

**ANNUAL REPORT OF THE
NATIONAL MEDICAL RESEARCH COUNCIL
(NMRC)**

2004

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CHAPTER 1

National Medical Research Council

Council Members

Chairman

Prof Woo Keng Thye

Emeritus Consultant, Department of Renal Medicine
Singapore General Hospital

Members

Assoc Prof Chew Suok Kai

Deputy Director of Medical Services
(Epidemiology and Disease Control)
Ministry of Health

Prof Barry Halliwell

Head, Department of Biochemistry
National University of Singapore

Prof Hong Wan Jin

Deputy Director
Institute of Molecular & Cell Biology

Prof Lee Eng Hin

Director, Division of Graduate Medical Studies
National University of Singapore

Assoc Prof London Lucien Ooi

Head, Surgical Oncology Department
National Cancer Centre

Assoc Prof Shazib Pervaiz

Vice-Dean (Research), Faculty of Medicine
National University of Singapore

Prof Soo Kee Chee

Director
National Cancer Centre

Assoc 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

Executive Committee

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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. 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

Together with key stakeholders and partners, the Council set the strategic plan for medical research in Singapore in 2003 for the next 5 years. It also aims to chart the future directions for medical research development in Singapore.

The NMRC Strategic Plan consists of 3 key elements:

1. Development of research landscape
2. Funding of manpower
3. Development of greater depth and breadth of clinical research expertise.

The Council also identified 7 focus areas for research as follows:

1. Vascular
2. Oncology
3. Infectious diseases (include public health)
4. Hepatology
5. Neurobiology and ageing
6. Ophthalmology and visual sciences
7. Child Health

FY2004 Budget and Expenditure

In FY2004, the NMRC was allocated a total of \$54.9 million for research expenditure, out of which \$49.9 million was obtained from MOH's Other Operating Expenses Budget and \$5.0 million was received as a generous donation from Singapore Totalisator Board (STB) for research projects and programmes. STB also provided an additional \$2.0 million in FY2004 for the Medical Research Fellowship and Scientist Award.

For this financial year, the expenditures for research programmes and projects i.e. Block Grants and Competitive Grants, were \$29.1million and \$23.6 million respectively; and the expenditure for Protected Time was \$0.1 million. An expenditure of \$1.6 million was incurred for Medical Research Fellowship and Scientist Awards.

Highlights of FY2004

NMRC-BMRC Joint Grant Call

In May 2004, MOH's National Medical Research Council (NMRC) collaborated with A*STAR's Biomedical Research Council (BMRC) to hold a joint grant call for research proposals. This joint effort serves to encourage synergy among the basic researchers and clinician scientists. (please refer to Chapter 3: Competitive Grants for more details)

NMRC-BMRC Clinician Scientist Investigator (CSI) Award

NMRC and BMRC jointly launched a new award which provides assistance to leading clinician-scientists who hope 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 inaugural exercise was held in September 2004, and a BMRC-NMRC CSI Joint Review Panel selected 5 Junior CSIs and 3 Senior CSIs. The Award funding would commence in FY2005.

Medical Research Travelling Fellowship

In July 2004, a one-time Medical Research Travelling Fellowship was launched, with the aim to assist young specialists to go abroad, visit research centres, attend research seminars to improve their knowledge and keep them abreast of latest updates in the field.

NMRC Peer Review Subcommittee Dialogue Session 2004

A Peer Review Subcommittee Dialogue Session was held on 6 April 2004 as a sharing session to discuss a) focus areas alignment and subcommittee composition, and b) improving IRG peer review process.

To improve the quality of the subcomm peer review, the 10 subcommittees were expanded to about 10 members in each Subcommittee.

DPM Tan's Visit to NMRC on 23 Nov 2004.

The Ministerial Committee on R&D, chaired by DPM Tony Tan, was reviewing R&D strategies & directions for Singapore. DPM Tan visited the National Medical Research Council on 23 Nov 2004 to understand its role and work in R&D, as part of his visits to R&D Institutions such as A*STAR, NUS and NTU.

Thematic Competitive Programme Grant

The Thematic Competitive Programme Grant is a new initiative proposed by DMS. The NMRC chairman has tasked a working committee to develop the framework for the grant, and the committee is currently looking into it.

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 2004, the NMRC received 297 applications. A total of 113 applications were approved, amounting to \$19.2 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 118 projects were completed with final reports submitted in FY 2004. Due to intellectual property (IP) and various issues, only 106 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 2004.

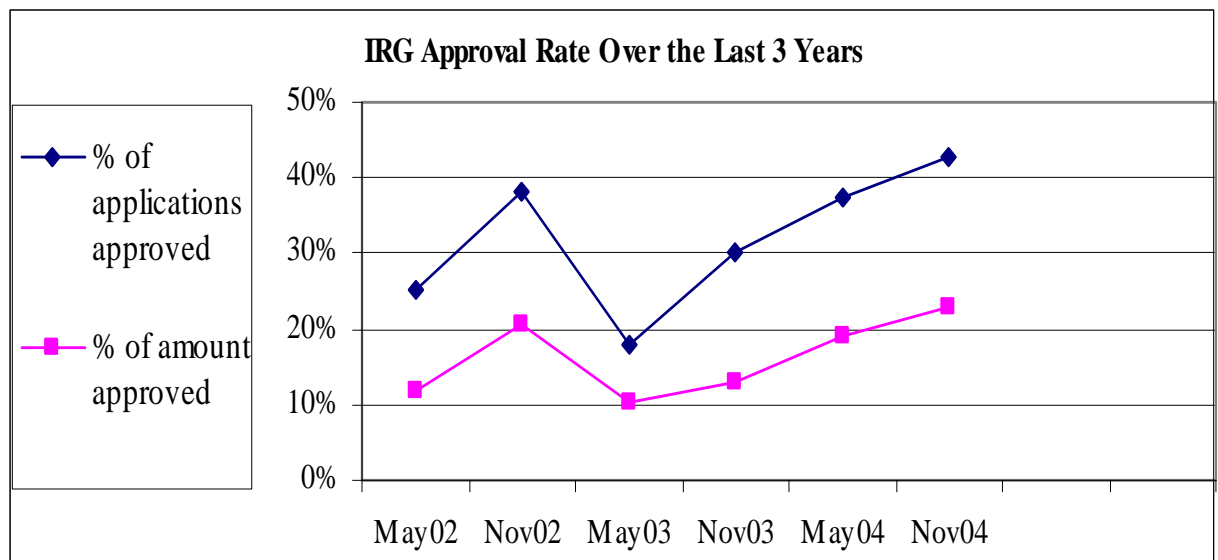
IRG Funding Exercises 2002-2004

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

- There is a general increase in the percentage of application approval. As compared to the 25% approval rate in May02 Exercise, the Nov04 Exercise shows a much higher approval rate of 43%.

Table 1
IRG 2002 - 2004

	IRG Funding Exercise					
	May02	Nov02	May03	Nov03	May04	Nov04
No. of applications received	123	163	227	173	145	126
Total amount applied for (\$millions)	42.7	50.1	77.7	65.9	42.3	46.0
No. of applications approved	31	62	41	52 *	54	54
Total amount approved (\$millions)	5.0	10.3	8.0	8.5	8.1	10.5
% of applications approved	25%	38%	18%	30%	37%	43%
% of amount approved	12%	21%	10%	13%	19%	23%



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

Applications in FY2004

A total of 271 applications were received by NMRC during the May04 and Nov04 Exercises. Out of the 271 applications, 108 projects were approved (please refer to Table 1).

Approved Projects in FY2004

Table 2 shows the number of IRG projects approved in FY2004, by institution.

Table 2
No. of Projects Approved, by Institution

Institutions	No. of Projects Approved in FY2004
Alexandra Hospital (AH)	2
Institute of Mental Health (IMH)	1
KK Women's & Children's Hospital (KKH)	3
National Cancer Centre (NCC)	13
National Neuroscience Institute(NNI)	7
Nanyang Technological University(NTU)	1
National University Hospital (NUH)	11
National University Medical Institutes (NUMI)	2
National University of Singapore (NUS)	44
Singapore Eye Research Institute (SERI)	2
Singapore General Hospital (SGH)	10
Singapore Health Services (SHS)	3
Singapore National Eye Centre(SNEC)	1
Tan Tock Seng Hospital (TTSH)	5
Total	105

Ongoing Projects in FY2004

A total of 323 projects were still ongoing at the close of FY2004. Table 3 on the next page shows the number of projects being carried out in each institution.

Project Findings Reported in FY2004

A total of 118 IRG projects reported their final findings in FY2004. Table 4 on the next page shows the number of IRG projects that reported final findings in FY2004, by institution.

Table 3
No. of IRG Projects at the end of FY2004, by Institution

Institutions	No. of IRG Projects Ongoing at the end of FY2004
Alexandra Hospital (AH)	4
Institute of Mental Health (IMH)	4
KK Women's & Children's Hospital (KKH)	4
Nanyang Polytechnic (NYP)	1
National Cancer Centre (NCC)	36
National Dental Centre (NDC)	1
National Heart Centre (NHC)	15
National Neuroscience Institute(NNI)	25
National Skin Centre (NSC)	1
Nanyang Technological University (NTU)	2
National University Hospital (NUH)	18
National University Medical Institutes(NUMI)	9
National University of Singapore (NUS)	132
Singapore Eye Research Institute (SERI)	8
Singapore General Hospital (SGH)	46
Singapore Health Services (SHS)	9
Singapore National Eye Centre(SNEC)	2
Tan Tock Seng Hospital (TTSH)	6
Total	323

Table 4
No. of IRG projects that reported final findings in FY2004, by Institution

Institution	Numbers of Projects completed in FY2004
AH	1
CTERU	1
IMH	3
KKH	2
NCC	6
NHC	2
NNI	4
NSC	1
NUMI	1
NUH	1
NUS	72
SGH	21
TTSH	1
WH	1
WH/IMH	1
Total	118

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 2004, 26 applications were received. 8 were approved amounting to \$2.6 million and are currently in progress.

Competitive Priority Grant (CPRG)

There is no grant call for this category in FY 2004.

CHAPTER 4

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. Since the inception of NMRC in 1994, NMRC has provided \$225.6 million for block grants. Currently, there are 22 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 FY2004. The names of the 15 institutions are listed in Table 5, as shown below.

Table 5
Institutions that received IBG funding in FY2004

	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 FY2004 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 FY2004

Core facilities

In FY2004, the IBG supported items required to improve the ventilation and environment of the facility, alarm systems for security and basic laboratory items to equip the common laboratory in the facility.

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 IBG is used to support the cost of education and training required for IACUC members.

Achievements / Research Outcomes

Overall, there has been an increase in the number of projects and research animals used from FY2003 to FY2004.

- 7 research groups used the Animal Research Facility.
- Total number of research projects which use the ARL facilities to house animals has increased from 11 to 13 in FY2004, including those using the Specific Pathogen Free (SPF) facility.
- More than 3200 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 the SHS-NHG Joint Management Committee.

In FY2004, CTERU's broad objective was to provide an infrastructure to promote GCP standard clinical research, evidence-based medicine research and epidemiological research in Singapore. With the funding support of the IBG, this objective was achieved by:

1. Initiating clinical investigations in collaboration with investigators island-wide and internationally.
2. Continuously developing and improving the planning, implementation, running and coordination of clinical investigations.
3. Maintaining and further developing biostatistical and epidemiological expertise in the design, methodology, analysis and reporting of clinical investigations.
4. Providing biostatistical consultations on site in CTERU's Institutions as well as providing further support needed as a result of these activities.
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 FY2004

CTERU's branches comprise Clinical Project Coordination (CPC), Biostatistics, Evidence-Based Medicine (EBM), Epidemiology, Training, Quality Assurance and Infotech/Admin. Some highlights from each branch are detailed on page 16 and 17.

Clinical Project Coordination / Biostatistics

Some project highlights of the Clinical Project Coordination and Biostatistics branches are as follows:

Project title	Progress / Outcomes
1. Randomised Phase III Trial of Radiotherapy versus Concurrent Chemo-Radiotherapy followed by Adjuvant Chemotherapy in Patients with AJCC/UICC (1997) Stage III and IV Nasopharyngeal Cancer of the Endemic Variety.	This trial confirmed an earlier study which showed a benefit of adding chemotherapy to radiotherapy in the treatment of nasopharyngeal cancer (NPC). Furthermore, our study showed that these conclusions were applicable to endemic NPC.
2. Acute primary angle closure: configuration of the drainage angle in the first year after laser peripheral iridotomy.	This study aimed to evaluate the changes in the configuration of the drainage angle in the first year after acute primary angle closure (APAC). A prospective observational case series was conducted whereby acute primary angle closure cases were treated with medical therapy followed by laser peripheral iridotomy (LPI). The study suggested that LPI was effective in preventing progressive closure of the angle in the first year after APAC.
3. A randomized controlled trial to compare calcipotriol with betamethasone valerate for the treatment of cutaneous lichen planus.	This was a randomized open-label trial comparing the effectiveness of calcipotriol 50 microg/g versus betamethasone 0.1% ointments twice daily for 12 weeks in patients with cutaneous lichen planus, with respect to thickness, pigmentation, clearance and pruritus. The study found that calcipotriol appears no more effective than betamethasone. The course of the disease appears to be affected in the same way by both treatments.
4. A Pilot Randomised Controlled Trial Of The Effectiveness And Safety Of Campath® As An Induction Agent For Prevention Of Graft Rejection And Preservation Of Renal Function In Patients Receiving Cadaveric Kidney Transplants	As per protocol, CyA trough levels were lower in CAMPATH patients post RTx (median trough level of 119 vs. 166 ng/mL at 6 months, CAMPATH vs. Standard; 95% CI -92 to -34). At 6 months post RTx, serum creatinine, graft and patient survivals, the incidence of biopsy proven acute rejection (25% vs. 20%, CAMPATH vs. Standard), overall treatment failure and severe and moderate infections were comparable. Whereas, all patients receiving Standard therapy required maintenance corticosteroids at 6 months, of the 17 of 20 with functioning grafts in CAMPATH, 15 (88%, 95% CI 53% to 97%) were steroid free. These results suggest that Alemtuzumab (Campath) is an effective induction agent that permits low dose steroid-free immunosuppression in RTx
5. A randomised, parallel, double-blind study comparing the lipid lowering effect of Xuezhikang (Lipascor) with Simvastatin in asymptomatic patients with hyperlipidaemia	This was a randomised double-blind parallel trial conducted among patients without pre-existing vascular disease or other important co-morbidities and hypercholesterolaemia. The study found that the traditional Chinese formulation, Xuezhikang (Lipascor) and simvastatin improved the lipid profile in the group of patients. However, due to small sample size, the data were not able to support the non-inferiority of Xuezhikang (Lipascor) compared with simvastatin at the doses studied.
6. Clinical Protocol for the Validation of the Mediwatch™ Ambulatory Blood Pressure Monitoring Device According to the Association for the Advancement of Medical Instrumentation Standard and European Society of Hypertension Protocol (ESH)	The study found that that Mediwatch met the required standard for the measurement of systolic and diastolic blood pressures, in the ESH Validation Protocol.

Evidence-Based Medicine (EBM) / Epidemiology

In collaboration with National Dental Centre (Dr Ken Tan, first author) and the University of Berne, Switzerland, EBM and Epidemiology published the most up-to-date and rigorous systematic review of the long-term survival and complication rates of fixed partial dentures (FPDs). Two evidence-based clinical practice nursing guidelines were published on urinary incontinence and oral hygiene.

Early operative debridement is a major determinant of outcome in necrotizing fasciitis. However, early recognition is difficult clinically. This study involved the development of a novel diagnostic scoring system (the LRINEC :Laboratory Risk Indicator for Necrotizing Fasciitis) to distinguish necrotizing fasciitis from other soft tissue infections based on laboratory tests routinely performed for the evaluation of severe soft tissue infections.

Training

During 2004, CTERU offered 43 courses including 9 SPSS and biostatistics research courses, 15 evidence-based medicine courses, 10 research methodology courses and 7 GCP courses, in response to the Clusters' requests. More than 1,000 health care professionals have benefited from these training activities.

Quality Assurance

Standard operating procedures have been prepared for the different departments to standardize procedures and integrate functions across the different sections. A database to collate information of all CTERU work has been set-up, and is also a tool for the measurement of certain performance metrics.

Infotech / Admin

The Clintrial data management system was upgraded from version 4.2 to 4.4 and moved to a new server. A paperless archiving system has been put in place for fast electronic archival of hard-copy documents. A web-based portal (APEX) has been put in place allowing for easy tracking of project work. The system also serves as a timesheet application, enabling the user to plan work and meetings. A brochure showing the tasks and abilities of CTERU was produced in-house, and the website has been re-designed in-house to reflect a more professional and contemporary image.

Summary of Achievements / Research Outcomes

In FY2004, CTERU's achievements are as follows:

- 80 inter-institutional collaborations
- Conducted 43 training courses for investigators and personnel involved in clinical research
- 37 publications, with 12 more publications submitted as at April 2005

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 FY2004, 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.

From late 2003, the DCR has helped clinicians from the relatively new Department of Rheumatology & Immunology to pursue wet-bench research by allocating some lab bench space within its current facilities and supporting some research projects through the DCR seed funds. The DCR also supported the recruitment of a Research Scientist to collaborate closely with the Multiple Myeloma Research Group. The Department's Neurobiology Laboratory continued to be productive in its research publications and its PI was awarded the inaugural SingHealth Excellent Researcher award in 2004.

Activities in FY2004

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 FY2004, DCR's resources were utilized by 71 SGH research projects and 25 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

41 small research grants were awarded. These small grants achieved 18 presentations, 7 publications and 1 award during FY2004.

Summary of Achievements / Research Outcomes

The Department's achievements are as follows:

- 36 papers were published in FY2004, with over 19 citations as at April 2005. The 30 papers published in FY2003 has over 78 citations, as at this date.
- 29 presentations at international conferences were made.
- An external award for research was won.
- 6 PhD research students were trained, as well as several undergraduates and Polytechnic students.
- At least 63 of the research projects supported by the Department had potential or direct clinical applications.
- There were approximately 25 inter-institutional collaborations.
- In terms of research infrastructure, a microarray facility had also been developed.

Department of Experimental Surgery (DES), Singapore General Hospital

Overview

The Department of Experimental Surgery (DES) functions as an open laboratory serving researchers in the SingHealth Cluster and throughout the nation to sustain long-term funded research activities in multi-disciplinary (and cross cluster) collaborative groups and with research institutions from other countries that have broad programme goals.

In FY2004, DES continued to extend its open laboratory concept for all researchers to conduct animal-based studies and training irrespective of their affiliations. Its 3 major facilities are:

1. Open Laboratory in Block 9 of Singapore General Hospital, which caters for research activities on animals and cadavers;
2. Clinical Skills Laboratory in Sembawang, which provides psychomotor skills training for clinicians; and
3. Animal Husbandry & Hospital in Sembawang, which offers facilities for big animal breeding and post-operative animal convalescence.

Together, the 3 facilities provide a comprehensive set-up of training and biomedical research.

The principal objective of the IBG is to sustain strong core manpower to service animal and cadaveric research. The core manpower is subjected to a continual education and training program involving talks and hands-on training experiences to upgrade skills and keep abreast of the latest technological advancement in biomedical sciences.

The core manpower is assigned to support the 8 research programmes, namely experimental oncology, diabetes, developmental implants, neurobiological, cadaveric research, animal model development, pharmacokinetics/toxicology and transplant immunology. To service the diverse research activities, the focus is on development of a manpower base with multi-tasking capability and individual specialization on a specific research programme, which will benefit from a high competency level of services.

Activities in FY2004

Services

In FY2004, DES serviced 42 research projects and 40 surgical skills training courses. Research projects are categorised into programmes to facilitate training and development of staff expertise to be specifically focused on respective programmes in order to raise level of competency services. Where research expertise is beyond the Department manpower's scope, assistance is obtained from Nuclear Medicine, Diagnostic Radiology and National Heart Centre, especially in the provision of bioimaging services.

Training of Manpower

With the legislation of NACLAR guidelines to govern animal research in Singapore, DES initiated intensive staff training and facilities improvement programme in order to conform to the set regulations. The core manpower is required to attend the course on Responsible Care & Use of Laboratory Animals.

Rigorous training for staff was conducted for the purpose of AAALAC accreditation, which contributed tremendously in elevating manpower research service capability to an even higher plane especially in veterinary sciences.

Core Facilities

The equipment purchased was for generalized application, especially for achieving good animal husbandry practices and improved surgical support. The additional equipment and renovations will upgrade existing facility to provide a total solution for animal research activities to be conducted under a single institution.

Focus on Translational Research

With DES linkage to SGH, its logical focus is on the promotion of translational research with the benefit of support from clinician scientists and a large patient base. In this aspect, we have attracted the participation of several institutions to conduct research on big animal models and non-human primates with anticipated progression to clinical trial. Collaborating institutions included NCC, NDC, NHC, SERI, NUS, NTU, DCR, Vanda Pharmaceuticals, Johns Hopkins, Maccine Pte Ltd, Embryon, Merlin MD, Biosensors and PsiOncology.

Summary of Achievements / Research outcomes

In FY2004, DES' research activities generated:

- 8 presentations
- 2 academic awards
- 20 publications of which 9 were published in FY2004.
- 2 books were also published
- 8 of the programmes/projects using DES' core facilities had direct or potential clinical applications
- DES was also involved in 36 institutional collaborations
- A PET Laboratory was set up in Block 9 of Singapore General Hospital, and will be fully operational in FY2005. PET scanning procedures will offer improved bioimaging analysis over current conventional procedures.

Institute of Mental Health (IMH)

Overview

The objectives of the Institute of Mental Health are to:

- 1) Create a research culture with a critical mass of committed researchers.
- 2) Train mental health professionals and research staff in research methodology
- 3) Maintain a research infrastructure which will provide administrative and technical support for research
- 4) Focus on key areas of research like early psychosis, psychiatric genetics, psychiatric epidemiology, child and adolescent psychiatry and health service research.

IMH's research strategy is to focus on key areas where the potential yield would be the greatest. It also aimed to collaborate with other renowned research centres. Certain key areas have been identified, such as psychiatric epidemiology and genetics, first-episode psychosis, child and adolescent psychiatry, and health service research. These areas will be the foci of their research activities. Small start-up and pilot projects are funded by the Research Unit. In order to train future researchers, courses in statistical analysis, psychiatric genetics and health services research were also conducted.

IMH uses the IBG funding to continue to build on what has been achieved, maintain the administrative infrastructure, encourage and train budding researchers and to continue its support to support senior researchers conducting clinically relevant research.

Activities in FY2004

Focused Areas of Research

In the past year, in order to promote research and nurture young investigators, IMH has continued to support a slew of pilot and start-up studies through the Institutional Block Grant. However, they also focused on a number of key areas. 7 areas have been identified based on the Institute's strengths which include: its position as the country's tertiary treatment centre for those with mental illnesses, its large patient population, the highest clinical expertise, and a well established research infrastructure. These areas are:

1. First-Episode Psychosis

This research programme is embedded in a clinical programme: the Early Psychosis Intervention Programme. The studies ranged from establishing the determinants of the duration of untreated psychosis (DUP), the predictors of outcome of this group of disorders, quality of life, weight gain, glucose and lipids abnormalities from the use of antipsychotic medications, and the comorbidity of other disorders with psychosis. A high rate of psychiatric comorbidity was found in the patients with first episode psychosis. Patients with psychiatric comorbidities were younger and had an earlier onset of illness. In addition, it was found that patients with a comorbid depressive syndrome had greater awareness of their mental illness, its social consequences and treatment efficacy; but had poorer overall quality of life, especially in the physical, psychological health, social relationships and environmental domains.

IMH has 7 published papers and 37 published abstracts from this body of work. One of the investigators was also awarded a Young Investigator Award.

2. Brain Imaging

IMH has established a brain imaging programme in collaboration with other centres which have sophisticated brain imaging technology. IMH has also managed to establish a database of brain scans. In collaboration with the National Neuroscience Institute, MRI studies are being conducted in schizophrenia patients and their first-degree relatives versus normal controls. To date, IMH has successfully obtained whole brain volumetric scans of 63 patients with first-episode psychosis, 12 first-degree non-psychotic relatives and 45 normal controls on a clinical 1.5 tesla and later the 3 tesla MR systems.

Preliminary analyses of hippocampal volumetry have shown significant volume reduction of right anterior hippocampus in patients with first-episode psychosis as compared to normal controls. There is a correlation between the duration of untreated psychosis and gender. It has also been found that bigger anterior hippocampus in patients with first-episode psychosis was associated with better performance of executive functioning. These findings have been presented and published as abstracts at conferences organized by the International Early Psychosis Association and Association of European Psychiatrists.

In collaboration with the Cognitive Neuroscience Laboratory and the National University of Singapore, a functional MRI study is being conducted to explore the effects of atypical antipsychotics on working memory in patients with schizophrenia.

Having set up this foundation in psychiatric neuroimaging, the Institute plans to apply for a competitive grant to do a longitudinal follow-up study of 300 subjects who have an ultra high-risk of developing schizophrenia. The research team hopes to elucidate the specific structural brain abnormalities that predict or are associated with conversion of prodromal symptoms to overt psychosis.

Furthermore, additional work done by an IMH clinician-researcher who was at Harvard Medical School had found an absence of regional specificity of the involvement of medial temporal lobe areas in schizophrenia. Two papers are currently under review.

3. Psychiatric Genetic Programme

A number of psychiatric disorders have a genetic basis although it is unlikely that a single gene is involved in these disorders. Rather, they are complex disorders with a number of causative genes interacting with environmental factors.

The team has focused on the genetics of schizophrenia - probably the most severe of all mental disorders. They have continued, and expanded on their previous work on a particular aspect of pharmacogenetics i.e. on a severe antipsychotic-induced movement disorder, tardive dyskinesia, among patients with schizophrenia. The current project will involve up to a thousand subjects. This study funded by a NMRC's Individual Research Grant, is a collaborative project with the Genome Institute of Singapore (GIS), the Singapore Tissue Network (STN), the Defence Medical Research Institute, and SUNY Upstate Medical University, New York. The intent is also to establish a high quality clinical database on various psychiatric disorders which is linked to a DNA bank. This will lay the foundation of a consortium where IMH will gather the high quality clinical data and GIS and STN will respectively provide technical expertise in cutting edge genotyping and DNA banking.

4. Psychiatric epidemiology

Epidemiological studies are important to understand the risk factors and provide information on the prevalence and incidence of psychiatric disorders to policy makers. This is especially pressing given the dearth of such information in Singapore.

The last year saw the completion of a landmark epidemiological study which set out to determine the lifetime prevalence of anxiety and depressive disorders in the adult population in Singapore. This study shows that anxiety and depressive disorders (lifetime prevalence of 7.1%) continue to significantly affect the adult population of Singapore. These important findings should drive effective allocation of resources for disease management. Early detection of these disorders in sub-populations at higher risk should result in improved treatment outcomes and reduced disability. Awareness of the risk factors and the use of suitable screening measures by primary care providers for at-risk individuals may also result in early detection, effective interventions, and reduced disability in individuals suffering from Depressive and Anxiety Disorders.

The findings were presented at the NHG ASM, and one of the papers won the Best Poster Award in the Doctors Category.

IMH has initiated a collaborative project between the Early Psychosis Intervention Programme and the Singapore Armed Forces. This large-scale epidemiological study of pre-enlistees for National Service will establish the prevalence of psychiatric morbidities in this population, while at the same time, develop and validate a screening instrument. The use of this instrument will enable a more accurate screening of this population prior to their entry into the army and ensure that more of those with existing but undetected psychiatric morbidity will be identified, and receive a detailed assessment for their fitness for military duties, and/or subsequent treatment.

5. Research in Child and Adolescent Psychiatry

There were three threads of research in child and adolescent psychiatry over the last year, namely, 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. In the past one year, a locally developed Singaporean Children Emotional Distress Scale, which is a brief 8-item parent-rated measure for children's emotional distress, has been extensively validated.

This project has yielded one conference paper and two manuscripts that have been submitted for journal review.

A current project aims at examining the validity of the Achenbach Child Behavioral Checklist (CBCL) in assessing various mental disorders in the local clinical context. In the first study, the original sub-scales in the CBCL that are directly relevant to the measurement of ADHD have not been found to be valid in the local context. Rather, only eight items from the CBCL have been found to be suitable for assessing ADHD locally. These findings which demonstrated the problems with using imported rating scales without considering the cultural validity of their use have been presented at the Asia-Pacific Forum on ADHD.

In epidemiological research, the work seeks to understand the determinants and distribution rates of emotional disorders in children and adolescent in Singapore. In 2004, effort has been concentrated on collecting data from about 2200 children and their parents and teachers on the children emotional mental health. Data collection has completed and analyses are currently underway. In addition, using data collected from a clinical epidemiological study conducted earlier, a paper on the parenting behavior of Singaporean parents and child outcomes has been published last year.

In intervention research, the work focuses on locating intervention programmes that are culturally suitable for the treatment of mental disorders with children and adolescents in

Singapore. Last year, in collaboration with the National Institute of Education, the effectiveness of a group social problem-solving skills treatment for children with disruptive behavior disorders has been evaluated. Besides generating two conference papers and a manuscript currently under journal review, this work has also led to the establishment of a much-needed Anger Management treatment program in the Child Guidance Clinic (CGC). Beyond these three threads of research, in the last year, CGC has also lent support to an external collaborator, the Nanyang Technological University, in conducting a psychosocial research on examining the resilience factors of Singaporean families in coping with major crises. This work has produced one published paper and six conference papers and strengthened ties between the hospital and the university. In sum, in the past year, research in child and adolescent psychiatry has been wide-ranging and dynamic. The Institute saw the total production of 11 conference papers and 4 manuscripts (2 published and 2 currently under review).

6. Health Service Research

The accessibility of care for IMH patients with first episode psychosis has been examined. It was found that the DUP of IMH patients was longer than that reported in studies done in the West. 24% of the patients had sought consultation with a traditional healer prior to consulting a psychiatrist, and the majority of patients have sought help from the primary health care sector rather than the psychiatric services. IMH tracked the changes in the DUP and referral pattern following the initiation of an Early Detection Programme and found significant shifts: reduction in DUP, an increase in self and family referrals and a fall in police referrals.

IMH, in collaboration with NTU, is evaluating the cost-effectiveness of the Early Psychosis Intervention Programme. One paper has been published and another is in print.

7. Drug Trials

IMH has 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 the last year, 4 industry-sponsored drug trials were initiated: One was a Phase 1 trial, three were Phase 3. IMH will continue to build on their experience and expertise in doing Phase 1 and 2 trials, as well as in investigator-initiated drug trials.

Summary of Achievements / Research outcomes

In FY2004, IMH's achievements are as follows:

- 6 papers were published in international peer review journals with impact factor greater than 2.0
- 68 papers were published in peer review journals with impact factor less than 2.0
- 32 presentations were made at international conferences
- 1 PhD student has been trained.
- 14 clinically-relevant research projects
- 5 drug trials
- 9 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

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 FY2004

Core facilities

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

Small Projects/ Start-up Grants

In FY2004, 9 projects and start-up grants were still ongoing, of which 8 were awarded in FY2004. A CPG on Oral Hygiene was completed, while 6 more CPGs on Venous Leg Ulcers, Central venous devices, Prevention of Falls, Breast Feeding for pre-term infants, Nasogastric feeding, and Prevention of Violence were still in progress.

Clinically relevant research

In FY2004, MOH-NRC core facilities supported 7 clinically-relevant studies, which resulted in potential or direct clinical applications.

Title	Achievement
Project funded by MOH-NRC	
Is Physical Cooling Necessary? A Nursing Study to Investigate the Effectiveness Of Tepid Sponging And Cold Compress In Fever Management Of Adult Patients	The study found that there were no significant differences in the subjects' mean change of temperature at 20 minutes, 1 hour and 4 hours after the intervention, between subjects who received physical cooling interventions and those who did not. It suggested that greater efforts should be made to support the body's beneficial physiological responses to infection and to base nursing interventions on thermoregulatory principles. Emphasis should be placed on close monitoring of temperature, adequate hydration etc instead of physical cooling measures that have not been shown to be effective.
Projects supported by MOH-NRC core facilities	
Randomised clinical trial comparing the use of Mepitel with conventional paraffin gauze as dressing material for patients with skin graft.	Although Mepitel® costs more than Paraffin gauze dressing, the potential benefits outweighed Paraffin gauze in terms of patient comfort and satisfaction, reduction on time spent on dressing changes, graft infection and graft take.
Routine Screening of MRSA for Elective CABG Surgery is not Necessary: A Retrospective Study	The study suggests that routine screening for MRSA for elective CABG is not required.
Close monitoring of discharged patients in the community by Community Psychiatric Nurses (CPN) helped in reduction of re-hospitalisation	The survey found that the mean length of stay for CPN-intervention admissions was shorter compared to before intervention admissions with no differences between discharges during and after CPN intervention.
Urinary Incontinence (UI) in Women: Prevalence and Factors Influencing their Health Behaviours	This study highlighted that UI affect women of all age groups. It is an important point that majority of them do not seek treatment. Thus, there is a pressing need to raise awareness among public and healthcare providers. Additional studies are therefore indicated.
A Descriptive Study on Quality of Life of Haemodialysis Patients	This study provides useful information for nurses in caring for ESRD patients. Identifying suitable coping skills may result in better adaptation leading to better QOL.
Perineal Cold Pad vs Oral Analgesics in the Relief of Post-Partum Perineal Wound Pain	This study showed that the use of cold gel pad, a non-invasive method was as effective in the reduction of perineal pain.

Inter-Institutional Collaboration

A multi-centre study, "A Retrospective Study of Falls and Fall Prevention Practices at General Hospitals in Singapore" was in progress.

Summary of Achievements / Research outcomes

In FY2004,

- 94 nursing studies were completed
- 16 papers were published
- 136 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. MOH-NRC core facilities supported 7 research projects which had potential or direct clinical applications as well as 1 multi-centre study.

National Birth Defects Registry (NBDR)

The National Birth Defect Registry (NBDR) was set up in 1993 and shifted to KKH in 1999. It has since become an important source of clinical data which provides important national information on birth defects, such as trends, risk factors, effect of prenatal diagnosis and intervention. The comprehensive reporting to the system includes live births, stillbirths and abortus with fetal anomalies.

A number of articles and papers have been written using data from NBDR. There has been media interest in data on the incidence of polydactyl and older mothers and birth defects risks, 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 currently in practice 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 been prepared with the aim to provide an overview of the annual changes in the population with regards to birth defects and other vital statistics. The statistical tables and figures on vital statistics will be of interest to academics, demographers and medical professionals. It also aims to collate information on a national scale and hopes to facilitate the planning and evaluation of antenatal screening, genetic counseling and pediatric medical and surgical services.

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 FY2004

Division of Medical Sciences Programme

The Division of Medical Sciences engages predominantly in translational research with a special interest in improved methods for early cancer diagnosis and novel treatments. It is host to a new initiative that mentors clinicians in research training for a year.

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 are ongoing. Women at high risk of breast and/or ovarian cancer are offered a clinical research service that includes screening for mutations in breast cancer genes, BRCA1 and BRCA2. Protein profiling of gastric fluid appears highly sensitive and specific in detecting gastric cancer and two biomarkers have been identified.

Innovations in cancer therapy

Clinical trials of photodynamic therapy for oral cavity and bladder cancer using novel photosensitizers are ongoing and show encouraging efficacy. DNA vaccines are in process for clinical trials in nasopharyngeal cancer. Chemotherapy has been optimized for Asian patients with glioblastoma multiforme and shown to be superior to conventional treatment regimens developed for Caucasian patients.

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 toaneuploidy has been identified as consistently upregulated in hepatocellular and other cancers, and thus may be a key driver of genomic instability. Hotspots for chromosomal breakpoints have

been identified in gastric cancer cell lines, providing clues to molecular pathogenesis. Brain tumour stem cells have been found to home to brain tumours in animal models and to have characteristics of chemoresistance.

The close juxtaposition of clinicians, clinician-scientists and cancer researchers enables the Division to keep a clear and consistent focus on addressing real problems in clinical oncology. To this end, the Centre seeks to direct limited resources to research which has real potential to alleviate the burden of cancer in our community.

Division of Cellular & Molecular Research Programme

Gene therapy represents a promising approach for the treatment of inherited or acquired diseases. However, 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. A novel series of Herpes Simplex Virus-1 (HSV-1) that confer specific gene expression that is controlled by cell cycle events has been engineered. Activation of genes within these viruses will only take place in actively proliferating cells e.g. cancerous cells. Further attempts have been made to improve these viruses to target a selected group of actively proliferating cells such as glioma cells. With these novel viral constructs, NCC hopes to achieve cell-type specific and cell cycle dependent transgene expression. The Centre is in the process of inserting various therapeutic genes into these viruses for cancer gene therapy experiments.

This Division has also established an integrated bioinformatics infrastructure for the production, storage, and analysis of DNA microarrays to perform large-scale genomic experiments. This 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. To exploit this core facility and in collaboration with various clinicians, tumor-specific genes for many human cancers that are common in Singapore have been characterized. The human cancers studied include cervical cancer, nasopharyngeal carcinoma, hepatocellular carcinoma, breast cancer and gastric cancer. The malfunction of some of these genes might be responsible for the development and metastasis of cancer. Some of these genes will be incorporated into novel viruses that have been engineered in the Division for testing their potential efficacy in treating human cancers. Novel approaches for the prevention and treatment of breast cancer using physiological signals that encourage terminal differentiation have been developed.

Clinical Trials & Epidemiological Sciences Programme

Biostatistics Unit

The Unit's main tasks include the provision of statistical support and training for clinical investigators, as well as the conduct of applied biostatistics research. Good statistical 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 Bayesian approaches have been applied 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 this unit has been responsible for providing the infrastructural support for our physicians to conduct clinical trials to international standards.

Some of the trials that this unit has 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 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.

Clinical Pharmacology

1. This unit completed a phase II study investigating the pharmacokinetic and pharmacodynamics of irinotecan (CPT-11) in NPC patients. Two main toxicities of CPT-11 are diarrhoea and myelosuppression which limits its use in cancer patients. Studies found that severe diarrhoea (grade 3 or 4) was uncommon in our population. Myelosuppression was however, more common and this was correlated with exposure levels to SN-38, the active and cytotoxic metabolite of CPT-11.
2. The influence of genetic factors that may be predictive of CPT-11 induced toxicity in cancer patients was also investigated. Preliminary analysis points to variations in certain genes that are present in some patients which predict an increased risk of myelosuppression following treatment with CPT-11. The Centre is in the process of validating this important finding in a larger population of cancer patients. They are also in the process of performing ethnic comparisons by including Caucasian subjects in the study.
3. Antiangiogenic agents cause tumour cells to die by preventing development of blood vessels that supply nutrients to tumour cells. The growth of new blood vessels, and hence tumour recurrence is a common problem following treatment with photodynamic therapy (PDT). Preclinical studies investigating the usefulness of antiangiogenic agents to enhance the therapeutic effectiveness of PDT have been completed. This study was done in collaboration with industry (SUGEN). Results show that adding antiangiogenic agents, following PDT treatment, delayed tumour growth and improved survival time.

4. Cyclosporin is an important drug used for patients undergoing heart and kidney transplants. It is important that patients receive the optimal dose and achieve therapeutic levels of the drug so as to minimise graft rejection. Results show that certain haplotypes (i.e. combination of SNPs) in the MDR1 gene influenced exposure levels to CycA in heart transplant patients. This finding has never been reported for CycA and was published in *Pharmacogenetics* 2003;13:89-95. This knowledge will enable better optimisation of cyclosporin levels for patients undergoing transplants. The Centre is now studying the applicability of this to other transplant patients e.g. bone marrow transplants in adult and paediatric patients.
5. The lab is also focusing on developing HPLC-based assay methods for monitoring of other immunosuppressive agents commonly used to prevent graft rejection as well as to prevent GVHD in cancer transplant patients.

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 300 research projects / clinical trials this FY. The 300 projects include 27 completed projects, 236 ongoing projects (including 78 NMRC Individual Research Grants / Extramural grants), 29 new projects, 3 projects that were halted pending further funding, and 5 withdrawn projects.
- These resulted in 124 publications, including 21 papers in press and 14 papers submitted for review.
- NCC published 25 international and 12 local conference papers, and gave 12 lectures as invited speakers.
- In terms of the quality of the research, 83 of these published papers were internationally ranked at Journal Impact Factor greater than or equal to 2.0
- In 2004, NCC Researchers also received 1 International & 8 National awards.
- 8 Masters research students and 30 PhD research students were trained and 10 post-doctoral researchers were employed
- 99% of the research supported by NCC had potential or direct clinical applications
- The IBG also supported 264 inter-institutional collaborations.

National Heart Centre (NHC)

Overview

For FY2004, the objectives of NHC's IBG were:

1. To promote and develop and expand the basic and molecular research capabilities of the National Heart Centre, especially in the area of stem cell research for the repair of the failing heart.
2. To consolidate and further equip the imaging and experimentation capability for large animal studies at the National Heart Centre i.e. to continue to update and improve our animal lab facilities.
3. To promote development of innovative mechanical devices for various common cardiac conditions and to bring them rapidly to patient care.
4. To continue to develop the tissue engineering facility with biomaterials engineers from Nanyang Technological University to identify and nurture technological solutions to cardiovascular diseases (particularly in the field of biodegradable polymers and nanotechnology).
5. To create and cultivate a research culture in the National Heart Centre conducive to training creative and talented scientist clinicians in the area of cardiovascular research.
6. To fund and maintain a critical mass of core research scientists to provide continuity of research at the National Heart Centre.
7. To integrate and facilitate various researches across disciplines, e.g. cardiologists and engineers, scientists and clinicians, cardiologist with other specialists, principal investigators with private businesses and government agencies.
8. To consolidate existing projects with renowned overseas investigators and promote further collaboration with them.
9. To bring successful projects rapidly to the patient, and for patent filing and eventual commercialization.

Activities in FY2004

The main core item purchased during this fiscal year was the Zeiss LSM confocal microscope. The equipment was installed and the staff were trained to use it. Images are being acquired in relation to the stem cell work and initial results are encouraging. (Objectives 1 & 2)

For experimental imaging, a fully trained research technologist has been hired and has helped to optimize the use of the imaging facilities, namely the digital c-arm and cardiac ultrasound. This is being used to good effect by collaborating with many other institutions to study the use of various innovative cardiac devices, molecular and gene therapy in experimental models. (Objective 1, 3 and 6)

NHC has also enhanced its information technology, publication facilities and statistical analysis ability. These have greatly enhanced their ability to produce top-notch abstracts and publications. (Objective 6)

Using equipment funded by IBG, a patent has been filed on 'Methods for ex-vivo differentiation of bone marrow stem cells to cardiac like cells'. (Objective 9)

Priority projects include:

1. Use of innovative polymers for drug and gene delivery in the cardiovascular system.
2. Stem Cell therapy for the repair of the failing heart.
3. Tissue engineering heart construct with stem cells as basic building blocks.
4. Innovative drugs for targeting vascular endothelial dysfunction and platelet function.
5. Gene therapy for therapeutic angiogenesis.

The projects will not be possible without the continued support of the manpower and core equipment funding from the IBG.

Summary of Achievements / Research outcomes

In FY2005, NHC's achievements were as follows:

- 15 papers were published, 9 of which were published in top 20% international peer review journals with impact factor greater than 2 and 6 were published in peer review journals with impact factor less than 2
- 14 presentations were made at international conferences
- 1 patent has been filed.
- A Masters research student and PhD research student have been trained.
- 3 research projects had potential or direct clinical applications
- 1 research facility was developed (as mentioned above)
- There had also been 2 inter-institutional collaborations.

National Neuroscience Institute (NNI)

Overview

The NNI's primary mission is to develop and advance neuroscience research to improve patient care, enhance the nation's health and establish an international reputation for medical excellence. The block grant is vital to this mission because it is the sole source of funding for the infrastructure underpinning the NNI's neuroscience research.

The objectives of the block grant are to fund the key components of the research infrastructure, comprising core equipment, administrative and support staff, and a faculty of core scientists and researchers. In addition, the block grant aims to support research training and education, as well as research collaborations and scientific presentations, especially at international levels.

Since its inception in 2000, the NNI has 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. These, in turn, is leading to notable research output and results. These achievements are a clear measure of the effectiveness of the block grant to the NNI's research effort.

Activities in FY2004

Research Infrastructure

Most large equipment needed for the new NNI laboratories (from 2001) have been acquired. Major equipment costs funded in FY2004 included the upgrading of the existing FACS Aria, genotyping/sequencing equipment, confocal microscope and HPLC equipment.

The NNI is reaching a critical mass of core scientists and researchers and a steady state of research administrative and other support staff. The research administration has taken on new duties in FY2004, including providing administrative support for two newly established institutional review boards, the NNI IRB and the TTSH-NNI IACUC.

The block grant provides support to activities promoting research collaborations between NNI scientists/researchers and leading international researchers and institutions. It also supported training and educational activities related to research.

Summary of Achievements / Research outcomes

The primary desired outcome is the improvement of 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, e.g. neuro-degenerative diseases, and is directed towards disease mechanisms and therapies, databases, epidemiological studies and treatment trials.

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

In FY2004, NNI's achievements are as follows:

- A total of 54 funded research projects were ongoing at NNI, of which 26 are funded by NMRC's Individual Research Grant (7 awarded in 2004).
- 7 clinical/drug trials were running at NNI-TTSH campus in FY2004, of which 5 were initiated during the year.
- 77 scientific publications were produced by NNI researchers, with 40 in the top 20% scientific journals with impact factor 2.0 and above.
- 121 scientific presentations were made at international and local scientific meetings.
- NNI added 3 MOUs, one each with Volume Interaction Pte Ltd, IMCB and NYP, to the 10 extant MOUs.

From the previous year, the increase in total individual research grant value was 40%, the increase in publications was 165%, and the increase in the number of presentations was 245%. These improvements are significant, taking into account the impact of SARS in 2003.

National University Medical Institutes (NUMI)

Overview

The National University Medical Institutes focused its efforts on (i) the development of centralized research facilities and services to biomedical users in the vicinity of the Clinical Research Centre, and (ii) the recruitment of research scientists to develop research programmes in cancer and cardiovascular diseases and ROS biology and apoptosis. Core facilities include Confocal Microscopy, DNA Sequencing, Flow Cytometry, in situ Hybridization, Media Preparation, Medical Communications, Store, Transgenic & Gene Knockout (Mouse Facility), and Workshop.

The continued success of our Core Services funded under the IBG is reflected by the steady increase in the number of end-users, not exclusively restricted to the Faculty of Medicine. NUMI's core facilities support hospitals, research institutes and national centres, and other organizations such as Defence Science & Technology Agency, Johns Hopkins Singapore, Lilly-NUS, Nanyang Technological University, and Singapore Science Centre.

Activities in FY2004

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

Cardiovascular Research Programme (CVR)

1. Characterization of xenomyoblasts (human skeletal myoblasts) transplantation for cardiac repair

Human skeletal myoblasts were intramyocardially transplanted into porcine heart model of chronic infarction using transient immunosuppression. Myoblasts successfully survived in porcine heart up to 30 weeks as shown by Lac-z expression. Human myoblasts have conditionally immunoprivileged status when transplanted for cardiac repair in a porcine heart model.

2. Assessment the efficacy of angiogenic gene carrying myoblasts for cardiac repair

Human skeletal myoblasts were transduced with angiogenic gene and transplanted into porcine heart. Transplantation of angiogenic gene carrying human skeletal myoblasts efficiently improved injured heart function with improved regional blood flow as compared with only myoblast transplantation.

3. Bone marrow derived stem cells for cardiac repair

Human bone marrow mesenchymal stem cells treated with 5-azacytidine differentiated into cardiomyocytes. Human sternum bone marrow cells from patients undergoing were found containing cardiomyogenic cells.

The Cardiovascular Research Programme collaborated with A/Prof Ge Ruowen, Department of Biological Sciences, NUS, who kindly provided adenoviral monocistronic vectors carrying either human VEGF165 or Ang-1 and bicistronic vectors concurrently carrying human VEGF165 and Ang-1. With the help of staff from National Heart Center,

animal heart function studies were performed at National Heart Center and Departmental of Experimental Surgery, Singapore General hospital.

Oncology Research Programme (ORI)

The focus of research in the Oncology Research Programme has been on four main cancers: gastric, breast, colorectal and leukemia. A summary of the progress in each of these areas are as follows:

1. 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 study. One-year funding for this project was obtained from the Singapore Cancer Syndicate. Both projects involved inter-institutional collaborations with NUH, IMCB, GIS and SGH.
2. Breast cancer - This project involves inter-institutional collaborations with NUH while a research grant application involving multi-disciplinary collaborative effort between NUS/NUH and John Hopkins University has been submitted to the University for consideration. The 2 projects currently being pursued are:
 - a. The study of methylation status of several genes involved in breast cancer that have been worked out in Prof Sukumar's lab in Johns Hopkins. The specific aim is to see whether there are ethnic differences in breast cancer formation/development of breast cancer.
 - b. Possible involvement of RUNX3 in breast cancer - the results obtained show that RUNX3 mRNA expression is lost specifically in 60% of breast cancer cell lines; and that silencing correlated with hypermethylation of the RUNX3 promoter. This project has received support from an NMRC grant since January 2003.
3. Colorectal Cancer - There is strong evidence that RUNX3 is likely to be involved in human colon cancer based upon the results of the RUNX team working on the mouse system, and another potential tumour suppressor gene, CC3. The involvement of these genes in colon cancer is being analyzed. Work is being done in the area of colorectal cancer and grant support has been successfully obtained from SCS, NUS ARF and NMRC to commence in 2005. This group has initiated inter-institutional collaboration with NUH, SGH, UWA and NCC.
4. Leukemia - The investigators are working on different areas of leukemia. The 2 main studies focus on development of mouse model of FPD/AML (Familial Platelet Disorder with propensity to Acute Myeloid Leukemia) and development of mouse model of Down's syndrome associated Acute Megakaryoblastic Leukemia (D-AMKL). Inter-institutional collaboration exists with scientists in NUH, IMCB and GIS.

Summary of Achievements / Research outcomes

NUMI's achievements in FY2004 are as follows:

- 300 published papers, including 5 by ORI and 13 by CVR
- 33 presentations at international conferences, of which 18 were by ORI and 15 were by CVR
- 1 patent filed by ORI

- 3 external awards for research won by CVR
- 3 masters research students and 3 PhD research students were trained, and 1 postdoctoral researcher was employed.
- 3 research projects were found to have clinical relevance.
- There were 9 inter-institutional collaborations by ORI and CVR
- ORI also developed a Translational Interface.

National University of Singapore (NUS)

Overview

The block grant for NUS (Yong Loo Lin School of Medicine) is used to fund start-up grants for new Faculty recruits (Assistant Professor and above) and small research proposals.

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 projects.

The funding for the start-up grants and pilot projects is meant for the purchase of small equipment and consumables. In the FY2004, the NMRC block grant supported 25 such projects. Below are some highlights of NUS's research activities in FY2004.

Highlights for FY2004

Drug-induced hepatotoxicity: Mitochondria as targets of drug toxicity in animal models of human disease

The overall aim of this new project was to define the role of mitochondria as a pivotal target in the hepatic toxicity of certain pharmaceutical drugs that have been associated with liver injury in humans. Indirect evidence had pointed to mitochondria, but detailed mechanistic studies and in vivo studies had not been performed previously. The focus was initially on the nonsteroidal anti-inflammatory drugs (NSAIDs) nimesulide and diclofenac. The experimental approach was multidimensional, including both in vitro and in vivo models.

Major finding:

The research team first established an in vitro system with isolated mouse liver mitochondria and could demonstrate that nimesulide induced mitochondrial toxicity, in particular induction of the permeability transition (which leads to apoptosis or necrosis) and other related mechanisms leading to mitochondrial dysfunction.

They next established an in vivo model using heterozygous superoxide dismutase 2 (Sod2^{+/-}) deficient mice (breeding colony and genotyping done in their lab). These mice exhibit clinically silent mitochondrial dysfunction and were used to mimic genetic abnormalities in mitochondria that may predispose individuals to drug-induced toxicity. At therapeutic doses of nimesulide given over a prolonged period of time, these mice developed significant mitochondrial oxidative changes that were not seen in normal wild-type mice treated with the same drug. In addition, highly increased numbers of hepatocytes undergoing apoptosis could be demonstrated. Collectively, these results demonstrate that underlying genetic abnormalities may predispose mice (and perhaps individual patients) to the precipitation of NSAID-induced mitochondrial injury and perhaps later overt organ toxicity. Future research will be aimed at finding evidence for these postulated changes in human mitochondria of susceptible patients.

These studies led to further funding (BMRC and NMRC grants) and the project, which is currently ongoing, has been expanded accordingly. Also, two Tier 1 (IF 5.6) publications (in Free Radical Biol Medicine) arose from these initial studies.

NMRC provided the seed grant support during the critical initial phase.

Development of a device for digit volumetry for use as an indicator of sympathetic function

Digit volume is dependant on tissue and physical factors. The most important physical factor is temperature which directly activates the sympathetic nervous system which in turn controls and adjusts blood flow via dilation or constriction of vessels. Blood tissue contributes to an estimated 30-50 % of the distal digit tip volume. Digit blood vessels are densely innervated and controlled by sympathetic nerves which can reduce blood flow by 100%.

Based on this, the research team set out to develop a medical device capable of measuring digit volume as a direct indicator of sympathetic function to the digit in the hand or foot.

Testing and construction of the device prototype was performed in healthy volunteers in the Department of Engineering. The research team was able to show that sympathetic activation results in a measurable drop in the digit tip volume. Results of the testing led to the application of a patent for possible exploitation as a commercial medical device. (Apparatus and method for non-invasively measuring digit volumetric changes. Filed in Singapore 25/06/2005 Singapore Patent application: 200503834-4).

Possible indications for use of the digit volumeter

Any process, be it pathological or physiological or a pharmaceutical agent that interferes with the sympathetic function to the digits (hand or foot) will likely result in abnormality of digit volumetry. Common pathological conditions would be all types of polyneuropathy in particular diabetic polyneuropathy, while less common ones are for eg. idiopathic small nerve fibre disease. Carpal tunnel syndrome also often involves hand sympathetic nerve fibres and the research team expects digit volumetry to be useful in the investigation of this disease and its elucidation.

Next step

The research team intends to test the device in specified medical conditions. To enable this, they are looking for an industrial partner and NMRC funding.

Fibroblast-activating factor: Molecular characterization of a putative virulence factor from Porphyromonas gingivalis causing periodontal disease

Periodontal diseases represent a group of inflammatory diseases of the gingiva and the supporting structures of the periodontium. Although the etiology of periodontal disease is still not completely understood, it is widely accepted that the disease occurs as a result of infection from the subgingival plaque bacteria, particularly Gram-negative anaerobes.

P. gingivalis is an anaerobic nonmotile, Gram-negative, rod-shaped, black pigment-forming bacterium highly associated with periodontitis. *P. gingivalis* has been shown to produce a variety of potential virulence factors such as capsule, fimbriae, lipopolysaccharides (LPS), proteases and several outer membrane proteins including fibroblast activating factor (FAF). These putative virulence factors have been shown to have an effect on host-parasite interaction in selected cell culture and animal models.

FAF is a novel 24-kDa outer membrane-associated protein from the outer membrane vesicles of *P. gingivalis*. It has been shown to have a significant proliferative stimulating effect on normal human gingival and skin fibroblasts. What role FAF plays in vivo in *P. gingivalis*-elicited infections is unclear. Since fibroblasts constitute the major portion of

cells in periodontal tissues, and play significant roles in controlling the metabolism of connective tissue and keeping the integrity of periodontal tissues, it supports the idea that FAF may function as a virulence factor of *P. gingivalis* by affecting the growth and protein synthesis of human gingival fibroblast and thus, interfering with the homeostasis of connective tissue. In addition to the destruction of the connective tissue of the periodontium, the resorption or destruction of alveolar bone is a common outcome of periodontal disease progression. Therefore, there is also a possibility that FAF may play a role as a second messenger for in bone resorptive activity in addition to having fibroblast-modulating effects.

The objective of this project is to study both the molecular and cellular aspects of the activities of FAF. The research team's role here is to focus on the molecular aspect by doing the cloning and examining the regulatory mechanism of the expression of *faf* from *P. gingivalis*. Prof Alistair Lax who is an expert on cellular microbiology from King's College Dental Institute will concentrate on the cellular aspect by looking at how recombinant FAF interacts with host eukaryotic cells including osteoblast cells during infections.

The role of statins immune cells interaction

Immunological-based, anti-inflammatory therapies have shown promise in the management of a number of inflammatory conditions such as asthma and rheumatoid arthritis. Increasing understanding of the pathophysiology of these diseases has revealed a number of potential checkpoints, including key mediators of lymphocyte adhesion, cytokines, and other immune molecules critical in the presentation of antigen and subsequent T cells activation. 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (Statins), are effective serum cholesterol-lowering agents, but may also possess immunomodulatory properties. The role of statins in immune cell-cell contact was studied 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 concentrations of statins. Production of pro- and anti-inflammatory cytokines such as IL-1 β , TNF α , IL-6, IL-10 were assessed by ELISA. The research team observed that dose-dependent inhibitory effect of statins on IL-1 β , TNF α , IL-6 cell-contact induced cytokine production while IL-10 remains unaffected. To verify the inhibition was not a cytotoxic effect, cell viability were be monitored throughout the experiment. In addition, they observed statins reduced cell surface adhesion and co-stimulatory molecules LFA-1/ICAM-1, CD40/CD40L expression by FACS analysis. Additional experiment is currently performed in which reversal of statins inhibitory effect will be studied by addition of cholesterol substrates including mevalonate (MVA).

Inter-institutional Collaboration/Conference Presentation

The start-up grant has provided the recipient with the necessary resources to perform the above experiments and established collaboration with colleagues at the Dept. of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital. Part of the data has been accepted for poster presentation at the American College of Rheumatology annual scientific meeting in San Diego, California, November 13-17, 2005.

Dissection of the signalling pathways in reactive nitrogen species- induce cell death

With the support of the above grant, experiments have been conducted in examining the role of c-Jun N-terminal kinases (JNK), an important member of the mitogen-activated protein kinase (MAPK) family in cell death initiated by reactive nitrogen species. Preliminary data suggest a rather complex relationship between JNK and cell death and the exact role of JNK is depending on the presence of other cell signaling

pathways such as nuclear factor-kappaB (NF-κB). Currently studies in mouse embryonic fibroblasts (MEF) as well as in human cancer cells are carried out.

This study is based on close collaboration with international collaborator Dr. Zheng-gang Liu from the National Cancer Institute (NCI), the National Institutes of Health (NIH), USA and Dr. Matt Whiteman from the Department of Biochemistry, NUS.

Based on the support of this start-up grant, the PI has successfully obtained an external competitive grant from BMRC.

One manuscript has been submitted to Free Radical Biology and Medicine, the top journal in the field of free radical research.

Summary of Achievements / Research Outcomes

In FY2004, NUS's achievements are as follows:

- 1 patent has been filed
- 2 Masters research students were trained
- 2 on-going inter-institutional collaborations with
 - King's College, London
 - NCI/NIH

Singapore Cardiac Data Bank (SCDB)

Overview

Singapore Cardiac Data Bank (SCDB) is a collaboration project and joint effort of the cardiac departments from Changi General Hospital, National Heart Centre, National University Hospital, Alexandra Hospital and Tan Tock Seng Hospital. Its aim was to contain vital statistical information used by the restructured hospitals for benchmarking, quality care and outcome management. Statistics provided by the SCDB enables comparative assessments against local and international cardiac care benchmarking in the future in the following areas: myocardial incidence, coronary intervention (angiography & angioplasty), electrophysiology and pacing (Electrophysiology/Ablation, pacemaker implantation, ICD implantation), cardiac surgery (CABG, valve surgery & minimally invasive surgery), etc.

Of particular national significance is the long-term tracking of the rates of myocardial infarction in Singapore, which is essential to assessment of national trends in heart disease patterns and long term health planning. A number of publications have been produced from the registry data.

The establishment of SCDB in 1999 enables the cardiac department and cardiac surgery departments from the various hospitals to hold National Medical Audit Meetings in Cardiology to review the workload, morbidity, mortality and make recommendation of changes in practice for cardiac specialties. It also benchmarks individual hospital quality care.

The clinical characteristics, risk factors, co-morbidity of cardiac information captured in SCDB enables hospitals to track the utilization of healthcare resources in terms of drug therapy and treatment outcomes, and monitor the related factors contributing to cardiac morbidity and mortality.

Coordinated Clinical Pathway (CCP) Acute Myocardial Infarction (AMI) project was the joint effort of the National Heart Centre (NHC) and SCDB, and has served as a general guideline for planned programme of patients' care and was implemented at the end of 1999. The introduction of CCP has dramatically improved the education of patients regarding coronary risk factors and cardiovascular rehabilitation. Feedback from patients and relatives indicated that they were more aware of the disease process as well as the importance of risk modification and were happy with this approach. They also recognized the value of attending cardiovascular rehabilitation. NHC subsequently implemented CCP Heart Failure and taken over CCP CABG from Singapore General Hospital.

Usage of SCDB data

Overall, the usage of SCDB data is as follows:

1. For National Medical Audit Meetings (Cardiovascular discipline), to review the workload, morbidity, mortality and complications of service included in the audit period, and make recommendations of changes (if any).
2. Submission of AMI progress status to Epidemiology and Disease Control Division (E&DC): Non-communicable diseases, Ministry of Health (MOH), for MOH policy and planning purposes.

3. Submission of AMI 28-day survival rate, Adult PTCA 30-day in-hospital survival rate and Adult CABG (alone) 30-day in-hospital survival rate to E&DC, MOH, for updating the members of DMS' meeting on the status of the National Disease Control Plans for major non-communicable diseases (including cardiac) and conditions.
4. Coordinated Clinical Pathway (CCP) for AMI, Heart Failure & CABG (selective patients): A collaboration project with NHC. It is a general guideline that represents a planned programme of care for patients with AMI, Heart Failure and CABG. It aims to monitor and evaluate the variance to ensure good clinical outcome and service, the appropriate use of resources and make recommendations for changes of practice (if any).
5. Lectures, talks, presentations for local/international conferences, for teaching, medical updates and education to medical staff in cardiac and non-cardiac disciplines.
6. Media/press interview/conferences for health promotion programmes, for health programmes and to provide education to the public.
7. To transfer selected AMI data to National Disease Registries Office (NDRO) as agreed by the head of NDRO (in discussion and progress.)
8. To set Singapore national benchmarking for cardiac specialties (in progress)
9. For constructing risk modelling for cardiovascular discipline (in progress)

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 internationally recognized high profile.

The major objective of the FY2004 block grant was to continue to maintain research facilities and scientific output within SERI's four established research divisions, namely, the Clinical Research Unit, the Epidemiological Unit, the Visual Psychophysics Unit and the Laboratory Sciences Unit. Research priorities remained as those most relevant to Asian ocular disorders such as myopia, angle closure glaucoma, ocular surface diseases and diabetes. In addition, an important objective of this IBG was to support the conduct of the 2nd SERI-ARVO International Meeting in vision research, which was held from 16 - 19 February 2005.

Activities in FY2004

Myopia

In myopia research, we continued our laboratory work on the role of muscarinic receptors and cell signaling studies in scleral fibroblasts, developed a pig model of myopia, explored interactions in putative myopia genes and environmental risk factors for myopia progression, and conducted a randomized trial on a new neurophysiological treatment for visual enhancement in both low myopia, and amblyopia.

Ocular Surface Stem Cells and Tissue Engineering

In our studies on ocular surface diseases, we accelerated work on ocular surface stem cell biology, stem cell ex vivo expansion and human clinical trials on cultured conjunctival stem cell transplantation and tissue engineering. We have been successful in developing bioengineered corneal and conjunctival tissue-equivalents by cultivating ocular surface stem cells on amniotic membranes. These findings have important clinical implications and are important for the development of a safe and effective bioengineered tissue-equivalent for clinical use.

Glaucoma

We continued to conduct clinical trials on acute angle closure, including exploratory studies on neuroprotective vaccination and various pressure-lowering drug trials and prophylactic laser iridotomy studies.

Diabetes and ocular vascular disorders

In diabetes and retinal and ocular vascular disorders, we conducted electrophysiology studies on macular and peripheral retinal disorders, epidemiological studies on the use of retinal imaging to detect vascular disease, and evaluated novel posterior segment drug delivery approaches for anti-angiogenesis therapies.

Ophthalmic Genetics Programme

In FY2004, SERI started an Ophthalmic Genetics program led by a consultant ophthalmologist with a PhD in Genetics. A new molecular genetics laboratory was set up,

staffed by a Senior Research Fellow and 2 laboratory technologists, and a database of patients and families with genetics disorders was also initiated. The main interests of ophthalmic genetics research in SERI are glaucoma, retinal dystrophies and corneal dystrophies. Projects initiated include linkage analysis of primary angle closure glaucoma pedigrees, the role of MYOC and CHX10 in angle closure glaucoma, molecular analysis of the retinal dystrophy genes PRPF31, CA4 and CYP4V2, and linkage analysis of pedigrees with Fuch's endothelial dystrophy.

Summary of Achievements / Research outcomes

In FY2004, SERI scientists and clinicians from both clusters accomplished the following:

- Published 120 scientific articles in peer reviewed ophthalmology and visual science journals
- Presented 150 scientific abstracts at local and international clinical and research meetings
- Initiated 46 new research projects
- Received a total of 5 awards for research excellence
- Trained 2 masters research students and 1 PhD research student, and employed 2 post-doctoral researchers
- 28 research projects had potential or direct clinical applications
- Developed and improved the research clinics with additional and replacement equipment, and 2 additional investigation rooms to meet increased demand
- Developed the new Ocular Genetics Laboratory, set up since March 2004
- SERI scientists and affiliated clinicians were also awarded a significant amount of extramural research funding, in individual research grants and commercially funded grants.

SERI was given the prestigious privilege to once again host the important international vision research meeting in Singapore in 2005. This meeting was jointly sponsored by the world's largest organisation for eye research, Association For Research In Vision And Ophthalmology (ARVO). ARVO has a membership of more than 10,500 members representing more than 60 countries. The 2nd meeting, was again judged a huge success, as it was attended by more than 700 delegates from 36 countries.

For the first time, selected abstracts from the meeting were compiled and printed as a supplement to the prestigious journal, American Journal of Ophthalmology with an impact factor of 2.258.

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

Overview

The main objective of the block grant is to provide administrative, scientific and technical support for NMRC related research conducted in TTSH. The block grant was instrumental in providing core manpower support for TTSH Clinical Research Unit (CRU) and the Infectious Disease Research Centre (IDRC).

CRU continues to provide central support for TTSH researchers working on NMRC-funded studies while IDRC continues to grow in strength and activity and has established itself as a regional centre of excellence in infectious disease research.

The manpower support, through the FY2004 IBG had helped researchers with the preparation of the grant application, study costing, actual conduct of the study, management of accounts for all ongoing NMRC projects, literature searching and preparation of the manuscript for publication.

IDRC was established in Oct 2000 to provide infrastructure to conduct infectious diseases clinical science research and clinical trials to internationally acceptable standards. Since its inception, there has been a tremendous growth of research in the department. The IDRC received favourable report by an audit team from NIH for its participation in the multinational ESPRIT Study. It continues to expand its link with TREATAsia, The Research, Education and Treatment for Asia project, a new regional collaborative research network for HIV research funded by the American Foundation of AIDS Research. IDRC had also secured an agreement with BMS to provide lifelong free Anti-HIV treatment to patients enrolled in BMS A1455 Stravudine study till November 2004.

Activities in FY2004

TTSH-CRU's achievements in FY2004 include:

- 17 papers published in top 20% international peer review journals with impact factor greater than 2.0, and 14 papers published in peer review journals with impact factor less than 2.0
- 31 presentations at international conferences
- 2 Masters research students and 2 PhD research students trained
- 64 clinically-relevant research projects
- The improvement 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. 7 Enabling Grants were awarded in FY2004.

Table 6
Institutions that received EG funding in FY2004

	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)

Each Enabling Grant recipient's research activities and outcome for FY2004 are as follows.

Alexandra Hospital (AH)

Overview

The FY2004 block grant was a pivotal resource from NMRC that was invaluable in helping Alexandra Hospital build up the basic foundation of clinically relevant research.

Activities in FY2004

Enhanced capability of molecular genetic laboratory

The FY04 EG has helped the laboratory upgrade its capability to perform medium through-put RT-PCR based genotyping. However, all existing equipment in the lab can only perform genotyping of known genetic variation. With the entry-level genetic analyzer funded by the block grant, AH will be able to explore the presence of novel genetic variations. Some of these variations are population specific.

The studies on the genetics of diabetic nephropathy have resulted in two presentations in a regional Human Genome (HUGO) pacific scientific meeting in Nov 2004. Additional abstracts have been accepted for presentation at the World Congress of Nephrology in June 05.

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 been presented at the European Arteriosclerosis Society scientific meeting in Apr 05. Additional abstracts have been accepted for presentation at the World Congress of Nephrology in June 05. With the enhanced capability from FY04 EG (e.g. RT-PCR), the investigators have started pursuing gene expression study on these cell lines.

Consolidating research in sports medicine and exercise physiology

A multi-disciplinary team of investigators from orthopedic surgery, sports medicine, physiotherapy and endocrinology has come 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 begun clinical studies on human volunteers and athletes. Preliminary results on influence of the abductor hallucis muscle on the medial arch of the foot have been accepted for presentation at International Federation of Foot and Ankle Surgeons' Triennial Meeting, Sept 2005. Research on the diagnostic value of clinical tests for supraspinatus injury has also shed some light on the possibility of the composite of 4 out of 6 tests available, having a high positive predictive value for supraspinatus injury.

Research manpower

The funded research nurse played a key role in the recruitment of study subjects. She has been instrumental in the recruitment and collection of biological samples of more than 1000 subjects with diabetes, more than 650 healthy subjects and has set up a diabetic foot syndrome database. She has also contributed to the smooth running of most of the FY04 small grants and NMRC IRG grants. In return, she 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 AH investigators. These included statistical courses, courses on cell culture, genetics and bio-informatics, and research writing. With the above development, AH has successfully attracted 5 undergraduate science and medical students to do their elective attachment with us for a period of 1 to 3 months.

The grant has also helped to support subscription to Blackwell Synergy (Medical and Nursing Collections) Journals and Cochrane Library.

Clinical trial research clinic

The physical availability of a research clinic is an important resource to investigators who wish to conduct clinical study but have space constraint in the usual service clinic.

Competitive grants

AH investigators have been awarded two competitive grants in 2004. The set up of research infrastructure using FY04 EG have enabled the smooth execution of other competitive grants from NHG and NMRC.

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

AH is witnessing the rise of research in the field of artificial blood replacement product, emergency airway management, age related macular degeneration and molecular marker for risk stratification in thyroid cancer.

Synergy

Inter-disciplinary collaboration is burgeoning among 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.

The block grant has made FY04 an exciting year for research development in AH.

Changi General Hospital (CGH)

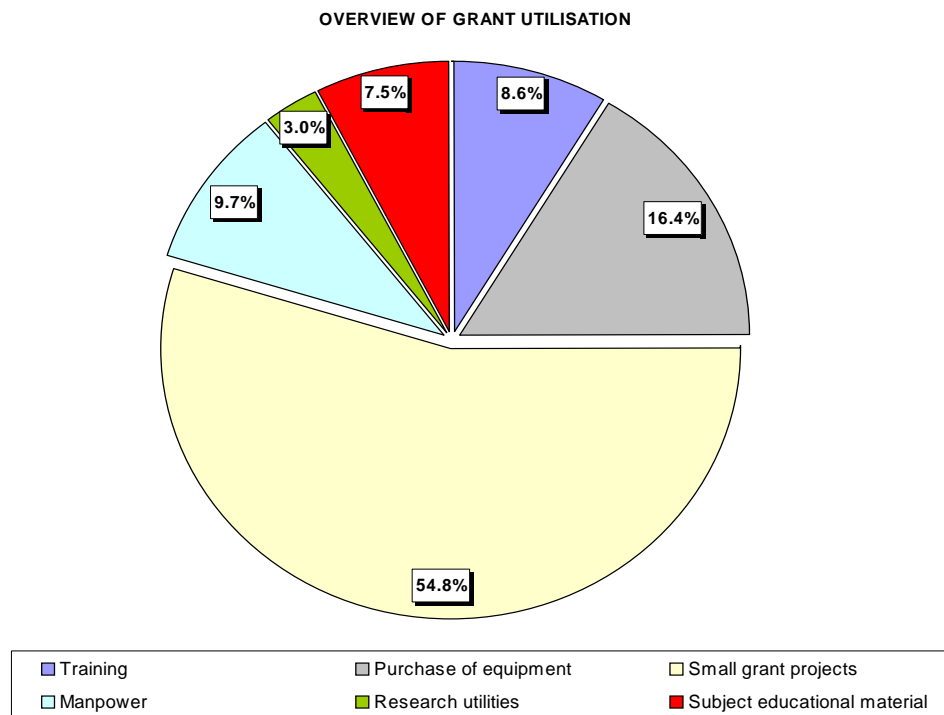
Overview

The objectives of the NMRC FY 2004 enabling grant were:

To further develop and enhance the research infrastructure;
To further develop the human resources for research work.

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

Activities in FY 2004



In FY 2004, CGH's activities and research outcomes are as follows:

- The Phase 1 clinical trial facilities have been improved. This helps CGH meet the stringent requirements of conducting the trials and complete the trials in a shorter time.
- CGH staff have been sent to Ethics seminars, clinical trial symposium, as well as overseas to learn new laboratory-based research techniques and to learn from other established phase 1 units. The training and exposure improved staff confidence and work efficiency.
- The article retrieval services with NUS were renewed, and the doctors have found the services helpful in obtaining references for their research work and paper writing.
- CGH's CTRU brochure was developed and printed to advertise their services to potential clients.
- A video was developed to educate trial subjects on "what is involved in clinical trials participation".

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

Overview

Since FY2003, KKH has enhanced its research infrastructure by putting in place a KKH research center, which amalgamates the research administrative group, nursing research unit and the new clinical trial unit under one roof. The centre is co-funded by KKH, the NMRC enabling grant, SingHealth research grants and commercial sponsored trials.

The centre oversees all clinical trials activity in KKH. This includes budget & contract negotiations with external sponsors for clinical trials and providing research nurses in coordinating simple clinical research. With the NMRC enabling fund for provision of research nurses, the clinical trial capability, quality and consistency has improved in KKH.

Activities in FY2004

Research databases and statistical consultation/analysis services

Research studies carried out require support in the form of statistical consultation/analysis or extensive disease databases.

In the year 2004, a total of 271 consultation-episodes were provided by KKH Research Centre. Majority of the consultation-episodes was on statistical analysis (being 83% of the activity) and 7% concern database support. On average, there were 23 consultations per month.

The centre supports researchers in developing research databases. 22 databases have been set up since 2000 and most are hosted in the server funded by the NMRC enabling grant.

Education and Training

The centre recognises the need to upgrade the skills and knowledge of clinicians on statistical analysis. In 2004, 4 in-house SPSS workshops were conducted with participants from various disciplines and 2 in-house research courses were conducted for nurses.

Laboratory-based research infrastructure

KKH laboratory based research infrastructure was enhanced in the later part of FY2003. As genetic disease has become an important area of health care and most genetic diseases present in childhood, KKH presents a unique opportunity to capture and study genetic diseases in Singapore. With the support from NMRC enabling grant and other funding sources, KKH has put together a comprehensive facility to support genetic based clinical research, including dHPLC, real time PCR, automated DNA extractor and DNA sequencer. A number of clinical specialists from different areas have embarked on novel projects studying mutations in various genetic diseases. Two researchers have been successful in gaining project funding from the NMRC to pursue interests in this area.

Summary of Achievements / Research Outcomes

KKH's research achievements/outcomes for FY2004 are as follows:

- 47 Publications

- 105 Presentations at international conferences
- 1 NMRC Research Scientist award
- 4 Research projects with potential/direct application
- 4 Inter-institutional collaboration
- 2 Research Infrastructure developed/improved

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

Overview

The objectives of the FY2004 enabling grant were to enable HSA to implement the following clinical trials regulatory initiatives in Singapore:

1. Training the clusters' institutional staff, and Institutional Review Board (IRB) members and administrators in preparing the institutions for accreditation in the area of human research protection. The training was conducted by, Dr Marjorie Speers, Executive Director, Association for the Accreditation of Human Research Protection Programs (AAHRPP) (<http://www.aahrpp.org>), which is a non-profit organisation based in the United States. Accreditation of the institutions would serve to improve the systems that protect the rights and welfare of trial subjects, hence raising the benchmark for human research protection in Singapore. It also improves the overall quality of research by creating an environment whereby high standards and practices are applied.
2. Keeping abreast with the advancing sciences and regulatory aspects in clinical trial matters through training and participation in educational conferences so as to ensure regulatory knowledge is kept relevant.
3. Enhance the review system for safety assessment of investigational drugs undergoing clinical trials in Singapore.

The initiatives have been made to ensure that the regulatory system is innovative, efficient and responsive to its environment, and will help to improve the overall quality of clinical research and human research protection in Singapore by consistently applying high standards and practices that are benchmarked against international standards.

Activities in FY2004

Core Manpower - Locum Pharmacist

Under the Medicines (Clinical Trials) Regulations 2000 and the Singapore Guideline for Good Clinical Practice, international serious adverse events that are unexpected and related to the investigational products studied in clinical trials have to be reported to the regulatory agency. These safety reports have to be sent to HSA on an expedited basis. HSA has to be notified no later than 7 calendar days after first knowledge, by the sponsor, of a fatal or life threatening event and a follow-up report has to be sent within the next 8 calendar days. For all other events, the initial notification period is 15 calendar days.

In order for meaningful evaluation of these safety reports, the information contained in the reports is entered into the Access database. When there are any signals that warrant further follow-up, Clinical Trials Branch (CTB) staff will contact the sponsor to provide more information and, if need be, CTB will request for additional follow-up, e.g., amendments to the protocol and/ or informed consent form.

The total number of reports that met the reporting criteria and have been entered into the database from (Apr 04 - Mar 05) is 4800 for initial reports and 3550 follow-up reports. The actual number of reports received is more than the above statistics. However, some of them do not meet the reporting criteria and are therefore not entered into the database.

Funds for a locum pharmacist were requested under this activity. The main responsibility of the locum pharmacist was to enter the safety information into the database, assist with the monthly reviews (including trend detection and sponsor follow-up) of the safety information gathered and generation of monthly statistics.

The framework for regulatory safety reporting, management and interventions was presented last year at the following meetings:

1. 4th Conference of Asia Pacific Economic Cooperation (APEC) Network on Pharmaceutical Regulation of Science - Seoul, Korea (22-23 Nov 2004) by Dr Gerard Wong, DD (PER), CDA, HSA.
2. IQPC Good Clinical Practices Conference 2004, Orchard Hotel, Singapore. Reporting and Management of Serious Adverse Events in Clinical Drug Trials - A Regulatory Perspective (24 Aug 2004) by Ms Dorothy Toh, Clinical Trials Branch, CDA, HSA

A paper was published on the regulatory safety reporting, management and interventions in the Regulatory Affairs Journal - Pharma:

Dorothy Toh S.L., Kerwin Low S.Y., John C. W. Lim, Julia Leong, Foo Yang Tong
How Singapore Regulates Safety Reporting from Clinical Trials
The Regulatory Affairs Journal - Pharma, October 2004, 15(10), 725-732

Below are some interventions and follow-ups from CTB for FY2004

- An investigational product for Breast Cancer showed an increase in the number of decreased left ventricular ejection fraction, with an approximate incidence of about 1.3 -1.4%. Company was asked to update informed consent form (ICF), in view of the potential risk, as it may be relevant to the patient's willingness to continue participation in the trial.
- Investigational oncology product: There were occurrences of tumour hemorrhage with life threatening and fatal outcomes. CTB requested that the ICF be updated to include this uncommon but potentially life threatening SAE, and to inform all doctors to be vigilant for signs of tumour necrosis and haemorrhage in subjects treated with this study drug.
- An investigational growth factor inhibitor: SAEs relating to blindness / partial blindness occurring with other neurological events and concern were shared by Data Safety Monitoring Board (DSMB). CTB requested for an ICF amendment for this trial and all existing patients were re-consented. In addition, an independent panel of neurologists was formed and the need for a protocol amendment was to be reviewed at a subsequent DSMB meeting. There was also inhibition of HERG channel assay in vitro, leading to a QTc study in healthy volunteers. CTB requested for ICF update to inform ongoing subjects at risk for QTc prolongation about this risk and documenting their consent if they wish to continue in the trial.
- A novel immunosuppressant, currently in trials. CTB noticed a trend in retinal / macular edema, one of which resulted in a disability. An Ophthalmology Advisory Group has confirmed an increased risk for the development of macular edema and recommended a protocol amendment, which is to be implemented immediately in the interest of patient safety.

Institutional Review Board (IRB) Training

IRB Ethics Training Workshop

CTB collaborated with A/Prof Jean-Paul Deslypere, Director of the Clinical Trials Epidemiology Research Unit (CTERU) and the 2 clusters to put together a programme for an ethics workshop on Saturday, 28 August 2004. Two prominent experts* in this area conducted the IRB Ethics Training Workshop. It served as a continuing education session and an update to the local ethics community on current ethical issues in medical research. In addition, both speakers also met with MOH Health Regulation Division (HRD) senior staff to update them on ethics review boards oversight / regulatory system in the US and Europe/International. Both experts were also invited to speak at an Advanced Good Clinical Practice (GCP) Course focusing on Quality Assurance, which was organized by Clinical Research Professional Group (comprising mainly industry players) under the auspices of the Singapore GCP programme, run by A/Prof Jean-Paul Deslypere.

* Prof Francis Crawley
Secretary General & Ethics Officer
European Forum for Good Clinical Practice (EFGCP)
<http://www.efgcp.org/index.php>

* Dr Melody Lin
International Director, Office for Human Research Protections (OHRP)
Department of Health & Human Services (DHHS), USA
<http://www.hhs.gov/ohrp/>

Visit by AAHRPP, 21-24 March 2005

This is the second trip by Dr Marjorie Speers, Executive Director from the Association for the Accreditation of Human Research Protection Programs (AAHRPP), USA, to meet with senior officials from the 2 clusters and MOH HRD to discuss how the institutions and clusters could be prepared and trained in order to seek accreditation. This visit is part of a three-year plan, now in its second year, outlined by HSA for the two clusters to seek accreditation in 2006, if they are ready. Dr Speers also conducted a two-day intensive training course for the clusters' institutional staff, and IRB members and administrators working on the accreditation self-assessment and application, and a one-day general IRB training session opened to all IRB members.

Conferences Attendance 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. Conference: DIA/EMEA Joint Meeting on Gene Therapy & Cell Therapy Product
2. IBC Conference: Pharmacovigilance and Adverse Events Reporting
3. EC ASEAN PPWG Training Workshop on Analytical Validation

Health Science Authority (HSA) - Small Grants

Overview

The objectives of the FY2004 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 FY2004

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

These research projects could be generally 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 FY2004 were:

Clinical Trials Support

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

To fund manpower such as the institution-wide posts of NDC nurse, research coordinator and data entry clerk.

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.

Activities for FY2004

Clinical Trial Support and Small Grants

In FY2004, the Enabling grant funded 22 small projects, 2 pilot projects and the organization of the "Research Strategic Plan Workshop on 31 July 2004 - Research Strategic Plan FY2005 -2007".

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 FY2004 are as follows:

- 4 published papers
- 9 Citations of papers published
- 7 Presentations at International Conferences
- 1 Research with potential/direct application
- 7 inter-institutional collaboration
- 1 Research Infrastructure improved - Research Resource Unit
- 4 MDS and 13 Advanced Specialty Trainees Trained

National Skin Centre (NSC)

Overview

The objectives of the NSC's enabling grant for FY 2004 were:

1. To consolidate the existing infrastructure for clinical trials.
2. To further support the establishment of the cell culture laboratory.
3. To provide an alternative funding source for researchers conducting small or pilot studies in areas of clinical importance.

Activities in FY2004

Manpower for Clinical Trials Support

The recruitment of additional manpower enabled greater oversight and better co-ordination of research activities in NSC. With the establishment of the NHG Domain Specific Review Boards in early 2004, this was especially crucial given the additional administrative processes required for research approval and the conduct of clinical trials. Timely updating and management of the 9 disease-specific databases was also ensured.

Cell Culture Laboratory

A study on the novel use of autologous human serum in the culture of human melanocytes was completed. This has important clinical significance in melanocyte transplantation for vitiligo patients, as it circumvents the traditional use of fetal calf serum. A pilot project on melanocyte-keratinocyte co-culture has also been completed, with the outcome of establishing a more physiological in-vitro culture model that can be used for future cell biology research.

Small Grants

The project on the "Molecular characterization of atypical mycobacterium species by PCR-RFLP" was completed successfully. The results of the study confirmed the validity of this technique in differentiating 8 species of atypical mycobacterium (MOTT) species. This PCR assay has been translated into clinical application, thus offering a more comprehensive diagnostic panel for mycobacterial infections, in addition to that for M.TB. NSC currently receives specimens from all the public and private hospitals in Singapore for PCR diagnosis of mycobacterial infections.

Other small grants continued to allow NSC registrars and younger doctors to conduct pilot studies such as immunotherapy for recalcitrant viral warts, histological analysis of urticarial vasculitis and extrammary Paget's disease and an epidemiological seroprevalence study of sexually transmitted diseases in the MSM community.

Summary of Achievements / Research Outcomes

NSC's research outcomes for FY2004 are summarised as follows:

- 4 presentations at regional/international conferences
- 1 application to NMRC competitive grant and 1 grant awarded by Singapore Cancer Syndicate
- 6 projects with direct or potential clinical applications
- 1 Masters research student trained

- 1 new product/process commercialised
- 3 inter-institutional collaborations
- 1 research facility developed/improved.

CHAPTER 5

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 2002 to 2004.

From 2002 to 2004,

- there was a 114% increase in publications for every million dollars expended
- there was a 125% increase in publications with impact factor greater than 2, for every million dollars expended.
- there was a 169% increase in the number of national and international awards clinched.
- all completed projects had clinical significance

Table 7
Research Output from Block/Competitive Grants

Year	2002	2003	2004
Expenditure* (\$'m)	55.2	49.7	52.9
Output			
Total no. of Publications	316	514	645
Publications with impact factor >2	113	177	240
No. of national and international awards	26	24	70
% of completed projects with clinical significance	100	100	100
Number of research scientists (including clinician-scientists)	Not available	112	136
Output per \$'m			
Publication per \$'m	5.7	10.3	12.2
Publications with impact factor >2 per \$'m	2.0	3.6	4.5

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

CHAPTER 6

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 by independent local and overseas reviewers and evaluated by the Fellowship subcommittee which will provide awarding recommendations to the Council.

AWARDS COMMENCING IN FY2004

Medical Research Fellowship Award

15 doctors commenced their NMRC Medical Research Fellowship in FY2004; 8 of which were for training leading to a degree whereas the other 7 were for training not leading to a degree.

Training leading to a degree (MSc/PhD)

1. Dr Ong Eng Hock Marcus from the Department of Emergency Medicine, SGH received a full-time fellowship for 12 months. His project at the Medical College of Virginia, USA was "The chest pain EMS house call program". Dr Ong's training would lead to a MSc.
2. Dr Ang Hui Chi Annette from the Department of Otolaryngology, NUH received a part-time fellowship for 14 months. Her project at the National University of Singapore was "Role of cell cycle regulator proteins and leukotrienes in the pathogenesis of nasal polyposis". Dr Ang's training would lead to a MSc.
3. Dr Oo Kian Kwan Kenneth from the Department of Otolaryngology, NUH received a part-time fellowship for 7 months. His project at the National University of Singapore was "Tissue engineered prefabricated vascularised flaps". Dr Oo's training would lead to a MSc.
4. Dr Tan Thuan Tong from the Department of Internal Medicine, SGH received a full-time fellowship for 24 months. His project at the Malmo University Hospital, Lund University, Sweden was "Host cell interactions of the respiratory pathogen *Moraxella catarrhalis*". Dr Tan's training would lead to a PhD.
5. Dr Pang Su Yin Grace from the Singhealth Services received a full-time fellowship for 36 months. Her project at the National University of Singapore, National Cancer Center, Singapore and University of Adelaide, Australia was

“To screen for variant SNPs in genes encoding opioid drug receptors in Asian cancer patients & to identify functional SNPs and determine their influence on the PK/PD of opioids in cancer patients”. Dr Pang’s training would lead to a PhD.

6. Dr Tan Kiat Tee Benita from the Department of General Surgery, SGH received a full-time fellowship for 36 months. Her project at the National University of Singapore, National Cancer Center, Singapore and Karolinska Institute, Sweden was “Gene expression profile of breast cancer with site-specific metastasis”. Dr Tan’s training would lead to a PhD.
7. Dr Tan Soo Yong from the Department of Pathology, SGH received a full-time fellowship for 36 months. His project at the University of Oxford, UK was “Novel cellular subsets in lymphoid tissue and relevance to the pathogenesis of lymphoma subtypes”. Dr Tan’s training would lead to a DPhil.
8. Dr Chong Kian Tai from the Department of Urology, TTSH received a part-time fellowship for 15 months. His project at the National University of Singapore was “Detection of cancer-specific peptides in prostate cancer”. Dr Chong’s training would lead to a MSc.

Training not leading to a degree

9. Dr Low Fatt Hoe Adrian from the Department of Medicine, NUS received a full-time fellowship for 12 months. His project at the Massachusetts General Hospital, USA was “The genetic basis of CAD, employing a proband-family strategy in premature CAD patients and consideration of gene-gene and gene-environment interactions”
10. Dr Chai Yui Hwei Josiah from NNI received a full-time fellowship for 8 months. His project at the University of Rochester, New York, USA was “Vascular adaptation in facioscapulohumeral muscular dystrophy: An immunohistochemical study”.
11. Dr Wong Chek Hooi from the Department of Geriatric Unit, SGH received a full-time fellowship for 8 months. His project at the Mc Gill University, Canada was “The determinants and components of frailty and clinical intervention for the prevention, treatment and care for the frail older person”.
12. Dr Tay Shian Chao from the Department of Hand Surgery, SGH received a full-time fellowship for 12 months. His project at the Mayo Clinic, Minnesota, USA was “Real-time motion analysis of wrist carpal kinematics utilizing a novel ultra-fast three-dimensional dynamic MRI / 64 detector CT scanner”.
13. Dr Lee Tswen Wen Victor from the Department of General Surgery, SGH received a full-time fellowship for 12 months. His project at the National Cancer Center, Singapore was “Elucidation of expression profiles of genes in alpha-fetoprotein positive and alpha-fetoprotein negative hepatocellular carcinoma by cDNA microarray analysis”.
14. Dr Au Wing Lok from NNI received a full-time fellowship for 6 months 27 days. His project at the Pacific Parkinson’s Research Center, Vancouver, Canada was “Surrogate markers of the cortical dopaminergic system in patients with Parkinson’s disease”.
15. Dr Chin Tan Min from the Department of Haematology-Oncology, NUH received a full-time fellowship for 6 months. Her project at the Oncology

Research Institute, Singapore was “Mutations of the EGFR gene in tumours and their therapeutic significance - a pharmacogenetics study”.

Medical Research Scientist Award

2 scientists commenced their NMRC Medical Research Scientist Award in FY2004. All were for training leading to a degree.

1. Ms Tay Yin Chih Cheryl from the Division of Medical Sciences, NCC received a full-time research scientist award for 36 months. Her project at the Monash University, Australia was “Isolation, characterization and propagation of multipotent endodermal stem cells”. Ms Tay’s training would lead to a PhD.
2. Ms Tai Lee Kian from the Department of Pathology, NUH received a part-time research scientist award for 21 months. Her project at the National University of Singapore was “Proteomics analysis of HER-2 / neu-linked protein profiles and signal patterns in tumor microenvironment”. Ms Tai’s training would lead to a MSc.

TRAINING COMPLETED IN FY2004

5 doctors completed their training under the Medical Research Fellowship in FY2004:

1. Dr Tay Kiat Hong Stacey from the Department of Paediatrics, NUS completed 12 months of training at the New York Presbyterian Hospital, New York, USA. Her projects were “Mutation screening in patients with COX deficiency and unknown molecular etiologies”, “Genotype-phenotype studies in patients with MELAS (mitochondrial encephalomyelopathy, lactic acidosis and stroke-like episodes)” & “Molecular genetics and phenotype of patients with muscle glycogenoses”.
2. Dr Chan Chung Yip from the Department of General Surgery, TTSH completed 12 months of training at the Northwestern University Medical School, Chicago, USA. His project was “Molecular biology of pancreatic cancer”.
3. Dr Tan Choon Kiat Nigel from NNI completed 8 months 19 days of training at the Epilepsy Research Institute, University of Melbourne, Australia. His project was “Susceptibility alleles and association studies in epilepsy”.
4. Dr Chuah Thuan Heng Charles from the Department of Haematology, SGH completed 12 months of training at the Imperial College London, UK. His project was “Novel combination therapies for selective elimination of CML cells”.
5. Dr Oo Kian Kwan Kenneth from NHG completed 7 months of training at the National University of Singapore. His project was “Tissue engineered prefabricated vascularised flaps”.

The abstracts of their reports are at Annex 2.

Medical Research Travelling Fellowships

The NMRC Medical Research Travelling Fellowships aim to assist young specialists to go abroad, visit research centers, attend research seminars to improve their knowledge and keep them abreast of latest updates in the field. The scheme is funded by donations made by Mr Jacob Ballas, Zeneca Pharma Singapore and Glaxco Wellcome Singapore.

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

Medical Research Travelling Fellowship

7 doctors/scientists were awarded the NMRC Medical Research Travelling Fellowship in FY2004. All of them completed their training and the abstracts of their reports are at Annex 3.

1. Mr Lim Kok Chye Alex from the Department of Pathology, NUH received the Zeneca Pharma Singapore Travelling Fellowship for the training on “2004 HUGO mutation detection” at the HUGO International Centre for Life, Newcastle, UK for a period of 5 days.
2. Dr Shim Se Ngie Winston from the Department of Research, NHC received the Glaxo Wellcome - NMRC Cardiology Travelling Fellowship for the training on “3D microscopy of living cells” at the University of British Columbia, Canada for a period of 15 days.
3. Dr Srilatha Balasubramanian from the Department of Obstetrics & Gynaecology, NUS received the Grace Ballas Medical Travelling Fellowship for the training on “Hemodynamic and cell culture models for female sexual dysfunction” at Chonnam National University Medical School, South Korea for a period of 14 days.
4. Dr Sudhakar Kundapur Venkatesh from the Department of Diagnostic Imaging, NUH received the Grace Ballas Medical Travelling Fellowship for the training on “MR colonoscopy techniques” at the University of Essen, Germany for a period of 14 days.
5. Dr Sim Shao-Jen Llewellyn from the Department of Diagnostic Radiology, SGH received the Grace Ballas Medical Travelling Fellowship for the training on “MRI-guided breast biopsy procedures and new MRI techniques” at the University of Bonn Medical Centre, Germany for a period of 14 days.
6. A/Prof Au Eong Kah Guan from the Department of Ophthalmology & Visual Sciences, AH received the Grace Ballas Medical Travelling Fellowship for the training on “The use of the maculometer for macular pigment research” at Waterford Institute of Technology & Waterford Regional Hospital, Ireland for a period of 14 days.
7. Dr Lim Swee Han from the Department of Emergency Medicine, SGH received the Grace Ballas Medical Travelling Fellowship for collaborative work with Dr Michael J. McCue in his NMRC funded project “Acute chest pain treatment and evaluation study (ACTION)” at the Medical College of Virginia, USA for a period of 14 days.

CHAPTER 7

Financial Report

Introduction

The NMRC was allocated \$232,192,500 under the Medical Research & Development Fund II (Fund II) for the period of FY1997 to FY2001.

Under Fund II, the NMRC could commit funding for new projects and programmes up to end of FY2001. The funding of the on-going projects and programmes committed under Fund II could continue until FY2004.

With effect from FY2002, the funding of Fund II 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 FY2004 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 FY2004.

On top of funding from the OOE budget, NMRC also obtains funds from Singapore Totalisator Board (STB), comprising annual donations of up to \$2 million for fellowship, and up to \$5 million for research projects and programmes.

Budget for FY2004

A total of \$54.9 million was allocated for research expenditure in FY2004. Table 8 shows the movement of budget allocated for research expenditure.

Table 8
Allocated Budget, FY2004

	Amount (\$)
MOH's OOE budget	49,940,080
STB's donations for research projects and programmes	5,000,000
Total budget	54,940,080

In addition, a donation of \$2,000,000.00 was received from STB in FY2004 for the Medical Research Fellowship and Scientist Award.

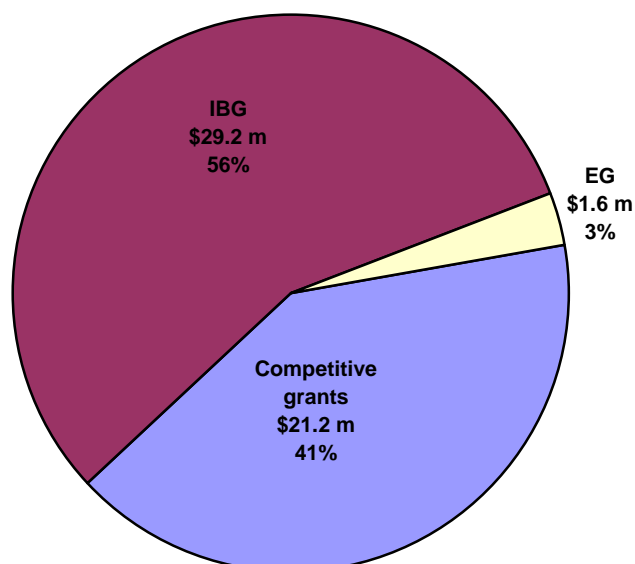
Commitments in FY2004

A total of \$51.9 million was committed in FY2004 with the breakdown as shown in Table 9.

Table 9
Commitments in FY2004

	Amount (\$)	% of total
<i>Competitive Grants</i>		
Individual Research Grants (IRG)	16,576,407.27	31.9%
Competitive Programme Grants (CPG)	2,611,578.05	5.0%
Supplementary Grants	1,993,107.22	3.9%
Sub-Total	21,181,092.54	40.8%
<i>Block Grants</i>		
Institutional Block Grants (IBG)	29,209,737.42	56.2%
Enabling Grants (EG)	1,557,651.00	3.0%
Sub-Total	30,767,388.42	59.2%
Total Commitments for FY2004	51,948,480.96	100.0%

Fig 1: FY2004 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, \$19.2 million was committed to 113 projects and programmes, comprising 105 Individual Research Grants (IRG) and 8 Competitive Programme Grants (CPG). The approved projects in FY2004 are listed in Annex 4.

Out of the 105 IRG approved in FY2004, 51 are applications received in Nov03 IRG funding exercise and 54 in May04 exercise.

In addition to amounts committed to IRG and CPG, \$2.0 million was also committed to 127 existing projects as supplementary grants to partially restore the budget reduction suffered by these projects at point of approval.

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

Table 10
Commitments for Competitive Grants by Institutions, FY2004

Institution	IRG		CPG		Supplementary Grant		Total	
	No. of Projects	Amount (\$)	No. of Projects	Amount (\$)	No. of Projects	Amount (\$)	No. of Projects	Amount (\$)
National University of Singapore	44	7,168,386.32	3	860,039.70	57	902,137.50	104	8,930,563.52
National Neuroscience Institute	7	1,812,327.10	2	671,486.00	10	166,112.15	19	2,649,925.25
National Cancer Centre	13	1,796,363.50	1	384,964.71	14	220,781.71	28	2,402,109.92
Singapore General Hospital	10	1,053,697.75	1	390,000.00	13	203,548.50	24	1,647,246.25
Singapore Eye Research Institute	2	695,681.03	1	305,087.64	3	47,990.45	6	1,048,759.12
National University Hospital	11	898,224.30	-	-	5	62,590.00	16	960,814.30
Tan Tock Seng Hospital	5	849,035.00	-	-	1	16,000.00	6	865,035.00
Singapore Health Services	3	647,500.00	-	-	6	95,996.91	9	743,496.91
National University Medical Institute	3	553,225.00	-	-	7	108,500.00	10	661,725.00
Alexandra Hospital	2	401,100.00	-	-	2	32,000.00	4	433,100.00
KK Women's & Children's Hospital	3	333,136.67	-	-	-	-	3	333,136.67
Nanyang Technological University	1	224,375.60	-	-	1	16,000.00	2	240,375.60
Institute of Mental Health	1	143,355.00	-	-	2	30,500.00	3	173,855.00
National Heart Centre	-	-	-	-	6	90,950.00	6	90,950.00
Total	105	16,576,407.27	8	2,611,578.05	127	1,993,107.22	240	21,181,092.54

Table 11

Commitments for IRG and CPG by area of research, FY2004

Area of Research	IRG		CPG	
	No. of Projects	Amount (\$)	No. of Projects	Amount (\$)
Cancer	21	3,418,634.42	2	634,060.05
Neuroscience	11	2,691,868.60	-	-
Epidemiology	3	900,027.50	-	-
Eye	3	875,681.03	-	-
Molecular Biology	6	748,829.50	1	281,509.00
Cardiovascular Diseases	4	736,665.00	-	-
Diagnostic Radiology	4	722,434.50	2	779,977.00
Immunology	4	707,971.50	-	-
Endocrinology	4	475,299.50	-	-
Psychiatry	3	473,470.00	-	-
Public Health Medicine	3	445,625.00	-	-
Paediatrics	5	410,766.67	-	-
Liver Diseases	1	392,000.00	1	286,650.00
Biochemistry	2	383,300.00	-	-
Orthopaedic Surgery	6	362,097.80	-	-
Renal Medicine	2	336,612.90	-	-
Pharmacology	2	296,488.00	-	-
Geriatric Medicine	2	280,060.00	-	-
Microbiology	3	275,281.00	1	305,087.64
Others	4	267,856.00	1	324,294.36
Plastic Surgery	2	245,600.00	-	-
Gastroenterology	1	224,375.60	-	-
Urology	2	216,426.25	-	-
Respiratory Diseases	1	210,500.00	-	-
Infectious Diseases	1	200,000.00	-	-
Emergency Medicine	1	111,036.50	-	-
Genetics	1	65,000.00	-	-
Allergy	1	50,000.00	-	-
Obstetrics & Gynaecology	1	50,000.00	-	-
Anaesthesia	1	2,500.00	-	-
Grand Total	105	16,576,407.27	8	2,611,578.05

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 FY2004, a total of \$29.2 million was committed for IBG and \$1.6 million was committed for EG, distributed as shown in Table 12.

Table 12
Commitment for IBG and EG by research centre/block vote, FY2004

Research Centre/Block Vote	Amount (\$)
IBG	
National Cancer Centre (NCC)	8,120,000.00
National Neuroscience Institute (NNI)	4,213,649.00
Singapore Eye Research Institute (SERI)	3,773,898.00
National University Medical Institute (NUMI)	3,840,000.00
Clinical Trials and Epidemiology Research Unit (CTERU)	2,619,883.00
Department of Clinical Research (DCR)	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) Block Vote	800,000.00
Department of Experimental Surgery (DES)	457,316.52
Institute of Mental Health/ Woodbridge Hospital (IMH/WH)	415,396.86
Tan Tock Seng Hospital - Clinical Research Unit (TTSH-CRU)	303,864.00
NNI-TTSH Animal Research Laboratory (ARL)	264,359.50
National Birth Defects Registry (NBDR)	242,130.54
Nursing Research Committee (NRC)	106,000.00
Total	29,209,737.42
EG	
KK Women's & Children's Hospital (KKH)	350,000.00
Alexandra Hospital (AH)	349,971.00
Changi General Hospital (CGH)	325,000.00
National Dental Centre (NDC)	207,000.00
National Skin Centre (NSC)	185,680.00
Health Sciences Authority (HSA)	140,000.00
Total	1,557,651.00
Total for IBG and EG	30,767,388.42

Research Expenditure for FY2004

Out of the \$54.9 million allocated for research expenditure, a total of \$53.3 million was utilized, representing a fund utilization rate of 97.02%. Of this, \$23.6 million was for competitive grants, \$27.7 million was for IBG, \$1.4 million for EG, \$0.1 million for protected time and the remaining \$0.5 million for other expenses.

Table 13 shows the distribution of research expenditure and Table 14, the expenditure for IBG and EG in FY2004.

Table 13
Research Expenditure, FY2004

Type of Expenditure	Amount Spent (\$)	% of Total Expenditure
Competitive Grants:		
IRG	20,712,422.57	
CPG	2,641,425.00	
CPRG	259,277.44	
Sub-Total	23,613,125.01	44.3%
IBG:		
NCC	8,119,971.26	
SERI	3,770,851.32	
NUMI	3,704,223.09	
NNI	3,671,096.51	
CTERU	2,517,393.32	
DCR	1,891,951.52	
SCDB	995,715.77	
NUS Block Vote	786,076.50	
NHC	714,439.43	
DES	437,326.42	
IMH/WH	370,466.86	
TTSH	261,711.74	
NNI-TTSH ARL	156,090.56	
NBDR	198,475.70	
NRC	98,550.74	
Sub-Total	27,694,340.74	52.0%
EG:		
AH	321,678.08	
CGH	316,270.23	
KKH	293,319.40	
NDC	186,703.11	
NSC	144,759.82	
HSA	113,801.05	
Sub-Total	1,376,531.69	2.6%
Protected Time	64,674.09	0.1%
Others:		
Patenting Cost	256,204.91	
Reviewers' Honorarium	193,687.86	
Clinical Practice Guidelines	95,894.53	
Scientist Meetings	11,000.00	
Sub-Total	556,787.30	1.0%
Total	53,305,458.83	100.0%

Fig 2: FY2004 Fund Distribution by Expenditure

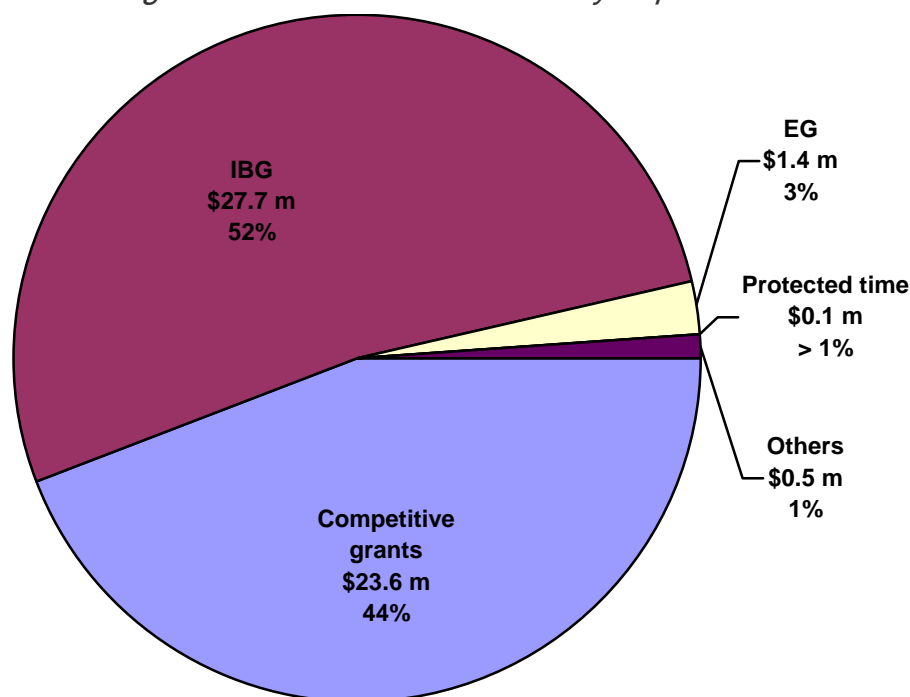


Table 14
Expenditure for IBG and EG, FY2004

Research Centre/ Block Vote	Manpower (\$)	Equipment (\$)	Other Expenses (\$)	Small Grants (\$)	Total (\$)
IBG					
NCC	5,573,821.14	111,671.85	2,434,478.27	-	8,119,971.26
NNI	2,133,711.77	382,284.32	1,155,100.42	-	3,671,096.51
SERI	2,150,373.48	225,467.00	1,270,345.84	124,665.00	3,770,851.32
NUMI	1,904,253.53	1,237,345.45	562,624.11	-	3,704,223.09
CTERU	1,463,553.68	479,269.47	529,625.23	44,944.94	2,517,393.32
DCR	1,142,412.66	183,043.70	275,993.63	290,501.53	1,891,951.52
SCDB	778,367.38	-	217,348.39	-	995,715.77
NHC	341,949.03	291,341.03	81,149.37	-	714,439.43
NUS Block Vote	-	-	-	786,076.50	786,076.50
DES	306,451.67	118,552.25	12,322.50	-	437,326.42
IMH/WH	198,906.81	37,935.72	125,584.76	8,039.57	370,466.86
TTSH	261,671.74	-	40.00	-	261,711.74
NNI-TTSH ARL	90,651.55	55,475.40	9,963.61	-	156,090.56
NBDR	167,342.70	-	31,133.00	-	198,475.70
NRC	-	60,057.20	-	38,493.54	98,550.74
Total	16,513,467.14	3,182,443.39	6,705,709.13	1,292,721.08	27,694,340.74
EG					
AH	91,442.95	98,753.00	19,549.14	111,932.99	321,678.08
CGH	22,216.41	50,091.30	67,717.38	176,245.14	316,270.23
KKH	128,542.15	4,075.00	10,059.36	150,642.89	293,319.40
NDC	90,884.16	-	9,990.10	85,828.85	186,703.11
NSC	88,729.50	-	2,096.05	53,934.27	144,759.82
HSA	13,998.25	-	49,802.80	50,000.00	113,801.05
Total	435,813.42	152,919.30	159,214.83	628,584.14	1,376,531.69
Grand Total	16,949,280.56	3,335,362.69	6,864,923.96	1,921,305.22	29,070,872.43

Table 15 shows the list of major equipment with funding of more than \$100,000 in FY2004.

Table 15
List of major equipment funded, FY2004

Description	Institution	Cost (\$)	Amount funded (\$)
Oracle Clinical® Perpetual Software Licence	CTERU	370,696.48	370,696.48
LSM 5 Pascal c/w Axiovert 200M Confocal Microscope	NHC	262,500.00	262,500.00
ESI System Version 4.2 INTL non-contact cardiovascular mapping system	NHC	169,050.00	169,050.00
Intera Quasar Dual Upgrade and its accessories for Philips Gyroscan Intera 3T MRI System	NNI	388,762.50	388,762.50
Flow Cytometer Beckman Coulter EPICS Altra with accessories	NUMI	514,500.00	514,500.00
New Multi-Photon Laser for Confocal Microscope	NUMI	275,100.00	275,100.00
PHERASTAR High End Microplate Reader & HTRF Optics Modules	NUS	145,561.50	145,561.50
MALDI Source for ABI Q-Star mass spectrometer	SERI	163,800.00	163,800.00
ACT Model Apex 396-DC Multiple Peptide Synthesizer	SERI	138,600.00	138,600.00
Small Animal Positron Emission Tomography (PET) unit	SGH	769,650.00	390,000.00
Medison Model SA 9900 Prime 3D/4D CFM Ultrasound Scanner Colour Doppler with Features	TTSH	122,350.00	122,350.00
Total		3,320,570.48	2,940,920.48

Medical Research Fellowship/Scientist Award

Table 16 shows the commitment and expenditure for Medical Research Fellowship and Scientist Award in FY2004. The expenditure includes those on commitments made before FY2004.

Table 16
Commitment and expenditure for medical research fellowship/scientist award, FY2004

	Commitment (\$)	Expenditure (\$)
Medical Research Fellowship & Scientist Award	1,846,231.71	1,546,239.93
Medical Research Travelling Fellowship	47,588.09	21,955.14
Total	1,893,819.80	1,568,195.07

ANNEXES

Annex 1: Abstracts of IRG & IBG Research Projects Completed in FY2004

<p>NMRC/0290/1998</p> <p>PI: Seow Ying Ying (SGH)</p>	<p>Deficient Expression of IgA FcαR (CD89) in patients with IgA nephritis</p> <p>This study sought to study IgA receptors, in particular the asialoglycoprotein receptor (ASGPR) and Fc-α receptor (or CD89). Renal proximal tubular epithelial cells (RPTEC) and human mesangial cells (HMC) of the kidney were used.</p> <p>The researchers cultivated the cells and performed reverse-transcription polymerase chain reaction, flow cytometry (FACS), immunocytology and ELISA. Immunohistochemical staining of renal biopsy specimens was then performed to study renal tubular ASGPR expression <i>in vivo</i>. Correlation between percentage tubules staining positive for ASGPR and different histological and clinical parameters were observed. This study also looked at CD89 polymorphisms in IgAN patients and results of these patients were compared against normal individuals.</p> <p>The researchers observed mRNA expression of ASGPR in both primary RPTEC as well as renal cortex. FACS immunocytology and ELISA showed presence of a functional ASGPR protein. <i>In vivo</i> expression of the RTEC ASGPR was also demonstrated in 3 normal controls which also show staining for ASGPR in their tubules.</p> <p>This study showed a strong association between <10% tubules staining and acute tubular necrosis (ATN) (p=0.000). The researchers also discovered expression of the ASGPR by human RPTEC. On top of this, it was observed that expression of ASGPR became almost non-existent in ATN.</p>
<p>NMRC/0327/1999</p> <p>PI: Chan Soh Ha (NUS)</p>	<p>Genetic construction and characterization of recombinant immunotoxins specifically directed at malignant B cells</p> <p>Acute Graft-versus-Host disease (GVHD) is a disease initiated by allogeneic T cells. T cells preferentially infiltrate certain organs, such as liver, skin and intestines, and cause serious damages to these organs while other organs are seldom affected. An animal model of GVHD was employed in this study using C57BL/6 mice (H-2b) as T cell donors and SCID mice (H-2d) as recipients. This study observed a distinct pattern of chemokine expression, which correlated with the infiltration pattern of alloreactive T cells in these target organs. This suggests that GVHD can be modulated by changing the micro-environmental chemokine repertoire. It was also observed that about 20% of donor T cells which, even for more than 5 days after homing to recipient secondary lymphoid organs, remained quiescent and non-proliferating. These non-proliferating T cells showed no proliferation when subjected to <i>in vitro</i> mixed lymphocyte culture, but were still able to induce GVHD upon transfer into secondary recipient mice. This implies that there is an alloreactive T cell population that does not respond to <i>in vitro</i> and initial <i>in vivo</i> alloantigenic stimulation, but can mount a delayed alloresponse <i>in vivo</i>.</p> <p>Amelioration of GVHD was attempted by using an <i>in vivo</i> transfection method to deliver and express an immunotoxin gene (DT390-IL-2) into the recipient mice after GVHD had been induced. This immunotoxin should specifically kill activated alloreactive T cells expressing CD25. Indeed, 3 of the 4 treated mice survived by day 90 post-transplantation, while all the 4 control mice and 4 mice treated with other different IT constructs died before day 50.</p>

<p>NMRC/0358/1999</p> <p>PI: Cheong Keng Fatt (NUS)</p>	<p>Hypothermia and traumatic brain injury</p> <p>The chief aims of the study were to validate the usefulness of moderate hypothermia (core temperature 34-35°C) in treatment of traumatic head injury. This project also hypothesizes that T81 may be associated with an elevated CSF concentration of cytokines.</p> <p>Ten patients who suffered from severe head injuries were chosen. The following criteria were met by all of these ten patients: their ICP was maintained below 20 mm Hg by using fluid restriction, hyperventilation, high-dose barbiturate therapy and the patient had a Glasgow Coma Scale score of 8 or less upon admission.</p> <p>After conventional therapies had been applied, the patients were divided randomly into two groups: the mild hypothermia group (HT group; 5 patients) and the normothermia group (NT group; 5 patients). The HT group received mild hypothermia (intracranial temperature 35 degrees C) therapy for 24 hours followed by rewarming at 1 degree C-per-day for 3 days, whereas the NT group were kept normothermic (intracranial temperature 37 degrees C). Specimens of cerebrospinal fluid (CSF) taken from an intraventricular catheter were analyzed for cytokines (tumor necrosis factor-alpha, IL-6, and IL-10). The two groups did not differ significantly in patient age, neurological status, or level of ICP.</p> <p>This study showed that there were no significant differences in daily changes in CSF concentrations of cytokines between the two groups. The two groups did not differ in their clinical outcomes and mortality rates. This indicates that mild hypothermia therapy does not convey any advantage over normothermia therapy in such patients.</p>
<p>NMRC/0369/1999</p> <p>PI: Damian Png (NUS)</p>	<p>The effect of chronic bladder outlet obstruction and spinal cord hemisection on expression of neuropeptides and nitric oxide synthase in the bladder wall, paravesical ganglia and spinal cord of the guinea pig and human bladder</p> <p>This project aimed to examine the effect of chronic partial outlet obstruction on the expression of neuronal nitric oxide synthase (nNOS). Intramural ganglion cells from the guinea pig bladder were used. Partial urethral ligation was done in young male guinea pigs. The animals were sacrificed at 2, 4, 6, 8 and 12 weeks after partial outlet obstruction and nNOS immunohistochemistry was carried out in the intramural neurons of the urinary bladder. This was compared to controls (normal and sham-operated). In addition, the mRNA expression of nNOS in the bladders of 4-week sham and operated animals was also investigated using real time, quantitative, reverse transcription combined with the polymerase chain reaction (qRT-PCR)</p> <p>2 weeks after urethral obstruction, a decrease in the number of nNOS positive intramural neurons was detected. This decrease was most drastic at 4 weeks; cell counting showed a 60.6% reduction in number of nNOS positive neurons as compared to controls. Some neurons appeared to undergo degenerative changes such as irregular outline, vacuolation and lysis. At 6 weeks, the number of nNOS positive neurons rose from its nadir level at 4 weeks and the increase was sustained till 12 weeks where the number of nNOS positive neurons was almost at the same level as that of the controls. qRT-PCR also showed a 42.4% down-regulation of nNOS expression at 4-week post-obstruction compared to the sham-operated controls.</p> <p>This project suggests that partial urethral ligation result in an initial decrease of nNOS positive neurons which may be due to actual neuronal loss and/or down-regulation of the enzyme. This may be attributed to regional hypoxia as a result of reduced blood flow consequent to high intravesical pressure created by partial ligation. The decrease in nNOS expression was followed by a compensatory increase in nNOS positive neurons in an attempt or mechanism to up-regulate nitric oxide bioactivity</p>

	following elevated bladder outlet resistance.
<p>NMRC/0381/1999</p> <p>PI: Christopher Chen (SGH)</p>	<p>Investigation of the histopathological and neurochemical features of an MK-801 induced NMDA receptor hypoactivity animal model.</p> <p>NMDA receptor hypoactivity has been put forward as a potential mechanism of the neurochemical alterations seen in Alzheimer's Disease (AD; Olney <i>et al.</i> 1997). This study evaluated a potential neurochemical model of AD by induced NMDA receptor hypoactivity.</p> <p>Swiss albino mice were injected intraperitoneally with a non-competitive NMDA antagonist, MK-801 (dizocipine), which has previously been shown to induce NMDA receptor hypoactivity as well as neuronal degeneration (Horvath <i>et al.</i> 1997). The animals were sacrificed three months later and saturation radioligand binding assays on neocortical and hippocampal brain homogenates preparations were performed.</p> <p>It was observed that MK-801 treated animals suffered loss of cholinergic M2 receptors, increased densities of serotonergic 5-HT_{2A}, and preserved levels of M1 and NMDA receptors. Certain aspects of these changes parallel those seen in AD (Mash <i>et al.</i> 1985, Lai <i>et al.</i> 2001).</p> <p>The researchers concluded that MK-801 treatment may be a potentially useful model in the elucidation of the mechanisms underlying neurochemical changes in AD.</p>
<p>NMRC/0399/2000</p> <p>PI: Li Qiu-Tian (NUS)</p>	<p>Liposome-encapsulated drugs for delivery to brain</p> <p>This project aimed to examine the efficacy of sulfatide-containing liposomes as carriers for the delivery of anticancer drugs (e.g., doxorubicin (DOX)) into the brain of experimental animals. <i>In vitro</i> studies showed that sulfatide is the essential component of liposomes for their effective uptake by glioblastoma cells. By sulfatide-mediated endocytosis, anticancer drug encapsulated in liposomes can be effectively delivered into the tumor cells and be accumulated in the nuclei, thereby leading to cytotoxicity. Nude mice with subcutaneous tumor xenografts were used in this project to examine the anti-glioblastoma efficacy of the formulated liposomal DOX.</p> <p>It was found that the tumors began growing at an accelerated rate approximately 3 weeks after inoculation and its growth was retarded after treatment with liposomal DOX. The survival time of the treated animals was extended by more than 30% as compared to animals treated with free DOX and commercially available liposomal DOX. Similar results have been obtained from nude mice which underwent intracerebral tumor xenografts, suggesting that the sulfatide-containing liposomes were able to pass through the blood brain barrier to target specifically the glioblastoma cells.</p> <p>These results may lead to the development of novel liposome-based ligand-targeted drug delivery systems (DDS) for treatment of gliomas.</p>
<p>NMRC/0403/2000</p> <p>PI: Victor H H Goh (NUS)</p>	<p>Efficacy and safety of growth hormone augmentation therapy in men and women with low GH</p> <p>The primary objective of this project was to evaluate whether a small dose of human recombinant hGH given to normal healthy men and women with low levels of hGH, as indicated by their serum IGF-1 levels, would be beneficial and whether it improves the well being of individuals.</p> <p>This project was a double-blind randomized trial carried out over 18 months. It was approved by the IRB of NUH and MOH which anactioned the study with a clinical trial certification. Written informed consent was obtained from each subject before commencement of the study. A total of 47 men and women were randomised into 2 groups for the first 6 months of</p>

the trial: a placebo and a GH-treated group at a ratio of 1:2 (placebo: treatment). After recruitment and initial screening, subjects were placed on an augmentation regime comprising thrice weekly self-administered injection of either placebo or hGH (2 unit/0.5ml of saline) subcutaneously just before sleep. After the first 6 months, the augmentation therapy ceased for 3 months. The second 6-month augmentation therapy began after 3 months. At this juncture, all subjects were placed on the treatment group.

An elaborate screening test battery was instituted and results were analysed using the repeated measure analysis. At baseline, a fasting blood sample was collected and various parameters were analysed on the blood samples. The parameters included lipid and triglyceride levels, kidney and liver functions, FBC, insulin, IGF-1, IGFBP3, PSA (for men), TSH, T3, T4, DHEAS, total T, SHBG, bioavailable-T, FSH, LH, osteocalcin, nTX, cortisol levels using a combination of in-house methods and commercial kits. At the same time, a full physical examination which includes B/P, pulse rates, a simple survey comprising of questions on possible symptoms as well as questions on supplements, exercise, sleep and sexual activities were administered. Each subject also completed a well being survey and an aging score survey. Anthropometric parameters which included body weight, height, waist and hip circumference were measured. Bone scans (at spinal L2-L4 and hip) and a whole body scan was carried out for each subject at baseline 6 months after the 1st and 2nd periods of therapy. Several functional tests for short-term memory, perceptual capacity, grip strength and lung capacity (a test of physical effort) were carried out. The test battery was repeated at 6, 9 and 18 months after the start of the trial.

A total of 47 subjects: 14 men and 33 women completed the 18-month trial. Preliminary results showed that after 6 months of augmentation therapy, levels of IGF-1 in individuals from the treatment group were significantly higher than those in the placebo group. After the 1st 6 months of therapy, results revealed that there were no adverse effects. Observational results indicated that most respondents experienced a better sleep quality in terms of increased duration and less awakening during the night. Some respondents reported being more energetic during the day and about 20% of men and women reported a more involved sex life in terms of frequency and enjoyment.

Using paired t analyses between baseline and post-6 month data in both GH and placebo groups, several parameters showed significant differences. In men, following 6 month of GH treatment, concentrations of both IGF-1 and IGFBP3 were significantly higher than corresponding baseline levels, while in the placebo group, there were no significant differences. In addition, men who underwent 6 months of GH treatment had significantly lower aging scores which indicated an increase in the sense of wellbeing.

The most significant changes brought about by GH treatment were in the lipid and body composition profiles. In men, the 6 months of GH treatment resulted in significant increases in total lean mass, hip BMD and total BMC, and significant increases in total fat mass, percent body fat (Siri fat), total cholesterol and LDL-cholesterol when compared to baseline levels.

In the placebo group, all parameters did not change over the 6 months of study. In women, on the other hand, 6 months of GH treatment resulted in significant increases in total fat mass, percent body fat (Siri fat), total cholesterol and LDL-cholesterol. In the placebo group most of the parameters measured showed no change during the 6 month of placebo treatment except for a significant increase in triglyceride and a significant decrease in HDL-cholesterol. In women, following 6-month of GH treatment, a significant decrease in diastolic blood pressure as compared to baseline levels was noted.

Overall, the preliminary results indicate that GH treatment that led to increased IGF-1 levels well within the median range in young reference might be beneficial to men and women with low levels of IGF-1. The doses and regime of administration used in this experiment appeared to be safe. However, these results cannot be extrapolated to therapies which last longer 12 months since this therapy only lasted for 12 months.

<p>NMRC/0404/2000</p> <p>PI: Wong Hee Kit (NUS)</p>	<p>Nerve regeneration and recovery following surgical decompression of sustained spinal nerve root compression : the role of neutropic agents in an experimental animal model (renewal)</p> <p>Selective spinal nerve drug injections may work by changing pathophysiological processes which are involved in nerve root compression. However studies on the basis of their uses have been limited. This study aimed to assess the behavioural and histological effects of Diclofenac sodium, Betamethasone, Neurobion, mix-Ganglioside and Riluzole in the nerve root compression animal model.</p> <p>The left fifth lumbar nerve roots were compressed in SD rats to study Parasis, Mechanical withdrawal threshold and the Thermal withdrawal latency at regular intervals. At the end of the experiment, the DRG sections were immunostained for Sub P and CGRP.</p> <p>It was observed that post-compression administration of Ganglioside resulted in increased sensitivity to mechanical stimuli in both the first three weeks and second three weeks treatment groups. Rats administered with Betamethasone during both post-compression time periods had decreased sensitivity to thermal stimuli. Application of Diclofenac, Cobalamin and Riluzole did not show a significant difference in behavioural parameters as compared to the controls. Betamethasone administered after a decompression surgery at the 3rd week also appeared to reduce thermal hyperalgesia. There was no statistical difference in histological grading for all groups as compared to the controls.</p> <p>This study suggests that response to nerve root compression surgery varies among different groups and individuals. Drug treatment makes them either hypoalgesic or hyperalgesic. The study also indicates the role of Ganglioside and Betamethasone in the patho-physiology of lumbar radiculopathy and nerve root compression. This animal model can be used to study the drugs involved in the patho-physiology of nerve root compression. The choice and timing of administration of medications may be important in outcome. Further studies are required to evaluate the significance and underlying pathological processes of these findings.</p>
<p>NMRC/0415/2000</p> <p>PI: Ho Bow (NUS)</p>	<p>Development of novel recombinant antigen as a diagnostic and epidemiological marker for helicobacter pylori infections</p> <p>Helicobacter pylori infects half of the world's population, yet the mystery surrounding the mechanism of pathogenesis of Helicobacter pylori is still unresolved. This is partly due to the genetic variation among strains present in different parts of the world.</p> <p>This project focused on two novel genes, hjs4 and bck2. hjs4 initially showed the ability to differentiate H. pylori isolates associated with peptic ulcer disease from non-ulcer dyspepsia. However, inconsistent RAPD finger-prints posed problem to the study. A second gene, bck2, efficiently differentiates H. pylori isolates into two main groups: Asian and non-Asian origin. Hence it can serve as an effective epidemiology marker. BCK2 is a surface protein and its 14th-16th amino acid residues are unique to this organism. The insertion sequence separates it from existing HS1V homologues. bck2 demonstrated an important role in pathogenesis because it assisted in the surface presentation of CagA, a known pathogenetic factor of H. pylori. Furthermore, the isogenic mutant H. pylori (bck2 knock-out) was unable to colonize in the Balb/c mice. Preliminary studies also showed that BCK2 protein can protect the mice against H. pylori colonization indicating BCK2 is a potential vaccine candidate against H. pylori infections.</p>

<p>NMRC/0416/2000</p> <p>PI: Kesavan Esuvaranathan (NUS)</p>	<p>Evaluation of a novel liposomal vector for multiple cytokine gene therapy in bladder cancer</p> <p>This project aimed to evaluate the efficacy of non-viral cytokine gene therapy through the use of a murine model for bladder cancer.</p> <p>All cytokine genes were cloned into the pBudCE4.1 mammalian expression system which can express 2 cytokine genes at the same time because it has 2 promoters. The researchers developed an easily monitored orthotopic model by producing murine bladder cancer cells that secrete the PSA antigen.</p> <p>The researchers managed to develop a liposomal transfection system which resulted in efficient transfection of urothelial tumor cells <i>in vitro</i> and <i>in vivo</i> and hence is better than adenoviral vectors whose transfection is dependant on receptor expression and is inhibited by the GAG layer. Single cytokine genes [TNF-α, IFN-γ, IFN-α, GM-CSF] were able to cure murine bladder tumors and BCG. The researchers also managed to develop an orthotopic model of bladder cancer with modified MB49 cells which secreted PSA. Hence, this led to the confirmation of the presence of tumors as early as 4 days after implantation, when the tumors were less than 0.3mm in size and this further permitted the monitoring of tumors throughout the study period. Mice cured with GM-CSF therapy produced high levels of GM-CSF and showed up-regulation of certain chemokines such as MCP-1, MIP-2, and TIMP-1 and the p40 sub-unit of IL-12.</p>
<p>NMRC/0418/2000</p> <p>PI: Soo Khee Chee (NCC)</p>	<p>Fluorescence endoscopy and multiphoton laser confocal fluorescence microscopy of early neoplasia in the nasopharynx, oral cavity, uterine-cervix and endometrium using ALA induced PPIX</p> <p>One objective of this study was to assess the efficacy and safety of 5-Aminolevulinic Acid (ALA) induced Protoporphyrin IX (PPIX) fluorescence endoscopy for the early detection of neoplasms in the oral cavity and the uterine-cervix. Another objective was to explore the relationship between the fluorescence intensity and the histopathological information of the diseased tissue. The researchers developed a digitized fluorescence endoscopic imaging system associated with digital image processing technique to enable on-line image acquisition and fluorescence quantification. PPIX fluorescence endoscopy and fluorescence image quantification were performed in 78 patients with a known malignancy or suspected lesions of the oral cavity (64 patients) and the uterine-cervix (14 patients). No skin photosensitization or side effects were found in patients who had undergone ALA-PPIX fluorescence endoscopy.</p> <p>Preliminary data from the clinical trials showed that the combination of quantifying PPIX fluorescence endoscopic images with the red-to-blue intensity ratio as a diagnostic algorithm could establish the ability of differentiation between benign and different stages of malignancies with high diagnostic accuracy (over 90%). Hence, there is a potential to significantly improve the noninvasive diagnosis and evaluation of early oral neoplasia <i>in vivo</i>. The digitised system and methodology of this project has been extended to bladder cancer detection and studies of drug formulation and pharmacokinetics of various photosensitizers in animal tumor models.</p>
<p>NMRC/0423/2000</p> <p>PI: Leena Gole (NUS)</p>	<p>Detection of low grade mosaicism in Turner's Syndrome using fluorescence in situ hybridization (FISH)</p> <p>Since 90 % of fetuses with 45,X genotype result in miscarriages in the first trimester, it stands to reason that the surviving babies born with 45,X may have a normal 46,XX cell line in their genetic make-up. Vice-versa, many patients with Turner like phenotype may show a normal karyotype cytogenetically. These low level mosaics may not be detected by routine</p>

	<p>cytogenetic techniques, but may be picked up in the interphase cells by fluorescent in-situ hybridization.</p> <p>The researchers have carried out both routine cytogenetics and FISH on 3 groups of patients: Group 1: Study group of 46,XX patients with some Turner stigmata (n=11). Group 2: Positive controls of 45,X Turner patients (n=17). Group3: Control group of normal fertile females (n=25).</p> <p>100 metaphases were analysed by routine G-banding techniques. 5000 interphase nuclei were analysed by fluorescent in-situ hybridization for the X chromosome in each sample. Comparing the X chromosome aneuploidy in controls and the study group, a cut-off level of 0.895% was obtained, above which low grade mosaicism could be classified as significant.</p>
<p>NMRC/0425/2000</p> <p>PI: Samuel S Chong (NUS)</p>	<p>Simplified molecular diagnostic testing for fragile X mental retardation syndrome</p> <p>Fragile X syndrome is the most common kind of inherited mental retardation. This syndrome is caused predominantly by hyperexpansion of a CGG trinucleotide repeat in the 5' untranslated region of the FMR1 gene. Current molecular diagnosis of this disorder relies on Southern blot technique which is both labor-intensive and expensive. As an alternative to Southern analysis, the researchers proposed the development and validation of a simplified PCR-based test which can detect the full spectrum of FMR1 genotypes. The researchers developed a methylation-specific PCR assay which involved the selective modification of unmethylated versus methylated genomic DNA by sodium bisulfite. This was followed by a triple PCR amplification to detect and size the modified methylated and non-methylated alleles. Amplification products were analyzed by agarose gel electrophoresis. Through the use of fluorophore-labeled primers, PCR products were detected and accurately sized on a genetic analyzer. A population survey of the FMR1 flanking haplotypes in the three major ethnic groups in Singapore and in several affected males was also performed.</p> <p>Both the triple ms-PCR assay and fluorescent fragment analysis successfully detected all normal, premutation and full mutation alleles of the FMR1 CGG repeat in the males and females. The haplotype survey suggests the absence of a founder fragile X chromosome in our population.</p>
<p>NMRC/0433/2000</p> <p>PI: Wong Wai Shiu Fred (NUS)</p> <p>Collaborators : Lee Edmund Jon Deon, Chang Chan Fong</p>	<p>Signal transduction antisense therapy for asthma in an animal model</p> <p>The objective of this project was to develop antisense oligonucleotide (ASO) targeted at the mRNAs of signaling molecules for the treatment of allergic airway inflammation.</p> <p>The researchers were involved in the development of ASO technology for several signaling molecules, inclusive of Syk and PLCγ. Research collaboration was also established with ISIS Pharmaceuticals of the USA to study p38α mitogen-activated protein kinase (MAPK) ASO in a mouse model of asthma. The researchers have put in most of their manpower to the <i>in vivo</i> work (translational research). The collaboration with ISIS Pharmaceuticals of the USA has facilitated the researchers' ASO study markedly and has generated substantial amount of data for publication and patent application.</p> <p>In addition, the researchers have also examined MAPK inhibitor and PI3K inhibitor on the expression of chemokine receptor 1 (CCR1) in myelomonocytic cells, and on anaphylactic responses in guinea pig <i>in vitro</i> and anti-inflammatory effects in mouse asthma model <i>in vivo</i>. The studies on CCR1 expression, anti-allergic effects and anti-inflammatory effects of MAPK inhibitor and PI3K inhibitor have been published. The manuscript for p38α MAPK ASO has been submitted for publication. Future plans of this laboratory will be to continue development of ASO for the treatment of allergic airway inflammation.</p>

<p>NMRC/0434/2000</p> <p>PI: Eng Hsi Ko Peter (SGH)</p> <p>Collaborators: Teo Keng Fong, Khoo Hsu Chin Daphne, Braverman Lewis E, Chin William</p>	<p>Effect of iodide on sodium iodide symporter gene transcription and protein expression</p> <p>This project aimed to find an <i>in vitro</i> cell model which shows NIS mRNA and or protein regulation by iodide. The researchers also aimed to characterize the mechanism of the regulation of NIS mRNA & protein.</p> <p>The researcher tested four different thyroid cell lines: KAT-50, Nthy-ori-3-1, FRTL-5 and PCCI-3. These cells were exposed to different concentrations of iodide in the culture media. After this, NIS mRNA and protein were extracted. NIS mRNA levels was measured by Northern blot and NIS protein was quantitated by Western blot. Nuclear run-off assays were carried out to determine the rate of transcription of the NIS mRNA. Protein half-life was quantitated with pulse chase experiments. FRTL-5, KAT-50 and Nthy-ori-3-1 did not show any change in the mRNA level with iodide. PCCL-3 cells grown in media containing iodide showed decreased NIS mRNA levels. When the PCCL-3 cells were subjected to nuclear run-off assays, there was no difference between the transcription of NIS mRNA in cells exposed to iodide versus the non-exposed cells. FRTL-5 cells showed that NIS protein was reduced when the cells were incubated with iodide and pulse chase experiments suggested that there was a decrease in NIS protein half-life.</p> <p>The researchers conclude that the FRTL-5 cell line is a good <i>in vitro</i> cell model to understand the mechanism regulation of NIS protein by iodide while the PCCL-3 thyroid cell line is a good <i>in vitro</i> cell model to explore the mechanism of regulation of NIS mRNA by iodide. Iodide did not seem to affect NIS mRNA transcription, suggesting that iodide may regulate NIS mRNA by affecting its stability. In FRTL-5 cells, iodide appeared to decrease NIS protein by increasing its turnover.</p>
<p>NMRC/0442/2000</p> <p>PI: Chua Kaw Yan (NUS)</p>	<p>Study of the immunopathogenesis and neurogenic inflammation of atopic dermatitis</p> <p>Pathogenesis of atopic dermatitis involved the interactions of immune and neuroendocrine systems. Here the researchers described a mouse model for atopic dermatitis with concomitant neurogenic inflammation. This was performed by epicutaneous sensitization with a dust mite allergen. Allergen patching resulted in localized dermatitis characterized by pronounced epidermal hyperplasia and spongiosis, which were associated with infiltration of eosinophils and neutrophils, degranulated mast cells, CD4+ and CD8+ T cells, and dendritic cells. There was increased innervation of CGRP and substance P in inflamed skins. Interactions between nerve fibers and mast cells were also observed, indicating the coexistence of neurogenic inflammation. Splenic T cells produced Th2-polarized cytokines in response to allergen stimulation <i>in vitro</i>, indicating systemic allergen sensitization.</p> <p>This is the first report of a mouse model of eczema accompanied by neurogenic inflammation, hence showing close resemblance to human allergic diseases. This work supported the notion that the skin is an important site for the initiation of primary allergen sensitization. On top of this, this model may also be useful for the study of other stress-associated neuroinflammatory skin disorders such as neurogenic pruritus and psoriasis.</p>
<p>NMRC/0444/2000</p> <p>PI: Lee Eng Hin (NUS)</p>	<p>The application of a bioresorbable 3D scaffold and mesenchymal stem cells for tissue engineering an osteochondral transplant</p> <p>This project strived to evaluate the repair potential and efficacy of a biphasic scaffold system seeded with mesenchymal stem cells in osteochondral defect of the rabbit model. The project can be divided into two portions: scaffold fabrication and <i>in vitro</i> culture of scaffold/mesenchymal cells construct. <i>In vivo</i> transplantation 3-D polycaprolactone (PCL) scaffold was fabricated by the Fused Deposition Modeling technique. This technique enabled the production of a highly</p>

	<p>reproducible and totally interconnected scaffold with different lay-down pattern and porosity. A number of mesenchymal stem cell culture protocols had been established successfully for the <i>in vitro</i> study. PCL scaffold showed good compatibility with bone marrow mesenchymal stem cells (BMSC) and it could support cell growth in a dynamic culture system. Osteogenic cells and chondrogenic cells which were co-cultured on the partitioned PCL scaffold could achieve an <i>in vitro</i> preliminary osteochondral construct. Bi-phasic scaffold concept was utilized in the <i>in vivo</i> study and this involved the use of different scaffold or materials as the cartilage part or the bony part. Osteochondral defects were created on the high load-bearing site---femoral medial condyle of adult New Zealand rabbit and then treated with bi-phasic scaffold (with or without allogenic BMCS). Implanted cell survival was tracked by fluorescent or Adeno-lacZ labeling. The repair tissue was evaluated by several techniques at 3 months, 6 months or 9 months after implantation.</p> <p>From gross, histological and biomechanical examination, the combination of PCL for cartilage portion and PCLTCP for bone portion showed better repair results. This indicates a promising alternative approach for osteochondral repair.</p>
<p>NMRC/0447/2000</p> <p>PI: Leong Khai Pang (TTSH)</p>	<p>Targeting the T lymphocyte in the treatment of asthma: investigations in the mouse model</p> <p>The researchers examined the effects of various agents on the mouse model of asthma, especially those concerning the T lymphocyte. The researchers also studied the effects of dexamethasone, lignocaine, cyclosporin A and tacrolimus (FK-506). It was found that intranasal lignocaine was effective in controlling airway hyperresponsiveness but had minimal effect on airway inflammation. This result discourages the use of lignocaine as monotherapy for asthma treatment. Tacrolimus was much more effective in reducing airway hyperresponsiveness and inflammation than cyclosporin even though both agents have extremely similar modes of action.</p> <p>Dissection of the differential actions of these agents may reveal cellular pathways crucial to the development of the disease.</p>
<p>NMRC/0452/2000</p> <p>PI: Roy Ashim C (NUS)</p> <p>Collaborators: Ng Soon Chye, Liao Wuxiang, Mongelli Joe Max</p>	<p>Mitochondrial DNA mutations and gestational diabetes mellitus</p> <p>Two hundred mitochondrial DNA (mtDNA) samples were isolated from 200 patients with gestational diabetes mellitus (GDM) and these samples were subsequently screened for mutations in the mitochondrial NADH dehydrogenase (ND) 3, ND 4, and ND4L genes using PCR based SSCP and DNA sequencing techniques. However, neither known nor novel mutations were detected in this mtDNA segments.</p> <p>These findings suggest that these segments of mtDNA are not involved in the pathogenesis of GDM, and hence have no clinical importance in the disease.</p>
<p>NMRC/0455/2000</p> <p>PI: Ho Ting Fei (NUS)</p> <p>Collaborator: Yip Chin-Ling William</p>	<p>Evaluation of foetal electro-cardiography and foetal heart rate variability</p> <p>This study had several aims: 1) to determine foetal ECG in normal fetuses from early gestational ages to term, 2) improve signal-processing to eliminate maternal signals so as to capture foetal ECG signals more accurately and 3) use spectral analysis of foetal ECG to derive foetal heart rate variability (HRV) as an indirect indicator of foetal cardiac autonomic control.</p> <p>A non-invasive foetal ECG system was used to measure foetal ECG from pregnant females transabdominally. Pregnant females (n=100) with normal fetuses were followed-up from 18 weeks gestation to term. Foetal ECG signals were used for signal processing and for the derivation of HRV.</p>

	<p>Changes of foetal ECG waveform, voltage and duration were measured and computed in relation to gestational age. Quantification of various foetal ECG variables provided a useful source of clinical reference for normal fetuses. Raw foetal ECG signals were used for the design of a new algorithm to improve signal-processing and to filter off maternal signals. An algorithm was designed for spectral analysis of foetal ECG. The derived HRV was then used to assess development of foetal autonomic cardiac control. These are initial accomplishments that precede future development of improved foetal ECG systems that have better signal processing ability and better clinical applications.</p>
<p>NMRC/0456/2000</p> <p>PI: Hooi Shing Chuan (NUS)</p> <p>Collaborators: Salto-Tellez Manuel, Leong Adrian Peng Kheong</p>	<p>Role of heparin/heparan sulfate interacting protein in colon cancer cell proliferation and differentiation</p> <p>Heparin interacting protein (HIP) is a cell surface protein that interacts with heparan sulfate side chains of proteins. It is involved in cell-cell and cell-extracellular matrix interactions and has been postulated to influence cell proliferation, migration and differentiation. The grant addressed the role of this protein in cancer cell differentiation and proliferation.</p> <p>The major achievements of the grant are:</p> <ol style="list-style-type: none"> 1. The researchers showed that HIP was mutated in a colorectal cancer cell line and in a liver metastatic tissue. Interestingly, the mutation involved the deletion of a 12-base sequence that encodes the heparin / heparan sulfate binding motif, suggesting that this motif plays an important role in cell adhesion and metastasis. The results were published in International Journal of Molecular Medicine 11(4):473-477, 2003. 2. The researchers also showed that HIP played a role in apoptosis induced by anticancer drugs. HIP expression correlated to the occurrence of apoptosis in cells treated with anticancer agents. Moreover, the knockdown of HIP expression by siRNA resulted in increased apoptosis of the cells. These cells were also more sensitive to drug-induced death. The results were published in Carcinogenesis (in press). <p>The researchers also extended the studies to another cell surface molecule (CD44 receptor for hyaluronate) that was thought to be involved in carcinogenesis, They showed that the expression of CD44 variants in colorectal carcinoma was increased in tumors and correlated to vascular and depth of invasion. The results were published in J Lab Clin Med 139(1):59-65, 2002.</p>
<p>NMRC/0457/2000</p> <p>PI: Esuvaranathan Kesavan (NUS)</p>	<p>A multicentre randomised controlled trial of BCG and interferon alpha-2b in the treatment of superficial bladder cancer</p> <p>The primary aims of this study were to determine whether “low-dose BCG plus Interferon-alpha” is more efficacious than standard dose BCG in patients who had a high risk of contracting superficial bladder cancer. If both prove to be equally efficacious, the researchers will then find out whether there is less toxicity associated with the lower dose. The researchers also aimed to identify individuals who had unsatisfactory responses to BCG. This was carried out through a blood test for HLA type and BCG genotype. Identification was also carried out through the analysis of urinary cytokines.</p> <p>Patients with superficial bladder cancer were randomized to low dose BCG (27 mg), low dose BCG (27 mg) and 10 MU interferon alpha-2b or standard dose BCG (81 mg). All treatment arms received an initial course of 9 intravesical instillations of BCG. Urine samples were collected before and after instillation 1,6,7 and 9. A blood sample was collected on instillation 1, 6 and 9. Follow-up comprised urine cytology, cystoscopy and biopsy at 3-monthly intervals. Patients who did not respond to the treatment or developed a superficial recurrence were randomized to low dose BCG or low-dose BCG plus interferon alpha-2b in a maintenance schedule of</p>

	<p>instillations at 6 monthly intervals for 3 years. As symptoms of bladder irritability and other adverse reactions could be subjective, the trial was double blinded, i.e. neither patient nor the physician knew which drug and dose was used. Blood samples were typed and stored for future genetic analysis. Urine samples were assayed for cytokines.</p> <p>A total of 140 patients were recruited in this randomized double-blinded controlled clinical trial. There were 64 patients in the standard dose BCG group, 32 patients in the low dose BCG group and 44 patients in the combination group. For the efficacy analysis, only 130 patients were evaluable. For standard, low dose and combination therapies, the recurrence rates at 12 months and 24 months were 14.6%, 10.7% and 5.6% and 29.7%, 15.4% and 12% respectively. The mean time to recurrence and 5 year estimates for percentage recurrence free status for combination therapy were 75.7 months and 84.8% respectively, as compared to standard dose therapy at 59.8 months and 53.3% respectively (p=0.04). The recurrence-free function Kaplan Meyer curves showed a statistically significant reduction in recurrence events in the combination therapy arm. The toxicity analysis was based on all patients who received therapies. It showed that a reduced dose of BCG coupled with interferon alpha 2b significantly reduced both systemic and local side effects. Systemic side effects (fever, malaise, lassitude, difficulties with work and activities) in standard dose BCG, low dose BCG and the combination therapy arm were 96.7%, 71.4% and 85.7% (p<0.01) respectively. Local side effects (dysuria, burning sensation, frequency, urgency, haematuria, nocturia, incontinence) in standard dose BCG, low dose BCG and the combination therapy arm were 100%, 92.9% and 95.2% (p<0.05) respectively. Urinary cytokine analysis revealed that patients who received BCG and Interferon alpha produced much higher levels of the urinary interferon gamma than those who only received BCG treatment. Interferon gamma production was associated with a positive anti-tumor response of BCG and this may explain the superiority of combined therapy as compared to only BCG therapy.</p> <p>In conclusion, the 5-year data suggest that intravesical low dose BCG, with the addition of IFNa, had a lower toxicity and superior durability and efficacy as compared to standard dose BCG in patients with superficial bladder cancer.</p>
<p>NMRC/0464/2000</p> <p>PI: Chang Chan Fong (NUS)</p> <p>Collaborator: Lee Hon Cheung</p>	<p>Expression cloning and functional expression of a novel endogenous ligand of human bone marrow stromal antigen 1/CD157</p> <p>CD157, a glycosylphosphatidylinositol-anchored protein, has previously been shown to mediate tyrosine phosphorylation of a 130 kDa protein (p130) in several cell lines.</p> <p>In this study, the researchers identified the p130 protein to be a focal adhesion kinase (FAK or pp125 (FAK)). FAK undergoes phosphorylation at Tyr-397 and Tyr-861 in intact MCA102 cells which were stably transfected with CD157 (MCA/CD157). MCA/CD157 cells displayed rounded and compact cell morphologies and exhibited a dispersed distribution. This is in contrast to a more closely associated and elongated spindle cell shape in the vector-transfected cells. MCA/CD157 cells proliferated at a rate 20-25% slower than the control cells. The results of this study demonstrate, for the first time, that FAK is a downstream signalling molecule of CD157. The researchers also demonstrated that CD157, independent of antibody crosslinking, undergoes dimerization with disulfide bond formation and localization in caveolae in CHO/CD157 and MCA/CD157 fibroblasts. However, the native CD157 induced in mHL-60 cells remains a monomer form. The structural integrity of caveolae is required for the association of CD157 with caveolin and CD157-mediated tyrosine kinase signalling in the fibroblasts.</p> <p>The researchers proposed that an overexpression of CD157 could lead to its dimerization and relocation to caveolae and further result in the initiation of</p>

	<p>signalling processes.</p>
<p>NMRC/0465/2000</p> <p>PI: Shen Han Ming (NUS)</p> <p>Collaborators: Chan Daniel W, Lin Zhong Ning, Wang Young(YongQiang)</p>	<p>Anti-cancer effects of parthenolide in human colorectal cancer and nasopharyngeal cancer cells: involvement of cyclooxygenase-2 and fatty acid synthase through the NF-kB pathway</p> <p>Parthenolide (PN) is a major sesquiterpene lactone of Chrysanthemum (Tanacetum parthanium) with known anti-inflammatory activities. The focus of this project was to systematically evaluate the anti-cancer activity of PN and the molecular mechanisms involved. The research work covered the following main aspects:</p> <p>(i)The mechanisms involved in PN-induced apoptosis in human colorectal cancer cells (ii)The inhibitory effect of PN on NF-kB activation (iii)The sensitization effect of PN on TNF-induced apoptosis in human cancer cells (iv)The anti-cancer activity of PN tested in a UVB-induced mouse skin cancer model.</p> <p>Data from this study provided convincing evidences that PN is a potent anti-cancer agent with great potential as a chemopreventive and chemotherapeutic agent.</p> <p>This project has led into a number of tangible outcomes:</p> <p>(i)Publications: Three papers have been accepted for publication in peer-reviewed leading international journals such as Carcinogenesis. Two more manuscripts are currently under preparation. (ii)Presentations: two presentations in international conferences and a number of invited talks for the PI in some prestigious research institutions in USA. (iii)Establishment of various laboratory techniques and animal models, including UVB-induced skin cancer model (iv)Training of Postgraduates: two PhD students were supported and trained under this research project. One laboratory technician was also recruited. (v)One major equipment was also purchased with the support of this grant.</p>
<p>NMRC/0466/2000</p> <p>PI: Wilder-Smith Einar (NUS)</p> <p>Collaborators: Ho King Hee, Natarajan Suneetha</p>	<p>A comparison of clinical, neurophysiological & histological methods for diagnosing & quantifying sensory & autonomic peripheral neuropathy</p> <p>This project proposed:</p> <ol style="list-style-type: none"> 1) To determine the diagnostic accuracy of intraepidermal nerve fiber density (IENFD) in sensory and autonomic peripheral neuropathies. 2) To correlate skin wrinkling, nerve conduction and sympathetic skin reflex measurement with intraepithelial nerve fiber density in sensory-autonomic neuropathy. <p>Patients with clinical neuropathy and the healthy volunteers underwent skin punch biopsy at the hypothenar region for estimation of IENFD by using PGP 9.5 antibodies. The clinical neuropathy score, water and EMLA® skin wrinkling correlated with sensory-motor nerve conduction of ulnar, peroneal sural nerves and sympathetic skin responses.</p> <p>Nerve conduction and skin biopsy was performed in 56 patients (34 male, 22 female; mean age 56 yrs, range 20-88), SSR in 43 (24 male, 19 female) with neuropathy. Etiology was diabetes mellitus (type 2) in 17. Five had diabetes and renal failure, 5 diabetes and alcohol. No cause was identified in 21 patients and a diagnosis of idiopathic small nerve fiber disease was made. Two were diagnosed with CIDP, 1 diabetes mellitus (type 1), 3 uremia, 1 genetic, 1 Guillan Barré. In neuropathy, IENFD nerve counts/mm ranged from 0.0-5.15. IENFD correlated significantly with sural sensory</p>

	<p>amp ($p=0.003$) and right hand SSR ($p=0.009$) but not peroneal nerve or sole SSR parameters ($p=0.632$). Correlation between IENFD and EMLA® wrinkling was significant ($p=0.023$) but not for water wrinkling ($p=0.521$). The positive predictive value of absent EMLA® wrinkling in identifying abnormal IENFD ($<1.5\text{mm}$) was 94 %. Mean IENFD from 40 healthy subjects was 3.07; 2 SD 1.56 (mean age 41; range 21-71, 30 Females, 10 Males; 24 Chinese, 5 Malay, 11 Indian).</p> <p>The researchers found that the parameters of small nerve fiber function, IENFD, EMLA® wrinkling and SSR showed good correlation with sensory neuropathy. For parameters of large nerve fiber function, IENFD only correlated with sural nerve amplitude. This study supports IENFD as a useful overall diagnostic parameter of sensory polyneuropathy in general and establishes EMLA® wrinkling as a screening test for small nerve fiber dysfunction.</p>
<p>NMRC/0467/2000</p> <p>PI: Wong Yee Chee (NUS)</p> <p>Collaborators: Shekhar Gangaraju Raja, Annamalai Loganath</p>	<p>Interaction between placental cell adhesion molecules and angiogenic factors in normal pregnancy, pre-eclampsia and fetal growth restriction</p> <p>Proper placentation is a prerequisite for normal fetal development and investigations were conducted on expression and secretion profiles of growth factors and cell adhesion molecules (CAMs). Studies on the pivotal angiogenic factors, angiogenin as well as PIGF, EGF and VEGF were conducted in normal and in pregnancies complicated by preeclampsia (PE) and fetal growth restriction (FGR).</p> <p>Angiogenin was identified for the first time to be produced in a gestation dependent manner with significantly increased levels of expression and secretion in PE and FGR. PIGF levels and mRNA transcripts were also enhanced in both conditions while VEGF secretion was below detectable limits. With regard to CAMs, levels of VCAM-1 and its mRNA were decreased in term placentae when compared to first trimester chorionic villi, but these levels were further decreased in FGR placenta, suggesting that diminished levels were associated with placental insufficiency. In contrast, levels of CAM-2 and P-Selectin were higher in term placentae compared to those of the first trimester and both CAMs were significantly decreased in PE and FGR. Moreover, experiments using hypoxia provided evidence for significantly enhanced expression and secretion of angiogenin with a concomitant loss of VCAM-1 by both explants and trophoblast cells in culture, thus indicating a role for these pivotal peptides in FGR. Uteroplacental insufficiency such as PE and FGR could be attributed to an inappropriate expression and secretion of CAMs and growth factors.</p>
<p>NMRC/0472/2000</p> <p>PI: Zhu Yi Zhun (NUS)</p> <p>Collaborator: Tan Kwong Huat, Benny</p>	<p>Investigating the mechanisms of the protective effects of Dan Shen, an extract from the root of salvia miltiorrhiza on myocardial infarction and stoke in experimental animals</p> <p>In this project, the researchers compared cardioprotective effects of DanShen (an extract from Salvia miltiorrhiza) against angiotensin-converting enzyme inhibitor, ramipril, in rats. With both treatment regimens, similar effects were observed: (1) a higher survival rate, (2) a significant reduction of infarct size, (3) significantly lower ratios of heart weight to the body weight as well as lower ratios of the left and right ventricular weights to body weight.</p> <p>DanShen showed some unique effects in the following aspects: (1) higher activities of antioxidant defense enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) and glutathione S-transferase (GST) in the liver of rats with acute myocardial infarction (AMI), (2) lower myocardial and hepatic TBARS values; (3) augmented VEGF mRNA expressions in the non-ischemic parts of rat hearts with</p>

	<p>AMI.</p> <p>These results were consistent with the findings of a slight increase in myocardial capillary density and the special distribution pattern of coronary blood vessels in DanShen-treated rats.</p>
<p>NMRC/0473/2000</p> <p>PI: Tay Sam Wah, Samuel (NUS)</p> <p>Collaborator: Dheen S Thameem</p>	<p>Molecular bases for gestational diabetes-induced changes in the nervous and visual systems of developing mouse embryos</p> <p>Maternal diabetes-induced malformations have been detected in all major organ systems including cardiovascular, gastrointestinal, genitourinary and neurological systems among which the neural tube defects involving forebrain, midbrain and hindbrain were more frequently reported in infants. The researchers have analyzed the molecular mechanisms of morphological changes in the developing forebrain of embryos derived from diabetic mice using immunohistochemistry, in situ hybridization, Real-time PCR, ELISA and cell-culture techniques. Morphological analysis revealed that embryos of diabetic pregnancy displayed a forebrain dysmorphogenesis. Expression of various genes that regulated early events of the forebrain patterning during embryogenesis was altered by maternal diabetes. It was concluded that altered expression of these genes may contribute to the forebrain malformations in embryos of diabetic mice. In addition, exposure of embryos to both maternal diabetes and a teratogen was linked to pathogenesis of neural tube defects during development. It was found that maternal diabetes aggravated the teratogen-induced inflammatory reaction in the developing neural tube. Inflammatory reactions in the neural tube were characterized by an increased number of brain macrophages and altered expression of inflammatory cytokines. Although a definitive link has yet to be elucidated, it was suggested that the increased rate of neural tube defects observed in embryos of diabetic mice exposed to the teratogen may be due to the upregulation of proinflammatory cytokines caused by maternal diabetes.</p>
<p>NMRC/0474/2000</p> <p>PI: Whiteman Matthew (NUS)</p>	<p>Mechanisms of the modulation of cellular behaviour by reactive species of nitrogen, chlorine and oxygen; analysis by high performance liquid chromatographic and fluorescence techniques</p> <p>Extensive evidence implicates the overproduction of free radicals and other reactive oxygen, nitrogen and chlorine species (ROS, RNS and RCS respectively) in numerous human pathologies involving, among other things, chronic inflammation (rheumatoid arthritis, inflammatory bowel disease) neurodegeneration (Parkinson's, Alzheimers, Motor Neurone, Huntington's Diseases) and cancer, as evidenced from depletion of endogenous antioxidants and increased formation of oxidised protein, lipid and DNA adducts. The effects of the above reactive species on ATP, GSH, GSSG, NAD⁺ levels and oxidative DNA damage were examined over a wide range of concentrations in various human cell models.</p> <p>Using fluorescence probes, the role of protein kinases, intracellular cation and pH alterations, poly(ADPribose) polymerase (PARP) and caspase activation, DNA strand breakage and formation of DNA lesions were investigated. HPLC was used to analyse nitrated, chlorinated and oxidised bio-markers of protein and DNA damage (3-nitrotyrosine, 6-nitrotryptophan, 8-nitroguanine, 3-chlorotyrosine and dityrosine) and lipid hydroperoxides. GC-MS analysis was used to assess the formation of oxidized amino acids and DNA bases. Additionally, techniques established by the researchers were used to identify, purify and directly assess the scavenging activities of potential therapeutic antioxidants from TCM and novel plant sources using HPLC and fluorescence spectroscopy.</p>

<p>NMRC/0476/2000</p> <p>PI: Ip-Yam Christian Pierre (SGH)</p> <p>Collaborators: Chew Tsong Huey Sophia, Chow Yew Hoong Mark</p>	<p>Comparison of non-invasive method of cardiac output measurement with invasive bolus thermodilution during thoracic surgery</p> <p>Non-invasive partial CO₂ rebreathing (NICO) is a relatively new alternative to thermodilution (TDCO) for measurement of cardiac output (CO). To investigate if NICO is effective and accurate during two- and one-lung ventilation (OLV) during thoracic surgery in the lateral position, 12 patients undergoing thoracotomy and OLV were selected for a prospective controlled trial. Paired measurements of CO were performed 1) two-lung ventilation in the supine position, 2) ten minutes after initiation of OLV in the lateral decubitus position and 3) after 30 minutes on OLV. There was moderate agreement between CO measurements obtained with NICO and TDCO although NICO showed a tendency to underestimate CO compared to TDCO at all measurement times.</p> <p>The researchers' data suggested that the NICO technique may be useful during thoracic surgery.</p>
<p>NMRC/0478/2000</p> <p>PI: Quak Seng Hock (NUS)</p> <p>Collaborators: Aw Marion Margaret Hui Yong, Lai Poh San</p>	<p>Molecular analysis of JAG1 gene in biliary atresia, paediatric liver disease and Alagille syndrome (AGS)</p> <p>Alagille syndrome (AGS) is one of the major forms of chronic liver disease in childhood with severe morbidity and mortality rate of 10-20%. This syndrome is associated with neonatal jaundice arising from paucity of bile ducts, and clinical manifestations affecting the eye, heart, face and lungs. Although this disorder should be considered in all infants with cholestasis, histologic diagnosis based on arteriohepatic dysplasia identified from liver biopsies is difficult or impossible in infancy. Most diagnosis is thus dependent on syndromatic manifestations. Hence, the main aim of this project was to determine the mutational basis of this disorder among local patients in order to establish a molecular strategy for diagnosis of patients clinically diagnosed with, or suggestive of AGS.</p> <p>Clinical phenotyping of local AGS patients showed involvement of at least three of the five presentations: abnormalities of liver (80%), heart (60%), vertebrae (47%), face (47%) and eye (20%). Molecular analysis showed presence of de novo JAG1 mutations, all of which involved insertion or deletion frameshifts, missense and nonsense mutations. 80% of these mutations were novel indicating that future molecular diagnosis would require screening of the entire gene in the absence of mutational hotspots. Novel informative exonic polymorphisms were identified which will allow for carrier and linkage analysis. Haplotype studies of the SNPs were carried out in 16 population control groups to provide genotype information useful for future linkage and association studies.</p> <p>The results of this project indicate that (1) molecular analysis of JAG1 is useful for confirmation of clinical cases of AGS due to the wide phenotypic variability of the disease, (2) JAG1 mutations in local patient population show heterogeneity in spectrum and location, with most affecting the EGF repeat domains critical in protein-protein interaction, and (3) possibility of involvement of other gene(s) besides JAG1 to account for the diversity of phenotypic manifestations and absence of JAG1 mutation in some patients.</p>
<p>NMRC/0485/2000</p> <p>PI: Ling Eng-Ang (NUS)</p> <p>Collaborator: Ng Yee Kong</p>	<p>Investigation of neuronal response and glial reaction in the central nervous system and its target visceral organs, with special reference to the urinary bladder, following occlusion of the middle cerebral artery</p> <p>The expression pattern of proinflammatory cytokines, neuronal nitric oxide synthase (nNOS), substance P (SP) and calcitonin gene related peptide (CGRP) in the spinal cord and the bladder in response to permanent middle cerebral artery occlusion (MCAO) was investigated. In this connection, the</p>

	<p>gene expression of tumor necrosis factor α (TNF-α), interleukin-1 β (IL-1β) and interleukin -6 in the lumbosacral spinal cord and the bladder as determined by real-time polymerase chain reaction was upregulated. In the spinal cord, the immunoreactivity of TNF-α and IL-1β was mainly localized in the ventral horn motoneurons contralateral to MCAO. In the bladder, TNF-α was mainly expressed in the inflammatory cells. The expression of nNOS immunoreactivity as well as nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d) staining in the spinal cord and bladder was also markedly increased in response to MCAO. Furthermore, the temporal and spatial expression of nNOS paralleled that of TNF-α and IL-1β in the spinal cord. On the other hand, there was no noticeable change in gene expression and immunoreactivity of SP and CGRP. The present results have shown that cytokines and nNOS expression are elevated in areas far removed from the primary site of ischemic infarct, namely, the lumbosacral spinal cord and bladder. This together with some neuronal deaths may be linked to the dysfunction of the latter in a clinical stroke. On the other hand, the apparent lack of SP and CGRP changes following MCAO suggests that the two neurotransmitters are not directly involved.</p>
<p>NMRC/0488/2000</p> <p>PI: Tan Chay Hoon (NUS)</p> <p>Collaborators: Lau Gilbert, Chong Siow Ann</p>	<p>Association studies in the genetics of suicidal behaviour</p> <p>The researchers studied the association between a single nucleotide polymorphism in the 5-HT receptor genes and suicidal behavior. In addition, the researchers also studied the CCKB gene expression in suicide and controls. Blood samples consisted of 333 confirmed suicide cases (mean age 43.6 SD=19.1) obtained from the Institute of Forensic Science and 110 controls (mean age 43.3 SD=16.3) recruited from the hospital. Ten samples of postmortem brain tissue consisted of suicide completers and age, sex-matched controls were obtained from Institute of Forensic Science.</p> <p>The project received ethic approval from the Director of Institute of Forensic Science and Medicine.</p> <p>The researchers reported a significant difference of 5-HTB receptor polymorphism between the control and suicide groups. In addition, CCKB gene expression is significantly higher in the cerebellum, cingulate gyrus and pre-frontal cortex of suicide when compared to the controls. (See attached publications)</p> <p>After this project, the researchers hope to:</p> <ol style="list-style-type: none"> 1. Use the 5-HT receptor gene 1B as a tool to predict suicidal behaviour in their psychiatric patients. 2. Identify new markers which could be used in the detection of patients at high risk for suicide in animal study.
<p>NMRC/0491/2000</p> <p>PI: Wong Meng Cheong (SGH)</p> <p>Collaborators: Wilder-Smith Einar, Ling Eng Ang, Chen Christopher Li-Hsian, Chang Hui Meng, Auchus Alexander P.</p>	<p>Ultrastructural endothelial abnormalities and stroke</p> <p>Endothelial dysfunction is a major feature of vascular disease, including stroke. The researchers sought to develop semi-quantitative parameters of ultrastructural endothelial dysfunction examining patients with stroke.</p> <p>Prospectively, 107 individuals underwent microvascular biopsy taken from the hypothalar region. 1184 microvessels consisting of 303 arterioles, 461 capillaries and 420 post-capillary venules from 87 consecutive inpatients admitted with ischemic stroke (61% hypertensive, 43% diabetic, 21% smokers) and 20 non-stroke controls were examined. Electron microscopy, computer software imaging aided standardized ultrastructural assessment. Multivariate linear regression analysis revealed that diabetes (p=0.002), smoking (p=0.004) were significant predictors of arteriolar endothelial blebbing. For post-capillary venule endothelial blebbing, diabetes (p=0.034), interaction of diabetes and smoking (p=0.03) were significant predictors. Capillary endothelial blebbing was not associated with diabetes, hypertension, smoking, age or presence of stroke. Aside from endothelial abnormalities, the researchers also separately described novel association of</p>

	<p>smooth muscle cell arterial hypertrophy with moya-moya stroke.</p> <p>In conclusion, this study demonstrated visible and quantifiable endothelial abnormalities in systemic microvessels, <i>in vivo</i>. Particularly diabetes and smoking were significant predictors of microvascular endothelial blebbing, highlighting the systemic nature of endothelial dysfunction in patients with cerebrovascular disease.</p>
<p>NMRC/0492/2000</p> <p>PI: Adaikan P. Ganesan (NUS)</p> <p>Collaborator: Ng Soon Chye</p>	<p>Comprehensive evaluation of the effects of oestrogen in male reproductive health and disease</p> <p>This project was initiated to explore the physiopharmacology of the so called “female hormone” oestrogen in male erectile function. The researchers found that long term oestradiol (E2) treatment (12 weeks) precipitated sexual behavioural deficits and significantly reduced intracavernous pressure response to erectile nerve stimulation in the rat model. These changes correlated directly with two to five folds elevation in serum E2 levels (and simultaneous reduction in T levels). Pretreatments with E2 and phytoestrogen daidzein impaired neurotransmitter mediated erectile function in rabbits seen as reduced relaxant responses to acetylcholine, nitroglycerine and nitergic neurotransmission and significantly potentiated noradrenaline induced antierecile contraction of the cavernosum. Histologically, trichrome staining highlighted the cavernosal connective tissue hyperplasia and decrease in smooth muscle in both models and in tissue culture studies, the cyclic guanosine monophosphate release was impaired by oestradiol. Exploratory immunohistochemistry proposed a genomic basis for these effects through the researchers’ pioneer identification of positive signals for nuclear ERα and ERβ receptors within the rabbit cavernosum. Hormone profile data of erectile dysfunction (ED) patients from Andrology Clinic, National University Hospital gave the clinical correlate for the experimental results.</p> <p>This project has also established the detrimental effect of both oestradiol and phytoestrogen on erectile function and has highlighted the endocrine disruptive effect of oestrogens including their negative impact on T levels and male sexual health.</p>
<p>NMRC/0493/2000</p> <p>PI: Ratha Mahendran (NUS)</p> <p>Collaborator: Esuvaranathan Kesavan</p>	<p>Is the Internalization of BCG by bladder cancer cells essential for successful therapy?</p> <p>This project sought to determine whether 1) the presence of internalized BCG will change the ability of bladder cancer cells to form tumors and/or the growth characteristics of the tumors so formed ie. vasculature; 2) internalized BCG increases the cytotoxic effects of PBLs against bladder cancer cells; 3) the cellular events induced by BCG internalization will eventually cause cell death and 4)the expression of mycobacterial genes could correlate with the induction of cells death.</p> <p>The methodology used was to clone the $\alpha 5$ gene, over-express it in bladder cancer cells (confirmed by flow cytometry) and use these cells to study changes in growth characteristics (monitored by measuring cell proliferation using labeled thymidine) and gene expression (using representational differential analysis) after exposure of cells to BCG. To confirm uptake FITC labeled BCG was used and uptake monitored by flow cytometry.</p> <p>Major accomplishments of this work were that the researchers did find a strong link between the expression of the $\alpha 5\beta 1$ integrins, internalization of BCG and cell death. Using RDA the researchers were able to identify changes in the expression of several genes, including $\beta 1$ integrin and GST after exposure of MGH bladder cancer cells to BCG.</p>

<p>NMRC/0494/2000</p> <p>PI: Wong Hee Kit (NUS)</p> <p>Collaborator: Goh Cho Hong James</p>	<p>The effects of load-carrying on the posture and gait of normal and scoliotic adolescents</p> <p>The aim of this study was to examine how unilateral load carrying while standing and walking, affects the spinal posture of normal and scoliotic adolescents. 28 adolescents aged 13.1 (SD 1.9) years participated in this study. 9 were normal and 19 had late onset idiopathic scoliosis (LOIS). Of the latter, 9 had thoracic curves; 3 had thoracolumbar curves; 4 had lumbar curves and 3 had double curves. All thoracic curves were convex to the right; and all thoracolumbar and lumbar curves were convex to the left. Mean Cobb angles of the main curves was 43.5 (SD 10.9) degrees.</p> <p>Subjects' postures were assessed in the following load carrying conditions: (1) carrying no load; (2) carrying 5kg (10-12% BW) on the right and (3) on the left shoulder. Spinal radiographs were used to assess the standing posture of 9 scoliotic subjects. Cobb and Perdriolle angles were measured. A VICON motion analysis system was used to assess the posture of all 28 subjects during standing and walking. External markers were placed on the spinous processes of C7, T4, T9, T12 and L3, and on the right and left PSIS. These vertebrae were selected because the end-vertebrae and apices of scoliotic curves typically present around these levels. Lateral flexion of the trunk, of the various spinal segments, and thoracic and lumbar curvature angles were calculated from marker coordinate data.</p> <p>The VICON system was found to be a viable method to assess coronal plane spinal motion during gait. The spine was most inclined to the opposite side of the pelvis at foot contact. This motion pattern was the same for all subjects and did not change with load carrying.</p> <p>Left load carrying increased thoracic Cobb angles in standing ($p=0.052$); induced and increased lumbar curvatures in both the normal and scoliotic spine during walking ($p<0.05$). Right load carrying increased thoracic Perdriolle angles in standing ($p<0.05$).</p> <p>Although all subjects laterally flexed their spines to the opposite side of the load ($p<0.05$), the mid to lower thoracic spine of the scoliotic subjects generally had smaller changes in lateral flexion angles with load carrying. This was due to the structural stiffness of the scoliotic spine. Consequently, greater compensatory lateral flexion occurred in the lower lumbar segments of the scoliotic spine, more so while standing than walking. While standing, the scoliotic subjects had greater changes in spinal posture when carrying load on one side than the other.</p> <p>Unilateral load carrying caused significant spinal lateral flexion; and aggravated spinal deformity in both normal and scoliotic adolescents. Although the long term effects of this increase in spinal curvature could not be determined in this study, it is recommended that the load carriage requirements of students be reduced and correct load carriage techniques be promoted.</p>
<p>NMRC/0496/2000</p> <p>PI: Poh Chit Laa (NUS)</p>	<p>Degradation of phenolic wastes by Pseudomonas species via the gentisate pathway: cosmid cloning and genetic organization of the genes in P25X and P35X</p> <p><i>Pseudomonas alcaligenes</i> NCBI 9867 (strain P25X) is a soil bacterium that is capable of degrading xylenols and cresols via the gentisate pathway. It was postulated that there were two gentisate 1,2-dioxygenases, one being constitutively expressed and the other inducible. The gene encoding gentisate 1,2-dioxygenase (GDO) was cloned and designated as XlnE. In a P25X xlnE knockout mutant, GDO activity was detected only when cells were grown in the presence of aromatic substrates, confirming that there was another inducible gentisate 1,2- dioxygenase.</p> <p>The <i>P. alcaligenes</i> P25X endogenous pRA2 plasmid utilizes several independent mechanisms to enhance plasmid stability. A detailed examination of the pRA2 par plasmid partitioning locus was carried out in this project. The par locus consists of two genes, parAB, that are co-</p>

	<p>transcribed from a σ70-like promoter sequence. ParB was found to repress the par promoter activity but parA had no effect on transcriptional activity. Primer extension analysis revealed that the par transcriptional start point was located 47 nucleotides upstream of the parA translational start codon. Based on this information, putative -10 and -35 transcriptional signals were identified, and their subsequent deletion resulted in a dramatic reduction in promoter activity. The par promoter region was also demonstrated to exert incompatibility towards a plasmid with an active pRA2 par system.</p>
<p>NMRC/0499/2000</p> <p>PI: Tan Theresa, Maychin (NUS)</p>	<p>Transport of sulphate conjugates</p> <p>Sulphotransferases (SULTs) catalyze the transfer of a sulphate group from 3'-phosphoadenosine 5'-phosphosulfate to the acceptor molecule. The acceptor may be an endogenous molecule or an exogenous compound. Although the process of sulphate conjugation is part of the detoxification process, certain procarcinogens are activated following sulphate conjugation. In addition certain SULT isoforms have been linked to increased incidences of cancer.</p> <p>In this study, Hep G2, a human hepatocarcinoma cell line, was used to study the sulphation and transport of sulphated phenolic metabolites (dopamine and p-nitrophenol). Following the incubation of HepG2 cells with Na235SO4 and either dopamine or p-nitrophenol, the net efflux of 27.4 + 1.4 pmol p-nitrophenyl sulphate/min/mg protein and 7.7 + 1.4 pmol dopamine sulphate/min/mg protein was observed.</p> <p>The effects of glucocorticoids on SULT activity and efflux of sulphate conjugates were also examined using dopamine and p-nitrophenol. Treatment with dexamethasone increased the net efflux of dopamine sulphate but decreased that of p-nitrophenyl sulphate. Further analysis showed that a) the sulphation process of p-nitrophenol was not affected by dexamethasone, while SULT1A3 transcripts and activity toward dopamine were induced and b) OATP (including OATP-B, D and E) and MRP transporters (including MRP 1, 2, 4 and 5) can be induced by dexamethasone. It is thus evident that both the generation as well as the transport of sulphate conjugates can be modulated by dexamethasone.</p>
<p>NMRC/0500/2000</p> <p>PI: Khoo Hsu Chin Daphne (SGH)</p> <p>Collaborators: Ho Su Chin, Eng Hsi Ko Peter, Lai Oi Fah, Bahn Rebecca</p>	<p>Role of thyroid stimulating immunoglobulins and thyroid peroxidase antibodies in the pathogenesis of Graves' ophthalmopathy(renewal)</p> <p>This project sought to investigate in an <i>in vitro</i> culture, the effect of TPO antibody and thyroid stimulating antibody present in the sera of Graves' disease patients on adipogenesis in human orbital fibroblasts. Human orbital fibroblasts grown in culture were induced to accumulate lipid using a pulsed chemical cocktail. The effect of addition of antibodies present in the patients sera, on adipogenesis in the fibroblasts was measured using a dye which stain triglycerides. The dye was extracted and measured spectrophotometrically.</p> <p>The researchers had successfully developed an <i>in vitro</i> thiazolidinone-free human orbital fibroblast adipogenesis model. In other laboratories only 5-10% of the orbital fibroblasts can be induced to accumulate lipid using thiazolidinone free protocols.</p>
<p>NMRC/0502/2000</p> <p>PI: Chang Chan Fong (NUS)</p>	<p>Studies of function and regulation of human ADP-ribosyl cyclases in normal and abnormal cells using inducible adenoviral gene expression system</p> <p>CD157 is a novel bone marrow stromal antigen that was found to possess both ADP-ribosyl cyclase and cADPR hydrolase activities. It is also able to act as a receptor to generate signals.</p> <p>In this study, recombinant adenovirus containing inserts CD157 and mutant CD157 (mCD157) was constructed in order to study the relationship</p>

	<p>between the cyclase activity and receptor function of CD157. mCD157, which has a higher cyclase activity, was developed by mutating wild type CD157 at two sites: Arg103 to Cys103, and Arg184 to Cys184. Using adenovirus infection with an optimal MOI of 10, overexpression of CD157 and mCD157 in COS-7 cells was found to mediate tyrosine phosphorylation of a p130 protein in the absence of ligand(s). However, the cyclase activity of CD157 was not found to be involved in this phosphorylation. The p130 protein was identified as focal adhesion kinase (FAK) and was phosphorylated on Tyr397 and Tyr861.</p>
<p>NMRC/0503/2000</p> <p>PI: Ashvin Thambyah (NUS)</p> <p>Collaborators: Thiagarajan P, Bose Kamal, Goh Cho Hong James</p>	<p>A study of mechanical factors related to osteoarthritis</p> <p>The loading of the knee in walking, stairclimbing and deep flexion were investigated in-vivo of normal subjects as well as those with unilateral anterior-cruciate-ligament (ACL) deficiency. The altered in-vivo knee joint kinematics was also studied using a novel approach with magnetic resonance imaging. The data from the in-vivo study was input and correlated to in-vitro models that measured joint contact areas and the topographical variation in cartilage properties on the tibial plateau.</p> <p>The findings indicate that knee kinematics and kinetics is activity-dependent. Stair climbing confirmed the importance of the ACL in influencing the loads about the tibiofemoral joint. It was found that contact area in relation to deep flexion activities resulted in stresses that bordered the critical limits that predispose the cartilage to structural damage. Correlating to the topographical variation in cartilage properties on the tibial plateau, it was found that some peripheral regions of cartilage and bone have unique properties. The risk of cartilage damage if tibiofemoral contact was altered accordingly as to engage the peripheral regions as required during deep flexion activities or as a result of ACL deficiency is real. The current study shows the importance of combining the tibiofemoral knee kinematics and kinetics studies in predicting the possible mechanical risk factors that leads to knee OA.</p>
<p>NMRC/0509/2001</p> <p>PI: Lin Valerie (SGH)</p> <p>Collaborator: Aw Swee Eng</p>	<p>Studies of progesterone receptor (PR)- gene therapy in PR - negative breast cancer</p> <p>Previous work demonstrated that re-activation of PR expression by transfection in Erand PR-negative breast cancer cells MDA-MB-231 enabled progesterone to strongly inhibit tumor growth both in vivo and in vitro. In this report, the researchers show that transfection of PR in Erand PR- positive cells MCF-7 exhibited antiestrogenic effect in a ligand-independent manner. Cell cycle analysis revealed a 50% reduction of s-phase fraction in PR-transfected MCF-7 cells treated with estradiol-17β compared to vehicle-treated controls after 72 h. Induction of the gene expression of pS2 and GREB1 by estradiol, two well-known estrogen target genes, was also significantly impaired. Promoter interference assay revealed that estradiol-17β- mediated ER binding to estrogen response elements (ERE) was also drastically impaired in PR-transfected MCF-7 cells. The transfected PR may also exert these antiestrogenic effects by modulating the metabolism of E2. After 72 h in culture, only one third of added E2 remains in the medium and the cytosol of PR-transfected cells compared to two thirds of that in the parental and the vector transfected MCF-7 cells. The findings suggest a novel mode of action by the progesterone receptor. This antiestrogenic effect of transfected PR also provides a potential therapeutic strategy for estrogen-dependent breast cancer. Studies using adenoviral-mediated PR gene delivery are in progress. The researchers have cloned PR cDNA into Transpose-Ad TM Adenoviral vector. High titre adenoviral particles expressing PR have been generated. The effect of PR gene therapy in hormone-dependent and hormone independent breast cancer using adenoviral vector delivery are being determined.</p>

<p>NMRC/0518/2001</p> <p>PI: Lim Su Chi (AH)</p> <p>Collaborators: Chew Tec Huan Stephen, Tan Hwee Huan</p>	<p>The effect of angiotensin converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) on the endothelial and renal function of subjects with type 2 diabetes</p> <p>The objective of this study was to evaluate the efficacy of Accupril (ACE inhibitor with specific action on tissue ACE) vs. Losartan (angiotensin receptor blocker, ARB) on the micro-circulatory endothelial function and renal albumin excretion of subjects with type 2 diabetes (T2DM).</p> <p>Fifty ARB- and ACEI-naive T2DM subjects with hypertension and/or significant albuminuria (>30mg/g creatinine) were given either 50 mg of Losartan (L) or 20 mg of Quinapril (Q) (50% maximum dose) for 4 weeks with 4 weeks wash-out period in-between interventions in a cross over fashion. The order of intervention was randomized and investigators involved in the measurement of the primary endpoints were masked to the intervention. The primary endpoints were changes in (1) albuminuria and (2) microcirculatory endothelial vascular reactivity. Secondary endpoints were changes in plasma markers of endothelial activation [i.e. serum soluble vascular cell adhesion molecule (sVCAM) and intercellular adhesion molecule (sICAM)], plasma transforming growth factors (TGFβ) and urinary TGFβ. The endothelial function was assessed safely and non-invasively by measuring the forearm superficial skin hyperemic response to the iontophoresis of 1% acetylcholine (produces endothelium dependent vasodilation) and 1% sodium nitroprusside (produces endothelium independent vasodilation). Plasma sICAM, sVCAMs, TGFβ and urinary TGFβ were measured using commercial ELISA assays (R&D systems)</p> <p>Main findings from this study include: The mean age (SD) was 54(10) year, BMI 27.1(4.6) kg/m², waist 92(13) cm, baseline systolic BP (SBP) 135(15) mmHg, diastolic BP (DBP) 83(9) mmHg, FPG 9.3(2.7) mM, HbA1c 8.3(1.8)%, serum potassium 4.2(0.4) mM, serum creatinine 76.4(17.9) μM, urinary albumin/creatinine ratio (ACR) 445(978) mg/g. Blood pressure reduction on both interventions was similar [SBP: L 3(14) vs. Q 2(12) mmHg, P=0.65; DBP: L 1(9) vs. Q 2(8) mmHg, P=0.66]. However, amelioration of albuminuria was significantly greater with Losartan [L vs. Q: -367 (973) vs. -21(318) mg/g, P=0.01]. Nevertheless, the differential efficacy in albuminuria reduction between Losartan and Accupril was not associated with any differences in changes of microcirculatory endothelial reactivity, markers of endothelial activations and TGFβ.</p> <p>The researchers conclude that 50 mg of Losartan had similar BP reduction but greater antiproteinuric effect than 20 mg of Quinapril in Asian subjects with T2DM. However, microcirculatory endothelial reactivity, markers of endothelial activation and TGFβ did not change appreciably with either treatment.</p>
<p>NMRC/0519/2001</p> <p>PI: Gopalakrishnakone P.</p> <p>Collaborator: Mohamed A. Jamal</p>	<p>Application of microarray technology to divulge the molecular mechanisms of drug resistance in mycobacteria</p> <p>In an effort to find the gene clusters and their regulatory networks that affect drug susceptibility in Mycobacterium smegmatis, a DNA microarray platform was used with selected genes. ORFs concerned with efflux mechanism, energy metabolism, oxidative stress response and drug resistance (especially the targets) were selected from the GenBank database, primers designed and amplified through PCR. The amplified oligos were then spotted on poly-L-lysine coated glass slides and hybridized with fluorescently labelled cDNA samples. Differential gene expression analysis based on a highly sensitive two colour hybridization assay showed, a high level expression (both in the drug resistant mutant & wild type) for genes concerned with energy metabolism and oxygen toxicity (oxidative stress response). In this study though the researchers included the oxidative stress response genes ahpC, katG and sodA, only</p>

	<p>sodA showed high level expression whereas the other two were at their basal level. Further, in accordance with the statement that out of two genes (secA1 & secA2) concerned with transport across cytoplasmic membrane of proteins having signal sequences at their amino termini, secA1 is essential and secA2 can be deleted; a high level expression was obtained for secA1 and a poor signal for secA2. As evidenced by many others, this study also confirmed the hypermutability of rpoB gene from the low signals (under expression) for rpoB in the mutant where the complete coding region of the rpoB gene of the <i>M. smegmatis</i> mc2 155 was sequenced and analyzed.</p>
<p>NMRC/0520/2001</p> <p>PI: Wilder-Smith Einar (NUS)</p> <p>Collaborators: Ng Yee Kong Wong Meng Cheong Ong Kian Chung Benjamin Xu Mei</p>	<p>Assessment of endothelial factors in stroke using skin biopsy</p> <p>The researchers sought to determine endothelial cell abnormality of the microvasculature (vessel < 400 microns in diameter) of patients with stroke by identifying and classifying endothelial abnormalities using Electron Microscopy.</p> <p>The methodology included an open, prospective, descriptive study of arteriolar, capillary and venuolar endothelial cell luminal surface changes occurring in prospective patients with stroke. All had 3-mm skin punch biopsy from the palmar aspect of the hand. Stroke classification was into either small or large vessel disease and stroke risk factors were identified.</p> <p>107 patients were investigated (87 stroke patients, 20 controls). Endothelial cell morphology was compared to the normal controls and a standardized endothelial scale was developed. The researchers have found and quantitated pathological aberrations of “endothelial blebbing” and “ghost cells” to correlate to stroke risk factors of hypertension, age and diabetes. In addition smooth muscle abnormality of “ghost cells” were described and linked to similar stroke risk factors. A bonus of the study was the identification of the first Singaporean family of CADASIL- a rare monogenic autosomal dominant stroke disorder and vascular parkinsonism in moya moya disease. Two major publications are being written detailing the outcome of this research. These will be submitted to major international journals.</p>
<p>NMRC/0521/2001</p> <p>PI: Koh Woon Puay (NUS)</p> <p>Collaborators: Lee Hin Peng Lee Edmund Jon Deoon Zhao Bin Knize Mark</p>	<p>Carcinogenic heterocyclic amines in the Chinese diet: development of an instrument for exposure assessment in population-based studies</p> <p>Heterocyclic aromatic amines (HAA) are formed when protein-rich foods are heated to high temperatures, and several of these compounds have been found to be mutagenic and carcinogenic <i>in vivo</i>, and associated with risk of cancers of the colon, breast, and lung in human populations.</p> <p>The primary objectives of the project were to develop an instrument to measure dietary heterocyclic amine exposure in Chinese populations.</p> <p>These involved two stages – measuring frequency and amount of meat consumed by the population, and determining the levels of heterocyclic amines in common meat dishes. Based on the results from analyzing 25 meats cooked as commonly consumed and in-person interviews of 515 randomly selected individuals in the population, the researchers estimate that mean HAA exposure from the Chinese diet is 49.95 ng/day from an average intake of 108.7g of meat. This is lower than in most Western populations. The researchers have also identified seven types of meat which contribute to about 90% of this intake, and this list can be applied in large-scale epidemiologic investigations to assess HAA exposure,</p>

	<p>as well as to public health interventions aimed at reducing exposure to these potential carcinogens in the diet.</p>
<p>NMRC/0522/2001</p> <p>PI: Lee How Sung (NUS)</p> <p>Collaborators: Kong Hwai Loong, Goh Boon Cher, Leow Chon Kar, Lim Seng Cheong Robert</p>	<p>Pharmacokinetic study of thalidomide in patients with unresectable hepatocellular carcinoma; an extension of phase II clinical trial of thalidomide in the treatment of unresectable hepatocellular carcinoma by cancer therapeutics research group</p> <p>Full Pharmacokinetics (PK) of Thalidomide (antiangiogenic agent) in liver cancer patients Phase II study had to be changed to just plasma thalidomide monitoring because this grant's approval came after the trial was nearly completed. Very few patients could be further recruited for samples for plasma thalidomide concentrations quantification.</p> <p>Thalidomide undergoes spontaneous hydrolysis at physiological pH. Sample stability had to be dealt with. The HPLC method of quantification of thalidomide in plasma was validated using FDA guidelines and the doses of thalidomide were increased weekly from 100 mg daily at bedtime, up to 800 mg daily (200, 200, 400 mg). Plasma thalidomide concentrations varied from a trough of 0.4 mg/L (100mg daily) to a high of 7.3 mg/L at the high dose. These values were not different from those reported by Eriksson T <i>et al</i> 1988 in healthy volunteers and Figg WD <i>et al</i> 1999 in elderly prostate cancer patients.</p> <p>Although the researchers' sample size was small, the results seemed to suggest that hepatic elimination of drug was not significantly changed in liver cancer patients to affect the plasma thalidomide concentrations.</p>
<p>NMRC/0526/2001</p> <p>PI: Nga Been Hen (NUS)</p> <p>Collaborator: Tan Hai Meng</p>	<p>Cloning of structural genes for the biosynthesis of antitumour anthracycline antibiotics by the actinomycete isolates NS3-166 and NC4 obtained from soil in Singapore. Characterisation of the chemical compounds produced by them</p> <p>The researchers isolated two strains of actinomycete, NS3-166 and NC4, from soil in 1996. These strains produced novel analogues of daunorubicin and doxorubicin (DNR and DOX) and tetracenomyacin C and elloramycin (TCMC and elloramycin) respectively. The chromosomal DNAs of NS3-166 and NC4 were shown to contain the ketoacyl synthase (KS) gene when analysed by Southern hybridisation with the act I gene (encoding the α and βketoacyl synthase of act I gene) of <i>Streptomyces coelicolor</i> M145 by probing. Thin layer chromatography analysis of the extracts of the culture of NS3-166 in ADI media grown at 30°C for 10 days with shaking at 200rpm showed that the extracts contained novel analogues of DNR and DOX. Thin layer chromatography of the extracts of the culture of NC4 grown in R2YENG at 30°C for 4 days showed that these contained novel analogues of TCMC and elloramycin.</p> <p>A genomic library of the chromosomal DNA of NS3-166 was made using the Sau3 AI cut fragments of the chromosomal DNA inserted into the cosmid pKC505. The library was screened to isolate clones that carried the DNR/DOX biosynthetic gene cluster. One positive clone which carried a 25kb insert of the chromosome fragment of NS3-166 was studied and was shown to carry twenty genes of the DNR/DOX biosynthetic gene cluster. These genes were sequenced. The amino acid sequence of the proteins encoded by these genes and of the corresponding genes of the known DNR/DOX producer, <i>Streptomyces peucetius</i> ATCC 29050 were compared. A genomic library of the chromosomal DNA of NC4 was made. A positive clone which carried genes of the TCMC and elloramycin biosynthetic gene cluster was studied. Twelve genes were characterized. The amino acid sequence of the proteins of the tcm C genes was compared with the amino acid sequence of the proteins of the corresponding genes of the known TCMC producer, <i>Streptomyces glaucescens</i> GLA. O.</p> <p>Experiments to test the toxicity of the polyketide compounds of NS3-166</p>

	<p>on Molt 4 cell-line cells showed that these were toxic to the cells when present at 14µg/ml. The extracts of the polyketide compounds of NS3-166 were introduced into DBA/2J mice (which had been treated with leukaemia cells) at a weekly interval and this increased the life-span of the mice by 45%.</p> <p>The researchers used a Streptomyces replicating plasmid which carried specific genes of the DNR/DOX biosynthetic gene cluster of NS3-166 and cells of NC4 were transformed with it. One genetically engineered transformant from this produced novel polyketide compounds which, when injected into DBA/2J mice treated with L1210 cells gave a high percentage increase of the life-span of the L1210 treated mice.</p>
<p>NMRC/0528/2001</p> <p>PI: Chew Tec Kuan Paul (NUH)</p> <p>Collaborators: Goh Cho Hong James, Shabana Noor, Peres Valerie Cornilleau</p>	<p>A study to assess the affect of glaucoma on postural control with age matched normal subjects</p> <p>This project measured the effect of Primary open angle glaucoma (POAG) on the visual contribution to postural steadiness in terms of visual stabilization ratio (VSR) and relate this measure to the (i) mean deviation (MD) and (ii) Advanced Glaucoma Intervention Study (AGIS) score, which quantify the visual field defect evaluated on the Humphreys visual field analyzer through DLS (differential light sensitivity).</p> <p>This project also seeked to compare the VSR of patients with age matched control subjects with normal vision.</p> <p>35 glaucoma patients and 21 age matched control subjects with normal vision participated in the study.</p> <p>The postural sway data was obtained with the subjects standing bare foot on the force measuring platform and also while standing on rubber foam. In both situations the subjects viewed a large visual stimulus screen. Foam was used to enhance the contribution of vision to stabilisation while cutting down the somatosensory input. The data was collected at the Orthopaedic Diagnostic Center (ODC), NUH.</p> <p>This study found out that for all subjects, the sway velocity was lower with vision than without vision, indicating the existence of a visual contribution to posture at all stages of glaucoma. This contribution was significantly lower for patients than for normals in monocular and binocular vision, and decreased with the MD, or as the AGIS scores increases. Among the maximum, minimum and average values of the two monocular MD, the MD of the eye with worsen vision presented the most significant negative correlation with the visual contribution to posture. The somatosensory contribution to postural steadiness was larger in patients, as compared to normal individuals in monocular or binocular vision.</p>
<p>NMRC/0529/2001</p> <p>PI: Xiao Zhi Cheng (SGH)</p> <p>Collaborators: Melitta Schachner, David Samuel, Ang Beng Ti Christopher, Zhu Kong Jie</p>	<p>Development of biocompatible artificial nerve growth guidance conduit for optic nerve transplantation</p> <p>Autografts have been extensively studied to facilitate optic nerve (ON) regeneration in animal experiments, but the same approach for clinical application to aid in autoregeneration has not yet to be attempted due to its obvious shortcomings. This study aimed to explore the guided regeneration by an artificial polyglycolic acid-chitosan conduit coated with recombinant L1-Fc. Consistent with the previous studies, <i>in vitro</i> assays showed that both chitosan, a natural biomaterial, and the neural cell adhesion molecule L1-Fc enhanced the neurite outgrowth. Rat optic nerve transection was used as an <i>in vivo</i> model. The implanted PGA-chitosan conduit was progressively degraded and absorbed and these was accompanied by significant axonal regeneration, as revealed by immunohistochemistry, anterograde and retrograde tracing. Moreover, polyglycolic acid-chitosan conduit coated with L1-Fc proved to be more effective in the promotion of axonal regeneration and remyelination. Taken together, the researchers demonstrated that the L1-Fc coated PGA-chitosan conduits provided a</p>

	compatible and supportive canal to guild the injured nerve regeneration and remyelination.
NMRC/0535/2001 PI: Jeyaseelan K (NUS) Collaborator: Armugam Arunmozhiarasi	Expression and functional studies on venom nerve growth factor Nerve growth factor (NGF) is a potent signaling protein that is important for growth and maintenance of neurons. The researchers have identified a novel NGF in the venom of Malayan spitting cobra, Naja sputatrix. In this project the researchers first purified this nerve growth factor and determined its N-terminal sequence. With this information the researchers cloned 2 cDNAs encoding cobra NGF by RT-PCR and then produced the recombinant NGF free of contamination from other venom component on a large scale using E.coli as a host. The recombinant protein has been purified, refolded and tested for biological activity using PC12 cells.
NMRC/0537/2001 PI: Cheng Christopher Wai Sam (SGH) Collaborators: Ng Wan Sing, Tan Puay Hoon, Thng Choon Hua	Trans-rectal prostate biopsy - a precise biopsy device for accurate prostate biopsy Transrectal ultrasound (TRUS) image-guidance and histopathological analysis are often used in the diagnosis of prostate cancer. However, the current systematic manual biopsy protocol is inaccurate and operator dependent, resulting in false-negative rate of around 35%. The performance of both biopsy and treatment of prostate cancer can be improved through better image guidance and robotic manipulation. In this project, the researchers aimed to develop a computer-controlled manipulator guided by pre-biopsy magnetic resonance spectroscopy imaging (MRSI) and real-time TRUS imaging. From July 2001 to July 2004, the NMRC Grant has enabled them to develop a prototype robotic prostate biopsy device guided by the above mentioned imaging system. They have also conducted a limited clinical trial (8 patients) with promising results. This project has generated one patent filing with another one being reviewed for filing; 2 international publications with another 2 manuscripts being reviewed for publication; 3 best clinical presentation awards in urological scientific conferences in 2003 and 2004. The researchers have successfully obtained an extension grant from NMRC for the further development (automation) of the robotic prostate biopsy device.
NMRC/0538/2001 PI: Xiao Zhi Cheng (SGH) Collaborators: Leong Seng Kee, Udo Bartsch	Evaluation of the role of neural cell adhesion and extracellular matrix molecules in modulating sodium channels during axonal development and regeneration: molecular mechanisms and therapeutic application for neurogenic pain and multiple sclerosis F3/contactin is identified as a functional ligand of the Notch receptor which promotes oligodendrocyte maturation. Cell adhesion and repulsion assays as well as biochemical approaches suggested that F3 and Notch interact and triggers the nuclear translocation of Notch intracellular domain (NICD). Notch1 and Notch2 are upregulated, but not HES1. In a co-culture system cellular processes of the oligodendrocyte cell line OLN-93 terminate and spread over the F3-transfected CHO cell bodies but pass across control CHO cells. The interaction also up-regulates MAG, which is independent on HES1. These results describe F3 as a novel ligand for Notch, a signaling paradigm which may be involved in myelination.
NMRC/0542/2001 PI: Gopalan Ganesan (NCC) Collaborators:	Studies on the role of AIK1 as an oncogene in the development of ovarian cancer AIK1 (aurora-A kinase) is an important member of the subfamily of aurora kinases that play essential roles in mitotic events. AIK1 is oncogenic and over-expressed in many types of malignancies. Human AIK1 over-expression in cultured cell lines results in centrosome hyper-amplification

<p>Hui Kam Man, Ho Tew Hong</p>	<p>and chromosomal instability. Normal functions of AIK1 include roles in G2/M progression, spindle assembly, modulation of mitotic spindle checkpoint and cytokinesis.</p> <p>In this study, the researchers found that AIK1 increased the expression of telomerase gene in near-normal ovarian surface epithelial cells, which could be a prelude to tumorigenesis. It was shown that overexpression of AIK1 led to decreased sensitivity of cancer cells to chemotherapeutic agent, paclitaxel. The researchers also observed that endogenous AIK1 levels in different cell lines did not correlate to their paclitaxel sensitivity. However, downregulation of AIK1 levels by siRNA techniques led to increased sensitivity in breast and ovarian cancer cell lines irrespective of the initial responsiveness to taxol. Both estrogen and progesterone induced the expression of AIK1 and the transforming potential of MCF7. This suggests that AIK1 could be involved in hormone-induced carcinogenesis. Thus, AIK1 inhibitors could be potentially useful in reduction of some side effects of HRT (hormone replacement therapy). They could also act adjuvants to chemotherapeutic drugs like paclitaxel during postoperative estrogen replacement therapy.</p>
<p>NMRC/0545/2001</p> <p>PI: Song Keang Peng (NUS)</p> <p>Collaborator: Ong Hui Lian Grace</p>	<p>Molecular studies and development of diagnostic tests for the periodontal diseases in Singapore</p> <p>Periodontal disease is a significant global public health concern. As the aging population of Singapore increases, the prevalence of periodontal disease is expected to rise as well.</p> <p>The main objectives of this project were (i) to study the prevalence of periodontal disease in Singapore, (ii) to identify new virulence factors associated with periodontal disease, (iii) to develop methods to monitor and detect progression of periodontal disease.</p> <p>The experimental procedures included various molecular techniques such as PCR, cloning, RT-PCR and real-time PCR. The researchers' results showed that real-time PCR could potentially be used as a sensitive and quantitative tool for the detection of <i>A. actinomycetemcomitans</i>, <i>P. gingivalis</i> and <i>T. forsythensis</i> present in periodontal samples. If the methodology is optimized, not only will it be more sensitive, the time it takes to complete the assay will also be shortened. The use of leukotoxin gene from <i>A. actinomycetemcomitans</i>, <i>prtC</i> gene from <i>P. gingivalis</i> and <i>prtH</i> gene from <i>T. forsythensis</i> as new targets for detection using PCR was examined and found to be useful. For example, leukotoxin was found to be expressed at the early growth phase of the bacteria, hence the presence of the bacteria at the diseased site could be established early during the onset of the infection.</p>
<p>NMRC/0548/2001</p> <p>PI: Gan Yunn Hwen (NUS)</p> <p>Collaborator: Mahendran Ratha</p>	<p>Signal transduction pathways mediated by Mycobacteria heat shock protein 65</p> <p>Heat shock proteins have emerged as agents capable of eliciting immune responses against cancers and viruses. They are able to deliver antigens into monocytes and dendritic cells to be presented on MHC class I molecules to cytotoxic T cells. The researchers have previously shown that mycobacteria heat shock protein 65 (Hsp65) could be complexed with tumor lysate <i>in vitro</i> and these complexes could immunize mice against a challenge of live tumor cells. The objective of this project was to understand the mechanism of action of heat shock proteins in enhancing antigen processing and presentation to T cells in an <i>in vitro</i> system.</p> <p>The researchers discovered that Hsp65 did not activate TLR4 nor bind to cell surface in a saturable manner on dendritic cells. The researchers demonstrated that many signaling activities of Hsp60 on monocytes and dendritic cells reported in the literature could be due to contaminating LPS. Furthermore, it was found that <i>Burkholderia pseudomallei</i> Hsp70 was superior to Hsp65 in promoting cross-presentation in dendritic cells. The</p>

	<p>mechanism did not involve TLR4 signaling, and heat shock proteins were able to enhance cross-presentation of peptides to T cells even on metabolically inactive dendritic cells. This suggested a physical interaction and promotion.</p>
<p>NMRC/0549/2001</p> <p>PI: Tan Chee Hong (NUS)</p> <p>Collaborator: Khoo Hoon Eng</p>	<p>Role of adenosine in cell death.</p> <p>Adenosine functions in a variety of physiological processes, including the modulation of cell growth and the induction of apoptosis.</p> <p>The researchers investigated the apoptotic effect of adenosine on a wide range of cell lines ranging from mammalian and human epithelial cancer cells, human neuronal cancer cells to human lymphocytes. The researchers obtained results which showed that adenosine-induced-apoptosis (AIA) is a universal physiological phenomenon in many tissues except in the neuronal cells where adenosine appeared to have no significant apoptotic effects.</p> <p>The key steps of the pathways leading to the AIA have been identified. The researchers showed that the elevation of cytosolic calcium, the decrease of mitochondrial membrane potential, the translocation of Bax, the release of cytochrome c and the activation of caspase 3 were downstream events leading to apoptosis. Based on the above findings, the researchers plotted the complete signaling pathway of adenosine-induced apoptosis. In addition to receptor-mediated and nucleoside-transporter-mediated AIA, the researchers also proposed a model of receptor-transporter co-mediated AIA.</p> <p>These findings should be useful in the design and development of new pharmacological agents (e.g. receptor agonists and antagonists) modulating apoptosis which, in turn, may be employed in antitumour therapy or in reducing cell death due to immunodeficiency or neurological diseases such as SCID, Parkinson's and Alzheimer's.</p>
<p>NMRC/0551/2001</p> <p>PI: Ratha Mahendran (NUS)</p> <p>Collaborator: Ong Adrian</p>	<p>Role of phospholipase-A2 inhibitors and/or its antibodies in the pathogenesis and prevention of surgically induced adhesions</p> <p>The project aimed to define the natural history, pathogenesis and progression of peritoneal adhesion formation. The researchers also studied the effect of PLA2 inhibitors in the reduction of the post-surgical peritoneal inflammatory response. A ventral hernia model in male Sprague Dawley rats was used to repair the abdominal defect with polypropylene mesh. Laparoscopic evaluation was used to perform repeated <i>in vivo</i> examinations of the peritoneal cavity. PLA2 inhibitors were directly administered to the site of surgical trauma using either miniosmotic pumps or hyaluronic acid gel as vehicle. The results demonstrated that a combined use of a physical barrier and PLA2 inhibitors at the site of peritoneal trauma attenuated the peritoneal inflammatory response. The minimum peritoneal residence time for effectiveness of the drug was 3-5 days post-surgery, a time that is critical in mesothelialisation of peritoneal defect. Polypropylene mesh serves as a potent and consistent stimulus for adhesion formation. Once the mesothelialisation of a prosthetic mesh was complete (at day 8), it was shown to be resistant to development of peritoneal adhesions. The sequential laparoscopic <i>in vivo</i> observations coincided with our scanning electron microscopy findings on mesothelial regeneration. The data shed additional light that would aid in the understanding of multifactorial process of peritoneal healing after surgery.</p>
<p>NMRC/0552/2001</p> <p>PI: Ong Biauwei Chi (SGH)</p> <p>Collaborator: Lai Oi Fah</p>	<p>Cytokines and inflammatory response in coronary artery bypass graft surgery: Is non-pump method better than cardiopulmonary bypass technique?</p> <p>The use of cardiopulmonary bypass (CPB) for coronary artery graft bypass surgery (CABG) has been the accepted method for many years. However it is of concern that contact with large areas of foreign material in the bypass circuit, hemodilution and hypothermia can stimulate a massive</p>

	<p>inflammatory response which can influence clinical outcomes.</p> <p>The aim of this study was to examine the cytokine levels in 2 groups of patients: those undergoing CABG with CPB and those undergoing CABG without CPB. Cytokine levels were taken at various time points during the surgery and up to 24 hours after surgery. Cytokine IL6, IL8, IL10 were measured. IL6 is a pro-inflammatory cytokine, IL8 is produced by the myocardium and indicates myocardial injury, IL10 is an anti-inflammatory cytokine.</p> <p>The results showed that off pump CABG had a lower and later rise in inflammatory cytokines which was balanced by a very low response in the anti inflammatory cytokines. Less myocardial IL 8 was found in off pump CABG. This may translate to better patient outcome and faster recovery. However the long term graft patency has to be investigated. Surgeon comfort and experience are also important in increasing the numbers of off pump CABG done with good outcome.</p>
<p>NMRC/0553/2001</p> <p>PI: Moore Xiao Lei (NCC)</p> <p>Collaborators: Wong Meng Cheong, Tan Boon Ooi Patrick, Sun Li</p>	<p>Analysis of 'homing' specificity of Endothelial Progenitor Cells to angiogenic sites of tumor, as a platform for future cell delivery of therapeutic genes</p> <p>Current treatment of malignant glioma brain tumors is unsatisfactory. Gene therapy holds much promise but more effective target-specific vectors are needed. Endothelial Progenitor Cells (EPCs) have <i>in vivo</i> homing specificity to angiogenic sites and are thus potential vehicles for site-specific gene therapy. However, there is lack of reports of EPCs homing to intracranial solid tumors. To explore potential of EPCs in glioma gene therapy, the researchers examined their biodistribution using SCID mice bearing orthotopic gliomas to determine homing specificity of EPCs under condition of intracranial solid tumors.</p> <p>CD34+ cells were isolated from human cord blood immunomagnetically, cultured in medium containing growth factors and characterized by immunocytochemistry and RT-PCR. Derived EPCs possessed endothelial markers and expressed endothelial-related genes. Following <i>in vitro</i> characterization, EPCs were labeled with a fluorogenic agent CFSE and intravenously injected into SCID mice bearing gliomas. Seven to fourteen days after EPC injection, mouse brains and other vital organs were examined for distribution of transplanted EPCs. As controls, CFSE labeled HUVECs or EPCs were intravenously injected into matched glioma SCID mice or non-tumor SCID mice, respectively.</p> <p>Fluorescence image analysis revealed that systemically transplanted EPCs 'homed' to brain tumors with significantly higher specificity than other organs within the experiment groups ($p < 0.001$) and anatomically matched brain sections from the control groups ($p < 0.001$). Thus this study demonstrates EPCs <i>in vivo</i> tropism for intracranial gliomas, with potential for cell delivery of site-specific brain tumor gene therapy.</p>
<p>NMRC/0554/2001</p> <p>PI: Bay Boon Huat (NUS)</p> <p>Collaborators: Mahendran Ratha, Dheen S Thameem</p>	<p>Development of non-pathogenic lactobacillus as a potential vector.</p> <p>In this study, the potential of non-pathogenic lactobacillus as a novel delivery system for DNA was elucidated. Normal and cancer cell lines were screened by flow cytometry, scanning and transmission electron microscopy and confocal microscopy in order to identify specific cell types which are susceptible to lactobacillus penetration. Of the various cell lines tested, internalization of Lactobacillus rhamnosus GG (LGG) was evident in the MGH bladder cancer cell line. <i>In vivo</i>, confocal microscopy of Green Fluorescent Protein (GFP)-expressing LGG revealed the internalization of this bacteria in epithelial cells of the small intestine and large intestine of germ free mice. These <i>in vivo</i> findings were verified by transmission electron microscopy. Functional studies showed that LGG and Lactobacillus casei Shirota (LcS) exerted cytotoxic effects in human bladder and colon cancer cell lines. The cytotoxicity of the bacteria was not dependent on bacterial-cell contact and the candidate cytotoxic molecule appears to be a small protein. A gene of interest, the interleukin-2 (IL-2)</p>

	<p>gene was successfully cloned into lactobacillus and preliminary results following transfer of the IL-2 gene into cells looks promising.</p>
<p>NMRC/0555/2001</p> <p>PI: Fong Kok Yong (SGH)</p> <p>Collaborators: Thumboo Julian, Suppiah P Sivalingam, Yoon Kam Hon, Koh Dow Rhoon, Sheila Vasoo</p>	<p>Pro-inflammatory and anti-inflammatory cytokines profiles in rheumatoid arthritis patients: Effect of methotrexate and genotype.</p> <p>The study aimed to determine the <i>in vitro</i> cytokines secretion profiles of RA peripheral mononuclear cells after stimulation by PHA and LPS under controlled conditions.</p> <p>When compared to normal individuals, the basal, 1-hr, 4-hr, 8-hr, 12-hr, 24-hr, 48-hr, and 72-hr IL-18 and TNF-α mRNA expressions were significantly elevated in RA patients. No significant differences were noted between HLA-DRB1*04 positive and negative patients. The presence of methotrexate did not affect the secretory profiles. The cytokines/receptors (IFN-γ, TGF-β, TNF-α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-18, sTNF-R1, sTNF-R2) profiles of a RA cohort were determined by ELISAs. TNF-α, IL-1β, IL-6, IL-8, IL-18 levels were significantly elevated in RA patients when compared to controls, while TGF-β (an immunoregulatory cytokine) levels were significantly depressed. When the RA patients were subsetted into active and inactive groups, there was no difference between the cytokine profiles noted. However, the soluble TNF receptors R1 and R2 were noted to be significantly elevated in those with inactive disease, providing a basis to explain the high TNF-α levels noted in patients in the remission state. When analysed according to the HLA-DRB1*04 positivity status, there was no significant difference noted.</p>
<p>NMRC/0556/2001</p> <p>PI: Lim Lay Cheng (SGH)</p> <p>Collaborators: How Gee Fung, Zhao Yi, Tan Li Tuan</p>	<p>Tandem duplications of the FLT3 receptor gene-association with adult acute myeloid leukemia.</p> <p>This study aimed to evaluate the distribution and frequency of FLT3 (FMS-like tyrosine kinase-3) mutations among patients of acute myeloid leukaemia (AML).</p> <p>A total of 221 adult patients were examined. Genomic DNA PCR assays were performed to detect ITDs (internal tandem duplications) and Asp835 (aspartate 835) mutations.</p> <p>The researchers found that FLT3/ITD and D835 mutations were detected in 21% (47/221) and 10% (22/221) AML patients respectively. Nucleotide sequencing showed all FLT3 mutations to be in-frame.</p> <p>Among the different FAB subtypes, FLT3/ITD mutations were most prevalent in patients with M1 morphology (45%). The majority of the patients with ITD or Asp835 mutations were found to be associated with either t (15;17) that was seen in AML M3 cases or AML patients with normal karyotypes.</p> <p>This study also suggests that the presence of FLT3 ITD was a poor prognostic factor in AML patients with normal cytogenetics. Thus analysis for FLT3 ITD presence is important in AML patients with normal cytogenetics as they are associated with poor outcome with autologous marrow transplant. There is a high relapse rate and possibly increased risk of refractory disease.</p>
<p>NMRC/0558/2001</p> <p>PI: Duan Wei (NUS)</p> <p>Collaborator: Qi Robert Z</p>	<p>Regulation of Serine/Threonine Protein Kinase PRK1 in Health and Diseases.</p> <p>Mammalian serine/threonine protein kinases, except for TGF-beta receptor kinase family, are intracellular proteins. PRK1/PKN is a member of the protein kinase C superfamily of serine/threonine kinases and is one of the first identified effectors for RhoA GTPase. Despite the pivotal roles Rho GTPases play in human physiology and disease development, the details of PRK1 in mediating signaling downstream of activated RhoA is largely unknown.</p> <p>In this project, the reseachers discovered a novel plasma membrane pool of</p>

	<p>PRK1. The phosphorylation of serine-377 of PRK1 is required for its integration into membranes. This integration is essential for PRK1 to function as a Rho effector because only the integral plasma membrane PRK1 is able to initiate RhoA-mediated and ligand-dependent transcriptional activation of the androgen receptor in human epithelial cells and to mediate RhoA-induced neurite retraction in mouse neuronal cells.</p> <p>These results advance the knowledge of mammalian signal transduction but also paved way to new effective therapy for neurodegenerative diseases and prostate cancer.</p>
<p>NMRC/0559/2001</p> <p>PI: Halliwell Barry (NUS)</p>	<p>Inhibition of proteasomal function as a mechanism of cell death in neurodegenerative disease. Induction by reactive oxygen species and the role of nitric oxide.</p> <p>The researchers' hypothesis was that impaired degradation of "unwanted" proteins by the ubiquitin-proteasome system is a major contributor to neuronal cell death in the major neurodegenerative diseases. The data obtained in the present project support this.</p> <p>The researchers showed that the proteasome played a key role in degrading oxidatively-damaged proteins and that too many such proteins can overload it and favour apoptosis. It was also found that several reactive species, especially 4-hydroxynonenal (HNE) and peroxynitrite, impaired proteasome function. The researchers also examined the effects of H₂S and sulphite, both neurotoxic agents. In turn, proteasome impairment led to formation of more reactive species, in a "vicious cycle".</p> <p>Studies on primary murine cortical neurons showed that low levels of proteasome inhibition activated transcription of "rescue genes" encoding heat-shock proteins, antioxidants and proteasome subunits. These events delayed cell death but they cannot prevent it. Cells with impaired proteasome function were also found to be more sensitive to a range of neurotoxins, including HNE, H₂O₂ rotenone and MPP+.</p> <p>Five papers have been published in J. Neurochem., one in Cellular and Molecular Life Sciences and two in J. Biol. Chem. (all tier 1 journals), another is in press in J. Neurochem and the final two will shortly be submitted.</p>
<p>NMRC/0560/2001</p> <p>PI: Jeyaseelan K (NUS)</p> <p>Collaborator: Armugam Arunmozhiarasi</p>	<p>Agonists and antagonists of aquaporins and related ion channels from toxins</p> <p>Appropriate regulation of membrane water permeability is a fundamental requirement of all living organisms. It is becoming apparent that specialized water-channel proteins, called aquaporins, determine transcellular water movements. Aquaporins are important in several pathophysiological conditions such as brain tumor, trauma, stroke, edema and disorders in lungs and kidneys. Toxins are known to contain natural inhibitors and activators to various cellular processes.</p> <p>The aim of this project was to identify such agonists and antagonists to aquaporins and related ion channels. Within the last 2.5 years, the researchers have identified the venoms that contain inhibitors and activators to water channels especially, aquaporin 1, 4, 5, 9 and potassium channel, Kir4.1 and have characterized some of these venom components. They have also examined the effect of a venom component, phospholipase in detail on the expression of water channel genes found in lungs.</p>

<p>NMRC/0565/2001</p> <p>PI: Goh James Cho Hong (NUS)</p> <p>Collaborators: Lee Eng Hin, Teoh Swee Hin, Chan Kwan Ho Casey</p>	<p>Use of synthetic porous biodegradable polymer sheets for ligament tissue engineering</p> <p>The study was divided into two parts: Part 1 focus on tissue engineering approach to Achilles tendon regeneration and Part 2 focus on tissue-engineered Anterior Cruciate Ligaments. The objectives for Part 1 was to determine the efficiency of knitted PGLA scaffolds and MSCs for tendon regeneration, and for Part 2 was to reconstruct Anterior Cruciate Ligament (ACL) with fabricated knitted PGLA scaffolds and MSCs.</p> <p>Part 1: The results showed that the bMSCs used in this study were multipotential, the implanted allogeneic bMSCs could survive as long as 8 weeks and were able to differentiate into spindle-shape cells after implantation. The bMSCs seeded knitted PLGA scaffold improved the structure and biomechanics of tendon repair. In summary, these results illustrated that the tissue engineering graft composed of bMSCs and knitted PLGA are promising substitutes for tendon repair.</p> <p>Part 2: It was also found that Poly-L-Lactic Acid (PLLA) yarns and PGLA (copolymer of Poly Lactic Acid and Poly Glycolic Acid) yarns were suitable materials and the knitted structure can provide sufficient mechanical properties while having adequate porosity for potential tissue in-grow. The in-vivo study demonstrated that the fabricated PLGA/PLLA knitted structures with cells has potential for ACL regeneration.</p>
<p>NMRC/0566/2001</p> <p>PI: Chow Kah Hoe Pierce (SGH)</p> <p>Collaborators: Yu Wing Kwong Sidney, Wall Darryl, Kotlovsky Anatoly, Cheow Peng Chung, Somanesan S., Song y, Tan Soo Yong</p>	<p>An investigative study on the efficacy of a novel anti-reflux biliary-enteric bypass construction in an animal model</p> <p>The Roux-en-Y biliary-enteric bypass is a relatively common higher surgical procedure in both pediatric and adult patients but a significant proportion of patients are incapacitated by recurrent episodes of cholangitis. Ascending reflux and infection through the biliary-enteric bypass, compounded by stasis and altered motility contributes to changes in the biliary epithelium with subsequent hyperplasia and dysplasia and late bile duct cancer complicating biliary-enteric anastomosis for benign disease. A more physiological biliary-enteric bypass conduit interposed between the biliary tree and the duodenum would overcome these known problems. In this study, the researchers constructed a novel biliary-enteric bypass based on principles used in the development of an anti-reflux ureteric valve using small bowel and investigated this in a pig model.</p> <p>Groups of 6 Yorkshire piglets weighing 15-20kg were used: (1) a jejunal narrowed valve mechanism was created by plication of the longitudinally myomectomized jejunal segment forming a narrowed lumen of 10mm in diameter; (2) a similar short segment with a intussuscepted valve of 1cm; (3) a Roux-en-Y hepaticojejunostomy (control); (4) sham. The piglets were all sacrificed at 5 months.</p> <p>Liver function test and HIDA scans demonstrated no significant biliary obstruction all groups. At the time of sacrifice, manometric assessment of the sham controls showed that the closing pressure of the ampulla was 27.5 cm H₂O (sham) 3.5 cm H₂O (control) 14 cm (Valve) and 16.5 (Narrowed) cm H₂O respectively. This novel biliary-enteric bypass is thus safe more physiological than the current Roux-en-Y hepaticojejunostomy used and can potentially can prevent ascending infection and the long-term risk of malignant change.</p>

<p>NMRC/0568/2001</p> <p>PI: Hui James Hoi Po (NUS)</p> <p>Collaborators: Lim Jit Kheng, Lim Lee Yong, Goh Cho Hong James, Lee Eng Hin</p>	<p>Intra-articular injection of microsphere-encapsulated chondroitin sulphate for the treatment of osteoarthritis in a rabbit model.</p> <p>This study aimed to evaluate the efficacy of intra-articular injection of chondroitin sulphate(CS) by hydrogel in prevention of osteoarthritis in adult rabbit models</p> <p>OA models were created with either a trochlea of condyle defect and a a-CD-EG 4400 hydrogel was selected as the CS carrier. There were 3 groups of rabbits; one injected with CS, one with hydrogel and the other with saline.</p> <p>The researchers concluded that intra-articular injection of CS carried by a-CD-EG 4400 is effective in preventing OA in rabbits by improving the histological properties of the knee joint.</p>
<p>NMRC/0569/2001</p> <p>PI: Tan Chee Eng (SGH)</p> <p>Collaborators: Lim Su Chi, Tan Hwee Huan, Lim Bee Choo</p>	<p>Effectiveness of nurse clinician case manager and telemedicine in the management of patients with uncontrolled diabetes mellitus.</p> <p>The proposed study was designed to explore the effectiveness of a model of nurse clinician case manager aided by telemedicine (to facilitate patient-care giver communication) in the management of 30 patients with uncontroled diabetes mellitus. This study sought to find out whether such model can help such patients to (1) improve their metabolic control and (2) to have better satisfaction (i.e. quality of life assessment).</p> <p>Using the same model, the researchers also studied the pattern of resource utilization in health care delivery The researchers found significant changes in weight and HbA1c by time ($p = 0.0105$ and $p < 0.0001$ respectively). Mean weight increased by time, while mean HbA1c decreased. Compared to baseline, the mean increase of weight at 1st & 2nd follow-up visits were 0.84 kg (95% CI -0.16 to 1.83, $p = 0.096$) and 1.75 (95% CI 0.54 to 2.96, $p = 0.007$) respectively. Compared with baseline, the mean decrease of HbA1c at 1st and 2nd follow-up visits were 1.26 (95% CI 0.81 to 1.71) and 1.19 (95% CI 0.69 to 1.70) respectively.</p> <p>The researchers concluded that telemedicine based therapeutic diabetes education may be effective in improving glycemic control among subjects with persistently uncontrolled diabetes.</p>
<p>NMRC/0570/2001</p> <p>PI: Lee Ann, Siew Gek (NCC)</p> <p>Collaborators: Hong Ga Sze, Seow Francis Choen, Yap Eric Peng Huat, Gray Joe W.</p>	<p>Identification of putative tumour suppressor genes involved in the carcinogenesis of breast and colorectal cancer.</p> <p>The aim of this project was to identify putative tumour suppressor genes involved in the carcinogenesis of breast and colorectal cancer. The researchers' previous work suggested the presence of tumour suppressor genes in that region. BAC clones from the deleted regions were selected and spotted on to microarrays. The researchers have completed array CGH analysis on 57 breast tumour samples and are currently analysing these results.</p> <p>The BAC clones from the chromosome 11q23 region have also been used in fluorescence in situ hybridisation (FISH) and array CGH experiments on breast cancer cell lines to determine if any of these have deletions at 11q23. Of the 11 cell lines studied, two were found to have deletions in this region.</p> <p>By using dual color FISH, the researchers have identified a region with increased amplification adjacent to the MLL gene in acute myeloid leukemia. These findings suggest that other gene(s) and not the MLL gene could be the target gene involved in the tumorigenesis of AML. By using the same strategy, the researchers have also found different deletions in myelodysplastic syndrome (MDS) as compared to chronic lymphocytic</p>

	leukemia (CLL), though these are cytogenetically indistinguishable. These findings suggest different molecular mechanisms for these diseases.
<p>NMRC/0572/2001</p> <p>PI: Chiam Peak Chiang (WH)</p> <p>Collaborators: Kua Ee Heok, Goh Lee Gan, Ng Tze Pin, Tan Lay Ling</p>	<p>Risk factors of depression in elderly people</p> <p>This study sought to examine prevalence and risk factors associated with depression in older adults</p> <p>The researchers analysed data of subjects with depression (N=48) and without depression (N=1044). It was a cross-sectional study of a national ethnically-stratified random sample of 1092 adults aged 60 years and above living in the community. Depression was diagnosed using the Geriatric Mental State Examination and Automated Geriatric Examination for Computer Assisted Taxonomy. Risk factors examined included social, economic and medical data. The prevalence of depression in the age groups 60-64 years, 65-74 years, ≥ 75 years were 2.2%, 3.3% and 3.9% respectively. Among the elderly who were ≥ 65 years old, the prevalence of depression in males and females was 3.2% and 3.8% respectively; the prevalence in Chinese, Malays and Indians was 2.8%, 6.5% and 6.8% respectively. Gender-ethnic interaction was statistically significant, being lowest in Chinese males (2.5%) and highest in Indian females (12.7%). Significant independent risk factors identified from weighted multivariate logistic regression analyses were Malay ethnicity, being self-employed, living in 1-2 room public housing, higher post-secondary educational level, and having 3 or more medical comorbidities.</p> <p>From this study, it was found that depression was not associated with gender, marital status and religion.</p>
<p>NMRC/0573/2001</p> <p>PI: Chua Hong Choon (IMH)</p> <p>Collaborators: Rathi Mahendran, Ng Tze Pin, Lee Theresa Mei Ying</p>	<p>An epidemiological Study of depression in Singapore.</p> <p>This landmark epidemiological study set out to determine the lifetime and recent prevalence of Depressive Disorders (Major Depressive Disorder and Dysthymia) in the adult population. A random sample, stratified by ethnicity, of adults aged 20-59 living in the community were screened for the presence of mental health disorder by using the General Health Questionnaire (GHQ-12). Individuals who scored ≥ 2 were administered the Schedule for Clinical Assessment in Neuropsychiatry (SCAN). This generated the DSM-IV diagnoses of Anxiety and Depressive Disorders. Of the 3875 individuals contacted, 2847 consented to participate in the study (Response Rate = 75.2%). The overall population weighted recent prevalence of Depressive Disorders was determined to be 4.9% (95% C.I. 3.7 – 6.2%) and lifetime prevalence of Depressive Disorders was determined to be 5.6% (95% C.I. 4.3 – 6.9%). Only 49.1% of individuals with mental health disorders (Anxiety and/or Depression) had sought any kind of mental health services. The most common sources for mental health services were General Practitioners, Psychiatrists, and Clergy. This study showed that depressive disorders continue to significantly affect the adult population of Singapore.</p> <p>These important findings should drive effective allocation of resources for disease management. Early detection of these disorders in sub-populations at higher risk should result in improved treatment outcomes and reduced disability.</p>
<p>NMRC/0588/2001</p> <p>PI: Goon Teik Jin Anthony (NSC)</p> <p>Collaborators: Goh Chee Leok, Ng See Ket, Leow Yung Hian</p>	<p>The atopy patch test to aeroallergens and pityrosporum orbiculare in patients with atopic dermatitis</p> <p>The full article is still being written. Currently data is with the statistician for further analysis. Partially-written article thus far has been attached.</p> <p>The role of allergy in atopic dermatitis is still controversial. The atopy patch test (APT) has been used to investigate the association between atopic dermatitis and aeroallergen allergy.</p>

	<p>This study aimed to determine the proportion of atopic dermatitis patients with positive patch tests to common local aeroallergens and to compare this to a control group.</p> <p>The researchers performed the APT, skin prick tests and IgE RAST tests on 73 atopic dermatitis patients and 38 non-atopic controls. The allergens used were house dust mite, cat dander, Bermuda grass and German cockroach.</p> <p>This study showed that only the APT for house dust mite showed a significant difference between the two groups. APT for house dust mite correlated with the RAST test, while APT for cat fur correlated with the SPT.</p> <p>This study concluded that the APT may be useful to evaluate aeroallergens in atopic dermatitis but work remains to be done to make it more reliable.</p>
<p>NMRC/0589/2001</p> <p>PI: Chong Siow Ann (WH/IMH)</p> <p>Collaborators: Verma Swapna Kamal, Sitoh Yih Yian</p>	<p>Correlation of the duration of untreated illness with structural brain abnormalities and cognitive impairment in patients with first-episode psychosis.</p> <p>The aims of this study were to examine the prevalence and patterns of structural brain abnormalities in minimally treated patients with first-episode psychosis as compared to normal controls and to look at the correlation between these structural brain abnormalities and clinical psychopathology.</p> <p>Consecutive referrals to the Early Psychosis Intervention Program were screened using the Structured Clinical Interview for DSM-IV diagnoses (SCID). A thorough clinical assessment was performed through the use of the Positive and Negative Syndrome in Schizophrenia (PANSS), and Global Assessment of Functioning scales (GAF). Neuropsychological performance was assessed using a cognitive battery of tests measuring cognitive aspects of attention, verbal memory and executive functioning. The duration of psychosis was determined from the time of onset of first psychotic symptoms (based on patient interview, corroborative history from family members and medical records) to the time of definitive diagnoses and treatment. Control subjects matched for age, gender, and handedness were recruited from the general population and screened with the non-patient version of the SCID. Both patients and controls underwent a high resolution MRI scan to evaluate the neuroanatomic substrate of disease.</p> <p>To date, volumes of bilateral, posterior and anterior hippocampal formation have been computed in 27 patients and 16 healthy controls. Compared to controls, the patients had statistically significant smaller mean right hippocampal and right anterior hippocampal volumes. There was a significant gender-by-diagnosis-by-hemisphere interaction for hippocampal volume. Hippocampal volume on the right was significantly smaller in female patients than in female controls. Male patients and male controls demonstrated no significant difference in hippocampal volume.</p> <p>Conclusion: These findings suggest that there may be a unique interaction between gender and the disease processes that lead to reductions in hippocampal volume in patients with schizophrenia.</p>
<p>NMRC/0592/2001</p> <p>PI: Lee Yuan Kun (NUS)</p> <p>Collaborator: Lu Jinhua</p>	<p>Host-bacteria and bacteria-bacteria interactions in human gastrointestinal tract</p> <p>It is the researchers' interest to understand the interaction between the host, probiotic bacteria and invading pathogens, in order to maximize the roles of probiotic bacteria in disease prevention and treatment. Intestinal cell line Caco-2 was used as the <i>in vitro</i> model and the BALB/c mouse used as the animal model. A carbohydrate interference method was developed for the evaluation of the binding property of bacteria on c cell and intestinal mucosal surface. It was reasoned that probiotic <i>Lactobacillus rhamnosus</i></p>

	<p>competes with <i>Escherichia coli</i> and <i>Salmonella</i> spp. through steric hindrance, whereas <i>L. casei</i> interferes the adhesion of the two pathogens through steric hindrance and receptor competition. The approach provided a scientific basis for the screening of potential probiotic bacteria and interpretation of competition for adhesion on human intestinal mucus surfaces. Displacement of adhered pathogens by the probiotics was slower than that of competition and exclusion. That is, probiotics were more effective in the prevention rather than treatment of diseases. The establishment of probiotic and other commensal bacteria in the intestinal tract correlated inversely to the diet dependent genotoxicity of fecal water. The specific growth rate of the probiotic bacteria in the intestinal environment ultimately determined the resident time of the bacteria in the intestinal tract.</p>
<p>NMRC/0594/2001</p> <p>PI: Chung Ching Ming Maxey (NUS)</p>	<p>Proteomics in human diseases: Application to hepatocellular carcinoma(HCC)</p> <p>Proteome analysis of human hepatocellular carcinoma (HCC) tissues was conducted using two dimensional - difference gel electrophoresis (2D-DIGE) coupled with mass spectrometry. Paired samples from the normal and tumor region of resected human liver were labeled with Cy3 and Cy5 respectively while the pooled standard sample was labeled with Cy2. After analysis by the DeCyder-DIA software, protein spots that exhibited at least a 2-fold difference in intensity were excised for in gel tryptic digestion and MALDI-TOF mass spectrometry. A total of 6 and 42 proteins were successfully identified from the well- and poorly-differentiated samples respectively. The majority of these proteins are related to detoxification/oxidative stress and metabolism. Three down-regulated metabolic enzymes, methionine adenosyltransferase (MAT), glycine N-methyltransferase (GNMT), and betaine-homocysteine S-methyltransferase (BHMT) that are involved in the methylation cycle in the liver are of special interest. Their expression levels, especially, MAT, seemed to have a major influence on the level of S-adenosylmethionine (AdoMet), a vital intermediate metabolite required for the proper functioning of the liver. Recent work showed that chronic deficiency in AdoMet in the liver results in spontaneous development of steatohepatitis and hepatocellular carcinoma, and hence the down-regulation of hepatic MAT in the researchers' HCC samples is in line with this observation. Moreover, when a comparison was made between the differentially expressed proteins from the researchers' human HCC samples and from the liver tissues of knockout mice deficient in MAT, there was a fairly good correlation between them.</p>
<p>NMRC/0597/2001</p> <p>PI: Adaikan P. Ganesan (NUS)</p> <p>Collaborators: Ng Soon Chye, Srilatha B.</p>	<p>Mechanism, pathophysiology and possible treatment options for female sexual disorders</p> <p>This project was initiated to identify the mechanisms of female sexual function in normal and postmenopausal animal models and to validate the possible therapeutic replacement and potential of phytoestrogen for sexual dysfunction in menopause. The project studied the functional responses of arousal and desire in rats as determinants of age (hormone) -related changes in sexual behaviour. Objective changes on genital blood flow in rabbits were also studied. In the rat model, the team found that similar to oestrogen, a combination of phytoestrogen isoflavine with progesterone revived normal sexual function or mating behaviour in ovariectomised female rats. The effects of isoflavine phytoestrogens (estrated from red clover) were compared with oestradiol in the rabbit model. The parameters included bone mineral density, uterine weight, body weight, genital blood flow and serum levels of testosterone and oestrogen on ovariectomised and normal rabbits. The researchers' results indicated that the use of red clover isoflavones in hormone replacement therapy could to an increase in bone mineral density, vaginal blood flow and uterine weight and may therefore be a viable alternative to traditional regimens using synthetic oestrogens. With similar mechanistic actions of oestrogens on specific pathways, this therapeutic intervention would replace the loss of positive effects of oestrogen in postmenopausal women while minimizing its negative effects.</p>

<p>NMRC/0598/2001</p> <p>PI: Shen Shali (NUS)</p>	<p>Characterisation and functional Exploration of a novel gene, hepn1, whose expression is down regulated in 79%(72/91) of human hepatocellular carcinoma</p> <p>In a previous pilot study, the researchers had examined genes associated with human hepatocellular carcinoma (HCC) by suppression subtractive hybridization. A novel transcript, designated as hepn1 was discovered in non-cancerous liver. Screening the expression of hepn1 in 91 HCC using RT-PCR, the researchers found that hepn1 was downregulated in 79% (72/91) of HCC (P < 0.001).</p> <p>In this study, the researchers aimed to characterize and explore the functional significance of hepn1 <i>in vitro</i>. The full-length hepn1 cDNA was isolated from normal liver through the technique of RACE (rapid amplification of cDNA ends) and its open reading frame was cloned into expression vectors. Transfection studies were carried out by individually expressing hepn1, V5-fused hepn1, and green fluorescent protein-fused hepn1 in HepG2 cells. Gene hepn1 was mapped to human chromosome 11q24; and the predicted gene product, a 10-kDa peptide with 88 amino acids, had no homology to known proteins. When transfected into HepG2 cells, hepn1 reduced cell viability to 37.5±2.5% (P = 0.001), and induced apoptosis with typical morphological changes as determined by Annexin V assay and fluorescence microscopy. The researchers' data showed that hepn1 is frequently silenced in HCC, and that exogenous hepn1 exhibits antiproliferative effect on HepG2 cells, suggesting that silencing of hepn1 may be associated with hepatocarcinogenesis.</p>
<p>NMRC/0600/2001</p> <p>PI: Halliwell Barry (NUS)</p> <p>Collaborators: Ong Choon Nam, Whiteman Matthew</p>	<p>Is Oxidative DNA damage a predictor of cancer development?</p> <p>This project achieved the development of a new methodology for the analysis of oxidative DNA damage that is suitable for large population studies. Measurement of oxidative DNA damage in an "at risk" population in China showed a relation of levels of oxidative DNA damage to a risk of cancer development.</p>
<p>NMRC/0601/2001</p> <p>PI: Wong Meng Cheong (SGH)</p> <p>Collaborators: Auchus Alexander P., Chang Hui Meng, Chen Christopher Li-Hsian, Xu Mei</p>	<p>The gene expression profile underlying endothelial dysfunction in a microvascular stroke syndrome</p> <p>Endothelial cell dysfunction is a major feature of cerebrovascular, cardiovascular and related diseases. Alterations of endothelial gene expression are believed to underpin this dysfunction. Practical, minimally invasive methods to "probe" endothelial gene transcription for an individual patient are lacking, but have potential to "customize" assessment and pharmacological treatment for an individual at risk of vascular disease. Stroke patients and Controls underwent endothelial cell RNA extraction, following Cutaneous Microvascular Biopsy Laser Capture Microdissection. After reverse transcription and amplification, ds-cDNA were subtractively hybridized to generate clones. Sequence determination, GenBank™, BLAST searches and bioinformatics tools were used for analysis.</p> <p>A differential endothelial gene expression library was established by the researchers. Twenty Up-regulated and five Down-regulated genes were found. Two Novel gene sequences (F147 & F85) were obtained. For novel gene F147, RACE was used to obtain the full length. No obvious ORF was found in the full length. The second novel gene F85 is part of a hypothetical protein. Using <i>in silico</i> methods, the team predicts that F85 is a novel Nuclear Protein, involved in transcriptional regulation of lipid metabolism. Using F85 RNA interference, the team established a cellular knockout model. Following F85 RNAi treatment, cell viability was decreased, particularly at 48 hr and 72 hr.</p>

<p>NMRC/0604/2001</p> <p>PI: Rajan Sandeep Kumar (NCC)</p> <p>Collaborators: Soo Khee Chee, Hong Ga Sze, Khoo Kei Siong, Epstein Richard, Wong Chow Yin</p>	<p>Characterization of clinical and therapeutic outcomes in high-risk primary breast cancers using quantitative measurements of telomerase activation</p> <p>Telomerase is an enzyme that stabilizes telomeres. During the process of malignant transformation, human cancer cells upregulate telomerase activity, thereby stabilizing the telomeric ends of chromosomes and immortalizing tumour cell growth. Telomerase is generally not expressed in somatic cells.</p> <p>In this study, quantitative telomerase expression was studied in 252 snap-frozen primary human breast cancer specimens by a novel RT-PCR based methodology. The enzyme value correlated with stage, 'T' size, 'N' stage, presence of metastases and survival. While the final statistical analysis of this data is underway, some clinically significant outcomes from this translational study are as follows:</p> <ol style="list-style-type: none"> 1. Telomerase expression in primary tumour correlated with the risk of metastases. Therefore the need for extensive staging investigations could be rationalized for overall cost saving. 2. Nodal stage was linked to telomerase expression. Therefore, tumors which express low levels of telomerase tend to have a lower risk of nodal metastases. This may reduce the need for lymph node dissections, hence lowering morbidities associated with lymph node dissections. 3. Tumors which express a low telomerase level generally have a good prognosis. Therefore there is no need for chemotherapy, especially when the tumors are positive for hormone receptors. 4. Tumors which express a high telomerase level generally have a poor prognosis. This is independent of the TNM stage. Hence they are an ideal group for novel therapies. 5. With the emergence of telomerase inhibitors & anti-hTERT immunotherapy, telomerase expression may be a predictive indicator for such therapies.
<p>NMRC/0606/2001</p> <p>PI: Tan Eng King (SGH)</p> <p>Collaborators: Ratnagopal Pavanni, Zhao Yi, Wong Meng Cheong, Lim Erle Chuen Hian</p>	<p>NURR1 gene mutations in Parkinson's disease</p> <p>In this study, the researchers performed sequence analysis of all the exons and exon-intron boundaries in familial and young-onset Parkinson's disease (PD). None of the patients carried any pathogenic mutation in the Nurr1 gene. The team demonstrated a 5 to 10% prevalence of the intron 7 +33 C->T variant among Malay and Indian PD and healthy controls, suggesting that this variant, which was previously described only in 1 Chinese patient, is not a silent mutation but a common polymorphic variant in some ethnic races.</p> <p>The team found three polymorphic loci (c -2922(C)2-3, IVS6 + 18insG and EX8 + 657 (9-10CA)) of the Nurr1 gene in their PD patients. They proceeded to perform a haplotype analysis in a case control study. 202 PD patients and 202 age, gender and race matched controls were studied. The team also found complete linkage disequilibrium between c. -2922(C) 2-3 and IVS6 + 18insG polymorphic loci (D=0.25). There were no differences in the haplotype frequencies between the cases and controls.</p> <p>Using real-time PCR, the Nurr1 mRNA levels in the lymphocytes did not significantly differ between the affected patient and controls.</p> <p>The data provide a strong evidence which suggests that unlike in some White populations, Nurr1 variability does not appear to be associated with PD in the Asian population and hence routine genetic screening is not cost effective.</p>

<p>NMRC/0609/2001</p> <p>PI: Tan Eng Looi Carolyn (KKH)</p> <p>Collaborator: Shanti Wasser</p>	<p>Expression profiling in human biliary atresia in comparison to other paediatric cholestatic disorders</p> <p>The main aim of this project was to identify genes that are differentially expressed or repressed in human biliary atresia and usage of these genes to develop an early detection system for biliary atresia in jaundiced neonates. The team had interrogated 25 Affymetrix Human HG-U133A and 10 Human HG-133B oligonucleotide microarray chips with biotinylated cRNA from 11 biliary atresia, 9 choledochal cyst and 5 other paediatric cholestatic livers. Data mining of the hybridization results using the Affymetrix Data Mining Tool Version 3.0 revealed at least 71 genes that were either more highly expressed or repressed in biliary atresia as compared to choledochal cyst or other paediatric cholestatic livers. Several candidate genes have been analyzed, by RT-PCR, in 21 biliary atresia, 14 choledochal cyst and 10 other paediatric cholestatic to confirm the results of the microarray analysis. In addition, the expression of some of these candidate genes have been analysed in animal models of biliary atresia and hepatic fibrosis.</p>
<p>NMRC/0610/2001</p> <p>PI: Yu Hanry (NUS)</p> <p>Collaborator: Gang Bao</p>	<p>Influence of extra-cellular micro-environment on cellular dynamics for tissue engineering</p> <p>Almost all tissue-engineering applications involve the use of normal and un-transformed mammalian cells. Most of these cells are anchorage-dependent which means that the extra-cellular microenvironment can greatly affect the way these cells behave. Therefore, understanding how the extra-cellular microenvironment influences the dynamic processes in these cells is critical in tissue engineering. Such understanding will allow us to better control the cellular behaviour when cells are seeded to scaffolds for tissue-engineered constructs as well as for large-scale production of un-disrupted cells for cell transplantation. The team have developed and optimized a large-scale non-disruptive three-dimensional culture and harvest system circumventing the conventional detachment requirements for anchorage-dependent mammalian cells commonly used in biomedical applications. The cells harvested from this system demonstrate improved attachment, morphology and functions over conventionally cultured cells, upon binding to ligand-conjugated polymer surfaces. The harvested cells can be re-encapsulated and allowed to proliferate again, or used immediately in applications.</p>
<p>NMRC/0613/2001</p> <p>PI: Jeyaseelan K (NUS)</p> <p>Collaborators: Strong Peter Nicholas, Armugam Arunmozhiarasi, Singh Mulkit</p>	<p>Anti-microbial and anti-parasitic peptides in scorpion hemolymph and venom</p> <p>The utilization of antimicrobial agents has played an important role in decreasing the mortality of certain bacterial/microbial derived diseases. However, the overuse of antibiotics has led to the rapid evolution of bacteria that are resistant to multiple drugs such that even vancomycin, the antibiotic of last resort, is no longer effective against such strains. One extremely promising area of new antibiotic design is the exploitation of natural peptide anti-microbial agents as templates for new therapeutic antibiotics. These agents are host defence molecules which play a key role in innate immunity against microorganisms and other pathogens. To date, more than 100 peptides with this property have been isolated from arthropods and amphibians. Scorpions, like insects fight against bacteria by producing anti-bacterial molecules.</p> <p>In this project, the researchers analyzed and identified the molecules that are responsible for this resistance. Two species of Indian scorpions,</p>

	<p>Mesobuthus tamulus and Heterometrus fulvipes, were evaluated for their anti-bacterial properties. The acidified hemolymphs from the scorpions were fractionated on a SepPak column followed by RP-HPLC. The antibacterial property was tested against a Gram-ve (Escherichia coli) and a Gram+ve (Micrococcus luteus) bacterial strain. Several fractions showed inhibitory effects on the growth of these bacteria. Further studies are required to clone the cDNAs encoding these peptides, express them in large quantities as recombinant proteins and also to test them on a variety of pathogenic bacteria to better evaluate their efficacies as anti-microbial agents.</p> <p>This project also resulted in the identification of peptides from scorpion venom that target Ca²⁺ activated potassium channels and chloride ion channels. These peptides have the potential to be developed into insect toxins.</p>
<p>NMRC/0615/2001</p> <p>PI: Chan Edwin Shih-Yen (CTERU)</p> <p>Collaborators: Suresh Shirley, Poon Choy Yoke</p>	<p>A randomised controlled trial to compare steroid with cyclosporine for the topical treatment of oral lichen planus (renewal)</p> <p>This study aimed to compare the effectiveness of topical steroid and topical cyclosporine in patients with histologically confirmed oral lichen planus. Effectiveness between these two drugs was compared with respect to the alleviation of pain, relief of symptoms, response rate and adverse events.</p> <p>Patients were randomised to receive either topical steroid (triamcinolone acetonide 0.1% in Orabase) or cyclosporine (Sandimmun Neoral containing 100 mg/ml). Medication was applied 3 times a day for 8 weeks. A marker lesion was assessed by visual scoring and grid measurement. Patient assessment of severity of pain and burning sensation were done using a visual analogue scale. Blood tests for patients on cyclosporine were done at 0, 2 and 8 weeks with whole blood cyclosporine levels at 2 and 8 weeks. Follow-up was for 1 year.</p> <p>This trial involved the National Dental Centre (Singapore), Seoul National University (South Korea), Madras Medical College & Government Dental College (India) and Chulalongkorn University (Thailand). The total accrual was 139 patients from the 4 centres.</p> <p>The study commenced in March 1998 and was able to recruit only 139 out of the required 200 patients. The recruitment dateline for this study was 31 December 2002. The data has been analysed and the manuscript is in the process of been submitted to various journals for publication.</p>

<p>NMRC/0616/2001</p> <p>PI: Hooi Shing Chuan (NUS)</p>	<p>Role of histone deacetylases in colorectal carcinogenesis and metastasis</p> <p>Histone deacetylases (HDACs) 1 and 2 share a high degree of homology and are known to co-exist within the same protein complexes. Despite their close association, studies have shown that each possesses unique functions. This project showed that in colorectal cancer, the upregulation of HDAC2 occurred early, at the polyp stage; was more robust and happened more frequently as compared to HDAC1. In cervical carcinoma, both HDACs1 and 2 expressions correlated with the severity of cervical dysplasias and invasive carcinomas. However, HDAC2 expression showed a clear demarcation of higher intensity staining at the transition region of dysplasia. Upon HDAC2 knockdown, cells displayed an increased number of cellular extensions reminiscent of cell differentiation. There was also an increase in apoptosis, associated with an increase in P21 expression. These results suggest that histone deacetylases, especially HDAC2, are important enzymes involved in the early events of carcinogenesis, making them candidate markers for tumor progression and targets for cancer therapy.</p>
<p>NMRC/0619/2001</p> <p>PI: James Goh (NUS)</p> <p>Collaborators: Dietmar Huttmacher Wern, Wong Hee Kit</p>	<p>The efficacy of BMP-7 & TGF-beta1 in directing the transformation of mesenchymal stem cells into bone - an in vitro study</p> <p>The goal of the project was to evaluate the quality and rate of formation of bone when bone marrow mesenchymal stem cells were exposed to rhBMP-2, in a biodegradable polymer scaffold <i>in vitro</i>. The project aimed to evaluate the effective dosage of rhBMP-2 to differentiate bone marrow mesenchymal stem cells from rabbits into bone tissue. There were 3 experimental groups: one consisted of cells alone with the carrier, one with rhBMP-2 (10ng/ml) and cells together with the carrier and the last group with rhBMP-2 (100ng/ml) and cells together with the carrier. The different mixtures were contained in a polycaprolactone-tricalcium phosphate (PCL-TCP) biodegradable polymer scaffold. Histological analyses were then performed to determine the rate and quality of bone formation at 7, 14, 21 and 28 days. It was found that rhBMP-2 is capable to differentiate bMSCs. It was observed that 100 ng/ml of rhBMP-2 was the most stimulative of differentiation as it produced the most amount of osteocalcin 7 days after stimulation. An important observation was that PCLTCP scaffolds proved to be osteoconductive, bioactive and non-toxic to cells in-vitro. Notably, PCL-TCP scaffolds seeded with differentiated bMSCs could sustain osteogenic expression in-vitro. Hence, the synergy of a purely osteoconductive PCL scaffold with bioactive TCP and rhBMP-2 could offer an exciting approach for bone regeneration.</p>
<p>NMRC/0620/2001</p> <p>PI: Wong Philip (NHC)</p> <p>Collaborators: Lim Soo Teik, Chew Steven, Lim Yean Leng, Gunasegaran Kurugulasigamoney, Chuah Seng Chye, Koh Tian Hai</p>	<p>Acetylcysteine in the prevention of Renal Impairment in Coronary Procedures (APRICate)</p> <p>It is known that administration of radiographic contrast during cardiac catheterisation and percutaneous coronary intervention (PCI) can cause contrast-induced nephropathy (CIN) in patients with chronic renal failure (CRF).</p> <p>The aim of this randomized, placebo-controlled study was to establish whether pre-treatment with oral NAC can prevent CIN in patients with CRF (baseline creatinine > 150 µmol/L). The patients in the NAC group received NAC 600mg BD (diluted in 50 mls of isotonic drink) for 3 days. All patients received intravenous hydration with 0.45% normal saline. Serum urea and creatinine were measured before, 24 hours & 48 hours after the procedure. The primary endpoint was the development of CIN (increase in serum creatinine > 25% above baseline, or >50µmol/L, 48 hours post-procedure).</p> <p>38 patients were recruited by April 2004, but data from 8 patients were</p>

	<p>incomplete for various reasons. The baseline clinical characteristics between the two groups were similar; with the exception of more biguanide use in the NAC group. There was no significant difference in CIN incidence in both groups; CIN occurred in 3 of 13 patients in the NAC group, and in 0 of 17 patients in the placebo group (p=0.07).</p> <p>From the results obtained, the researchers concluded that NAC did not prevent contrast-induced nephropathy.</p>
<p>NMRC/0630/2002</p> <p>PI: Lo Ngai Nung (SGH)</p> <p>Collaborators: Divakaran Sheeja Tay Beng Kang</p>	<p>Investigation of low wear rate sliding pair for loaded orthopaedic bearings</p> <p>One of the current orthopaedic implants of metal sliding against UHMWPE produce relatively high wear debris from the polymer surface and this leads to failure of the implant after few years. Hence artificial joints with Co-Cr-Mo sliding against Co-Cr-Mo have been developed to overcome the polymer wear problem. However, there is uncertainty of Cr dissolution, potential carcinogenicity and whether it causes wear. In order to overcome the above drawbacks, the researchers studied the feasibility of DLC coating on one or both the sliding surfaces.</p> <p>The adhesion of DLC coating on different orthopaedic materials was studied and it was discovered that unlike SS 316L and Cr-Co-Mo alloy, Ti and Ti-alloy were not good substrate materials for DLC coating. Subsequently the researchers went on to investigate the tribological behaviour of DLC coated Co-Cr-Mo against uncoated UHMWPE. However, the results suggested that the friction and wear of DLC coated Co-Cr-Mo slid against UHMWPE did not show any favorable improvement over that of uncoated Co-Cr-Mo. Hence the researchers evaluated the tribological performance of DLC coated metal (Co-Cr-Mo) /metal (Co-Cr-Mo) sliding pairs. A detailed tribological evaluation of DLC sliding against DLC revealed that low stress single-layer DLC sliding against the same material would make a perfect sliding pair with low friction and wear. Since the DLC against DLC exhibited good tribological behaviour, the researchers also evaluated the tribology of DLC coated UHMWPE against DLC coated Co-Cr-Mo. The results were found to be excellent and suggested that DLC coatings on the sliding surfaces of Co-Cr-Mo/UHMWPE would also prolong the lifetime of Co-Cr-Mo/UHMWPE.</p>
<p>NMRC/0635/2002</p> <p>PI: Whiteman Matthew (NUS)</p> <p>Collaborators: Halliwell Barry, Das De Shama,l Goh Cho Hong James</p>	<p>Nitric Oxide and peroxynitrite in ageing: Mediators of bone and cartilage damage in osteoporosis and osteoarthritis?</p> <p>Nitric oxide (\bulletNO) and peroxynitrite (ONOO\cdot) are important mediators of bone and joint cell functions. In chondrocytes, \bulletNO mediates apoptosis and inhibits cartilage synthesis. In bone, \bulletNO stimulates osteoblast differentiation and inhibits osteoclastic bone resorption. However, the effects of \bulletNO can be controlled by superoxide (O$2\bullet$-) through the formation of the cytotoxic agent peroxynitrite (ONOO\cdot). The effects of ONOO\cdot on bone and joint function are unknown. ONOO\cdot formation <i>in vivo</i> can be detected by measurement of its bio-marker, 3-nitrotyrosine and elevated levels of this nitrated amino acid are observed in several bone and joint disorders. Hence, this team aimed to investigate the interaction of \bulletNO, O$2\bullet$- and ONOO\cdot and the mechanisms of cell death by using human cells in culture.</p> <p>The major and novel findings of this project were: (1) ONOO\cdot induces extensive mitochondrial dysfunction, mitochondrial permeability transition, calcium overload and apoptotic cell death by a</p>

	<p>mechanism(s) that does not involve caspase but calcium-dependent cysteine proteases (calpains) (2004; FASEB J. 18, 1395-1397)</p> <p>(2) ONOO⁻-modified extracellular matrix components could illicit a cell response through a p38 / ERK1/2–NF-κB pathway forming IL-1β, TNF-α, PGE2 and •NO; components well documented to modulate bone resorption, ECM degradation and inflammation. (2005; J. Bone Min. Res. In prep; 2005; Arthrit. Rheum. In prep).</p> <p>(3) NO2Cl, an additional reactive nitrogen species formed in the joint is not cytotoxic (2002; Proc. Natl. Acad. Sci. USA. 99, 12061-12066) and (2003; Arthrit. Rheum. 48, 3140-3150) and unlikely to be a contributor to the extensive tyrosine nitration observed in the joints of OA patients (2003; J. Biol. Chem. 278, 8380-8384)</p>
<p>NMRC/0641/2002</p> <p>PI: Chua Hong Choon (IMH)</p> <p>Collaborators: Lim Eng Choon Leslie, Fones Calvin Soon Leng, Ng Tze Pin, Kua Ee Heok</p>	<p>Anxiety Disorders in Singapore: A community survey</p> <p>This landmark epidemiological study set out to determine the lifetime and recent prevalence of Anxiety Disorders (Generalised Anxiety Disorder, Panic Disorder, with and without Agoraphobia, and Social Anxiety Disorder) in the adult population. A random sample, stratified by ethnicity, of adults aged 20-59 living in the community were screened for the presence of mental health disorder with the Genral Health Questionnaire (GHQ-12). People who scored more than or equal to 2 were administered the Schedule for Clinical Assessment in Neuropsychiatry (SCAN). This helped to generate the DSM-IV diagnoses of Anxiety and Depressive Disorders. Of the 3875 individuals contacted, 2847 consented to participate in the study (Response Rate = 75.2%). The overall population weighted recent prevalence of Anxiety Disorders was determined to be 2.3% (95% C.I. 1.6 - 3.1%) and lifetime prevalence of Anxiety Disorders was determined to be 3.4% (95% C.I. 2.4 - 9.3%). Only 49.1% of those with mental health disorders (Anxiety and/or Depression) had sought any kind of mental health services. The most common sources for mental health services were the General Practitioners, Psychiatrists, and Clergy. This study showed that anxiety disorders continue to significantly affect the adult population of Singapore. These important findings should drive effective allocation of resources for disease management. Early detection of these disorders in sub-populations at higher risk should result in improved treatment outcomes and reduced disability.</p>
<p>NMRC/0642/2002</p> <p>PI: Lee Yuan Kun (NUS)</p> <p>Collaborators: Ng Mah Lee Mary, Lim Chor Kiang, Kwang Jimmy</p>	<p>Gene expression and colonization of lactic acid bacteria in gastrointestinal tract.</p> <p>The researchers aimed to study the suitability and feasibility of lactic acid bacteria as antigen delivery vehicles for oral immunization purpose.</p> <p>Fluorescein labeled Lactobacillus casei (LcS) was fed to BALB/c mice. The bacterial cells were recovered from various sections of the intestinal tract, and the residential time of the bacterium was in the order of duodenum, colon, jejunum and ileum, with the average doubling time being 4.10, 5.59, 4.8 and 4.56 days respectively. A 75 kDa fragment of transmissible gastroenteritis coronavirus (TGEV) spike glycoprotein S was cloned into a Lactobacillus/E. coli shuttle vector whereby the expression and secretion of the glycoprotein S from the recombinant lactobacilli was detected via immunoblotting. Oral immunization of Balb/c mice with the recombinant LcS induced both local mucosal and systemic immune responses against TGEV, attaining the maximum titers at 32 days post oral intubations. The induced antibodies demonstrated neutralizing effects on TGEV infection.</p> <p>The study indicates that lactobacilli are potential vaccine delivery vehicles for coronavirus antigens.</p>

<p>NMRC/0646/2002</p> <p>PI: Lee Yuan Kun (NUS)</p> <p>Collaborators: Ooi Eng Eong, Tan Tinh-Hui Esther</p>	<p>Ecology of Legionella in Singapore</p> <p>The main objective of this project was to study the distribution of Legionella in natural and man-made water sources in Singapore. Three methods of detection were used in the qualitative study of the distribution of Legionella: (i) multiplex PCR, (ii) immunofluorescence, and (iii) culture method.</p> <p>In total, 61 samples were taken from 51 random sites distributed around Singapore. Legionella was found to be ubiquitous in the environmental water bodies and there was no obvious localization of Legionella on this island. Equal ratio of L. pneumophila serotype 1 and serotype 2-14 was isolated. One L. pneumophila of serotypes which did not belong to serotype 1-14 was isolated.</p> <p>The existence of Legionella in these water bodies was not affected by its brackishness and by whether the water body was man-made or not. However, the culturability of L. pneumophila of all serotypes except serotype 1 was enhanced in man-made water bodies, while L. pneumophila serotype 1 was the prevailing strain in brackish water of low salinity. Native microorganisms appeared to serve as effective amplifiers for Legionella.</p> <p>This study has important implication in effective management of water sources for preventing the dispersion of pathogenic Legionella serotype 1.</p>
<p>NMRC/0652/2002</p> <p>PI: Kwek Kenneth (KKH)</p> <p>Collaborators: Yeo Seow Heong, George Zakar Tamas, Read Mark, Walters William</p>	<p>The evaluation of the isoprostane, 8-Epi-prostaglandin F2a in placental pathophysiology</p> <p>This study aimed to investigate the vaso-active effects of an isoprostane upon pregnant myometrial vasculature, and to compare this with the effects on placental vasculature. This is important as recent studies suggest that unchecked cellular oxidation and lipid peroxidation result in increases in isoprostanes which could play a major role in the pathophysiology of pre-eclampsia and other vascular diseases.</p> <p>The researchers' experiments were conducted using a small vessel myograph, and confirmed the vaso-active effects of the isoprostane in the placental vessels. Myometrial (systemic) vessels displayed an increased responsiveness to the isoprostane, with a similar maximal contractility as placental vessels. This suggests a possible pathophysiological role of isoprostanes in vascular diseases such as pre-eclampsia.</p> <p>The researchers also initiated the novel investigation of whether the isoprostane affected myometrial contractility as this indirectly affects uterine and placental blood flow, and could also suggest a pathophysiological role in preterm labour. The team found that the isoprostane is a potent stimulator of myometrial contractions, and can elicit a significant increase in contraction amplitude and a slightly increased contraction frequency.</p> <p>This study was completed and validated while the PI was in Australia and the data has been published in the journal Placenta* and has been presented at several local meetings and an international meeting (Annual Pacific Rim Meeting on Perinatal Medicine 2002, in Australia)</p> <p>The novel use of a small vessel myograph to study myometrial contractility has led to a second project evaluating the effects of alpha-adrenoceptor agonists on myometrial contractility. The manuscript has been accepted for publication in the journal Anaesthesia.</p> <p>* Vasoactive effects of 8-epi-prostaglandin F(2alpha) in isolated human placental conduit and resistance blood vessels in vitro. Placenta. 2001 Jul;22(6):526-33.</p>

<p>NMRC/0668/2002</p> <p>PI: Melendez Alirio J. (NUS)</p>	<p>Studies on the anaphylatoxin activation of neutrophils and macrophages through their C5a receptor</p> <p>Anaphylatoxins activate immune cells to trigger the release of proinflammatory mediators which can lead to the pathology of several immune-inflammatory diseases. However, the intracellular signaling pathways triggered by anaphylatoxins on immune effector-cells are not well understood. The central theme of this project was to examine the intracellular signaling pathways initiated by C5a stimulation in myeloid cells and relate these to the changes in intracellular calcium concentrations, NADPH oxidase activity, PKC activation, Sphingosine kinase activation, cytokine production/release, degranulation and cell motility. The researchers utilized a wide range of biochemical, molecular and cell biology techniques in order to uncover the intracellular molecules involved in the C5a triggered responses.</p> <p>These researchers were the first to discover that the intracellular signaling molecule SPHK1 (sphingosine kinase1) plays a key role in C5a-triggered intracellular signaling pathways coupled to the physiological responses in human neutrophils. The researchers demonstrated that C5a receptor activation rapidly stimulates sphingosine kinase activity in primary human neutrophils and human macrophages. The researchers also showed that SPHK1 is important for Ca²⁺ release from internal stores (triggered by C5a), degranulation, activation of NADPH-oxidative burst, chemotaxis, and cytokine production.</p> <p>These findings were published last year in high-impact international journals (The Journal of Biochemical Biology, and the Journal of Immunology), and another article is currently under review.</p> <p>These results suggest that SPHK1 plays an important role in the immune-inflammatory pathologies triggered by anaphylatoxins, and points out SPHK1 as a potential therapeutic target for the treatment of diseases associated with neutrophil and macrophage hyper-activation.</p>
<p>NMRC/0672/2002</p> <p>PI: Yu Hanry (NUS)</p> <p>Collaborator: Kuleshova Lilia</p>	<p>Vitrification of hepatocyte spheroids and encapsulated hepatocytes</p> <p>Cryopreservation permits pooling of donor cells to reach a critical cell number and the transportation of these cells to different locations for patient use. A current approach to cryopreservation involves formation of ice crystals that compromise cell survival and a controlled rate machine. However, the medical cost associated with the “freezing” machine is high. Vitrification is another efficient approach that has not been previously explored and reported because the development of vitrification involves special knowledge of the nature of low temperature biology and expertise in composing solutions, cryomedical technology.</p> <p>These researchers developed a way to achieve vitreous cryopreservation of complex tissue-engineered structures such as hepatocytes cultured in novel microencapsulated system. The researchers also developed a vitrification protocol in which containers with pre-treated encapsulated hepatocytes could be directly immersed into liquid nitrogen. The vitrification treatment had no impact on viability of cells and capsule survival rate was 100%. It is the first time that high numbers of tissue engineered constructs can be preserved by vitrification simultaneously with high efficacy. A practical benefit of developed vitrification procedure is that it is less time consuming since it involves direct immersion into liquid nitrogen (-196°C) without sophisticated and expensive cooling equipment, making the method easy to use clinically.</p>

<p>NMRC/0675/2002</p> <p>PI: Ho Ting Fei (NUS)</p> <p>Collaborators: Lee Ee Lian, Seow Mollie, Liow Pei Hsiang, Cheng Eng Teck Samuel</p>	<p>Prevalence and clinical study of eating disorders in young females</p> <p>The hypotheses of this study include:</p> <ol style="list-style-type: none"> 1) Prevalence of eating disorders (ED) in young females in Singapore is as high as that in the West. 2) Various psychosocial and cultural factors are positively correlated with preference for thinness or the development of ED 3) Clinical or physiological parameters correlate with the severity of ED <p>The study cohort consisted of 4461 females (ages 12-26 years). In Phase I of the study, questionnaires (EAT & EDI) were used to identify those at risk of eating disorders (ED). Assessment of the socio-demographic, psychological and behavioural characteristics, attitudes towards eating, dieting and body image of the subjects were also done. In Phase II, clinical, nutritional and diagnostic assessments (EDE) were conducted on individuals who were at risk of having ED. Age specific controls were also included in Phase II.</p> <p>Some preliminary results done by these researchers indicate that:</p> <ol style="list-style-type: none"> (i) Prevalence of individuals who were at risk of getting ED (7.4%) is comparable to that of the West (ii) Significant personal and behavioral risk factors may predispose young females to ED <p>Ongoing analyses of data will give further insight into the clinical presentation of those at risk and those with ED. Accomplishments by these researchers include the publication of findings from this study in several local and international conference papers which have been or will be presented/ published in 2004 and 2005.</p>
<p>NMRC/0678/2002</p> <p>PI: Tachibana Shinro (NUS)</p> <p>Collaborators: Rama Sethuraman, Joseph Tessa, Siau Chiang, Lee Tat Leang, Wong Peter Tsun Hon</p>	<p>Characterization of clinically significant peptides present in human cerebrospinal fluid (CSF)</p> <p>In this study, the peptides fractions of CSF samples obtained from chronic pain patients were purified by an ODS analytical column followed by a microbore Phenyl column. The purified peptides were so unstable that even at -30 °C, the researchers were unable to obtain any sequences by mass sequencing. Eventually, the researchers were able to find some compounds which could stabilize these peptides, and this allowed them to sequence four peptides, which they have tentatively assigned as #54(Met-O of #55), #55, #56 and #68. Although the first three peptides were partial sequences of some known proteins, but their physiological roles have yet to be elucidated. #68 is a new peptide. Spontaneous locomotion monitoring systems were set up in mice for screening. The CNS activities of the many fractions obtained from HPLC purification steps were studied by intracerebral ventricular (icv) administration. A new quantitative HPLC method for physiological amino acids present in CSF was developed, which allow them to analyze 23 amino acids including GABA, taurine and citrulline in CSF. This method has been published in the journal Clinical Chemistry. Using labor pain as an acute pain model, the researchers compared the amounts of these amino acids in women at term pregnancy with pain versus no-pain (control).</p> <p>The researchers' results showed that at least two mechanisms, with and without nitric oxide were being involved in mechanism of labor pain (manuscript submitted to Anesthesiology).</p>
<p>NMRC/0743/2003</p> <p>PI: Cheung Yin Bun (NCC)</p> <p>Collaborators: Thumboo Julian, Wee Joseph Tien Seng,</p>	<p>Variability of health-related quality-of-life scores in cancer patients: A comparative study of three major instruments</p> <p>Sample size requirements depend critically on the variability of the outcome measures. This study aimed to assess variability and sample size requirements of the three major quality of life questionnaires in oncology research, namely, the FACT-G, FLIC and EORTC QLQ-C30. The</p>

<p>Khoo Kei Siong, Goh Cynthia Ruth Nee Fung</p>	<p>researchers conducted a randomized experiment in which about 1300 cancer patients filled out two of the three questionnaires. Quality of life as measured by EORTC QLQ-C30 tend to show larger coefficient of variation, smaller effect size, and lower reliability over time than that measured by the FACT-G and FLIC. Using the EORTC QLQ-C30 may require a sample size 57% and 33% larger than using the FACT-G and FLIC respectively. In addition, the researchers' analysis confirmed the equivalence of the Chinese and English versions of the questionnaires, with a few exceptions of small differences. These researchers also found that interviewer-administration tended to biased upward the estimate of quality of life. Last but not least, the researchers found that the pattern of response and non-response to a question about sexual life was very different between the Singaporean and western populations, and that the commonly used algorithm for imputation of missing values is likely to be biased.</p>
<p>NMRC/SRG/002/2003</p> <p>PI: Bishop George D (NUS)</p>	<p>Public understanding and responses to Severe Acute Respiratory Syndrome (SARS): A cross-national comparative Study</p> <p>This project was concerned with public responses to the 2003 SARS outbreak and its aftermath. The objectives of this project were to examine the beliefs and behaviours of members of the lay public towards SARS using data collected in both affected and unaffected areas during the SARS outbreak as well as one year later. In line with these objectives surveys were conducted using questionnaire protocols developed by an international consortium of behavioural sciences researchers recruited during the outbreak by the PI.</p> <p>Results of these questionnaires showed that, although there were significant differences in responses to SARS between affected and unaffected areas, by and large, the understanding and response to SARS was realistic both during the outbreak and one year later. Examination of coping strategies indicated that people tended to use more passive strategies as compared to active ones. Worry appeared to be a key factor in perceptions and responses to the outbreak with those highest in worry being the ones most likely to take precautions as well as to avoid specific groups of people. Finally, comparison of responses to SARS with responses to other diseases indicated that responses to SARS were reflective of individual's characteristic ways of dealing with disease threats.</p>
<p>NNI/0004/1999</p> <p>PI: Sitoh Yih Yian (NNI)</p>	<p>Functional MRI reading in normal and dyslexic subjects</p> <p>The researchers applied fMRI to study the neuroanatomical substrates involved in reading English and Chinese, both in normal subjects and in those with developmental reading disability ie dyslexics.</p> <p>With the advent of very high field 3T MRI and its superior image acquisition, the study which was initially intended to be performed on a 1.5T MR system has been transferred to the new 3T platform. Language fMRI paradigms have been incorporated into the more advanced fMRI audio-visual system on the 3T system at the NNI. These have been successfully used in both research and clinical cases, especially in the pre-surgical planning for epilepsy surgery, tumour and arteriovenous malformation surgery. With further system upgrades to the 3T scanner completed, novel fMRI scans using parallel imaging or SENSE technology with less image distortion and in a faster scan time have been acquired successfully and have now become routine. This is important for patient/subject comfort arising from a shorter scan time. Another emerging new MR technique, diffusion tensor imaging (DTI), has also been added to the fMRI protocol whereby the major connecting white matter fibre tracts are delineated non-invasively with both clinical and research relevance.</p> <p>Data incorporating both fMRI and DTI with MR tractography have been presented at premier international conferences such as the Human Brain</p>

	<p>Mapping Conferences in 2003 and 2004, as well as the Annual Meeting of the International Society for Magnetic Resonance in Medicine - Technologists Section 2004. Other presentations at the National Healthcare Group Annual Scientific Congress 2003 and SingHealth Scientific Congress 2004 locally were made, with the NHG 2003 work shortlisted as one of the Finalists for the Best Oral Presentation for Scientific Paper in the Surgery category. 3 papers on various aspects of the work have been published (one local and two international journals). Two other manuscripts to international journals have generated favourable reviews. Final revisions to the researchers' work are in process.</p>
<p>NNI/0008/2000</p> <p>PI: Soong Tuck Wah (NNI)</p>	<p>Molecular studies of voltage-gated calcium channel disorders and examination of possible endogenous ligands</p> <p>The objectives were to understand the function of voltage-gated calcium (Cav) channels in physiology and in channelopathies, and to search for possible endogenous ligands from brain extracts.</p> <p>The researchers investigated the proteomic diversity of the Cav 1 subunit generated by alternative splicing and employed Fugu genomics to identify transcriptional regulatory elements. Using transcript-scanning and patch clamp electrophysiology, the researchers have identified a vast array of splice variants of the Cav1.2 and Cav2.1 channels. The splice variants demonstrated altered biophysical properties and one alternatively spliced exon exhibited cell-specific localization it underlies a key shift in activation potential in smooth muscle. These results are important references for understanding the dynamic expression of the plethora of Cav channel proteomic variations and will contribute to our understanding of the fine-tuning of channel functions to specific neurophysiological signals. Using SSCP, dHPLC and DNA sequencing methods, we have probed the genes of skeletal muscle potassium, calcium and sodium channels and sodium/potassium ATPase for mutations, but found no association with Thyrotoxic Periodic Paralysis. Nonetheless, the researchers discovered a potassium channel gene polymorphism in which a patient displayed homozygous mutation. Brain extract was subject to HPLC separation and a crude fraction has been shown to inhibit the P/Q-type calcium channel.</p>
<p>NNI/0010/2000</p> <p>PI: Peter Hwang Ying Khai (NNI)</p>	<p>Evaluation of a novel biodegradable nerve guide conduit for peripheral nerve regeneration in an animal model: a pre-clinical study</p> <p>The project aimed to develop an advanced prototype of nerve guide conduits (NGCs), a device used to repair injured nerves. Two innovative approaches have been developed and tested in rats. The first one incorporated a controlled protein release system into the NGC, which provided a sustained effect of nerve growth factors during regeneration of peripheral nerve through NGCs. The second approach adopted a gene therapy concept and used gene delivery vectors to provide long term effects of nerve growth factor. The above pre-clinical, animal studies have generated data which is useful in refining NGC design to meet the requirements in clinical trials, which may serve as the foundation for more multi-centre trials, petition for regulatory approval, manufacturing (GMP) and other actions to make a NGC into useful commercial products. Such a process will be re-iterated for all other generations of the NGC when they are ready for testing.</p>

Annex 2: Abstracts of Completed Projects under NMRC-STB Medical Research Fellowship/Scientist Award in FY2004

<p>Chan Chung Yip (Department of General Surgery, TTSH)</p> <p>Place of training: Northwestern University, Chicago, IL, USA</p>	<p>The molecular biology of pancreatic cancer</p> <p>Through this study, Dr Chan hoped to meet a few objectives. Firstly, he hoped to acquire technical skills and experimental design knowledge, particularly in the fields of molecular biology and functional genomics. He also hoped to explore and identify an area of research interest which had potential for further research and development upon the completion of this programme. Last but not least, he hoped to complete an in-depth study of a research topic as a thesis submission for the MD programme in the National University of Singapore.</p> <p>During the two years in the laboratory, Dr Chan was involved in several projects, out of which the project “<i>In silico</i> and functional characterization of a novel gene discovered in a pancreatic cancer cell model” proved to be the most promising.</p> <p>In this project, genes which had been differentially expressed after treatment with various agents were identified through oligonucleotide microarray. Dr Chan and his co-workers focused on the hypothetical proteins.</p> <p>After transient transfection of non-cancer cells, it was found that cells transfected with one of the hypothetical genes showed differential growth dynamics. This gene was then characterized and was found to be upregulated upon exposure to the phorbol ester TPA. After this, Dr Chan et al cloned and sequenced full length transcripts of this gene using 5’ and 3’ RACE. The full length sequence of this gene has been deposited in the NCBI Genbank. <i>In silico</i> characterization of this novel gene was done, after which the open reading frame and amino acid sequence of the gene was deduced. Computational analysis of the amino acid sequence suggested that it conformed to a single-pass transmembrane topology and comparison to its orthologues in mouse and chicken was then made. Dr Chan et al then investigated the mechanism of induction of this gene upon exposure to TPA. It was found that pretreatment of the gene with actinomycin D did not change degradation kinetics of the message after induction with TPA. With the help of a reporter gene luciferase assay, it was found that the mode of induction was at the promoter level. The above findings have been published in BBRC.</p> <p>The next step was to perform functional characterization of the novel gene which the researchers had named TTMP (TPA induced TransMembrane Protein). Stable cell lines carrying both the full length protein and a N-terminal truncated protein were established. Interestingly, in cell proliferation assays, the full length protein was found to confer a growth retardation effect as compared to empty vector transfected controls. On the other hand, the N-terminal truncated protein caused an increase in cell proliferation compared to controls. The cell proliferation assays were performed using cell counting and thymidine incorporation studies. Through cell cycle analysis, Dr Chan and his co-workers found that the full length protein induced G1 phase arrest when transfected into pancreatic cancer cell line CD18. When the expressed protein was extracted and analysed on immunoblotting, the full length transcript was found to be of a larger molecular size than predicted. The researchers hypothesized that the protein underwent post-translational modification. Using deglycosylation assays, the protein was seen to be N-glycosylated and further step-wise deletion of the N-terminal showed that glycosylation was present on every asparagine residue on the N-terminal end. Through co-immunofluorescence, the researchers also demonstrated that the protein was localized to the endoplasmic reticulum. This <i>in vitro</i> evidence agreed with the <i>in silico</i> prediction of its intracellular localization. Transcript levels of the protein in various normal tissues were analysed using realtime PCR on cDNA from a commercial source, and interestingly, this was found to be the highest in normal pancreatic tissue. Dr Chan et al are in the process of putting together a second paper based on the above results.</p> <p>A third part of the project was to study the promoter region of the gene. Using deletion constructs of the promoter cloned into the luciferase reporter vector, the core promoter region was identified. Further mutational analysis of the core promoter region showed that 2 putative Sp1 binding sites were responsible for basal activity of the gene. Physical interaction of Sp1 proteins was demonstrated using gel-shift assays.</p>
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**Chuah Thuan Heng
Charles
(Department of
Haematology, SGH)**

**Place of training: Imperial
College London, UK**

Novel combination therapies for selective elimination of CML cells

Chronic myeloid leukemia (CML) is a malignant haematopoietic stem cell disorder characterized by the reciprocal translocation of chromosomes 9 and 22, the molecular consequence of which is the Bcr-Abl oncoprotein. Imatinib mesylate, a tyrosine kinase inhibitor that binds to the ATP-binding site of Abl, has been shown to be therapeutically efficient in all stages of CML. Although imatinib mesylate has revolutionized the treatment of chronic myeloid leukemia (CML), resistance to the drug as relapse after an initial response or persistence of disease remains a therapeutic challenge. In order to overcome this, alternative or additional targeting of signaling pathways downstream of Bcr-Abl may provide the best option for improving clinical response. Bisphosphonates, such as zoledronate, have been shown to inhibit the oncogenicity of Ras, an important downstream effector of Bcr-Abl.

In this project, Dr Chuah examined whether imatinib-resistant CML cell lines and primary CML progenitors exhibit cross-resistance to zoledronate, a third generation bisphosphonate and the effect of the combination of imatinib and zoledronate. He showed that zoledronate was equally effective in inhibiting the proliferation and clonogenicity of both imatinib-sensitive and -resistant CML cells, regardless of their mechanism of resistance. This was achieved by the induction of S-phase cell cycle arrest and apoptosis, through the inhibition of prenylation of Ras and Ras-related proteins by zoledronate. The combination of imatinib and zoledronate also augmented the activity of either drug alone and this occurred in imatinib-resistant CML cells as well. The results revealed that resistance to imatinib is not associated with resistance to zoledronate and the combination of both drugs was additive or synergistic, even in imatinib-resistant cells.

Dr Chuah was attached to the Hammersmith Hospital's Department of Haematology's research laboratory under the supervision of Professor Junia Melo, who has a strong interest in the molecular biology and targeted therapy of CML. The Hammersmith Hospital is the tertiary referral hospital for chronic myeloid leukaemia for London and south England. As such, there is a wealth of clinical and research material in CML. Apart from working on his research project, Dr Chuah also aimed to learn various molecular biology techniques and to gain exposure in a laboratory-based research environment. The techniques which he learnt and became competent at included cell culture, cell proliferation assays, clonogenicity assays, flow cytometry for apoptosis and cell cycle analysis, gene sequencing for mutations, Western blotting and in vivo murine experiments. The results of the work were presented as an oral presentation at the 2003 American Society of Hematology 45th Annual Meeting for which Dr Chuah was awarded an ASH Travel Award. The results have also been recently submitted for publication. Dr Chuah will be submitting his MD thesis soon and will be returning to London for the viva in 2005. Based on the promising in vitro data, a phase I/II clinical trial has been started at the Hammersmith Hospital using the imatinib/zoledronate combination.

**Oo Kian Kwan Kenneth
(NUS)**

**Place of training:
National University of
Singapore, Singapore**

Tissue engineered prefabricated vascularised flaps

In current clinical practice there is a constant demand for autologous tissue in reconstruction. Common sources of autologous tissue used in head and neck surgery include the pectoralis major flap, radial forearm flap, free fibular flap and increasingly the perforator flaps e.g. anteriorlateral thigh flap. Advances in microsurgical techniques have allowed a wider repertoire of autologous tissue transfers with less donor site morbidity. Nevertheless, autologous tissue transfers still result in donor-site morbidity and steep learning curves often limits its use especially in the case of the perforator flaps. Furthermore, the harvested flap requires surgical manipulation in order to obtain the desired morphology whereas prefabrication would address this problem by constructing a three-dimensional (3D) scaffold that matches the defect *before* it is implanted into its vascular pedicle.

Currently, *in vitro* engineered tissue that has been re-implanted *in vivo* are either avascular or thin enough to obtain sufficient nutrients by diffusion from surrounding vessels (e.g. cartilage, artificial skin, blood vessels, heart valves). Tissues that need to be transferred from one part of the body to another as three-dimensional constructs with their own vascular supply need to be prefabricated by either wrapping vascularized soft tissue around the construct or placing a vascular pedicle within the tissue to be transferred so that angiogenic outgrowth may allow successful microvascular transfer subsequently.

Therefore, a distinct alternative would be one which uses tissue engineering techniques. This consists of a vascular supply, scaffold and mesenchymal stem cells to generate a prefabricated flap that can be used to address the many pressing problems that harvesting autologous tissue entails.

Current techniques have shown that prefabricating a soft tissue flap is possible by either using an arteriovenous (AV) shunt loop or an arteriovenous bundle as a vascular carrier. PLGA has been shown to be suitable matrix for seeding human dermal fibroblasts (HDF). Therefore, it is possible that by combining a ligated arteriovenous bundle with PLGA seeded with fibroblasts (i.e. PLGA-HDF), a vascularised soft tissue flap can be produced.

5 nude rats at 12-15 weeks of age were used for the experiment. 3 pairs of PLGA-HDF constructs were sandwiched around the ligated femoral artery and vein of the nude rat. Two pairs of unseeded PLGA constructs were sandwiched around the ligated femoral artery and vein of the nude rat. All sandwiched constructs were carefully wrapped with polycaprolactone sheet to separate the constructs from surrounding capillary ingrowth. 4 weeks after implantation, the constructs were harvested and studied.

This experiment attempted to generate a prefabricated vascularized soft tissue flap *in vivo* by providing vascular supply through an arteriovenous bundle. Dr Oo and his co-worker also wanted to demonstrate the *in vivo* use of PLGA-HDF construct as a suitable construct for generating a prefabricated flap. With this model, it was hoped that tissue of increased size and complexity may be engineered *without* the use of intrinsic soft tissue to generate the flap. Eventually, larger myocutaneous defects may potentially be reconstructed with tissue engineered flaps.

Results showed that all five post-implanted constructs did not demonstrate significant contraction or distortion. For routine histology, capillary outsprouting was clearly demonstrated in all five pedicles, mainly from the venous supply. Cellular proliferation and apparent tissue volume was greater in the PLGA-HDF constructs as compared to the plain PLGA constructs. PLGA fibres were mostly broken down in the HDF seeded constructs as compared to the plain constructs. Masson Trichrome study demonstrated greater collagen formation in the PLGA-HDF constructs as compared to the unseeded constructs. Cell tracer studies indicated that HDFs seeded on PLGA remained viable after 4 weeks of implantation *in vivo*. In conclusion, PLGA-HDF with a vascular pedicle provides a viable tissue engineered prefabricated vascularized soft tissue flap.

<p>Tay Kiat Hong Stacey (Dept of Paediatrics, NUS)</p> <p>Place of training: Department of Neurology, Columbia University, New York and New York Presbyterian Hospital, New York.</p>	<p>(i) Mutation screening in patients with COX deficiency and unknown molecular etiologies</p> <p>53 patients with isolated cytochrome c oxidase deficiency, and no mutations in previously described genes such as the mitochondrial COX subunits, nuclear DNA COX assembly genes such as SURF1, SCO1, SCO2, COX10 and COX15 were screened by single stranded conformational polymorphisms (SSCP) and direct sequencing of COX16, COX19 and PET191 genes. No mutations were found in this group of genes for these patients. The results have been published (SKH Tay, C Nesti, M Mancuso, EA Schon, S Shanske, E Bonilla, M Davidson, S DiMauro. Studies of COX16, COX19 and PET191 in Human Cytochrome c Oxidase Deficiency. Arch Neurol, Arch Neurol. 2004 Dec;61(12):1935-7.). Four patients with novel SURF1 mutations and unusual clinical phenotypes, such as renal presentations with Leigh syndrome, as well as ragged red fibers on muscle biopsy were reported and the paper has been accepted by the Journal of Child Neurology. Also, the researchers reported the finding of early fetal lethality associated with SCO2 mutations, a condition of fatal infantile cardioencephalomyelopathy. The paper has been published (SKH Tay, S Shanske, P Kaplan, S DiMauro. Mutations in SCO2, a COX Assembly Gene, are Associated with Early Fetal Lethality. Arch Neurol 2004, Arch Neurol. 2004 Jun;61(6):950-2.)</p> <p>(ii) Genotype-phenotype studies in patients with MELAS (mitochondrial encephalomyelopathy, lactic acidosis and stroke-like episodes)</p> <p>The clinical phenotype and assessment of mutation load in multiple tissues in 2 families with the rarer T3271C mutation were described and the paper has been accepted by the Journal of Child Neurology. Further publications are pending on 2 families with MELAS A3243G mutation with unusual clinical manifestations, namely large vessel vasculopathy and Kearns-Sayre phenotype. The papers are currently being written.</p> <p>(iii) Molecular genetics and phenotype of patients with muscle glycogenoses</p> <p>2 patients with infantile brancher enzyme deficiency (Glycogen Storage Disease type IV) were studied and the molecular, biochemical and pathological features in these patients were reported. The results have been published in Neuromuscular disorders (Tay SK, Akman HO, Chung WK, Pike MG, Muntoni F, Hays AP, Shanske S, Valberg SJ, Mickelson JR, Tanji K, DiMauro S. Fatal infantile neuromuscular presentation of glycogen storage disease type IV. Neuromuscul Disord. 2004 Apr;14(4):253-60). Also, 3 patients with early onset cardiomyopathy and glycogen deposition in the heart were studied. One patient had GBE1 mutations that are still in the process of being delineated, and the other 2 patients have a new glycogen storage disease. The researchers are currently trying to find the molecular basis for this disease. There were 2 patients with adult polyglucosan body disease and brancher enzyme deficiency, with only one mutation found. The paper has been accepted by Muscle and Nerve. There was a patient with McArdle's Disease (GSD V) who was a manifesting heterozygote. The family is currently being studied still for silent mutations or polymorphisms.</p> <p>Tangible improvements in medical care and treatment:</p> <p>Dr Tay has gained tremendously from the experience of conducting research in mitochondrial disorders and the muscle glycogenoses with Dr Salvatore DiMauro in Columbia University. They are continuing an active collaboration and Dr Tay will be studying patients with similar disorders in Singapore under his advice and guidance. Hitherto these patients have never had a genetic diagnosis made and improvements to Singapore's diagnostic capabilities and more appropriate clinical management of these patients are being done.</p>
<p>Tan Choon Kiat Nigel (Dept of Neurology, NNI)</p> <p>Place of training: Epilepsy Research Centre, University of Melbourne, Australia</p>	<p>Susceptibility alleles and association studies in epilepsy</p> <p>Dr Tan's 8-month long NMRC fellowship was an extension of his HMDP medical fellowship for 2003 at the Epilepsy Research Centre, Melbourne (ERC).. He worked under Professor Samuel F Berkovic, a leading authority on epilepsy genetics. Other investigators involved were A/Prof Ingrid E Scheffer (also from the ERC), Professor John C Mulley and Sarah Heron, who were the molecular geneticists from a collaborating center in Adelaide.</p>

Association studies:

Dr Tan’s research projects involved genetic association studies in the complex epilepsies (as opposed to monogenic epilepsies). Association studies are used to dissect the genetic basis of complex diseases (such as asthma or Parkinson’s disease). The rapid evolution of methodology and statistics in this field implies that conduct of such studies has to be scientifically robust. Replication of initial positive association studies using independent populations is crucial to validate initial reports. This is because methodological inadequacies in earlier studies have led to spurious genetic associations.

Dr Tan’s role in these studies was to design the study methodology, recruit the subjects, and to perform the statistics. Two studies were performed and this involved over 1000 subjects. Both studies were replication studies which aimed to test if published genetic associations were replicable in an independent population, on the basis that the replication study was performed carefully in accordance with recent guidelines.

The first replication study examined the putative association between a silent polymorphism in the drug transporter gene ABCB1 and pharmacoresistance in epilepsy; this project formed the basis of Dr Tan’s NMRC application. Dr Tan and his co-workers did not confirm the findings from a UK group. Their results have been published in Neurology. Their study was also the topic of an editorial on association studies in the same issue. The second replication study examined the validity of a reported association between a variant in the GABA(B) receptor 1 gene and susceptibility to temporal lobe epilepsy. Dr Tan et al did not find a similar association. The paper will be published later this year. A review paper was also published, summarizing and critically reviewing over 50 association studies in epilepsy.

Familial temporal lobe epilepsy:

Besides association studies in complex diseases, a project was also conducted in a monogenic epilepsy – autosomal dominant familial temporal lobe epilepsy (fTLE). No gene for this condition has yet to be found.

Mutations in both intragenic and promoter regions of the PTEN gene result in autosomal dominant familial cancer syndromes. Epilepsy is also seen in these mutation carriers, though the mechanism is unknown. PTEN knockout mice have seizures and brain malformations similar to those seen in fTLE; Dr Tan’s study hypothesized that unrecognized mutations in PTEN may cause fTLE. Dr Tan and his co-workers screened 41 carefully phenotyped fTLE families for intragenic and promoter region mutations in PTEN; none have been found. The manuscript is currently in preparation.

Benefits:

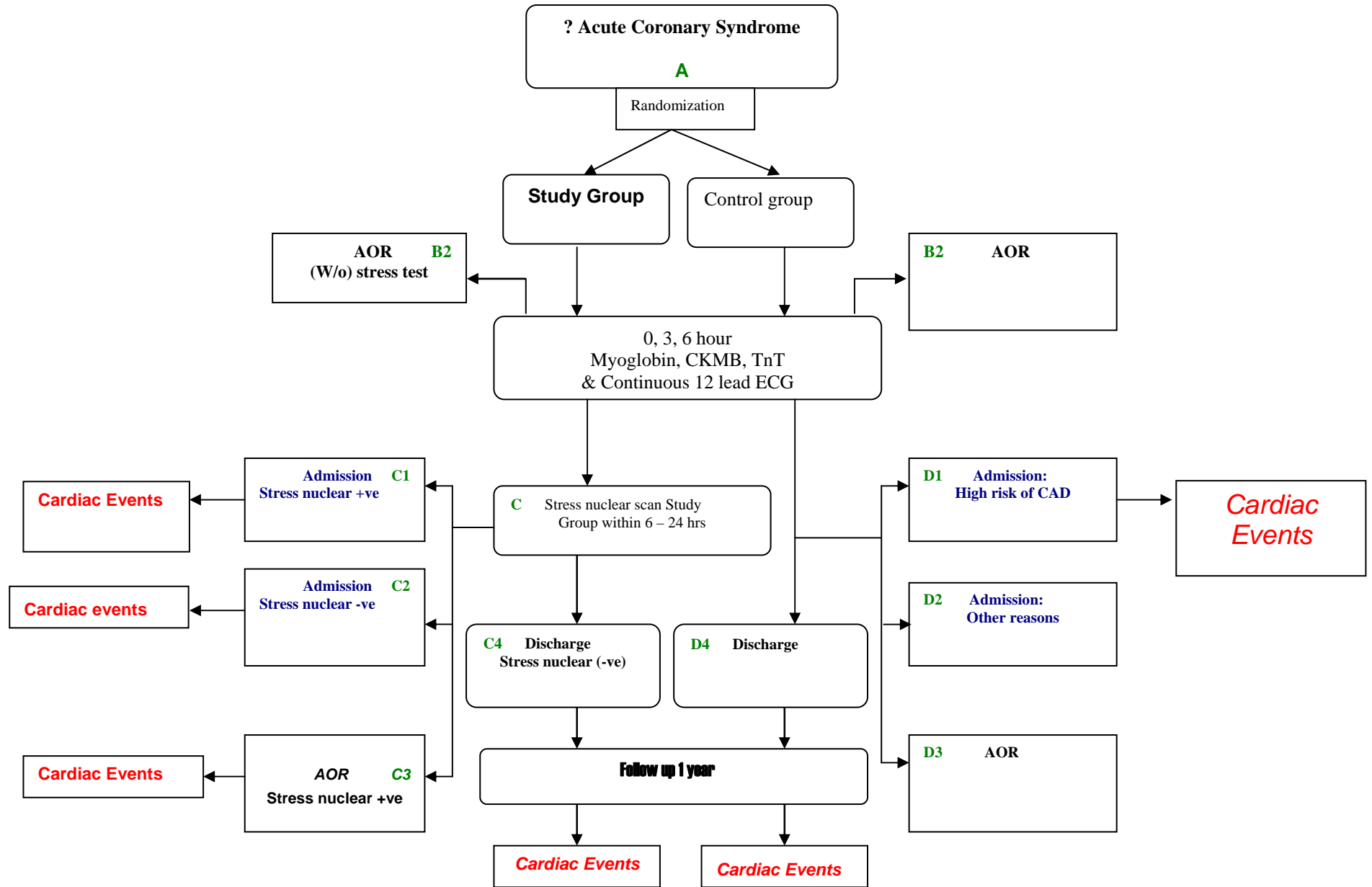
The major diseases that result in the greatest disease burden (diabetes, asthma, stroke, epilepsy) are genetically complex, and dissection of their genetic basis remains challenging. The research experience gained in Melbourne has been invaluable in understanding the genetic basis of complex diseases, as well as designing and conducting association studies to dissect this genetic basis. This will hopefully translate into the ability to conduct similar studies in Singapore, not just for epilepsy, but for other common neurological diseases such as stroke, in conjunction with GIS.

Annex 3: Abstracts of Completed Projects under NMRC-STB Medical Research Travelling Fellowship in FY2004

<p>Associate Professor Au Eong Kah Guan</p> <p>Place of training: Waterford Institute of Technology & Waterford Regional Hospital, Ireland</p>	<p>Macular pigment research attachment</p> <p>The purpose of the Grace Ballas Medical Research Travelling Fellowship was to study the set-up of a Macular Pigment Laboratory and to learn relevant techniques related to macular pigment research in the Waterford Institute of Technology and Waterford Regional Hospital in Waterford, Republic of Ireland.</p> <p>During the attachment, A/P Au learnt and practiced two different methods of measuring macular pigment levels clinically in patients: one using the maculometer and the other, Raman spectroscope. A/P Au also observed the follow-up visits of patients participating in a clinical trial on dietary supplementation of macular pigment. In addition, A/P was also introduced to laboratory equipment and techniques used to measure serum lutein and zeaxanthin (the macular pigments) as well as other carotenoids.</p> <p>A/P Au found this attachment useful because it gave him a good overview of macular pigment research and familiarity with the 2 equipment used for clinical measurement of macular pigment levels. He plans to start a Macular Pigment Laboratory to conduct macular pigment research in Singapore and has obtained a small NMRC grant to purchase equipment that measures macular pigment.</p>
<p>Mr Lim Kok Chye, Alex</p> <p>Place of training: HUGO International Centre for life, Newcastle, UK</p>	<p>4th HUGO 2004 mutation detection training course</p> <p>The 4th HUGO 2004 Mutation Detection training course was conducted at the International Center for LIFE, Times Square, Newcastle upon Tyne, UK from 3rd to 6th September 2004. The lectures covered the Human Genome Mutation Database (HGMD), RNA-based mutation detection (Genotype to Phenotype) and, Protein Truncation Test (PTT); The laboratory workshop demonstrated on DNA extraction using the <i>GeneCatcher</i> Kit, and single nucleotide polymorphism (SNP) and mutation detection using the ABI 310 capillary electrophoresis system, Denaturing HPLC (DHLPC), Denaturing Gradient gel Electrophoresis, Multiplex Ligation-dependent Probe Amplification, and Pyro-sequencing method. Software Mutation Surveyor and Staden package were demonstrated on mutation sequence analysis and detection of new mutation.</p> <p>Both Human Genome Mutation Database (HGMD) (www.hgmd.org) and Locus-Specific Databases (LSDB) (www.hgvs.org/dblist/dblist.html) are established web sites that contained published gene mutations and comprehensive core data on germ-line mutations associated with human inherited disease. Mutation Surveyor software (SoftGenetics Technologies) is the latest DNA mutation sequence analysis software that detects a mutation in a given DNA sequence precisely and could detect both homozygous and heterozygous for point mutation or base deletions. Protein Truncation Test (PTT) is used in vitro transcription and translation functional assay to monitor mutated proteins generated from mutation cDNA that cause premature translation termination in cell culture. The truncated protein was analyzed by mass spectrometry (MALDI-TOF). High-resolution Thermal Denaturation (Melting) Chemistry (HRTD) mutation detection method used a higher fluorescent saturation dyes like the LC Green to characterize the thermal denaturation (melting) profile of an amplified PCR product which varies depending on the specific DNA mutation in disease. The instrument, HR-1 (Idahotech), is used for DB/HRTD mutation detection</p> <p>Mr Lim's current project involved the identification of a receptor expression in white blood cells and hepatocarcinoma tissues. Mr Lim and his co-workers hoped to sequence the cDNA obtained from RNA present in the white blood cells and hepatocarcinoma tissues. Primers will be designed to</p>

	<p>amplify the full length cDNA so that the sequence of the cDNA could be analyzed by the ABI310 sequencing machine. The sequencing trace data can then be used in conjunction with the Mutation Surveyor programme to identify any point mutation or nonsense mutation (premature termination) in the cDNA gene. Since the cDNA gene contains only exons and no intron, this allows functional assay analysis like PTT Functional assay to be carried out at translation level. This assay could help assess the pathogenesis of such mutation in the receptor, especially in hepatocarcinoma. When the region of mutation on the cDNA is identified, DB/HRTD assay or a real time PCR assay can be used to screen for similar mutation in patients.</p>
<p>Dr Lim Swee Han</p> <p>Place of training: Medical College of Virginia, USA</p>	<p>Collaboration purposes in the area of cost-effective analysis study</p> <p>The aim of this training was to design cost-effective analysis of Acute Chest Pain Treatment and Evaluation Study (ACTION) Trial. Decision on data collection points was also made. (Please refer to the attached flowchart)</p> <p>DATA EXTRACTION</p> <p>Firstly, the entire cost of care per patient during ED visit within the six hours of care for all patients in both study & control was identified. Resident, attending review, investigations – FBC, U/E/Cr/S, CXR, Troponin T 0, 3, 6. ECG 0, 3, 6.</p> <p>Next, the cost per admission for patients admitted was identified. (cost per admission includes all cost for ward, length of stay (LOS), cost ancillary services, overhead and any other costs incurred during the hospital visit)</p> <p>Lastly, each diagnostic resource used by all patients in both study & control group subjects was identified (angiogram, stress echo, stress nuclear, resting echo, resting stress nuclear scan & exercises test) including their cost per test.</p>

FLOWCHART (Collaboration purposes in the area of cost-effective analysis study, Dr Lim Swee Han)



<p>Shim Se Ngie Winston</p> <p>Place of training: University of British Columbia, Canada</p>	<p>3D microscopy of living cells</p> <p>The course offered by the University of British Columbia focused on specialized techniques in cell imaging with latest equipment and techniques in fluorescence microscopy. This included confocal laser scanning microscopy, deconvolution methods, digital image processing and time-lapse imaging of living specimens.</p> <p>This training covered both theory and hands-on experiments. Emphasis was placed on live cell imaging. Special considerations were placed in sample preparation, equipment set-up and image acquisition. Furthermore, dynamic functional imaging, such as calcium imaging was introduced. Multi-photon imaging of live whole animal was also demonstrated. These real-time functional imaging techniques are crucial in understanding the dynamic and kinetic of live cells in disease and normal settings.</p> <p>This course also emphasized on proper processing of the images into meaningful and presentable data. Of particular interest was the demonstration on how data extraction could be carried out from standard imaging procedures using modern imaging software and hardware. This full exploitation of acquired data is most likely to be a driving force in the development of new knowledge, even from already well-studied systems/subjects.</p> <p>This appreciation of the immense power of modern microscopy techniques has implication in most of Dr Shim's morphometry studies, data deconvolution, data measurement/display experiments. Furthermore, there is a plan to set up calcium imaging capability in the Stem Cell Laboratory to study the dynamic changes of calcium levels in stem cells prior to commitment into a particular lineage. This will aid in directed differentiation of stem cells toward cardiomyocytes.</p>
<p>Sim Shao-Jen Llewellyn</p> <p>Place of training: University of Bonn, Germany</p>	<p>Breast MRI and MR-guided breast biopsy</p> <p>Breast MR imaging has gained increasing importance for its ability to diagnosis primary and recurrent breast cancer, for staging and, more recently, for screening of high familial risk women. The latter was one of the 2 major aims of Dr Sim's research. Dr Sim also aimed to develop a method of MRI-guided breast biopsy.</p> <p>For this training, Dr Sim frequently worked with Prof Kuhl. Typically, Breast MRI examinations were performed either on a full-day or half-day basis and approximately 10 cases were done daily. The attending resident would collect the cases at the end of each half-day session to check with Prof Kuhl. Dr Sim learnt the technical aspects of the MRI breast examination performed on a 1.5 Tesla Philips Gyroscan unit from the resident and the MRI technologist who performed and checked the MRI cases in the MRI control room. At the end of each half-day session, Dr Sim would sit with Prof Kuhl who checked the residents' accumulated MRI cases.</p> <p>Dr Sim learnt various aspects of Breast MRI which includes:</p> <ol style="list-style-type: none"> 1) technical requirements and recommendations 2) the pros and cons of different image acquisition techniques 3) common technical pitfalls 4) image interpretation guidelines 5) typical and unusual findings in benign and malignant breast disease 6) established and evolving clinical indications for Breast MRI

	<p>7) influence of hormonal stimulation 8) typical pitfalls and artifacts (and strategies to avoid them)</p> <p>Dr Sim also learnt to operate a new battery-powered vacuum-assisted automatic 10G core needle device. He observed a MRI-guided breast biopsy which was performed using this technique and had some hands-on with the device. However, he did not perform the procedure on a patient. No MRI-guided needle localisation or semi-automatic core needle biopsies were performed while Dr Sim was in the university. However, these techniques are gradually being replaced by the vacuum-assisted core needle biopsy that he had observed.</p> <p>A day was spent with Assistant Prof Claudia Leutner who was in charge of conventional breast imaging, for example, mammography, breast ultrasound and conventional image-guided breast biopsy. Dr Sim sat with her for the screening mammography cases and discussed aspects of breast cancer screening. The discussion also touched on a difficult case where US-guided biopsy was planned for a suspicious MRI-detected breast lesion.</p> <p>From this study trip, Dr Sim also managed to pick up useful tips concerning Breast MRI and MRI-guided breast biopsy from Dr Nuschin Morakkabati. With her help, Dr Sim gained access to their center's digital archive of interesting MRI breast cases (almost 100 of them) performed in their center with histopathological correlation. Most of these cases also had mammographic and sonographic correlation. Dr Sim found this very helpful, especially when Prof Kuhl was away to attend to other matters.</p> <p>Dr Sim felt that the knowledge gained from Prof Kuhl and her faculty would be readily applied in his NMRC research on Breast MRI screening in women with high familial risk of breast cancer.</p> <p>After the study trip to Bonn, Dr Sim is looking into the modification of current Breast MRI scanning protocols in Singapore. He hopes to achieve high quality images as seen in Bonn. He also learnt to interpret breast MRI for such a difficult category of well women with confidence. This helps to improve the positive predictive value of the MRI study and prevents unnecessary breast biopsies and worry for the women involved in the study. Last but not least, Dr Sim and his co-workers have already taken steps to equip themselves with the latest devices seen in Bonn for MRI-guided biopsy to be performed on their own MRI unit under the research setting.</p>
<p>Dr. Srilatha Balasubramanian</p> <p>Place of training: Chonnam National University Medical School, South Korea</p>	<p>Hemodynamic and cell culture models for female sexual dysfunction</p> <p>Summary of Training: There have been limited pathophysiological investigations of female sexual dysfunctions reported in literature so far. An <i>in vivo</i> animal model to study female sexual arousal disorder (FSAD) was developed by Dr. Kwangsung Park, Professor of Urology, Chonnam National University Hospital, Kwangju, South Korea. Dr Balasubramanian found this to be a viable animal model to record physiological and hemodynamic changes in vagina following pelvic nerve stimulation, administration of vasoactive agents/physiological modulators and organic pathological states. The training during the attachment consisted of the following:</p> <p>1. Hemodynamic Study: <i>In vivo</i> experiments were carried out in normal (n=2, control) and diabetic (n=2) female Sprague Dawley rats. Through careful surgical exploration under ketamine-xylazine anaesthesia, the pelvic nerve was stimulated using a bipolar platinum wire electrode (7V, 0.8msec and 16Hz delivered for 20 seconds). The laser Doppler flowmeter probe (Transonic Systems #HL-D1021) was positioned inside the vagina and the resting vaginal engorgement (blood flow data) was recorded using PowerLab Chart v.3.6 software. There was simultaneous recording of mean arterial blood pressure. This hemodynamic study indicated that electric field stimulation (EFS) resulted in an increase in mean vaginal mucosal blood flow in the control rats from 14 ml/min/100g in the quiescent state (prior to</p>

	<p>EFS) to 22 ml/min/100g following stimulation. In diabetic rats, the pelvic nerve mediated peak vaginal blood flow was much less indicating the negative impact of this metabolic disorder on female sexual function.</p> <p>2. Primary Cell Culture and Cyclic Adenosine Monophosphate and cyclic Guanosine Monophosphate Assays: Clitoral biopsies were obtained from consenting women undergoing clitoroplasty for adrenal hyperplasia. Clitoral cavernosal smooth muscle cells were cultured using Dulbeccos' modified eagle medium (DMEM) fortified with 10% foetal calf serum, antibiotic (penicillin 100units/ml and streptomycin 100µg/ml) and antifungal (amphotericin B 250ng/ml) agents. Cells from primary cultures were plated at a density of 2×10^5 cells in 24-wells culture plates. At confluence, cells were washed in plain DMEM and incubated for 1 hour in the same medium. To inhibit cAMP hydrolysis, these cells were incubated with isobutyl methyl xanthine for 15 minutes before addition of forskolin, a direct adenylyl cyclase activator. To inhibit cGMP hydrolysis, cells were incubated with sildenafil for 15 minutes prior to incubation with sodium nitroprusside. To terminate the reaction, the medium was aspirated at 15 minutes and 3ml of cold trichloroacetic acid (6%) was added to the cells with the well plate placed on ice. The cells were then scraped and lysed and the levels of the respective cyclic nucleotide evaluated by enzyme immunoassay (assay kit protocol and spectrophotometer).</p> <p>3. At the Clinical Setting:</p> <ol style="list-style-type: none"> Dr Balasubramanian was an observer at the outpatient clinic of Urology Department where male and female sexual dysfunction cases were seen by Dr. Kwangsung Park. Dr Balasubramanian was an observer at the operation theatre where urological surgeries were performed by Dr. Kwangsung Park and his team. <p>Dr Balasubramanian felt that the expertise gained from the hemodynamic study is useful for the interpretation of changes in genital blood flow and the tissue culture experiments can be extrapolated to evaluate changes in enzyme activities and signal transduction pathways in pathological states. The training was particularly relevant to the NMRC funded project on "mechanism, pathophysiology and possible treatment options for female sexual disorders" of which she was the collaborator.</p>
<p>Sudhakar Kundapur Venkatesh</p> <p>Place of training: University of Essen, Germany</p>	<p>MR colonography</p> <p>MR Colonography studies are performed daily at the Department of Diagnostic and Interventional Radiology, University of Essen, Germany. During the fellowship, Dr Venkatesh observed the routine MR Colonography performed in clinically indicated patients and in patients who were undergoing research MR Colonography studies. The technique for the routine clinical indicated that patients differed in the bowel preparation. The MR imaging technique was the same for both groups of patients. After the imaging, Dr Venkatesh was involved in the assessment of images for preliminary reports to be given to the patients. Dr Venkatesh then read the cases and verified his findings with the experts.</p> <p>The research group at Essen is now validating their results of fecal tagging with routine screening patients for acceptance and for image quality.</p> <p>Dr Venkatesh and his co-workers would try to use Singapore food products and foodstuff for fecal tagging to render the signal from the feces to the minimum for their study on MR Colonography. The primary objective of the study was to avoid bowel preparation, which many patients find unpleasant. The standard MR imaging protocol for MR Colonography used at Essen will be followed. Dr Venkatesh is also looking towards for collaboration with the researchers from Essen in his study.</p>

	Dr Venkatesh found the fellowship training to be very helpful and the learning experience helped him and his co-workers to plan and make improvement in their study protocol on MR Colonography.
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Annex 4: Research Projects Approved by NMRC in FY2004

Alexandra Hospital (AH)

NMRC/0863/2004

PI: Lim Su Chi

Epidemiological study of the metabolic syndrome and microangiopathies in Asians (An ancillary study of the Singapore Prospective Study Program, SP2)

NMRC/0878/2004

PI: Subramaniam Tavintharan

The Effects of Simvastatin on Coenzyme Q in the Hep G2 cell culture system

Institute of Mental Health (IMH)

NMRC/0834/2004

PI: Chong Siow Ann

Pharmacogenetics of tardive dyskinesia

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

NMRC/0873/2004

PI: Mahadev Arjandas

Monkey Bars are for Monkeys: A study on Playground Equipment related Extremity Fractures in Singapore. PART 2

NMRC/0884/2004

PI: Law Hai Yang

Screening of α globin gene mutation causing α -thalassaemia using denaturing High Pressure Liquid Chromatography (dHPLC) and SNaPShot analysis

NMRC/0888/2004

PI: Chui Chan Hon

Genetic and molecular status in paediatric patients with embryonal tumors of the nervous system in Singapore - a collaborative study between KKH and NUH

National Cancer Centre (NCC)

NMRC/0822/2004

PI: Goh Cynthia Ruth Nee Fung

Preference-based assessment of quality of life and quality-adjusted life-years in cancer patients

NMRC/0837/2004

PI: Chong Fook Hin Vincent

Imaging-based Tumour Volumetric Analysis

NMRC/0841/2004

PI: Loong Susan Li Er

An investigation into DNA repair abnormalities in lymphoblastoid cell lines from patients with nasal NK/T non-Hodgkin's lymphoma

NMRC/0842/2004

PI: Sabapathy Kanaga

Elucidating the functional significance of p53 codon 72 polymorphism in cancer predisposition and therapeutic response

NMRC/0843/2004

PI: Lee Ann Siew Gek

Identification of putative tumour suppressor genes involved in the carcinogenesis of breast and colorectal cancer (renewal)

NMRC/0854/2004

PI: Hui Kam Man

To develop novel molecular diagnostic and therapeutic markers for non-small lung adenocarcinoma

NMRC/0885/2004

PI: Chowbay Balram

To investigate the interaction of single nucleotide polymorphisms (SNPs) in CYP2C8, CYP3A4 and MDR1 genes and their impact on the pharmacokinetics and pharmacodynamics of paclitaxel in Asian cancer patients

NMRC/0886/2004

PI: Tan Say Beng

Practical Bayesian Methods for Clinical Trials

NMRC/0887/2004

PI: Huynh Hung

Functional Characterization of HuUO-44 an estrogen regulated membrane-associated protein, as a Biomarker for Ovarian Cancer Prognosis, Diagnosis and Treatment

NMRC/0896/2004

PI: Lee Ann Siew Gek

Molecular mechanisms of streptomycin and ethambutol resistance in drug resistant Mycobacterium tuberculosis isolates from Singapore

NMRC/0909/2004

PI: Tan Terence Wee Kiat

An investigation into the role of molecular marker(s) as prognostic indicator and therapeutic target in undifferentiated nasopharyngeal carcinoma

NMRC/0915/2004

PI: Soo Khee Chee

Endoscopy and 2 Photon Laser Confocal Fluorescence Microscopy of Early Neoplasia in the Oral Cavity using Hypericin

NMRC/0923/2004

PI: Ong Yew Kuang Simon

A Phase 1 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/CPG/005/2004

PI: Wong Wai Keong

Developing an integrated platform for multi-disciplinary translational gastric cancer research: correlating genotypes, transcription profiles and histopathology with clinical oncology and surgical outcomes

National Neuroscience Institute (NNI)

NMRC/0821/2004

PI: Lim Kah Leong

Understanding how alterations in parkin function contribute to the development of Parkinson's disease

NMRC/0855/2004

PI: Golay Xavier

Understanding the coupling between cerebral blood flow and metabolism in interictal epileptical spikes

NMRC/0864/2004

PI: Lo Yew Long

Cervical spondylotic myelopathy: clinical, electrophysiological and imaging study in a large series

NMRC/0869/2004

PI: Taupin Philippe

In vivo and in vitro characterization of adult neurogenesis in a model of mouse deficient for the activity of the neural stem cell factor CCG

NMRC/0883/2004

PI: Gan Robert N.

Aspirin resistance among patients with first-ever or recurrent stroke

NMRC/0904/2004

PI: Wang Chee Meng Ernest

Efficacy of clot thrombolysis in intraventricular haemorrhage

NMRC/0919/2004

PI: Golay Xavier

Collateral perfusion in first episode stroke patients measured by regional MR perfusion imaging may help define patients at risk for further ischemic event

NMRC/CPG/008/2004

PI: Yu Wei Ping

Transcriptional regulation of genes associated with common neurological diseases: a comparative functional genomics study using fugu genome as a model

NMRC/CPG/009/2004

PI: Golay Xavier

Fast and Strong Gradient System for Advanced Applications in High Field Magnetic Resonance Imaging

Nanyang Technological University (NTU)

NMRC/0827/2004

PI: Phee Soo Jay Louis

Development of robotic system to enhance therapeutic GI endoscopic procedures

National University Hospital (NUH)

NMRC/0824/2004

PI: Wong Thien Chong Marcus

End-to-side anastomoses for stretch expanded polytetrafluorethylene in a rabbit epigastric free flap model

NMRC/0825/2004

PI: Hee Hwan Tak

Mesenchymal stem cell implantation slows down intervertebral disc degeneration in a rabbit model

NMRC/0844/2004

PI: Mow Benjamin, Ming Fook

In vitro study of CYC202 on nasopharyngeal carcinoma (NPC) cell lines

NMRC/0853/2004

PI: Loy Chong Jin

Role of estrogen receptor alpha/beta and phyto-flavonoids in the treatment of uterine fibroids

NMRC/0862/2004

PI: Tagore Rajat

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

NMRC/0872/2004

PI: Goh Eugene Yu-Yuen

The effects of different doses of lignocaine on coagulation and fibrinolysis in parturients. An in vitro assessment using thromboelastography

NMRC/0892/2004

PI: Liew Choon Fong Stanley

Euglycaemic clamp study of the effects of thiazolidinediones in two local ethnic Groups

NMRC/0893/2004

PI: Ho Yvonne Yi-Wan

Technetium-99m sestamibi scintimammography for prediction of multidrug resistance expression and neoadjuvant chemotherapy response in locally advanced/metastatic breast cancer: correlation with dynamic MRI, MR spectroscopy, gene expression and genotyping studies.

NMRC/0894/2004

PI: Lim Aymeric Yu-Tang

The influence of bone marrows derived mesenchymal stromal cells on rate of tendon healing in rabbits (related to NMRC/0751/2003)

NMRC/0895/2004

PI: Looi Kok Poh

Investigating the kinematics of the wrist and that of the scaphoid relative to the lunate, after a novel repair of the dorsal scapho-lunate interosseous ligament in a scapho-lunate disassociation.

NMRC/0922/2004

PI: Ooi Shirley Beng Suat

Incremental value of troponin T, heart-type Fatty Acid-Binding Protein, creatine kinase-MB mass, electrocardiogram and myoglobin (TroFCEM Study) in rapid bedside diagnosis of acute coronary syndrome in chest pain patients presenting to an emergency department

National University Medical Institutes (NUMI)

NMRC/0847/2004

PI: Yamamura Yasuko

Roles of STAT3 activation in development of H.pylori-associated gastric carcinoma

NMRC/0848/2004

PI: Khan Md. Matiullah

Targeting the conformational rearrangement of N-CoR protein for therapeutic intervention in Acute Promyelocytic Leukemia (APL)

National University of Singapore (NUS)

NMRC/0823/2004

PI: Zhu Yi Zhun

Is hydrogen sulfide cardioprotective or destructive in ischemic heart disease?

NMRC/0826/2004

PI: Poh Chit Laa

Development of novel DNA vaccines against Pseudomonas aeruginosa and elimination of virulence by antisense RNA

NMRC/0828/2004

PI: Mahendran Ratha

The role of mycobacterial PTPs in microbe -epithelial/immune cell interactions

NMRC/0829/2004

PI: Lee Edmund Jon Deoon

Population survey of AChE and BChE activities and its genetic correlation against AChE and BChE mutations: neurological implications

NMRC/0830/2004

PI: Wei Changli

The role of interleukin-13 in the pathogenesis of minimal change nephrotic syndrome and its underlying molecular mechanisms

NMRC/0831/2004

PI: Ahsan Jamil Kazi

Study of functional interaction between Nociceptin and Nocistatin in regulating pain perception pathways

NMRC/0832/2004

PI: Pereira Barry P

Determining the moment arms and lines of action of skeletal muscles that cross the forearm axis

NMRC/0833/2004

PI: Duan Wei

A novel therapeutic target of prostate cancer: role of PRK1 kinase in the progression and invasion of prostate cancer

NMRC/0838/2004

PI: Lee Jen Mai Jeannette

Singapore Cardiovascular Cohort Study

NMRC/0845/2004

PI: Wang Zheng Ming Dennis

Efficacy evaluation of locally delivered growth factors on transplanted islets engraftment by using diabetic animal models

NMRC/0846/2004

PI: Ng Tze Pin

Randomized controlled trial of a community-based early psychiatric intervention strategy (CEPIS) to screen and manage depression in the elderly

NMRC/0849/2004

PI: Liang Fengyi

Cellular expression of RIM genes in rat CNS and functional characterization of RIM3y in nociception

NMRC/0850/2004

PI: Ng Peng Keat Daniel

Genetic and environmental risk factors for diabetic nephropathy among Singaporeans with Type 2 diabetes mellitus

NMRC/0851/2004

PI: Wang De Yun

Pathogenesis of nasal polyposis: role of leukotrenes in recruitment and activation of CD8+ T cells (Continuation of study NMRC/0396/1999)

NMRC/0852/2004

PI: Chua Kaw Yan

Development of a lactobacilli-based oral vaccine for prevention and treatment of allergic diseases

NMRC/0865/2004

PI: Tan Kim Siang Luke

Tissue engineered prefabricated vascularised bone flaps

NMRC/0866/2004

PI: Yang Robert Hong Yuan

Molecular dissection of apoptotic pathways in the fission yeast

NMRC/0867/2004

PI: Dawe Gavin Stewart

Can fetal neural stem cell transplants to the glaucomatous rat eye enhance light-flash evoked responses in the brain?

NMRC/0868/2004

PI: Esuvaranathan Kesavan

Intravesical interferon alpha and BCG immunotherapy for patients with recurrent bladder cancer after previous BCG therapy

NMRC/0870/2004

PI: Tan Hao Yang

Apolipoprotein D in first-episode schizophrenia: clinical and cognitive correlates

NMRC/0871/2004

PI: Pervaiz Shazib

Mechanisms of anti-apoptotic activity of Resveratrol in human leukemia cells: Clinical implications for the use of Resveratrol in combination chemotherapy Regimens

NMRC/0874/2004

PI: Soong Richie Chuan Teck

Clinical Relevance of Thymidylate Synthase Gene Variants

NMRC/0875/2004

PI: Tan Kok Kiong

Development of Cell Manipulation with Electro-Activation System for Nuclear Reprogramming

NMRC/0876/2004

PI: Schwarz Herbert

Analysis of growth and selection advantages which tumor cells gain by expressing CD137 as a neoantigen. Evaluation of a novel therapeutic approach.

NMRC/0877/2004

PI: Lu Jinhua

Understand the roles of Beta₂-microglobulin in dendritic cell macropinocytosis and assess its role as a potential enhancer for subunit vaccines

NMRC/0880/2004

PI: Bhatia Madhav

Acute pancreatitis and associated lung injury: the role of nitric oxide as a potential therapeutic target

NMRC/0881/2004

PI: Bian Jinsong

Androgen regulates HERG/IKr expression and function: why women are at higher risk than men for developing arrhythmias?

NMRC/0889/2004

PI: Huang Canhua

The function of RUNX3 in hepatocarcinogenesis

NMRC/0890/2004

PI: Aw Marion Margaret Hui Yong

A longitudinal study on infectious risks and immune response to vaccination in Singapore infants enrolled in a placebo-controlled, randomised study of probiotic supplementation from birth

NMRC/0891/2004

PI: Lim Yaw Chyn

Novel receptor-ligand interactions that mediate tumor cell adhesion to endothelial cell from different organ sites

NMRC/0897/2004

PI: Seow Ling Hui Adeline

LUNG CANCER IN SINGAPORE CHINESE WOMEN: THE ROLE OF ESTROGENS AND THEIR INTERACTION WITH GENETIC AND ENVIRONMENT FACTORS (The Genes, Environment and Lung cancer (GEL) Study)

NMRC/0898/2004

PI: Tay Kiat Hong Stacey

Screening of mitochondrial DNA and nuclear DNA gene mutations in patients with mitochondrial encephalomyopathies

NMRC/0902/2004

PI: Yu Hanry

Regulation of Hepatocyte Functions in Co-culture with Non-parenchymal Cells

NMRC/0905/2004

PI: Tan Kwong Huat, Benny

Investigation into the mechanisms of pancreatoprotective and hypoglycaemic effects of *Andrographis paniculata* and its diterpenoids in diabetic animals

NMRC/0908/2004

PI: Esuvaranathan Kesavan

Evaluation of intravesical gene transfer using a novel liposome-based preparation in a porcine model

NMRC/0910/2004

PI: Hande M Prakash

Maintenance of Telomere-Chromosome Integrity by DNA Repair/Recombination and DNA Damage Signalling Factors in Mammalian Cells: Role of Breast Cancer Genes

NMRC/0911/2004

PI: Goh Daniel Yam Thiam

Evaluation of the effect of a low density gas (Helium) in the alleviation of upper airway obstruction in children with obstructive sleep apnea syndrome.

NMRC/0912/2004

PI: Lai Poh San

Application of aminoglycosides in inducing mutation read-throughs for molecular therapy in Duchenne muscular dystrophy patients

NMRC/0916/2004

PI: Lee Edmund Jon Deoon

Contribution of Drug Transporters and CYP450 Pharmacogenetics to Statin Myotoxicity

NMRC/0918/2004

PI: Lim Li Chern Dawn

A Study on the Paediatric Prevalence of Adverse Drug Reaction and Drug Allergy in Singapore

NMRC/0920/2004

PI: Van Bever Hugo PS

The influence of fever on early life wheeze: creating a predictive index for identifying wheezy infants at risk of persistent wheeze and likely asthma at preschool age

NMRC/0921/2004

PI: Das De Shamal

Assessment of insufficiency fractures and incident knee osteoarthritis in pre and post-menopausal women using dual energy x-ray absorptiometry (DXA)

NMRC/0924/2004

PI: Chia Kee Seng

Follow-up of the Singapore Breast Screening Project: Efficacy, Disease Progression and Mammographic Density

NMRC/0925/2004

PI: Zhu Yi Zhun

Cross talk between two neuromodulators: the anxiogenic action of CCK requires CRF1 receptor

NMRC/CPG/003/2004

PI: Raghunath Michael

The National Group on Fibrovascular Disorders Programme (NFDP)

NMRC/CPG/004/2004

PI: Yip Wai Cheong George

Expression analyses and functional studies of syndecans and metallothioneins as biomarkers and regulators of breast cancer

NMRC/CPG/010/2004

PI: Boelsterli Urs Alex

Identifying Molecular Mechanisms of Drug-induced Liver Injury in Immortalized Human Hepatocyte Cultures Expressing Liver-specific Genes: Focus on MOMP (Mitochondrial Outer Membrane Permeabilization)

Singapore Eye Research Institute (SERI)

NMRC/0906/2004

PI: Aung Tin

Investigating the genetic basis of primary angle closure glaucoma

NMRC/0914/2004

PI: Wong Tien Yin

Retinal microvascular signs in acute stroke: association with stroke subtype and Prognosis

NMRC/CPG/007/2004

PI: Beuerman Roger W.

Singapore Consortium for Antimicrobial Peptides (SCAMP)

Singapore General Hospital (SGH)

NMRC/0835/2004

PI: Ng Lay Guat

Study of efficacy of Botulinum toxin A on treatment of patient with non-neurogenic detrusor instability

NMRC/0840/2004

PI: Fong Kok Yong

Brain reactive antibodies in systemic lupus erythematosus: Characterisation of neuronal membrane antigens and correlation with neuropsychiatric manifestations

NMRC/0856/2004

PI: Xiao Zhi Cheng

Microarray analysis of genes involved in axon growth using mutant mice

NMRC/0857/2004

PI: Chan Ling Ling

Neurogenic hypertension in hemifacial spasm: Imaging with MR-CISS and MRA

NMRC/0858/2004

PI: Lee Seng Teik

Cultivation and morphogenesis of stem cells from hair follicle, epidermis and cord blood in three-dimensional skin culture and wound healing models

NMRC/0859/2004

PI: Cheng Christopher Wai Sam

Trans-rectal ultrasound prostate biopsy - A precise biopsy device for accurate prostate biopsy

NMRC/0861/2004

PI: Anantharaman Venkataraman

A Multicenter, prospective, randomised study comparing the efficacy of high versus low biphasic energy defibrillation in patients with cardiac arrest (HILOBED)

NMRC/0901/2004

PI: Song Colin

A bilayered scaffold for the development of composite skin construct

NMRC/0903/2004

PI: Hsu Li Yang

A molecular and clinical study of methicillin-resistant staphylococcus aureus (MRSA) strains in Singapore

NMRC/0913/2004

PI: Tien Sim Leng

Characterisation of mutations of the essential regions of the FVIII gene

NMRC/CPG/006/2004

PI: Chow Kah Hoe Pierce

Development of a collaborative program for non-invasive molecular imaging of living in vivo models using micro-PET technology

Singapore Health Services (SHS)

NMRC/0836/2004

PI: Tan Eng King

Adenosine a2a receptors and caffeine intake in Parkinson's disease

NMRC/0900/2004

PI: Tan Eng King

Identification and functional analysis of a novel Parkin splice variant in sporadic Parkinson's Disease

NMRC/0917/2004

PI: Hwang Ying Khee William

Phase II trial on the anti-tumour potential of umbilical cord blood transplantation for high-risk acute myeloid leukemia with a novel reduced-intensity conditioning regimen

Singapore National Eye Centre (SNEC)

NMRC/0839/2004

PI: Aung Tin

Prophylactic laser iridotomy for eyes with narrow drainage angles: A randomized controlled trial

Tan Tock Seng Hospital (TTSH)

NMRC/0860/2004

PI: Wang Yee Tang Sonny

Tuberculin skin test reactivity and peripheral blood mononuclear gamma interferon responses to mycobacterium tuberculosis specific proteins in medical and nursing students

NMRC/0879/2004

PI: Chee Cynthia Bin Eng

Evaluation of the performance of the tuberculin skin test for contact investigation in an intermediate TB burden country with mass BCG vaccination using an assay measuring T-cell interferon-gamma response to Mycobacterium tuberculosis-specific antigens (CLINISPOT-TB assay)

NMRC/0882/2004

PI: Sitoh Yih Yiow

Falls risk and epidemiology in the elderly and the impact of falls on health related quality of life and falls efficacy

NMRC/0899/2004

PI: Leong Yi Onn Ian

Outcomes of patients admitted to community hospitals: a study of factors affecting discharge destination, variance in the length of stay and rehabilitation efficiency

NMRC/0907/2004

PI: Wang Yee Tang Sonny

TB Transmission patterns in Singapore using molecular methods: Finding opportunities for TB control intervention

Annex 5: Publications arising from Block Grants and Competitive Grants

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

- 1 *See SJ, Levin VA, Yung AWK, Hess KR, Groves MD
13-cis-retinoic acid in the treatment of recurrent glioblastoma multiforme
Neuro-Oncology, 2004; 6(3): 25-8
- 2 Bhatia M and Wallig MA
1-cyano-2-hydroxy-3-butene: a plant nitrile that induces apoptosis in pancreatic acinar cells and reduces the severity of acute pancreatitis
Novel Compounds from Natural Products in the New Millennium: Potential & Challenges (Book chapter) 2004:130-38
- 3 *Huynh H, Nguyen TH, Panasci L, Do P
2-Chloroethyl-3-sarcosinamide-1-nitrosourea (SarCNU) inhibits prostate carcinoma cell growth via p53-dependent and p53-independent pathways
Cancer 2004; 101(12): 2881-91
- 4 Li AZJ, Tan L, Chan ESY
5 Year Study of FPDs – A Preliminary Report of Patient Satisfaction
J Dent Res 2004; 83: Spec Iss B
- 5 Wai Hoe Ng, Peter Mitchell, Lara Tickell, Andrew Kaye
A Case of Hyperdense Diploic Epidermoid Cyst on CT Scan Mimicking Meningioma
J Clin Neurosci 2004; 11(8): 930-1
- 6 Wong ZW, Leong SS, Tan T, Mancer K
A case of metastatic squamous cell carcinoma of the hypopharynx manifesting as acute abdomen
Ann Acad Med Singapore 2004; 33(3): 356-8
- 7 CY Loh, SS Chao, YH Chan, DY Wang
A clinical survey on compliance in the treatment of rhinitis using nasalsteroids
Allergy 2004
- 8 Johnny Eng, Chua HC, Sitoh YY, Arul E, Teo BC, Venketasubramanian N
A comparative study of duplex ultrasonography versus angiography in detection of extracranial internal carotid artery stenosis in a local population
J Clin Neurosci 2004; 11(Suppl 1): S75
- 9 Tan YM, Wong WK, Ooi LL
A comparison of two surgical strategies for the emergency treatment of gallstone ileus
Singapore Med J 2004; 45(2): 69-72
- 10 *T Umapathi (2nd Author)
A controlled investigation of the cause of chronic idiopathic axonal polyneuropathy
Brain 2004; 127(Pt 8):1723-30
- 11 *Cheung YB, Machin D, Karlberg J, Khoo KS
A longitudinal study of pediatric body mass index values predicted health in middle age
J Clin Epidemiol 2004; 57(12): 1316-22

- 12 *Zhang X, Vincent AS, Halliwell B, and Wong KP
A mechanism of sukfite neurotoxicity: direct inhibition of glutamate dehydrogenase
J Biological Chemsitry 2004; 279(41): 43035-45
- 13 *Yu K, Lee CH, Tan PH, Hong GS, Wee SB, Wong CY, Tan P
A molecular signature of the Nottingham prognostic index in breast cancer
Cancer Res 2004; 64(9): 2962-8
- 14 *Ying GW, Lee CG, Lee EJ
A naturally occurring -263G/C variant of the human AA-NAT gene and overnight
melatonin production
Mol Genet Metab 2004; 81(1): 65-9
- 15 Moh CH, Lee SK, Pang NL, Kwek CP, Kam WF, Juhana Bte MT, Kalayarasi
A Novel Approach to Managing Patients with High Temperature – A Quality Circle
Effort
Singapore Nursing Journal 2004; 31(1): 4-7
- 16 *EC Pica, ZAD Pramono, PS Lai, WCYee
A novel desmin mutation S13F in a case of spheroid body myopathy with desmin
storage
Neuromuscular Disorders 2004/14: 565
- 17 *Ang P, Lim IHK, Tan PH, Ho GH, Lee ASG
A novel germline BRCA1 mutation identified in a Chinese patient with breast and
ovarian cancer
Eur J Human Genet 2003; 11(1): 64
- 18 *Wong TY, Knudtson MD, Klein R, Klein BE, Hubbard LD
A prospective cohort study of retinal arteriolar narrowing and mortality
Am J Epidemiol 2004; 159(9): 819-25
- 19 *Tay E, Andreou P, Xing W, Bunce C, Aung T, Franks WA
A questionnaire survey of patient acceptability of optic disc imaging by HRT II and
GDx
Br J Ophthalmol 2004; 88(5): 719-20
- 20 CTS Theng, SH Tan, CL Goh, S Suresh, HB Wong, D Machin
A randomized controlled trial to compare calcipotriol with betamethasone valerate for
the treatment of cutaneous lichen planus
Journal of Dermatological Treatment 2004; 15(3): 141-5
- 21 *WYK Hwang, L-P Koh, HJ Ng, PHC Tan, CTH Chuah, SC Fook, H Chow, KW Tan, C
Wong, CH Tan, Y-T Goh
A randomized trial of amifostine as a cytoprotectant for patients receiving
myeloablative therapy for allogeneic hematopoietic stem cell
Bone Marrow Transplantation 2004; 34(1): 51-6
- 22 Husain R, Clarke JC, Seah SK, Khaw PT
A review of trabeculectomy in East Asian people-the influence of race
Eye 2004
- 23 Ma Dongrui, Yang Ennan, S.T.Lee
A Review: The Location, Molecular Characterisation and Multipotency of Hair Follicle
Epidermal Stem Cells
Annals of the Academy Medicine of Singapore 2004/33; 784-8

- 24 Chong SA, Lee C, Bird L, Verma S
A risk reduction approach for schizophrenia: the early psychoais intervention programme
Annals Academy of Medicine 2004; 33: 630-5
- 25 Thong PSP, Bay BH, Watt F, Tan PH, Soo KC, Olivo M
A study on hypericin photodynamic therapy induced cell death: Novel complementary techniques used and initial results
Acta BioOptica et Informatica Medica 2004; 10: 36
- 26 SL Seng, PS Lim, MY Ng, HB Wong, SC Emmanuel
A study on SARS awareness and health seeking behaviour – findings from a sampled population attending National Healthcare Group Polyclinics
Annals Academy of Medicine 2004; 33(5): 623-9
- 27 Lee P L, Ong A K, Grace C, Authilaskhmy NM Sri Rahayu
A study on the management of hospitalised diabetes mellitus patients on blood glucose monitoring in CGH
Singapore Nursing Journal 2004; 31(3)
- 28 Eddy Cheong Seng Giap, Stephanie MC Fook-Chong, Rita Pant
A study to assess the normal values of ovarian volume for women in Singapore using transabdominal ultrasound
SGH Proceedings 2004; 13(3)
- 29 Pjetursson BE, Tan K, Lang NP, Brägger U, Egger M, Zwahlen M
A Systematic Review of the Survival and Complication Rates of Fixed Partial Dentures (FPDs) After an Obeservation Period of at Least 5 Years I. Implant-Supported FPDs
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79	Chen, Jiun-Han	130	Dolezalova, Pavla
80	Chen, Xihua	131	Donahue, Tammy Haut
81	Cheng, Lingyun	132	Dorman, Todd
82	Chesney, Russell W.	133	Dougherty, Thomas
83	Cheung, Bernard MY	134	Dressman, Marlene
84	Cheung, Kam-Lau	135	Drolet, Guy
85	Cheung, Lim Kwong	136	Drouva, Sophia V.
86	Chiu, Ray Chu-Jeng	137	Du Toit, Eugene (Joss)
87	Choy, Kwong Wai Richard	138	DuBois, Raymond

139	Dudley, Gary	190	Haines, Stephen J
140	Dudley, Samuel C	191	Hakem, Razqallah
141	Duesberg, Peter	192	Halling, Anders
142	Duiverman, Eric J	193	Hammond, Geoffrey Lewis
143	Ent, Fred Van Der	194	Hamutcu Ersu, Refika
144	Eschenhagen, Thomas	195	Han, Kwang-Hyub
145	Ewald, Ben	196	Hans-Joachim, Schmoll
146	Fagarasanu, Mircea	197	Harness, Jay K.
147	Fan, Arthur Yin	198	Harvey, Alan L.
148	Fan, Dorothy	199	Heath, Andrew W
149	Federman, Daniel	200	Heidegger, Thomas
150	Fenlon, Michael R	201	Hepp, Urs
151	Ferguson, Thomas B.	202	Hermida, Jean-Sylvain
152	Ferrero, Richard L.	203	Higgins, Trefor
153	Filmus, Jorge	204	Hillman, David
154	Finnegan, Maureen	205	Hinman, Channing
155	Fischer, Joan	206	Hirohito, Kita
156	Fliegel, Larry	207	Hirvonen, Ari
157	Foell, Juergen	208	Hitchings, Roger A
158	Fokkens, Wytse J.	209	Ho, Yik Hong
159	Fountoulakis, KN	210	Hodsdon, Michael
160	Framme, Carsten	211	Hoffman, John R.
161	Frentzel, Stefan	212	Hoffman, Steven A.
162	Friedl, Andreas	213	Holloway, Andrew
163	Fuller, Frederick J.	214	Holmstrom, Hans
164	Gabrielli, Brian	215	Holz, George G
165	Gal, Peter	216	Holzer, Gerold
166	Ganesh, Sudha K	217	Homer, Robert J.
167	Gangur, Venu	218	Hondermarck, Hubert
168	Garrett, Michelle D.	219	Hoon, Dave
169	Geraedts, Joep P M	220	Hoshi, Toshinori
170	Gessner, Christian	221	Huang, Li-Min
171	Gilfix, Brian M.	222	Huang, Suber S
172	Goel, Vijay	223	Huang, Yu
173	Going, James J.	224	Hung, CR
174	Goitz, Robert J	225	Iles, Ray K.
175	Goldfarb, Lev	226	Ironside, James W.
176	Gomer, Charles J	227	Isik, Frank
177	Gopal, Ajay K.	228	Jagannath, Chinnaswamy
178	Gorelik, Eli	229	Jankauskas, Rimantas
179	Gothenburg, Agnes Wold	230	Jenkin, Grant A.
180	Graeff, Richard	231	Jensen, Troels Staehelin
181	Greaves, Mel F.	232	Jin, J-P
182	Greenspan, Phillip	233	John Wilson, David
183	Griffin, Constance A.	234	Johnson, Mary Ann
184	Groettrup, Marcus	235	Juang, Jyh-Lyh Jerry
185	Guillouzo, Andre	236	Jürchott, Karsten
186	Guldan, Georgia S	237	Kanter, Lena
187	Gutmann, David H.	238	Kasimir-Bauer, Sabine
188	Guyuron, Bahman	239	Katellaris, Peter
189	Hague, Angela	240	Katsanis, Emmanuel

241	Kauppinen, Risto	292	Lipkowski, Andrzej
242	Kemp, Christopher	293	Litaker, David
243	Kempermann, Gerd	294	Littarru, Gian Paolo
244	Kennedy, Martin A.	295	Liu, Jianqi
245	Khairallah, Moncef	296	Liu, Leroy F.
246	Khudyakov, Yuri E	297	Liu, Mingyao
247	Kim, Chunsung	298	Lo, Kwok Wai
248	Kim, Jason K	299	Loeb, Lawrence A.
249	King, Paul H	300	Ludewig, Gabriele
250	Kirwan, John P.	301	Luk, Keith
251	Kitlinska, Joanna	302	Lundgren, Erik
252	Kleinberger, Tamar	303	Lynch, Richard G.
253	Kneipp, Katrin	304	Lyu, Rong-Kuo
254	Koh, Gou Young	305	M. Robyn, Andersen
255	Kondo, Eisaku	306	MacPherson, Ross
256	Kong, Tony Ah-Ng	307	Macri, Joseph
257	Kopecky, Kenneth J.	308	Madhok, Ashish
258	Koschinsky, Marlys	309	Mahady, Gail B
259	Kotiw, Michael	310	Malas, Stavros
260	Kountakis, Stil	311	Malberti, Fabio
261	Krag, David	312	Mann, Derek A
262	Krajinovic, Maja	313	Mantulin, William W
263	Krauss, Joachim Kurt	314	Margison, Geoff P
264	Kroemer, Guido	315	Margo, Curtis
265	Krohn, Knut	316	Marino, Michele
266	Kwan, Chiu Yin David	317	Marra, Kacey
267	Kwong, Lai-wan Dora	318	Martin, Brook
268	La Thangue, Nicholas B.	319	Martins, Ralph N
269	Lacroix, Steve	320	Marx, Christian
270	Lai, Ching-Lung	321	Mbagwu, Godwin O.
271	Lam, Wai Man Wynnie	322	McCord, Fraser
272	Landis, William J.	323	McCormick, Joseph Benford
273	Lansky, Alexandra	324	McCullough, Peter A.
274	Lau, Chu Pak	325	McDermott, Hugh J
275	Lau, Wan Yee Joseph	326	McKenzie, Matthew
276	Lee, Daniel	327	McLoon, Linda
277	Lee, Wing Yan Michael	328	McMillan, Trevor J
278	Lee, Young Hwan	329	McMinn, Peter
279	Lees, George	330	McPherson, David D
280	Lei, Chang Moh Clarence	331	Medina-Acosta, Enrique
281	Lei, Yu	332	Meininger, Cynthia J
282	Leira, Rogelio	333	Menger, Michael D
283	LeRoy, Bruce E	334	Miao, Carol H.
284	L'Esperance, James O.	335	Miller, Michael
285	Leung, Pak Heng George	336	Minagar, Alireza
286	Leung, Ting Fan	337	Mirkhani, Hossein
287	Lew, Daniel J.	338	Mitsiadis, Thimios A
288	Lewin-Kowalik, Joanna	339	Miyazono, Kohei
289	Liapis, Christos D	340	Mizuno, Hiroshi
290	Lin, Ching-Shwun	341	Mocanu, Mihaela Mariana
291	Lindeman, Robert	342	Moore, Xiao Lei Shirley

343	Morgan, Andrew J	394	Pérez- Novo, Claudina A.
344	Morrisett, Joel D.	395	Perez-Vizcaino, Francisco
345	Moutet, Francois	396	Perillo, Alessandro
346	Mueller, Thomas	397	Perretti, Mauro
347	Muench, Gerald	398	Perrie, Yvonne
348	Muller, Stefan	399	Pfeiffer, Per
349	Murphy, Christopher Raymond	400	Pienkowski, David
350	Musch, David C	401	Pietrojusti, Antonio
351	Narayan, Satya	402	Pileggi, Antonello
352	Naritomi, Hiroaki	403	Pinder, Sarah
353	Nelson, Andrew John	404	Pipe, Steven
354	Nelson, Edward L.	405	Pitard, Bruno
355	Nemes, Attila	406	Plant, Giles W
356	Nerlich, Andreas	407	Platt, Bettina
357	Ng, Anthony	408	Pollack, Charles
358	Ng, Daniel Kwok-Keung	409	Pollock, Carol
359	Ng, KF Jacobus	410	Poolsup, Nalinee
360	Ngan Kee, Warwick Dean	411	Porter, James E
361	Ngan, Y S Hextan	412	Potchen, E. James
362	Nicolai, Thomas	413	Poulsen, Lars K
363	Noguchi, Masayuki	414	Proctor, Lavinia
364	Nordström, Anna	415	Rainer, Timothy Hudson
365	Norton, Robert	416	Rajewsky, Manfred F.
366	Novak, Natalija	417	Ramachandra, Murali
367	Nowak, Romana	418	Ramesh, R
368	Oberley, Larry W.	419	Ramirez, Franceso
369	Oberley, Terry D	420	Rebeiz, Elie E
370	O'Connor, Andrea J.	421	Reek, Sven
371	O'Donnell, Michael	422	Reid, Gregor
372	Ogris, Manfred	423	Reid, Kenneth BM
373	Okhuysen, Pablo C.	424	Reinmuth, Niels
374	Olver, Ian	425	Rhodes, Daniela
375	Ono, Santa Jeremy	426	Rice, Alison
376	Oreffo, Richard	427	Rice, Frances
377	Orentas, Rimas J.	428	Richardson, Ann
378	Osterhoff, Martin	429	Rieder, Michael
379	Pallen, Catherine	430	Rinaldo, Piero
380	Palotas, Andras	431	Roberts, Timothy P
381	Pang, Chi-Pui Calvin	432	Robertson, Stephen
382	Papa, Sergio	433	Rong, Zhou
383	Papapetropoulos, Andreas	434	Ross, Ian B
384	Papka, Raymond E.	435	Rossi, Renato Enzo
385	Pardo, Inês	436	Roy, Hemant K.
386	Park, Jeong Mi	437	Russell, Fraser D
387	Passalacqua, Giovanni	438	Sairam, M Ram
388	Passaniti, Antonino	439	Salles, Jean Pierre
389	Patchefsky, Arthur S.	440	Salvini, Filippo
390	Paterson, Ian	441	Sanders, Esmond J
391	Pelker, Richard R.	442	Sanderson, John Elsby
392	PENAULT-LLORCA, Frederique	443	Sang, Nianli
393	Perdigón, Gabriela	444	Sarchielli, Paola

445	Sathian, Krish	496	Thompson, Nancy
446	Sauter, Edward R.	497	Toi, Masakazu
447	Schell, Mark A.	498	Tonacchera, Massimo
448	Schetz, John A.	499	Tsai, Ray Jui-fang
449	Schillaci, Orazio	500	TSE, Hung-Fat
450	Schmidt, Christopher	501	Turturro, Francesco
451	Schulz, Rainer	502	Tyrrell, Rex M
452	Schwab, Jan	503	Ung, Owen
453	Sean, Collins	504	Vaarala, Outi
454	Segel, Leigh D	505	Vallejo, Manuel C
455	Semma, Masanori	506	Vallieres, Luc
456	Shaoul, Ron	507	Van der Vijver, Marc
457	Sharma, M P	508	van Dijk, Diederik
458	Shay, Jerry W.	509	Vekemans, Johan
459	Sheldon, Stephen H	510	Venook, Alan
460	Shortman, Ken	511	Vercesi, Anibal
461	Sieb, Joern P	512	Vergnolle, Nathalie
462	Simic, Mima	513	Vicart, Patrick
463	Simmonds, Monique S.J.	514	Vickers, James
464	Simon, Julian	515	Virji, Mumtaz
465	Simpson, Hamish	516	Virshup, David M.
466	Sims, Stephen	517	Von Eyben, Finn Edler
467	Singh, Bruce	518	Vona-Davis, Linda
468	Smith, Ross C.	519	W. Orth, Michael
469	Smith, Stephen W	520	Wadhwa, Renu
470	Somasundaram, Siva	521	Wallace, John L.
471	Soslowsky, Louis	522	Walsh, Ed
472	Speed, Cathy. A.	523	Walsh, W.R.
473	Stegmann, Thomas J	524	Walworth, Nancy C.
474	Steinke, John	525	Wang, Michael Y
475	Stevens, Michael	526	Wang, Xuejun
476	Stewart, Duncan J	527	Ward, Philip B
477	Stewart, Elizabeth A.	528	Watson, Sue A.
478	Stone, Trevor W	529	Watson, Timothy
479	Stupack, Dwayne G	530	Weissman, Sherman M.
480	Surbek, Daniel	531	Weller, Michael
481	Suzuki, Ken	532	Welter, Jean F.
482	Syrjanen, KJ	533	Wener, Mark
483	Taegtmeier, Heinrich	534	Werner, Haim
484	Taj-Aldeen, Saad J.	535	Weston, Gareth
485	Tam, Kwong Hang Paul	536	Wewer, Ulla M.
486	Tanaka, Ken-ichi	537	Whalen, Christopher
487	Tang, Nelson Leung Sang	538	Wheelhouse, Richard
488	Tang, Weihong	539	White, Nick
489	Tatarkiewicz, Krystyna	540	Whiteman, Suzanne
490	Taupenot, Laurent	541	Williams, Ann C.
491	Tavassoli, Mahvash	542	Wilner, Joel
492	Tayles, Nancy	543	Windsor, John A
493	Taylor, Eric	544	Wingard, Deborah
494	Theodossiou, T.	545	Wintermark, Max
495	Thomas, Walter	546	Wixler, Viktor

547	Wolf, Steven L	559	Xiao, Yun Xu
548	Wong, Chun Nei Virginia	560	Xie, Xiao-Song
549	Wong, HC Albert	561	Ye, Zu Cheng
550	Wong, Lee-Jun C.	562	Yew, David Tai Wai
551	Wong, Norman C W	563	Yoder, Mervin C
552	Wong, Shiu Man, Jude	564	Yu, Nai-Teng
553	Wong, TM	565	Zacharin, Margaret
554	Wong, WK Gary	566	Žádníková, Raja
555	Wongratanacheewin, Surasakdi	567	Zalewski, Peter
556	Woo, Kong Sang John	568	Zeps, Nikolajs
557	Wood, Charles E.	569	Zhang, James X
558	Woods, Marion	570	Zhivotovsky, Boris