

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

2003

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Immunology and Urology
The Children's Medical Institute
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Introduction

MISSION

The National Medical Research Council (NMRC) was set up in 1994 with the mandate to engender the growth of research talent, to support high quality clinical research, and to improve the quality of medical care and human health in Singapore. The NMRC is a Ministry of Health (MOH) unit and MOH provides secretariat support to the NMRC.

STRUCTURE OF NMRC

The current Council of 12 members is appointed by the Minister for Health. The Chairman of the current Council is Professor Woo Keng Thye, Singapore General Hospital. It comprises representatives from the universities and leading medical and scientific institutions in Singapore. The Council is assisted by the Executive Committee, Peer Review Committee and Fellowship Committee.

The Executive Committee was appointed by the Council to provide scientific inputs to assist the Council in making funding decisions.

10 Peer Review Subcommittees in the following respective fields assist the Executive Committee in making funding recommendations:

- (i) Immunology/Microbiology
- (ii) Pathology/Inflammation/Oncology/Nuclear Medicine
- (iii) Biochemistry/Cell and Molecular Biology
- (iv) Epidemiology/Health Sciences/Public Health & Health Services
- (v) Peripheral, Central, Sensory & Cellular Nervous System/Mental Health
- (vi) Genetics/Paediatrics/Reproduction
- (vii) Cardiovascular/Respiratory
- (viii) Renal/Endocrine/Pharmacology
- (ix) GIT/Liver/Nutrition
- (x) Dentistry/Surgery/Ophthalmology

FY2003 BUDGET & EXPENDITURE

In FY2003, the NMRC was allocated a total of \$54.3 million for research expenditure, out of which \$49.3 million was obtained from MOH's Other Operating Expenses Budget and \$5 million was received as a generous donation from Singapore Totalisator Board (Tote Board) for research projects and programmes. The Tote Board also provided an additional \$1.7 million in FY2003 for the Medical Research Fellowship and Scientist Award.

In FY2003, the expenditures for research programmes and projects i.e. Block Grants and Competitive Grants, were \$30.4 million and \$15.6 million respectively; and the expenditure for Protected Time was \$2.4 million. An expenditure of \$1.2 million was incurred for Medical Research Fellowship and Scientist Awards.

HIGHLIGHTS OF FY2003

NMRC Strategic Planning Retreat 14-15 March 2003

The NMRC Strategic Retreat was held from 14 to 15 March 2003, and is the first such Retreat since NMRC's inception in 1994. The event was a major milestone which allowed the Council and key stakeholders and partners to reflect and debate on the needs of biomedical research in Singapore, as well as strategise in order to enhance the level of research and its benefits to Singaporeans.

The present Council set the strategic plan for medical research in Singapore over the next 5 years, as well as charted future directions for medical research development in Singapore.

The NMRC Strategic Plan consists of 3 key elements:

- (a) Development of research landscape.
 - i. Focusing on specific areas of research so that funds would be allocated to support these research programmes throughout
 - ii. Scaling down of Institutional Block Grants
 - iii. Continuous provision of competitive grants
 - iv. Ensuring efficient and coordinated use of limited funds.
- (b) Funding of manpower.
 - i. Building up a critical mass of clinician scientists.
- (c) Development of greater depth and breadth of clinical research expertise.
 - i. Address weak interface between hospitals and basic research, as evident from the SARS episode
 - ii. Partnership between basic science researchers and clinical research expertise
 - iii. Effective collaboration between NMRC and Biomedical Research Council (BMRC).

New Grant Categories

The Council reviewed its policies with regards to competitive grants, block grants, programme grants and fellowships, and created 3 new grant categories, the **Enabling Grant**, the **Competitive Priority Grant** and the **Competitive Programme Grant**

Enabling Grant

Enabling grants was set up to help institutions to build up research capabilities and nurture a research culture through providing grants for clinical trials support and pilot studies. In 2003, it was given to Alexandra Hospital, Changi General Hospital, Health Science Authority, KK Women's and Children Hospital, National Dental Centre and National Skin Centre.

Competitive Priority Grant

The Competitive Priority Grant (CPRG) was created in FY2003 to provide for research on important national health issues, one example being the SARS research grant.

Competitive Programme Grant

The Competitive Programme Grant (CPG) was put in place to provide for research teams to conduct medical research programmes (a group of projects) of specific research areas or objectives.

Cessation of Protected Time Scheme

Initiated by the NMRC in 1997, the **Protected Time Scheme (PTS)** enabled institutions to employ replacement doctors or arrange for the necessary coverage for the clinical duties of clinicians who take time off for research. The **Revised Protected Time Scheme (PTS)** was introduced in FY2001 to fund protected time based on the time spent by the Principal Investigator (PI) on a specific project.

Practical problems were faced in the administration of the grant and the PTS was ceased. To ease the transition, the Council would still honour previously approved protected time (until their expiry in FY2004), and would consider protected time applications made during the period of FY2003, for projects approved in FY2001 and FY2002.

Initiating NMRC-BMRC Collaboration

Biomedical research and development in Singapore is driven mainly by A*STAR and NMRC. Both establishments play an important role in sustaining R&D activities in Singapore. The NMRC is responsible for the funding of medical research in Singapore while BMRC of A*STAR is responsible for the funding of research in the biomedical Sciences in Singapore. Both organizations will complement each other in developing talent and infrastructure for research. This would eventually culminate in excellent Science, which, given the capability to exploit, would result in useful clinical applications and commercialization. NMRC-BMRC collaborations were initiated in FY2003 and plans for a joint grant exercise and clinician scientist investigator scheme are currently underway.

Competitive Grants

OVERVIEW

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** (since 1994)
- **Competitive Priority Research Grant** (incepted in FY2003)
- **Competitive Programme Grant** (incepted in FY2003)

Since the inception of NMRC in 1994, a total of 866 competitive projects amounting to \$168 million have been approved. Of this total, 449 projects have been completed, and 338 are still on-going. At the end of FY2003, a total of \$90 million has been expended, with outstanding commitments of \$44 million. There has been a marked increase in the number of applications each year – with 231 applications in 2001, 286 applications in 2002, and 423 applications in 2003.

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) For the strict purpose of objectivity, reviewers recommended by the Principal Investigator of the grant application will not be invited to review the proposal.
- 3) To safeguard against any situational bias, reviewers from the same institution as the Principal Investigators, Co-Principal Investigators and collaborators will not be selected.

- 4) Overseas reviewers are invited when there is limited local expertise in certain areas such as stem cell research and skin research.
- 5) A third reviewer 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:

- (xi) Immunology/Microbiology
- (xii) Pathology/Inflammation/Oncology/Nuclear Medicine
- (xiii) Biochemistry/Cell and Molecular Biology
- (xiv) Epidemiology/Health Sciences/Public Health & Health Services
- (xv) Peripheral, Central, Sensory & Cellular Nervous System/Mental Health
- (xvi) Genetics/Paediatrics/Reproduction
- (xvii) Cardiovascular/Respiratory
- (xviii) Renal/Endocrine/Pharmacology
- (xix) GIT/Liver/Nutrition
- (xx) 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, 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 their research findings and achievements is submitted when a project is completed. Each project is required to report on key performance indicators as described in Chapter 4: Summary of Research Output.

IRG Funding Exercises 2001-2003

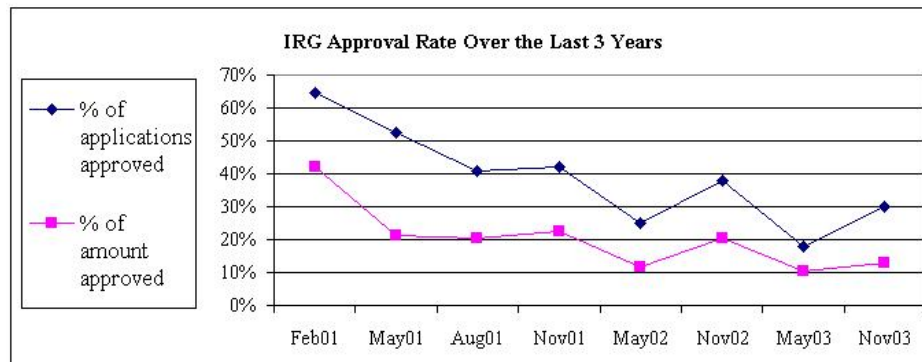
Table 1 presents the statistics of each IRG Funding Exercise over the last three years. Between the Feb01 Exercise and the Nov03 Exercise,

- There has been a general increase in the number of applications, although there was a drop from 227 applications in the May03 Exercise to 173 applications during the Nov03 Exercise.

- Approval rate of applications has more than halved, from 65% (Feb01) to 30% (Nov03).
- Total amount applied for has increased from \$32.5 million to \$65.9 million,
- Total amount approved has decreased from \$13.7 million to \$8.5 million.

Table 1
IRG 2001 – 2003

	IRG Funding Exercise							
	Feb01	May01	Aug01	Nov01	May02	Nov02	May03	Nov03
No. of applications received	51	57	61	62	123	163	227	173
Total amount applied for (\$'millions)	32.5	26.7	17.0	21.4	42.7	50.1	77.7	65.9
No. of applications approved	33	30	25	26	31	62	41	52
Total amount approved (\$'millions)	13.7	5.7	3.5	4.8	5.0	10.3	8.0	8.5
% of applications approved	65%	53%	41%	42%	25%	38%	18%	30%
% of amount approved	42%	21%	20%	23%	12%	21%	10%	13%



The reduction in approval rate over the years is due to increasing competitiveness (as evident in the rising number of applications) and the reduction of available funds, as NMRC's funding source was switched from Development Fund to Other Operating Expenses (OOE) Fund with effect from FY2002.

Applications in FY2003

A total of 400 applications were received by NMRC during the May03 and Nov 03 Exercises. 93 applications out of the 400 were approved. (Please refer to Table 1.)

Approved Projects in FY2003

107 IRG projects were approved by NMRC in FY2003. Out of the 107 IRGs approved in FY2003, 41 are applications received in May03 IRG funding exercise, 61 in Nov02 exercise, 1 in May02 exercise, 1 in Nov01 exercise, 1 in Aug01 exercise and 2 in May01. Table 2 shows the number of IRG projects approved, by institution.

Table 2
No. of IRG Projects Approved, by Institution

Institutions	No. of IRG Projects Approved in FY2003
Alexandra Hospital (AH)	1
Institute of Mental Health (IMH)	1
KK Women's & Children's Hospital (KKH)	2
National Cancer Centre (NCC)	14
National Environment Agency (NEA)	1
National Heart Centre (NHC)	8
National Neuroscience Institute (NNI)	11
National University Hospital (NUH)	7
National University Medical Institutes (NUMI)	4
National University of Singapore (NUS)	35
Singapore Eye Research Institute (SERI)	2
Singapore General Hospital (SGH)	15
Singapore Health Services (SHS)	5
Tan Tock Seng Hospital (TTSH)	1
Total	107

Ongoing Projects in FY2003

A total of 338 projects were still ongoing at the close of FY2003. Table 3 on the next page shows the number of IRG applications ongoing, by institution.

Project Findings Reported in FY2003

A total of 95 IRG projects reported their final findings in FY2003. Table 4 on the next page shows the number of IRG projects that reported final findings in FY2003, by institution.

Table 3*No. of IRG Projects Ongoing at the end of FY2003, by Institution*

Institutions	No. of IRG Projects Ongoing at the end of FY2003
Alexandra Hospital (AH)	3
Clinical Trials & Epidemiology Research Unit (CTERU)	1
Institute of Mental Health (IMH)	9
KK Women's & Children's Hospital (KKH)	6
Nanyang Polytechnic (NYP)	1
National Cancer Centre (NCC)	29
National Dental Centre (NDC)	1
National Environment Agency (NEA)	1
National Heart Centre (NHC)	17
National Neuroscience Institute (NNI)	19
National Skin Centre (NSC)	2
Nanyang Technological University (NTU)	1
National University Hospital (NUH)	11
National University Medical Institutes (NUMI)	6
National University of Singapore (NUS)	154
Singapore Eye Research Institute (SERI)	6
Singapore General Hospital (SGH)	61
Singapore Health Services (SHS)	6
Singapore National Eye Centre (SNEC)	1
Tan Tock Seng Hospital (TTSH)	3
Total	338

Table 4*No. of IRG projects that reported final findings in FY2003, by Institution*

Institutions	No. of IRG Projects Completed in FY2003
Alexandra Hospital (AH)	1
KK Women's & Children's Hospital (KKH)	1
National Cancer Centre (NCC)	4
National Heart Centre (NHC)	3
National Skin Centre (NSC)	2
National University Hospital (NUH)	5
National University of Singapore (NUS)	56
Singapore General Hospital (SGH)	19
Tan Tock Seng Hospital (TTSH)	4
Total	95

Research Outcome: Highlights of FY2003

Research outcomes have grown steadily since the inception of the IRG. The following abstracts are the highlights of research outcomes from IRG projects completed in FY2003. (See Annex 1 – “Abstracts of IRG & Block Grant Research Projects completed in FY2003” for the comprehensive list.)

<i>Project No. & PI</i>	<i>Project Title & Abstract</i>
<p>NMRC/0372/1999 Lim Su Chi (AH)</p>	<p>The effect of d-alpha-tocopherol (vitamin E) on the endothelial of subjects with Type 2 diabetes</p> <p>The objective of this study is to evaluate the efficacy of vitamin E on the endothelial function of subjects with type 2 diabetes. 100 patients with type 2 diabetes were enrolled in a randomized, double-blind, placebo controlled trial and followed them for 3 months. 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). Blood specimens was also obtained from each subject for the measurement of glucose, HBA1c, lipid profile and markers of endothelial activation - vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM) and oxidative stress (Coenzyme Q10). Ninety eight patients completed the study. Two patients were lost to follow up – one due to religious consideration, another due to relapse of previously stable seizure disorder. The data suggested that even at a daily dose of 1,600 IU of vitamin E (resulting in a tow fold increment in plasma vitamin E levels in those subjects taking the active intervention), there was no demonstrable improvement in any of the above markers. Contrary to previous belief, recent metanalysis from major clinical trials suggested that vitamin E supplements could not improve cardiovascular morbidity and mortality. The data may have provided the possible underlying explanation i.e. vitamin E supplement even at high dose, could not improve the endothelial function of subjects with type 2 diabetes.</p>

<i>Project No. & PI</i>	<i>Project Title & Abstract</i>
<p>NMRC/0302/1998 Prof Soo Khee Chee & Dr Pierce Chow (NCC)</p>	<p>Randomised trial of Tamoxifen versus placebo for the treatment of inoperable hepatocellular carcinoma</p> <p>Hepatocellular carcinoma (HCC) is endemic in the Asia-Pacific region. Surgery is the only treatment modality that significantly prolongs survival but almost 90% of patients are inoperable at diagnosis. Tamoxifen (TMX) is believed to retard HCC positive for estrogen receptor (ER), but previous phase III trials in inoperable HCC have been conflicting and inconclusive. Most HCCs are also ER negative. Tamoxifen at higher doses, is however, known to retard HCC through ER-independent mechanisms.</p> <p>The objective of the project was to assess the role of high-dose TMX versus placebo (p) in the treatment of inoperable HCC with survival as the primary endpoint and quality of life (QoL) as the secondary end-point.</p> <p>The methodology used was a prospective double-blind controlled randomized trial with TMX 120mg/day in the study arm and P in the control arm and an intermediate dose arm of TMX 60 mg/day to assess possible dose-response. Randomisation was done through the data center in Singapore. Trial safety and quality controlled was ensured via site audits and an independent Data Monitoring Committee. QoL of patients was assessed using the EORTC QLQ-C30 questionnaire.</p> <p>10 centres in 9 countries (Myanmar, Hong Kong, Singapore, Thailand, Indonesia, Malaysia, South Korea, New Zealand, Australia) entered 329 patients. Reported adverse drug reaction was 3% and 8 patients were lost to follow-up. The 3-month survival rates for P, TMX60 and TMX 120 were 44%, 41% and 35% respectively with significant trend difference in crude survival rates across the 3 treatment regimens (p=0.011). There is a significantly higher risk of death in TMX120 as compared with P (HR:1.39;95% CI of HR: 1.07 to 1.81).</p> <p>In conclusion, TMX does not prolong survival in inoperable HCC and has a negative impact with increasing dose. Changed international clinical practice with respect to the treatment of inoperable hepatocellular carcinoma. The practice of treating such patients with tamoxifen was found to be detrimental.</p>

Project No. & PI	Project Title & Abstract
	<p>The trial resulted in the formation of an Asia-Pacific multi-national cancer trials group with its data centre in Singapore which continued to carry out further <i>collaborative</i> clinical trial (current AHCC02 trial) in this field, to address a disease, which although relatively unimportant in the West, is endemic in the Asia-Pacific.</p>
<p>NMRC/0546/2001 Dr Cheung Yin Bun (NCC)</p>	<p>Shortening quality-of-life measurement scales : methods and application to cancer research</p> <p>A practically useful measure of quality of life should be simple and quick to complete. Based on a study of 140 cancer patients, a short version of the Functional Living Index – Cancer (FLIC) was developed, and called the Quick-FLIC. The methodology of shortening the instrument involved both multivariate statistical techniques and clinical judgments. In another study of 190 cancer patients, the measurement properties of the Quick-FLIC were assessed. The patients filled in a retest questionnaire on average two weeks after baseline to assess test-retest reliability and responsiveness to change. The Quick-FLIC scores correlated well with the Functional Assessment of Chronic Therapy – General scores ($r = 0.78$). Patients with different treatment status, performance status and self-rated health had significantly different Quick-FLIC scores in the expected directions (ANOVA; each $P < 0.001$). Internal consistency (Cronbach's $\alpha = 0.87$) and test-retest reliability (intra-class correlation = 0.81) were also satisfactory. The measure was responsive to changes in health status ($P < 0.001$). The Quick-FLIC is a valid and reliable measure of health-related quality of life of cancer patients. The shortening of established health-related quality of life instruments should be considered in order to reduce the burden of having patients to answer lengthy questionnaires.</p>
<p>NMRC/0571/2001 Dr Patrick Tan (NCC)</p>	<p>Computational modelling of biological signalling pathways</p> <p>Conserved metabolic networks such as glycolysis are often regulated in different tissues, species, and diseases by cell-type specific molecular pathways. The project presents a systematic methodology for identifying the point-of-interaction between these specific pathways and the conserved network through the comparison of predicted and experimentally determined metabolic</p>

Project No. & PI	Project Title & Abstract
	<p>phenotypes. The methodology employs a semi-empirical approach to create deterministic, quantitative models that can predict the 'metabolic phenotype' of a particular cell type in terms of its steady-state metabolite concentration profile. In a series of proof-of-concept experiments, a glycolytic simulation was used to predict the existence of species-specific and environmentally-regulated metabolic circuits in various cells types (erythrocytes, myocytes and <i>Tbrucei</i>). A similar approach, applied to a rat animal model of diabetes, identified the polyol pathway as a major regulator of glycolysis in diabetic rat hearts, and accurately predicted the metabolic effects of treating both normal and diabetic rat muscle cells with aldose reductase inhibitor zolprestat. The study suggests that quantitative computational techniques can be successfully used for biological pathway discovery and the prediction of complex metabolic phenotypes.</p> <p>Filing of an international patent application of the computational modelling of signalling pathways is currently in progress. A start-up company, <i>Systome Therapeutics</i>, has also been established to apply this technology to reduce the cost and improve the efficiency of drug development. This will reduce the overall cost of drugs, and accelerate the rate by which new and better drugs are identified.</p>
<p>NMRC/0439/2000 Brownyn Kingwell (NHC)</p>	<p>Studies on the functional mechanical properties of large conduit arteries and their potential therapeutic impact in cardiovascular disease</p> <p>This project established a clinical arterial function laboratory within the National Heart Centre, which is capable of performing non-invasive assessments of arterial function -- a newly identified independent risk marker for cardiovascular disease. The ability to assess such properties holds potential for clinical research and for the longer-term use in risk stratification and assessment of treatment.</p> <p>Increased arterial stiffness causes increased blood pressure and the differential effects of blood pressure medications that interfere with the rennin-angiotensin system were studied. Decreasing the amount of angiotensin II in the blood is well known to decrease blood pressure and have other beneficial effects on health. Effects on arterial mechanical properties of</p>

Project No. & PI	Project Title & Abstract
	<p>newer agents targeting this system are unknown. The study compared the effects of angiotensin converting enzyme inhibition, direct angiotensin 2 receptor blockade and placebo medication on blood pressure and, uniquely, on arterial mechanics in a Chinese population. Aortic function was measured in hypertensives using a latin-square experimental design with all participants receiving all treatments. As specified in the project plan, analysis was performed after completion of data collection. Initial analysis supports the hypothesis that the point of interference in the angiotensin system has no effect on blood pressure effect or arterial mechanical properties.</p> <p>The laboratory has an ongoing place in cardiovascular research within the centre and the techniques established and staff who have been trained are being used in ongoing projects.</p>
<p>NMRC/0504/2000 Tan Suat Hoon (NSC)</p>	<p>Detection of clonal TCR gamma chain gene re-arrangements in cutaneous T-cell lymphoproliferative disorders by PCR/DGGE</p> <p>The distinction between a malignant lymphoma and benign reactive infiltrate is a challenge for the dermatopathologist. The molecular analysis of TCR γ-chain gene rearrangements has emerged as an important diagnostic tool, to complement histology and immunophenotyping in the diagnosis of T-cell lymphoid infiltrates. The main objective of this project was to establish the technique of clonal PCR detection of TCR γ-chain gene rearrangements in cutaneous T-cell lymphoproliferative disorders and to explore its usefulness with respect to the types of cutaneous T-cell lymphomas, stage of mycosis fungoides, and in the pre-diagnostic stage of cutaneous T-cell lymphomas (CTCL).</p> <p>A total of 86 skin biopsy specimens from 38 patients diagnosed to have CTCL were examined for TCR γ-chain gene rearrangements using the following primer sets: Vγ2, Vγ9, Vγ10 and Vγ11, and Jγ2, Jγp, Jγp1 and Jγp2. For each case, 4 separate PCR reactions were performed on the paraffin sections or frozen tissue. The specimens were grouped as follows:</p> <p>Mycosis fungoides (MF) / Sezary syndrome - 62 cases Non-MF lymphomas - 12 cases</p>

Project No. & PI	Project Title & Abstract
	<p>Pre-diagnostic inflammatory dermatitis - 12 cases</p> <p>Another 14 cases including subacute dermatitis, chronic dermatitis, psoriasis, lichen planus and insect bites were also included in the analysis.</p> <p>The PCR positivity rate was 72.6% (45 cases) for mycosis fungoides, 66.7% (8 cases) for non-MF lymphomas and 33.3% (4 cases) for inflammatory dermatitis. Non-MF lymphomas comprise lymphomatoid papulosis, CD30 + cutaneous T-cell lymphoma (CTCL), T/NK cell lymphoma and pleomorphic CTCL. Inflammatory dermatitis comprise mainly biopsies of other sites from patients who had MF / non-MF or previous biopsies when histology was suggestive or equivocal. In MF, PCR positivity rate was 62.1% in patch stage vs. 85.7% in plaque stage vs. 80% in erythrodermic MF / Sezary syndrome. All the 14 cases of non-lymphoma cases were PCR-negative.</p> <p>The research is the process of offering PCR detection of clonal TCR gene rearrangements and JH heavy chain gene rearrangements as an adjunctive diagnostic test for lymphomas, complementing immunohistology.</p>
<p>NMRC/0021/1994</p> <p>NMRC/0065/1995</p> <p>NMRC/0108/1995</p> <p>A/Prof Yong Eu Leong (NUS)</p>	<p>RNA splicing and human androgen receptor gene mutations</p> <p>Treatment of defective sperm production due to mutations in the androgen receptor gene</p> <p>Molecular mechanisms of androgen receptor mutations in the aetiology of male infertility</p> <p>The principal investigator's laboratory is focused exclusively on the identification and characterization of androgen receptor (AR) mutations associated with human disease. Over 300 pedigrees have been screened for mutations of the AR gene and dozens of mutations/polymorphisms that lead to varying degrees of androgen insensitivity (AIS), from testicular feminization, to minimal AIS associated solely with depressed spermatogenesis and male infertility, have been identified. To characterize their effects, the team has recreated these mutants ARs and systematically examined their effects on every aspect of AR function.</p>

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	<p>Most of the cases of complete AIS have mutations in the DNA and ligand-binding domains and cause disease by disrupting DNA- or ligand binding. However, cases in the minimal AIS group are most interesting as they do not have demonstrable defects in ligand binding even though they are located in the LBD. These mutations are in sub-domains of the AR that by comparisons with available crystallographic data from other steroid receptors, are implicated in interactions with coactivators but which do not actually form part of the ligand-binding pocket. It has been confirmed that the molecular pathogenesis of AR mutations associated with male infertility has two mechanisms. Firstly, the mutations reduce direct interactions of the LBD with coactivator proteins like TIF2. This was most clearly observed in the two-hybrid system, when mutant AR, liganded to DHT, had only half the ability of WT to interact with TIF2. Secondly, these mutations disrupt TAD-LBD interactions; the function of the full-length receptor is impaired, perhaps by disrupting the efficient recruitment of coactivators that normally bind to the TAD in a hormone-independent manner. The third possibility is that TIF2 mediates the linking of AR LBD to the TAD, resulting in a more stable ternary complex with improved transactivation activity. These studies for the first time prove that protein-protein interactions between AR coactivators can lead to human disease. This groundbreaking work has led to many high impact publications. The PI was awarded National University of Singapore Researcher of the Year 1998 and the NSTB Ministerial Citation for research excellence to the PI by DPM Tony Tan in 1999.</p>
<p>NMRC/0383/1999 Dr Evelyn Koay (NUS)</p>	<p>Novel molecular biological approaches for the diagnosis of pre-eclampsia : Measurement of fetal DNA in maternal serum or plasma</p> <p>Many Dukes' B (Stage II) cancer patients die from disease recurrence, due to early tumour spread, which is undetectable by histomorphological examination. The aim of the study was to determine whether quantifying the nodal expression of 3 tumour markers (carcinoembryonic antigen/CEA, cytokeratin-20/CK-20, guanylyl cyclase C/GCC) in colorectal cancer (CRC) would improve the accuracy of stratifying Dukes' B patients into different prognosis groups. The team questioned whether using a single biomarker in one</p>

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	<p>tissue type for the detection of micrometastases, as reported by others, was adequately representative, due to tumour heterogeneity. The team studied 175 frozen lymph nodes and 158 formalin-fixed, paraffin-embedded lymph nodes from 28 CRC cases and obtained gene expression data using CEA, CK-20 and GCC-specific quantitative real-time PCR (R-PCR). There was considerable discordance in the positive detection of the 3 biomarkers in frozen versus fixed tissues in 11 Dukes' B CRC assessed by morphological evaluation. The one patient with full concordances in all 3 markers with both tissue types suffered a fatal relapse within 2 years. These results clearly demonstrated the heterogeneity of biomarker gene expression and the importance of using multiple (at least three) markers and both FT and PET tissues, to precisely predict the metastatic potential of Dukes' B CRC.</p>
<p>NMRC/0296/1998 Chang Hui Meng (SGH)</p>	<p>Food (feed or ordinary diet) trial</p> <p>FOOD is a multi-centre (154 sites) "family" of trials aiming to answer 3 important questions about feeding of patients after stroke: (FOOD I) Does nutritional supplementation increase the proportion of patients with stroke who survive without disability? (FOOD II) Does early initiation of tube feeding (nasogastric [NG] or percutaneous endoscopic gastrostomy [PEG] in patients who are unable to take an adequate diet orally increase the proportion of patients with stroke who survive without severe disability? (FOOD III) Is feeding via a PEG tube instead of the traditional NG tube associated with improved outcomes after stroke? Over 5000 patients have been recruited worldwide, and recruitment was closed in 2004. Overall results will be reported in May 2004. Observational data of 3012 patients from FOOD revealed that poor nutritional status on admission for stroke predicted for poor outcomes.</p> <p>At SGH, the team participated in FOOD II & III. Over 3 years from December 1998 to November 2001, 83 patients were recruited in FOOD trial. Sixty-nine patients were recruited into FOOD II and 14 (8 PEGs and 6 NGs) into FOOD III. During this period, it was established that 17% of the stroke patients were dysphagic within 24 hours of admission, decreasing to 10% after 7 days. It was also found that dysphagia was associated with large strokes, chest infections and predicted for poorer outcomes. These results were</p>

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	<p>presented at 2 regional meetings (Singapore and Thailand) in 1999.</p> <p>Because of the impact of dysphagia on stroke patients, Neurology nursing staff learnt to screen dysphagia in all acute stroke patients in 1999. Since 2000, it became standard practice for nursing staff to screen dysphagia in all stroke patients, 24 hours a day.</p> <p><u>Direct/potential clinical applications of the research project</u></p> <p>Locally, as a result of FOOD trial,</p> <ol style="list-style-type: none"> 1. The data shows that dysphagia was present in 17% of stroke admissions, reducing to 10% after 1 week. 2. Dysphagic patients at SGH also had poorer stroke outcomes. These patients had larger strokes, and were more likely to develop chest infections up to 3 months post-stroke. <p>Following on these findings, neurology nurses have been trained in dysphagia screening to provide 24 hour swallowing assessment to all acute strokes.</p> <p>The tangible improvements in medical care and treatment arising from the project are as follows:</p> <p>At SGH,</p> <ol style="list-style-type: none"> 1. All stroke patients receive an immediate dysphagia screener, regardless of admission time, administered by a trained nurse. Clerking doctors are informed of patient's dysphagic status, and the most appropriate route of feeding ordered, until further review by speech therapist. This will minimise the risk of patients aspirating from inappropriate feeding. 2. Nursing staff have a heightened awareness of dysphagia in Neurology ward. 3. Speech therapists need not review every stroke patient for dysphagia and can concentrate on patients with significant dysphagia and dysphasia.
<p>NMRC/0712/2002 Foo Keong Tatt (SGH)</p>	<p>The natural history of prostatic disease and the selection of patients with symptomatic benign prostatic hyperplasia (BPH) for different modalities of treatment</p> <p>The proposed aim of the study was to improve the treatment of BPH by analyzing in a prospective manner</p>

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	<p>the outcomes of conservative and medical therapy. An earlier phase of the study had looked into improving the outcome of surgical treatment. This was achieved by the successful formulation of a system of classification based on symptoms and life style scores and uroflowmetry and post-void residual urine volumes termed staging. Further refinement was possible by grading the prostate according to its protrusion into the bladder on transabdominal ultrasound.</p> <p>As proposed for this phase of the study, these concepts are now applied to patients on conservative and medical therapy. Medical therapy is attractive and often times the first recommended treatment, as it is non-invasive. However, the long term cost of treatment is high if it is prescribed indiscriminately to all patients and final outcomes may be poor.</p> <p>This may only become obvious on longer follow-up and is the objective of this study.</p> <p>There is a total of 272 patients in the database who had their international prostate symptoms score (IPSS), quality of life index (QoL), uroflowmetry, residual urine volume and intravesical prostatic protrusion measured by transabdominal ultrasound scan meticulously documented by the data clerk. Based on these data, a few important findings on the natural history of BPH were discovered.</p> <p>Grade of prostatic protrusion is the best predictor of whether patients with lower urinary tract symptoms suggestive of BPH would fail from conservative treatment.</p> <p>Based on the same theory, it could be predicted whether a patient with acute retention of urine could be successfully treated without a catheter.</p> <p>Patients with minimal to moderate intravesical protrusion of the prostate demonstrated an improvement in their maximum flow rates with medical therapy. Those with severe intravesical prostate protrusion however experienced a decline in their flow rate in spite of medical therapy.</p> <p>Those patients with high grade intravesical prostatic protrusion with good uroflow rate were actually</p>

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	<p>obstructed when they were subjected to urodynamics testing.</p> <p>These results would therefore support the use of intravesical prostatic protrusion measured by transabdominal ultrasound scan as a useful guide in selecting patients who would be best suited to medical therapy; thus improving treatment outcomes and reducing wasteful long term therapy in those least likely to benefit from such treatment.</p>
<p>NMRC/0482/2000 Howe Tet Sen (SGH)</p>	<p>Pattern analysis & machine intelligence in the detection of fractures in digital radiology</p> <p>The project's aim is to develop a computer system for automated screening and detection of bone fractures in digital x-ray images. The system is designed to analyze digital x-ray images of the bones and perform the following tasks:</p> <ol style="list-style-type: none"> 1. Determines whether the bones are healthy or fractured, and computes confidence of the assessment; 2. Identify cases suspected of fractures and highlight the possible areas where fractures may have occurred. <p>In addition, the project aims to provide a computer system and associated software that perform the following tasks:</p> <ol style="list-style-type: none"> 1. Reads digital x-ray images stored in an external storage device. 2. Identifies the regions of the images where the bones of interests are located. 3. Determines whether the bones of interests are fractured, and measures the confidence of the assessment. 4. For images that contain possibly fractured bones, marks the locations where fractures area suspected. 5. Displays on an output device the results of the automated analysis, such as whether the bones of interests area fractured, and the associated confidence, the locations of suspected fractures, and alerting the doctors to the suspected fractures. <p>The project uses a combination of two or more methods including Active Contour (i.e. Snake) method, each examining different aspects of the x-ray image of the bone, increasing the confidence of the assessment</p>

<i>Project No. & PI</i>	<i>Project Title & Abstract</i>
	<p>accuracy.</p> <p>This research has potential for development of automated hip detection system for use in clinical setting. An initial patent application covering the technology has been filed in US.</p>
<p>NMRC/0428/2000 Daphne Khoo (SGH)</p>	<p>Ethnic differences in autoimmune thyroid disease – the role of TSH-receptor mutations</p> <p>Thyrotropin (TSH) receptor (TSHr) mutations have been investigated in relation to Graves’ disease (GD) genetic susceptibility under the hypothesis that a modified antigen may have novel immunogenic properties. The prevalence of three germline polymorphisms —D36H, P52T, and D727E — were studied in a cohort of multiracial GD patients together with their associations with disease state, Graves’ ophthalmopathy, and thyroid autoantibodies titers.</p> <p>Polymerase chain reaction products of exon 1 and 10e of the TSHr were generated from 164 GD patients (109 Chinese, 34 Malays, and 21 Indians) and 240 individuals with no thyroid illnesses (74 Chinese, 84 Malays, and 82 Indians). Mutations were detected by single-strand conformational polymorphism and confirmed with direct sequencing.</p> <p>The D36H mutation was absent, while significant ethnic differences in the distribution of the P52T and D727E mutations were found. The levels of thyroid autoantibodies also differed significantly amongst the three ethnic groups, with the Indian cohort having the lowest titer. Both the P52T and D727E mutations were not associated with GD. An intron mutation, C/G+63IVS1, was detected and showed significant association with GD. Overall, it conferred a twofold increase risk of GD, while subgroup analysis showed increased odds ratios of 2.4 for Chinese (p = 0.008) and 2.8 for Indian (p = 0.049) but not for the Malay ethnic group.</p> <p>Together with recent identification of disease susceptibility markers in the region of the TSHr gene, these results are supportive of genetic factors existing in this region that may be in linkage disequilibrium with the inheritance of various TSHr polymorphisms.</p>

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	<p>The study led to the discovery of significant association of Graves' disease with an intron region of the TSH receptor gene.</p>
<p>NMRC/0204/1997 Lee Seng Teik (SGH)</p>	<p>The in-vitro investigations of the aqueous extract from the leaves of Chromoneala Odorala (formerly Eupatorium Odoratum), a herbal remedy for the treatment of burns and wounds</p> <p>The achievement of this project is the development of reliable <i>in-vitro</i> systems for fast and low-cost screening of novel pharmaceutical drugs for wound healing and fibrotic scar prevention. Using <i>in-vitro</i> models of wound healing research, the effectiveness of the extract from a medicinal plant, <i>Chromolaena odorata</i>, which has enhanced <i>in-vivo</i> wound healing, was investigated. By investigating different aspects of the healing process, the extract was found to enhance the proliferation of keratinocytes, fibroblasts and endothelial cells. The extract induced keratinocyte migration and production of fibronectin and other adhesion proteins. The extract showed strong antioxidant properties, protecting cultured skin cells from oxidative damage. The phenolic compounds were identified as the active components in the extract. This work could also provide the explanation for the observed clinical efficacy of this plant extract in burns and wound healing.</p> <p>The other interesting and significant data of this work is the elucidation of the role of IGF-I system in epidermal-dermal interaction of keloid pathogenesis. Using an <i>in-vitro</i> double chamber co-culture model, it was demonstrated for the first time that the IGF-I system was highly activated in the presence of epidermis, especially in epidermis derived from keloid scars. This work has contributed to a better understanding of the IGF-I system in keloid pathogenesis, especially the role of the overlying epidermis, which has not been appreciated before. A possible inference to be drawn from this work is that modulating the production of the IGF-I system may represent a novel approach in the treatment of keloid and other excessive scars.</p> <p>The most significant development is the discovery of a phytochemical, quercetin, for the treatment of keloid and hypertrophic scars. Quercetin is a well-known dietary</p>

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	<p>compound with multiple bioactivities including antioxidant and anticancer properties. Using <i>in-vitro</i> models for anti-scar research experimentation, it was found that quercetin is the most effective compound out of ten different dietary compounds which were studied or investigated in detail. Quercetin inhibited the proliferation, collagen deposition and contraction of pathological fibroblasts derived from keloids and hypertrophic scars. At the molecular level, quercetin was shown to effectively block the signal transduction pathways of IGF-I and TGF-β systems, which are established systems causing pathological fibrosis and scar formation. The next step will be the formulation and development of a delivery system of quercetin for clinical trials.</p> <p>The studies led to establishment & improvement of skin culture techniques in treatment of burns victims.</p> <p>Patent filing in the US and EPO is in progress for a composition containing a flavonoid glycone and method for using same as anti-proliferative.</p>
<p>NMRC/0284/1998 Mathew Sebastian (SGH)</p>	<p>The effect of arteriovenous graft configuration on blood flow dynamics & its consequent contribution to the development of fibrointimal hyperplasia and stenosis</p> <p>The failure of prosthetic arteriovenous (AV) grafts used for dialysis in renal patients is due to fibrointimal hyperplasia (FIH) at the venous anastomosis causing stenosis and subsequent obstruction. Pharmacological intervention poses a possible solution. Angiotensin peptides attenuate FIH in rat carotid arteries that had undergone balloon intimal ablation. Similar intervention might also decrease FIH in prosthetic AV grafts.</p> <p>The methodology was to investigate four groups of experimental animals – 2 controls and 2 experimental. The control groups had grafts implanted in 2 different configurations. One was prone to early failure and abandoned. The experimental groups were given des-aspartate angiotensin for a total of 14 days following graft implantation in 2 different concentrations (C1 & C2) and the grafts monitored weekly by duplex scanning until they were completely thrombosed.</p>

<i>Project No. & PI</i>	<i>Project Title & Abstract</i>
	<p>It was found that median time to obstruction for the ipsilateral looped graft was 4 weeks (range 3-10), contralateral looped grafts 19 weeks (range 11-21). With the peptide, graft life was 9.5 (range 4-10) weeks (C1) and 40 weeks (C2). On obstruction, the animals were sacrificed, the grafts harvested and the neointima explanted in tissue culture.</p> <p>Uptake of tritiated thymidine and phenylalanine as a marker of DNA and protein synthesis respectively in the explanted cells did not show any significant difference with the addition of specific receptor antagonists or mitogens.</p> <p>With the addition of des-aspartate angiotensin I, intimal hyperplasia was inhibited and graft potency extended to more than double that for the control group. Once validated, this finding is of great significance for patients with end-stage renal failure on haemodialysis who currently need graft revisions every 18-24 months or so due to FIH at the venous end. Although the result has not yet been published, it has potential to improve clinical service in vascular access for dialysis.</p>
<p>NMRC 0575/2001 Tan Eng King (SGH)</p>	<p>Analysis of Parkin gene mutations in Parkinson's Disease</p> <p>Mutations of Parkin, DJ-1 and other candidate genes may be associated with young onset Parkinson's disease (YOPD) and autosomal recessive PD (ARPD) patients. The objectives were to analyse for pathogenic mutations of Parkin, DJ-1 and other related candidate genes in YOPD and ARPD in the patients and to determine if any genetic variants increase the risk of PD.</p> <p>The methods were to conduct sequence analysis of the exons and exon-intron boundaries of the Parkin and DJ-1 genes in YOPD and ARPD patients and in controls. Gene expression analysis was also carried out for genetic variants found. 65 index YOPD and ARPD patients were examined for Parkin and DJ-1 gene mutations. No pathogenic mutations were found. However, novel Parkin splice variants which may increase the risk of PD were identified. In addition, a number of intronic and exonic variants were also found. Other candidate genes related to PD in case control studies were analysed, but no significant association with PD was found.</p>

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	<p>In conclusion, DJ-1 mutations are likely to be confined to certain genetically isolated populations and hence routine screening for DJ-1 in all PD patients may not be cost-effective. However, abnormal Parkin expression may increase risk of PD. Parkin gene screening is suggested, especially in the younger PD patients.</p> <p>The research provided new data in an Asian population regarding Parkin and related gene mutations in PD. More importantly, it identified new variants which may contribute to disease causation.</p> <p>Immediate clinical applications include</p> <ol style="list-style-type: none"> a) Parkin gene analysis should be primarily restricted to young onset and young PD patients. Genetic testing amongst the older patients will not be cost-effective. b) Closer monitoring of at-risk individuals with specific genotypes and preventive medications should be considered. <p>Long term applications include</p> <ol style="list-style-type: none"> a) Studies on these gene variants in cell culture and animal models with a view to developing therapeutic targets.
<p>NMRC/0489/2000 Gerrard Teoh (SGH)</p>	<p>Regulation of proliferation and survival of multiple myeloma cells by Ku86/Ku86 variant via signals that mediate immunoglobulin isotype class switch recombination</p> <p>The proliferation and survival of multiple myeloma (MM) cells is regulated by numerous factors. Prior studies done by the researchers have demonstrated that triggering via CD40 induces the expression of a novel cell membrane antigen (Ag), Ku86, as well as variants of this Ag (Ku86v) in the majority of patient MM cells. Since CD40 plus interleukin-4 (IL-4) are the most potent signals that mediate normal immunoglobulin (Ig) isotype class switch recombination (CSR), and this process requires the Ku86 protein, it was hypothesized that Ku86 and/or Ku86v protein could be abnormally regulated by these signals that mediate Ig isotype CSR. Moreover, since CD40 is well known to induce the proliferation and survival of MM cells, it was further hypothesized that</p>

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	<p>abnormally regulated Ig isotype CSR could be related to process of tumorigenesis in MM. In this study, it was first demonstrated that CD40 signal transduction was indeed decoupled from IL-4 in MM cells, but not in normal B cells. Next, a potentially oncogenic Ku86v protein, Ku86v-C, was identified in at least 3 human MM cell lines. The DNA and protein sequences of this novel Ag are currently being analyzed using two-dimensional gel electrophoresis (2DGE), high-performance liquid chromatography, mass spectrometry, DNA cloning and sequencing (data is currently embargoed for patent application). In addition, since Ku86 is an important enzyme regulating the repair by non-homologous end joining (NHEJ) of broken double stranded DNA, the team also demonstrated that DNA double strand break repair (DSBR) was indeed abnormal in CD40 activated MM cells. These data suggest that abnormal CD40 induced growth and survival of MM cells could be associated with genomic instability and clonal evolution in MM. The findings therefore suggest that Ku86v-C could be a potential target for therapeutic intervention. Accordingly, the team are using hybridoma technology and phage library systems to produce monoclonal antibodies (mAb) which specifically target Ku86v-C (NMRC/0632/2002, and others). Moreover, the team is planning on using novel methods, including panhandle polymerase chain reaction (PCR), in the near future to study genomic instability and clonal evolution in CD40-triggered MM cells in the future.</p>
<p>NMRC/0632/2002 Gerrard Teoh (SGH)</p>	<p>The generation of novel monoclonal antibodies to tumour-specific antigens expressed on multiple myeloma cells</p> <p>Monoclonal antibodies (mAb) are among the most specific immunological substances that can be used to treat diseases, including cancer. <i>In vitro</i> bulk preparation of murine mAbs was made possible with the discovery of hybridoma technology in 1975 by Nobel laureates, Drs Georges Kohler and Cesar Milstein. The team previously used a modified version of the original Kohler and Milstein hybridoma method, and successfully produced a number of murine mAbs that recognized antigens (Ag) on the cell membrane of CD40 activated multiple myeloma (MM) cells. These mAbs included the 5E2 anti-Ku86 and the 6D11 anti-glucose regulated peptide 94 (GRP94) mAbs. Importantly, functional studies subsequently demonstrated inhibitory</p>

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	<p>(or blocking) properties of 5E2 mAb on cytoadhesion and interleukin-6 (IL-6) secretion of MM and bone marrow stromal cells, suggesting that 5E2 anti-Ku86 mAb could potentially be used therapeutically to treat MM. More recent data further suggested that 5E2 anti-Ku86 mAb could in fact mediate tumor rejection (data is currently embargoed for patent application), paving the way for the development of such mAbs for serotherapy in MM. In order to refine the antigenic targeting of murine mAbs produced in this fashion, a second generation fusion study (i.e. Fusion01A, NMRC/0632/2002) was performed in May 2003, using purified CD40-induced MM cell membrane Ags as immunogens. This strategy of producing anti-tumor mAbs as well as the immunological relevance of molecules (e.g. heat shock proteins) that are identified using this hybridoma strategy, has been reviewed recently by the team. Importantly, Fusion01A was the first somatic hybridization performed in the Hybridoma Facility, SingHealth, at the Outram Campus. The data (also embargoed for patent application) demonstrated that it was feasible to use this strategy to produce mAbs of high anti-tumor specificity. Accordingly, Fusion01B was initiated a year later (May 2004), and included further refinements to the strategy. Currently, greater than 800 original initiating hybridoma clones are being selected using indirect immunofluorescence flow cytometric analysis, Western immunoblotting and propidium iodide staining. There were 168 (>20%) positive hybridoma clones in the first round of screening, and these are currently being subcloned and further selected. The team is optimistic that an mAb of interest and clinical relevance will be identified in Fusion01B. In conclusion, this study (Fusion01A) has provided great insights into the development of hybridomas for mAb production, and marks a milestone in the field of Immunology and translational research in the Outram Campus. It is hoped that clinical-grade mAbs which can be used to treat patients with MM and other diseases will also one day be produced in the current good manufacturing practice (cGMP) facility, SingHealth.</p>
<p>NMRC/0497/2000 Wilder-Smith Annelies (TTSH)</p>	<p>An epidemiological study of the acquisition of N. meningitidis by Hajj travellers and transmission to household contacts via nasopharyngeal carriage</p> <p>An international outbreak among pilgrims returning from</p>

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	<p>the Hajj (pilgrimage to Mecca) and their close contacts was caused by W135 N.meningitidis. The extent of transmission of N.meningitidis in Hajj pilgrims and their contacts was investigated, in order to provide evidence for developing a rational public health policy.</p> <p>The methodology used was, tonsillopharyngeal swabs were taken from Singaporean pilgrims before, and from pilgrims and their household contacts after the Hajj 2001. Serogrouping and pulsed field gel electrophoresis was performed on meningococcal isolates. The prevalence of meningococcal carriage was 0.5% in departing pilgrims and 17% in returning pilgrims. 90% of isolates in Hajj returnees were a single clone identified as a serogroup W135 in most cases, and identical to the strain which caused Hajj-associated invasive meningococcal disease in Singapore. The transmission rate from returning pilgrims to household contacts was 13%. Based on the carriage rate and national epidemiological data, it is estimated that 1 in 120 unvaccinated carriers develop invasive disease.</p> <p>In interpretation of the findings, intense transmission of a single clone of W135 N.meningitidis occurred during the 2001 Hajj. The strain appears to be virulent and can attain high carriage rates. Vaccination covering W135 N.meningitidis should be mandatory for all Hajj pilgrims and recommended to household contacts. The findings support a policy of administering antibiotics to pilgrims prior to their return to eradicate carriage and thereby protect household contacts.</p> <p>The study made the important observation of a high carrier rate of virulent new strain of W135N meningitis in pilgrims returning to Singapore and a high rate of transmission to unvaccinated household contacts.</p>
<p>NMRC/0557/2001 Richard Bellamy (TTSH)</p>	<p>Epidemiology of mycobacterium tuberculosis development of semi-automated, fluorescent-based strain-typing system suitable for construction of a digital database</p> <p>The objectives of this project are to adapt a recently introduced genotyping method for Mycobacterium tuberculosis (Mtb) which is based on the variable-number tandem repeats of mycobacterial interspersed repetitive units (MIRU-VNTR) and to study the genetic</p>

<i>Project No. & PI</i>	<i>Project Title & Abstract</i>
	<p>diversity of Mtb isolates in Singapore using this method. This semi-automated high throughput MIRU-VNTR typing method is to amplify 12 VNTR loci by PCR followed by DNA fragment size analysis on an ABI PRISM Genetic Analyzer using Genescan™ and Genotyper™ software. This method has been successfully established in the laboratory and 303 Mtb isolates have been analysed. These isolates displayed 184 distinct MIRU-VNTR genetic patterns which identify 148 unique isolates and 155 isolates in 36 clusters. Interestingly, a dominant cluster pattern was the same as the representative patterns of China and Malaysia, suggesting the population and geographic relatedness in Singapore, China and Malaysia. The results confirm that MIRU-VNTR typing is a useful method, especially for Mtb isolates with low copy numbers of IS6110; and the results obtained by this method are reproducible, portable, and globally comparable, therefore, suitable for construction of a digital database.</p> <p>This typing method could be used to identify M tuberculosis transmission in hospitals and communities and to confirm whether a reactivation or new infection in a new M tuberculosis patient.</p>

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 and recommendation by the Exco, before they are approved by the Council.

Two research programmes under the supervision of Singapore Eye Research Institute (SERI) and Department of Clinical Research (DCR), SGH, applied and were awarded the Competitive Programme Grant in FY2003. SERI’s programme has 7 collaborators, and DCR has 20 collaborators working in tandem. Both programmes are currently in progress.

COMPETITIVE PRIORITY GRANT (CPRG)

The Competitive Priority Grant (CPRG) was put in place by NMRC in FY2003 to fund high priority research on important national health issues, such as SARS. NMRC set aside \$0.5 million for SARS research.

21 SARS research applications amounting to \$3,353,839 were received. 6 were approved and are currently in progress.

Block Grants

OVERVIEW

Block grants are provided to facilitate the development of core manpower and research capabilities and to 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:

- (a) Core manpower
- (b) Equipment necessary to establish specific areas of research
- (c) Small grants to stimulate research activity.

For mature research institutions, the block grants provide for:

- (a) Core manpower support to run critical research services for the institution
- (b) Core equipment to support general research facilities for the institution
- (c) Small grants for new and pilot projects, especially for new investigators

Block grants are awarded on a yearly basis, and any unutilised funds will lapse at the end of the financial year. Since the inception of NMRC in 1994, NMRC has provided \$197 million for 24 block grants. Currently, there are 21 ongoing 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 FY2003.

Table 5
Institutions that received IBG funding in FY2003

	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 and outcome for FY2003 is detailed in the following sections.

Animal Research Laboratory (NNI-TTSH ARL)

Introduction

Beginning its operations in the first quarter of 2002 and jointly managed by the National Neuroscience Institute (NNI) and Tan Tock Seng Hospital (TTSH), the Animal Research Laboratories provide care and housing for small animals that are essential for medical research at the NNI and TTSH. The ARL block grant supports infrastructure needs of the Laboratories, providing for the manpower and core equipment necessary for its establishment and operations.

In FY2003, the ARL aimed to continue to expand its services and maintain a high level of service and standards.

Activities in FY2003

SPF Facility

Equipment was purchased for special needs: specifically, the expansion of the SPF (specific pathogen free) facility required an additional air purifier system and security protection. The facility is for the housing of transgenic, knockout and immunocompromised animals. The SPF facility accepted its first animals for research studies, following the completion of renovations, and screening of test animals to fulfil quality control requirements. Animals from 2 research projects were housed in the SPF facility.

Support of Surgical Training

The ARL is involved in supporting surgical training courses in basic and advanced abdominal and urological surgical procedures organised by TTSH which employ animals. ARL provides temporary animal housing and manpower assistance during these courses.

Institutional Animal Care and User Committees

ARL is aligning its organisation, protocol and procedures for animal care and use in research to the guidelines of the National Advisory Committee for Laboratory and Animal Research (NACLAR), and has initiated measures to set up Institutional Animal Care and Use Committees.

Research Progress/Outcome

The total number of research projects using the ARL facilities to house animals has increased from 2 to 11 in FY2003, including those using the SPF facility. The ARL housed more than 3000 animals during this period. Most of the animal research studies supported by the ARL apply therapeutic studies in animal models, which may support or lead to therapeutic trials on humans. The majority are currently in progress.

Clinical Trials & Epidemiology Research Unit (CTERU)

Introduction

Established in 1996 with funding from NMRC, the Clinical Trials & Epidemiological Research Unit's (CTERU) primary objective is to provide the biostatistical, epidemiological, evidence base and operational backbone of academic clinical research investigations in Singapore. The block grant supports the ongoing work of the Unit so that collaborations with the healthcare community are undertaken in a timely fashion and to the highest international standards; leading through research to evidence based clinical decisions to the benefit of Singapore citizens.

The block grant funds a critical mass of key clinical research infrastructure and expertise in one location that would not be cost-effective for individual hospitals or institutions to maintain in isolation. These include:

- a) Research expertise in biostatistics, clinical project management, database design and management, data analysis, interpretation & report writing, Research design, database searching, critical appraisal of literature, systematic reviews, meta-analysis and epidemiology
- b) Core facilities such as an industry standard clinical trials database and management system, a 24-hr web randomization service, a phone randomization service, statistical & Evidence Based Medicine (EBM) software, specialized research literature databases, data-entry workstations for external collaborators to enter data
- c) Collaborative research projects from single-centre studies to multi-centre/national Research Clinical Trials (RCT), systematic reviews & meta-analysis, national surveys and clinical audits, clinical practice guideline development with MOH, postgraduate training in clinical research methodology and statistics, expert consultancy to journals, hospital, cluster and regulatory bodies.

Professional Activities in FY2003

Clinical Trials, Epidemiological and Evidence Based Medicine Projects

CTERU has a continuous roll-over of Clinical trials, and Epidemiological and Evidence Based Medicine projects done in collaboration with public healthcare institutions, MOH and the private sector. In addition, ad hoc consultancy and 'clinics', and an extensive support of postgraduate training continues to require a substantial input from the Unit. The Unit also supports Singapore clinical research infrastructure through participation at the level of NMRC, BMRC, CDE/CPA, Hospital & Cluster R&D Committees, Hospital & Cluster IRBs or DSRBs, Clinical Trials Coordinating Committee and MOH.

As at March 2004, 52 Clinical Trials were supported by CTERU. 18 clinical trials were closed, 6 were completed, 18 were open and 10 were at the design stage.

CTERU staff also supported a total of 27 Epidemiological Studies, where 13 were in progress, 9 were preparing for publication, 2 had been submitted for publication, 2 were at the design stage, and 1 had been suspended.

23 Evidence Based Activities were completed with the participation of CTERU staff: 6 Reviewed Protocols were in progress and 4 Clinical Practice Guidelines (CPG) were completed, with 6 still in progress.

19 projects were supported by the Evidence-Based Medicine Section for the International Conference on Evidence-based Medicine incorporating the 10th Annual Singapore General Hospital-Stanford University Hospital Joint Update.

Training courses, Papers and Abstracts/Presentations/Posters

In FY2003, CTERU conducted or was involved in 35 training courses conducted in Singapore, on: Evidence Based Medicine, Good Clinical Practices, SPSS and Biostatistics, Epidemiology, Research Design, writing research proposals, logistical issues in research, statistical analysis, systematic review, Nursing Clinical Practice Guidelines and nursing research, among other conferences and workshops.

During this period, the Unit published 59 papers, and also conducted 6 talks and 5 abstracts/presentations/posters, 2 of which won awards for oral presentation.

Department of Clinical Research (DCR), SGH

Introduction

The Department of Clinical Research (DCR) was established in 1990 under the Ministry of Health and has been funded by NMRC since 1994. The Department was transferred to Singapore General Hospital (SGH) in 1999, and came under the Division of Research in 2001. In FY2003, the DCR met its main objectives:

1. To be the core basic research facility of SGH
2. To promote laboratory-based research
3. To assist clinicians in pursuing research interest
4. To provide scientific and technical expertise through a team of research scientists and technicians
5. To provide financial support through seed funding for small research projects

Activities in FY2003

DCR Research Equipment & Resource Centre

The core research equipment funded by the block grant is used by all researchers within the hospital for individual research projects funded by NMRC, BMRC or SingHealth. More than 70 projects were being supported by the DCR's facilities in FY2003. These facilities are:

- Cell Culture Labs (2)
- Molecular Biology Labs (2)
- Flow Cytometry Labs (2)
- Analytical & Endocrine Labs (2)
- Confocal Microscopy Lab
- Automatic DNA Sequencing & Real-Time PCR Lab
- Radioactive Lab
- Electrophysiology Lab
- Microarray Lab (New)
- Common Utilities & Chemical Rooms
- Cold Room

The DCR's heavily-utilised Resource Centre, with over 500 titles and 20 scientific journals, provides extensive coverage in all research areas. The DCR's extensive facilities provide clinicians returning from overseas training with the means to continue the pursuit of their research interests.

Small/Start-up Grants

A block vote under the DCR IBG goes towards providing seed money for small research projects. A total of 43 grants were awarded in FY2003.

Research Manpower

The Department funds a team of research scientists, with varied interests in molecular biology, molecular neurobiology, haematology, immunology, endocrinology, pathology and biochemistry; collaborating with clinicians, overseeing the operation of major core equipments and providing technical advice and training.

A biostatistician provides researchers of basic science, clinical and epidemiological research with statistical assistance from the planning stage and preparation of grant proposals to the statistical reporting for publications.

Training & Research Networking

For interaction between clinicians, clinician-scientists, research scientists and research technologists, the DCR's active Journal Club held 7 meetings in FY2003. The journal club meetings give a platform for members or invited speakers to share findings or impart specialised skills. In addition, 4 seminars were organised in FY2003 to update researchers on latest technologies and recent advances in life sciences and medical research.

Staff members were involved in training undergraduate and postgraduate students. Several end-users' training sessions were also conducted for optimum and proper usage of specialised equipment.

Research outcome

A significant milestone in basic research for the DCR in 2003 was a publication made in CELL, a prestigious US-based scientific journal of high impact factor (27.254), on the groundbreaking research conducted at its Neurobiology Lab. Associate Professor Dr. Xiao Zhi Cheng led a team of researchers in exploring the degenerative diseases that affect the central nervous system and achieved international recognition with this publication. Within the same week, a second paper was accepted by EMBO, another international journal of high impact factor (10.698). These excellent achievements were the result of collaborative effort with an international team of scientists.

FY2003 was a fruitful year for the Department, which met its targeted performance indicators with 30 publications, 8 postgraduates and 4 undergraduates trained.

Department of Experimental Surgery (DES), SGH

Introduction

The Department of Experimental Surgery (DES) aims to have a comprehensive experimental surgery and related research facilities and services which are capable of conducting a wide range of research and training activities. The Department functions as an open laboratory serving researchers in the SingHealth cluster and throughout the nation.

The Department's facilities are:

- The Open Laboratory, a prefabricated structure in SGH which houses the rodent and primate holding centre, research laboratories and an administrative wing;
- The Cadaveric Repository, which generates cold room storage for cadavers and workstations for the conduct of biomechanical and anatomical research, and;
- The Animal Husbandry & Hospital (AH&H) in Sembawang, which provides breeding, quarantine and convalescing spaces for post operative animals.

The DES continues to focus its research direction on the following programs: experimental oncology, viral hepatitis, pancreatic transplantation, engineered tissue replacement and anatomical biomechanics.

It is also the mission of the DES to encourage and promote collaborative studies with multi-disciplinary research groups that are geared towards clinical applications and healthcare development. These collaborations allow the pooling of expertise and tap on the resources of individual members and their Institutions for synergy and greater scientific output.

Activities in FY2003

Efforts towards international standards and accreditation

The SGH Institutional Animal Care & Use Committee (IACUC), formed in October 2002, conducted its first program and site inspection review and evaluation of the facilities in the DES in August 2003. The Association for Accreditation & Assessment of Laboratory Animal Care (AAALAC) conducted and evaluated the animal care and use program of DES in December 2003. SGH Occupational Health Safety Accreditation (OHSA) team conducted its audit exercise in January 2004.

All these activities are in line with the DES's effort to achieve international standards and accreditation, and are in compliance with the national guidelines of National Advisory Committee on Laboratory Animal Research (NACLAR). International standards accreditation will attract international academic and industrial collaboration.

Plans for expansion and re-designation of Clinical Skills Laboratory

The Medical Board in SGH gave provisional approval in the capital budget for FY2004 to expand and re-designate the Clinical Skills Laboratory to a Learning Skills Centre with the addition of approximately 240m² training spaces which incorporates structural design for radiological procedure.

Training

Manpower capability was improved with the implementation of proficiency in safe animal handling and husbandry procedures. The staff have also undergone mandatory training courses in basic radiation safety, microsurgery, basic surgical skills and participated in online AALAS courses.

Due to the SARS outbreak, several scheduled courses were cancelled and future courses placed on hold. Nevertheless, 20 surgical skills training workshops was still hosted in the Clinical Skills Laboratory during the year.

Others

Maccine Pte Ltd, a spin-off entity of the University of Monash, Australia, leased spaces in DES for the set up of a non-human primate centre for CRO activities and contacted our specialized services to fulfill their contractual obligations.

Research Activities and Outcome

For FY2003, 35 research projects were implemented, which generated 10 publications and 6 research awards. 6 contracted and collaborative research projects were conducted with local and overseas companies in the areas of pre-clinical trial evaluation of drugs and devices. These include research activities involving pSiOncology Pte Ltd, the first research spin-off company in SGH which is a joint-venture between SGH, Biotech Research Ventures Pte Ltd (BRV) and pSiMedica of the United Kingdom.

The Department of Experimental Surgery is well positioned to become a principal research institution with strengths in animal and cadaveric models.

Institute of Mental Health (IMH)

Introduction

The Institute of Mental Health aims to nurture a thriving research culture which conducts clinically relevant research with a critical mass of committed researchers; and to establish itself as an internationally renowned Research Centre.

The grant supports research administration staff, training conducted in research methodologies, statistical analysis and ethical issues, and research activities; where the strategy is to focus on key areas where potential yield would be greatest and collaborate with other renowned research centres. These key areas are psychiatric epidemiology, brain imaging, psychiatric genetics, clinical drug trials and health service research.

Activities in FY2003

Psychiatric Epidemiology

Psychiatric epidemiological studies are important for understanding risk factors and prevalence rates, and are especially vital in providing data for the formulation of health policies. A community survey on the prevalence of depressive disorders, anxiety disorders and dementia was recently completed and a study on the mental health of school children is ongoing.

Brain Imaging

Brain imaging studies examine the structural abnormalities of individuals with psychosis and those at high risk of developing this disorder. A hitherto unreported abnormality was found in the hippocampus of those with first episode psychosis. IMH aims to establish a Neuropsychiatric programme in collaboration with the National Neuroscience Institute and the University of Melbourne.

Psychiatric Genetics

Psychiatric genetics and the emerging field of pharmacogenetics examine the contribution of genetic factors in a patient's response to medications. In collaboration with Defence Medical Research Institute, IMH has made an in-depth study of the genetics of tardive dyskinesia, one of the most severe side effects of antipsychotic treatment. At present, IMH is also in discussion with the Genome Institute of Singapore (GIS), Singapore Tissue Network (STN) and Harvard Medical School, to develop an ongoing genetic programme that capitalises on its rich clinical pool, the cutting edge technology of GIS and STN, and the research expertise of Harvard Medical School.

Clinical Drug Trials

With the IBG, IMH has been able to establish an infrastructure for clinical drug trials and attract a number of industry-sponsored trials. These studies allow IMH patients to have access to new and potentially more effective drugs, provide training to Investigators on conducting studies while observing good clinical practices (GCPs), increase the profile of the Institute, and generate income.

Research Progress/Outcomes

The outcomes of IMH's research in FY2003 are detailed as follows:

- a) In the wake of the SARS epidemic, a nation-wide survey on the psychological effects of SARS was conducted among hospital and primary health care workers. A high prevalence of psychiatric morbidity and perception of stigma was found among health care workers, highlighting the importance of protecting front-line care givers both physically and mentally, to combat SARS effectively.
- b) A study on *Untreated psychosis: duration and causes* established the duration of untreated psychosis in Singapore and the pathways to care taken by psychiatric patients. It helped in establishing the EPIP programme funded by MOH.
- c) A pilot study developed a culturally relevant and sensitive cognitive behavioural therapy (CBT) for children in Singapore with anxiety. There is currently an ongoing group in child guidance clinic on the CBT developed by the Principal Investigators.
- d) A study on the *Association of psychotropic drugs and other risk factors with QTc lengthening* established the role of psychotropic drugs in QTc lengthening in the local context, and went on to highlight the importance of ECG monitoring in psychiatric patients.
- e) A study of *Abnormalities in glucose regulation during treatment with atypical antipsychotics and lipid abnormalities with atypical antipsychotics* noted a significant weight and BMI increase in patients treated with anti-psychotics. The need for monitoring and use of psychoeducation programmes has been highlighted and adopted in the hospital. Patients with pre-existing risk factors for diabetes are monitored carefully when started on second-generation anti-psychotics.
- f) The results of a study on *Obsessive Compulsive Symptoms (OCS) and atypical antipsychotic use* will alert clinicians to the extent of the problem of de novo OCS with atypical antipsychotic use amongst local patients, leading to its early diagnosis and treatment.

Summary of Research Output

In sum, the research achievements in FY2003 were 3 drug trials, 37 publications; 54 presentations; 1 completed PhD awarded by University College London, 2 ongoing PhDs, 1 ongoing MD; and collaborative studies with 4 other centers.

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

Introduction

The block grant enables the MOH-Nursing Research Committee (MOH-NRC) to better promote research activities and formulate evidence-based guidelines on critical areas of nursing care, with the objective of improving the standard of nursing care.

In FY2003, the block grant funds were 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 and research studies and activities. The block grant consisted of 3 broad categories: 1) provision of core resources; 2) funding of research projects; and 3) funding for 9 CPG development projects.

Activities in FY2003

Provision of Core Resources

Core equipment such as books, databases, subscriptions, a form processing software and a document scanner were purchased during FY2003. These were used for supporting research projects and the development and implementation of CPGs.

Research Projects

32 nursing studies were completed by nurses in 2003. 10 articles were published in peer-reviewed journals and 62 presentations were made in institutions, national and international seminars and conferences. The majority of these projects utilized the resources funded by the block grant.

CPG Development Projects

The CPG “Nursing Management of Patients with Urinary Incontinence” was published in December 2003. This CPG was officially launched by Chief Nursing Officer in Mar 04. A re-print of the CPG “Management of Breastfeeding for Healthy Full-term Infants” was made in December 2003.

The Nursing Branch is currently working with seven guideline workgroups to produce CPG for the following topics:

- Oral Hygiene Care for Dependent Patients
- Prevention of Infections Related to Central Venous Devices in Children
- Nursing Management of Venous Leg Ulcers
- Prevention of Fall in Institutions
- Management of Breastfeeding for Pre-Term Infants
- Nursing Management of Patients on Nasogastric Tube
- Nursing Management of Patients with Potentially Violent Behaviours

National Birth Defects Registry (NBDR)

The National Birth Defect Registry was set up in 1993 and shifted to KK Women's and Children's Hospital in 1999. NBDR has become an important source of clinical data, providing important national information on birth defects, its trends, risk factors, and the effect of prenatal diagnosis and intervention. Comprehensive ascertainment of live births, stillbirths and abortus with fetal anomalies are included in the reporting to the system.

A number of articles and papers have been written using data from NBDR, and there has been much media interest in information such as the incidence of polydactyl, older mothers and associated birth defects risks. Many requests have been made for relevant processed data from the Registry by various medical professionals, for use in their planning and work, such as data on cleft lip and palate (plastic surgeons), occupational effects (workplace epidemiologists) and Down syndromes (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. More requests for information from the media and from professional bodies in Singapore will be expected.

Annual reports are prepared with the aim to provide an overview of the annual changes in the population with birth defects and other vital statistics, and will prove useful for academics, demographers and medical professionals. The Annual Report also aims to collate information on a national scale and hopes to facilitate the planning and evaluation of antenatal screening, genetic counseling and paediatric medical and surgical services.

National Cancer Centre (NCC)

Introduction

NCC conducts research leading to clinical applications in oncology. The ultimate aim is to improve the survival and quality of life of cancer patients. Research programmes and projects in NCC are conducted under its three research divisions – the Division of Cellular & Molecular Research (CMR), the Division of Medical Sciences (DMS) and the Division of Clinical Trials & Epidemiological Sciences (CTE).

Activities in FY2003

In FY2003, the NCC block grant supported the completion of 20 research projects/clinical trials, 161 ongoing or new projects, and 19 projects funded by NMRC competitive grants. 119 publications, 66 international conference papers, 22 local conference papers, 23 lectures as invited speakers, 5 international awards and 4 local awards have resulted. Some of the highlights of the research outcome are below.

Clinical Trials and Epidemiological Sciences Programme

The Clinical Trials and Epidemiological Sciences Programme has applied Bayesian statistical approaches to clinical trials, to guard against inappropriate early trial termination and in the design of randomised trials for rare cancers.

Shorter Quality of Life (QoL) measurement scales have also been developed by the programme, which allow for the easier and less expensive collection of QoL data in clinical care and clinical research.

With regards to life-course modelling, the programme identified that a person's paediatric body mass index could be used to accurately predict obesity and the tendency to be overweight in middle-age – opening up the possibility of early intervention programs.

Clinical trials have (1) resulted in improved patient outcomes such as improved survival in a randomized trial of chemo-radiotherapy (RT) vs. radiotherapy for nasopharyngeal cancer (NPC); (2) provided patients with alternative treatments to surgery such as 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); and (4) definitively shown that certain treatments were of no benefit, such as Tamoxifen in liver cancers. Patients have even been provided with access to the latest medicines before they were made commercially available. One such example is Gleevec, which prolongs the lives of patients with a previously uniformly fatal cancer.

A Phase II study of the pharmacokinetic and pharmacodynamics of irinotecan (CPT-11) in NPC patients was completed. Two main toxicities limiting the use of CPT-11 in cancer patients are diarrhoea and myelosuppression. Severe diarrhoea (grade 3 or 4) is uncommon in our population, while myelosuppression is more common. This was correlated with exposure levels to SN-38, the active and cytotoxic metabolite of CPT-11.

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 study is currently validating the finding in a larger population of cancer patients.

In collaboration with SUGEN, a preclinical study has shown that adding antiangiogenic agents, following photodynamic therapy, delays tumour growth and improves survival time.

In heart and kidney transplants, it is important that patients receive the optimal dose of cyclosporin, achieving therapeutic levels of the drug to minimise graft rejection. Results show that certain haplotypes (i.e. combination of SNPs [single nucleotide polymorphisms]) in the MDR1 gene influence exposure levels to cyclin A (CycA) in heart transplant patients. This knowledge will better enable clinicians to optimise the cyclosporin levels for patients undergoing transplants. This may be extended to include bone marrow transplant patients, if studies can prove its applicability.

HPLC(high performance liquid chromatography)-based assay methods are being developed to monitor other immunosuppressive agents commonly used to prevent graft rejection, as well as to prevent GVHD (grafts versus host disease) in cancer transplant patients.

Division of Medical Sciences Programme

Clinical trials are in progress to exploit increased sensitivity of fluorescence urine cytology for bladder cancer detection, and fluorescence endomicroscopy for the early diagnosis of oral and cervical cancer. A clinical research service with genotyping of breast cancer genes is now being offered to women at high-risk of breast and/or ovarian cancer. A diagnostic for gastric cancer using patient samples is being validated in collaboration with CIPHERGEN Biosystems Inc. and a large medical centre in Yunnan, China.

A Phase I/II trial of reduced-intensity blood stem cell transplantation for metastatic nasopharyngeal cancer showed encouraging clinical efficacy. The treatment of solid tumours (bladder and oral cancers) with photo-sensitizers is also under clinical trial, with good results.

Cellular & Molecular Research Programme

Gene therapy represents a promising approach for the treatment of inherited or acquired diseases. A novel series of Herpes Simplex Virus-1 (HSV-1) that confers specific gene expression that is controlled by cell cycle events has been engineered. NCC research is in the process of inserting various therapeutic genes into these viruses for cancer gene therapy experiments.

An integrated bioinformatics infrastructure for the production, storage and analysis of DNA microarrays to perform large scale genomic experiments has been established, and tumour-specific genes have been characterised for common cancers in Singapore, such as cervical cancer, nasopharyngeal carcinoma, hepatocellular carcinoma, breast cancer and gastric cancer. NCC research has also developed novel approaches for the prevention and treatment of breast cancer using physiological signals that encourage terminal differentiation.

National Heart Centre (NHC)

Introduction

The National Heart Centre's objectives for FY2003 were:

- 1) To promote and develop basic and molecular research capabilities, especially in the area of stem cell research for the repair of the failing heart;
- 2) To expand the imaging and experimentation capability for large animal studies at the National Heart Centre i.e. to update and improve our animal lab facilities;
- 3) To promote development of innovative mechanical devices for various common cardiac conditions e.g. minimally invasive devices for cell replacement therapy and to deliver successful ones to the practicing cardiologist and patients;
- 4) To set up a tissue engineering facility (the ability to grow human tissue mixed with mechanical scaffolding for organ replacement therapy) with biomaterials engineers to identify and nurture technological solutions for cardiovascular diseases;
- 5) To create a research culture (particularly translational research from the bench to bedside) in the National Heart Centre that is 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 business and government agencies;
- 8) To consolidate existing projects with renowned overseas investigators and promote further collaboration with them.

Activities in FY2003

Experimental Angiographic and Imaging Suite

A large part of the funding for FY2003 (Core Equipment) was used for expanding the imaging and experimentation capability for large animal studies at the National Heart centre. A GE 9800 Digital C-arm fluoroscopic camera was purchased and an angiographic suite set up. NHC has started using this imaging tool for many large animal studies involving stem cell transplantation as well as testing of interventional devices such as stents. In addition, an Echocardiogram machine with necessary attachments for imaging hearts of large and small animals was purchased. These two imaging modalities alone have greatly improved the ability of NHC research to test and experiment on cutting edge minimally invasive technology.

Improvement of Wet Lab at School of Nursing, SingHealth Research Facilities

The Vascular Biology Consortium, consisting of collaboration between NHC, National Neuroscience Institute, Baker Heart Research Institute and Howard Florey Institute, Australia, has moved into the Wet Lab, which is located at the School of Nursing, SingHealth Research Facilities (sited on the Outram Campus). The laboratory was updated in terms of basic equipment such as freezers, fridges, Gel Doc system etc.

The six wet labs located at the NHC building were also updated with equipment such as a Cryostat for microscopic work.

Core Research Manpower

The block grant continues to fund core research manpower, supporting principal investigators and upcoming scientists who have good productivity in research. With funding support for core research manpower, NHC is able to maintain a critical mass of core research scientists to provide continuity of research at the NHC.

The FY2003 block grant has helped NHC to better support the existing Principal Investigators with the development and advancement of their projects, and also to promote further research collaboration and future commercialization.

Research output

22 projects were being supported by NHC core facilities in FY2003. 17 publications, 11 conferences presentations and 4 scientific awards were achieved during this period.

National Neuroscience Institute (NNI)

Introduction

The National Neuroscience Institute's (NNI) mission is to develop neuroscience research to improve patient care by advancing knowledge in neuroscience. NNI's neuroscience research will promote national health and medical excellence, the Singapore Biomedical Initiative and the international reputation of Singapore in medical care and research.

In support of this mission, the IBG is the sole source of funding to NNI for its entire research infrastructure: including core equipment, core scientists/researchers and support staff, and a research administration. In addition, it supports training, collaborations, presentations and library facilities, which are intended to enhance research expertise and outcomes.

Activities in FY2003

Manpower Strategy for Research

The grant continues to support the manpower critical to the development of neuroscience research. Manpower support is now increasingly aligned to a more focused research strategy and direction: to foster researchers and research groups collaborating in research fields of vital importance and in which NNI has particular strengths, such as Parkinson's disease (neurodegenerative disorders), molecular genetics, stem cells and neuroradiology.

Two new principal investigators from Singapore and the United States of America joined the fold in FY2003.

New Equipment in Support of Neuroscience Research

The NNI continued to build up its range of strategic core equipment at the start of FY2003 with the block grant funds. These include:

- a) The FACS Aria Flow Cytometer which has the capability to sort rare cell types, such as adult stem cells.
- b) 2 units of CO2 incubators and a 3-loop solenoid coil to adapt MRI scanning for small animal imaging
- c) Basic laboratory equipment for start up of new PIs' laboratories and for use by central research support services
- d) Equipment to meet increased security needs of the research laboratories, namely surveillance cameras

The grant underpins NNI's research programmes and projects (all of which are funded by competitive grants) by providing the infrastructure and other support without which none of them may proceed.

Research Outcome

NNI's research in FY2003 encompassed a total of 37 projects, of which 11 were newly awarded by NMRC's competitive grant. They cover the range of basic neuroscience studies, translational research studies to clinical studies, including epidemiological studies and databases.

A total of 29 publications and 35 scientific presentations were put forward by the research. Two Memorandums of Understanding with private entities were signed.

At the end of FY2003, 14 clinical trials were concluded and 15 clinical trials, both academic and commercial, were ongoing, with assistance from the NNI research administrative staff. While the trials involve a wide range of neurological disorders, experience is particularly strong in stroke, with 18 stroke trials to date. These trials, in which patients are invited to participate, bring the latest therapy to Singapore, and place NNI and Singapore favourably as the leading centre for clinical trials in the region.

National University Medical Institute (NUMI)

Introduction

NUMI focused its efforts to 1) develop centralized research facilities and services for biomedical users in the locality of the Clinical Research Centre; and 2) recruit research scientists to develop research programmes in cancer and cardiovascular diseases. NUMI's facilities are funded by the block grant and include Confocal Microscopy, DNA sequencing, flow cytometry, in situ Hybridization, Media preparation, Medical Communications, Store, Transgenic and Gene Knockout (Mouse Facility) and Workshop. The steady increase in the number of end-users, who are not exclusively restricted to the Faculty of Medicine, is reflective of continued success of these services.

The overall objectives of the NUMI block grant are two-fold: to sustain and enhance the capabilities of NUMI Core facilities and to maintain support for the research programmes supported by the block grant, which are namely, the Cardiovascular Research Programme and the Oncology Research Programme.

Activities in FY2003

Cardiovascular Research Programme

A major part of the research program that is currently being run is based on human myoblast and allogenic bone marrow cell transplantation in relation to cellular cardiomyoplasty in small and large animal models of myocardial infarction. Myogenic donor cell transplantation for cardiac repair is a potential new strategy to regenerate irreversibly damaged cardiac tissues and structures.

The team has successfully developed a pig heart model of myocardial infarction by coronary artery ligation. Human skeletal myoblasts were provided by Cell Transplant Pvt Ltd, Singapore. The cells were transduced with angiogenic growth factors, which were developed and provided by a collaborator from DBS, National University of Singapore. The cells carrying angiogenic growth factors were transplanted in the infarcted myocardium of the pig which was immunosuppressed to allow xenomyoblast survival post transplantation. This is a novel approach to combine angiogenesis and heart cell therapy for cardiac repair. The team has used the same strategy for the treatment of peripheral vascular disease in the hind limb ischemia model in a rabbit. The results of these studies have already been presented at various regional and International scientific meetings. The project is presently engaged in elucidation of molecular basis of this new therapeutic strategy and the role of various cytokines in the donor cell survival. These findings will have far reaching implications on optimization of transplantation conditions and the clinical outcome of the procedure.

The Cardiovascular Research Programme has achieved 5 presentations and 2 awards.

Oncology Research Programme

The focus of research in the Oncology Research Programme has been on 4 main cancers: gastric, breast, colorectal and leukemia.

Two main studies are being conducted on Gastric Cancer. Both projects involved inter-institutional collaborations with NUH, IMCB, GIS and SGH. They are:

- 1) Examining the role of RUNX3 in human gastric cancer, with the objective to do a retrospective study using archived tissue to examine the methylation of the RUNX3 gene and the expression of MUC6, CDX2, MUC2, PCNA and a few others, to see whether they can be used in the early detection of gastric cancer.
- 2) A study of a cohort of 2,000 high risk patients by examining their biopsy specimens following the results obtained in the first study.

The Breast Cancer programme also involves collaboration with NUH, and is exploring collaboration with the Karolinska Institute. The 2 projects currently being pursued are:

- 1) The study of the methylation status of several genes involved in breast cancer; the specific aim is to see whether there are ethnic differences in breast cancer formation/development of breast cancer; and
- 2) Possible involvement of RUNX3 in breast cancer – inactivation of RUNX3 was found in about 30% of breast cancer.

The multi-disciplinary team is also seeking to develop a method of early detection of breast cancer using serum from patients and through the analysis of the methylation of a set of genes.

Since there is strong evidence that RUNX3 is likely to be involved in human colon cancer based upon the results from the RUNX team in IMCB working on the mouse system, and another potential tumour suppressor gene, CC3, the Colorectal Cancer project is analysing the involvement of these genes in colon cancer. Inter-institutional collaboration has been initiated with the Dept of Colorectal Surgery in SGH.

There are 2 main studies in area of Leukemia:

- 1) Development of the mouse model of FPD/AML (Familial Platelet Disorder with propensity to Acute Myeloid Leukemia)
- 2) 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.

Most of the studies above are translational in nature given the mandate of the Oncology Research Institute to further research in the area of translational medicine and strengthen the research capability of clinicians. The Oncology Research Programme has achieved a total of 5 publications, 20 presentations and 1 award in FY2003. A patent is also being filed.

National University of Singapore (NUS)

Introduction

The NUS Block Vote was used to fund small and start up grants submitted to the Faculty of Medicine. It provides for new academic staff to conduct pilot studies and assists new faculty members in setting up their laboratories while waiting for the approval of their major grants. The block grant tides the new academic staff over this period. The following are some highlights of the achievements of the 38 small and start-up projects being funded in FY2003.

Highlights of FY2003

Processing pathway of nociception and nocistatin from prepronociception

Pain is a multi-dimensional sensory experience that is intrinsically unpleasant and associated with hurting and soreness. Chronic pain is usually associated with any damage or lesions to nervous system. Nociceptin (NCP) and nocistatin (NST) are two neuropeptides derived from the same precursor protein that exhibit opposing effects on spinal neurotransmission and nociception. Given the existence of NCP and NST on the same prepronociceptin, which play opposite roles in pain transmission in central actions, it will be crucial to identify the conditions under which the peptides are released, and the circuitry on which they act. Little is known about the sites of precursor synthesis, cleavage and maturation into final products in human CNS. Knowledge on these precursor polypeptides, their most active forms and further modifications are very important in understanding the pain response. The human nociceptin precursor is known to have at least four putative processing points, consisting of double basic amino acid sequences, and NST is located at the upstream of NCP just flanked by Lys.ARG. It will be clarified whether NCP and NST are equally released as their matured forms or separately processed, which suggests the mechanisms of chronic pain perception and provide helpful hints for therapeutics.

Effects of tumour necrosis factor on the development, formation, function and characteristics of osteoclasts

It is envisaged that the models to be developed and set up will provide valuable tools for further research into the mechanisms of bone resorption and bone turnover. In the light of possible interactions that TNF α may have with the fundamental cellular processes that control osteoclast formation and thus bone turnover, research that furthers the elucidation of such interactions may have significance in the understanding of the basic processes of bone balance, and in the development of potential therapeutic strategies against clinical conditions of accelerated bone loss.

Elucidation of functional metallothionein isoforms in breast myoepithelial, premalignant and malignant cells in vitro

The MT-2A isoform is a potential target for the development of cancer therapeutics.

Environmental endotoxin exposure and its relationship with atopy and allergy symptoms in the first two years of life

Since allergy symptoms are not well studied in this age group in Singapore, the data can be used to propose appropriate treatment guidelines. Indonesia is expected to complete the database of the Phase I cross-sectional survey and is now preparing for Phase II and III. This study was highlighted during November 2003's Asia Pacific Association of Pediatric Allergy, Respiratory or Immunology (APAPARI) workshop and a call for regional participation was made.

The expression of IL-6 in the nerve fibers in the myocardium in response to biomechanical stimuli might be a novel target to treat heart failure

Proinflammatory cytokines are believed to be implicated in the development of heart disease but clinical trials showed that anti-cytokine therapy failed to provide beneficial roles in heart diseases, suggesting the incomplete understanding of the cytokines in heart diseases. It is noted that most studies of cytokines in the heart disease are mainly focused on the myocardium or circulation. The present study suggested that the investigation of cytokines should be extended to the cytokines induced in the central nervous system; it should be noted that current anti-cytokine drugs cannot reach the CNS because of the existence of blood-brain barrier. Therefore, the cytokines in the CNS might be the novel role to treat heart diseases.

The effects of different heparins & activators on activated clotting time

The research project has shown that porcine heparins tend to produce lower activated clotting time tests with MAX-ACT activator, compared to celite and kaolin activators. Bovine heparins did not produce any difference in activated clotting time tests for the 3 activators. Traditionally, an activated clotting time of 4 seconds is used as an indicator of adequate anti-coagulation to go on cardiopulmonary bypass for cardiac surgery. Celite or kaolin activators were used to produce this activated clotting time result. The introduction of activator MAX-ACT into clinical practice has prompted the question whether the traditional value of 400 seconds for activated clotting time is still applicable for this new activator. MAX-ACT would produce a lower activated clotting time than celite or kaolin and lead to additional heparins being administered to the patients to achieve an activated clotting time above 400 seconds when it is not necessary. In the post-operative period, these extra heparins may potentiate bleeding and surgical re-exploration from insufficient reversal with protamine. This may lead to considerable morbidities and mortalities.

The creation of the standard heparin concentration-activated clotting time curves for the various heparins and activators would be useful for the estimation of heparin concentration from activated clotting time tests. This knowledge is used to guide anti-coagulation therapy during cardiopulmonary bypass and reversal of heparin effects with protamine.

Singapore Cardiac Data Bank (SCDB)

Introduction

Established in 1999, the Singapore Cardiac Data Bank (SCDB) is a collaboration project and joint effort among the Cardiac Department 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 hospital for benchmarking, quality care and outcome management. Statistics provided by SCDB enables comparative assessments against local and international cardiac care benchmarking in the future in the following areas: myocardial infarction incidence, adult coronary intervention (angiography & angioplasty), electrophysiology & pacing (Electrophysiology /Ablation, pacemaker, ICD implantation), adult 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, essential for assessing national trends in heart disease patterns and long-term health planning. Starting as the Singapore Myocardial Infarction Registry in 1987, it is the only comprehensive nation-wide myocardial infarct registry. A number of publications have been produced from the registry data.

Applications of Data

National Medical Audit Meetings in Cardiology

SCDB enables the Cardiac Department and Cardiac Surgery Department from the various hospitals to hold National Medical Audit Meetings in Cardiology to review the workload, morbidity, mortality and recommendation of changes in practice for cardiac specialties. It also benchmarks individual hospital quality care.

Tracking of utilisation of healthcare resources

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 outcome and monitor the related factors contributed to cardiac morbidity and mortality.

Ongoing application of CCP AMI Project

The Coordinated Clinical Pathway (CCP) Acute Myocardial Infarction (AMI) project, a joint effort of National Heart Centre (NHC) and SCDB, has served as a general guideline for planned program of patients' care and was implemented at the end of year 1999 at NHC. 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 recognised the value of attending cardiovascular rehabilitation. NHC has subsequently implemented CCP Heart Failure in April 2002 and officially took over CCP CABG from Quality Management Dept, Singapore General Hospital in April 2002.

A new revised CCP CABG form was initiated by the CCP Committee Members and implemented at NHC on 1 June 2002.

SCDB's role is to target the selected outcome and variance for evaluation as proposed and agreed by the CCP team, which consists of Cardiologists, Cardiac Surgeons, nurses, pharmacists, dieticians, physiotherapists, medical social workers and SCDB staff. Statistical updates are provided by SCDB on quarterly and annual bases.

Submission of AMI figures to Ministry of Health

AMI figures are also submitted on a quarterly and yearly basis to the Epidemiology and Disease Control Division (E&DC): Non-communicable diseases of the Ministry of Health (MOH), for the purposes of MOH policy and planning.

Lectures, talks, presentation for local/international conferences

SCDB data is used by various hospitals for lectures, talks and presentation for local and international conferences, for the purposes of teaching, medical update, and education of medical staff in both cardiac and non-cardiac disciplines.

Others

Adhoc requests have been made for SCDB data from Cardiologists and Cardiac Surgeons for department and subspecialty audit sessions, disease treatment outcome and management.

SCDB data has been requested by hospitals for the media, press interviews and conferences, as well as for health promotion programs.

The transfer of selected AMI data to the National Disease Registries Office (NDRO) is under discussion and in progress.

Singapore Eye Research Institute (SERI)

Introduction

In the relatively short time since its inception, SERI has established an internationally recognized high profile and is the leading centre in South Asia for eye and visual science research. Appointed as a NUS affiliated institute in 2003, SERI acts as a national centre for eye research in Singapore, coordinating research among ophthalmology units across the medical Clusters, the Defence Medical Research Institute and the Department of Optometry of the Singapore Polytechnic.

The major objectives of the SERI block grant in FY2003 were 1) to further develop the four established research core competencies of SERI, namely, the Clinical Research Unit, the Epidemiological Unit, the Visual Psychophysics Unit and the Laboratory Sciences Unit, to enhance and facilitate the conduct of high quality visual science and ophthalmic clinical and translational research; and 2) to initiate integrated planning for the Second Combined Meeting between SERI, and the Association for Research in Vision and Ophthalmology (ARVO), to be held in February 2005.

Activities in FY2003

Clinical Research Unit

The Clinical Research Unit is staffed by research ophthalmologists, optometrists and clinical trial coordinators and equipped to conduct ophthalmic clinical trials and interventional studies in ophthalmology. The Unit conducted several clinical trials in the last year, including:

- a) the successfully-completed ATOM study, a Research Clinical Trial (RCT) on the use of atropine eye-drops in controlling myopia progression in schoolchildren (which proved conclusively that myopia progression in children can be controlled),
- b) a pivotal ocular surface transplantation procedure on the successful use of our cultivated conjunctival stem cell equivalents, tissue-engineered by our SERI Tissue Culture Lab and performed in collaboration with the Outram Campus Stem Cell Research Group.
- c) a RCT on acute angle closure treatment with either laser iridotomy or phacoemulsification (ACLIPS Trial)
- d) a study (initiated by the Unit) on a novel artificial corneal procedure in which a tooth is used to implant an artificial prosthetic cornea into the eye with severe end-stage anterior segment disease (the Osteo-odonto Keratoprosthesis (OOKP) procedure; the first in SE Asia.

Epidemiological Unit

Consisting of a team of clinicians and research optometrists led by two ocular epidemiologists, the Epidemiology Unit evaluates risk factors for ocular disorders of major public health importance in Singapore and Asia, which include myopia, diabetic retinopathy and angle closure glaucoma. The following were carried out in 2003:

- a) Continued assessment of myopia and refractive errors in our longitudinal cohort study of 2000 schoolchildren (SCORM)
- b) Completion of a prevalence survey of visual impairment and ocular disease in the Riau Islands, South Sumatra, Indonesia.

Visual Psychophysics Unit

The Visual Psychophysics Unit focuses on visual function and the improvement of visual performance. Studies in 2003 included:

- a) A RCT comparing lasik with excimer laser photorefractive keratectomy (PRK) in military vocations,
- b) The launch of a new neural visual improvement technology, NeuroVision, with a pilot study on visual improvement in low myopes.

In addition, several electrophysiological studies on retinal disorders and high myopia were also carried out.

Laboratory Sciences Unit

The Laboratory Sciences Unit comprises several integrated laboratories supporting vision researchers across Singapore. The on-site availability of expertise and instrumentation allows new researchers to become active quickly. SERI Lab supports the research of 5 major grants, 3 principal investigators, and a host of smaller seed grant projects. The individual facilities include:

- a) The Cell and Molecular Biology Laboratory
- b) The Analytical Chemistry Laboratory (now the Proteomics and Microanalytical Laboratory)
- c) The Tissue Culture Laboratory
- d) The Animal Laboratory, which includes the SERI-Experimental Surgery Primate Facility

Summary of Research Outcomes

In the period of January 2003 to March 2004, SERI achieved its highest productivity to date in terms of scientific research output. SERI scientists and clinicians published 94 scientific articles in peer reviewed ophthalmology and visual science journals (with significant proportion of articles published in high impact journals), presented 175 scientific abstracts at local and international clinical and research meetings, and initiated 51 new research projects.

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

Introduction

The FY2003 block grant was instrumental in providing essential core manpower support for TTSH CRU and Infectious Disease Research Centre (IDRC) to support NMRC studies.

The CRU continued to provide central support for TTSH researchers working on NMRC-funded studies. The IDRC continued to grow in strength and activity and has established itself as a regional centre of excellence in Infectious Diseases research.

Main Achievements in FY2003

TTSH received a highly favourable report by an audit team from the National Institute of Health (NIH), US for its participation in the multinational ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomized International Trial) study.

TTSH was selected as the only Asian site to participate in Phase III multi-centre trial of a once daily protease inhibitor. The study has been extended for another 48 weeks and is a pivotal licensing study for Food Drug Authority (FDA) submission.

The IDRC continued to expand its links with TREATAsia, The Research, Education And Treatment for Asia project, a new regional collaborative research network for HIV research funded by the American Foundation for AIDS Research.

8 papers arising from original research work conducted at TTSH under NMRC funding were published in 2003 in the Lancet and British Medical Journal as well as several other high impact journals.

An agreement was also secured with Bristol Myers Squibb (BMS) to provide lifelong free Anti-HIV treatment to patients enrolled in BMS A1455 Stavudine study. This study has been extended to November 2004.

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. 6 institutions were awarded Enabling Grants in FY2003.

Table 6
Institutions that received EG funding in FY2003

	Institutions
1	Alexandra Hospital (AH)
2	Changi General Hospital (CGH)
3	KK Women's & Children's Hospital (KKH)
4	Health Sciences Authority (HSA)
5	National Dental Centre (NDC)
6	National Skin Centre (NSC)

Each Enabling Grant recipient's research activities and outcome for FY2003 are as follows.

Alexandra Hospital (AH)

Introduction

FY2003 is the first year that Alexandra Hospital (AH) received Enabling Grant Funding from NMRC. The Enabling Grant came at an opportune time as the Hospital gathered its momentum in the development of clinically relevant research. The mission of the Hospital is to improve health and reduce illness through patient-centred quality healthcare that is accessible and seamless, comprehensive, appropriate and cost effective, in an environment of continuous learning and relevant research.

Activities in FY2003

Building up core facilities

The FY2003 Enabling Grant has helped AH in building the basic infrastructure needed for clinical research. The basic equipping of the molecular genetic laboratory and the metabolic cell culture laboratory was completed. (Both facilities were not available previously.) These facilities provide AH with the means to pursue clinical and molecular research in diabetes-related research. Availability of the new cryopreservation capability also allows for storage of biological samples that can be utilised for potential research that may translate to improved clinical care. . The Clinical Trial Research Clinic has also been established, and there are a number of ongoing clinical trials in the hospital. This has attracted the attention of pharmaceutical companies.

The set up of the research clinic, molecular genetic laboratory and metabolic cell culture laboratory have enabled the researchers in the Hospital to successfully obtain competitive grants from NHG and NMRC.

Research Manpower and training

The Research Nurse funded by the Enabling Grant has played a pivotal role in the smooth running of most of the FY2003 start-up research projects; and has, in turn gained valuable clinical research experience.

The vibrant research culture in AH has successfully attracted two undergraduate medical students to do research attachments and one of whom has made significant research findings. Senior physicians are also pursuing postgraduate studies in the fields of genetic and molecular epidemiology and bioinformatics.

Research Outcomes

Single nucleotide polymorphisms pivotal in metabolism have been successfully genotyped. The Enabling Grant has also enabled AH to jumpstart research in sports medicine, exercise physiology and emergency medicine.

Changi General Hospital (CGH)

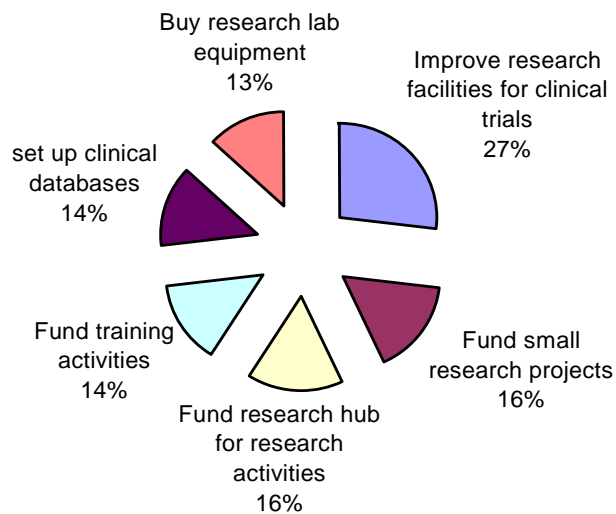
Introduction

CGH is continuously promoting a research culture among the clinicians, nursing and paramedical staff. In FY2003, Changi General Hospital set out to 1) further develop their research infrastructure, 2) make the resources readily available to the users, 3) build up databases for easy data retrieval and 4) have better trained personnel to support the clinicians and their research work. CGH's aim is to cultivate a notable and significant research environment, in line with the Government's vision for Singapore to become a premier centre for biomedical research.

Activities in FY2003

The objectives of the NMRC Enabling Grant for FY2003 were met.

The grant was used to: buy research laboratory equipment and improve research facilities for clinical trials; fund small research projects, a research hub for research activities and training activities; and also to set up clinical databases.



The improved facilities have enabled CGH to conduct trials with more demanding requirements. The provision of training for staff has resulted in greater awareness of Ethics and Good Clinical Practice requirements, and a good appreciation of software such as the reference manager, EndNote, as well as the upgraded SPSS version. The research hub supported the preparation of research papers and presentations, and two poster presentations have been made by the small research projects funded.

Health Sciences Authority (HSA)

Introduction

The Health Sciences Authority reviewed a new regulatory framework for clinical drug trials, which was approved by the Director of Medical Services and Chairmen of Medical Boards in November 2002. This framework aims to ensure high standards of clinical research in Singapore via a range of new initiatives:

- a) IRB verification and Trial Centre Licensing to improve the accountability of institutions and IRBs in hospitals where clinical trials are conducted.
- b) GCP inspections as part of a quality assurance process at trial sites and institutions, allowing HSA to have a better overview and assess the compliance of clinical drug trials with regulations and the Singapore Guideline for GCP.
- c) Enhance the review system for safety-assessment of investigational drugs undergoing clinical trials in Singapore.

FY2003 marks the first year of funding by NMRC, and the objective of the grant is to enable HSA to be sufficiently trained and resourced in order to implement the new initiatives.

Activities in FY2003

A summary of the activities funded under the enabling grant and their correlation to the revised clinical trials regulatory framework initiatives is shown in the table below.

No	Activities funded by the enabling grant	Correlation to new framework
1	Experts from the international benchmarked agencies to train staff from HSA and the IRBs on IRB verification, Trial Centre Licensing and GCP audits.	Initiatives (a) & (b)
2	Conference attendance by HSA staff.	Initiatives (a), (b), & (c)
3	Setting up of a new safety database.	Initiative (c)
4	A part-time pharmacist (0.5 full time equivalent) to assist with setting up the new database, data entry, activities surrounding safety reports.	

In conclusion, the initiatives under the new framework have been formulated 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.

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

Introduction

In FY2003, the KKH Enabling Grant was to go towards the maintenance, development and building upon of current research infrastructure in the hospital, so as to provide consistent long-term support for medical research in the areas of obstetrics, gynaecology, neonatology and paediatrics.

KK Women's and Children's Hospital aims to become a regional and international medical centre with a strong research culture and high quality research output, and also, to become a hospital where research techniques are instinctively used to answer clinical questions and objective research outcomes form the basis for clinical practice and policy. KKH's area of focus is on clinical research, with the objective of developing evidence based practice through the conduct of international clinical trials and epidemiological studies.

Activities in FY2003

Establishment of KKH Research Centre

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

The centre oversees and coordinates all clinical trials activity in KKH. With the NMRC enabling fund for provision of research nurses, the clinical trial capability quality and consistence has improved in KKH.

Databases for support of research studies

All research studies require heavy support in the form of either statistical consultation/analysis or extensive disease databases. With the help of the KKH Research Centre, 19 databases have been set up and most are hosted in the server funded by the NMRC enabling grant.

Training

The Research Centre recognised the need for clinicians to upgrade their skills and knowledge on statistical analysis. In 2003, 8 SPSS in-house workshops were conducted with participants from various disciplines.

Enhancement of laboratory-based research infrastructure

There was further enhancement in KKH laboratory based research infrastructure in the later part of FY2003. Genetic disease has become an important area of health care and most genetic diseases present in childhood. As such, 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 base clinical research, including dHPLC, real time PCR, automated DNA extractor and DNA sequencer. A number of clinical specialists from different areas have embarked on new projects studying mutations in various genetic diseases.

National Dental Centre (NDC)

Introduction

FY2003 was the first year of block grant funding from NMRC. The objectives of the National Dental Centre Enabling Grant in FY2003 were:

- (a) Clinical Trial Support
 - 1) fund the NDC Research Resource Unit which assist clinicians in their research activities
 - 2) fund the secretariat support for NDC Research Ethics Committee to carry out its regulatory and monitory functions
 - 3) fund the institution-wide post of NDC Nurse/Research Coordinator
 - 4) fund bio-statistical consultation services
- (b) Small Grants
 - 5) fund small projects, inclusive of protected time in addition to materials and miscellaneous supplies
 - 6) provide seed funding for pilot projects within the institution

Activities in FY2003

Clinical Trials Support and Small grants

The Enabling Grant funded clinical trial support for two investigator-initiated randomized clinical trials at the Centre, 26 small projects, and 2 pilot projects.

Manpower for clinical trials support was funded under the grant, as well as equipment such as SPSS “Data Entry Enterprise Service and Endnote” software, Chinese Richwin 2000 software, and an upgrade of IBM Personal Computers for the Research Resource Unit.

Research Outcome

17 presentations and 1 publication have arisen from the research so far.

National Skin Centre (NSC)

Introduction

NSC aims to further develop its core research capabilities, focusing on the areas of clinical trials and molecular dermatopathology. The objectives for the NSC Enabling Grant for its first year of funding are to:

- a) Establish an infrastructure for the conduct of clinical trials
- b) Consolidate the establishment of a molecular dermatopathology laboratory
- c) Encourage and nurture the junior staff in the undertaking of research.

Activities in FY2003

Increased Efficiency in Clinical Trials

Additional manpower that was recruited has increased the efficiency of clinical trials, such as by assisting in eliciting informed consent from trial subjects and ensuring that all protocols are filled up. The secretariat assisted in tracking ongoing projects and the utilisation rate of funds, providing an overview of research progress for all NSC projects.

Building up Support Infrastructure

The clinical trials office purchased essential office equipment, and an SPSS (LAN version) was procured after the implementation of the EMR (electronic medical records) system. The SPSS will be used by doctors and paramedical staff, and will enhance research in epidemiological and clinical studies and help in the formulation of clinical guidelines and policies.

Research Progress/Outcome

The small grants provided start-up funds for building up existing capabilities in molecular diagnosis. The project, "*Identification of atypical mycobacterium species using a PCR protocol, combined with restriction fragment length polymorphism*" resulted in the optimization of the PCR protocol for identification of atypical mycobacteria in archival tissue specimens. NSC intends to further assess its validity in clinical specimens.

A second project, "*Identification of T-cell clones in lymphoproliferative disorders, comparing current PCR protocol, with a gene scan system which uses capillary fluorescence electrophoresis*" has shown that current PCR protocol compares favourably with that using a system that has been touted to increase sensitivity and resolution. This will see its application in cases where there is diagnostic difficulty based on histomorphology and immunohistochemistry.

Other small grants have helped stimulate research interest in young NSC registrars. Many studies will be presented at an upcoming Asian-Australasian Regional Conference of Dermatology held in Singapore.

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 2001 to 2003.

From 2001 to 2003,

- there was a 157% *increase* in publications for every million dollars expended;
- 140% *increase* in publications with impact factor greater than 2, for every million dollars expended.
- the number of national and international awards has been *stable*, at 20 or more.
- *all* completed projects had clinical significance

Table 7
Research Output from Block/Competitive Grants

Year	2001	2002	2003
Expenditure* (\$'m)	54.8	55.2	49.7
Output			
Total no. of Publications	220	316	514
Publications with impact factor >2	83	113	177
No. of national and international awards	20	26	24
% of completed projects with clinical significance	100	100	100
Number of research scientists (including clinician-scientists)	Not available	Not available	112
Output per \$'m			
Publication per \$'m	4.0	5.7	10.3
Publications with impact factor >2 per \$'m	1.5	2.0	3.6

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

NMRC-Singapore Totalisator Board Medical Research Fellowship/Scientist Award

INTRODUCTION

The NMRC Medical Research Fellowship and Scientist Award 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 (Tote Board).

All applications for fellowship and scientist award are assessed by independent local and overseas reviewers and evaluated by the Fellowship subcommittee, who will provide awarding recommendations to the Council.

AWARDS COMMENCING IN FY2003

Medical Research Fellowship Award

10 doctors commenced their NMRC-Tote Board Medical Research Fellowship in FY2003, which were either new awards or extensions to existing awards. 6 of which were for training leading to a degree whereas the other four were for training not leading to a degree.

Training leading to a degree (MD/PhD)

1. Dr Shanker Pasupathy from the Department of General Surgery, SGH received a full-time fellowship for 12 months. His project at the Leeds General Infirmary, UK was "The effects of warm-up on walking distance, platelet activation and platelet-neutrophil aggregation in claudicants". Dr Shanker Pasupathy's training would lead to a PhD.
2. Dr Leong Hoe Nam from the Department of Internal Medicine, SGH received a full-time fellowship for 36 months. His project at the Royal Free and University College Medical School, London, UK was "Studies on the viral host relationship of Human Herpesvirus 6 (HHV6) using DNA microarray technology". Dr Leong's training would lead to a PhD.
3. Dr Yap Peng Leng Karen from the Department of Surgical Oncology, NCC received a part-time fellowship for 48 months. Her project at the National University of Singapore and Karolinska Institute, Singapore and Sweden respectively, was "Genetic Epidemiology of Breast Cancer". Dr Yap's training would lead to a PhD.
4. Dr Chuah Thuan Heng Charles from the Department of Haematology, SGH received a full-time fellowship for 12 months. His project at the Imperial College London, UK was "Novel combination therapies for selective in vitro elimination of leukaemic progenitor cells in chronic myeloid leukaemia". Dr Chuah's training would lead to a MD.

5. Dr Chong Tsung Wen from the Department of Urology, SGH was awarded a 12-month extension to his full-time fellowship. His project at the University of Oxford, UK was “To study the natural T cell responses to a novel tumour antigen G250 in renal cancer patients”.
6. Dr Narayanan Gopalakrishna Iyer from the Department of Surgery, SGH was awarded a 6-month extension to his full-time fellowship at the University of Cambridge, UK. His project was “Role of p300 in the p53 pathway”.

Training not leading to a degree

7. Dr Tan Choon Kiat Nigel from NNI received a full-time fellowship for 8 months 19 days. His project at the Epilepsy Research Institute, University of Melbourne, Australia was “Polymorphisms in refractory epilepsy – An association study”.
8. Dr Tan Sing Huang from the Department of Haematology-Oncology, NUH received a full-time fellowship for 4 months. Her project at the Institute of Molecular and Cell Biology (IMCB), Singapore, was “Detection of tumour cells in blood samples of patients by methylation specific polymerase reaction (MSP) for tumour suppressor genes including *RUNX3*”.
9. Dr Tay Kiat Hong Stacey from the Department of Paediatrics, NUS received a full-time fellowship for 12 months. Her project at the New York Presbyterian Hospital, USA was “Extensive mutation screening of patients with mitochondrial disease characterized by isolated cytochrome oxidase b deficiency”.
10. Dr Chan Chung Yip from the Department of General Surgery, TTSH received a full-time fellowship for 12 months. His project at the Northwestern University Medical School, USA was “The role of immune mediators and acute phase proteins in pancreatic cancer cachexia”.

Medical Research Scientist Award

No medical research scientist award were given in FY2003.

TRAINING COMPLETED IN FY2003

Medical Research Fellowship Award

12 doctors completed their training under the Medical Research Fellowship in FY2003:

1. Dr Chua Soo Yeng Benjamin from the Department of General Surgery, SGH completed 22 months of training at the Duke Clinical Research Institute, Durham, USA. His projects were “Peripheral vascular disease (PVD): Is it a risk factor for mortality in end-stage renal disease (ESRD)?” and “Associations between clinical performance benchmarks, profit structure and mortality in US dialysis units”.

2. Dr Guo Changming from the Department of Orthopaedics, SGH completed 12 months of training at the Brigham and Women's Hospital, Harvard Medical School, USA. His project was "Bone marrow derived mesenchymal stem cell (MSC) for tissue engineering".
3. Dr Shek Pei Chi Lynette from the Department of Paediatrics, NUS completed 11 months of training at the Mount Sinai School of Medicine, New York, USA and Telethon Institute for Child Health Research, Perth, Australia. Her projects were "Natural history of food allergy", "Cow milk specific T and B cell responses" and "Cord blood responses to allergens".
4. Dr Tan Sing Huang from the Department of Haematology-Oncology, NUH completed 4 months of training at the Institute of Molecular and Cell Biology (IMCB), Singapore. Her project was "Detection of tumour cells in blood samples of patients by Methylation Specific Polymerase Reaction (MSP) for tumour suppressor genes including *RUNX3*".
5. Dr Tong Khim Leng from the Department of Medicine, CGH completed 12 months of training at the University of Virginia Health System, USA. His project was "Detection of non-critical coronary stenosis at rest with myocardial contrast echocardiography".
6. Dr Chan Ching Wan from the Department of Surgery, SGH completed 42 months of training at the University of Bristol, UK. Her project was "Apoptosis in breast cancer cells".
7. Dr Narayanan Gopalakrishna Iyer from the Department of Surgery, SGH completed 48 months of training at the University of Cambridge, UK. His project was "Role of p300 in the p53 pathway".
8. Dr Chong Tsung Wen from the Department of Urology, SGH completed 36 months of training at the University of Oxford, UK. His research project was "To study the natural T cell responses to a novel tumour antigen G250 in renal cancer patients".
9. Dr Ng Chung Fai Jeremy from the Department of Surgery, SGH completed 24 months of training at the University of London, UK. His research projects were "Differential expression patterns of the insulin-like growth factor II gene in human colorectal cancer" and "Prediction of radiotherapy response in rectal cancer patients using global gene expression profiling".
10. Dr Shanker Pasupathy from the Department of General Surgery, SGH completed 12 months of training at the Leeds General Infirmary, UK. His research project was "The effects of warm-up on walking distance, platelet activation and platelet-neutrophil aggregation in claudicants".
11. Dr Wong Seng Cheong Alvin from the Department of Haematology-Oncology, NUH completed 6 months of training at the Bunting-Blaustein Cancer Research Building, Johns Hopkins, USA. His research project was "RNA interference of Epstein-Barr virus nuclear antigen 1".

12. Dr Tan Soo Yong from the Department of Pathology & Laboratory Medicine, TTSH completed 6 months of training at the University of Oxford, UK. His research project were “Immunophenotype of follicular center cells”, “Immunophenotypic characterization of interfollicular CD30 cells” and “Advances in the use of immunohistochemistry in skin biopsies”.

The abstracts of their reports are at Annex 2.

Medical Research Scientist Award

3 recipients of the Medical Research Scientist Award completed their training in FY2003:

1. Dr Loh Pui Kwan Donus from IMH completed 12 months of training at the University College London, UK. His project was “Auras in temporal lobe epilepsy: The problem with classification of auras, and the relationship between auras and psychopathology after temporal lobectomy”.
2. Dr Gao Ge from NHC completed her 12 months of training at Cardiovascular Medicine of Yale University, USA. Her project was “Proinflammatory mRNA stabilization by adhesion receptor engagement in macrophages”.
3. Dr Wong Boon Seng from the Department of Biochemistry, NUS completed his 26 months of training at the Case Western Reserve University, Cleveland, Ohio, USA. His project was “Construction and characterization of novel neuronal cell lines derived from gene-knockout mice”.

The abstracts of their reports are at Annex 2.

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 FY2003 OOE Budget allocated to NMRC was used to fund both on-going projects and programmes committed under Fund II and in FY2002, as well as new initiatives in FY2003.

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

BUDGET FOR FY2003

A total of \$54.3 million was allocated for research expenditure in FY2003. Table 8 shows the movement of budget allocated for research expenditure.

Table 8
Movement of Allocated Budget, FY2003

	Amount (\$)
MOH's OOE budget	50,250,000
Transfer of Secretariat budget to MOH	(917,020)
Final OOE budget	49,332,980
Add: Tote Board's donations for research projects and programmes	5,000,000
Total budget	54,332,980

In addition, a donation of \$1,669,656.65 was received from Tote Board in FY2003 for the Medical Research Fellowship and Scientist Award.

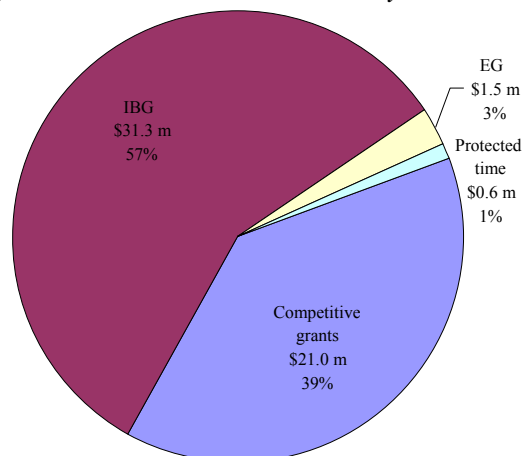
COMMITMENTS

A total of \$54.4 million was committed in FY2003 with the breakdown as shown in Table 9.

Table 9
Commitments in FY2003

	Amount (\$)	% of total
Competitive Grants		
Individual Research Grants (IRG)	19,341,716.94	35.5%
Competitive Programme Grants (CPG)	1,195,930.00	2.2%
Competitive Priority Grants (CPRG)	473,520.39	0.9%
Sub-Total	21,011,167.33	38.6%
Block Grants		
Institutional Block Grants (IBG)	31,250,854.18	57.5%
Enabling Grants (EG)	1,510,461.00	2.8%
Sub-Total	32,761,315.18	60.3%
Protected Time	598,932.60	1.1%
Total Commitments for FY2003	54,371,415.11	100.0%

Fig 1: FY2003 Fund Distribution by Commitments



Competitive Grants

Competitive grants are awarded to researchers over a period of up to 3 years. Of the competitive grants awarded, \$21.0 million was committed to 115 projects and programmes, comprising 107 Individual Research Grants (IRG), 2 Competitive Programme Grants (CPG) and 6 Competitive Priority Grants (CPRG). The approved projects in FY2003 are listed in Annex 3.

Out of the 107 IRG approved in FY2003, 41 are applications received in May03 IRG funding exercise, 61 in Nov02 exercise, 1 in May02 exercise, 1 in Nov01 exercise, 1 in Aug01 exercise and 2 in May01 exercise.

The distribution of the competitive grants awarded by institutions and area/type of research are depicted in Tables 10 to 13 respectively.

Table 10
Commitments for Competitive Grants by Institutions, FY2003

Institution	IRG		CPG		CPRG		Total	
	No. of Projects	Amount (\$)	No. of Projects	Amount (\$)	No. of Projects	Amount (\$)	No. of Projects	Amount (\$)
National University of Singapore	35	5,632,423.80	-	-	2	129,700.00	37	5,762,123.80
National Cancer Centre	14	3,021,756.32	-	-	-	-	14	3,021,756.32
National Neuroscience Institute	11	2,866,970.12	-	-	-	-	11	2,866,970.12
Singapore General Hospital	15	1,866,779.50	1	530,000.00	1	118,692.00	17	2,515,471.50
National Heart Centre	8	2,134,259.00	-	-	-	-	8	2,134,259.00
Singapore Eye Research Institute	2	987,451.00	1	665,930.00	-	-	3	1,653,381.00
National University Medical Institute	4	1,156,611.00	-	-	-	-	4	1,156,611.00
Singapore Health Services	5	666,390.00	-	-	-	-	5	666,390.00
National University Hospital	7	618,212.00	-	-	-	-	7	618,212.00
KK Women's & Children's Hospital	2	203,880.00	-	-	-	-	2	203,880.00
Institute of Mental Health	1	59,094.00	-	-	1	100,000.00	2	159,094.00
Nanyang Technological University	-	-	-	-	1	72,600.00	1	72,600.00
Alexandra Hospital	1	66,881.00	-	-	-	-	1	66,881.00
Tan Tock Seng Hospital	1	11,869.20	-	-	1	52,528.39	2	64,397.59
National Environment Agency	1	49,140.00	-	-	-	-	1	49,140.00
Total	107	19,341,716.94	2	1,195,930.00	6	473,520.39	115	21,011,167.33

Table 11*Commitments for IRG by area of research, FY2003*

Area of Research	No. of Projects	Amount (\$)
Cancer	18	3,690,507.98
Neuroscience	15	3,400,025.12
Cardiovascular Diseases	14	2,761,889.00
Molecular Biology	7	1,336,252.00
Endocrinology	5	881,937.00
Biochemistry	3	847,388.34
Pharmacology	4	798,439.00
Epidemiology	2	648,222.00
Haematology	3	644,517.00
Immunology	4	620,868.00
Microbiology	3	574,312.00
Liver Diseases	2	470,767.00
Diagnostic Radiology	3	397,054.50
Orthopaedic Surgery	3	363,705.00
Genetics	4	363,646.80
Psychiatry	2	249,542.00
Paediatrics	1	241,000.00
Otolaryngology	2	181,821.00
Others	3	156,491.00
Plastic Surgery	1	150,645.00
Urology	1	124,530.00
Obstetrics & Gynaecology	1	123,120.00
Dentistry	1	114,125.00
Anaesthesia	2	103,325.00
Respiratory Diseases	1	54,218.00
Dermatology	1	31,500.00
Colorectal Surgery	1	11,869.20
Grand Total	107	19,341,716.94

Table 12*Commitments for CPG by type of research, FY2003*

Type of Research	No. of Projects	Amount (\$)
Proteomics facilities	1	665,930.00
Microarray facilities	1	530,000.00
Total	2	1,195,930.00

Table 13*Commitments for CPRG by type of research, FY2003*

Type of Research	No. of Projects	Amount (\$)
SARS research	6	473,520.39

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 FY2003, a total of \$31.3 million was committed for IBG and \$1.5 million was committed for EG, distributed as shown in Table 14.

Table 14
Commitment for IBG and EG by research centre/block vote, FY2003

Research Centre/Block Vote	Amount (\$)
IBG	
National Cancer Centre (NCC)	9,798,904.99
National Neuroscience Institute (NNI)	4,473,120.00
Singapore Eye Research Institute (SERI)	3,959,199.51
National University Medical Institute (NUMI)	3,850,000.00
Clinical Trials and Epidemiology Research Unit (CTERU)	2,623,900.00
Department of Clinical Research (DCR)	1,801,000.00
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)	459,262.00
Institute of Mental Health/ Woodbridge Hospital (IMH/WH)	414,622.43
Tan Tock Seng Hospital – Clinical Research Unit (TTSH-CRU)	359,200.00
NNI-TTSH Animal Research Laboratory (ARL)	265,000.00
National Birth Defects Registry (NBDR)	242,287.25
Nursing Research Committee (NRC)	72,118.00
Total	31,250,854.18
EG	
Alexandra Hospital (AH)	343,450.00
Changi General Hospital (CGH)	320,000.00
KK Women's & Children's Hospital (KKH)	315,500.00
National Dental Centre (NDC)	244,561.00
National Skin Centre (NSC)	164,000.00
Health Sciences Authority (HSA)	122,950.00
Total	1,510,461.00
Total for IBG and EG	32,761,315.18

FY2003 RESEARCH EXPENDITURE

Out of the \$54.3 million allocated for research expenditure, a total of \$50.5 million was utilized, representing a fund utilization rate of 92.91%. Of this, \$15.6 million was for competitive grants, \$29.0 million was for IBG, \$1.4 million for EG, \$2.4 million for protected time and the remaining \$2.1 million for other expenses. The lower utilization rate was due to a delay in ongoing IRG activities as a result of SARS outbreak in FY2003.

Table 15 shows the distribution of research expenditure and Table 16, the expenditure for IBG and EG in FY2003.

Table 15
Research Expenditure, FY2003

Type of Expenditure	Amount Spent (\$)	% of Total Expenditure
Competitive Grants:		
IRG	14,522,738.00	
CPG	1,071,147.92	
CPRG	22,206.17	
Sub-Total	15,616,092.09	30.9%
IBG:		
NCC	9,798,883.52	
NNI	4,246,022.75	
SERI	3,947,307.49	
NUMI	2,869,509.84	
CTERU	2,450,316.88	
DCR	1,753,329.49	
SCDB	734,761.25	
NHC	1,025,193.60	
NUS Block Vote	781,696.23	
DES	327,526.87	
IMH/WH	205,357.44	
TTSH	354,075.00	
NNI-TTSH ARL	174,071.46	
NBDR	223,535.79	
NRC	71,701.54	
Sub-Total	28,963,289.15	57.4%
EG:		
AH	285,692.11	
CGH	314,943.65	
KKH	314,176.94	
NDC	240,970.45	
NSC	144,027.38	
HSA	100,901.06	
Sub-Total	1,400,711.59	2.8%
Protected Time	2,360,563.36	4.7%
Others:		
GST Returned to IRAS (Note 1)	1,389,990.85	
Reviewers' Honorarium	133,314.28	
Patenting Cost	263,818.76	
Clinical Practice Guidelines	79,559.99	
Fellowship/Scientist Awards	276,055.67	
Sub-Total	2,142,739.55	4.2%
Total	50,483,395.74	100.0%

Note 1: Inland Revenue Authority of Singapore (IRAS) had previously ruled that GST for research activities is non-claimable for input GST. The amount previously claimed incorrectly from IRAS between FY2000 to FY2002 was returned to IRAS in FY2003. Out of the \$1,389,990.85 returned, \$261,420.08 relates to IRG, \$1,020,679.59 relates to IBG, \$106,738.85 relates to protected time and \$1,152.33 relates to others expenses.

Fig 2: FY2003 Fund Distribution by Expenditure

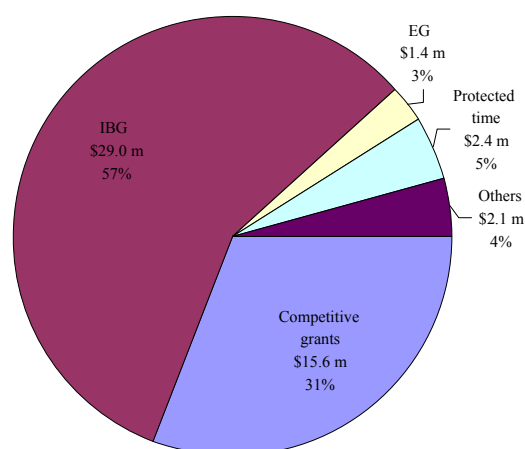


Table 16
Expenditure for IBG and EG, FY2003

Research Centre/ Block Vote	Manpower (\$)	Equipment (\$)	Other Expenses (\$)	Total (\$)
IBG				
NCC	6,483,770.06	224,927.23	3,090,186.23	9,798,883.52
NNI	1,875,084.65	998,844.89	1,372,093.21	4,246,022.75
SERI	2,012,745.28	516,687.54	1,417,874.67	3,947,307.49
NUMI	1,741,934.53	851,715.38	275,859.93	2,869,509.84
CTERU	1,602,016.19	104,338.32	743,962.37	2,450,316.88
DCR	1,154,431.57	-	598,897.92	1,753,329.49
SCDB	701,795.56	-	32,965.69	734,761.25
NHC	337,282.53	633,369.52	54,541.55	1,025,193.60
NUS Block Vote	20,244.03	199,133.03	562,319.17	781,696.23
DES	273,250.37	54,276.50	-	327,526.87
IMH/WH	93,520.14	23,259.00	88,578.30	205,357.44
TTSH	349,200.00	-	4,875.00	354,075.00
NNI-TTSH ARL	81,049.08	47,279.25	45,743.13	174,071.46
NBDR	167,296.13	24,936.80	31,302.86	223,535.79
NRC	-	61,191.36	10,510.18	71,701.54
Total	16,893,620.12	3,739,958.82	8,329,710.21	28,963,289.15
EG				
AH	16,424.35	234,987.55	34,280.21	285,692.11
CGH	52,346.00	170,717.90	91,879.75	314,943.65
KKH	90,500.00	186,306.75	37,370.19	314,176.94
NDC	160,259.67	9,423.75	71,287.03	240,970.45
NSC	55,091.00	26,071.04	62,865.34	144,027.38
HSA	18,109.97	-	82,791.09	100,901.06
Total	392,730.99	627,506.99	380,473.61	1,400,711.59
Grand Total	17,286,351.11	4,367,465.81	8,710,183.82	30,364,000.74

Table 17 shows the list of major equipment with funding of more than \$100,000 in FY2003.

Table 17
List of major equipment funded, FY2003

Description	Institution	Cost (\$)	Amount funded (\$)
GE Vivid 7 Ultrasound Scanner System	NHC	209,475.00	209,475.00
GE OEC 9800 Super C-Arm Cardiac System and accessories	NHC	367,952.00	267,952.00
BD FACSAria Flow Cytometer	NNI	733,425.00	733,425.00
DHPLC-Transgenomic WAVE® Nucleic Acid Fragment Analysis System 3500 with Navigator	KKH	164,850.00	164,850.00
Cyan LX Dual Laser Flow Cytometer	NUMI	228,800.00	228,800.00
Upgrade of LSM 510 VIS Confocal Microscope to LSM 510 VIS/META	NUMI	100,000.00	100,000.00
FV500 Confocal Microscope	NUMI	286,520.00	286,520.00
Affymetrix GeneChip Scanner 3000	SGH	398,161.92	398,161.92
Medical Proteomics Facility-Qstar Pro System Package and Nano LC System	SERI	691,600.00	665,930.00
Total		3,180,783.92	3,055,113.92

MEDICAL RESEARCH FELLOWSHIP/SCIENTIST AWARD

Table 18 shows the commitment and expenditure for Medical Research Fellowship and Scientist Award in FY2003. The expenditure includes those on commitments made before FY2003.

Table 18
Commitment and expenditure for medical research fellowship/scientist award, FY2003

	Commitment (\$)	Expenditure (\$)
Medical Research Fellowship & Scientist Award	2,275,199.99	1,246,617.07

ANNEXES

Annex 1: Abstracts of IRG & Block Grant Research Projects Completed in FY2003

Individual Research Grant (IRG) Research Projects

<p>NMRC/0021/1994 NMRC/0065/1995 NMRC/0108/1995</p> <p>PI: Yong Eu Leong (NUS)</p>	<p>RNA Splicing and Human Androgen Receptor Gene Mutations</p> <p>Three NMRC projects were amalgamated into one at the suggestion of NMRC. The principal investigator's laboratory focused exclusively on the identification and characterization of androgen receptor (AR) mutations associated with human disease. Over 300 pedigrees have been screened for mutations of the AR gene; and dozens of mutations/polymorphisms that lead to varying degrees of androgen insensitivity (AIS), from testicular feminization to minimal AIS associated solely with depressed spermatogenesis and male infertility, have been identified. To characterize their effects, these mutants ARs have been recreated and their effects on every aspect of AR function. Most of the cases of complete AIS have mutations in the DNA and ligand-binding domains, and cause disease by disrupting DNA- or ligand binding. However, cases in the minimal AIS group are most interesting as they do not have demonstrable defects in ligand binding even though they are located in the LBD. These mutations are in sub-domains of the AR, that by comparisons with available crystallographic data from other steroid receptors are implicated in interactions with coactivators but which do not actually form part of the ligand-binding pocket. It has been confirmed that the molecular pathogenesis of AR mutations associated with male infertility has two mechanisms. Firstly, the mutations reduce direct interactions of the LBD with coactivator proteins like TIF2. This was most clearly observed in the two-hybrid system, when mutant AR, liganded to DHT, had only half the ability of WT to interact with TIF2. Secondly, these mutations disrupt TAD-LBD interactions; the function of the full-length receptor is impaired, perhaps by disrupting the efficient recruitment of coactivators that normally bind to the TAD in a hormone-independent manner. The third possibility is that TIF2 mediates the linking of AR LBD to the TAD, resulting in a more stable ternary complex with improved transactivation activity. These studies prove for the first time that protein-protein interactions between AR coactivators can lead to human disease. This groundbreaking work has led to many high impact publications. The PI was awarded National University of Singapore Researcher of the Year 1998 and the NSTB Ministerial Citation for research excellence to the PI by DPM Tony Tan in 1999.</p>
<p>NMRC/0182/1996</p> <p>PI: Wong Meng Cheong (SGH)</p>	<p>Gene Therapy for Brain Tumours</p> <p>This study sought to develop gene therapy for tumours. Current therapies for malignant gliomas are surgery, radiation therapy and chemotherapy. However, in spite of treatment, almost all patients with Glioblastoma Multiforme die about 9 to 18 months after diagnosis. Gene therapy has potential to improve the current dismal outcomes. Major achievements have included a platform presentation at the American Academy of Neurology Annual Meeting, a poster presentation at the Gene Therapy Meeting (USA), winning the SGH Scientist Award, and 2 full length papers in Journal of Neuroscience Research to date. These cover pro-apoptotic, antisense, and antiangiogenic gene therapy strategies.</p>

<p>NMRC/0184/1996</p> <p>PI: Wong Meng Cheong (SGH)</p>	<p>Immunofluorescence study of Protein Kinase C and Benzodiazepine receptors in human high and low grade astrocytomas</p> <p>The study set out to study brain tumours, specifically the astrocytoma subtype. Five presentations were achieved as the major accomplishments and these also (a) established an experimental glioma model, (b) developed subcellular fluorescence localization techniques, (c) developed techniques to assess chemotherapy resistance and (d) assessed glioma growth.</p>
<p>NMRC/0199/1997</p> <p>PI: Arijit Biswasn (NUS)</p>	<p>Effect of NORPLANT Subdermal Contraceptive Implants on Lipid Metabolism - A Randomised Controlled Study</p> <p>Increased risk of coronary heart disease (CHD) is associated epidemiologically with changes in serum lipids and lipoproteins. Since progestins are known to alter metabolism, it is important to study the effects of long term use of progestin releasing contraceptive implants, like the Jadelle ® system, on serum lipids major apolipoproteins. Little controlled data is available on the effects of laevonorgestrel-releasing implants on these lipoproteins. The objective of this study was to evaluate the effects of 2-years use of Jadelle ® (Norplant-II) contraceptive implants on serum lipids including major lipoproteins and apolipoproteins, which are markers of cardio-vascular risk. One hundred healthy Singaporean women requiring long-term contraception were recruited for this study. After obtaining informed consent, they were randomized to receive either Jadelle ® implant (study group) or intrauterine device, Nova-T 380 (control group). Fasting blood samples were drawn pre-insertion, at 1, 6, 12, 18 and 24 months and before removal. Parameters that were tested included Total Cholesterol (TC), High density lipoprotein cholesterol (HDL-C), Low density lipoprotein cholesterol (LDL-C), Triglyceride (TG), Apolipoprotein A-1 (Apo A-1), Apolipoprotein B (Apo B) and Lipoprotein-A (Lp-a). The results showed that compared to non-steroidal intrauterine device users, there were significant changes in serum lipids and lipoproteins with long-term (2-years) use of levonorgestrel releasing subdermal contraceptive implant – Jadelle ® (Norplant-II). However, the changes were mainly in the form of a significant lowering of total cholesterol and serum lipid fractions including apolipoproteins in the Jadelle users at the end of two years of use. There was no significant change in the lipid ratios (Total cholesterol / HDL ratio, LDL/HDL ratio, Apolipoprotein A1/B ratio) in either group. The results of the study shows that there is no increased serum lipid related cardiovascular risk in users of Jadelle contraceptive implants.</p>
<p>NMRC/0204/1997</p> <p>PI: Lee Seng Teik (SGH)</p>	<p>The in vitro investigations of the aqueous extract from the leaves of Chromonaela Odorata (formerly Eupatorium Odoratum), a herbal remedy for the treatment of burns and wounds</p> <p>The achievement of this project is the development of reliable in-vitro systems for fast and low-cost screening of novel pharmaceutical drugs for wound healing and fibrotic scar prevention. Using in-vitro models of wound healing research, the effectiveness of the extract from a medicinal plant, Chromolaena odorata, which has enhanced in-vivo wound healing, was investigated. By investigating different aspects of the healing process, the extract was found to enhance the proliferation of keratinocytes, fibroblasts and endothelial cells. The</p>

	<p>extract induced keratinocyte migration and production of fibronectin and other adhesion proteins. The extract showed strong antioxidant properties, protecting cultured skin cells from oxidative damage. The phenolic compounds were identified as the active components in the extract. This work could also provide the explanation for the observed clinical efficacy of this plant extract in burns and wound healing.</p> <p>The other interesting and significant data of this work is the elucidation of the role of IGF-I system in epidermal-dermal interaction of keloid pathogenesis. Using an in-vitro double chamber co-culture model, it was demonstrated for the first time that IGF-I system was highly activated in the presence of epidermis, especially in epidermis derived from keloid scars. This work has contributed to a better understanding of the IGF-I system in keloid pathogenesis, especially the role of the overlying epidermis, which has not been appreciated before. A possible inference to be drawn from this work is that modulating the production of the IGF-I system may represent a novel approach in the treatment of keloid and other excessive scars.</p> <p>The most significant development is the discovery of a phytochemical, quercetin, for the treatment of keloid and hypertrophic scars. Quercetin is a well-known dietary compound with multiple bioactivities including antioxidant and anticancer properties. Using in-vitro models for anti-scar research experimentation, it was found that quercetin is the most effective compound out of ten different dietary compounds which were studied or investigated in detail. Quercetin inhibited the proliferation, collagen deposition and contraction of pathological fibroblasts derived from keloids and hypertrophic scars. At the molecular level, quercetin was shown to effectively block the signal transduction pathways of IGF-I and TGF-β systems, which are established systems causing pathological fibrosis and scar formation. The next step will be the formulation and the development of a delivery system of quercetin for clinical trials.</p>
<p>NMRC/0205/1997</p> <p>PI: Soo Khee Chee (NCC)</p>	<p>Surgery and Adjuvant Radiotherapy versus Concurrent Chemo-Radiotherapy for Resectable (NonMetastatic) Stage III/IV Head and Neck Cancer</p> <p>This is a Phase III randomised trial comparing radical surgery with chemoradiotherapy for patients with locally advanced squamous cell cancers of the head and neck. The aim was to compare the difference in survival/disease-free survival as well as organ preservation rates between the two treatment modalities. The trial reached its objectives and was closed on February 28 2002, after accruing 119 patients within a 5-year time frame.</p> <p>The researchers expect to be able to present preliminary survival data in May 2003. This is the first and only randomised trial in the world to address this question, and the researchers expect it to add objective evidence to the various treatment alternatives for patients with that cancer.</p>
<p>NMRC/0222/1997</p> <p>PI: Chia Chin Soon John (NUS)</p>	<p>Role of the University of Wisconsin cold storage(UW) solution on the bone muscle, nerve and skin in limb preservation</p> <p>Replantation of major limb amputations has been a serious challenge in reconstructive surgery. Complications often arise due to prolonged</p>

	<p>ischaemia (post-ischaemic syndrome – Steinau, 1988). The success of the replantation depends on how ischaemic damage can be minimized.</p> <p>One option effectively used in organ transplantation is the University of Wisconsin Cold Storage (UW) Solution. The project investigated the efficacy of using UW solution on various tissues to determine if the ischaemic time (warm and cold) can be prolonged.</p> <p>The project looked at two specific tissues, skin flaps and peripheral nerves, and these were also critical to the survival of the replanted amputated limb. The findings from the study on skin flaps found no effect in improving the survival of the ischaemic skin flaps in rats. The researchers suggest that the perfusion of the tissue with UW Solution will probably not prevent the no-reflow phenomenon of the skin flap. A second study on peripheral nerve preservation to determine the regenerative potential of the nerve grafts at 5 weeks after 1-week storage in either UW Solution or Saline Solution was done. No significant differences was found between the two preservations conditions and its effects on the regenerative potential, although significant difference on their regenerative potential were observed between the two cold storage medium at 3 days.</p> <p>This study provides some new limits to the use of UW solution of preserving whole amputated limbs. Its clinical use might still be warranted and advantageous over 1 to 2 days, as shown by other authors. More work is required to assess its efficacy in preserving other tissues at various storage times, particularly muscle and vasculature.</p>
<p>NMRC/0231/1997</p> <p>PI: Lee Bee Wah (NUS)</p>	<p>Immunological characterization, molecular cloning, sequencing and expression of allergens of the storage mite, <i>Blomia tropicalis</i> : Towards the development of diagnostic and therapeutic tools for tropical allergy</p> <p>The objectives of the study were to characterize, clone, express and sequence the allergenic components of this mite using recombinant cDNA technology and immunochemical methods.</p> <p>Pure colony cultures of <i>B tropicalis</i> were obtained from mite cultures of house dust. The immunochemical nature of its antigens was analyzed via polyacrylamide-gel electrophoresis, isoelectric focusing, Western blotting and peptide sequencing. Cloning of the major allergens was carried out by extraction of poly-A RNA from mite cultures, followed by the construction of a cDNA expression library. Immunoscreening of expressed cDNA were carried out using positive sera (containing <i>B tropicalis</i>-specific IgE) as probes. The positive clones were purified, sequenced and expressed. The expressed recombinant proteins were evaluated for their allergenicity using both the immunochemical methods described earlier and via skin prick tests and ELISA. Populations in the East Asia region were tested for sensitization to these recombinant allergens.</p> <p>The pertinent findings have shown that the dust mite <i>Blomia tropicalis</i> is a very important mite allergen in this region. Several novel allergen clones have been identified. This research was achieved with collaborative efforts funded by the Bioprocessing Technology Centre and the Ministry of Education, through a flagship project.</p>

<p>NMRC/0259/1997</p> <p>PI: Ling Lieng His (NUS)</p>	<p>Three-dimensional reconstruction of effective regurgitant orifice area in mitral regurgitation: Comparison with the proximal isovelocity surface area (PISA) and quantitative echo-doppler methods</p> <p>By synthesizing multiple tomographic images, three dimensional (3-D) reconstruction can demonstrate the exact spatial orientation of anatomical structures. The researchers proposed to compare effective regurgitant orifice area (EROA) measured by 3-D techniques with that derived using proximal isovelocity surface area (PISA) and other quantitative Doppler-echocardiographic methods. 3-D datasets of 42 patients with mitral regurgitation (MR) due to flail mitral leaflets were acquired via transesophageal echocardiography (TEE), and Doppler echocardiographic data obtained near-simultaneously by transthoracic echocardiography (TTE). The 3-D datasets have been post-processed, reconstructed and archived digitally. Analysis of these datasets has been hampered by software which was cumbersome to use and proved suboptimal in assessing EROA. As of July 2003, Tom Tec released the latest version of their 3-D software (4-D RT) to the project, which allows near real-time interaction with the reconstructed dataset. Work is in progress to complete analysis using this new software.</p>
<p>NMRC/0263/1997</p> <p>PI: Quah Thuan Chong (NUS)</p>	<p>The study of novel oncogene fusion transcripts in childhood leukaemia and its use as minimal residual disease markers</p> <p>Childhood acute lymphoblastic leukaemia (ALL) is the most common form of childhood cancer and is highly curable (~ 75% EFS locally). The researchers studied the use of oncogene fusion and IgH rearrangement markers as highly sensitive prognostic markers in the management of childhood ALL. They found that the combination of multiplex rt-PCR and DNA index is superior to conventional karyotyping in treatment of childhood ALL, as the latter misses out >20% of submicroscopic translocations. This is important as karyotyping is both cumbersome and has poor yield. Using IgH receptors as markers of minimal residual diseases, the researchers found that they could accurately predict the patient's risk of relapse within 1 month of starting therapy, allowing them to tailor therapy to commensurate with patient's risk of relapse in their current treatment study on childhood ALL. It was found that the frequency of thiopurine methyltransferase deficient alleles is much less frequent in Asians (3%) than in Caucasians (10%) and African Americans (5%). This helps the researchers to adjust therapy emphasizing more on altering the dose of methotrexate than mercaptopurine.</p>
<p>NMRC/0268/1998</p> <p>PI: Teo Wee Siong (NHC)</p>	<p>A pilot study to compare biphasic versus monophasic shocks with the Automatic External Defibrillator in out-of-hospital cardiac arrest patients</p> <p>This was a pilot study where the aim was to see if biphasic defibrillation will enhance the survival of patients with out-of-hospital cardiac arrest. The initial animal studies had suggested that the success of defibrillation with biphasic shocks was less time dependent. The project was hampered by the slash in funding and we were not able to buy enough defibrillators to equip all the ambulances with the biphasic defibrillator. In the end only 2 ambulances were given the defibrillators. The project was started in April 1999 and stopped by December 1999. During that period, there</p>

	<p>were only 15 out of hospital cardiac arrest attending to by the 2 ambulances. Of these however only one of the patients had a shockable rhythm but the patient died subsequently. The researchers were hence unable to prove that the biphasic defibrillator was superior to conventional monophasic defibrillators in successfully resuscitating patients with out-of-hospital cardiac arrest.</p> <p>The main limitation of the study is the very poor result of out-of-hospital cardiac arrest in Singapore. The majority of the patients (about 98%) are not successfully resuscitated because of the delay from the time of arrest until CPR and defibrillation is given. Hence most of the patients are in asystolic cardiac arrest which is a non-shockable rhythm and thus the researchers were unable to demonstrate the superior efficacy of biphasic defibrillation.</p>
<p>NMRC/0271/1998</p> <p>PI: Ho Ting Fei (NUS)</p>	<p>Assessment of Lung Volumes and Mechanics in Infants and Young Children with Congenital Heart Disease</p> <p>The main objectives of the study were to determine the relationship between lung mechanics and cardiopulmonary haemodynamics in infants and children with congenital heart diseases; to understand the cardiopulmonary pathophysiology of such conditions and assess the progress of lung development and function with medical or surgical management of such patients.</p> <p>Lung function was measured non-invasively using a face mask over the face of each patient. During quiet breathing, passive respiratory mechanics and lung flow-volume relationship were determined. Pulmonary compliance and airway resistance were derived. Serial measurements were conducted to follow the progress of the patients.</p> <p>The main findings relate to the differences in airflow dynamics, lung compliance and airway resistance of patients with mild to severe left-to-right shunts. Patients with significantly large L-R shunts often had various combinations of attenuation of airflow rates, low lung compliance and high airway resistance.</p> <p>Such information was useful to the understanding of pathophysiology and helped in the management and decision-making process with regards to choosing between medical or surgical treatment.</p>
<p>NMRC/0283/1998</p> <p>PI: Teoh Ming Keng (SGH)</p>	<p>Aortic aneurysm expansion study</p> <p>The purpose of this study was to assess the mean diameter of the abdominal aorta in relation to age, sex and cardiovascular disease in Singapore. This will assist in the development of more appropriate guidelines for elective repair of abdominal aortic aneurysms. The study will also help define the true incidence of aortic aneurysms and the pattern of this disease in Singapore. This will not only enable evaluation of the role of screening but also identify the various high-risk groups that may justify screening.</p> <p>From 1998 to March 2003, a total of 995 patients have been recruited into the study from the Vascular Studies Unit (ultrasound Scan) and the Diagnostic Radiology Department (CT scan).</p> <p>The aorta was adequately visualized in 970 patients (97%). When the aneurysms were excluded, the ultrasound scan showed that the</p>

	<p>AP diameters of the abdominal aorta in the renal artery level were larger in the cardiovascular group (1.58cm) than in the non-cardiovascular group (1.45cm). CT scan showed a similar relationship between the cardiovascular and non-cardiovascular groups. The prevalence of AAA in the population among Singaporeans with cardiovascular disease was 4.0% and 11.5% in male aged 65 and above with cardiovascular disease.</p> <p>The finding that the aorta AP diameters of Singaporeans are significantly smaller compared to Caucasians suggests the need to adopt our own set of reference values for normal individuals and those with aneurysms. Screening for AAA during lower extremity arterial evaluation using ultrasound in male aged 65 and above with cardiovascular disease is cost-effective and should be considered an appropriate and valuable addition to the examination protocol.</p>
<p>NMRC/0284/1998</p> <p>PI: Mathew George Sebastian (SGH)</p>	<p>The effect of Arteriovenous graft configurations on blood flow dynamics and its consequent contribution to the development of fibrointimal hyperplasia and stenosis</p> <p>The failure of prosthetic arteriovenous (AV) grafts used for dialysis in renal patients is due to fibrointimal hyperplasia (FIH) at the venous anastomosis causing stenosis and subsequent obstruction. Pharmacological intervention poses a possible solution. Angiotensin peptides attenuate FIH in rat carotid arteries that had undergone balloon intimal ablation. Similar intervention might also decrease FIH in prosthetic AV grafts.</p> <p>The methodology was to investigate four groups of experimental animals – 2 controls and 2 experimental. The control groups had grafts implanted in 2 different configurations. One was prone to early failure and abandoned. The experimental groups were given des-aspartate angiotensin for a total of 14 days following graft implantation in 2 different concentrations (C1 & C2) and the grafts monitored weekly by duplex scanning until they were completely thrombosed.</p> <p>It was found that median time to obstruction for the ipsilateral looped graft was 4 weeks (range 3-10), contralateral looped grafts 19 weeks (range 11-21). With the peptide, graft life was 9.5 (range 4-10) weeks (C1) and 40 weeks (C2). On obstruction, the animals were sacrificed, the grafts harvested and the neointima explanted in tissue culture.</p> <p>Uptake of tritiated thymidine and phenylalanine as a marker of DNA and protein synthesis respectively in the explanted cells did not show any significant difference with the addition of specific receptor antagonists or mitogens.</p> <p>With the addition of des-aspartate angiotensin I, intimal hyperplasia was inhibited and graft potency extended to more than double that for the control group. Once validated, this finding is of great significance for patients with end-stage renal failure on haemodialysis who currently need graft revisions every 18-24 months or so due to FIH at the venous end. Although the result has not yet been published, it has potential to improve clinical service in vascular access for dialysis.</p>

<p>NMRC/0296/1998</p> <p>PI: Chang Hui Meng (SGH)</p>	<p>FOOD (Feed or Ordinary Diet) Trial</p> <p>FOOD is a multicentre (154 sites) “family” of trials aiming to answer 3 important questions about feeding of patients after stroke: (FOOD I) Does nutritional supplementation increase the proportion of patients with stroke who survive without disability? (FOOD II) Does early initiation of tube feeding (nasogastric [NG] or percutaneous endoscopic gastrostomy [PEG] in patients who are unable to take an adequate diet orally increase the proportion of patients with stroke who survive without severe disability? (FOOD III) Is feeding via a PEG tube instead of the traditional NG tube associated with improved outcomes after stroke? Over 5000 patients have been recruited worldwide, and recruitment was closed in 2004. Overall results will be reported in May 2004. Observational data of 3012 patients from FOOD revealed that poor nutritional status on admission for stroke predicted for poor outcomes.</p> <p>At SGH, we participated in FOOD II & III. Over 3 years from December 1998 to November 2001, 83 patients were recruited in FOOD trial. Sixty-nine patients were recruited into FOOD II and 14 (8 PEGs and 6 NGs) into FOOD III. During this period, we established that 17% of our stroke patients were dysphagic within 24 hours of admission, decreasing to 10% after 7 days. We also found that dysphagia was associated with large strokes, chest infections and predicted for poorer outcomes. These results were presented at 2 regional meetings (Singapore and Thailand) in 1999.</p> <p>Because of the impact of dysphagia on stroke patients, Neurology nursing staff learnt to screen dysphagia in all acute stroke patients in 1999. Since 2000, it became standard practice for nursing staff to screen dysphagia in all stroke patients, 24 hours a day.</p> <p><u>Direct/potential clinical applications of the research project</u> Locally, as a result of FOOD trial,</p> <ol style="list-style-type: none"> 1. The data shows that dysphagia was present in 17% of stroke admissions, reducing to 10% after 1 week. 2. Dysphagic patients at SGH also had poorer stroke outcomes. These patients had larger strokes, and were more likely to develop chest infections up to 3 months post-stroke. <p>Following on these findings, neurology nurses have been trained in dysphagia screening to provide 24 hour swallowing assessment to all acute strokes.</p> <p>The tangible improvements in medical care and treatment arising from the project are as follows:</p> <p>At SGH,</p> <ol style="list-style-type: none"> 1. All stroke patients receive an immediate dysphagia screener, regardless of admission time, administered by a trained nurse. Clerking doctors are informed of patient’s dysphagic status, and the most appropriate route of feeding ordered, until further review by speech therapist. This will minimise the risk of patients aspirating from inappropriate feeding. 2. Nursing staff have a heightened awareness of dysphagia in Neurology ward. 3. Speech therapists need not review every stroke patient for dysphagia and can concentrate on patients with significant dysphagia and dysphasia.
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<p>NMRC/0302/1998</p> <p>PI: Soo Khee Chee (NCC)</p>	<p>Randomised Trial of Tamoxifen vs Placebo for the Treatment of Inoperable Hepatocellular Carcinoma</p> <p>Hepatocellular carcinoma (HCC) is endemic in the Asia-Pacific region. Surgery is the only treatment modality that significantly prolongs survival but almost 90% of patients are inoperable at diagnosis. Tamoxifen (TMX) is believed to retard HCC positive for estrogen receptor (ER), but previous phase III trials in inoperable HCC have been conflicting and inconclusive. Most HCCs are also ER negative. Tamoxifen at higher doses, is however, known to retard HCC through ER-independent mechanisms.</p> <p>The objective of the project was to assess the role of high-dose TMX versus placebo (p) in the treatment of inoperable HCC with survival as the primary endpoint and quality of life (QoL) as the secondary end-point.</p> <p>The methodology used was a prospective double-blind controlled randomized trial with TMX 120mg/day in the study arm and P in the control arm and an intermediate dose arm of TMX 60 mg/day to assess possible dose-response. Randomisation was done through the data center in Singapore. Trial safety and quality controlled was ensured via site audits and an independent Data Monitoring Committee. QoL of patients was assessed using the EORTC QLQ-C30 questionnaire.</p> <p>10 centres in 9 countries (Myanmar, Hong Kong, Singapore, Thailand, Indonesia, Malaysia, South Korea, New Zealand, Australia) entered 329 patients. Reported adverse drug reaction was 3% and 8 patients were lost to follow-up. The 3-month survival rates for P, TMX60 and TMX 120 were 44%, 41% and 35% respectively with significant trend difference in crude survival rates across the 3 treatment regimens (p=0.011). There is a significantly higher risk of death in TMX120 as compared with P (HR:1.39;95% CI of HR: 1.07 to 1.81).</p> <p>In conclusion, TMX does not prolong survival in inoperable HCC and has a negative impact with increasing dose. Changed international clinical practice with respect to the treatment of inoperable hepatocellular carcinoma. The practice of treating such patients with tamoxifen was found to be detrimental.</p> <p>The trial resulted in the formation of an Asia-Pacific multi-national cancer trials group with its data centre in Singapore which continued to carry out further <i>collaborative</i> clinical trial (current AHCC02 trial) in this field, to address a disease, which although relatively unimportant in the West, is endemic in the Asia-Pacific.</p>
<p>NMRC/0306/1998</p> <p>PI: Goh Cho Hong James</p>	<p>Development of a biomechanical model of the stump-Prosthesis for transfemoral amputees</p> <p>The main objective of the project was to generate a Finite Element (FE) model of the amputee's stump which is capable of predicting the pressure distribution at the patient/prosthesis interface. Such knowledge would predict the quality of socket fit, prior to manufacture. This would allow a reduction of fitting errors and hence improve delivery of service to the physically disabled population. The model would also aid prosthetists and bioengineers in the design of prosthetic sockets and components for the artificial limb. The specific achievements and progress of this study are:</p>

	<ol style="list-style-type: none"> 1. Investigated methods and successfully acquired the geometry of the amputee stump for FE modeling. 2. Developed integration tool for commercially available prosthetic CAD software and FE software. 3. Designed and developed stump/socket interface pressure measurement systems and techniques. 4. Validated the FE model prediction by comparing experimental data recorded during the clinical trial. 5. Developed FE model with the potential for incorporation to commercially available Computer Aided Design and Manufacturing (CAD/CAM) system for prosthetics.
<p>NMRC/0307/1998</p> <p>PI: Lee Tat Leang (NUH)</p>	<p>Effect of Acupuncture on Cutaneous Blood Flow</p> <p>Acupuncture is an integral part of Traditional Chinese Medicine. It is widely used throughout the world for many disease states especially for the treatment of pain, whereby its efficacy can be explained by either local effect (trigger point release) and/or systemic effect attributable to the release of biochemical mediators (endorphins, serotonin etc) and activation of known anti-nociceptive neuro-circuits (spinal gate control mechanism, central descending inhibitory pathways and diffuse noxious inhibitory control). However, the physiological understanding of acupuncture treatment for functioning disorders is still incomplete, although there is existing data to support that acupuncture can activate the autonomic nervous system. This project aimed to study the effect of electroacupuncture on cutaneous blood flow (as the surrogate of sympathetic activity). The increase in skin temperature secondary to increase in cutaneous blood flow was assessed using infrared thermography. A total of sixty patients with neck and arm pain were recruited for the study. Electroacupuncture at acupoints GB 21, SI 11, GB 20, and EX-B2 using 15 Hz dense-disperse stimulation resulted in a significant vasodilatory effect on the upper limbs. The increase was maximum at 20 to 25 minutes during the acupuncture treatment. This phenomenon was not observed in a healthy control group. This finding suggests an effect of acupuncture on the sympathetic nervous system. In addition, infrared thermography may be a useful means to follow the progress of disease process, and the response to acupuncture therapy. The researchers are currently studying the relationship of vasomotor changes and treatment efficacy to acupuncture.</p>
<p>NMRC/0310/1998</p> <p>PI: Melvin Look Chee Meng (TTSH)</p>	<p>p53 as a prognostic marker in gastric cancer</p> <p>Apoptosis is a highly regulated form of programmed cell death thought to be involved in cell turnover for various tumours. The p53 tumour suppressor gene is believed to control apoptosis by regulating the expression of the apoptosis associated genes bcl-2 and bax. The role of this in gastric cancer is not fully understood. The researchers examined 232 archival samples of gastric carcinomas for the over-expression of p53, the over-expression of the bcl-2 and bax proteins, as well as directly for the presence of apoptotic cells by the TUNEL methodology. There were 38.8% (using DO-7 anti p53 antibody) and 34.1% (using 1801 anti p53 antibody) p53 protein over-expression. Bcl-2 expression was found in 30.6% of the samples and bax was tested in 57.3%. Apoptotic cells were found in 35% of the samples. The involvement of p53 mutations in this study was also investigated. p53 mutations in 232 gastric cancer were examined by polymerase chain reaction-single strand conformation polymorphism</p>

	<p>(PCR-SSCP) analysis and sequencing. Mutations were detected in 56 of 232 (24.1%) cases, in exon 5 (10.3%), exon 6 (1.3%) , exon 7 (5.6%) and exon8 (6.5%). No mutations were detected in both exons 4 and 9. Polymorphism was found in condon 72 of exon 4 (CGC to CCC) in 23% of samples.</p>
<p>NMRC/0312/1998 PI: Ling Lieng His (NUS)</p>	<p>Coronary artery calcification as a surrogate for atherosclerosis: the clinical role of ultrafast computed tomography in a multi-ethnic population without proven coronary artery disease</p> <p>This study evaluates the incremental value of EBCT calcium score (CS) over conventional clinical variables in predicting the presence of coronary artery disease (CAD).</p> <p>252 patients (65% males, mean age 55±10 years) with suspected CAD who had selective coronary angiography were examined. Sequential 3-mm images were acquired using the Imatron C-100 scanner and CS calculated using the method of Agatston. Quantitative coronary angiography was performed and plaque burden derived.</p> <p>Significant CAD (≥50% diameter stenosis of a major epicardial vessel) was present in 52% of cases. Only 60% of patients diagnosed as stable angina pectoris and 68% as unstable angina had CAD. There was a significant correlation between CS and total plaque area (r=0.54, p<0.0001). All patients with CS >650 had CAD whereas only 7% with CS<1 had CAD. Areas under the receiver operating characteristic (ROC) curves were 0.86 (95% confidence intervals [CI] 0.81-0.91) for CS and 0.66 (95% CI 0.59-0.72) for traditional risk factors. In univariate analyses, predictors of CAD included CS (p<0.0001), cigarette smoking (p=0.0003), age (p=0.0004) and diabetes mellitus (p=0.0097). In a multivariate model, only 2 variables retained independent predictive value: CS ($\chi^2=22.8$, p<0.0001) and smoking ($\chi^2=9.8$, p=0.001).</p> <p>The conclusion is that CS provides incremental value in identifying CAD and may help stratify need for further invasive testing.</p>
<p>NMRC/0322/1998 PI: Yap Hui Kim (NUS)</p>	<p>Role of IL-3 as a modulator of monocyte production of a vascular permeability factor in idiopathic nephrotic syndrome of childhood</p> <p>It had previously been shown that lymphocyte (CD4+ and CD8+) gene expression of IL_13 was increased in children with steroid-responsive nephrotic syndrome (SRNS) in the relapse phase. As IL-13 has important immunomodulatory effects on monocytes, the researchers postulated that IL-13 may act on monocytes to produce a vascular permeability factor important in the pathogenesis of nephritic syndrome. Thus this project was aimed at (a) identifying monocyte functional abnormalities related to the increased IL-13 expression in relapse; and (b) determining differentially expressed gene(s) in monocytes in relapse, particularly those upregulated by IL-13.</p> <p>The researchers first examined the possible relationship between increased lymphocyte IL-13 gene expression and the proinflammatory monokines, in particular IL-8 and TNF-α, and monocyte CD14 expression. Both cross-sectional and paired data showed that IL-8 and TNF-α were decreased in LPS-stimulated</p>

	<p>monocytes from SRNS patients during relapse, as compared to remission and normal controls. Moreover, it was associated with suppression of monocyte surface CD14 expression, as well as lower levels of soluble CD14. These results point to a major anti-inflammatory effect of IL-13 in an LPS-driven system.</p> <p>The research also showed that SRNS patients had lower 5-LO expression in relapse, compared to remission, using real-time quantitative RT-PCR. As the 5-LO pathway is a major route of arachidonic acid formation leading to leukotriene production, the decreased 5-LO levels in relapse should be suggestive of reduced pro-inflammatory LT synthesis consistent with the absence of inflammatory cells in MCNS.</p> <p>In order to identify putative monocyte genes that may be upregulated by IL-13, the researchers examined the differently expressed gene(s) induced by recombinant human IL-13 on a monocyte cell-line 28SC, using differential display RT-PCR. The researchers identified a gene B3.0, coding for a novel protein, AD024, which is mapped to chromosome 2. In order to determine if this could be a putative vascular permeability factor in MCNS, they then analyzed its expression on 18 patient-pairs with SRNS and found significant higher levels in relapse as compared to remission and normal controls. Further work is undergoing to define the role of this protein, AD024, in the pathogenesis of MCNS.</p>
<p>NMRC/0336/1999</p> <p>PI: Ong Choon Nan (NUS)</p>	<p>Mechanistic studies on the antioxidative and anti-carcinogenic effects of green and black tea flavonoids</p> <p>EGCG, one of the main components and an isoflavonoids has been found to be able to decrease the effect of oxidant, hydrogen peroxide. This event also linked to the decrease in PGE2 levels. These cellular changes of H₂O₂ production and PGE2 were significantly correlated with the observed decrease in cellular proliferation. This finding suggests there is a link between the ability of EGCG to alter the intracellular redox status, PGE2 production and cellular proliferation. Further investigation of whether or not it is due to the antioxidant activities that tea flavonoids may inhibit COX-2 expression will be carried out. Another flavonoid in green tea, leuteolin, on the other hand, was found to be able to cause apoptosis via the mitochondrial pathway.</p>
<p>NMRC/0339/1999</p> <p>PI: Fong Yoke Fai (NUS)</p>	<p>A novel regimen to achieve amenorrhea using the levonorgestrel-releasing intrauterine system for combined hormone replacement therapy in premenopausal women and its correlation with mRNA expression of IGF-1, IGF-II and IGFBP-1 in the endometrium</p> <p>The objective of this study was to assess the effectiveness of a novel regimen in achieving amenorrhea using the levonorgestrel-releasing intrauterine system (LNG_IUS) in combined hormone replacement therapy (HRT).</p> <p>The hypothesis was that compared to the standard regime of oral continuous combined HRT, a new regimen of the LNG-IUS inserted 3 months before the commencement of estrogens is better in terms of: producing a period free regime, acceptability, incidence of menstrual disturbances, occurrence of systemic side effects, effects on liver function, lipid and carbohydrate metabolism and protection against endometrial hyperplasia.</p>

	<p>Women with menopausal symptoms requiring HRT were randomized into one of three treatment groups: (i) LNG-IUS and daily oral estrogen started simultaneously; (ii) LNG-IUS inserted 3 months before commencing estrogens; (iii) Continuous combined oral progestogen and estrogen.</p> <p>The bleeding pattern, amenorrhea and discontinuation rates were assessed at 0, 3, 6 and 12 months. Other secondary parameters such as lipid profile, liver function, fasting glucose and clinical parameters such as weight and blood pressure are also assessed.</p> <p>A total of 69 (23 in each arm) menopausal women were recruited and followed up for 12 months. In the oral group the continuation rate was 56.5% at 12 months. This contrasts with 78.3% at 12 months for both the LNG-IUS groups.</p> <p>The study concluded that the use of the LNG-IUS in combined HRT gives a higher rate of amenorrhea and may be helpful in improving compliance with HRT.</p>
<p>NMRC/0344/1999 PI: Christopher Chen (SGH)</p>	<p>A study of the clinical and neuropathological correlates of g-amino butyric acid GABAA, GABAB receptor alterations in Alzheimer's disease</p> <p>Preclinical studies have demonstrated an involvement of the GABAA / benzodiazepine (BZ) as well as GABAB receptors in cognition and behavior. However, the status of cortical GABAA / BZ and GABAB receptors in relation to cognitive and behavioral symptoms in dementias such as Alzheimer Disease is not known.</p> <p>Using radioligand binding assays to postmortem tissues, the researchers measured the affinity and density of GABAA / BZ sites in the temporal cortex, as well as GABAB receptors in the frontal cortex of a cohort of dementia patients prospectively assessed for behavioral symptoms, and correlated the neurochemical findings with clinical features.</p> <p>Both GABAA / BZ as well as GABAB sites were not significantly altered in dementia compared with controls, in agreement with previous postmortem studies. Within the dementia group, however, the density of BZ binding sites in the temporal cortex is higher in severely depressed patients than in non-depressed patients. Surprisingly, the neurochemical measures were not related to other neuropsychiatric behaviors or to cognitive decline, suggesting that GABAergic neurotransmission do not play a direct role in these behaviors in dementia. Taken together, the results suggest for the first time that the state of GABAergic receptors may be risk factors or markers of behavioral disturbance in dementia.</p>
<p>NMRC/0346/1999 PI: Kuldip Singh (NUS)</p>	<p>Use of the levonorgestrel-releasing intrauterine system in the treatment of menorrhagia: influence on mRNA and antigen expression of plasminogen activators and plasminogen activator inhibitors in the endometrium</p> <p>The objective of the study was to assess the effectiveness of the levonorgestrel-releasing intrauterine system (LNG-IUS) in the treatment of menorrhagia.</p> <p>The study hypothesized that the LNG-IUS system causes significant</p>

	<p>changes in levels of activators and inhibitors of the fibrinolytic system within the endometrial tissue resulting in marked reduction in menstrual blood loss.</p> <p>Women referred to the gynaecological clinic for the problem would be recruited; menstrual blood (MBL) would then be quantified according to a pictorial blood loss assessment chart. Those with a score of 100 and more will be included in the trial and will be fitted with the LNGH-IUS.</p> <p>A total of 45 patients were admitted, 15 with uterine fibroids, 15 with adenomyosis and 15 with menorrhagia due to dysfunctional uterine bleeding. They were all followed-up for 12 months. The continuation rate was above 90% at the end of 12 months with majority achieving a reduction in menstrual blood loss.</p> <p>The study concluded that use of the LNG-IUS is effective in marked reduction in menstrual blood loss in women with documented menorrhagia.</p>
<p>NMRC/0348/1999</p> <p>PI: Chan Soh Ha (NUS)</p> <p>Collaborators: Yap Eu Hian, Ren Ee Chee</p>	<p>Role of interleukin-18 and its responsive T cells in autoimmune diabetes</p> <p>In the present study using NOD mice as the diabetes model, the researchers defined the changes in expression pattern of cytokines, chemokines and chemokine receptors over time, and how it correlates with the stage-wise progression of insulinitis to diabetes. The mice were divided into 3 age groups which correspond generally to different immunopathology of the islets of Langerhans, namely pre-insulinitis, established insulinitis and destructive insulinitis. Th1 cytokines (IFN-g, IL-12, IL-18) and chemokines (MIP-1a, IP-10) levels in serum, spleen and pancreas were determined. Interestingly, pre-insulinitic mice showed the highest level of IL-18, IP-10 and MIP-1a than their diabetic counterparts while the reverse is true for the expression of IL-12. There is no difference in IFN-g expression across the designated age groups and genders. On the other hand, while splenic and pancreatic elevation of IL-18 in the prediabetic group was significantly higher than the diabetic group, the reverse was observed when comparing serum level of IL-18. In general, female mice also showed higher cytokine expressions than their male counterparts in to the same disease stage. The study suggested that those cytokines showed elevated expression in the pre-insulinitis group indicated an association with the early phase of insulinitis, and those elevated at a later stage indicated association with ongoing insulinitis. The expression of various chemokine receptors in spleen and pancreas of diabetic and non-diabetic mice was also investigated. Lastly, an immunotoxin – MIP-1aPE38KDEL, was also constructed and tested to determine if they can ameliorate insulinitis by specifically eliminating the autoreactive CCR5+ cells.</p>
<p>NMRC/0350/1999</p> <p>PI: Cheah Peh Yean (SGH)</p>	<p>Assessing the anti-cancer effect of NSAIDs in colorectal cancer tumour using an individualised histoculture system</p> <p>Epidemiological and animal studies have shown that nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin can reduce the incidence of death from CRC by 50%. However, individual tumors often have varying chemosensitivity. The study successfully established an in vivo-like 3-dimensional histoculture system for assessing chemosensitivity of individual colorectal cancer (CRC) to</p>

	<p>chemotherapeutic drugs. The histoculture system was used to assess the anti-proliferative effect of sodium salicylate, an aspirin metabolite, by the bromodeoxyuridine (BrdU) immunohistochemical labeling assay. The dose-response of individual cancers to sodium salicylate can be categorized into 4 groups, ranging from the most sensitive to the least sensitive. 60% of the cancers (Groups A and B) show concentration-effect relationship with sodium salicylate within the clinically relevant concentrations, suggesting that sodium salicylate has anti-proliferative effect on majority of the histocultured cancers. The varying chemosensitivity is possibly due to individual differences in the cancers, thus highlighting the advantage of the histoculture system in customizing chemotherapy to individual patient. By staining with anti-Poly (ADP-ribose) polymerase (PARP) p85 fragment antibody, the researchers did not find any concentration-dependent increase in apoptotic index in sodium salicylate-treated sections over control, suggesting that sodium salicylate did not induce caspase-activated apoptosis in the histoculture system.</p>
<p>NMRC/0351/1999 PI: Lim Sok Bee (KKH)</p>	<p>Singapore NICU Network: mortality and morbidity of a national cohort of very low birth weight infants</p> <p>Population based studies on the provision of care and outcome of high-risk preterm neonates are essential in evaluating perinatal care services and NICU programmes, and also for perinatal counselling.</p> <p>The aims of the project were 1) to determine incidence of morbidity and mortality of a geographic cohort of Very Low Birth Weight (VLBW) infants in Singapore and to assess variations in clinical care practices and outcomes among participating hospitals; 2) to establish foundation of a NICU network in Singapore for subsequent collaborative multicentre research.</p> <p>All live born VLBW infants born between 1 July 2001 and 30 June 2002 in the eight major hospitals in Singapore were recruited. Data was collected prospectively on obstetric and neonatal demographic profile and neonatal mortality and morbidity. During the study period, 334 VLBWs were recruited. Common causes associated with preterm delivery were PIH(24%), PPROM(28%) and APH(15%). 62(19%) babies were born through assisted conception.</p> <p>The mean gestational age was 28.9 ± 2.8 weeks and mean birthweight was 1107 ± 262 gms. 122 (36.5%) of the cohort were ≤ 1 kg at birth and 70 (21%) were born extremely preterm ≤ 26 weeks. Overall survival for the entire cohort was 93% with improving survival with increasing birth weight and gestational age. Common neonatal morbidity included HMD (46%), PDA(37%), CLD at 36 weeks (6.6%), severe ROP (6.1%) and severe IVH (4%).</p> <p>108(89%) of the 122 ELBW were born in the 3 restructured hospitals compared to 14 (11%) in the 5 private hospitals ($p < 0.01$). Similarly, 60 (85%) of the 70 ELGA babies ≤ 26 weeks were delivered in the restructured hospitals versus 10 (25%) in the private hospitals. Mortality was not significantly different among the different hospitals.</p> <p>In conclusion, the study has been invaluable in understanding demographic profile, morbidity and mortality of national cohort of VLBW babies. This data will be used for auditing, quality improvement and to aid in deriving potentially better practices to</p>

	improve outcome in different centres.
<p>NMRC/0352/1999</p> <p>PI: Eugene Sim Kwang Wei (NUS)</p>	<p>Transfer of embryonic stem cells and fetal cardiomyocytes into ischaemic adult hearts with a view to a long term cure for myocardial damage</p> <p>The project studied the safety and efficacy of adult rabbit stem cells for myocardial repair and its transformation into cardiomyocytes by directed differentiation with 5-azacytidine (5 AZA). In the vitro study, adult stem cells were isolated from the fatty tissues of rabbits and were chemically induced in vitro, using various concentrations of 5-aza, into cardiomyocytes. The 5-aza treated stem cells immunostained positive for cardiomyocytes. The 5-aza treated stem cells immunostained positive for cardiomyocyte specific markers including myosin heavy chain, α-actinin and cardiac troponin-I. The transformed cells maintained their phenotype for up to 2 months of observation after treatment with 5-aza. These observations reveal the potential of fatty tissue derived adult stem cells for chemical transformation into cardiomyocytes and may be exploited as a potential source of autologous stem cells for myocardial repair.</p> <p>For in vivo characterization, the transformed cells were transplanted into the heart of SCID (Severe Combined Immune Deficient) mice. For post transplant identification, the cells were labelled with lac-z reporter gene using an engineered recombinant retroviral vector. The lac-z transduced cells were transplanted intramyocardially by the infra-diaphragmatic approach. The animals were euthanized at 4-8 weeks post-transplantation and the heart was removed. Histochemical studies revealed the presence of lac-z positive cells with sustained gene expression in the myocardium. Immunostaining for cardiomyocyte specific β-myosin heavy chain and cardiac troponin-I was positive. The study showed that adult SC could be transformed into cardiomyocyte like cells and may be a potential source for cells for an auto transplantation and myococardial repair.</p>
<p>NMRC/0359/1999</p> <p>PI: Lee Tat Leang (NUS)</p>	<p>Determination of the pathophysiological roles of the analgesic peptide nocistatin and its possible clinical application</p> <p>Morphine, a major component of opium, is a powerful analgesic that has been used for centuries for the treatment of pain. However, though morphine and other opioids are very effective in the treatment of pain produced by tissue injury, such as post-operative pain, the neuropathic pain associated with nerve injury is often unresponsive to opioids. Drugs currently being used for treatment of neuropathic pain also present many undesirable side-effects. Nocistatin (NST) is a new neuropeptide first isolated from bovine brain in 1998 and has been shown to be involved in pain modulation. It is processed from prepronociceptin, a precursor of another neuropeptide, Nociceptin/Orphanin FQ (NCP). NCP has been shown in animals to produce allodynia and hyperalgesia, and NST has been shown to counter these effects. NST dose not act on the opioid receptors, hence NST-like drugs should be devoid of the side effects associated with opioid therapy. The research team was the first group to report the presence of NST in human, mouse and rat brain tissues and in human CSF. In addition, they also identified a new NST-17 isoform in humans. They also developed a highly sensitive RIA detection technique to enable them to identify both NST and NCP in a small amount of CSF (1mL)</p>

	<p>The team was also successful in expressing and purifying mouse NST using two related plant viral vectors (odontoglossum ringspot virus and tobacco mosaic virus).</p>
<p>NMRC/0362/1999</p> <p>PI: Lee Eng Hin (NUS)</p>	<p>Use of cultured mesenchymal stem cells on repair of chondral defects in humans</p> <p>The objectives of the study were to investigate the effect of cultured Chondrocytes & MSCs on the treatment of growth arrest in children and cartilage defects in adults.</p> <p>Chondrocytes are isolated from cartilage and MSCs from bone marrow, cultured in vitro under strictly sterile conditions in the lab, and allowed to proliferate approximately 3 to 5 weeks to significant amounts (10 to 20 million cells) before autologous cell implantation.</p> <p>Post-operative assessment includes survey evaluation and MRI. Patients were to be questioned and examined with regards to their ability to perform vocational and vocational activities. Magnetic Resonance Imaging is performed at 12 months after operation to assess the quality of healing of the defect.</p> <p>More than 86% of the patients have shown significant improvement in the post-operative assessments. Also, patients will be expected to experience improved joint performance, thus resuming the quality of life. There have been no adverse events or complications following implantation in all our patients.</p>
<p>NMRC/0365/1999</p> <p>PI: Samuel S Chong (NUS)</p>	<p>Development of simplified and highly sensitive molecular diagnostic testing for alpha-thalassaemia</p> <p>The alpha-thalasseмии represent one of the most common single gene disorders in man. Despite the existence of protocols for rapid detection of many of the common deletional determinants of a-thalassaemia using the polymerase chain reaction (PCR), Southern blot analysis continues to be relied upon as the standard test platform in many clinical diagnostic laboratories. This is due in large measure to reliability and reproducibility issues for many of the published PCR tests, and the multiple PCR tests required in order to screen a patient for deletions. A simplified multiplex PCR test to detect 7 common deletional determinants of a-thalassaemia [-(a)3.7, -(a)4.2, -(a)20.5, --SEA, --MED, --FIL, and --THAI] has been developed. Complementary reagents for use as positive controls in the diagnostic laboratory have been developed. Also, a multiplex minisequencing assay has been developed to detect commonly encountered point mutations in a-thalassaemia. An automated fluorescent sequencing test to screen for rare mutations in the a2 and a1 globin genes has also been developed. To complement the a-thalassaemia molecular tests, a multiplex minisequencing assay to detect 15 common b-thalassaemia mutations was developed.</p>
<p>NMRC/0372/1999</p> <p>PI: Lim Su Chi (AH)</p>	<p>The effect of d-alpha-tocopherol (vitamin E) on the endothelial of subjects with type 2 diabetes</p> <p>The objective of this study is to evaluate the efficacy of vitamin E on the endothelial function of subjects with type 2 diabetes. 100 patients with type 2 diabetes were enrolled in a randomized, double-blind placebo controlled trial and followed them for 3 months. The endothelial function was assessed safely and non-invasively by measuring the forearm superficial skin hyperemic response to the</p>

	<p>iontophoresis of 1% acetylcholine (produces endothelium dependent vasodilation) and 1% sodium nitroprusside (produces endothelium independent vasodilation). Blood specimens was also obtained from each subject for the measurement of glucose, HBA1c, lipid profile and markers of endothelial activation – vascular cell adhesion molecule (VCAM), intercellular adhesion molecule (ICAM) and oxidative stress (Coenzyme Q10). Ninety eight patients completed the study. Two patients were lost to follow up – one due to religious consideration, another due to relapse of previously stable seizure disorder. The data suggested that even at a daily dose of 1,600 IU of vitamin E (resulting in a tow fold increment in plasma vitamin E levels in those subjects taking the active intervention), there was no demonstrable improvement in any of the above markers. Contrary to previous belief, recent metanalysis from major clinical trials suggested that vitamin E supplements could not improve cardiovascular morbidity and mortality. The data may have provided the possible underlying explanation i.e. vitamin E supplement even at high dose, could not improve the endothelial function of subjects with type 2 diabetes.</p>
<p>NMRC/0376/1999 PI: Goh Cho Hong James (NUS)</p>	<p>Biomechanical evaluation of the pressure cast (PCAST) prosthetic socket for trans-tibial amputee</p> <p>The project aims to develop a new pressure cast (Pcast) technique to fabricate prosthetic sockets for transtibial amputees. Clinical trials and biomechanical evaluation of the socket fabricated was done to access the feasibility of this new technique and to determine the performance of the new socket.</p> <p>24 subjects participated in the clinical trials. 13 of the 24 subjects were successfully fitted with the PCast socket. 11 of the 13 were “first time fit”. From the result of questionnaire and interview, 54.55% of the subjects preferred the PCast prosthesis N 68.88% of the subjects felt that PCast prosthesis performed better or equivalent to the PTB socket. The remaining subjects preferred the PTB design.</p> <p>For the biomechanical evaluation of the PCast socket, 4 subjects were fitted with both the PCast and the PTB sockets. Pressure and gait measurements were done simultaneously when the subject is in a normal standing position and during walking.</p> <p>The PCast socket did not exhibit ‘a hydrostatic pressure profile’ as expected. Though some subjects exhibited similar pressure profiles for both sockets, the hypothesis to ‘let nature determine the most natural and realistic pressure distribution’ may hold true, though reasons for it not occurring in all subjects need more research. 2 other subjects exhibited different pressure profiles: subjects wearing the PTB socket showed a higher pressure profile at the proximal brim of the socket while the PCast socket exhibited more distal end pressures.</p> <p>With the PCast and PTB sockets developed from different schools of thought, the best socket would be one that suit a patient’s stump condition, activity level and rehabilitation needs.</p>
<p>NMRC/0377/1999 PI: Kesavan Esuvaranathan (NUS)</p>	<p>A randomised controlled double-blind trial to determine the efficacy of orally administered theophylline in assisting the passage of ureteric calculi</p>

	<p>The efficacy of theophylline in assisting the spontaneous passage of uterine stones without the need for surgical intervention was assessed in this study. 50 eligible patients with single ureteric calculi were randomized to receive either oral theophylline or identical placebo for a period of 8 weeks. The efficacy of theophylline was assessed in terms of passing rate, incidence of pain.</p> <p>Out of 50 patients 31 patients received theophylline and 19 received placebo. Out of the total number of patients recruited 14 patients dropped out of the trial for reasons not related to adverse events. Of the remaining, 42% and 35% of those receiving placebo and theophylline respectively passed their ureteric calculus. 62.5% and 78% passed their ureteric calculi within the first 4 weeks of the trial for patients receiving placebo and theophylline respectively.</p> <p>The incidence of pain was higher for patients receiving theophylline (44.4%) as compared to patients receiving placebo (33.3%). However, the usage of naproxen and buscopan was found to be lower for the patients receiving theophylline than those receiving placebo. This could be due to the fact that theophylline is facilitating the movement of the calculus resulting in a higher incidence of pain and at the same time reducing the intensity of pain by diluting the ureter.</p> <p>In conclusion, the numbers achieved so far are small but they indicate that theophylline may help in the spontaneous passage of ureteric calculi with less pain. A larger number of patients are required, to determine if the results obtained are significant.</p>
<p>NMRC/0378/1999 PI: Kuldip Singh (NUS)</p>	<p>Effect of the levonorgestrel releasing intrauterine system (LNG-IUS) on lipid metabolism - a randomised controlled study</p> <p>The objective was to study the effect on the levonorgestrel-releasing intrauterine system (LNG-IUS) on lipid metabolism as markers of cardiovascular risks.</p> <p>A total of 100 women were recruited – 50 using the LNG-IUS system and 50 using a non-steroidal intrauterine device as controls. Following insertion of the intrauterine device, the women were followed up at 1, 6, 12, 18 and 24 months. Blood was drawn preinsertion and at 1, 6, 12, 18, 24 months. Parameters tested include Total Cholesterol, High Density Lipoprotein Cholesterol, Low Density Lipoprotein Cholesterol, Triglycerides and severe apolipoproteins.</p> <p>Analyses of the results show clearly that the effect on levonorgestrel when used on an intrauterine system has no adverse effect on lipid metabolism. This is in accordance with previous findings when levonorgestrel is used orally or as subdermal implant.</p>
<p>NMRC/0383/1999 PI: Evelyn Koay (NUS)</p>	<p>Novel molecular biological approaches for the diagnosis of pre-eclampsia : Measurement of fetal DNA in maternal serum or plasma</p> <p>Revised title: Quantitative detection of tumour-derived biomarker gene expression in nodal micrometastases in patients with colorectal cancer in relation to tumour re-staging.</p> <p>Many Dukes' B (Stage II) cancer patients die from disease</p>

	<p>recurrence, due to early tumour spread, which is undetectable by histomorphological examination. The aim was to determine whether quantifying the nodal expression of 3 tumour markers (carcinoembryonic antigen/CEA, cytokeratin-20/CK-20, guanylyl cyclase C/GCC) in colorectal cancer (CRC) would improve the accuracy of stratifying Dukes' B patients into different prognosis groups. The researchers questioned whether using a single biomarker in one tissue type for the detection of micrometastases, as reported by others, was adequately representative, due to tumour heterogeneity. 175 frozen lymph nodes and 158 formalin-fixed, paraffin-embedded lymph nodes from 28 CRC cases were studied and gene expression data obtained using CEA, CK-20 and GCC-specific quantitative real-time PCR (R-PCR). Considerable discordance was found in the positive detection of the 3 biomarkers in frozen versus fixed tissues in 11 Dukes' B CRC assessed by morphological evaluation. The one patient with full concordances in all 3 markers with both tissue types suffered a fatal relapse within 2 years. These results clearly demonstrated the heterogeneity of biomarker gene expression and the importance of using multiple (at least three) markers and both FT and PET tissues, to precisely predict the metastatic potential of Dukes' B CRC.</p>
<p>NMRC/0386/1999</p> <p>PI: Goh Yam Thiam Daniel (NUS)</p> <p>Collaborator: Dr Wang De Yun</p>	<p>Vorner-adenoidal distance and acoustic reflectometry as measures of upper airway patency : A predictive factor of obstructive sleep apnea syndrome in children</p> <p>The gold standard for diagnosis of obstructive sleep apnea syndrome (OSAS) in children is the overnight polysomnogram, which is costly, time-consuming and of limited availability. This study aims to evaluate an OSA score, acoustic rhinometry and vomer-adenoidal distance (VAD) as a screening tool. Patients referred for suspected OSAS underwent standard polysomnography and the proposed screening tests. 121 children (46% with OSA) were recruited between June 2000 and July 2002. The median age was 7.9years (range 5 months to 16years). The average OSA score was +1.27 for those with OSAS while the non-OSAS based on polysomnography was +0.121 (p<0.001). The correlation coefficient between the OSA scores and OSA severity was 0.566 (p<0.005). The average score for VAD was 6.25 and 3.14 for OSAS and non-OSAS children respectively (p<0.05). The acoustic reflectometry measurement of the narrowest cross-sectional area at >2cm distance (an average of right and left sides) was 0.782cm² and 0.604cm² in the OSA and non-OSA subjects respectively (p<0.05). It was concluded that the OSA score, VAD and acoustic rhinometry are useful screening tools for children with OSAS. Further studies are needed to apply these in clinical practice.</p>
<p>NMRC/0388/1999</p> <p>PI: Foo Keong Tatt (SGH)</p>	<p>The Natural History of Prostatic Disease and the selection of patients with symptomatic benign prostatic hyperplasia for different modalities of treatment (renewal)</p> <p>This is the continuation of a previous study looking at the natural history of patients with BPH. The proposed aim of the present study was to improve the treatment of BPH by analyzing in a prospective manner the outcomes of conservative and medical therapy. An earlier phase of the study had looked into improving the outcome of surgical treatment. This was achieved by the successful formulation of a system of classification based on symptoms and life style scores</p>

	<p>and uroflowmetry and post-void residual urine volumes termed staging. Further refinement was possible by grading the prostate according to its protrusion into the bladder on transabdominal ultrasound.</p> <p>As proposed for this phase of the study, these concepts are now applied to patients on conservative and medical therapy. Medical therapy is attractive and oftentimes the first recommended treatment, as it is non-invasive. However, the long term cost of treatment is high if it is prescribed indiscriminately to all patients and final outcomes may be poor.</p> <p>This may only become obvious on longer follow-up and is the objective of this study.</p> <p>There are a total of 272 patients in the database who had their international prostate symptoms score (IPSS), quality of life index (QoL), uroflowmetry, residual urine volume and intravesical prostatic protrusion measured by transabdominal ultrasound scan and meticulously documented by the data clerk. Based on these data, a few important findings on the natural history of BPH were discovered:</p> <ol style="list-style-type: none"> 1. Grade of prostatic protrusion is the best predictor of whether patients with lower urinary tract symptoms suggestive of BPH would fail from conservative treatment. 2. Based on the same theory, it could be predicted whether a patient with acute retention of urine could be successfully tried without a catheter. 3. Patients with minimal to moderate intravesical protrusion of the prostate demonstrated an improvement in their maximum flow rates with medical therapy. Those with severe intravesical prostate protrusion however, experienced a decline in their flow rate in spite of medical therapy. 4. Those patients with high grade intravesical prostatic protrusion with good uroflow rate were actually obstructed when they were subjected to urodynamics testing. <p>These results would therefore support the use of intravesical prostatic protrusion measured by transabdominal ultrasound scan as a useful guide in selecting patients who would be best suited to medical therapy; thus improving treatment outcomes and reducing wasteful long term therapy in those least likely to benefit from such treatment.</p>
<p>NMRC/0394/1999 PI: Adrian Low Fatt Hoe (NUS)</p>	<p>The role of non-traditional cardiovascular risk factors in the pathogenesis of coronary artery disease among the various ethnic groups in Singapore</p> <p>It is known that Indians in Singapore have higher risk for coronary artery disease compared to the other races. The data documents higher prevalence of H.pylori seropositivity and CRP levels among Indians. CRP is a marker of inflammation and the elevated levels suggest elevated inflammatory activity as a possible cause for the increased cardiovascular risk among Indians. The basis for these findings however remains unclear. Infection (by H.pylori) leading to plaque vulnerability is a possibility. Among the whole patient cohort, the data does not suggest homocysteine levels, Lp(a) levels or C.pneumoniae infection to be significant risk factors.</p> <p>There are few studies evaluating the importance of these non-</p>

	<p>traditional cardiovascular risk factors in the Asian population and this study will add to the growing literature on these novel cardiovascular risk factors in the pathogenesis of coronary artery disease. Much analysis, however, remains to be performed and this includes follow-up data and subgroup analysis, determining the impact of various H.pylori strains, as well as looking at the impact of these risk factors among patients with chest pain complaint but without myocardial infarction, etc. The researchers hope to present further data in upcoming meetings.</p>
<p>NMRC/0396/1999 PI: Wang De Yun (NUS)</p>	<p>The role of proinflammatory cells and cytokines in the pathogenesis of sinusitis and nasal polyps with immunohistochemical characterization</p> <p><u>Pattern of mucosal inflammation and relationship to inhalant allergy in patients with chronic rhinosinusitis or nasal polyps</u></p> <p>Chronic sinusitis is a common chronic disease that is often associated with nasal polyposis. Although there have been advances in pharmacologic and surgical therapies, the recurrence rate is still unacceptably high. This may be due to incomplete understanding of the etiology and pathogenic mechanisms of these diseases. The researchers studied the cellular mechanisms of chronic sinusitis and nasal polyps using an immunohistochemical characterization of a panel of cell surface makers for inflammatory cells (CD4+, CD8+, CD1a+, CD19+, tryptase, major basic protein, neutrophil elastase) in pairs of inflamed sinus mucosa (16 patients) or nasal polyp tissue (38 patients) and middle turbinate mucosa of the same side. Serum specific IgE antibodies to a panel of common allergens were also tested by RAST. Results showed that cell patterns in sinus mucosa or polyp tissue and the turbinate mucosa were very similar with an infiltration of eosinophil, CD8+ cells (suppressor/cytotoxic T cells) and mast cells. Atopy is found only in up to 40-50% of the study patients. In conclusion, the study demonstrates that nasal polyps and chronic sinusitis are inflammatory diseases, which can not be explained solely by IgE-mediated allergy. A similar pattern of mucosal inflammation is found both in middle turbinate and inflamed sinus mucosa/polyps tissue; suggesting a diffuse mucosal involvement.</p> <p><u>Trichophyton rubrum, an Important Fungal Allergen in the Pathogenesis of Nasal Polyposis and Sinusitis</u></p> <p>Fungi have been recognized as an important pathogen in sinusitis and nasal polyposis. In addition to major fungal allergens (i.e., Aspergillus spp., Candida albicans, Cladosporium spp., etc), Trichophyton rubrum is known to be the most common dermatophyte fungi, which causes both nail and skin infection. However, its role in the pathogenesis of sinusitis and nasal polyposis has not been reported. Serum IgE-mediated reaction to Trichophyton rubrum was determined using immunodot blot and western blot in (a) 56 patients with nasal polyposis; (b) 10 patients with chronic sinusitis; and (c) 48 healthy controls with non-atopic and no history of nasal polyposis/sinusitis. The incidence of positive reaction to Trichophyton rubrum was significantly (P<0.01) higher in patients with nasal polyposis and chronic sinusitis than the healthy controls. A positive reaction to Trichophyton rubrum was confirmed by two techniques in 90% (9/10) patients with chronic sinusitis, 94.6% (53/56) patients with nasal polyposis, and 18.75% (9/48) of healthy subjects. In addition, two novel 15 kDa and 60 kDa IgE-binding</p>

	<p>proteins from <i>Trichophyton rubrum</i> were identified. The study demonstrates a high incidence of IgE-mediated allergy to <i>Trichophyton rubrum</i> in patients with nasal polyposis and chronic sinusitis. The exact role of <i>Trichophyton rubrum</i> in the pathogenesis of chronic sinusitis and polyp formation will need further investigation.</p>
<p>NMRC/0406/2000</p> <p>PI: Ruan Run Sheng (NUS)</p>	<p>Inner ear gene transfer for treatment of profound hearing loss</p> <p>The aim of this project is to study the feasibility of introducing the genes for neurotrophic factors, like BDNF and NT-3, into the cochlea. The guinea pig was used as an animal model. HSVlac expressing <i>Escherichia coli</i> β-galactosidase/EGFP-GOI served as reporter genes. Non-virus such as lipofectamine and nanoparticles and adenovirus genomic backbone were used as vectors for the gene transfer experiment. The vectors were placed on the round window membrane, the distribution of the reporter transgenes was detected morphologically, Western blot was applied to quantify the transgene expression, and hearing was monitored by sequentially recording auditory brainstem response. With nanoparticle/adenovirus, the distribution of the reporter transgene was confirmed throughout the cochlea from the basal to the apical turn, and Western blot analysis indicated significant reporter gene expression 14 days following vector application. There was no hair cell loss or hearing impairment noted after the gene transfer. The utility of nanomaterial-mediated GDNF gene transfer was also assessed in animals with kanamycin-induced hearing loss. The Western blot indicated significant upregulation of GDNF protein 11 days following vector inoculation on the round window membrane. ABR threshold shift was remarkably suppressed in the GDNF gene transfer group compared with the control group. These results suggest that nanoparticles/adenovirus is useful for cochlear gene transfer through intact round window membrane.</p>
<p>NMRC/0407/2000</p> <p>PI: Chew Fook Tim (NUS)</p>	<p>Characterization of important airborne fungal spore allergens of the Singapore environment</p> <p>The aim of the project was to identify and characterize the allergenic components of major fungal allergens present in the Singapore environment. Within the allotted grant period, the team was able to 1) define further, the species present within the different genera of airborne fungi in Singapore and to optimize the culture and growth conditions for mass production of these fungal species; 2) immunochemically characterize various fungal allergens; 3) identify, clone, express and characterise several novel allergens from <i>Curvularia lunata</i>; and 4) study Cross-reactivity between different <i>Curvularia</i> species.</p>
<p>NMRC/0408/2000</p> <p>PI: Heng Chew Kiat (NUS)</p>	<p>Novel genetic variation screening in the newly cloned Acyl Coenzyme: a cholesterol Acyltransferase2 (ACAT2) gene in the three ethnic groups in Singapore and their impact on plasma lipid factors in relation to coronary artery disease</p> <p>Screening of all the exon and intron sequences of the ACAT2 gene was completed. A total of 7 novel single nucleotide polymorphisms (SNPs) were identified. Two of these have been genotyped in the population. Both have significant association with plasma lipid profiles. The team is currently carrying out functional studies to</p>

	<p>determine if the SNP directly affects ACAT2 enzyme activity. In addition to the ACAT2 gene, the ATP-binding cassette transporter gene (ABCA1) was screened. One novel SNP was found at the 3' untranslated region. This SNP, together with four other known ones were genotyped and a paper has been published in Human Genetics (Tan et al 2004) reporting some interesting associations with plasma lipid profile levels. Human Genetics has an impact factor of at least 3.4 as at 2000. The findings in this project have been presented at three conferences, one of which was at the Annual Meeting of the American Society of Human Genetics in 2001.</p>
<p>NMRC/0409/2000 PI: Liew Lip Nyin (NUS)</p>	<p>DNA vaccine for allergic asthma - study of mechanisms and optimization of gene transfer using cDNA encoding for a major mite allergen, Der p1</p> <p>Der p 1 is a major trigger of mite allergy and atopic asthma worldwide. As a first step in the design of a Der p 1 DNA vaccine, the immunogenicity of the N-terminal domain, the C-terminal domain and the whole molecule of mature Der p 1 allergen encoded by variant plasmid constructs was assessed. A long lasting but below ideal level of Th1 predominant IgG2a was elicited in animals injected with plasmid encoding the N-terminal domain or the mature molecule of Der p 1. To tackle this inefficiency, in-vivo electroporation was incorporated into the DNA intramuscular injection and significant levels of Der p 1-specific IgG2a were induced. However, concerning the infeasibility of in-vivo electroporation in clinical trial, a new immunization regime with the use of DNA-prime-protein-boost strategy and a new construct DERp1-LAMP chimeric gene that possesses the capability of targeting the endogenously synthesized Der p 1 molecules into the MHC class II trafficking pathway was developed. This new regime was evaluated using a murine asthma model and results showed that significant suppression of Th2 immune responses and airway hyperresponsiveness in this asthma model was achieved. As part of the vital data, these results had been filed for a US patent.</p>
<p>NMRC/0411/2000 PI: Eugene Sim Kwang Wei (NUS)</p>	<p>Effect of myocardial laser revascularization and gene therapy on chronic myocardial ischemia</p> <p>It was hypothesized that Ang-1 might be an angiogenic inducer, similar to VEGF. This experimental study compared neovascularization in chronic ischemic myocardium induced by adenovirus-mediated gene transfer of Ang-1 (AdAng-1) and VEGF165 (AdVEGF165).</p> <p>A porcine model of chronic myocardial ischemia was established. Animals were randomized to four groups: ischemic control (without further interventions), AdNull (null adenoviral vector), AdAng-1, and AdVEGF165. Adenoviral vectors were injected directly into the ischemic myocardium along the free wall of left ventricle. Animals were sacrificed 3 months later. Myocardial blood flow measurements were performed with fluorescent microspheres, before and after treatment. Collateral development was assessed by ex vivo angiography after treatment. The vascular density of treated areas was compared.</p> <p>Ex vivo angiography showed collateral formation in most of the animals. The average vascular density of AdAng-1 and AdVEGF group was significantly higher than those of the other two groups. Increase of regional blood flow after administration was significantly</p>

	<p>higher in AdAng-1 group than VEGF group.</p> <p>It was concluded that administration of adenoviral vector coding for Ang-1 or VEGF enhances angiogenesis in chronic ischemic myocardium. Compared with VEGF, additional Ang-1 is beneficial to the formation of sustained, functional and “healthy” collaterals.</p>
<p>NMRC/0414/2000</p> <p>PI: Fred Wong Wai Shiu (NUS)</p>	<p>Effects of tyrosine inhibitors on experimental models of asthma: from gene expression to whole animal</p> <p>The specific aims of this project were to examine the effects of inhibitors of the tyrosine kinase signaling cascade on experimental models of asthma, ranging from gene expression to whole animal study. Most of the objectives set forth in this project were achieved. The team investigated the effects of genistein, a broad-spectrum tyrosine kinase inhibitor; piceatannol, a Syk-selective tyrosine kinase inhibitor; U0126, a mitogen-activated protein kinase (MAPK) kinase inhibitor; and PD169316, a p38 MAPK inhibitor in both in vivo and in vitro models of asthma. A manuscript entitled “Anti-inflammatory Effects of Genistein, a protein tyrosine kinase Inhibitor, on an In Vivo Guinea Pig Model of Asthma” has been published in the American Journal of Respiratory and Critical Care Medicine (IF=6.5). An in vitro study has also been conducted examining Syk-selective tyrosine kinase inhibitor on antigen-induced bronchial contraction and release of histamine and leukotrienes from chopped lung preparation. A manuscript entitled “Piceatannol, a Syk-selective tyrosine kinase inhibitor, attenuated antigen challenge of guinea pig airways in vitro” has also been published in the European Journal of Pharmacology (IF=2.3). In addition, the study comparing p44/42 MAPK inhibitor with p38 MAPK inhibitor in in vitro model of asthma was completed. A manuscript entitled “Inhibitor of p42/44 mitogen-activated protein kinase (MAPK) kinase, but not p38 MAPK, attenuated antigen challenge of guinea-pig airways in vitro” has been submitted to Allergy for publication. Under this grant, 1 review article was published in the journal Biochemica & Biophysica Acta, and another was published in a book series entitled “Recent Research Development in Immunology”.</p>
<p>NMRC/0417/2000</p> <p>PI: Ho Khok Yu (NUS)</p>	<p>The effects of sleep disturbance and melatonin on bowel functions in female nurses on different shift duties and in women with irritable bowel syndrome</p> <p><u>Functional bowel disorders (FBD) are related to sleep disturbances in night shift nurses</u></p> <p>The aim of the study was to compare the frequency and severity of bowel disturbances between night and day shift nurses and to determine if FBD were related to sleep disturbances. Sixty day shift and 58 night shift nurses were recruited. Each was surveyed using questionnaires to determine the frequency and severity of gastrointestinal symptoms, sleep disturbances and psychological distress.</p> <p>FBD were more common among the night shift nurses compared with their day shift counterparts. The FBD symptoms and sleep disturbances were also more severe among the night shift group than the day shift group. The FBD symptom score was positively and independently correlated with the sleep disturbance score. These findings suggested that the increased frequency and severity of FBD symptoms among the night shift nurses might be due to their</p>

disrupted sleep patterns.

Which factors make persons with bowel symptoms see their doctors?

The objective of the study was to determine the factors that influence health-seeking behaviour of persons with bowel symptoms. 130 unselected nurses were interviewed using a gastrointestinal questionnaire. Factors that were potentially predictive of health-seeking behaviour, i.e., scores for FBD symptoms, sleep, abdominal pain, gastric symptoms, anxiety, depression and well-being were analyzed. In conclusion, the severity of bowel symptoms and abdominal pain predicted which patients with bowel symptoms would seek medical help.

Melatonin improved bowel symptoms in female patients with irritable bowel syndrome (IBS): a double-blind placebo-controlled study.

The objective of the study was to determine its potential therapeutic effects in IBS. 17 female patients with IBS were randomized to receive either melatonin 3 mg nocte or identically appearing placebo 1 nocte for 8 weeks, followed by a 4-week washout period and placebo or melatonin in the reverse order for another 8 weeks. Results: Improvements in mean IBS scores and mean global evaluation of IBS symptoms were significantly greater after treatment with melatonin than with placebo therapy. Percent response was also greater in the melatonin treated arm than in the placebo treated arm. The study concluded that oral melatonin is a promising therapeutic agent in irritable bowel syndrome. It is most effective in relieving abdominal pain, abdominal distension and abnormal sensation of defecation in female patients with IBS.

The effect of melatonin on colonic transit time of health volunteers and irritable bowel syndrome patients

The objective of the study was to investigate the effects of melatonin on gut transit times of healthy subjects and IBS patients. The colonic transit times (CTT) of 17 normal controls AND 17 IBS patients were measured. Saliva melatonin and urine aMT6s (6-sulphatoxy melatonin) were measured by ELISA tests. In healthy controls, CTT was positively correlated with endogenous melatonin levels and was prolonged following administration of oral melatonin. In IBS patients, no relationship could be demonstrated between CTT and endogenous melatonin level. Despite this, the effect of exogenous melatonin on CTT in IBS patients warrants further investigation. The paper has been submitted as an abstract in United European Gastro Week, Nov 2003.

IBS patients have disturbed melatonin rhythm

Saliva melatonin levels of IBS patients and normal controls were analyzed. IBS patients had significantly lower fasting saliva melatonin levels than the levels of age and sex matched normal controls. It was concluded that the IBS patients have disturbed melatonin rhythm.

<p>NMRC/0420/2000</p> <p>PI: Victor H H Goh (NUS)</p>	<p>An animal model to evaluate the feasibility and to optimize the conditions for in utero cord blood stem cell transplantation using an inbred guinea pig strain</p> <p>The project started off by using the guinea pig as a model to evaluate the feasibility as well as to optimize the conditions for in utero cord blood stem cell transplantation. In the initial evaluation, the XY chromosomes were used as markers for the possible chimerism. Without such markers, it would not be possible to know the extent of engraftment of the cord stem cells in the recipient animals. After several attempts, the project was not able to distinguish the sex chromosomes from autosomes of the guinea pig. Even the use of the FISH techniques did not yield positive results. The main reason for such failure was that no hybridization of the guinea pig's XY chromosomes with either the mouse or human XY probes was used.</p> <p>Following the failed attempt with the guinea pig model, the researchers next tried the primate model using the Macaques. The team was fortunate to ride on the study of Professor SC Ng who was working on the Macaques, and thus was able to obtain blood samples from the primate. In order for a greater degree of success, it would be necessary to import inbred Macaques. But this possibility was faced with insurmountable problems: chiefly, the difficulty of identifying a source, importing them, and the lack of available housing facility. Other difficulties included the fact that Macques have a relatively long gestation period and small litter size which are not ideal for such a study. In addition, more elaborate anaesthetic procedures during cord blood transplantation would be needed.</p> <p>Works on the hybridization of the primate XY chromosomes with the available human probes only resulted in the positive hybridization with the X probe, while the Y was not easily identifiable. Confocal microscopy was made use of to view the hybridization, and even with its use, the signal for the Y was extremely low.</p> <p>Faced with insurmountable difficulties for this project, and the successful cord blood stem cells transplant in human reported, the continuation of this project is not feasible and relevant.</p>
<p>NMRC/0422/2000</p> <p>PI: R N V Prasad (NUS)</p>	<p>Changes in the coagulation and fibrinolytic levels during the menstrual cycle and in patients with menorrhagia</p> <p>The coagulation and fibrinolytic variables were determined within the four phases of the menstrual cycle (menstruation, follicular, mid-cycle or early secretory phase, and luteal) in 29 healthy women with normal menstrual cycle of between 28 and 30 days. The subjects were further divided into those with Body Mass Index (BMI) of less than (n=21) and above (n=8) 25 kg/m² defined as overweight (WHO 1998). The statistical analysis by ANOVA showed no significant differences in the parameters studied between the four different phases of the menstrual cycle, including fibrinolytic response by venous-occlusion in both groups of cohorts. The collated data from the four periods of the menstrual cycle in each group was compared. No significant differences were seen for platelets, beta-thromboglobulin, tissue plasminogen activator (t-PA) activity, urokinase like -PA and protein C levels between the two groups of cohorts. However, in cohorts with BMI >25kg/ m² showed significant increase in fibrinogen (P=0.008), Factor VIII (P=0.005), plasminogen (P=0.003), D-dimer (P=0.045), t-PA antigen (P<0.001),</p>

	<p>PA Inhibitor-1 ($P < 0.001$), vonwillebrand Factor (vWF) ($P < 0.001$), total protein S ($P < 0.001$) and free protein S ($P = 0.04$) levels were seen. Decreased antithrombin III antigen ($P = 0.01$) levels with shortened clotting time ($P = 0.02$) and enhanced clot elasticity ($P = 0.001$) determined in the computerized Thrombelastograph were observed. The study demonstrated that systemic coagulation and fibrinolytic variables are not influenced by hormonal changes occurring during the menstrual cycle in our Asian women. The effects of being overweight on the vascular-endothelial and hepatic systems are evident by the increased levels of FVII, vWF, t-PA, PAI-1 and fibrinogen.</p>
<p>NMRC/0424/2000</p> <p>PI: Sim Meng Kwoon (NUS)</p>	<p>Angiotensins and cardiac infarction</p> <p>The aim of the study was to determine if des-aspartate-angiotensin I (DAA-I), an endogenous angiotensin peptide, could attenuate the infarct size and transmural extent in experimentally-induced cardiac infarction in rats.</p> <p>Earlier studies from the laboratory showed that DAA-I attenuates experimentally-induced cardiac hypertrophy and neointima formation. Angiotensin II is implicated in the cardiac hypertrophy, neointima formation and cardiac infarction. DAA-I acts as an antagonist on the angiotensin AT1 receptor and elicits responses opposing the deleterious actions of angiotensin II, and in this way improves the angiotensin-implicated pathologies. DAA-I was found to significantly attenuate the infarct size and transmural extent in experimentally-infarcted rat hearts. The attenuation was dose-dependent and DAA-I, though a peptide, was effective orally. The maximum effective dose was 1524 nmole/kg/day for 14 days.</p> <p>The attenuation was inhibited by indomethacin, indicating that prostaglandins mediate the cardioprotection actions of DAA-I. The activity of aminopeptidase X, an enzyme that specifically converts angiotensin I to DAA-I, had also been found to be significantly elevated in infarcted tissues of the rat heart, suggesting that the level of DAA-I could be physiologically regulated to cope with the pathology.</p> <p>DAA-I exerts cardioprotective actions that are mediated via the same indomethacin-sensitive angiotensin AT1 receptors that mediate its anti-cardiac hypertrophic and anti-neointimal actions. The findings demonstrate for the first time, the ability of an endogenous angiotensin peptide to attenuate the infarct size in an infarcted heart.</p> <p>The novel findings have been patented in the United States.</p>
<p>NMRC/0428/2000</p> <p>PI: Khoo Hsu Chin Daphne (SGH)</p>	<p>Ethnic differences in autoimmune thyroid disease - the role of TSH-receptor mutations</p> <p>Thyrotropin (TSH) receptor (TSHr) mutations have been investigated in relation to Graves' disease (GD) genetic susceptibility, under the hypothesis that a modified antigen may have novel immunogenic properties. The prevalence of three germline polymorphisms – D36H, P52T, and D727E – were studied in a cohort of multiracial GD patients, together with their associations with disease state, Graves' ophthalmopathy, and thyroid autoantibodies titers.</p> <p>Polymerase chain reaction products of exon 1 and 10e of the TSHr were generated from 164 GD patients (109 Chinese, 34 Malays, and</p>

	<p>21 Indians) and 240 individuals with no thyroid illnesses (74 Chinese, 84 Malays, and 82 Indians). Mutations were detected by single-strand conformational polymorphism and confirmed with direct sequencing.</p> <p>The D36H mutation was absent, while significant ethnic differences in the distribution of the P52T and D727E mutations were found. The levels of thyroid autoantibodies also differed significantly amongst the three ethnic groups, with the Indian cohort having the lowest titer. Both the P52T and D727E mutations were not associated with GD. An intron mutation, C/G+63IVS1, was detected and showed significant association with GD. Overall, it conferred a twofold increase risk of GD, while subgroup analysis showed increased odds ratios of 2.4 for Chinese (p = 0.008) and 2.8 for Indian (p = 0.049) but not for the Malay ethnic group.</p> <p>Together with recent identification of disease susceptibility markers in the region of the TSHr gene, these results are supportive of genetic factors existing in this region that may be in linkage disequilibrium with the inheritance of various TSHr polymorphisms.</p>
<p>NMRC/0430/2000</p> <p>PI: Valerie Lin (SGH)</p>	<p>Comprehensive identification of progesterone-regulated genes for therapeutic application in the unique progesterone receptor (PR)-transfected breast cancer cell models</p> <p>The inactivation of ER and PR expression is characteristic of hormone-independent breast cancer. A potential therapeutic intervention for this type of breast cancer is to re-activate the expression of ER or PR gene so as to restore the response of the cancer cells to hormonal treatment. It was previously reported that re-activation of PR expression in MDA-MB-231 cells by transfection enables progesterone to inhibit markedly the growth of PR-transfected cells and to induce remarkable cell spreading and focal adhesions. This study was designed to understand the molecular mechanisms of progesterone action. The results revealed that progesterone mediates diverse molecular pathways. Growth inhibition and focal adhesion are mediated by distinct mechanisms. Growth inhibition could be resulting from increased expression of CDK inhibitors such as p21WAF1/CIP1 and p27, decreased expression of cyclins and decreased activation of mitogen-activated protein kinase (p42/44 MAPK). On the other hand, focal adhesion is mediated by beta 1 integrin that had no effect on cell growth and the expression of growth regulators such as cyclins and CDK inhibitors. Whole genome analysis of gene expression in ABC28 cells using Affymetrix Genechips (~30,000 gene spots) revealed over 1000 progesterone-regulated genes in PR-transfected MDA-MB-231 cell line ABC28. 70% of these genes were previously not known to be progesterone targets. More than 500 of these progesterone targets are of unknown functions, est sequences or hypothetical proteins. The exposed progesterone-regulated genes cover a wide range of biochemical functions such as cell-cell and cell-matrix inhibition, signal transduction, lipid and carbohydrate metabolism, cell cycle and apoptosis and gene transcription. Realtime PCR analysis of a sample of 50 genes confirmed over 92% of the genes tested. These progesterone targets represent 'road signs' of progesterone-mediated biochemical pathways and some of them may be targets for drug intervention.</p>

<p>NMRC/0439/2000</p> <p>PI: Kingwell Brownyn (NHC)</p> <p>Collaborators: Koh Tian Hai Cameron James</p>	<p>Studies on the functional mechanical properties of large conduit arteries and their potential therapeutic impact in cardiovascular disease</p> <p>This project established a clinical arterial function laboratory within the National Heart Centre that is capable of performing non-invasive assessments of arterial function, a newly identified independent risk marker for cardiovascular disease. The ability to assess such properties holds potential for clinical research, and in the longer-term use in risk stratification and assessment of treatment.</p> <p>Increased arterial stiffness causes increased blood pressure and the differential effects of blood pressure medications that interfere with the rennin-angiotensin system were studied. Decreasing the amount of angiotensin II in the blood is well known to decrease blood pressure and to have other beneficial effects on health. Effects on arterial mechanical properties of newer agents targeting this system are unknown. The study compared the effects of angiotensin converting enzyme inhibition, direct angiotensin 2 receptor blockade and placebo medication on blood pressure and, uniquely, on arterial mechanics in a Chinese population. Aortic function was measured in hypertensives using a latin-square experimental design with all participants receiving all treatments. As specified in the project plan, analysis was performed after completion of data collection. Initial analysis supports the hypothesis that the point of interference in the angiotensin system has no effect on blood pressure effect or arterial mechanical properties.</p> <p>The laboratory has an ongoing place in cardiovascular research within the center and the techniques that have been established and staff who have been trained are involved in ongoing projects.</p>
<p>NMRC/0449/2000</p> <p>PI: Ho Khek Yu (NUS)</p>	<p>The association of HLA class antigens and autoantibodies with achalasia in Singaporean patients</p> <p>The aims of the project were to:</p> <ol style="list-style-type: none"> 1. To determine whether associations exist between achalasia and specific HLA Class II genetic subtypes in the local population. 2. If this was so, to determine if such an association occurs in a race-specific manner. 3. To determine the prevalence of specific autoantibodies in this group of patients with achalasia. <p>45 patients diagnosed with achalasia were recruited into the study. 10 mls of citrated, peripheral venous blood was obtained. The sample was processed and genomic DNA extracted by the salting-out method. HLA-DRB1 and DQ typing will be performed by the PCR-RFLP method. The allelic frequencies were compared to the control group of the same ethnic origin. The plasma obtained was stored at minus 700 C until ready for autoantibodies determination. The following autoantibodies: Anti-SSA, Anti-SSB, Anti-Sm, Anti-RNP, Anti-Thyroglobulin and Anti-TPO were determined by ELISA. Blood samples from 40 randomly selected healthy controls were also assayed to validate the manufacturer's negative cutoff value.</p> <p>The collection of samples has been completed and preliminary results have been obtained.</p>

<p>NMRC/0450/2000</p> <p>PI: Lee Kok Onn (NUS)</p> <p>Collaborators: Hoffman Andrew, Quah Thuan Chong</p>	<p>Genomic imprinting of insulin-like growth factor II and childhood acute leukaemia</p> <p>The loss of imprinting of the IGF-II gene is a concomitant event of some (but not all) childhood malignancies, and is thought to enhance tumour growth through increased expression of autocrine IGF-II, a known mitogenic factor. Some reports have suggested that this was present in adult acute myeloid leukemia and our own previous studies demonstrated specific changes in childhood acute lymphoblastic leukemia (ALL) in levels of IGF binding proteins with a higher affinity for IGF-II (How et al, 1999). In the present study, the prevalence of loss of IGF-II imprinting (LOI) in childhood ALL was investigated; and the expression of endogenous IGF-II anti-sense RNA (AS-RNA) in acute leukemic cells of childhood ALL was further investigated. After ethics approval, the team obtained excess (otherwise discarded) leukemic cells from bone marrow aspirates obtained for diagnostic and staging purposes from 45 children with ALL, and in 10 control children who had marrow aspirates for other conditions. Additional marrow samples were obtained from some of these children at various time intervals after induction of remission by chemotherapy when they had further assessment of their disease state. The study used validated methodology: PCR of genomic DNA, RT-PCR to generate cDNA to study IGF-II expression, and digestion of the transcripts with HinfI, which was then further digested with ApaI. Digests were analysed by SDS-PAGE. Only 4 samples (<10%) had the polymorphism which permitted study of IGF-II imprinting (compared to expected 25% from studies in Caucasian populations) – and no loss of imprinting was found in any of the samples of patients or controls. Endogenous IGFII AS RNA was not expressed in any of the leukemic cells. However preliminary studies identified another imprinted gene's endogenous AS RNA (PEG1/MEST) in some of the samples. The expression of this AS RNA was characterised and studied in a variety of tissues. In conclusion, IGF-II gene polymorphisms are significantly less prevalent in Singapore children than in Caucasian children; and loss of IGF-II gene imprinting is not likely to have a major role in childhood ALL.</p>
<p>NMRC/0459/2000</p> <p>PI: Lim Thiam Chye (NUS)</p> <p>Collaborators: Chou Ning, Dietmar Hutmacher Wern, Jan-Trorsten Schantz</p>	<p>The experimental evaluation of a tissue engineered bone graft for cranial reconstruction</p> <p>The ideal reconstructive material for the craniofacial skeleton remains elusive. Bone autograft is the standard but its shortcomings e.g. donor site morbidity, material scarcity, poor graft calibre and handling characteristics, and graft resorption are significant clinical problems. A logical solution would be the ready availability of autogenous tissue transplants with no donor site morbidity, perfectly matched to the defect for reconstruction, highly biocompatible, and which is eventually remodeled by the host bone.</p> <p>Bone generation by autogenous cell transplantation is one of the most promising tissue engineering techniques being developed. Osteoprogenitor cells obtained from an individual patient can be grown in culture and seeded onto a three-dimensional scaffold that will slowly resorb as the bone structures grow and assimilate in vivo. The 3D scaffold provides the necessary support for cells to multiply, differentiate, produce extracellular matrix, and defines the overall shape of the new bone.</p> <p>The objective of the interdisciplinary team was to apply the above</p>

	<p>concept for tissue engineering to a bone graft for craniofacial reconstruction of a critical size defect in a rabbit model. This was carried out in New Zealand White rabbits where bilateral parietal critical size defects were created. On the basis of computed tomography scans, customized PCL scaffolds were fabricated, using a rapid prototyping technology. Osteoblasts (group I) and mesenchymal progenitor cells (group II) were seeded in combination with a fibrin glue suspension into 40 PCL scaffolds. After incubating for 3 days in static culture, the PCL scaffold–cell constructs and unseeded control were implanted into 15- mm-diameter calvarial defects. Reconstruction of the cranium and bone formation was evaluated after 3 months. In vivo results indicated osseous tissue integration within the implant and functionally stable restoration of the calvarium. Islands of early bone formation could be observed in X-ray radiographs and in histological sections. Implants showed a high cell: ECM ratio and a dense vascular network. Mechanical testing of the reconstructed area revealed partial integration with the surrounding corticocancellous calvarial bone. The amount (area) of calcification, measured by clinical computed tomography, indicated that cell-seeded constructs measured about 60% more than unrepaired or unseeded scaffolds. This demonstrates that 1) Customized biodegradable polymeric implants may be used to deliver osteoprogenitor cells and enhance bone formation in critical-sized defects in vivo; 2) Rapid prototyping technology can be utilised to produce scaffolds for the functional and aesthetic reconstruction of complex craniofacial defects.</p>
<p>NMRC/0462/2000</p> <p>PI: Tan Chee Eng (SGH)</p> <p>Collaborators: Packard C J, Ordovas J M, Arthur Thomas, Chew Suok Kai, Loh Li Ming</p>	<p>The impact of the Taq 1B polymorphism of the cholesterol ester transfer protein gene on enzyme activity & lipid profile in the Singapore population</p> <p>In Singapore, Indians have the highest rates of coronary heart disease (CHD) the lowest HDL- concentrations compared to Malays and Chinese. The cholesterol ester transfer protein (CETP) locus is an important candidate gene in the pathogenesis of CHD. Variants at this locus are associated with variation in HDL-C concentration.</p> <p>The aim of the study was to determine the association between the TaqIB and –629C>A polymorphisms at the CETP locus and HDL-C concentration in Chinese, Malays and Indians living in Singapore. The B2 and the A-629 alleles were associated with increased HDL-C concentrations and differed in frequency between ethnic groups. However, these differences in allele frequencies did not explain the ethnic differences in HDL-C. The study also identified a novel gene-diet interaction between the CETP polymorphisms, HDL-C and dietary. Homozygotes for the B2 allele exhibited high levels of HDL-C in the presence of higher dietary cholesterol intake.</p> <p>As a consequence of this project, the team has also been able to extend their work to involve other candidate gene loci. This has resulted in several invitations to speak at regional and international meetings, 3 additional publications to date and an invitation to write a review on gene-diet interactions as they pertain to lipid metabolism. This review will appear in Current Opinions in Lipidology in Feb 2004 and is based largely on work carried out in the Singapore population.</p>

<p>NMRC/0463/2000</p> <p>PI: Ong Wei Yi (NUS)</p> <p>Collaborators: Halliwell Barry, Loh Teck Peng, Goh Siang Hiong</p>	<p>Roles of calcium dependent and calcium independent phospholipase A2 in kainate induced neuronal degeneration</p> <p>Brain tissue contains multiple forms of intracellular phospholipase A(2) (PLA(2)) activity that differ from each other in many ways including their response to specific inhibitors. The systematic administration of kainic acid to rats produces a marked increase in cPLA(2) activity in neurons and astrocytes. This is associated with increased lipid peroxidation as evidenced by accumulation of 4-hydroxynonenal (4-HNE) modified proteins. The present study describes the effect of specific inhibitors of Ca(2+)-dependent or Ca(2+)-independent PLA(2) on kainite-induced excitotoxic injury in rat hippocampal slices. Specific inhibitors of Ca(2+)-dependent PLA(2) prevented the decrease of neuronal marker, GluR1, and increase in cPLA(2) and 4-HNEimmunoreactivities in slices treated with kainate. This shows that cPLA2 plays an important role in kainite-induced neurotoxicity and that cPLA2 inhibitors can be used to protect hippocampal slices from damage induced kainate.</p>
<p>NMRC/0467/2000</p> <p>PI: Wong Yee Chee (NUS)</p>	<p>Interaction between placental cell adhesion molecules and angiogenic factors in normal pregnancy, preeclampsia 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). 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 placenate, 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/0470/2000</p> <p>PI: Tan Kun Kiang Henry (NUS)</p> <p>Collaborators: Kumarasinghe Gamini, Wang De Yun</p>	<p>The etiology and pathogenesis of otitis media in Singapore</p> <p>Otitis media with effusion (OME) has been extensively studied. However, its pathogenesis is not fully elucidated. Controversies remain on its relation to (1) adenoid size, (2) eustachian tube occlusion by adenoid enlargement and (3) allergy. Furthermore, while the bacteriology of middle ear effusion (MEE) and adenoid have been well described in the West, no local (Singapore) data are available. Such information is important for the treatment of OME</p>

	<p>and post-operative purulent otorrhea.</p> <p>112 children with OME who needed surgical intervention over a 3-year period from 2000-2003 were studied. Bacteriology of the MEE, adenoid size as estimated by rigid nasopharyngoscopy with an Adenoid Picture Scale or by clinical flexible nasopharyngoscopy or lateral neck soft tissue x-ray and allergy with radioallergosorbent test (RAST) were assessed. The immunological and morphological structure of adenoid tissue will be studied by several experiments involving flow of cytometry, confocal microscopy, immunohistochemical staining, light microscopy, fluorescent microscopy and electron microscopy.</p> <p>Children's ages ranged from 3 months to 13.5 years with a mean age of 4.9. There were 61 males and 51 females. Races include Chinese 76, Malay 21, Indian 8 and 7others.</p> <p>Adenoid hypertrophy (grades 3 and 4) was found in 40% of patients, suggesting that other mechanisms than Eustachian tube occlusion by adenoid enlargement are also important etiologic factors.</p> <p>RAST was performed in 44 patients and allergy to common allergens (i.e. house dust mites) is evident in only 34% (15 out of 44 cases).</p> <p>Only 61 children had middle ear fluid culture results. A variety of organisms were isolated. A large proportion (23%) was coagulase negative staphylococci (CNS) and about 15% did not grow any organism. Although the specimens were collected under ideal conditions, contamination is still possible. So, organisms such as coagulase negative staphylococcus, <i>Achromobacter xylosoxus</i>, <i>Serratia marcescens</i>, <i>Acinetobacter lowffi</i> and <i>Pseudomonas aeruginosa</i> should be considered as non pathogens unless there is a secondary cause. Out of the specimens that did not grow any organism, at least some of them would have been due to viral infections or due to prior antibiotics. At the same time, it is possible that there were some mixed infections (viral and bacteria) as described in other studies.</p> <p>The results of our findings are similar and consistent with the other studies. The commonest organisms include strep pneumoniae (10.3%), staph aureus (8.6%), haemophilus influenzae (6.9%), morexella catarrharis (5.2%) etc.</p> <p>20 cases had nasal purulence at the time of surgery, indicating rhinitis or rhinosinusitis. 16 of the 20 cases involved both nasal fossae. This indicates that about one fifth of the cases could be secondary to sinonasal infection. Treatment of the infection with antibiotics may result in resolution of the OME. Likewise, taking a child for myringotomy and ventilation tube insertion under general anaesthesia without examining the nose may miss the cause of the OME.</p> <p>From this study, one case of plastic foreign body in the right nose with infection was noted without prior medical history. This was noted only with EUA nose in the study. Two cases of significant deviated nasal septum which were most likely causes of the OME were also noted. The team recommends simultaneous examination of the nose and postnasal space when myringotomy and ventilation tube insertion is done for children. This can give the examiner a complete assessment of the cause of the OME especially when the adenoid size is assessed. From this study, the cause of OME is</p>
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	<p>multifactorial. Its management needs consideration of multiple factors.</p>
<p>NMRC/0472/2000</p> <p>PI: Zhu Yi Zhun (NUS)</p>	<p>Investigating the mechanisms of the protective effects of DanShen, an extract from the root of salvia miltiorrhiza myocardial infarction and stroke in experimental animals</p> <p>The present project compared cardioprotective effects of DanShen (an extract from <i>Salvia miltiorrhiza</i>) and the angiotensin-converting enzyme inhibitor, ramipril, in rats. With both treatment regimens, DanShen- and ramipril 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 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 AMI. 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/0475/2000</p> <p>PI: Liem Lie Kuo (SGH)</p> <p>Collaborator: Choong Hui Lin Lina</p>	<p>Dihydropyrimidine dehydrogenase deficiency in Singapore: screening of a healthy population and implications for 5-fluorouracil-based chemotherapy</p> <p>Dihydropyrimidine dehydrogenase (EC 1.3.1.2 DPD) is critical in a rate-limiting step in the catabolism of 5-Fluorouracil (5-FUra) and accounts for 80-90% of the drug's clearance. Thus, the level of this enzyme is an important determinant in predicting toxicity associated with the use of 5-Fura and potentially for predicting patients whose tumours are most likely to respond to treatment with 5-Ufra. Thus tumours with high DPD levels are relatively resistant to 5-Fura (1). Early recognition of this serious pharmacogenetic syndrome may allow for the modification of future chemotherapy by avoiding further life-threatening toxicities (2-3) and by designing better DPD-inhibitors. A recent study has shown that DPD activity in peripheral blood mononuclear cells could be used as a pharmacologically relevant marker of total body DPD activity (4). However, the data of DPD activity has not previously been reported in healthy Singaporeans. Cancer patients with DPD deficiency were found to have elevated uracil levels (5). In our study to determine the plasma uracil from whole blood collected from 167 Singapore cancer subjects who had not been treated with 5-Fura and 43 non-cancer Chinese, it was found that the plasma uracil concentration in Singapore cancer subjects is higher compared with Caucasian cancer subjects (6) The future direction is to screen for DPD deficiency in healthy Singaporeans. The team hopes to determine the population characteristics of DPD activity in healthy Singaporeans, quantify the plasma uracil concentration in each sample and establish a database for DPD deficiency in healthy Singaporeans. This will help oncologists administer better therapies to patients with cancer who are treated with 5-fluoropyrimidines.</p>

<p>NMRC/0482/2000</p> <p>PI: Howe Tat Sen (SGH)</p> <p>Collaborators: Leow Wee Kheng, Sung Kah Kay, Hsu Wynne</p>	<p>Pattern analysis & machine intelligence in the detection of fractures in digital radiology</p> <p>The project's aim was to get a computer to automatically recognise hip fractures on digital X-rays. The project was divided into a number of discrete parts: segmentation of the bone, measurement of neck shaft angles and texture analysis. Segmentation of the proximal femur was done by using active contour algorithms (snakes) as described by Kass et Al. Measurement of neck shaft angles provided an accuracy of greater than 90% with more that 60% of the fractures detected. The main source of error was: some fractures did not alter the neck shaft angle. The third part of the project involved texture analysis and frequency domain analysis. The resulting texture maps were analysed with principle component analysis. The result of this method had an accuracy similar to that obtained by measuring the neck shaft angle, 96.3% of training images and 93.5% of testing images are correctly classified. The fracture detection rate was 46.2%. The two methods combined provided a higher accuracy than either method in isolation. A combined accuracy of 95.4% was obtained, with 76.9% of the fractures detected.</p>
<p>NMRC/0486/2000</p> <p>PI: Wong Soon Tee (NUS)</p>	<p>Investigation of HFH 11 gene expression in normal skin and psoriasis</p> <p>The objective of the proposed research was to test the hypothesis that: "HFH 11 plays a key role in mediating proliferative signals in hyperproliferative keratinocytes in psoriasis".</p> <p>The researchers have shown that HFH 11 is highly expressed in suprabasal keratinocytes of psoriatic skin. Using HFH 11 gene specific RT-PCR, and they were able to amplify the correct size product from the RNAs extracted from all the psoriatic skin specimens. Subsequent sequencing confirmed that the amplified products are HFH 11. In-situ hybridization with anti-sense riboprobe showed strong signal at the suprabasal layers of the psoriatic keratinocytes and immunohistochemistry also showed suprabasal staining with anti-HFH 11 Mpp2 antibodies. These evidences suggest that HFH 11, which has been shown to play a significant role in the regulation of cell cycling and proliferation, may play an active role in mediating proliferative signals in hyperproliferative keratinocytes in psoriasis. Unfortunately, the researchers were not able to produce a Northern blot to lend further support to the hypothesis. A northern blot showing differential expression of HFH 11 psoriatic skin specimen would be the last piece of jigsaw puzzle in the whole experiment.</p> <p>In summary, the experiments suggest that HFH 11 is likely to be differentially expressed in psoriasis.</p>
<p>NMRC/0489/2000</p> <p>PI: Gerrard Teoh (SGH)</p>	<p>Regulation of proliferation and survival of multiple myeloma cells by Ku86/Ku86 variant via signals that mediate immunoglobulin isotype class switch recombination</p> <p>The proliferation and survival of multiple myeloma (MM) cells is regulated by numerous factors. Prior studies done by the researchers have demonstrated that triggering via CD40 induces the expression of a novel cell membrane antigen (Ag), Ku86, as well as variants of this Ag (Ku86v) in the majority of patient MM cells. Since CD40 plus interleukin-4 (IL-4) are the most potent signals that mediate</p>

	<p>normal immunoglobulin (Ig) isotype class switch recombination (CSR), and this process requires the Ku86 protein, it was hypothesized that Ku86 and/or Ku86v protein could be abnormally regulated by these signals that mediate Ig isotype CSR. Moreover, since CD40 is well known to induce the proliferation and survival of MM cells, we further hypothesized that abnormally regulated Ig isotype CSR could be related to process of tumorigenesis in MM. In this study, it was first demonstrated that CD40 signal transduction was indeed decoupled from IL-4 in MM cells, but not in normal B cells. Next, a potentially oncogenic Ku86v protein, Ku86v-C, was identified in at least 3 human MM cell lines. The DNA and protein sequences of this novel Ag are currently being analyzed using two-dimensional gel electrophoresis (2DGE), high-performance liquid chromatography, mass spectrometry, DNA cloning and sequencing (data is currently embargoed for patent application). In addition, since Ku86 is an important enzyme regulating the repair by non-homologous end joining (NHEJ) of broken double stranded DNA, the team also demonstrated that DNA double strand break repair (DSBR) was indeed abnormal in CD40 activated MM cells. These data suggest that abnormal CD40 induced growth and survival of MM cells could be associated with genomic instability and clonal evolution in MM. The findings therefore suggest that Ku86v-C could be a potential target for therapeutic intervention. Accordingly, we are using hybridoma technology and phage library systems to produce monoclonal antibodies (mAb) which specifically target Ku86v-C (NMRC/0632/2002, and others). Moreover, the team is planning on using novel methods, including panhandle polymerase chain reaction (PCR), in the near future to study genomic instability and clonal evolution in CD40-triggered MM cells in the future.</p>
<p>NMRC/0490/2000</p> <p>PI: Tan Theresa, Maychin (NUS)</p> <p>Collaborators: Leow Chon Kar, Wee Aileen, Sit Kim Ping</p>	<p>Energy homeostasis and oxidative stress in cirrhotic rat liver and following liver resection</p> <p>In man, hepatectomy is often carried out on a cirrhotic liver. The mitochondrial function in cirrhotic livers shows a variety of changes as compared to control livers. This study aims to investigate how mitochondrial respiratory function and antioxidant capacity change, following partial hepatectomy of cirrhotic livers.</p> <p>10 week-old male Wistar-Furth rats were injected intra-peritoneally with 300mg thioacetamide / kg body weight thrice weekly for ten weeks. Controls received no treatment. The rats were then rested for a week before undergoing 70% hepatectomy. At 3, 6, 24, 48 and 72 hours following hepatectomy, the livers were harvested.</p> <p>There were significant decreases in the mitochondrial respiratory control ratios (using succinate as the substrate) at 6h up till 48h post resection in cirrhotic rats compared to that of the corresponding controls. Further examination revealed that following resection, both NADH-linked respiration and FADH₂-linked respiration were affected.</p> <p>Impaired mitochondrial antioxidant capacity was also evident. Mitochondrial malondialdehyde level was increased while lowered mitochondrial superoxide dismutase was observed at 24h. Mitochondrial GSH levels and mitochondrial glutathione peroxidase activity were reduced at all time points.</p> <p>In conclusion, when compared to the controls, cirrhotic livers have diminished oxidative phosphorylation capabilities and impaired</p>

	antioxidant defenses following partial hepatectomy. If critical, both of these factors could then impede liver regeneration.
<p>NMRC/0491/2000</p> <p>PI: Wong Meng Cheong (SGH)</p>	<p>Ultrastructural endothelial abnormalities and stroke</p> <p>Endothelial dysfunction is a major feature of vascular disease, including stroke. The project 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 hypothenar 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 group also separately described novel association of smooth muscle cell arterial hypertrophy with moya-moya stroke.</p> <p>The study demonstrated visible and quantifiable endothelial abnormalities in systemic microvessels, in vivo. Diabetes and smoking, in particular, were significant predictors of microvascular endothelial blebbing, highlighting the systemic nature of endothelial dysfunction in patients with cerebrovascular disease.</p>
<p>NMRC/0496/2000</p> <p>PI: Poh Chit Laa (NUS)</p>	<p>Degradation of phenolic wastes by <i>Pseudomonas</i> 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 <i>XlnE</i>. In a P25X <i>xlnE</i> 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 <i>par</i> plasmid partitioning locus was carried out in this project. The <i>par</i> locus consists of two genes, <i>parAB</i>, that are co-transcribed from a σ^{70}-like promoter sequence. <i>ParB</i> was found to repress the <i>par</i> promoter activity but <i>parA</i> had no effect on transcriptional activity. Primer extension analysis revealed that the <i>par</i> transcriptional start point was located 47 nucleotides upstream of the <i>parA</i> 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 <i>par</i> promoter region was also demonstrated to exert incompatibility towards a plasmid with an active pRA2 <i>par</i> system.</p>

<p>NMRC/0497/2000</p> <p>PI: Wilder-Smith Annelies (TTSH)</p> <p>Collaborators Nick Paton, Barkham Timothy</p>	<p>An epidemiological study of the acquisition of N. meningitidis by Hajj travellers and transmission to household contacts via nasopharyngeal carriage</p> <p>An international outbreak among pilgrims returning from the Hajj (pilgrimage to Mecca) and their close contacts was caused by W135 N.meningitidis. The extent of transmission of N.meningitidis in Hajj pilgrims and their contacts was investigated, in order to provide evidence for developing a rational public health policy. Tonsillopharyngeal swabs were taken from Singaporean pilgrims before and from pilgrims and their household contacts after the Hajj 2001. Serogrouping and pulsed field gel electrophoresis was performed on meningococcal isolates. The prevalence of meningococcal carriage was 0.5% in departing pilgrims and 17% in returning pilgrims. 90% of isolates in Hajj returnees were a single clone identified as a serogroup W135 in most cases, and identical to the strain which caused Hajj associated invasive meningococcal disease in Singapore. The transmission rate from returning pilgrims to household contacts was 13%. Based on the carriage rate and national epidemiological data, it is estimated that 1 in 120 unvaccinated carriers develop invasive disease. Intense transmission of a single clone of W135 N.meningitidis occurred during the 2001 Hajj. The strain appears to be virulent and can attain high carriage rates. Vaccination covering W135 N.meningitidis should be mandatory for all Hajj pilgrims and recommended to household contacts. The findings support a policy of administering antibiotics to pilgrims prior to their return to eradicate carriage and thereby protect household contacts.</p>
<p>NMRC/0498/2000</p> <p>PI: Yang Er Bin (SGH)</p> <p>Collaborators: Mack Peter, Zhang Kai</p>	<p>Expression and mutations on growth factors, their receptors and tumour suppression genes during the hepatocarcinogenesis of tree shrews infected with human HBV and exposed to aflatoxin B1 and in human hepatocellular carcinoma (HCC)</p> <p>HCC is one of the major killer diseases in South-East Asia. Infection with HBV and exposure to aflatoxin B1 are thought to be two major factors in the development of HCC. This project investigated expression and mutations of growth factors, their receptor, and tumour suppressor genes in human HCC and during the hepatocarcinogenesis of tree shrews. It was found that M6P/IGF2R was involved in HBV-associated hepatocarcinogenesis by the regulation of its expression level. In the development of HBV-associated HCC, M6P/IGF2R mutation was not a major agent. Significantly more microsatellite alterations in serum a-fetoprotein (AFP)-positive cases were observed than those in serum AFP-negative cases, suggesting that microsatellite alterations in HCC may be involved in the regulation of AFP expression. In addition, the project established a cDNA array system for the analysis of 150 genes involved in major signal transduction pathways in tree shrews. Now, the system is being used to analyze gene expression in HBV- and aflatoxin B1-associated HCC in tree shrews.</p>
<p>NMRC/0501/2000</p> <p>PI: Ho Ting Fei (NUS)</p> <p>Collaborator: Wang May Choo</p>	<p>Assessment of perceptions of body image, dietary patterns and psychosocial profiles of young Chinese females</p> <p>The main objectives of this study were to examine the following hypotheses:</p>

	<ul style="list-style-type: none"> • Preference for thinness increases with obesity • “Westernisation” is positively associated with preference for thinness • Low self-esteem is positively associated with preference for thinness • Females with early or subclinical eating disorders have associated psychological changes e.g. menstrual cycle changes, cardiovascular changes <p>Young females between 12-25 years old were randomly sampled. A cohort of 4500 females was recruited from various institutions and schools. Questionnaires were administered to these subjects to identify those who are at risk of developing of Eating Disorders (ED) and to assess the risk factors associated with ED. Both the Eating Disorder Inventory (EDI) and Eating Attitude Test (EAT) were used as screening tools to identify those at risk for ED. Concurrently, females with ED were assessed for their anthropometric measurements and cardiovascular profiles to examine the differences between those with Anorexia Nervosa and Bulimia Nervosa.</p> <p>The data is still being processed and analysed. Preliminary analysis revealed relevant information related to the hypotheses:</p> <ul style="list-style-type: none"> • About 5% to 6% of young females between 12-25 years old are at risk of ED. This is based on analysis of their scores for EAT and EDI questionnaires. • Significant proportions of females have an inclination towards inappropriately low BMI. • Certain risk factors may predispose young females to ED. These are fair/poor relationship with their fathers; previous attempts to diet and using more than one method to diet • Females with anorexia nervosa and bulimia nervosa differ in their clinical profiles. Those with anorexia nervosa had significantly lower BMI and less subcutaneous fat when compared to controls. They also had significantly lower heart rates, systolic and diastolic blood pressures. Those with bulimia nervosa tended to be heavier and had increased subcutaneous fat compared to healthy controls. <p>The major accomplishments of this project are two papers were presented at the recent 37th Malaysia –Singapore Congress of Medicine in September 2003. These papers are:</p> <ul style="list-style-type: none"> • Psychosocial and behavioural profiles of females at risk for developing eating disorders • Cardiovascular and anthropometric profiles of females with eating disorders <p>Data analysis is in progress to prepare papers for publication and presentation at future conferences. The study has been expanded to include a much larger population of subjects and to assess other epidemiological and clinical aspects of Eating Disorders. This is now under a separate grant from NMRC.</p>
<p>NMRC/0504/2000</p> <p>PI: Tan Suat Hoon (NSC)</p> <p>Collaborators: Sun Yongjiang,</p>	<p>Detection of clonal TCR gamma chain gene rearrangements in cutaneous T-cell lymphoproliferative disorders by PCR/DGGE</p> <p>The distinction between a malignant lymphoma and benign reactive infiltrate is a challenge for the dermatopathologist. The molecular analysis of TCR γ-chain gene rearrangements has emerged as an</p>

<p>Giam Yoke Chin</p>	<p>important diagnostic tool, to complement histology and immunophenotyping in the diagnosis of T-cell lymphoid infiltrates. The main objective of this project was to establish the technique of clonal PCR detection of TCR γ-chain gene rearrangements in cutaneous T-cell lymphoproliferative disorders in our laboratory and to explore its usefulness with respect to the types of cutaneous T-cell lymphomas, stage of mycosis fungoides, and in the pre-diagnostic stage of cutaneous T-cell lymphomas (CTCL).</p> <p>A total of 86 skin biopsy specimens from 38 patients diagnosed to have CTCL were examined for TCR γ-chain gene rearrangements using the following primer sets: Vγ2, Vγ9, Vγ10 and Vγ11, and Jγ2, Jγp, Jγp1 and Jγp2. For each case, 4 separate PCR reactions were performed on the paraffin sections or frozen tissue. The specimens were grouped as follows:</p> <p>Mycosis fungoides (MF) / Sezary syndrome - 62 cases Non-MF lymphomas - 12 cases Pre-diagnostic inflammatory dermatitis - 12 cases</p> <p>Another 14 cases including subacute dermatitis, chronic dermatitis, psoriasis, lichen planus and insect bites were also included in the analysis.</p> <p>The PCR positivity rate was 72.6% (45 cases) for mycosis fungoides, 66.7% (8 cases) for non-MF lymphomas and 33.3% (4 cases) for inflammatory dermatitis. Non-MF lymphomas comprise lymphomatoid papulosis, CD30 + cutaneous T-cell lymphoma (CTCL), T/NK cell lymphoma and pleomorphic CTCL. Inflammatory dermatitis comprise mainly biopsies of other sites from patients who had MF / non-MF or previous biopsies when histology was suggestive or equivocal. In MF, PCR positivity rate was 62.1% in patch stage vs. 85.7% in plaque stage vs. 80% in erythrodermic MF / Sezary syndrome. All the 14 cases of non-lymphoma cases were PCR-negative.</p> <p>The research is the process of offering PCR detection of clonal TCR gene rearrangements and JH heavy chain gene rearrangements as an adjunctive diagnostic test for lymphomas, complementing immunohistology.</p>
<p>NMRC/0510/2001</p> <p>PI: Mak Koon Hou (NHC)</p> <p>Collaborators: Lim Yean Leng, Ng Tze Pin</p>	<p>A single-centre observational study to evaluate trends in resource utilisation and cost on patients with acute myocardial infarction</p> <p>The objective of the study was to describe resource utilisation in the management of patients with acute myocardial infarction in terms of time in the hospital, use of diagnostic procedures, and use of therapeutic procedures up to a 1-year follow-up period.</p> <p>The study is based on the patients with acute myocardial infarction (AMI) in National Heart Centre during the period of 1998 to 1999. A database of 448 AMI patients was being collected. Follow-up information on death, recurrent hospitalisation and utilisation of invasive cardiac procedures were obtained. The total expenditure of each 448 patients was computed. The total cost included both inpatient and outpatient cost over the one-year period.</p> <p>The resource utilisation measurement throughout the study period will be based on Percutaneous Transluminal Coronary Angioplasty (PTCA) and Coronary Artery Bypass Grafting (CABG). The</p>

	<p>outcome was being described in terms of resource utilisation, that is, length of stay, procedures and percentages of mortality and reinfarction.</p> <p>The average cost of the 448 AMI patients was about \$16 000. 84% of the patients were hospitalised between 1 to 10 days and the average cost spent for this group of patients is about \$14 000. 4.69% of patients had reinfarction over the one-year of study. The mortality rate was found to be 20.8%. The different usage of drugs was determined for the different ethnic groups.</p>
<p>NMRC/0511/2001</p> <p>PI: Tan Wan Cheng (NUS)</p> <p>Collaborators: Lee Szu Hee, Qiu Diwen, Sandford Andrew</p>	<p>Ethnic differences in polymorphisms in candidate genes associated with asthma severity</p> <p>The objective of the study was to compare a panel of specific polymorphisms associated with asthma severity in three ethnic populations in Singapore and relating these to phenotypic markers of severity of asthma.</p> <p>A case control study of 327 asthmatics (152 Chinese, 76 Malay and 88 Indian) [ratio of near fatal asthma to acute asthma = 1:3] and 363 control subjects (157 Chinese, 100 Malay and 103 Indian) was conducted. Demographic and clinical details were collected by a structured questionnaire. In addition, atopy was determined by skin prick test to the 21 common allergens and by measurement of serum Ig E, and baseline lung function tests were performed. Genomic DNA was extracted and quantified from venous blood. Genotyping of Single nucleotide polymorphisms [SNIPS] of IL4a, IL4R, TNFa, FceRIB, two B2 adrenergic receptor (B2-AR) polymorphisms, and PAF acetylhydrolase was performed.</p> <p>The main findings were that FceRIB gene polymorphism E237G and B2-AR gene polymorphism Arg16Gly may be risk factors for asthma in Chinese and Malay populations while Gln27Glu polymorphism is associated with asthma in the Indian population. These differential findings are important for understanding asthma etiology in these three Asian populations and can lead to future differential strategies in therapeutic interventions.</p>
<p>NMRC/0512/2001</p> <p>PI: Lee Soo Chin (NUH)</p> <p>Collaborators: Koay Evelyn SC, Kong Hwai Loong, Leong Adrian Peng Kheong, Salto-Tellez Manuel, Sng Jen Hwei, Wong Eu Li John</p>	<p>Prevalence of germline mutations in the hMLH1 and hMSH2 genes in Singaporean colorectal cancer patients suspected clinically to have hereditary non-polyposis colorectal cancer and correlation with clinical and family history & tumor microsatellite status</p> <p>Hereditary non-polyposis colorectal cancer (HNPCC) is the most common known form of hereditary colorectal cancer (CRC), and is predominantly due to germline mutations in the mismatch repair genes <i>hMLH1</i> and <i>hMSH2</i>. Data of the prevalence and spectrum of <i>hMLH1</i> and <i>hMSH2</i> mutations in Asian populations is sparse. Singaporean CRC patients diagnosed below age 40, and/or with strong familial cancer clustering suggestive of HNPCC, were recruited for germline <i>hMLH1</i> and <i>hMSH2</i> sequencing. When available, the patient's colon cancer tissues were tested for microsatellite instability (MSI) and immunohistochemically stained for the hMLH1 and hMSH2 proteins. Forty-six unrelated high-risk patients, of Chinese, Malay, or Indian ethnicity, were recruited. Five different deleterious <i>hMLH1</i> and two deleterious <i>hMSH2</i> mutations have been identified in six Chinese, one Malay, and two Indians</p>

	<p>(9/46, 20%). Of these, two <i>hMLH1</i> and one <i>hMSH2</i> deleterious mutations were novel, and two deleterious <i>hMLH1</i> mutations were recurrent in two unrelated families each. The previously reported <i>T1151A (Val384Asp)</i> missense mutation in Chinese occurred in 3/23 (13%) of the Chinese patients. In addition, five other novel <i>hMSH2</i> exonic missense mutations of uncertain significance were identified, of which two showed linkage, and occurred in 3/23 (13%) Chinese patients, but was not found in a screen of 44 Chinese healthy blood donors. The core promoter regions of the <i>hMLH1</i> and <i>hMSH2</i> genes were sequenced, and the <i>hMLH1</i> -93G→A and the <i>hMSH2</i> -118C→T variants previously described in Japanese were identified.</p> <p>In addition, the novel <i>hMLH1</i> -28A→G variant was found in a Chinese patient. The <i>hMLH1</i> and <i>hMSH2</i> mutation data in our Malay and Indian families represents the first such data in these ethnic groups. 11/35 (31%) patients had MSI-high tumors, while 4/27 (15%) patients had loss of expression of the hMLH1 or hMSH2 proteins in their tumors. Family history was the strongest predictor for a positive gene test. The correlation between <i>hMLH1/hMSH2</i> germline status and tumor microsatellite instability status was good though imperfect, while tumor hMLH1/hMSH2 immunohistochemical staining appears to have limited clinical utility in this pre-selected high-risk population.</p> <p>The study concluded that novel and recurring <i>hMLH1</i> and <i>hMSH2</i> mutations occur in Singaporean HNPCC families, and family history remains the strongest predictor of a positive gene test. This information is relevant when selecting patients for gene testing and in formulating molecular diagnostic strategies for HNPCC in Asia.</p>
<p>NMRC/0515/2001</p> <p>PI: Goon Teik Jin Anthony (NSC)</p> <p>Collaborators: Goh Chee Leok, Tan Suat Hoon, Sun Yongjiang</p>	<p>Detection of disease-specific epitopes in pityriasis rosea, pityriasis lichenoides chronica, urticaria and mycosis fungoides using a screening phage displayed random peptide library</p> <p>This new method is based on identification of antibodies to a multitude of epitopes that may be present in patients' sera. The DNA sequences of these epitopes can then be determined and matched with sequences of known viruses in DNA libraries currently available. The team managed to obtain and analyze the sera of 12 pityriasis rosea patients. After 2 rounds of biopanning, amplification and purification, they were unable to isolate any clones from the ELISA. Only the positive control was positive.</p>
<p>NMRC/0527/2001</p> <p>PI: Wilder-Smith Einar (NUS)</p> <p>Collaborators: Ong Kian Chung Benjamin, Tan Joo Hui</p>	<p>Vasomotor reflex testing in healthy volunteers</p> <p>The vasomotor reflex of small and large vessels is a useful indicator of small nerve fibre function. This study investigates the repeatability and the effect of gender, weight, height, blood pressure and skin temperature on the vasomotor reflex of large and small vessels in healthy adults. Bilateral skin vasomotor reflexes of the 2nd and 4th digit tip and vasomotor reflexes of the radial, ulnar and brachial artery were tested using the inspiratory gasp method under standard conditions. To determine test variability, repeat tests were performed after 3 to 14 days. Gender, weight, height, blood pressure and skin temperature were recorded and correlated with vasomotor reflexes. Test variability for vasomotor reflexes in percents were: 2nd digit 17;16; 4th digit 14;12; radial artery 9;10; ulnar artery 13;12; brachial artery 11;13 (right; left respectively). Gender, weight, height, blood pressure and skin temperature had no significant effect on skin and</p>

	<p>muscle vasomotor reflexes (p for all >0.1).</p> <p>This study concluded that vasomotor reflexes of small and large vessels have good repeatability and are not affected by gender, weight, height, blood pressure and skin temperature.</p>
<p>NMRC/0546/2001</p> <p>PI: Cheung Yin Bun (NCC)</p> <p>Collaborators: Khoo Kei Siong, Epstein Richard, Goh Cynthia Ruth Nee Fung, Loke See Wah Wong Lea Choung</p>	<p>Shortening quality-of-life measurement scales: methods and application to cancer research</p> <p>A practically useful measure of quality of life should be simple and quick to complete. Based on a study of 140 cancer patients, a short version of the Functional Living Index – Cancer (FLIC) was developed, called Quick-FLIC. The methodology of shortening the instrument involved both multivariate statistical techniques and clinical judgments. In another study of 190 cancer patients, the measurement properties of the Quick-FLIC were assessed. The patients filled in a retest questionnaire on average two weeks after baseline to assess test-retest reliability and responsiveness to change. The Quick-FLIC scores correlated well with the Functional Assessment of Chronic Therapy – General scores ($r=0.78$). Patients with different treatment status, performance status and self-rated health had significantly different Quick-FLIC scores in the expected directions (ANOVA; each $P<0.001$). Internal consistency (Cronbach's $\alpha = 0.87$) and test-retest reliability (intra-class correlation = 0.81) were also satisfactory. The measure was responsive to changes in health status ($P<0.001$). The Quick-FLIC is a valid and reliable measure of health-related quality of life of cancer patients. The shortening of established health-related quality of life instruments should be considered in order to reduce the burden of having patients to answer lengthy questionnaires.</p>
<p>NMRC/0550/2001</p> <p>PI: Lim Beng Hai (NUS)</p> <p>Collaborators: Poston Tim, Burdet Etienne, Sarimuthu Rita</p>	<p>Digital pre-training for microsurgery</p> <p>The project recreated micromanipulation tasks in a virtual environment that magnifies hand manipulation as in a surgical microscope, measures in detail the motions of the hand-held device representing surgical forceps, and provides immediate visual and quantitative feedback to the user for acquiring or assessing the subskills that underlie surgical technique, such as close following of a planned curved motion and minimizing tremor. The user looks into a stereoscopic 3D setting, reaches in to 'grasp' a virtual curved 'needle' and passes it through a 'membrane' as in performing a suture. The original intent to study the impact of such virtual training on student acquisition of surgical skill was deferred in favour of a trial with seventeen surgeons to analyze expert hand motions (targets of training plan design) and assess different efficacies for the same standard task of different needle shapes. This preliminary trial with a forceps-like grasping geometry revealed a number of necessary improvements such as a needle-holder-like angled grasp whereby the device is turned in the fingers, rather than the hand. Maintaining subject conformity with protocol, for statistically useful data, requires the immediate analysis and feedback that has now been implemented, for test when SARS ceases to complicate collaboration.</p>
<p>NMRC/0553/2001</p> <p>PI: Moore Xiao Lei (NCC)</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.</p>

	<p>Gene therapy has much promise, but effective target-specific vectors are needed. Endothelial Progenitor Cells (EPCs) have in vivo homing specificity to angiogenic sites and are thus potential vehicles for site-specific gene therapy. However, reports of EPCs homing to intracranial solid tumors are lacking. To explore potential of EPCs in glioma gene therapy, the study 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 in vitro characterization, EPCs were labelled 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. 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, the study demonstrates EPCs in vivo tropism for intracranial gliomas, with potential for cell delivery of site-specific brain tumor gene therapy.</p>
<p>NMRC/0557/2001</p> <p>PI: Richard Bellamy (TTSH)</p>	<p>Epidemiology of Mycobacterium tuberculosis: development of a semi-automated, fluorescent-based strain-typing system suitable for construction of a digital database</p> <p>The objectives of this project were to adapt a recently introduced genotyping method for Mycobacterium tuberculosis (Mtb) which is based on the variable-number tandem repeats of mycobacterial interspersed repetitive units (MIRU-VNTR) and to study the genetic diversity of Mtb isolates in Singapore using this method. This semi-automated high throughput MIRU-VNTR typing method is to amplify 12 VNTR loci by PCR followed by DNA fragment size analysis on an ABI PRISM Genetic Analyzer using GenescanTM and GenotyperTM soft ware. The team has successfully established this method in their laboratory and analyzed 303 Mtb isolates. These isolates displayed 184 distinct MIRU-VNTR genetic patterns which identify 148 unique isolates and 155 isolates in 36 clusters. Interestingly, a dominant cluster pattern was the same as the representative patterns of China and Malaysia, suggesting the population and geographic relatedness in Singapore, China and Malaysia.</p> <p>The results confirm that MIRU-VNTR typing is a useful method, especially for Mtb isolates with low copy numbers of IS6110; and the results obtained by this method are reproducible, portable, and globally comparable, therefore, suitable for construction of a digital database.</p>
<p>NMRC/0564/2001</p> <p>PI: P. Gopalakrishnakone (NUS)</p>	<p>Multidisciplinary approach to design of a potent anti-inflammatory agent for therapeutic applications</p> <p>The project aimed to define the active region of the anti-toxic/anti-inflammatory protein by expression of fusion proteins corresponding</p>

	<p>to predicted active domains of the protein and/or using the corresponding synthetic peptides, followed by optimization of the resultant drug by means of structural studies. Based on structural homologies, the candidate peptide with the most potent PLA2-inhibitory activity was synthesized, and its therapeutic potential examined in transgenic mice that spontaneously develops an erosive polyarthritis. The results demonstrate attenuation of rheumatoid arthritis (RA) by treatment with the lead peptide P-NT.II, and suggest a pivotal role for secretory PLA2 inhibitors in the mediation of joint inflammation in this disease. A time-course study on ultrastructural changes confirms the beneficial effect of the peptide on synovial inflammation and joint destruction. P-NT.II also provides protective capacity towards kainate-induced neuronal injury as evidenced by hippocampal organotypic cultures. Structure-based design was then applied to the lead peptide for optimization using X-ray crystallographic techniques. A complex between daboiatoxin, a toxic sPLA2 purified from <i>D. russelli siamensis</i> venom, and P-NT.II was co-crystallized to determine the three-dimensional structure by molecular-replacement method. The resulting data should aid in the development of peptidic drugs with improved potency for commercial exploitation. Patent filing is in progress.</p>
<p>NMRC/0571/2001</p> <p>PI: Tan Patrick (DMRI)</p> <p>Collaborator: Lim Mong King</p>	<p>Computational Modelling of Biological Signaling Pathways</p> <p>Conserved metabolic networks such as glycolysis are often regulated in different tissues, species, and diseases by cell-type specific molecular pathways. The project presents a systematic methodology for identifying the point-of-interaction between these specific pathways and the conserved network through the comparison of predicted and experimentally determined metabolic phenotypes. The methodology employs a semi-empirical approach to create deterministic, quantitative models that can predict the 'metabolic phenotype' of a particular cell type in terms of its steady-state metabolite concentration profile. In a series of proof-of-concept experiments, a glycolytic simulation was used to predict the existence of species-specific and environmentally-regulated metabolic circuits in various cells types (erythrocytes, myocytes and <i>Tbrucei</i>). A similar approach, applied to a rat animal model of diabetes, identified the polyol pathway as a major regulator of glycolysis in diabetic rat hearts, and accurately predicted the metabolic effects of treating both normal and diabetic rat muscle cells with aldose reductase inhibitor zolprestat. The study suggests that quantitative computational techniques can be successfully used for biological pathway discovery and the prediction of complex metabolic phenotypes. A start-up company, <i>Systome Therapeutics</i>, has been established to commercialise this technology.</p> <p>Filing of an international patent application of the computational modelling of signalling pathways is currently in progress. A start-up company has also been established to apply this technology to reduce the cost and improve the efficiency of drug development. This will reduce the overall cost of drugs, and accelerate the rate by which new and better drugs are identified.</p>
<p>NMRC/0575/2001</p> <p>PI: Tan Eng King (SGH)</p>	<p>Analysis of Parkin Gene Mutations in Parkinson's Disease</p> <p>Mutations of Parkin, DJ-1 and other candidate genes may be associated with young onset Parkinson's disease (YOPD) and</p>

<p>Collaborators: Ratnagopal Pavanni, Zhao Yi, Wong Meng Cheong, Lim Erle Chuen Hian</p>	<p>autosomal recessive PD (ARPD) patients. The objectives were to analyse for pathogenic mutations of Parkin, DJ-1 and other related candidate genes in YOPD and ARPD in the patients and to determine if any genetic variants increase the risk of PD.</p> <p>The methods were to conduct sequence analysis of the exons and exon-intron boundaries of the Parkin and DJ-1 genes in YOPD and ARPD patients and in controls. Gene expression analysis was also carried out for genetic variants found. 65 index YOPD and ARPD patients were examined for Parkin and DJ-1 gene mutations. No pathogenic mutations were found. However, novel Parkin splice variants which may increase the risk of PD were identified. In addition, a number of intronic and exonic variants were also found. Other candidate genes related to PD in case control studies were analysed, but no significant association with PD was found.</p> <p>In conclusion, DJ-1 mutations are likely to be confined to certain genetically isolated populations and hence routine screening for DJ-1 in all PD patients may not be cost-effective. However, abnormal Parkin expression may increase risk of PD. Parkin gene screening is suggested, especially in the younger PD patients.</p> <p>The research provided new data in an Asian population regarding Parkin and related gene mutations in PD. More importantly, it identified new variants which may contribute to disease causation.</p> <p>Immediate clinical applications include</p> <ol style="list-style-type: none"> a) Parkin gene analysis should be primarily restricted to young onset and young PD patients. Genetic testing amongst the older patients will not be cost-effective. b) Closer monitoring of at-risk individuals with specific genotypes and preventive medications should be considered. <p>Long term applications include</p> <ol style="list-style-type: none"> a) Studies on these gene variants in cell culture and animal models with a view to developing therapeutic targets.
<p>NMRC/0587/2001</p> <p>PI: Wilder-Smith Annelies (TTSH)</p>	<p>Epidemiology of the meningococcal transmission during Hajj 2001: Investigation of the epidemic strain of Neisseria meningitidis by Multilocus Sequence Typing.qn</p> <p>An international outbreak of W135 meningococcal disease occurred during the annual Hajj pilgrimages in 2000 and 2001 in Saudi Arabia. Previously, a 15% acquisition rate of W135 meningococcal carriage in pilgrims returning from the Hajj 2001 was documented. The study set out to determine the acquisition rate of meningococcal carriage for the Hajj 2002.</p> <p>Tonsillopharyngeal swabs were taken from pilgrims before departure and after return from the Hajj 2002. Serogrouping and multilocus sequence testing was performed on all meningococcal isolates and compared with the strains isolated from returning Singaporean pilgrims from the Hajj 2001.</p> <p>The pre Hajj carriage was 2.6% (4 out of 198). Two of the 156 returning pilgrims (1.3%) were carriers, and both isolates were serogroup W135 and were of the MLST type 'ST 192' and 'ST 32/ET5', as opposed to the ET 37 ST 11 clone that was identified in</p>

	<p>90% of all carriage in the year 2001 Hajj.</p> <p>The study documented the absence of carriage of ET 37 ST 11 <i>N. meningitidis</i> W135 in returning pilgrims after the Hajj 2002 in comparison to the reported 15% carriage of this strain in returning pilgrims after the Hajj 2001. It would appear that the epidemiology of carriage is changing or has been controlled by vaccination and a policy of antibiotic administration to incoming pilgrims from high-risk countries.</p>
<p>NMRC/0588/2001</p> <p>PI: Goon Teik Jin Anthony (NSC)</p>	<p>The atopy patch test to aeroallergens and pityrosporum orbiculare in patients with atopic dermatitis</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. The objective of the study was to determine the proportion of atopic dermatitis patients with positive patch tests to common local aeroallergens and to compare this to a control group. The APT, skin prick tests and IgE RAST tests were performed on 73 atopic dermatitis patients and 38 non-atopic controls. The allergens used were house dust mite, cat dander, Bermuda grass and German cockroach. 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. In conclusion, 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/0590/2001</p> <p>PI: Ong Wei Yi (NUS)</p> <p>Collaborators: Halliwell Barry</p>	<p>Gas Chromatography/Mass Spectrometry Analyses of Cholesterol and Cholesterol Oxidation Products (COPs) in the Rat Hippocampus after Kainate Induced Neuronal Injury and Toxicity of COPs in Hippocampal Slice Cultures.</p> <p>Little is known about changes in sterols, in particular cholesterol, and cholesterol oxidation products (COPs) in oxidative injury in neural tissues. The researchers have therefore examined changes in cholesterol and COPs using a model of excitotoxic injury. Intracerebroventricular injections of kainate in rats resulted in an increase in immunoreactivity to cholesterol in the affected CA fields of the hippocampus. The increase was confirmed by increased filipin staining of cholesterol in adjacent sections from the same animals, and in hippocampal slice or neuronal cultures after kainate treatment. In neuronal cultures, addition of lovastatin, an inhibitor of cholesterol synthesis, attenuated the increased filipin staining after kainate treatment, indicating that the increase in cholesterol could involve increased cholesterol synthesis. Furthermore, gas chromatographic mass spectrometric (GC/MS) analysis of cholesterol and COPs in kainate-injected rat brain showed a marked increase in cholesterol and COPs including 7-ketocholesterol, 3 days after kainate treatment. The addition of some COPs, including 7-ketocholesterol and cholesterol epoxides to hippocampal slices resulted in neuronal injury as reflected by decreased staining of a neuronal marker in the affected CA fields. The ability of these COPs to produce neuronal injury was attenuated by glutathione, suggesting that oxidative mechanisms are involved in neuronal injury induced by these products. These results, together with GC/MS results that showed significant increase in 7-ketocholesterol at 3 days post-kainate injury</p>

	<p>suggest that 7-ketocholesterol may be a factor in aggravating oxidative damage to neurons, after the initial stages of kainate-induced neuronal injury.</p>
<p>NMRC/0615/2001</p> <p>PI: Poon Choy Yoke (NDC)</p> <p>Collaborator: Chan Shih Yen, Edwin (CTERU)</p>	<p>A Randomised Controlled Trial To Compare Steroid With Cyclosporine For The Topical Treatment Of Oral Lichen Planus</p> <p>The study aim was to compare the effectiveness of topical steroid and topical cyclosporine in patients with histologically confirmed oral lichen planus with respect to alleviation of pain, relief of symptoms, response rate and adverse events.</p> <p>Patients were randomised to 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>The 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 study closed to recruitment on 31 December 2002. The data has been analysed. The manuscript is in the process of been submitted to journals for publication.</p>
<p>NMRC/0623/2002</p> <p>PI: Sim Meng Kwoon (NUS)</p>	<p>Cardiovascular actions of angiotensin IV</p> <p>The project was a focused research and the objectives were achieved. Angiotensin IV, administered orally or intravenously, has been shown to significantly attenuate the development of experimentally-induced cardiac hypertrophy in rats in a dose-dependent manner. The anti-cardiac hypertrophic action was completely inhibited by 46µmol of indomethacin but not by divalinal-angiotensin IV (a specific angiotensin AT4 receptor antagonist) indicating that angiotensin IV acts via a novel receptor that is mediated by prostaglandin/s and not via the angiotensin AT4 receptor. The anti-cardiac hypertrophic action of angiotensin IV was also confirmed by its ability to significantly inhibit the incorporation of [³ H]-phenylalanine in cultured cardiomyocytes. Similarly, the in vitro action was also inhibited by indomethacin and not by divalinal-angiotensin IV. In balloon catheter-injured rat carotid artery, angiotensin IV significantly and dose-dependently attenuates the development of neointima formation. These two findings are novel and NUS is in the process of filing a patent on the use of angiotensin IV for the treatment and prevention of cardiac hypertrophy and neointima formation or restenosis.</p>

<p>NMRC/0637/2002</p> <p>PI: Mongelli Joe Max (NUS)</p> <p>Collaborators: Loganath A, Shekhar Gangaraju Raja</p>	<p>Functional Significance of Fas-FasL Pathway of Apoptosis in Normal and Malignant Trophoblasts</p> <p>The cell surface molecule Fas (CD95) is a member of the tumour necrosis factor receptor family. Ligation of the Fas receptor can lead to induction of apoptosis in several cell types. The expression of Fas and its ligand (FasL) has been identified in normal human placenta. The study examined Fas and FasL expression on the immortalized human choriocarcinoma cell lines, BeWo and NJG. Receptor and ligand expression were demonstrated using specific antibodies and multiple techniques, including immunocytochemistry, confocal immunofluorescence microscopy, immunoblots, and reverse transcription-polymerase chain reaction (RT-PCR). Immunohistochemical staining demonstrated that both cell lines expressed cell surface Fas and FasL. Expression of mRNA for Fas and FasL using RT-PCR and presence of FasL by immunoblot provided further confirmation of these apoptosis inducers. Data from this study indicates for the first time that human choriocarcinoma cell subtypes co-express both Fas and FasL. It is envisaged that expression of these molecules could have important implications in the regulation of immune evasion in gestational trophoblastic diseases. In addition, in these FasL positive choriocarcinoma cells when co-cultured with Fas-sensitive Jurkat cells induced apoptosis in the latter thereby indicating that the tumour cells could evade immune attack and possess immune privilege essential to survival in host tissue.</p>
<p>NMRC/0679/2002</p> <p>PI: Tan Tze Siong (NUH)</p> <p>Collaborators: Siau Chiang, Lim Aymeric Yu-Tang, Ng Huey Ping, Pua Hwee Leng</p>	<p>Study of neurotoxic potential of Ropivacaine using a percutaneous rat sciatic nerve block model</p> <p>Previous animal studies suggest that all local anaesthetic are neurotoxic at high concentrations. The addition of epinephrine increased the incidence of neurotoxicity, leading to the postulation that vasoconstriction also played a role in the development of local anaesthetic-induced neurotoxicity. Ropivacaine, available at concentrations of 0.2% to 1%, caused vasoconstriction after local infiltration. Hence, administration of high concentration ropivacaine may be associated with risk of neurotoxicity. The team aimed to investigate whether ropivacaine at doses up to 1% concentration caused histological nerve damage using a percutaneous rat sciatic nerve block model. Forty Sprague-Dawley rats are divided into 4 groups. Each rat receives 0.2ml of the following drugs during sciatic-nerve block. Group 1: Normal saline, Group 2: 2% lignocaine, Group 3 0.25% ropivacaine, group 4 1% ropivacaine. On day 7, the rats were sacrificed and the sciatic nerve excised and evaluated for histological nerve damage via light and electron microscopy. Histological examinations revealed no conclusive abnormalities suggestive of neurotoxicity in all groups. Although ropivacaine, at up to 1%, did not cause significant myelin sheath degeneration in the rat sciatic nerve block model, further investigations incorporating nerve physiology studies in humans are required to explore the role of ropivacaine 1% in peripheral nerve blocks.</p>
<p>NNI/0001/1999</p> <p>PI: Sitoh Yih Yian (NNI)</p>	<p>Magnetic Resonance Spectroscopy in Alzheimer's Disease</p> <p>Alzheimer's Disease (AD) accounts for more than 40% of dementias in the elderly. Clinical diagnosis is presently based on the NINCDS-ADRDA criteria supplemented by CT or MRI findings. The project</p>

	<p>prospectively studied 19 patients with clinically diagnosed early AD and 30 controls matched for sex and age. All had proton magnetic resonance spectroscopy (MRS) and volumetry of the hippocampus performed to provide insight into the brain metabolic and structural changes in early AD. The project also analysed if Apolipoprotein ε4 (ApoE) genotype, a risk factor for AD, has influence on the diagnostic utility of MRS and MR volumetry. The projected 30 normal volunteers had been studied, but recruitment of early AD patients had been difficult, with only 19 subjects enrolled. A number of early AD patients deemed suitable on clinically indicated CT scans were subsequently found unsuitable due to factors such as inability to remain still for the period of MR scanning or declined consent. For ApoE status, of 29 normal controls, only 6 were positive, versus 9 which were positive out of 17 AD subjects. This is statistically significant at $p=0.0364$. Compared to controls, AD patients showed a 2.02% decrease in NAA/Cr and an 8.21% increase in Cho/Cr ratios. No statistical significance was observed. However, a significant difference in the mean ratio of ml/Cr was observed between the groups; the AD patient was 18.16% higher than the control group ($p=0.008$). In addition, the average group hippocampal volumetry measurements of the AD patients were significantly lower than the control group ($p<0.001$). Comparing mean cerebral volumes between the 2 groups, there was a statistically significant difference ($p<0.05$); with smaller total cerebral volumes in the early AD group versus normal controls. The data was presented at the 4th Asian-Oceanian Congress of Neuroradiology and Head & Neck Radiology and won the overall Bronze award for Scientific Exhibitions.</p>
<p>NNI/0003/1999 PI: Lim Choie Choie (NNI)</p>	<p>Nipah Virus Infection of the CNS - Prospective Magnetic Resonance Imaging in an Emerging Disease</p> <p>The Nipah virus is a previously unknown pig-borne virus that caused an outbreak of fatal encephalitis in Malaysia and Singapore. Follow up MR imaging in patients affected by the outbreak revealed small lesions within the white matter, some of which were positive on diffusion-weighted MR imaging. Transient punctate cortical abnormalities were seen, but most brain lesions disappeared or were smaller over 18 months; no new lesions were detected. One patient developed Horner syndrome, caused by a spinal cord lesion. Two patients had residual visual symptoms, and ophthalmologic examination revealed retinal artery obstruction. Patients developed depression; personality changes, chronic fatigue syndrome and dysthymia, and neuropsychological testing showed deficits in attention, verbal and/or visual memory. On brain imaging, a second group of asymptomatic seropositive workers showed lesions similar to those in encephalitis patients. The MR imaging appearance of Nipah virus is unlike other viral encephalitides, and is likely caused by occlusion of small blood vessels. In addition, the virus also affects the retinal blood vessels and causes late clinical and radiological findings in the spinal cord. This study expands the clinical spectrum of manifestations of this disease to include psychiatric and cognitive effects, and subclinical infection.</p>
<p>NNI/0005/1999 PI: Yee Woon Chee (NNI)</p>	<p>Autoantibodies to gangliosides, glycosaminoglycans and galactocerebrosides in the Guillain Barre syndrome</p> <p>The primary aim of the study was to look for evidence of autoantibodies to neural antigens in the Guillain Barre syndrome</p>

	<p>(GBS). A secondary aim was to apply tests developed in the study for clinical use. Sera from patients with GBS and normal controls were assayed using ELISA for IgG and IgM antibodies to gangliosides (GM1, GM2, GM3, GD3, GD1a, GD1b, GT1b, GQ1b) and glycosaminoglycans (heparan sulfate). Over two years (1999 and 2000), 61 cases of GBS were identified, of which 22 (36%) had the Miller Fisher variant (MFS).</p> <p>67% of the GBS cases had elevated titres of one or more anti-ganglioside antibodies. The most common autoantibody was IgG anti-GQ1b antibody, with raised titres occurring in 41% of GBS cases and 90% of MFS variant cases. Anti-GM1 and anti-heparan sulfate antibodies were uncommon. These findings provide evidence of geographical variation in the relative frequency of GBS clinical variants and anti-ganglioside antibodies. They indicate the differential clinical utility of these antibodies in GBS in Singapore. As an outcome of the study, three of the assays, namely ELISA for IgG anti-GQ1b antibody, IgG anti-GM1 antibody and IgM anti-GM1 antibody, are available for the first time as clinical diagnostic tests at the NNI.</p>
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Block Grant Research Projects

<p>F2/S025/NHC/002/1999</p> <p>PI: Yan Ming (NHC)</p> <p>Collaborators: He Guo-Wei, Lim Yean Leng</p>	<p>Characterization alpha1-adrenoceptor subtypes in human coronary artery bypass grafts</p> <p>The human radial artery (RA), internal mammary artery (IMA) and saphenous vein (SV) are the most commonly used coronary artery bypass grafts, and their spasm was observed in the patients with coronary artery bypass surgery both intraoperatively and postoperatively. Norepinephrine activates the α_1-adrenoceptor (AR)-induced contraction and spasm of human coronary artery bypass grafts. The aim of this project was to identify α_1-AR subtypes (α_{1A}, α_{1B}, and α_{1D}) in human coronary artery grafts.</p> <p>RT-PCR was employed to study genes expression of α_1-AR subtypes and DNA-DNA hybridization analysis of the PCR productions. The functional affinities for α_1-AR antagonist were used in the analysis of α_1-AR subtypes in human coronary artery bypass grafts.</p> <p>The major finding is that α_{1A}-AR is the major subtype in human RA, α_{1B} is the predominant subtype in human IMA, and α_{1A}- and α_{1B}-AR are major subtypes in human SV. Therefore, the optimal α_1-AR subtype antagonists such as α_{1A}-AR antagonist for AR and α_{1B}-AR antagonist for IMA, may be used to prevent coronary artery bypass spasm in the clinical setting. In 2000, the investigator was invited to present this work at Conference of CSANZ of Australia (speaker). Four papers have been published in this study.</p>
<p>F2/S037/NHC/013/2001</p> <p>PI: Xiong Zhuo Wei (NHC)</p> <p>Collaborators: Mak Koon Hou Lim Yean Leng Wahlqvst Mark L</p>	<p>Genetic effects of apo(a) and apoE in coronary heart disease (CHD) in Singapore populations</p> <p>The aim of this project was to investigate the role of the apolipoprotein(a) [apo(a)] and apolipoprotein E (apoE) polymorphisms on the development of coronary heart disease (CHD) susceptibility in the Singapore population, and their relations to plasma lipid and lipoprotein levels. Subjects with chest pain or other indications undergoing coronary angiography in three ethnic populations (Chinese, Malays and South Asians) were designed for this study. 280 Chinese patients, 20 Malays and 56 South Asian patients with CHD have been studied. 300 normal Chinese subjects, 21 Malays and 11 South Asians subjects were investigated as a control. Lp(a) concentrations have been measured using radioimmunoassay (RIA). Apo(a) phenotypes have been assessed using SDS-PAGE and ECL western blotting. LPA and APOE genotypes have been analyzed using pulsed-field gel electrophoresis (PFGE) and polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique. The expression of apo(a) and apoE in partial cases has been assessed using RT-PCR. All statistical analysis was performed using SPSS.</p>
<p>NUMI/0018 PI: Henry Yu (NUMI)</p>	<p>Organelle-Specificity of the Microtubule-Based Transport Machinery on Phagosome and other Intracellular Organelles</p> <p>This current work focuses on understanding the kinectin functions</p>

	<p>in cell motility by looking carefully at different kinectin isoforms, their interacting partners and what happen when these interactions are disrupted. The researchers have characterized the kinectin-kinesin interaction to be via a region covering parts of the kinectin variable domain 3 and 4. They have also investigated the functions in endoplasmic reticulum of a kinectin isoform lacking variable domain 4 which cannot bind to kinesin. A yeast two-hybrid screening and a number of in vitro and in vivo assays have elucidated an important role of kinectin to anchor the translation elongation factor-1δ on endoplasmic reticulum. The researchers also engaged in detail studies of the kinectin functions in organelles such as mitochondria, endoplasmic reticulum and golgi apparatus, and a model of how organelles utilizes motors and motor-anchors a la carte has been proposed. To further investigate the specificities of kinectin isoforms, the researchers have identified and analyzed a collection of novel kinectin isoform cDNAs expressed at different developmental stages of the mouse nervous system.</p> <p>A unified and expanded view of kinectin functions in cell motility and protein biosynthesis has emerged from these studies.</p>
<p>NUMI/0020 PI: Lim Sai Kiang (NUMI)</p>	<p>Roles of Haptoglobin in Hemolysis and Inflammation and Their Implications in Atherosclerosis</p> <p>The primary aim in this project was to understand the roles of haptoglobin in hemolysis and inflammation, and their implication in atherosclerosis. The researchers first observed that haptoglobin neutralizes the oxidative potential of free hemoglobin and reduces hemoglobin-mediated oxidative damages in the kidneys during hemolysis. To better understand oxidation-mediated tissue damages, the team also studied the role of other physiological anti-oxidants e.g. PON-1, regulators of lipid metabolism that contributed to formation of lipid peroxides e.g. PPARα and vasoactive enzymes such as ACE that modulate tissue oxygenation and ischemia. It was demonstrated that many of these genes were regulated in tandem with haptoglobin during inflammation and in a gender specific manner. It was also demonstrated that haptoglobin plays a role in arterial remodeling during inflammation and tissue damage and is regulated via TLR4 during inflammation.</p>
<p>NUMI/0021 PI: Lu Jinhua (NUMI)</p>	<p>Novel Ligands and Functional Regulation of Integrin, A Virtonectin Receptor involved in Angiogenesis, Virus Infection and Potentially in Phagocytosis of Microbes and Apoptotic Cells by Cytohesin-4, A Novel Cytoplasmic Protein Containing Sec7 and PH Domain</p> <p>Integrin avb5 is expressed on both macrophages and dendritic cells. The main objectives of this project are: 1) characterization of the interaction between cytohesin-4 and integrin avb5 and how this interaction may modulate avb5-mediated cell adhesion and migration; and 2) expression of the extracellular domains of integrin avb5 as a soluble probe for the identification of novel avb5 ligands. In this project, a novel cytoplasmic protein, cytohesin-4, was cloned and shown using the yeast two hybrid system to interact with the cytoplasmic domain of the integrin b5 subunit. Cytohesin-4 was also shown to co-precipitate with b5</p>

	<p>and its over-expression increases avb5-mediated adhesion and reduces cell migration. Cytohesin-4 is predominantly expressed in myeloid cells, i.e. macrophages and dendritic cells and the role of cytohesin-4 in these cells is currently under investigation. Another major aspect of this project involves the expression of the extracellular domains of av and b5 as soluble dimers and use of soluble avb5 to identify novel ligands. Avb5 was successfully expressed and shown to bind to vitronectin and osteopontin. With this soluble avb5 probe, a venom toxin has been shown as a ligand for avb5, which can be developed into an inhibitor of avb5-mediated cell migration, a process associated with tumor metastasis to the lung. The specific binding site is currently being mapped. A novel application of the soluble avb5 expression system was its application in the dimerization of toll-like receptors for signaling studies. Much progress has been made in this aspect and a new grant has been awarded to extend the application of the system in the expression of constitutively active TLRs and IL-1R.</p>
<p>NUMI/0022 PI: Li Guodong (NUMI)</p>	<p>Mechanisms Underlying Defective Intracellular Ca²⁺ Homeostasis in the Endothelial Cells Chronically Exposed to High Glucose</p> <p>This project investigated the molecular mechanisms underlying dysfunctional endothelial cells in diabetes. Hyperglycemia and dyslipidemia are the two major metabolic disorders that are the primary causes for many of diabetic cardiovascular complications. Overwhelming evidence indicates that the impairment of endothelium is involved in the pathogenesis of these diseases and that the diminished endothelium-dependent vascular relaxation is the early indicator of endothelium dysfunction. Production of nitric oxide (NO) by endothelial cells (ECs) plays a key role in endothelium-mediated vascular relaxation. Thus the researchers studied how high glucose (HG) and high fatty acids (HF) on receptor-agonist-induced NO production and the possible alterations of signaling pathways implicated in this scenario. The results revealed that exposure of ECs to HG or HF significantly reduced NO production evoked by receptor agonists that activate phospholipase C, an effect in both time- and dose-dependent manner. The diminished NO formation was probably due to the reduced elevations of intracellular free Ca²⁺ levels ([Ca²⁺]_i) under these conditions, a close correlation was observed between [Ca²⁺]_i increases and NO generation in intact ECs. Furthermore, it was found that one of the products of phospholipase C, Ins(1,4,5)P₃ which leads to [Ca²⁺]_i rises, was also decreased following HG culture. Further study suggested that this abnormality might be due to a reduction of receptor number. Importantly, application of PKC inhibitors relieved the alterations caused by HG culture in ECs. The findings have shed some light on the understanding of pathogenesis of dysfunctional ECs under diabetic conditions. The data from this project have been accepted for oral presentation at prestigious international conferences on diabetes research and published as conference papers. Three full manuscripts have been submitted or are nearly completed for publication.</p>
<p>NUMI/0023 PI: Marie-Veronique Clement (NUMI)</p>	<p>Regulation of Tumor Cell Response to Apoptosis by Reactive Oxygen Intermediates</p> <p>Previous observations had demonstrated that an increase in the intracellular reactive oxygen species (ROS), in particular</p>

	<p>superoxide anion (O₂⁻), inhibits tumor cell response to a variety of apoptotic triggers including anti-cancer drugs. Using the bladder carcinoma cell line T24, and M14 melanoma cells tailored to express constitutively active wild type and mutant forms of Rac1, we investigated if activation of the Rasoncogene leads to inhibition of apoptosis through Rac1-dependent production of O₂⁻. Intracellular level of O₂⁻ was determined using a lucigenin-based chemiluminescence assay, and sensitivity of these cell lines to a commonly used chemotherapeutic agent etoposide was correlated with the intracellular levels of O₂⁻. The results showed that Rac-mediated production of O₂⁻ could inhibit apoptosis triggered by chemotherapeutic agents, hence suggesting a new role for the Rac/oxidase/O₂⁻ signalling pathway, previously shown to be associated with mitogenic signalling in transformed fibroblasts. These results suggest that scavenging intracellular O₂⁻ in addition to inhibiting proliferation, may increase tumor cell sensitivity to a variety of apoptotic triggers, including anti-cancer drugs and the CD95-receptor. The second part of this proposal aimed at investigating the potential use of antioxidants such as ascorbate or Vitamine C as part of a combination chemotherapy regimen to enhance the efficacy of anti-tumor drugs. The experiments showed that unfortunately the effects of ascorbate in vivo could not be predicted from studies on cultured cells. Indeed, ascorbate was toxic in tissue culture due to production of H₂O₂ in the culture medium.</p>
<p>SERI/004</p> <p>PI: Roger Beuerman (SERI)</p>	<p>Aetiology of Myopia</p> <p>This project has developed a new animal model of myopia using the mouse. This was the primary goal of the project and the project has been successful in showing that experimental myopia in the mouse can be induced using two methods: lid-suture and the attachment of a negative contact lens. The results have validated the significance of the effect in several hundred mice. Since the mouse genome is well known, methods such as gene array and proteomics can be used for investigative tools. This model represents the first time that there is an opportunity to understand the biological basis of myopia. In fact, for pre-clinical drug development the mouse will likely be the model of choice. In the second goal, the researchers have used atropine to investigate the functional genomics and biology of the scleral fibroblast and that both human and mouse scleral fibroblasts have at least four types of muscarinic receptors which are blocked by atropine. Atropine also decreases axial length in the mouse model of myopia. In future studies, gene array methods will be used to determine which genes participate in the development and progression of myopia and for testing new drugs, test the use of specific muscarinic blockers and detail the pathways participating in experimental myopia.</p>
<p>SERI/005</p> <p>PI: Saw Seang Mei (SERI)</p>	<p>Changes in the Refractive Components in Myopia and Emmetropic Eyes: A Two Centre Study</p> <p>The objective of the study was to evaluate the environmental and genetic risk factors for myopia in Singapore and Xiamen school children</p> <p>1979 children in Primary 1 to 3 were recruited from 3 schools in Singapore to participate in a concurrent cohort study. In a parallel and similar fashion, 400 children from 4 schools in Xiamen were</p>

	<p>recruited in a parallel cohort. Information on nearwork, parental myopia, intelligence, night lighting, and other risk factors were obtained from a parent-administered questionnaire at baseline in both cohorts. Yearly eye examinations were performed in the schools and the following examinations were performed: uncorrected and presenting logMAR visual acuity readings, cycloplegia was administered using 1% cyclopentolate solution, stand-alone autorefraction and A-scan biometry measures. The children in Singapore and Xiamen will be followed yearly till Year 6.</p> <p>The prevalence rates of myopia were highest in Singapore, followed by Xiamen city, and Xiamen countryside. The major environmental risk factors for myopia (reading in books per week), height, and fetal growth have been identified and defined in this Asian population. Children who read more books per week and who had parents who were myopic had higher risks of myopia, suggesting possible gene-environment interaction.</p>
<p>SERI/006</p> <p>PI: Roger Beuerman (SERI)</p>	<p>Analysis of Ocular Surface and Human Tears in Normal and Diseased Eyes</p> <p>This project has developed microanalytical chemistry to a) study corneal and ocular surface disorders such as pterygium and dry eye, b) perform drug bioavailability studies for intraocular drug delivery, and c) evaluate biochemical abnormalities in myopic eyes. Main laboratory techniques used include High Performance Liquid Chromatography (HPLC), and electrospray Liquid Chromatography-Mass Spectrometry (LCMS), for quantitative biochemical determination. Some recent inexpensive modifications of equipment have allowed the researchers to carry out 2-D liquid chromatography.</p> <p>The researchers have competed successfully for two new NMRC grants which have allowed them to purchase a new ABI Q-Star XL mass spectrometer and a peptide synthesizer making this laboratory a high level proteomics facility. The use of the facility will be opened to others on the SGH campus to the extent that they can with the limited funds granted. Rapid evaluation of tear protein profiles by surface-enhanced laser desorption ionization-time of flight (SELDI-TOF) ProteinChip technology has led to the discovery of new tear proteins. The researchers assisted in the development of a pilot study to perform chorioretinal fluorescein angiography via a novel inhalational route in an animal model and in a study of the penetration of atropine into the eye, which may be useful for regulating the dose of atropine for children. The collaborations include pharmaceutical companies as well as local researchers.</p> <p>The emphasis is becoming more aligned to the area of proteomic biomarkers and the discovery of novel proteins that can be used for diagnosis of inflammatory and infectious disease. To reflect the emphasis on proteomics the title of the area of research has been changed to "Tear Microanalysis and Proteomics". The study has recently shown that defensins and similar proteins, which are considered natural antibiotics, are upregulated on the surface of the eye following ocular surface surgery in humans. These productive studies will be continued and an active program in ocular drug delivery will be maintained.</p>

	<p>An important outcome of the five year project has been the establishment of this laboratory, the Microanalytical Chemistry Laboratory, as a core laboratory for SERI. This laboratory has been successful in linking with clinicians to perform translational research projects, such as the team's studies in anterior segment and posterior segment drug delivery in various aspects of clinical ophthalmology, including ocular infections, cataract surgery antibiotic prophylaxis, post-surgical anti-inflammatory treatments and corneal transplantation immunology. This laboratory epitomizes an important principle of the Institute in utilizing the cost-effective core laboratory approach to assisting multiple clinical and translational research projects, while performing important fundamental research goals of the Institute.</p>
<p>SERI/007 PI: Donald Tan (SERI)</p>	<p>Atropine in the Treatment of Myopia (ATOM) STUDY</p> <p>The Atropine in the Treatment of Myopia (ATOM) study is a randomized, double-masked, placebo-controlled trial designed to assess the safety and efficacy of topical 1% atropine in controlling the progression of myopia in children.</p> <p>Four hundred children aged 6-12 years, with myopia of -1 D to -6 D, were enrolled after informed consent and randomly assigned to receive either 1 % atropine eye drop or Ioptotears once nightly. Only one eye of each child was chosen for treatment. Each subject was followed-up at 4-monthly intervals for 2 years and all subjects were followed up for an additional 12 months after cessation of treatment.</p> <p>346 (86.5%) subjects completed the 2-year study. After 2 years, the mean myopia progression and axial elongation in the placebo-control eyes were $-1.20D \pm 0.69D$ and $+0.38mm \pm 0.38mm$ respectively. In the atropine treated eyes, myopia progression was only $-0.28D \pm 0.92D$ while the axial length remained essentially unchanged compared to baseline ($-0.02mm \pm 0.35mm$). The differences in both myopia progression ($-0.92D$ 95% CI -0.77 to $-1.07D$) and axial elongation ($0.39mm$ 95% CI 0.32 to $0.47mm$) between the two groups were both statistically ($p < 0.0001$) and clinically significant. This data confirms that atropine is highly effective in reducing myopia progression and axial elongation. Safety data also revealed that this treatment is safe, with no clinically significant adverse events.</p> <p>The ATOM study is the largest randomized controlled trial of its kind to date and the results provide strong evidence that childhood myopia progression and axial elongation can be controlled through pharmacological means such as topical atropine. We now have a viable and effective treatment for myopia progression in children, and a final RCT to evaluate reduced dosages and concentrations of atropine is planned, to determine the final treatment algorithms for widespread clinical use.</p>
<p>SERI/008 PI: Chan Wing Kwong (SNEC)</p>	<p>Singapore National Eye Centre Lasik Assessment Trial</p> <p>The Singapore National Eye Centre Laser In-Situ Keratomileusis Assessment Trial (SLAST) was a prospective, non-randomised, open ended clinical trial to assess the efficacy, predictability, stability and safety of LASIK surgery for the correction of myopia</p>

	<p>and astigmatism. LASIK is an ophthalmic surgical procedure that involves using a microkeratome to make a central partial thickness corneal flap of 9mm diameter and 160μ thickness that is hinged superiorly. This flap is reflected and a computer controlled excimer laser beam applied to the exposed corneal stroma to correct myopia and astigmatism. Post-operative attainment of good vision without the need for optical aids is rapid and pain free.</p> <p>Between February 1998 and March 2003, a total of 9980 LASIK procedures were done for the correction of myopia and astigmatism in 5065 patients. The results were excellent with the best results in terms of efficacy, predictability, safety and stability obtained in those eyes with myopia between -1D to -5D. The success of SLAST has established LASIK as the preferred surgical method of choice for the permanent correction of myopia with or without astigmatism in SNEC and Singapore.</p> <p>SLAST has resulted in the publication of 6 papers in peer reviewed journals and 26 presentations in local and international conferences. It has also established SNEC's reputation as an international clinical trial and reference centre for refractive surgery procedures where the team has participated in 2 other global multicentre clinical trials in refractive surgery.</p>
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Annex 2: Abstracts of Completed Projects under NMRC-Tote Board Medical Research Fellowship/Scientist Award in FY2003

<p>Chan Ching Wan (Department of Surgery, SGH)</p> <p>Place of training: University of Bristol, UK</p>	<p>Apoptosis in Breast Cancer Cells</p> <p>The importance of apoptosis as a means of homeostasis and maintaining genomic integrity, as well as the ability of cancer cells to escape this failsafe mechanism, has long been the subject of intense investigation. To investigate the possibility that prolactin might enable breast cancer cells to survive apoptotic insults, T47-D and MCF-7 cells were stimulated with ceramide (C2). In addition, the ability of prolactin was assessed to improve cell survival. Morphological studies and cell survival assays demonstrated a significant survival effect in T47-D cells exposed to prolactin. Because prolactin activates the Jak2-STAT5 pathway, a model was then created in which the role of this pathway in apoptosis could be investigated. An initial attempt to inhibit dexamethasone-induced apoptosis in a human leukaemic cell line (CEM-C7) by establishing a stable clone expressing the prolactin receptor (for activating the JAK2-STAT5 pathway) was unsuccessful. Next, stable clones of breast cancer cells over-expressing STAT5b were established. Despite increased STAT5 signalling after prolactin stimulation, no enhancement of survival was demonstrated, implying that STAT5b is not responsible for survival following ceramide exposure. Surprisingly, increased STAT5 activation, following prolactin stimulation, actually increased cell death.</p> <p>The second half of this project involved investigation and characterization of the newly identified Met protein, which was showed to induce apoptosis in breast cancer cells as well as in other cell lines. Met is structurally related to SAF-B – which attaches to DNA at scaffold / matrix attachment regions and is thought to be involved in DNA transcription or mRNA processing. Met was shown to be confined to the nucleus, and partially co-localized with SAF-B, but not with splicing factor speckles. Signalling assays show that Met down-regulates transcriptional activity within cells.</p>
<p>Dr Chong Tsung Wen (Department of Urology, SGH)</p> <p>Place of training: Tumour Immunology group, University of Oxford, John Radcliffe Hospital, Oxford UK</p>	<p>To study the natural T cell responses to a novel tumour antigen G250 in Renal Cancer patients</p> <p>The project consisted of obtaining peripheral blood lymphocytes (PBL) and tumour infiltrating lymphocytes (TIL) from renal cancer patients. The patients were accrued from attendances at the Department of Urology and Uro-oncology, Churchill Hospital, Oxford. Frozen peripheral blood mononuclear cells (PBMC) were thawed and expanded in vitro with cytokine supplements and periodic peptide specific re-stimulation to obtain PBL. TIL were obtained from fresh tumour specimens and expanded. Following in vitro expansion of PBL and TIL, peptide specific responses were detected through IFN γ secretion assays (ELISpot) and further confirmed with tetramer staining and flow cytometric analysis. ELISpot and FACS data were correlated to G250 staining on immunohistochemistry of corresponding paraffin sections of tumour.</p> <p>T cell lines were cultivated from patients and healthy donors to assess differences in activation status (tetramer combined with intracellular cytokine staining and flow cytometric analysis), and cytotoxicity assays. Target cells in killing assays consisted of</p>

	<p>allogeneic HLA-A*0201 or autologous B cells infected with recombinant virus encoding human G250, or labeled with peptide.</p> <p>Autologous renal cancer cell lines (generated from fresh tumour samples) were used as targets in cytotoxicity/ ELISpot assays, to assess processing and presentation of the relevant epitopes by the tumour. T cell line has been previously established from a healthy donor which recognizes a specific G250 HLA-A*0201 restricted epitope, through in vitro priming with autologous professional antigen presenting cells. Also, several novel tetramers have been generated, enabling flow cytometric analysis of specific T cell responses to G250 both in vitro and ex vivo. In addition, a recombinant modified Vaccinia Ankara (MVA) virus encoding for human G250 has also been generated, thus allowing for transduction of antigen presenting cells as targets for G250 specific T cells.</p>
<p>Dr Chua Soo Yeng Benjamin (Department of General Surgery, SGH)</p> <p>Place of training: Duke Clinical Research Institute, Durham, USA</p>	<p>Peripheral vascular disease (PVD): Is it a risk factor for mortality in end-stage renal disease (ESRD)?</p> <p>PVD is associated with adverse outcomes in ESRD. This project determined whether differences in performance measures existed between patients with/without PVD and their relationship to mortality with PVD. Alternative PVD definitions were tested in survival models to determine categorization biases. 6920 patients were analyzed in a merged USRDS-Clinical Performance Measures database. Demographic and clinical variables were stratified by PVD status and compared using Student's t- and x2 tests. Associations between variables and presence of PVD were identified with logistic regression. The relationship between PVD and mortality was explored with models using PVD defined by CMS's Form 2728, ICD-9 diagnosis and procedures.</p> <p>It was found that PVD was associated with increasing age, male gender, white race, diabetes, tobacco use, lower BMI, shorter dialysis duration, percutaneous catheters, decreasing albumin and transferrin saturation ($p < 0.05$). In an unadjusted survival model, PVD defined by Form 2728 was associated with a hazards ratio (HR) 1.50 ($p < 0.0001$). Controlling for demographic and process of care variables attenuated the risk of PVD (figure 1). Use of ICD-9 diagnosis and procedure codes resulted in unadjusted HRs 2.40 and 2.35 ($p < 0.0001$) respectively, that remained significantly associated with risk of death in models adjusted for demographic variables. PVD is variably associated with mortality in the ESRD population, depending on definition of PVD. A uniform definition of PVD in ESRD is needed before drawing conclusions regarding its independent death association.</p> <p>Associations between clinical performance benchmarks, profit structure, and mortality in US dialysis units</p> <p>External financial pressures have forced many providers of haemodialysis to modify their cost base. Cost containment pressures may be greater in for-profit versus not-for-profit dialysis units. Previous studies have observed that haemodialysis patient mortality is greater in for-profit dialysis units, but have not captured information about clinical performance benchmarks for haemodialysis patients across units with different profit status. Moreover, the period studied in previous analyses preceded the</p>

	<p>introduction of national quality improvement programs in Medicare-certified dialysis units.</p> <p>By utilizing data from 1995-2000, the US Renal Data System and the Centres for Medicare & Medicaid Services' End Stage Renal Disease Clinical Performance Measures (CPM) project, haemodialysis units were categorized as for-profit or not-for-profit. Selected clinical variables were stratified on profit status and compared. The associations with all-cause mortality were tested using Cox proportional hazards regression.</p> <p>The results showed that although a greater proportion of haemodialysis patients in for-profit dialysis units met the established clinical performance benchmarks of care, their survival was less. The findings herein suggest that cost-containing interventions implemented in for-profit dialysis units have not impaired their ability to deliver performance benchmarks and do not account for survival differences.</p>
<p>Dr Gao Ge (NHC)</p> <p>Place of training: Cardiovascular Medicine of Yale University, USA</p>	<p>Proinflammatory mRNA Stabilization by Adhesion Receptor Engagement in Macrophages</p> <p>Monocyte adhesion to the endothelium is one of the earliest events in atherosclerosis. Firm leukocyte adhesion is mediated by both beta-1 and beta-2 integrins. In addition to their adhesive properties, integrins are potent transmembrane signaling molecules, although their role in proinflammatory gene expression has not been defined. A "consensus sequence" within the transcripts encoding many "athero-relevant", proinflammatory molecules is an adenylate- and uridylylate- rich element (ARE) within the 3'-untranslated region. This is a vigorous target of endogenous RNAses, thereby minimizing functional gene expression.</p> <p>This project addressed whether beta-2 integrin engagement in cells of the monocyte/macrophage lineage affects the half-life of transcripts encoding cytokines/chemokines that play roles in monocyte recruitment, migration, differentiation, and inflammatory effector function, all key events in atherosclerosis.</p> <p>Steady-state mRNA levels of MCP-1, its receptor CCR2, M-CSF, TNF-alpha and IL-1beta (all ARE-bearing transcripts) are up to 7 folds greater ($p < 0.01$) in murine macrophage RAW264.7 cells and bone marrow-derived murine macrophages, when bound to recombinant mouse ICAM-1-coated dishes, compared with poly-L-lysine-coated controls. mRNA decay experiments performed in transcription-arrested cells demonstrated the expected rapid 60 min decay of transcripts in control-bound cells.</p> <p>In contrast, beta-2 integrin engagement induced marked mRNA stabilization over the 60 min period. Immunofluorescence microscopy on both RAW264.7 cells and bone marrow macrophages displayed beta-2 integrin-induced rapid (30 min) nuclear-to-cytoplasmic translocation of HuR, an ARE-binding, mRNA-stabilizing protein, that is constitutively abundant in the macrophage nucleus. Real-time RT-PCR of transcripts specifically bound to immunoprecipitated HuR demonstrated up to a 588-fold increase ($p < 0.01$) in TNF-alpha and M-CSF mRNA in ICAM-1-bound cells, relative to controls.</p>

	<p>This work demonstrated a physiologically/ pathologically relevant signalling consequence of adhesion receptor engagement in murine macrophages, and established the foundation for further study in animal models of vascular remodelling and atherosclerosis.</p>
<p>Guo Changming (Department of Orthopaedics, SGH)</p> <p>Place of training: Brigham and Women's Hospital, Harvard Medical School, USA</p>	<p>Bone marrow derived mesenchymal stem cell (MSC) for tissue engineering</p> <p>3 projects with bone marrow derived stem cells were done during the course of the year.</p> <p>The first of which entailed the characterization of surface markers present on human MSC. The specific aim of the study was to determine the variability of certain surface proteins present on MSC generated with human AB serum within an individual and between individuals. The surface markers were identified with FACS analysis and the ability of the MSC to be chondroinduced and osteoinduced were demonstrated with histology and immunohistochemistry. We found that our isolation method yielded a population of cells that were negative for common hematopoietic markers CD3, CD19, CD31, CD34, CD45, CD56 and previously unreported, CD138. The intra individual variability of the method was less than 5%. Significant positive markers include CD13, CD90 and CD105. They were expressed by more than 96% of the cells and the coefficient of variation of these markers was less than 6.2%. Other markers present such as CD9, CD10, CD44, CD49a, CD71 and HLA-DR demonstrated a large variability between patients. Our analysis also showed that the distribution of the markers do not correlate with the sex or age of the patient. This project is done with collaboration between Brigham and Women's Hospital and Dana Faber Cell Manipulation Facility, a GMP facility.</p> <p>The aim of the second project was to study the effect of collagen I versus II scaffolds, duration (1 and 4 weeks) and the effect of insulin like growth factor-1 (IGF-1) and fibroblast growth factor-2 (FGF-2) at various doses on chondroinduced canine MSC in a three dimensional collagen GAG scaffolds. Final diameter, weight gained, GAG and DNA content and protein and DNA biosynthesis rates were measured. The results showed that MSCs grown in a collagen type II scaffold for 4 weeks were superior than growing them on a type I scaffold and for 1 week. This project is done with collaboration between Harvard, MIT and the Veterans Administration hospital.</p> <p>The third project was to incorporate the lessons learnt in the earlier two projects to tissue engineer in vitro an immature chondroinduced MSC-seeded construct that when implanted will undergo maturation and remodelling into articular cartilage in vivo. The aim of the third project was to compare the effect of sequential supplementation of IGF-1 at 100ng/ml and FGF-2 at 10ng/ml on canine MSC seeded in a type II collagen GAG scaffold. FGF-2 showed increased cell mediated contraction and DNA increase compared to the other 2 groups whilst although the IGF-1 showed significant histological neocartilage development although there was no statistical difference in GAG or DNA increase compared to controls. This project is done with collaboration between Harvard, MIT and the Veterans Administration hospital.</p>

<p>Loh Pui Kwan Donus (IMH)</p> <p>Place of training: Institute of Neurology, University College London, UK</p>	<p>Research Project: Auras in temporal lobe epilepsy: The problem with classification of auras, and the relationship between auras and psychopathology after temporal lobectomy</p> <p>Auras have been defined and classified in different ways in past studies. Study 1 attempted to verify if the objective expectations of clinicians and researchers as represented in aura classifications, matched patients' subjective reports of auras. The aura descriptions of 114 patients with temporal lobe epilepsy (TLE) were recorded and categorized in a self-developed aura classification, the Aura Tree. Factor analysis could not be performed as poor correlations between aura sensations meant that groups of auras could not be statistically derived. It was suggested that the expectations of clinicians and researchers might not match the subjective experiences of patients.</p> <p>Study 2 investigated the short and long term effects of temporal lobectomy on the relationship between auras and psychopathology. Pre-surgical and short-term follow-up information was collected via patients' case notes. A questionnaire was constructed to collect long-term follow-up information from 61 patients. Results obtained however revealed trends that were difficult to analyze and interpret. This could be attributed to a number of methodological concerns which were discussed.</p> <p>In summary, the findings of both studies were not conclusive; instead they have contributed more controversies into this area of research. In addition, it highlighted to clinicians that there is a need for TLE patients to be counselled about the possible consequences of temporal lobe lobectomy. Postoperative medical and psychological care can be structured for a patient with particular preoperative symptoms.</p> <p>Library Project: The neuropsychiatry of basal ganglia disorders</p> <p>The neuropsychiatric symptoms that accompanied motor symptoms have recently received much attention, where attempts are focused in elucidating its role as a co-morbid symptom. A small meta-analysis of prevalence rates cited in current reviews and articles was compiled, and further summarized into a spectrum of symptoms. Following qualitative analysis, this review observed that hyperkinetic behaviour tends to co-occur with hyperkinetic movement disorders. This was similarly observed for hypokinetic behaviour and movement disorders. It also suggested that the "on-off" phenomenon observed in Parkinson's disease might be a credible 'human' model in explaining the overlap of neuropsychiatric symptoms in both hyper- and hypo-kinetic disorders.</p> <p>In clarifying co-morbidity of motor and neuropsychiatric symptoms following basal ganglia disorders, this review hoped to help the clinician improve on making differential diagnosis and thus, better therapeutic interventions.</p>
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<p>Shek Pei-Chi Lynette (Department of Paediatrics, NUS)</p> <p>Place of training: Mount Sinai School of Medicine, New York, USA</p>	<p>Natural History of Food Allergy</p> <p>The aim of the project was to see if measuring specific-IgE to food over time could predict the development of tolerance. Patients with egg and cow milk allergy who underwent double-blind, placebo-controlled food challenges were included in the study. Specific IgE (sIgE) levels were determined from stored serum samples obtained at the time of the food challenges.</p> <p>It was found that the rate of decrease in food-specific IgE levels over time was predictive of the likelihood of developing tolerance in milk and egg allergy. Using these results, a model was developed for predicting the likelihood of developing tolerance in milk and egg allergy based on the decrease in food-specific IgE over time. The likelihood estimates derived from this study could aid clinicians in times of food challenges, and in prognosticating the likelihood of development of tolerance in food allergy.</p> <p>Cow milk specific T and B cell responses</p> <p>The aim of the study was to determine IgE, IgA, IgG₁ and IgG₄ antibody levels and lymphocyte proliferative responses to α-casein, β-casein, κ-casein, α-lactalbumin and β-lactoglobulin in patients with IgE- and non-IgE-mediated cow milk allergy (CMA). Antibodies to casein and whey proteins were measured using ELISA. Lymphocyte proliferation was performed in the usual way.</p> <p>A distinct pattern of humoral antibody response was found in the different forms of CMA. Patients with IgE-mediated CMA had an elevated polyisotypic response to cow milk protein. A relative lack of specific IgG₄ production was also found in patients with enterocolitis syndrome. In general, caseins appeared to be the predominant allergen in CMA patients. The identification of major milk allergens can help in developing allergens for diagnosis and immunotherapy in CMA.</p> <p>Cord blood responses to allergens</p> <p>The last 5 months of my fellowship were spent in Perth, Australia at the Telethon Institute for Child Health Research. There, the techniques of cord blood collection and processing under the supervision of Prof Patrick Holt were taught. Work on cord blood cells will be continued in Singapore in an attempt to find immune markers that may predict the development of atrophy in Singapore children.</p>
<p>Dr Narayanan Gopalakrishna Iyer (Department of Surgery, SGH)</p> <p>Place of training: University of Cambridge, UK</p>	<p>Role of p300 in the p53 pathway</p> <p>Activation of the tumour suppressor p53 by DNA damage induces either cell cycle arrest or apoptosis. This p53-mediated cell fate is mediated by a balance of factors that favour arrest (such as p21 and 14-3-3σ) versus pro-apoptotic factors (such as Puma, Noxa and bax). However, what determines the choice between cytostasis and apoptosis remains unclear.</p> <p>To determine the role of the E1A-binding p300 nucleoprotein in p53-determined cell fate, the <i>EP300</i> gene in HCT116 was targeted by homologous recombination, to generate cells null for p300 protein (p300⁻ cells). HCT116 is a colorectal cell line, wild type for</p>

	<p>p53 and has a well-characterized DNA damage response. As a result, it has been extensively used in gene targeting experiments to dissect the p53 pathway.</p> <p>Comparing the isogenic cell lines, absence of p300 resulted in reduced p53 acetylation in response to DNA damage, showing that p300 is indeed the main p53 acetylase. Furthermore, p53 stability was increased in after damage, where p53 protein levels were sustained for a prolonged period compared to HCT116. This was secondary to blunted mdm2 activation and the absence of p300, as both mdm2 and p300 are key mediators of p53 ubiquitination and degradation.</p> <p>Analyses of p53 downstream targets demonstrated that loss of p300 results in a failure to transactivate p21 coupled with a disproportionate increase in Puma levels, seen in expression analyses by real time RT-PCR and Western blots. This combination of prolonged p53 activation, loss of a p21 response and augmented activation of Puma act in combination to alter the cell fate of HCT116, promoting apoptosis over arrest in response to UV irradiation mediated damage. The increased sensitivity leading to apoptosis of p300⁻ cells extends to other DNA damaging agents including doxorubicin, etoposide and 5 FU. Xenograft models showed that loss of p300 promotes chemo-sensitivity of tumors to doxorubicin, compared to parental HCT116.</p> <p>These results showed that p300 is a key modulator of the p53 response that functions by altering the balance between p21 and Puma. <i>In vivo</i> experiments provide compelling evidence that p300 loss increases sensitivity of tumours to doxorubicin suggesting that p300 inhibition may be utilized in a therapeutic setting to promote chemo-sensitivity.</p>
<p>Ng Chung Fai Jeremy (Department of Surgery, SGH)</p> <p>Place of training: University of London, UK</p>	<p>Differential expression patterns of the insulin-like growth factor II gene in human colorectal cancer</p> <p>Tumour development and metastasis are associated with altered gene expression profiles. The aim of this study was to identify the transcriptional differences in normal, tumour and metastatic tissue. Oligonucleotide arrays were used to identify differential expression patterns of insulin-like growth factor 2 (IGF 2) between 139 primary colorectal tumour and 42 tumour adjacent mucosa specimens from colorectal cancer (CRC) patients. The expression levels of the IGF2 gene were significantly increased in primary tumours compared with adjacent mucosae. This was concordant with our real-time RT-PCR quantification of 48 matched tumour-mucosa samples.</p> <p>IGF2 expression levels were also measured by RT-PCR quantitative analysis in 18 liver metastases and 10 normal tissues from patients without cancer. The mRNA levels were significantly under-expressed in liver metastases compared with either colorectal tumours or adjacent normal mucosae. The non-malignant normal tissue expressed significantly lower IGF 2 levels than adjacent normal and this was not due to a field effect originating from the tumour. In addition, our microarray data demonstrated that IGF 2 expression was down-regulated in sporadic microsatellite instability (MSI-H) CRC and parallels under-expression of hMLH1 and IGF 2 receptor (IGF2R) genes in these patients.</p>

	<p>It was then concluded that IGF 2 plays an important role in CRC development. Also, individuals with loss of genomic imprinting (LOI) causing over-expression of IGF 2 may be at greater risk of developing CRC. Understanding how IGF 2 is implicated in tumour development and metastasis may provide a novel therapeutic target to be used in clinical practice.</p> <p>Prediction of radiotherapy response in rectal cancer patients using global gene expression profiling</p> <p>Pre-operative radiotherapy reduces local recurrence in rectal cancer patients. However, patient response is not uniform and cannot be reliably predicted. Recent advances in DNA microarray technology allow global gene expression profiling. The aim of this project is therefore to define a gene expression ‘signature’ that predicts for response to radiotherapy in rectal cancers using 2 approaches.</p> <p>The first approach was to allow 2 blinded pathologists to assess the histopathological response to radiotherapy, using the Rectal Cancer Regression Grade, a 3-point scale quantifying the pathological effects of radiotherapy treatment. The degree of response was then correlated to microarray data using supervised hierarchical clustering. The second approach was then to use an unsupervised hierarchical clustering method to separate tumour transcriptomes between the post-irradiation rectal cancer patients who developed local recurrence and those who had a disease-free survival of more than 2 years. The validity of the results of microarray experiments is confirmed by comparing with quantitative real-time RT-PCR analyses of selected genes.</p> <p>There is a clear difference in gene expression between tumours that demonstrate a significant pathological response and those that display minimal response. However, this difference was not translated to patient outcome. The underlying biology of the tumour, as differentiated by a transcriptome-based approach affords a better correlation with patient outcome. Further recruitment of patients will enable the delineation of a more robust gene expression ‘signature’ that, when assayed at diagnosis, will allow more accurate patient selection for neoadjuvant radiotherapy.</p>
<p>Dr Shanker Pasupathy (Department of General Surgery, SGH)</p> <p>Place of training: Leeds General Infirmary, UK</p>	<p>The effects of warm-up on walking distance, platelet activation and platelet-neutrophil aggregation in claudicants</p> <p>The aim of the project was to investigate the warm-up phenomenon in patients with intermittent claudication.</p> <p>16 subjects were recruited for two treadmill exercise tests each, one preceded by a warm-up. Exercise continued until maximal leg pain (claudicants) or exhaustion (controls). Pre-, 5 and 60 minutes post-exercise blood samples were taken for flow cytometric analysis of platelet fibrinogen binding, P-selectin expression, platelet-leucocyte aggregation (PLA) and platelet-neutrophil aggregation (PNA) with and without ADP agonist stimulation. Wilcoxon signed-rank test was used for statistical analysis.</p> <p>The results obtained showed that 8 claudicants (median age 63 yrs (<i>inter-quartile range 61,70</i>, 2 men) and 8 healthy controls (63.5 yrs (<i>61,70.5</i>), 3 men) exercised for a longer period after warm-up</p>

	<p>(claudicants 6.95 (6.21,7.95) vs. 7.86 (7.46,9.00) minutes, $p=0.012$, controls 7.81 (6.16,9.40) vs. 9.03 (6.85,9.41) minutes $p=0.008$). Platelet fibrinogen binding and P-selectin expression was increased after exercise in both groups (claudicants fibrinogen binding: 1.11%(0.8,2.46) vs. 2.63%(1.49,4.00) $p=0.008$; P-selectin : 0.68%(0.48,0.80) vs. 1.11%(0.79,1.52) $p=0.028$). Neither agonist stimulation nor warm-up altered this response. PLA and PNA were similarly increased (claudicants PLA 7.6% (6.45,9.73) vs. 12.99% (9.10,24.64)$p=0.004$; PNA 6.76% (5.64,7.92) vs. 10.15% (8.15,21.20) $p=0.012$) although 60 minutes post-exercise levels of PLA [14.51%(10.0,22.0) $p=0.004$] and PNA [9.41(8.29,14.78) $p=0.017$] remained high only in claudicants (but recovered to baseline levels when preceded by warm-up). Warm-up also significantly desensitised PNA after 10uM ADP stimulation at all time points.</p> <p>Thus, it can be concluded that warm-up increases the exercise capacity of both claudicants and controls. Exercise induces a thrombo-inflammatory response with PLA and PNA persistently elevated after 60 minutes in claudicants, an effect diminished after warm-up.</p>
<p>Dr Tan Sing Huang (Department of Haematology-Oncology, NUH)</p> <p>Place of training: Institute of Molecular and Cell Biology, Singapore</p>	<p>Detection of tumour cells in blood samples of patients by methylation specific polymerase reaction (MSP) for tumour suppressor genes including <i>RUNX3</i></p> <p>The aims of the project were to determine the presence and frequency of methylation of tumour suppressor genes, including <i>RUNX3</i>, <i>p16</i>, <i>RASSF1A</i>, <i>CDH1</i> and <i>hMLH1</i> in cancer patients (namely breast, non-small cell lung, small cell lung, gastric, pancreatic, colorectal and hepatocellular cancers) by carrying out MSP on their plasma, serum and buffy coat. Also, the optimal conditions necessary for detection of methylation status were determined in the genes studied.</p> <p>There has been considerable interest recently in the area of epigenetic changes contributing to the process of carcinogenesis. Molecular evidence has emerged recently of aberrant methylation of cytosine in promoter CpG islands, causing abnormal silencing of vital tumour suppressor genes in cancer cells. This relationship between <i>RUNX3</i> and carcinogenesis has already been extensively studied in the context of gastric cancer where it was found that 45-60% of human gastric cancer cells do not express <i>RUNX3</i> due to hypermethylation and hemizygous deletion of the <i>RUNX3</i> promoter region.¹ Tumourigenicity of human gastric cancer cell lines was found to be inversely related to the level of <i>RUNX3</i> expression, a mutation (R122C) within the Runt domain abolishing the tumour-suppressive effect of <i>RUNX3</i>.¹</p> <p>Furthermore, <i>RUNX3</i> has also been reported to be lost in 20% of lung cancer cell lines and tissue samples,² 70% of bile duct cancer cell lines, 75% of pancreatic cancer cell lines,³ 70% of liver cancer cell lines (Ida et al, unpublished data) and 50% of breast cancer cell lines (Lau QC et al, unpublished data) due to hypermethylation of the CpG islands. 50% of sporadic colon cancer is also associated with <i>RUNX3</i> (Inoue et al, unpublished data). These data suggested that <i>RUNX3</i> plays a part in various types of cancers.</p> <p>This project planned to analyze <i>RUNX3</i> with blood samples of</p>

	<p>patients with cancer. These analyses consist of examination of genomic DNA from tumour cells to examine the methylation status of the <i>RUNX3</i> promoter region. The results obtained in the analyses would be particularly of benefit to elucidate the mechanism of carcinogenesis and could lead to improvements in their treatment, the discovery of new diagnostic tests for cancer or development of targeted therapies.</p> <p>MSP is able to target not only <i>RUNX3</i> but <i>p16</i>, <i>RASSF1A</i>, <i>CDH-1</i> and <i>hMLH1</i> as well. This improves the sensitivity of cancer cell detection and can provide molecular classification of cancers.</p>
<p>Tan Soo Yong (Department of Pathology & Laboratory Medicine, TTSH)</p> <p>Place of training: University of Oxford, UK</p>	<p>Immunophenotype of follicular center cells</p> <p>A variety of multi-labelling techniques were used in immunohistochemistry including double immunoenzymatic and double immunofluorescent staining, as well as combined immunoenzymatic and immunofluorescent methods. A late germinal center cell not previously characterized was identified, demonstrating a unique immunophenotype.</p> <p>Immunophenotypic characterization of inter-follicular CD30 cells</p> <p>CD30 is a tyrosine kinase receptor expressed in a number of human lymphoid tumours such as anaplastic large cell lymphoma, Hodgkin lymphoma and cutaneous lymphoproliferative disorders such as lymphomatoid papulosis. Whilst it has been known that scattered CD30+ cells exist in the interfollicular region of the reactive lymph node, its nature is still uncertain. By multiple immunolabelling techniques, it was found that the interfollicular CD30+ cells is a heterogenous population with expression of both T- and B-cell markers, as well as a number of B-cell associated transcription factors. This project is part of an ongoing collaboration with Dr Teresa Marafioti of Oxford and fellow researchers in Berlin.</p> <p>Advances in the use of immunohistochemistry in skin biopsies</p> <p>Traditionally, immunohistochemistry in dermatopathology is limited largely to immunofluorescence on fresh, skin biopsy specimens in the study of bullous diseases. After collaborated in a paper studying the usefulness of various methods in immunohistochemistry and fluorescent in situ hybridization in paraffin-embedded tissue sections, it was shown that it is possible to achieve satisfactory results using skin biopsies of lymphomatoid papulosis as an example.</p> <p>The protocols for double immunofluorescent labeling and fluorescent in situ hybridization (FISH) have been optimized and the initial results with FISH using split-apart translocation probes for Burkitt lymphoma have been encouraging. In addition, this project has managed to successfully combine the techniques of immunoperoxidase with double immunofluorescent labelling to achieve triple-colour, multi-immunolabelling.</p>

<p>Dr Tong Khim Leng (Department of Medicine, CGH)</p> <p>Place of training: University of Virginia Health System, USA</p>	<p>Detection of Non-critical Coronary Stenosis at Rest with Myocardial Contrast Echocardiography</p> <p>It was hypothesized that autoregulatory changes in arteriolar blood volume that develop spontaneously distal to a stenosis can be detected by analyzing phasic changes in contrast enhancement with myocardial contrast echocardiography (MCE), allowing the detection of coronary stenosis at rest without recourse to stress. MCE was performed in 24 patients with suspected or known left anterior descending artery stenosis using bolus injections of Definity and high mechanical index real-time power modulation. Patients were divided into 4 groups by stenosis severity on QCA: Group 1 (n = 5) had normal coronary arteries, Group 2 (n = 6) had mild stenoses (36 ± 13%), Group 3 (n = 6) had moderate stenoses (66 ± 5%) and Group 4 (n = 5) had severe stenoses (85 ± 5%) (p < 0.001 between groups). A progressive increase in the background-subtracted systolic/diastolic AI ratio was noted from Group 1 to Group 4 patients. Using a receiver-operator characteristic curve, a systolic/diastolic AI ratio of > 0.30 provided a sensitivity and specificity of 83% and 100%, respectively, for the detection of coronary stenosis > 50% severity.</p> <p>It was concluded that both the presence and relative severity of a physiologically significant coronary stenosis can be detected at rest in patients with suspected coronary artery disease (CAD) using phasic changes in myocardial AI on MCE.</p> <p>The clinical implication of this is that CAD is the leading cause of death in the world. The current means of diagnosing CAD are tedious because they require some form of pharmacological or exercise stress. MCE could offer the ability to detect the presence and severity of CAD at rest.</p> <p>This project was presented as featured poster presentation at the American College of Cardiology Scientific Session 2004. It was carried out in collaboration with Dr. Kevin Wei (MD, FACC), Dr. Sanjiv Kaul (MD, FACC), Dr. Eric Powers (MD, FACC), Dr. Michael Ragosta (MD, FACC) and Todd Belcik (RDCS).</p>
<p>Dr Wong Boon Seng (National University Medical Institutes and Department of Biochemistry, NUS)</p> <p>Place of training: Institute of Pathology, Case Western Reserve University, Cleveland, Ohio, USA</p>	<p>Construction and characterisation of novel neuronal cell lines derived from gene-knockout mice.</p> <p>The availability of mice homozygous for the targeted disruption of the prion protein (<i>Prnp</i>^{-/-}) and amyloid precursor protein (<i>App</i>^{-/-}) genes have facilitated the study of these two proteins in an <i>in vivo</i> environment to examine the phenotype exerted by the absence of these genes during neuro-development and neuro-degeneration at the tissue level. However, similar advances have been lacking at the cellular level, although culturing of primary cells from these knockout mice has enabled <i>ex vivo</i> investigation for short periods of time.</p> <p>During the extended period of my fellowship, two immortalized neuronal cell models derived from the cerebellum of <i>Prnp</i>^{-/-} and <i>App</i>^{-/-} mice had been established and characterized respectively. The characterisation work was partly performed during my fellowship period in US and was continued when I joined NUS.</p> <p>During the early stages of the primary culture, most non-neuronal</p>

	<p>cells were removed with cytosine arabinoside. After transformation, the absence of either the <i>Prnp</i> or <i>App</i> gene was confirmed by gene amplification using genomic DNA and mRNA extracted from the respective cells, alongside appropriate controls. The lack of prion protein (PrP) or amyloid precursor protein (APP) expression in the respective cell lysates and cell surface was verified by immunoblotting and flow cytometry. Further separation of the transformed <i>Prnp</i>^{-/-} and <i>App</i>^{-/-} cells into neuronal and non-neuronal populations was performed based on the presence or absence of cellular reaction with a neuronal surface antigen using fluorescence activated cell sorting (FACS). Isolated neuronal and non-neuronal cells were propagated to obtain clonal cell lines.</p> <p>The origin of the neuronal clone was established by the reactivity of cellular lysates with anti-MAP2 and the lack of interaction with anti-GFAP (Glial Fibrillary Acidic Protein). MAP2 is the major microtubule associated protein of the brain tissues, thereby serving as a useful neuronal marker. Interestingly, the molecular size (~70kDa) that was observed is of the MAP2c subtype that is only present in newborn. Indeed, our neuronal cell lines were derived from mice at postnatal day 4.</p> <p>The “creation” of these immortalized neuronal cell lines will enable us to examine the cellular biology of PrP and APP in a knockout environment for a prolonged period of time and they will serve as good models for my ongoing investigation on the biology of prions and Alzheimer’s diseases.</p>
<p>Dr Wong Seng Cheong Alvin (Department of Haematology-Oncology, NUH)</p> <p>Place of training: Bunting-Blaustein Cancer Research Building, Johns Hopkins, USA</p>	<p>RNA Interference of Epstein-Barr virus nuclear antigen 1</p> <p>RNA interference (RNAi) is a novel technique used in silencing of specific gene expression. Epstein-Barr virus (EBV) nuclear antigen 1 (EBNA1) is required for maintenance and replication of the viral episome and is expressed in all EBV-associated tumours. This project investigated the feasibility of using RNAi to silence EBNA1 gene expression.</p> <p>EBNA1-specific short-interfering RNA (siRNA) duplexes were designed using appropriate software and synthesized commercially. SiRNA duplexes specific to 2 sites on the EBNA1 genome were tested. The duplexes were transfected into an EBV-negative breast cancer cell-line (MCF-7) together with a green fluorescent protein (GFP) and EBNA1 fusion-protein DNA expression vector, using a liposomal protocol. The cells were analyzed at 48 hours by fluorescent microscopy, and Western blotting. Subsequently, DNA expression vector for the equivalent short-hairpin RNA (shRNA) was made. The shRNA sequence was designed and the oligonucleotides synthesized, annealed, and inserted into a plasmid vector, downstream to an RNA polymerase III promoter. The shRNA vector was transfected into MCF-7 together with GFP-EBNA1 vector, using a liposomal protocol. Transfected cells were analysed at 72 hours. Finally, the promoter-shRNA fragment was cut out and re-inserted into an ori-P containing plasmid. EBNA1 is known to bind to the ori-P sequence of the viral episome for its maintenance. An ori-P containing vector would potentially be specific for EBV-positive cells and also a more stable expression system. We tested the ori-P containing vector in our GFP-EBNA1 expression system.</p>

	<p>It was found that MCF-7 cells transfected with GFP-EBNA1 expression vector alone produced green signal under fluorescent microscopy. Co-transfection with siRNA duplexes against EBNA1 caused a marked reduction in the amount of green signal. Western blotting with anti-GFP antibody showed a marked reduction in amount of fusion protein in the cells co-transfected with siRNA duplexes. Results were confirmed using antibody against EBNA1. Similar results were obtained with cloned shRNA expression vectors. Preliminary experiments with the ori-P containing vector demonstrated good transfection rates in previously difficult-to-transfect EBV-positive cell lines, using both liposomal and novel electroporation techniques.</p> <p>The silencing of EBNA1 by RNA interference was demonstrated using both siRNA duplexes and shRNA expression vectors. Studies are ongoing to investigate the effects of EBNA1 silencing in EBV-infected cell lines such as Burkitt's lymphoma and Nasopharyngeal Cancer (NPC) cell lines.</p>
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Annex 3: Research Projects Approved by NMRC in FY2003

Alexandra Hospital

NMRC/0802/2003

PI: Lim, Su Chi

A randomised, double-blind, placebo controlled trial to assess the efficacy of 12 weeks of coenzyme Q10 at 200mg per day on the micro-circulatory endothelial function of 80 subjects with type 2 diabetes

Institute of Mental Health

NMRC/0745/2003

PI: Woo, Siew Choo Bernardine

Mental Health of Primary School in Singapore

NMRC/SRG/004/2003

PI: Fung, Shuen Sheng Daniel

Understanding resilience in the face of crisis: The Aftermath of SARS

KK Women's & Children's Hospital

NMRC/0733/2003

PI: Yeow, Kok Leng Vincent

A Randomised Controlled Trial Comparing Speech and Growth Outcomes between 2 Different Techniques and 2 Different Timings of Surgery in the Management of Clefts of the Secondary Palate

NMRC/0757/2003

PI: Tee, Wen Sim Nancy

To detect evidence of Mycoplasma pneumoniae infection in acute central nervous system diseases

Nanyang Technological University

NMRC/SRG/001/2003

PI: Lescar, Julien

Enzymatic and Structural studies of the SARS-associated coronavirus 3C-like protease as an aid for drug design

National Cancer Centre

NMRC/0715/2003

PI: Hui, Kam Man

Analysis of gene expression profiles for human undifferentiated nasopharyngeal carcinoma (NPC)

NMRC/0725/2003

PI: Lam, Paula Y P

New strategies to enhance gene therapy efficiency in cancer gene therapy

NMRC/0726/2003

PI: Lee, Caroline Guat Lay

Molecular Elucidation of Proteins that interact with FAT10 in the Carcinogenesis Process

NMRC/0727/2003

PI: Rajan, Sandeep Kumar

To evaluate the improvement in anemia, response to treatment, quality of life, Vascular Endothelial Growth Factor (VEGF) expression and cognitive function of cancer patients undergoing chemotherapy and treated with recombinant human erythropoietin

NMRC/0740/2003

PI: Hui, Kam Man

Development of nanoparticle-DNA complexes (nanoplex) for efficient gene delivery

NMRC/0743/2003

PI: Cheung, Yin Bun

Variability of Health-Related Quality-of-Life Scores in Cancer Patients: A Comparative Study of Three Major Instruments

NMRC/0761/2003

PI: Wong, Meng Cheong

Development and Characterization of Endothelial Progenitor Cells from Genetically Engineered Human Embryonic Stem Cells

NMRC/0762/2003

PI: Hung, The Huynh

The role of insulin-like growth factor binding protein 3 in early detection and treatment of hepatocellular carcinoma

NMRC/0763/2003

PI: Lee, Ann Siew Gek

Identifying recurrent BRCA1 Mutations in Breast Cancer Patients in Singapore for Improved Susceptibility Testing

NMRC/0764/2003

PI: Ang, Peter Cher Siang

In vivo detection of multidrug resistant phenotype in breast cancer patients for neoadjuvant chemotherapy by scintimammography using ^{99m}Tc-sestamibi scan and MDR1 genotyping

NMRC/0807/2003

PI: Kon, Oi Lian

Chromosomal rearrangements in gastric cancer: Molecular and functional studies of signature translocations

NMRC/0813/2003

PI: Hui, Kam Man

Immune system and cancer: the role of Cytotoxic T Lymphocytes and perforin in cancer resistance

NMRC/0814/2003

PI: Chowbay, Balram

To investigate the influence of MDR1 haplotypes on enterocyte and hepatic expression of P-glycoprotein, CYP3A4 and CYP3A5

NMRC/0815/2003

PI: Gopalan, Ganesan

Validation of Aurora-A kinase interacting protein (AIP) as an anti-tumor target

National Environmental Agency

NMRC/0724/2003

PI: Tang, Kin Fai

Establishment and functional study of human CD34+ dendritic cell lines from peripheral blood monocytic cells by HESS-5 and a cytokine cocktail

National Heart Centre

NMRC/0720/2003

PI: Lim, Tai Tian

Comprehensive approach to evaluate novel components and approaches to prevent vascular restenosis

NMRC/0721/2003

PI: Chin-Dusting, Jaye

Identifying the L-arginine Transporter and Targeting Patients as High Cardiovascular Risk with eNOS Polymorphisms for Therapeutic Restoration of Endothelial Function: Implications of Ethnicity

NMRC/0722/2003

PI: Dusting, Gregory J.

Function of NADPH Oxidase and Nox in Human Arteries - Gene Targets for oxidative stress

NMRC/0729/2003

PI: Shim, Winston Se Ngie

Isolation and Characterization of Sternum Bone Marrow Derived Stem Cells from Patients Undergoing Coronary Artery Bypass Graft Surgery – Extracellular Matrix Dependent Cardiomyogenic Differentiation of Adult Human Mesenchymal Stem Cells

NMRC/0730/2003

PI: Shim, Winston Se Ngie

Combined Angiogenic Effects of Vascular Endothelial Growth Factor and the Angioproteins on Chronic Ischemic Myocardium in a Porcine Model

NMRC/0801/2003

PI: Koh, Tian Hai

The structural and genetic basis of large artery stiffening in cardiovascular and cerebrovascular disease; risk prediction and therapeutic targeting

NMRC/0809/2003

PI: Wei, Heming

Identification of Fatty Acids Profiles as a Novel Cardiovascular Risk in Singapore

NMRC/0810/2003

PI: Wong, Philip En Hou

Rejuvenating the failing heart: a minimally invasive method of repopulating cardiomyocytes using the Biosense NOGA intramyocardial mapping and injection system

National Neuroscience Institute

NMRC/0723/2003

PI: Auchus, Alexander P.

Vitapops – Magnetic Resonance Imaging Substudy

NMRC/0731/2003

PI: Tang, Feng-Ru

Expression of Protein Kinase C Isoforms in the Hippocampus of Patients with Temporal Lobe Epilepsy

NMRC/0735/2003

PI: Feng, Zhi Wei

Neuronal differentiation of adult bone marrow stem cell: Application for treatment of stroke

NMRC/0742/2003

PI: Soong, Tuck Wah

Characterization of the genetic basis and the pathophysiology of primary and acquired periodic paralysis: thyrotoxic, familial and idiopathic causes

NMRC/0752/2003

PI: Lim, Shih Hui

Mesial Temporal Structures and Psychopathology in Epilepsy - A MRI Volumetry Study

NMRC/0768/2003

PI: Burgunder, Jean-Marc

Molecular analysis of the effects of sarcoglycan mutations

NMRC/0776/2003

PI: Lim, Kah Leong

The role of familial Parkinson's disease-linked gene product, parkin, in Lewy Body formation and dopaminergic neuronal death in Parkinson's disease

NMRC/0777/2003

PI: Tang, Feng-Ru

Prevention of Learning and Memory Impairment by the Agonists and Antagonists of Metabotropic Glutamate Receptors in the Animal Model of Temporal Lobe Epilepsy

NMRC/0778/2003

PI: Ng, Hua Bak Ivan

In vivo-Microdialysis-Aid to defining and Optimization of Cerebral perfusion Pressure in Head Injury

NMRC/0795/2003

PI: Lim, Choie Cheio Tchoyoson

Diffusion weighted magnetic resonance imaging: Visualising normal and diseased white matter

NMRC/0816/2003

PI: Chen, Christopher Li-Hsian

A case-control study of genes affecting homocysteine metabolism in Singaporean stroke patients

National University Hospital

NMRC/0713/2003

PI: Chai, Ping

Multi-slice Computed Tomography for detecting and Quantitating Thoracic Aortic Atheromas: Comparison with Transoesophageal Echocardiography

NMRC/0736/2003

PI: Lee, Soo Chin

Characterizing the functional significance of novel hMLH1 and hMSH2 missense mutations in Singaporean HNPCC families

NMRC/0744/2003

PI: Mukherjee, J J

Prevalence of Reversible Endocrine Causes of Hypertension in Type 2 Diabetic Patients with Poorly Controlled Blood Pressure

NMRC/0749/2003

PI: Tan, Kim Siang Luke

EBV DNA (RT-PCR) predictor of nasopharyngeal cancer. Early detection of nasopharyngeal cancer with EBV-DUAL

NMRC/0769/2003

PI: Lau, Philip Tsau Choong

Validation of the sentinel node biopsy for operable breast cancer following neoadjuvant chemotherapy

NMRC/0774/2003

PI: Phua, Jason

N-terminal pro B-Type Natriuretic Peptide (NT-proBNP) levels in severe sepsis and septic shock

NMRC/0791/2003

PI: Poon, Keah How

Characterization of processing and secretion mechanisms on pain-related neuropeptides, nociceptin and nocistatin, in NS20Y cell culture

National University Medical Institutes

NMRC/0746/2003

PI: Haider, Khawaja Husnain

Lipofection of human VEGF165 in human skeletal myoblasts for angiomyogenesis: Making it safer for the ailing heart

NMRC/0784/2003

PI: Wong, Boon Seng

Genetic influence on prion protein: an insight to neurodegenerative diseases

NMRC/0790/2003

PI: Khan, Md. Matiullah

Role of aberrant proteolysis in the pathogenesis of Acute Promyelocytic Leukemia (APL)

NMRC/0803/2003

PI: Li, GuoDong

Molecular mechanism for the activation of Rac1 and downstream effectors by glucose stimulation in the regulation of insulin secretion from islet beta-cells

National University of Singapore

NMRC/0717/2003

PI: Quak, Seng Hock

Hepatitis B immune status in children - a decade after mass vaccination

NMRC/0719/2003

PI: Zhu, Yi Zhun

Cardioprotective effects of active ingredients isolated from *Salviae Miltiorrhizae* after myocardial infarction in rats

NMRC/0732/2003

PI: Chong, Samuel Siong-Chuan

Molecular Basis of Nonsense-Mediated mRNA Decay (NMD) in Beta-Thalassemia

NMRC/0737/2003

PI: Chang, Chan Fong

Functional roles of CD38/ADP-ribosyl cyclase and its metabolites in the rat models of liver cirrhosis

NMRC/0738/2003

PI: Pervaiz, Shazib

Interplay between Intracellular Redox Status and Pro-apoptotic Protein Bax during Drug-induced Tumor Cell Death: Potential Implications for Cancer Chemotherapy.

NMRC/0739/2003

PI: Tan, Kevin S W

Cell and Molecular Biology of the human intestinal protozoan parasite *Blastocystis hominis*: replication, cell death, pathogenesis and genetic tools.

NMRC/0741/2003

PI: Wilder-Smith, Einar

Effect of transdermal botulinum toxin on sweat secretion in subjects with hyperhidrosis

NMRC/0747/2003

PI: Lim, Thiam Chye

Adipose-derived Mesenchymal Cells for Bone Reconstruction: A preliminary study in a Mouse Model.

NMRC/0748/2003

PI: Sim, Eugene Kwang Wei

Intramyocardial engraftment of skeletal myoblast for cardiac repair: Optimization of transplantation conditions.

NMRC/0751/2003

PI: Lim, Beng Hai

The influence of bone marrow derived mesenchymal stromal cells on rate of tendon healing in rabbits.

NMRC/0754/2003

PI: Wong, Peter T.H.

Molecular mechanisms of the CCK2 receptor in the regulation of fear and anxiety: Generation and analysis of an inducible CCK2 gene deletion in mouse

NMRC/0765/2003

PI: Sim, Meng Kwoon

Angiotensins and cardiac infarction

NMRC/0766/2003

PI: Wang, Nai-dy

Assessment of C/EBPa Gene Knock-in Mouse Embryonic Stem Cells for the Ability to Differentiate into Hepatocytes *in vivo* and Assessment of these Stem Cell-derived Hepatocytes for Resistance to Tumourigenesis.

NMRC/0770/2003

PI: Lim, Lum Peng

Prospective study of Periodontal disease risk markers and treatment outcome of a Periodontal programme for adult diabetics in Singapore.

NMRC/0771/2003

PI: Joseph, Tessy

Processing pathway of nociceptin and nocistatin from prepronociceptin

NMRC/0772/2003

PI: Yip, Wai Cheong George

Characterisation of the biological roles of different heparin sulphate species in breast cancer development and metastasis

NMRC/0773/2003

PI: Loke, Kah Yin

Characterization of CYP 11B1 Mutations in 11-Beta hydroxylase deficiency

NMRC/0779/2003

PI: Wang, Shih-chang

Features of Tumour Aggression in Ductal Carcinoma In Situ of the Breast: Correlation between *in vivo* Magnetic Resonance Imaging, *in vitro* Magnetic Resonance Spectroscopy, Histology and Gene Expression Analysis

NMRC/0780/2003

PI: Lee, Alan Yiu-wah

The significance of cell adhesion molecule L1 in Axon-glia interaction and its implication in Axonopathy

NMRC/0781/2003

PI: Wenk, Markus R

Lipidomics of neuronal membranes – Identification of lipids involved in neurosecretion and neurodegenerative diseases

NMRC/0782/2003

PI: Liou, Yih-Cherng

The Prolyl Isomerase Pin 1 function in the regulation of Tau phosphorylation and Alzheimer's disease

NMRC/0783/2003

PI: Hewitt, Robert

The role of RUNX3 as a tumour suppressor in human colorectal cancer

NMRC/0785/2003

PI: Liu, Eugene Hern Choon

The effects of nocistatin on the central nervous system and the distribution of nocistatin receptors in the brain and spinal cord, in the mouse

NMRC/0786/2003

PI: Yeong, Foong May

The role of chromosome condensation in maintenance of genomic stability

NMRC/0787/2003

PI: Bhatia, Madhav

Apoptosis of pancreatic acinar cells and acute pancreatitis

NMRC/0788/2003

PI: He, Beiping

Interaction between aggregate-bearing neurons and microglial toxicity in the pathogenesis of adult-onset neurodegenerative diseases

NMRC/0789/2003

PI: Lau, Quek Choon

Role of RUNX3 in breast cancer

NMRC/0792/2003

PI: Ng, Yee Kong

Exercise induced glial reactions in the brain, and their roles in relation to changes of cytokines

NMRC/0793/2003

PI: Yong, Eu Leong

Pre-clinical studies using hormone-responsive bioassays as surrogate biomarkers to measure selective estrogen receptor modulator (SERM) activity in serum following oral administration of flavonoid-enriched traditional Chinese herbal extracts

NMRC/0794/2003

PI: Lee, Eng Hin

The study of gene-enhanced bone marrow mesenchymal stem cells for articular cartilage repair in pig model

NMRC/0804/2003

PI: Sng, Jen Hwei

Prevalence of the founder BRCA1 mutation c.2845insA in Singapore Malay breast and ovarian patients unselected for family history

NMRC/0811/2003

PI: Lee, Yuan Kun

Modulation of the development and progression of cancer by Lactobacilli

NMRC/0812/2003

PI: Wong, Hee Kit

Gene expression in substained lumbar spinal nerve root compression neuropathy: An evaluation of novel gene detection techniques in an experimental animal model

NMRC/0817/2003

PI: Melendez, Alirio J.

Dissecting the roles of FcγRs-mediated signalling and antigen presentation in health and disease

NMRC/0818/2003

PI: Wang, De Yun

Clinical and immunologic effects of sublingual immunotherapy in patients with persistent allergic rhinitis: a double-blind, placebo controlled study

NMRC/SRG/002/2003

PI: Bishop, George D

Public Understanding and Responses to Severe Acute Respiratory Syndrome (SARS): A Cross-national Comparative Study

NMRC/SRG/005/2003

PI: Yong, Eu Leong

Screening and characterization of phyto-flavonoids and defined traditional chinese herbal extracts for anti-SARS coronavirus activity and their use as therapeutic agents

Singapore Eye Research Institute

NMRC/0796/2003

PI: Wong, Tien Yin

The Singapore Malay Eye Survey (SIMES)

NMRC/0808/2003

PI: Zhou, Lei

Proteomics of Ocular Antimicrobial Proteins

NMRC/CPG/002/2003

PI: Beuerman, Roger

Singhealth Medical Proteomics Facility

Singapore General Hospital

NMRC/0714/2003

PI: Lee, Lai Heng

Venous Thromboembolism in Singapore - A National Collaborative Study on Incidence, Etiology and Risk Factors of Symptomatic Cases

NMRC/0716/2003

PI: Cheah, Foong Koon

Correlation of coronary artery calcium burden (determined by multi-detector CT scan) with coronary artery angiography and coronary events in the Singapore population

NMRC/0718/2003

PI: Lau, Weber Kam On

Open versus Laparoscopic (da Vinci robotic system) Radical Prostatectomy: A Prospective Randomised Controlled Trial

NMRC/0728/2003

PI: Goh, Su-Yen

A study to compare the effects of progressive resistance training vs aerobic training on the metabolic profile with type 2 diabetes mellitus

NMRC/0755/2003

PI: Tan, Bee Yee

Morbidity following Diagnosis and Treatment of Patients with Colorectal Cancer- a Prospective Study comparing 2 Rehabilitation Programmes

NMRC/0759/2003

PI: Howe, Tet Sen

Automated Computer Detection of Fractures on Digital X-rays

NMRC/0760/2003

PI: Chan, Ling Ling

Diffusion Tensor Imaging in Parkinsonian Disorders

NMRC/0767/2003

PI: Cheng, Christopher Wai Sam

Differential expression of a novel Vascular Endothelial Growth Factor isoform, VEGF165b, in transitional cell carcinoma of the bladder

NMRC/0775/2003

PI: Sim, Shao-Jen Llewellyn

Breast MRI screening for women with a high hereditary risk of breast cancer

NMRC/0797/2003

PI: Lau, Weber Kam On

Photodynamic therapy of refractory bladder carcinoma using hypericin

NMRC/0798/2003

PI: Lee, Pyng

Mitomycin-C in the treatment of recurrent tracheobronchial stenosis

NMRC/0805/2003

PI: Wong, Wai Pong

Physiological, functional and psychological effects of country line dancing on older women: a randomised controlled study

NMRC/0806/2003

PI: Tay, Sun Kuie

Diagnostic Potential of Prosaposin and Fibulin-1 in Endometriosis

NMRC/0819/2003

PI: Lim, Leslie

Cognitive behaviour therapy of depressed post-myocardial infarction patients; effects on cardiovascular and haematological measurements

NMRC/0820/2003

PI: Lau, Pang Cheng David

Efficacy of percutaneous hyaluronic-acid (HA) injection to improve voice and swallowing in patients with unilateral vocal-fold paralysis (UVFP). A prospective randomized controlled blinded trial comparing HA of two different molecular weights.

NMRC/CPG/001/2003

PI: Aw, Swee Eng

Setting up a Core Affymetrix Microarray Facility for SGH

NMRC/SRG/003/2003

PI: Tan, Puay Hoon

Pathology of renal changes in SARS: insights into pathogenesis

Singapore Health Services

NMRC/0734/2003

PI: Teoh, Gerrard Kheng Hoe

Regulation of Proliferation and Survival of Multiple Myeloma Cells by Ku86/Ku86 Variant via Signals that Mediate Immunoglobulin Isotype Class Switch Recombination (formerly NMRC/0489/2000)

NMRC/0756/2003

PI: Ho, Su Chin

Generation of mouse model of Graves' disease by genetic immunization: A study to identify factors important for generation of thyroid autoimmunity by i) modifying the target antigen TSH receptor ii) modulating the cytokine profile and iii) evaluating the effect of dietary iodine

NMRC/0758/2003

PI: Hwang, Ying Khee William

Humanization of Murine Anti-Ku86v Monoclonal Antibody for Serotherapy in Multiple Myeloma

NMRC/0799/2003

PI: Teoh, Gerrard Kheng Hoe

Use of the superconducting quantum interference device (SQUID) magnetometer for the measurement of antibody affinity for antigens expressed on multiple myeloma cells

NMRC/0800/2003

PI: Ho, Su Chin

Generation of mouse models of Graves' ophthalmopathy and the evaluation of cytokine profiles participating in disease pathogenesis of Graves' ophthalmopathy

Tan Tock Seng Hospital

NMRC/0750/2003

PI: Sim, Richard

Surgical management of the short bowel syndrome by a novel technique of recirculating loop and adjustable valve: An experimental study in pigs

NMRC/SRG/006/2003

PI: Tan, Soo Yong

Detection of infectious agents in biopsy and cytological specimens of patients with SARS-like symptoms: use of immunohistochemistry and insitu hybridization

Annex 4: Publications arising from Block Grants and Competitive Grants

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

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Long-term Follow-up and Outcome of Extremely Low Birth Weight (ELBW) Infants.
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541 Yoder, Mervin C
542 Yoshikawa, Hisao
543 Yu, Chack Yung
544 Yu, Nai-Teng
545 Yu, Victor
546 Zalewski, Peter
547 Zeps, Nikolajs
548 Zhang, James X
549 Zhang, Wei
550 Zhao, Richard Yuqi
551 Zincke, Horst