ANNUAL REPORT OF THE NATIONAL MEDICAL RESEARCH COUNCIL (NMRC)

2005

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National Medical Research Council

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National University Hospital

A/Prof Tay Eng Hseon
Chairman of Medical Board
KK Women's & Children's Hospital

A/Prof Lam Kong Peng
Acting Executive Director of Biomedical Research Council (BMRC)

Executive Committee

Chairman	**Prof Woo Keng Thye** Emeritus Consultant, Department of Renal Medicine Singapore General Hospital
Members	**Prof Barry Halliwell** Deputy President (Research and Technology) National University of Singapore
	Prof Soo Kee Chee Director National Cancer Centre
	Prof Donald Tan Director Singapore Eye Research Institute
	Dr Stephen D Wise Director Lilly-NUS Centre for Clinical Pharmacology
	Prof Yap Hui Kim Head, Division of Paediatric Nephrology Immunology and Urology The Children's Medical Institute National University Hospital

CHAPTER 2
Introduction

NMRC's Mission and Strategy

Since its inception in 1994, the National Medical Research Council's (NMRC) mission has been to engender the growth of research talent, support high quality clinical research, and improve the quality of medical care and human health in Singapore. NMRC is a unit of the Ministry of Health (MOH), and MOH provides secretariat support to the Council.

The present Council is chaired by Professor Woo Keng Thye, Singapore General Hospital, and comprises representatives from the universities and leading medical and scientific institutions in Singapore. The Council was appointed by the Minister for Health in Feb 2003 for a 3 year term. Councilship was extended for another one year in Feb 2006 till Feb 2007. Its mission includes:

- To lead, promote and co-ordinate clinical research nationally.
- To identify and prioritise areas of clinical research to be undertaken
- To propose an annual budget for clinical research to MOH.
- To decide on the allocation of funds for clinical research activities.
- To co-ordinate and facilitate the efficient use of research facilities, manpower and funds.
- To evaluate the outcomes of research studies, including the clinical applications of the research findings.

The Council is assisted by the Executive Committee, which provides funding recommendations to aid the Council, and the Fellowship Subcommittee and 10 Peer Review Committees which provide scientific inputs. The 10 Peer Review Subcommittees are grouped as follows:

1. Immunology/Microbiology
2. Pathology/Inflammation/Oncology/Nuclear Medicine
3. Biochemistry/Cell and Molecular Biology
4. Epidemiology/Health Sciences/Public Health & Health Services
5. Peripheral, Central, Sensory & Cellular Nervous System/Mental Health
6. Genetics/Paediatrics/Reproduction
7. Cardiovascular/Respiratory
8. Renal/Endocrine/Pharmacology
9. GIT/Liver/Nutrition
10. Dentistry/Surgery/Ophthalmology

FY2005 Budget and Expenditure

In FY2005, the NMRC was allocated a total of $51.6 million for research expenditure, out of which $49.1 million was obtained from MOH's Other Operating Expenses Budget and $2.5 million was received as a generous donation from Singapore Totalisator Board (STB) for research projects and programmes.

For this financial year, the expenditures for research programmes and projects i.e. Block Grants and Competitive Grants, were $28.5 million and $22.1 million respectively; and the expenditure for Protected Time of the Clinical Scientist Investigators was $0.44 million. An expenditure of $1.65 million was incurred for Medical Research Fellowship and Scientist Awards.

CHAPTER 3
Competitive Grants

Introduction

Competitive grants are provided to researchers for carrying out specific research projects and programmes. The grants are awarded based on the scientific merits of the projects.

The three competitive grant categories are the:

- Individual Research Grant
- Competitive Priority Research Grant
- Competitive Programme Grant

In FY 2005, the NMRC received 293 applications. A total of 119 applications were approved, amounting to $21.8 million and are currently in progress.

Individual Research Grant (IRG)

Introduction

Individual Research Grants (IRG) are provided to researchers for carrying out specific research projects. The grants are awarded based on the scientific merits of the projects. A systematic reviewing, approving and monitoring system is in place to administer the IRG.

Current Reviewing, Approving and Monitoring System

(a) Reviewing

The reviewing process for IRG applications has evolved into a stringent and robust two-step system of review and assessment

The NMRC Secretariat selects appropriate reviewers (at least 2 for each application) from a local and overseas pool of reviewers, with the following guiding principles:

1. Reviewers are selected by matching the expertise of the reviewer to the grant application, according to the research area of the application.

2. To safeguard against any situational bias, reviewers from the same institution as the Principal Investigators, Co-Principal Investigators and collaborators will not be selected.

3. More reviewers will be assigned in the event of great disparity in reviewers' grading.

Following the first round of review by external reviewers, the 10 peer review subspecialty committees, which comprise representatives from the various institutions, will then assess the research proposals based on the comments given by the reviewers on the proposals. Each subspecialty committee will rank the proposals under its own subspecialty and make funding recommendations to the Executive Committee or the Council. The 10 subspecialty areas are as follows:

1. Immunology/Microbiology
2. Pathology/Inflammation/Oncology/Nuclear Medicine
3. Biochemistry/Cell and Molecular Biology
4. Epidemiology/Health Sciences/Public Health & Health Services
5. Peripheral, Central, Sensory & Cellular Nervous System/Mental Health
6. Genetics/Paediatrics/Reproduction
7. Cardiovascular/Respiratory
8. Renal/Endocrine/Pharmacology
9. GIT/Liver/Nutrition
10. Dentistry/Surgery/Ophthalmology

(b) Approval

Both the Executive Committee and the Council are vested with approving authority, depending on the grant amount. Grant amounts of up to $500,000 are approved at the Executive Committee level, and proposals above $500,000 are approved at the level of the Council.

(c) Monitoring

Approved projects are tracked and monitored on an annual basis. This is carried out through progress reports submitted by the Principal Investigators. Requests for grant variations or extensions are accepted upon review of their progress.

A final report on the researchers' findings and achievements is submitted when a project is completed. Each project is required to report on key performance indicators. A total of 86 projects were completed with final reports submitted in FY 2005. Due to intellectual property (IP) and various issues, only 79 abstracts of completed projects will be published in this report.

The abstracts are described in Annex 1: Abstracts of IRG & Block Grant Research Projects Completed in FY 2005.

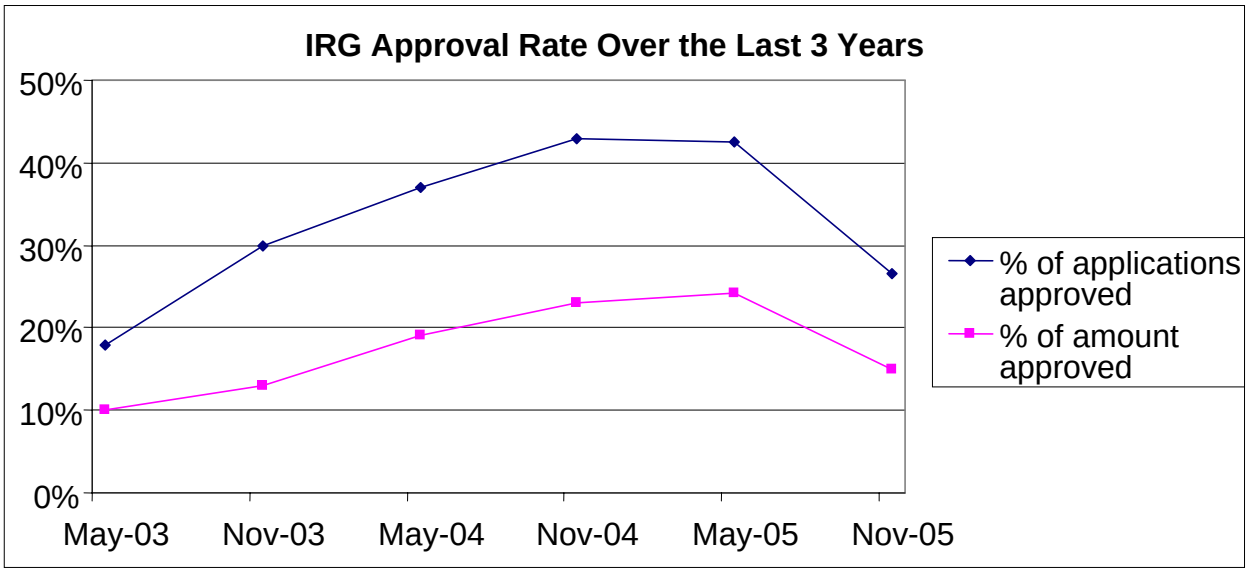
IRG Funding Exercises 2003-2005

Table 1 presents the statistics of each IRG Funding Exercise over the last three years.

- There is a decrease in the percentage of application approval in Nov05 Exercise as compared to the Nov03 and Nov04 Exercises. However, May05 Exercise shows a significantly higher approval rate of 42.6% as compared to 18% and 37% in the May03 and May04 Exercises respectively.

Table 1
IRG 2003 - 2005

	IRG Funding Exercise					
	May03	**Nov03**	**May04**	**Nov04**	**May05**	**Nov05**
No. of applications received Total amount applied for ($'millions)	227 77.7	173 65.9	145 42.3	126 46.0	115 34.6	162 67.8
No. of applications approved Total amount approved ($'millions)	41 8.0	52 * 8.5	54 8.1	54 10.5	49 8.4	43 10.1
% of applications approved % of amount approved	18% 10%	30% 13%	37% 19%	43% 23%	42.6% 24.3%	26.5% 14.9%



*: Reported as 52 projects in FY2003's Annual Report. 1 project was withdrawn since.

Applications in FY2005

A total of 277 applications were received by NMRC during the May05 and Nov05 Exercises. Out of the 277 applications, 92 projects were approved (please refer to Table 1).

Approved Projects in FY2005

Table 2 shows the number of IRG projects approved in FY2005, by instituition.

Table 2
No. of IRG Projects Approved in FY2005, by Institution

Institutions	No. of Projects Approved in FY2005
Changi General Hospital (CGH)	2
CTERU	1
Institute of Mental Health (IMH)	2
KK Women's & Children's Hospital (KKH)	2
National Cancer Centre (NCC)	14
National Neuoscience Institute(NNI)	9
National Skin Centre(NSC)	1
Nanyang Technological University(NTU)	1
National University Hospital (NUH)	9
National University of Singapore (NUS)	41
Singapore Eye Research Institute (SERI)	3
Singapore General Hospital (SGH)	13
Singapore National Eye Centre(SNEC)	1
Tan Tock Seng Hospital (TTSH)	4
Total	**103**

Ongoing Projects in FY2005

A total of 361 projects were still ongoing at the close of FY2005. Table 3 on the next page shows the number of projects being carried out in each institution.

Project Findings Reported in FY2005

A total of 86 IRG projects reported their final findings in FY2005. Table 4 on the next page shows the number of IRG projects that reported final findings in FY2005, by instituition.

Table 3

On-going Research Projects at the end of FY2005, by Institution

Institutions	No. of IRG Projects Ongoing at the end of FY2005
Alexandra Hospital (AH)	3
Institute of Mental Health (IMH)	4
KK Women's & Children's Hospital (KKH)	8
Changi General Hospital (CGH)	1
Nanyang Polytechnic (NYP)	1
National Cancer Centre (NCC)	40
National Dental Centre (NDC)	1
National Heart Centre (NHC)	11
National Neuroscience Institute(NNI)	32
National Skin Centre (NSC)	3
Nanyang Technological University (NTU)	5
National University Hospital (NUH)	21
National University Medical Institutes(NUMI)	8
National University of Singapore (NUS)	144
Singapore Eye Research Institute (SERI)	9
Singapore General Hospital (SGH)	45
Singapore Health Services (SHS)	11
Singapore National Eye Centre(SNEC)	3
Tan Tock Seng Hospital (TTSH)	11
Total	**361**

Table 4

No. of projects reported final findings in FY2005, by Institution

Institution	Numbers of Projects completed in FY2005
AH	1
IMH	1
KKH	1
NCC	11
NDC	1
NHC	3
NNI	5
NUH	3
NUS	30
SERI	2
SGH	25
SHS	2
SNEC	1
Total	**86**

Competitive Programme Grant (CPG)

Introduction

The Competitive Programme Grant (CPG) was set up in FY2003 to fund research programmes on vital health-related areas.

A “Research Programme” is defined as research in which several interdependent projects by co-investigators address an important theme or question, and a “Programme Grant” is defined as the funding of several independent projects as a programme where there are significant scientific advantages over funding these same projects on an individual basis.

Similar to the IRG, the CPG has a finite lifetime and is led by a Principal Investigator.

Review & Approval

CPG applications go through a process of peer review by external reviewers similar to the peer review process of IRG applications and recommendation by the Exco, before they are approved by the Council.

In FY 2005, 16 applications were received. All 16 applications were approved amounting to $2.9 million and are currently in progress.

Competitive Priority Grant (CPRG)

There is no grant call for this category in FY 2005.

C H A P T E R 4

Clinician-Scientist Investigator (CSI) Award

A*STAR's Biomedical Research Council (BMRC) and MOH's National Medical Research Council (NMRC) have launched a new award that will provide assistance to leading clinician-scientists hoping to translate basic research into tangible treatment therapies for their patients.

Targeted at outstanding clinician-scientists with a record of research excellence and who show good potential to become research leaders, the BMRC-NMRC Clinician-Scientist Investigator (CSI) Award is designed to support the career development of clinician-scientists, and promote clinical and translational research in Singapore.

The Award provides between three and five years support to clinician-scientists working in public hospitals and disease centres, including part of the recipient's salary commensurate with the amount of time spent on research.

The Award is divided into two categories, to cater to both senior clinician-scientists who demonstrate a consistent, high level of productivity and leadership (Category A), as well as younger clinician-scientists who show good potential to become independent researchers and who can develop careers in translational medicine (Category B).

8 awardees commenced their CSI award in FY2004:

Name	Host institution	Category
Dr Goh Boon Cher	NUH	Category A
Dr Yong Eu Leong	NUS/ NUH	Category A
Dr Michael Chee	SingHealth	Category A
Dr Allen Yeoh Eng Juh	NUS/ NUH	Category B
Dr Lynette Shek	NUS/ NUH	Category B
Dr Aung Tin	NUS/ SERI	Category B
Dr Tan Eng King	SingHealth	Category B
Dr Tai E Shyong	SingHealth	Category B

C H A P T E R 5
Block Grants

Introduction

NMRC's block grants facilitate the development of core manpower and research capabilities and fund research programmes carried out by the various research institutions. The goal of block grant funding is to enable the institutions to develop sufficient research capabilities to compete for competitive grants.

For institutions starting on research, block grants help to provide:

1. Core manpower
2. Equipment necessary to establish specific areas of research
3. Small grants to stimulate research activity.

For mature research institutions, the block grants provide for:

1. Core manpower support to run critical research services for the institution
2. Core equipment to support general research facilities for the institution
3. Small grants for new and pilot projects, especially for new investigators

Block grants are awarded annually and any unutilised funds will lapse at the end of the financial year. Currently, there are 23 block grants in two block grant categories: the **Institutional Block Grant** and the **Enabling Grant**.

Institutional Block Grant (IBG)

Institutional Block Grants (IBG) are provided to restructured hospitals and public research institutions to facilitate the development of core expertise and research capabilities.15 institutions received IBG funding in FY2005. The names of the se instituitions are listed in Table 5, as shown below.

Table 5
Institutions that received IBG funding in FY2005

	Institutions
1	Animal Research Laboratories (NNI-TTSH ARL)
2	Clinical Trials & Epidemiology Research Unit (CTERU)
3	Department of Clinical Research (DCR), SGH
4	Department of Experimental Surgery (DES), SGH
5	Institute of Mental Health (IMH)
6	MOH Nursing Research Committee (MOH-NRC)
7	National Birth Defects Registry (NBDR)
8	National Cancer Centre (NCC)
9	National Heart Centre (NHC)
10	National Neuroscience Institute (NNI)
11	National University Medical Institutes (NUMI)
12	National University of Singapore (NUS)
13	Singapore Cardiac Data Bank (SCDB)
14	Singapore Eye Research Institute (SERI)
15	Tan Tock Seng Hospital Clinical Research Unit (TTSH-CRU)

Each Institutional Block Grant recipient's research activities for FY2005 are detailed in the following sections.

Animal Research Laboratory (NNI-TTSH ARL)

Overview

The Animal Research Laboratory (ARL) is jointly managed by National Neuroscience Institute (NNI) and Tan Tock Seng Hospital (TTSH). It provides central animal care and housing services for all researchers and doctors at both institutions. Surgical skills training courses conducted by both institutions involving the use of animals also depend on the ARL.

The IBG funds the infrastructure and organizational needs of the ARL. ARL's objective is to provide reliable, efficient and reputable services for animal research at NNI and TTSH.

Activities in FY2005

Core facilities

In FY2005, the IBG supported items required to improve the ventilation and environment of the facility, and new alarm systems for monitoring of environmental parameters in the respective animal holding rooms.

TTSH-NNI Institutional Animal Care and Use Committee

An important activity supported by the IBG was the establishment of the TTSH-NNI Institutional Animal Care and Use Committee (IACUC) covering ethical oversight for animal care and utilization at the two institutions as well as the operational oversight of the Animal Research Facility.

The TTSH-NNI IACUC continues to be supported under the IBG, in terms of cost of education and training required for the IACUC members.

Achievements / Research Outcomes

In FY2005, NNI-TTSH ARL's achievements are as follows:

- 27 teams/individuals used the Animal Research Facility.
- 42 research projects use the ARL facilities to house animals, 6 out which made use of the Specific Pathogen Free (SPF) facility.
- About 3020 animals were housed in the facility.

Clinical Trials & Epidemiological Research Unit (CTERU)

Overview

The Clinical Trials & Epidemiological Research Unit was established in 1996 with funding from NMRC, and is managed by a Joint Management Committee including representatives from both healthcare clusters.

In FY2005, CTERU's broad objective was to provide essential infrastructure to enable clinical trials, evidence-based medicine and epidemiological studies in Singapore to be conducted according to established international standards. With the funding support of the IBG, this objective was achieved by:

1. Collaborating with investigators in Singapore and internationally in the conduct of clinical trials and other clinical research projects.

2. Providing expertise and support in the areas of research design, project management, data-management and statistical analysis/reporting.

3. Running biostatistical consultation clinics, made available to all Singapore investigators.

4. Carrying out systematic reviews and providing support for the development of clinical practice guidelines

5. Planning, providing and participating in post-graduate training of doctors, nurses and other healthcare professionals.

6. Publishing and presenting research results nationally and internationally.

Activities in FY2005

Much of CTERU's activities in FY2005 fall in the area of Clinical Trials as well as Evidence-Based Medicine/Epidemiology. Biostatistical support and training activities also continued to feature very prominently.

Clinical Trials

Some project highlights are as follows:

Project title	Progress / Outcomes
A Randomised Controlled Trial to Compare Steroid with Cyclosporine for the Topical Treatment of Oral Lichen Planus	139 biopsy-proven OLP patients were randomly assigned to cyclosporine (68) or steroid (71) applied onto the target lesion and affected areas. Although clinical response, pain, burning sensation, area of reticulation, erythema and ulceration at week 4 were all worse in patients receiving cyclosporine than in those receiving steroid the differences were not statistically significant. The study concludes that topical cyclosporine appears no more effective than steroid in the treatment of oral lichen planus. Manuscript was accepted by Oral surgery, oral Medicine, Oral pathology, Oral radiology and Endontology.
A Double-Blind Placebo Controlled Randomised Trial of Combination α-Interferon and Thymosin-α-1 versus α-Interferon Alone for Chronic Active Hepatitis B	98 subjects were randomly assigned to combination (48) or monotherapy (50) treatment group. There was no statistically significant advantage to combination with respect to time to HBeAG loss nor HBEAG seroconversion, changes in histology, normalization of ALT or loss of HBV DNA. In conclusion, this trial showed a 17.8% improvement in HBeAg loss rates with combination over interferon monotherapy that could indicate a potential clinically important difference that would need confirmation in subsequent trials. The manuscript was accepted by Antiviral Therapy.
A Randomised Controlled Trial to Compare Antenatal Preparation and Postnatal Counseling Strategies for Improving Breastfeeding Rates	450 mothers were randomly assigned 3 groups: the control group received standard hospital care; the antenatal group received breastfeeding educational materials and watched a breastfeeding video; the postnatal group received two postnatal counselling sessions by a lactation consultant. The preliminary report of the breastfeeding rates up to 6 weeks after delivery indicates that the postnatal counselling is more effective than antenatal education. The study is on going and in follow up stage. Study will conclude when all subjects complete one year postnatal follow up.
Phase II Trial of Infusional Gemcitabine in Combination with Carboplatin in Chemo-Naïve Advanced Non-Small Cell Lung Cancer (CTRGL08)	76 subjects were randomly assigned to one of the two treatment groups: fixed rate Gemcitabine 750mg/m2 over 75 minutes (arm A) or Gemcitabine 1000 mg/m2 over 30 minutes (arm B) on days 1 and 8 every three week cycle. The study concludes that the saturability of dFdCTP accumulation in Arm A suggests optimal delivery of Gemcitabine is achieved using fixed rate infusion compared to 30 min infusion. Fixed dose rate Gemcitabine is active and feasible, supporting the concept of fixed dosing rate of Gemcitabine in advanced NSCLC. However, this entails a longer infusion time with associated higher costs involved. The manuscript was accepted by Annals of Oncology.

Evidence-Based Medicine (EBM) / Epidemiology

In collaboration with the Department of Emergency Medicine (Dr Lim Swee Han, PI) EBM reported the results from the Acute Chest Pain Evaluation (ACTION) trial on the utility of cardiac enzymes for prediction of short and mid-term outcomes for patients presenting with acute chest pain. One multi-disciplinary evidence-based clinical practice guideline on Prevention of Falls in Hospitals & Long-term care facilities was published in collaboration with MOH. A non-invasive histology prediction algorithm for patients with chronic hepatitis B was published in collaboration with NUH.

Summary of Achievements / Research Outcomes

In FY2005, CTERU's achievements are as follows:

- 79 inter-institutional collaborations, including 38 clinical trials.
- Conducted 26 training courses in areas such as biostatistics, research methodology and GCP
- 3 weekly half day biostatistical clinics
- 31 publications

Department of Clinical Research (DCR), Singapore General Hospital

Overview

The Department of Clinical Research (DCR) has been funded by NMRC since 1994 and is one of three departments under the Division of Research of the Singapore General Hospital. In FY2005, the Department continued to function as a core basic research facility in the Hospital, supporting laboratory-based research activities and collaborating closely with researchers in the hospital and research institutions under the SingHealth Cluster.

The IBG supports the Department's core research manpower and facilities, including the expenses required for the running of 17 research laboratories at 2 locations: the Administrative Office and the Resource Centre. A portion of the funds is also set aside for seed funding of small research projects. This aims to encourage young clinicians returning from overseas training to pursue their research interest and to support existing researchers in the Hospital.

Activities in FY2005

Laboratory-based research & collaborative projects

DCR continues to promote laboratory-based research, assist clinicians in pursuing their interest in research and provide technical and scientific manpower through collaborative projects. Their core manpower have been actively involved in laboratory-based research in multi-disciplines such as molecular diagnosis and management of metabolic diseases and infectious diseases, cell transplantation and tissue engineering, central nervous system regeneration and neurochemical studies, as well as cancer research and cellular pathological studies.

Core Facilities & Statistical Consultation Services

The Department's core facilities include the Molecular Biology Laboratories, DNA Automatic Sequencing Laboratory, Analytical Laboratory, Endocrine Laboratory, Flow Cytometry Laboratories, Cell Culture Laboratories, Laser Scanning Confocal Microscopy Room, Photographic Dark Room, Radioactive Laboratory and Electrophysiology Laboratory. In FY2005, DCR's resources were utilized by over 70 SGH research projects and 31 research projects administered by other institutions.

In addition, 56 projects utilized their statistical consultation services on design, data analysis, results interpretation, paper editing and review.

Small Grants

40 small research grants were awarded. These small grants achieved 12 presentations and 2 publications during FY2005.

Summary of Achievements / Research Outcomes

The Department's achievements are as follows:

- 40 papers were published in FY2005, with 11 citations as at April 2006. The 36 papers published in FY2004 have 89 citations, as at this date.
- 22 presentations at international conferences were made.
- An external award for research was won.

- 7 PhD research students were trained, as well as several undergraduates and Polytechnic students.
- At least 50 of the research projects supported by the Department had potential or direct clinical applications.
- There were approximately 13 inter-institutional collaborations.

Department of Experimental Surgery (DES), Singapore General Hospital

Overview

In FY2005, the new research emphasis of the Department of Experimental Surgery (DES) was on the development of bio-imaging capabilities to better service translational research activities especially in the field of experimental oncology but also in other translational research fields. Bio-imaging, especially of small animals is an emerging research technology. The main focus of DES's activities was in optimising images and protocols and the creation of new animal models suitable for such imaging. These activities were carried out using the Siemens R4 micro-PET scan, which was acquired by SGH on 20 June 2005 under a collaborative program funded NMRC. A micro-CT scan, another new bio-imaging tool suitable for application on small animal models was also loaned from J.Morita, Japan under a collaborative research agreement with that company. J Morita has previously set up an office in Singapore after having been approached by EDB.

Both the micro-PET and micro-CT scanners are installed at the Animal Bio-imaging Centre within the premises of the Dept for Experimental Surgery and a proposal will be submitted to acquire another bio-image scanner, a Bio-photonic Imager in due course. The cyclotron support provided by the Dept of Nuclear Medicine in SGH which was co-located in the Outram campus, was crucial to the success of the micro-PET scan program. These bio-imaging facilities will, together with the existing fluoroscopy and the gamma camera in DES, provide translational and basic researchers with a full range of bio-imaging tools within the location of an established comprehensive animal research centre.

To support the research activities that follows the acquisition of these new capabilities in bio-imaging, the NMRC-IBG was utilised to develop core manpower comprising scientists, veterinarians, research associates and other veterinary care personnel. These additional core personnel are crucial to ensure that new IACUC approved projects arising from the bio-imaging capabilities are carried out in a manner compliant with newly-enforced NACLAR guidelines.

An important milestone in DES history was the official visit by a 2-member audit team from AAALAC[1] International on 9 and 10 March 2006 to conduct program review and site inspection for accreditation. Drs Kathy Laber and John Bradfield assessed the Deparment favourably. Physical deficiencies noted by this team were speedily rectified through additional funds made available by senior management in SGH and DES awarded full accreditation by AAALAC International on 22 June 2006. It is the first of only 2 such institutions in Singapore to be AAALAC accredited, the other being a commercial CRO.

Activities in FY2005

Research Services

In FY2005, DES carried out 44 research projects on its premises and 25 clinical skills training courses. Research services were streamlined to emphasis joint collaborative studies that create intellectual capital for the institution. Research projects carried out on the basis of fee-for-service only was de-emphasized and was carried out only when excess capacity was available.

Research efforts were organised into 6 focus areas namely:

1. experimental oncology
2. neurobiology
3. cadaveric research
4. trauma
5. pancreatic transplantation
6. medical devices.

Manpower Development

Core manpower underwent continual professional education upgrading with a program covering overseas training attachments, an on site training scheme and participation at lectures and courses related to the fields of veterinary sciences, biostatistics and biomedical technologies. Staff also underwent mandatory in-house updates on biosafety, occupational health & safety, emergency crisis management and animal husbandry to keep current with latest legal and safety guidelines for animal research in Singapore.

National and International recognition

Achieving full AAALAC accreditation is an affirmative endorsement that the personnel, protocols, facilities and animal program in DES are benchmarked to the highest international standards. The Deparment attracted collaboration with academic and industrial partners both within Singapore and internationally

DES is also the centre for cadaver repository and research in Singhealth and in this capacity, through the Ministry of Health, was involved in the assignment and distribution of cadavers to other institutions in Singapore.

Focus on Translational Research

The existing expertise and facilities within DES are fundamental to DES's strengths in animal and cadaver-based pre-clinical studies. The early involvement of expert clinicians in such projects allows for for rapid translation into early-phase clinical trials. In this respect, DES is the only centre in Singapore that has the expertise and capability for the large animal models including nonhuman primates, which are crucial to translational research projects, especially those involving medical devices. In FY2005, seven pre-clinical research projects with the potential to rapidly move into early-phase clinical trials were carried out in DES utilising the manpower funded by NMRC-IBG.

Three pre-clinical research projects completed at DES went on to clinical trials (bench-to-bedside) namely:

"Diabetes treatment with transplanted islet cells"
PI: Prof Bernie Tuch of Diabetes Transplant Unit, University of New South Wales

"Autologous heart valve implantation"
PI: Drs Tan Tieng Ee and Tony Yeo of NHC and NTU respectively

Brachytherapy in hepatocellular and pancreatic carcinoma.
PI: A/Prof Pierce Chow, SGH. Collaborative project with PsiOncology Pte Ltd which has gone on to successfully complete a phase IIA trial.

Summary of Achievements / Research outcomes

In FY2005, DES' research activities generated:

- 25 scientific presentations
- 3 academic awards
- 19 publications of which 9 were published in FY2005.
- 8 of the programmes/projects using DES' core facilities had direct or potential clinical applications
- DES was also involved in 25 institutional collaborations
- An Animal Bioimaging Centre was established and was equipped with micro-PET and micro-CT with plans for a bio-photonic image to provide comprehensive bio-imaging support for translational research
- DES was awarded full accreditation by AAALAC International on 22 June 2006.

[1]AAALAC: Association for the Assessment and Accreditation of Laboratory Animal Care, International.

Institute of Mental Health (IMH)

Overview

The Institute of Mental Health is the largest provider of mental health care in the country. It has a range of clinical expertise for the treatment of the various mental disorders.

With the continued support from the National Medical Research Council in the form of an annual block grant, IMH has taken the initial step and built the foundation of the infrastructure for research.

Once the foundation of the infrastructure was laid, the next step was to identify a few key areas of research to focus on, i.e. psychiatric genetics, neuroimaging, clinical drug trials and health service research. These areas were selected to optimally leverage on IMH's strength as the largest provider of mental health care especially to those with severe mental illnesses. IMH has a patient population and service structure that is highly unique across the world. It has accessibility to a large pool of ethnically homogeneous patients with limited mobility, detailed medical records, and a high level of clinical expertise.

Aims:

- To carry out world-class translation and clinical research in mental health.
- To foster collaboration between basic scientists and clinicians by providing support for joint research programs.
- Be the nucleus for future growth and development of other forms of research in Singapore (epidemiology, health service research), and facilitate other local, regional and international collaboration.

IMH continues to encourage and support research across the board with small start-up and pilot projects. Courses and seminars in research-related topics were conducted. A year-long training programme in research for the Medical Officers and Registrars was also initiated. Two of IMH's researchers have gone to United States of America for training in genetics and addiction research.

Activities in FY2005

Focused Areas of Research

The following areas have been identified based on the Institute's strengths: its position as the country's tertiary treatment centre for those with mental illnesses, its large patient population, the highest clinical expertise at a national level, and a well established research infrastructure. These areas are:

First-Episode Psychosis

This is an ongoing programme which has successfully integrated research into a clinical programme: the Early Psychosis Intervention Programme. There is a wide range of studies: including biological, psychosocial and psychopharmacological studies – one of the latter found a high rate of weight gain and glucose dysregulation among patients with the antipsychotics - with no differences found between the classes of antipsychotics.

Cognitive imaging

The etiology of many psychiatric illnesses will be determined through identification of the structural, functional and neurochemical aberrations that occur in the human brain. Neuroimaging studies include structural (structural MRI) studies, functional (functional MRI, PET or SPECT) studies, neurochemical (magnetic resonance spectroscopy) and connectivity (diffusion tensor imaging) studies. Neuroimaging technologies will also serve as essential complements to genetic studies in elucidating the neurobiological basis of psychiatric illnesses and to treatment studies in determining the impact of pharmacologic treatments on brain function.

IMH established a series of brain imaging studies in collaboration with the National Neuroscience Institute, the Singapore Brain Imaging Consortium (SBIC), as well as Nanyang Technology University that investigate markers of psychosis and developing techniques to enhance and better analyse brain images. It recently completed a study looking at structural brain abnormalities in patients with first-episode psychosis as compared to controls. Analysis of hippocampal volumetry has shown significant volume reduction of right anterior hippocampus in patients with first-episode psychosis as compared to normal controls. Currently IMH is also assessing hippocampal volume in first-degree relatives of schizophrenic patients; this would help IMH explore whether there is a genetic diathesis to this abnormality. IMH has ongoing projects that use cutting edge technologies such as the diffuse tensor imaging and functional MRI to explore parietal lobe connectivity using in patients who experience symptoms of passivity as well as the effects of atypical antipsychotics on working memory respectively in patients with schizophrenia.

Psychiatric Genomics and Genetics

The genetic factors underlying the etiology and manifestation of psychiatric disorders, as well as pharmacogenetics are in the forefront of psychiatric research globally. Singapore has the opportunity to be a world leader in this domain because of the unique characteristics of its population, the consolidated organization of psychiatric services, the sophisticated technology that is available in the Genome Institute of Singapore, and the infrastructure available from the Singapore Tissue Network. It is estimated that there is almost no place in the world where the clinical population and technical capabilities coexist in such a compact manner. IMH already launched its genetics research programme with the pharmacogenetic study on tardive dyskinesia – a serious and common side-effect arising from antipsychotic treatment. This study, conducted in collaboration with the Genome Institute of Singapore and the Singapore Tissue Network, is but the first stage in establishing a psychiatric genetic programme that will establish a genetic bank linked to high-quality clinical databases of key psychiatric disorders. The completion of the Tardive Dyskinesia project will create a bank of 1,000 subjects with schizophrenia.

The practical offshoot of this research is the precise identification of at-risk individuals for psychiatric disorders, and the possibility of tailoring therapeutics to maximize effect and minimize toxicity

Psychiatric epidemiology

In collaboration with the Diabetic Centre of Alexandra Hospital, IMH has embarked on a study of 1,000 patients with types 1 and 2 diabetes mellitus to examine the prevalence of depression, its associated complications and the pattern of service utilization.

It also has a collaborative study with the Singapore Armed Forces in developing a screening instrument for psychiatric morbidity and establishing the rates mental illnesses among young male adults.

Research in Child and Adolescent Psychiatry

2005 saw the continuation of three threads of research in child and adolescent psychiatry. These were measurement research, epidemiological research and intervention research.

In measurement research, the work focuses on developing culturally appropriate measurement rating scales, and assessing the cultural appropriateness of existing measurement rating scales for their use among local children and adolescent populations. IMH validated a general screening tool, the Child Behaviour Checklist and its subsidiary tool for teachers, the Teacher Rating Scale. As a result, it is now the local distributors of the scale for Singapore and Malaysia. In addition, IMH further validated its Anxiety and Depression scales for Children, which have been used in several studies.

In epidemiological research, the work seeks to understand the determinants and prevalence of emotional and behavioural disorders in children aged 6 to 12 in Singapore. Data was collected from 2141 children and their parents and teachers on the children's mental health. 12.5% of the children were found to have mental health problems, the main risk factors being lower intellectual ability and parents being single or divorced. These findings will be presented at an international child psychiatry conference and at the NHG ASM later this year. In addition, using data collected from a clinical epidemiological study conducted earlier, a paper on the parenting behaviour of Singaporean parents and child outcomes has been published in 2005.

In intervention research, the work focuses on developing culturally appropriate psychological interventions that has resulted in the development of cognitive behavioural therapies for anger, anxiety and selective mutism. In addition, the department has embarked on a clinical trial of Ziprasidone for adolescents, which is the first clinical trial for adolescents in a treatment trial for mental illness in youths.

Health Service Research

IMH has initiated an array of studies that examined the accessibility of their care, as well on the impact of clinical pathways, and clinical programmes on the quality of care and their cost effectiveness.

IMH, in collaboration with NTU, is evaluating the cost-effectiveness of the Early Psychosis Intervention Programme.

Drug Trials

IMH continued to attract a large number of drug trials from the pharma industry. Its Clinical Trial Unit (also supported under the IBG) continues to provide high level support and co-ordination of these trials. All staff in this Unit are trained and certified in Good Clinical Practice (GCP).

In 2005, IMH see itself embarking on its first investigator-initiated trial. IMH will continue to build on their experience and expertise in early Phase trials, as well as in investigator-initiated drug trials.

Summary of Achievements / Research outcomes

In FY2005, IMH's achievements are as follows:

- 7 papers were published in international peer review journals with impact factor greater than 2.0
- 19 papers were published in peer review journals with impact factor less than 2.0
- 26 abstracts published
- 14 presentations were made at international conferences
- 1 PhD student, 1 MD, and 1 MSc student have been trained
- 13 clinically-relevant research projects
- 2 external awards for research at National level
- 13 inter-institutional collaborations. IMH's collaborations were with Genome Institute of Singapore, Singapore Tissue Network, National Neuroscience Institute, Cognitive Neuroscience Laboratory, Singapore Armed Forces, Clinical Trials and Epidemiology Research Unit, University of Melbourne, SUNY Upstate Medical University in New York, Nanyang Technological University, Alexandra Hospital, National University Singapore, Biomedical Imaging Laboratory, Duke University

Ministry of Health – Nursing Research Committee (MOH-NRC)

Overview

The block grant for the MOH Nursing Research Committee (MOH-NRC) was used to provide research resources and literature databases for use by nurses in Singapore. It was also used to fund Clinical Practice Guideline (CPG) development activities and research studies and activities.

Activities in FY2005

Core facilities

An OVID database subscription was purchased for the support of research projects and CPG development.

Small Projects/ Start-up Grants

In FY2005, 7 projects and start-up grants were ongoing, of which 5 were awarded in FY2005. A CPG on Prevention of Falls was completed, while 7 more CPGs on Prevention of Infections Related to Cental Venous Devices in Children, Breastfeeding for Pre-term Infants, Nasogastric Tube Feeding, Nursing Patients with Potentially Violent Behaviours, Nursing Management of Venous Leg Ulcers, Prevention of Deep Vein Thrombosis and Nursing Patients with Tracheostomy were still in progress.

Clinically relevant research

In FY2005, MOH-NRC core facilities supported 8 clinically-relevant studies, which resulted in potential or direct clinical applications.

Title	Achievement
Project funded by MOH-NRC	
Music Therapy: As an Intervention in Reducing Anxiety and Improving Physiological Parameters of Acute Myocardial Infarct Patients in Coronary Care Unit	This study concludes that music therapy can reduce heart rate and respiration rate of patients with AMI. It can also slightly reduce the anxiety level but the result was not statistically significant. The findings suggest that music therapy may be implemented as a nursing intervention to reduce cardiac workload for AMI patients.
Projects supported by MOH-NRC core facilities	
Impact Of An Acute Stroke Unit Care - A Controlled Study	This study showed that the use of a clinical pathway for patients admitted with stroke and managed in an acute stroke unit provides a systematic management plan and had shown to reduce complications and mortality with improved functional ability.
Examining the Efficacy of Programmed Breathing Technique as a Pain Relief Measure for Patient Who Is Receiving Subcutaneous GCSF (Neupogen)	This study showed that haematology patients who performed Programmed Breathing Technique (PBT) during the administration of subcutaneous Neupogen injection experienced less pain than those who did not.
A Descriptive Study on Factors That Influence the Decision of Postnatal Mothers to Breast Feed	Findings show that factors within the social environment, a return to work and support from family and friends are significant influences on early cessation. To improve the rate of breastfeeding, initiatives such as frequent home visits and telephone follow up to reinforce education, starting a breastfeeding support group and improve the working environment to make it more breastfeeding friendly should be explored
Effectiveness of Surgical Bra in the Immediate Post Operative Phase for Breast Cancer Patients	This study showed that the surgical bra provided better support and comfort for the chest wall of patients post-breast surgery. The findings also showed a significant increase in the volume of fluid drained in the surgical bra group but further evaluation is needed to observe for any seroma formation after removal of drain.
Effect of pelvic floor re-education on duration and degree of urinary incontinence after robot assisted laparoscopic prostatectomy	Urinary incontinence is a significant cause of postoperative morbidity after a radical prostatectomy. Using the Incontinence Grading System, the experimental group achieved improvement in both duration and degree of continence (Chi-square p= 0.02) to that of the control group at 12 months.

A Study on Knowledge, Attitude and Practice of Diabetes Mellitus patients in Polyclinics	This study provides useful information for nurses caring for Diabetic patients. It reinforces that regular assessment of patients' skills and knowledge is important in order to identify specific patient characteristic that may help them to improve in self-care.
Promoting Continence in the Nursing Homes - Weaning off Diapers for Residents	This study showed that with targeted planning and concerted efforts from all care staff to offer toileting regimes to suitable residents in a nursing home, almost all could be weaned off their diapers.

Inter-Institutional Collaboration

A multi-centre study, "A Retrospective Study of Falls and Fall Prevention Practices at General Hospitals in Singapore" had been completed and another multi-centre study "A Multicentred Study to Evaluate the Effectiveness of A Tailored Multifaceted Strategy for Implementation of Clinical Practice Guidelines in Singapore" was in progress.

Summary of Achievements / Research outcomes

In FY2005,

- At least 79 nursing research studies from public institutions were conducted.
- 18 papers were published
- 107 presentations were made in institutions, national and international conferences.

The majority of these projects were not directly funded by the IBG, but utilized the resources funded by the IBG.

National Birth Defects Registry (NBDR)

The National Birth Defect Registry (NBDR) was set up in 1993 and shifted to KK Women's and Children's Hospital in 1999. It has since become an important source of clinical data providing important national information on birth defects such as epidemiological trends, risk factors and the effects of prenatal diagnosis and intervention. Notification of birth defects to the registry is comprehensive and includes live births, stillbirths and abortuses with fetal anomalies.

A number of articles and papers have been written using data from NBDR. There has been media interest in the incidences of polydactyly and the association of increased maternal age with birth defects, as well as numerous requests for relevant processed data from the Registry by various medical professionals for the purpose of planning and work. The data requested includes data on cleft lip & palate (plastic surgeons), occupational effects (workplace epidemiologists) and Down Syndrome (maternal fetal medicine).

This ongoing national database is an important clinical application that helps to monitor and improve clinical service and healthcare of the nation. Its usefulness will be enhanced with time as more data are collected and methodology improves. It is expected that there will be more requests for information from the media and from professional bodies in Singapore.

The block grant supports the production of NBDR's Annual Report. The Report is prepared with the aim to provide an overview of the annual changes in the population with regards to birth defects. The statistical tables and figures will be of interest to academics, demographers and medical professionals. This collation of information on a nation-wide scale will hopefully facilitate the planning and evaluation of antenatal screening, genetic counseling and pediatric medical and surgical services in the country.

National Cancer Centre (NCC)

Overview

The National Cancer Centre emphasizes multi-disciplinary research and is actively engaged in basic, clinical and translational cancer research that can potentially be applied to improve clinical care.

The Centre's research divisions - the Division of Cellular and Molecular Research, the Division of Medical Sciences, and the Division of Clinical Trials & Epidemiological Sciences, are staffed by full-time scientists who work in collaboration with cancer specialists of various disciplines.

The Division of Cellular and Molecular Research is engaged in gene therapy, gene knockouts and transcriptional regulation of genes. The Division of Medical Sciences fosters translational research with the objective of applying advances in basic research (including new diagnostic and therapeutic technologies) to clinical care. The Division of Clinical Trials & Epidemiological Sciences applies the latest advances to the treatment of patients, providing consultancy in biostatistics, clinical trial design and execution. This Division investigates the epidemiology of cancers, and maintains databases that combine epidemiological information with treatment and survival data.

Activities in FY2005

Division of Medical Sciences Programme

The Division of Medical Sciences engages predominantly in translational research with special interest in improved methods for early cancer diagnosis and novel treatments. It is also host to young clinicians who undertake research training.

Developing novel cancer diagnostics

The Division is the leader in Singapore in pioneering non-invasive optical methods for cancer diagnosis. Clinical studies focusing on early diagnosis of oral cavity and bladder cancer combining various spectroscopic and optical imaging approaches are being pursued as optical biopsy techniques. Novel formulations of drug-induced fluorescence, white light diffuse reflectance and tissue autofluorescence are combined for online optical diagnosis. Nanophotonics for optical molecular imaging of early cancer is being pioneered. In DNA-based diagnosis, clinical research service is offered for women at high risk of breast and/or ovarian cancer that includes screening for mutations in the cancer susceptibility genes, *BRCA*1 and *BRCA*2. Novel mutations have been identified that may be important in Asian populations. The Division has expanded its proteomic approaches for biomarker discovery in gastric cancer tissues and in gastric fluids.

Innovations in cancer therapy

Clinical trials of photodynamic therapy for head and neck cancer and bladder cancer using novel photosensitizer formulations are ongoing and show encouraging efficacy. Brain tumour chemotherapy regimens customized for Asians have been developed. DNA vaccines for nasopharyngeal cancer are in ongoing clinical trials.

Pharmacogenomics

The influence of genetic polymorphisms on pharmacokinetics and pharmacodynamics of chemotherapeutic agents, and pharmacological factors underlying interethnic differences in drug responses are active areas of investigation. The Clinical Pharmacology Laboratory supports and collaborates closely with the NCC Dept. of Medical Oncology in several Phase I/II clinical trials. Strategies have been developed to identify polymorphisms in drug transport genes of functional significance that could be useful for association studies.

Molecular and cell biology of cancer

Understanding the pathways of carcinogenesis is essential to advances in cancer care. To this end, work in the Division also focuses on understanding the multifarious aspects of the cancer cell. For example, a protein whose overexpression leads to aneuploidy has been identified as consistently upregulated in hepatocellular and other cancers, and thus may be a key driver of genomic instability. Hot spots for chromosomal breakpoints have been identified in gastric cancer cell lines, providing clues to molecular pathogenesis. Progenitor cells have been found to home to brain tumours in animal models. Brain tumour stem cells have characteristics of chemoresistance and specific DNA damage signaling profile. MicroRNA expression in several cancer types and their role in oncogenesis are recent initiatives.

Close juxtaposition of clinicians, clinician-scientists and cancer researchers enables the Division to keep its focus consistently and clearly on addressing real problems in clinical oncology. To this end, the Division seek to direct its limited resources to research that have real potential to alleviate the burden of cancer in the community.

Division of Cellular & Molecular Research Programme

The Division of Cellular & Molecular Research is an active research department within the National Cancer Centre, Singapore. The close proximity of the research laboratories to the clinics within the National Cancer Centre allows a collegial, collaborative and productive scientific and clinical research environment to forge research in translational biomedical science. The Division's interests are wide-ranging and encompass Molecular Diagnosis of Human Cancers, DNA Repair, Molecular Endocrinology, Molecular Carcinogenesis, Cancer Genomics, Cancer Proteomics, Biological Imaging, Bacterial Pathogens, Gene Therapy, and Immunotherapy. The Division engages in vigorous basic clinical & translational research leading to novel clinical applications in oncology including innovative diagnostic tests, novel cancer prevention and treatment protocols, and genomic-based personalized treatment in oncology. The strategy is to focus on testing the applicability of scientific discoveries to solve clinical problems.

One of the most difficult hurdles in achieving effective gene therapy is the requirement for the use of efficient vehicles to deliver the gene of interest into target cells. In the **Gene Vector Laboratory**, the feasibility of designing better viral vectors for therapeutic gene delivery is being explored. The group has engineered a series of novel Herpes Simplex Virus-1 (HSV-1) with gene expression that is controlled by cell cycle events. Consequently, the specific activation of transgenes carried within these viruses will only take place in actively proliferating cancerous cells.

The **Laboratory of Cancer Genomics** has exploited the in-house integrated bioinformatics infrastructure set up within the Division for the production, storage, and analysis of large-scale genomic data generated from DNA microarrays that allows the integration and processing of sample data from multiple different technology platforms associated with all different aspects of microarray production, from receipt of clones or probes from external vendors to microarray fabrication/printing. In collaboration with

various clinicians, the laboratory has characterized tumor-specific genes for many human cancers that are common in Singapore. The human cancers being studied include cervical cancer, nasopharyngeal carcinoma, hepatocellular carcinoma, lung carcinoma, and breast cancer. The malfunction of some of these genes might be responsible for the development and metastasis of cancer. The group is incorporating some of these genes into the novel viruses that have been engineered in the Gene Vector Laboratory in order to test their potential applications for treating human cancers.

The **Laboratory of Molecular Development** utilizes genome-wide technologies such as DNA microarrays to discover genes or gene subsets that may be of diagnostic or therapeutic value in adult cancers. The group applies genome-targeted technologies such as DNA microarrays to investigate conditions that are highly represented amongst ethnic groups common in the South-East Asian region but which are less represented in Caucasian populations, or conditions whose clinical manifestations differ between these populations. Examples of diseases that are currently being investigated by the group (either directly or with our collaborators) include gastric, naso-pharyngeal, and breast cancer. The group has identified a gene expression signature associated with poor prognosis in breast cancers. The identification of such a signature, at the point of diagnosis, may allow clinicians to pre-select individuals for more aggressive treatment regimens. The group is also applying the genetic tools available in *C. elegans* to investigate host-pathogen interactions.

The **Laboratory of Molecular Endocrinology** is interested to identify new genes with gene products that could potentially aid the early diagnosis of cancers. This group is studying the function of novel genes that include the OKL38, a tumor suppressor gene; UO-44 which exhibits expression that is tightly regulated by hormones; and ps20, a growth inhibitor. The group is also studying serum markers that could potentially serve as biomarkers for the early detection of hepatocellular carcinoma. A HCC xenograft model has also been established by the group for the identification of novel pre-clinical drugs in the areas of anti-angiogenesis activities specifically in the context of the MEK/ERK pathway, VEGF receptor, survivin and cdc-2.

Oncogenes play an important role in the development of human cancers. The **Laboratory of Gene Structure and Expression** has isolated the aurora-A oncogene. Over-expression of aurora-A protein results in centrosome hyper-amplification and aneuploidy. Aneuploidy is a hallmark of metastasis, for example in gastric cancer, and is associated with poor prognosis. In addition, it has recently been reported that over-expression of aurora-A resulted in poor response to therapeutic agents, such as taxol, that target the spindle checkpoint. This group is engaged in the identification and characterization of potential suppressors of aurora-A and the involvement of aurora-A in hormone-mediated carcinogenesis.

The tumor suppressor gene p53 is considered to be one of the most significant of all genes in cancer because mutations of this gene are found in more than half of all human cancers. In normal cells, p53 regulates cell growth by controlling cell proliferation and cell death. Mutations in p53 lead to the loss of these growth suppressive functions, thus leading to uncontrolled growth. The main objective of the **Laboratory of Molecular Carcinogenesis** is to elucidate the biochemical and biological processes that underlie the ability of p53 to act as a tumor suppressor. In particular, the group is interested in studying the mechanisms by which the activity of p53 is regulated by environmental agents that cause cellular stress, and the involvement of post-translational modifications of p53 in determining the biological effects of its activation. “Knock-in” mice models and genetic screens are being employed to achieve these goals. Unlike p53 which is mutated in more than 50% of all human cancers, its relative, the p73 tumour suppressor gene, is not mutated but over-expressed in many cancers. The cause and consequence of overexpression of p73 is at present unclear. The group is also focusing on understanding the regulation of p73, particularly with reference to its ability to induce cell

death. The objective is to try to "activate" p73 in human cancers thereby harnessing its ability to induce cell death in the eradication of the disease.

Cancer, at its very core, is a genetic disease. Recently, its molecular underpinnings have been traced to a group of genes coding for proteins that mediate cell cycle progression, DNA repair, programmed suicide (apoptosis) and the 'upstream' cell membrane signalling and transduction regulatory cascades. Collectively, these systems form a complex, interconnected homeostatic circuitry - denoted genome maintenance network (GMN) - that enables a human cell to sense and respond to different types of genotoxic stress (e.g. solar UV rays or toxic chemicals). The primary aim of the **Laboratory of Genome Maintenance** is to gain mechanistic insight into the genome maintenance network, i.e., the complex homeostatic circuitry comprising interconnected cell cycle control, DNA repair and apoptotic processes that enable a human cell to sense and respond to DNA damage. To this end, the Laboratory has made considerable progress in the identification of novel candidate substrates of ATM protein kinase, the DNA damage-sensing product of the *ATM* gene mutated in the rare cancer-predisposition and radiotherapy-sensitivity syndrome ataxia-telangiectasia (AT). In related work, the Laboratory has continued to investigate the molecular basis of the severe, late side effects routinely encountered by a small percentage (5%) of cancer patients who have undergone curative radiotherapy.

In summary, the department of Cellular and Molecular Research focuses on performing vigorous basic & translational research leading to clinical applications in oncology including diagnostic innovations, novel treatments, methods for cancer prevention and genomic oncology.

Clinical Trials & Epidemiological Sciences Programme

Biostatistics Unit

The Unit's main tasks include the provision of statistical and epidemiological support and training for clinical investigators, as well as the conduct of applied biostatistics research.

Good statistical and epidemiological input is required to ensure that the data from research projects are correctly analyzed and interpreted. This will prevent inappropriate conclusions being drawn from research findings.

As for applied biostatistics research, a key area of research is the application of Bayesian statistical approaches to clinical trials. Such methods allow for the formal incorporation of relevant external sources of information into the design, conduct and analysis of a trial. This enables more informed decisions to be made. Among the applications to which the Unit has applied Bayesian approaches are the design of early phase clinical trials and the conduct of randomised trials for rare cancers.

Clinical Trials Office and Clinical Trials Compliance Unit

In order to practice evidence-based medicine, clinical trials must first be conducted to obtain quality data to reach accurate conclusions with regards to treatment. NCC has conducted over a hundred clinical trials since 1999 and the Unit has been responsible for providing the infrastructural support for its physicians to conduct clinical trials to international standards.

Some of the trials that this Unit helped to conduct have:

1. resulted in improved patient outcomes (e.g. survival – randomized trial of chemo-RT vs RT for NPC)
2. provided patients with alternative treatments to surgery (e.g. Surgery vs chemo-RT for head and neck cancers)
3. shown the efficacy of certain new drugs in certain cancers common in this region (e.g. gemcitabine in NPC)
4. definitively shown that certain treatments were of no benefit (e.g. tamoxifen in liver cancers)
5. provided patients with access to the latest medicines even before they were commercially available (e.g. Gleevec, a new drug which has prolonged the lives of some of the patients who had a type of cancer which was previously uniformly fatal).
6. enabled patients who have benefited in a study treatment to continue the study treatment in an open-label extension protocol (e.g. IRESSA vs Supportive Care in lung cancers and SU011248 in gastric cancers)

The Clinical Trials Office functions as the secretariat for the Institutional Review Board (IRB) and the Clinical Trials Steering Committee. It ensures that only well-designed, ethical and scientifically-sound protocols are allowed to be used on patients to optimize trial resources and to ensure patient safety and confidentiality. The IRB has reviewed a total of 139 clinical studies and 188 lab-based research since it started its function in 1999.

Summary of Achievements / Research outcomes

The major outcomes of NCC's research efforts this FY can be summarized as follows:

- In terms of the volume of research activities, the IBG provided support for 338 research projects / clinical trials this FY. The 300 projects include 30 completed projects, 236 ongoing projects (including 68 NMRC Individual Research Grants / Extramural grants), 38 new projects, 2 projects that were halted pending further funding, and 5 withdrawn projects.
- These resulted in 161 publications, including 17 papers in press and 15 papers submitted for review.
- NCC published 54 international and 27 local conference papers, and gave 42 lectures as invited speakers.
- In terms of the quality of the research, 97 of these published papers were internationally ranked at Journal Impact Factor greater than or equal to 2.0
- In FY 2005, NCC Researchers also received 3 International and 5 National awards.
- 10 Masters research students and 33 PhD research students were trained/undergoing training and 10 post-doctoral researchers were employed
- 99% of the research supported by NCC had potential or direct clinical applications
- The IBG also supported 374 inter-institutional collaborations.

National Heart Centre (NHC)

Overview

For FY2005, the objectives of NHC's IBG were:

1. To expand the basic and molecular research capabilities of the National Heart Centre

2. To develop, test and commercialize innovative mechanical devices for various common cardiac conditions and to bring them rapidly to patient care.

3. To establish a core team for the tissue engineering facility with biomaterials engineers from Nanyang Technological University to identify and nurture technological solutions to cardiovascular diseases.

4. To cultivate a research culture in the National Heart Centre conducive to training creative and talented scientist clinicians in the area of cardiovascular research.

5. To fund and maintain a critical mass of core research scientists to provide continuity of research at the National Heart Centre.

6. To integrate and facilitate various researches across disciplines: e.g. cardiologists and engineers, scientists and clinicians, cardiologist with other specialists, principal investigators with private business and government agencies.

7. To consolidate existing projects with renowned and established overseas investigators and promote further collaboration with them.

8. To bring successful projects rapidly to the patient, and for patent filing and eventual commercialization

Activities in FY2005

NHC has continued to fund its entire basic research staff from the IBG. It continues to focus on the following research interests.

1. Stem cell and other cell based therapy for the repair of the failing heart.
2. Gene therapy for therapeutic angiogenesis.
3. Use of innovative polymer delivery systems for drug and gene delivery in the cardiovascular system, including a biodegradable polymeric coronary stent
4. Understanding vascular endothelial inflammation and dysfunction and developing therapeutic targets for the vulnerable plaque
5. Antibody engineering for therapeutic purposes (antiplatelet agents) and for therapeutic homing of cell based therapy
6. Tissue engineering artificial heart muscle and heart valves for transplant.

Summary of Achievements / Research outcomes

In FY2005, NHC's achievements were as follows:

- 8 papers were published, 5 of which were published in top 20% international peer review journals with impact factor greater than 2 and 3 were published in peer review journals with impact factor less than 2
- 27 presentations were made at international conferences
- 1 patent has been filed.
- 6 external rewards for research have been clinched at national and international levels
- A Masters research student and PhD research student have been trained.
- 5 research projects had potential or direct clinical applications
- 2 research facilities were developed
- There had also been 6 inter-institutional collaborations.
- 1 company span off

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National Neuroscience Institute (NNI)

Overview

The IBG is vital to NNI's mission to develop and advance of neuroscience research to improve patient care, enhance the nation's health and establish an international reputation for medical excellence. It is the only source of funding for the infrastructure underpinning the NNI's neuroscience research.

The objectives of the IBG are to fund the vital components of the NNI's research infrastructure, including core equipment, administrative and other support staff, and, most critically, a faculty of core scientists and researchers. The IBG will also support research training and education, research collaborations and international scientific presentations.

Since its inception in late 2000, the NNI has effectively set up its neuroscience research laboratories, recruited a core team of talented neuroscientists, supported the development of a vigorous research faculty and provided effective research administration and governance, all leading to laudable research output and results. These achievements are a clear measure of the effectiveness of the NMRC's IBG to the NNI's research effort.

Activities in FY2005

Research Infrastructure

The core equipment budget in FY2005 supported the purchase of new core/communal equipment and the upgrading of existing infrastructure equipment. Items purchased included the FPLC system, additional CO_2 incubators, the Gel Documentation System, X-ray film developers, core refrigerators/freezers, upgrading of existing software tools and startup equipment for the scientists.

The IBG also supported research scientists, basic supporting research staff, and research administration for NNI research infrastructure and general operations, the NNI IRB Secretariat and the NNI-TTSH IACUC Secretariat.

On top of these, IBG also promoted research collaboration between thescientists/researchers and leading international researchers and institutions. In addition, the IBG also supported training and educational activities related to research.

Summary of Achievements / Research outcomes

The primary desired outcome of the IBG is that NNI Research improves the clinical care of patients with neurological diseases. To this end, research at NNI is disease centred and focused, especially on diseases of major concern in Singapore, eg. neuro-degenerative diseases, and directed towards disease mechanisms and therapies, databases, epidemiological studies and treatment trials.

. Secondary desired outcomes include the training and career development of research staff, the development of an international reputation for research and contribution to Singapore's Biomedical Initiative.

In FY2005, NNI's achievements are as follows:

- A total of 69 funded research projects were ongoing at NNI, of which 38 are funded by NMRC's Individual Research Grant
- 12 ongoing clinical/drug trials linked to industry, with 4 new clinical/drug trials initiated during the year.
- 89 scientific publications were produced by NNI researchers, with 44 in the top 20% scientific journals with impact factor 2.0 and above.
- 93 scientific presentations were made at international and local scientific meetings.
- NNI added 1 MOU with Volume Interaction Pte Ltd to the 10 extant MOUs.

National University Medical Institutes (NUMI)

Overview

The overall objective of the National University Medical Institutes (NUMI) is to (i) strengthen existing translational programs and develop new niche areas pertinent to clinical medicine, and (ii) to provide state-of-the-art Core research facilities and services to cater to the needs of biomedical researchers at School of Medicine (SoM) and NUS. The latter include Confocal Microscopy, DNA Sequencing, Flow Cytometry, in situ Hybridization, Medical Communications, NUMI Store, Small Mouse Facility, and Translational Interface.

One of NUMI's focuses is to commit to the development of cancer biology program. This resulted in a very strong Oncology Research Institute (ORI). ORI has expanded and done exceedingly well in attracting top-notch scientists to Singapore, as well as setting up a state-of-the-art Core Translational Interface (TRI) facility within NUMI for clinician scientists/scientists at SoM.

A second focus is cardiovascular biology and NUMI is currently working to build up the critical mass to move this forward.

The continued success of Core Services funded under the IBG is reflected by the steady increase in the number of end-users, not exclusively restricted to the Yong Loo Lin School of Medicine. NUMI anticipates this trend to continue and hence the need for continued support for upgrading its Core services within the School of Medicine. With the growing technological advances, a faculty level state-of-the art Core facility is an essential requirement.

Activities in FY2005

NUMI's ongoing research programmes are the Cardiovascular Research Programme, Oncology Research Programme and ROS Biology Programme. Below are abstracts of their progress.

Cardiovascular Research Programme (CVR)

1. Myoblast therapy for cardiac repair

   Xeno-transplanted human skeletal myoblasts successfully survived in rat and porcine heart without immunosuppression and the survival rate was further enhanced by transient immunosuppression. Human skeletal myoblasts have conditionally immunopriviledged status. Fusion between myoblasts and pig cardiomyocytes is the mechanism of the surviving human skeletal myoblasts in pig heart

2. Myoblasts as carriers of angiogenic genes for cardiac repair

   Human skeletal myoblasts were transduced with either Cholesterol: DOTAP liposome (CD liposome) or polyethylenimine (PEI) carrying $VEGF_{165}$ or Ang-1. It was found that that transfection of homogenously mixed and suspended skeletal myoblasts significantly increased transfection efficiency (up to 30%) with a prolonged expression period (up to 24 days). The angiogenic gene transduced skeletal myoblasts efficiently improved injured heart function with improved regional blood flow as compared with only myoblast transplantation.

   Studies found that PEI transfected HSM expressed h $VEGF_{165}$ up to day-18 (5 ng/ml) with peak at day-1 (25 ng/ml) with >90% cell viability. Animal studies revealed

increased blood vessel density, improved blood flow and ejection fraction after transplantation of PEI mediated VEGF transfected skeletal myoblasts.

3. Embryonic stem cell for cardiac repair

Human embryonic stem cell line---H1 was induced to form embryoid bodies (EBs) by culturing them in low attachment plates for 7, 14 and 21 days. Adenoviral vector expressing human $VEGF_{165}$ gene (Ad-h$VEGF_{165}$) was used to transduce the EBs. Endothelial expression was optimal in 14-day EBs. Maximum transduction efficiency in the 14-day EBs with high cell viability was achieved by 4-hour exposure of the EBs to virus for three consecutive days. Combination of the optimal endothelial expression and $VEGF_{165}$ gene transduction in 14-day EBs showed the highest expression for vascular markers in both immunostaining and RT-PCR results. ELISA data also showed a significant upregulation in $VEGF_{165}$ protein in these transduced 14-day EBs.

<u>Oncology Research Programme (ORI)</u>

The focus of research in the Oncology Research Institute has been on 4 main cancers: gastric, breast, colorectal and leukemia as there is critical mass in NUS/NUH in these 4 areas. The ORI has therefore sought to be internationally competitive in these 4 areas. A summary of the progress in each of these areas are as follows:

Gastric cancer – 2 main studies are being conducted. The first examines the role of RUNX3 in human gastric cancer. The second is a study of a cohort of 4,000 high risk patients by examining their biopsy specimens following the results obtained in the first study. Both have good grant support from the SCS and BMRC, and involve inter-institutional collaborations with NUH, IMCB, GIS and SGH. The ORI gastric cancer team is also one of the main contributors to the national gastric cancer program, involving NUS/NUH, IMCB, GIS & BII, and is a member in the Fred Hutchinson Cancer Research Centre's International Cancer Biomarker Consortium.

Breast cancer – Prof Sara Sukumar, Sidney Kimmel Comprehensive Cancer Center in Johns Hopkins, is leading the breast cancer program at ORI. Inter-institutional collaboration is mainly with NUH while extension of collaboration with GIS is being explored for 2006. The 2 projects currently being pursued are:

- The study of the methylation status of several genes involved in breast cancer. The specific aim is to see whether there are ethnic differences in breast cancer formation/development of breast cancer. In 2005, the team discovered that the incidence of point mutations in PIK3CA, the A3140G substitution in particular, in Singapore breast cancers are among the most frequent reported to date for any gene in breast cancer.

- Involvement of RUNX3 in breast cancer – inactivation of RUNX3 was found in about 30% of breast cancer. This project has successfully concluded.

Colorectal cancer – In 2005, Dr Manuel Salto-Tellez was tasked to head the colorectal program team in order to broaden the scope and interest of CRC, to encourage a more direct link with translational research, increase the involvement of more researchers/projects, as up to 2005 the work had almost exclusively been centred on RUNX3 involvement in CRC. Inter-institutional collaboration has been initiated with SGH, TTSH and JHS.

Leukemia - The main studies focus on therapeutic targeting of AML and investigating the molecular mechanisms underlying AML pathogenesis. The projects are supported by grants from SCS and BMRC and inter-institutional collaboration exists among

scientists in NUH, IMCB and GIS.

Summary of Achievements / Research outcomes (by CVR and/or ORI)

NUMI's achievements in FY2005 are as follows:

- 50 published papers, including 33 by ORI and 17 by CVR.
- 22 citations of published papers from ORI.
- 74 presentations at international conferences, of which 59 were by ORI and 15 were by CVR
- 1 patent filed by ORI
- 5 external awards for research won by CVR
- 2 masters research students and 2 PhD research students were trained, and 3 postdoctoral researchers were employed.
- There were 5 inter-institutional collaborations by ORI and CVR
- 1 research facility is developed or improved.

ROS Biology Program

The program aims to identify mechanisms of redox-mediated pathways pertinent to cancer, and other disease states. To that end the PIs are involved in a variety of extramurally funded programs to enhance our understanding of these pathways for use as biomarkers of disease or targets for novel drug design. Following is a list of projects under the various PIs.

1. Regulation of death signaling in tumor cells by intracellular ROS.
2. The role of NHE-1 and PPAR-gamma in tumor cell sensitivity to apoptosis.
3. Functional proteomics of cell death and survival signaling in tumor cells.
4. Study on redox active compounds and their mechanism of action.

Research Output and Awards

- Published about 15 papers in 2005-06.
- Brought in approximately S$1.5M in funding from extra-mural sources.
- The 2 senior PIs (A/Profs Pervaiz and Clement) were jointly awarded the University Outstanding researcher Award for their contribution to the understanding of ROS-dependent signaling in tumor cells.
- Invited presentations at international and local conferences (A/Ps Pervaiz and Clement).

National University of Singapore (NUS)

Overview

The block grant for NUS's School of Medicine is used to fund start-up grants for new Faculty recruits (Assistant Professor and above) and small research proposals not exceeding $25,000.

Start-up grants help new Faculty recruits to set up their laboratories while waiting for the results of major grant applications. The small grants are primarily utilized to conduct pilot or preliminary studies which would aid Principal Investigators in applying for larger grants based on the outcome of their findings.

The funding for the start-up grants and pilot projects is meant for the purchase of small equipment and consumables. In the fiscal year 2005, the NMRC block grant supported 21 such projects.

Highlights

Title: Saliva as a Reliable Source of Genomic DNA for Modern Genetic Studies

Large population-based studies, involving hundreds to thousands of study subjects, are crucial in the search for the genetic determinants underlying common complex diseases. Genetic material, in the form of genomic DNA, is typically obtained from blood samples, a collection method which is invasive, painful and generally disliked by study subjects. For population or community studies, especially among children, less invasive methods are preferable, as this will likely result in higher study participation rates. As such, NUS researchers explored the viability of saliva as a potential source of human genomic DNA by testing a newly available kit (Oragene) that has been specifically designed for the collection of saliva samples and their subsequent genomic DNA extraction. The Oragene method was evaluated in terms of genomic DNA yield from whole saliva. In addition, the effect of diverse storage conditions (including different storage temperatures for varying periods of time prior to DNA extraction and analyses) was examined to determine if these conditions substantially impact on DNA yield and quality using a variety of methods including spectrophotometry, PCR-RFLP and Taqman-based real-time amplification methods.

Main Findings

The major conclusion was that saliva is undoubtedly a viable source of genomic DNA for human genetic epidemiological studies. Specifically, the researchers' results demonstrated that saliva may be conveniently stored for up to 6 months at room temperature and yet still yielded DNA of adequate yield and quality. Overall average DNA yield from 2 ml of saliva was 35.5 µg and purity was acceptable and comparable across all storage conditions. Differences in storage conditions did not impact DNA quality in real time PCR experiments and genotyping fidelity remained undiminished. These researchers' finding regarding the use of saliva as a source of DNA was shared with the scientific community through presentation at the Combined Scientific Meeting 2005 organized by SingHealth, National Healthcare Group, and the National University of Singapore and by formal publication in the journal Clinica Chimica Acta 2006, vol 367, 81-85.

Title: Investigating the roles of gelsolin in tumourigenesis

The funding provided contributed a major portion of the resources necessary to set up the new laboratory, as well as to embark on this novel startup project at the NUS. NUS researchers suggested the possibility that gelsolin might act as an anti-oncogene in tumours, as it is often downregulated in tumour samples. The specific project aims to test if this might be true and the tumour mechanisms gelsolin might interfere, with including signaling pathways (eg. protein kinases). The objectives are to characterize gelsolin expression in tumour cell lines, identify those with 'normal', up- or down-regulated gelsolin levels and modulate gelsolin levels artificially in these. If gelsolin alters tumourigenic potential in these modified cell lines, we expect to see changes in cellular behaviour and possibly phenotype, as well as altered protein expression (including signaling proteins).

Main findings:

The researchers have characterized the expression of gelsolin in several tumour cell lines by immunochemistry and have identified potentially important changes that could be relevant to cellular invasion and metastasis. It appears that gelsolin is especially highly expressed in tumour cell lines that exhibit potential for dissemination. This is one aspect of gelsolin biology which will be explored for future work, as it suggests that intervention directed towards gelsolin may be explored as part of therapy for tumours that currently have poor prognosis. The researchers are also characterizing tumour cell lines for reduced gelsolin expression to enable us to select lines suitable for analysis of changes in signaling.

Expansion of research findings funded:

Since completion of the grant, NUS researchers have been able to secure the following grant that will follow up on their preliminary work:

NMRC Pilot Study approved August 2006 (S$100,000 for 1 year): Investigating the anti-oncogenic and oncogenic roles of gelsolin in the development of tumours.

Main collaborator in this grant: Dr Sutherland Maciver (Biomedical Sciences, University of Edinburgh). The researchers are actively working with him to design and test protein expression systems that can be used to alter gelsolin expression in tumour cell lines.

Title: The role of statins in immune-cells interaction

Cell-cell contact between T lymphocytes and monocytes represents an important mechanism in perpetuating chronic disease in Rheumatoid Arthritis (RA). T cells isolated from RA synovial fluid or mitogen activated T cells induce pro-inflammatory cytokines and matirix metalloproteinases (MMPs) production by monocytes via a cell contact-mediated mechanism. 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (Statins), are effective serum cholesterol-lowering agents, but also posses immunomodulatory properties. NUS researchers studied the role of statins in immune cell-cell contact by using reconstituted cell culture assays in which PHA/PMA-activated Jurkat T cells were fixed in paraformaldehyde and co-cultured with human monocytic cell lines (i.e. U937, THP-1) in the presence of increasing doses of statins. Production of pro- and anti-inflammatory cytokines such as IL-1beta, $TNF_{\alpha,}$ ILI_{β}, IL-6, IL-10 were assessed by ELISA. Mitogen activated fixed Jurkat T cells induced significant TNF_{α}, ILI_{β}, IL-6, MCP-1 and MMP-9 production by U937 cells via cell-cell contact. Such production can be inhibited by statins in a dose-dependent manner. AlamaBlue was performed throughout the experiment to confirm cell viability was not affected by statins. Mitogen activated T

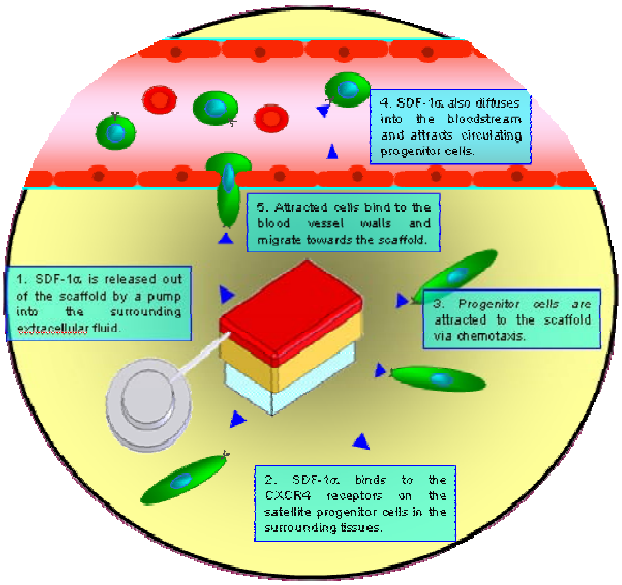
cells trigger p38 MAPK phosphorlyation in U937 cells upon cell-cell contact, and can be inhibited by pretreatment of statins as assessed by FACS analysis.

Collaboration/Conference Presentation

Research collaboration was established a result of this start-up grant with colleagues at the Dept. of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital. Part of the data has been presented at the American College of Rheumatology annual scientific meeting in San Diego, California, November 13-17, 2005.

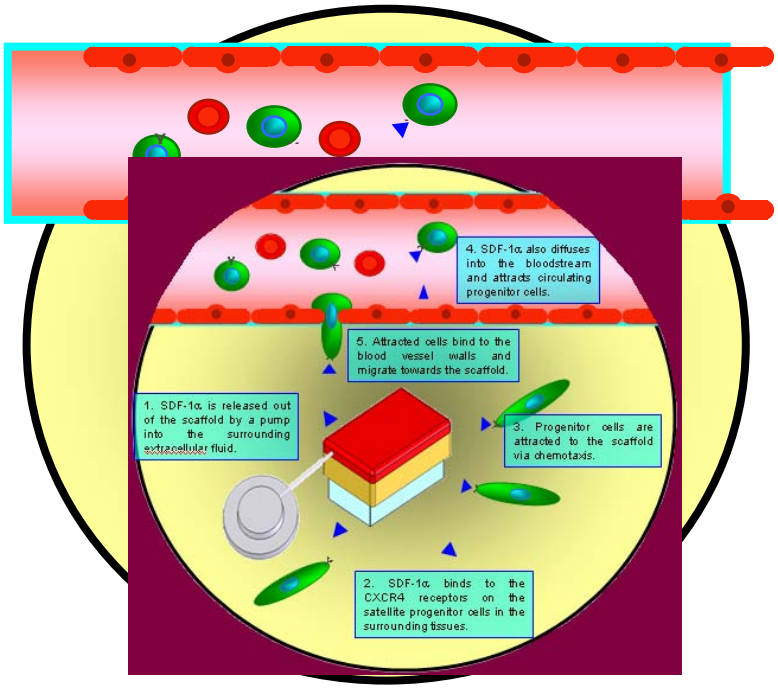
Title: Characterization of the migratory potential of mesenchymal precursor cells

Cell guidance is a tissue engineering concept which acts to create a biomimetic environment leading to site specific tissue function. The objective of this combined in vitro and in vivo study was to chemotactically attract mesenchymal cells into 3D scaffolds for in situ bone tissue formation. The concept recapitulates certain embryonic events like (1) site directed cell homing, (2) angiogenesis, (3) tissue differentiation and mineralization.
In this study, chemokines were released into a polycaprolactone scaffold in a controlled and sustained manner through microneedles into specific sites of the scaffold to create a biomimetic environment for bone tissue formation.The focus of the in vitro studies will be based on cell homing of the mesenchymal progenitor cells (MPCs) using Stromal Cell-derived Factor-1晁 (SDF-1晁). Following the in vitro studies a controlled drug delivery system was implanted subcutaneously into Wistar rats to provide a biomimentic environment for cell chemotaxis and osteogenic differentiation.



Conclusion

SDF-1a has been shown to induce chemotaxis of MPCs into a PCL scaffold to promote cellular ingrowth. The ability to promote site-directed homing of stem cells has great potential in the clinical setting. Progenitor cells can be directed to aid repair in specific sites of tissue damage via SDF-1a. NUS researchers plan to perform in vivo studies and also use Vascular Endothelial Growth factor to increase vascularization of the scaffold for nutrient delivery.



In vitro Experiments
The cells were seeded onto the bottom layer of the polycaprolactone scaffold in fibrin glue (Baxter) (G). The whole set-up is assembled (H) and cultured in DMEM (10% FBS, 1% PS) (I) and 100ng/ml of SDF-1α is injected into the system daily for 15 days (J). For the control scaffolds, Phosphate Buffer Solution is released instead. After 15 days the system is disassembled and the scaffolds are stained with Fluorescein Diacetate and Propidium Idodide and viewed under confocal microscopy. The scaffolds are also viewed using Scanning Electron Microscopy to detect any migrated cells.

Summary of Achievements / Research Outcomes

- 3 papers published in international peer review journals (with impact factor greater than 2.0)
- 12 on-going inter-institutional collaborations set-up such as with
  - University of California
  - University of Gothenburg, Sweden
  - Cambridge University
  - University of Edinburgh
  - St Luke's Hospital
  - Local hospitals and research centres

Singapore Cardiac Data Bank (SCDB)

Singapore Cardiac Data Bank (SCDB) was established in 1999. It is a collaboration project and joint effort of cardiac departments from Changi General Hospital, National Heart Centre, National University Hospital, Alexandra Hospital and Tan Tock Seng Hospital.

The primary objectives of SCDB are to provide Ministry with data to support its healthcare planning and policy, national cardiovascular disease management plans as well as National Medical Audit Meeting (Cardiovascular Discipline) to improve quality of cardiovascular care.

National Medical Audit Meeting in various cardiac specialties are held during the year for Cardiac Clinicians and Surgeons to review workload, morbidity, mortality, complication of service included in the audit period and recommendation changes in practice of cardiac specialties.

The cardiac information captured in SCDB is important and enables hospitals to monitor and understand the trends, demographics, clinical characteristics, current management, define treatment strategies associated with best clinical outcomes and most efficient use of resources.

The cardiac data also evaluates and insures the quality of respective procedures/surgeries. Analysis of major outcomes and process-of-care measures that impact respective procedure. The outcome data helps individual hospitals to target specific areas for clinical practice improvement, obtain an accurate reflection of practice patterns.

There have been a number of publications produced from SCDB data in the international journals and conferences since it was established.

Singapore Eye Research Institute (SERI)

Overview

SERI is the leading centre in South Asia for ophthalmic and visual science research. In the relatively short time since its inception SERI has established an international reputation as an eye research center of excellence with an internationally recognized high profile.

The major objective of FY2005's IBG is to maintain the level of activity and scientific output within the four established research divisions, namely, the Clinical Research Unit, the Epidemiological Unit, the Visual Psychophysics Unit and the Laboratory Sciences Unit. Within these units, SERI will continue to develop its major initiatives in ocular proteomics, genomics, ocular stem cell biology, ocular drug delivery, development of animal models of ocular diseases, visual performance studies and clinical trials in ophthalmic pharmaceuticals, lasers and surgery. Research priorities remain those most relevant to Asian eye disease such as myopia, angle closure glaucoma, ocular surface diseases and diabetes.

Activities in FY2005

Myopia research

A second large-scale clinical trial on the use of atropine eyedrops in school age children to retard myopia progression, and to determine the bioavailability of atropine to optimize atropine usage was initiated. Additionally, laboratory work continued on the role of cellular pharmacological receptor and pathways for atropine on the scleral fibroblasts, including use of the current pig and mouse models of myopia. SERI's randomized clinical trials on NeuroVision treatment in low and mid-myopic individuals in the SAF are currently mid-way. Plans are currently underway to develop a randomized controlled trial on the use of NeuroVision treatment in schoolchildren with progressive myopia. SERI's epidemiology studies on school myopia continued to progress unabated, and it published a total of 6 papers relating to myopia research this year.

Ocular Surface diseases

Having proven its concept of cultivating cultured conjunctival equivalents for conjunctival and ocular surface reconstruction, SERI's efforts this year focused on evaluating the ability of the conjunctival constructs in replacing corneal epithelium in limbal stem cell deficiency, and re-evaluate concepts of conjunctival epithelial transdifferentiation in these eyes. SERI successfully performed cultured conjunctival transplants as corneal surface replacements in 4 eyes of 3 patients this year. Proteomic tear and ocular surface work will continue to evaluate new ocular defensins and biomarkers for dry eye disease, and early results of SERI's work on antimicrobial peptides are promising and need to be followed up. Four publications in this field of research were published this year. In addition, one of SERI's key stem cell clinician scientists was awarded the 2005 Singapore National Academy of Sciences (SNAS) Young Scientist Award for his contribution to the program.

Glaucoma

Clinical trials on acute angle closure glaucoma, including evaluation of new technology for population screening, and SERI's new RCT on the use of prophylactic laser iridotomy in preventing acute angle closure glaucoma in high risk patients were performed this year. Genetic studies relevant to glaucoma including linkage studies and the identification of candidate genes continued to be major programs underway. A total of 8 publications relating to glaucoma research were published this year.

Diabetes, retinal vascular disorders and a new retinal stem cell program

SERI's main focus remained the epidemiological study of retinal vascular disease such as diabetic and hypertensive retinapathy as a predictor for cardiac or cerebrovascular disease, using retinal imaging as a screening modality. In addition, work relating to ocular angiogenesis progressed well with regards to its pig model of retinal capillary closure and its rat model of retinal hypoxia. In addition, SERI initiated a new retinal stem cell research program this year, headed by Dr Henry Klassen. Over 64 scientific articles in this field were published this year, and A/Prof Wong was awarded both the Woodward Medal for Science and Technology at the University of Melbourne, and the Fred Hollows Lecture in Ophthalmic and Visual Science at the Australian Ophthalmic and Visual Sciences Meeting in Australia, this year, for his work in retinal vascular disease epidemiology.

Psychophysics and Visual Neuroscience

Studies on multifocal ERG in myopia were completed this year, with 3 publications on retinal electrophysiological function in high myopia, myopia associated with retinitis pigmentosa, and in myopia study subjects treated with atropine eyedrops to retard myopia progression. Studies currently ongoing in electrophysiology include projects on optic neuritis, diabetic macula edema and post-retinal detachment surgery.

Several perceptual learning studies evaluating NeuroVision treatment in low and mid-myopia and post-refractive surgery are currently in progress, including 2 RCTs with the SAF on visual improvement and contrast sensitivity enhancment in military subjects.

Summary of Achievements / Research outcomes

In FY2005, SERI scientists and clinicians from both clusters accomplished the following:

- Published 129 scientific articles in peer reviewed ophthalmology and visual science journals
- Presented 80 scientific abstracts at local and international clinical and research meetings
- Initiated 42 new research projects
- Received a total of 4 awards for research excellence
- Trained 1 masters research student and 1 PhD research student
- 1 new product/process is commercialized
- 14 research projects had potential or direct clinical applications
- 89 inter-instituitional collaborations
- 4 research facilities are developed or improved

Tan Tock Seng Hospital – Clinical Research Unit (TTSH-CRU)

Overview

The main objective of the Institutional Block Grant (IBG) 2005 is to provide administrative, scientific and technical support in (i) promoting growth of research talent and research culture in Tan Tock Seng Hospital, (ii) developing research programmes that have genuine potential of output in terms of high quality publications and improvement in medical care and health.

The FY2005 IBG had been instrumental in providing essential core manpower support for TTSH Clinical Research Unit (CRU), Infectious Disease Research Centre (IDRC) and additional support for TTSH Research Laboratories. As a result, TTSH continued to grow in strength and activity and to provide central support for TTSH researchers working on NMRC funded studies and investigator-initiated studies.

The manpower support, through FY2005 IBG has helped researchers with literature searching, preparation of the grant application, study costing, actual conduct of the study, management of accounts, statistical analysis and advice and preparation of the manuscript for publication and conference presentation.

The manpower support has also assisted CRU in forming the Publication team comprising of the medical statistician, research executive (project) and administrative assistant. The publication team was set up, in view of the increasing need of assistance in grant submission, statistical analysis, management of data and study and the writing of publications. This team will assist investigator-initiated studies.

The form processing solution purchased through the FY2005 IBG will be helping TTSH to improve on the deliverables in the future. This form processing solution is a cost-effective way of managing research data. Besides minimizing the number of errors in data entry, it would also minimize the need to hire more data management personnel with the expected increase in research data in future.

The FY2005 IBG had also helped to purchase the necessary parts in building 5 cost-effective prototypes of the vacuum wound system which facilitates coverage of wounds that are difficult to manage, reduces patient discomfort, reduces dressing changes, provides biologically favourable healing milieu and provides a closed wound system that protects patients and staff from contamination. It is still in the process of being built. The first prototype had shown good results so far. If found effective,it will provide a breakthrough for a cost-effective treatment of infected wounds. Currently, the systems available in the market involve a significant costs estimated at about $400 per day.

Since the CRU and IDRC establishment, there had been tremendous growth of research activity within the hospital. They provide the infrastructure to conduct clinical research and clinical trials to internationally acceptable standards. In fact, the institution has received favourable report from audit teams in the pharmaceutical industries and NIH for its participation in the multinational ESPRIT Study. It continues to expand its link with TREATAsia, (The Research, Education Aand Treatment for Asia project) a new regional collaborative research network for HIV research funded by the American Foundation of AIDS Research. The Institution will continue its collaborative research effort with other institutions.

Activities in FY2005

TTSH-CRU's achievements in FY2005 include:

- 22 papers published in top 20% international peer review journals with impact factor greater than 2.0, and 64 papers published in peer review journals with impact factor less than 2.0
- 20 presentations at international conferences
- 99 clinically-relevant research projects
- 16 inter-institutional collaborations
- Development of Infrastructure of 2 research facilities

Enabling Grant (EG)

The Enabling Grant was set up in 2003 and is given to institutions to build up research capabilities and nurture a research culture through providing grants for clinical trials support and pilot studies. 8 Enabling Grants were awarded in FY2005.

Table 6

Institutions that received EG funding in FY2005

	Institutions
1	Alexandra Hospital (AH)
2	Changi General Hospital (CGH)
3	KK Women's & Children's Hospital (KKH)
4	Health Sciences Authority (HSA) – Clinical Trials Support
5	Health Sciences Authority (HSA) – Small Grants
6	National Dental Centre (NDC)
7	National Skin Centre (NSC)
8	National University Hospital (NUH)

Each Enabling Grant recipient's research activities and outcome for FY2005 are as follows.

Alexandra Hospital (AH)

Overview

The NMRC FY05 enabling grant (EG) has made 2005 another remarkable year in helping the institution build up the basic foundation of clinically relevant research.

Activities in FY2005

Consolidated capability of molecular genetic laboratory

The FY05 EG transformed the laboratory into a modern molecular genetic laboratory equipped to perform a good range of genetic analyses including multi-channel nucleotide sequencing and multiplex PCR genotyping. Together with previous years' EG which allowed the setting up of RT-PCR based genotyping, the genetic lab is now a somewhat self-sufficient medium through-put molecular genetic lab. The large number of blood samples collected over the past 5 years can now be studied in various genetic epidemiological studies. All these resources when put together have greatly enhanced AH's probability of success in the application of competitive funding which in turn attracted collaborations from leading research institutions such as the Genome Institute of Singapore (GIS) and National University of Singapore (NUS).

Enhanced capability of metabolic cell culture laboratory

The metabolic cell culture laboratory now maintains stable HepG2 and HUVEC (human umbilical vein endothelial cell) cell lines and is routinely harvesting intracellular organelles such as mitochondria and microsomes for biochemical and molecular studies in the field of diabetes and lipid metabolism. Studies done have laid the foundation for successful application of competitive funding and publications. A Consultant from Dept of Medicine, who directed AH's cell culture lab, was one of first batch of five NHG investigators, who were awarded both Mentorship & Assessment Program (MAP) and Research Investigator Scientist Enabler (RISE) Program from NHG.

Consolidating research in sports medicine and exercise physiology

A multi-disciplinary team of investigators from orthopedic surgery, sports medicine, physiotherapy and endocrinology has came together to provide the critical mass sufficient to lift this area of research off the ground in AH. They have set up a core exercise physiology laboratory and started clinical studies on human volunteers and athletes. The facilities were also employed to help in understanding exercise physiology in type 1 diabetes patients engaged in highly competitive sports.

Research nurses.

The 2 funded research nurses played pivotal role in the recruitment of study subjects. They have been instrumental in the recruitment and collection of biological samples of > 500 subjects with carefully phenotyped diabetes. They have also contributed to the smooth running of most of the FY05 small grants. In return, they gained an enormous amount of clinical and epidemiological research experience and has attended both basic and advanced GCP.

Research training

AH continued to fund research related training to enhance the research capability of our investigators. These included statistical courses, courses on genetics and research writing. With the above development, the institution has successfully attracted four undergraduate medical students to do their elective attachment for a period of 1 month. Five staff (4 of them clincians) from AH are pursuing advanced training in research in the field of genetic and molecular epidemiology, phsyiotherapy (both leading eventually to PhD) and bioinformatics (leading to MSc), cell culture/lipodology and islet cell biology .

Clinical trial research clinic

The physical availability of a research clinic is an important resource to investigators who wish to conduct clinical study but has space constraint in the usual service clinic. EG FY05 has continued to support the day-to-day operations of this research clinic.

Competitive grants

AH investigators have been awarded eight new competitive grants in 2005. The set up of research infrastructure using FY05 EG have enabled the smooth execution of other competitive grants from NHG and NMRC.

Jump start research in geriatric medicine, ocular visual science, molecular oncology of thyroid cancer and biomechanics

AH is witnessing the rise of research in the field of cognitive impairment, age related macular degeneration and molecular marker for risk stratification in thyroid cancer. Two senior orthopedic surgeons are also deeply keen in developing research in clinical biomechanics and are working towards setting a biomechanic laboratoy in the new hospital at Yishun.

Synergy

Inter-disciplinary collaboration is sprouting between physicians, surgeons, allied health and clinical laboratories. For instance, the multi-disciplinary team in sports medicine (probably unique in Singapore) exemplifies the synergy that AH strongly encourages. The synergy between molecular genetic and cell culture laboratories has paved the ways towards functional genetics and molecular oncology of thyroid cancer.

The enabling grant has made FY05 another exciting year for research development in AH. The above landmark development will certainly empowered AH to take a significant step forward in the development of clinically relevant research.

Summary of Achievements/Research Outcomes

AH's research achievements/outcomes for FY2005 are as follows:

- 4 papers published in top 20% international peer review journals with impact factor greater than 2.0
- 5 presentations at international conferences
- 2 external awards for research at national and international level
- 8 competitive research grants were awarded from NMRC, BMRC or industry, the total quantum being $486,100

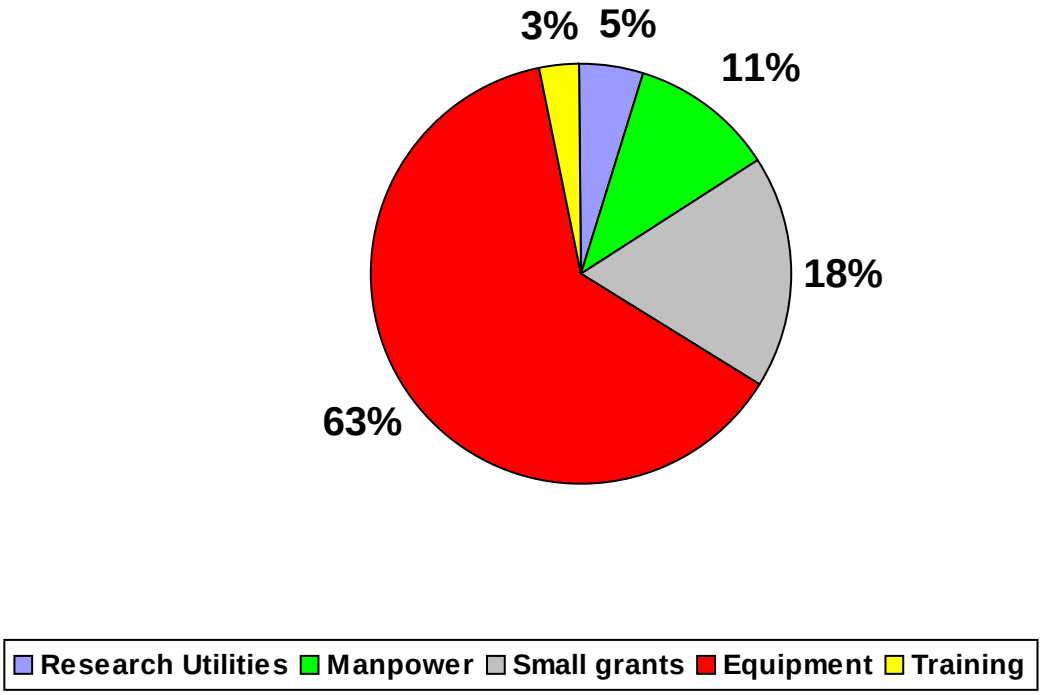
Changi General Hospital (CGH)

Overview

The objectives of the NMRC FY2005 enabling grant were:

To further upgrade the clinical trial facilities to become more competitive;
To further develop the human resources for research work;
To encourage and fund more staff to conduct pilot and start-up research projects

An overview of the grants utilisation (in percentage) is as shown on the pie chart:



Activities in FY 2005

CGH achieved the following research outcomes with the NMRC FY2005 enabling grant :

- The Phase 1 clinical trial facilities have been improved. This helps CGH to be more self-sufficient and able to meet the stringent requirements of conducting the trials and complete the trials in a shorter time.
- The manpower resources help to share the workload and improve project management.
- The staff attended research forum and PK workshops organised in-house, and other external seminars and courses on research and ethics. This training and educational programs improved staff confidence and work efficiency.
- The research hub facilities have been strengthened, the bibliograpgy software was upgraded, statistics books were made available, the article retrieval services with NUS were renewed, and the doctors have found them useful for their research work and paper writing.
- 1 paper published in peer-reviewed journal.
- 4 presentations at international conferences

- 5 projects were found to have clinical relevance
- 2 research infrastructure were developed or improved

KK Women's & Children's Hospital (KKH)

Overview

The enabling grant, being in two components has stimulated research activities within the institution in both clinical and non clinical trials. It has provided the 2 crucial elements in promotion and supportive maintenance of research activities; i.e. through

1. overall research administration, facilitation and coordination
2. project grants for equipments and consumables

Activities in FY2005

a) Clinical trial Management
   - Overseeing clinical trials, i.e. contract and budget negotiations as well as trial and staff administration

b) Laboratory Activities
   - Supporting Institution's Tissue Banking activities, i.e. management/storage of bio-materials
   - Conduct of basic science research; collaborations between clinicians and scientists.

c) Education and Training
   Research training is made possible through on-going courses funded through the grant. They include courses on GCP training, database creation/MS Access and SPSS (Statistical Package for Social Science). From the centre, the training activities conducted are:
   - General research training was conducted in 2005 to various KKH staff. It included planning, proposal writing and data analyses using SPSS
   - Research Seminar on topics ranging from literature review, grant writing, statistics to manuscript writing in 2006 for all medical staff across the clusters.
   - Research nurses are also trained specifically on their roles and functions in clinical drug trials, ranging from documentation, drug storage and consent taking

d) Research databases and statistical consultations
   - Data management is integral in research studies. This involves database support especially in large disease registries. To date there are 28 databases set up by the centre for such purpose.
   - Statistical support in the form of sampling calculations, randomizations and analysis are conducted in-house on requests.

Summary of Achievements/ Research Outcomes

KKH's research achievements/outcomes are as follows:

- 34 publications
- 83 presentations
- 5 research with direct applications
- 5 inter-institutional collaborations
- 1 research infrastructure developed

Health Science Authority – Clinical Trials Support (HSA-CT)

Overview

The objectives of the IBG for FY2005 were to support the following activities:

- Modification to the current online clinical trials licensing system (PRISM) to cater to the clinical trials framework
- Training of HSA professional staff through participation in conferences to maintain regulatory knowledge and keeping pace with the advances in clinical trial matters.

Activities in FY2005

Modification to the current online clinical trials licensing system (PRISM) to cater to the clinical trials framework

This fund was initially requested to support the change of framework in PRISM (PO - HSA000EPO05000444), which costs $56,480. However, the initial proposal to revise the clinical trials framework could not be implemented due to legal considerations. Hence, the description of the item has been revised as per the variation request in Jan 2006 to "Modification to the current online clinical trials licensing system (PRISM) to cater to the clinical trials framework". This would accurately reflect the ongoing development in PRISM to support the current clinical trials framework. The Clinical Trials Branch (CTB) in HSA has also implemented administrative changes such as the parallel submission system and altered the current format of the Clinical Trial Certificate (CTC) to reduce administrative workload. The amended format takes the form of a notification email/ fax to inform the applicant that the trial can proceed. Hence all applications received from Jan 2006 would be approved electronically and HSA will cease to issue hard copy CTCs.

The funds allocated in this area have greatly enabled HSA to enhance the system both for external and internal customers:

1. Improvement in the user-friendliness of the system: CTCs and import licenses are available online, and applicants are also able to view the history of approvals for CTC extensions.
2. Reduced administrative workload: Without hard copies of the CTCs, less time is administrative details. In addition, reminders for extension of the CTCs have also been automated.
3. Increase in database efficiency: The Intranet Enquiry Function has been enhanced to allow officers to search for the various information and these searches can be customized for the specific query.

Seminars, programmes and forums attended by HSA staff

To enhance the regulatory competencies and review expertise in view of the new initiatives, CTB's regulatory evaluators attended the following conferences and training:

1. Thailand Seminar: Understanding the 9 ICH Safety & ICH Efficacy Guidelines
2. Attachment programme to Ministry of Health, Labour and Welfare (MHLW), Japan
3. Signal Detection and Risk Management Strategies
4. Phacilitate Cell and Gene Therapy Forum 2006

Health Science Authority (HSA) – Small Grants

Overview

The objectives of the FY2005 enabling grant were to assist HSA in its effort to develop and promote a vibrant research culture as well as a strong research capability in order to support and attain regulatory and service excellence in the following areas:

- health products regulation (pharmaceutical products, complementary medicines, cosmetic products, irradiating apparatus and materials and medical devices);
- transfusion medicine practices and bloodbanking;
- forensic science and medicine investigations;
- quality and safety analysis of pharmaceuticals.

Activities in FY2005

The EG was mainly used to fund the purchase of test samples, reference materials, laboratory consumables and reagents in support of the research projects while the research manpower, administrative and management costs were borne by HSA.

These research projects could generally be categorized as:

- Development and enhancement of test methodologies – this is to strengthen the quality assessment and regulatory surveillance of health products;
- Enhancement of regulatory systems – this is to improve product safety, encourage rational drug use and healthcare delivery in Singapore;
- Development of forensic examinations of physical evidence, questioned documents, controlled substances (narcotics) and toxicology analysis;
- Development of measures to increase safety of blood transfusion and alternative strategies to the use of homologous blood and use of new biomedical technologies to generate safer and more effective components of blood for human use.

National Dental Centre (NDC)

Overview

The objectives of the National Dental Centre Enabling Grant in FY2005 were:

Clinical Trials Support

To fund the NDC Research Resource Unit which assists clinicians in their research activities.

To fund research manpower such as research administrative staff and research nurse / coordinator.

To fund research advisor which directs the research directions and programme for NDC.

Small Grants

To fund small projects, inclusive of protected time in addition to materials and supplies.

To provide seed funding for pilot projects within the institution.

To fund the thematic research programme "TL Modular Endoprosthetic Replacement of Mandibular Defects" in its pilot phase.

Activities for FY2005

Clinical Trial Support and Small Grants

In FY2005, the Enabling Grant funded 24 small projects, 2 pilot projects and set up 1 thematic research programme "TL Modular Endoprosthetic Replacement of Mandibular Defects".

The Enabling Grant also provided Clinical Trial Support for one investigator-initiated randomized trial at the Centre.

Summary of Research Achievements/Outcomes

NDC's research achievements/outcomes for FY2005 are as follows:

- 1 paper published in peer review journal
- 9 Citations of papers published
- 7 Presentations at International Conferences
- 1 Research with potential/direct application
- 17 inter-institutional collaboration
- 1 Research Infrastructure improved – Research Resource Unit & Research Coordination Section
- 5 MDS and 13 Advanced Specialty Trainees Trained

National Skin Centre (NSC)

Overview

The objectives of the Enabling Grant for FY 2005 were:

1. To support the existing infrastructure for clinical trials, along GCP guidelines
2. To further develop the cell culture laboratory for research into cutaneous biology and physiology in Asians
3. To enhance current capabilities in molecular diagnostics, with mycobacteria PCR tests as our niche area
4. To provide alternative funding source for researchers who are conducting small or pilot studies in areas of clinical importance

Activities in FY2005

Infrastructure / Manpower Support for Clinical Trials

The full-time Clinical Trial Coordinator and Research Executive were crucial in overseeing, co-ordinating and ensuring that research activities in NSC were conducted along GCP guidelines and with adherence to research protocols. The research executive was the chief laison officer with external funding agencies, pharmaceutical companies, HSA and domain-specific review board. The Data Entry Clerk was responsible for updating and managing the disease specific databases.

Cell Culture Laboratory

A pilot project using autologous transplantation of cultured melanocytes in the treatment of vitiligo in 9 patients was completed with encouraging results. Further research work on establishing a melanocyte-keratinocyte co-culture system started in 2004 was continued in 2005, to optimize the ratio of cell seeding and cell characterization by immunostaining. This has further spawned the initiation of a collaborative research pilot project between GIS and NSC in the development of a skin toxicogenomics system utilizong gene expression profiling which will require NSC's expertise in culturing keratinocytes. Another in-vitro skin model using reconstructed epidermis to study melanocyte and keratinocyte interactions is also being developed to enhance understanding of melanin synthesis and transfer in Asians and this model will have potential in the screening of active molecules in the treatment of the pigmentary disorders. The recruitment of a trained research assistant experienced in cell culture techniques was essential to conduct this specialized laboratory work.

Molecular Diagnostics

The PCR laboratory continues to play a vital role in the identification of tuberculous and non-tuberculous mycobacterial infections in Singapore. A project examining the effects of different fixatives and fixation times on DNA amplification from paraffin embedded tissues was completed in 2005. NSC has also embarked on a project utilizing a multiplex PCR protocol for a more rapid identification of mycobacteria. These projects are aimed to enhance the quality of PCR testing, increased laboratory cost efficiency and a faster turnaround time.

Small Grants

Funding for small grants enabled NSC's young doctors and registrars to initiate several new research projects. A clinical, ultrastructural and biochemical study of autosomal recessive congenital ichthyosis was pursued in collaboration with several German institutions in Muenster, Heidelberg and Cologne, and the Tissue Modulation Laboratory, NUS. A collaborative project with the NUH Molecular Diagnostics Centre on acute non-gonoccocal urethritis found that mycoplasma genitalium plays an important role in local patients patients. The project on allergic contact dermatitis found that a sensitization rate of 60% in chronic leg ulcer patients, many of whom were sensitized to traditional Chinese medicaments as well as modern dressings, such as hydrocolloids and intrasite gel. This new knowledge will allow NSC to develop a specific leg ulcer patch test series for NSC.

Summary of Achievements / Research Outcomes

NSC's research outcomes for FY2005 are summarised as follows:

- 5 presentations at local conference
- 1 presentation at overseas conference
- 1 competitive grant awarded from NMRC,BMRC or industry with a quantum of $77,000
- 6 projects with direct or potential clinical applications
- 3 inter-institutional collaborations
- 2 research facility developed/improved.

National University Hospital (NUH)

Overview

The primary objective of the EG was to develop further the current services and facilities of the Clinical Trials Unit (CTU) to facilitate the conduct of early phase trials. This was to be accomplished through: training and development of skills of CTU staff to conduct early phase clinical trials, development of specialized services and improvement on the existing equipment and infrastructure of CTU

Activities in FY2005

Training and development of skills of CTU staff

This was achieved by inviting overseas experts from the United Kingdom to give talks to clinical research co-ordinators and provide consultation on CTU's existing services, facilities and infrastructure. The experts reviewed CTU's work processes and shared on quality assurance measures, competency framework of staff and clinical research facilities in UK. As a result of the visit, CTU is refining some of its departmental SOPs and setting up a competency framework program for clinical research co-ordinators.

CTU provided clinical research expertise, equipment and facilities for the conduct of 2 early phase clinical trials, 1 Phase III trial and 2 Observational studies by NUH / NUS researchers. These studies are all PI-initiated studies.

Development of Specialized Services

The CTU has set up an internal audit program for Principal Investigator-initiated studies and has audited 2 studies so far. Quality assurance policies have been formally implemented.

CTU has also started providing data entry services and trial administrative support for PI-initiated studies. To date, data entry for 3 studies have been completed and trial administrative support is being provided for 1 study.

To provide support for the specialized services, a clinical research co-ordinator was hired. In addition, this extra FTE provided additional support to the CTU to cope with the increase in the number of clinical trials managed by CTU in FY05 (increased by 30%, thereby surpassing the target of 20%).

Improvement of Existing Equipment and Infrastructure

New medical equipment for use in clinical research was purchased to facilitate and enhance the conduct of clinical trials in CTU. Due to an increase in clinical trial activities, additional equipment (eg freezer, ECG machine, Patient Bedside Monitoring System) had to be purchased.

Office equipment and supplies were also purchased for the additional manpower.

A security and surveillance system was installed to enhance the security of the CTU and to limit the movement of trial volunteers within the CTU, thereby allowing clinical trials to be conducted within a controlled environment

Summary of Achievements / Research outcomes

In FY2005, NUH's achievements are as follows:

- Research staff were trained through overseas training/attachment programs. Quality assurance programs and specialized services were developed. Training in early phase clinical trials also took place.
- 2 early phase trials, 1 Phase III trial and 2 observational studies were conducted by NUS/NUH researchers

C H A P T E R 6
Summary of Research Output

Research Output from Block Grants & Competitive Grants

Research output is measured by the following indicators:

- the total number of publications
- publications with impact factor greater than 2
- number of national and international awards
- % of completed projects with clinical significance
- number of research scientists (including clinician-scientists) funded (with effect from 2003)

The table below is a summary of the total research output from Block Grants and Competitive Grants from 2003 to 2005.

From 2003 to 2005

- there was a 83.5% increase in publications for every million dollars expended
- there was a 112.8% increase in publications with impact factor greater than 2, for every million dollars expended.
- all completed projects had clinical significance

Table 7

Research Output from Block/Competitive Grants

Year	2003	2004	2005
Expenditure* ($'m)	49.7	52.9	51.6
Output			
Total no. of Publications	514	645	975
Publications with impact factor >2	177	240	395
No. of national and international awards	24	70	19
% of completed projects with clinical significance	100	100	100
Number of research scientists (including clinician-scientists)	112	136	168
Output per $'m			
Publication per $'m	10.3	12.2	18.9
Publications with impact factor >2 per $'m	3.6	4.5	7.66

- *Includes expenditure on competitive grants, block grants and protected time as these expenses are directly attributable to competitive and block grant activities.*

C H A P T E R 7
NMRC-STB Medical Research Fellowship/Scientist Awards

NMRC Medical Research Fellowship/Scientist Award

Introduction

The NMRC Medical Research Fellowship and Scientist Awards are awarded to aspiring and talented researchers to enable them to receive research training in their areas of interest or to pursue an MSc or PhD in health and medical research in leading local or overseas institutions. The scheme is funded by donations made by the Singapore Totalisator Board (STB), Hong Leong Foundation and Lee Foundation.

All applications for fellowships and scientist awards are assessed and evaluated by the Fellowship subcommittee which will provide awarding recommendations to the Council.

Awards commencing in FY2005

Medical Research Fellowship Award

5 doctors commenced their NMRC Medical Research Fellowship in FY2005; 3 of which were for training leading to a degree whereas the other 2 were for training not leading to a degree.

Training leading to a degree (MSc/PhD)

1. Dr Tan Ern Yu from the Department of General Surgery, TTSH received a full-time fellowship for 24 months. Her project at the John Radcliffe Hospital, University of Oxford, UK was "The role of vasculogenesis in the various stages of breast tumour development". Dr Tan's training would lead to a MSc.

2. Dr Cheng I-Cheng Mark from the Department of Clinical Epidemiology, TTSH received a full-time fellowship for 36 months. His project at the London School of Hygiene and Tropical Medicine, UK was "Modeling the rapid emergence of antimicrobial resistant gonorrhoea in the United Kingdom". Dr Cheng's training would lead to a PhD.

3. Dr Lim Su Chi from the Department of Medicine, AH received a part-time fellowship for 36 months. His project at the National University of Singapore was "Molecular and genetic epidemiology of diabetic nephropathy". Dr Lim's training would lead to a PhD.

Training not leading to a degree

4. Dr Koh Fang Yung Angela from the Department of Medicine, AH received a full-time fellowship for 24 months. Her project at the Joslin Diabetes Center, University of Alberta, USA was "Islet Cell Transplant: An exciting treatment possibility for diabetes mellitus"

5. Dr Ang Pek Kiang Leonard from the Department of Ophthalmology, NUS received a full-time fellowship for 4 months. His project at the Massachusetts Eye and Ear Infirmary, Boston, USA was "The role of angiogenic and anti-angiogenic factors in ocular neovascularization".

Medical Research Scientist Award

8 scientists commenced their NMRC Medical Research Scientist Award in FY2005; 7 of which were for training leading to a degree whereas 1 was for training not leading to a degree.

Training leading to a degree (MSc/PhD)

1. Ms Tan Ai Lin Shawna, formerly from the Department of Obstetrics & Gynaecology, NUS, received a full-time research scientist award for 36 months. Her project at the University of Sydney, Australia was "The role of micro RNAs in normal and neoplastic cellular physiology". Ms Tan's training would lead to a PhD.

2. Mr Chong Yok Rue Desmond received a full-time research scientist award for 36 months. His project at the Imperial College London, UK was "Analysis of fixation and bone remodelling in the proximal tibia after implantation of a knee prosthesis". Mr Chong's training would lead to a PhD.

3. Ms Wong Hwee Bee from the Department of Biostatistics, CTERU received a part-time research scientist award for 36 months. Her project at the National University of Singapore was "Changes in refraction and biometry in emmetropic and myopic children: the SCORM study". Ms Wong's training would lead to a PhD.

4. Mr Loo Liat Hui from KKH received a part-time research scientist award for 36 months. His project at the National Technological University, Singapore was "Isolation and genetic characterization of Metapneumovirus isolated from pederiatric patients in Singapore". Mr Loo's training would lead to a PhD.

5. Mr Wang Ling Zhi from the Department of Haematology-Oncology, NUH received a part-time research scientist award for 20 months. His project at the National University of Singapore was "Gemcitabine Pharmacokinetics-Pharmacodynamics (PK-PD) in solid tumors: A bench to bedside approach". Mr Wang's training would lead to a PhD.

6. Ms Chua Li Ming Constance from the Division of Medical Sciences, NCC received a part-time research scientist award for 36 months. Her project at the National University of Singapore was "Cancer stem cells in the brain: Mechanisms of Chemoresistance". Ms Chua's training would lead to a PhD.

7. Ms Cheng Shi Yuan from the Division of Medical Sciences, NCC received a part-time research scientist award for 36 months. Her project at the National University of Singapore was "BRCT protein Ect2 is a mediator of the DNA damage-induced S phase checkpoint". Ms Cheng's training would lead to a PhD.

Training not leading to a degree

8. Dr Lam Yeng Po Paula from the Department of Cell & Molecular Research, NCC received a full-time research scientist award for 3 months. Her project at the University of Zurich, Switzerland was "Construction of a replicative competent HSV-1 vectors that could deliver gene expression in a cell cycle-dependent manner".

Training Completed in FY2005

11 completed their training under the Medical Research Fellowship/Scientist Award in FY2005:

1. Dr Low Fatt Hoe Adrian from the Department of Medicine, NUS completed 12 months of training at the Massachusetts General Hospital, USA. His project was "The Genetics of Acute Myocardial Infarction".

2. Dr Ong Eng Hock Marcus from the Department of Emergency Medicine, SGH completed 12 months of training at the Medical College of Virginia, USA. His projects were "Comparison of circumferential chest compression and standard cardio-pulmonary resuscitation in out-of-hospital cardiac arrest" and "Controlled therapeutic hypothermia post-cardiac arrest compared to standard intensive care unit therapy".

3. Dr Ang Hui Chi Annette from the Department of Otolaryngology, NUH completed 14 months of part-time training at the National University of Singapore. Her project was "Nasal polyposis: A immunohistochemical study of cell cycle proteins in epithelial proliferation".

4. Dr Chai Yui Huei Josiah from the Department of Neurology, NNI completed 8 months of training at the University of Rochester, USA. His project was "Vascular adaptation in Fascioscapulohumeral Muscular Dystrophy – An Immunohistochemical Study".

5. Dr Wong Chek Hooi from the Department of Geriatric Unit, SGH completed 8 months of training at the McGill University, Canada. His project was "The determinants and components of frailty and clinical intervention for the prevention of frailty in older persons".

6. Dr Tay Shian Chao from the Department of Hand Surgery, SGH completed 12 months of training at the Mayo Clinic College of Medicine, USA. His project was "Three dimensional dynamic in-vivo motion studies of the wrist using a ultrafast 64-slice computed tomographic scanner".

7. Dr Lee Tswen Wen Victor from the Department of General Surgery, SGH completed 12 months of training at the National Cancer Centre, Singapore. His project was "Elucidation of expression profiles of genes in alpha-fetoprotein positive and alpha-fetoprotein negative hepatocellular carcinoma by cDNA microarray analysis".

8. Dr Au Wing Lok from the Department of Neurology, NNI completed 7 months of training at the Pacific Parkinson's Research Centre, Vancouver, Canada. His project was "Surrogate markers of the cortical dopaminergic system in patients with Parkinson's disease".

9. Dr Lam Yeng Po Paula from the Department of Cell & Molecular Research, NCC completed 3 months of training at the University of Zurich, Switzerland.

Her project was “Construction of a replicative competent HSV-1 vectors that could deliver gene expression in a cell cycle-dependent manner”.

10. Dr Chin Tan Min from the Department of Haematology-Oncology, NUH completed 6 months of training at the Oncology Research Institute, Singapore. Her project was “Mutations of the EGFR gene in tumours and their therapeutic significance – a pharmacogenetics study”.

11. Dr Ang Pek Kiang Leonard from the Department of Ophthalmology, NUS completed 4 months 25 days of training at the Massachusetts Eye and Ear Infirmary, Boston, USA. His projects were “Dohlman-Doane keratoprosthesis surgery for the treatment of severe cornea and ocular surface disease”, “New refractive surgical procedures for the correction of refractive error” and “The role of angiogenic and anti-angiogenic factors in ocular neovascularization”.

The abstracts of their reports are at Annex 2.

CHAPTER 8
Financial Report

Introduction

Since FY2002, NMRC fund was subsumed under MOH's Other Operating Expenses (OOE) Budget.

Under the OOE Budget funding structure, budget allocated to the NMRC is approved on an annual basis, has to be expended within the financial year; and no roll-over of un-utilised budget is allowed.

The FY2005 OOE Budget allocated to NMRC was used to fund both on-going projects and programmes committed in previous years, as well as new initiatives in FY2005.

On top of funding from the OOE budget, NMRC also obtains fund from Singapore Totalisator Board (STB) of an amount up to $2.5 million for research projects and programmes.

Budget for FY2005

A total of $51.6 million was allocated for research expenditure in FY2005. Table 8 shows the movement of budget allocated for research expenditure.

Table 8
Allocated Budget, FY2005

	Amount ($)
MOH's OOE budget	49,072,000
STB's donations for research projects and programmes	2,500,000
Total budget	**51,572,000**

Commitments in FY2005

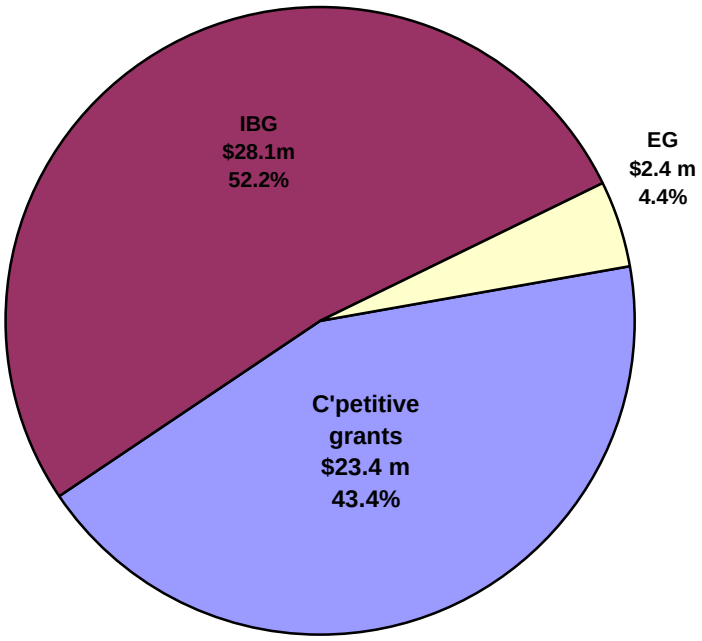
A total of $53.8 million was committed in FY2005 with the breakdown as shown in Table 9.

Table 9
Commitments in FY2005

	Amount ($)	% of total
Competitive Grants		
Individual Research Grants (IRG)	18,913,889.16	35.14%
Supplementary Grants	683,466.63	1.26%
Competitive Programme Grants (CPG)	2,876,212.60	5.34%
Clinician Scientist Investigator Award (CSI) - Projects	450,000.00*	0.84%
Clinician Scientist Investigator Award (CSI) - Salary	450,000.00*	0.84%
Sub-Total	**23,373,568.39**	**43.42%**
Block Grants		
Institutional Block Grants (IBG)	28,084,400.09	52.18%
Enabling Grants (EG)	2,368,692.00	4.40%
Sub-Total	**30,453,092.09**	**56.58%**
Total Commitments for FY2005	**53,826,660.48**	**100.00%**

*CSI commitment is an estimated proportional amount for FY2005

Fig 1: FY2005 Fund Distribution by Commitments



Competitive Grants

Competitive grants are awarded to researchers over a period of up to 3 years. Of the competitive grants awarded, $21.8 million was committed to 119 projects, comprising 103 Individual Research Grants (IRG) and 16 Competitive Programme Grants (CPG).

Out of the 103 IRG approved in FY2005, 54 are applications received in Nov04 IRG funding exercise and 49 in May05 exercise.

In addition to amounts committed to IRG and CPG, $0.68m was also committed to 44 existing projects as supplementary grants to partially restore the budget reduction suffered by these projects at point of approval.

Clinician Scientist Investigator Award (CSI) is a new initiative jointly implemented by NMRC and BMRC, NMRC has committed to 5 junior CSI projects of amount $1m.

The approved IRG, CPG and CSI projects in FY2005 are listed in Annex 3.

The distribution of the competitive grants awarded by institutions and area of research are depicted in Tables 10 and Table 11 respectively.

Table 10

Commitments for Competitive Grants (Projects) by Institutions, FY2005

	IRG		Supplementary		CPG		CSI		Total	
Institution	No. of Projects	Amount ($)	No. of Projects	Amount ($)	No. of Projects	Amount ($)	No. of Projects	Amount ($)	No. of Projects	Amount ($)
NUS	41	8,889,536.97	23	354,500.00	6	1,130,210.00	2	397,635.00	72	10,771,881.97
NCC	14	2,849,699.00	5	79,940.00	0	0	0	0	19	2,929,639.00
SGH	13	2,403,240.00	3	47,928.00	1	50,000.00	0	0	17	2,501,168.00
NNI	9	1,709,580.09	3	47,984.15	2	147,661.60	0	0	14	1,905,225.84
NTU	1	400,700.00	0	0	2	647,024.00	0	0	3	1,047,724.00
NUH	9	452,023.60	3	47,907.68	2	528,860.00	0	0	14	1,028,791.28
SERI	3	784,453.00	1	15,976.80	0	0	0	0	4	800,429.80
TTSH	4	390,740.00	2	28,000.00	2	234,817.00	0	0	8	653,557.00
SNEC	1	280,475.00	0	0	0	0	1	200,000.00	2	480,475.00
SHS	0	0	1	16,000.00	0	0	2	399,522.00	3	415,522.00
IMH	2	367,877.00	0	0	0	0	0	0	2	367,877.00
KKH	2	192,550.00	2	29,230.00	1	137,640.00	0	0	5	359,420.00
CTERU	1	79,310.00	0	0	0	0	0	0	1	79,310.00
NSC	1	77,000.00	0	0	0	0	0	0	1	77,000.00
CGH	2	36,704.50	0	0	0	0	0	0	2	36,704.50
AH	0	0	1	16,000.00	0	0	0	0	1	16,000.00
Total	**103**	**18,913,889.16**	**44**	**683,466.63**	**16**	**2,876,212.60**	**5**	**997,157.00**	**168**	**23,470,725.39**

Table 11

Commitments for IRG, CSI and CPG by area of research, FY2005

Area	IRG		CSI		CPG	
	No. of Projects	Amount($)	No. of Projects	Amount($)	No. of Projects	Amount($)
Cancer	20	3,558,295.60			3	749,110.00
Neuroscience	9	2,294,656.00	1	200,000.00	2	378,501.60
Eye	6	1,578,128.00	1	200,000.00		
Paediatrics	7	1,346,105.00	2	397,635.00	1	228,270.00
Molecular Biology	7	1,315,390.00			1	307,524.00
Physiology	4	1,278,200.00				
Epidemiology	5	1,202,373.37				
Pharmacology	5	1,012,253.00			2	100,000.00
Microbiology	3	644,305.00				
Immunology	2	572,500.00			1	50,000.00
Genetics	3	559,117.09			1	238,410.00
Biochemistry	3	529,426.00			2	533,557.00
Orthopaedic Surgery	3	479,384.00				
Obstetrics & Gynaecology	2	386,490.00			1	137,640.00
Psychiatry	2	367,877.00				
Respiratory Diseases	2	342,910.00				
Colorectal Surgery	1	273,500.00				
General Surgery	3	241,769.60				
Anaesthesia	2	225,519.00				
Cardiovascular Diseases	2	197,358.00				
Haematology	1	173,270.00			1	50,000.00
Infectious Diseases	3	150,543.00				
Others	3	85,149.50				
Otolaryngology	2	54,200.00				
Plastic Surgery	1	25,695.00				
Neonatology	1	13,475.00				
Dermatology	1	6,000.00				
Endocrinology			1	199,522.00		
Pathology					1	103,200.00
Total	**103**	**18,913,889.16**	**5**	**997,157.00**	**16**	**2,876,212.60**

Block Grants

The commitment for Institutional Block Grants (IBG) and Enabling Grants (EG) was given on an annual basis, and any unutilised commitments will lapse at the end of the financial year. In FY2005, a total of $28.1 million was committed for IBG and $2.4 million was committed for EG, distributed as shown in Table 12.

Table 12

Commitment for IBG and EG by Research Centre block vote, FY2005

	Amount ($)
Research Centre Block Vote	**30,453,092.09**
IBG	***28,084,400.09***
National Cancer Centre (NCC)	7,715,470.00
National University Medical Institute (NUMI)	3,360,000.00
National Neuroscience Institute (NNI)	3,941,280.50
Singapore Eye Research Institute (SERI)	3,778,380.00
Clinical Trials and Epidemiology Research Unit (CTERU)	2,619,765.69
Department of Clinical Research (SGH)	1,921,000.00
Singapore Cardiac Data Bank (SCDB)	1,099,424.00
National Heart Centre (NHC)	1,032,816.00
National University of Singapore (NUS)	800,000.00
Department of Experimental Surgery (SGH)	521,419.24
Tan Tock Seng Clinical Research Unit (CRU)	284,600.00
Institute of Mental Health (IMH)	415,420.60
NNI-TTSH Animal facilities (ARL)	265,000.00
National Birth Defect Registry (NBDR)	223,824.06
Nursing Research Committee	106,000.00
Enabling Grants	***2,368,692.00***
Alexandra Hospital (AH)	609,962.00
Changi General Hospital (CGH)	587,427.00
Health Science Authority (HSA)	140,883.00
KK Women's & Children's Hospital (KKH)	350,000.00
National Dental Centre (NDC)	325,200.00
National Skin Centre (NSC)	222,220.00
National University Hospital (NUH)	133,000.00

Research Expenditure for FY2005

Out of the $51.6 million allocated for research expenditure, a total of $51.6 million was utilized, representing a fund utilization rate of 100%. Of this, $22.1 million was for competitive grants, $26.3 million was for IBG, $2.3 million for EG, $0.6 million for CSI and the remaining $0.3 million for other expenses.

Table 13 shows the distribution of research expenditure and Table 14, the expenditure for IBG and EG in FY2005.

Fig 2: FY2005 Fund Distribution by Expenditure

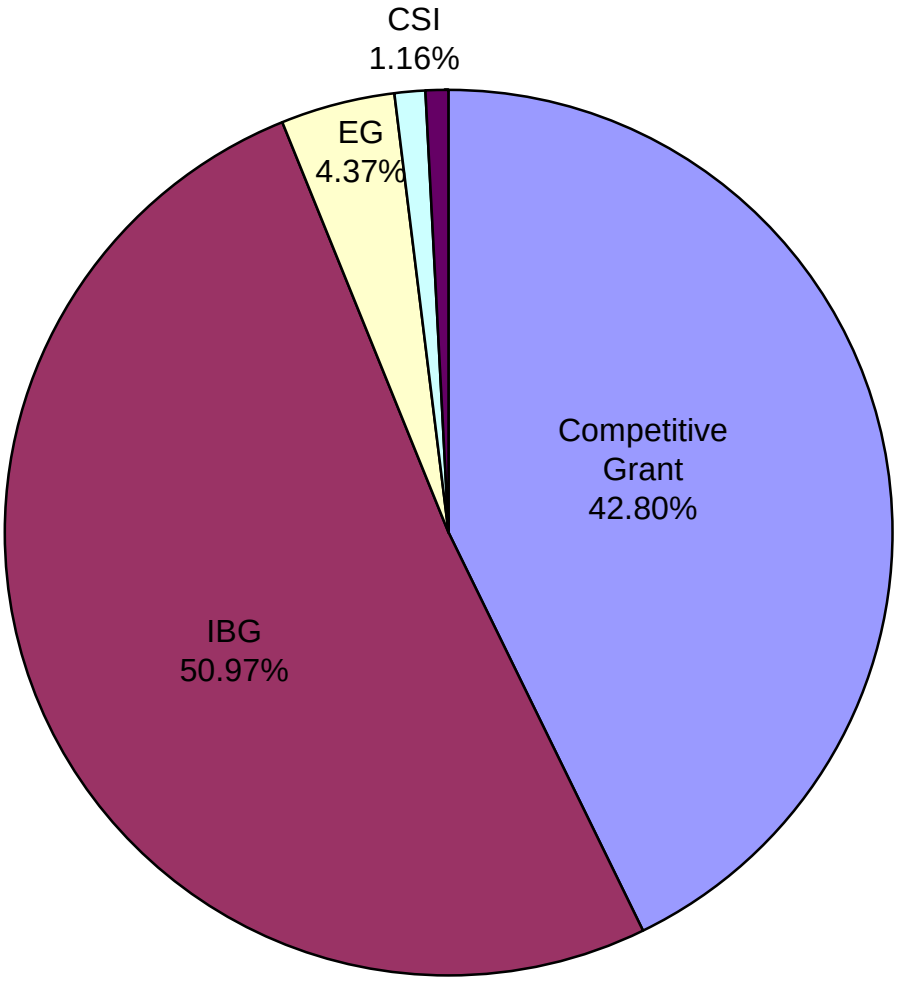


Table 13
Research Expenditure, FY2005

Type of Grant	Amount of Expenditure ($)	% of Total Expenditure
Competitive Grants	***22,071,236.62***	***42.80%***
Research Projects / Programmes (IRG)	**18,454,105.00**	
Supplementary Grant	**648,351.62**	
Competitive Programme Grant (CPG)	**2,777,751.98**	
SARS Grant	**191,028.02**	
CSI Award	***598,032.84***	***1.16%***
CSI Research Projects	154,576.62	
CSI Protected Time	443,456.22	
IBG	***26,285,031.73***	***50.97%***
National Cancer Centre (NCC)	7,715,392.98	
National Neuroscience Institute (NNI)	3,782,766.41	
Singapore Eye Research Institute (SERI)	3,778,031.42	
National University Medical Institute (NUMI)	2,898,969.28	
Clinical Trials and Epidemiology Research Unit (CTERU)	2,129,320.48	
Department of Clinical Research (SGH)	1,902,147.35	
National Heart Centre (NHC)	951,677.66	
Singapore Cardiac Data Bank (SCDB)	873,163.95	
National University of Singapore (NUS)	571,449.15	
Department of Experimental Surgery (SGH)	521,008.24	
Institute of Mental Health (IMH)	405,988.64	
Tan Tock Seng Clinical Research Unit (CRU)	274,875.40	
National Birth Defect Registry (NBDR)	218,329.77	
NNI-TTSH Animal facilities (ARL)	162,308.46	
Nursing Research Committee	99,602.54	
Enabling Grants	***2,255,268.88***	***4.37%***
Alexandra Hospital (AH)	587,078.18	
Changi General Hospital (CGH)	575,387.68	
KK Women's & Children's Hospital (KKH)	343,738.86	
National Dental Centre (NDC)	309,702.47	
National Skin Centre (NSC)	170,993.52	
Health Science Authority (HSA)	136,548.39	
National University Hospital (NUH)	131,819.78	
Others	***361,570.16***	***0.70%***
Reviewers' Honorarium	77,576.84	
Patenting Cost	241,699.41	
Scientific Meetings	42,293.91	
TOTAL	**51,571,140.23**	**100.00%**

Table 14

Expenditure for IBG and EG, FY2005

Institution Block Vote	Manpower ($)	Equipment ($)	Other Expenses ($)	Small Grant ($)	Total
IBG					
NCC	5,254,733.00	326,294.30	2,134,365.68	-	7,715,392.98
NNI	2,330,017.96	314,458.13	1,138,290.32	-	3,782,766.41
SERI	2,195,420.00	447,121.50	1,077,828.92	57,661.00	3,778,031.42
NUMI	2,049,251.56	352,027.41	497,690.31	-	2,898,969.28
CTERU	1,645,450.49	10,868.00	473,001.99	-	2,129,320.48
DCR	1,139,457.72	209,063.93	257,761.81	295,863.89	1,902,147.35
NHC	501,130.11	351,609.60	98,937.95	-	951,677.66
SCDB	774,618.36	-	98,545.59	-	873,163.95
NUS	-	-	-	571,449.15	571,449.15
DES	340,000.00	134,589.00	46,419.24	-	521,008.24
IMH	209,297.03	49,933.50	124,262.37	22,495.74	405,988.64
TTSH	227,616.40	8,972.00	38,287.00	-	274,875.40
NBDR	180,834.96	-	37,494.81	-	218,329.77
NNI-TTSH ARL	94,259.79	2,849.50	65,199.17	-	162,308.46
NRC	-	60,564.78	-	39,037.76	99,602.54
Total	***16,942,087.38***	***2,268,351.65***	***6,088,085.16***	***986,507.54***	***26,285,031.73***
EG					
AH	70,999.28	340,553.28	25,781.52	149,744.10	587,078.18
CGH	63,481.00	219,326.90	195,701.07	96,878.71	575,387.68
KKH	129,853.72	15,949.50	10,000.00	187,935.64	343,738.86
NDC	98,671.10	-	52,110.88	158,920.49	309,702.47
NSC	91,884.66	-	10,763.22	68,345.64	170,993.52
NUH	15,449.38	108,150.80	8,219.60	-	131,819.78
HSACT	-	-	75,665.39	-	75,665.39
HSA	-	-	-	60,883.00	60,883.00
Total	***470,339.14***	***683,980.48***	***378,241.68***	***722,707.58***	***2,255,268.88***
Grand Total	**17,412,426.52**	**2,952,332.13**	**6,466,326.84**	**1,709,215.12**	**28,540,300.61**

Table 15 shows the list of major equipment with funding of more than $100,000 in FY2005.

Table 15
List of major equipment funded, FY2005

Description	Institution	Cost ($)	Amount Funded ($)
FACSAria Sorter	NHC	347,550.00	347,550.00
Applied Biosystems 3130xl Genetic Analyzer	AH	256,500.00	256,500.00
1 x Upgrade Olympus FV500 to a filtered-based FV1000	NUMI	231,000.00	231,000.00
OmniSwitch 7800 for NCCResearch (Level 5 & 6)	NCC	121,724.40	121,724.40
Renovations to Animal Holding Unit	NCC	115,500.00	115,500.00
Health Management System	CGH	109,725.00	109,725.00
Purchase of data mining software	CGH	100,000.00	100,000.00
Total		**1,281,999.40**	**1,281,999.40**

Medical Research Fellowship/Scientist Award

Table 16 shows the commitment and expenditure for Medical Research Fellowship and Scientist Award in FY2005. The expenditure includes those on commitments made before FY2005.

Table 16
Commitment and expenditure for medical research fellowship/scientist award, FY2005

	Commitment ($)	Expenditure ($)
Medical Research Fellowship & Scientist Award	1,603,334.10	1,627,766.66
Medical Research Travelling Fellowship	-	23,032.95
Total	**1,603,334.10**	**1,650,799.61**

A N N E X E S

Annex 1: Abstracts of IRG & IBG Research Projects Completed in FY2005

F2/S037/NHC/005/2000 **PI:** Chong Beng H (NHC) **Collaborator:** Lim Yean Leng		**Development of anti-GPIb-IX antibody fragments for the treatment of coronary heart disease** This project was based on a mouse monoclonal antibody, AK2 which binds strongly to human platelet receptor, GPIbα, at the N-terminus between residues Leu36 and Gln59. AK2 inhibits both botrocetin and ristocetin-dependent and also shear-dependent interactions between von Willebrand Factor (vWF) and GPIbα. Therefore, AK2 is potentially a very useful drug for treatment of heart disease as it can effectively block GPIb/vWF-mediated platelet thrombus formation in the coronary arteries in patients with acute coronary syndrome and patients undergoing coronary angioplasty. However, an intact mouse antibody is not suitable for human therapy because it may induce an immune response in human subjects and its Fc domain may cause complement-mediated adverse effects. Thus, antibody fragments without the Fc domain (Fab and single chain Fv, scFv), are generated and "humanized"using loop grafting technique to reduce 'human anti-mouse antibody" or HAMA response. The researchers have successfully produced several anti-GPIb fragments, namely three human-mouse chimeric Fabs and three humanized scFvs. All these anibody fragments display strong inhibition of vWF-GPIbα interaction, including ristocetin-induced platelet agglutination. The work is now ready to proceed into the next stage of pre-clinical studies (e.g. studies with animal models of arterial thrombosis) prior to human clinical trials.
NMRC/0326/1999 **PI:** Vernon Oh (NUS)		**Establishment of families of Singaporean Chinese subjects to identify candidate genes in essential hypertension by genomic search (renewal)** The project rigorously characterized over 640 hypertensive families comprising individuals, sibling-pairs, and parents-offspring trios, and similar numbers of normotensive controls, from the adult non-obese, non-diabetic, Chinese community in Singapore. The second important objective was to establish two resources, one of biographic information and DNA from the hypertensive patients and the other from the healthy control subjects. Thirdly, the researchers compared genotypes of limited numbers of gene markers between the two populations. By July 2005 they processed a total of 644 hypertensive individuals, and 451 normotensive control subjects, making an aggregate population of 1095 individuals. They worked with Dr Eric Yap, a senior molecular geneticist, to study appropriate candidate genes. In 2004-05 they published 4 conference papers from the project. To date, the researchers have published 16 conference abstracts reporting the project's results in scientific meetings. In 2004, haplotype analysis of single nucleotide polymorphism markers for the β 2-adrenergic receptor gene showed significant associations of specific haplotypes with hypertensive patients and normotensive control subjects. An international journal, Journal of Hypertension, published their paper in November 2004 on the results for the β2-adrenoceptor gene genotypes and haplotypes in their Singapore Chinese cohort. Other papers will flow from the clinical and DNA databases produced by the project. The researchers can now compare non-obese hypertension genotypes with those from metabolic syndrome patients.

NMRC/0426/2000 **PI:** Chua Kim Lee (NUS)		**Membrane proteins and drug resistance in burkholderia psuedomallei** Multidrug efflux pumps of the resistance-nodulation-division (RND) family are important determinants of antimicrobial resistance in many gram-negative bacterial pathogens. This project identified two RND pumps in Burkholderia pseudomallei, the causative agent of melioidosis. BpeAB-OprB is responsible for conferring antimicrobial resistance to aminoglycosides and macrolides. Expression of bpeAB-oprB is inducible by the substrates it recognizes, upon entry into stationary phase, and by certain cellular metabolites. Expression of bpeAB-oprB is regulated locally by BpeR, a member of the TetR family of repressors, whilst the expression of bpeR was similarly induced at stationary phase. The second pump, BpeEF-OprC conferred resistance to chloramphenicol, a clinically relevant antibiotic. Overexpression of bpeEF-oprC resulted in 64-fold increase in chloramphenicol resistance whilst significantly decreased resistance to streptomycin, erythromycin, ceftazidime and ofloxacin. A clinical isolate which overexpresses the BpeEF-OprC pump also showed significant increase in resistance to chloramphenicol. The bpeAB null mutant and the bpeR-overexpressing strain were defective in extracellular production of acyl-homoserine lactones, the B.pseudomallei quorum sensing autoinducers. BpeAB-OprB function is likewise necessary for optimal production of quorum sensing-controlled virulence factors such as siderophore and phospholipase C, and for biofilm formation. Cell invasion and cytotoxicity towards human lung epithelial (A549) and human macrophage (THP-1) cells were also significantly attenuated in both the bpeAB mutant and bpeR-overexpressing strains, thus demonstrating that the possibility of attenuating B. pseudomallei virulence, as well as enhancing its susceptibility to commonly used antibiotics, using inhibitors of the BpeAB-OprB efflux pump.
NMRC/0431/2000 **PI:** Kanaga Sabapathy (NCC)		**Clinical implications of p53 : effect on prognosis, tumour progression and chemotherapy response** p53 is probably the most important tumour suppressor gene product in humans that regulates cell growth and hence, is mutated in about 50% of all human cancers. This proposal, written about 5 years ago, aimed at performing a systematic analysis to evaluate if p53 (or its functions) can serve as a reliable molecular indicator for cancer predisposition and response to anti-cancers drugs. Firstly, the role of a polymorphism at codon 72 of p53, which results in either the arginine (72R) or proline (72P) form of p53, was evaluated. The researchers studies indicated that the expression of these p53 polymorphs is selectively regulated in Asians compared to Caucasians. These data suggest that the expression status of p53 polymorphs can be utilized to predict cancer predisposition. Secondly, they have also evaluated the effect of six p53 hot-spot mutations, in conjunction with the codon 72 polymorphism, for their response to a variety of anti-cancer drugs, either alone or in combination. The researchers data revealed the existence of mutation-specific effects on responsiveness to various drugs, which indicate that molecular determination of p53 status in cancer patients would improve cancer therapeutic outcome. Finally, their data also demonstrate that the two different p53 polymorphs have differential ability to repair damaged DNA. Together, the data suggests that the status of codon 72 polymorphism and p53 mutations can be used as a means to predict susceptibility to cancer, as well as response to anti-cancer chemotherapy. This study has thus achieved its initial objectives and would provide a basis for future retrospective and prospective studies aiming at cancer predisposition prediction, and evaluation of the most appropriate and effective therapeutic measures for each individual cancer patient, based on p53 status.

NMRC/0437/2000 **PI:** Vincent Yeow (SGH) **Collaborators:** Khoo Kian Ming Andrew, Phan Toan Thang, See Patrick, Zhang Ji Tuan, Ong Yee Siang		**In vivo fabrication of tissue engineered bone using polymer scaffolds and vascular endothelial growth factor** The study aimed to produce clinically useful bone using tissue engineering with a nanostructure biomaterial, Biosilicon three-dimensional (3D) scaffold, for application in surgical reconstruction. The researchers cultured and created human osteoblast cell line for the aim of in vivo fabrication of tissue engineering bone using Biosilicon 3-D scaffold. Consequently they seeded and cultured human osteoblast cells onto Biosilicon disc for 4 weeks in vitro and conducted non-invasive evaluation of cell growth using the BD oxygen biosensor system and analysis of DNA content using the Picogreen Assay Kit. They also observed cell attachment and viability using SEM and confocal laser scanning microscope. Cell viability and adherence assays using BD Oxygen Biosensor System, Confocal Laser Microscope and SEM demonstrated that these cells were perfectly viable and adherence onto biosilicon disc throughout 4 weeks. The growth of osteoblasts was similar with that of chondrocytes. It is believed that Bisilicon should be considered as new nanostructure biomaterials for bone and cartilage tissue engineering application in the near future.
NMRC/0453/2000 **PI:** Loke Kah Yin (NUS) **Collaborators:** Goh Cho Hong James, Saw Seang Mei, Lee Yung Seng		**Characterising normative values for areal and volumetric bone mineral density and body composition in Singapore children and adolescents: towards an accurate assessment of therapeutic intervention in chronic paediatric disease and childhood obesity** The researchers recruited 496 subjects, of which 174 were Chinese boys and 181 were Chinese girls. They achieved their aim of collecting data from at least 150 Chinese boys and 150 Chinese girls to establish race-specific reference values for Chinese children. However, they only recruited 81 Malays and 60 Indians (target was 300 children from each race). Subject recruitment was initially slow but steady, and participation rate increased during school holidays. The researchers had not been successful in recruiting subjects from the schools they initially identified. However, they were fortunate that many subjects have responded to their appeal for volunteers via e-mails and notices circulated within the hospital and the University. The data will be analysed to produce normative reference range, which will be representative of their local paediatric population. The reference chart will help doctors to manage children with bone disorders as well as various chronic diseases which affect bone growth and mineral accretion. They will also study the association and correlation with various parameters/factors and publish their findings in a peer reviewed journal. Unfortunately the lack of adequate number of subjects from the minority race will not allow them to produce race-specific reference ranges. The preliminary data was analysed and presented in the 23rd International Congress of Pediatrics in 2001. The researchers employed one part-time research nurse, whose salary is partly funded by this grant.

NMRC/0477/2000 **PI:** Chee Michael (SGH) **Collaborators:** Caplan David, Sriram N, Hennig Jeurgen		**Foundation grant for the establishment of human cognition laboratory** The researchers work on language processing provides empirical evidence to show the co-location of different languages in the brain. It demonstrated the effect proficiency has on modifying how brain is recruited suggesting the beneficial effects of constant training in the wiring of the brain. They demonstrated one neural basis for why some people are better at acquiring new languages compared to others. The work on aging shows that elderly persons process visual scenes differently from young persons and that experience modulates how reduced processing resources are allocated in the elderly. Behavioral training may thus achieve desirable benefits in improving visual analysis skills amongst the aged.
NMRC/0479/2000 **PI:** Tan Wee Kiat (NDC) **Collaborators:** Tahir Md. Azharashi. Md., Chan Yiong Huak, Tan Hee Hon, Lim Beng Choo		**A randomised controlled trial to evaluate the safety of MTA VS formocresol as a pulpotomy agent in primary teeth** The study is a randomized controlled clinical trial to compare the safety and preliminary efficacy of a root canal medicament, Mineral Trioxide Aggregate (MTA) as a pulpotomy agent in primary teeth with Formocresol as a control. Safety was defined as absence of acute or chronic inflammation detected clinically and radiologically, and where possible, through histological evaluation of the pulp to these agents. Preliminary efficacy was assessed by presence of dentine bridge formation, radiologically and histologically. A two arm study comprising 56 patients was conducted. Inclusion criteria are children between ages of 3 and 9 years with mechanical or carious pulp exposures, deemed to have occurred when there is a bleeding point from the pulp and can be penetrated with a probe. There should be no history of spontaneous pain nor pathological signs detected clinically or radiographically. Teeth pulpotomised with formocresol were done in 1 visit and restored with amalgam. In the MTA group, the cement was applied over the pulpotomised site, covered with a moist cotton pellet and dressed with IRM for 2 weeks, after which the cotton pellet was removed before final restoration with amalgam. Review visits were at 1mth, 2mth, 4mth 6mth and 1year. Radiographs were taken at every visit except the 4th month.
NMRC/0507/2001 **PI:** Cheah Peh Yean (SGH) **Collaborators:** Eu Kong Weng, Seow Francis Choen		**The use of p27 and other molecular markers in predicting survival in colorectal cancer** The objective of this project is to find a panel of bio-markers that can predict colorectal cancer (CRC) risk and survival in sporadic CRC patients through protein immunohistochemistry in association with patients' clinicopathological features and survival. The researchers showed that the combined expressions of p27 and nuclear β -catenin (but not c-myc and cyclin D1) were significantly correlated with disease specific survival by both univariate and multivariate analysis, suggesting that p27 and β -catenin are potential prognostic markers for management and therapeutic intervention. These two bio-markers are currently being validated with larger sample sets in a different center. In addition, genotyping of single nucleotide polymorphism (SNP) of potential bio-markers using a case-control design was performed. They showed that the GG genotype of cyclin D1 G870A SNP was associated with increased risk and advanced CRC in Singapore sporadic cancer patients. Moreover, young (aged 50 or less) male GG patients had significantly worse disease-specific survival than young male AA/AG patients indicating an interaction between genotype and gender. Further, the identification of young CRC patients without dominant family history enabled them to embark on genome-wide expression profiling to identify a panel of bio-markers for early onset CRC

NMRC/0508/2001 **PI:** Nather Aziz (NUS) **Collaborators:** Ho Kee Hai, Wang Li Hui		**Using tissue engineering to produce biologically active bone allografts for orthopaedic surgery and oral and maxillo-facial surgery** **Objectives** : To evaluate the effect of the PRP on the biological healing of large weight bearing cortical bone allograft in adult rabbits **Methodology:** 36 Adult New Zealand White Rabbits were used for the study. A 1.2cm of cortical bone segment was excised from the rabbit's right tibia. The defect was replaced by an autograft, allograft or allograft impregnated with PRP. Internal fixation was performed using a 9-hole Mini Plate, re-enforced with cerclage wires over the segment. Observation periods for each model were 12, 16, and 24 weeks. Specimens procured were tested for union and undecalcified sectioning of 5-10µ was done. Staining of the sections was done using Von Kossa and Toluidine Blue. **Results:** Union at host graft junctions with autograft was observed at 12 weeks. Allograft union occurred at 16 weeks onwards. When PRP is added to allograft, union occurred at both junctions at 12 weeks. Addition of PRP to allograft showed high resorption activity in the cortex of allograft, as compared to autograft or allograft alone.
NMRC/0513/2001 **PI:** Yeoh Kian Hian (NUS) **Collaborator:** Wang De Yun		**Clinical manifestations of food allergy - a double blind, placebo controlled food challenge study** This study aimed to investigate the clinical manifestations of food allergy using a double-blind, placebo-controlled food challenge (DBPCFC).Twenty patients, 6 males and 14 females and aged from 25 to 61 years (mean age of 46 years), with food allergy completed this study. Their diagnosis of food allergy was based on the coordination between a typical medical history and a positive intra-dermal progressive dilution food test (IPDFT). All patients were interviewed by a dietitian, and were then subjected to open food challenges to confirm their allergic response to the allergic food. DBPCFC was conducted on two days, separated by an interval of 5-7 days. Two natural meals (breakfast and lunch) were served each day, containing either allergic food or placebo in a double-blind, randomized manner. The results showed that 13 patients (75%) developed typical symptoms after challenge with allergic food, while 7 patients (35%) had symptoms with placebo. In addition, the 13 patients had statistically significant higher symptom score than the 7 placebo-responding patients. The symptoms involved multiple organs, such as nasal symptoms (n=12), throat (phlegm or irritation) (n=8), headache (n=7), lungs (n=3), eye (n=5), abdominal bloating (n=1) and urticaria (n=1). The IPDFT was positive to all the 20 foods challenged positive. The sIGE was positive to just one food, while the SPT was positive to two foods. The sensitivity (95% CI) of the three diagnostic tests was 86 -100% for IPDFT, 1.5 - 36% for SPT, and 0.1 - 25% for serum sIgE determination. In conclusion this is the first study to utilize DBPCFC with natural foods to confirm the existence of food allergy in IPDFT positive patients. Most patients showed simultaneous, multiple organ involvement of the nose, nervous system, throat, and lung. The mechanisms underlying the observed symptoms need to be further studied, since no significant differences in serum inflammatory markers were identified.
NMRC/0516/2001 **PI:** Chong Fook Hin Vincent (SGH) **Collaborators:** Chan Tony, Wee Joseph Tien Seng,		**Nasopharyngeal carcinoma : 3D imaging for staging and treatment planning** **Methodology:** A tumour-volume measurement software was developed for the purpose of this project. It was validated on a phantom model prior to clinical studies. Sixty-nine patients with histology-proven nasopharyngeal carcinoma (NPC) were recruited and the tumour volumes were measured using a semi-automated threshold and connectedness-based seed-growing (SG) algorithm and a

Rajapakse Jagath Chandana, Wong Toh Jui, Rumpel Helmut, Lin Feng, Chua Eu Jin		knowledge-based fuzzy clustering (KBFC) algorithm. The volumes of another 18 patients with histology-proven tongue carcinomas were assessed using manual tracing, SG algorithm and semi-automated region deformation (snake) algorithm. The data were recorded for analysis of inter-operator variance and inter-observer reliability at volume and pixel levels. **Results:** There was no significant inter-operator variance using the semi-automated method. Hence, the semi-automated computer method could be used for measuring tumor-volume and the assessment of treatment response. **Accomplishment:** MRI-based tumour volume measurement techniques are currently developed to monitor response to treatment. The results have been reported in brain tumours and gynaecological malignancies. The researchers were the first to validate computer-based measurement techniques for head and neck tumours.
NMRC/0517/2001 **PI:** Lim Swee Han (SGH) **Collaborators:** Lim Yean Leng, Chua Siang Jin Terrance, Seldrup Jorgen, Sundram Felix, Anantharaman Venkataraman		**Short stay chest pain evaluation and treament unit (CPETU) project - acronym ACTION (Acute chest pain treament and evaluation study)** **Aim :** To compare the incidence of adverse cardiac event (CE) among patients discharged after evaluation through short stay chest pain evaluation protocol with mandatory stress nuclear scan or conventional protocol. **Method :** Design Randomised controlled trial. Participants Patients presenting to Emergency Department (ED) with chest pain or symptoms suggestive of angina with a 12 lead ECG non-diagnostic for myocardial ischaemia or infarction (AMI). Invervention ECG and blood test for CKMB and Troponin T were done at 0, 3, 6 hours. Patients in the study group who had a negative 6 hour evaluation underwent tetrofosmin scan within 24 hours, and positive result were admitted. In the control group, patients with high or moderate risk for CAD were admitted. End points CE - cardiac death, ventricular fibrillation, AMI, cardiogenic shock or coronary revascularisation (CR) in 1 year. **Results :** 1,005 patients were randomised to mandatory nuclear scan and 504 patients to the control group. There was no significant difference in the rate of CE or CR between the study group and the control group. There was a higher admission rate in the control group vs study group. **Conclusion:** Diagnostic strategies incorporating acute stress nuclear scan was safe and reduction of hospital admission for ED patients with chest pain.
NMRC/0530/2001 **PI:** Ooi Choon Jin (SGH)		**Regulation of mucosal permeability and tight junction proteins in intestinal epithelial cells in inflammation** Disordered intestinal permeability may play a role in inflammatory bowel diseases. Whether barrier dysfunction contributes to primary initiation of inflammation, or occurs secondarily following inflammation, it is likely that loss of intestinal barrier function may allow for the propagation and amplification of the cascade of the inflammatory process. The researchers study aims include identifying integral cytokines, either acting singly or in concert, responsible for the changes in intestinal permeability. The methodology to study trans-epithelial resistance (TER) in vitro employs a technique of growing T84 cells in a monolayer on a Transwell insert. This further allows for polarisation in that stimulation from different cytokines can be employed either from the apical or basolateral aspects. This is important to ascertain changes on TER and tight junctions. Moreover, tight junctions studied consisted of major cytoplasmic (ZO-1) and trans-memebrane proteins including occludin and claudin-1. These proteins are studied from the differential protein expression, immunolocalisation and messenger RNA. Their

		studies showed changes in TER and differential expression in tight junction protein expression and immuno-localisation. Data on these have been presented in Asian Pacific Digestive Week in Beijing 2004 and updated work will be presented in Digestive Disease Week in Chicago, IL, USA on 16 May 2005.
NMRC/0533/2001 **PI:** Tan Say Beng (NCC) **Collaborators:** Machin David, Khoo Kei Siong		**Practical Bayesian methods for clinical trials** The main objective of this project was to improve clinical trial methodology. Inefficient or incorrect design/analysis at any stage of the trial process can have severe consequences on the final decision made, resulting in patient care being compromised. Bayesian approaches provide an alternative to traditional statistical approaches for clinical trials. Proponents claim that they allow for clinical trials to be better designed/analysed, and can also incorporate external sources of relevant information. The project resulted in 10 publications and 3 conference abstracts. The publications included some in leading clinical journals like the BMJ and the Journal of Clinical Oncology, as well as good biostatistics journals such as Statistics in Medicine and Controlled Clinical Trials. The team was also invited to contribute an entry to the Encyclopedia of Biopharmaceutical Statistics on the work. There was also interest from researchers in other institutions, with the PI being invited to give talks on topics related to the project at institutions including Queen Mary University of London and NUS. The European Medicine Agency's Committee for Medical Products also made reference to some of their work in one of their new guidelines. The project also helped with the training of three postgraduate students from NTU.
NMRC/0534/2001 **PI:** Zhu Cong Ju (NCC) **Collaborators:** Li Yong Biao, Wong Meng Cheong, Foo Kok Siu		**Chemotherapy induced glioma endothelial cell global gene expression** Malignant gliomas are the most common type of primary brain tumors. Prognosis of malignant gliomas remains dismal, despite conventional therapy. The researchers study was to use transcription profiling to identify novel genes underpinning oncogenicity and chemosensitivity of malignant gliomas. The researchers have achieved their major goals as follows: 1) Isolation and in vitro culture of glioma associated endothelial cells; 2) Global transcription profiling of chemotherapy (temozolomide) induced differential gene expression and establishment of relevant database with detailed annotation; 3) Novel identification of epithelial transforming sequence 2 (ECT2) gene which has important function in glioma oncogenicity and chemosensitivity. These findings have significant implication in the understanding of gliomagenesis and improvement of glioma chemotherapy.
NMRC/0536/2001 **PI:** Nather Aziz (NUS) **Collaborators:** Wong David HC, Wong Hee Kit		**Role of OP 1 in enchancing anterior lumbar interbody fusion using allografts** **Objectives:** To evaluate the effect of the Mesenchymal Stem Cells (MSC) on the biological healing of large weight bearing cortical bone allograft in adult rabbits Methodology - 36 Adult New Zealand White Rabbits were used for the study. A 1.2cm of cortical bone segment was excised from the rabbit's right tibia. The defect was replaced by an autograft, allograft or allograft impregnated with MSC. Internal fixation was performed using a 9-hole Mini Plate, re-enforced with cerclage wires over the segment. Observation periods for each model were 12, 16, and 24 weeks. Specimens procured were tested for union and undecalcified sectioning of 5-10µ was done. Staining of the sections was done using Von Kossa and Toluidine Blue.

		Results: Union at host graft junctions with autograft was observed at 12 weeks. Allograft union occurred at 16 weeks onwards. When MSC is added to allograft, union occurred at both junctions at 12 weeks. Addition of MSC to allograft showed high resorption activity in the cortex of allograft, as compared to autograft or allograft alone.
NMRC/0541/2001 **PI:** Hung The Huynh (NCC) **Collaborator:** Soo Khee Chee		**Purification and characterization of growth inhibitor (BEGI) for breast cancer cells** The researchers report the purification of BEGI, a uterine derived secreted protein having growth inhibitory properties. BEGI appears to inhibit human breast cancer cell lines that are estrogen-receptor negative. Sequence analysis revealed that BEGI protein shares 98% identical to ps20 growth inhibitor isolated from urogenital sinus mesenchymal cells. BEGI (ps20) belongs to family composed primarily secreted serine protease inhibitors. Full length of BEGI cDNA was isolated from both rat and human uterus cDNA library. BEGI mRNA was detected in various female rat tissues with highest expression in the lung and heart. Two BEGI transcripts were detected in rat mammary tissue and BEGI mRNA levels gradually declined as pregnancy advanced. In normal mammary gland and DMBA-induced mammary tumours BEGI expression was suppressed by estradiol while antiestrogens, ICI 182780 and tamoxifen, upregulated it. Induction of BEGI expression by antiestrogens was correlated with apoptosis. Polyclonal antibody against purified BEGI recognised proteins with molecular mass of 24, 27 and 29 kDa. BEGI secretion from primary mammary cells was significantly reduced following growth factor treatment including IGF-I, IGF-II, insulin and TGF-α. Although purified BEGI potently inhibits breast cancer cell proliferation, bacterial recombinant BEGI exhibits no growth suppression suggesting post-translational modification of BEGI determines its activity. In BEGI-transfected MCF-7 cells, acceleration of apoptosis was observed upon growth factor depletion. The results indicate that BEGI is a growth inhibitor and apoptotic factor for breast epithelial cells in vitro and suggest that absence of BEGI expression in breast tumours would facilitate tumour growth and progression. The researchers findings have a considerable potential relevance to breast cancer pathophysiology and treatment. Further characterisation of BEGI may advance their current understanding on the role of BEGI in controlling mammary epithelial cell proliferation and apoptosis.
NMRC/0544/2001 **PI:** Ang Su Yin Angelina (KKH) **Collaborators:** Chin Hoong Chor, Goh Siang Hiong, Anantharaman Venkataraman, Heng Mok Kwee Derrick, Ng Kee Chong, Tan Eng Looi Carolyn, Tan Ngiap Chuen, Wee Keng Poh		**Epidemiology and prevention of unintentional childhood injuries in Singapore** 1) To study the epidemiology of unintentional childhood injuries in Singapore. 2) To establish a childhood unintentional injuries surveillance system. **Methodology:** All children 0-16 years old, being managed for unintentional childhood injuries or poisoning from February 2002 to January 2004, at the Emergency Departments of KKH and SGH, 2 SingHealth polyclinics and the Forensic Medicine Department, Health Sciences Authority, were included. A data dictionary was compiled. ICD-9 and E codes, ICECI (International Classification of External Cause of Injuries) codes, AIS (Abbreviated Injury Scale) codes and derived Injury Severity Scores (ISS), and PTS (Pediatric Trauma Score) were used. A customized database software was established. **Results:** There are 19073 cases. The male to female ratio is 1.67:1. There were 28 deaths (0.15% of the cohort). The age specific mortality rates ranged from 0- 5.6/ 100,000 populations per year. The commonest causes of death were motor vehicle injuries, drowning and falling from high rise

		buildings. Home, school, playground and road injuries caused significant morbidity. **Conclusions:** A childhood unintentional injuries surveillance system using the WHO/ CDC guidelines on essential data sets and ICECI codes was established. This has yielded valuable detailed data on injury causation, useful for guiding injury prevention programs in the local context.
NMRC/0577/2001 **PI:** Ng Puay Yong (NNI) **Collaborators:** Ng Puay Yong, Teo Gek Choo Jennifer, Yee Woon Chee, Hui Kim Hoong Francis, Ng Wai Hoe, Wang Chee Meng Ernest		**Vascular endothelial growth factor and receptor expression in cerebral arteriovenous malformations (AVM) of the brain** The pathogenesis of cerebral arteriovenous malformations (CAVMs) is controversial but is characterized phenotypically to be that of direct arteriovenous shunts without an intervening capillary bed. The researchers hypothesized that cerebral avms may abnormally express ephrinB2 and EphB4 in its endothelium. They studied 11 cerebral AVMS obtained from surgical resection by the senior author. The specimens were compared with 2 arterial and 3 venous controls for ephrinB2 and EphB4 respectively. Semiquantitative RT- PCR and Western blot were performed. EphrinB2 mRNA expression in CAVMs was higher than controls although not statistically significant ($p=0.072$); EphB4 mRNA expression was significantly lower than controls ($p<0.05$). EphrinB2 protein was expressed in all the CAVMs; protein expression was noted to be significantly less than controls ($p<0.05$). The level of expression between the specimens was not markedly different. EphB4 protein was expressed in only 5 of the CAVMs; protein expression was significantly reduced as compared to controls ($p<0.05$). Analysis of ephrinB2 and EphB4 expression with age, sex, GCS, symptom presentation (hemorrhagic vs non-hemorrhagic) and nidus size yielded no significant associations ($p>0.05$). EphrinB2 and EphB4 expression is abnormally low in CAVMs raising the possibility that abnormal paracrine(local cues) may be responsible in the pathogenesis of CAVMs by affecting EphrinB2-EphB4 interaction required for the proper morphogenesis of capillary beds during embryologic development.
NMRC/0579/2001 **PI:** Soong Tuck Wah (NNI) **Collaborator:** Lee Kam Yiu Timothy		**Determination of the role of iron in the cell death of dopaminergic neurons in hemi-parkinsonian rats** The aim of the project was to explore the interactions between environmental and genetic factors associated with Parkinson's disease (PD), which will hence shed some light on understanding the selective dopaminergic toxicity in PD. The researchers used the divalent metal transporter 1 (DMT1) as a tool for cellular iron-overloading. Human SH-SY5Y and rat PC12 cells were used to characterize DMT1 and to determine synergistic toxicity of iron and α-synuclein (α-syn). DMT1, expressed either by stable transfection or transduction using adenovirus, markedly ($P< 0.01$) enhanced the iron uptake as examined by 55Fe-uptake assay. In SH-SY5Y DMT1-stable cell line, extensive ($P<0.01$) cell death was observed after treatment with 5 mM FeCl2 as compared with control. In addition, PC12 cells stably expressing mutant α-syn (A53T) were dose-dependently more prone to FeCl2 toxicity. These suggest that DMT1 was able to enhance the iron-mediated cellular toxicity and expression of mutant α-syn (A53T) further aggravated the DMT1-mediated iron toxicity. On the other hand, nitric oxide (NO), which is found to be increased in PD, has been shown to be a potent agent that modifies an array of proteins, thus disturbing their physiological functions. They are currently exploring the role of NO in the regulation of DMT1 activity.
NMRC/0583/2001		**Functional analysis of Ncr1p, a NPC1 ortholog in the yeast Saccharomyces cerevisiae**

PI: Yang Robert Hong Yuan (NUS) **Collaborators:** Munn Alan L, Li Qiu-Tian		The Niemann Pick C1 protein (NPC1) plays a key role in the intracellular trafficking of low density lipoprotein (LDL) derived cholesterol in mammalian cells. Ncr1p is a homolog of NPC1 in the budding yeast Saccharomyces cerevisiae. In this study, we show that Ncr1p is a vacuolar membrane protein that transits through the biosynthetic vacuole protein sorting (VPS) pathway. The absence of Ncr1p appeared to have no effect on fluid phase and receptor mediated endocytosis, biosynthetic delivery to the vacuole, retrograde transport from endosome to Golgi and ubiquitin and non-ubiquitin dependent multivesicular sorting. On the other hand, the researchers show that the sterol esterification activities in wild type, are1Δ or are2Δyeast strains increased by more than three fold upon acute glucose starvation. The maximum induction of sterol esterification activity of the are2Δ strain, but not that of the wild type or are1Δ strain, was dependent upon a functional Ncr1p. There was no difference between are2Δ and are2Δncr1Δ strains in sterol esterification activity when measured in vitro. In addition, there was ~50% more vacuolar free ergosterol in the are2Δncr1Δ strain than in the are2Δ strain upon glucose starvation. Their results suggest that Ncr1p, like its mammalian counterpart, regulates subcellular sterol transport out of the vacuole.
NMRC/0585/2001 **PI:** Jeyaseelan K (NUS) **Collaborator:** Armugam Arunmozhiarasi		**Construction of DNA and protein databases and development of potential therapeutic agents from toxin genes** Components isolated from toxic principles in animal venoms have provided opportunities to develop many new innovative treatments either as drugs or starting points for the discovery of new therapies. The objective of this project is to continue with their search for more cDNAs encoding novel products that have therapeutic potentials. During the course of this investigation, the reseachers have constructed DNA and protein databases as useful points of references for drug discovery. Specific genes encoding biologically active products have also been examined more closely. cDNAs encoding chloride ion channels from scorpion as well as pre/post synaptic neurotoxins from Bungarus sp., have been cloned and characterized. A comprehensive Database for neurotoxins has also been created. (http://sdmc.i2r.astar.edu.sg/Templar/DB/snake_neurotoxin). Several muscarinic toxin like peptides and cDNAs have also been identified from Bungarus
NMRC/0586/2001 **PI:** Roy Ashim C (NUS) **Collaborators:** Liao Wuxiang, Ng Soon Chye		**Genetic variability of estrogen receptor genes and human reproductive disorders** One hundred Chinese women of which 50 had idiopathic infertility, 25 had PCOS and 25 had ovulatory dysfunction other than PCOS were screened for unknown mutations and polymorphisms in all the exons and introns of estrogen receptor alpha (ER-α) gene using DHPLC and PCR-based DNA sequencing. No novel mutations or polymorphisms were detected. Therefore, it appears that ER-α gene missense or nonsense mutations are not involved in the infertility of local Chinese women. Among the known ER-α gene polymorphisms, the PvuII and XbaI polymorphisms have recently gained immense popularity for their potential associations with various clinical manifestations that might be related to estrogen exposure. It is speculated that these polymorphisms may alter the functions of the estrogen receptors. Therefore, the researchers evaluated their possible associations with PCOS in 111 Chinese PCOS patients and 102 Chinese controls using PCR-based RFLP. Their results showed that PvuII polymorphism and not XbaI polymorphism was significantly associated with PCOS ($p=0.27$), while their compound homozygote, PvuII-XbaI showed stronger association with the disease ($p<0.001$). LH/FSH ratio was significantly decreased in PCOS patients homozygous for PvuII polymorphism and also in PvuII-XbaI compound homozygous patients compared to non homozygous

		patients (p=0.026). Though within the normal range, serum levels of testosterone were significantly increased and of prolactin decreased (p=0.002) in patients homozygous for PvuII polymorphism. There were no statistically significant changes in the hormone levels in XbaI polymorphic patients. This study suggests that the detection of homozygous PvuII polymorphism, and compound homozygous PvuII-XbaI polymorphism of ER-α gene may be used as markers in the early diagnosis of PCOS. Finally, they screened the 5'-untranslated region and 3'-untranslated region of ER-α gene for mutation in women with PCOS (n=20), DUB (n=2) and amenorrhea (n=2), and identified four novel mutations in the 5'untranslated region (G deletion at nt 31, C insertion between 42 and 45, 53 and 56, 67 and 70) and four in the 3'-untranslated region (G5002N, T51056, C51780N and T53831N)) of the gene. An association study of these mutations in the untranslated regions of ER-α gene with reproductive disorders leading to infertility remains to be done.
NMRC/0596/2001 **PI:** Xiao Zhi Cheng (SGH) **Collaborators:** David Samuel, Ang Beng Ti Christopher		**Identification and therapeutic use of the peptides of tenascin-R for neuroprotection after CNS injury** Microglia are the principal immune effected cells of the central nervous system. In the normal brain microglia is in a quiescent state, with short branched processes. Following injury they exhibit various behavious, including activation, cell division, and migration to the injured sits. It is reported that tenascin-R presented in the perineuronal net of motoneurons becomes downregulated in the lesioned nucleus, and tenascin-R has antiadhesion properties for activated microglia. But it is not clear which domain of tenascin-R has function to repel activated microglia. The receptor for tenascin-R on the microglia has not also been elucidated. The researchers investigated how extracellular matrix (ECM) molecules, such as Tenascin-R (TN-R), play roles in neuroprotection via modulating microglia, one of main players in the response to brain injury. In both cell adhesion and Transwell invasion/migration assays, microglia adhered pronouncedly to FN6-8 and FG domains, but were repelled by EGFL domain, compared with other TN-R domains and GST as controls. Moreover, PKA involved in the EGFL induced microglia anti-adhesion, while PKC involved in FG6-8 induced microglia adhesion, implicating that the microglia are activated by TN-R through different pathways. Interestingly, the activated microglia displayed a similar cytokine expression pattern, in which CINC-2, CINC-3 and TNF-α were significantly up-regulated, and the conditioned mediums promoted neurite outgrowth of both N1E115 cells and cortical neurons after either EGFL or FN6-8 stimulation. These observations indicate that TN-R plays a role in neuroprotection through its distinct domains coordinately modulating the microglia function during the CNS regeneration.
NMRC/0599/2001 **PI:** Wong Peter T.H. (NUS) **Collaborators:** Ng Yee Kong, Wong Wai Shiu Fred, Zhu Yi Zhun		**The roles of endothelin receptors expressed in neurons and microglia in the acute phase of brain ischemia.** The cortical expression of endothelin receptors was found to increase rapidly after experimental stroke in rat. ETA receptors were expressed in neurons while ETB receptors were expressed in microglia/macrophages. These findings showed that endothelins released during cerebral ischemia may play an important role by affecting the functions of neurons and microglia, in addition to their known effects on the blood vessels. ETB receptors are expressed in primary culture of microglial cells as well as in BV2 cells (a mouse microglial cell line). This is consistent with their findings in vivo after stroke. On the other hand, both ETA and ETB receptors are expressed in primary rat neuron with the ETB receptors being expressed to a greater extent. This is contrary to the in vivo finding that ETA receptors were selectively expressed in neuron. It is possible that ETB receptors were expressed in the neurons ex vivo. Functional studies, however, showed that ET-1 (up to 10μM) did not alter intracellular calcium concentration in these neurons as well as primary rat microglia and BV-2 (mouse microglia cell line). ET-1 also did not alter cell viability in hypoxic conditions used to simulate stroke in vitro. This lack of

		effect suggests non-involvement of these ET receptors in cell death.
NMRC/0612/2001 **PI:** Bay Boon Huat (NUS) **Collaborators:** Tan Puay Hoon, Chow Tak Kwong Vincent		**Evaluation of metallothioneine as a molecular and prognostic biomarker of breast cancer** Metallothioneins (MTs), a group of cysteine-rich intracellular proteins, are known to influence the fundamental cellular processes of proliferation and death. In humans, there are at least 10 functional genes which encode 4 groups of MT proteins (MT-1, MT-2, MT-3 and MT-4). MT protein expression was evaluated by immunohistochemistry and confirmed by immunoelectron microscopy. The MT protein was present in all the breast tumor sections and exhibited both nuclear and cytoplasmic staining. The MT-2A isoform was the most abundant isoform and observed to be differentially up-regulated in the invasive phenotype. The MT-1E isoform was found to be present in estrogen-receptor-negative breast cancer cell lines but not detectable in the estrogen-receptor-positive cell lines. Direct sequencing of the RT-PCR products revealed the occurrence of a variant MT-1H isoform. As MT is a known antioxidant, the expression of MT and its correlation with apoptosis was compared with 2 established antioxidants, viz., bcl-2 and Glutathione-S-Transferase-pi (GST-pi). There was no significant correlation of MT with apoptosis but a positive correlation was noted with bcl-2 and GST-pi. When analyzed with clinico-pathological parameters, MT correlated with histological grade whereas bcl-2 correlated with hormonal status and tumor grade. The expression of MT and associated markers, GST-pi and YB-1 protein were analyzed in relation to adjuvant chemotherapy, recurrence and disease free survival. All three markers had prognostic significance.
NMRC/0618/2001 **PI:** Chatterjee Subroto (NHC) **Collaborators:** Seldrup Jorgen, Xiong Zhuo Wei, Wei Heming		**Platelet Endothelial Cell Adhesion Molecule Polymorphism and Cardiovascular Disease Risk in Singaporeans.** Association of platelet-endothelial cell adhesion molecule-1 (PECAM-1) gene polymorphism in multi-ethnic populations in Singapore was explored. Gene polymorphism C+373G (L125V) is associated with coronary artery disease (CAD) in all three populations in Singapore. Moreover the serum level of sPECAM-1 was also markedly elevated in CAD patients. The study in Chinese [1] and Asian Indians [2] are either published or in press. The functional impact of PECAM-1 gene polymorphisms on atherogenesis has been confirmed with endothelial cell-like cell line (Ren cells) over-expressing various PECAM-1 genotypes [3]. C-reactive protein (CRP) is a well-known chronic inflammatory marker which is also elevated in their CAD in Chinese [4] and associated with elevated levels of sPECAM-1. Further, the roles of PECAM-1 have been explored at cellular level, the researchers found it is involved in CRP- [5] and TNF-α [6] induced endothelial inflammation and mediates the anti-inflammatory effect of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) [6]. A PECAM-1 gene transcript missing the 7th exon has been identified and an antibody raised against the peptide encoding the 5th (Ig)-like domain in PECAM-1 was found with potential therapeutic value [7]. Also a novel lipid second messenger lactosylceramide was found to recruit protein kinase C (PKC) and phospholipase A-2 to induce PECAM-1 gene/protein expression [8]. They concluded that PECAM-1 gene polymorphism and soluble level could serve as novel risk factors for CAD (please find the publication list in the order from 1~8).
NMRC/0621/2001 **PI:** Lee Kok Onn (NUS) **Collaborator:** Ng Wai Yoong		**Investigating ion channel gene mutations and expression in hypokalemic thyrotoxic periodic paralysis** Patients with proven observed hypokalemic thyrotoxic periodic paralysis had whole blood taken, which were then used for DNA and RNA extraction. For controls, DNA and RNA were similarly obtained from male patients with thyrotoxicosis for at least 2 years of follow-up with no episodes of

		hypokalaemia or paralysis. Studies of gene mutations reported in familial periodic paralysis, and other ion channels were carried out. Mutations studied in these patients included: KCNE3; KCNJ2; SCN4A; CACNA1S. There were no consistent mutations found in the study group compared to the control group in any of the genes studied. These findings do not agree with some of the previous studies of mutations reported (SCNA4: Lane 35 al, 2004; KCNE3: Dias Da Silva et al 2002).
NMRC/0626/2002 **PI:** Tan Chee Kiat (SGH) **Collaborators:** Ooi London Lucien Peng Jin, Chung Yaw Fui Alex, Chow Wan Cheng, Chow Kah Hoe Pierce, Zhao Yi, Ng Han Seong		**A prospective study to determine the significance of serological markers of previous Hepatitis B infection in patients with hepatocellular carcinoma** Results show that patients who have recovered from previous acute hepatitis B infection and later develop HCC have evidence of viral genome in the normal and tumour liver tissues. This implies that the researchers should consider all patients with serological evidence of previous hepatitis B infection as being still at risk of developing HCC.
NMRC/0627/2002 **PI:** Lee Seng Teik (SGH) **Collaborators:** Tham Hsien Jen Colin, Phan Toan Thang, Huynh The Hung, Sun Li		**Cultivation and Characterization of Human Epidermal Stem Cells for Tissue Engineering of Epidermis and Living Composite Skin** The objective of this project is to characterize the human epidermal stem cells, and investigate the potential of developing composite skin with these stem cells. In this study, the researchers defined their methods of isolating and cultivating of epidermal keratinocytes from human skin and hair follicle, successfully isolated and cultured clonogenic keratinocytes from human skin epidermis and hair follicle bulge region, excluding other cells contamination in cell culture. In identifying the molecular markers for human epidermal stem cells, previously suggested molecular markers, such as b1-integrin, a6-integrin, transcript factor P63 and cytokeratin15 are studied; they also investigated the potential of identifying epidermal stem cells with Hoechst excluding assay (side population cells) in human skin. With the in vitro culture model, they compared the efficiency of identifying epidermal stem cells with these molecular markers and Hoechst excluding method. The in vitro results strongly suggest that side population cells possess enriched stem cell properties, and these cells might be the putative epidermal stem cells.
NMRC/0628/2002 **PI:** Wong Meng Cheong (NCC) **Collaborators:** Tan Patrick Huat Chye, Sun Li, Lu Jia		**Endothelial Progenitor Cells: A novel and promising cell vehicle for temporal-and-spatial-specific gene therapy** Gene therapy has increasingly become translated from bench to clinic. Worldwide, hundreds of patients with malignant brain tumours have been treated with clinical gene therapy protocols. However, much refinement is needed to improve therapeutic efficacy. A major obstacle to gene therapy is the issue of targeted delivery. Anti-angiogenic therapies are increasingly used to treat patients with various cancers. In this study, the researchers derived endothelial progenitor cells, demonstrating their in vitro morphological, gene expression and protein characteristics, as well as their high efficiency targeting to the vasculature of brain tumours in an in vivo model.
NMRC/0638/2002 **PI:** Cheah Peh Yean (SGH)		**Further dissection of the role of the adenomatous polyposis coli (APC) gene and search for other candidate genes in the colorectal carcinomas (CRC)** Familial adenomatous polyposis (FAP) is a heritable form of colorectal cancer

Collaborators: Cao Xia, Sivaswaren Christina Rudduck, Tien Sim Leng, Eu Kong Weng, Seow Francis Choen, Hong Yi		caused by autosomal dominant inheritance of the mutated adenomatous polyposis coli (APC) gene. The researchers used the protein truncaton test (PTT) and direct sequencing techniques to successfully detect APC germline mutations from 46/57 unrelated FAP families. For the remaining families, they performed the new multiplex ligation-dependent amplification (MLPA) technique, which identifies large deletion undetectable by PTT. Genomic deletions were found in 3 families. Differential expression at polymorphic codons 486(TAC/T) and 545(GCA/G) of APC was detected in another family. Thus, in total, APC germline mutations were detected in 50/57 families. Phenotypic analyses revealed that APC mutation negative patients have unique features that distinguished them from APC mutation positive patients. One sub-group has mixed hyperplastic and adenomatous polyps and was renamed Hereditary Mixed Polyposis Syndrome (HMPS). The putative locus for HMPS in the Ashkenazi families has recently been remapped to a haplotype between D15S1007 and D15S118. They showed by haplotype and linkage analyses that the Ashkenazi haplotype is not associated with HMPS in Singapore families. The researchers then performed whole genome linkage search with the new GeneChip Human Mapping 10K Array and successfully identified BMPR1A as the disease causing gene in Singapore HMPS families.
NMRC/0639/2002 **PI:** Koh Tse Hsien (SGH) **Collaborators:** Wang Grace Chee Yeng, Tan Ai Ling, Song Keang Peng		**Epidemiological study of clostridium difficile infections in hospital and the community** 1. incidence of C. difficile disease 2. presence of toxin A negative/toxin B positive strains 3. antimicrobial susceptibility 4. whether strains are clonal or sporadic **Methodology:** Stool samples from patients with diarrhoea were tested for toxin A and B by enzyme immunoassay. C. difficile was isolated by inoculation of stool onto agar plates. Culture filtrates were assayed for toxin A and toxin B. PCR was used to confirm the presence of toxin A and B genes. Isolates were typed by PCR ribotyping. Antimicrobial susceptibility to clindamycin, metronidazole and vancomycin were determined by Etest. **Major accomplishments:** The researchers established the incidence of C. difficile disease in their hospital to be low (about 2-2.8 cases per 1000 discharges). This is the first accurate figure for a south-east asian country to their knowledge. They determined that toxin A negative/toxin B positive strains are present in Singapore. This has implications for the choice of diagnostic test. They confirmed that C. difficile here remain susceptible to metronidazole and vancomycin which are the drugs of choice. They also now know that many of the strains isolated in hospital are clonal, implying spread by breakdown in infection control.
NMRC/0649/2002 **PI:** Roy Ashim C (NUS) **Collaborator:** Ng Soon Chye		**Poor response to ovarian stimulation with follicle-stimulating hormone: possible genetic causes** One hundred seven Singapore women of which 36 were poor responders to ovarian stimulation with FSH were compared with 71 good responders recruited at their IVF centre. Since polymorphisms are population specific, in this study, the researchers aimed to screen Singapore Chinese women with poor response to ovarian stimulation with FSH for previously identified FSHR conjugated variants in German population, Thr307/Asn680, Thr307/Ser680, Ala307/Asn680 and Ala307/Ser680, and compare the results with that of good responders. IVF patients were screened for unknown mutations and polymorphisms in all the exons and introns of FSH receptor gene using DHPLC and PCR-based DNA sequencing. A novel mutation was discovered in the 3' UTR. A single nucleotide 2135C deletion was observed in both poor responder (n=16) and good responder (n=13) groups studied. While mutations affecting FSHR are sporadic, polymorphism of the FSHR

		gene seems to be a common phenomenon. To date, six inactivating and only one activating mutation have been detected in the FSHR gene. The integrity of each FSHR segment is required for proper expression of the fully active protein and for normal gonadal function.The ovarian response to FSH stimulation in assisted reproduction is variable, ranging from hyporesponse to hyperresponse, with the possible complication of ovarian hyperstimulation (OHS); it would be of great benefit to predict the response of the patients to FSH. To date, no clear-cut predictors of ovarian responsiveness to FSH have been identified. Perez et. al. (2000) had investigated the role of two distinct FSHR variants, Thr307/Asn680 and Ala307/Ser680, in the response to FSH in 161 ovulatory women below the age of 40 undergoing controlled ovarian stimulation. In their study, DNA was extracted from the peripheral blood leucocytes. PCR was used to amplify the desired fragments of coding regions of the regions of the FSHR gene. Restriction fragment length polymorphism (RFLP) was used to determine the distribution of polymorphisms. DNA sequencing was performed to confirm the polymorphisms and to identify other mutations. This study suggests that the detection of Homozygous Ser680/Ser680, and Homozygous Thr307/Thr307 polymorphism of FSH receptor gene may be used as markers in the early diagnosis of poor reponse to Ovarian stimulation.
NMRC/0654/2002 **PI:** Philip Iau Tsau Choong (NUS) **Collaborators:** Lee Soo Chin, Wong Eu Li John		**The prevalence of large exon rearrangements in the BRCA1 gene in Asian early onset and familial breast cancer patients** **Objective:** Large genomic rearrangements account for about 10% to 15% of BRCA1 gene mutations. Up to 45 BRCA rearrangements have been described to date, all of which have been reported in Caucasian populations of predominantly Western European descent. At present, no data exists on the presence of BRCA genomic rearrangement in any Asian population. This objective of this study was to investigate the presence of BRCA1 rearrangements among Singapore patients with early onset or familial history of breast or ovarian cancer. **Methodology:** MLPA was used to screen 100 Singapore patients, tested negative for deleterious BRCA1 mutations by the conventional PCR-based mutation detection methods, for BRCA1 genomic rearrangements. Long range PCR and direct sequencing were used to characterise the rearrangements detected. **Results:** Two novel BRCA1 exon rearrangements were detected by MLPA. Characterisation of these rearrangements showed an exon 13-15 deletion (10.1 kbp in size), presumed to be the result of an Alu-mediated recombination event and an exon 13 duplication different from the founder mutation reported in Western populations. **Major accomplishments:** This study presents the first genomic rearrangements to be described in an Asian population. Given the increasing number of rearrangements reported in recent years and their contribution to the BRCA mutation spectrum, the suitability of including rearrangement analysis within the BRCA mutation screening protocols in Asian populations should be evaluated.
NMRC/0658/2002 **PI:** Eugene Sim Kwang Wei (NUS)		**Auto Transplantation of Mesenchymal Stem Cell into Chronically Failing Heart-Porcine Model** The researchers have successfully isolated and cultured of human bone marrow mesenchymal stem cells (BMMSC) from human sternal bone during coronary

Collaborators: Rangappa Sunil, Teh Ming, El Oakley Reida, Lee Eng Hin		artery bypass grafting. Human BMMSC were induced to differentiate into cardiomyocyte-like cells after treated with differentiation medium. Human BMMSC labeled with Lac-z reported gene were intramyocardially transplanted into the heart of SCID mice. The cells were found inhibated in the heart of SCID mice and expressed myosin heavy chain. Rabbit BMMSC were isolated from iliac bone The rabbit BMMSC were transplanted into rabbit heart model of myocardial infarction. Lac-z or BrdU positive cells were observed in transplanted rabbit heart. BMMSC survived in the center and peri-infarction area. The donor cells were found following the tissue architecture. Bone marrow mesenchymal stem cells were also observed in the walls of the vasculature suggesting that bone marrow cells differentiated into endothelial cells or smooth muscle cells. Immunostaining for von Willebrand factor VIII showed that bone marrow mesenchymal stem cell transplantation increased regional blood vessel density compared with control animals.
NMRC/0664/2002 **PI:** Lee Tat Leang (NUS) **Collaborators:** Tachibana Shinro, Wong Peter Tsun Hon, Ricos Michael Geoge, Tay Sam Wah Samuel		**Analysis of the levels of Nocistatin and Nociceptin, in animal models of chronic pain** Nocistatin (NST) and nociceptin (NCP) have been detected in the central nervous system of humans and rodents. It is also known that these molecules may have a role in pain transmission. Although the widely held model is that NCP is pronociception and that NST is involved in countering the effects of NCP by normalizing the pain threshold. There are data to suggest both neuropeptides could play dual roles depending on the dose, animal models and routes of administration. There is no report that documents the levels of NST and NCP simultaneously. Furthermore, there is emerging new data to suggest that many other amino acids (other than glutamate, aspartate, GABA and glycine) such as proline and D-serine are also involved in pain transmission. The main objective of their study is trying to establish a correlations between NST and NCP levels in a chronic pain animal model, in addition, the researchers also try to develop a simple quantitative method which will allow them to simultaneously determine many amino acids which are unknown or recently implicated to play a role in pain modulation. Their project involved cannulation of the right lateral cerebral ventricle and collection of microdialysates from normal rats (control) and neuropathic rats (partial sciatic nerve ligation). The microdialysates were tested for NST and NCP by RIA and for amino acids analysis. The results showed that the levels of NST and NCP decreased in the neuropathic rat model compared to control rats, however, the variances were too big to draw a definitive conclusion. The amino acids analysis revealed no significant differences amongst all the amino acids between the 2 groups. The interaction between NST, NCP and pain related amino acids (aspartate, glutamate, asparagines, glutamine, citrulline, glycine, GABA and taurine) were studied by analyzing the amino acids levels, following intra-cerebral ventricular injection of different doses of NST and NCP (0.1, 1 and 10 nmol). The results showed that both peptides had no effect on pain related amino acids except a significant increase in GABA following the injection of NST.
NMRC/0665/2002 **PI:** Donald Tan Tiang Hwee (SNEC) **Collaborators:** Phan Toan Thang,		**Tissue Engineering of Conjuctival Stem Cells** Their objectives were to develop a viable conjunctival epithelial cell culture facility, to develop safer methods for conjunctival epithelial stem cell propagation, to investigate the in vitro and in vivo proliferative capacity of human conjunctival epithelial cells cultured in serum-free media, to develop conjunctival epithelial equivalents with improved proliferative and structural properties, and to compare this with current methods that utilize serum-

Beuerman Roger W., Lavker Robert		containing media and 3T3 feeder layers. The reseachers demonstrated that cells cultivated in serum-free media had similar proliferative capacities as cells that were cultivated in serum-containing media. The degree of epithelial stratification was similar in both conditions. They developed bioengineered conjunctival epithelial equivalents by cultivating conjunctival epithelial cells on human amniotic membrane (HAM) using a multistep serum-free culture system. They showed that epithelial equivalents cultivated in serum-free media were more proliferative than those cultivated in serum-containing media. Cells that were air-lifted for 6 and 12 days had a reduced proliferative capacity compared to submerged cultures. Following transplantation, the serum-free derived epithelial equivalents demonstrated a significant increase in proliferation and stratification. These serum-free cultivated conjunctival cells retained their in vivo characteristics and expressed K4, K19 and MUC5AC. The presence of MUC5AC mRNA in these cells was confirmed by RT-PCR. Electron microscopy demonstrated a basal lamina with numerous hemidesmosomes, which are important for maintaining graft integrity following transplantation. The use of a multistep serum-free culture system to develop a transplantable conjunctival epithelial equivalent was found to improve the proliferative and structural properties of the cultivated cells. These are crucial for enhancing graft-take and regeneration of the conjunctival surface following transplantation. The use of a serum-free culture system represents a significant advancement over current culture methods when considering clinical transplantation, as it reduces the risks of zoonotic infection and xenograft rejection. These findings have important clinical implications and are important in the development of a safe and effective bioengineered tissue-equivalent for clinical use. They have established a full-fledged tissue culture facility that supports their conjunctival and corneal epithelial stem cell and tissue engineering research. Their invention has been filed as a patent and is currently in progress. The researchers have to date published 3 scientific articles and presented 14 papers or posters at scientific meetings. In addition, the study investigators have received 8 local and international awards for this work.
NMRC/0666/2002 **PI:** Lui Hock Foong (SGH)		**1) A study into the haemodynamic response of a local population of patients with liver cirrhosis to propranolol;** **2) A study into the effect of lamivudine on portal pressures using invasive haemodynamic measurements** The current standard for assessing portal pressure is by invasive pressure studies. We designed 2 studies using this tool to address unanswered questions of chronic liver disease that are of clinical and local relevance. 1. Hepatitis B is the most common cause of liver cirrhosis, which in turn leads to portal hypertension. Lamivudine, a nucleoside analogue, inhibits RNA polymerase and therefore HBV replication. It improves inflammation and fibrosis and promotes HBV seroconversion. The researchers postulate that portal hypertension will also improve with lamivudine treatment. This study will measure the splanchnic and systemic pressures before and 1 year after lamivudine treatment in patients with liver cirrhosis. 2. Propranolol is the standard treatment of oesophageal varices that have never bled. However there is uncertainty if the dose-response varies with ethnicity. If this is true, it will impact current treatment recommendations, which are based on studies involving mainly Caucasian patients. This study will study the haemodynamic response, as determined by invasive pressure studies, of a group of local patients and comparing the results with those performed, using an identical protocol, in a Caucasian population.

NMRC/0667/2002 **PI:** Yap Keng Bee (AH) **Collaborators:** Ng Tze Pin, Tan Chay Hoon, Low Adrian		**A community survey of elderly subjects with atrial fibrillation: associated risk factors and treatment preferences** **Aims & objectives:** The prevalence of atrial fibrillation (AF) in Asian populations appears to be lower than in the West, according to limited data. A community study was conducted to estimate the prevalence of atrial fibrillation in elderly Chinese in Singapore, and examine associated cardiac precursors, risk factors and anti-coagulant therapy. **Method and results:** Whole survey area population screening of 1839 elderly Chinese residents aged 55 and above in South-East region of Singapore with single ECG recording and echocardiography. The estimated overall prevalence of 1.5% (95% CI, 1.1 to 2.2) was higher in men (2.6%) than in women (0.6%) and only increased sharply to 5.8% in those aged $\geq$ 80; lower than age standardized rates in Western populations by half; consistent with similarly low prevalence reported in Korea and China. Only a third (10/26) was known cases, and 3/10 was on anti-coagulant therapy, the rest on anti-platelet therapy. AF was significantly associated in multivariate analyses with male gender (OR=4.10), heart failure (OR=3.11) and stroke (OR=3.60). **Conclusion:** These data suggest consistently low prevalence of AF in Asian populations which should be further investigated. Anti-coagulant therapy also appears to be under-used.
NMRC/0676/2002 **PI:** Low Wong Kein (SGH) **Collaborators:** Prabhu Anitha, Goh Yau Hong, Teoh Gerrard Kheng Hoe		**Generation and characterization of human nasopharyngeal carcinoma cell lines** A total of 20 (100% accrual) fresh patients' nasopharyngeal carcinoma (NPC) post-nasal space (PNS) biopsy tissues were processed. Tissue culture methodology was progressively improved from the original protocol for the generation of long-term culture of multiple myeloma (MM) cell lines, i.e. using proprietary methodology (details embargoed for patent application). These modifications to the protocol permitted long term healthy tumor cell growth, prevention of overgrowth of feeder cells and prevention of contamination. The researchers successfully produced 5 long-term (>6 months) human NPC cell cultures. Of these, one (SGH-NPC1) achieved log phase growth with >30 passages. Immunophenotyping; light, confocal and electron microscopy; karyotyping; p53 status; serum-dependence and colony assays; and in vivo tumorigenesis in severe combined immunodeficiency (SCID) mice confirmed that SGH-NPC1 was an epithelial tumor. Unfortunately, the SGH-NPC1 NPC cell line did not express Epstein-Barr virus (EBV) encoded RNA-1 (EBER-1). The xenograft-derived tumor cell line was named SGH-NPC2 and has achieved >10 passages. This too was EBV negative. They believe that both SGH-NPC1 and SGH-NPC2 cell lines are authentic human NPC cell lines. They set the stage for the development of immunotherapeutic strategies for the treatment of NPC, e.g. patient-specific anti-NPC cell-based vaccines.
NMRC/0677/2002 **PI:** Lim Swee Han (SGH) **Collaborators:** Tan Hock Heng, Anantharaman Venkataraman, Tan Eng Hoe, Seldrup Jorgen, Chan Yiong Huak,		**Cardiac arrest and resuscitation epidemiology in Singapore: A prehospital study, phase II (CAREII)** Cardiac Arrest and Resuscitation Epidemiology in Singapore: A prehospital study, phase II (CARE II) was a multicentre observational study. The objectives of CARE II were: to describe the epidemiology of all out-of-hospital cardiac arrest (OHCA) in Singapore and to evaluate the effectiveness of prehospital intravenous (IV) adrenaline given by the Singapore Civil Defence Force (SCDF) paramedics. During phase I, ambulance paramedics were only capable of providing CPR and defibrillation. In phase II, the researchers measured the effect of the

Lim Swee Han, Manning Peter George, Ng Kheng Siang, Ong Victor Yeok Kein, Tham Lai Peng Sharon		introduction intravenous adrenaline to the prehospital management of cardiac arrest. The SCDF Ambulance Service implemented these new interventions on 15 October 2003. Data collected was compared against baseline data obtained in CARE phase I. In phase II they also expanded the study to include patients conveyed by their own transport, private ambulances and traumatic cardiac arrests. 1980 patients were enrolled into the study and 1591 (80.4%) of the data were completed. 121 (7.6%) of the subjects survived to hospital admission, 23 (1.4%) of the subjects survived to 30 days post cardiac arrest. 152 (9.6%) of the cases were actually conveyed by private transport and private ambulances while the rest by SCDF emergency ambulances. To date, 5 publications have been achieved from the CARE study. The main phase II study analysis is pending.
NMRC/0681/2002 **PI:** Samuel Tay Sam Wah (NUS) **Collaborators:** Dheen S Thameen, He Beiping		**Indirected transplantaion of Mesenchymal stem cells into the hypoglossal nuclei after unilateral nerve avulsion - Prototype model for treating neurodegenrative diseases** The present study involved the use of bone marrow stem cells (mesenchymal stem cells) for culture in conditioned media. Mesenchymal stem cells (MSCs) were characterized and identified using specific staining for markers using CFDA-SE fluorescent dye, Alizarin red, Oil Red "O" and Nestin. MSCs stained for nestin (a marker for neurons) were cultured through 3-4 passages and then sorted by flow cytometry. The pre-selected cells were then cultured to confluency and used for transplantation into the brain. Left hypoglossal nerve avulsion was performed, the right side served as a control for each experimental animal. Immediately after nerve avulsion, the pre-selected MSCs (106 cells) were then injected stereotaxically into both lateral ventricles of the brain. Animals were sacrificed at 1 week and 2 weeks post-operation. Results showed that CFDA-SE positive fluorescent cells were localized in the injured left hypoglossal nucleus, with no labeled cells found in the right normal hypoglossal nucleus and in the sham-operated animals. It has been found that interaction between SDF-1 and CXCR4, and between fractalkine and CX3CR1 are responsible for the migration of MSCs into the damaged hypoglossal nucleus.
NMRC/0684/2002 **PI:** Benny Tan Kwong Huat (NUS)		**Studies in animal models of Type II diabetes bioactive compounds from Morinda officinalis and Pereskia grandifolia with effects on blood glucose, lipids and antioxidant levels** The project involved the evaluation of two plants, Morinda officinalis and Averrhoa bilimbi (replacing Pereskia grandifolia) for their antidiabetic effects in animals with streptozotocin (STZ)-induced diabetes. The studies showed that the semi-purified fractions of A bilimbi extract produced a hypoglycaemic effect in the STZ-diabetic rats and that this effect was likely to be due to the combined effect of magnesium and niacin, which are present in large amounts in the semi-purified fraction of the leat extract. The water fraction of Morinda extract improved glucose tolerance in STZ-diabetic rats as well as the drug, metformin. It also reduced fasting blood glucose when given for 10 days to these rats. The mechanism of this hypoglycaemic effect was investigated and insulin release was excluded. Possible causes were attributed to reduced hepatic glucose (as shown by reduced activity of hepatic glucose 6 phosphatase in Morinda-treated rats), as well as elevated hepatic glycogen stores (indicating either increased glucose uptake by the liver or reduced glycogen breakdown). The water fraction of Morinda also had significant antioxidant effects, causing significant increases in reduced glutathione, catalase and sodium dismutase.

NMRC/0687/2002 **PI:** Wilson Wang Ee Jen (NUS) **Collaborator:** Kandiah Satkunanantham		**Investigation of Vascular Endothelial Growth Factor (VEGF) and Vascular Endothelial Growth Factor Receptor (VEGFR) expression in osteoarthritic articular cartilage** Vascular endothelial growth factor (VEGF) is an angiogenic favtor that may be involved in the development of osteoarthritis, though its exact role, as well as its expression and roles in growing and mature articular cartilage remain uncertain. This study was performed to determine the spatiotemporal expression of VEGF and VEGF receptor in articular cartilage and to improve their understanding of its roles in articular cartilage physiology. The guinea pig model of spontaneous osteoarthritis was used. Tibal plateaus from guinea pigs of various ages were obtained: 2 months, 6 months and 12 months, representing growing, mature and osteoarthritic cartilage. Expressions of VEGF and VEGF receptor were determined by immunohistochemistry. Specimens from the 2 month group showed VEGF and VEGFR expression in the superficial layer of the articular cartilage. This result is a new finding not previously reported and may have implications in the understanding of cartilage physiology, with potential downstream applications in tissue engineering. The researchers also confirmed that specimens from 6 months showed no VEGF, while specimens from 12 months showed VEGF and VEGFR specifically in areas of osteoarthritis. This demostrated a theme of re-expression of early growth factors in senescence, a recurrent pattern in nature but one not previously reported with VEGF in articular cartilage.
NMRC/0689/2002 **PI:** Kesavan Esuvaranathan (NUS) **Collaborator:** Ratha Mahendran		**Urine analysis for prognostic indicators of response to therapy in bladder cancer patients receiving intravesical BCG instillations** The aim of this project was to identify non-responders to BCG immunotherapy as early as possible by analysis of urinary proteins using SELDI-TOF-MS technology. The researchers analyzed samples from n=39 patients (19 responders and 20 non-responders) which were obtained before the start of BCG therapy. The samples were applied onto an anion (Q10) and a cation (CM10) chip. The spectra generated was analysed with a special computer program. For analysis the responders and non-responders were split into the training and test groups. Key protein spectra components larger than 2kD from the training group were determined and used to generate a linear discriminant model that separated the responders and non-responders perfectly on the training set. Their model used only four protein spectral components and was based on two responder and two non-responder cases in the training set. When applied to the test set that contained the remaining 17 responder and 18 non-responder cases, they obtained the same 100% success, i.e. they were able to correctly predict which patients would or would not respond to BCG immunotherapy. The identification of these discriminatory proteins and the analysis of a bigger pool of patient samples should confirm their value as prognostic indicators of response to BCG immunotherapy.

NMRC/0691/2002 **PI:** Christopher Chen Li-Hsian (SGH) **Collaborators:** Chang Hui Meng, Wong Meng Cheong, Auchus Alexander P.		**A Multi-centre, Randomised, Controlled Study Comparing Nadroparin Calcium (Fraxiparine) 3,800 Axa iu/0.4ml Twice Daily with Aspirin 160mg Once Daily for the Treatment of Acute Ischaemic Stroke (FISS-tris Study)** Funding approval was obtained at the end of November 2002. The researchers began utilizing the funding from 1/1/2003. Unfortunately, recruitment of patients as well as research staff was severely disrupted by the SARS outbreak. A trial coordinator and research sonographer were eventually employed in October 2003 after the acute stroke service returned to pre-SARS standards. Due to the sterling efforts of the Stroke Trials Unit, they achieved their recruitment targets and recruitment ceased in September 2004. Their site contributed 114 patients towards the global total of 599 patients. They also recruited 44 patients to the FISS-tris MES substudy. Follow-up was completed by end March 2005. The preliminary results of the main study and FISS-tris MES substudy were presented at the European Stroke Congress in Bologna in May 2005
NMRC/0695/2002 **PI:** Saw Seang Mei (SERI) **Collaborators:** Wu Hui Min, Tong Louis, Carkeet Andrew, Chua Wei Han, Hong Ching Ye, Chia Kee Seng, Yap Eric Peng Huat, Koh David Soo Quee, Katz Joanne, Stone Richard		**Changes in the Refractive Components in Myopia and Emmetropic Eyes: A Two-centre Study** **Objectives:** 1) To document the incidence rates and longitudinal changes in refraction and biometry parameters in Singapore schoolchildren 2) To evaluate in a prospective and repeated fashion the risk factors for onset myopia and links with ocular biometry parameters 3) To evaluate the effects of specific genes and environment on myopia incidence and progression in children. **Methods:** A total of 1979 children aged 7 to 9 were recruited from three schools in the Singapore Cohort study Of the Risk factors for Myopia (SCORM) in 1999 and 2001. Parent-administered questionnaires assessed risk factor status and yearly eye examinations were conducted in the schools. Digital retinal photography and the genetic analysis of the DNA buccal samples will be performed. Major accomplishments: Several risk factors such as nearwork, intelligence quotient (IQ), birth parameters and breastfeeding were associated with myopia. **Clinical significance:** This is one of the most comprehensive and longest cohorts. Further quantification of the extent of pathologic myopia and the incidence and progression of myopia will facilitate their understanding of eye growth in Asian children. These findings will provide useful and valuable scientific information for clinicians and other health care professionals.
NMRC/0704/2002 **PI:** Ho Khek Yu (NUS) **Collaborators:** Sivaraman Pary, Rajnakova Andrea, Lim Seng Gee		**The role of gastric mucosa cyclo-oxygenase and prostaglandin in the pathogenesis of gastroduadenitis and ulcer disease in uremic patients** **Background/Aims:** Gastroduodenitis and ulcers are common in uremia. Their pathogenesis is unknown but gastroduodenal lesions found in uremia are similar to those that result from ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs induce gastropathy primarily via inhibition of the cyclo-oxygenenase (COX) enzymes, which thereby reduce gastroprotective prostaglandin. The researchers investigated if a similar phenomenon occurs in uremia.

		Methods: Thirty-nine uremic patients were compared to 36 patients presenting with non-ulcer dyspepsia (NUD). Another group of 21 patients who had peptic ulcer disease (PUD) due to NSAID ingestion acted as a secondary control. All patients underwent gastroduodenoscopy. Biopsies were taken from the antrum for COX-1, COX-2 and prostaglandin E2 (PGE2) analysis. Expressions of COX isoforms were detected using immunohistochemistry and compared between groups using chi-square test. PGE2 levels were determined using enzyme immunoassay and expressed as ng/mg protein. Difference in PGE2 levels were computed using Mann-Whitney U-test. **Results:** PGE2 level (median and interquantile range) in uremic patients was 5.24 (1.97–7.82)ng/mg. This compares with 8.93 (2.30–12.00)ng/mg in NSAID ingesting PUD patients, and 19.22 (13.30–35.80)ng/mg in NUD patients. As in the NSAID ingesting PUD patients, PGE2 levels in uremic patients were significantly depressed ($P < 0.001$) when compared to NUD patients. However, no difference was observed in the gastric expression of COX-1 and COX-2 in both PUD (COX 1: 71.4%, $P = 0.87$; COX 2: 90.5%, $P = 0.63$) and uremic patients (COX 1: 59.0%, $P = 0.35$; COX 2: 89.7%, $P = 0.63$) when compared to NUD controls (COX 1: 69.4%; COX 2: 86.1%). **Conclusions:** Decrease in gastroprotective PGE2 levels in uremia may explain, at least in part, the pathogenesis of gastroduodenitis and ulcer disease in these patients. Although the exact mechanism is unclear, the similarity in the reduction of PGE2 to that in NSAID induced ulcerogenesis suggests that administration of exogenous prostaglandin might help in the alleviation of gastroduodenopathy in uremic patients.
NMRC/0718/2003 **PI:** Weber Lau Kam On (SGH) **Collaborators:** Sidney Yip Kam Hung, Khin Lay Wei, Christopher Cheng Wai Sam, John Yuen Shyi Peng		**Open versus Laparoscopic (da Vinci robotic system) Radical Prostatectomy: A Prospective Randomised Controlled Trial** The robot-assisted versus open prostatectomy study evaluates the role of robotic assisted surgery in the management of cancer of the prostate, where surgeons can perform complex prostatectomy with a reduced learning curve compared with conventional laparoscopic surgery. The comparison of the peri-operative parameters between patients undergoing robot-assisted prostatectomy and open surgery showed significant reduction in transfusion rate as well as pain score post-operatively. Robotic-assisted prostatectomy is now well received by the patients, the public as well as the surgical community. It has evolved to become the primary modality of surgical treatment for patients with localised carcinoma of prostate in their institute. To date, > 170 prostatectomies have been performed since the introduction of the robotic system in 2003, with good functional results. The long term oncological outcome remains to be revealed in years down the road. At this juncture, their goals include continuous refinement of technique, especially regarding nerve preservation (to preserve sex potency) and early return of continence.

NMRC/0727/2003 **PI:** See Hui Ti (NCC) **Collaborators:** Chew Lita Sui Tjien, Donald Yeo Hong Huang, Christopher Chen Li-Hsian, Gao Fei		**To evaluate the improvement in anemia, response to treatment, quality of life, Vascular Endothelial Growth Factor (VEGF) expression and cognitive function of cancer patients undergoing chemotherapy and treated with recombinant human erythroprotein** 45 were found eligible; however due to the high cost of recombinant erythropoietin, only 5 have consented for treatment. This is despite the negotiation with the manufacturer that has allowed first four injections to be provided free for this trial purpose (previously communicated to NMRC). In the limited sample size there was a rise in HB 0.7 to 1.8g/dl in 2-4 weeks. FACT-AN score showed an universal improvement with application of hemoglobin and there seems to be improving trends in the following cognitive domains: attention span; verbal memory, visual memory, visuoconstruction, processing speed and executive function. The most consistent pattern of improving cognitive scores appears to be in speed of information processing and executive functioning.
NMRC/0734/2003 **PI:** Gerrard Teoh Kheng Hoe (SHS) **Collaborators:** Susan Loong Li Er, William Hwang Ying Khee, Charles Gullo		**Regulation of Proliferation and Survival of Multiple Myeloma Cells by Ku86/Ku86 Variant via Signals that Mediate Immunoglobulin Isotype Class Switch Recombination** The researchers studied the biological responses of multiple myeloma (MM) cells under conditions that maximally induced immunoglobulin heavy chain (IgH) isotype class switch recombination (CSR), to determine if these signals mediated malignant transformation, growth, survival and clonal evolution. Specifically, they triggered MM cell lines via CD40 and/or interleukin-4 (IL-4), and found abnormal decoupling of CD40/IL-4 signaling pathways. Moreover, activation of MM cells via CD40 alone was sufficient to induce genomic instability. They next identified a novel protein, Ku86v-C, in at least 3 human MM cell lines, which was associated, both constitutively as well as temporally during CD40 activation with the pro-oncogenic protein, Bcl2. Since Bcl2 is the most important anti-apoptotic protein in MM, these data suggest that Ku86v-C could potentially be involved in the sustained survival of MM cells. Interestingly and unexpectedly, Ku86v-C protein was also expressed on the surface of MM cells, again both constitutively as well as following CD40 activation; suggesting that Ku86v-C could potentially be used as a target for anti-MM serotherapy. They next isolated Ku86v-C protein from cell membrane extracts of CD40-triggered MM cells and are in the process of identifying its molecular sequence. Preliminary results suggest that it is a post-translationally modified protein.

NMRC/0736/2003 **PI:** Lee Soo Chin (NUH) **Collaborators:** Adrian Leong Peng Kheong, Salto-Tellez Manuel, Elaine Lim Hsuen, Robert Yang Hong Yuan, Goh Boon Cher, Evelyn Koay SC, Theresa Tan May Chin, John Wong Eu Li		**Characterizing the functional signifiance of novel hMLH1 and hMSH2 missense mustations in Singaporean HNPCC famillies.** **Background:** Hereditary non-polyposis colorectal cancer (HNPCC) is the commonest known form of hereditary colorectal cancer (CRC) in Singapore. Mutations in MLH1/MSH2 account for up to 90% of identifiable mutations in HNPCC. They previously identified 23 MLH1/MSH2 mutations in 46 suspected HNPCC probands, of which nine were novel, and four were recurrent in Chinese. Aims: The goal of this research proposal is to (1) study a larger cohort of HNPCC probands to detect additional mutations, (2) elucidate the functional significance of novel MLH1/MSH2 mutations identified. **Methodology:** High-risk CRC patients were recruited for MLH1/MSH2 sequencing, and recurring mutations tested in cancer-free or low-risk cancer controls. Functional studies of mutations in cell lines are ongoing. Results: 29 high-risk cancer patients were recruited and comprehensive sequencing completed for 14 patients. Five additional mutations were identified. Two previously reported MSH2 recurring mutations in Chinese familial CRC patients were found to be rare or absent in healthy controls, low-risk CRC patients, and nasopharyngeal cancer patients, suggesting possible correlation between these mutations and familial CRC. Site-directed mutagenesis has been successful for two MLH1 and 3 MSH2 mutations. Transfection of wild-type and mutant MLH1/MSH2 into colorectal cancer cell lines is now ongoing for functional characterization.
NMRC/0740/2003 **PI:** Hui Kam Man (NCC) **Collaborators:** Ooi Choo Ping, Freddy Boey Yin Chiang		**Development of nanoparticle-DNA complexes (nanoplex) for efficient gene delivery** The researchers have explored the ability of nano-sized bio-ceramic particles including silica (SiO2, approx. 10nm, and = -53mV), hydroxyapatite (approx. 50nm, and = -21.05mV), and zirconia (approx. 100nm, and = +57.5mV) to act as synthetic gene carriers. Due to the extended size of hydrated DNA and its negative charge density, it is difficult for naked DNA to enter the nucleus where transgene expression could take place. They have tested various polycations to modulate the charges of the nanoparticles so they could interact with DNA to produce nearly charge-neutral DNA-nanoparticle complexes. Among the polycations tested, protamine sulfate (PS) was able to produce stable DNA-nanoparticle complexes with SiO2 both in vitro and in vivo and mediated good reporter gene expression when introduced into different human cancer cell lines. They have also employed the SiO2-PS DNA complexes for in vivo gene delivery experiments and observed that the SiO2-PS DNA complexes could target transgene expression specifically to the spleen. From time course studies, it was determined that transgene expression in the spleen could last up to 48h. Since the spleen plays a vital role in immune regulations, the potential of the SiO2-PS DNA complexes to modulate immune responses is being examined.

NMRC/0744/2003 **PI:** Mukherjee J J (NUH) **Collaborators:** Thai Ah Chuan, Florence Tan Hui Sieng, Lim Pin, Khoo Chin Meng, Khin Saw Myint		**Prevalence of Reversible Endocrine Causes of Hypertension in Type 2 Diabetic Patients with Poorly Controlled Blood Pressure.** Aggressive blood pressure control significantly reduces cardiovascular morbidity and mortality amongst diabetic patients. However, adequate BP control is achieved in only a small proportion of diabetics. Recent evidence suggests that 5-8% of adult hypertensive patients have underlying primary hyperaldosteronism (PHA). The researchers therefore prospectively evaluated the prevalence of secondary endocrine causes of hypertension, in particular PHA, in 100 patients [41 males; median age 58 yrs (range 27-74)] with type 2 DM with poorly controlled BP. Median duration of DM and hypertension was 9.5 (0.6-36) and 10 yrs (1-40) respectively. Median number of antihypertensives in use was 3 (2–5), majority (35%) being on three drugs. They found a high prevalence of PHA (14%) in these type 2 diabetic patients with poorly controlled BP. Unlike previous studies, they did not find a high prevalence of Cushing's syndrome. They therefore recommend screening for PHA, using a random PAC to PRA ratio, in all type 2 diabetic patients with difficult to control BP. Identification and treatment of this reversible form of hypertension will have a significant impact in the management of a subset of diabetics with hypertension. Screening for Cushing's syndrome and pheochromocytoma should only be undertaken in the presence of suggestive clinical features.
NMRC/0758/2003 **PI:** William Hwang Ying Khee (SHS) **Collaborators:** Gerrard Teoh Kheng Hoe, Tham Su Chin, Ho Su Chin, Patrick Tan Huat Chye, Li Sun		**Humanization of Murine Anti-Ku86v Monoclonal Antibody for Serotherapy in Multiple Myeloma** The objective of this grant was to facilitate the humanization of an anti-Ku86 monoclonal antibody for serotherapy in multiple myeloma. The anti-Ku86 murine antibody previously produced by their co-Investigator Dr Gerrard Teoh, who demonstrated the ability to induce growth arrest of CD40 activated myeloma cells. However, the murine hybridoma production has been delayed due to issues of contamination of the clone. Consequently, the researchers embarked on an alternative strategy to facilitate the production of a humanized anti-Ku86 antibody. Full length Ku86 was first cloned from a human myeloma cell line by RT-PCR. A histidine tag was added to the 3' end and cloned into a mammalian expression vector (see findings). The vector was transfected into a COS expression cell line, from which they have derived pure Ku86 antigen by purification of the supernatant through a Nickel column. The Griffin human phage antibody library (obtained with permission of the UK Medical Research Council) was used to pan for an anti-Ku86 human monoclonal antibody. While some interesting high affinity clones were isolated, they were also found to have truncated variable chain genes and therefore unsuitable for immunoglobulin synthesis. Isolation of high affinity clones by phage display has now recommenced using a new phage library (Tomlinson) from the UK MRC.
NMRC/0767/2003 **PI:** Christopher Cheng Wai Sam (SGH) **Collaborators:** Tan Puay Hoon, Marto Sugiono, Zhao Yi		**Differential expression of a novel Vascular Endothelial Growth Factor isoform, VEGF165b, in transitional cell carcinoma of the bladder** The aim of the present study was to find out the expression of the novel isoform, vascular endothelial growth factor VEGF165b in Transitional Cell Carcinoma (TCC) of the bladder, comparing it to the benign part of the same organ, and determine whether it is downregulated as reported in Renal Cell Carcinoma. For this, an estimated sample size of 34 patients with TCC bladder were recruited and samples obtained from them after surgical procedure (TURBT or total cystectomy). Total RNA was extracted and cDNA (complementary DNA) synthesized using reverse transcriptase. Exon 9

		containing isoforms was amplified by real-time quantitative PCR (polymerase chain reaction) using specific primers designed to detect only VEGF isoforms that contained the novel exon. Cloning and sequencing confirmed the identity of the amplicon. Beta-actin was taken as internal control and the Ct values of VEGF165b were compared with Ct values of beta-actin for both cancer and benign tissues and the difference in expression was determined. Significant difference was considered present if the expression of VEGF165b was at least 8 times lower or higher than the internal control. The expression of VEGF 165b was significantly higher in TCC bladder (28/34) than that of the benign tissues. In vitro transcription translation protein expression showed the presence of VEGF165b in all the highly expressed bladder tumors confirming the presence of VEGF165b in TCC of bladder. However, there was no significant difference between grading and staging with respect to the VEGF165b isoform expression. Thus, VEGF 165b was not downregulated as in Renal Cell Carcinoma and may not be anti-angiogenic as reported in RCC study.
NMRC/0771/2003 **PI:** Joseph Tessy (NUS) **Collaborators:** Shinro Tachibana, Lee Tat Leang, Peter Wong Tsun Hon, Yong Eu Leong		**Processing pathway of nociceptin and nocistatin from prepronociceptin.** Nocistatin (NST) and nociceptin/Orphanin FQ (NCP) are two important bio-peptides derived from the precursor protein prepronociceptin (ppNCP), involved in several central nervous system (CNS) functions including pain transmission. In the first part of the project, the researchers studied the structure of NST from human brain tissue and cerebrospinal fluid (CSF) samples. NST and NCP were isolated from human brain and CSF samples by affinity chromatography combined with HPLC. Mass spectrometry was used for the identification and characterization of the peptides. The presence of two different forms of mature nocistatin (NST-17 and NST-30) and a possible N-terminal methionine cleaved NST- 29 were confirmed by both radioimmunoassay and mass spectrometry. Affinity chromatography, HPLC and mass spectrometry methods used in this study were highly sensitive and suitable for identification of actual chemical structures and quantification of very small amount of peptides in biological samples (published in peptides; Joseph et al., 2006). In the second part of the project, the partial sciatic nerve ligation (neuropathic pain models) was performed on male Sprague-Dawley rats and hyperalgesia was determined using a plantar apparatus. Rats, which showed significant hyperagelgesia of the ligated limb, were used as neuropathic pain group. The whole brain tissue extract and serum were used for the quantitative analysis of ppNCP, NST and NCP by RIA. Their data indicate that NST, NCP and their precursor protein play an important role in the neuropathic pain mechanism, which is located at multiple sites, and the up regulation of NST in the brain and serum of neuropathic rats support the antinociceptive function of the NST. (preparing this part of the work for publication; enclosed a draft). Using the same strategy as human brain tissue, they have also identified the actual mature form of rat NST (NST-35). The processing of NST and NCP from ppNCP is still continuing and they may complete in few months time and will be able to publish soon as short communication. The present findings may help for the search for new treatment of neuropathic pain, which is often poorly managed by current therapies.
NMRC/0773/2003 **PI:** Loke Kah Yin (NUS)		**Characterization of CYP 11B1 Mutations in 11-Beta hydroxylase deficiency** The 11-β hydroxylase deficient form accounts for 5-8% of congenital adrenal hyperplasia. The identical presentation of genital ambiguity (females) and pseudoprecocious puberty (males) can lead to misdiagnosis, since hypertension, the clinical hallmark of 11-β hydroxylase deficiency is variable, and biochemical confirmation is not available locally. The research objective was to perform molecular characterization of CYP11B1 mutations in suspected Singapore patients and referrals from abroad. The CYP11B1 gene was PCR amplified and sequenced in 6 patients. Two previously described mutations

		were discovered (Q356X, Q338X). Two novel mutations (R374, R454C) were also characterized by cloning into the mammalian expression vector, pBudCE4. The constructs were co-transfected with wild type CYP21B expression plasmid into Griptite 293 MSR cells. Tritium labeled 17α-hydroxyprogesterone was first converted to 11-deoxycortisol by wild type 21-hydroxylase (from the co-transfected CYP21B expression plasmid), which then acted as the substrate for CYP22B1 and its mutants. The substrate was incubated for 48 hours prior to analysis with thin layer chromatography to ensure complete conversion of 17α-hydroxyprogesterone to 11-deoxycortisol and cortisol. Both the mutant CYP11B1 alleles (R374W, R454C) exhibited null enzyme activity towards 11-deoxycortisol. Molecular characterization of CYP11B1 has been established for the diagnosis of 11-β hydroxylase deficiency. Two novel CYP11B1 mutations have been characterized.
NMRC/0792/2003 **PI:** Ng Yee Kong (NUS) **Collaborators:** Peter Wong Tsun Hon, Ang Eng-Tat		**Exercise induced glial reactions in the brain, and their roles in relation to changes of cytokines** The aims of the project were to investigate how exercise may induce intrinsic immunological changes in the central nervous system (CNS), and how this change in the microenvironment may be beneficial or detrimental to the regeneration process. Glial cells are immunoregulatory agents and a source of cytokines. These mediators regulate glial cell activation in an auto- and/or para-crine fashions. This led them to hypothesize that the manner of microglial and astrocytic activation or deactivation resulting from exercise- induced dysregulation of cytokines could be related to neural degeneration, regeneration or protection in normal as well as pathological conditions such as that after ischemic stroke. The researchers have used rats' treadmill running and the middle cerebral artery occlusion (MCAO) as the experimental models for runners and stroke respectively. They compared the runners and the control (nonrunners), as well as runners-stroke and nonrunners stroke, using immunohistochemistry, real time PCR and Western blot to study changes of expression of various cytokines. Their results indicated that the runners exhibited less immunoreactivity and reduced numbers of glial cells within the HDB compared with the nonrunners. Interestingly, the mRNA and protein levels of tumor necrosis factor-alpha, interleukin (IL)-1beta, IL-6 and interferon-gamma, were significantly downregulated in the runner. Their data also suggest albeit with some inconsistency that the runners/MCAO rats had benefited from running. These observations suggest that running can result in changes to the microenvironment, in which the microglia and astrocytes exist in a state of quiescence concomitant with a reduced expression of pro-inflammatory cytokines that may lead to beneficial effects seen in ischemic stroke induced by MCAO.
NMRC/0795/2003 **PI:** Lim Choie Cheio (NNI) **Collaborators:** Hong Yin, Ng Yee Kong, Yeo Tseng Tsai, Sitoh Yih Yian, Francis Hui Kim Hoong		**Diffusion weighted magnetic resonance imaging : Visualising normal and diseased white matter** Using MR diffusion methods at 3T, diffusion tensor imaging (DTI) can be successfully carried out in the brain. White matter information, including functional neural connections, can be inferred in normal volunteers and patients with brain tumors. However, many difficulties remain especially lack of robust analysis software and biological correlations.
NMRC/0805/2003 **PI:** Wong Wai Pong (SGH) **Collaborator:** Singh Maria A Fiatarone		**Physiological, functional and psychological effects of country line dancing on older women: a randomised controlled study** Leisure activities like social dancing are well attended by older persons. However, the effects of such activities on the physical health and quality of life are not well–established. The aim of this trial was to investigate the efficacy of country line dancing (CLD) (a form of social dance) relative to sham exercise

		[stretching (S)] in older community-dwelling women selected for self-reported physical limitations. The primary outcome was six-minute walk distance (6MWD), and secondary outcomes included strength, balance, gait, range of motion, depression, self-efficacy, quality of life and disability. Thirty-eight community-dwelling older women were recruited and randomized to either CLD or S. They attended supervised classes twice a week, one hour per session for six months. Both assessors for outcome measures and subjects were blind to allocations of interventions and intention of this investigation respectively. No adverse events occurred during exercise. Preliminary results suggest that there were trends for greater improvements in some outcomes with CLD, but no statistically significant physical or psychological benefits have yet been demonstrated in this ongoing clinical trial.
NMRC/0852/2004 **PI:** Chua Kaw Yan (NUS) **Collaborator:** Lee Yuan Kun		**Development of a lactobacilli-based oral vaccine for prevention and treatment of allergic diseases** Der p 2 is one of the major house dust mite allergen involved in the induction of mite polysensitization in allergic subjects leading to allergic asthma, rhinitis and atopic dermatitis. Present treatment for allergic diseases is unsatisfactory, thus the need for improved vaccine strategies. Recent studies have shown the protective role of gut microflora in the induction of tolerance and sensitization to dust mite allergens. Thus the objective of this research is to exploit the safe probiotic nature, intrinsic adjuvancity that drives pro-Th1 immunity and immuno-modulatory properties of gram positive lactic acid bacteria (eg. lactobacilli) as a delivery vehicle for development of oral vaccine against allergic diseases. Their group is the first to express a full-length Der p2 major allergen gene in lactobacilli. The research focus of this one year pilot project was to evaluate the efficacy of recombinant L.casei expressing Der p2 (Lc/Dp2) as a prophylactic reagent in an oral-prime-protein-boost strategy on abn experimental mouse asthma model. Mice were oral primed by feeding with NaHCO3 buffer, L.casei/pLP500 (Lc/V) or L.casei/Derp2 (Lc/Dp2) and boosted with two subcutaneous immunization of Der p2 protein on the second and third week. Subsequently, these mice were sensitized by three epicutaneous patching followed by two aerosol challenges with Der p2. Mice fed with Lc/Dp2 showed attenuation of Der p2-specific IgE and IgG1 level after aerosol challenge. Overall T-cells cytokine profile of Lc/Dp2 fed mice, compared to the wildtype or NaHCO3 fed group exhibited suppression of Th-2 and pro-inflammatory cytokines, substantial TGF-β production in spleen and mesenteric lymph nodes cells and reduced splenic Der p2-specific T-cells proliferation, indicative of T-regulatory cells and tolerance induction. In addition, these mice showed significant reduction in neutrophils recruitment, a decrease in proinflammatory (TNF-α and Th-2 cytokines (IL-5, IL-13, IL-10, IL-4) in the bronchoalveolar lavage fluid (BALF) with a concurrent decrease in lung inflammation demonstrated by lung histology and total cell count in BALF, indicating an overall attenuation of allergic responses in mice fed with Lc/Dp2. The result from this pilot study will serve as a basis for future work in exploring the mechanism of immune regulation rendered by these recombinant lactobacilli.

NMRC/0854/2004 **PI:** Hui Kam Man (NCC) **Collaborator:** Eng Cher Tiew Philip		**To develop novel molecular diagnostic and therapeutic markers for non-small lung adenocarcinoma** Non-small cell lung carcinoma comprises about 80% of all human lung cancers. This is further subdivided into various subtypes including squamous cell carcinoma, adenocarcinoma, and large cell carcinoma, as well as, others. The incidence of adenocarcinoma has been steadily increasing, comprising about 50% of all non-small cell lung adenocarcinoma seen currently. While the stage at diagnosis has prognostic and therapeutic implications, histopathological analyses could not predict clinical response to chemotherapy. Therefore, although the improvement in survival with the use of chemotherapy in these patients was statistically significant, these results are interpreted by the oncologists with a certain degree of skepticisms. This stems from the fact that, in general, it is not easy to predict tumour behaviour. The management principles of non-small cell lung adenocarcinoma are still based primarily on the anatomical distribution of the disease and hence its resectability. In this proposal, the researchers have combined clinical and gene expression data with the objective to stratify disease patterns and treatment outcomes as well as the development of novel diagnostic and therapeutic markers.
NMRC/0861/2004 **PI:** Anantharaman (SGH) **Collaborators:** Charles Rabind Anthony, Teo Wee Siong, Tiruchittampalam Mohan, Lingamanaicker Jayaram, Suresh Shirley, Wu Yingjuan, Ng Kenneth Kwan Chung, Lim Swee Han, Chua Siang Jin Terrance, Kam Ruth, Chan Kim Chai, Tay Seow Yian, Manning Peter George		**A Multicenter, prospective, randomised study comparing the efficacy of high versus low biphasic energy defibrillation in patients with cardiac arrest (HILOBED)** The HILOBED study was designed to test the effectiveness of high-energy biphasic versus low-energy biphasic defibrillation for patients who have collapsed as a result of Ventricular Fibrillation in an in-hospital environment. The study is still ongoing. After a period of community and public consultations and publicity in the print and broadcast media, the trial got off the ground. To date a total of 66 patients have been recruited. Basically, patients presenting in either Emergency Departments or Cardiology Wards in the participating sites with ventricular fibrillation would undergo biphasic defibrillation with either low-energy shocks beginning at 150 joules, or high-energy shocks beginning at 200 joules. Primary endpoints would be Return of Spontaneous Circulation and survival at 24 hours. Secondary endpoints would be survival at 30 days and evidence of myocardial damage as a result of the defibrillation. Involving seven study sites in four medical campuses, this is the only such in-hospital study on this issue being conducted anywhere in the world. The study is expected to be completed in early 2007. Whatever the results of the trial, they will have major implications on defibrillation energy guidelines for collapsed patients.
NMRC/0862/2004 **PI:** Tagore Rajat (NUH) **Collaborators:** Saw Sharon, Chan Yiong Huak		**A cross sectional study to correlate cardiac dysfunction and severity of renal failure with new biochemical markers i.e brain natriuretic peptide (BNP, NT proBNP) in patients with chronic kidney disease** A cross sectional study of adults with chronic kidney disease [CKD] with [GFR] glomerular filtration rate between 15 and 60ml/min, without evidence of cardiac dysfunction. A correlation of 2 Dimensional echocardiographic [2DE] assessment of myocardial function with sensitive, well studied [in non CKD population] biochemical markers i.e. natriuretic peptides were studied in 150 patients, euvolemic and asymptomatic [for cardiac dysfunction] from renal clinic. In addition to various relevant biochemical tests, N Terminal Pro B Type Natiuretic peptide [NT Pro BNP] and B Type Natiuretic peptide [BNP] were assayed with standard commercially available kits at recruitment and on the day of echocardiography. The following were the main observations so far. In absence of clinical and 2DE evidence of myocardial dysfunction, there was a negative correlation of GFR with NT pro BNP [-0.397, P= 0.001], BNP did

		not show any significant correlation [-0.072, P=0.435]. BNP may therefore be a better biochemical marker than NT pro BNP in absence of the affect of GFR. Myocardial systolic function is retained even in advanced CKD. GFR negatively correlates with severity of diastolic dysfunction and [P<0.05] and with visual left ventricular ejection fraction, but not with LV Mass Index [r= -0.055, P= 0.5] and circulating BNP.
NMRC/0864/2004 **PI:** Lo Yew Long (NNI) (SGH) **Collaborators:** Tan Seang Beng, Chan Ling Ling, Tan Chong Tien		**Cervical spondylotic myelopathy: clinical, electrophysiological and imaging study in a large series** Cervical spondylotic myelopathy (CSM) is a common degenerative mechanical compression of the cervical cord, with impingement by osteo-cartilagineous elements within the spinal canal. It is mostly a gradual process in which patients present at various clinical stages of severity.There are no large series addressing systematic correlation between transcranial magnetic stimulation (TMS) findings and MRI abnormalities in patients with various degrees of CSM since the introduction of both techniques in the last decade. This study aims to critically analyze the actual correlation of TMS findings with the degree of cord compression on MRI scans in patients presenting with symptoms and signs suggestive of cervical myelopathy. The researchers defined the technique of pectoralis major nerve conduction and demonstrated its value in differentiating brachial plexopathy from cervical root lesions. Building on this finding, they found that pectoralis major motor evoked potentials from TMS were useful for electrophysiological evaluation of cord compression in CS. While TMS is not a substitute for MRI, it is of value as a rapid, inexpensive and non-invasive technique for screening patients before MRI studies. They are currently studying the value of preoperative TMS in relation to surgical outcome for CSM patients.
NMRC/0867/2004 **PI:** Dawe Gavin Stewart (NUS) **Collaborators:** Tan Tiang Hwee Donald, Ahmed Sohail, Chew Tec Kuan Paul, Ng Yee Kong		**Can fetal neural stem cell tranplants to the glaucomatous rat eye enhance light-flash evoked responses in the brain?** Glaucoma is the world's leading cause of irreversible blindness. Elevated intraocular pressure (IOP) results in progressive loss of the visual field. In many cases, raised IOP can be controlled pharmacologically or surgically and the degeneration slowed or halted. However, currently, the damage which has already occurred before presentation cannot be reversed. The aim of this project is to explore the potential of intraocular stem cell transplants to reverse the loss of vision in glaucoma. The researchers transplanted fetal neural stem cells (NSCs) from enhanced green fluorescent protein transgenic mice into the eyes of rats with an episcleral vein cautery (EVC) model of glaucoma and IOP controlled with timolol. NSCs survived in timolol-treated eyes and showed morphological and immunohistochemical evidence of differentiation. Light flashes to shamtransplanted glaucomatous eyes resulted in reduced cortical visual evoked potentials compared to control eyes. In some, but not all eyes, NSCs improved visual evoked potentials. Further investigations would be required to determine whether the improvement was attributable to replacement of retinal ganglion cells projecting to the brain or to increased connectivity or neuroprotection within the retina permitting host retinal ganglion cells that had survived glaucoma to contribute to stronger visual evoked potentials.
NMRC/0903/2004 **PI:** Hsu Li Yang (SGH) **Collaborators:**		**A molecular and clinical study of methicillin-resistant staphylococcus aureus (MRSA) strains in Singapore** **Objectives:** To study the epidemiology and molecular characteristics of methicillin-resistant Staphylococcus aureus (MRSA) strains isolated in restructured

Lin Tzer Pin Raymond, Tee Nancy Wen Sim		hospitals in Singapore. **Methodology:** Consecutive MRSA strains isolated from clinical specimens obtained at KKWCH, NUH and SGH for the month of May 2005 were collected and tested. In addition, strains fulfilling criteria for community-associated MRSA (CA-MRSA) irregardless of date of isolation were also submitted by collaborating microbiology laboratories. All strains were confirmed as S. aureus and typed via pulsed-field gel electrophoresis, multi-locus variable-number tandem-repeat analysis, and multilocus sequence typing. All strains were also tested for carriage of different types of staphylococcal chromosome cassette mec as well as susceptibility to the antibiotics vancomycin and mupirocin via the E-test method. Selected isolates further underwent toxin gene profiling via multiplex PCR methods. Brief clinical and epidemiological data of each patient from whom the respective MRSA strains were isolated were also collated via chart review. **Results:** Typing of healthcare-associated MRSA (HA-MRSA) clearly defined the two major local clones as ST239-MRSA-III and ST22-MRSA-IV. ST22 HA-MRSA had only appeared in Singapore since 2003, but currently accounts for 30% to 45% of all HA-MRSA locally. It is less frequently associated with severe invasive infections, and appeared to be associated with less mortality than ST239 HA-MRSA.CA-MRSA rates had increased progressively and dramatically over the past 2 years in Singapore. The majority of strains belonged to ST30-MRSA-IVc, and were associated with cutaneous abscesses in young adults. **Follow-up:** Typing databases for both HA- and CA-MRSA have been established. It is clear that the local situation with the latter organism needs to be monitored closely.
NMRC/0939/2005 **PI:** Toh Chee Keong (NCC) **Collaborator:** Chuah Khoon Leong		**Identifying the prevalence and prognostic significance of non-tobacco related factors in non-small cell lung cancer: development of an etiology-based epidemiological database** The objective of the study is to examine representative histological specimens of non-small cell lung cancer in order to identify possible etiological factors other than smoking that could be potentially important in their population. The researchers are performing immunohistochemical staining for estrogen/progesterone/Her-2 receptors on lung cancer tissues as well as doing in-situ hybridization for human papillomavirus and ebstein-barr virus on the tissues. They will look at the differences in prevalence of these factors between smokers and never-smokers as well as between men and women with lung cancer. The project is still on-going, thus results are still pending.
NMRC/CPG/001/2003 **PI:** Aw Swee Eng (SGH) **Collaborators:** Tan Eng King, Tien Sim Leng, Cheah Peh Yean, Xiao Zhi-Cheng, Lai Mitchell K P, Woo Keng Thye, Khoo Daphne, Sun Li, Tan Guet Khim		**Setting up a Core Affymetrix Microarray Facility for SGH** The Department of Clinical Research (DCR) is grateful to the support received from the National Medical Research Council for the acquisition and set up of a Core Microarray Facility on the Outram Campus for communal use by researchers within Singapore General Hospital (SGH). It has proven to be useful for gene expression profiling and other genomics experimentation and analysis, and enhanced further progress in clinical research and that of the projects utilizing it. As the Affymetrix system is the leader in the industry of genechip analysis, and hence used by many other research institutions, it has also greatly facilitated collaboration across institutions.The programme was smoothly implemented since it was awarded in October 2003. An experienced DCR Research Scientist, Dr Michelle Tan has been assigned to oversee the general operation of the system and the

		availability of a local Affymetrix Application Specialist ensures that the system is optimally utilised and proper training is conducted. Around February 2004, the programme received additional support from SingHealth Cluster Research Fund (about S$30,000) and the Department purchased the Spotfire Microarray Analysis software as well as the Genechip DNA Analysis Software for human mapping 10K array analysis. In addition, in March 2006, the DCR optimize available funds from its Institutional Block Grant (IBG) in FY2005 to purchase the Genomatix ChipInspector/BiblioSpherePE Package (about S$60,000), a new online scientific software for the complex analysis of many Affymetrix data. This complements specific features beyond the initial microarray data output processed using the Affymetrix Data Mining Software.
NMRC/CPG/009/2004 **PI:** Golay Xavier (NNI) **Collaborators:** Sitoh Yih Yian, Rajapakse Jagath Chandana, Lim Choie Cheio Tchoyoson, Lim Shih Hui		**Fast and Strong Gradient System for Advanced Applications in High Field Magnetic Resonance Imaging** This project was put together in order to get an advanced gradient system for NNI's 3T MRI system. Thanks to this grant, the researchers got the upgrade, and it is being used on a daily basis on patients. Thanks to this gradient system, they managed to reach all their objectives in terms of increased signal-to-noise ratio, reduced acoustic noise in heavy-duty sequences, and improved overall image quality.
NMRC/SRG/003/2003 **PI:** Tan Puay Hoon (SGH) **Collaborators:** Tan Soo Yong, Chiang Shih Chuin Gilbert, Chong Pek Yoon Angela, Chui Paul, Bay Boon Huat		**Pathology of renal changes in SARS: insights into pathogenesis** **Objectives:** There is scant data on the morphologic impact of severe acute respiratory syndrome (SARS) on the kidney. The researchers aimed to detail renal histologic and ultrastructural alterations in individuals afflicted by SARS, and to understand the pathogenetic mechanisms. **Methodology:** Kidney tissues from autopsies were pathologically reviewed for alterations in renal glomeruli, tubulointerstitium and vessels. Inflammatory infiltrates within the interstitium, immune deposits in different renal structures were characterised immunohistochemically. Electron microscopy of reprocessed paraffin embedded kidney material was performed to determine the presence or otherwise of viral particles, virally driven changes in cellular organelles, and immune complexes in the different renal structures. **Results:** Out of 6 autopsies evaluated, 2 revealed thrombotic microangiopathy with glomerular and arteriolar fibrin thrombi. Acute tubular necrosis was observed in 4 cases. The interstitium was mostly oedematous with patchy lymphocytic aggregates. Vessels were otherwise unremarkable. No cytopathic alterations were seen histologically. Immunohistochemistry showed tubular casts highlighted with IgA. Lymphocytic infiltrates were T-immunophenotype with admixed plasma. Electron microscopy disclosed numerous lysosomes within tubular epithelial cells, without convincing viral inclusions. **Conclusions:** Though tubular damage and thrombosis in the kidneys may be aetiologically

		related to SARS, their findings do not unequivocally verify this link, and it is possible that these changes are pre-terminal.
NMRC/SRG/004/2003 **PI:** Fung Shuen Sheng Daniel (IMH) **Collaborators:** Wang Adrian, Fones Calvin Soon Leng, Chen Cecilia, Kwek Seow Khee		**Understanding resilience in the face of crisis: The Aftermath of SARS** The project attempted to identify personal resilience and resilience factors within the family that helped health care workers deal with adverse conditions, such as during the outbreak of SARS in Singapore. Nurses who worked in the SARS-affected hospitals were recruited in the study. This was a two-phase study, with phase one utilizing semi-structured interviews to elicit responses from 30 nurses and some of their family members on how they have coped during the SARS outbreak. The responses were coded into frequencies and constituted the basis to construct a family resilience questionnaire for phase 2 of the study. Phase two involved distributing the questionnaires to 111 nurses and 77 family members. Results indicated that family resilience predicted psychological health above and beyond individual resilience. Factor analysis found that family resilience consisted of five elements: (1) Family solidarity (family bonding and care), (2) Meaning-making (make sense of the situation), (3) Spirituality-faith in God, (4) Spirituality-Ancestors worship, (5) Emotion regulation. Analyses performed at the family system level revealed that the level of family resilience and the extent of having a shared perception on family resilience played an important role in the adaptation and well-being of the individuals.
NMRC/SRG/006/2003 **PI:** Tan Soo Yong (SGH) **Collaborator:** Kok Elsie		**Detection of infectious agents in biopsy and cytological specimens of patients with SARS-like symptoms: use of immunohistochemistry and insitu hybridisation** **Aim:** To evaluate and select a panel of antibodies for the detection and diagnosis of infectious agents in serious respiratory infections that may mimic SARS. **Methodology:** Biopsy and cytology specimens received from patients with respiratory symptoms were studied. A panel of antibodies and probes was tested on any remaining specimen after standard diagnostic procedures were completed. The study aimed to assess the efficacy of such a diagnostic panel in the early detection of various infective agents that may give rise to SARS-like conditions. **Results:** Immunohistochemistry and insitu hybridization using a selected panel of antibodies and probes proved to be useful in the identification of common respiratory viruses in cytological and histological specimens. **Relevance to clinical medicine:** Detection of respiratory viruses by molecular methods is now the standard modality of investigation. However, there are instances when the only material available is paraffin embedded tissue sections, especially in autopsy settings. This study has identified suitable reagents and established protocols for detection of common respiratory viruses.
SERI/009 **PI:**		**Developing Molecular Tests for Rapid Identification of Clinical Pathogens Causing Severe Ocular Infections**

Chan Tat Keong (SERI)		The main objective of this study is to develop a rapid molecular diagnostic tool for the detection of important pathogens from ocular isolates. In their study, the researchers investigated the utility of nested PCR (both conventional and real-time) in severe ocular infections, including endophthalmitis, keratitis, scleritis and conjunctivitis. In all of the clinical specimens analyzed, PCR improved the detection by 65% as compared to that of culture (25%). The organisms in the PCR-positive specimens were further identified by using specific primers. They further proved that by using real-time PCR with SYBR Green system on selected clinical ocular specimens, the results obtained were the same as those of conventional PCR. Above that, quantitative data of the pathogen load could also be obtained by real-time PCR. A subgroup of the ocular specimens analyzed in their study were obtained from the study of "The effect of preoperative Povidone-Iodine with or without preoperative topical Tobramycin on anterior chamber bacterial contamination during elective cataract surgery" (S.P.Chee et al). A total number of 400 patients were randomly divided into two treatment arms: Group A patients were given preoperative tobramycin in the eye undergoing cataract surgery while Group B patients were only given placebo eye drops or normal saline. All patients were subjected to preoperative povidone-iodine treatment to remove any normal flora from ocular surface. In conclusion, the nested PCR protocol they developed in this study has a great potential to be used as a reliable and rapid diagnostic method for ocular infections. Furthermore, real-time PCR can be applied to a wider range of ocular infections due to its extreme speed and quantitative nature of the data obtained.
NMRC/0246/1997 **PI:** Mahesh Choolani (NUS)		**Diagnosis of fetal growth retardation using 3-dimensional assessment of fetal liver volumes** Three dimensional fetal ultrasound is effective for the visualisation of fetal congenital defects, but not yet precise enough for volumetric measurements of fetal organs for the accurate diagnosis of fetal growth restriction. Three dimensional fetal ultrasound is a useful adjunct, and in some cases superior, to standard two-dimensional sonography for fetal anatomic visualisation. It has an additional important role in the appropriate counselling of couples owing to a more natural surface rendition of the fetal anomalies.

NMRC/0581/2001 **PI:** Low Chian Ming (NUS) **Collaborators:** Stephen F. Traynelis Xiaodong Cheng Jim Snyder Hisato Jingami K Swaminathan		**Structural and functional studies of glutamate receptor proximal N-terminal domain** Objectives – The researchers hypothesized that the proximal N-teminal domain (hereby called ATD; called LIVBPlike domain in original grant proposal) of NMDA receptor can operate as a discrete modulator binding domain as well as play a role in oligomerization of the receptor. Methodology – Bacteria expression of isolated ATDs of NMDA receptor subunits, biochemical binding assays to demonstrate ATD specific binding to respective ligands, attempt protein crystallization and patch-clamp electrophysiology analyses of the ATD in NMDA receptor. Major accomplishments – Their lab has successfully (a) Project achievements: Fully characterized ATD of NR2B and partially on ATD of NR2A and demonstrated ATD can form discrete modulator binding domain as well as can form dimer biochemically, setup and promoted patch-clamp electrophysiology capabilities in their lab and Singapore, attempted protein crystallization of ATD of NR2B. (b) Manpower (total 22; 17 are Singaporeans): trained 9 research assistants, 2 postdoctoral fellows, 3 Honours students, 2 UROPS, 2 PhD students, 1 undergraduate student (now NGS scholar) and 3 polytechnic attachment students. (c) Publications: 3 international publications, 5 posters and 2 oral presentations. Other relevant information – Awards: Young Investigator Award, Asian-Pacific Society for Neurochemistry and Young Investigator Award, The Japanese Society for Neurochemistry.

Annex 2: Abstracts of Completed Projects under NMRC-STB Medical Research Fellowship/Scientist Award in FY2005

Dr Adrian Low Fatt Hoe (Dept of Medicine, NUS) **Place of training: Massachusetts General Hospital, USA**		**The genetics of acute myocardial infarction** During his 2 years at the Cardiovascular Research Center and Massachusetts General Hospital, Dr Low was engaged in several research projects. These include: 1. The study of progeric genes in patients with premature coronary artery disease. 2. Genetic and novel biomarkers in patients with atrial fibrillation. 3. The pleiotropic effects of statins, employing the zebrafish as a novel biological system to test the varied chemical pathways. 4. The clinical application of optical coherence tomography in the evaluation of vulnerable plaques. In the course of the above projects, Dr Low underwent comprehensive training in the methods of human genetic studies which included patient enrollment, characterization of phenotype and genetic epidemiology and molecular genetic analysis. Drs Calum MacRae and Christopher O'Donnell (Deputy director, Framingham Heart Study) initiated a project in 1999 evaluating the genetics of patients with premature coronary artery disease. Dr Low, Dr MacRae and Dr O'Donnell began a systematic analysis of the 500 patients that were recruited. This included studying novel pathogenic mechanisms. Specifically, they evaluated the hypothesis that common variants in progeric syndrome genes may be associated with premature coronary artery disease. Using a combination of TaqMan probes and direct sequencing, they did not identify any significant differences in a preliminary screen of 295 probands when compared to a population of patients without coronary artery disease; this work has been published. Dr Low cooperated with Dr Patrick Ellinor and identified several novel biomarkers including C-reactive protein, natriuretic peptides, and apelin among patients with lone atrial fibrillation. The results from this study have also been published. Experience was gained in the multiple ELISA assays which were a fundamental technique in the research. In addition to the aforementioned projects, Dr Low was also using the zebrafish as a model system for studying vascular biology. This experience has included a wide range of vascular and molecular biology techniques including bioinformatics, small molecule screens, assay development, genomic analyses, cDNA and genomic cloning, in situ and quantitaive RNA analysis, transgenesis, and morpholino 'knockdown' experiments. He is currently in the process of writing up and publishing the research findings. In his clinical year, Dr Low also became involved in a project with Dr Ik-Kyung Jang. The project involved optical coherence tomography which is a novel technique enabling "in vivo histology" of coronary arteries. They are also currently writing up the project for submission to a reputed journal. Since Dr Low's return to Singapore, he continued to keep up to date with his research interests and has just submitted a BMRC grant (with Prof. Chia Kee Seng and Dr Tai E Shyong as collaborators) to study the genetics of acute myocardial infarction in the multi-ethnic population of Singapore. Dr Low is currently involved in projects which deal with the study of non-traditional cardiovascular risk factors and the conception and evaluation of a novel thrombectomy device by collaborating with engineers from the Nanyang Technological University.

Dr Ang Hui Chi Annette (Dept of Otolaryngology, NUH) **Place of training: National University of Singapore**		**Nasal polyposis: A immunohistochemical study of cell cycle proteins in epithelial proliferation** Nasal polyposis is thought to be a multifactorial disease of the nasal mucosa, which is characterised clinically by the presence of oedematous masses in the nasal and paranasal cavities. The disease is well-known to recur despite recent advances in medical and surgical management. The precise mechanisms underlying the pathogenesis of nasal polyposis are not clearly understood. In this thesis, a literature review of recent theories of pathogenesis, histopathology and current management of nasal polyposis is presented. Findings of an immunohistochemical study of polypoidal epitheliumin in relation to its proliferation index and expression of cell cycle markers are also presented. Twenty-five specimens of nasal polyp mucosa and 10 specimens of normal, non-polypoidal inferior turbinate mucosa were investigated using technique of immunohistochemistry. The exact protocols used in Dr Ang's experiments are presented. The immunostaining of Ki-67, p21, p27, p53 and p63 within nasal polyp mucosa and inferior turbinate mucosa were obtained. Quantification of results was performed by 2 independent observers. Comparison of means between the 2 groups was performed using 2-sample t-test. The immunohistochemical and numerical results are presented. Multiple regression of the various immunolabelling indexes (p21, p27, p53 and p63) vs. proliferation (Ki67) index was analysed. Dr Ang's team detected a statistically significant higher proliferation index in nasal polyp mucosa. In addition, the expression of cell cycle proteins p21, p27 and p63 were significantly decreased as compared to that of non-polypoidal mucosa. Dr Ang's team failed to detect any significant difference in p53 expression in nasal polyps, in contrast to previous authors in this field. More importantly, using multiple regression, Dr Ang's team confirmed that the assessment of p21 and p27 immunolabelling indexes together is a useful predictor of Ki67 activity (increased proliferation) in nasal polyps but not in non-polypoidal mucosa. A discussion of the results in the light of recent findings of the roles of the above cell cycle markers is presented. It is likely that with down regulation of p21 and p27, dysregulation of epithelial proliferation is present in the diseased nasal polyp mucosa. Perhaps, p21 and p27 may be used as plausible predictors of biological behaviour of nasal polyps. The downregulation of p63 suggests a dysregulation in the differentiation pattern of nasal polyps as compared to non-polypoidal mucosa.
Dr Au Wing Lok (Dept of Neurology, NNI) **Place of training: Parkinson's Research Centre, University of British Columbia, Vancouver, Canada**		**Surrogate markers of the cortical dopaminergic system in patients with Parkinson's disease** This work was part of a larger study to examine the spatio-temporal compensatory mechanisms in Parkinson's disease (PD) using electroencephalography (EEG), electromyography (EMG), and functional magnetic resonance imaging (fMRI). In the NMRC proposal, Dr Au's team aim to identify surrogate markers of cortical dopaminergic activity with high temporal resolution in patients with PD using EEG. The secondary aims were to study the effects of dopamine on the frontal midline theta (FMT), and to correlate the error detection process with FMT.The study was divided into three phases: a) design and set-up of experiment, b) data collection, and c) data analysis **Phase 1: Design and set-up of experiment** As there has been no study on FMT in PD patients, Dr Au's team had to create novel study paradigms and digital signal processing algorithms to isolate the FMT on EEG. These works were done in collaboration with the Master students from the Medical Physics Department and the Electrical and Computer Engineering Department. **Phase 2: Data collection** Dr Au's team recruited 14 patients with mild to moderate PD and 10 age-matched normal

		volunteers. Subjects with atypical parkinsonism, psychiatric disorders, and those on antidepressants, sleeping tablets or dopamine blocking agents were excluded from the study. All subjects underwent continuous joystick tracking tasks of varying difficulties, while EEGs were being recorded. PD patients had two studies in a day, one before and the other after levodopa medication. Control subjects had only one EEG study. Dr Au's team also collected surface EMG data as part of a related study. **Phase 3: Data analysis** In the original proposal, Dr Au's team aimed to analyze the data using a novel form of independent component analysis (ICA) developed by Dr Rajapakse. ICA is a technique that can be applied on EEG data to isolate the various source components that are active in the brain and/or muscles while a subject is performing a certain task. However, there were technical issues to be resolved, and given the time constraints, the supervisors had decided to use another form of ICA (mexica) with digital signal processing algorithms written by Dr McKeown. **Results** Using mexica, Dr Au's team were able to extract independent components with scalp mapping over the midline regions in all subjects. Frontal midline theta (near Fz) were present in 60% of control subjects, 71.4% of PD patients after overnight withdrawal of antiparkinson medications, and 57.1% of PD patients after levodopa was given. The central midline theta (near Cz) were present in 90% of control subjects, 71.4% of patients in the 'off' state, and 78.6% of patients in the 'on' phase. During tracking tasks, the frontal theta powers (6-7Hz) were significantly increased in both control and PD subjects. This is consistent with current observations of increase FMT during tasks that demand concentration and attention. Levodopa medication, however, had unreliable influence on FMT bursting (McKeown MJ and Au WL. Society for Psychophysiological Research Symposium, Lisbon, Portugal, Sep 22-25, 2005). Instead, Dr Au's team found a relationship between the central 4-6Hz theta powers and the underlying dopaminergic activity. The central theta powers correlated positively with the UPDRS motor scores in the 'off' state, and were reduced after levodopa was given. The powers were also increased during tasks with greater observed errors among PD patients after overnight withdrawal of antiparkinson medication. These findings suggest a resemblance between the central midline theta and the error-related negativity (ERN), the latter being generated as a result of phasic decrease in dopamine during 'worse than expected' situations. The findings suggest a negative relationship between the central midline theta powers and the cortical dopaminergic activities (Au et al. Manuscript in preparation) **Improvements in medical care and treatment arising from the project:** EEG is a noninvasive tool commonly used in clinical neurology. By applying ICA and other digital signal processing algorithms to the EEG data, Dr Au's team may isolate certain rhythms from other types of ongoing EEG activity. The techniques allow them to study these rhythms in detail and to correlate with underlying brain processes. In particular, the team observed a negative relationship between the central midline theta powers and the cortical dopaminergic activities. The preliminary findings are encouraging, suggesting possible surrogate markers of cortical dopaminergic system. The ultimate goal is to utilize neurophysiological and neuroimaging data to study underlying brain processes in Parkinson's disease and other neurodegenerative conditions. Better understanding of these processes and their characteristics will ultimately translate to better care and management for the patients.
Dr Chai Yui Chuei Josiah (Dept of Neurology, NNI) **Place of training: University of Rochester, USA**		**Vascular adaptation in Fascioscapulohumeral Muscular Dystrophy – An Immunohistochemical Study** **Background:** Fascioscapulohumeral muscular dystrophy (FSHD) is the third most common form of muscular dystrophy. Although the genetic lesion has been identified to be due to deletions of DNA tandem repeat (D4Z4) on chromosome 4q35, the cellular mechanism involved in the pathophysiology is unknown. Prior microarray analysis suggests an overexpression of vascular smooth muscle gene. Further, most FSHD individuals have subclinical retinal telangiectasias and have muscle biopsy specimens showing inflammatory infiltrates surrounding perimysial blood vessels. These suggest vasculopathy as a pathophysiologic mechanism common to both.

		Objective and Methods: Dr Chai's team decided to explore this hypothesis that vasculopathy contributes to the pathogenesis of FSHD by independent methods: a) Applying immunofluorescence (IF) to muscle sections for protein that is disease specific and appears biologically relevant. b) Investigating FSHD-specific changes in skeletal muscle microvasculature in muscle sections by IF using smooth muscle and endothelial cell markers. Needle muscle biopsy samples of genetically confirmed FSHD patients were obtained and processed for histopathological analysis using light microscope. Confirmations at the protein level using IF are then performed for differentially expressed genes that are deemed of biologic significance for FSHD. One of the genes which is involve in angiogenesis and found to be specifically upregulated in FSHD is Endoglin or CD105. This is a cell-surface glycoprotein recently identified as an optimal indicator of proliferation of human endothelial cells, including vascular smooth muscle cells. In addition to looking at the protein products of dysregulated genes, proteins known to be upregulated during vascular remodeling are also studied --- namely VEGF, VEGF receptors (VEGF-R1 and VEGF-R2), IL-8, Tie-1 and Angiotensin-2. Additional signs of vascular remodeling are investigated by looking at quantitative changes in the microvasculature (capillary density). Capillaries are immunohistochemically stained using Ulex-FITC viewed under a fluorescent microscope and the image is captured using a video camera. The images are then analysed using advanced imaging software (MetaView) to perform quantitative morphometric analysis and deconvolution microscopy. **Results:** CD105 was found to co-localise very well with Ulex, both of which stained the muscle capillary endothelium. However, no obvious qualitative difference was noted between FSHD specimen, normal or disease controls. The other angiogenesis markers co-localised less well but there were again no significant qualitative differences between the specimens. Even in FSHD muscle specimen with inflammatory cells seen, CD105 was not seen to be upregulated. One possibility is that that the upregulation of CD105 seen in the microarray study may be due to an inflammatory response rather than a vasculopathy. However, staining muscle biopsy specimens of inflammatory muscle disease (e.g. Dermatomyositis) with CD105 failed to show any significant difference in capillary staining pattern compared to the controls. Despite the negative immunohistochemical study, the role of vasculopathy has not been conclusively excluded. This study is still ongoing and the next phase is to analyse the microvascular density. **Learning opportunities:** The most important and clinically relevant benefit to Dr Chai is the ability to read muscle histopathology and to apply immunohistochemical staining methods. Although the numbers of muscle diseases that can be diagnosed by genetic tests are ever increasing, there remains a need to be skilled in these areas. This is because not all genetic tests are readily available or are sensitive. Coupled with the explosion in knowledge in the molecular genetics aspect of muscular dystrophies is the identification of their protein products, its structural location in the muscle fiber, its relation with other muscle proteins and the extracellular matrix. This allows for more precise diagnosis by immunohistochemical techniques. Indeed, not only is it complementary to the genetic test, it also helps in understanding of the molecular pathophysiology of the neuromuscular condition in question.
Dr Chin Tan Min (Dept of Haematology-Oncology, NUH) **Place of training: Oncology Research Institute, Singapore**		**Mutations of the *EGFR* gene in tumours and their therapeutic significance – a pharmacogenetics study** This project was done in the Oncology Research Institute (ORI), Translational Interface laboratory (TI), under the supervision of Dr Richie Soong, Senior Scientist, Head of TI. The work was done over the period of fellowship, from January 2005 to July 2005. The data from recent publication (IDEAL1 and IDEAL 2) (Fukuoka et al 2003; Kris et al 2003) reported encouraging response rates in NSCLC patients who were refractory to first and second line chemotherapy. These were exciting results given the limited therapy available for patients refractory to platinum, docetaxol, and of late alimta. In addition, the

		clinical efficacy appeared to parallel that of standard second line chemotherapy with a much better toxicity profile. Despite the promising clinical benefit, it was disappointing that only a cohort of 10-20% of Caucasian patients responded well. The question on most clinicians' minds was thus how to better identify this cohort of patients since Erlotinib and Gefitinb were expensive, costing $4000-$5000 per month. It soon was known that the clinical characteristics of patients who had favourable response are that of female, non-smokers with broncho-alveolar carcinoma. East Asians also seemed to have a much higher chance of response. Subsequent publications suggested that EGFR mutations in exons 18-21 were associated with better clinical response, with some even suggesting a better overall survival. With this in mind, Dr Chin's team set out to develop a method which can detect these mutations with a view to using this as a possible molecular tool for prediction of response to EGFR small molecule inhibitors. The gold standard for mutation detection is sequencing, and it was used in most published literature reporting EGFR mutations. However, sequencing is expensive, time consuming and insensitive to high background, thus making it a sub-optimal method of mutation detection. This is especially important given that most NSCLC patients are diagnosed on small biopsies; fine needle aspirates (FNA) and pleural fluid cytology with small amount of DNA, thus necessitating a more sensitive method. In BRCA1 and hMLH1 studies, DHPLC has been shown to be a cost-efficient alternative to sequencing with a lower limit for detecting minority alleles. Moreover, the high throughput nature of DHPLC would make it a suitable method for diagnostic work in lung cancer, the most common of all cancers. The goal of this study was to optimize a DHPLC assay for detecting EGFR mutations. Numerous PCR and DHPLC paramaters were rigorously tested to identify optimal running conditions. Using this assay, 162 lung cancer samples from Singapore, Perth and Japan were screened for mutations in exons 18-21 of EGFR. The detection limit of DHPLC was compared to sequencing in mixing experiments. Small biopsies, FNAs and cell blocks from pleural fluid were also examined to test the feasibility of EGFR mutations by DHPLC in small samples. DHPLC detected most of the commonly described mutations, namely deletions around codons 746-752 in Exon 19, T-G substitutions at codon 858 in Exon 21 and single nucleotide substitutions at codon 718 in Exon 18. Sequence variants at codons 719, 720, 836 were also detected. DHPLC detected mutations in a 1:500 mutant: wild-type mixture, whereas sequencing was only able to detect mutations in a 1:5 mutant: wild-type mixture. Mutations were also detected in small biopsies, and their presence correlated with good responders to Gefitinib. Cost analysis showed DHPLC can reduce expenses by 20%. **Results and novel findings applicable to therapeutics with small molecule inhibitors:** The results obtained showed that DHPLC can detect most of the commonly described EGFR mutations which were detected by sequencing. Importantly, given its lower detection limit and thus improved sensitivity over the current method of sequencing, Dr Chin's team believe that it may therefore explain for patients who were known responders to Erlotinib or Gefitinib, but were thought not to have the mutations based on sequencing. Hence DHPLC may be a cost-efficient and sensitive alternative for detecting EGFR mutations for future EGFR inhibitor response prediction. This work is currently being written up for publication, and has been submitted for the combined scientific meeting in November 2005, Singapore.
Dr Lam Yeng Po Paula (Dept of Cell and Molecular Research, NCC) **Place of training: University of Zurich, Switzerland**		**Construction of a replicative competent herpes simplex virus type 1 (HSV-1) vectors that could deliver gene expression in a cell cycle-dependent manner** In the research field of human gene therapy, manipulation of the viral genome is the key to improving viral vectors for delivering therapeutic genes specifically to the site of disease. In previous studies, Dr Lam's team reported on the generation of a novel HSV-1 amplicon vector that could mediate transgene expression in a cell type-specific and cell cycle-dependent manner both *in vitro* and *in vivo*. Despite the desirable feature of these vectors to trigger the transcription activities of therapeutic genes in the event of rapidly

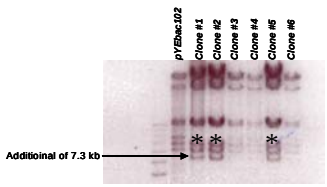
dividing tumor cells, these vectors are replication defective and faced with challenges of relatively low titre for potential clinical application.

Recently, several laboratories reported the cloning of herpes simplex virus type-I (HSV-1) genomes into an F-factor plasmid found in *E.coli* as bacterial artificial chromosome (BAC). This technique allows mutagenesis of the viral genome in *E.coli* using the bacterial reconstitution machinery. The reconstitution of infectious virus is achieved by transfection of the BAC plasmid into mammalian cells, thereby allowing the generation of desired mutant viruses more easily and quickly. Thus, the objective of this study is to reconstitute the cell cycle-specific regulatory elements in the context of a recombinant BAC vector containing the full-length infectious HSV genome via BAC recombination engineering. It is anticipated that in the scenario of a cancerous mass where intratumoral administration represents a feasible modality of viral vector delivery, it would be more relevant to generate high titre viruses so as to achieve a favorable virus to tumor cells ratio for efficient tumor cell killing.

With the support from NMRC-Hong Leong Foundation Medical Research, three strategies of BAC DNA recombination were attempted to compare the recombination efficiency. Most of the recombinant HSV-1 vectors adopted for human clinical trials are either deleted in UL39 (also known as ICP6), γ34.5 (also known as ICP34.5) or both. Such ICP6 mutant viruses depend on the complementation of ribonucleotide reductase activities by the infected cells. As ribonucleotide reductase transcription is strictly regulated by E2F that has been "freed" of Rb inhibition, which is in turn, regulated by p16. It is therefore implicated that UL39-mutant HSV-1 would alsoreplicate specifically in cells with defects in the p16 tumor-suppressor pathway. Indeed, these mutant viruses have been reported to replicate with a viral titre that is approximately 100-fold greater in tumor cells compared with normal cells (Chase et al., 1998; Yoon et al., 2000). Thus, the first step in Dr Lam's strategy is to knock out UL39 in the infectious molecular BAC clone, pYEbac102. This BAC clone contains a full-length infectious clone of HSV-1 strain F in which a BAC vector flanked by *lox*P sites was inserted into the intergenic region between U_L3 and U_L4. Viruses reconstituted from pYEbac102 replicates efficiently as the wild-type virus and exhibited wild-type virulence in mice on intracerebral inoculation (Tanaka et al., 2003).

The efficiency of BAC recombineering was reported to be high using the *gal*K selection method (Warming S et al., 2005). Dr Lam initiated the study using *galK* BAC recombineering with the support from NMRC-Hong Leong Foundation Medical Research Scientist Award (17th June til 17th September, 2005). 50% of the selected clones were positive ICP6-deleted pYEbac102 clones containing a selectable marker in place of the ICP6 gene.

Below is a figure of HindIII restriction enzyme mapping of ICP6-deleted pYEbac102 clones #1, 2, and 5 derived from method C. The 9.4 kb fragments from parental pYEbac102 were lost (as represented by *), the recombinants contained an additional 7.3 kb, indicating that these are potential positive recombinants harboring the selectable marker kanamycin gene while loosing the UL39 gene.



Future studies

The next step of the study would be to insert cell cycle-regulatory elements that have been amplified as PCR products and electroporated into newly generated recombinant pYEbac102ΔUL39 (Fig.2) that were made competent. In parallel, a vector without the cell cycle regulatory elements will also be constructed, pYEbacICP6p-luc. Depending on results of characterizing these mutants *in vitro* and *in vivo*, more HSV-1 mutants may be constructed.

		Problems encountered HSV-1 genome is highly GC-rich, it is difficult to obtain the desired specific PCR products. As a result, screening of colonies is rather tedious with many false positives. In addition, the complete gene sequence of HSV-1 strain F is unknown. This has further complicated the design of primers. **Concluding remark** Recombinant BAC pYEbac102 containing a deletion of UL39 has been successfully constructed, namely pYEbac102ΔUL39. Two versions were created; one flanking an antibiotic kanamycin selection marker while the other contain the *gal* gene. Since Dr Lam's return, she continued with the work where cell cycle-regulatory elements have been amplified as PCR products and electroporated into newly generated recombinant pYEbac102ΔUL39 that were made competent. Although this work is still at its preliminary stage, Dr Lam is hopeful that continual research could lead to improved viral vectors for potential brain tumor therapy. Dr Lam thank NMRC for its kind support for these studies.
Dr Lee Tswen Wen Victor (Dept of Surgery, SGH) **Place of training: National Cancer Centre, Singapore**		**Elucidation of expression profiles of genes in alpha-fetoprotein positive and alpha-fetoprotein negative hepatocellular carcinoma by cDNA microarray analysis** Hepatocellular carcinoma (HCC) is a leading cause of cancer death worldwide and current treatment options remain limited. Surgical resection is the mainstay of treatment. However the majority of patients are diagnosed late and surgery is precluded from its management. Among patients who undergo surgical extirpation, 50% will suffer recurrent disease. Present clinico-pathological classification of HCC is of limited value in predicting treatment outcomes and there is little known about the genetic alterations responsible for specific phenotypes of HCC, particularly with regard to alpha-fetoprotein (AFP) expression. AFP is expressed in 50% of cases, and has been shown to be useful in prognosticating patients with HCC. Patients with high AFP titres have larger tumours, poorer median survival and more aggressive biological behaviour characterized by higher grade tumours, multifocality and high recurrence rate. Dr Lee's team hypothesize that AFP positive and AFP negative liver tumors represent two distinct molecular subtypes of liver cancer and provide preliminary data supporting this possibility. They propose to utilize DNA microarray technology to further test this hypothesis on a larger set of liver specimens. Through gene expression profiling, Dr Lee's team aim to uncover specific molecular derangements and help identify potential targets for therapeutic intervention predicated upon the different phenotypes of hepatocellular carcinoma. Hence, Dr Lee's team proposed study to perform gene expression profiling of these two clinical phenotypes of HCC may contribute to a better understanding of liver carcinogenesis and allow directed therapy. **Clinical results** **1. Validation of correlation of AFP levels with histopathological features of HCC in our local population** Dr Lee's team reviewed their clinico-pathological data for hepatocellular carcinomas over the previous 6 years to validate the working hypothesis that there is a clinically different behaviour in AFP-negative and AFP-positive HCCs correlating with different histopathological features (manuscript under review), the study is summarized below. **Objective** The clinical study aimed at correlating AFP expression at two levels – AFP negative (< 20 ng/ml) and AFP positive (>20 ng/ml) with histopathological features, recurrence and survival studies in the local population. **Material and methods** The clinical records of all patients with primary HCCs who underwent surgical resection from 1999 to 2004 were retrieved from our computerized HCC database. The following histopathological features were recorded: tumour size, tumour grade (Edmonson grading), multifocality, presence of encapsulation, and presence of vascular invasion. Tumour

		recurrence was defined based on follow-up imaging examinations with ultrasonography or computed tomography, bone scans and serum AFP elevation. Early recurrence was documented as the presence of recurrence within 12 months from the time of surgical resection. The mean survival of both groups were calculated using Kaplan-Meier survival tables, and difference in survival calculated using log-rank analysis. **Results** There were 280 primary HCCs surgically resected in Singapore General Hospital from 1999 to 2004. Among them, 212 cases (75.7%) were associated with hepatitis B virus infection, which formed the basis of this study. Two patients were excluded as preoperative chemoembolisation was performed precluding adequate histopathological examination. There were 173 males and 37 females with a male:female ratio of 4.7:1. The median age was 62 years (range, 30 to 84 years). Serum AFP levels were normal (<20 ng/ml) in 87 cases (41.4%) and elevated (>20 ng/ml) in 123 cases (58.6%). Histopathological features that correlated with elevated AFP levels included the following: larger tumour size (p=0.002), higher tumour grade (p=0.011), presence of vascular invasion (p=0.002), and multifocality (p=0.002). The presence of cirrhosis (p=0.767) and fibrous encapsulation (p=0.343) did not correlate with elevated AFP levels. Of the 131 patients available for analysis of early recurrence, elevated AFP level was significantly associated with early recurrence (p=0.008). Mean survival was significantly longer in the cohort with normal AFP levels (65.8 months) compared to the cohort with elevated AFP levels (47.5 months) (p<0.001). **Conclusion** Dr Lee's team conclude that AFP expression in viral hepatitis B related HCCs correlates with poor histopathological features, early recurrence and poor prognosis. **2. Initial molecular profiling work on 11 clinical samples** Dr Lee's team performed gene expression profiling of an initial 11 liver cancer samples utilizing Affymetrix U-133A chips. The clinicopathological characteristics of the profiled 11 tumours with AFP positive and AFP negative expression is representative of the earlier cohort described with regards to vascular invasion and tumour recurrence. The tumour size in both these groups were comparable, as such tumour size is not a significant discriminator (p=0.529). Hence, tumour size is not a confounding variable in our analysis for gene selection. This deliberate selection of tumour samples attempts to ensure that the difference in the two groups is related the different observed tumour features, and is not related to tumour size. There were 2 main cluster groups in which one cluster included only AFP positive tumours (n=4), while the other cluster included both AFP negative (n=5) and AFP positive (n=2) tumours. This cluster analysis supports the hypothesis that molecular profiling is able to identify a subclass of HCC that had more aggressive biological behaviour characterized by vascular invasion and high recurrence rate. Of note, this subclass of HCCs were all AFP positive tumour samples. Dr Lee's team completed molecular profiling of their intended sample size of 38 liver cancer samples. Provisional bioinformatics analysis has been performed for these samples. They are in the process of validating their results with immunohistochemistry and real-time PCR. They intend to present our work at the upcoming AACR (American Association of Cancer Research) meeting next year. Their work is presently successfully funded by the NMRC/0986/2005 grant.
Dr Ang Pek Kiang Leonard (Dept of Ophthalmology, NUS) **Place of training: Dept of Ophthalmology, Harvard Medical School, Massachusetts Eye and Ear Infirmary, Boston, USA**		**1. Dohlman-Doane keratoprosthesis surgery for the treatment of severe cornea and ocular surface disease** Keratoprosthesis surgery (artificial cornea) is performed to restore vision for severe blinding corneal diseases that are at too high a risk of graft failure for conventional corneal transplantation. The Dohlman-Doane keratoprosthesis was designed and developed by Prof Claes Dohlman, and stands today as probably the most widely used and most successful keratoprosthesis available. During the fellowship, Dr Ang learnt the surgical techniques involved in performing the type I and type II Boston keratoprosthesis procedures, as well as the pre- and post-operative management of these patients. Dr Ang's team also evaluated the safety and efficacy of this procedure for the treatment of

		complicated corneal cases and severe ocular surface disorders. They performed a retrospective review of patients operated from 1997 to 2004 and evaluated the long-term clinical course and outcome of these patients. In many severe blinding corneal diseases, where further keratoplasty appears futile, this method of treatment may prove to be the best option for achieving visual rehabilitation. **2. <u>New refractive surgical procedures for the correction of refractive error</u>** LASIK is the current leading refractive surgical procedure. However, because of the potential risks related to the use of a microkeratome, the creation of a stromal flap, and the risk of corneal ectasia, there is a recent trend towards surface ablation for correcting refractive errors. Epithelial laser in situ keratomileusis (Epi-LASIK) is a new surface ablative procedure, in which an epithelial flap is created and preserved, without having to cut a stromal flap. This may combine the advantages of both LASIK and PRK, while at the same time overcoming some of their problems. Dr Ang learnt the surgical technique and management of patients undergoing Epi-LASIK, and evaluated the clinical results for the initial series of eyes that underwent Epi-LASIK for the correction of myopia over a 1-year period. These results suggest that this new refractive procedure appears to be safe and effective for the treatment of myopia and myopic astigmatism. **3. <u>The role of angiogenic and anti-angiogenic factors in ocular neovascularization</u>** Neovascularization in the cornea results in opacification, scarring, and a loss of visual acuity. It is a severely disabling condition, resulting in loss of the immunologic privilege of the cornea and in visual impairment. The cornea is a powerful model for investigating the in vivo regulation of blood vessel growth. Prof Azar's team has been involved in studying the role of angiogenic and anti-angiogenic factors in corneal neovascularization. This includes investigating the role of metalloproteinases (MMP-7 AND -14) in corneal neovascularization. In addition, his team is also involved in characterising the effect of bFGF-induced mouse corneal neovascularization with hemilimbal and hemiepithelial debridement, and studying the role of VEGF-A and VEGF-C in the regulation of corneal neovascularization in the limbal deficiency model. A better understanding of the factors that modulate wound healing and neovascularization would improve our ability to treat patients with eye disease. **IMPROVEMENTS IN MEDICAL CARE AND TREATMENT** The knowledge and expertise acquired during this fellowship would be useful for expanding the capabilities of SNEC and SERI, and will allow Dr Ang to better manage many severe blinding conditions that do poorly with conventional therapy. In addition, it has also enabled Dr Ang to forge stronger ties between his institute, SNEC, and the staff at Harvard Medical School, Massachusetts Eye and Ear Infirmary, which would serve as a stepping stone for future collaboration in clinical and basic cornea and ocular surface research.
Dr Ong Eng Hock Marcus (Dept of Emergency Medicine, SGH) **Place of training: Medical College of Virginia, USA**		**<u>Comparison of Circumferential Chest Compression and Standard Cardio-Pulmonary Resuscitation in Out-of-Hospital Cardiac Arrest</u>** **<u>Purpose</u>** The AutoPulse™ (Revivant Corporation, Sunnyvale, CA) is a novel non-invasive circumferential chest compression device. Dr Ong's team aimed to compare the resuscitation outcomes with Circumferential Chest Compression CPR (Autopulse-CPR) and Standard CPR (STD-CPR) in Out-of-Hospital Cardiac Arrest (OHCA). **<u>Design</u>** Dr Ong's team conducted a phased, non-randomized, observational, before and after type evaluation of the Autopulse-CPR device in adult OHCA. Historical control data was obtained using OHCA patients who received standard manual CPR (STD-CPR).

Results

During the period January 2001 to March 2005, there were 500 cases during the standard CPR (STD-CPR) phase and 408 cases during the autopulse (CCC-CPR) phase. In the CCC-CPR phase, the Autopulse was applied for 52.6% of cardiac arrest cases. Patients in the two phases were comparable in all respects except for a slightly faster response time (mean difference of 32 seconds) in the CCC-CPR group. There was significantly higher ROSC in the CCC-CPR group (30.1%) compared to the STD-CPR group (20.4%), adjusted OR 1.66, 95%CI [1.21, 2.29]. The adjusted OR for survival to hospital admission in the CCC-CPR group (16.5%) compared to the STD-CPR group (10.3%) was 1.59, 95%CI [1.05, 2.43]. The adjusted OR for survival to hospital discharge in the CCC-CPR group (7.4%) compared to the STD-CPR group (2.8%), was 1.69, 95%CI [1.63, 1.76]. There was no significant difference between the two groups in CPC (p-value 0.75) and OPC (p-value 0.72). The Number Needed to Treat (NNT) for the unadjusted outcome survival to discharge was 21 (95% CI 13, 59).

Conclusion

This study provides the first real-world evidence that adoption of this device in an EMS setting can lead to improved outcomes in cardiac arrest.

Presentations and Publication

(i) 8 Aug 2005 Virginia Commonwealth University, Department of Epidemiology and Community Health Research Day
(ii) 24 Aug 2005 Virginia Commonwealth University, Department of Emergency Medicine Grand Rounds
For submission and presentation at the Society for Academic Emergency Medicine annual scientific meeting 2006, San Francisco
Submitted to the journal JAMA for publication.
*This is the first large scale clinical trial of an experimental mechanical CPR device that has potential to greatly improve current treatment of cardiac arrest

Controlled Therapeutic Hypothermia Post-Cardiac Arrest Compared to Standard Intensive Care Unit Therapy

Objectives

Dr Ong's team describes a prospective series of post-resuscitation patients treated on a controlled therapeutic hypothermia protocol. Survival to hospital discharge and neurological status was compared with age-gender matched controls that received conventional post-resuscitation care treatment.

Design

Inclusion criteria included: sustained return of spontaneous circulation (ROSC) after cardiac arrest, age 18 years and older, females age below 50 years with a negative pregnancy test, hemodynamically stable and patient comatose or unresponsive post-resuscitation.

Results

For the period February 2004 to April 2005, there were 15 consecutive patients treated on the hypothermia protocol in addition to conventional post-resuscitation treatment. Dr Ong's team selected 30 controls that had received conventional post-resuscitation treatment not including hypothermia. Mean time from initiation of hypothermia to achievement of target temperature 34 degrees Celsius was 261.7 minutes (SD 181.9 minutes). Mean time from initiation of hypothermia to achievement of rewarming at 36 degrees Celsius was 31.3 hours (SD 11.4 hours). Forty percent of hypothermia patients had at least a brief period of status epilepticus that was detected by continuous EEG monitoring. There was a significantly improved survival in the hypothermia group (80.0%) compared with controls (40.0%), p-value 0.0167, Fisher's exact test (2-tailed). The crude odds ratio (OR) for survival in the hypothermia group compared to controls was 2.4 (95% CI, 1.3-5.0). The adjusted OR for survival was 4.1 (95% CI, 1.5-21.2). A higher number of patients recovered with intact neurological function with hypothermia using the Cerebral Performance Category (CPC) assessment compared to controls (p-

		value 0.04). However there was no significant difference in Overall Performance Category (OPC) assessment between the two groups (p-value 0.97). **Conclusion** These results provide further support for the use of controlled hypothermia post-resuscitation and suggest the need for continuous EEG monitoring to detect and treat status epilepticus during hypothermia if paralytic agents are used.
Dr Tay Shian Chao (Dept of Hand Surgery, SGH) **Place of training: Mayo Clinic College of Medicine, USA**		**Three dimensional dynamic *in-vivo* motion studies of the wrist using a ultrafast 64-slice computed tomographic scanner** The aim of the project was to advance musculoskeletal imaging using ultra fast computerized tomography. The 64-slice CT scanner available in Mayo Clinic CIC has a gantry rotation time of 0.33 seconds which affords it a temporal resolution of 0.165 s. With such capability, it had become possible to perform CT scans of the heart even while it is beating. This has allowed cardiologists to look for coronary artery calcifications and myocardial wall abnormalities. Dr Tay's project was to develop this technology to perform real-time musculoskeletal imaging during wrist motion. The first part of Dr Tay's project was performed using a CT resolution phantom. In the second part, a cadaveric wrist was used. Motion was achieved using a custom-made motion simulator which performed periodic motion with the wrist/phantom mounted on. The scanner used was a 64-slice CT scanner (Siemens Somatom Sensation). The CT scanner protocol required for 4-dimensional imaging of a periodically moving wrist joint was developed and refined. The protocol that was eventually selected after going through several options was based on retrospective cardiac gating using a factory-customized table pitch of 0.1. Simulated ECG signals synchronized with the motion were produced by the motion simulator to allow temporal reconstructions. From the CT phantom studies, Dr Tay's team was able to define the relationship between motion velocity and motion artifacts in the CT images. They discovered that, for our setup, the frequency of motion should be 30 cycles per minute with amplitude of motion of the phantom of not more than 20 mm. This works out to a maximum motion velocity of 20 mm/s for 4D scanning. The best images were achieved at the ends of motion, when the phantom velocity was slower. This was a finding that was similar to cardiac imaging where the best images were during diastole. The proof of concept was performed using a cadaveric wrist and they found that with the wrist moving at 30 cycles per minute in radioulnar deviation, they were able to resolve both the proximal carpal and the midcarpal joint spaces. Proximal and distal intercarpal joint spaces were also well resolved. The 4D nature of the images meant that a large amount of image data was generated. Sufficient disk storage space was important. Having powerful computers was also important to process and analyze the image data. Good computational and image processing software eg. (MATLAB and Analyze) were required. Two manuscript drafts on this project have been completed and will be submitted for publication in the near future. Dr Tay's initial assumptions in the requirements of the motion simulator did not turn out to be correct and hence the motion simulator had to be revised a few times. Retrospective gated CT technology is currently the most viable means to advance musculoskeletal imaging for small joints into the 4th dimension. The ability to have high spatial resolution (0.6 mm) 3D images of joints in motion will significantly improve their investigative and diagnostic capabilities. Patients with previously un-diagnosable wrist pain may benefit and our understanding of wrist kinematics will be improved. This development could also be expanded to the study of other joints with small motion amplitudes such as the temporamandibular joints, other joints in the hand and wrist, ankle and foot joints, and perhaps the spine. The advent of 128-slice CT scanners in 2006 would also indicate further improvements in image acquisitions and quality.
Dr Wong Chek Hooi		**The determinants and components of frailty and clinical**

(Geriatric Unit, SGH) **Place of training:** **McGill University, Canada**		**intervention for the prevention of frailty in older persons** **(i) The FrFrdata substudy: Estimating the prevalence of frailty using self-reported measures from a database in Montreal** The first aim of this project is to estimate the prevalence of frailty in a community sample of elderly in Montreal based on the proposed characteristics by Fried et al (2001). The characteristics are shrinking/sarcopenia, weakness, poor endurance/exhaustion, slowness and low physical activity. The second aim is to explore the relationship between frailty and sociodemographic variables, Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADL) disability and comorbidity. The last aim is to compare results with the secondary analyses conducted by Gried et al (2001). Results showed that prevalence of frailty in cohort was 7.4%. Frailty was also shown to be associated with the female genderr, those with lower income, lower educational attainment, more chronic diseases and ADL and IADL disability. In addition, frailty is correlated with cardiovascular risk factors and arthritis and is dissociated from comorbidity and disability. These findings are important as the study has its utility in verifying and replicating the initial work on frailty done by Fried et al. As far as Dr Wong's team know, this is the first project that utilizes only self-reported measures to operationalize the frailty characteristics, This is vital in studies where performance measures could be impractical like long term care facilities and large population based studies. The study contributes to frailty research by reinforcing the importance of conceptual and operational clarification in the used of hypothesized characteristics. This study will serve as a foundation of a larger study (the Frdata study) leading to a collaborative effort among 10 international longitudinal studies on aging from Canada, the United States, Netherlands, Italy and Israel. This study will also contribute to the development of the Canadian Longitudinal Study on Ageing (CLSA). Both the FrFrdata substudy and the larger Frdata study are funded by the Canadian Institutes of Health Research (CIHR). **(ii) The effects of a later-life educational health promotion program on body composition and physical performance measures of older adults** The aim of this project is to implement a later-life health promotion program which is based on the concept of successful aging and behavioral change for older persons and evaluate its effects on body composition and physical performance. Results showed that participants improved gait speed, chair rise time and body composition. This study contributes to further the evidence that a later-life health promotion is feasible with participants improving in terms of physical performance and body composition. The study is in line with the recent declaration by WHO on the 58th World Health Assembly, 2005 on strengthening active and healthy ageing in promoting research for health promotion throughout the life course. The study has in implications in preserving physical function in an ageing population and in the prevention of frailty.

Annex 3: Research Projects Approved by NMRC in FY2006

Changi General Hospital

NMRC/0959/2005

PI: Goh, Soon Noi
Post Acute Care of the Elderly - The Interface Between Hospital and Community. A Utilization Study of Post Acute Care Services

NMRC/0979/2005

PI: Tan, Thean Yen
A study of the in-vitro activity of antifungal agents on bloodstream isolates of yeasts in Singapore

Clinical Trials & Epidemiology Research Unit

NMRC/0980/2005

PI: Deslypere, Jean-Paul
Ethnic Differences in Abdominal Fat Distribution and levels of sex hormone and their Relationship with Type 2 Diabetes and Metabolic Syndrome In Three Ethnic Groups In Singapore - A Pilot Study for A Population Based Cross-Sectional Study and Longitudinal Study on Metabolic Syndrome

Institute of Mental Health

NMRC/0967/2005

PI: Chong, Siow Ann
Depression and Diabetes Mellitus: Prevalence, cost and impact on treatment

NMRC/1002/2005

PI: Sung, Min
A Randomized Controlled Trial on the Effect of Cognitive-Behavioral Therapy for High-Functioning Children with Autistic Spectrum Disorders

KK Women's & Children's Hospital

NMRC/0942/2005

PI: Liew, Woei Kang
The Effect of Kawasaki Disease on Atopy in Children

NMRC/0981/2005

PI: Lai, Hwei Meeng Angeline
Screening for Fibroblast Growth Factor Receptor (FGFR) Mutations in Patients with Craniosynostosis

NMRC/CPG/015/2005

PI: Sia, Tiong Heng, Alex
μ-opiod receptor gene and catechol-O-methyltransferase gene polymorphisms in Asian populations and their effects on pain perception and analgesic requirement post - operatively

National Cancer Centre

NMRC/0931/2005

PI: Tang, Soo Leng Carol
Cancer stem cells in the brain: Mechanisms of chemoresistance

NMRC/0934/2005

PI: Hui, Kam Man
Characterization of murine HDMCP through targeted gene deletion by homologous recombination

NMRC/0935/2005

PI: Ho, Meng Fatt
Mapping the Gastric Cancer Proteome to Delineate Molecular Pathogenesis, Identify Tumor-Associated Biomarkers and Novel Therapeutic Targets

NMRC/0939/2005

PI: Toh, Chee Keong
Identifying the prevalence and prognostic significance of non-tobacco related factors in non-small cell lung cancer: development of an etiology-based epidemiological database

NMRC/0941/2005

PI: Lim, Wan Teck Darren
Viral carcinogens and EGFR mutations in lung cancer in Singapore

NMRC/0964/2005

PI: Zhu, Cong Ju
Study of novel function of epithelial cell transforming sequence 2 (ECT2) oncogene in glioma cell cycle progression and chemosensitivity

NMRC/0968/2005

PI: Sabapathy, Kanaga
Role and regulation of the structural and functional homologue of the p53 tumour-suppressor, p73

NMRC/0986/2005

PI: Lee, Victor Tswen Wen
An Alpha-fetoprotein-based molecular taxonomy of liver cancer: Identification of candidate therapeutic targets in subtypes of aggressive hepatocellular carcinoma

NMRC/0990/2005

PI: Lee, Ann Siew Gek
Molecular epidemiology of drug resistant Mycobacterium tuberculosis isolates from Singapore

NMRC/0991/2005

PI: Loong, Susan Li Er
Biochemical characterization of radiosensitive lymphoblastoid cell lines defective in DNA double strand break re-joining after ionizing radiation

NMRC/0992/2005

PI: Kon, Oi Lian
Cellular ontogeny of human gastric cancer: An investigation of putative gastric cancer stem cells

NMRC/0993/2005

PI: Lee, Caroline Guat Lay
Genetic and Genomic Approaches to Predicting Drug Response in Advanced Colorectal Cancer Patients

NMRC/0994/2005

PI: Ong, Yew Kuang Simon
A Phase I Dose-Finding Study Using A Chronomodulated Dose-Intensified Regimen Of Xeloda and Oxaliplatin (Xelox) As Either A First- Or Second-Line Therapy In Patients With Advanced Metastatic Colorectal Cancer.

NMRC/0997/2005

PI: Wong, Meng Cheong
Significance of quiescent cell population in chemotherapeutic response of human malignant gliomas

National Neuroscience Institute

NMRC/0936/2005

PI: Chen, Christopher Li-Hsian
A prospective study of vascular cognitive impairment in Singaporean stroke patients: ESPRIT (European & Australasian Stroke Prevention in Reversible Ischaemia Trial) Cognition Sub-Study.

NMRC/0937/2005

PI: Lim, Kah Leong
Using the 350-fold compacted Fugu parkin gene as a model to understand the regulation of human parkin gene expression

NMRC/0938/2005

PI: Dwi Pramono, Zacharias Aloysius
Development of Antisense Oligonucleotides for Molecular Therapy of Duchenne Muscular Dystrophy

NMRC/0943/2005

PI: Ng, Hua Bak Ivan
Improving neuroplasticity in traumatic brain injury - DNA vaccination in a rat study

NMRC/0944/2005

PI: Yu, Wei Ping
Functional Study of NRSF/REST in the central nervous system

NMRC/0960/2005

PI: Tang, Feng-Ru
Reorganization of the Hippocampal Memory Networks Following the Environmental Enrichment in Immature and Adult Mice after Pilocarpine Induced Status Epilepticus

NMRC/0995/2005

PI: Tan, Chew Seng Louis
Valvular heart disease amongst Parkinson's disease patients treated with Bromocriptine and Pergolide

NMRC/0996/2005

PI: Feng, Zhi Wei
Characterization and therapeutic evaluation of neuronal and myogenic progenitor-like cells cloned from bone marrow stromal cells in stroke and muscular dystrophy models

NMRC/0998/2005

PI: Tan, Choon Kiat Nigel
What is the extent of publication bias in epilepsy genetic association studies?

NMRC/CPG/012/2005

PI: Lo, Yew Long
Multidisciplinary spinal cord program grant

NMRC/CPG/017/2005

PI: Feng, Zhi Wei
Design, synthesis and evaluation of new analogs of anticancer drug, cisplatin

National Skin Centre

NMRC/1001/2005

PI: Goh, Boon Kee
Transplantation of Autologous Non-cultured Epidermal Cell Suspensions For Treatment of Vitiligo

Nanyang Technological University

NMRC/0956/2005

PI: Sugrue, Richard
Isolation and genetic characterisation of a Metapneumovirus isolated from pederiatric patients in Singapore

NMRC/CPG/016/2005

PI: Preiser, Peter Rainer
Establishment of a malaria microarray facility to study and identify parasite genes that are potential targets for an intervention strategy

NMRC/CPG/020/2005

PI: Konishi, Shiro
Search for Regulatory Mechanisms in Central GABAergic Inhibitory Synapses and Drug Therapies from TCM (Traditional Chinese Medicines) for Neurological Diseases related to Inhibitory Synapses in the Brain

National University Hospital

NMRC/0928/2005

PI: Lee, Suyin Pamelia Joan
Time versus event-related sterility: linen and pouch packaging remain sterile over a year of storage and handling.

NMRC/0929/2005

PI: S/O Sritharan Naidu, Shenthilkumar
Use of a long length, small diameter ePTFE graft to create a low flow venous system in an animal model

NMRC/0957/2005

PI: Peng, Yeong Pin
Image enhanced patient database with Pictorial User Interface for the musculoskeletal system

NMRC/0978/2005

PI: Goh, Siok Ying
To determine the bone mineralization and bone strength of children with chronic diseases using Dual X-Ray Absorptiometry (DEXA) and the paediatric Contact Ultrasonic Bone Analyser (CUBAResearch), and to determine its association with chronic steroid therapy

NMRC/0999/2005

PI: Ng, Peng Mei Yvonne
Postprandial changes in Superior Mesenteric Artery (SMA) blood flow velocities at first enteral feed to predict feeding tolerance in preterms 26 - 35 weeks gestation.

NMRC/1000/2005

PI: Lin, Tzer Pin Raymond
Detection of plasmid-mediated quinolone resistance associated with the qnr gene and characterizing its associated genetic elements

NMRC/1003/2005

PI: Niduvaje, Krishnamoorthy
Measurement of cerebellar vermis size by cranial ultrasonography to estimate the gestational age of newborns at birth

NMRC/1011/2005

PI: Peng, Yeong Pin
Use of the rat hindlimb model
1) As an ideal teaching and training model for extremity replantation
2) To investigate the effects of steroids in reducing ischaemia reperfusion injuries in skeletal muscles in major limb replantation

NMRC/1020/2005

PI: Ho, Khek Yu
Clinical evaluation of novel biological markers for the prediction of severe acute pancreatitis

NMRC/CPG/011/2005

PI: Chen, Chien-Shing
Clinical cellular immunotherapy program project-Novel applications for hematologic and oncologic cancers

NMRC/CPG/014/2005

PI: Lin, Tzer Pin Raymond
Investigating the genomics of new strains of virulent community-acquired Staphylococcus aureus isolated in Singapore

National University of Singapore

NMRC/0945/2005

PI: Tachibana, Shinro
Re-evaluation of amino acids analysis in cerebrospinal fluid to find possible correlations with different pain states

NMRC/0946/2005

PI: Liang, Fengyi
Functional roles of CROSP myelin protein in molecular specialization of the node of Ranvier

NMRC/0947/2005

PI: Clement, Marie-Veronique
Regulation of the Na+/H+ exchanger 1, NHE-1 gene expression by activation of PPARgamma receptor in the human breast cancer cell line MCF-7

NMRC/0948/2005

PI: Tan, May Chin Theresa
Regulation of multidrug resistance protein (MRP) transporters by xenobiotics

NMRC/0949/2005

PI: Shen, Han Ming
Luteolin and its Analogues as Chemosensitizers in Cancer Chemotherapy

NMRC/0950/2005

PI: Lu, Jinhua
Mechanisms of C1q Contribution to the Prevention of Systemic Lupus Erythematosus (SLE)-like Diseases: Insights from the Unique Mechanism of C1q Biosynthesis

NMRC/0951/2005

PI: Lim, Lay Hong Renee
Lactobacilli-based oral vaccine: A model to study the induction and role of regulatory cells in the ablation of allergic diseases

NMRC/0952/2005

PI: Lee, Edmund Jon Deoon
Functional and Genetic diversity in the Concentrative Nucleoside Transporter in Singapore population and Herbal interaction

NMRC/0953/2005

PI: Bhatia, Madhav
Substance P as a mediator of inflammation in sepsis

NMRC/0954/2005

PI: Schwarz, Herbert
Characterization of the gene expression profile and the activation stage induced by CD137 in hematopoietic stem cells

NMRC/0955/2005

PI: Sng, Jen Hwei
Screening for complex genomic rearrangements in the BRCA2 gene of Singaporean patients presenting with early-onset breast cancer with or without family history

NMRC/0962/2005

PI: Alonso, Sylvie
Development of live recombinant vaccines against avian influenza virus: Use of Bordetella pertussis as a nasal delivery vehicle

NMRC/0963/2005

PI: Hui, James Hoi Po
Intraarticular therapy of encapsulated hyaluronan with chrondroitin sulfate or mesenchymal stem cells for osteoarthritis of the knee

NMRC/0965/2005

PI: Chao, Siew Shuen
The Role of Fungus in Allergic Rhinitis

NMRC/0966/2005

PI: Lim, Lina Hsiu Kim
The effectiveness of a naturally occurring compound on leukocyte activation in allergy: Role of Annexin-1

NMRC/0969/2005

PI: Lee, Shao Chin
Characterizing the resveratrol-evoked, Bax- and p53-independent apoptosis signaling cascades: in relevance to the therapeutic development of resvertrol in treating drug-resistant cancers

NMRC/0970/2005

PI: Goh, Cho Hong James
RNAi for tendon healing: Synthetic small interfering RNA decrease type V collagen synthesis for growing larger collagen fibrils

NMRC/0971/2005

PI: Lee, Bee Wah
A 2 year prospective study of stool microbiota in two diverse cohorts of Asian (Singaporean and Vietnamese) newborns and its influence on allergy development

NMRC/0972/2005

PI: Lee, Beng Huat Martin
Molecular mechanisms underlying SUMO-mediated repression of SF-1 by DP103 and PIAS proteins

NMRC/0973/2005

PI: Pervaiz, Shazib
Mechanism of defective drug-induced apoptotic signaling in B cell lymphomas

NMRC/0974/2005

PI: Choolani, Mahesh A
Human fetal mesenchymal stem cells for intrauterine treatment of mucopolysaccharidoses

NMRC/0977/2005

PI: Sim, Khe Guan
Impact of absence of TRIP-Br2 on growth and development: characterization of TRIP-Br2 knockout mouse as a model for common human disease(s)

NMRC/1007/2005

PI: Lim, Aymeric Yu-Tang
Retrograde flow venous flaps - A potentially reliable resurfacing tool?

NMRC/1008/2005

PI: Wang, De Yun
Role of Staphylococcus aureus superantigens (enterotoxin) in the pathogenesis of chronic rhinosinusitis and nasal polyposis

NMRC/1009/2005

PI: Saw, Seang Mei
Preschool Refractive Error, Amblyopia, and Strabismus in Singapore study

NMRC/1010/2005

PI: Wong, Boon Seng
Characterizing the carbohydrate composition on apolipoprotein E using inbred and knockout animal models as potential biomarkers for atherosclerosis

NMRC/1012/2005

PI: Chua, Kim Lee
Burkholderia pseudomallei Multidrug Efflux Pumps

NMRC/1013/2005

PI: Wong, Mee Lian
Sexually transmitted infections and high risk sexual behaviours among adolescents in Singapore

NMRC/1014/2005

PI: Lee, Edmund Jon Deoon
The effects of ethnicity and PEPT2 transporter genetics on single oral dose pharmacokinetics of cephalexin and ceftriaxone

NMRC/1015/2005

PI: Seeram, Ramakrishna
Polymer Nanofiber Conduits for Peripheral Nerve Regeneration

NMRC/1016/2005

PI: Chua, Kaw Yan
Mechanistic Study of the Stimulatory and Adjuvant Effects of a Fungal Immunomodulatory Protein in Tumor immunotherapy

NMRC/1017/2005

PI: Yeoh, Eng Juh Allen
A risk-stratified multicentre childhood acute myeloid leukemia study using the modified MRC AML 10 backbone with anthracycline reduction, and minimal residual disease and cardiomyopathy assessments

NMRC/1018/2005

PI: Ng, Peng Keat Daniel
Genetic and Environmental Risk Factors For Diabetic Nephropathy Among Singaporeans with Type 2 Diabetes Mellitus: Role Of Inflammatory Genes

NMRC/1019/2005

PI: Bay, Boon Huat
The Y-box binding protein, YB-1 as a novel prognostic biomarker and predictor of chemoresistance in adjuvant chemotherapy for breast cancer and radioresistance in nasopharyngeal cancer.

NMRC/1021/2005

PI: Joseph, Tessy
Identification and characterization of nocistatin receptor protein

NMRC/1022/2005

PI: Lee, Eng Hin
Development of xeno-/ serum- free medium to improve the safety and quality of human chondrocyte culture for clinical autologous chondrocyte implantation

NMRC/1023/2005

PI: Yip, Wai Cheong George
Analysis of heparan sulphation patterns as biomarkers of breast cancer and as regulators of tumour cell behaviour

NMRC/1024/2005

PI: Low, Chian Ming
Regulation of dopamine-dependant intracellular trafficking of N-methyl-D-aspartate receptor subunits and their co-localization with D1 receptor

NMRC/1025/2005

PI: Zhu, Yi Zhun
Role of Monocyte/ macrophage derived-angiogenic factors in ischemic disease

NMRC/1026/2005

PI: Phan, Toan Thang
Transcriptional program differences between keloid and normal skin derived keratinocytes and fibroblasts: A cDNA microarray analysis

NMRC/1027/2005

PI: Goh, Daniel Yam Thiam
The identification and evaluation of cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations and polymorphisms in Asians with chronic pulmonary disease

NMRC/CPG/013/2005

PI: Gopalakrishnakone, P.
Therapeutic Effectiveness of Biopeptides on Inflammatory Joints in Rheumatoid Arthritis

NMRC/CPG/018/2005

PI: Zhu, Yi Zhun
Studies on purified Chinese herbal compounds from Salvia miltiorrhizae (SM) and Herba leonuri (HL): antioxidant therapeutic effects in ischemic heart disease

NMRC/CPG/021/2005

PI: Pervaiz, Shazib
Program to study the regulation of cellular stress signaling by reactive oxygen species and its role in malignant transformation

NMRC/CPG/022/2005

PI: Yap, Hui Kim
Genetics of Pediatric Renal Diseases

NMRC/CPG/023/2005

PI: Liou, Yih-Cherng
Molecular Mechanisms governing leukemia: a quest for novel therapeutic targets

NMRC/CPG/024/2005

PI: Wong, Wai Shiu Fred
Proteomics programme to identify pathogenic molecules and therapeutic targets in animal models of stroke, myocardial infarction and chronic obstructive pulmonary disease

NMRC/CSI/0004/2005

PI: Yeoh, Eng Juh Allen
Developing New Molecular Signatures for Disease Prognostication for Childhood Acute Lymphoblastic Leukemia Using Gene Expression Profiling

NMRC/CSI/0005/2005

PI: Shek, Lynette Pei Chi
Cord Blood Mononuclear Cell Responses to Probiotics as a Predictor for and Potential Therapeutic Tool in Allergic Diseases

Singapore Eye Research Institute

NMRC/0940/2005

PI: Aung, Tin
The identification of genes causing corneal endothelial dystrophies

NMRC/0958/2005

PI: Beuerman, Roger W.
Molecular characterization of anti-muscarinic therapy for myopia using specific muscarinic receptor knockout mouse model

NMRC/0982/2005

PI: Beuerman, Roger W.
Quantitative Proteomics of Tear Biomarkers for Dry Eye

Singapore General Hospital

NMRC/0926/2005

PI: Greaves, Malcolm Watson
Psoriasis and the eye: prevalence of eye disease in Singaporean Asian patients with psoriasis: a controlled study

NMRC/0930/2005

PI: Tan, Guet Khim
Identification and characterization of hypoxia-inducible factor-1 alpha target genes with aberrant DNA methylation in hepatocellular carcinoma (HCC)

NMRC/0932/2005

PI: Lai, Mitchell K P
A common pathway to plagues and tangles in Alzheimer's Disease: The role of Gq/11-coupled neurotransmitter receptors in amyloid protein processing and tau phosphorylation

NMRC/0933/2005

PI: Tay, Sun Kuie
Dissection of the molecular pathways modulated by fibulin-1C and 1D using RNAi and GeneChip analysis

NMRC/0961/2005

PI: Chow, Kah Hoe Pierce
Protein biomarker discovery of liver cancer progression in a monkey model

NMRC/0976/2005

PI: Xiao, Zhi-Cheng
Evaluation of the inductive role of F3/NB-3 in oligodendrocyte differentiation from neural stem cells in the PLP transgenic mice, a chronic demyelination animal model

NMRC/0983/2005

PI: Lim, Puay Cheng Valerie
Stuttering in English and Mandarin Bilingual Speakers

NMRC/0984/2005

PI: Koh, Liang Piu
Using serum galactomannan levels to guide early anti-fungal therapy in haematology patients at risk of invasive aspergillosis

NMRC/0985/2005

PI: Zhang, Kai
In vivo study of plant polyphenols as sensitizers for cancer chemotherapy

NMRC/0987/2005

PI: Xiao, Zhi-Cheng
Study of the physiological functions of oligodendrocyte myelin glycoprotein (OMgp) in CNS development and regeneration

NMRC/0988/2005

PI: Cheah, Peh Yean
Exploring the use of the Affymetrix arrays for the search of new candidate genes in young colorectal cancer patient

NMRC/0989/2005

PI: Ong, Marcus Eng Hock
Cardiac Arrest and Resuscitation Epidemiology in Singapore: The geographic epidemiology of out-of-hospital cardiac arrest and its implications for ambulance deployment (phase III)

NMRC/CPG/025/2005

PI: Koh, Boon Chai Mickey
A multi-disciplinary programme grant investigating the process of autoimmunity: A pilot study and scientific analysis of autologous haematopoietic stem cell transplantation (AHSCT) and graft manipulation in re-setting the immune rheostat in patients with systemic lupus erythematosus (SLE)

WITHDRAWN PI: Dhingra, Narender K
Replacement of degenerating retinal neurons by stem cells or retinal prosthesis: A study on connectivity and signal processing in retinal ganglion cells

Singapore Health Services

NMRC/CSI/0001/2005

PI: Tan, Eng King
Analysis of Alpha Synuclein in Parkinson's Disease

NMRC/CSI/0002/2005

PI: Tai, E Shyong
Inflammation, immunity and risk factors for cardiovascular disease in Chinese, Malays and Indians living in Singapore

Singapore National Eye Centre

NMRC/0975/2005

PI: Saw, Seang Mei
Changes in the refractive components in myopic and emmetropic eyes: the teenage years

NMRC/CSI/0003/2005

PI: Aung, Tin
A Search For Quantitative Trait Loci in Angle Closure Glaucoma

Tan Tock Seng Hospital

NMRC/0927/2005

PI: Hossain, Iqbal
Risk factors and incidence of retinal hemorrhages in dengue fever

NMRC/1004/2005

PI: Chee, Cynthia Bin Eng
The evaluation of T-cell immune response to specific TB antigens, as measured utilizing two commercially available interferon-gamma release assays, for the monitoring of response to TB treatment and as a surrogate marker of cure and predictor of relapse

NMRC/1005/2005

PI: Seong, Peck Suet
Lifetime Cost of Care for Human Immunodeficiency Virus Patients

NMRC/1006/2005

PI: Lee, Vernon Jian Ming
Predictors of Severity, Outcomes, and Costs in Dengue Fever Hospitalisations

NMRC/CPG/019/2005

PI: Khoo, Keng Meng
The localization and functional characterization of ocular CD38: A study of its role in the calcium signaling processes in the human eye.

NMRC/CPG/026/2005

PI: Howe, Hwee Siew
Developing a composite index for predicting outcomes in systemic lupus erythematosus

Annex 4: Publications arising from Block Grants and Competitive Grants

(*refers to journals with impact factor 2 or above)

1. *Biswas A, Chia D, Wong YC
Three-dimensional sonographic diagnosis of cephalothoracopagus janiceps twins at 13 weeks
Ultrasound Obstet Gynecol 2003; 18(3): 289-90

2. *Anandakumar C, Mohammed NB, Chua TM, Wong YC, Chia D
First-trimester prenatal diagnosis of omphalocele using three-dimensional ultrasonography
Ultrasound Obstet Gynecol 2002; 20(6): 635-6

3. Mohammed NB, Biswas A
Three-dimensional ultrasound in prenatal counselling of congenital talipes equinovarus
Int J Gynaecol Obstet 2002; 79(1): 63-5

4. Anandakumar C, Mohammed NB
Three-dimensional transvaginal sonographic diagnosis of asymptomatic interstitial pregnancy at 6 weeks of gestation
Acta Obstet Gynecol Scand 2004; 83(4): 408-10

5. *Wee J, Tan EH, Tai BC, Wong HB, Leong SS, Tan T, Chua ET, Yang E, Lee KM, Fong KW, Tan HS, Lee KS, Loong S, Sethi V, Chua EJ, Machin D.
Randomized trial of radiotherapy versus concurrent chemoradiotherapy followed by adjuvant chemotherapy in patients with American Joint Committee on Cancer/International Union against cancer stage III and IV nasopharyngeal cancer of the endemic variety.
Journal of Clinical Oncology 2005 Sep20; 23(27): 6730-8

6. Monica Garcia-Alloza, Shirley W Tsang, Francisco J Gil-Bea, Paul T Francis, Mitchell K Lai, Beatriz Macros, Christopher P Chen, Maria J Ramirez
Involvement of the GABAergic system in depressive symptoms of Alzheimer's disease
Journal of Neurobiology of Aging 2006/27: 1110-1117

7. *Kang Chen, Guang Wen Sun, Kim Lee Chua and Yunn-Hwen Gan
Modified Virulence of Antibiotic-Induced Burkholderia pseudomallei Filaments
Antimicrobial Agents and Chemotherapy 2005; 3(49): 1002-9

8. *Ying Ying Chan nd Kim Lee Chua
The Burkholderia pseudomallei BpeAB-OprB efflux pump: expression and impact on quorum sensing and virulence
Journal of Bacteriology 2005; 14(187): 4707-19

9. *Siddique MM, Balram C, Fischer ML, Aggarwal M, Tan A, Tan P, Soo KC and Sabapathy K
Evidence for selective expression of the p53 codon 72 polymorphs: implications in cancer development
Cancer, Epidemiology, Biomarkers & Prevention

10. *Faina Vikhanskaya, MM Siddique, Ming Kei Lee, Massimo Broggini and Kanaga Sabapathy
Evaluation of the combined effect of p53 codon 72 polymorphism and hot-spot mutations in response to anticancer drugs
Clinical Cancer Research 2005/11/2: 4348-56

11. *Siddique MM and Sabapathy K
p53-dependent DNA-repair is affected by the codon 72
Oncogene

12. Chee MW
Brain differences between bilinguals of differing proficiency: an empirical look at an emotional issue
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