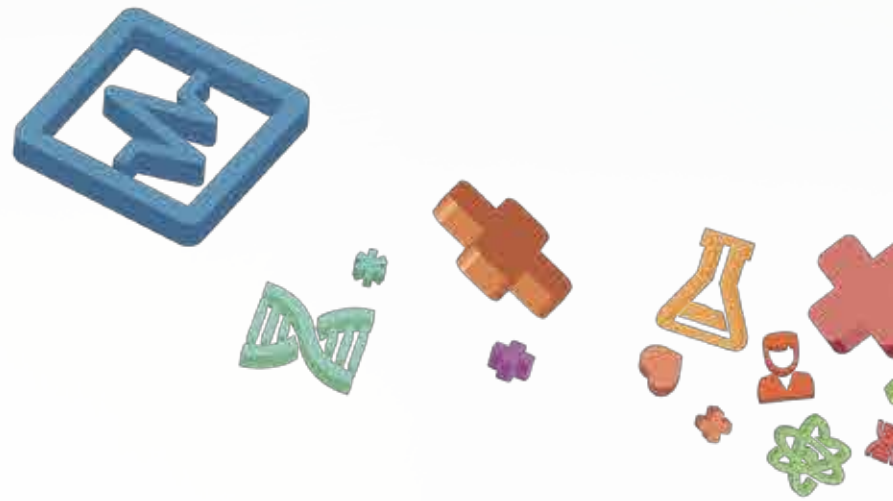


RESEARCH FOR A BETTER FUTURE



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Promoting Research Excellence

To promote excellence in translational and clinical research, nurture a vibrant research community of clinicians and scientists in Singapore, and enhance knowledge translation for health and economic outcomes.



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NMRC hopes to provide a conducive environment to attract new clinician scientists and retain existing ones to do research.

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Message from Chairman

Generating solutions for patients in the real world

Biomedical and healthcare research is not a luxury as opposed to common thinking. At National Medical Research Council (NMRC), our priority is to support Translational and Clinical Research (TCR) to result in significant improvements in healthcare. There has been a 15% increase in funding under the Research, Innovation and Enterprise 2015 (RIE2015) plan to improve the health of Singaporeans through enhancement of the existing healthcare system through preventive measures, early diagnosis and cost-effective treatments.

Investment in biomedical research started in 2000 in Singapore, when research funding in many countries were stagnant or declining. Today, Singapore is committed to biomedical and healthcare research due to the ageing population and shortage of healthcare providers and hence, need to build a more effective health system for better patient outcomes.

In the immediate future, NMRC's short-term goal is to discover medicine that can translate in the shortest time into the hands of patients for treatment. NMRC hopes to provide a conducive environment to attract new clinician scientists and retain existing ones to do research. NMRC forms a platform where clinician scientists can congregate to do research, apply for necessary funding, have access to facilities and tap on to connections with the pharmaceutical industries and hospitals. The National Health Innovation Centre was incubated to get in investments early, and to carry out practical research in products, medicine and diagnostic testing.

For the ecosystem to succeed, manpower is integral. Hence, NMRC places emphasis on talent development with the hope to train 160 clinician scientists at the end of

the funding period in 2015. Through forming multifunctional teams, the clinician scientists focus on speciality areas working on common protocols, research projects databases and talent plans.

At the end of the chain are hospitals and NMRC aims to come up with effective ways to treat a large number of people in the shortest time possible. Besides identifying the treatment methods, other aspects such as treatment procedures are other important areas looked at.

NMRC hopes to identify key research priorities for Singapore, to concentrate research and development resources on the greatest health and economic outputs. More specifically, NMRC is interested in studying cures to conditions and infectious diseases common in Singapore. For example, dengue, which is a disease prevalent in Southeast Asia, can lead to global collaborations. Testing grants have been awarded to researchers to develop treatments to prevent complications and ways to neutralize the dengue virus.

At NMRC, we recognize that achieving results in TCR requires a long-term commitment. Successes rarely come overnight, but instead require years of dedication and diligent work. Research takes some 15 to 30 years of hard work to arrive at a successful outcome. Hence it is imperative to create a greater awareness of the importance of research among the general public, to educate them on the long-term goals and benefits of researches.

In a nutshell, our role is to get things organized and focus on outcomes, to move research into the real world as quickly as possible for better health.

Prof. Ranga Krishnan

Chairman

Message from Executive Director

Providing a conducive environment for research growth

The National Medical Research Council (NMRC) has been promoting and supporting biomedical research in Singapore (BMS) since 1994.

In 2013, we continued to support the various BMS funding programmes under the Research, Innovation and Enterprise 2015 (RIE2015) funding tranche. The year saw nearly \$340 million in research grants and awards being given out. These included several new Translational and Clinical Research (TCR) Flagship Programmes in areas such as Parkinson's Disease and Lymphoma, as well as many other smaller grants covering a wide range of research areas and diseases of importance to Singapore. Developing and supporting BMS research talents continued to be a priority for NMRC, with 27 awardees receiving our Human Capital Awards and 17 awardees funded under our Talent Development Programmes.

However, the availability of funding and talent are only two of the enablers necessary to support good research. Another important component is having in place systems and processes that are conducive to the conduct of research. In 2013, NMRC supported the work of the Clinical Trials Working Group, which reviewed the bottlenecks and proposed solutions to improve the clinical trial environment in Singapore. The Working Group's recommendations received strong endorsement from the various BMS stakeholders and are now in the process of being rolled out. Together with the launch of the Clinical Trials Grant and the renewal of funding for the Singapore

Clinical Research Institute and the Investigational Medicines Units, NMRC hopes to facilitate the conduct of impactful clinical trials in Singapore through these initiatives.

The year also saw work begin on the planning for the next funding tranche beginning in 2016 (RIE2020). NMRC has developed its strategy for RIE2020, focusing on healthcare research. NMRC's vision for healthcare research is to deliver better health outcomes for Singaporeans. This is especially important as Singapore faces challenges such as an ageing population and a rising burden of chronic diseases. BMS research has the potential to generate academic, economic as well as health outcomes. While all of these outcomes are important in their own right, the priority for NMRC as part of the Ministry of Health (MOH), is on supporting research that will ultimately lead to healthcare benefits for Singaporeans. This will be a key consideration in the planning of NMRC's programmes for RIE2020.

It has been a fulfilling year for NMRC and a privilege for us to have had the opportunity to work with and serve the healthcare and BMS community. NMRC's work would not be possible without the strong support of the leadership and colleagues in MOH, the NMRC Board, the healthcare community and other government agencies and stakeholders. We are deeply appreciative of all the support we have received and look forward to continuing work with everyone in the year ahead.

A/Prof. Tan Say Beng

Executive Director

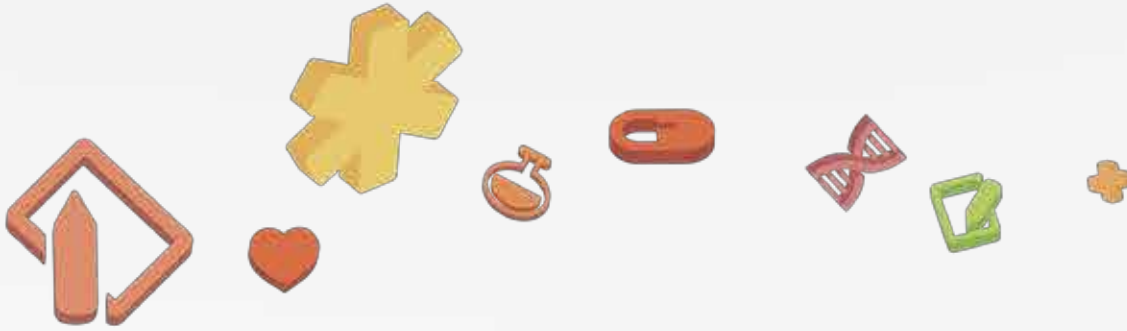


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NMRC's vision for healthcare research is to deliver better health outcomes for Singaporeans.

”





Established in 1994, the National Medical Research Council oversees the development and advancement of Translational and Clinical Research (TCR) in Singapore. It provides competitive research funds to publicly funded healthcare institutions, awards competitive research funds for programmes and projects, supports the development of core clinical research infrastructures, is responsible for the development of clinician scientists through awards and fellowships, and fosters interactions and knowledge exchange among researchers.

In 2006, the Ministry of Health established a new mandate to support TCR in areas where Singapore has great potential. With this in mind, NMRC's role is ever more important in leading, promoting, coordinating, and funding TCR in Singapore. NMRC-funded research has led to interdisciplinary partnerships and international collaborations, helping to boost the role played by Singapore's biomedical sector on the global stage.

Under the Research, Innovation and Enterprise (RIE2015) plan, Singapore has earmarked \$16.1 billion over a five-year period (2011–2015) to fund research and innovation in a variety of sectors, including biomedical and life sciences research. NMRC is one of the beneficiaries of this boost in funding, reinforcing the Council's mandate as the champion for TCR in Singapore.

Human capital plays a key role in the success of Singapore's TCR industry. Having a critical mass of clinician scientists is crucial for providing thought leadership and driving the translation of bench discoveries to bedside applications to improve human health. As such, NMRC actively supports clinician scientists with funding through research grants, human capital awards and talent development programmes. Under Singapore's Biomedical Sciences (BMS) Initiative Phase III (2011–2015), NMRC is stepping up its efforts to boost the number of clinician scientists in Singapore from around 80 in 2010 to 160 by 2015.

Since its inception, NMRC has supported over 300 clinicians with scholarships, fellowships and various talent development awards. The Council has also built up the TCR capabilities in Singapore through the funding of more than 1,900 competitive research projects and 13 TCR Flagship Programmes. To ensure that the budget is appropriately managed and optimally utilized, NMRC also evaluates the outcomes of the research projects it funds and facilitates the commercialization of research findings.

NMRC Board

The NMRC Board advises the Council on the formulation of strategies and priorities to promote excellence in TCR in Singapore with the objective of improving human health. By overseeing the implementation of the research programmes approved by the MOH and the Biomedical Sciences Executive Committee (BMS Exco), the Board ensures that the Council is being effectively managed to meet its mission and key performance targets. The Board also ensures that governance frameworks are in place such that NMRC's budget is appropriately managed and optimally utilized.

As of FY13, the NMRC Board consists of 16 members.

Board Members



Prof. Ranga Krishnan

Chairman
National Medical Research Council



A/Prof. Benjamin Ong

Director of Medical Services
Ministry of Health



Prof. Edward Holmes

Deputy Executive Chairman
Biomedical Research Council



Prof. Ivy Ng

Group Chief Executive Officer
SingHealth



A/Prof. Tan Say Beng

Executive Director
National Medical Research Council



Dr. Anand Tharmaratnam

*Senior Vice President and
Head of Clinical Development*
Quintiles Asia-Pacific



Prof. John Wong Eu Li

Chief Executive
National University Health System



A/Prof. Chong Siow Ann

Vice Chairman
Medical Board (Research),
Institute of Mental Health



Prof. Ian D. Graham

Professor
Epidemiology and Community
Medicine, University of Ottawa



Prof. Dermot P. Kelleher

Dean
Lee Kong Chian School of Medicine,
National Technological University



Dr. Benjamin Seet

Executive Director
Biomedical Research Council



Prof. Patrick Sissons

Regius Professor Emeritus of Physics
Department of Medicine,
University of Cambridge



Prof. Donald Tan

Director
Singapore National Eye Centre



Prof. Wong Tien Yin

Director
Singapore Eye Research Institute



A/Prof. Allen Yeoh Eng Juh

Senior Consultant
Department of Paediatrics,
National University of Singapore



A/Prof. Yeoh Khay Guan

Dean
Yong Loo Lin School of Medicine,
National University of Singapore

NMRC Portfolio

Under Singapore's Biomedical Sciences (BMS) Initiative Phase III (2011–2015), NMRC continues to drive TCR through sustained and strategic investment in three key areas: research grants, talent development programmes, and knowledge exchange and enablers.

Talent Development Programmes

In order to grow, nurture and anchor the pool of clinician scientists in Singapore, NMRC offers a range of human capital awards and talent development programmes aimed at supporting individuals in their research and career progression. These awards and programmes include:

Human Capital Awards

- + Singapore Translational Research (STaR) Investigator Award
- + Clinician Scientist Award (CSA)
- + Transition Award (TA)
- + Clinician Investigator Salary Support Programme (CISSP)

Talent Development Programmes

- + MOH Healthcare Research Scholarship (PhD)
- + MOH Research Scholarship (Master of Clinical Investigation)
- + NMRC Research Training Fellowship

Research Grants

NMRC directly supports research initiatives through a series of competitive grants. These grants are defined as either strategic/thematic or investigator-led, allowing NMRC to support specific areas of research as well as promising individual researchers. The grants include:

Strategic/Thematic

- + TCR Flagship Programme
- + Centre Grant

Investigator-led

- + Clinician Scientist Individual Research Grant (CS-IRG)
- + Clinician Scientist Individual Research Grant New Investigator Grant (CS-IRG-NIG)
- + Cooperative Basic Research Grant (CBRG)
- + Cooperative Basic Research Grant New Investigator Grant (CBRG-NIG)
- + Bedside & Bench Grant (B&B)
- + Health Services Research Competitive Research Grant (HSR-CRG)
- + Health Services Research New Investigator Grant (HSR-NIG)

Knowledge Exchange and Enablers

NMRC strives to grow and strengthen Singapore's TCR ecosystem by facilitating various events and platforms that foster interactions and knowledge exchange among researchers, supporting the development of core clinical research infrastructure and implementing new strategic research grant initiatives. These include:

- + Clinical Trial Grant (CTG)
- + Ministry of Health Industry Alignment Fund (MOH IAF)
- + Singapore Clinical Research Institute (SCRI)
- + Investigational Medicine Units (IMUs) at SingHealth Services (SHS) and National University Hospital System (NUHS)
- + Animal Research Facilities (ARF) at SingHealth Services (SHS) and National University Hospital System (NUHS)
- + Nationalized Animal Research Facility (NLARF)



NMRC Funding Framework

Talent Development Programmes

- Singapore Translational Research (STaR) Investigator Award
- Clinician Scientist Award (CSA)
- Transition Award (TA)
- Clinician Investigator Salary Support Programme (CISSP)
- MOH Healthcare Research Scholarship (PhD)
- MOH Healthcare Research Scholarship (Master of Clinical Investigation)
- NMRC Research Training Fellowship

Research Grants

Strategic/ Thematic

- Translational and Clinical Research (TCR) Flagship Programme
- Centre Grant (CG)

Investigator-led Research

- Clinician Scientist Individual Research Grant (CS-IRG)
- Clinician Scientist Individual Research Grant New Investigator Grant (CS-IRG-NIG)
- Cooperative Basic Research Grant (CBRG)
- Cooperative Basic Research Grant New Investigator Grant (CBRG-NIG)
- Bedside & Bench Grant (B&B)
- Health Services Research Competitive Research Grant (HSR CRG)
- Health Services Research New Investigator Grant (HSR-NIG)

Strategic Research Grant Initiatives and Infrastructure Grants

- Clinical Trial Grant (CTG)
- Ministry of Health Industry Alignment Fund (MOH IAF)
- Singapore Clinical Research Institute (SCRI)
- Investigational Medicine Units (IMUs)
- Animal Research Facilities (ARF)
- Nationalized Animal Research Facility (NLARF)



A key objective in BMS Initiative Phase III is to grow the pool of clinician scientists in Singapore. Clinician scientists play a critical role in TCR: their close interactions with patients enable them to identify gaps related to causes, diagnoses and treatment of diseases, while their experience and expertise as scientists allow them to frame these clinical insights as relevant research questions.

NMRC recognizes the need to train and develop clinician scientists who are able to plug these knowledge gaps and, over time, develop breakthrough research that will eventually result in positive outcomes for patients.

Through its Human Capital Awards and Talent Development Programmes, NMRC offers comprehensive support to clinician scientists at every stage of their career, ranging from fellowship and scholarship programmes to sponsor budding clinician scientists for local or overseas training to prestigious awards to support excellent TCR researchers. These awards and programmes include:

Human Capital Awards

- Singapore Translational Research (STaR) Investigator Award
- Clinician Scientist Award (CSA)
- Transition Award (TA)
- Clinician Investigator Salary Support Programme (CISSP)

Talent Development Programmes

- MOH Healthcare Research Scholarship (PhD)
- MOH Healthcare Research Scholarship (Master of Clinical Investigation)
- NMRC Research Training Fellowship



Human Capital Awards

Singapore Translational Research (STaR) Investigator Award

The prestigious STaR Investigator Award is the highest level of NMRC's Human Capital Awards. Designed to recruit and nurture world-class clinician scientists to undertake cutting-edge TCR in Singapore, the STaR Investigator Award includes five-year funding for the researcher's salary, an annual budget for research support and a one-time start-up grant.

Clinician Scientist Award (CSA)

The CSA is structured to develop local research talent and give clinician scientists valuable protected time to focus on their research. The Senior Investigator (SI) level of the CSA offers funding for up to five years, catering to senior doctors who are already actively involved in highly productive research. The Investigator (INV) level offers funding for three years and targets younger doctors with the potential to become independent investigators. The CSA provides funding for salary support, together with a competitive research grant.

Transition Award (TA)

The TA is designed to help budding clinician scientists who have just completed formal research training. This award provides research funding and salary support to help recipients build up their research capabilities by facilitating their transition to a stable, independent research position, which will in turn enhance their ability to successfully obtain independent research support later on. The TA is non-renewable, as awardees are encouraged to apply for national level independent research grants after they have completed this award.

Clinician Investigator Salary Support Programme (CISSP)

The CISSP supports clinical research by providing funding for the clinicians' research time in the form of salary support or full-time-equivalent (FTE). In recognition of the support from clinical departments for their clinicians' time and participation in clinical research, the awarded funding is channelled to the respective departments, which are given flexibility in using the funds to support clinical research.

Singapore Translational Research (STaR) Investigator Award Awardees



Professor Salvatore Albani
Director
SingHealth Translational Immunology and Inflammation Centre
Senior Clinician Scientist
KK Women's and Children's Hospital
Professor
Duke-NUS Graduate Medical School

A Precision Medicine Approach to Understand and Predict Responsiveness to Therapy in Human Arthritis

Predictive biomarkers of treatment responsiveness in human autoimmune arthritis are missing. Knowledge of the immunological and epigenetic mechanisms driving disease pathogenesis and determining resistance to therapy is insufficient. Prof. Albani and team have developed an approach (Immunomics), which is based on the identification of immune variables that cluster meaningfully.

By means of this, an immune function predictive or confirmatory of a given clinical status (i.e. responsiveness to therapy) can be defined. They have also applied Immunomics to a clinical trial, which tested responses to an anti-TNF in patients with active JIA who failed MTX. This has led to the identification of an immune signature or training set that predicts responsiveness to anti-TNF. This solves a need in a very large patient population.

Firstly, this solves a crucial unmet medical need in an underserved paediatric disease. Secondly, the knowledge gained can be subsequently applied to adult rheumatoid arthritis. Part of Prof. Albani's vision is to translate knowledge of molecular immune mechanisms into targeted therapies. This multidisciplinary approach to understanding the pathogenesis of human arthritis has the potential to generate new diagnostic and therapeutic tools for the benefit of patients in Singapore. In addition, increased efficiency and reduced costs will drive tangible outcomes for healthcare in Singapore and justify investments in biologic therapies.

T-Cell Receptor Mediated Immune Therapy in Chronic Hepatitis B and Hepatocellular carcinoma (HCC)

Immunotherapies are increasingly becoming a key component of mainstream clinical practice. The adoptive transfer of T-cells that are able to recognize tumour antigens have shown clinical efficacy in melanoma and leukaemia.

Patients with chronic HBV infection or with HBV-related HCC have a defective HBV-specific T-cell response. Prof. Bertoletti and team have developed methods to reconstitute the defective hepatitis B virus (HBV)-specific T-cell immunity using a library of T-cell receptors (TCRs) that allow the engineering of TCR-redirectioned T-cells with the capacity to recognize and kill HBV-expressing normal or transformed hepatocytes. The aim of the STaR award is to establish therapeutic platforms for personalized immune-based treatments of CHB infections, and of its neoplastic consequence, HCC.

They have also planned to develop new methods to produce TCR-expressing lymphocytes, and test the clinical feasibility of TCR-mediated therapy. Theoretical and practical knowledge derived from these aims should significantly move the field of adoptive immunotherapy forward and extend it to other areas of infectious diseases and oncology.



Professor Antonio Bertoletti
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Infection and Immunity Programme,
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A*STAR
Visiting Professor
Emerging Infectious Disease Programme,
Duke-NUS Medical School



Professor Michael Chee
Professor
**Centre for Cognitive Neuroscience
 Neuroscience and Behavioral
 Disorders Programme,
 Duke-NUS Graduate Medical School**

Sleep Deprivation, Information Processing Capacity and Decision Making: From Mechanisms to Intervention and Across Life

Adequate sleep is fundamental to human health and well-being but many East Asian children and working adults are sleeping less than their predecessors.

Prof. Chee's prior research has shown that sleep deprivation (SD) affects task-related brain activity corresponding to impaired selective attention, visual processing capacity, visual short-term memory, executive function and choice behaviour. In the renewal award, he will extend his work with the goal of improving human cognitive performance, well-being and health across different groups and lifespan.

In furthering this fundamental discovery, Prof. Chee will continue exploring the neurobehavioural mechanisms underlying degraded visual information processing during

SD. This will be guided by the overarching idea that the sleep-deprived brain can adaptively reallocate impoverished processing resources in the service of goal-directed behaviour. With sleep-deprived participants, Prof. Chee will explore the temporal constraints on visual processing, determine how information processing is affected by emotional stimuli, and investigate how processing capacity varies from moment to moment. This research will involve young adults and engage fMRI, EEG and behavioural tests in different combinations.

In his work that seeks to clarify the relationship between sleep duration and quality on cognition and health, Prof. Chee will study adolescents and older adults over weeks to years. Adolescents will be evaluated through a mixture of survey and controlled quasi-laboratory settings using a range of mobile technologies and behavioural measures. Older adults from an existing longitudinal ageing study will be evaluated using neuropsychological tests, structural brain imaging and measures of intrinsic connectivity.

With the aim of evaluating the benefits of promising interventions, Prof. Chee will evaluate the benefits of sleep extension in adolescents and slow-wave sleep enhancement in older adults.

To sum up, Prof. Chee and team will seek to gain clarity about the impact of short sleep across the lifespan and allow at-risk people to benefit from fundamental research that seeks to improve sleep and cognitive performance for all.

Research in Parkinson's Disease and Movement Disorders

Prof. Tan's research is supported by a national integrated neurological service helmed by clinicians and clinician scientists together with an extensive research network of local and international collaborators. Prof. Tan's group is involved in the identification of genes involved in movement disorders (such as Parkinson's Disease and essential tremor) with a focus on whole-genome and exome analysis and massive parallel sequencing. Building on these potential genetic discoveries, his group focuses on the interaction of the various molecular pathways using different in vitro and in vivo models (Mouse and Drosophila), with the aim at identifying early markers and to explore potential therapeutic interventions through the selection of viable targets.

One of the key research focus is on peroxidases, a group of antioxidants. The therapeutic studies will involve the generation of bigenic Drosophila models carrying a Parkinson's Disease kinase gene and various peroxiredoxin isoforms and evaluation of the motor, behavioural and immunohistological features in the Drosophila and subsequent proof-of-principle drug challenges. Separately, studies on specific miRNA targets linked to Parkinson's Disease genes will be investigated in the mouse models,



Professor Tan Eng King
*Senior Consultant Neurologist and
 Research Director*
**National Neuroscience Institute
 Professor and Deputy Director
 Neuroscience Programme,
 Duke-NUS Graduate Medical School
 Honorary Professor
 Lee Kong Chian School of Medicine**

with validation in human fibroblasts and other human samples. Prof. Tan's research intersects across the different domains in the national translational research programme in Movement Disorders and his efforts will further facilitate the development of different therapeutic strategies in Parkinson's Disease and related disorders.

Translational Studies of Stem Cells

Prof. Suda and team will base their work on the hypothesis that the bone marrow (BM) microenvironment, known as the stem cells niche, is essential to the maintenance of haematopoietic stem cells (HSC) quiescence in cell cycle and regulates the fate of HSCs. The studies aim for the regulation of stem cells by niche as niche therapy. The team will dissect the niche as a functional unit of stem cell regulation, and aim to expand stem cells using ex vivo artificial niches and improve the method of BM transplantation. First, the team will dissect the cellular and molecular character of the endosteal and perivascular niches, and clarify the direct negative feedback from progenitor cells to HSCs. This will elucidate the haematopoietic homeostasis of stem cells. Second, they hope to develop methods for maintaining and expanding stem cells ex vivo by reducing mitochondrial reactive oxygen species production. This process will involve the integration of various methodologies including metabolome analysis, bioimaging and bioinformatics. In particular, the team will establish state-of-the-art metabolomics technology in HSCs in NUS.

They will also clarify whether stem cell and niche-ageing relates to pathogenesis of malignancies. They will identify leukaemic and multiple myeloma stem cells and their niches in seeking to develop a novel treatment for these intractable diseases. They will further study abnormal cytokine networks in chronic myelogenous leukaemia and the vascular and osteoblastic niches in myeloma. Migration of cancer stem cells is another challenge with potentially



Professor Toshio Suda
Professor
Department of Medicine,
Cancer Science Institute of Singapore
National University Health System

high impact. They will extend their study on HSC migration to cancer metastasis by introducing the concept of epithelial cell suppression for stem cell expansion. Moreover, the team will investigate the onset and progression of myelofibrosis and other fibrotic disorders (liver cirrhosis and pulmonary fibrosis). These studies will elucidate the pathophysiology of diseases and would provide critical clues to develop novel treatment and preemptive measures for the diseases.



Professor Daniel G. Tenen
Director
Cancer Science Institute of Singapore
Distinguished Professor
Department of Medicine,
National University of Singapore

Targeting Stem Cell Genes in Haematopoietic Stem Cell (HSC) Expansion and Cancer

Prof. Tenen's research is based on targeting normal and cancer cells using stem cell marker/factor(s), focusing on 2 genes: CD34 and SALL4.

CD34 is a stem cell marker on normal HSC. Prof. Tenen and team tested several human CD34 antibodies (hCD34ab) and observed that one unique antibody has the ability to eliminate haematopoietic stem progenitor cells

(HSPCs) in vivo (patent applied). Pre-treatment with this antibody augments engraftment in a murine bone marrow transplantation (BMT) model. They will further characterize and develop a translational application of this hCD34ab as a novel non-toxic BMT conditioning using our unique human CD34 transgenic (hCD34tg) mouse model.

SALL4 is a stem cell factor shared by embryonic stem cells (ESC) and HSC. It is not expressed in adult tissues but reactivated in many solid tumours, such as HCC. They were able to use it as a novel oncofetal protein marker in identifying a subset of aggressive HCC patients (New England Journal of Medicine). Most importantly, they have also identified a therapeutic peptide that can effectively target the oncogenic functions of SALL4 (US patent PCT/SG2012/000347). Intriguingly, treatment of human

CD34+ HSC with the SALL4 peptide leads to expansion of these cells ex vivo and enhanced engraftment in vivo (US patent no: 61/707,756). Prof. Tenen and team are now furthering their work by screening for small molecule peptide mimetics targeting SALL4-expressing cancers and expanding HSC.

Overall, their targeting stem cell marker/factor approach will lead to highly selective cancer or HSC-specific and non-toxic clinical translation applications.

Regulation of Wnt Secretion

Over the past grant period, Prof. Virshup and team found that all human Wnts require palmitoleation by the ER-resident O-acyltransferase PORCN, and that this palmitoleation is required for all Wnts to be transported to the cell surface by the carrier protein, WLS. Prof. Virshup and team identified a key mechanism required for the release of Wnts from cells. In collaboration with Prof. Alex Matter and the Experimental Therapeutics Center, they developed and are patenting novel pharmacologically optimized nanomolar inhibitors of Wnt secretion that can be used in both discovery and potentially, in the treatment of Wnt-high disorders.

Major insights into the source of Wnts in the stem cell niche came from their study of intestinal epithelium and BM of mice homeostasis using mice with a floxed allele of PORCN. This current proposal builds on the collaborations and tools generated over the past grant period to translate new knowledge on Wnt secretion into therapeutic advances.



Professor David M. Virshup
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Programme in Cancer and Stem Cell Biology
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Professor and Senior Consultant
Ophthalmologist
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Group Director
SingHealth Office of Research
Vice-Dean
Office of Clinical Sciences,
Duke-NUS Graduate Medical School
Head
Department of Ophthalmology,
National University of Singapore

Singapore Diabetic Retinopathy Epidemiology, Biomarkers and Imaging (Dream) Programme

Diabetic retinopathy is a common complication of diabetes and a major public health problem in Singapore and globally. The overall objective of the Dream programme is to determine the epidemiology of diabetic retinopathy in Asians and the relationship of early diabetic retinopathy signs to the risk of future diabetes, using prospective data amongst the three major Asian ethnic groups (Chinese, Indians, Malays) in Singapore. Such information provides important public health data for Singapore and countries in Asia.

Prof. Wong and team will also discover novel biochemical and genetic biomarkers of diabetic retinopathy using state-of-the-art approaches with stored serum/DNA. Finally, they will develop a new retinal imaging software that combines the assessment of retinal vascular features with automated diabetic retinopathy detection built on a "cloud" platform to determine if retinal imaging may be used to predict response to new therapy in patients with diabetic retinopathy. The Dream programme is based on an international interdisciplinary team and targets a national research priority area in Singapore.

Clinician Scientist Award (CSA) Awardees

Influence of Midlife Diet and Lifestyle Factors on Telomere Attrition and Accumulation of Chromosomal DNA Damage in Biological Ageing

Biological ageing is the process of accumulative damage to molecular and cellular structure, disrupting metabolism over time and resulting in disease and death. This proposal will investigate how midlife factors in diet and lifestyle, as well as subsequent modifications, affect rate of biological ageing as measured by change in telomere length and accumulation of chromosomal DNA damage in circulating leucocytes.

A/Prof. Koh and team plan to conduct the project among a subcohort of 1,000 participants from the Singapore Chinese Health Study, an ongoing, population-based prospective cohort established between 1993 and 1998. Diet and lifestyle factors of interest will be studied individually, and for their interactive effects on biological ageing. Findings from this project may provide scientific evidence for direct diet and lifestyle interventions, and inform the development of nutraceutical or functional food for the preservation of health and prevention of disease among the elderly.



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Heart Failure Clinical Studies

Heart failure is the final common pathway of a myriad of heart diseases. As increasing number of patients survive their acute cardiac conditions (such as acute coronary syndrome or valve disease), many will progress to chronic heart failure, which is a debilitating and deadly condition. Survival rates for patients with heart failure are comparable to most cancers. Until two decades ago, heart failure was assumed to be synonymous with pump failure, where ejection fraction is reduced – also called heart failure with reduced ejection fraction (HFREF). However, numerous studies have now demonstrated that heart failure can exist with preserved EF (HFPEF) – and that this syndrome of HFPEF is just as common and deadly as HFREF.² Even more significantly, it remains unclear why some patients develop HFREF, where traditional anti-failure therapy is highly effective; while others develop HFPEF, where there is still no proven therapy. A/Prof. Lam and team plans to understand the Asian phenotype of heart failure (HF) through large observational studies, and focus on novel therapeutic areas in pilot clinical trials. A/Prof. Lam and team hopes findings from the project will advance the fundamental understanding of the epidemiology, pathophysiology and outcomes of HF in Asia, and address important treatment gaps.

A Randomized Controlled Trial Phase II Clinical Trial to Evaluate the Effects of Faropenem With or Without Clavulanic Acid on Clinical, Microbiological, Immunological, Imaging and Pharmacokinetic Outcome Measure in Patients with Pulmonary Tuberculosis

Tuberculosis (TB) remains to be one of the leading causes of mortality from an infectious disease worldwide with approximately 2 million deaths annually. There is an urgent need to identify new drugs, especially drugs with activity against persistent organisms that may enable shorter treatment regimens.

This clinical trial will test whether an established oral antibiotic, developed for the treatment of other bacterial infections and that has activity in the test tube against TB, has activity in patients with TB. As well as addressing this important clinical question, the trial will also examine a range of novel scientific outcome parameters that have the potential to improve the ways that potential new TB drugs are evaluated.



Professor Nicholas Paton (CSA-SI)
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Cancer and Stem Cell Biology Signature Research Programme,
Duke-NUS Graduate Medical School
National Cancer Centre Singapore
Department of Haematology,
Singapore General Hospital

Overcoming Resistance to Targeted Therapies in Blast Phase Chronic Myelogenous Leukaemia

Early stage chronic myelogenous leukaemia (CML) responds well to tyrosine kinase inhibitors (TKI) targeting the oncogenic BCR-ABL kinase, while TKI resistance causes late stage blast crisis (BC) CML to be uniformly fatal. The long-term goal of this project is to develop new drugs that prolong the survival of BC CML patients. BC is

characterized by elevated β -catenin signalling in granulocyte macrophage progenitors, which enables this population to self-renew and function as leukaemia stem cells (LSC), and act as a reservoir for resistance. A/Prof. Ong's group recently identified an MNK-eIF4E axis that activates the β -catenin-driven self-renewal programme in BC LSCs but not normal haematopoietic stem cells (HSC). Most importantly, his group determined that small molecule MNK kinase inhibitors can overcome TKI resistance and extinguish the self-renewal capacity of BC LSCs.

In collaboration with the Experimental Therapeutics Centre, his group has developed a series of highly potent compounds with dual-specificity against the MNK and BCR-ABL kinases. These compounds inhibit β -catenin signaling in BC LSCs, but not HSCs, and completely abrogate the self-renewal capacity of the former at nanomolar concentrations. In further studies, his group has determined that overexpression of the splicing factor, SRSF1, contributes to the activation of the MNK-eIF4E- β -catenin axis. Here, his group found that SRSF1 promotes the generation of the MNK2b isoform, and that SRSF1 is also required for eIF4E-dependent β -catenin activation. Finally, his group broadened their work to include common Wnt-regulated epithelial cancers, and discovered that the MNK kinases contribute to β -catenin activation in breast, gastric, and colon cancers. Accordingly, the specific aims in this proposal are to: (i) test the efficacy of dual-specific small molecule inhibitors of the BCRABL and MNK kinases against BC CML, (ii) determine the mechanisms by which SRSF1 activates the MNK-eIF4E axis in BC CML and (iii) identify epithelial cancers in which the MNK-eIF4E- β -catenin axis is operative, and determine their sensitivity to MNK kinase inhibitors.

Hormonal Regulation of Hepatic Lipophagy, β -Oxidation, and Gluconeogenesis

Non-alcoholic fatty liver disease (NAFLD) is a major pandemic throughout the world with rates of more than 30% of the adults in Western and Asian countries. It is commonly found in patients with obesity and diabetes. It represents a spectrum of disorders ranging from fatty liver to hepatitis and cirrhosis. Inappropriate glucose production also occurs in NAFLD. Currently, there is no treatment for NAFLD other than diet and exercise.

Recently, A/Prof. Yen and team found that thyroid hormone (TH), epinephrine, and caffeine stimulates hepatic autophagy. Moreover, this autophagy involves the ingestion of lipid from fat droplets by autophagosomes that subsequently fuses with lysosomes to form autolysosomes (lipophagy). Triglycerides within autolysosomes are hydrolysed into fatty acids that undergo β -oxidation by nearby mitochondria. Defects in autophagy have been associated with NAFLD in several genetic model systems. They have also found that TH stimulates gluconeogenesis through a novel transcriptional pathway involving the activation of SIRT1 followed by its deacetylation of FOXO1. The latter then binds the two main genes involved in gluconeogenesis – glucose-6-phosphatase (G6Pase) and phosphoenolpyruvate carboxykinase (PEPCK) – to the promoters, and activated their transcription. During the next five years, A/Prof. Yen's laboratory will study drug and hormone regulation of fatty acid oxidation as well as glucose production in normal and fatty liver. They will study



**Associate Professor
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Cardiovascular and Metabolic
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the molecular, cellular, and metabolic mechanisms that are employed by drugs and hormones to regulate autophagy, fatty acid oxidation, and gluconeogenesis. They believe that by understanding these processes, they may be able to identify novel drug targets for the treatment of NAFLD as well as to improve its detection and treatment.

Integrative Profiling to Refine Risk Assignment in Childhood Acute Lymphoblastic Leukaemia

Contemporary high throughput methodologies like global gene expression profiling and targeted next-generation sequencing are now sufficiently affordable for clinical use. A/Prof. Yeoh and team aim to use these new platforms to characterize genetic alterations that are clinically significant in children of Asian ancestry with acute lymphocytic leukaemia (ALL). They also aim to use these platforms to develop a highly personalized and practical treatment regimen for these children based on algorithms incorporating minimal residual disease (MRD), genetic features of the leukaemic cells, and host genetic variants in the context of the MA-SPORE 2010 protocol.

Early response to treatment as determined by MRD quantitative strategies – ability to detect submicroscopic leukaemia – is the most significant prognostic in ALL. However, current allele-specific MRD quantitation using real-time quantitative PCR has limited sensitivity of only 0.01%. In addition, clonal evolution where the PCR MRD marker is lost may occur, risking relapse.

The team will use sequence-based, instead of allele-specific MRD quantitation strategies centered on next-generation sequencing with at least another 10-fold improvement in sensitivity and specificity to risk-assign children (<18 years old) with newly diagnosed ALL in the multi-centre MA-SPORE ALL 2010. We will study and minimize clonal evolution of markers to determine if this improved methodology will improve treatment outcome.



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In addition to the current IgH/TCR/IgK receptor antigen rearrangements, they will develop new MRD markers. To this end, every patient will have at least one MRD marker of 10-fold increase in sensitivity without compromise in specificity (<0.001%) for risk assignment and hence, treatment intensity and outcome can be optimized for every patient.



**Associate Professor
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Towards Patient-Tailored Therapy for Glioblastoma: Application of a Reactive Oxygen Species-Based Quantitative Index to Guide Management

Glioblastoma is the most common malignant primary brain tumour and its prognosis remains dismal. A/Prof. Ang and team recently showed that patient-derived glioma-propagating cells (GPCs) contain transcriptomic information that dictates primary tumour behaviour. They then investigated redox-based mechanisms governing chemoresistance as it has been documented that elevated

O_2^- (superoxide) promotes tumour cell growth. Their work describes how variations in $O_2^-:H_2O_2$ (superoxide:hydrogen peroxide) ratio lead to a heterogeneous pattern of response to chemotherapy. Pharmacological and genetic manipulation of this ratio sensitized GPCs to drug-induced apoptosis. They further demonstrated that gene signatures related to changes in redox levels and hence, response to chemotherapy were associated with patient survival.

In this proposal, A/Prof. Ang and team asked if the ROS gene signature associated with chemoresistance can: (i) act as a biomarker for redox-driven, resistant patient tumours; and (ii) reveal genes required to perpetuate tumourigenicity. They will analyze differentially regulated genes using four criterias: Those most highly variable, different from normal brain tissue, show survival-relatedness and have a novel role in brain tumours. They anticipate that chemoresistance will manifest as a cooperativity network, since gene expression drives brain tumour disease progression and clinical outcome. They will then utilize a custom-designed lentiviral shRNA library to determine under-represented shRNA clones which perpetuate in vitro and in vivo serial tumour formation. These candidate genes will be studied using assays that measure GPC activity and function, and subsequently validate in orthotopic animal models. Additionally, the clinical relevance of these genes will be established using patient glioma databases.

This study will establish a method to stratify redox-driven, chemo-resistant patient tumours and provide evidence that the ROS resistance gene signature contributes to the molecular heterogeneity of gliomas, underscoring the limitation of relying solely on morphology-based, histological approaches to diagnose and treat patients. This will facilitate the development of patient-tailored therapy in subsequent projects.

Tailored Prediction of Risk and Outcome for Breast Cancer in South East Asia

A modified Gail model with additional information on breast cancer density and genetic risk variants will be built using data from the Singapore Breast Screening Project and Singapore Breast Cancer Cohort. The model will be evaluated in a hypothetical cohort of Singaporean women and the team will assess the calibration and discrimination of the models as well as estimate the number of cancers detected and number of screening mammograms. Stage I-III patients in Singapore-Malaysia Breast Cancer Cohort with information on tumour characteristics and follow-up will be used to validate Adjuvant! Online. Test for agreement and receiver operating characteristic analysis will be used to evaluate the performance. If overestimation is observed, a new model will be developed using the Size+Nodes+Prognostic Factors method to estimate 15-year Kaplan-Meier breast cancer death rate and effect of adjuvant therapy. Pathological complete response rates of tumours after neo-adjuvant therapy will be compared in a prospective study of women with and without reduced breast density.



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In a historical cohort of patients who have undergone adjuvant therapy, a five-year relative survival in relation to the change in breast density will be calculated, adjusting for hormonal and reproductive covariates. A/Prof. Hartman and team hope to develop a breast cancer risk assessment tool and evaluate its efficiency in a tailored screening programme, build a prognostic model to predict survival and effect of treatment to aid treatment decision making for early breast cancer patients and determine the association between therapy, breast density and mortality.



Dr. Ng Kar Hui (CSA-INV)
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Next Generation Sequencing and Mechanistic Understanding for the Diagnosis and Management of Primary Glomerular Disease in Singapore

Diseases involving the kidney filter (glomerular disease) is an important cause of renal failure in Singapore. Current

treatment is often non-directed using drugs which suppresses the immune system. Only a proportion of patients responded to these drugs. There is currently no method to predict which patient will respond. Lack of directed treatment is due to poor understanding of the disease process. Dr. Ng and team hypothesized that a proportion of these diseases occur due to gene defects. As of now, there are about 25-30 genes known to be involved in glomerular disease. There are probably many more undiscovered genes. They hypothesize that the gene pattern in Asian patients with glomerular disease are different from those in Caucasians. Next generation sequencing is a new technique that allows the team to screen all 20,000 genes in a person at the same time. This will allow them to discover novel genes which have never been known to cause glomerular disease, and to identify gene patterns in Asian patients.

In the preliminary study, they have identified a family with hereditary glomerular disease. Using exome sequencing, they have identified the gene angiotensin (AMOT) as a novel candidate gene. This project aims to study the role of angiotensin in glomerular disease, using cultured cells, rat and mouse models. In addition, they aim to perform exome sequencing in 30 Singapore paediatric patients with glomerular disease that are likely to be genetic in origin.

This study may allow the team to identify novel genes which may be important in glomerular disease, and these may be important targets for new drug developments.



Associate Professor Marcus Ong (CSA-INV)
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International Multi-Centre Controlled Interventional Trial to Increase Out-of-Hospital Cardiac Arrest Survival by Implementation of a Dispatcher-Assisted Cardio-Pulmonary Resuscitation Package (Pan-Asian Resuscitation Outcomes Study Phase 2)

Out-of-Hospital Cardiac Arrest (OHCA) is a global health concern. In Asia, survival rates are low, ranging between

2-7%. Research has shown that for every minute OHCA is left unattended, chances of survival will decrease by 10%. There is currently good research that indicates survival can be improved by early Cardiopulmonary Resuscitation (CPR) and defibrillation. However, with the exception of Japan, bystander CPR rates in Asia are low, and range from 1.7 to 20.6%.

In recent years, Dispatcher-Assisted Cardiopulmonary Resuscitation (DA-CPR) has emerged as a potentially cost-effective intervention to increase bystander CPR and thus, survival from OHCA. When a bystander calls the emergency medical response number to request for help, this creates an opportunity for early identification of OHCA and provision of bystander CPR.

The overall aim of the project is to increase the bystander CPR rate and thus the survival rate for OHCA in the Asia-Pacific with the implementation of DA-CPR by 5% compared to historical controls and Emergency Medical Services (EMS) systems without DA-CPR.

The secondary aim of the study is to assess the incremental cost-effectiveness of a comprehensive step-up, system-level DA-CPR package on survival to discharge for OHCA compared to a basic DA-CPR package.

A/Prof. Ong and team also aim to assess the impact of a comprehensive DA-CPR package on neurologically intact (Cerebral Performance Category 1 or 2) survival for OHCA in Singapore.



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Exploration of the Therapeutic Utility of Targeting Isoprenylcysteine Carboxymethyl Transferase (Icmt) in Human Cancers and Development of Predictive Biomarkers to Identify Icmt Inhibitor Responsive Cancers

Despite recent progress in the understanding of cancer cells signalling and in the development of targeted therapies, most aggressive solid tumours remain difficult to eradicate through chemotherapeutic intervention. Identification of novel molecular targets, development of target-specific therapies, and stratification of cancer patients

according to the molecular signatures of individual tumours, are critical components to conquer this heterogeneous and complex disease.

Among the known cancer driving oncoproteins, Ras family of GTPases are infamous examples. Ras activation alone leads to more than one-third of malignant transformations, much higher in some other solid tumours, such as pancreatic cancers. It has been extremely challenging to target these GTPases directly, mainly due to their intrinsic biochemical properties. Therefore, targeting the post-translational modification process of these proteins has emerged as important anticancer strategy. Isoprenylcysteine carboxyl methyltransferase (Icmt) is a unique enzyme catalyzing the last step of the prenylation modification of Ras GTPase; it is now recognized that this C-terminal carboxymethylation is indispensable for Ras functions. Evidence from both genetic and pharmacologic suppression of Icmt function strongly supports the potential of Icmt as a therapeutic target.

Dr. Wang and team have developed specific small molecule inhibitors of Icmt that selectively inhibit proliferation and induce cell death of many cancer cells, likely by targeting oncogenic processes to which these cells are addicted. In addition, these inhibitors have demonstrated significant antiproliferative efficacy in vivo with reasonable tolerability and pharmacokinetic properties. The focuses of Dr. Wang's research group are to identify molecular mechanisms through which Icmt inhibitor impact on cancer cells proliferation and survival, and the characteristics of cancer cells that are most responsive to Icmt inhibitor treatment.

Transition Award Awardees

Respiratory Dialysis; Simple Carbon Dioxide Removal for Patients with Respiratory Failure

Conventional treatment for respiratory failure involves the application of mechanical ventilation; however, mechanical ventilation also worsens the underlying lung condition. For example, in patients with acute respiratory distress syndrome, ventilation-induced lung injury triggers a cascade of events that can result in multi-organ failure and death.

The proposal aims to develop novel respiratory support technology for critically ill patients with respiratory failure. By adapting existing dialysis systems to remove carbon dioxide, Dr. Cove hopes to demonstrate that carbon dioxide dialysis is a viable adjunctive support system in patients with respiratory failure.



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The role of PAX4 genetic polymorphism in the pathogenesis of Type 2 Diabetes Mellitus (T2DM)

A single nucleotide polymorphism (SNP) in the PAX4 gene (rs2233580) has been found to have a strong association with T2DM, which is unique to East Asians. This SNP results in an amino acid substitution (R192H) that is predicted to cause a moderate loss of function of the PAX4 protein, a key factor in β -cell differentiation, maturation and survival. This 192H allele has an allele frequency of 12% in

East Asians, with an odds ratio of 1.7 per allele. The mechanism underlying this association is unknown.

This study aims to examine the effect of this R192H variant on β and α -cell function in human subjects. The hypothesis is that individuals with the 192H allele will have lower β -cell function and hyperglucagonemia compared with matched controls. Dr. Kao and team also hypothesize that T2DM patients with this variant will be leaner, exhibit earlier β -cell failure and therefore have a younger age of onset of DM, and a higher likelihood of being on insulin therapy. This study represents a unique opportunity to understand the role of PAX4 in human metabolism and the more prominent β -cell defect observed in East Asian T2DM patients. This variant may also represent a method for identifying patients who would benefit from disease-modifying therapies that target the β -cell and α -cell, such as incretin-based therapies, or novel therapies such as glucagon receptor antagonists (stratified medicine).

Delineating Oncogenic Pathways of Natural Killer/T-Cell Lymphoma and Identification of Prognostic and Clinical Importance

Extranodal nasal-type natural killer T-cell lymphoma (NKTCL) is an aggressive EBV-associated lymphoma which is prevalent in Asia. To date, the pathogenesis of this tumour remains unclear and there are no effective treatment modalities or reliable markers to predict outcome and treatment response.

In this study, A/Prof. Ng and team will delineate the role of the important oncogenic pathways, such as upregulation of EZH2 via MYC activation, JAK3 /STAT5 and NF-KB pathways, which the team and others have identified in a large cohort of NKTCL and correlate with clinical parameters to identify prognostically distinct subsets. In the intestinal tract, it may be difficult to distinguish NKTCL from other closely related T/NK cell lymphomas that are similarly prevalent in Asia. They will also compare the molecular

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signature of NKTCL involving the intestine with other primary intestinal T-cell lymphoma that are prevalent in Asia, such as enteropathy associated T-cell lymphoma, using gene expression profiling. They will identify genes that are differentially expressed and perform bioinformatics target prediction with subsequent functional validation to identify essential target genes and signaling pathways that are deregulated in each of these entities. In doing so, they hope to uncover a molecular signature that can be applied for the diagnostics of intestinal T/NK cell lymphomas in Asia.

Antifungal Resistance Diagnosis – Moving Forward with Molecular Techniques for Point of Care Therapeutics

Candidemia ranks as the fourth most common cause of nosocomial bloodstream infections and have a profound impact on patient outcomes. The crude mortality is in the excess of 60%; attributable mortality is estimated to be as high as 47%. As there is a significant mortality benefit to administering appropriate and adequate therapy in a timely manner within 24 to 48 hours, in vitro antifungal susceptibility testing plays an increasingly critical role in predicting therapeutic failures and to optimize treatment outcomes. However, susceptibility testing is not routinely performed, requiring 48 to 72 hours following identification, which often comes too late to influence an appropriate and timely decision for patient management and hence clinical outcomes.

Echinocandin has become the preferred front-line therapy against *Candida* species that demonstrate decreased susceptibility to azoles and such isolates are becoming increasingly common today, despite the fact that azole is still an option. The limited spectrum of resistance mutations identified for echinocandin and azoles resistance in *Candida* is ideally suited for the development of robust diagnostic assays. This proposal aims to successfully reduce the turnaround time in evaluating echinocandin and azole susceptibilities via the identification of azoles and echinocandin resistance from high throughput PCR, qRT-PCR and sequencing, directly from blood, thus making routine in vitro susceptibility testing timely and clinically feasible. The development of this technology can be



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spurred off for commercialization, which will be in high demand in the current era of tremendous advances in healthcare technology, such as the widespread use of invasive medical devices and broad-spectrum antimicrobials as well as the intensive employment of transplant and oncological medicine. Institution of adequate and appropriate antifungal therapy can then be hastened to improve patient outcomes.



Dr. Joanne Ngeow Yuen Yie
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Metagenomic and Methylation Profiling of Gastrointestinal Non-Hodgkin's Syndrome

Epidemiologically, the incidence of non-Hodgkin's lymphoma (NHL) shows tremendous geographical variation. There is increasing evidence for Dr. Joanne and team to view humans as ecosystems living in a symbiotic relationship with the microflora in human's body. Evidence

from these metagenomic studies show that disruption of the homeostasis between the microbiota and the host can have a more important role than host genetics in the development of diseases.

As antigenic stimulation is an important precursor to the development of NHL, Dr. Ngeow and team hypothesize that host-gene-microbiome interactions increase susceptibility to NHL via immune/inflammatory or other mechanisms resulting in epigenetic alterations and consequently initiate tumourigenesis. Using cases of gastrointestinal related NHL, they will explore the microbiome including the virome of the tumour using high-throughput sequencing. Their study is innovative on many fronts. For the first time, they are attempting to comprehensively catalogue the microbiome associated with gastrointestinal NHL. If successful, their study will provide novel insights into the complex epidemiology behind gastrointestinal NHL. Should distinct microbiomic/metabolomic signatures exist between normal and tumour tissue or between different histological subsets? These may be developed into potential biomarkers for disease detection and novel treatment options.

Comprehensive Pain Programme to Determine Mechanism of Transition of Acute to Chronic Postsurgical Pain-Functional Brain Imaging, Quantitative Sensory Testing, Psychological and Genetic Screening: Prospective Cohort Study

Chronic pain affects 9% of Singapore's population, resulting in major socioeconomic burden. Chronic postsurgical pain (CPSP) that persists for over 3 months could be related to nerve injury, making this a strategic model to study the transition of acute to chronic pain. CPSP occurs in up to 32% after hysterectomy. Over 600,000 hysterectomies were performed in the U.S. in the year of 2003, causing CPSP to be a significant problem. One possible mechanism is central sensitization or increased pain sensitivity due to nerve injury as the pathophysiologic pathway.

Dr. Sng and team will perform this prospective cohort study to determine whether increased central sensitization and negative psychological experience are involved in the transition of acute to chronic pain after hysterectomy. Women undergoing hysterectomy will undergo physical pain testing. Pain catastrophising (negative thoughts of pain) and state trait anxiety scoring will be assessed for the impact of negative cognitive-affective experience on CPSP. A phone survey will be performed at 4 months to determine



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the primary outcome of CPSP. Functional brain imaging using arterial spin labelling will be used to delineate cerebral blood flow using arterial spin labelling, functional connectivity and structural connectivity to evaluate insula-anterior cingulate cortex differences. The results of this study will help to elucidate potential mechanisms of CPSP development that will guide the team in future studies on potential novel therapeutic targets.

Integrated Molecular Analysis of Cancer (IMAC)

It is becoming increasingly clear that genetic heterogeneity in gynaecological cancer underpins the observed variations in patient outcomes. Hence, the ability to characterize the unique genetic features of each patient's tumour will be a critical step to identifying the optimal therapeutic strategy for the individual.

The aim of Dr. Tan's study is to evaluate the impact of molecular profiling information on potentially actionable mutations/activated molecular pathways in gynaecological cancers. The hypothesis here is that molecular profiling will improve the outcome of novel targeted-agent treatments in clinical trials by allowing Dr. Tan and team to select the patients with the right tumours for these treatments. Patients who consent to participate in this study will have their tumour specimens, blood, and pleural or ascitic fluid collected. Molecular profiling of tumour cells will be performed using Next-Generation Sequencing (NGS), or SNP-arrays, immunohistochemistry and/or other relevant techniques to identify mutations, copy number aberrations, gene expression and protein expression levels that may determine the suitability of each patient for targeted therapies. Clinical data to be collected include baseline patient and tumour characteristics, treatment regimen(s) administered, time on treatment(s), and survival. Progression free survival (PFS) and overall response rates (ORR) on matched targeted therapy based on molecular profiling compared with PFS on previous non-targeted therapy, and PFS and ORR on matched therapy versus non-matched therapy will be compared to assess the clinical impact of molecular profiling in these patients.



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Dr. Tan and team envisage that by characterizing the genetic mechanisms and molecular pathways driving oncogenesis and tumour progression in different primary/recurrent gynaecological cancers, the differences in tumour behaviour and optimization of therapy can be addressed earlier. Rather than a 'one size fits all' treatment approach, it thus fulfills the promise of personalized cancer medicine.

The Effectiveness of Strength and Balance Training in Patients with Diabetic Peripheral Neuropathy on Quality of Life and Functional Status: A Randomized Controlled Trial with Cost-Utility Analysis

Individuals with Diabetic Peripheral Neuropathy (DPN) comprise 16-24% of patients with diabetes mellitus in Singapore, and this is set to rise with the increasing prevalence of diabetes. DPN is associated with reduction in health-related quality of life (HRQoL), specifically in the domains of physical functioning and physical role. However, there is currently no intervention that targets individuals with DPN for improvements in HRQoL and functional status. The study by Dr. Kavita and team aims to test the effectiveness of a structured strength and balance training intervention in: (i) improving the physical health component summary (PCS) measure of health related quality of life, (ii) functional status, and (iii) assessing cost-utility of the intervention, in individuals with DPN.

Using a randomized controlled trial design, 2 months of home-based strength and balance training will be provided to subjects on the intervention arm. The training intervention will target muscle strength and a range of



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motion at ankle and foot, static and dynamic balance and endurance for functional mobility. If the proposed training proves beneficial, it can offer clinicians and patients a cost-effective tool in the management of DPN.



Dr. Zhou Zhidong
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Therapeutic Targets in Parkinson's Disease

Parkinson's Disease (PD) is the most common neurodegenerative condition seen at the National Neuroscience Institute. Mutations of LRRK2 represent the most common cause of both familial and sporadic forms of

PD. No bona fide substrates and therapeutic targets of LRRK2 have been identified. Dr. Zhou and team hopes to identify new therapeutic targets that can be potentially used for clinical studies in PD patients.

Dr. Zhou and team have identified two novel potential LRRK2 substrates (LRRK2-Int1 and NTX) that are linked to dopaminergic degeneration and hypothesized that mutant LRRK2 contributes to dopaminergic neuron degeneration via altered binding and phosphorylation of LRRK2-Int1 and its nuclear transporter X (NTX), leading to subsequent up-regulation of tyrosine hydroxylase (TH) and dopamine (DA) levels in dopaminergic neurons and dopamine neuronal degeneration.

In human cell line studies, the team will investigate the interactions of wild type (WT) and mutant LRRK2 with LRRK2-Int1 and NTX, using co-immunoprecipitation experiments. They will also investigate whether LRRK2 can phosphorylate LRRK2 substrates; whether LRRK2 can influence LRRK2-Int1 nucleus translocation and subsequent alteration of TH and DA levels in dopaminergic cells. Transgenic *Drosophila* over expressing human WT and mutant LRRK2 and LRRK2 substrates as well as transgenic mice with WT and mutant LRRK2 will be studied. These PD models will be exposed to LRRK2 inhibitors and potential therapeutic compounds to assess their ability to rescue mutant LRRK2 induced dopaminergic neuron degeneration.

Talent Development Programmes

MOH Healthcare Research Scholarship (PhD)

This scholarship provides support to Basic Specialist Trainees, Advanced Specialist Trainees and Residents who wish to enrol in a PhD programme locally or overseas. It is targeted at young clinicians who want to pursue a career in translational and clinical research. The scholarship provides funding for salary, tuition fees and a maintenance allowance (for overseas PhDs), as well as protected time for research during the clinical training period. A seed funding for post-doctoral research is also available.

MOH Healthcare Research Scholarship (MCI)

This scholarship aims to encourage clinicians to pursue advanced clinical research training through the Master of Clinical Investigation (MCI) programme at the Yong Loo Lin School of Medicine, National University of Singapore. The scholarship covers the tuition and research fees for the programme.

NMRC Research Training Fellowship

The NMRC Research Training Fellowship aims to provide doctors and health science professionals with the training necessary to become clinician scientists. Medical doctors registered with the Singapore Medical Council, dental surgeons registered with the Singapore Dental Board, health science professionals and biostatisticians are all eligible to apply. The fellowship covers both overseas research training and graduate research degree programmes at local or overseas institutions. Awardees of the fellowship receive funding for salary and tuition fees for local graduate degree programmes, or allowances and other benefits in line with the host institution's policies for overseas research attachments.



List of Awardees for 2013

NMRC Research Training Fellowship

Awarded in 2013

There were nine awardees under the NMRC Research Training Fellowship in 2013: two awardees are undergoing training leading to a PhD, two awardees are undergoing training leading to a Master's degree, and five awardees are doing an overseas research attachment.

Name	Institution and Type of Training	Area of Research and Project
Ms. Hu Jing	NCCS Master's Degree (Part-time overseas)	CANCER Adaptive radiotherapy planning for local-regionally advanced nasopharyngeal carcinoma – a dosimetric comparison amongst intensity-modulated radiation therapy, RapidArc™, helical tomotherapy and intensity-modulated proton therapy
Mr. Eric Pang Pei Ping	NCCS PhD Degree (Full-time overseas)	CANCER Evaluation of the use of a non-invasive 3D ultrasound clarity system in real-time tracking of the target volume in prostate RapidArc™ therapy
Ms. Connie Yip Siew Poh	NCCS PhD Degree (Full-time overseas)	CANCER Imaging Tumour Heterogeneity with a Multimodality Functional Approach in Primary Oesophageal Cancer
Dr. Lee Eng Sing	NHGP Master's Degree (Part-time overseas)	MENTAL HEALTH Multimorbidity in primary care and its association with depression, anxiety and quality of life (MDAQ)
Dr. Louis Chai Yi Ann	NUHS Fellowship (Full-time overseas)	INFLAMMATORY AND IMMUNE SYSTEM Diagnostics of Immunodeficiency Diseases in Adults
Dr. Kewin Siah Tien Ho	NUHS Fellowship (Full-time overseas)	ORAL AND GASTROINTESTINAL Using multimodal brain imaging to identify the brain substrate underlying language dependent IBS symptom reporting between Chinese and Caucasians, and between two Chinese populations, speaking Mandarin and English
Ms. Christine Teng Bee Choon	NUS Fellowship (Full-time overseas)	INFECTION Rapid identification and susceptibility testing of pathogens growing in blood culture bottles – a quality improvement theragnostic stewardship project
Dr. Candice Chan Yuen Yue	SGH PhD Degree (Full-time local)	RESPIRATORY INFECTION Addressing diagnostic dilemmas in immunocompromised patients with pneumonia
Mr. Tan Ek Khoon	SGH Fellowship (Full-time overseas)	INFLAMMATORY AND IMMUNE SYSTEM Hepatic oval cells and their roles in liver regeneration after ischemic reperfusion injury
Dr. Tay Kae Jack	SGH Fellowship (Full-time overseas)	RENAL AND UROGENITAL MRI-fusion biopsy with cell cycle proliferation signature assessment: A novel approach to active surveillance in prostate cancer

Completed in 2013

One awardee completed his training under the NMRC Research Training Fellowship in 2013.

Name	Institution and Type of Training	Area of Research and Project
Dr. Eric Chan Chun Yong	NUS Fellowship (Full-time overseas)	EAR Elucidation of the nature of oxidative damage to hepatocellular mitochondrial proteins by quinone imine metabolites of drugs

NRF-MOH Healthcare Research Scholarship (PhD)

Completed in 2013

Three awardees completed their training under the NRF-MOH Healthcare Research Scholarship (PhD) in 2013.

Name	Institution and Department	Area of Research and Project
Dr. Samintharaj Kumar	MOHH Plastic and Reconstructive Surgery	CARDIOVASCULAR Molecular analysis of coronal craniosynostosis in a murine model for Crouzon syndrome
Dr. Catherine Ong Wei Min	NUHS Medicine	INFLAMMATORY AND IMMUNE SYSTEM Neutrophils and the regulation of matrix metalloproteinases in tuberculosis
Dr. Johnny Ong Chin-Ann	SGH General Surgery	CANCER Identification of a Novel Therapeutic Strategy from molecular stratification of oesophageal adenocarcinoma

MOH Healthcare Research Scholarship (MCI)

Awarded in 2013

There were nine awardees under the NRF-MOH Healthcare Research Scholarship (MCI) for the NUS Master of Clinical Investigation in 2013.

Name	Institution and Department	Project
Dr. Liew Tau Ming	IMH Geriatric Psychiatry	PSYCHIATRY Grief Research In Dementia Family caregivers
Dr. Aziah Ahmad	NCCS Medical Oncology	CANCER Asian 90-day mortality predictors to select oncology patients in phase 1 clinical trials
Dr. Yeo Tee Joo	NUHS Otolaryngology – Head and Neck Surgery	CARDIOVASCULAR Pilot Randomized Controlled Trial of Ferric Carboxymaltose in Asians with Heart Failure (the PRACTICE-ASIA-HF study)
Dr. Lin Bingyuan Jeremy	NUHS Department of Paediatrics	MUSCOSKELETAL Evaluation of Skeletal Muscle Growth and Regeneration in Children with Spastic Cerebral Palsy
Dr. Liu Yu-Chi	SERI Tissue Engineering and Stem Cell Research Group	EYE Ultrathin corneal grafts for endothelial corneal transplantation prepared by a low-pulse energy, high-frequency femtosecond laser with endothelial approach
Dr. Siak Jyh Kuen Jay	SNEC Training and Education	INFLAMMATORY AND IMMUNE SYSTEM Immunosenescence in Immunocompetent Individuals with Ocular Cytomegalovirus Infection
Dr. Wong Chee Wai	SNEC Training and Education	OPHTHALMOLOGY The associations of scleral and choroidal thickness with myopic maculopathy
Dr. Aung Myint Oo	TTSH General Surgery	SURGERY Study on Microbiota of Chinese male patients who underwent Roux-en-Y gastric bypass surgery
Dr. Tu Tian Ming	TTSH/NNI Neurology	STROKE T-allele variant of rs2200733 on chromosome 4q25 as a Predictor of Paroxysmal Atrial Fibrillation in Acute Ischemic Stroke

Completed in 2013

Nine awardees completed their NUS Master of Clinical Investigation training under the NRF-MOH Healthcare Research Scholarship (MCI) in 2013.

Name	Institution and Department	Project
Dr. Hey Hwee Weng Dennis	NUHS Orthopaedic Surgery	MUSCULOSKELETAL Comparison of two techniques in obtaining lumbar spine flexion and extension x-rays
Dr. Nadira Binte Hamid	NHCS Cardiology	CARDIOVASCULAR Prospective Study on the Validation of the New Adenosine Independent Index of Stenosis Severity from Coronary Wave-Intensity Analysis in the Asian Population
Dr. Colin Ngeow	St Luke's Hospital Medical Services	INFLAMMATORY AND IMMUNE SYSTEM Will an isolation and decolonization bundle reduce Methicillin-resistant Staphylococcus aureus (MRSA) transmission rates in Intermediate-Long Term Care?
Dr. Go Yun Yun	NHCS Cardiology	CARDIOVASCULAR What are the mechanisms of increased mortality following acute myocardial infarction in patients with diabetes mellitus?
Dr. Goh Jia Jun	NNI Neurosurgery	CARDIOVASCULAR A Randomized Controlled Trial to Study the Effectiveness of Red Blood Cells (RBC) Transfusion on Brain Tissue Oxygenation in patients with Traumatic Brain Injury and Anaemia
Dr. Goh Ting Hui Angeline	NUHS Medicine	RENAL Validation of glomerular filtration rate estimation equations in kidney transplant recipients
Dr. Dharmaraj Rajesh Babu	NUHS Surgery	SURGERY Quantitative flow assessment of lower extremity endovascular interventions by iFlow
Dr. Tay Bee Gek, Laura	TTSH Geriatric Medicine	GERIATRIC Serial changes in blood-based Biomarkers and Frailty State Transitions among community-dwelling older adults with early Alzheimer's Disease in a multi-modal rehabilitation programme
Dr. Wu Mei Wen, Fiona	NUHS Urology	CANCER The use of intravesical <i>Lactobacillus rhamnosus</i> GG as a safe and efficacious alternative treatment for bladder transitional cell carcinoma

Clinician Scientists in the Spotlight

CUTTING TIME TO SAVE LIVES

With the common use of antibiotics, microorganisms become drug resistant, resulting in the need to develop new antibiotics to treat them. Making matters worse, in the United States, insurance companies rule out reimbursements for such scenarios, which escalates medical costs.

Dr. Andrea Kwa, a specialist pharmacist in Infectious Diseases at SGH, came into the picture to look into this problem. She subsequently received the Transition Award (TA) funded under NMRC for her research in antifungal resistance diagnosis that consisted of molecular technologies for point-of-care therapies.

With the TA grant, she carried out antifungal resistance research. She helped patients who developed difficult-to-treat nosocomial infections due to fungi. She shared, "Many a times, patients who go through multiple surgeries due to cancer or transplants, or patients who have abdominal operations may get serious fungal infections. The same goes for patients with burn injuries and diabetes." Using molecular methods, she was able to diagnose the susceptibilities of candida within 24 hours, which guided the appropriate and adequate use of antifungals, resulting in

improved efficacy of treatment programs where doctors often have to race against time to save lives. Line this against the older method to test fungi infections which required 4 to 5 days and you see a stark difference. "Some patients develop infections due to low immunity and die from such infections, instead of the initial primary medical problem which patients come to the hospital for, drawing the example of patients who go for bone marrow transplants," she added.

Currently a specialist pharmacist at SGH, Dr. Kwa takes care of patients who have very difficult-to-treat infections, e.g. invasive fungal diseases and multi-drug resistant bacteria infections. Besides her daily clinical work which involves thorough clinical review of drugs prescribed to critically-ill patients and making sure that patients are appropriately and adequately dosed, she is also actively involved in research studies. While she has lamented that the lack of adequate laboratory space can be a problem in Singapore for young researchers, she is grateful for the support of SGH & Duke-NUS in paving the way that led to her successful clinched NMRC TA grant that provides for more facility resources.

She pointed out that difficult-to-treat and resistant fungal infections are on the rise, and there is a huge amount of research interest currently in fungal infections. Pharmaceutical industries are disinterested in resistant bacteria infections research, as they believe that we are fighting a losing war in resistant infections. As a result, there is no more new antibiotics in any pharmaceutical companies' pipeline. Hence, grants and research are imperative in such areas, in order to support the study and in the long run, translate to treatment. Dr. Kwa's team is also involved in recycling of antibiotics where the team hopes to work out the ideal old antibiotics in combination, to combat very resistant infections which otherwise single old antibiotics are useless against.



Associate Professor Andrea Kwa

*Pharmacy Clinician Scientist and
Specialist Pharmacist
Department of Pharmacy,
Singapore General Hospital*

*Associate Professor
Emerging Infectious Diseases
Duke-NUS Graduate Medical School*

RESEARCH THAT GOES A LONG WAY

The research that Dr. Mikael Hartman conducts may not bring in direct monetary value but it is an integral aspect to determine the reason why women are developing breast cancer, and how to effectively treat them.

For his epidemiology work in tailored predictions of risk and outcome for breast cancer in South East Asia, he was awarded the CSA – Investigator by NMRC. The award recognizes individuals with outstanding contributions to clinical and translational research work relating to their fields of speciality, especially if the research resulted in the understanding of diseases with potential positive outcomes on healthcare delivery.

He said that his research largely involved “finding out how common things are, and what are the determinants of how common things can be”. A practising breast cancer surgeon in NUH, he wears the hat of an epidemiologist in research.

His research is two-pronged: researching on models of patients who are going to develop breast cancer and those who will suffer badly from this disease. He said: “For epidemiology studies, there is no drug at the end of the research. Funding is important to spur research simply for the good of the people.”

On the positive health outcomes of his research, he elaborated that with the findings of risk models, doctors can more accurately predict patients who will develop breast cancer and hence, allow early diagnosis and treatment for these patients. In addition, his research hopes to allow doctors to identify the degree of treatment the patient needs for a cost-effective treatment with minimal side effects. He illustrated: “For breast cancer patients who have a spread of cancer to the lymph nodes, only 15 out of 100 patients will benefit from chemotherapy.”

Already, researchers are taking data from NUH to compare against the Breast Cancer Association Consortium, a research body run by Cambridge and have identified more than 60 genetic markers that are associated with breast cancer. Blood samples from cancer patients and non-cancer patients are also compared to check DNA differences.

A challenge faced in research include the gathering of data from various hospitals to get sufficient evidence for cohort studies, for a substantial research. “We need to sit down and have coffee with colleagues from different hospitals as we require a lot of data,” he said.

Dr. Mikael Hartman is from Sweden and he has been practicing in Singapore since 2009. He currently heads a research group of more than ten members including four PhD students and leads the Singapore Breast Cancer Cohort and the Singapore-Malaysia Breast Cancer Working Group.

Associate Professor Mikael Hartman

*Senior Consultant
Breast and Trauma Surgery,
National University Hospital*

*Associate Professor
Saw Swee Hock School of Public Health,
National University of Singapore*





Associate Professor Allen Yeoh
*Senior Consultant and Associate Professor
 Division of Haematology-Oncology,
 Department of Paediatrics,
 Khoo Teck Puat-National University
 Children's Medical Institute,
 National University Hospital
 Yong Loo Lin School of Medicine,
 National University of Singapore
 National University Cancer Institute Singapore,
 National University Health System*

LESS IS MORE

Sometimes less can be better. That was what A/Prof. Allen Yeoh looked into—to discover possibilities of paring down side-effects of existing treatments for children suffering from leukaemia so as to boost their survival rates.

His research on integrative profiling to refine risk assignment in childhood acute lymphoblastic leukaemia earned him the CSA-Senior Investigator from NMRC. Calling it “precision medicine”, he said treatment could be adjusted accordingly in patients depending on the prevalence of cancer cells. “We are able to reduce treatment in 85% of our patients. And among the developed countries, we are using the least treatment,” he shared.

His findings were based on a study involving some 556 children in NUH, KK Women’s and Children’s Hospital in Singapore, University of Malaya Medical Centre and Sime Darby Medical Centre in Subang Jaya.

His team also found out that among the leukaemia patients who received treatment, 20% would develop a relapse while 80% had a full recovery. His studies involved looking into methods to identify this 20% cohort, and using the necessary treatment to help them fight the cancer. He looks at bone marrow tissues of children below 18 years of age, with a large majority of the cohort falling under the 2 to 6 years age group.

Other significant studies included duplicating adult treatment methods used on children, such as those done on teenagers. A/Prof. Yeoh said: “We had some patients in their early 20s. Now, doctors in Tan Tock Seng Hospital and NUH are collaborating on ways we could transfer similar treatment styles from the adult patients.”

A/Prof. Yeoh was awarded the CSA award in 2000 and this year, the renewal of his CSA award funded research which was an extension of the project proposed during his first CSA award. The longer time frame worked in favour, including time to build collaborations with the hospitals in Malaysia which took seven years, for his team of researchers as it allowed them to plan the studies to achieve their aims.

A/Prof. Yeoh is passionate about his research and said the prognosis and efficacy of treatment of childhood cancer is better especially since children have a faster recovery rate compared to the adult patients. Even though he juggles a busy schedule with his routine clinical duties, research work and various academic and teaching duties, A/Prof. Yeoh hopes to continue to improve the care for children with leukaemia and to mentor junior doctors for the betterment of more patients.

TACKLING A COMMON DISEASE

Though the prevalence of Hepatitis B has decreased over the years due to the mandatory requirement for all children to take the Hepatitis B vaccine, there are 2 to 3% of the population that are on life-long medication due to the disease.

The backbone of Prof. Bertoletti's research experience is the development of a novel, targeted therapeutic platform to induce tolerance in immune-mediated diseases. Prof. Bertoletti hopes to eradicate this problem by studying gene responses and was awarded the STaR-Investigator Award, the highest accolade of NMRC's Human Capital Awards.

"We hope to find out why there are differential responses where in Hepatitis B-positive patients, some subjects manifest symptoms while others do not," he pointed out. He also explained that the human system has cells that recognize infected cells and immediately defends the body by killing them. In layman terms, his team's role is to reconstitute the immune response in order to counteract against the disease.

His research, known as "T-Cell Receptor Mediated Immune Therapy in Chronic Hepatitis B and Hepatocellular carcinoma", investigating strategies to treat chronic Hepatitis B virus (HBV) infection. In particular, he studied the function of T-cells in the liver environment and found the

molecular mechanisms responsible for T-cell exhaustion. His team also looked at ways to restore HBV specific immunity in chronic HBV patients, and to increase the chances of cytokinase or drugs into infected hepatocytes.

He said the STaR Investigator Award allowed him "peace of mind" with the funding of his salary and project for 5 years and a one-time start-up grant. "Research work can be constrained by grants which fund 2 to 3 years. The NMRC grant gives me adequate time and support required to conduct the research," he offered. He added that the STaR Investigator Award is part of a broader plan to develop a Translational Immunology and Inflammation Centre, with SingHealth, KKH and Duke-NUS as the principal stakeholders. Essentially, the aim of the award is to forge collaborations, as well as create and maximize synergies.

Reiterating that Hepatitis B can lead to liver cancer, he underscored the interest in other parts of Asia such as China and Indonesia. Hence, his research will not only benefit local patients but also the relevant industries too.

He is thankful of the support for research in Singapore. As part of the criteria for the STaR Investigator Award, Prof. Bertoletti has to spend a significant amount of time in Singapore, where he has made many friends in the medical and scientific community.

Professor Antonio Bertoletti

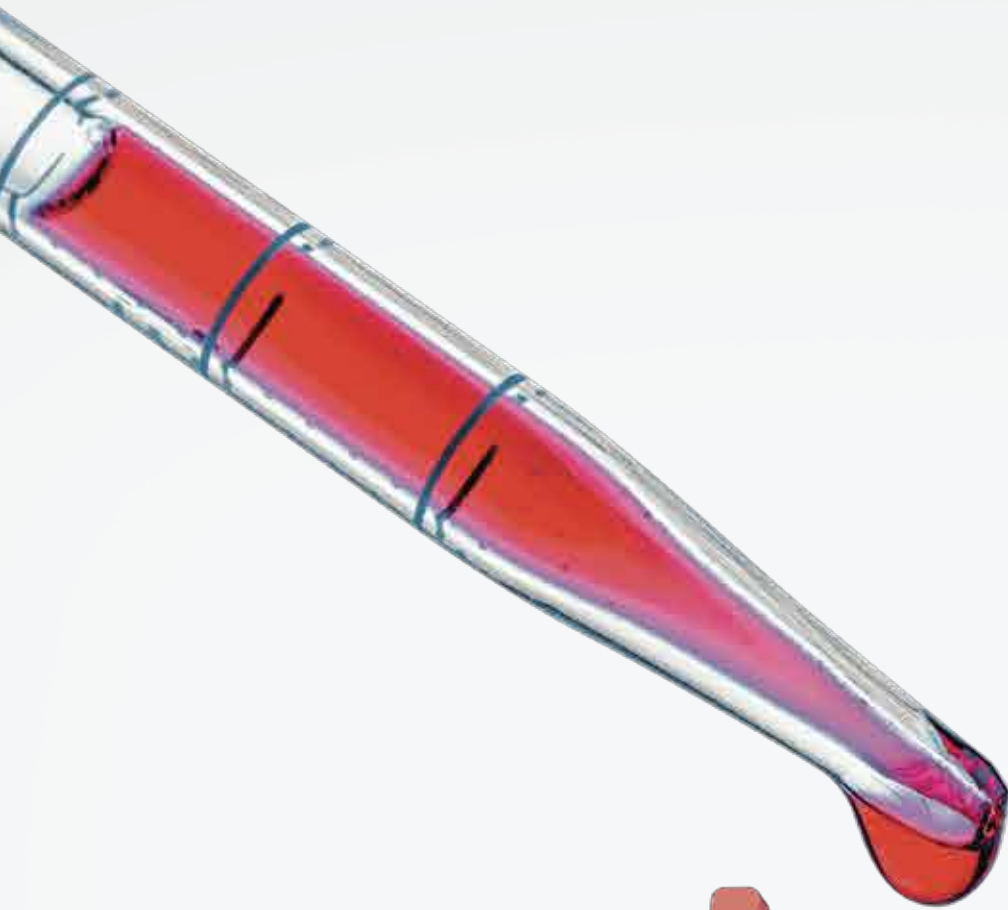
Director

*Infection and Immunity Programme
Singapore Institute for Clinical Sciences, A*STAR*

Visiting Professor

*Emerging Infectious Disease Programme,
Duke-NUS Graduate Medical School*





Research Grants

*Funding Translational and
Clinical Research and
Health Services Research*

The funding of translational and clinical research (TCR) is one of the core pillars of NMRC's mandate. To carry out this function, NMRC offers several grant programmes that support small-scale and large-scale Singapore-based research initiatives covering a broad spectrum of biomedical sciences.

NMRC's grant programmes are divided into two main categories:

- 1 Strategic/programmatic research
- 2 Investigator-led research

The first category consists of TCR Flagship Programmes and Centre Grants. TCR Flagship Programmes provide significant levels of funding to large-scale strategic studies that span across the spectrum of basic TCR. Centre Grants are awarded via a performance-based competitive mechanism to provide core research funding to clinical institutions with the aim to strengthen the overall research competitiveness of the institutions.

The second category supports different types of investigator-led studies via the following grant schemes:

- + **Clinician Scientist Individual Research Grant (CS-IRG)**
- + **Clinician Scientist Individual Research Grant New Investigator Grant (CS-IRG-NIG)**
- + **Cooperative Basic Research Grant (CBRG)**
- + **Cooperative Basic Research Grant New Investigator Grant (CBRG-NIG)**
- + **Bedside & Bench Grant (B&B)**
- + **Health Services Research Competitive Research Grant (HSR-CRG)**
- + **Health Services Research New Investigator Grant (HSR-NIG)**
- + **Individual Research Grant (IRG)***
- + **Exploratory/Developmental Grant (EDG)***

*While there are still ongoing projects that were funded via the IRG, EDG and NIG schemes, the final grant call for these schemes were held in May 2011. The newer grant schemes were launched in November 2011.

To ensure that its limited funds are put to the best possible use by funding the best science, NMRC awards all of its research grants on a competitive, peer-reviewed basis.



Strategic/Thematic Research

Translational and Clinical Research (TCR) Flagship Programme

The TCR Flagship Programme is a strategic initiative that was launched by NMRC in 2007 to fund TCR in key disease areas that are clinically relevant to Singapore. The programme's aims are:

- ✦ To bring together the best complementary research strengths in hospitals, national disease centres, universities and A*STAR research institutes to focus on diseases or research themes of strategic importance.
- ✦ To build up a critical mass of experienced high-level researchers to facilitate a broader research platform, and increase collaboration both locally and internationally.
- ✦ To establish Singapore as a global leader in the study of key strategic medical research fields by integrating, coordinating and leveraging the full spectrum of research capabilities in Singapore from basic science to clinical research in a comprehensive manner.

Under the S&T2010 funding, five TCR Flagship Programmes in the areas of gastric cancer, neuroscience (schizophrenia), eye diseases, infectious diseases (dengue) and metabolic diseases, were each awarded \$25 million to carry out research over a period of five years under the leadership of a well-qualified clinician scientist.

In view of the success of these programmes, further funding of \$175 million has been secured from the National Research Foundation's (NRF) Research, Innovation and Enterprise 2015 (RIE2015), Open Collaborative Funds (OCF) for this important initiative. The money will be distributed across three grant calls to provide opportunities for new programmes to be funded and existing programmes to be renewed on a competitive basis.

Under RIE2015, two tiers of TCR Flagship Programme funding are available:

Tier 1: Capped at \$9 million, inclusive of indirect costs, over a period of five years.

Tier 2: Capped at \$25 million, inclusive of indirect costs, over a period of five years.

Progress update

As of Q1 CY2014, a total of thirteen TCR Flagship Programmes have been awarded: five funded under the S&T2010 funding, and eight under the RIE2015 framework (four Tier 1 Programmes and four Tier 2 Programmes). Three of the Tier 2 awards were renewals of the pioneer TCR Flagship Programmes under the S&T2010 funding.

Overview of TCR Flagship Programmes awarded as of 31 March 2014

S/N	Lead PI and Institution	Area of Research	Title	Year of Award
01	A/Prof. Yeoh Khay Guan NUS	Oncology (Gastric Cancer)	The Singapore Gastric Cancer Consortium – Improving Outcomes for Our Patients	2007
02	A/Prof. Chong Siow Ann IMH	Neuroscience (Schizophrenia)	Vulnerability, Disease Progression, and Treatment in Schizophrenia and Related Psychosis	2008
03	Prof. Donald Tan SERI	Eye Diseases	Singapore Eye Research Institute TRIOS Programme (Translational Research Innovations in Ocular Surgery)	2008
04	A/Prof. Chong Yap Seng NUS	Metabolic Diseases	Developmental Pathways to Metabolic Diseases	2008
05	A/Prof. Leo Yee Sin TTSH	Infectious Diseases (Dengue)	Scientific Exploration, Translational Research, Operational Evaluation of Disease Prevention and Preventative Measures Through New Treatment Strategies Against Dengue (STOP Dengue)	2008
06	Prof. Mark Richards NUHS	Cardiovascular Diseases	Genetic Predisposition, Epigenetic Change, MicroRNA Profiling and Experimental Therapies in Heart Failure	2013 (Tier 1)
07	A/Prof. Tan Eng Huat NCCS	Oncology (Lung Cancer)	Non-Small Cell Lung Cancer: Targeting Cancer Stem Cell and Drug Resistance	2013 (Tier 1)
08	Prof. Donald Tan SERI	Eye Diseases	Eye Surgery and Innovative Technologies (EyeSITE)	2013 (Tier 2)
09	A/Prof. Yeoh Khay Guan NUHS	Oncology (Gastric Cancer)	Singapore Gastric Cancer Consortium – Redefining Gastric Cancer Management	2013 (Tier 2)
10	A/Prof. Lim Soon Thye NCCS	Oncology (Lymphoma)	National Lymphoma Translational Research Programme: From Genomics to Therapeutics	2014 (Tier 1)
11	Prof. Nicholas Paton NUHS	Infectious Diseases (Tuberculosis)	Singapore Programme of Research to Investigate New Approaches – to drug discovery and clinical translation – to deliver improved treatments for Tuberculosis (SPRINT)	2014 (Tier 1)
12	A/Prof. Chong Yap Seng NUHS	Metabolic Diseases	Developmental Pathways to Health and Diseases: Metabolic, Neurodevelopment and Related Outcomes	2014 (Tier 2)
13	Prof. Tan Eng King NNI	Neuroscience (Parkinson's Disease)	National Parkinson's Disease TCR Programme	2014 (Tier 2)

Key achievements of the five pioneer TCR Flagship Programmes under the S&T2010 funding

Human Capital		Intellectual Capital	
PhD students trained and graduated:	27	Invention disclosures:	30
Master's degree students trained and graduated:	19	Publications in peer-reviewed journals:	498
Postdoctorals employed:	76	Presentations at major conferences:	814
		Patents (primary & secondary) applications filed:	72
		Patents granted:	8
		Patents commercialized:	2
Industry Relevance			
Industry funding:	\$29.815 million (cash) \$7.346 million (in-kind)		
Spin-offs and start-ups emerging from research programmes:	12		
Clinical trials initiated:	22		

► **Neuroscience TCR Flagship Programme:
Vulnerability, Disease Progression, and Treatment
in Schizophrenia and Related Psychoses**

Launched in July 2008, this TCR Flagship Programme aims to identify key genetic, biological, cognitive, clinical and social risk factors for psychotic disorders, and to establish the efficacy and safety of a neurocognitive-enhancing agent for patients with schizophrenia. The programme comprises three projects:

- 1 A comprehensive genetic study of schizophrenia and its neurocognitive impairments.
- 2 The Longitudinal Youth-At-Risk Study (LYRIKS), a public health initiative that aims to identify the biomarkers of disease vulnerability, progression and therapeutic response for psychosis.

- 3 A double-blind randomized clinical trial to evaluate the efficacy and safety of a putative neurocognitive-enhancing agent for patients with schizophrenia.

Principal Investigator:
A/Prof. Chong Siow Ann
Institute of Mental Health



► **Infectious Diseases TCR Flagship Programme:
Scientific Exploration, Translational Research,
Operational Evaluation of Disease Prevention
and Preventative Measures Through New
Treatment Strategies Against Dengue
(STOP Dengue)**

Launched in December 2008, this TCR Flagship Programme has a simple objective: to stop dengue by studying the major gaps in treatment and management of dengue diseases. Specifically, the programme aims to:

- 1 Create a global centre of excellence for the clinical study and management of dengue diseases.
- 2 Improve dengue prevention through epidemiological studies and entomological control.
- 3 Elucidate pathogenesis of adult dengue diseases and identify those at risk of poor outcomes from dengue through better diagnostic and prognostic tools.
- 4 Improve clinical management of dengue illness through evaluation of current therapeutic strategies and development of new ways to treat dengue.

Principal Investigator:
A/Prof. Leo Yee Sin
Communicable Disease Centre,
Tan Tock Seng Hospital



► **Eye Diseases TCR Flagship Programme:
Eye Surgery and Innovative Technologies
(EyeSITE)**

Launched in August 2013, this Tier 2 TCR Flagship Programme is a continuation of the previous eye diseases TCR flagship programme, named Translational Research Innovations in Ocular Surgery (TRIOS), carried out from July 2008 to July 2013. It builds on the notable achievements of the previous programme with aims to develop novel clinical therapies and diagnostic applications to help alleviate ocular morbidity from major eye diseases, including corneal disease, infection, glaucoma, refractive errors and retinal disorders. The specific objectives are:

- 1 To develop new classes of antimicrobial small peptide and peptoid molecules that will help treat various types of corneal infection.
- 2 To develop sustained drug delivery carriers to provide prolonged drug release without relying on patient compliance.

Principal Investigator:
Prof. Donald Tan
Singapore National Eye Centre



- 3 To develop a novel artificial cornea to treat severe corneal blindness via a bionic cornea programme.
- 4 To develop a new treatment for keratectasia, keratoconus and presbyopia utilizing femtosecond laser refractive technology.
- 5 To develop new diagnostic and prognostic approaches to primary angle closure glaucoma (PACG).

► **Gastric Cancer TCR Flagship Programme:
Singapore Gastric Cancer Consortium (SGCC)
– Redefining Gastric Cancer Management**

Launched in February 2013, this Tier 2 TCR Flagship Programme is a continuation of the previous gastric cancer TCR Flagship Programme carried out by SGCC from August 2007 to January 2012. It builds on the notable achievements of the previous programme with aims to improve the management of gastric cancer and patient outcomes for those suffering from the disease through research spanning three key themes:

- 1 **Early detection** – This theme will focus on developing a cost-effective gastric cancer screening strategy for Singapore patients by identifying suitable blood-based diagnostic biomarkers from candidate biomarkers identified in a previously assembled pre-disease high-risk cohort (Gastric Cancer Epidemiology Programme).
- 2 **Therapeutics** – This theme will focus on new and ongoing clinical trials aimed at establishing the clinical usefulness of the genomic classifications of gastric cancer previously discovered by the team to be able to predict patient's survival and drug responses in cell lines and patients, and testing the efficacy of new treatment options. The ultimate aim is to improve treatment.

Principal Investigator:

A/Prof. Yeoh Khay Guan

Yong Loo Lin School of Medicine,
National University of Singapore



- 3 **Gastric carcinogenesis** – This theme will focus on understanding the molecular biology of gastric cancer. The team aims to identify new therapeutic targets and early detection biomarkers through the use of animal models that faithfully recapitulate various aspects of gastric cancer development, including transitions from normal gastric tissue to precancerous states and eventual cancer.

► **Cardiovascular Diseases TCR Flagship Programme:
Genetic Predislection, Epigenetic Change,
MicroRNA Profiling and Experimental
Therapies in Heart Failure**

Launched in March 2013, this Tier 1 TCR Flagship Programme aims to improve the understanding of inherited factors for risk of heart failure, with a view to improving prediction of heart disease and identifying new treatments. This will be achieved through genetic studies and the identification of specific gene products.

The research under this programme will focus on four key areas:

- 1 Differences in genetic background.

- 2 Different activation and de-activation of genes (epigenetics).
- 3 The role of intermediate gene products (microRNAs).
- 4 The potential of gene targets.

Principal Investigator:

Prof. Mark Richards

Cardiovascular Research Institute,
National University Health System



► **Lung Cancer TCR Flagship Programme:
Non-Small Cell Lung Cancer: Targeting Cancer
Stem Cell and Drug Resistance**

Launched in March 2013, this Tier 1 TCR Flagship Programme, which focuses primarily on individuals with lung cancer who have never smoked (termed "never-smokers"), has the following four objectives:

- 1 To conduct a comprehensive analysis of the cancer genome of never-smokers with lung cancer in order to gain a complete or near-complete view of the genomic mutations.
- 2 To look for novel genomic mutations other than those already known that can potentially be treated by new targeted agents. These new targeted agents can be used in combination with standard treatment in order to enhance the efficacy of standard therapies, thereby prolonging quality survival.
- 3 To determine the spectrum of acquired genomic alterations that can contribute to the onset of resistance to targeted agents and to design rational clinical studies combining newer targeted agents with standard therapies to address these mechanisms of resistance in patients.
- 4 To understand more deeply the behaviour of cancer stem cells that are believed to be the source of cancer cell proliferation and to develop strategies to target this subset of cancer cells that may lead to more durable remission of lung cancer and therefore improve survival outcomes.



Principal Investigator:

A/Prof. Tan Eng Huat

Department of Medical
Oncology (Research),
National Cancer Centre
Singapore

► **Metabolic Diseases TCR Flagship Programme: Developmental Pathways to Health and Disease: Metabolic, Neurodevelopment and Related Outcomes**

In January 2014, NMRC awarded Tier 2 funding for this TCR Flagship Programme focused on metabolic diseases and neurodevelopment. This new programme is a continuation of the previous metabolic diseases TCR Flagship Programme launched in June 2009. It aims to understand how pregnancy and early childhood conditions affect later growth and development, as well as metabolic, neurodevelopmental and other disorders, which have major public health and economic importance, not only in Asia, but globally. The research will span across 4 themes, conducting studies directly designed with the goals of developing public health, clinical and commercially-valuable, testable interventions to reduce the burden of childhood obesity, non-communicable diseases, and improve neurodevelopmental outcomes in children:

- 1 **Metabolic outcomes of early development influences** – The theme will focus on continuing the study of children in the Growing Up in Singapore Towards healthy Outcomes (GUSTO) cohort. The children will be between 4 and 9 years of age which is a critical phase in metabolic development.
- 2 **Maternal health and offspring neurodevelopment** – This theme will focus on identifying the relevant intermediate pathways by which specific risk factors influence early neurodevelopment, mental health and capacity, thus identifying critical targets for intervention, as well as defining naturally-occurring conditions that promote resilience within children.
- 3 **Pre-conceptual and early influences on maternal and offspring health** – This theme will focus on pre- and periconceptual influences through a second cohort, **GUSTO-Mum**, that will be set up based on the extant infrastructure of GUSTO.
- 4 **Therapeutic reversal of developmental programming in non-human primate (NHP) models** – This theme will focus on ‘proof of concept’ studies that inform potential clinical interventions.

This programme builds on the notable achievements of the previous metabolic diseases TCR Flagship Programme, which includes:

- Establishment of one of the deepest phenotype birth cohorts in the world (GUSTO) investigating how conditions of early life induced epigenetic changes that, in turn, associate with specific developmental outcomes. This cohort leveraged substantial nutritional industry co-funding and energized Singapore’s thrust in nutritional sciences.
- Establishment of an NHP platform for related studies.



Principal Investigator:
A/Prof. Chong Yap Seng
Yong Loo Lin School of Medicine,
National University of Singapore

► **Parkinson's Disease TCR Flagship Programme:
TCR Programme in Parkinson's Disease**



Principal Investigator:
Prof. Tan Eng King
Department of Neurology,
National Neuroscience Institute

In January 2014, NMRC awarded Tier 2 funding for this TCR Flagship Programme focused on Parkinson's Disease (PD). The overall aim of the programme is to reduce the economic burden of PD through identifying factors or markers that can facilitate early diagnosis, disease monitoring, drug screening and development of patient-centered individualized treatment regimes, and cellular replacement therapies. These will be achieved through five integrated themes:

- 1 **Clinical and Epidemiology** – The theme will focus on conducting prospective population cohort and developing body sensor devices and novel signal processing techniques.
- 2 **Genetics** – This theme will focus on conducting large scale population-based whole genome and exome sequencing and genomic studies.
- 3 **Disease Models/Pathophysiology** – This theme will focus on developing specific and novel disease in vivo models (Mouse, Drosophila), particularly those that are unique or simulate disease models in ethnic Chinese.
- 4 **Stem cells and Brain Transplant** – This theme will focus on developing human disease models using patient stem cells and augmenting effective cellular replacement/brain transplant therapies in animal models for potential clinical application.

- 5 **Experimental Therapeutics** – This theme will focus on conducting drug screening in both animal and human stem cell models, and evaluating new drugs in preclinical/clinical models through joint industrial collaborations.

This programme leverages on the clinical expertise of clinicians and clinician scientists, and the disease and domain specific skills of its local clinical and basic science researchers. At the same time, it also takes advantage of the contemporary technological platforms and infrastructure support available in Singapore, and the team's extensive international collaborative network. The intent is to forge a Bench to Bedside translational programme with the ultimate objective of reducing the economic burden of PD through better and more cost effective healthcare delivery. These outcomes will be measured by early diagnosis, better disease monitoring, reducing disease and drug complications, improved quality of life through better counseling and management, and the development of potentially new and more effective therapies. Development of an international acclaimed academic centre for PD will facilitate regional and international patient referral to both our public and private institutions, bringing further economic benefits to Singapore.

► **Lymphoma TCR Flagship Programme:
National Lymphoma Translational Research Programme: From Genomics to Therapeutics**

In January 2014, NMRC awarded Tier 1 funding for this TCR Flagship Programme focused on lymphoma. The aim of the programme is to provide fundamental understanding of disease mechanisms that can be translated into novel diagnostic and therapeutic strategies to improve survival in patients with lymphoma. The research will span across 3 themes to do the following:

- 1 Using the latest molecular technologies to help understand the molecular mechanisms driving these cancers, and how genetic and environmental factors, particularly, infections contribute to the risk of developing lymphomas.
- 2 Performing experiments to translate genetic findings into practical targets that can be used to improve diagnosis and treatment.
- 3 Translating research findings for daily clinical use through the development of a simple laboratory technique that can classify and prognosticate lymphomas better as well as through the conducting of clinical trials that test targets discovered.

This programme will meet the needs of both lymphoma clinicians in Singapore, Asia and in fact, worldwide. Not only will the successful pursuit of the TCR programme set up the first genomics programme in haematological

malignancies in Singapore, but will also expectedly bring about better care for Singaporeans by enabling access to novel drugs and treatments. It is also envisaged that this programme will serve to nurture future clinician researchers and scientists; foster a vibrant national consortium that will facilitate ongoing expansion of translational cancer research in Singapore; consolidate Singapore's cancer network and at the same time, allow its expansion throughout multiple nations in Asia; and set up Singapore as the leader in therapeutic trials in lymphoma research in Asia.

The team comprises national and international basic scientists and clinicians with expertise in molecular epidemiology, next generation sequencing, molecular pathology, bioinformatics and clinical trials. Importantly, the proposed studies leverage on their existing Singapore Lymphoma Study Group (comprising of clinicians, pathologists, epidemiologists and scientists from all institutes across Singapore such as NCCS, NUHS, Cancer Science Institute, SGH, Duke-NUS, Genome Institute of Singapore, and TTSH), Asian Lymphoma Study Group (comprising of centres from Hong Kong, Korea, Taiwan, China, Malaysia, Indonesia and Thailand) and international collaborators from United States (the National Institute of Health, University of Nebraska and Genomic Medicine Institute, Cleveland Clinic).

Principal Investigator:
A/Prof. Lim Soon Thye
Department of Medical Oncology,
National Cancer Centre Singapore



► **Tuberculosis TCR Flagship Programme:
Singapore Programme of Research to Investigate New Approaches – to drug discovery
and clinical translation – to deliver improved treatments for Tuberculosis (SPRINT)**

In January 2014, NMRC awarded Tier 1 funding for this TCR Flagship Programme focused on tuberculosis (TB). The overall aim of the programme is to investigate new approaches to overcome obstacles that stand in the way of delivering improved treatments for TB. The research will span across 3 themes to do the following:

- 1 Utilizing novel approaches based on chemical genetics to identify promising compounds that will then be developed with industry partnership, into new drugs for pre-clinical and clinical development.
- 2 Identifying existing drugs – licensed for other indications – that have activity against TB targets and take these forward into early clinical trials.
- 3 Assessing the potential of a new imaging method, PET/MRI used with different labels that can detect cellular metabolic activity, to assess anti-TB drug activity and seek to create a novel monoclonal antibody PET label that may have additional value for imaging TB lesions.
- 4 Establishing an Asian TB clinical trials network to strengthen research capacity in the region.

- 5 Conducting a proof of concept clinical trial to test a new immune-based adjunctive treatment for drug sensitive TB and a phase 2/3 clinical trial to test a 2 month treatment regimen for drug-sensitive TB that will optimize the use of new and old drugs in an innovative strategic approach.

The cutting-edge research within this programme has the potential to transform TB medical science, accelerating the development and evaluation of new TB drugs and improving the clinical management of TB in Asia and globally, with additional applications in many other disease areas.

Lead Principal Investigator Prof. Nicholas Paton is an infectious diseases clinical trialist with extensive experience of investigator-initiated trials from proof of concept through to large-scale randomized clinical trials. Theme Principal Investigator Prof. Thomas Dick worked in the pharmaceutical industry, heading TB research, drug discovery and development at Novartis for eight years, prior to joining NUS in 2011. Theme Principal Investigator Prof. Alex Matter, has 38 years of experience in the industry (oncology & ID areas) including head of Oncology at Novartis, Basel and was head of the anti-infective drug discovery programme at Novartis Institute for Tropical Diseases.



Principal Investigator:
Prof. Nicholas Paton
Yong Loo Lin School of Medicine,
National University of Singapore

Centre Grant Funding Framework

The aim of the revised Centre Grant (CG) funding framework is to provide core funding support to the public hospitals and national disease-specific centres to build up their core research capabilities in terms of common research platforms, shared equipment and core research manpower. One of the key aspects of the CG funding model is to also provide longer-term research funding to sustain core research activities in the eligible research institutions.

The revised CG funding framework adopts a competitive performance-based mechanism to award funding. It evolved from two previous NMRC research funding frameworks: the Institutional Block Grant/Enabling Block Grant (IBG/EG)¹ and the Centre Grant/Programmatic Project Grant (CG/PPG)², with integration of key successful components from the previous models.

NMRC launched the first grant call of the revised CG funding framework in August 2012 and received applications from 17 eligible centres/institutions. Each application underwent two levels of evaluation: first, looking at the institution's research performance over the past three years, and second, assessing the institution's proposed four-year strategy for building up its core research capabilities.

CGs with a funding quantum ranging from \$3 million (for developing centres) to \$26 million (established centres) were awarded to the 17 eligible centres/institutions for a four-year funding period from 1 April 2013 to 31 March 2017. All the CG awardees will be subjected to a mid-term review in FY2015 by the Centre Grant Evaluation Panel and the Centre Grant Scientific Advisory Board.

Investigator-led Research

Over the past three years, NMRC has funded a total of 529 investigator-led research projects via the Individual Research Grant (IRG) scheme (251 grants), Exploratory/Developmental Grant (EDG) scheme (141 grants) and New Investigator Grant (NIG) scheme (137 grants). The final grant call for these three schemes was held in May 2011.

To date, these projects have generated more than 3,000 high impact journal papers and contributed to the training and local employment of about 370 PhD-level scientists.

In addition, NMRC has also funded investigator-led research via the following five grant schemes launched in 2011:

Clinician Scientist-Individual Research Grants

Clinician Scientist-Individual Research Grant (CS-IRG) is provided to clinician scientists to enable them to carry out medical research on a specifically defined topic for a period of three years in a local public institution. The focus of the research should be translational and clinical in nature. The quantum supported for CS-IRG is up to \$1.5 million over a period of three years. CS-IRG grant calls are made twice per year, with closing dates on 1 June and 1 December.

Period	Proposals Reviewed	Grants Awarded	Total Sum Awarded (\$ in millions)
Nov 2012	69	14	17.8
May 2013	64	14	17.8
Total	133	28	35.6

Clinician Scientist-Individual Research Grant New Investigator Grant

The CS-IRG New Investigator Grant (CS-IRG-NIG) is a sub-category of the CS-IRG that is targeted specifically at new clinical investigators. The CS-IRG-NIG is intended to serve as a career stepping stone, providing new investigators with their first independent national-level grant. Applicants with substantial research experience are not eligible to apply for this grant. The quantum supported for CS-IRG-NIGs is up to \$200,000 over a period of two years.

Period	Proposals Reviewed	Grants Awarded	Total Sum Awarded (\$ in millions)
Nov 2012	23	9	1.99
May 2013	22	8	1.86
Total	45	17	3.85

Cooperative Basic Research Grant

Cooperative Basic Research Grant (CBRG) is provided to non-clinician researchers to carry out basic TCR that is relevant to human health, as well as research that looks at the causes, consequences, diagnosis and treatment of human diseases. CBRG also aims to promote basic biomedical sciences (BMS) research collaborations across institutions in Singapore. The quantum supported for CBRG is up to \$1.5 million over a period of three years. CBRG grant calls are made once a year, with the closing date on 1 December.

Period	Proposals Reviewed	Grants Awarded	Total Sum Awarded (\$ in millions)
Nov 2012	134	28	36.14

Cooperative Basic Research Grant New Investigator Grant

The Cooperative Basic Research Grant New Investigator Grant (CBRG-NIG) is a sub-category of the CBRG that is targeted specifically at new non-clinical investigators. The CBRG-NIG is intended to serve as a career stepping stone, providing new investigators with their first independent national-level grant. Applicants with substantial research experience are not eligible to apply for this grant. The quantum supported for CBRG-NIGs is up to \$200,000 over a period of two years.

Period	Proposals Reviewed	Grants Awarded	Total Sum Awarded (\$ in millions)
Nov 2012	31	9	2.16

Bedside & Bench Grants

Bedside & Bench (B&B) Grant aims to foster closer interactions between basic scientists and clinicians in order to translate scientific discoveries in the laboratory into clinically useful and commercially viable applications to improve health outcomes.

For B&B Grant, each Co-Principal Investigator must provide symmetrical intellectual input for the project. Partnerships with industry collaborators are strongly encouraged and additional consideration will be given to proposals that demonstrate industrial interest or engagement. The scheme supports up to \$5 million per project depending on the host institutions of the Co-Principal Investigators, with funding provided for up to three years. B&B grant calls are made once a year, with the closing date for submissions of Letters of Intent in mid-January.

Period	Letters of Intent Received	Full Proposals Reviewed	Grants Awarded	Total Sum Awarded (\$ in millions)
Sep 2012	44	12	5	12.34 ³

Health Services Research Competitive Research Grants

The Health Services Research Competitive Research Grant (HSR CRG) is a MOH research grant established in 2009. This Competitive Research Grant aims to promote the conduct of HSR and enable the translation of HSR findings into policy and practice. The quantum supported for HSR CRG is up to \$1 million over a period of two years. HSR CRG grant calls are made once a year, with the closing date on 1 June.

Period	Proposals Reviewed	Grants Awarded	Total Sum Awarded (\$ in millions)
May 2013	38	10	4.0

Health Services Research New Investigator Grant

The New Investigator Grant (HSR-NIG) subcategory of the HSR CRG was launched in Nov 2012 with the aim to support new HSR researchers. The quantum supported for this new subcategory is \$100,000 over 2 years. The HSR-NIG grant calls are made once a year, with the closing date on 1 December.

Period	Proposals Reviewed	Grants Awarded	Total Sum Awarded (\$ in millions)
Nov 2012	14	6	0.719

¹ The IBG/EG scheme was launched in 1994 and it provided annual block funding to national disease-specific centres and research units in public hospitals.

² The CG/PPG scheme was implemented in 2009 to replace the IBG/EG scheme. CGs/PPGs were awarded through a competitive scientific review process to support research programmes involving a team of investigators working towards a central research theme, as well as being awarded to administration units.

³ This includes \$3.73 million in funding from the Biomedical Research Council (BMRC) for B&B projects that involve BMRC scientists.

Knowledge Exchange and Enablers



Strengthening the TCR Landscape

The growing biomedical sciences (BMS) landscape in Singapore has to be constantly reviewed and strengthened to support the growing TCR carried out by our clinical research community.

In view of the researchers' need for support in strategic investigator-led research and collaborative research with industry, NMRC has launched two new competitive research grants initiatives.

Clinical Trial Grant

The Clinical Trial Grant (CTG), launched in late 2012, is intended to support clinicians carrying out clinical trial studies for the development of novel therapies, moving promising ideas from bench to bedside, to improve health outcomes. There are three schemes under the CTG programme:

- 1 The **Co-Development Scheme (Co-D)** supports clinical trial projects carried out via a public-private partnership (PPP) model in which a clinician collaborates with an industry partner. The clinician can apply for Co-D funding for 50 percent or less of the total project cost. An industry partner must provide co-investment (either cash or in-kind contributions) representing 50 percent or more of the total project cost. The quantum for Co-D funding is up to \$5 million over five years. The Co-D scheme is open throughout the year.
- 2 The **Investigator-Initiated Trials – Early Phase Scheme (IIT-E)** supports investigator-initiated Phase I and II clinical trials carried out by clinicians. The scheme is intended to support the development of locally produced assets, ideas and compounds. Partnership with industry for carrying out the trial is optional. The intellectual property must reside in Singapore. The quantum for IIT-E funding is up to \$5 million over five years. The IIT-E scheme grant calls are made twice a year, with closing dates on 1 June and 1 December.
- 3 The **Investigator-Initiated Trials – Late Phase Scheme (IIT-L)** supports investigator-initiated Phase III and IV clinical trials carried out by clinicians. Partnership with industry for carrying out the trial is optional. The quantum for IIT-L funding is up to \$2 million over five years. The IIT-L scheme grant calls are made twice a year, with closing dates on 1 June and 1 December.

Period	Proposals Reviewed	Grants Awarded	Total Sum Awarded (\$ in millions)
2013	14	3	4.54

Ministry of Health Industry Alignment Fund

The Ministry of Health Industry Alignment Fund (MOH IAF) aims to strengthen public-private collaboration in biomedical sciences (BMS) research and encourage commercially relevant research for better health outcomes. This programme was jointly developed with the Singapore Economic Development Board and comprises of 2 schemes:

- 1 The **Category 1 (Cat 1)** funding under the MOH IAF is launched in early 2013 to support both clinicians and non-clinicians in their partnerships with industry in pre-clinical and clinical research. Joint funding from industry is a prerequisite, with an industry partner covering at least 70 percent of the total project cost via cash or in-kind contributions. The quantum for MOH IAF Cat 1 funding is up to \$500,000 for pre-clinical projects and \$1 million for clinical projects. In the case of projects involving both pre-clinical and clinical research, the funding quantum is up to \$1.5 million. Cat 1 funding is provided for up to two years. The Cat 1 funding is open throughout the year.
- 2 The **Category 2 (Cat 2)** funding under the MOH IAF is launched in late 2013 to support both clinicians and non-clinicians in developing pre-clinical and clinical platforms or programmes that will pre-position Singapore as a desirable location for the industry to undertake TCR activities. Industry interest is a prerequisite. Cat 2 funding is up to \$3 million and is provided for up to three years. There is one pilot grant call in 2013 (future call is to be confirmed).

Period	Proposals Reviewed	Grants Awarded	Total Sum Awarded (\$ in millions)	Industry Dollars Attracted (\$ in millions)
2013	2	2	0.322	1.257
2014	7	7	1.255	2.713
Total	9	9	1.577	3.97



Events



National Medical Excellence Awards 2013

The National Medical Excellence Awards (NMEA) is held annually to honour and recognize clinicians, clinician scientists and healthcare professionals for their valuable contributions toward medical excellence in the areas of clinical care, clinical research, clinical quality, training and mentorship in Singapore. The awards also provide an opportunity to celebrate successes and hold up role models for the younger generation of clinicians and clinician researchers.

In 2013, the NMEA recognized six individuals and a four member team for their outstanding contributions to medical research, training and clinical practice. Awards were given out for the following six categories:

- ✦ **National Outstanding Clinician Award**
- ✦ **National Outstanding Clinician Scientist Award**
- ✦ **National Outstanding Clinician Mentor Award**
- ✦ **National Outstanding Clinician Educator Award**
- ✦ **National Outstanding Clinical Quality Activist Award**
- ✦ **National Clinical Excellence Team Award**

The recipients of this year's awards represented a wide range of disciplines, including cardiology, rheumatology, gastroenterology, oncology, emergency medicine and infectious diseases. Despite their diverse backgrounds, the award winners all share a common commitment to excellence, which is reflected in their selfless dedication to raising the standards of medicine even higher in Singapore.



NMEA 2013 Award Winners

National Outstanding Clinician Award 2013

Associate Professor Terence Chua is currently the Deputy Medical Director and Senior Consultant, Department of Cardiology at the National Heart Centre Singapore (NHCS). A/Prof. Chua's main clinical contribution has been in cardiac imaging, particularly nuclear cardiology, a specialized non-invasive test for assessment of heart function and blood flow, which helps in diagnosis, prognostication and decision-making in heart disease. He established Singapore's first cardiac-dedicated nuclear imaging laboratory in 1994, in collaboration with SGH's department of nuclear medicine. Under his stewardship, nuclear cardiology at NHCS has grown to be among the highest cardiac nuclear imaging volume centres in the world, with over 9,000 tests performed each year. He helped to organize many workshops in the region and successfully engaged and attracted young doctors to this less popular subspecialty. A/Prof. Chua also collaborated with his radiology colleagues to develop cardiac computed tomography services at NHCS.

A/Prof. Chua's passion in Academic Medicine sees his involvement in supporting the Singapore Cardiac Data Bank. He contributes actively to clinical trials, has many

**Associate Professor
Terrance Chua Siang Jin**
Department of Cardiology,
National Heart Centre
Singapore



publications in scientific and medical literature, and is also on the editorial board of various journals.

To many of his patients and colleagues, A/Prof. Chua is an epitome of humility and commitment. He is routinely seen checking on his patients on Sundays and public holidays. A believer in quality improvement, A/Prof. Chua's belief in quality improvement is evidenced by the many initiatives to improve the delivery of cardiac care. These included a fast-track priority appointment system for patients with symptoms suggestive of heart disease; and regular teaching sessions for primary care doctors to facilitate right siting of care. His selfless dedication and genuine care for the patients won him numerous service quality awards and the prestigious Healthcare Humanity Award in 2005.



**Professor
Fong Kok Yong**
Department of Rheumatology
& Immunology,
Singapore General Hospital

National Outstanding Clinician Award 2013

Professor Fong Kok Yong is Chairman, Medical Board (CMB), and Senior Consultant with the Department of Rheumatology & Immunology at the Singapore General Hospital (SGH); Group Director for Medical at SingHealth; Professor and Senior Associate Dean of the Duke-NUS Graduate Medical School and Adjunct Professor, Yong Loo Lin School of Medicine (YLLSOM) at the National University of Singapore (NUS).

Prof. Fong stands head and shoulders above his peers in playing a pivotal role in advocating and advancing better treatment and care for patients through new and effective methods of delivery, research and education. Prof. Fong introduced concept of a nurse clinician-and-educator when he joined SGH 10 years ago as an integral member of the

rheumatology care team. That was a novel idea but his intention was clear: to enhance patient care. Today, the nurse clinician is an important and accepted presence in many multidisciplinary clinics, augmenting the work of clinicians to deliver better care. More recently, Prof. Fong takes the vision of excellent patient care one step further with the establishment of the Autoimmunity and Rheumatology Centre in SGH in May this year that brings together quality patient care, education and research under one roof.

Under his leadership as the Acting Chairman of SGH research division, Prof. Fong doubled the number of trials that the SGH Clinical Trials and Resource Centre can support, within the span of three years. When he was SingHealth Group Director for Clinical Research, he successfully coordinated the application of a five-year, \$10 million research infrastructure grant to set up the SingHealth Investigational Medicine Unit on SGH Campus in 2010. Prof. Fong's visionary leadership also saw to the implementation of the Medicine Academic Clinical Program (ACP) aimed at furthering research and teaching.

National Outstanding Clinician Scientist Award 2013



**Associate Professor
Yeoh Khay Guan**
Department of Gastroenterology
& Hepatology,
Yong Loo Lin School of Medicine,
National University Health System

Associate Professor Yeoh Khay Guan is a pioneering clinician-scientist, an accomplished gastroenterologist and a dedicated educator and mentor. His research translates scientific discoveries into clinical applications, improving outcomes for patients.

A/Prof. Yeoh leads the Singapore Gastric Cancer Consortium (SGCC), which is carrying out research to improve the early detection and treatment of gastric cancer – the second leading cause of cancer death worldwide. The group brings together clinicians from various hospitals and scientists from the local universities and research institutes. The consortium was awarded the first national TCR Flagship Programme by the NMRC, and successfully renewed its grant award this year.

Under his leadership, the team has made ground breaking research findings in the early detection and genomic profiling of gastric cancer. The achievements of the consortium have made Singapore and A/Prof. Yeoh one of the thought leaders in gastric cancer internationally. Research by his team demonstrated that endoscopic screening is able to successfully detect early gastric cancer. In collaboration with other scientists in his team he has also pioneered new imaging methods and biomarkers for better detection of early gastric cancer. The group has successfully attracted international collaboration from overseas universities and academic centres, leading pharmaceutical companies and industry.

As Dean of the NUS Yong Loo Lin School of Medicine (YLLSOM), A/Prof. Yeoh oversees the curriculum and training of medical students to be the next generation of doctors. He has also nurtured and mentored many clinician educators and clinician scientists in NUHS. He serves on several national committees for medical research and training, and he is also a member of the NMRC Board as well as the MOH Specialists Accreditation Board and Specialist Training Committee for Gastroenterology.

National Outstanding Clinician Mentor Award 2013

Associate Professor Quah Thuan Chong is Head and Senior Consultant of the Division of Paediatric Haematology-Oncology, Khoo Teck Puat-National University Children's Medical Institute at the National University Hospital.

A/Prof. Quah has learned much from his beloved mentor, the late Professor Wong Hock Boon, to be an all-round paediatrician, and to have a life-long hunger for learning – not only in paediatrics or medicine, but also in all areas of life. He has tried to instill this love of learning in his students and young doctors, not only in Singapore but also beyond. He has maintained regular contact with a group of young paediatric oncologists from the Asean region and other parts of the world, sending them regular updates on important topics and answering their questions on patient care.

He pioneered the Clinical Fellowship Programme in Paediatric Oncology that has since benefited numerous clinical fellows from the region, such as Philippines, Brunei, Vietnam and Indonesia. Following the success of the Programme, he went on to spearhead the development of a structured two-year training programme to complement

**Associate Professor
Quah Thuan Chong**
Department of Paediatric
Haematology-Oncology,
National University Health System



the one-year clinical fellowship. This programme eventually became the second paediatric sub-specialty Diploma endorsed by the College in Paediatrics and Child Health, Academy of Medicine Singapore.

As the Head of the Division of Paediatric Haematology-Oncology at NUH, A/Prof. Quah has led both hospital and Singapore teams to initiate international collaborations, one of which is the MA-SPORE clinical trials, which resulted in significant improvement in the cure rates for children with acute lymphoblastic and myeloid leukaemia.

National Outstanding Clinician Educator Award 2013



**Associate Professor
Koo Wen Hsin**
Division of Medical
Oncology,
National Cancer
Centre Singapore

Associate Professor Koo Wen Hsin is the Deputy Director and Senior Consultant (Division of Medical Oncology) at the National Cancer Centre Singapore (NCCS), as well as the Associate Programme Director for Singhealth Internal Medicine residency and Singhealth Group Director for Education. A/Prof. Koo also holds academic positions in the Duke-NUS Graduate Medical School and the Yong Loo Lin School of Medicine (YLLSOM) at the National University of Singapore (NUS).

As the Singhealth Group Director for Education, A/Prof. Koo had set up the Academic Medicine Education Institute (AMEI), which will help transform Singapore into an international education hub for medical education. As the

chairman for the Medical Oncology Specialist Training Committee for several years, he successfully guided the various institutions in transiting to senior residency in medical oncology. His ability to strategize and his collaborative style also improved educational activities in the campus across all levels by helping set up and providing oncologic training to physicians at many hospitals.

Affectionately referred to as “Grand Master” by his peers and juniors in NCCS, A/Prof. Koo has been instrumental in grooming a succession of oncologists to further their specialist skills not just by taking on research projects and getting them published in high impact factor journals, but also in winning international awards. He has been nominated as the Outstanding Faculty for Learning for at least three consecutive years and twice by the graduating class to perform the hooding ceremony. He also plays an active role in the education of oncology nurses and lecturers for the Master of Nursing Course at NUS and the Palliative courses at Singapore Hospice Council. He is a believer of lifelong learning and embarked on several courses with his latest addition – an Executive MBA from the Singapore Management University (SMU).

National Outstanding Clinician Educator Award 2013

Associate Professor Shirley Ooi is a Senior Consultant and former Head of the Emergency Medicine Department (EMD) at the National University Hospital (NUH). She is an Associate Professor with the NUS Yong Loo Lin School of Medicine (YLLSOM), Designated Institutional Official (DIO) of the National University Health System (NUHS) Residency Program and also an Adjunct Professor at the University Kebangsaan Malaysia Department of Emergency Medicine.

Apart from being a respected Emergency Medicine (EM) physician, A/Prof. Ooi is a passionate educator. She had also won the National Medical Excellence Team Award in 2011 as a team member for her contributions in reducing median door-to-door balloon time for ST elevation myocardial infarction patients present at the EMD.

A prolific writer, A/Prof. Ooi has contributed chapters in overseas EM textbooks and written/co-edited three books to share her knowledge on EM, including the Guide to the Essentials in Emergency Medicine, which has sold more than 13,000 copies internationally. A/Prof. Ooi is active in research and has published more than 30 peer-reviewed journal articles. She is a long-serving member of the Singapore Medical Journal editorial board, and is active in several other editorial boards. Her work in research has also garnered her several international research awards. As the DIO of the NUHS Residency Program, A/Prof. Ooi is instrumental in the implementation of the various specialty



**Associate Professor
Shirley Ooi Beng Suat**
Department of Emergency
Medicine,
National University Health
System

programmes and the success of the ACGME-International accreditation of all its 14 programmes. Under her leadership, a further 10 programmes have been rolled out on 1 July 2013.

Balancing her role as a senior clinician educator-administrator, A/Prof. Ooi continues to be an active EM senior consultant, and clinical teacher. She ensures to continue contributing to ground level teaching, clocking over 200 hours of scheduled teaching (excluding bedside supervision) and is appointed core faculty in the NUHS EM Residency Program. Her students include local and international medical undergraduates, trainees/residents, nurses and non-trainee medical officers.

National Outstanding Clinical Quality Activist Award 2013



**Associate Professor
Quek Swee Chye**
Division of Paediatric
Cardiology,
National University
Hospital

Associate Professor Quek Swee Chye is the champion of quality improvement and patient safety at the National University Hospital (NUH). Over the years, he has spearheaded significant and innovative clinical improvement programmes that were later shared with other healthcare institutions, resulting in increased productivity and patient safety.

Under A/Prof. Quek's strong leadership, NUH became the first hospital in Singapore to receive the Joint Commission International (JCI) accreditation in 2004. This year, he once again led NUH to become the first hospital in Singapore and in the region to achieve the new Academic Medical Centre standards, the "Gold Seal" accreditation, newly introduced by the JCI. A/Prof. Quek also serves as a

Visiting Senior Consultant to the Standards and Quality Improvement Division at the Ministry of Health since April 2008, where he contributes to quality improvement and patient safety on a broader front.

He is credited with being instrumental in driving the use of clinical indicators and benchmarking in Singapore. Under A/Prof. Quek's initiative, NUH became the first hospital in Singapore to publish its clinical indicators on its website in 2006. This set the stage for the Singapore public to access healthcare indicators, which was useful not just for the public's benefit, but also essential in helping clinicians drive many areas of improvements of patient safety and clinical care within their own practice.

As a clinician, A/Prof. Quek is well known both locally and overseas as a respected paediatric cardiologist. He heads and oversees the paediatric cardiology programme at NUH. His work has been published extensively in peer-reviewed journals, and he has been invited to speak at many scientific international conferences. He is a reviewer for reputable international journals including Heart and the International Journal of Cardiology; and local journals such as Annals of Academy of Medicine, Singapore (AAMS). For several years now, A/Prof. Quek has been invited to serve as a reviewer of abstracts for BMJ's International Forum on Quality and Safety in Healthcare.

National Clinical Excellence Team Award 2013

Associate Professor Dale Fisher
Associate Professor Raymond Lin
Ms. Cathrine Teo
Ms. Lisa Ang
National University Hospital

Methicillin-resistant *Staphylococcus aureus* (MRSA) is endemic in Singapore and worldwide hospitals. Colonization with MRSA is a risk factor for subsequent clinical infection and the burden of MRSA is heavy.

A team headed by Associate Professor Dale Fisher was formed in 2006 to look for a complete solution to deal with MRSA infections in the National University Hospital (NUH). It has been instrumental in spearheading several initiatives and MRSA control measures, including active surveillance to identify ward-based acquisition, audits and novel hand hygiene publicity campaigns to reduce MRSA infection rates in the hospital. By working closely with bed management and ward staff, all identified patients at NUH with MRSA colonization or infection are isolated or grouped. This "MRSA bundle of interventions" took three years to roll out hospital wide.

As the programme was rolled out in a sustainable and acceptable way, MRSA acquisitions began falling. There was also a significant drop in bacteremias, and other clinical infections, while the hospital's hand hygiene compliance rate rose significantly. The team successfully oversaw change across the hospital, while continuing all the usual and necessary hospital infection control efforts.



Awareness on the importance of hand hygiene in saving lives was raised amongst staff, patients, visitors and the general public through innovative efforts such as a hand hygiene mascot, display of a replica of a patient's bed showing areas where germs are present, a large external banner on the hospital façade, a video featuring real stories of patients and families who have been affected by MRSA, and a series of posters and comic strips to reinforce the message. The team had just completed its third bi-annual staff hand hygiene training and credentialing involving over 6,000 staff in a week. Efforts towards prevention of MRSA acquisition and infection are now embedded in the culture of clinical medicine at NUH with sustainable practices and results.

The experience and results of these measures at NUH have been published in established peer-reviewed journals, and presented at both local and international conferences. It has taken major efforts from many at NUH.

NMRC Awards Ceremony and Research Symposium 2014



In 2014, the NMRC Awards Ceremony and Research Symposium were held concurrently during a one-and-a-half day event that attracted about 450 leading clinician scientists, researchers and other key players in the field of biomedical research. Held at the Grand Copthorne Waterfront Hotel on 26 and 27 February 2014, the event recognized the clinicians and researchers for their achievements and contributions to improving care for patients, and also to provide a useful platform for networking and collaborations amongst the many individuals from the healthcare institutions, academia and industry.

One of the Ministry of Health's key priorities for this year is delivering Healthcare 2020, which aims to improve healthcare accessibility, affordability and quality in Singapore. With the theme "Research and Innovation for Better Health", NMRC hopes that this year's event provides the platform for fostering stronger collaborations towards research excellence and better healthcare outcomes.

Awards Presentation

The first half of Day One featured an awards presentation for NMRC's Human Capital Awards and Talent Development Programmes, which was graced by Mrs Tan Ching Yee, Permanent Secretary for Health.

This was followed by experience sharing sessions by the STaR Investigator awardees, each with different clinical and research backgrounds, and different experiences, sharing some of their insights from their journey. The TCR Flagship Lead Principal Investigators also presented their achievements thus far.

Featured Workshops & Exhibitions

Day One workshops kick-started after the awards presentation, with parallel sessions for clinical trials and industry partnerships & commercialization. The day ended off with a wine and cheese reception, a platform for industry and clinical and research community participants to expand their network and explore collaboration opportunities after the forum discussions.

The workshops continued on Day Two with parallel sessions for Health Services Research and Stratified Medicine & Clinical Research Networks, all of which are key areas in fostering new directions in translational biomedical research. Over the one and a half days, there were a total of 25 speakers featured from healthcare institutions and industries.

Participants also had a chance to visit the exhibition booths during break times, and these booths showcased the services and latest projects undertaken by various institutions, such as Singapore Clinical Research Institute (SCRI), Clinician Scientist Xchange, SHS Investigational Medicine Unit, NUHS Investigational Medicine Unit and existing TCR programmes in areas of gastric cancer, eye, metabolic diseases, dengue and neuroscience.



Biomedical Sciences International Advisory Council Meeting 2013

On 17 Oct 2013, Singapore's Biomedical Sciences International Advisory Council (BMS IAC) held its annual meeting to discuss the progress of Singapore's BMS Initiative and the synergy of efforts of the BMS research players in Singapore. The IAC members also facilitated discussions amongst the local research community to gather inputs for the planning and developing of the national BMS Strategy for RIE2020.

Chaired by Sir Richard Sykes, the BMS IAC members commended Singapore's good progress in BMS and highlighted that the subsequent phase of work would be to determine the strategy to stay competitive and maintain such progress, as well as to review holistically and assess if Singapore was fit for the purpose envisioned for the BMS Initiative.

Updates in Singapore BMS Governance Framework

The BMS Initiative is coordinated by the BMS Executive Committee (EXCO), chaired by the Chairman of the Agency for Science, Technology and Research (A*STAR) and the Permanent Secretary for Health. The BMS IAC noted that the BMS EXCO was reconstituted in February 2013 to oversee the national BMS Initiative, as part of the national



effort to exercise more coherent strategic oversight of all Singapore BMS research funds. Senior representatives from ministries/agencies funding BMS research were appointed to the reconstituted BMS EXCO. A Scientific Strategy Group (SSG) was also established in August 2013 to provide national strategic framing inputs to the BMS EXCO.



Progress in BMS efforts

BMS has been a strategic initiative for Singapore since its inauguration in 2000 and the opening of Biopolis in 2003. As one of the key pillars of Singapore's economy, the BMS manufacturing output and value-added in 2012 was \$29.4B and \$15.3B respectively, and is now the largest manufacturing sector in Singapore by VA contribution. Business Expenditure on R&D (BERD) has also grown to \$553M in 2011, with a 21% CAGR since 2000. The sector now employs more than 20,000 people and contributes 5.25% of the Singapore GDP.

Beyond economic impact, Singapore has developed excellent clinical research capabilities in the public hospitals and research institutes over the past years. Initiatives have also been put in place to groom clinician scientists and support their research. MOH's investment in TCR has also generated promising results that have made a positive impact on healthcare.



Overview of Fund Commitment in FY 2013



\$66.2 million

Strategic Research Grant Programmes

- 2 Tier One TCR Flagships (\$9M each)
- 2 Tier Two TCR Flagships (\$25M and \$23.18M)

\$86.7 million

Individual PI-initiated Research Grants (inclusive of New Investigator Grants)

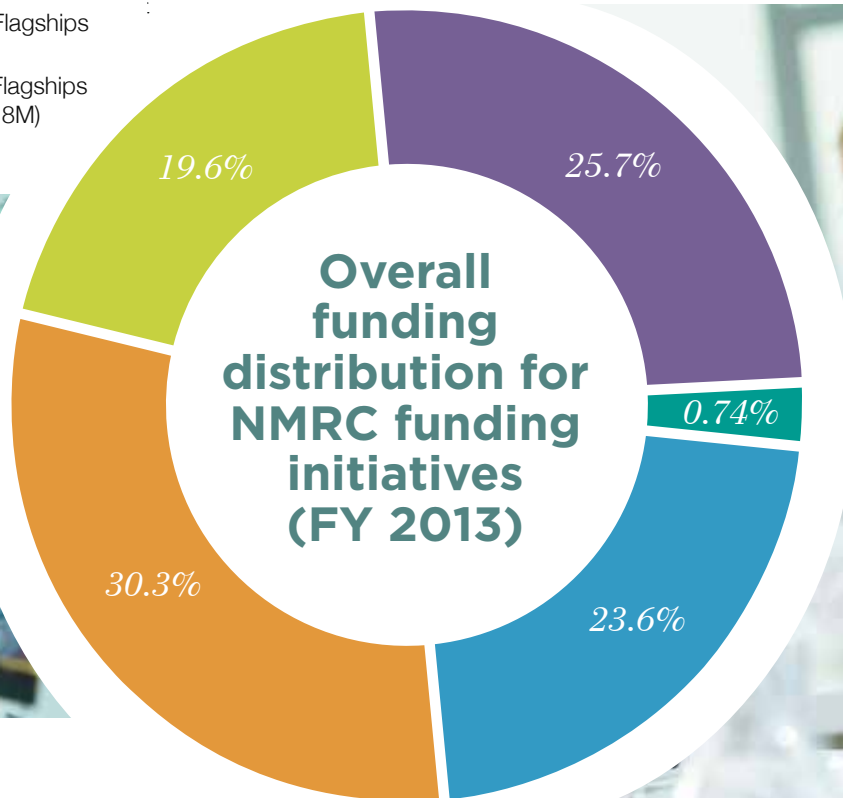
- B&B – 5 projects
- CBRG – 28 projects
- CS-IRG – 28 projects
- NIG – 26 projects



\$2.5 million

Talent Development

- 17 scholars / fellows



\$102.2 million

Human Capital

- CSA – 11 awardees
- STaR – 7 awardees
- TA – 9 awardees

\$79.6 million

Enablers & Infrastructure

- CTG – \$7.2M
- IMUs – \$10M
- IRB – \$845,877
- MOH IAF – \$1.6M
- Research Space Funding – \$20M
- SCRI – \$40M

