active; slow accrual; complicated CRF.

**Project Title:** Severe Aplastic Anemia. (RAC# 2021-084).

**Investigators:** H Zahrani, M Aljurf, P Seth, A Behainy, G Dawsari, S Zaidi, E Colcol, I El Hassan

**Project Description**

Anemia database.

**Progress**

Active; accrue approx. 10 per month and follow-up.

**Project Title:** Acute Lymphocytic Leukemia (ALL) 1423 Protocol. (RAC# 2021-050)

**Investigators:** E Sahovic, et al.

**Project Description**

Leukemia database (ALL).

**Progress**

Active; accrue approx. 10 per month and follow-up.

**Project Title:** Prospective Database for Chronic Myelogenous Leukemia. (RAC# 2051-056)

**Investigators:** N Chaudhri, et al.

**Project Description**

Chronic Myelogenous Leukemia Database.

**Progress**

Active; continuous accrual.

**Project Title:** Prospective Database for Acute Myeloblastic Leukemia. (RAC# 2051-057)

**Investigators:** N Chaudhri, et al.

**Project Description**

Acute Myeloblastic Leukemia (AML).

**Progress**

Active; continuous accrual.

**Project Title:** Retrospective Assessment of Head and Neck Sarcoma and Prognostic Factors Evaluation. (RAC# 206-1073)

**Investigators:** Abdelsalam M, et al.

**Project Title:** A SU011248 Expanded Access Protocol for Systematic Therapy of Patients with Metastatic Renal Cell Carcinoma Who Are Ineligible for Participation in Other SU011248 Protocols but May Derive Benefit from Treatment of SU011248. (RAC# 206-1043)

**Investigators:** Bazarbashi S, Abdelsalam M, et al.

**Project Title:** T Cell Rich B Cell Non Hodgkin’s Lymphoma – Presentation, Treatment Outcome and Prognostic Factors. (RAC# 206-1020)

**Investigators:** Akhtar S, et al.
Project Title: Investigating the Role of the Actin-Bundling Protein (Fascin) in Regulating Dendritic Cells Migration Cancer Metastasis. (RAC# 206-0016)

Investigators: Twegieri T, et al.

Project Title: Retrospective Evaluation of High Dose Chemotherapy and Autologous Stem Cell Transplantation in Patient with Hodgkin’s Lymphoma. (RAC# 205-1050)

Investigators: Akhtar S, et al.

Project Title: Effect of Radiation Therapy on Autologous Peripheral Blood Stem Cell (CD34+cells) Collection in Patients with Relapsed or Refractory Diffuse Large Cell Lymphoma and Hodgkin’s Lymphoma. (RAC# 205-1024)

Investigators: Maghfoor M, et al.

Project Title: First line Bevacizumab and Chemotherapy in Metastatic Cancer of the Colon or Rectum. First BEAT (Bevacizumab Expanded Access Trial). (RAC# 204-1082)

Investigators: Bazarbashi S, et al.

Project Title: Cytogenetic Analysis of Bone Marrow Specimens Prior to High Dose Chemotherapy and Autologous Stem Cell Transplant in Patients with Non-Hodgkin’s Lymphoma and Hodgkin’s Lymphoma. (RAC# 204-1050)

Investigators: Akhtar S, et al.

Project Description

Search Protocol.

Progress

Active, rapid accrual.

Project Title: Retrospective Evaluation of Primary Central Nervous System Lymphoma. (RAC# 204-1034)


Project Title: Use of 18F-Flourodeoxyglucose (FDG) Positron Emission Tomography (PET) as a Predictor of Residual Disease and Subsequent Relapse in Patients with Non Hodgkin’s Lymphoma (NHL) and Hodgkin’s Lymphoma (HD) Undergoing High Dose Chemotherapy (HDC) and Peripheral Blood Stem Cell Transplant (PB SCT). (RAC#204-1015)

Investigators: Akhtar S

Project Description

Research Protocol.

Progress

Active, rapid accrual

Project Title: Gene-environment Interaction: TP3 Gene Mutation Spectrum in Breast Cancer in Saudi Arabia. (RAC#204-0037)

Investigators: Twegieri T. et al.

Project Title: Using Support Vector Machines for Prognosis and Survival Prediction in Breast Cancer. (RAC# 204-0006)

Investigators: Twegieri T. et al.
Project Title: Phase II Study of Vincristine, Adriamycin, Actinomycin, Ifosfamide Combination Chemotherapy in Ewing’s Sarcoma. (RAC# 203-1065)


Project Title: Basic Research Project for Evaluation of Anti-Tumor Activity of Gamma/Delta T-Cell in Cancer Patients. (RAC# 203-022)


Project Title: Investigation of the B7-H1 Molecular Expression by Breast Cancer and Myeloid Dendritic Cells of Saudi Breast Cancer Patients and Blockade of the Molecule as an Approach for Cancer Immunotherapy. (RAC# 203-0034)

Investigators: Twegieri T, et al.

Project Title: Synovial Sarcoma: A Retrospective Analysis of Prognostic Factor and Treatment Outcome. (RAC# 202-1086)


Project Title: Metaplastic Breast Cancer Clinical Presentation Treatment Results and Prognostic Factors. (RAC# 202-1080)


Project Title: Retrospective Review of Outpatient Management of Adult Ewing’s Sarcoma. (RAC# 202-1061)


Project Title: Phase II Trial of Concurrent Administration of Intravesical BCG and Interferon Alpha-2B in the Treatment and Prevention of Recurrence if Superficial Transitional Cell Carcinoma of the Urinary Bladder. (RAC# 201-1073)


Project Title: Retrospective Review of all Cases of Post-Transplant Lymphoproliferative Disorders (PTLD). (RAC# 201-1063)


Project Title: Calypso Protocol - AMulti-National, Randomized, Phase II, GCG Intergroup Study Comparing Pegylated Liposomal Doxorubicin (CAELYX® and Carboplatin vs Paclitaxel and Carboplatin in Patients with Epithelial Ovarian Cancer in Late Relapse (>6months). (RAC# 201-1062)

Investigators: Rehman K, et al.

Project Title: A Pilot Trial of Pre-Operative Chemo-Radiotherapy Using Capecitabine (Xeloda) and External Beam Radiation Followed by Definitive Surgery in Patients with Localized (Non-Metastatic) Rectal Cancer. (RAC# 201-1031)

Investigators: Rehman K, et al.
Project Description
Research Protocol.

Progress
For Follow-up, closed for accrual.

Project Title: Contribution of Authors from Low and Middle-Income Countries to Palliative Care Research. (RAC# 2060-032)
Investigators: S. Alsirafy, M. Al-Shahri

Project Title: Electrolyte Abnormalities Among Cancer Patients in the Palliative Care Setting. (RAC# 2061-001)
Investigators: S. Alsirafy, M. Al-Shahri, A. Hassan, M. Hidayatullah, H. Ghanem

Project Title: Prospective Data Collection of Newly Diagnosed Nasopharyngeal CA Cases
Investigators: Al Rajhi, Al Amro, Memon

Project Description
Nasopharyngeal cancer database.

Progress
Active, continuous accrual.

PROTOCOLS

Project Title: Organ Preservation: Weekly Carboplatin & Taxol with Concurrent RT for Locally Advanced Laryngeal & Hypolaryngeal Cancer. (RAC# 0971-024)
Investigators: Al-Amro and Memon

Project Description
Protocol.

Progress
Follow up only.

Project Title: Phase III: Assess Conventional RT With Conventional Plus Accelerated Boost RT in the Treatment of Nasopharyngeal Cancer. (RAC# 0971-004)
Investigators: Dr. Al-Amro and Dr. Al-Rajhi

Projection Description
Protocol.

Progress
Survival Follow up only.

Project Title: Randomized Multicenter Study of 5 vs 6 Weekly Fraction of RT in the Treatment of SCC of the Head and Neck. (RAC# 0981-019)
Investigators: Dr. Al-Amro and Dr. Al-Rajhi

Project Description
International.

Progress
Follow up only.
RESEARCH STUDY

Project Title: Cervix Carcinoma, HPV Infection, Genetic Predisposition and Biomarkers of Response to Chemo-radiation Therapy (RAC# 2060-029)


REGISTRY

Project Title: International Bone Marrow Registry (Autologous Transplant)

Investigators: Section of Adult Hematology/BMT

Project Description

Registry (BMT-Autologous Transplant).

Progress

Continuous accrual, NP CRF 2500 to 3000 variables. FU CRF-1000 variables; active; accrue approximately 30 per year and follow-up.

Project Title: European Bone Marrow Registry

Investigators: Adult and Pediatric Hematology

Project Description

Registry (BMT).

Progress

Active; continuous accrual.

Project Title: Post Operative Adjuvant Chemotherapy Followed by Adjuvant Tamoxifen vs Nil for Patients with Operable Breast Cancer – EORTC. (RAC#93-107)

Investigators: A Ezzat, S Bazarbashi, M Raja

Project Description


Progress

Follow-up only.

Project Title: Using Support Vector Machines for Prognosis and Survival Prediction in Breast Cancer. (RAC# 2040-006)

Investigators: T Twegieri, et al.

Project Description


Progress

Complete.

Project Title: Open Label, Randomized, Multicenter Study to Evaluate the Use of Zoledronic Acid in the Prevention of Cancer Treatment Related Bone Loss in Postmenopausal Women with ER+ and/or Pgr+ Breast Cancer Receiving Letrozole as Adjuvant Therapy. (RAC#2031-089)

Investigators: D Ajarim, T Twegieri
Project Description

Progress
Inactive.

Project Title: Phase II Study of Neoadjuvant Chemotherapy with Doxorubicin, Followed by Oxetaxel-Cisplatin in Locally Advanced Breast Cancer. (RAC# 2011-022)

Investigators: A Ezzat, et al.

Project Description

Progress
Closed for accrual; for FU and TX completion.

Project Title: Use of FDG PET as Predictor of Residual Disease and Subsequent Relapse in Patients with NHL and HD Undergoing HDC and ASCT. (RAC# 2041-051)

Investigators: S Akhtar, I Iqbal, A Ezzat, S Bazarbashi, D Ajarim, I Maghfoor, A El-Weshi, M Rahal

Project Description
Prospective Research Protocol-Lymphoma.

Progress
Active.

Project Title: Randomized Phase II Trial on Primary Chemotherapy with High-Dose Methotrexate, Alone or Associated with High Dose Cytarabine, Followed by Response and Age Tailored Radiotherapy for Immunocompetent Patients with Newly Diagnosed Primary Nervous System Lymphoma.

Investigators: A Abdelsalam, et al.

Project Description
International study; prospective research protocol-Lymphoma.

Progress
Pending RAC #approval.
Project Title: Loss to Follow-Up in Lymphoma Patients.


Project Description
Prospective Research Protocol-Lymphoma.

Progress
Closed; 2nd paper publication.

Project Title: (Phase II): Adjuvant and Neoadjuvant Chemotherapy in Operable Epidermoid Esophageal Cancer. (RAC# 981-021)

Investigators: Bazarbashi, T Amin, S Bakheet, A Ezzat, El Fadda, C Pai, D Ajarim, M Raja, M Rahal, M Memon, Raningwala, M El Foudeh, J Powe

Project Description
Prospective Research Protocol-Esophageal cancer

Progress
Follow-up; closed for accrual.

Project Title: Randomized Phase III Trial of Surgery Alone or Surgery Plus Peoperative Gemcitabine-Cisplatin in Clinical Early Stages of Non-Small Cell Lung Cancer. (RAC# 2031-059)

Investigators: K Rehman, et al.

Project Description
Prospective Research Protocol-Lung Cancer.

Progress
Follow-up only.

Project Title: (Phase III): Assess Conventional RT With Conventional Plus Accelerated Boost RT in the Treatment of Nasopharyngeal CA. (RAC# 0971-004)

Investigators: A Al-Amro, N Al-Rajhi

Project Description
Prospective Research Protocol-Nasopharyngeal Cancer.

Progress
Survival follow-up only.

Project Title: Randomized Multicenter Study of 5 vs. 6 Weekly Fraction of RT in the Treatment of SCC of the Head and Neck. (RAC# 0981-019).

Investigators: A Al-Amro, N Al-Rajhi

Project Description
Prospective Research Protocol-Head and Neck.

Progress
Follow-up only.

Project Title: Organ Preservation: Weekly Carboplatin and Taxol with Concurrent RT for Locally Advanced Lryngeal and Hypopharyngeal Carcinoma. (RAC# 0971-024).

Investigators: A Al-Amro, M Memon
Project Description

Prospective Research Protocol-Laryngeal and Hypopharyngeal Cancer.

Progress

Active; very slow accrual.

Project Title: Phase II, Trial of Concurrent Administration of Intravesical BCG and Interferon in the Treatment and Prevention of Recurrence of Superficial Transitional Carcinoma of the Urinary Bladder. (RAC# 2011-073).

Investigators: S Bazarbashi, et al.

Project Description

Prospective Research Protocol-Urinary Cancer

Progress: Active; slow accrual.

Project Title: Multi-National, Randomized, Phase III, GCIG Intergroup Study Comparing Pegylated Liposomal Doxorubicin (CAELYX®) and Carboplatin vs. Paclitaxel and Carboplatin in Patients with Epithelial Ovarian Cancer in Late Relapse. (RAC# 2051-062)

Investigators: K Rehman

Project Description

Prospective Research Protocol-Ovarian Cancer

Progress

New International Study.

Project Title: Phase III, Study of Cisplatin and RTX vs. RTX Alone in Squamous Cell Carcinoma of Cervix

Investigators: K Rehman, et al.

Project Description

Prospective Research Protocol-Cervical Cancer.

Progress

Follow-up only.

Project Title: Randomized Trial of Chemotherapy With or Without Granulocyte Stimulating Factor in Operable Osteosarcoma. (RAC# 931-009)


Project Description

Prospective Research Protocol-Sarcoma.

Progress

Follow-up only.

Project Title: Randomized Study for the Treatment of Ewing’s Sarcoma of the Bone (EORTC). (RAC# 931-025)


Project Description

Prospective Research Protocol-Sarcoma.
Progress
Follow-up only.

Project Title: Phase II Pilot Study of Vincristine, Adriamycin, Actinomycin D, Ifosfamide Combination Chemotherapy in Ewing's Sarcoma (RAC# 2031-065)

Investigators: M Memon, Raja, et al.

Project Description
Prospective Research Protocol-Sarcoma.

Progress
Active; slow accrual.

Project Title: Pilot Trial of Pre-Operative Chemo/RT Using Xeloda and External Beam RT Followed by Definite Surgery in Patients with Localized Rectal CA. (RAC# 2011-031)

Investigators: S Bazarbashi, et al.

Project Description
Prospective Research Protocol-Colon/colorectal cancer.

Progress
Active.

Project Title: First-Line Bevacizumab and Chemotherapy in Metastatic Cancer of the Colon or Rectum (International Study). (RAC# 2041-082).

Investigators: S Bazarbashi, et al.

Project Description
Prospective Research Protocol-HSCT.

Progress
Follow-up only.

Project Title: Induction of Mixed Hemopoietic Chimerism in pts Using Fludarabine, Low Dose TBI, PBSC Infusion and Post Transplant in Immunosuppression w/CSA and Mycophenolate Mofetil. (RAC# 2001-051)

Investigators: M Aljurf, H Al Omar, M Gyger, R Stuart, E Sahovic, Al-Homaidi

Project Description
Prospective Research Protocol-HSCT.
Progress

Active; very slow accrual.

Project Title: Prospective Randomized Trial of Marrow vs Filgastrim Mobilized Peripheral bld Progenitor Cells in HLA-Matched Related Allogenic Transplant Wax with Short Course Methotrexate & CSA as Prophylaxis for Acute Graft vs. Host Disease. (RAC#1998-014).

Investigators: M Aljurf, E Sahovic, M Gyger, R Stuart, F Al Sharif, N Chaudhri, and F Mohareb

Project Description

Prospective Research Protocol-HSCT.

Progress

Follow-up only.

Project Title: Prospective Study on combination immunotherapy for the treatment of aplastic anemia-Pilot Study. (RAC#2041-008).

Investigators: H Al Zahrani, et al.

Project Description

Prospective Research Protocol-Anemia.

Progress

Pending RAC #approval.

Project Title: Acute Lymphoblastic Leukemia 1423 Protocol. (RAC# 2021-050)

Investigators: E Sahovic, et al.

Project Description

Prospective Research Protocol-ALL.

Progress

Follow-up only.

RETROSPECTIVE STUDIES


4. H Al Omar. BCR/ABL Translocation status and T-Cell stimulation capacity of dendritic cell derived from CD34+ and CD34-bone marrow compartments from patients with chronic myeloid leukemia. (RAC# 990 029).


10. S Akhtar, et al. Effect of radiation therapy on autologous peripheral blood stem cell (CD34+ cells) collection in patients with relapsed or refractory diffuse large cell lymphoma and Hodgkin’s lymphoma. (RAC# 2051024)


19. F Hussain et al., Breast Cancer among Young Saudi Women.

PROSPECTIVE STUDIES


FUTURE RESEARCH DIRECTION

- Promote well designed clinical/transitional research activities.
- Establish firm collaboration and break barriers with Research Center and other related organizations.
- Establish membership and collaboration with national, regional and international research working groups.
- Expand and maximize utilization of available database for certain tumor sites in research direction and bench marking.
- Establish a refresher course for the Clinical Research Coordinators to achieve CCRP certification.
- Establish more international multicenter clinical research trials in collaboration with myriads of cooperative groups.
- To host an international symposium on hematological malignancies.
- Develop a comprehensive translational research program to faster opportunities for continuous research between oncologists and basic medical scientists at the Research Centre to enhance clinical applicability of research findings.
PUBLICATIONS


PRESENTATIONS / CONGRESS PROCEEDINGS

1. Quality versus Quantity of Life, Dr. S. Brown, 1st End of Life Care Mini Symposium, National Guard Hospital, Riyadh, May 2006.

2. Pain Management in the Patient with Cancer, Dr. M. Al-Shahri, King Fahad Central Hospital, Giza, KSA, March 2006.


4. Introduction to Palliative Care, Dr. M. Al-Shahri, Nursing Oncology Course, Military Hospital, Dammam, KSA 30 March 2006.

5. Applied Palliative Care: Case Studies, Dr. M. Al-Shahri, Nursing Oncology Course, Military Hospital, Dammam, KSA, 30 March 2006.

6. Rules of Dealing with Patients with Far Advanced and Life-Threatening Diseases, Dr. M. Al-Shahri, Symposium on Appropriate Treatment of Patients, King Fahad Conventional Center, Riyadh, KSA (In Arabic), 04 April 2006.


8. End of Life Care, Dr. M. El-Foudeh, Grand Round (Outreach Program) King Fahad Specialist Hospital, Jeddah, March 2006.


11. Contribution of Authors from Low & Middle-Income Countries of Palliative Care Research, Dr. S. Alsirafy and Dr. M. Al-Shahri, UICC World Cancer Congress, Washington, D.C; USA, July 2006. Oral Presentation.

12. Electrolyte Abnormalities Hospitalized Adult Cancer Patients upon referral to Palliative Care, Dr. S. Alsirafy, Dr. M. Al-Shahri, Dr. A. Hassan, Dr. M. Hidayatullah, Dr. H. Ghanem, Multinational Association for Supportive Care in Cancer and the International Society for Oral Oncology (MASCC/ISOO) 18th Annual Symposium, Toronto, Canada, June 2006. Poster Presentation.


16. Prostate Cancer Guidelines of Treatment, Dr. A. Al-Hebshi, A Clinical Update on Prostate Cancer, Northwest Armed Forces Hospital, Tabuk, Saudi Arabia, 22 November 2006.


20. Radiotherapy in Nasopharyngeal Carcinoma, Dr. N. Al-Rajhi, King Saud University, April 2006.
The
King Faisal Heart Institute

Director
Charles Canver

Deputy Director
Mohammed Al Amri
The Department of

King Faisal Heart Institute

The King Faisal Heart Institute (KFHI) is committed to excellence in patient care, teaching, and research. Its mandate involves undertaking research on the challenges of cardiovascular diseases facing the people of Saudi Arabia.

At the end of 2006, the KFHI had 30 approved/ongoing research projects and 7 newly submitted research projects under review. These projects included retrospective records review and analysis, registries, interventional, diagnostic, basic research, and animal studies. All sections of the KFHI have research proposals as follows: adult cardiology = 8, adult cardiovascular surgery = 7, pediatric cardiology = 9, pediatric cardiovascular surgery = 8, databases which include adult and pediatric surgery or adult and pediatric cardiology = 5.

RESEARCH PROJECTS

Project Title: E-Select Registry. RAC # 2061077

Principal Investigator: Fawaz Al Turki

Project Description

This multi-center observational study (500 centers worldwide) will collect national profiles and epidemiological data on patients who received Cordis Sirolimus-Eluting Stents (SES). The aims of this post-marketing study are:

a. To investigate the long-term effects, safety and performance efficiency of the SES in routine clinical practice;
b. To assess the frequency and duration of acute or chronic coronary syndrome related events;
c. To describe and measure the incidence of acute, sub-acute and late stent thrombosis and major adverse cardiac events (MACE);
d. To identify the predictors of acute, sub-acute and late stent thrombosis and MACE;
e. To analyze the stent performance data in patient sub-populations for diabetes, in-stent restenosis, acute myocardial infarction & multivessel coronary disease.
Progress
This study is under review by the RAC.

Project Title: PANORAMA: An Observational Study. RAC # 2061075

Principal Investigator: Majid Al Fayyadh

Project Description
This study will collect epidemiological data on patients who have medtronic implantable pulse generators and implantable cardioverters/defibrillators.

The aims of this post-marketing study are:

a. To investigate the long-term operation of the devices and device features;
b. To assess the frequency and duration of heart-failure related hospitalizations;
c. To analyze temporal aspects of cardiovascular events and symptoms;
d. To describe the incidence and prevalence of ventricular and atrial arrhythmias;
e. To associate cardiovascular events and symptoms with device data and diagnostics;
f. To determine programming preferences considering physical assessment variables and pathologies;
g. To build a prognostic model of time to death by using population baseline variables as predictors.

Project Title: NT-Pro-Brain Natriuretic Peptide (BNP) Levels in Neonates With and Without Cardiac Disease – a New Method to Detect Cardiac Causes of Respiratory Insufficiency in Neonates. RAC # 2061068

Principal Investigator: Ghassan Siblini

Project Description
This prospective randomized, stratified study will measure and assess blood NT-Pro-BNP levels which are elevated only in full-term and premature neonates who are oxygen or ventilator dependant due to hemodynamically significant large left-to-right shunts. Determination of NT-Pro-BNP levels will allow physicians to differentiate cardiac from non-cardiac causes of oxygen/ventilator dependence when an echocardiographic diagnosis may not be available.

The aim of the study is to confirm the normative levels of NT-Pro-BNP and Troponin-T in a sample of healthy Saudi neonates and premature infants and to compare these values to NT-Pro-BNP levels in premature infants with congenital heart disease.

Progress
This study is under review by the RAC.

Project Title: The Impact of Palliative Procedures on the Growth of Pulmonary Arteries in Pulmonary Atresia with Ventricular Septal Defect. RAC # 2061041

Principal Investigators: Akram Allam and Ahmad Sallehuddin
Project Description

This retrospective study will evaluate the impact on the growth of the neo- pulmonary artery and major aorto-pulmonary collateral arteries, following various palliative approaches in patients with pulmonary atresia with ventricular septal defect, and identify the most successful method.

Progress

Patients who underwent this procedure from 1998 to 2004 have been identified. Medical records and KFHI databases are being reviewed.

Project Title: Losartan for the Prevention of Atrial Fibrillation in Patients with Rheumatic Valvular Heart Disease in the Perioperative Period of Valve Surgery. RAC # 2061035

Principal Investigator: Suleiman Kharabsheh

Project Description

This randomized, open-label study will evaluate the potential effect of losartan in preventing atrial fibrillation in patients over the age of 14 years with rheumatic valve heart disease who undergo valve surgery.

Progress

This study is under review by the RAC.

Project Title: Prospective Trial of Endoscopic versus Conventional Vein Harvesting Techniques for CABG: Morphology and Post-Operative Outcome. RAC # 2061034

Principal Investigator: Muhammed Tamim

Project Description

This prospective study will assess whether minimally invasive endoscopic harvesting of the saphenous vein performed at the KFSH&RC reduces harvesting site tissue damage and morbidity. The study will also compare the histological properties of saphenous veins harvested conventionally with saphenous veins harvested endoscopically.

Progress

This study is under review by the RAC.

Project Title: Early and Long-term Outcomes and Follow-up of Mechanical Valve Replacement in Patients Less than 15 Years of Age. RAC # 2061029

Principal Investigator: Elias Saad

Project Description

This retrospective review will analyze the data of patients up to 15 years of age who underwent mechanical valve prosthesis implantation procedures. Three groups will be studied based on their age: Group I: 2 years of age and younger, Group II: 2 to 5 years, and Group III: 5 to 15 years. The study will document long-term clinical outcomes and valve-associated complications.

Progress

Patients who underwent valve procedures from 1988 to 2004 have been identified. Data is being collected from medical records, the valve registry database, and the echo database.
Project Title: Results of Heart Valve Surgery for Infective Endocarditis. RAC # 2061019

Principal Investigator: Shahid Khan

Project Description

This retrospective chart analysis will review the medical records of KFSH&RC patients with infective endocarditis who required surgical intervention. Both native and prosthetic valve endocarditis (NVE and PVE) will be included. The changes in incidence over the years, common organisms involved, and the factors affecting outcomes will be studied.

Progress

This study is under review by the RAC.

Project Title: Are Palliative and Reconstructive Procedures Effective in Promoting Growth of Pulmonary Arteries in Cases of Pulmonary Atresia (PA), Ventricular Septal Defect (VSD) and Major Aorto-Pulmonary Collaterals (MAPCs)? RAC # 2061018

Principal Investigator: Fareed Khouqeer

Project Description

This retrospective study will review and analyse all consecutive cases of PA with VSD and MAPCs treated at the KFSH&RC over the last 10 years. A detailed description of the pulmonary artery anatomy, the abnormal arborization and the collaterals will be done for each case based on cardiac catheterization findings. The influence of PA morphology and other factors on the final outcomes will be studied.

The different palliative and reconstructive procedures offered to patients and the effect of each approach in enhancing pulmonary arteries growth will also be studied.

Progress

Subjects have been identified and the data obtained from their medical records and the catheterization database is being reviewed.

Project Title: Clopidogrel and Hemorrhage in Coronary Artery Bypass Grafting (CABG): A Retrospective Study. RAC # 2061004

Principal Investigator: Shahid Khan

Project Description

This retrospective study will evaluate KFSH&RC patients who received Clopidogrel (an anti-platelet agent) and who underwent CABG. The aims are to determine the effect of clopidogrel on blood loss during surgery, and to describe Clopidogrel-associated morbidity and mortality.

Progress

The preliminary work of identifying patients for this study is currently being done.

Project Title: Redo Coronary Artery Bypass: Why so Infrequent? RAC # 2061002

Principal Investigators: Fareed Khouqeer and Mohammed Kandeel

Project Description

This retrospective chart review will study the redo coronary artery bypass graft (CABG) procedures performed at the KFSH&RC. The Project will describe the techniques used and attempt to identify the factors which may affect the frequency of “Redo-CABG” surgeries.
Progress

Appropriate patient records have been identified for this study and data is being collected.

Project Title: Laboratory Study: The Effects of Levosimendan on the Vasomotricity of Human Radial Artery (RA) *In Vitro*. RAC # 2060020

Principal Investigator: Charles Canver

Project Description

Levosimendan is a potent inotropic agent with known vasodilatory effects on coronary arteries in vitro and in vivo. Although the preoperative administration of levosimendan improves the cardiac hemodynamic conditions in patients undergoing coronary artery bypass graft surgery, a direct effect of the drug on human bypass graft arteries has not yet been demonstrated. This *in vitro* study, will study the effects of levosimendan on the mechanical properties of RA conduits.

Progress

This study is currently under review by the King Abdulaziz City for Science and Technology (KACST).

Project Title: Pilot Study: Evaluation of a Modified Technique of Heterotopic Heart Transplantation in the Dog & Rat. RAC # 2060019

Principal Investigator: Charles Canver

Project Description

Using the dog as an animal model, this feasibility study is evaluating a reproducible and easy to manage heterotopic heart transplantation model that will be used in future research projects. The purpose of this model is to provide adequate hemodynamic performance of the donor heart without disturbing the overall stability of homeostatic conditions. This model will be used to study xenotransplantation and transplant without immunosuppression.

Progress

To date one dog has undergone exploratory surgery.

Project Title: *Chlamydia Pneumoniae* Deoxyribonucleic Acid (*C. Pneumoniae* DNA) & Coronary Artery Disease: A Pilot Study. RAC # 2051061

Principal Investigator: Walid Hassan

Project Description

This prospective, randomized pilot-study will primarily focus on:

a. the detection of *C. Pneumoniae* DNA in coronary sinus blood samples,

b. the underlining correlation, if any, between *C. Pneumoniae* DNA and an increased risk of atherosclerosis, and

c. determining the effects of *C. Pneumoniae* on levels of other cardiac markers such as CRP, BNP, Angiotensin II and Troponin T.

The results of this study may help us to understand the underlying inflammatory process associated with atherosclerosis and *C. Pneumoniae*.

Progress

The study is under review by the RAC.
Project Title: Long-term Outcome of Aortic Valve Replacement Using the Ross Procedure in KFHI. RAC # 2051055

Principal Investigator: Zohair Al Halees

Project Description

This retrospective study examines the Ross procedure technique used to replace diseased or defective aortic valves with the patient’s own healthy pulmonary valve, which in turn is replaced by a homograft. The study focuses on the long term follow-up of patients who had surgery from Jan 1990 to Dec 2004, for event free survival rate, re-operation(s) on the autograft and/or homograft, associated morbidities and mortality, and factors affecting long term survival of the valve replacement technique.

Progress

Data collection is completed and is currently being analyzed.

Project Title: Permanent Pacing in Pediatric Patients: The King Faisal Specialist Hospital Experience. RAC # 2051040

Principal Investigator: Majid Al Fayyadh

Project Description

This is a retrospective review to evaluate the experience and long term results of pacemaker therapy in children treated at the KFSH&RC.

Progress

The medical records of relevant patients have been identified and data collection and analysis are ongoing, including subgroup analysis.

Project Title: Long-Term Outcome of Mitral Valve Repair Versus Mitral Valve Replacement Using Mechanical and Bioprosthetic Valves. RAC # 2051016

Principal Investigator: Zohair Al Halees

Project Description

This retrospective review is studying the long-term effect of mitral valve repairs versus mitral valve replacement using mechanical and/or bioprosthetic valves. The aims of the study are to:

a. compare the event-free survival periods associated with mitral valve repairs and replacement,
b. describe the incidences of redo repairs and redo replacements,
c. identify the factors contributing to the need for redo surgeries,
d. study the above factors on mortality and morbidity.

Progress

Mitral valve repair and replacement cases with or without tricuspid valve repair/replacement from Jan 1988 to Dec 2004 have been identified. Data cleaning and analysis are ongoing.

Project Title: Percutaneous Ventricular Septal Defect (VSD) Closure: The KFSH&RC Experience. RAC # 2041070

Principal Investigators: Mansour Al Joufan and Fadel Al Fadley

Project Description

The aim of this retrospective review was to further examine the safety and effectiveness profiles of the Amplatzer device used in VSD closing.
Progress

This study has been completed and a final report has been submitted to the RAC.

Project Title: Does Modified Ultrafiltration Affect the Clinical Outcome Following Congenital Heart Surgery?. RAC # 2041065

Principal Investigator: Ahmad Sallehuddin

Project Description

This is a prospective, randomized, double-blinded study comparing conventional with modified ultrafiltration in patients undergoing cardiac surgery.

Progress

Recruitment of the targeted number of subjects for this study has been completed. Data analysis is ongoing.

Project Title: Incidence of Diastolic Heart Failure (DHF) in the Elderly. RAC # 2041043

Principal Investigator: Fayez El Shaer

Project Description

DHF with preserved systolic function is a unique and challenging disease. Several studies have shown age to be the most important factor in diastolic filling. This study will assess the prevalence, patient characteristics, morbidity and prognosis in elderly patients with DHF in comparison to systolic heart failure.

Progress

Data collection for this retrospective review has been completed. The final report has been submitted to the RAC.

Project Title: The Impact of the Right Ventricle to Pulmonary Artery Shunt on the Early Outcomes of the Modified Norwood Procedure. RAC # 2041041

Principal Investigator: Ahmad Sallehuddin

Project Description

This retrospective review is studying the outcomes of patients with right ventricle to pulmonary artery shunt who underwent a modified Norwood Procedure.

Progress

Data has been collected and is currently being validated.

Project Title: Effect of Percutaneous Coronary Intervention (PCI) on Diabetic Patients. RAC # 2031082

Principal Investigator: Walid Hassan

Project Description

This retrospective study is analyzing the effect of PCI in diabetic patients with coronary artery disease. The analysis includes an assessment of the status of the coronary artery stents, the rate of restenosis, progression of or neo-atherosclerosis and factors affecting regional wall motion and ejection fractions.
Project Title: Is Myomectomy Justifiable in Preventing Recurrence of Discrete Subaortic Obstruction?. RAC # 2031072

Principal Investigator: Ahmad Sallehuddin

Project Description

This is a retrospective study of patients with atrioventricular valve regurgitation who underwent a modified Fontan operation from 1986 to 2001 at the KFSH&RC. The aim of the study is to compare the occurrence of subaortic obstruction to the incidence of myomectomy for discrete subaortic stenosis.

Progress

Data collection is ongoing.

Project Title: Tetralogy of Fallot (TOF): A Retrospective Chart Review. RAC # 2031061

Principal Investigator: Saud Al Oufi

Project Description

A retrospective review of medical records of patients with TOF treated at the KFSH&RC. Patient progress is studied using data from clinical follow-up visits and echocardiography appointments.

Progress

The data has been collected and validated and is presently being analyzed.

Project Title: Establishing Atrioventricular Synchrony in Dogs with Surgically Created Complete Atrio-Ventricular (AV) Block. RAC # 2031019

Principal Investigator: Majid Al Fayyadh

Project Description

Using the dog as an animal model, this project is studying the possibility of creating an electrical AV connection in addition to or as an alternative to the AV node. 10 dogs will be utilized; serial electrocardiograms will be performed and studied for patterns of conductivity.

Progress

8 surgeries were performed with and without growth factor injection; serial ECGs were obtained during the follow-up period.

Project Title: Retrospective Medical Records Review of Truncus Arteriosus. RAC # 2031015

Principal Investigator: Ahmed AlOmrani

Project Description

The purpose of this retrospective study is to analyze the data of neonates and infants who underwent primary repair of a truncus arteriosus anomaly at the KFSH&RC from 1990 to 2000.

Progress

Data collection for this project has been difficult. The final report, requesting an extension, has been submitted to the RAC.
Project Title: Fate of Bicuspid Neo-Aortic Valve in Arterial Switch Operation. RAC # 2021058

Principal Investigator: Shahid Khan

Project Description

This project is studying the long term integrity of the bicuspid pulmonary valve when used as an aortic valve in an arterial switch operation (ASO). Data from the medical records of patients who underwent an ASO between 1986 and 2001 is being collected and analyzed.

Progress

Data has been collected from over 80% of the records identified for this study.

Project Title: Outcomes of Contegra Grafts. RAC # 2021049

Principal Investigator: Ahmad Sallehuddin

Project Description

This retrospective review is examining the outcomes of patients who received the contegra biological valved conduit as an alternative to homografts.

Progress

Data collection and verification are on-going.

Project Title: Optimal Approach of Atrioventricular Insufficiency in Fontan Patients. RAC # 2021017

Principal Investigator: Ahmad Sallehuddin

Project Description

This retrospective review was conducted to evaluate the outcome of patients less than 2 years of age who underwent a modified Fontan operation from 1986 to 2001.

Progress

Data collection and analysis have been completed. The final report has been submitted to the RAC.

Project Title: KFHI Surgery Registry. RAC # 2001058

Principal Investigator: Zohair Al Halees

Project Description

This registry includes all cardiovascular surgical procedures performed at the KFSH&RC and is utilized as a valuable research and program administrative tool.

Progress

This is an ongoing registry.

Project Title: Percutaneous Transluminal Coronary Angioplasty (PTCA) Registry. RAC # 2001057

Principal Investigator: Hani Al Sergani

Project Description

This is an ongoing Registry of patients who underwent PTCA at the KFSH&RC. The objective is to examine revascularization strategies for coronary artery disease and the outcomes of interventions for patients with acute coronary syndrome and chronic coronary insufficiency.
Progress

Data collection is ongoing and has been useful in establishing KFHI guidelines for:

a. the use of bare and drug eluding stents
b. techniques for percutaneous intervention in high risk patients
c. the use of intracoronary IIb/IIIa agents for high risk complex lesions.

Project Title: Valve Registry. RAC # 2001055

Principal Investigator: Zohair Al Halees

Project Description

This registry includes data on KFSH&RC patients (both adult and pediatric) who have undergone valve surgery. Data on these patients’ pre-operative, peri-operative, post-operative and follow-up course is collected and including data on events such as thromboembolism, endocarditis, rhythm variations, anticoagulation, anticoagulation-related bleeding, readmissions, re-operations, symptomology and medications.

Progress

While the registry continues to grow, there are presently over 7000 patients in it. The data are entered in Apollo data integrating system, which is being utilized partially yet and other parallel valve databases.

The data is used for quantitative and qualitative analysis, quality improvement, departmental statistics, for publications and abstract presentations.

There are multiple ongoing projects under the umbrella of this registry.

Project Title: Mitral Balloon Valvotomy Registry Database. RAC # 2001054

Principal Investigator: Mohammed Fawzy

Project Description

This registry includes, short, intermediate and long-term follow-up data on patients who underwent a mitral balloon valvotomy procedure.

Progress

18 years of follow-up data has been collected and updated on an ongoing basis. The goal is to complete 20 years of long-term assessment for this group of patients.

Project Title: Pediatric Heart Catheterization Registry. RAC # 2001053

Principal Investigator: Fadel Al Fadley

Project Description

The aim of this project is to establish a registry for all diagnostic and interventional pediatric cardiac catheterizations performed at the KFSH&RC.

Progress

Data collection is ongoing.

Project Title: Congenital Heart Disease Registry. RAC # 991026

Principal Investigators: Mansour Al Jufan and Zohair Al-Halees

Project Description

This Registry is a collaborative project between the KFHI and the Biostatistics, Epidemiology
and Scientific Computing Department, Research Centre.

**Progress**

Data collection is ongoing.

**Project Title:** Evaluation of Cardiac Adaptive Signaling in Left Ventricular Overload Disease.  
**RAC #** 990004

**Principal Investigator:** Nduna Dzimiri

**Project Description**

This basic research project, using the ventricular overload (LVO) as a disease model, is investigating the mechanisms regulating the sequence of events involved in the progression of, or recovery from, cardiac disease. Specifically this study will examine:

- Altered gene expression by differential display techniques.
- Altered regulatory and signaling proteins by two-dimensional gel electrophoresis and related techniques.
- Mechanisms that regulate the sequence of events leading to heart failure.

**Progress**

This project is ongoing.

**Project Title:** Clinical Trial of Glycar Quadrileaflet Mitral Valve (QMV) in Patients Requiring Mitral Valve Replacement.  
**RAC #** 0971023

**Principal Investigator:** Zohair Al Halees

**Project Description**

The aim of this multi-centre, prospective study is to evaluate the (QMV) for:

- Feasibility of clinical insertion.
- Early mortality.
- Symptomatic benefit.
- Early valve related complications.
- Hemodynamic performance.
- Durability.

**Progress**

Data has been collected on 75% of the total number of patients targeted for this study. The study will be closed at the KFSH&RC in 2007 and a final report submitted to the RAC.

**FUTURE RESEARCH DIRECTIONS**

The KFHI has developed a 5-year strategic research plan (SRP) designed to promote and enhance basic and applied research, and to take advantage of the aspects of the KFSH&RC as a JCIA accredited hospital and a leader in healthcare in the Middle East.

The goal of this plan is to develop and sustain significant, internationally acknowledged research in several thematic areas. The KFHI plans to significantly increase its research capacity in each of these areas over the next five years and to become recognized internationally for its high caliber research.

The KFHI’s objective is to increase scientific knowledge of cardiovascular diseases, including their epidemiology, risk and risk factors, prevention, detection and diagnosis, treatment and prognosis.
This objective will be achieved in the context of the KFSH&RC healthcare organizations which provide care in diverse patient care settings, as well as utilizing community-based healthcare resources. The SP will also take advantage of existing integrated data systems from within the KFHI and other KFSH&RC resources.

PUBLICATIONS

2006 Publications and International Presentations by Staff of the KFHI include:

November


October


September

4. ME Fawzy, M Mansour, H Sergani, F El Shaer, and C Canver. Do we need to Stent Discrete Coarctation of the Aorta: 17-year Follow-up Results of Balloon Coarctation Angioplasty. World Congress of Cardiology, Barcelona, Spain, Sept 3-6, 2006.
5. ME Fawzy, M Shoukri, W Hassan, M Al Amri, M Kandeel, A Eldali, and C Canver. Long-Term Results (up to 16 years) of Mitral Balloon Valvuloplasty in a Series of 518 Patients and Predictors of Long-Term Outcome. World Congress of Cardiology, Barcelona, Spain, Sept 3-6, 2006.


7. ME Fawzy, H Sergani, W Hassan, A Badr, M Shahid, M Al Amri, M Kandeel, and C Canver. What is the Best Option of Treatment for Patients with Severe Mitral Stenosis Associated with Severe Tricuspid Regurgitation? World Congress of Cardiology, Barcelona, Spain, Sept 3-6, 2006.


9. W Hassan, M Awad, M Fawzy, M Nawaz, S Malik, F El Shaer, M Shoukri, C Canver Long-Term Effects (up to 18 Years) of Balloon Angioplasty of Coarctation of Aorta on Systemic Hypertension and LV Hypertrophy in Adolescents and Adults. World Congress of Cardiology, Barcelona, Spain, Sept 3-6, 2006.

August


2. ME Fawzy, M Shoukri, W Hassan, M Al Amri, M Kandeel, A Eldali, C Canver. Long-Term Results (up to 16.5 years) of Mitral Balloon Valvuloplasty in a Series of 518 Patients and Predictors of Long-Term Outcome. European Heart Journal Supplementary, Aug 2006.


June


May


3. W Hassan, M Fawzy, H Al Sergani, F El Shaer, A Alomrani, C Canver. Long-Term (up to 17 years) outcome of Pulmonary Balloon Valvuloplasty in Adults on Regression of Severe Infundibular Stenosis and Severe Tricuspid Regurgitation. Society for Cardiovascular Angiography and Interventions’ 29th Annual Scientific Sessions - Chicago, IL, USA May 10-13, 2006.


March

1. ME Fawzy, H Al Sergani, F El Shaer, M Monsour, A Osman, C Canver. Regression of Severe Infundibular Stenosis and Severe Tricuspid Regurgitation after Pulmonary Balloon Valvuloplasty. 55th Annual Scientific Session, American College of Cardiology - Atlanta, Georgia Mar 11-14, 2006.

2. ME Fawzy, H Al Sergani, F El Shaer, M Monsour, A Osman, C Canver. Long-Term (up to 17-years) Outcome of Pulmonary Balloon Valvuloplasty in Adults. 55th Annual Scientific Session, American College of Cardiology - Atlanta, Georgia Mar 11-14, 2006.


February

1. ME Fawzy, H Al Sergani, F El Shaer, M Monsour, A Osman, C Canver. Regression of Severe Infundibular Stenosis and Severe Tricuspid Regurgitation After Pulmonary Balloon Valvuloplasty Long-Term (up to 17-years) Outcome of Pulmonary Balloon Valvuloplasty in Adults. Supplement A in the Journal of the American College of Cardiology, Vol. 47; No.4. Feb 21, 2006.

The
Liver Transplant and Hepatobiliary and Pancreatic Surgery

Chairman
Mohammed Al Sebayel

Deputy Chairman
Mohammed Al Sofayan
The research activities in the Department of Liver Transplant are evolving, but not at the same pace as the progress of its infrastructure and clinical activities. All members are showing interest in research and will resume this year a regular monthly research meeting, creating databases, and establishing collaborations with other departments including the Research Centre. Articles were published in the year 2006, in both local and international journals. Abstracts were accepted and presented in international meetings. Research projects are being presented in the research meetings of the department and a deadline was assigned for each idea to assess its progress. These projects involve both transplant hepatology and transplant surgery in addition to donor issues, with special emphasis on ideas that help the program development. However, research productivity can be improved once the problem of shortage of staff is solved and with the increase in the number of patients transplanted.

ACTIVE RESEARCH PROJECTS

Project Title: Survival Following Cadaveric Versus Living Donor

Investigators: Mohammed Al Sebayel, Hatem Khalaf, Mohammed Al Sofayan, et. al.

Project Description

Survival was compare between cadaveric versus living related liver transplantation between April 2001 to present.

Progress

Presented for poster presentation to ILTS (International Liver Transplant Society) Meeting held in Milan, Italy on May 2006. In the process of writing the whole manuscript.

Project Title: Evaluation of Donors for Living Donor Liver Transplantation: The role of Protocol Biopsy in Detecting Macrovesicular Steatosis

Investigators: Mohammed Al Sebayel, Hamad Al Bahili, Mohammed Al Omran, et. al.
Liver Transplant and Hepatobiliary and Pancreatic Surgery

Project Description

Reporting the incidence of significant macrovesicular steatosis in donors with body mass index and 28 or less. Between May 2001 to November 2005, 100 consecutive donors with BMI of 28 or less were biopsied after all the other criterial for donation were met, including detailed radiological evaluation. All liver biopsies were evaluated by two independent pathologists. Donors with more than 10% macrovesicular steatosis were rejected from donation in our program.

Progress

Presented for poster presentation to ILTS (International Liver Transplantation Society) Meeting held in Milan, Italy on May 2006. In the process of writing the whole manuscript.

Project Title: Aggressive Hepatitis B Recurrent in Post Transplant Patients with and without HBIG

Investigator: Mohammed Al Sebayel

Project Description

This project describes difference in recurrent in Hep. B beween three cohorts of patients, patients receiving HBIG, patients receiving Lamivudine and HBIG, and patients who are not receiving prophylaxis. The aim of the study is to find out the usefulness of Hep. B prophylaxis on long-term basis i.e. more than a year after liver transplant.

Progress

Data have been collected and are at the stage of analysis.

Project Title: Functional Status of Donors Following LDLT

Investigators: Mohammed Al Sebayel, Mr. Majid Nasif

Project Description

This project based on interviewing living donors through questionnaire which was designed in order to find functional status of donors after transplantation both from psychological, physical and mental perspective.

Progress

20 out of 30 subjects have been interviewed so far over the phone and will proceed in data analysis.

Project Title: Multi-Center: Randomized Open-Label Study to Compare the Outcome of Hep. C Patients Following LRLT and Cadaveric Liver Transplantation Receiving Either Neoral or Tacrolimus

Investigator: Mohammed Al Sofayan

Project Description

To evaluate the value of neoral in reducing the recurrence rate and improving patient and graft survival.

Progress

Writing protocols.

Project Title: Nuclear Imaging of Transplanted Liver: is it Helpful in the Immediate Post Transplant Period
Investigator: Mohammed Al Sofayan

Project Description

Evaluating the natural behavior immediately following transplantation. No similar study has been conducted before.

Progress

Analyzing data.

Project Title: Post Transplant Lymphoproliferative Disorders in Liver in Liver Transplant Patients at KFSHRC

Investigator: Mohammed Al Sofayan

Project Description

Descriptive study of PTLD in our transplant group and the marked response following treatment with Anti-CD20.

Progress

Analyzing data and writing paper.

Project Title: Living Donor Evaluation

Investigator: Mohammed Al Sofayan

Project Description

Look at the correlation of each demographic factors, cost analysis of donor work-up, correlation between CT with liver biopsy and look at the estimated weight in the CT and the actual weights as well as look at the anatomy of right posterior segment and the middle hepatic vein.

Investigator: Mohammed Al Sofayan

Project Description

Case report presenting the effectivity of Rituximab with Sirolimus based immunosuppressive regimen in treating PTLD.

Project Title: Successful Living Related Donor Kidney Transplantation After Treatment of Post Transplant Lymphoproliferative Disorder (PTLD) Using Humanized Anti-CD20 Monoclononal Antibody (Rituximab)

Investigators: Mohammed Al Saghier, Ayman abdo, Ibrahm Al Hassoun et.al

Project Description

Case report presenting the effectivity of Rituximab with Sirolimus based immunosuppressive regimen in treating PTLD.

Progress

Presented for poster presentation to ILTS (International Liver Transplantation Society) meeting held in Milan in Italy on May 2006. In the process of writing the whole manuscript.

Project Title: Risk of Progression of Neurowilson's Disease After Orthopedic Liver Transplantation (OLT): Case Report

Investigators: Mohammed Al Saghier, Ayman Abdo, Mohammed Al Sofayan

Project Description

Case report presenting the beneficial role of sirolimus as a primary immunosuppresson for Neurowildson's patient post liver transplantation to avoid Tacrolimus neurotoxicity.
Progress

Presented for poster presentation to ILTS (International Liver Transplantation Society) meeting held in Milan, Italy on May 2006. In the process of writing the whole manuscript.

Project Title: Early Post Right Lobe Living Related Liver Transplant Venous Outlet Obstruction Treated with Balloon Dilatation Followed by Severe ARDS: Case Report

Investigator: Mohamed Al Saghier Ayman Abdo, Mohammed Al Sofayan

Project Description

Case report presenting the beneficial role of Sirolimus as a primary immunosuppression for Neurowildson’s patient post liver transplantation to avoid Tacrolimus neurotoxicity.

Progress

Presented for poster presentation to ILTS (International Liver Transplantation Society) meeting held in Milan, Italy on May 2006. In the process of writing the whole manuscript.

Project Title: The Outcome of Hepatitis C Recurrent on Arab Ethnic Race: Post Liver Transplantation with Genotype 1 and 4

Investigators: Mohammed Al Sagheir, Ayman Abdo, Mohammed Al Sofayan, et. al.

Project Description

Reviewed 81 patients with HCV at time of transplantation (between July and May 2005). To look at negative predictive variables associated with recurrent post orthotopic liver transplantation and the necessity of preemptive therapy of first year with presence of high recurrence rate to control virus load especially with potent immunosuppression.

Progress

At stage of data collection

Project Title: Non-Heart Beating Liver Recipients Outcome

Investigators: Mohammed Al Sagheir, Yasser El-Sheikh

Project Description

This is analysis and follow-up of 17 patients who were transplanted abroad (China) and being follow-up at KFSHRC. The aim of the study is to compare and analyze post-operative biliary and vascular problems and Mortality & Morbidity post liver transplant in non-hear beating donors.
Progress

Data has been collected and at stage for analysis.

Project Title: The Accuracy of Two Different Methods in Estimating the Right Graft Volume After Adult-to-Adult Living Donor Liver Transplantation

Investigators: Hatem Khalaf, Yusuf Kadhi

Project Description

Evaluation of the accuracy of two different methods in preoperative assessment of right graft volume in AALDLT. Between Jan. 2003 and Dec. 2005, out of 27 AALDTs performed at KFSHRC, right graft volume and percentage were both preoperatively calculated in all donors using CT scan dedicated software (Tissue Volume revision V1.0.12H developed General Electric). The right graft volume was preoperatively estimated using two different methods; the first was the radiological volume (RV) given by CT scan and the second was a calculated volume (CV)-PERCENTAGE % of the right graft (given by CT scan) x standard liver volume (calculated by Makuuchi formula – Volume (mL)=706.2 x Body Surface Area (m2)+2.4. Both methods were subsequently compared to the actual volume (AV) measured during the surgery. The Graft Recipient Weight Ration (GRWR) was also calculated using all three volumes (RV, CV, and AV) Lin’s 1989 concordance correlation coefficient (CCC) was used to measure the agreement between AV and RV as well as between the AV and CV. This was repeated using the GRWR measurements. In our experience, the use of CV has shown a good correlation with AV. Therefore, using CV in conjunction with RV might be of value in a more accurate estimation of right volume for AALDLT.

Progress

Accepted for publication: Transplantation Proceedings.

Project Title: Biliary Complications Following Cadaveric Versus Living Donor Liver Transplantation: A Single Center Experience

Investigators: Hatem Khalaf

Project Description

Between April 2001 and Dec. 2005, a total of 81 LTs were performed at KFSHRC (47 CLTs and 34 LDLTs). Chi Square Test was used for statistical analysis. In our experience, the incidence of biliary complications was significantly higher in the LDLT group compared to the CLT group.

Progress

Presented for oral presentation to ILTS (International Liver Transplantation Society) meeting held in Milan, Italy on May 2006. Submitted the whole manuscript for publication on 2006.

Project Title: Outcome of Saudi Patients Undergoing Cadaveric Liver Transplantation in China

Investigators: M Al Saghier, A Abdo, Y Sheikh1, A Al Saghier, M Neimatallah, M Al Sofayn1, A Nadir, H Khalaf, M Al Sebayel

Project Description

Intend to describe the outcome of patients transplanted in China and followed in King Faisal Specialist Hospital and Research Centre in Riyadh.
Project Title: HCV Genotype 4 Recurrence Post Liver Transplantation

Investigators: Hatim Mudawi, Ahmed Helmy, Mahmoud Saleh, Hatem Khalaf, Hamad Al Bahili, Yaser Al Sheikh, Yaser Medhat, Mohammad Al Saghier, Mohammad Al Sofayan, Mohammad Al Sebayel, and Ayman A Abdo

Project Description

All patients who have received liver transplantation for hepatitis C (whether locally or abroad) and were followed in the period from 1991 to end of 2006, were reviewed and suggests that HCV recurrence post liver transplantation in genotype 4 patients is not significantly different from other genotypes.

Progress

Submitted for publication (Jan. 2007).

Project Title: Biochemical and Virological Response to Adefovir in Patients With Lamivudine-Resistant Hepatitis B Virus YMDD Mutant Before and After Liver Transplant

Investigators: A Helmy, A Abdo, H Mutawi, H Al Ashgar, K Al Qahtani, M Al Quaiz, M Al Saghier, M Al Sofayan, H Khalaf, M Al Sebayel

Project Description

To describe the efficacy and safety of ADV therapy in patients with pre and post transplantation and its response to HbeAg negative patients.

Progress

Presented as ORAL presentation at 10th Middle East Society of Organ Transplantation at Kuwait, Dec. 2006. In process of writing the whole manuscript.

Project Title: Liver Transplantation for Autoimmune Hepatitis: A Single Center Experience

Investigators: H Khalaf, W Al Mourad, Y El-Sheikh, M Al Sofayan, A Abdo, A Helmy, H Al Bahili, M Al Saghier, M Al Sebayel

Project Description

To present the KFSHRC experience with Liver Transplantation (LT) for Autoimmune Hepatitis from April 2001 to Aug. 2006.
Progress

Presented as poster presentation at 10th Middle East Society of Organ Transplantation at Kuwait, Dec. 2006. In process of writing the whole manuscript. Submitted the whole manuscript for publication on Nov. 2006. Accepted for publication: Transplantation Proceedings.

Project Title: Donor Outcome After Live Liver Donation: A Single Center Experience

Investigators: H Khalaf, M Al Sofayan, H Al Bahili, Y El Sheikh, M Al Sagher, A Helmy, A Abdo, A Al Sebayel

Project Description

To evaluate the donor outcome and morbidity after donor hepatectomy for LDLT at KFSHRC between April 2001 to August 2006.

Progress

Presented as an oral presentation at 10th Middle East Society of Organ Transplantation at Kuwait, Dec. 2006. Submitted the whole manuscript for publication on Nov. 2006.

Project Title: Morbidity After Living Donor Hepatectomy for Liver Transplantation: A Single Center Experience

Investigators: H Khalaf, M Al Sebayel, M Al Sofayan

Project Description

Collecting data for all living donors for living donor liver transplantation in terms of morbidity and quality of life after donation.

Progress

Accepted for publication: Transplantation Proceedings.

Project Title: Correlation Between CT, MRI, and Liver Biopsy on Potential Living Donor

Investigators: H Al Bahili, M Al Sofayan, et al.

Project Description

Correlate the fat percentage shown by CT/MRI and liver biopsy before proceeding for surgery.

Progress

At stage of collecting data.

Project Title: Combined Living Donor Liver & Kidney Transplant for Hyperoxyluria

Investigators: H Al Bahili, M Al Sagher, H Khalaf, M Al Sofayan, K Al Shaibani, Ali Al Malaq

Project Description

Case report of two patients with PH1 underwent liver transplantation followed by kidney transplantation few months later.

Progress

Presented for oral presentation to ILTS (International Liver Transplantation Society) Meeting held in Milan, Italy on May 2006. Submitted the whole manuscript for publication on 2006.
FUTURE RESEARCH PROJECTS

1. Establish a solid, sound, and sustained Research Infra-Structure and Tools (RIST) including:
   a. Databases. (In progress) These involves Donors Database, Operative Database, Pre-transplant Database, Post-transplant Database in addition to Disease-or project-specific databases, Sample & Tissue Banks (in collaboration with the Research Centre).
   b. Recruiting a research nurse/ coordinator or assistant. Activating the “Liver Transplant Research Group” involving department members and scientists from the Research Centre.
   c. Local, national, and international collaborations such as Pan-Arab Liver Transplant Congress in Riyadh on 14-15 March 2007.
   d. Continue our regular research meetings, in addition to applying for funding.

2. Finish the ongoing research projects and case reports.

3. Start new research projects that cover both observational, interventional and prospective studies that cover both the clinical and the basic science sides of research. The target is 4-6 projects per year (not including observational or retrospective studies), that concentrate on specific topic, and utilize available expertise in the Research Centre. Everyone is encouraged to apply, and is advised to focus on local problems.

4. More appearance and participation in World Literature and Scientific Meeting. Each member of the department is encouraged to publish his abstracts, full articles, one review article, and one case report/commentary annually, in addition to targeting specific conferences.

PUBLICATIONS (2006)


Accepted Abstracts for International Conference Presentations

1st PanArab Liver Transplantation Congress March 2006 (Cairo, Egypt)

ILTS (International Liver Transplant Society Meeting on May 2006 (Milan, Italy)

10th Middle East Society of Organ Transplantation Meeting on Dec.’06 (Kuwait)

1. Hepatitis C Recurrence in LDLT vs. DDLT: Preliminary Data in Genotype 4 (Poster Presentation – PanARab & ILTS)
2. Cadaveric Donation for Liver Transplantation: 5 years experience at KFSHRC, Riyadh, Saudi Arabia (Poster Presentation– PanARab & ILTS)
3. Survival Following Cadaveric Versus Living Donor Liver Transplantation: A Single Center Experience (Poster Presentation– PanARab & ILTS)
5. The Outcome of Hepatitis C Recurrence on Arab Ethnic Race: Post Liver Transplantation with Genotype 1 and 4 (Poster Presentation– PanARab & ILTS)
6. Early Post Right Lobe Living Related Liver Transplant Versus Venous Outlet Obstruction Treated with Balloon Dilatation Followed by Severe ARDS: Case Report (Poster Presentation– PanARab & ILTS)
7. Risk of Progression of Neurowilson’s Disease After Orthotopic Liver Transplantation (OLT): Case Report (Poster Presentation– PanARab & ILTS)
9. The Accuracy of Two Different Methods in estimating the right graft volume after adult-to-adult living donor liver transplantation (Poster Presentation– PanARab & ILTS)
10. Biliary Complications Following Cadaveric Versus Living Donor Liver Transplantation: A Single Center Experience (Oral Presentation– PanARab & ILTS)
11. Combined Living Donor and Kidney Transplantation for Hyperoxyluria: KFSHRC Experience (Poster Presentation– PanARab & ILTS)
12. Markedly Increased Serum CA 19-9 in Autoimmune Hepatitis Despite Absence of Malignancy: With Complete Normalization After Liver Transplantation (Poster Presentation– PanARab & ILTS)
14. Experience with Liver Transplantation at King Faisal Specialist Hospital & Research Centre (Oral-MESOT).
The Department of Medical Genetics

Interim Chairman
Zuhair Rahbeeni
RESEARCH PROJECTS

Project Title: Molecular genetic analysis of five inherited metabolic disorders frequently encountered in the metabolic clinic - (RAC# 2020011)


Progress

Hydroxy-Methyl-Glutaryl Co-A-Lyase (HMG) deficiency: Apart from the common mutation that was reported in the previous report, two additional mutations were identified in the samples analyzed. One is a novel mutation (IVS6+1G>A) and the other has been reported previously. These mutations together account for over 90% of the abnormal alleles of HMG. This information will now enable us to perform large scale molecular testing for this disorder. The molecular assay for the common mutation is now established at ADL. This has allowed us to achieve the goals of the projects.

Argininosuccinic Aciduria (ASL): Apart from the common mutation that was reported in the previous report, 5 additional mutations were identified in the samples analyzed. This accounts for over 90% of the abnormal alleles of ASL. This information will now enable us to perform large scale molecular testing for this disorder. The molecular assay for the common mutation is now established at ADL. Two abstracts and one publication were completed after approval from ORA. Couple of families with this disorder are enrolled now in the preimplantation diagnosis service, allowing us to achieve yet another important goal of the project.

Propionic Acidemia (PPA): The common mutation G117D was found to account for 42% of the samples successfully tested. 5 additional (some novel) mutations are identified. Work is still going on to identify more mutations. As a result of the project, prenatal diagnosis and preimplantation diagnosis was made available for some families. The molecular assay for the common mutation is now established at ADL.

Methylmalonic Aciduria (MMA): There are three main genes involved in MMA-MMAA, MMAB and MUT. The first two have been screened and no mutation has been identified. Mut gene identified 2 common mutations so far.
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<th>Metabolic Disease</th>
<th>Gene</th>
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<tr>
<td>Argino-succinic Aciduria (ASA)</td>
<td>ASL</td>
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**Project Title:** Di George Syndrome: A Retrospective Study of 35 Cases From Saudi Arabia. (RAC# 2051 022)

**Investigators:** Zuhair Rahbeeni (PI), M. Anwar Iqbal, Zuhair Al-Hassnan, Fawzia Al-Sharief

**Progress**

Seventeen patients with DiGeorge syndrome (DS) were enrolled in the study. The age at diagnosis ranged from birth to 25 years. Family history was positive for 22q deletion in one patient, 3 patients had family history of CHD and one had a sibling who died in infancy with unknown diagnosis, and another one had a sibling who died at 3 months of age with diagnosis of Wilson's disease. Clinical findings can be summarized as follows:

- Of the 8 patients who had IgG analysis, 2 had ↓ IgG and 6 had normal IgG.
- Heart lesions: Tetralogy of Fallot (55%), Coarctation of aorta and interrupted aortic arch (21.09%), VSD, ASD and PDA (30%), Peripheral pulmonary stenosis (8.3%), Truncus arteriosus (7.6%).

Our result confirmed the close association of conotruncal heart disorders and the diagnosis of DiGeorge syndrome. In terms of overall phenotype, we noted that most children who had CHD and dysmorphic anomalies had 22q11.2 deletion. We recommend the following strategy for DGS diagnosis in our patients: (1) A standard karyotype for all cases, (2) FISH test for detecting micro deletion 22q11.2.

A future goal of this study will be the screening of 22q11 deletion in patients with isolated defect of CHD or hypocalcemia or repeated infection. Our findings also indicate that some CHD is hardly associated with the deletion as zero cases associated with TGA.

**Project Title:** Role of the DFNB1 Locus in Hereditary Deafness Within the Saudi Population. (RAC# 2040039)

**Investigators:** K. Taibah (PI), B. Meyer, M. Al-Owain, F. Imtiaz, Shelley J. Kennedy

**Project Description**

Over 70% of hearing loss is non-syndromic, with the majority being autosomal recessive (AR) in nature. Mutations in the GJB2 (connexin 26) gene and GJB6 (connexin 30) gene are reported to cause greater than 50% of cases of AR non-syndromic hearing loss in North America, with an estimated carrier frequency of 1 in 33. This study examined the frequency of mutations in these genes in individuals affected by non-syndromic AR hearing loss within...
the Saudi population. To date, less than 5% (3 of 135 patients) of affected Saudi individuals have been identified to have a mutation after complete sequencing of both \(GJB2\) and \(GJB6\). This finding was not wholly unexpected, as other hereditary diseases, such as cystic fibrosis, have unique genetic mutations within the Saudi population. Given that mutations in \(GJB2\) and \(GJB6\) have been excluded as the cause of non-syndromic AR hearing loss for the majority of Saudi families, we are now identifying families suitable for whole genome scanning to try and identify causative genes for hearing loss within this population. The findings of this study will be relevant to the newborn and premarital screening programs within the Kingdom.

Progress

- Blood has been collected and banked on 143 patients.
- The entire coding regions of \(GJB2\) and \(GJB6\) have been sequenced for 135 patients.
- 3 cases were identified to be homozygous for the common 35delG mutation in \(GJB2\).
- No other mutations in \(GJB2\) and \(GJB6\) have been identified.
- As exclusion of a mutation in a gene with 100% confidence is not possible based on sequencing the coding region alone, we genotyped 3 closely linked microsatellite loci to \(GJB2\) and \(GJB6\) for each patient. The majority of our patients have consanguineous parents. Therefore, \(GJB2\) and \(GJB6\) can be excluded if heterozygosity is detected for these tightly linked markers.
- Genotyping for these three markers has been completed on 64 of 143 patients.

Future Direction

Results of this study to date have revealed that mutations in \(GJB2\) and \(GJB6\) are not the cause of the majority of non-syndromic AR hearing loss in the Kingdom of Saudi Arabia. Blood samples are now being collected from a minimum of 6 family members in those families identified to have 3 or more affected individuals. These blood samples will be used to perform whole genome linkage analysis via 10K SNP Chip Affymetrix Genotyping. Results of this analysis may permit the identification of genes previously identified in the literature to cause non-syndromic AR hearing loss or may lead to the identification of novel genes.

Identification of the genes causing non-syndromic AR hearing loss in the Kingdom of Saudi Arabia will permit accurate genetic counselling. At the family level, mutation identification in the causative genes will allow for the option of carrier testing for extended family members and future spouses. This will help identify couples at risk to have a child with hearing loss within families known to have non-syndromic AR hearing loss. Couples identified to be at 25% risk who do not wish to have a child with hearing loss will have the option of pursuing preimplantation genetic diagnosis. At the general population level, these results may have direct application to newborn and pre-marital screening programs.

Project Title: Genetic Mapping and Characterization of Nonsyndromic X-linked Mental Retardation in Saudi Families. RAC # 2050 018)

Investigators: Zuhair Al-Hassnan (PI), Mohammed FaiyazUl-Haque (Co-PI), Nadia Sakati, Mohammed Al-Owain, Abdelghani Tbakh, Mohammed Al-Dosari, Fawzia Al-Sharief, Eissa Faqeih

Project Description

The main objective of this research project is to identify genes responsible for X-linked mental retardation in Saudi families. Scientific study is
not available on this form of mental retardation in our population and genetic screening of population specific gene loci for MRX patients is not possible. Therefore, an etiological diagnosis cannot be made, leaving families without a practical genetic counselling or reproductive options. Detecting the causative mutations in affected families will serve several clinical purposes in such incurable disease. It will enable clinicians to confirm the diagnosis, apply preventive measures such as preimplantation genetic diagnosis, and screen at-risk family members for carrier status, and then targeted premarital screening could be implemented on individual families.

Progress

- We have enrolled one family (XMR-01). Samples were collected after taking the consent.
- We have acquired the materials necessary for linkage analysis including: primers, buffers, chemicals for sequencing, etc.
- Device a plan for implementation of the linkage analysis on the enrolled family.
- Calculated the theoretical lod score which turned to be 2.8.
- No preliminary result yet as the procedure of linkage is still ongoing.

Future Direction

- Assess the results of linkage analysis on the family # MRX-01.
- Extend the project by enrolling more families, collect their samples, and calculate their lod score after devising the appropriate plan for each family.

Project Title: L-2-Hydroxyglutaric Aciduria: Clinical, Biochemical and Molecular Analysis in a Large Saudi Family. (RAC# 2050013)

Investigators: Moeen Al-Sayed (PI), E. Faqieh (Co-PI), M Ul Haque, A. Alduraihem, N.M. Saleh, H.A. Abalkhail, Mohammed Al-Owain

Progress

3 consanguineous families with L-2-hydroxyglutaric aciduria are included so far. We studied 15 individuals and sequenced the entire coding regions and exon–intron boundaries which revealed two different homozygous mutations in both families. In 1st family and 2nd family, we identified a novel single bp deletion “A1015” in exon 8, resulting in a frameshift in the translated protein and replacement of 12 novel amino acids before a premature termination. The mutation was found in a homozygous state in all 8 affected individuals. In the 3rd family, mutation analysis in 1 affected individual revealed a homozygous C1319A transition at codon 440, which changes serine a hydrophilic acidically charged residue to Tyrosine a basically charged residue in a conserved low complexity region of gene. We also found that the two mutations are located in a highly conserved area across the multiple species which suggests that the substituted residues are important for protein folding and/or enzyme catalysis and may effect the pre-processing and folding mechanism of the protein inside the mitochondria

Project Title: Molecular Look on Early Infantile Primary Lactic Acidosis: Pilot Study. (RAC# 2050009)

Project Description

This study aims to understand the molecular basis of the onset and progression of the infantile primary lactic acidosis in the affected patients using microarray technology, mutation analysis and apoptosis specific assays. We will be analyzing the gene expression patterns and trying to determine the gene signatures specific to the onset and
progression of this important disease at the early stages of the pathogenesis. Also, we will be utilizing the MitoLight Kit and DNA fragment analysis to determine the beginning and advancement of the apoptosis in the patients. To be able to achieve our goals, we will be performing these experiments periodically during the early stages of the disease onset and progression. Once the disease specific gene signatures are identified and stages of the apoptosis are clarified, we will characterize the significant genes of interest involved in this important disease. Furthermore, we will be doing mutation analysis for the mtDNA genes and nuclear genes known to involve in this disease.

**Investigators:** Mohammad Al-Owain (PI), Namik Kaya (Co-PI), Zuhair Rahbeeni, Pinar Ozand, Moeen Al-Sayed, Muhammad Faiyaz Al-Haque, Zuhair Al-Hassnan, Mehmet S. Inan, Saleh Al-Alaiyan, Khaled Abu-Amero, Ali Al-Odaib, Abdulghani Tbakhı

**Progress**

We have collected 5 cases (goal for 10 cases) of infantile primary lactic acidosis.

**Future Direction**

We have performed the gene expression studies on the 5 patients that have been recruited and is being analyzed. Meanwhile, we will continue to collect the required number of cases, an additional five cases. We have applied for an extension of the project for another year.

**Project Title:** Hereditary Tyrosinemia Type 1: Clinical, Biochemical and Molecular characterization with emphasis on response to NTBC. (RAC# 2050 022)

**Investigators:** Moeen Al-Sayed (PI), Faiqa Imtiaz (Co-PI), Mohamed Rashed, Zuhair Rahbeeni, Zuhair Al-Hassnan, Mohammad Al-Owain

**Project Title: Clinical, Biochemical, and Molecular Profiles of Saudi Patients with Dihydropyrimidine Dehydrogenase Deficiency. (RAC# 2050 021)**

**Investigators:** Zuhair Al-Hassnan (PI), Mohamed Rashed (Co-PI), Mohammed Faiyaz-Ul-Haque, Mohammed Al-Owain, Amal A. Saadallah, Osama Y. Al-Dirbashi, Zuhair Rahbeeni, Moeen Al-Sayed, Abdelghani Tbakhı

**Project Description**

This project aims to characterize the clinical phenotype, describe the biochemical profiles, and identify the disease-causing mutations in Saudi patients with DPD deficiency. Illustrating
the clinical and biochemical profiles will further clarify such a highly variable disease. Detecting the causative mutations in affected families will serve several clinical purposes in such incurable disease. It will enable clinicians to confirm the diagnosis, apply preventive measures such as preimplantation genetic diagnosis, and screen at-risk family members for carrier status, and then targeted premarital screening could be implemented on individual families.

**Progress**

- We have enrolled one family (DPD-01).
- The family was interviewed and affected members were examined and their charts were reviewed.
- Urine samples were tested by GC/MS and the highly excreted uracil and thymine were detected.
- Both pyrimidines (uracil and thymine) and dihydropyrimidines (dihydouracil and dihydrothymine) were quantified using LC-MS/MS and confirmed the DPD deficiency.
- Blood samples were collected from the patients for genomic DNA extraction.
- We have acquired the materials necessary for the DNA test: primers, buffers, chemicals for sequencing, etc.
- Search for mutation is still ongoing.

**Future Direction:**

- Identify the mutation in family # DPD-01.
- Expand the project by enrolling more families.

**Project Title:** Clinical, Biochemical and Molecular Profiles of Saudi Patients with Medium Chain Acyl CoA Dehydrogenase (MCAD) Deficiency. (RAC# 2050 037)

**Investigators:** Zuhair Al-Hassnan (PI), Mohamed Rashed (Co-PI), Zuhair Rahbeeni, Faiqa Imitiaz, Moeen Al-Sayed, Mohammed Al-Owain, Mohammed Al-Amoudi

**Project Description**

This project aims at better clinical and biochemical characterization of the MCAD phenotype in the Saudi population. It aims also at the identification of the disease-causing mutations in Saudi patients with MCAD. Improvement of the biochemical characterization of the MCAD phenotype will be extremely useful for the Saudi newborn screening program to reduce false-positive results and thus reduce recall rate. The biochemical and clinical characterization of the phenotype will be also useful for selective screening of patients suspected with fatty acid oxidation defects. It may also lead to detection of other MCAD cases in siblings from affected families. Detecting the causative mutations in affected families will serve several clinical purposes in such a potentially fatal disease. It will enable clinicians to confirm the diagnosis, apply preventive measures such as preimplantation genetic diagnosis, and screen at-risk family members for carrier status. Targeted premarital screening could then be implemented on individual families. Identification of carries by DNA testing will be followed by screening children of carrier parents for MCAD deficiency so prompt medical intervention could be implemented on positive cases.

**Progress**

- We have enrolled four patients with MCAD deficiency who were detected by the National Lab for Newborn Screening.
- We have acquired the materials necessary for the DNA testing: primers, buffers, chemicals for sequencing...etc.
- Blood samples were collected from the patients for genomic DNA extraction.
After sequencing the genomic DNA, two novel mutations have been identified (T121I and C116Y).

Future Direction

- The National Lab for Newborn Screening has been detecting more cases with MCAD deficiency and we will enroll them in the study.
- Extend the project for another year.
- Identify the mutations in the newly enrolled cases.

Project Title: Clinical and Molecular Characterization of Patients with Inherited Arrhythmogenic Disorders. (RAC# 2050 035)

Investigators: Zuhair Al-Hassnan (PI), Majid Al-Fayyadh (Co-PI), Brian Meyer (Co-PI), Yaseen Mallawi, Waleed Al Manea, Mohammed Al-Owain

Project Description

It is estimated that a significant percentage of sudden deaths are the result of unrecognized inherited arrhythmogenic disorders. In the last decade, there has been a momentous progress in understanding the genetic bases of these disorders. The identification of genes underlying the inherited arrhythmogenic disorders has provided major practical information. The detection of a mutation allows us to establish the diagnosis independently from the electrocardiographic features and the arrhythmic manifestations. The molecular data has been used as a parameter for risk stratification and hence, to tailor accordingly the therapeutic approach and have preemptive medical intervention for asymptomatic cases. In this research project, we aim at identifying genes responsible for inherited arrhythmogenic disorders in our population. This will provide molecular characterization of patients with known syndromes as well as those with novel non-described phenotypes.

Families with inherited arrhythmogenic disorders will be recruited for the study from the clinical service at King Faisal Heart Institute. After clinical data collection, patients will be stratified based on their phenotypes and inheritance patterns, and accordingly molecular characterization will be undertaken by either direct mutation screening of the candidate gene or whole genome linkage analysis.

Project Title: The Spectrum of Sphingolipid Activator Protein Deficiency in Children with Neuroregression. (RAC# 2061 036)

Investigators: Zuhair Al-Hassnan (PI), Mohammed Faiyaz-Ul-Haque, Hesham Aldhalaan, Mohammed Al-Owain

Project Description

Neurodegenerative disorders are amongst the most common reasons for referrals to the Genetics and Pediatric Neurology Services at King Faisal Specialist Hospital and Research Centre. Over the past few years, we have identified patients with sphingolipid activator protein deficiency secondary to mutated PSAP gene. Mutated PSAP resulting in SAP deficiency is known to cause atypical variants of metachromatic leukodystrophy and Gaucher disease. In this study, we aim at retrospectively
reviewing the clinical and molecular spectrum of those cases that were confirmed by DNA test to have SAP deficiency. It is expected to provide insight into the clinical spectrum of this underdiagnosed neurodegenerative disorder in our population.

Progress

Retrospective analysis of the phenotypic features and molecular findings in patients with SAP deficiency is in progress.

PUBLICATIONS

Manuscripts (published)


Manuscripts (accepted)


3. ZN Al-Hassnan, M Budhaim, B Lach, H Aldhalaan. Muscle Phosphofructokinase Deficiency with Neonatal Seizures and Nonprogressive Course. (J Child Neurol - accepted)
Manuscripts (submitted / in preparation)


Abstracts / Poster Presentations

The Department of Medicine

Interim Chairman
Magid Halim
The following is a summary of the section’s research projects during 2006.

Project Title: Hepatitis B Virus Genotypes in Saudi Arabia


Background: The natural history, disease activity, response to treatment and hepatocellular carcinoma related to hepatitis B may depend on the hepatitis virus genotype. There are no published reports on the prevalence of different HBV genotypes in Saudi Arabia. We report our initial experience with HBV genotyping in Saudi population.

Materials & Methods: HBV genotyping was performed on randomly collected sera of HBV PCR positive patient’s samples of HBV related liver disease by using INNO-LiPA; a line probe assay. (INNO-LiPA HBV Genotyping assay, Innogenetics N.V., Ghent, Belgium). The sera were also tested for ALT, HBsAg, HBV viral load and HBeAg status.

Results: Out of the 35 samples tested for HBV genotyping, 33 (94%) were HBV genotype D, one was genotype A (3%) and one was of mixed genotypes A/D. ALT value ranged from 13U/L to 1135 IU/L with mean ALT of 134 for genotype D and ALT value of 129 IU/L for genotype A. Fifty-two percentage of the genotype D had ALT value of more than 60 IU/L. HBeAg was tested on 33 samples and was positive in 15/33 (47%). HBV viral load ranged from 3000 copies/ml to more than 100 million copies/ml. The mean viral load in genotype D was 6,960,920 copies/ml. In fifteen patients (45.5%) with genotype D HBV viral load was above 100-million copies/ml. Viral load was 57,991,904 copies/ml in genotype A.

Conclusions: HBV genotype D is the commonest HBV genotype in sample of patients tested at KFSHRC. Further studies should be conducted on a larger number of samples to study the overall prevalence of HBV genotypes in Saudi Arabia.

Keywords: HBV Genotype, Hepatitis B, Chronic Hepatitis
Project Title: Efficacy of Combination Therapy With PEG-Interferon α-2a (Pegasys) Plus Ribavirin in the Treatment of Chronic Hepatitis C: A Retrospective Study

Investigators: Hamad Alashgar, Khalid E Alsawat, Mohammed Q Khan, Naser Elkum, Saleim Dahab, Musthafa C Peedikayil, Abdullah Alshehri, Abdullah Alkalbani, Mohammed Al Fadda, Ingvar Kagevi, Mohammed Al Quaiz, Mohammad Rezeig Khalid Alkahtani

Background: This is the first large scale retrospective study in Saudi population, planned to assess the efficacy and safety of Pegasys (Peginterferon α-2a) and Ribavirin combination in the treatment of chronic hepatitis C, at KFSH & RC, Riyadh.

Aim of the study: The primary objective is to evaluate the response rate of combination therapy (Peginterferon α-2a and Ribavirin) in chronic HCV, and secondary objective is to analyze the effect of HCV genotype, HCV RNA Level (quantitative), and histological staging on the success of viral eradication.

Materials & Methods: All patients who were diagnosed to have chronic Hepatitis C and treated by Pegasys (Peginterferon α-2a) 180 μgm and Ribavirin 800-1200 mg daily, since 2003 at KFSH & RC, were included in the study. Their records were evaluated for the Early virological response (at least 2-log decline of the HCV RNA level by 12 weeks on treatment), end of treatment response (ETR) after 48 weeks of treatment, and sustained virological response (SVR) is the persistence of negative HCV RNA 6 months after stopping the treatment. The patients who did not respond (non-responders) or who responded but relapsed within 72-96 weeks of follow up were also included in the study and analyzed. The clinical and biochemical data were extracted from the patient’s file and put it on the demographic data sheet.

Results: A total of 335 consecutive patients were included. Clinical, biochemical, and virological parameters at time 0 (pre-treatment), and at 12, 24, 48, and 72 weeks post-treatment were recorded. The mean ± SD age was 49.1±13.0 years; 229 (68.4%) were males, mean ± SD body mass index was 27.8±7.4, 148 (44.2%) were genotype 4, 30 (9.0%) were genotype 2 or 3, 85 (25.4%) were diabetic, 25 (7.5%) had renal impairment, 136 (40.6%) previously received Interferon ± Ribavirin therapy, and 247 (73.7%) underwent pre-treatment liver biopsy. Early viral response (≥2-log10 HCV-RNA decline 12 weeks post-treatment) was achieved in 253 (75.3%) Non-response and incomplete treatment (due to side effects or lost of follow-up) occurred in 71 (21.2%), and 56 (16.7%) patients respectively.

Patients who completed treatment were 208 (62.09%), of them 150 (72.1%) achieved sustained viral response (SVR; persistently negative HCV RNA PCR 6 months after the end of treatment response). That is 44.8% and 21.2% of all patients (n=335) respectively. Compared to relapsers, patients with SVR were significantly younger (p=0.001), less diabetics (p=0.030) had higher serum albumin (p=0.008), had less pre-treatment inflammatory grade (p=0.010), were genotype 2 or 3 (p=0.036), and more treatment-naïve (p=0.001). However, in stepwise multivariate logistic regression analysis, only higher serum albumin, genotype 2 or 3, and being treatment-naïve were independent predictors of SVR (p=0.024, p=0.008, p=0.002 respectively).

Conclusions: The overall SVR achieved in this study was 53.9% but in predominantly genotype 4 Saudi populations was 43.7%. SVR rates were significantly higher in treatment-naïve patients, than those with history of previous treatment with Interferon. The study is still continuing and the final results will be released in the department of medicine research day.

3 keywords: Chronic Hepatitis C, PEG-interferon α-2a, Ribavirin
Results: A total of 93 patient's records were searched to assess the efficacy & safety of Pegasys and Ribavirin combination treatment. The number of patients reduced to 82 (88.1%), when 9 (9.6%) patients were excluded from the study because they were unable to complete the full course of treatment. Sustained Virological Response (SVR) was observed in 53.7%, End of treatment Response (ETR) 74.6%, ETR but relapsed after 72-96 weeks was 20.8% and Non-responders after 48 weeks of therapy were 25.3%. In total 8 patients did not complete the prescribed 48 weeks treatment protocol due to adverse side effects (8.5%). One patient had an early virological response (EVR) but still waiting for ETR. The commonest Genotype was Type 4 (63%) followed by Type 1 (19.3%), Mixed type (8.06%), type 2 and 5 (3.22% each) and Genotype 3 and 6 (1.61% each). The SVR for Genotype-4 was 43%, Genotype-1 was 18%, Genotype 2,3 and 5 were 100%, Mixed Genotype was 40%. 58 treated patients were naïve and 35 with the previous history of interferon treatment. The sustained virological response in previously treated patient was 37% (less than naïve-patients). Hemoglobin, leukocyte and neutrophil levels decreased significantly during treatment, but returned to baseline after the end of treatment. ALT levels decreased significantly during treatment in patients with and without an SVR. 41.9 % of patients experienced adverse events like neutropenia, anemia, and thrombocytopenia. There was no death reported.

Materials & Methods: 67 years old lady was admitted to hospital with history of generalized abdominal pain and jaundice of 3 months duration. She had also history of undocumented fever, weight loss and anorexia. She had no previous history of jaundice. She has been taking Cilazapril for Hypertension, simvastatin for dyslipidemia, L-thyroxine for hypothyroidism since many years. She had undergone appendicectomy 10 years back and hysterectomy and bilateral salpingoophorectomy about 5 years back, which was complicated by a vesico-vaginal fistula. She had been treated with nitrofurantoin 100 mg and phenazopyridine 3 months prior to the onset of jaundice for recurrent urinary tract infections. At admission, she was jaundiced, but no other signs of stigmata of chronic liver disease or signs of decompensated liver disease. Vital signs were normal.

Liver was palpable 2 cm below the costal margins. Laboratory data included Hemoglobin of 63 g/dL, white blood cell count 6.10 x10^9/L, platelet count 254 x10^9/L, PT of 47.4 seconds and PTT of 82.8 seconds and INR 3.8 and reticuloocyte count of 91.6 x10^9/L. Creatinine 68 umol/L, albumin of 15 g/L, total bilirubin 167 umol/L, lactic acid 2.5 mmol/L, haptoglobin 0.17 g/L, Lactate dehydrogenase of 1306, alanine aminotransferase 206 u/L, aspartate aminotransferase 690 u/L, alkaline phosphatase 298 u/L, Gamma glutamyl transferase of 188 u/L, serum copper of 7.6 umol/L and ceruloplasmin level of 179 mg/L. She was HBsAg, HCV ELISA, IgM HAV, IgM HEV, SMA, LKM and HIV ELISA negative. ANA was high with titre of 1:640, IgG level was elevated with a 35.8 g/L level and IgA and IgM
Ultrasound study of abdomen showed a coarse heterogeneous liver with no focal lesion and gall bladder wall thickening, patent hepatic and portal veins. During the stay in the hospital, developed grade IV hepatic coma and coagulopathy worsened. Transjugular liver biopsy revealed picture of fulminant hepatitis. She was taken for cadaveric liver transplantation, and was failed because of severely atherosclerotic arteries. She died 3RD postoperative day.

3 keywords: Nitrofurantoin, adverse reactions, fulminant hepatitis and hepatotoxicity.

Discussion: Nitrofurantoin is well known to cause various kinds of liver injuries including hepatocellular damage, chronic hepatitis, cirrhosis, and cholestasis(1,2). There has been reports of immune mediated liver and lung injury with positive antinuclear antibodies and anti-smooth-muscle antibodies and the absence of any possible cause except for nitrofurantoin treatment(3). It was postulated that a breakdown product of the drug or the drug itself complexed to an endogenous peptide is presented by the class I HLA antigen on the hepatocyte cell membrane, inducing cytotoxic T cell activation and subsequently, hepatocyte death as mechanism of liver injury(4). Reported cases of death related to nitrofurantoin are with continuation of the drug despite development of jaundice(2) as it was again evident in our case.

This case and other reported cases show the potentiality of nitrofurantoin to cause various types of liver injury and even fatality. Hypergammaglobulinemia and serological markers of autoimmune markers can be seen in these patients. The care is required to differentiate between these 2 conditions. Utmost caution is required when prescribing nitrofurantoin for long term prophylaxis in elderly females(2) and timely stopping of the drug will avoid morbidity and mortality.

Project Title: Efficacy of Peginterferon α-2a, in HbeAg-Negative Chronic Hepatitis B: Naïve Versus Lamivudine Resistance Patients. (RAC#2051 015)


Project Description

To study pegasys in cases of chronic HBV precore mutant.

Progress

A multi center study is in progress and have endorsed 14 patients for the last 4 months.

Project Title: Intragastric Balloon in Obese Patients; KFSH&RC Experience. (RAC# 2051 038)

Investigators: K Kahtani, M Q Khan, N Elkum, H Al Ashgar, B Fahad, M S Al sofayan S Abdulrahman, S Dahab
Project Description

To evaluate the effectiveness tolerance and safety of a bioenteric entragastric balloon (BIB) for the treatment of obesity as adjunct to diet, physical training and behavioral modifications in Saudi patient who failed to respond to diet and physical activity alone.

Progress

The retrospective study of intragastric balloon in obese patients experience in KFSH&RC is under progress. 200 patients who received intragastric balloon, their data has been expected and tabulated in the data sheet and the final result is still pending. However, prospective study is not started as the assurance from the administration required supplying another 200 BIB balloon.

Project Title: Efficacy of Combination Therapy With PEG-Interferon Alfa-2a (Pegasys) R Plus Ribavirin in the Treatment of Chronic Hepatitis C. (RAC# 2051 035)

Investigators: H Al Ashgar, K Al Sawat, N Elkum, M Q Khan, S Dahab, M Al Fadda, I Kagevi

Project Description

To evaluate the response rate in our patients with chronic HCV who had been treated with this regimen (combination of pegylated interferon alfa-2a (Pegasys, Roche Pharmaceuticals) and Ribavirin).

Progress

Final Report has been submitted. Two abstracts have been submitted to the Asian Pacific Association for the Study of Liver Meeting (APASL) that will be held in Japan March 2007, and currently writing manuscript for publication.

FUTURE RESEARCH DIRECTION

- Complete the currently on-going projects
- Establish new research projects on hot topics such as non-alcoholic steatohepatitis, liver cancer and GI mucosal immunity and peptides, hemodynamics of portal hypertension, hepatitis B, colonoscopy, and inflammatory bowel disease.
- Launch a research meeting every 2-4 weeks.
- Establish local and national collaborations
- Establish research infrastructure including:
  - Data bank
  - Tissue bank
  - Serum/plasma bank
  - Full-time or part-time research nurse, coordinator or assistant.

Three projects were written, and now under the process of approval from the Research Advisory Council in KFSH&RC.

Project 1: A retrospective analysis of inflammatory bowel disease at a tertiary center in Saudi Arabia.
Principal Investigator: Dr. Mohammed Al Fadda, MD.

Project 2: A retrospective analysis of value, appropriateness and yield of colonoscopy in a tertiary center in Saudi Arabia.
Principal Investigator: Dr. Mohammed Al Fadda, MD.

Project 3: A 10-year retrospective analysis of different therapeutic modalities in chronic hepatitis B virus infection in a tertiary center in Saudi Arabia.
Principal Investigator: Dr. Hamad Al Ashgar, MD.
Human tuberculosis (TB), one of the most widespread infectious diseases, is the leading cause of death due to a single infectious agent among adults in the world. Despite tremendous improvements in the diagnosis of TB, little is known about the pathophysiology of TB in healthy individuals. Elucidation of the regulatory role of cytokines is important in understanding the pathophysiology of TB as well as in the induction of protective immunity.

In this study, we propose a three-fold approach to investigate the regulatory role of cytokines in patients with various manifestations of TB (pulmonary, extrapulmonary, and coinfection of TB with AIDS). In the first approach, common cytokines relative to TB manifestation will be detected by cytokine antibody array technology. In the second approach, cytokines identified above will be quantified by ELISA and correlated with the clinical manifestation of TB. In the third approach, the patterns of cytokine gene expression and protein level will be studied in vitro by using mononuclear cells as target cells.

The threshold detection of cytokines in the above approaches would provide insights into possible means of immune intervention as well as in the prediction of TB status. Thus, the compendium knowledge of cytokines profile would enhance our judgment about the prognosis of TB and pave the way towards future use of cytokines as treatment adjuvants in the control of TB. Further, anticipated differences in cytokine responses between pulmonary and extrapulmonary TB might be of great diagnostic value at certain stages of TB progression.
RESEARCH PROJECT

Project Title: Cytokine Responses of Patients with Tuberculosis in the Kingdom of Saudi Arabia. RAC # 2030 001 (KACST Grant, AT-26-41)

Investigators: Abdullah Al Hokail, MD, ABIM (Diplomate), Mohamed G. Elfaki, BVSc, MS, PhD (USA)

Progress

Ongoing.

FUTURE RESEARCH DIRECTION

- Studies on cytokine responses in human infected with tuberculosis.
- Modulation of adaptive immunity to infectious diseases by cytokines.
- Studies on host-parasite interaction at cellular and molecular level.
The Department of Neurosciences

Interim Chairman
Saeed Bohlega

Duputy Chairman
Imaduddin Kanaan
The Department of Neurosciences

The Department of Neurosciences attends patients for tertiary care in the areas of Neurosurgery, Neurology, Pediatric Neurology and Psychiatry. The Section of Neurophysiology provides state-of-the-art services, including intraoperative monitoring, corticography and magnetic brain stimulation. The Department comprises 25 consultants in these various specialties. There is an active residency training program in neurology and neurosurgery. A fellowship program exists in psychiatry and pediatric neurology.

RESEARCH PROJECTS

Project Title: Neuroendoscopic Training for Residents, Fellows and Neurosurgeons (Level 2). RAC# 206 2002

Investigators: Jalaluddin

Project Description

There are several models for teaching and training neuroendoscopy, including phantom and cadaver, but there is no report in literature of a small animal (or rat) model for neuroendoscopy. We will develop this rat model for Neuroendoscopy Training (Level 2). The peritoneal cavity of an anesthetized rat will be used to mimic hydrocephalus and 5 – 20ml of fluid / colloid will be injected into the omentum and / or mesentery to mimic the arachnoid and colloid cysts of the brain. These cysts will be resected with the help of endoscope and it will be used for teaching and Neuroendoscopy training. This rat model will be a good tool for learning neuroendoscopic procedures.
Project Title: Neurological Manifestations of the Antiphospholipid Syndrome in Children and Adolescents. RAC# 206 1051

Investigators: Chedrawi, Dhalaan, Muhaizea, Dossari, Ghomraoui, Hassar, Bashiri

Project Description

The Antiphospholipid Syndrome (APS) is a heterogeneous disorder characterized by vascular thrombosis and pregnancy morbidity. Neurological complications of APS are quite common, frequently in the form of cerebrovascular accidents; however involvement of the nervous system can be quite varied. Recent advances in our understanding of the pathophysiology of APS have paved the way for new criteria for the diagnosis of this condition. A wealth of information is currently available on the involvement of the central nervous system in adults with APS. Unfortunately, only scant data exists regarding the neurological involvement in children and adolescents. In this proposal, we intend to describe the neurological manifestations of APS, to characterize their incidence, and to determine the most effective form of therapy for the primary and secondary prevention of stroke in the pediatric and adolescent population in Saudi Arabia.

Project Title: Neuromuscular Pathology in Pediatrics, KFSHRC Experience. RAC# 206 1050

Investigators: Muhaizea, Hindi, Chedrawi, Dadabo, Dhalaan, Dossari, Ghomraoui, Ali, Otaif

Project Description

Neuromuscular diseases constitute a heterogeneous group of disorders encountered in pediatric neurology. Accurate diagnosis requires muscle biopsy in most cases. Knowledge about epidemiology of the different subcategories is essential in planning prospective studies and proper budget allocation for hospitals. We intend to review KFSHRC experience in neuromuscular disorders over the period of 1990-2005 in children who underwent a diagnostic muscle biopsy. This will be a basis for starting prospective and long-term follow-up studies.

Project Title: Childhood Stroke in Saudi Arabia: Etiology, Course and Recurrence Rates. RAC# 206 1038

Investigators: Dossari, Muhaizea, Dhalaan, Chedrawi, Ghomraoui, Baleegh, Mokeem

Project Description

Childhood stroke importance is derived not only from the fact that it is one of the top ten reasons for death in children, but also in the fact that around 20 to 35% of infant stroke survivors will go on to have another stroke, and more than two-thirds of survivors will have neurological deficits or seizures. These reasons make the study of specific risk factors associated stroke and with its recurrence very important for any prevention or intervention measures. The data regarding childhood in Saudi Arabia is very scarce. We propose a retrospective review of all children diagnosed with stroke who were seen and followed up at a major tertiary care hospital in Saudi Arabia. We think that the data derived from this the study would be quite helpful in designing future prospective studies dealing with idiopathic stroke and with primary and secondary prevention strategies.

Project Title: The Spectrum of Sphingolipid Activator Protein Deficiency in Children with Neuroregression. RAC# 206 1036

Investigators: AlHassnan, M Faiyez Ul-Haque, Dhalaan, M Al-Owain
Project Title: A phase III, Randomized, Double-Blind, Three-Arm, Placebo-Controlled, Multi-Centre Study to Evaluate the Safety and Efficacy of Oral Cladribine in Subjects with Relapsing-Remitting Multiple Sclerosis (RRMS). RAC# 2061028

Investigators: Bohlega, Abdulrahman Al-Reshaid

Project Description

The primary objective of the study is to evaluate the efficacy of cladribine versus placebo in the reduction of qualifying relapse rate during 96 weeks of treatment in subjects with RRMS. The secondary objective is:

- To assess the effect of cladribine on progression of disability in subjects with RRMS.
- To assess the effect of cladribine in reducing lesion activity compared to placebo as measured by magnetic resonance imaging (MRI) in subjects with RRMS.
- To assess the safety of cladribine in subjects with RRMS.
- To assess population pharmacokinetics in subjects with RRMS.
- To identify DNA polymorphisms or gene expression profiles associated with certain traits (i.e. response, adverse events) of cladribine used in the treatment of multiple sclerosis as well as potential susceptibility loci for multiple sclerosis.

Project Title: Clobazam Efficacy, Tolerability and Address Effects in Saudi Children with Intractable Epilepsy. RAC# 2061007

Investigator: Yamani

Project Title: Gene mapping of x-linked diseases with mitochondrial abnormalities. RAC# 2060018

Investigators: AbuAmero, Al-Semari, Wakil, Muhaizea

Project Title: Identification of Genes Involving Novel Genetic Diseases with Some Neurological Implications in Consanguineous Families

Investigators: Kaya, Dhalaan, Sakati, AbuAmero

Project Title: Molecular Genetic and Genomic Studies in Epilepsy

Investigators: Kaya, Dhalaan

Project Title: A Study to Examine Concordance Between the Neuropsychological Data and the EEG, PET, MRI Findings in the Presurgery Evaluation of Candidates for Epilepsy Surgery. RAC# 2061080
Investigators: Hassan, Al Semari, Al-Khawajah

Project Title: Neurological Complications of Nesidioblastosis. RAC# 2061071

Investigators: Dhalaan, Otaibi, Mohammed Al Dosari, Mohammed Al Muhaizea, Aziza Chedrawi, Rahma Al Hassar, Bassam bin Abbas

Project Description

Nesidioblastosis, also known as persistent hyperinsulinemic hypoglycemia of infancy (PHHI), is believed to be the most common cause of hyperinsulinemia in neonates. It is common in Saudi Arabia with incidence 1/2675 live birth. It can occur either sporadic or familial autosomal recessive. Severe hypoglycemia may produce brain injury in certain areas of cerebral cortex. It is not clear whether the mechanism of neurologic insult in patients with PHHI is related to hypoglycemia or hyperinsulinemia. The neurologic aspect are not well described in terms of extent of neurologic damage and developmental consequences or pathophysiological mechanisms of brain injury. In this retrospective study, we aim to review the neurological, neuropsychological, neurophysiological, and neuroimaging effects of nesidioblastosis on the central nervous system in children.

FUTURE RESEARCH DIRECTION

- To focus on national experience in neurogenetics, movement disorders, epilepsy, neuromuscular, neurometabolic and epidemiological studies.
- Provide assistance and support to make research attractive.
  o help in proposal submission and follow up
  o work in groups, by section or intradepartmental collaborations

- o activate departmental research committee
- o designate research coordinator and academic secretary
- o provide annual and semi-annual section report on ongoing research
- o support and motivate physicians with good research

PUBLICATIONS


The Department of Obstetrics and Gynecology

Chairman
Adnan R. Munkarah
RESEARCH PROJECTS

Project Title: Infertility Treatment Outcome in Sub-Groups of Obese Population. RAC# 2061013

Investigators: Khalid Awartani, MD, Samar Nahas, MD, Masheal Al Deary, MD, Saad Al Hassan, MD and Serdar Coskun, DVM, PhD

Project Description

In Saudi females at childbearing age, obesity is seen 38% of females attending our IVF centre. The objective of this study is to compare the outcome of the IVF or ICSI treatment in obese patients (BMI=30-34.9 kg/m²) to that in morbid obese population (BMI≥35 kg/m²). It was conducted as retrospective cohort study for all patients who is undergoing their first cycle of IVF or ICSI treatment, and had long follicular pituitary down regulation protocol we had 406 obese patients and 141 morbid obese patient, 20-40 years old, and had no living children.

Result

There was a higher cancellation rate in morbid obese women compared to the obese women (28.3% vs. 19%). Morbid obese patients had lower clinical pregnancy rate per started cycle (19.9 % vs. 28.6 %). Based on this we suggest that appropriate counseling should be provided to the couples before initiation of this expensive and invasive therapy in morbid obese women.

Progress

Manuscript preparation.
Project Title: Effect of Weight Loss in Morbidly Obese Infertile Women on IVF Outcome. RAC# 2061032

Investigators: Nada Al Sahan, MD, Masheal Al Deary, MD, Saad Al Hassan, MD, Serdar Coskun, DVM, PhD and Khalid Awartani, MD

Project Description

In Saudi females at childbearing age, obesity is commonly encountered. In our centre it has been reported that around 10% of the women are suffering from morbid obesity which carry high cancellation rate and low pregnancy rate. So the objective of the study is to assess the effect of significant weight loss in the morbidly obese (BMI≥35) population to obese (BMI<35) on IVF outcome. It was retrospective cohort study to compare the outcome in morbid obese women after weight loss to those who did not lose weight in the following IVF cycles. Among 79 women who had resumed their IVF treatment, 23 women lost weight to BMI <35kg/m and they had 37 IVF cycles (group A). The other 56 women did not lose weight and had 98 IVF cycles (group B). The women in group A were significantly younger (31.1 vs 35.5 years, P =0.001). Average BMI for group A was 33.1±1.2 vs 37.9±2.5 kg/m 2 for group B, P=0.001. Group A had more favorable outcome during the IVF treatment, They required less HMG for stimulation, they had higher number of oocytes retrieved, and less cancellation rate (5.7% vs 21 % for group B, P=0.03). There was a better clinical pregnancy rate in group A 24.3% vs 16.3% in group B. We Conclude that younger women are more able to lose weight, changing from morbidly obese status to even the obese status will positively affect various parameters in IVF treatment cycles.

Progress

Manuscript preparation.

Project Title: Can Empty Follicle Syndrome Be Predicted? RAC# 2050145

Investigators: Sameera Madan, MD, Rafat Al Rejjal, MD, Saad Al Hassan, MD, Khalid Awartani, MD and Serdar Coskun, DVM, PhD

Project Description

Failure to retrieve oocytes from mature ovarian follicles in normal responders during IVF treatment is described as empty follicle syndrome (EFS). In the literature there is no clear information on the underlying mechanisms, or distinctive patients or cycle characteristics, or future IVF outcome for these women. We did a retrospective study to assess the common characteristics of patients with EFS, and their prognosis, we had 26 patients during the study period had EFS. 78% of them were having primary infertility, their demographic features did not differ from that of the control group. Cycle characteristics was not different from the control group. 13 patients (50%) did not repeat any further cycles. The other 13 patients (50%) under went in total 32 cycles. We found that clinical pregnancy rate of 6.25% per future started cycle if EFS is encountered. So we conclude that EFS is sporadic event it can be seen in the first IVF treatment cycle, or even in patients who had successful cycles and even pregnancy before. There is no predictable feature for its occurrence, patients who had this event have poor pregnancy outcome in futures cycles .

Progress

Manuscript preparation.

Project Title: Prevalence of Hepatitis HCV and HBV in the IVF Population In the Kingdom of Saudi Arabia Between Years 2002 to 2005. RAC# 2061012
Investigators: Zainab Al Abdullah, MD, Serdar Coskun, DVM, PhD, Masheal Al Deary, MD, Saad Al Hassan, MD and Khalid Awartani, MD

Project Description

The American society for reproductive medicine request from IVF programs to test couples routinely for HCV and HbsAg to reduce the potential risk for transmission to an uninfected partner, baby, and disease-free gametes in the same laboratory. The background information regarding prevalence of these infections in the IVF population will be important for generating guidelines for screening and to determine the cost effectiveness of the modulation of practice. The objective of this study is to assess the prevalence of HCV and HBV in the IVF population in the Kingdom of Saudi Arabia. During the study period, there were 4,442 patients screened (2,221 males and 2,221 females). Hepatitis B seroprevalence rate was 5.9% (263 patients), they were 166 males (7.5%) and 97 females (4.4%). Compared to historical data from the general population where 26,606 blood donors were screened for HBV, with seroprevalence rate of 5.1%, the IVF population had higher rate with P=0.03. There were 62 patients with seropositive screen for hepatitis C, giving a seroprevalence rate of 1.4% in the IVF population. There were 30 females (1.35%), and 32 males (1.44%) seropositive for HCV. In the general population the seroprevalence rate was 0.7% from 113,993 blood donors from all over the country, this difference was statistically significant, P<0.001.

Conclusion

HBV and HCV are highly prevalent in the IVF population, even more than the general population, all IVF programs are urged to screen these couples before starting treatment cycles most importantly if gametes and embryos cryopreservation service are offered.

Progress

Manuscript preparation.

Project Title: In Vitro oocytes Maturation and Fertilization of Polycystic Ovarian Syndrome Women. RAC# 2011053

Investigators: Saad Al Hassan, MD, Khalid Awartani, MD, Rafat Al Rejjal, MD and Serdar Coskun, DVM, PhD

Project Description

Current IVF treatment involving in vivo oocyte maturation with the help of the gonadotropin hormone stimulation, this project is aiming to assess the pregnancy outcome with aspiration of immature eggs with subsequent maturation in the laboratory. If good pregnancy outcome achieved, this will be less risky treatment for patients with avoidance of short term and long term risks associated with hormonal stimulation.

Progress

Data collection is ongoing.

Project Title: Gene Expression Profiling of Granulose Cells From Patients Undergoing Infertility Treatment. RAC# 2050204

Investigators: Serdar Coskun, DVM, PhD, Pinar Ozand, MD, PhD, Mahmet Inan PhD , Rafat Al Rejjal, MD, Saad Al Hassan, MD and Khalid Awartani, MD

Project Description

Patients undergoing infertility treatment will have different response to ovarian stimulation, in this study would like to assess if differences in gene
expression profiling at the granulosa cells in normal responders will explain the either the over responder or the poor responder women.

**Progress**

Data collection is ongoing.

**Project Title:** Toward the Understanding of Sperm Role in Fertilization and Early Embryonic Development, a Pilot Study. RAC# 2040040

**Investigators:** Namic Kaga, PhD, Serdar Coskun, DVM, PhD, Mahmet Inan PhD, Hind All-mayman, Bs and Saad Al Hassan, MD

**Project Description**

The sperms from patient with unexplained infertility undergoing IVF/ICSI treatment will be tested to the level of mRNA; their level will be correlated with pregnancy outcome of the treatment cycle. If this correlation is documented then the factors can up-regulate or down-regulate the mRNA level will be assessed in future for hope in interventional options.

**Progress**

Data collection is ongoing.
The Section of

Perinatology

RESEARCH PROJECTS

Project Title: Chromosomal Abnormalities and Pregnancy Outcome in Fetuses with Increased Nuchal Translucency in Saudi Population. RAC# 2061074

Principal Investigator: Wesam I. Kurdi, MD
Co-Principal Investigator: Maha Al Tuwaijri, MD

Project Description

The measurement of fetal nuchal translucency (NT) thickness at 10-14 weeks of gestation has been established as a sensitive, accurate and effective method of screening for chromosomal abnormalities. In addition, several studies have reported on the association of increased NT with major cardiac defects, other structural defects and rare genetic syndromes. Despite the higher incidence of genetic disorders in Saudi Arabia, which is thought to be related to the high rate of consanguineous marriages, there is no study, to our knowledge, assessing the significance of increased nuchal translucency in Saudi population. Our study is a retrospective review of all cases with increased fetal nuchal translucency, their pregnancy course, outcome and diagnosis.

Progress

Data collection is ongoing.
Project Title: Non-Immune Fetal Hydrops (NIH): A Challenge for Prenatal Diagnosis and Management Retrospective Study. RAC# 2061058

Principal Investigator: Majed Faden, MD
Co-Investigators: Wesam I. Kurdi, MD, Rubina Khan, MD, Maha Al Nemer, MD, Samir Ghoureb, MD, Saleh Al-Alayan, MD and Ahmed Al-Ameri, MD

Project Description

Non-immune hydrops fetalis (NIH) is a description of fetuses with sonographic demonstration of fluid collection in at least two different fetal compartments or single effusion combined with fetal anasarca. The reported incidence of NIH is 1 in 1500 to 1 in 4000 deliveries. It is a non-specific finding in a wide variety of fetal and maternal disorders, including hematological, genetic, chromosomal, cardiovascular, renal, pulmonary, gastrointestinal, hepatic, metabolic abnormalities, congenital infection and malformations of placenta or umbilical cord. Although many causes of fetal hydrops are responsive to therapy with reversal of hydrops and survival, the mortality of fetal hydrops generally remain high. Estimates of mortality vary between 60% and 90%. Prenatal diagnosis of some causes of NIH is well established in chorionic villi and amnioncytes. Awareness of diseases causing hydrops is useful as it gives an opportunity for risk evaluation, genetic counseling to parent and targeted prenatal diagnosis for at-risk pregnancies. Our study is a retrospective review of all cases with NIFH maternal workup, fetal and neonatal outcome. The aim of this research is to evaluate the etiology, prognosis and outcome of fetuses with NIH, our diagnostic work-up and their yield.

Progress

Data collection is ongoing.

Project Title: The 2-Hour Postprandial Glucose Test: An Evaluation of the Accuracy of This Screening Test for Gestational Diabetes. RAC# 2051043

Principal Investigator: Rubina Khan, MD
Co-Principal Investigators: Shahida Mushtaq, MD, Assistant, Dept of OB/GYN
Co-Investigators: Wesam I. Kurdi, MD, Maha Al Nemer, MD and Maha Tulbah, MD

Project Description

Gestational diabetes mellitus is a common medical complication and metabolic disorder in pregnancy, occurring in 1-14% of patients depending on the population described and criteria used for diagnosis. Adverse maternal fetal outcomes will increase (fetal macrosomia, pre-eclampsia, caesarean section and birth trauma in pregnancy). 30-50% of women with glucose intolerance during pregnancy will develop diabetes later in life. This emphasized in large blind trial conducted by Toronto-tri hospital gestational diabetic project. This trial also showed an unequivocal graded relationship between the fasting plasma glucose concentrations and with variety of adverse outcomes. Identifying women susceptible to gestational diabetes is particularly important not only to prevent perinatal morbidity but also to improve long-term outcome for the mother and her child. Our aim of this study is to evaluate the accuracy of the 2-hour postprandial plasma glucose test as a screening test for gestational diabetes compare the result of this screening test to the gold standard diagnostic test which is 75g OGGT.
Project Title:  KFSHRC Experience in Prenatal Diagnosis. RAC# 2051042

Principal Investigator: Nadia Al Hazmi, MD
Co-Investigators: Wesam I. Kurdi, MD, Maha Al Nemer, MD, Rubina Khan, MD and Alya Al Kaff, MD

Project Description

Congenital and hereditary malformations are considered one of the main causes of mortality and morbidity, they result in suffering, emotional distress and economic burden for individuals, families and society. Medical Progress has not yet made it possible to cure a great many hereditary disorders, the best that can be done is to prolong life slightly and improve its quality to a limited degree. The aim of this research is to study the KFSHRC experience with prenatal diagnostic procedures, common genetic diseases encountered, and obstacles in specimen handling.

Progress

Data collection is ongoing and the final report should be submitted by 12 June 2007.

Project Title: The Prevention of Preterm Delivery in Women With Cervical Incompetence; Multicenter Randomized Controlled Trial. RAC# 2061016

Principal Investigator: Wesam I. Kurdi, MD
Co Investigators: Rubina Khan, MD, Maha Tulbah, MD and Maha Al Nemer, MD

Project Description

Preterm labor is the leading cause of perinatal morbidity and mortality. Strategies for reducing the incidence of preterm labor and delivery have focused on educating both physicians and patients about the risks for preterm labor and methods of detecting preterm cervical dilatation. The prevention of preterm delivery is a major desiderate in contemporary obstetrics. The research efforts have been punctuated by several ineffective intervention proposals. More recently, new areas of proposed preventive strategy have arisen, focusing on cervical competence. The purpose of this study is to determine if addition of cervical occlusion to routine prophylactic cervical cerclage is associated with a significant prolongation of pregnancy. The protocol is a large, simply designed, randomized-controlled, pragmatic multicentre trial, to confirm or refute the anticipated benefits of cervical occlusion vs. single cerclage. Additionally, the collaboration will give the opportunity to give a more detailed characterization of the group of women at repeated risk of preterm labor.

Progress

Recruiting patients.
Ovarian cancer is the fourth most common killer in women. Data regarding patient and tumor characteristics of ovarian cancer in the Arab world in general and Saudi Arabia specifically are completely lacking. Yet the statistics published by the National Cancer Registry in the Kingdom reveal that the disease does represent a significant problem. Therefore, this study looks at the molecular characteristics of epithelial ovarian cancer in Saudi patients as it is very important not only to understand the clinical behavior of these tumors but also to determine the appropriateness of using biologic therapy in these patients.

RESEARCH PROJECTS

Project Title: A detailed study of patients and tumor characteristics of epithelial ovarian cancer in Saudi Women. KACST and RAC# 2051067

Principal Investigator: Adnan Munkarah, MD
Co-Principal Investigator: Ismail Al Badawi, MD
Co Investigators: Jamal Al Subhi, MD, Hany Salem, MD and Wafa Ajoor, MD

Progress

In the stage of data collection and was approved by KACST for budgeting.

Future Research Direction

This study will provide the necessary data for future studies investigating ovarian cancer in the Saudi and Middle Eastern populations.
Project Title: Ovarian Function Preservation After Laparoscopic Ovarian Transposition. RAC # 2061026

Principal Investigator: Ismail Al Badawi, MD
Co-Investigators: Adnan Munkarah, MD, Jamal Al Subhi, MD, Hany Salem, MD, Khalid Balaraj, MD and Ala Abduljabbar, MD

Project Description

With Progress in early detection of pelvic malignancy and better treatment outcome, the quality of life issues become an important target to aim for when planning the treatment. Some pelvic malignancies affecting women in their reproductive years involve pelvic radiation therapy which leads to ovarian failure. In the past most of those women had managed their menopausal symptoms and osteoporosis with the conventional hormone replacement therapy (HRT). But, since the Women’s Health Initiative (WHI) study came out there was a major reluctance to use HRT. Laparoscopic ovarian transposition came as an alternative to preserve the ovarian function in pre-menopausal women with pelvic neoplasm requiring pelvic radiation therapy and avoiding the use of conventional HRT.

Progress

A total of 18 cases collected and agreed to extend it for one year to collect a total of 25 cases.

Future Research Direction

The study will assess the preservation of ovarian function following laparoscopic ovarian transposition.

Project Title: Clinical Proteomics: Development of Novel Biomarkers for Transitional Ovarian and Breast Cancer

Principal Investigators: Hany Salem, MD and Abdulkareem Alaiya, MD
Co-Investigators: Jamal Al Subhi, MD, Ismail Al Badawi, MD, Adnan Munkarah, MD

Project Description

Ovarian cancer is a major cause of morbidity and mortality in women in many parts of the world. Despite advances made in career treatment, the overall mortality rates for most solid tumors including ovarian cancer remain unchanged. The mortality rate is similar across different countries, and approximately 60% of the women would die of the disease. Cancer proteomics is an aspect of biomedical research and will be an important contribution to our understanding of tumor biology. The aim of this project is to use proteomics approach to identify polypeptides that significantly differ in their concentrations between cells, tissue, serum and plasma, reflecting different stages of the disease and response to therapy.

Progress

A total of 48 cases was collected and a request was submitted to RAC to extend it for one more year to collect the target total number of cases (70 cases).

Future Research Direction

The study will provide the necessary data that is needed for further study or investigation for ovarian cancer and clinical proteomics of novel biomarkers for Saudi women.
Project Title: Molecular Signatures of Diffuse Large B-Cell Lymphoma, Lung and Ovarian Cancer. RAC# 2060008

Principal Investigators: Kawla Al Kuraya, MD and Adnan Munkarah, MD
Co-Investigators: Jamal Al Subhi, MD, Ismail Al Badawi, MD, Hany Salem, MD and Asma’a Tulbah, MD

Project Description

The clinical course of individual cancers is driven by the sum of molecular alterations in cancer cells. Accordingly, studies analyzing the expression of thousands of genes in tumors using cDNA and tissue microarrays have suggested a clinical relevance of the molecular signatures of cancers. However, limited information is available for many cancer types. Moreover, as increasing data suggest there are significant molecular differences between the differences between the same tumor types from patients of different ethnic backgrounds. It is unclear to what extent conclusions from foreign studies will apply to Saudi cancer patients. The proposed pilot project is intended to look for molecular signatures (or individual gene alterations) in diffuse large B-cell lymphoma (DLBCL), lung neoplasias and ovarian cancer based upon DNA alterations including LOH, gene amplification and expression analysis based upon tissue and cDNA microarrays. Qualitative evidence will be sought for differences in the molecular signature of the above tumor types in Saudi and European patients. This study will provide the basis for future projects aimed at investigating the correlation of molecular profiles of tumor subtypes with clinical parameters such as response to treatment and survival. In addition, larger studies based upon data from this project will establish ethnic diversity in the molecular profiles of different tumor subtypes. The discovery of significant molecular differences between Saudi and Caucasians cancers would challenge the current practice of treating Saudi cancer patients according to Western protocols.

Progress

Data collection is underway.

Future Research Direction

This research is a pilot study which will show the important information about molecular signatures of the diffused large pieces lymphoma and specimen of them in the lung and ovarian cancer.
The Department of Otolaryngology

Chairman
Abdullah Al Otieschan

Deputy Chairman
Mohammed Abuzeid
Autosomal recessive genes are responsible for about 80% of hereditary non-syndromic deafness of pre-lingual onset. DFNB1, caused primarily by mutations in the GJB2 gene are responsible for approximately 50% of pre-lingual, recessive deafness in various populations. To date, 738 patients/family members and 80 families are enrolled and analysis of 500 individuals strongly suggests that DFNB1 does not play a dominant role (~2-5%) in non-syndromic hereditary deafness in the Saudi population. This accelerated our efforts to conduct prioritized linkage analysis on 11 families (with 3 or more affected members) using Affymetrix 10K Array SNP technology. Typical results (shown as a high LOD score) allow identification of a particular region on a specific chromosome, which contains the gene causing the underlying molecular defect in a particular family. Currently, using a candidate gene approach, we have identified the disease-causing mutations in 2 families and have identified strong candidates in remaining families that provided high LOD scores on various chromosomes, which will be discussed in detail. Identification of the most common forms of hereditary deafness, their incidence and distribution in the Saudi population and application of this knowledge to newborn and pre-marital screening will have a major impact upon early management of hereditary deafness.

SUMMARY OF THE UNIT’S 2006 REPORT

For 2006, the Otology and Communication Disorders had been contacted to study the role of DFNB1 locus in hereditary deafness within the Saudi Population as the sole research study in the unit.
RESEARCH PROJECTS

Project Title: Role of the DFNB1 Locus in Hereditary Deafness Within the Saudi Population

Principal Investigators: Khalid Taibah, MBChB, FRCS and Bryan Meyer, PhD
Co-Investigators: Faiqa Imtiaz, PhD, Mohammad Al-Owain, MB, Shelly Kenedy, MS, CG-C, Ghada Bin Khamis and Shaza Saleh

Aim

To identify the most common forms of hereditary deafness in the Saudi population.

Project Description

Autosomal recessive genes are responsible for about 80% of hereditary non-syndromic deafness of pre-lingual onset. DFNB1, caused primarily by mutations in the GJB2 gene are responsible for approximately 50% of pre-lingual, recessive deafness in various populations. To date, 738 patients/family members and 80 families are enrolled and analysis of 500 individuals strongly suggests that DFNB1 does not play a dominant role (~2-5%) in non-syndromic hereditary deafness in the Saudi population. This accelerated our efforts to conduct prioritized linkage analysis on 11 families (with 3 or more affected members) using Affymetrix 10K Array SNP technology. Typical results (shown as a high LOD score) allow identification of a particular region on a specific chromosome, which contains the gene causing the underlying molecular defect in a particular family. Currently, using a candidate gene approach, we have identified the disease-causing mutations in 2 families and have identified strong candidates in remaining families that provided high LOD scores on various chromosomes, which will be discussed in detail. Identification of the most common forms of hereditary deafness, their incidence and distribution in the Saudi population and application of this knowledge to newborn and pre-marital screening will have a major impact upon early management of hereditary deafness.

Progress

New patients are continued to be screened on a weekly basis in the unit and more families are being enrolled in the study.

Only research projects initiated during the year 2006 and ongoing projects of the previous years shall be included. Please do not include projects that were completed prior to year 2006.

FUTURE RESEARCH DIRECTION

To enlarge the project scope in order to study approximately 200 families to determine genes involved in deafness in the Saudi Population. Application of our study to newborn and pre-marital screening will have a major impact upon early intervention and prevention of hereditary deafness in Saudi Arabia.
The Department of Pathology and Laborator Medicine

Chairman
Fouad Al Dayel

Deputy Chairman
Abdelghani Tbakhi
RESEARCH PROJECTS

Project Title: Grading of Follicular Lymphoma Using Flow Cytometry

Investigators: Walid A. Mourad, MD, FCAP, FRCPA; Faisal Rawas, MT(ASCP) QCYM, MS(CLS); Mohamed Shoukri, PhD; Abdelghani Tbakhi, MD, FCAP; Mohammad Al Omari, MD; Asma Tulbah, MD, FRCPA; Fouad Al Dayel, MD, FRCPA

Background

The treatment and prognosis of follicular lymphoma (FL) is dependent on the grade of the disease. In the World Health Organization classification of lymphoma, grading of FL into low grade (1 and 2) and high grade (3) is recommended. Grading of FL is possible in excision biopsy; histological grading is subjective and inconsistent. Grading is extremely difficult in needle core biopsies and fine needle aspirates. We attempted to grade FL using flow cytometry (FCM) and CD19/forward scatter.

Materials and Methods

Cases of FL seen in our institution and submitted for FCM were evaluated for the percentage of cells detected beyond the 500-channel mark (on a 1024 scale) on a CD19/forward scatter dot plot. We hypothesized that these cells most likely represent centroblasts and their percentage would reflect the grade of the disease. Histological grading of the lymphoma on the open biopsies constituted the reference for FL grade.

Results

Thirty-six cases of FL, including 22 males and 14 females, ranging in age from 19 to 92 years (median, 42 years), were studied. There were 17 cases of low grade (grade 1; n=10 and grade 2; n=7) and 19 cases of high grade (grade 3) FL. The percentage of cells identified beyond the 500-channel mark on CD19/forward scatter dot plot ranged from 0.12% to 12.55% (median, 4.9%) in low grade (grade 1 and 2) whereas the percentage of those cells in high grade FL ranged from 6.22% to 51.95% (median, 21%; P=0.00001).
Conclusion

Our findings suggest that using a CD19/forward scatter dot plot can help identify centroblasts in FL making grading possible on FCM, especially in small biopsies and fine needle aspirates.

Project Title: Novel Mutations in Three Large Saudi Families Affected with L-2-Hydroxyglutaric Aciduria. RAC# -1070-26

Investigators: Muhammad Faiyaz-Ul-Haque1, Eissa Faqieh, Halah Abdullah Abalkhail1, Adel Alduraihem, Mohamed Al-Owain, Abdelghani Tahkhil1, Mohammed Rashed, and Moeen Al-Sayed

Here we report 3 extended consanguineous families from different geographical regions of Saudi Arabia, displaying the typical features of L-2-Hydroxyglutaric aciduria encoded by L-2-hydroxyglutarate dehydrogenase (L2HGDH), a rare autosomal recessive neurometabolic disorder characterized by mild psychomotor delay in the first years of life, followed by progressive cerebellar ataxia, dysarthria and moderate to severe mental deterioration. We studied 9 patients, from 3 families (A, B & C) with L2HGDH gene and sequenced the entire coding regions and exon–intron boundaries which revealed novel homozygous mutations in all 3 families. In family-A & B, we identified a novel single bp deletion “A1015” in exon 8, resulting in a frameshift in the translated protein and replacement of 12 novel amino acids before a premature termination. The mutation was found in a homozygous state in all 7 available affected individuals from family-A & B and was heterozygous in all unaffected carrier parents. In family-C, mutation analysis in 2 affected individuals revealed a homozygous C1319A transition at codon 440, which changes Serine a hydrophilic acidically charged residue to Tyrosine a basically charged residue in a conserve low complexity region of gene. To our knowledge, this is the first report of mutation analysis of the L2HGDH gene from Saudi Arabia. The two mutations are located in a highly conserved area across the multiple species suggest that the substituted residues are important for protein folding and/or enzyme catalysis and may effect the pre- processing and folding mechanism of the protein inside the mitochondria.

Project Title: Simultaneous LC-MS-MS Determination of Cyclosporine A, Tacrolimus, and Sirolimus in Whole Blood as Well as Mycophenolic Acid in Plasma Using Common Pretreatment Procedure. PUB# 2060 080

Investigators: Maciej J. Bogusz, Eid Al Enazi, Huda Hassan, Jamil Abdel-Jawwad, Jamal Al Ruwaily, Mohammed Al Tufail

The purpose of the study was to develop rapid and simple procedure for simultaneous determination of cyclosporine A (CsA), tacrolimus (TCR), and sirolimus (SIR) in whole blood and mycophenolic acid (MPA) in plasma. Ascomycin, cyclosporine D, and desmethoxyriolimus were used as internal standards (IS) for TCR, CsA and MPA, and SIR, respectively. Six-level blood calibrators were used for CsA (47-1725 ng/ml), TCR (2.1-38.8 ng/ml), and SIR (2.4-39.6 ng/ml). Four-level calibrators were used for MPA (0.15-5.48 µg/ml). Four levels of quality control (QC) standards were used. Calibrators and QC standards were obtained commercially.

Sample preparation based on simple precipitation of 100 µl of sample, followed by centrifugation. HPLC was performed on ChromSpher π column, 30x3mm, in gradient of ammonium formate buffer-methanol at 0.8 ml flow rate. Total run time was 3.7 min. ESI-MS-MS (MRM) was performed in positive ion mode. Ammoniated adducts of protonated molecules were used as precursor ions for all analytes.
The limits of quantitation were: 1 ng/ml for TCR and SIR, 20 ng/ml for CsA, and 0.1 µg/ml for MPA. MPA was fully separated from its glucuronide. Possible metabolites of CsA, TCR, or SIR did not interfere with target compounds or internal standards.

Chromatograms showing mass traces of target compounds and internal standards in various clinical samples.

The method was applied for everyday determination of immunosuppressive drugs among transplant patients (up to 130 samples daily) and was published in *Journal of Chromatography B* vol. 850, pp. 471-480, 2007.
The Department of Pediatric Hematology / Oncology

Chairman
Kwesi Sackey, MD

Deputy Chairman
Mohammed Al-Mahr, MD
Research activity in the Department has continued this year. Although the number of publications this year is marginally lower than the previous year there has been more progress towards the establishment of the infrastructure and mechanisms for quality research.

The Central Data Unit (CDU) in the Department, was established in 2005 with the primary objective of developing a comprehensive Patient Information Management System (PIMS) for the collection and storage of clinical data used to evaluate our treatment efforts, providing well organized information in a timely fashion. The PIMS is designed to include disease entity specific databases in a 3-tiered fashion, with each tier housing expanded and more specific data. These disease-entity specific databases are linked through Tier 1 (the Core Module), which comprises of information common to all disease subtypes. Database development is proceeding at a satisfactory rate and is concurrently being populated prospectively. Also, retrospective data previously collected on several RAC approved studies has been reformatted and ported in to populate the new databases.

There are currently Twenty (20) RAC approved projects active in the Department. Department members co-authored eight (8) publications and presented eleven (11) research abstracts during 2006. With many of the active studies approaching completion, it is anticipated that many more publications will be forthcoming.
RESEARCH PROJECTS

Project Title: Prospective Evaluation of Risk-Adapted Therapy for Pediatric Patients with Non-Lymphoblastic Non-Hodgkin Lymphoma (PNHL05). RAC # 2051-018


Project Description

This study is a prospective clinical trial based on the results of the retrospective evaluation of NHL at our institution (RAC# 2011-047). The primary objective of the study is to determine if treatment intensity for pediatric patients with non-lymphoblastic non-Hodgkin’s Lymphoma can be stratified based on the relative risk for relapse to reduce treatment-related toxicity, while maintaining the high cure rates. The specific aims of the study are as follows:

1. To determine the practicability of prospectively grouping NHL patients into risk categories that cross stage boundaries.
2. To determine the relative percentage distribution for the different risk groups in patients with non-lymphoblastic NHL.
3. To determine the outcome (RFS, EFS and OS) for patients non-lymphoblastic NHL treated on risk adapted therapy.
4. To determine if reduction in the dose intensity and duration of treatment for patients with Risk Group B disease (HR stage II and LR stage III) can be achieved without impact on the stage specific disease cure rates.
5. To determine if reduction in the dose and volume of CNS-directed radiation therapy for patients with CNS disease at presentation can be achieved without a negative impact on disease outcome.
6. To determine the relative short-term and long-term toxicity associated with the risk-adapted treatment protocols for non-lymphoblastic NHL.
7. To determine if other biological parameters, such as LDH level, Ki67 expression or proliferative index, could help further define the risk assignment for patients with non-lymphoblastic NHL.

Progress During 2006

Patient accrual on this study started in January 2006 and to date 12 patients had been enrolled. Several of these patients have actually completed their therapy and are now continuing on post-therapy follow-up. Others are currently receiving their protocol therapy.

Future Plans

To continue to accrue and enroll patients.

Project Title: Retrospective Review of Pediatric Patients Diagnosed with Hodgkin Lymphoma Treated at KFSH&RC, January 1975 to December 2002. RAC# 2041-046

Investigators: Rajah Sabbah, Asim Belgaumi, Amani Al Kofide, Yasser Khafaga, Rubina J Malik, Nacey Joseph

Project Description

Therapy improvements have resulted in the disease free survival for patients with HL increasing to a point where over 80-90% can expect to be cured. This, however, has been achieved at a significant toxic cost, and these patients suffer significant long-term toxic effects of therapy. This has prompted clinical investigators to devise treatment strategies that focus on reduction in toxicity without impinging
on the cure rates. The pediatric oncologists at our institution followed a similar strategy. With this review we would like to evaluate, in a very large cohort of young patients, the distribution of HL in terms of age, stage and histological subtype, comparing these results with published data from other regions in the world. Also, we will be able to determine the outcome, in terms of both the disease and the toxic complications, according to the type of therapy received (radiation or chemotherapy alone, combined modality therapy, lower dose radiation, ABVD vs. other regimens, etc).

Progress During 2006

Chart review and data entry was completed and analysis of the data is ongoing. Between January 1975 and December 2003, 495 patients under the age of 14 years were treated for Hodgkin Lymphoma at our institution. Data for 35 of these patients was unavailable and 92 were diagnosed elsewhere and had initiated therapy there. These patients were referred to our institution either for radiation therapy alone, for continuation of first line chemotherapy, or at the time of relapse for second line therapy. These patients were not included in the analysis. The remaining 368 patients were diagnosed and received all their treatment at our institution. The 10-year overall survival for the group is 90.5%, with an EFS of 78%. Subset analysis of the group is continuing and has so far resulted in the presentation of two abstracts.


Future Plans

Continued subset analysis for the whole group will be undertaken. The data that was presented in abstract form is being written as a manuscript for publication. We expect that the results of this study will enable us to plan and develop a prospective clinical protocol for the treatment of children with Hodgkin Lymphoma.

Project Title: Retrospective Review of The Outcome of Pediatric Acute Lymphoblastic Leukemia at KFHS&RC, 1999 - 2004. RAC#2051-065

Investigators: Asim Belgaumi, Hassan El-Solh, Mohammed Al-Mahr, Mahasen Al-Saleh, Abdur Rahman Al-Musa, Amel Al-Seraifi, Ali Al-Ahmari

Project Description

Acute lymphoblastic leukemia is the most common malignancy in children accounting for over 25% of childhood cancers and 75% of all leukemia. With current multi-agent, intensive chemotherapy the majority of these patients can expect to be cured. For certain sub-groups the cure rates now exceed 90%, and the EFS for all patients in most studies exceed 65%. This success in treatment of childhood ALL, has resulted from a progressive, step-wise understanding of the behavior of the leukemic cells and their response to different modalities of therapy.

The identification of risk factors and their interactions have allowed us to categorize patients based on their risk for relapse, and to administer risk-adapted
therapy. Risk-adapted therapy allows us to reduce treatment intensity for those patients expected to do well with less intensive treatment. At KFSH&RC the Pediatric Leukemia Program has used this strategy for the past several years. In late 1998, this stratification was revisited and new guidelines were established for diagnosis, risk stratification and treatment assignment. In this study we propose to evaluate the outcome of these patients, specifically looking at the various risk based sub-types and the specific treatment strategies applied to them.

This is a retrospective study, the primary objective of which is to determine the outcome (overall survival, relapse free survival and event free survival) of patients with acute lymphoblastic leukemia treated at KFSH&RC with risk-adapted therapy.

**Progress in 2006**

Data collection for the ALL patients diagnosed and treated between 1999 and 2004 was completed and the analysis has been initiated. Briefly, 411 patients were included in the analysis. 341 were diagnosed as precursor B-cell ALL, 53 T-cell ALL and 17 Biphenotypic acute leukemia. The OS and EFS for all patients was 79.9 and 71.1%, respectively. Further subset analysis was conducted looking at specific subtypes of ALL and prognostic indicators in relation to outcome of children with ALL in Saudi Arabia. This has resulted in the presentation of four research abstracts.


**Future Plans**

The results of that were presented in abstract form are now being written up as manuscripts for publication. Further analysis of the data, looking more in depth at the distribution of prognostic indicators and their impact on outcome is currently being undertaken. Also, we are reviewing the data of those patients who relapsed to determine the outcome of second and third line therapy used for our ALL patients. The results of this study is also being utilized to develop a new strategy of treatment for our patients and will hopefully result in an in-house prospective clinical trial for ALL.

**Project Title: Translational Initiatives in Lymphoid Malignancy. RAC# 2020-015**

**Investigators:** Asim Belgaumi A, Shahabuddin Khan, Khawla Al Kuraya, Azhar Hussain, Khalid AbuKhabar, Khalid Siraj, Hassan El Solh
Aims

The overall scientific goal of the proposal is a comprehensive approach to the characterization of ALL in pediatric patients from the Kingdom of Saudi Arabia. This shall be achieved by developing individual projects within a program that focuses on various facets of the biological heterogeneity of leukemia, and by extending state-of-the-art studies to childhood leukemia in this region.

Project Description

This is a translational research project that is a collaborative effort between the Department of Pediatric Hematology/Oncology and the Research Centre at KFNCCC&R. This study aims to comprehensively study molecular characteristics of the leukemic cells in patients with ALL and correlate the findings with clinical features. It is expected that such a study will allow us to better characterize childhood ALL seen in this region, establish and confirm molecular prognostic variables and develop better diagnostic and screening methodologies.

Until now, a total of 197 patients have been enrolled on this study. From these patients we have received 70 bone marrow, 31 peripheral blood and over 1000 CSF samples. These samples have been processed and stored for analysis. In addition to the samples we have been collecting clinical data regarding the diagnostic workup, treatment assignment, response to therapy and outcome. This information is collected prospectively and entered in the Leukemia database.

Progress During 2006 and Future Direction

We have performed Real-time RT-PCR experiments on 77 ALL samples to detect the four more common chromosomal translocations that are prevalent in ALL patients. They include:

- $t(12;21)(p113;q22)$ : TEL/AML1 fusion gene
- $t(9;22)(q34;q11)$ : BCR/ABL fusion gene
- $t(4;11)(q21;q23)$ : MLL1/AF4 fusion gene
- $t(1;19)(q23;p13)$ : E2A/PBX1 fusion gene

In addition, these samples have also been processed for their gene expression profile by Affymetrix gene expression analyzer. Currently, the data is being analyzed using 3 different softwares.

WHO-based Molecular Sub-Classification of Childhood ALL

Sample that are being collected are processed into RNA, DNA and proteins and the remaining samples are frozen down in liquid Nitrogen for later use. To date, we have collected more than 100 bone marrow and 50 peripheral blood diagnostic samples. RNA has been extracted from these collected samples and reverse transcribed into cDNA to study the common genetic translocations that are found in the ALL population by Real-time RT-PCR. Sub-classification of the ALL is necessary as the treatment modalities differ with different translocations. Of the various translocations commonly identified, in many studies $t(12;21)$ has been associated with poor prognosis and therefore requires a more extensive treatment protocol.

Profiling of Expression on Microarrays

Based on clinical data, 77 Acute Lymphoblastic Leukemia (ALL) samples have been analyzed for microarray expression studies to detect any genetic variation in correlation with risk stratification and clinical prognostic variables to select molecular prognostic markers as well as target genes for improved therapy. This study is currently ongoing with a target of collecting 100 samples of ALL. Comparison studies are also being done to compare the gene expression profile between normal and ALL samples.
Another study that has been initiated is the detection of TdT+ cells in the CSF of ALL patients to detect CNS involvement. We have shown that Quantitative RT-PCR allows greater sensitivity and also allows quantification of TdT in CSF, which may prove to be clinically significant. We have thus established a quantitative assay and generated a standard curve using serial dilutions of a precursor B-cell ALL cell line (REH) that expresses TdT. To date, we have already collected more than 1000 samples that are being processed into cDNA for further studies.

**Expression of Pro and Anti-Apoptotic Genes in Childhood B-Cell ALL**

Mammalian cells undergo programmed cell death by orchestrated interactions involving multiple independent pathways. At least one of the pathway, the p53 pathway has been found to be compromised in many lymphoid malignancies. Non-p53-dependent loss of apoptotic regulation may also contribute to the genesis and/or progression of leukemia. We are therefore studying the expression of pro- and anti-apoptotic genes at the cDNA and the protein level to provide information on how these two pieces of the expression profile correlate with each other. We will be targeting the Bcl-2, IAP and the caspase families of protein. We intend to use this to follow up only those candidate genes that have strict correlation between the transcript and protein levels, and their expression levels will then be correlated with response and subtypes.

**Project Title: A Prospective Study of Invasive Fungal Infection Among Pediatric Patients 0-14 Years of Age with Hematological Malignancies at KFSH&Rc and KFNCUC&R. RAC # 2041 006**

**Investigators:** Ibrahim Bin Hussain, Asim Belgaumi, Hasan Shahin, Ali Al Ahmari, Mohammed Gamal El Din, Sahar Al Thawadi, Mouhab Ayas, Elma Al Modvar, Zakariya Habib, Amel Al Seraihy, Rajeev Sathiapalan, Sami Hajjar, Sulaiman Jumaah, Khalid Al Mane, Husn Frayha, Irene Barron, Haysam Tufenkeji, Hassan El Solh

**Project Description**

The patterns of incidence of invasive fungal infection in patients with hematological malignancies have changed over the past few years. This notion was supported by a retrospective study that was conducted on our patients. This study is being conducted to determine the incidence of fungal infection in patients with hematological malignancies in KSA, whether the rate and pattern of fungal colonization could predict the development of invasive infection, and to determine if galactomannin assay could be used as a sensitive tool to predict infection in this patient population.

This study involves prospective collection of data regarding the development of clinically evident invasive fungal infection in these patients, along with evaluation of routine surface and orifice cultures for the detection of fungal colonization. In addition serially collected peripheral blood samples are also being tested using the Galactomannin assay.

**Progress in 2006**

A total of 116 patients have been enrolled on this study and their samples have been collected. This cohort includes 60 ALL patients, 20 AML patients and 36 patients with hematological disorders post SCT. The samples for these patients were collected and the microbiological tests are currently being completed.

**Future Plans**

Once the microbiological tests have been completed the results of these tests will be compared to the clinical data and an interim analysis will be done.
Based on the result of the interim analysis a decision will be made regarding the future course of the study.

**Project Title: P-Glycoprotein in Childhood ALL In KSA: A Prospective Study of Expression And A Correlation With Outcome. RAC# 2001 004**

**Investigators:** Abdallah Al Nasser, Khalid Al Hussein, Nasser El Kum, Zuha Al Mukhlafi, Fawaz Al Kassim, Mustafa Khalaf, Hassan El Solh, Raghad Al Saad

**Objectives**

The main objective of this study is to establish and standardize a system for the detection of P-glycoprotein at diagnosis and relapse in children with ALL. This is being conducted by flow-cytometry using bone marrow and peripheral blood samples containing leukemic blasts. The results will help determine the prevalence of p-glycoprotein expression in pediatric ALL seen in the Kingdom and will be compared against known prognostic variables in ALL. The outcome of patients with p-glycoprotein expression will be compared to those without expression.

**Progress During 2006**

To date 139 patients have been enrolled in the study. 32 cases were non-analyzable due to various reasons and the remaining have been subjected to flow-cytometry to determine p-glycoprotein expression.

**Future plans**

While patients will continue to be enrolled on the study, an interim analysis will be done to determine if the number accrued can result in significance.

**Project Title: Acute Myeloid Leukemia in Patients with Down’s Syndrome; Experience at KFSH&RC, KSA. RAC# 2051 044**

**Investigators:** Mahasen Saleh, Ashraf Radwan, Hassan El Solh, Mohammed Al Mahr, Asim Belgaumi, Abdulrahman Al Musa, Ibrahim El Hassan

**Project Description**

Patients with Down’s Syndrome have a greater risk of developing leukemia, in particular AML. In addition, these patients are more sensitive to the toxicity of leukemia directed chemotherapy and are at a greater risk of developing infectious complications. This is a retrospective study which looks at the outcome and toxicity of patients with Down’s Syndrome with AML who received two different treatment protocols.

**Progress During 2006**

The chart review and analysis of the data was completed. A total of 17 patients were identified with DS and AML. Ten were treated according to a standard protocol used for non-DS patients while 7 were treated on a less intensive protocol. The clinical characteristics of the two groups were similar. The DFS for the two groups was not found to be statistically significantly different (70% and 67.7% respectively). However, significantly more toxicity was found in the group treated with standard chemotherapy as compared to the lower intensity therapy.

**Future Plans**

This study was completed and the results will be used to direct future therapy in children with DS who have AML. The results of the study are currently being written up as a manuscript for publication.
Project Title: Retrospective Review of Pediatric Patients Diagnosed with AML and Treated at KFSh&Rc (January 1998- July 2002). RAC# 2031 037

Investigators: Mohammed Al Mahr, Ashraf Radwan, Asim Belgaumi, Mouhab Ayas, Mahasen Saleh

Acute Myeloid Leukemia (AML) is an aggressive form of leukemia that is seen in about one third of all pediatric cases of leukemia. Treatment of AML requires intensive chemotherapy and in a significant proportion of patients the use of allogeneic SCT is recommended. Patients at our institution have been treated with intensive chemotherapy followed by related donor transplantation when a suitable donor was available. Those patients who did not have a donor were treated with chemotherapy alone. This study was a retrospective review of the outcome of these patients at our institution.

Progress in 2006

Chart review of these patients and the analysis of the data were completed. The results showed that between 1998 and 2002, 103 patients were diagnosed and treated. The 5-year OS for the whole group was determined at 55.7%, and the EFS at 42.7%. No significant differences in the OS or the EFS could be determined for those who were treated with chemotherapy alone as compared to those who underwent SCT. This study was closed during this year.

Future plans

The results of this review have determined the direction we will be taking in terms of treatment strategies for our AML patients. Manuscript preparation is in progress to publish the results.

Project Title: The expression of MMP-9, TIMP-1 and correlation of TIMP-1 and IL-10 in pre-Bpediatric ALL. RAC# 2010 029

Investigators: Mona Al Quwaidi, Abdallah Al Nasser, Allison Sinclair, Khalid Al Hussein, Mouhab Ayas, Hassan El Solh, Christopher Alviedo

Project Description

This study was part of the PhD thesis for the principal investigator. It seeks to assess the expression of TIMP-1, MMP-9 and IL-10 in leukemia cell lines by RT-PCR and Western Block. In addition, the expression will be assessed in patient leukemic cell samples.

Progress during 2006

The target number of 150 leukemia patient samples and 10 normal bone marrow samples was achieved. The assays were all completed and the draft thesis is currently under preparation.

Future plans

The thesis will be submitted for review at the Sussex University, Brighton, UK, and subsequently prepared as a manuscript for publication.

Project Title: Flow-Cytometric Analysis of Minimal Residual disease in Pediatric ALL in the Kingdom of Saudi Arabia: A Prospective Study of Expression and Correlation with Outcome. RAC# 2001 007

Investigators: Abdallah Al Nasser, Khalid Al Hussein, Nasser El Kum, Tarek Owaidah, Fawaz Al Kasim, Mustafa Khalaf, Hassan El Solh, Christopher Alviedo, Raghad Al Saad
Aims

This study aims to introduce flow cytometry as a methodology for the detection of minimal residual disease in newly diagnosed patients with ALL at our institution. The results of the analysis will be compared with the conventional morphological study of the bone marrow at the end of induction, and with the outcome of the patients.

Progress in 2006

143 evaluable cases have been collected and tested to date. Further enrollment and sample collection is currently underway.

Future plans

Continue patient accrual and sample collection to reach the target number of 250. An interim analysis of the results will be conducted during the current year.

Project Title: An Open-Labeled, Multi-Center Study on the Efficacy and Safety of Long-Term Treatment with ICL670 (20mg-30mg/kg/day) in Beta Thalassemia Patients with Transfusional Hemosiderosis. RAC# 2041 038

Investigator: Abdullah Al Jefri

Project Description

This study is part of a multi-center, single arm, sequential trial design, aimed at studying the efficacy and safety during the trial period. Data were collected over the period of treatment with ICL670 for patients with transfusional iron overload who failed other iron chelators such as desferoxamine (DFO)/ deferiprone (non-compliance, poor tolerance, lack of response). ICL670 is an N-substituted bis-hydroxyphenyl-triazole, a new class of tridentate iron chelator. The drug is orally active with good tolerability and potency in mobilizing tissue iron and promoting iron excretion as demonstrated in vivo and in vitro models. The dose is 20-30 mg/kg given as a single daily dose.

The primary objective is to evaluate the effects of the ICL670 treatment on the liver iron content (LIC) as assessment by liver biopsy after one year of administration in Beta thalassemia patients with transfusional hemosiderosis unable to be treated with DFO. Secondary objective is to evaluate the tolerability profile of ICL670, assessing various iron surrogate markers and potential use of MRI as a noninvasive assessment of (LIC). In addition the study also assesses the drug usage compliance and quality of life and patient global assessment.

Progress in 2006

Twenty patients (age range 5-22 yrs) fulfilled the eligibility criteria and were enrolled in the study between February and June 2005. Patients had a pre-treatment initial assessment followed by regular monitoring and evaluations including physical exam, endocrine assessment and also a broad range testing of blood and urine on monthly basis. All patients underwent liver biopsy procedure at the beginning and at the end of one year of the study to quantify the iron content. In addition, patients also had simultaneous MRI of the liver for the same purpose. Patients were followed with a patient questionnaire, global assessment forms, and drug return recording form to assess compliance. All patients are currently continuing on the drug for the second year without any problems related to the drug. All of them except one had a remarkable decline in the (LIC), following one year of treatment with excellent compliance. The mean drop in LIC following one year of treatment is 52% (range 25-79%). At the beginning of the treatment few patients developed few minor side effects. Five patients
developed nausea and diarrhea of two days duration, three patients had skin rash, which resolved after one week, seven patients developed mild increased in serum creatinine (within the normal range), which resolved with modification of the dose.

So far we have concluded that ICL670 is an effective and safe iron chelator, with only minor side effects. This has resulted in significant increase in the compliance and the resultant decline in LIC.

Future Plans

The study period of the drug has been extended in order to continue to follow these patients for a longer duration. This will allow us to determine the continued chelation potential of this drug and its long-term toxicity profile.

Project Title: Pharmacokinetics of Methotrexate in Children with ALL- Correlation With Outcome. RAC # 2021 004

Investigators: Abdallah Al Nasser MD, Samir AlRawithy, PhD, Mohammed Shoukri, PhD Hassan El-Solh, MD (for the members of PHO)

Project Description

Methotrexate is an important constituent of the treatment of pediatric ALL. There are differences, however, in the sensitivity of the leukemic cells to the drug between the various immunophenotypic subtypes of ALL. There are also differences regarding the population pharmacogenetics of the metabolism of the drug with concerns relating to increased toxicity and lower efficacy of methotrexate in our population. This study aims to introduce and standardize an assay for measurement of the steady state plasma MTX level in patients with ALL. This will help study if a difference in drug elimination exists within our patient population that is different from that seen elsewhere, and to prospectively determine if the difference in MTX pharmacokinetics affects outcome.

Progress in 2006

Pediatric patients with ALL who are treated on protocols including high- or intermediate-dose methotrexate are continuing to be enrolled on this study. Peripheral blood samples are being collected, processed and stored for patients immediately following the completion of the 24-hour methotrexate infusion. Approximately 8-10 samples are collected for each patient over the course of the first year of therapy. These samples will be tested for the methotrexate level in batches of 60, as they become available.

Future plans

There will be continued accrual of patients for the coming year. Once the planned accrual is complete, the results of the methotrexate levels will be correlated against patient characteristics and outcome.

Project Title: PCR Assay for Detection & Quantification of Fungal Infections in Pediatric Patients with Acute Leukemia & Myelodysplastic Syndrome. RAC# 2021 054


Project Description

This prospective translational study was started with the aims of detecting fungal infection by PCR assay as a surrogate marker of fungemia and to determine if quantitative and kinetic characters
of PCR positivity will allow early detection and treatment. The investigators were able to develop a monochrome, multiplex, real-time PCR assay for the identification and quantification of 5 common fungal species.

**Progress in 2006**

Accrual of 19 patients was completed. Clinical, laboratory including PCR results and radiological information has been collected for these patients. Future plans An interim analysis will be undertaken to decide on the future course of action to be pursued for this study.

**Project Title: GVHD in Saudi Children Post Allogeneic HLA-Matched Stem Cell Transplantation. RAC # 205 1008**

**Investigators:** M. Ayas, A. Khairy Radwan, M. Al Mahr, A. Al Seraihy, A. Al Jefri, S. Al. Rifai, S. Markiz, I. El Hassan

**Project Description**

To study the incidence of GVHD (Acute and Chronic) in all children who were offered allogeneic stem cell transplantation from matched related donors at KFSHRC and to correlate it with other factors such as primary disease , HLA degree of compatibility, donor relationship (Phenotype and Genotype), patient’s age, recipient’s age and sex, dose of CD+34 stem cells received, dose of CD3 cells received, conditioning regimen, prophylactic immune-suppression, and the use of intravenous immune-globulin.

**Progress during 2006**

Data was collected and the proposal was finalized.

**Future Plans**

The data have been collected and submitted to the research and biostatistics department. Awaiting analysis.

**Project Title: Allogeneic Stem Cell Transplantation Using Cord Blood as the Source of the Stemcells. RAC # 203 1002**

**Investigators:** M. Ayas, H. El-Solh, M. Al-Mahr, S. Rifai, A. Al-Jefri, F. A. Al-Ahmari

**Project Description**

This study is a prospective clinical. The end point of the study are explained in the original protocol: a. Evaluate the mortality and incidence of GVHD in recipients of cord blood transplants b. Evaluate the engraftment rate The incidence of complications, engraftment, and mortality will be compared with the international data published

**Progress during 2006**

17 patients were accrued during 2006; the incidence of adverse events in our patients is as follows:

<table>
<thead>
<tr>
<th>Event</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute GVHD grade II or higher</td>
<td>19.3%</td>
</tr>
<tr>
<td>Veno-occlusive disease of liver</td>
<td>7.3 %</td>
</tr>
<tr>
<td>Hemorrhagic cystitis</td>
<td>9.8%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>48.8%</td>
</tr>
</tbody>
</table>

All figures are comparable with the international published data As to the causes of death of our patients thus far:

- Relapse of original disease
- Acute GVHD
- Infection
Future Plans

To continue to accrue and enroll patients.

Project Title: Allogeneic Stem Cell Transplantation in Patients With Fanconi Anemia, the King Faisal Specialist Hospital & Research Centre Experience. RAC # 206 1037


Project Description

Allogeneic Stem Cell Transplantation (SCT) is the only curative modality for bone marrow failure in patients (pts) with Fanconi Anemia (FA). The optimal conditioning regimen however is not determined. FA pts with myelodysplasia or clonal abnormality at the time of SCT are usually conditioned with more intensive regimens. Because of the prevalence of this disorder in our society, King Faisal Specialist Hospital has been a leading center in providing allogeneic SCT for these patients. Over the years, KFSHRC has used different regimens to condition FA patients to prepare them for SCT; the last was a RAC approved study launched for patients’ accrual in May 1999 using low dose cyclophosphamide, antithymocyte globulin (ATG) with no radiation therapy. We study our experience in 62 transplants over a period of 10 years.

Progress during 2006

Proposal was finalized, data collected, manuscript written.

Future Plans

Manuscript submitted to Pediatric Blood and Cancer, accepted provisionally.

Project Title: Retrospective Review of Pediatric Neuroblastoma Treated at KFSH&RC 1975-2004. RAC # 2051032


Project Description

The study is a review of all cases of Neuroblastoma treated at King Faisal Specialist Hospital & Research Centre between 1975 to 2004. The overall survival and disease free survival to all patients and to patient less than 1 year of age and older than 1 year will be reported. The disease free survival and survival will be reported according to the stage and N-myc amplification. The outcome of patient with high-risk, intermediate risk, and low risk group will be reported as well as the outcome of treatment of high risk group with chemotherapy and surgery only versus chemotherapy surgery auto SCT Retinoic acid.

Progress during 2006

400 out of 437 cases have been reviewed and entered for data analysis; charts for 8 cases could not be located and 29 cases are pending reviews.

Future Plans

After reviewing the last 29 cases, we will submit the cases for data analysis and then it will be reported as an abstract and manuscript for publication.

Project Title: Thrombosis in Childhood Leukemia at KFSHRC and KFNCCCR, 01 January 2000 to 30 December 2003. RAC # 2031 051
Investigators: M. Saleh, H. El-Solh, A. Radwan, El-Hassan, A. Maculangan

Project Description

This involved a retrospective review of all cases of Acute Lymphoblastic Leukemia seen at KFSHRC & KFCCCNR, from January 2000 to December 2003. This study aimed to determine the prevalence and the rates of thrombotic event in children with acute leukemia, to determine the risk factors that might contribute in the occurrence of thrombosis among these patients, to determine short and long term complications (from 6 months to 2 years) following treatment of thrombosis, to evaluate the effectiveness of treatment directed to thrombosis (anti-coagulants with or without surgical intervention), and to draw guidelines for the prevention and the management of thrombosis within the context of a pediatric patient with acute leukemia at various stages of chemotherapy.

Cancer in itself has an important role in promoting thrombosis. In this retrospective study among 263 patients seen at King Faisal Hospital and King Fahd Center for Children’s Cancer, from January 2000 - December 2003, the prevalence rate was noted to be 7.6%. Risk factors noted were line insertion, L-asparaginase, infections and post-operative conditions. Complications necessitated line removal in 60% of patients. The evaluation of treatment effectiveness data not available because it was not persistent and consistent. In this study the following guidelines were drawn.

Guidelines

1. All patients with ALL who have line inserted should have normal saline flush every 8 hours while patient is admitted and every 4-6 weeks for out-patients.

2. Periodic physical examination at the line insertion should be done for any evidence of redness or swelling.

3. Regularly check for blood return from Central line and it should be taken seriously in its absence. Investigation should be done promptly by requesting for a dye study followed by ultrasound and/or venogram.

4. If line was proved to be blocked by a clot, line should be removed and maintained on anti-coagulant medication for a month.

5. If there is a proven DVT, anti-coagulant should be started immediately and this would last for 3-6 months with ultrasound follow up.

Progress during 2006

Statistical analysis was already done and is already due for submission to RAC.

Future Plans

Thrombosis had been noted to lead to more serious complications and therefore early diagnosis and treatment is necessary for patients safety. As an oncologist, I have a deep concern for my patients and would still continue to do research on thrombosis until enough information is obtained to contribute significantly to prevention and early intervention.

Project Title: Hemophilia & Von Willebrand’s Disease Registry. RAC # 2041-040

Investigators: M. Saleh, T. Owaidah, A. Al Musa, H. Zahrani, P. Seth, Z. Al Khayal, M. Abu Riash

Project Description

The Hemophilia Care at King Faisal Specialist Hospital and Research Centre, run by the Departments of Pediatric Hematology-Oncology,
Adult Oncology and Pathology and Laboratory Medicine is a well-established Hematology comprehensive program aiming to deliver excellent patient care. A registry is proposed to unify and complete data collection in this area. The World Federation of Hemophilia has accredited the program during the congress meeting in Spain last May 2002.

It is designed to facilitate management and analysis of data of patients with bleeding disorders.

**Progress during 2006**

During this period of the registry, we tried to register all patients seen here in KFSHRC. And we were able to find patients seen as early as 1976. We were able to register 176 (80%) patients with hemophilia and 42 (19%) patients with Von Willebrand’s disease. For this period, we concentrated more of the hemophilia patients and we started to gather all the data possible. There were 137 patient with hemophilia A and 39 patients were Hemophilia B cases.

Analysis of the data for the hemophilic group, 33 patient are mild, 55 have moderate severity and 81 patients developed severe hemophilia that is <0.01 IU/ml of Factor activity. hepatitis in hemophilia were more common than in VWD. Among the hemophilic patients, 13 (7.39 %) patients were infected with Hepatitis B, 88 (50 %) reactive with hepatitis C, 8 (4.54 %) patients were reactive with hepatitis A and 31 (17.61 %) were noted to have HIV.

Since the advent of immunizations for hepatitis B and hepatitis A we found out that 118 (67.05 %) were immune with hepatitis B and 75 (42.61 %) have immunity to Hepatitis A. There were some lacking information of the status of some patients who were already lost to follow up.

In the hemophilic group, 14 (7.95%) patients developed Intra-cranial hemorrhage, 74 (42.05 %) developed target joints. 58 (32.95 %) patients developed inhibitors.

**Future Plans**

We plan to continue collecting data and update the database on a timely manner.

**Project Title**: Retrospective Review of Pediatric Ewing’s Sarcoma (ES) and Primitive Neuroectodermal Tumor (PNET) Treated with the POG 9354 Protocol at KFSH&RC 1994-2004. RAC 205 1015


**Background**

Ewings Sarcoma and Primitive Neuroectodermal Tumor are relatively common pediatric tumors which occur mainly in the second decade of life. Ewings Sarcoma usually arises in bone and most often at the soft tissue extension while PNET may arise in bone or soft tissue. They are linked to a common chromosomal translocations (t11:22). The treatment modality of these tumors include chemotherapy, radiation therapy and surgery depending on the location of the tumor and possibility of resection of the tumor. Since January 1995, we used a common chemotherapy protocol for Ewings Sarcoma and PNET at KFSH&RC. This protocol was modified from the POG/CCG protocol using the standard arm which consist of vincristine adriamycin and cytoxan alternating with ifosfamide and VP16 every three weeks for a total of 48 weeks plus evaluation at week 12 for local control which could be either by surgery or
radiation therapy or both. This retrospective review will cover the period of 10 years since the initiation of protocol until the end of 2004.

**Aims**

The aim of the study is to determine the relative percentage of cases with each histology, the presence and type of metastasis, possibility of resection of the primary tumor and finally the outcome in terms of event free survival and overall survival of these patients, depending on site of disease, presence of metastasis, resectability of tumor and the size of the original tumor.

**Progress during 2006**

There were 130 cases with Ewings Sarcoma / PNET treated during this study period. So far, 16 patients have been reviewed from the charts and the review process is still ongoing.

**Future Plans**

At the end of the review of these charts, the data will be entered and then analysis of the data will proceed to answer the aims of the study as stated.

**FUTURE RESEARCH DIRECTION**

Research activity in the department has continued to grow. There is now a move from retrospective review to the development of prospective studies of our patients and their outcomes. This has certainly been assisted by the establishment of the Central Data Unit, and by the desire of the staff for better quality research. We have continued to foster and expand our research collaboration with the Research Centre and with other sister Departments in the Hospital. The fruits of this endeavor will clearly be visible in the forthcoming years.
The Department of Pediatrics

Chairman
Saleh Al Mofadda
RESEARCH PROJECTS

Project Title: PCR Assay for Detection & Quantification of Fungal Infections in Pediatric Patients with Acute Leukemia & Myelodysplastic Syndrome. RAC# 2021-054

Principal Investigator: Rajeeve Sathiapalan
Co-Principal Investigator: Ibrahim Bin-Hussain
Co-Investigators: Asim Belgaumi, Mohammed Qutub, Ahmed Al Ahmari, Faisal Kurdi, Sahar Al-Thawadi

Project Description

The increasing frequency of fungal infections and high mortality associated with disseminated fungal disease has underlined the importance of rapid detection of pathogenic fungi. Early identification and quantification of fungal load may help to improve the outcome of invasive fungal disease while rationalizing the use of antifungal agents. Conventional identification methods based on phenotypic features are often time-consuming and depend largely on the skill and experience of personnel involved.

Real-time PCR assay has been shown to be a highly sensitive, specific and quantifiable diagnostic tool for the detection of fungi, albeit expensive. To minimize costs and extend application of real-time PCR assay to quantification of fungal load, we developed two duplex and one single probe free LightCycler® PCR assays. This assay utilizes species-specific primers and SYBR Green, without sequence-specific fluorescence energy transfer hybridization probes.

The LightCycler® system helps in analysis of the melting temperature of amplicons. We were able to demonstrate, in this study, that each fungal species has a characteristic melting temperature, which facilitates identification. The melting temperature for Candida albicans, Candida krusei, Candida tropicalis, Aspergillus flavus and Aspergillus fumigatus in our assays were 85.7°C ±0.7°C, 87.1°C ±0.8°C, 83.5°C ±0.9°C, 92.8°C ±0.8°C 92.7 ±0.8, respectively. Furthermore, the melting temperatures of each amplicon in our duplex LightCycler PCR panels were separate with a difference of 7°C between Candida albicans and Aspergillus flavus and 3.6 °C between Candida krusei and Candida tropicalis. These differences ensure reliable identification of each fungal species.
In summary, a low-cost, highly specific and sensitive LightCycler-based real-time PCR assay was developed for rapid and early detection of *Candida albicans*, *Candida krusei*, *Candida tropicalis*, *Aspergillus flavus* and *Aspergillus fumigatus* species and for quantification of the fungal load.

**Progress During 2006**

a. 19 pediatric patients with AML or andS have been enrolled in the study from 20 December 2004. These study patients have had blood samples collected for PCR analysis at various time points as specified in the study-design. As these patients were enrolled in another RAC approved study [RAC # 2041-006] blood samples were also collected for galactomannan assay and surveillance cultures taken from various body sites.

b. The samples were coded being a blinded study and submitted for their respective analyses.

c. Unfortunately, new patient accrual for the study had to be terminated in February 2007, when clinical research coordinator, Dr.Tabassum Akram left the institution. The part-time CRC completed required blood sample collections for patients already enrolled in the study.

d. A new CRC has been appointed and assigned for the study recently.

**Future Plans**

a. We propose to carry out an interim-analysis of the PCR results of the 19 study patients and see its correlation with the study objectives. If it shows unequivocal benefit for patients, further accrual of patients will be terminated and the PCR assay will be accepted as a standard assay for evaluation of pediatric cancer patient with fever and neutropenia.

b. If however, the results are inconclusive and demand more patient numbers, patient accrual will be restarted as the necessary personnel for the same has been recruited.

**Project Title:** A Retrospective Study of Pediatrics Candida Bloodstream Infectious at KFSHRC, January 2001- December 2004. RAC# 205-1020

**Principal Investigator:** Ibrahim Bin-Hussain

**Co-Principal Investigator:** Amal Aidaroos

**Co-Investigators:** Mary Louise Guy, Sahar Al Thawadi, Hail Abdely

**Background:** Candida species are important blood stream pathogens that are being isolated with increasing frequency. Despite the availability of effective antifungal therapy, the mortality rate associated with candida infection remains high.

**Objective:** To describe the epidemiology of candidemia in the pediatric group at the King Faisal Specialist Hospital & Research Centre (KFSH&RC), in relation to underlying medical condition, predisposing factors, concurrent infection antimicrobial agent, antifungal treatment and outcome.

**Method:** Retrospective chart review of all patients with candida blood stream infections age 0-14 years at KFSH&RC utilizing microbiology and infection control databases for the period January 2001 - December 2004.

**Progress During 2006**

Total of 141 pediatric patients with positive blood culture for candida spp. 91.4% were Saudi & 57.4% were males. The majority of them 34% in the Hematology/Oncology ward followed by 21.2% in the pediatric intensive care unit (PICU). 47.5% of the cases presented with fever and 24.1% with hypotension.
Most of the patients 85.8% had central venous lines which were removed after candidemia in 75.8% with survival of 56.7%. Other risk factors like total parenteral nutrition (TPN) recorded in 45.4% of the patients & 51.7% received >3 antibiotics. Dissemination of the fungal infection occurred in 22.7% and the mortality because of candidemia alone is 2% and candidemia as contributing factor for mortality in addition to other causes in 17%.

**Conclusion:** Candida is a major cause of blood stream infections at KFSH&RC, contribution to mortality in 19%.

*Candida albicans* is the predominant pathogen followed by *C. Tropicalis* and *C. parapsillosis*.

CVL is an important risk factor and its removal improves outcome.

**Project Title:** A Prospective Study of Invasive Fungal Infections Among Pediatric Patients 0-14 Years of Age with Hematological Malignancies at KFSH&RC and KFNCCC&R. RAC# 2041-006

**Principal Investigator:** Ibrahim Bin-Hussin  
**Co-Principal Investigators:** Hassan. Shahin, Asim Belgaumi  
**Co-Investigators:** Ali Al Ahmari, Mohammed Gamal-Eldin, Sahar Al Thawadi, Amal Seraihy, Mouhab Ayas, Zakariya Habib, Suliman Al Jumaah, Rajeev Sathiapalan, Sami Al Hajjar, Khalid Manea, Hsus Frayha, Haysams Tufenkeji, Hassan El Solh, Hussein Bagalb

**Project Description**

Invasive fungal infections are increasing in prevalence and present an enormous challenge to healthcare professionals. Systemic fungal infections are a main cause of morbidity and mortality in patients with haematological malignancies and neutropenia. Systemic fungal infection can be treated most effectively when early, definitive diagnosis can be made. Recently, significant advances have been made in the development and evaluation of newer methods for early and specific diagnosis of fungal infection. Galactomannan (GM) is a soluble aspergillus antigen, a major aspergillar cell wall constituent. Screening for circulating GM had been used to predict invasive aspergillus infection in immunocompromised patients as well as to predict the prognosis of invasive aspergillosis. GM assay for fungi is expected to facilitate early detection and treatment of invasive mycoses and eventually translate to superior outcome of therapy in high-risk patients.

Very few reports have addressed the question of colonization, GM assay versus invasive fungal infection in pediatrics, the study should contribute to our understanding of infection dynamics in high-risk paediatric patients. The results of the GM assay, and fungal colonization will be correlated with culture, pathology and radiology results and the clinical course of the patients. This will demonstrate the sensitivity, specificity, positive and negative predictive value of the assay. Quantitative Galactomannan monitoring of the patient can assess the effectiveness of antifungal therapy. Patients who are refractory to conventional antifungal agents can be identified early and therapies altered.

**Objectives**

- Determine the incidence of IFI in this population.
- Assess the rate and risk factors related to fungal colonization and relationship to IFI.
- Assess the sensitivity and specificity of Galactomannan assay in predicting IFI in pediatric patients and its utility in monitoring response to therapy.
• Determine if there is a relationship between the colonization galactomannan positivity and the occurrence of fungal infection.
• Develop insights into the selection of antifungal prophylaxis based on disease categories and colonization.

**Progress During 2006**

The Total of 116 patients were collected, among them are 60 patients with ALL and 20 patients with AML and 36 patients with SCT.

We are now in the process of doing an interim analysis of the results of the accrued 116 patients and see the results correlation with the study objectives.

**Future Plans**

If the results are inconclusive and requiring more patient numbers then more patients will be accrued to be involved in the study.

If the results are unequivocal for the benefit of the patients, it will be applied as a standard for evaluation and management for pediatric patients with ALL, AML or patients going for SCT who are at risk for fungal infection.

**Project Title:** NT-PRO-Brain-Natriuretic Peptide Levels in Neonate With and Without Cardiac Diseases - A New Method to Detect Cardiac Causes of Respiratory Insufficiency in Neonates

**Principal Investigators:** Ghassan Siblini, Mahmood Alasmi and Jalaluddin Bhuiyan

B-type Natriuretic peptide (BNP) is a cardiac hormone secreted mainly by the ventricles in response to volume expansion and pressure load. Pro-BNP is the parent polypeptide that is cleaved into the bioactive C-terminal peptide; Brain Natriuretic peptide (BNP); and an amino-terminal fragment called N-Terminal Pro-Brain Natriuretic peptide (NT-ProBNP) which has a longer half life than BNP.

**Aim:** To get blood levels of NT-Pro BNP for oxygen or ventilator dependant premature neonates to prove that it is elevated in neonates with heart disease causing large left to right shunts (e.g., large PDA).

**Methods:** After obtaining parental consent, blood levels of NT-ProBNP will be obtained within 24 hours of birth for a total of 60 premature infants less than 34 weeks of gestation. If clinical signs of PDA would be found, another level will be obtained in addition to an echocardiogram. If PDA is significant and requiring medical or surgical closure a third level will be obtained 3 days after an ECHO shows PDA is closed or small. In infants with no clinical signs of PDA, an ECHO will be performed at DOL 3 and if no or small insignificant PDA will be found, blood levels of NT-ProBNP will be obtained at time of discharge.

**Workplan:** Blood will be taken as stated in the Methods above after informed consent obtained, and then taken to the department of clinical biochemistry where a Log-book will be kept of all medical record numbers of patients having NT-Pro BNP levels at NICU. After having the number of levels obtained for statistical analysis, we ill stop the study and review the echocardiographic findings with correlation to NT-Pro BNP levels. Normative data will be analyzed as well.

**Statistical Analyses:** will include both descriptive and inferential statistics. The data will be analyzed by grouping patients with relevant numerical parameters into various clinical groups, and subjecting acquired data, whether parametric or
Pediatrics

non-parametric to statistical analysis. Appropriate statistical procedures will be adapted to determine significance, using a p-value of less than 0.05 as the cut off level for significance. Analysis will be performed with SAS Statistical Software (SAS version 9, Statistical Analysis System SAS Institute Inc., Cary, NC, USA).

Project Title: Familial Arthropathy in Saudi Arabian Children: Demographic, Clinical, and Biochemical Features

Investigator: Al-Mayouf SM

Project Description

Familial arthropathy comprises a heterogeneous group of arthropathies. It can be either an inflammatory or a noninflammatory condition. The worldwide frequency of these disorders is unknown.

Project Title: Molecular Genetic Characterization of Nephrotic Syndrome in Saudi Arabia. RAC# 2050 045

Principal Investigator: Mohammed Aldahmesh
Co-Principal Investigator: Ibrahim Al Hassoun
Co-Investigator: Brian Meyer, Abbas Al Abbad, Hamad Al Mojalli, and Kate Collison

Project Description

Nephrotic syndrome is very common in the Saudi population and often results in end-stage renal disease (ESRD) that requires dialysis and transplantation which is costly both in social and economic terms. Prevention remains the gold standard for management in many of these disorders. In general, more than 40% of renal disease is associated with a genetic aetiology. In many hereditary renal disorders, underlying genes are well documented. However, very little is known about which of these genes underlie nephritic syndrome in Saudi patients. In addition, the relevant mutations of these genes in Saudi patients are yet to be identified. It is also possible that in some families, novel genes giving rise to renal disease may be identified.

Several podocyte genes have been implicated in nephrotic syndrome progressing to ESRD. These data have re-enforced the central role of podocytes in the glomerular filtration barrier and contributed to the understanding of processes, the breakdown of which lead to nephrotic syndrome. Nephrotic syndrome in children may present congenitally, at birth, in the first 3 months or later in life. Steroid-resistance is a feature of nephrotic syndrome occurring in a high proportion of children less than 3 months old. This is in contrast to older children where only around 10% are steroid-resistant.

Patients will be categorized into three groups according to clinical and family histories.

Project Title: Progressive Sclerodermatous Skin Changes in a Child with Phenylketonuria.

Investigators: Al-Mayouf SM and Al-Owain MA

Project Description

We report a child with phenylketonuria and unusually severe sclerodermatous skin changes. It is likely that prompt and aggressive therapy for these skin changes and phenylketonuria may have modified the clinical course.

Project Title: Systemic Lupus Erythematosus Following Acute Lymphocytic Leukemia

Investigators: Sulaiman Al Mayouf and Amal Serayth
Pediatrics

Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder of autoimmune origin, characterized by a wide variety of association and an unpredictable course. The association of SLE and myeloproliferative and lymphoproliferative malignancies is widely reported in the adult literature. Most of the data show that the malignancy is detected after the diagnosis and treatment of SLE. However, the development of SLE has been described following treatment of different types of malignancies. There is only scarce information available as to the association of both disease conditions in children. We report here a girl with SLE diagnosed 4 years after acute lymphocytic leukemia (ALL) was successfully treated.

Project Title Novel Arab Mutations Underlying Nephrogenic Diabetes Insipidus

Investigators: Carroll, Pamela; Al-Mojalli, Hamad; Al-Abbad, Abbas; Al-Hassoun, Ibrahim; Al-Hamed, Mohamed; Al-Amr, Rana; Butt, Abdul Islam; Meyer, Brian Francis

Project Description

Nephrogenic Diabetes Insipidus (NDI), is genetically heterogeneous and may be inherited in an X-linked or autosomal recessive manner. We aimed to investigate the molecular basis of NDI among Arab families.

Project Title: Underlying Molecular Genetic Defects of Severe Combined Immunodeficiencies (SCID) in Saudi Arabia. RAC# 2060 0120

Principal Investigators: Hamoud Al-Mousa, Osama Alsmadi

Co-Investigators: Abdulaziz Al-Ghonaium, Hasan Al-Dheki, Hassan Al-Rayes, Saleh Al-Muhsen, Rand Arnaout, Abdelghani Tbakh, Dorota Monies, Salma Wakil

Project Description

Severe combined Immunodeficiencies (SCID) represent the most severe form of primary Immunodeficiencies. At least ten different forms of human SCID have now been recognized and can be grouped according to inheritance, phenotype, and for some of them, identification of the mutated genes. All SCID phenotypes are seen in the Kingdom, but up to date the underlying molecular genetic defects of those patients are not identified. The specific aim of this study is to identify the underlying molecular genetic defects of SCID in Saudi Arabia. All retrospective and prospective patients with the diagnosis of SCID under follow-up at KFSH&RC in primary immunodeficiency clinics or the post bone marrow transplantation clinic will be identified. Based on SCID phenotype, individuals will be screened for mutations in most likely genes that fit the clinical and laboratory presentation of SCID. Families of patient’s negative for mutations of the known SCID genes who demonstrate a strong family history will be utilized for subsequent linkage analysis depending upon statistical power of pedigrees and accessibility to family members that may identify novel genetic defects. It is expected that data resulting from this study will benefit future counseling and newborn screening programs.

Progress During 2006

Up to date, more than 40 families with SCID disease had been studied, mutations in RAG1, RAG2, Artemis, Jak3 and ADA genes have been identified; some were novel mutations. Few families had no
identified mutations in known disease causing genes and will be candidate for whole genome linkage analysis.

**Future Plans**

The research will identify the underlying molecular genetic defects of SCID in Saudi Arabia which can help in the genetic counseling, prevention of disease recurrence by offering pre-implantation diagnosis and hopefully identify novel genetic defects that can cause SCID.

**PUBLICATIONS**

The Department of Radiology

Chairman
Hamad Al Suhaibani

Deputy Chairman
Yusuf Al Kadhi
RESEARCH PROJECTS

Project Title: 18F-FDG PET/CT Applications in Children, One Year Experience in a Tertiary Care Setting

Investigators: Moheieldin M. Abouzied, Hussain Meer, Naima AlBulushi, Abdulaziz Alsugair, Tarek Munshy, Rushana Parker, Ayman Rifai

Project Description

[18F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) is recognized as a powerful imaging technique for a variety of disease conditions, mainly cancer, in adults. FDG PET-CT is also emerging as an important tool in evaluating children with a number of cancer diseases.

This paper focuses on our experience in implementing PET-CT in a tertiary care pediatric referral center.

Methods: During the period of October 2005 to May 2006, a total of 146 children with different types of cancer disease were scanned. Using 8 slice PET/CT system (Discovery T5;GE), utilizing low Kvp (80kVp), with 75 mA, slice thickness of 3.75 mm, and pitch of 1.67: 1. Patients were scanned following the administration of 0.3 mCi/Kg of 18F-FDG and after 60 minutes acquisition time, patients were scanned from base of the skull to mid thigh, unless indicated otherwise by the nuclear medicine physician to include the brain and the lower limbs. General anesthesia was performed to all patients less than 7 years to avoid excessive movement which affect the image registration and scan quality.

Results: PET/CT was performed for 146 children, average age of 16 years (range 2 months to 18 years), 80 boys and 66 girls. The majority (83 children) 57% had lymphoma (HD and NHL) followed by 36 children with sarcoma (25%). Other types of cancer diseases included neuroblastoma (13), wilms tumor (7), nasopharyngeal carcinoma (4) and others (3).
Neurological applications included 32 children; 21 with brain tumors and 11 with epilepsy. Children were referred for PET/CT to assess the response to therapy in 42% of the cases, to role out recurrent disease in 33% of the cases and finally for the initial staging in 25% of the cases.

Potential sites of pitfalls and image artifacts included brown fat uptake in 62% of the cases, thymus uptake in 82%, bowel uptake in 21% and finally genitourinary uptake in only 13%.

**Conclusion:** FDG PET has been shown to be useful in the imaging evaluation of many pediatric tumors. It is expected that the future data will show that FDG PET/CT does contribute unique valuable information for the care of childhood tumors.

**Progress**

Submitted to Society of Nuclear Medicine on December 2006. Presented at the 2nd Gulf Nuclear Medicine Meeting on 6-8 November 2006.

**Project Title:** Quantification of Bone Metastasis in Whole Body Images of $^{18}$F-FDG PET/CT

**Investigators:** Abouzeid, Mohei M, Demirkaya, Omer, Rifai, Ayman

**Project Description**

Oral Presentation. Presented at the 2nd Gulf Nuclear Medicine Meeting on 6-8 November 2006.

**Objectives:** To develop a method to qualify the metabolic changes induced by the different types of bone metastasis in cancer patients using whole-body PET/CT images. The quantitative parameters along with the structural changes seen by CT bone window may serve as a useful tool in assessing the tumor response of bone metastases to therapy.

**Methods:** Twenty five cancer patients with no prior history of chemo or radiotherapy who had definite bone metastases documented by PET/CT using an 8 slide PET/CT system (Discovery ST, GE) and other conventional modalities were selected for the study. PET and CT images were resampled to the same pixel size. Then the bone structure was segmented simply using a threshold of 150 Hounsfield unit. After the segmentation, the maximum SUV in the bone region in each slice was computed. Then the ROIs in PET slices were identified using the 50% of the corresponding maximum SUVs. The ROIs only within the bone were identified using the segmented bone mask. The lesion statistics including the average CT values were computed from the PET and CT images using these ROIs. The final results were saved into an excel file. The identified lesions were subjected to the visual confirmation of a nuclear medicine physician experienced in PET/CT who also described the structural changes in the CT bone window whether lytic, sclerotic or mixed type.

**Results:** 149 bony lesions have been processed using our method in 25 patients (8 females, 17 males, mean age of 42.4 years, 13 head and neck carcinoma, 5 with lymphoma, 3 with sarcoma and 4 other types of carcinoma). Quantitatively, the mean SUV for the lytic, sclerotic mixed and lesions with no structural changes were 6.88, 6.13, 6.79 and 6.27, respectively. On the other hand, the corresponding average CT values in Hounsfield units for the same lesions were 156.9, 266.7, 230.4, and 251.2, respectively. The automated method depicted all the lesions defined as bone metastases by the nuclear medicine physician.

**Conclusion:** The automated method (with minimal user interference) provides a convenient way to process images and give a valuable functional and structural description of the different types of bone metastases that might serve as a useful tool in monitoring and assessing the therapy response.
Progress

Submitted to Society of Nuclear Medicine on December 2006.

Project Title: Value of PET Scan for Semi Qualitative Assessment of Myocardial Viability Before CABG is Maintained in Diabetic With Severely Impaired IV Function

Investigators: Ayman Rifai, Mohei Eldin Abouzeid

Project Description

Oral presentation and article.

Progress

Accepted for publication on 24 October 2006 at British Journal of Vascular Diseases.

Project Title: The Role of F-18-Fluorodeoxyglucose Positron Emission Tomography In the Initial Evaluation of Differentiated Thyroid Cancer

Investigators: Ali S Alzahrani, Mohei Eldin Abouzeid, Suzan Abdel Salam, Gamal Mohamed, Ayman Rifai, Abdualaziz AlSugair, Tarik Amin

Project Description

Objectives: To compare FDG PET with diagnostic radioiodine whole body scanning (DxWBS) in newly diagnosed PTC patients, hypothesizing that FDG PET is more likely to disclose locoregional and distant metastases. We also studied the radiopathological correlation in those patients who underwent completion neck surgery following FDG PET and assessed whether positive results on FDG PET at the initial management correlate with long-term outcome of PTC.

Patients and Methods: FDG PET scans performed in 31 newly diagnosed PTC patients who underwent Thyroidectomy of variable degrees and were referred to our hospital for further management. DxWBS and FDG PET scanning were performed in 26 patients (group 1) and the 26 pairs of scans were compared. In the other 5 patients FDG PET scanning was done without DxWBS because they were found to have significant residual tissue on neck Ultrasonography. These 5 patients as well as 12 patients from group 1, whose initial surgery was found incomplete, underwent completion neck surgery (group 2). In this group, the results of FDG PET in the neck region were compared with the histopathological examination of the completion neck surgery. Finally, the results of FDG PET scans in the whole study patients were correlated with the long-term outcome of PTC.

Results: Overall, 23 (74.2%) of the 31 FDG PET scans were positive. Of the 26 FDG PET scans in group 1, 18 scans (69.2%) were positive while 8 scans (30.8%) were negative. A total of 40 foci were seen in the 18 positive FDG PET scans. The corresponding 26 DxWBS showed a total of 47 foci. In contrast to FDG PET scans which showed 26 foci (65%) of uptake outside the thyroid bed, 45 foci (95.7%) of uptake on DxWBS were in the thyroid bed while 2 foci (4.3%) were in cervical lymph nodes and no focus was seen outside the neck area (p < 0.000). Only 3 scan pairs (11.5%) were identical. The other 20 scan pairs showed additional foci on either scans or were completely discordant. Of 17 patients who underwent completion neck surgery (group 2), 11 had positive FDG PET scans in the neck region and histopathological examination of the subsequent surgery was positive while 2 patients had negative FDG PET scans and negative histopathological examination. The other 4 patients showed discordant
results. There was a clear correlation between FDG PET results, the stage of the disease and long-term outcome; seven of the 8 negative FDG PET scans were in stage 1 while all patients with disease higher than stage 1 (7 patients) had positive scans. Over all median follow-up period of 30 months (10-48), 7 out of 8 patients (87.5%) with negative FDG PET scans were in remission compared with only 10 of 23 patients (43.5%) with positive FDG PET scans (p 0.045).

Conclusion: FDG PET scans are frequently positive at the initial evaluation of PTC. In contrast to DXWBS which reveals uptake mostly in the thyroid bed region, FDG PET is more likely to reveal lymph node or distant metastases. There is a high radiopathological correlation of FDG PET scanning. FDG PET positively correlates with the stage of the disease and long-term outcome.

Project Title: Role of 18F-FDG PET-CT in the Follow-Up of Pediatric Patients with Sarcoma Following Neoadjuvant Chemoradiotherapy

Investigators: Moheieldin M. Abouzied, Naima AlBulushi, Husain Meer, Abdulaziz AlSugair, Tariq Munshy, Ruchana Parker, Mohamed AlRuwaili, and Ayman Rifai

Project Description

Objectives: Recent advances have improved sarcoma evaluation in children particularly with the advent of MRI and F-18 fluorodeoxyglucose positron emission tomography (FDG PET). Accurate assessment of the local control of the disease along with the exclusion of distant metastases can allow the limb/organ salvage surgery. The aim of the study is to evaluate the accuracy of PET/CT in assessment of the local control of the disease and excluding the distant metastases post neoadjuvant chemoradiotherapy.

Methods: Twenty nine consecutive PET-CT scans were performed in twenty three patients, (18 boys and 5 girls), average age 8 years (range 8 months to 18 years). 14 children had Ewing’s sarcoma, 5 rhabdomyosarcoma, 2 synovial sarcoma, and 2 osteosarcoma. Whole body PET-CT was performed approximately 60 minutes post injection of 0.3 mCi/Kg of 18F-FDG using an 8 slice PET/CT system (Discovery TS;GE) and utilizing low Kvp (80kVp), with 75 mA, Slice thickness of 3.75 mm, and Pitch of 1.675:1.

Histology (n=11) or follow-up clinically and radiologically (n=12) for at least 6 months were employed as the standard of reference for imaging findings.
**Results:** In detecting the local control of the disease; PET-CT was true negative in 19 patients in excluding local residual disease. Only one false negative study in a patient who developed local recurrence at four months post scanning with an overall negative predictive value is 95%. On the other hand, PET-CT was true positive in two patients and false positive in one patient in whom the histopathological examination revealed fibroblastic proliferation and no viable tumor with an overall positive predictive value of 67%.

Furthermore, PET-CT depicted distant lung metastases in two patients and bone metastases in one patient precluding further limb salvage surgery.

**Conclusion:** PET/CT is a safe and useful modality with high diagnostic accuracy in children age group with sarcoma particularly in excluding residual disease post chemoradiotherapy and assessing the distant metastases.
Project Title: Accelerated Myelination in Infants with Immediate Postnatal Onset of Seizures and Cortical Dysplasia

Investigators: Patay Zoltan, Al-Dossary Nasser, Al-Dossary Fatma

Project Description

Purpose: To present unusual MRI signal changes in cerebral white matter underlying areas of cortical dysplasia in patients with early postnatal onset of seizures.

Case Report: Three female patients with qualifying imaging abnormalities and clinical manifestations are presented. All had immediate postnatal onset of seizures. The patients had initial MRI work-up using 1.5 T MRI units at the ages of 5 days, 8 days and 12 weeks. Studies included T1-weighted inversion recovery and T2-weighted fast spin-echo sequences. Two of the patients also had diffusion-weighted imaging studies (b: 1000). One patient had further follow-up imaging at ages of 2 and 6 years.

Imaging Finding: In cerebral white matter underlying cortical areas with suspected dysplasia unusual, ill-defined T1 hyper, and T2 hypointensities were found. Diffusion-weighted images suggested abnormal restriction of water diffusion compared to corresponding areas in the contralateral hemisphere. Follow-up studies in one patient showed progressive "normalization" of white matter signal changes and later, development of abnormal T2 hyperintensities.

Summary: The described early signal changes likely represent abnormal, accelerated myelination, possible due to increased regional perfusion and metabolism and/or frequent functional stimuli of neuroaxonal units due to repetitive electric activity in the epileptogenic cerebral cortex. One may even speculate that because of the presence of immediate postnatal changes in myelination, the pathological process, including seizures, may have started in the prenatal period. Recognition of these early signal changes may be helpful in diagnosing cortical dysplasia or perhaps in a broader sense, epileptogenic foci of any other nature in the often challenging neonatal period. Our observations also suggest that the signal changes may later undergo a "fogging" phenomenon, before the more typical T2-hyperintense chronic white matter damage develops.
Progress

ASNR (Submitted 2006).

Project Title: MR Imaging Evidence of Anterior Commissure Involvement in X-linked Adrenoleukodystrophy (X-ALD)

Investigators: Patay Zoltan, Al-Dossary Nasser, Rawah, Elham, Al-Dossary Fatma

Project Description

Purpose: To present MR imaging evidence of involvement of the anterior commissure in patients with X-ALD, and discuss its potential diagnostic and histopathological relevance.

Case Report: The clinical and imaging files of 7 males patients (age range: 4-16 years) with laboratory confirmed (elevated VLCFA levels) X-ALD were reviewed. All MR imaging studies were carried out on a 1.5 T MRI unit and included non-enhanced T1 and T2-weighted, as well as contrast-enhanced T1-weighted sequences.

Imaging findings: Besides the characteristic parieto-occipital white matter abnormalities seen in all patients, in two patients (6 and 12 years old) we found MR imaging evidence of involvement of the anterior commissure, best shown on sagittal T2-weighted images. In one patient the post-contrast images clearly showed additional signal enhancement within the lesion area.

Summary: Involvement of the anterior commissure in X-ALD is an inconsistent but potentially useful MR imaging finding. To the best of our knowledge, this lesion pattern element has not been described in neuroradiological literature. Because of the demonstration of signal enhancement on post-contrast images in one of the cases, we believe that the lesion corresponds to primary inflammatory and/or demyelinating changes (Schaumberg zone 2 phenomena), rather than secondary axonal degeneration. Identification of lesion involvement within the anterior commissure may have differential diagnostic implication in cases of X-ALD with atypical MR imaging presentation.

Progress

ASNR (Submitted 2006).

Project Title: Diffusion-Weighted Imaging Diagnosis of Bilateral Posterior Cerebral Artery Territory Infarctions in a Patient with Giant Colloid Cyst of the 3rd Ventricle Presenting With Acute Hydrocephalus and Cortical Blindness

Investigators: Patay Zoltan, Al-Dossary Nasser, Kanaan Imaduddin

Progress

An article was written and submitted on March 22, 2006 to the British Journal of Neurosurgery.
Project Title: Congenital Lateral Torsion of Tibia and Fibula with Ball and Socket Ankle Joint, Lateral Talus Subluxation and Peroneal Tendons Dislocations in Hyper Lax Children, A New Deformity

Investigators: Al Barrag M, Al Otaibi L, Wade W

Progress

An article was written and submitted on January 2007 to the Journal of Pediatric Orthopedics.
The
Renal Transplant Unit

Director
Khalid Al Meshari
The

Renal Transplant Unit

The King Faisal Specialist Hospital and Research Centre has the largest Renal Transplant Program in the Kingdom and in the Region. On average, 140 kidney transplants are done annually. The scope of our services is quite diverse and includes: transplanting highly sensitized patients with positive cross-match; low body weight pediatric patients; and kidneys with difficult vascular anastomosis (en-block kidneys, kidneys with multiple services, small sized kidneys). The above services can only be offered at KFSH&RC.

We have recently started solid organ pancreas transplantation simultaneously with or after kidney transplantation for patients with Type I diabetes mellitus. We are the only program in the Region that does such transplants. Six transplants have so far been performed.

The Renal Transplant Program at KFSH&RC as such measures up to the top 10% of international renal transplant programs.
RESEARCH PROJECTS

Project Title: Sirolimus Protocol 0468H1-316. A Randomized, Open-Label, Comparative Evaluation of Conversion From Calcineurin Inhibitors to Sirolimus Versus Continued Use of Calcineurin Inhibitors to Renal Allograft Recipients. RAC # 2031054

Investigators: Khalid Al Meshari, Khaled Hamawi, Hazem El Gamal, Abdulghani Tbakh, Abdulrahman Bin Muammar

Project Description

The largest multi-center study to evaluate renal allograft function in recipients who use calcineurin based immunosuppression therapy versus a group who are converted to sirolimus immunosuppressive regimen.

Progress

Enrollment has ended. Study follow up has been extended to 4 years from the time of conversion.

Project Title: Islet Cells Transplantation: Collaboration Between Geneva University Hospital and King Faisal Specialist Hospital and Research Centre (following Edmonton Protocol)

Investigators: Abdulrahman Al Nuaim, Khalid Al Meshari, Hussein Raef, Ahmed Chaballout, Hamad Al Suhaibani, Abdelghani Tbakh, Aman Al Fadhli, Khaled Hamawi

Project Description

Performing islet cells transplantation in selected sub-group of type I diabetic subject following Edmonton immunosuppressive protocol. Isolation of islets is done in collaboration with university of Geneva.

Progress

To date, two patients have been selected. Arrangements with Saudi Center for Organ Transplantation (SCOT) and University of Geneva has been finalized. A new islet cell isolation lab at KFSH&RC was established.

Project Title: Determination of Polymorphism (S) in Genes Controlling the Immune Responses in Saudi Renal Transplant Patients. Proposal # 2041 081

Investigators: Khalid Al Meshari, Abdelghani Tbakh, Khalid Al Hussein

Project Description

Examining the features and polymorphism of some of the immune genes such as MHC, cytokines and KIR genes in relation to renal transplant outcome.

Progress

Patient sera were collected. Standardization of laboratory methodology in Research Centre has been documented.

FUTURE RESEARCH DIRECTION

We are in the process of implementing a new database system for renal transplant recipients. This will allow us to conduct a number of studies to evaluate our current medical practice and to direct future improvements.

Future studies will focus on survival data and innovative immunosuppressive protocols.
PUBLICATIONS

The Department of Surgery

Chairman
Saif Al Sobhi

Deputy Chairman
Fuad Hashem
The Department of

Surgery

RESEARCH ACTIVITIES SUMMARY

The Department of Surgery’s involvement in research activities continues to be promising in 2006. Our staff had an extensive participation in promoting research awareness, initiating new research projects, clinical, basic science, evidence-based, prospective and retrospective case reports, either individually or in collaboration with colleagues and other departments, and presenting their findings and outcomes in national and international meetings, either as invited speakers or presenters, and published them in peer and renowned journals. Below is the summary of our research and publications for 2006:

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Other highlights of our research activities are:

- Organized three (3) Surgical Update Symposia in local hospitals in Madina, Al Baha and Qurayat, in collaboration with Health Outreach Services.
- Conducted the 2nd Annual Saudi Colorectal Surgery Forum, with 800 attendees in 2006. Due to its success, this 3-day event is extended to a week-long meeting for next year to include workshops.
- Conducted the 6th Annual Research and Residents Day – received 31 abstracts; accepted 16 for presentation; registered 240 attendees.
- Conducted two (2) Anastomosis Workshops for our surgical residents using the Animal Lab Facility of the Research Centre provided hands-on training for open and laparoscopic procedures.
- Workshop on Minimally Invasive Surgery Techniques and Procedures (Proposal 2022006) – Staff invited as faculty members.
- First Cumulative Report of Cleft Lip and Palate/Craniofacial Registry – The Kingdom’s first registry on craniofacial anomalies including clef lip and palate, started in 1999 and continuously updated by Dr. Ali al Malaq, Consultant, Plastic Surgery, with the rest of the CLT Team. This registry will be a base for future epidemiological study which will have positive impact on the health care of CLP patients.
- Microsurgery Training (Proposal 2022007) – Conducted every Wednesday with the Plastic Surgery residents, if they are not committed to OR and clinics.
- Training of Vascular Residents on Suturing Techniques (Proposal #2032004) – reactivated and approved.
- Creation of Familial Polyposis Registry (Colorectal) – request submitted for executive management approval.
- Joint Staff Appointment of Dr. Saud Al Shanafey as a Clinical Epidemiologist Scientist in the Biostatistics Epidemiology and Scientific Computing Department of the Research Centre.

RESEARCH PROJECTS

Project Title: Genetics Classification of Thyroid Cancer (RAC# 2060 002: KACST Project# MB#26-01)

Investigators: Saif Al Sobhi S, Mehmet Inan, Mohammed Dababo, Laila Al-Alwan, Abdulghani Kohailan, Hadeel Ar-Rawaf

Project Description

Cancer is a multistage and very complex genetic disorder that can develop and spread out into different organs and cells of human body. While thyroid cancer is an uncommon tumor that represents only 1% of all new human malignancies in the rest of the world, it is second common type of cancer in the women in the Kingdom of Saudi Arabia. In the Kingdom, thyroid carcinomas are responsible for over 600 new diagnoses each year. Identification of characteristic gene signature of thyroid cancers may help to understand molecular mechanisms that might be responsible for the aggressive behavior of tumors with possible translation implementation.

In this project, we plan to utilize high-density Single Nucleotide Polymorphisms (SNP) and gene expression arrays to identify chromosomal abnormalities in thyroid cancer that can establish the fundamental link between genetic abnormalities and gene expression in thyroid cancer. Our impression is that genetic modifications involve in modification of tumor suppressor genes and oncogenes that are directly implicated in thyroid cancer development and progression.
The project involves the following aims:

1. To Study complete gene expression (at exon level) profiling of 100 thyroid cancer patients.
2. To perform high density genotyping on which gene expression analysis studied.
3. To correlate the genetic abnormalities to the gene expression profiling in order to find gene markers for diagnosis, prognosis, and ultimately gene therapy.

Project Progress

Samples of thyroid cancer, and in most cases matched normal thyroid tissue arising from the same patients with thyroid cancer have been collected through the Department of Surgery at King Faisal Specialist Hospital and Research Centre. So far, 124 patients have been enrolled to this project and a total of 195 samples have been collected for SNP analysis. Of these, 120 samples are from various thyroid cancer tissue and 90 samples are from normal thyroid tissue. All samples collected have been also fixed and embedded in paraffin for histopathological analysis. After a careful investigation and classification, 114 samples had been chosen for further SNP analysis. Off these, 35 patients have normal and tumor tissues (35 normal tissue and 35 tumor tissues), 22 patients have normal tissues only, and 22 patients have tumor tissues only. All these selected samples have been processed for DNA isolation and they are ready for SNP microarray analysis. DNA quantity and quality of these samples have been checked in Functional Genomics Lab. Currently, we are in process of running Affymetrix 500K SNP arrays and we are planning to complete the preliminary analysis in the next two months.

We have also collected 195 samples from thyroid cancer patients and isolated RNA to perform transcriptomic analysis by using Affymetrix Exon arrays. In this regard, 35 well characterized tumor and their matching normal tissue have been processed for exon array analysis. Since integrity of RNA is very crucial for a reliable result, quality control of each sample was checked by using RNA 6000 Nano Lab on Chip of Agilent 2100 Bioanalyzer Instrument (FigXXX). 1 microgram of total RNA used for production of cDNA and subsequently cRNA. Finally, the single stranded DNA was labeled and now, all the samples are ready for hybridization with whole transcriptome arrays.

Some additional work related to genetic analysis and the microarray studies remain to be completed. These studies will be completed by 15 February 2008.

Project Title: Prevention and Treatment of a Painful Neuromas of the Superficial Radial Nerve by the End-To-Side Nerve Repair Concept: An Experimental Study in a Rat Model and Clinical Experience in 30 Patients

Investigator: Prof. Mohammed Al Qattan

Project Description

End-to-side nerve repair has been utilized in nerve reconstruction but has never been examined as a method for treating painful neuromas. This paper studies the utilization of the end-to-side nerve repair concept in the prevention and treatment of painful neuromas.

A total of 20 rats were divided into 2 groups (10 rats per group). In group A, the tibial nerve was divided and left lying in the subcutaneous tissue. In group B, the cut ends of the tibial nerve were sutured to the adjacent peroneal nerve in an end-to-side fashion. Evaluation was performed 90 days after nerve injury.

For group A, the proximal end of the tibial nerve formed a “classic” neuroma and the distal end showed a degenerated nerve. In group B, the proximal end
of the tibial nerve formed a “non-classic” neuroma and the nerve healed into the peroneal nerve with continuity of the epineurium of the 2 nerves. The distal end of the tibial nerve in group B showed evidence of axonal regeneration. Clinical experience utilizing the same technique in the prevention and treatment of painful neuromas of the superficial radial nerve is presented in 30 patients. All patients remained pain-free at the final follow up (range 1-7 years, mean = 4 years).

Progress

Concluded that the end-to-side nerve repair concept may be utilized for the management of painful neuromas. Paper was presented at the 6th Annual Surgical Research and Residents Day, 14 December 2004, and awarded the “Best Paper.”

Project Title: Adrenalectomy for Pheochromocytoma a Comparative Study in the Era of Laparoscopic Surgery: KFSHRC Experience

Investigators: Hadi Al Mutairi, Saif Al Sobhi

Project Description

Pheochromocytomas are rare tumors of chromaffin cell origin. Prior to the year 2000, we managed this tumor using open adrenalectomy. After year 2000, we shifted to the laparoscopic approach. We report our experience before and after the year 2000 in a comparative study.

Retrospective review of patients managed for pheochromocytoma between 1998 and 2005 was conducted. Demographic and clinical data were retrieved. Results showed that a total of 24 cases were managed on that period. Mean age of diagnosis was 42y. There were 10 men and 14 women. The average tumor size was 6.7cm; 15 cases were managed by laparoscopic approach and 2 cases were converted to open, while the rest were managed using the open technique. Mean Blood Pressure (BP) before diagnosis was 175/83mm Hg, and mean postoperative BP was 134/70. Mean operative time for the laparoscopic procedures was 120min compared to 219 min for the open technique.

After follow up of 3 years, no recurrence has been documented in our series in either group. Morbidities included atelactasis (8%), Pulmonary Embolism (0.5%), all in the open group. No wound infection or arrhythmias occurred and no mortality.

Progress

Concluded and data shows that the laparoscopic approach is as effective as the open one. Moreover the laparoscopic approach is minimally invasive and provide quicker recovery and less post operative morbidity. Paper was presented at the 6th Annual Surgical Research and Residents Day, 14 December 2006, and awarded the “Best Research Paper of the Year.” Abstract has been submitted to the International Surgery Week 2007 Meeting scheduled in August 2007.

Project Title: Role of Flourine – 18 Fluorodeoxyglucose Positron Emission Tomography in Thymic Pathology


Project Description To Evaluate the Utilization of Position Emission Tomography (PET) Scan With Fluoro-18 Fluorodeoxyglucose (FDG) in Thymic Tathlogy

Twenty-five consecutive patients with thymic pathology underwent FDG-PET after being evaluated by computed tomography (CT). The indication for CT was myasthenia gravis in 10,
anterior mediastinal mass in 7 and recurrent thymic tumor after surgical excision in 8 patients. The results of PET were compared with results obtained by CT, and histopathologic examination of the surgical specimens.

All mediastinal abnormal thymic tissue showed FDG uptakes. FDG-PET managed to differentiate between thymic hyperplasia and thymoma in myasthenia gravis group (n=10) in which CT images were questionable in 2 patients. Both CT and FDG-PET showed 7 patients with thymoma presented as anterior mediastinal mass. However, PET scan predicted thymic carcinoma in 1 patient. PET was superior to CT scan in localization of recurrent thymoma in 2 patients, and equal to CT in detecting metastatic lesions in 6 patients during the follow up after thymoma excision.

Progress

Concluded that in myasthenia gravis, selective use of FDG-PET is useful in differentiating thymoma from hyperplasia especially when CT scan is controversial. FDG-PET may differentiate thymoma from thymic carcinoma. FDG-PET is also useful in follow up patients who underwent thymoma excision when there is suspicion of recurrence or metastasis. Accepted for publication in European Journal of Cardiothoracic Surgery.

RESEARCH ACTIVITIES

Breast Surgery

Project Title: Open-Label Study of Bevacizumab (AVASTIN) plus Taxane Monotherapy or In Combination for the first-line treatment of patients with locally recurrent or metastatic breast cancer. Investigators: Al Sayed A, Ajarim D, Twegieri T, Al Shabanah M, Al Malik O

Endocrine Surgery


Project Title: Genetic Classification of Thyroid Cancer (RAC#2060 002) Investigators: Inan M, Al Sobhi S, Dabobo M, Al-Alwan L, Kohailan A, Ar-Rawaf H

Project Title: Surgical Treatment of Renal Hyperparathyroidism: 3-Year Review (ongoing). Investigators: Al-Anezi N, Chaaban M, Al Sobhi S

Project Title: Laparoscopic Adrenalectomy: KFSH&RC Experience (completed; paper in preparation). Investigators: Al Ahdal H, Al Sobhi S, Al Fehaily M

Project Title: Thyroid cancer in children: The Hospital of Sick Children Experience (completed; paper in preparation). Investigator: Al Fehaily M

Colorectal Surgery

Project Title: A Multicenter, Open-label, Randomized Comparative Study of Tigecycline Vs. Ceftriaxone Sodium Plus Metronidazole for the Treatment of Hospitalized Patients with Complicated Intra-abdominal Infection. Investigators: Al Hokail A, N. Al Sanea
**Project Title:** Hereditary non Polyposis Colorectal Cancer: Molecular and Histochemical Screening in Saudi Colorectal Cancer Families.  
**Investigators:** Abalkhail H, Al Sanea N

**Project Title:** Preservation of Ovarian Function Following Laparoscopic Ovarian Transposition.  
**Investigators:** Al Badawi I, Munkarah A, Al Subhi J, Salem H, Abdul Jabbar A, Balaraj K

**Project Title:** Colorectal Wound Infection Study (ongoing).  
**Investigators:** Al Saleh I, Abdul Jabbar A, Al Sanea N

**Project Title:** DNA Damage Due to Polyclinic Aromatic Hydrocarbons Exposure Among Colon Cancer Patients and Its Possible Role in Inducting Carcinogenesis (ongoing).  
**Investigators:** Al Saleh I, Abdul Jabbar A, Al Sanea N

**Project Title:** Endorectal Ultrasound in Staging Rectal Cancer (ongoing).  
**Investigators:** Al Alem I, Al Sanea N

**Project Title:** A review of 100 consecutive patients referred to King Faisal specialist Hospital & Research Centre for colorectal cancer (ongoing).  
**Investigator:** Abdul Jabbar A

**Project Title:** Role of carcinogens in Saudi diet. Ongoing phasel study, 2002-present (ongoing).  
**Investigator:** Al Sanea N

**Project Title:** Effect of antioxidants in the Arabic Black Seed on colorectal cancer. Experimental study using an animal model, 2003-present (ongoing).  
**Investigator:** Al Sanea N

**General & Minimally Invasive Surgery**

**Project Title:** Laparoscopic Longitudinal Gastrectomy as Primary Treatment of Morbid Obesity.  
**Investigators:** F. Bamehriz, A. Salem, P. O’Regan

**Project Title:** Results of Sleeve Gastrectomy for Morbid Obesity (KFSHRC Experience).  
**Investigators:** F. Bamehriz, A. Salem, P. O’Regan

**Project Title:** Staple Line Leak Following Laparoscopic Longitudinal Gastrectomy for the Surgical Treatment of Morbid Obesity.  
**Investigators:** F. Bamehriz, A. Salem, P. O’Regan

**Project Title:** Once-Daily vs Multiple-Daily Dose Aminoglycosides in Obese Patients.  
**Investigator:** F. Bamehriz

**Project Title:** The Feasibility of Spinal Anesthesia for Laparoscopic General Abdominal Procedures in Critically-Ill Patients (ongoing).  
**Investigators:** F. Bamehriz, A. Salem, P. O’Regan

**Project Title:** Laparoscopic Repair of Para-duodenal Hernias Presenting with Small Bowel Obstruction.  
**Investigators:** F. Bamehriz, A. Salem

**Project Title:** Laparoscopic Management of Benign Splenic Cyst: Case Report  
**Investigators:** A Salem, W Kattan, M Al Saghier

**Project Title:** Prevention of Laparoscopic Puncture Site Hernia (in progress).  
**Investigator:** P. O’Regan

**Project Title:** Prevention of Incisional Hernia in Laparotomy Wounds by Routine Bolstering with Mesh (in progress).  
**Investigator:** P. O’Regan
**Project Title:** Elastic Band Ligation of Hemorrhoids with the O'Regan Ligator (Update in progress).
**Investigator:** P. O'Regan

**Project Title:** Tensiometric Evaluation of Laparotomy Wounds in the Dog Reinforced with Mesh Compared to Non-Reinforced Wounds (in progress)
**Investigator:** P. O'Regan

**Project Title:** Outcome of Laparoscopic Vertical Banded Gastroplasty at KFSH&RC (ongoing)
**Investigators:** D. Hijazi, A. Salem, F. Bamehriz, P. O'Regan

**Project Title:** Early Outcome of the Feasibility of Laparoscopic Assisted Gastrostomy for Gastric Cancer at KFSH&RC (ongoing)
**Investigators:** F. Bamehriz, A. Salem, P. O'Regan

**Project Title:** Intra-peritoneal bupivicaine and morphine alone and in combination with diclofenac for postoperative morphine sparring analgesia in patients undergoing vertical banded gastroplasty (ongoing).
**Investigators:** Y. Ali, H. Al Ouﬁ, H. Negmi, M. Sadek, M. Rabie, F. Bamehriz, A. Salem

**Ophthalmic Surgery**

**Project Title:** Study of the Association Between HLA-DRB1 Alleles and Vogt-Koyanagi-Harada Disease in Saudi Patients (RAC#2050034).
**Investigator:** Tabbara K

**Project Title:** Treatment of Corneal Cystine Crystals in Nephropathic Cystinosis by Topical 0.5% Cysteamine Eye Drops. (Reference # 2041034) ongoing.
**Investigators:** A Al Hemidan, I Al Hassoun, M Alwaily, S Al Haddab, E Al Sabban, S Al Hazzaa

**Project Title:** Chorioretinitis in Patient with Chronic Granulomatous Disease of Children.
**Investigators:** A Al Shehri, S Al Mohsen, A Al Hemidan

**Project Title:** Use of Cysteamine Eye Drops in the Management of Cystinosis Crystal Deposits.
**Investigators:** A Al Hemidan, I Al Hassoun, M Alwaily, S Al Haddab, E Al Sabban, S Al Hazzaa

**Pediatric Surgery**

**Project Title:** Laparoscopic Restoration of Aesophageal Continuity.
**Investigator:** Z Habib

**Project Title:** Short Bowel Syndrome Management – Experience at KFSH&RC.
**Investigator:** Z Habib

**Project Title:** Multimodality Management for Unresectable Solid Tumours.
**Investigator:** Z Habib

**Project Title:** Laparoscopic Duodenoduodenostomy in a Situs Inversus Totalis – Newborn.
**Investigators:** Z Habib, M Awan

**Project Title:** Meckel’s Diverticulum Perforation in Neonates: Case Report and Literature Review.
**Investigator:** Z. Habib, M. Kolar, A. Ameri

**Project Title:** Relation between breast feeding and Wilms’ tumor.
**Investigator:** S Al Shanafey

**Project Title:** Renal Tumors in Infants (outcome study).
**Investigator:** S Al Shanafey
**Surgery**

**Project Title:** Persistent Hyperinsulinemic Hypoglycemia of Infancy (Nesidioblastosis): Pathological Stratification.
**Investigator:** S Al Shanafey

**Project Title:** Nissen Fundoplication in Infants (outcome study).
**Investigator:** S Al Shanafey

**Project Title:** Satisfaction of surgical residents with their training: survey - (in progress).
**Investigator:** S Al Shanafey

**Project Title:** Laparoscopic adrenalectomy: an update (outcome study) – (in progress).
**Investigator:** S Al Shanafey

**Plastic Surgery**

**Project Title:** Patency of Internal Jugular Vein Following Reconstruction with Free Flap.
**Investigators:** F Al Subhi, F Hashem, A Al Saai, M. Qattan, M. Al Suhaibani

**Project Title:** Palatal fistula post palatoplasty at KFSH&RC (ongoing; progress for presentation in Cleft Lip & Palate Symposium in March 2007).
**Investigator:** A. Al Malaq

**Renal Transplant Surgery**

**Project Title:** Vascular Thrombosis in Renal Transplant (completed).
**Investigators:** A Al Hefdhi, A. Chaballout, S. Raza, I. Al Mesahri, K. Al Shaibabani

**Project Title:** Vascular Complications in Renal Transplant (ongoing).
**Investigator:** A Okda

**Thoracic Surgery**

**Project Title:** Cardiac Tamponade: A fatal rare complication of maximal thymectomy (ongoing).
**Investigator:** M Rafay

**Project Title:** Chest wall myositis ossificans: A diagnostic dilemma for osteogenic sarcoma (ongoing).
**Investigators:** M Rafay, K Al Kattan

**Project Title:** The role of plasmapheresis in myasthenia gravis (ongoing).
**Investigators:** M Rafay, K Al Kattan

**Project Title:** Left pneumonectomy syndrome, correction by muscle interposition (ongoing).
**Investigators:** M Rafay, K Al Kattan

**Project Title:** Pneumonectomy for destroyed lung in children, short-term consequences (ongoing).
**Investigator:** H. El Bawab

**Vascular Surgery**

**Project Title:** Endovascular Treatment of Aortioliac Aneurysms: Middle East Early Experience (ongoing).
**Investigator:** A Okda

**Project Title:** Scratic Artery Aneurysm: Case Report (ongoing).
**Investigator:** A Okda

**Project Title:** Ruptured Iliac Artery Aneurysm in Takayasu’s Arthritis: Case Report (ongoing).
**Investigator:** A Okda

**Project Title:** Internal Carotid Artery Aneurysms: KFSH&RC Experience (ongoing).
**Investigator:** A Okda
Project Title: Spinal Stimulation as a Modality for Treatment of Critically Ischaemic Limbs (ongoing).
Investigator: A Okda

Project Title: Increase level of homocystein and peripheral vascular disease in Saudi Arabia (ongoing).
Investigators: M. Saati, B. Safi

PUBLICATIONS

Breast Surgery


Colorectal Surgery


General & Minimally Invasive Surgery


Ophthalmic Surgery


Pediatric Surgery


Plastic Surgery


### Renal Transplant Surgery

**Book Chapter**


**Letter to Editor**


**Accepted for Publication**


3. Al Hazzaa SAF, Chaudhri N, Seth P and Gyger M. Bone Marrow Transplantation In the Absence of Radiation Therapy. Accepted in *Retina*. (In Revision).

4. Al-Hazzaa SAF, Glynn MW and Bale AE. A Genetic Variant of Usher Syndrome in a Saudi Family. Accepted in the *Journal of Medical Genetics*. (In Revision).

5. Al Hazzaa, SAF, Ozand PT. Convoluted Retinal Veins as a Distinguished Electroreptinograms as a sign of Ethylmalonic Aciduria. Accepted in *Ophthalmology* (In Revision).


7. Al Nassar S., Bowel atresia x-linked disease. Accepted for publication in *J Indian Association of Pediatric Surgery*.


In Preparation for Publication (Manuscripts in process)


6. S Al Muhsen, A Al Hemidan. The prevalence of Chorioretinal lesions in patients with Chronic Granulomatous Disease CGCD. (Reference # 2041032) - Manuscript in progress

7. Al Hazzaa SAF and Iqbal MA. Retinoblastoma and Retinoma Occurring in a Child with a Translocation and Deletion of the Long Arm of Chromosome 13 – In revision

8. Al Hazzaa SAF and Ozand PT. Retinal Vascular Tortuosity in Homocystinuria Caused by Methylene tetrahydrofolate Reductase Deficiency - In revision

9. Al Hazzaa SAF and Mikkonen PA. Candida Retinitis in Bare Lymphocyte Syndrome - In revision

10. Chaves-Carballo E, Dabbagh O, Al Watban J, Al-Hazzaa SAF. Unusual Retinal Abnormalities in MRI Study of Late-Infantile Neuronal Ceroid Lipofuscinosis (LINCL) - In revision

Abstracts / Papers Presented

Breast Surgery


Endocrine Surgery


2. Al Sobhi S, “Redo Surgery and Neck Dissection for Thyroid Disease,” Surgical Update Symposium, 03-05 April 2006, O hud General Hospital, Madinah General Hospital, Madinah Saudi Arabia; Surgical Update Symposium, 15-17 May 2006, Quaryat General Hospital, Quaryat, Saudi Arabia.


9. Al Fehaily M, “Thyroid Disorder” Residents’ Clinical Presentation, 08 February 2006, Department of Surgery, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia.

10. Al Saghier M. Neuro-Endocrine Tumor, Surgical Grand Rounds, 08 March 2006, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia.

Colorectal Surgery


5. Abduljabbar A. Large Bowel Obstruction. Mini-Symposium on Colorectal Disease, April 2006, King Faisal Specialist Hospital, Riyadh, Saudi Arabia.


General & Minimally Invasive Surgery


3. Bamehriz F. Updates in Gastric Cancer. Surgical Update Symposium, Madinah General Hospital, 03-05 April 2006, Madinah, Saudi Arabia; Surgical Update Symposium, 15-17 May 2006, Gurayat General Hospital, Gurayat, Saudi Arabia.


Ophthalmic Surgery


Pediatric Surgery


4. Habib Z. “Multi Modality Management for Unresectable Tumors”, Grand Rounds, Department of Pediatric Hematology/Oncology, 13 December 2006, KFSH & RC.

5. Habib Z. Pediatric Oncology and Surgical Therapy. Surgical Update Symposium, Madinah General Hospital, 03-05 April 2006, Madinah, Saudi Arabia.

6. Habib, Z. Fundoplication Technique and Video, 3rd Advance Pediatric Minimally invasive Surgery Course, 13-14 December 2006, College of Medicine, King Saud University, Riyadh, Saudi Arabia.


Plastic Surgery


5. Malaq, A. “Wound Healing Between Science & Practice” King Saud University Hospital, 06 September 2006.


7. Al-Malaq A. Cleft Lip & Palate. Surgical Update Symposium, 03-05 April 2006, Madinah General Hospital, Madinah, Saudi Arabia; Surgical Update Symposium, 15-17 May 2006, Gurayat General Hospital, Gurayat, Saudi Arabia; Surgical Update Symposium, 21-
22 November 2006, King Fahad Hospital, Al-Baha, Saudi Arabia.

Renal Transplant Surgery


2. Raza S. Re-implantation of the Transplanted Kidney, Surgical Grand Rounds, 06 December 2006, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia.


Thoracic Surgery


2. El-Bawab H. Lung Transplant. Surgical Update Symposium, 03-05 April 2006, Madinah


Vascular Surgery


Poster Presentation


FUTURE RESEARCH DIRECTION

The Department will continue to enhance commitment to research activities, especially among our junior staff so that they can build their career on solid foundation, clinical knowledge and evidence-based medicine.

For next year, we aim to accomplish the following:

- Mandate residents to initiate research proposals at beginning of the year, to be supervised and precept by a consultant, for submission and presentation in the Annual Surgical Research Day held at the end of the year.
- Commencement of training of vascular residents on suturing techniques (Proposal #2032004).
- Creation of Familial Polyposis Registry (Colorectal).
- Submit the following research projects for approval of the RAC:
  - Once-Daily vs Multiple-Daily Dose Aminoglycosides in Obese Patients
    Investigator: F. Bamehriz
  - Relation between breast feeding and Wilms’ tumor
    Investigator: S Al Shanafey
  - Renal tumors in infants (outcome study)
    Investigator: S Al Shanafey
  - Persistent Hyperinsulinemic Hypoglycemia of Infancy (Nesidioblastosis): Pathological stratification
    Investigator: S Al Shanafey
  - Nissen Fundoplication in infants (outcome study)
The Department of Urology

Chairman
Kamal Hanash
Tamsulosin proved clinically useful for the facilitation of spontaneous ureteric stone discharge. We set out to study the effect of tamsulosin on ureteric pressure in the anesthetized dog to elucidate the mechanism by which tamsulosin provides its effect.

Ten mongrel dogs were divided into two equal groups. Under general anesthesia a midline abdominal incision was made and bladder opened. Ureteric catheters were inserted into the ureters and pressure recorded. Partial obstruction was created by venting one ureteric catheter with a 23 gauge needle through a 3 way connection. Intravenous saline infusion was kept constant at 10 ml/kg/hour. After 30 minutes, intradudenal tamsulosin 30 ug/kg B.W. was administered via a gastrostomy tube. The control group received saline alone. Blood pressure, ureteric pressure, ureteric peristalsis per minute and amplitude of peristalsis were monitored and measured before and 30, 60, 90, 120, 150 and 180 minutes after drug administration. Data were compared between control and drug groups using ANOVA.

There was no significant difference in all measured parameters between the two groups.

Conclusions: In vivo study on dog ureter, no effect of tamsulosin could be documented explaining its facilitator stone expulsion effect. Further evaluation of the intramural ureter is the next step.
RESEARCH PROJECT

Project Title: Tamsulosin effect on the peristasis of completely and partially obstructed ureter in the anesthetized dog.

Investigators: Raouf M. Seyam, Walid Al Taweel, Alaa Mokhtar, Rafat Alsayed and Kamal A. Hanash

Project Description

Experimental animal study in the anesthetized dug evaluating the effect of intradudenal administration of the selective alpha 1 adrenergic blocker tamsulosin on the peristalsis of the partially and completely obstructed ureters.

Progress

Ten animals were studied and no difference could be found between saline and tamsulosin on the ureteric peristalsis.

FUTURE RESEARCH DIRECTION

We will evaluate the effect of tamsulosin on the most distal part of the ureter and ureteric orifice.
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