NMRC National Medical Research Council
Singapore

ANNUAL REPORT FY2021-FY2022

HEALTHCARE TRANSFORMATION THROUGH INNOVATION

CONTENTS

MESSAGE FROM CHAIRMAN

Adapting, Balancing and Collaborating

When Singapore started its healthcare journey, it focused on building the research infrastructure. The nation started with basic research: studying and understanding diseases, and building a cadre of scientists. Research has since evolved into the development of cures and treatments, and is now moving on into prevention by improving population health. As the main driver for research on patient care in Singapore, we at the National Medical Research Council (NMRC) have kept up with the ways in which global and healthcare needs are evolving, and very closely coordinate our operations with the Ministry of Health's (MOH's) plans for a healthy Singapore.

When the COVID-19 pandemic first made its presence known two years ago, we had to start from square one: from identifying symptoms to analysing diagnostics, managing treatments to creating vaccinations, and then planning for contingencies. But we managed to do this very quickly. The key was to start early and plan, and then improve the speed at which research was conducted.

Now that the situation has eased, the main challenge going forward would be managing public perception and meeting their expectations. A similar situation like COVID-19 can arrive very quickly, so we must prepare for what lies ahead. There will be challenges we cannot foresee or predict, but the lessons that the pandemic has taught us—such as the importance of adaptability—will help us to prepare for them.

The Research, Innovation and Enterprise 2025 (RIE2025) advocates moving forward, not just focusing on what we did before. Our next step is turning findings into real-world applications and prevention, and that means engaging additional researchers who can turn research into application. At the middle mark of RIE2025, NMRC is growing faster than expected with regard to the three strategic foci. We can achieve more because we already know what to do, and the pace has also become much faster. The biggest issue then is bringing all the research together. National-level programmes such as the Singapore Translational Cancer Consortium (STCC) and Precision Health Research, Singapore (PRECISE) have been set up to facilitate multi-institutional collaborations in a synergistic and integrated manner.

Singapore is experiencing rapid growth and has attained real progress. Our healthcare infrastructure is now better established with various institutions working together towards the common goal of transforming our healthcare system. I am excited to see how we can take individual projects to the next level with these collaborations—this is going to be a big change in our research landscape.

We will continue fostering the next generation by preparing for unexpected situations, developing new treatments and cultivating a culture of questioning and research. There were not many clinician scientists at the beginning, but the pool has gotten much bigger, as has its impact. It is time for the next generations to take the lead and continue elevating Singapore's healthcare scene, for the benefit of our country and our people.

Prof Ranga Krishnan
Chairman, NMRC

"Singapore is now known as a place for biomedical research; NMRC played a significant role in making this happen."

"Capitalise on the new ways of working and other changes brought about by the pandemic to support research..."

MESSAGE FROM EXECUTIVE DIRECTOR

Staying Responsive and Focused

COVID-19 has changed the world and, like many others, NMRC has responded accordingly with new initiatives and changes to the way we work. However, certain fundamentals will never change. These include the need to always be anchored in good science, prioritise what we support, identify and nurture talent, facilitate collaborations, and be focused on the desired outcomes.

RIE2025 is now well in progress and NMRC has been able to carry out our core responsibilities of supporting it, in spite of the challenges arising from the pandemic.

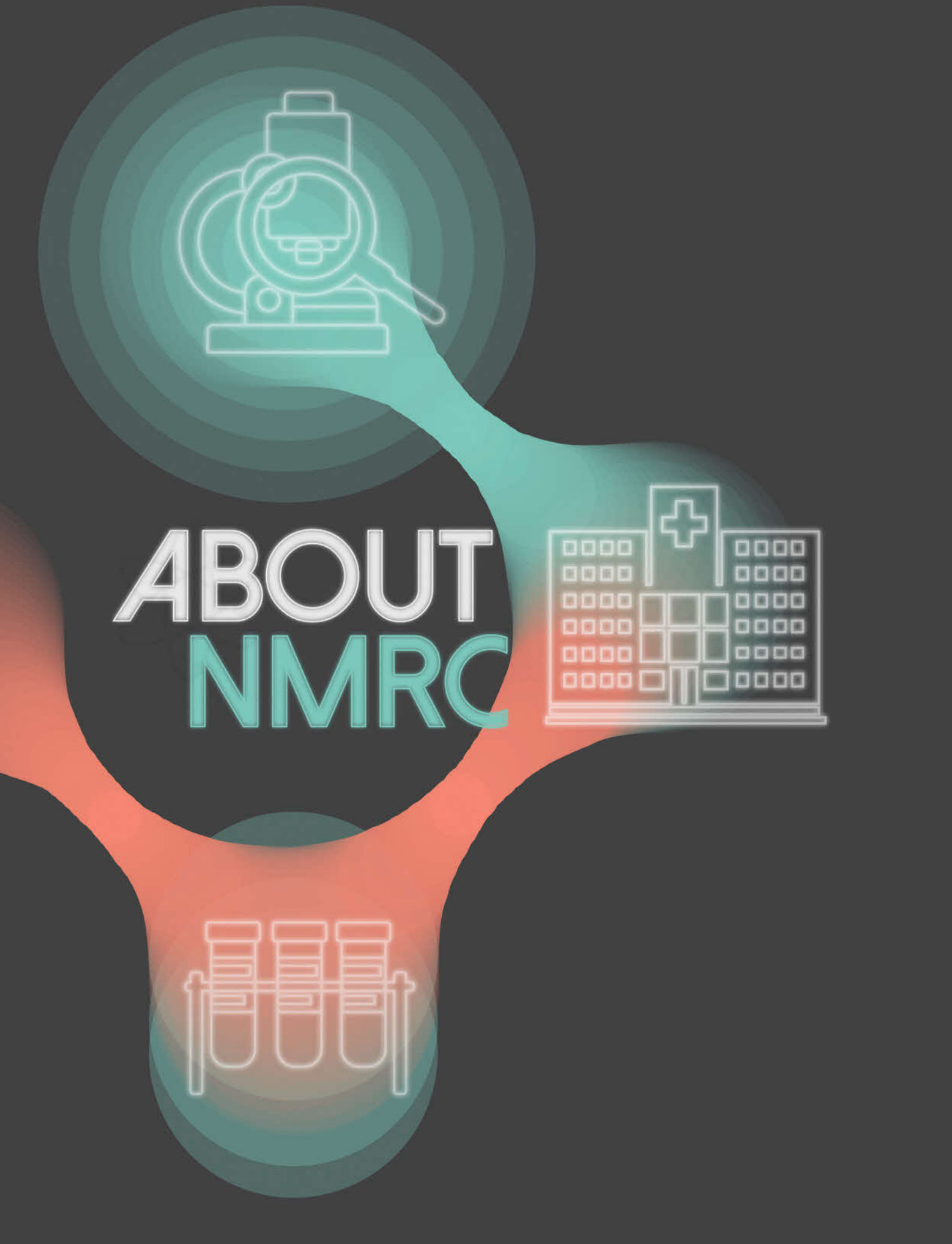
In line with Singapore's emphasis on population health, we launched a new Population Health Research Grant to support the research community as it works with MOH and other stakeholders to ask and answer questions that can impact policy as the country rolls out its population health initiatives.

We also introduced greater differentiation in our clinician scientist schemes. In particular, they now explicitly recognise clinician scientists whose work primarily aim to influence healthcare policies, as well as clinician innovators who help commercialise ideas and seek to have them adopted in practice. We also recognise the critical role played by nurses and allied health professionals in research and innovation, and have made changes to our various schemes to allow us to be more successful in building up clinician scientists in this community.

As we move on from COVID-19, we will capitalise on the new ways of working and other changes brought about by the pandemic to support research in areas such as digital health and healthcare applications of artificial intelligence. We will also continue to refine our existing processes, including allowing for expedited reviews where appropriate, and remote participation at review panels on a regular basis.

I am immensely proud of how NMRC has responded to the COVID-19 pandemic, in being responsive to both the research and non-research needs of combating the pandemic, while at the same time continuing to support our business-as-usual work. This would not have been possible without the strong support of the NMRC Chairman and Board, MOH leadership and colleagues, the National Research Foundation (NRF), our partners in the academic and healthcare institutions and all our other stakeholders. Finally, the NMRC team forms the bedrock of all we do here at NMRC, and I take the opportunity to again express my appreciation for all their dedication and hard work. I look forward to continuing to work closely with the team and our stakeholders to ensure that research makes a real difference and impact in the health of our population.

Prof Tan Say Beng
Executive Director, NMRC


ABOUT
NMRC

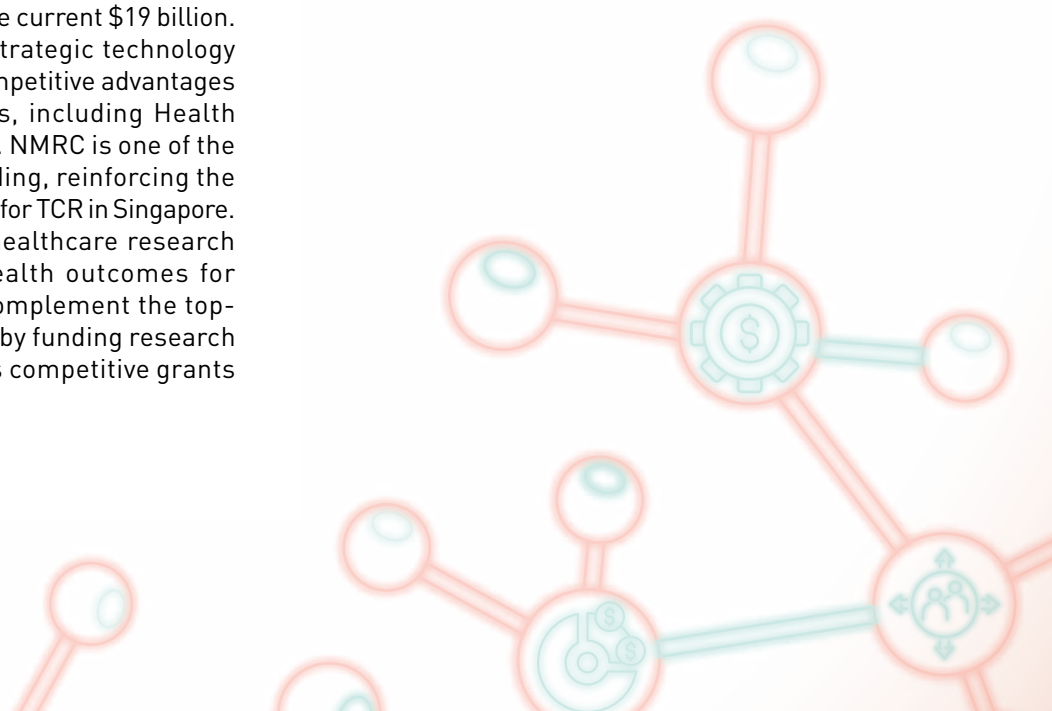
Established in 1994, NMRC has been overseeing the development and advancement of Translational and Clinical Research (TCR) in Singapore. It provides competitive research funds to publicly funded healthcare institutions, awards competitive research funds for programmes and projects, supports the development of core clinical research infrastructure, is responsible for the development of clinician scientists through awards and fellowships, and fosters interaction and knowledge exchange among researchers.

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

The Research, Innovation and Enterprise 2015 (RIE2015) Plan aimed for greater integration of activities across the entire Biomedical Sciences (BMS) community, including private- and public-sector performers, hospitals and government agencies. NMRC spearheaded these investments to realise long-term health and wealth outcomes.

Under the Research, Innovation and Enterprise 2020 (RIE2020) Plan, Singapore saw continued support for research, with an increase in investment from $16 billion in the previous tranche to the current $19 billion. Funding was prioritised in four strategic technology domains where Singapore had competitive advantages and/or important national needs, including Health and Biomedical Sciences (HBMS). NMRC is one of the beneficiaries of this boost in funding, reinforcing the Council's mandate as the champion for TCR in Singapore. It spearheads MOH's vision for healthcare research to deliver better health and wealth outcomes for Singaporeans. NMRC will also complement the top-down directed strategic research by funding research proposals received by the various competitive grants and awards administered.

In the current RIE2025 Plan, the funding allocation has been increased to $25 billion, with continued support for basic research, an expanded scope to better drive economic growth post-pandemic, and address our national needs and strengthen technology translation and enterprise innovation capabilities. The HBMS domain will be expanded into Human Health and Potential (HHP), where it builds on good progress in HBMS and additionally strategises efforts towards enabling Singaporeans to enjoy good health, and to realise their full potential. In alignment with the RIE2025 vision and changing health priorities, there will be key shifts to MOH's strategic thrusts towards transforming and protecting health. NMRC continues to be one of the major funding agencies and departments under MOH to support and realise the goals of the HHP and MOH's objectives through the administration of the various infrastructure and grant-funding schemes.



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 MOH and the Human Health and Potential Executive Committee, 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 utilised. As of 1 Sep 2023, the NMRC Board consists of 17 members.

Prof Ranga Krishnan
Chairman
National Medical Research Council, Ministry of Health

Prof Tan Say Beng
Executive Director
National Medical Research Council, Ministry of Health

Prof Kenneth Mak
Director-General of Health
Ministry of Health

Prof Ivy Ng
Group Chief Executive Officer
Singapore Health Services

Prof Yeoh Khay Guan
Chief Executive
National University Health System

Prof Chong Yap Seng
Dean
Yong Loo Lin School of Medicine, National University of Singapore

Prof Thomas Coffman
Dean
Duke-NUS Medical School

Prof Tan Sze Wee
Assistant Chief Executive
Biomedical Research Council, Agency for Science, Technology and Research

Prof Joseph Sung
Dean
Lee Kong Chian School of Medicine, Nanyang Technological University

Prof Edward Holmes
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Prof John Lavis
Canada Research Chair in Evidence-informed Health Systems
McMaster Health Forum

Prof Leo Yee-Sin
Senior Advisor
National Healthcare Group

Prof Michael Merson
Wolfgang Joklik Professor, Global Health
Duke University

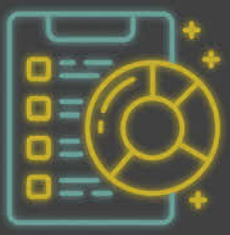
Prof Benjamin Seet
Deputy Group Chief Executive Officer (Education and Research) and Group Chief Research Officer
National Healthcare Group

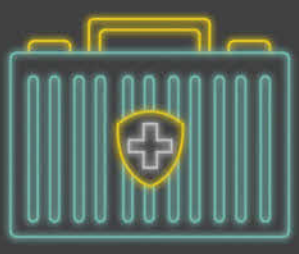
Prof Wong Tien Yin
Founding Head and Chair Professor
Tsinghua Medicine

Ms Amy Schulman
Managing Partner
Polaris Partners

Prof Teo Yik Ying
Dean
Saw Swee Hock School of Public Health, National University of Singapore

NMRC FUNDING PORTFOLIO





NMRC drives TCR through sustained and strategic investment in three key areas: (i) Human Capital Awards and Talent Pipeline Programmes, (ii) Research Grant Programmes (Project-based), and (iii) Research Enablers and Infrastructure Initiatives.

The active NMRC grant programmes and initiatives in FY2021 and FY2022^ are:

Human Capital Awards and Talent Pipeline Programmes

Human Capital Awards

- Singapore Translational Research (STaR) Investigator Award
- Clinician Scientist Award (CSA)
- HPHSR[1] Clinician Scientist Award (HCSA)
- Clinician Innovator Award (CIA)

Talent Pipeline Programmes

- Transition Award (TA)
- NMRC Research Training Fellowship (RTF)

Research Grant Programmes (Project-based)

- Centre Grant (CG)
- Clinical Trial Grant (CTG)
- Clinician Scientist-Individual Research Grant (CS-IRG)
- Clinician Scientist-Individual Research Grant-New Investigator Category (CS-IRG-NIG)
- Population Health Research Grant (PHRG)
- Population Health Research Grant-New Investigator Grant (PHRG-NIG)

Open Fund

- Large Collaborative Grant (LCG)
- Individual Research Grant (IRG)
- Young Individual Research Grant (YIRG)

Research Enablers and Infrastructure Initiatives

- Consortium for Clinical Research and Innovation, Singapore (CRIS)
- National Health Innovation Centre Singapore (NHIC)[2]
- National Large Animal Research Facility (NLARF)
- Programme for Research in Epidemic Preparedness And REsponse (PREPARE)

Enablers and Infrastructure Support for Clinical Trials-related Activities

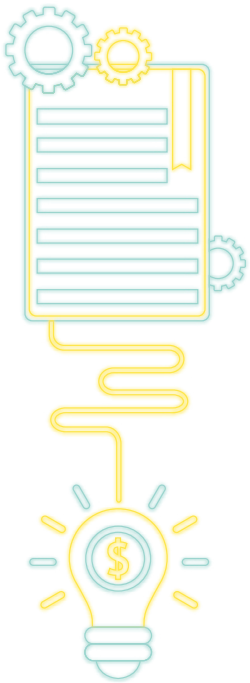
- Bioethics Advisory Committee (BAC)
- Clinical Research Coordinator (CRC)[3]
- Centre for Biomedical Ethics (CBmE)[4]
- Investigational Medicine Unit (IMU)
- Institutional Review Board (IRB)
- Singapore Clinical Research Institute (SCRI)[2]

National Clinical Translational Programmes

- Cardiovascular Disease National Collaborative Enterprise (CADENCE)[2]
- Precision Health Research, Singapore (PRECISE)[2]
- Singapore Translational Cancer Consortium (STCC)[2]

Strategic Datasets and Data-sharing Infrastructure

- National Cohorts Office (NCO)



^Funding sources: MOH, RIE2020 and RIE2020 White Space, RIE2025 and RIE2025 White Space

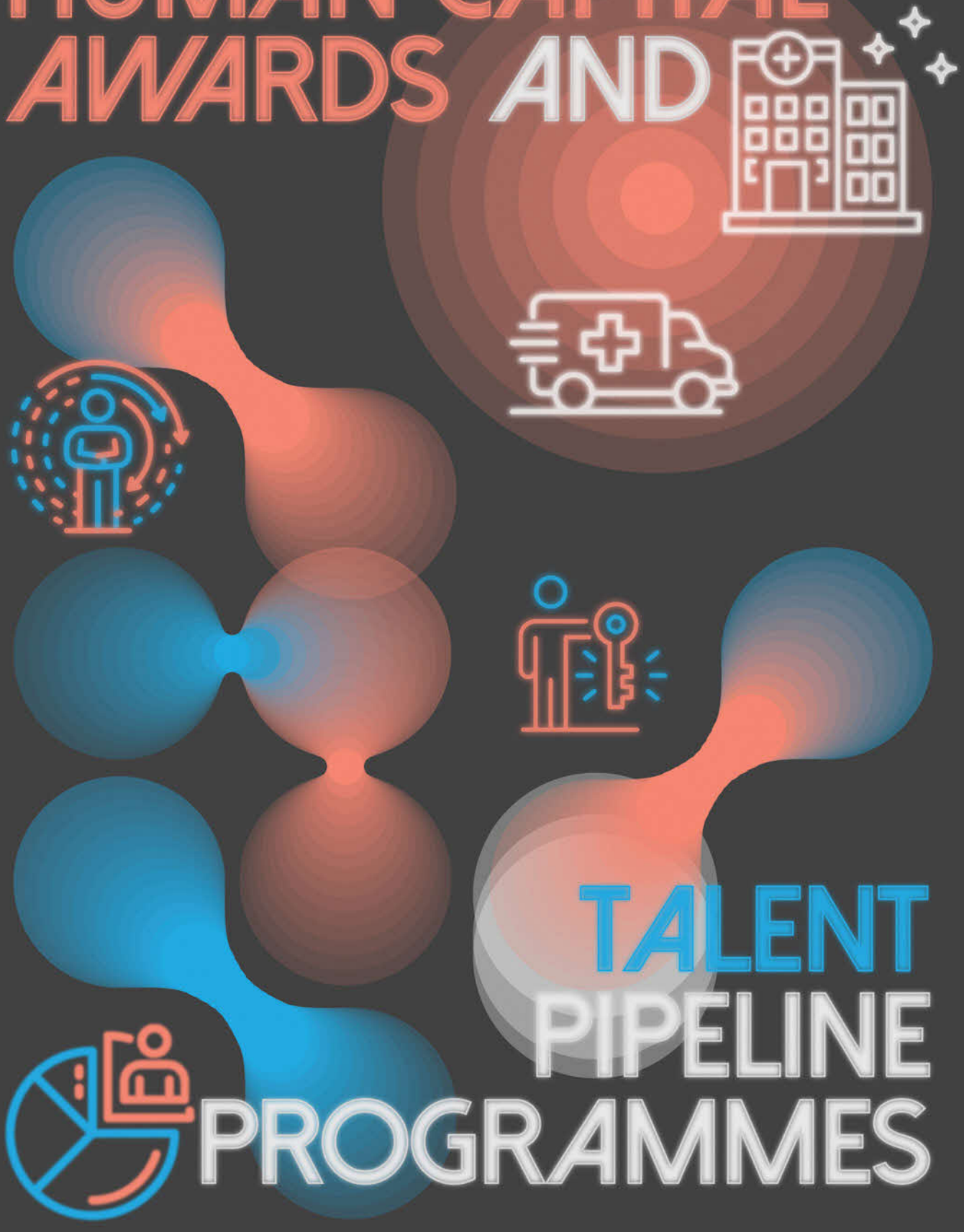
[1]Health Promotion, Preventive/Population Health and Health Services Research

[2]CRIS programme

[3]Funding for SCRI and clusters in support of CRCs

[4]For the Science, Health and Policy-Relevant Ethics in Singapore (SHAPES) programme

HUMAN CAPITAL AWARDS AND TALENT PIPELINE PROGRAMMES



NURTURING A VIBRANT AND DIVERSE COMMUNITY OF CLINICIAN SCIENTISTS

Talent is one of the seven RIE2025 HHP strategic thrusts. Singapore aims to grow, recruit and diversify clinician scientists who will advance its strategic goals in RIE2025's HHP domain.

Clinician scientists play a critical role in TCR, research in Health Promotion, Preventive Health, Population Health and Health Services Research (HPHSR), and/or Health Technology.

NMRC recognises the need to train and develop clinician scientists who are able to plug knowledge gaps and, over time, develop breakthrough research that will translate into impactful health outcomes.

To help Singapore nurture a vibrant and diverse community of clinician scientists, NMRC has put in place various human capital awards and talent pipeline programmes aimed at supporting individuals in their research and career progression.

The active Human Capital Awards and Talent Pipeline Programmes in FY2021 and FY2022 are:

Human Capital Awards

- Singapore Translational Research (STaR) Investigator Award
- Clinician Scientist Award (CSA)
- HPHSR Clinician Scientist Award (HCSA)
- Clinician Innovator Award (CIA)

Talent Pipeline Programmes

- Transition Award (TA)
- NMRC Research Training Fellowship (RTF)

HUMAN CAPITAL AWARDS

Singapore Translational Research (STaR) Investigator Award

The STaR Investigator Award is the most prestigious of the Human Capital Awards (HCAs). The HCAs recognise and support internationally renowned and outstanding investigators in TCR, HPHSR and/or Health Technology. The STaR Investigator Award provides up to five years of funding for salary and grant support.

Clinician Scientist Award (CSA)

The CSA is structured for local research talent to undertake internationally competitive TCR. It provides clinician scientists with valuable protected time to focus on their research. The Senior Investigator (SI) tier of the CSA offers up to five years of funding to support senior clinician scientists who are active in highly productive research. The Investigator (INV) tier offers three years of funding and targets younger clinician scientists with the potential to become leaders in their particular field of clinical research. Both funding tiers provide salary and grant support.

HPHSR Clinician Scientist Award (HCSA)

The HCSA is a new programme introduced in RIE2025 to develop the local research talent in the areas of HPHSR, bringing about significant and sustainable impact to health outcomes of the nation. There are two tiers of award: the SI tier for senior clinician scientists who have demonstrated sustained high levels of productivity and leadership in this field, and the INV tier for clinician scientists with the potential to become leaders in this field of research. Both funding tiers provide salary and grant support.

Clinician Innovator Award (CIA)

The CIA is a revamped version of the Clinician Innovator Development Award (CIDA) introduced in RIE2025 to develop local research talent with healthcare innovation ideas in fields such as disease diagnosis, medical treatment and/or improvement of human health and quality of lives. There are also two tiers of award offered: the SI tier for senior clinician innovators who have demonstrated an excellent track record in healthcare innovation, and the INV tier for clinician innovators with potential healthcare innovation ideas and require funding to generate pilot data. Both funding tiers provide salary and grant support.

SINGAPORE TRANSLATIONAL RESEARCH INVESTIGATOR AWARD RECIPIENTS

PROF DARIO CAMPANA

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

Cell Therapy of Cancer

Immunotherapy is gaining increasing prominence in oncology. The overall hypothesis underlying our research is that precisely directed immune cell therapy can yield better outcomes than standard treatment in patients with cancer, and with less toxicity. Research under two previously granted STaR awards resulted in first-in-human clinical trials, publications, awards, patents and the founding of three biotechnology companies. It also allowed for the training of numerous students and research fellows, and inspired considerable philanthropic support. This application builds on recent ideas backed by extensive preliminary data. It relies on a laboratory with a solid track record in translational research, and a dedicated cell therapy facility managed by a team with proven expertise in the preparation of clinical-grade cell products. The aims are:

Aim 1: Evaluating a novel chimeric antigen receptor (CAR)-T cell therapy for T-cell acute lymphoblastic leukemia and lymphoblastic lymphoma, aggressive diseases which lack effective immunotherapy. The studies stem from our patented technology, and are supported by very encouraging early clinical results.

Aim 2: Developing a novel cell therapy for acute myeloid leukemia (AML). A major obstacle to CAR-T cell therapy of AML is immunophenotypic heterogeneity of leukemic cells. An existing array of CARs made in our laboratory against CD123, CD70 and CD7 will be complemented by new CARs using an extensive database of AML surface marker profiles, including leukemia stem cells (Aim 2a). The activity of these new CAR-T cells will be studied alone and in combination with natural killer (NK) cells expressing an NKG2D chimeric receptor and membrane-bound interleukin-15 (Aim 2b).

These studies will lead to a clinical trial of CAR-T and NK cells in patients with relapse or refractory AML. The research proposed should generate new treatment options for patients with T-cell and myeloid malignancies and, if successful, will revolutionise their clinical management.

A/PROF CHRISTOPHER CHEN LI HSIAN

Associate Professor
Yong Loo Lin School of Medicine, National University of Singapore

Visiting Senior Consultant
Department of Psychological Medicine, National University Hospital

Validating Existing and Emerging Multi-modal Biomarkers of Vascular Cognitive Impairment

The focus of this study is on vascular cognitive impairment (VCI), which recognises that the mechanisms involved in VCI are complex and heterogenous: not only large or small cerebral vessel disease resulting in overt strokes or covert lesions such as microinfarcts, microhemorrhages, and white matter injury, but also neurodegeneration and Alzheimer's Disease (AD) pathology.

Project 1: Neurobehavioral & Structural magnetic resonance imaging (MRI) mMarkers for Cognitive Impairment & Dementia has specific aims which continue in the Harmonisation cohort's examination of the potential diagnostic and prognostic value of neurobehavioral and structural MRI markers for cognitive impairment and dementia as well as underlying pathophysiological mechanisms, and building existing as well as new international collaborations. This project will study, in a cohort of 700 subjects with up to five years longitudinal follow-up, the independent and joint associations of structural & functional MRI, retinal imaging, blood and neurobehavioural markers with risk of cognitive decline, dementia and vascular events.

Project 2: Multimodal MRI-based Network Breakdown and Progression Prediction in Cognitive Impairment and Dementia examines longitudinal brain network breakdown and microstructural changes using multimodal MRI and evaluate their interactions with AD & cerebrovascular pathology and contribution to cognitive and behavioral decline in patients with no, mild cognitive impairment and dementia.

Project 3: Retinal Markers for Cognitive Impairment and Dementia determines the relationship of these novel retinal imaging measures over time to the progression and development of VCI and other imaging markers of dementia, with a goal to determine the potential diagnostic and prognostic value of retinal imaging.

Project 4: Blood Markers for Cognitive Impairment and Dementia specifically aims to develop novel blood-based biomarkers of oxidative stress, vascular disease and neurodegeneration, and to examine their potential diagnostic and prognostic value for cognitive impairment and dementia.

PROF GOH BOON CHER

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

Senior Consultant
Department of Haematology-Oncology, National University Cancer Institute, Singapore

Advancing Therapeutics against Squamous Cell Carcinoma of the Head and Neck and Endemic Nasopharyngeal Carcinoma

Squamous cell carcinoma (SCCHN) and undifferentiated nasopharyngeal carcinoma (NPC) are the most common head and neck cancers in Singapore, and carry a significant burden of morbidity and mortality. This proposal brings together a group of highly qualified investigators with critically relevant expertise to collaborate on advancing therapeutics. The group has already established productive collaborations that have laid the foundations for this grant, and consists of senior as well as junior Principal Investigators (PIs) who ensure a diversity of experience and innovation. We will validate two projects in SCCHN.

First, we have shown that a polymorphism in C-MET gene occurs commonly in East Asians and South Asians and, through mutation at the Sema binding domain of MET, which causes conformational change and increased affinity for HER2, leading to strong oncogenic signalling. METN375S promotes aggressiveness in SCCHN and results in shorter relapse free survival, and we will conduct a clinical trial to study HER2 inhibitors in METN375S positive SCCHN.

Second, we have shown that the S4 strand of p53 is commonly mutated, and through structural simulations we predict the oncogenic gain of function with potential for therapeutic intervention. Through computational modelling of the mutants, we will evaluate the hypothesis that binding of chemical groups can reverse their oncogenic phenotype. In NPC, we will comprehensively map the tumour microenvironment of treatment-resistant NPC at the single cell resolution and the 3-D chromatin organisation to understand epigenomic regulation. Through this, we would design therapeutic interventions that can be assessed in clinical trials. The proposal will also advance our current efforts in vaccines against NPC through two delivery technologies: an efficient CD137L-DC already evaluated in a clinical trial, and a more tractable red blood cell-derived exosome. We will evaluate expressed viral antigens and tumour neoepitopes identified through our transcriptomic profiling of NPCs, prioritising them using an ex vivo high throughput immunogenicity reporter system.

PROF DEREK JOHN HAUSENLOY

Professor
Cardiovascular & Metabolic Disorders, Duke-NUS Medical School

Research Director
Senior Consultant Cardiologist & Clinician Scientist, National Heart Centre Singapore

New Treatments and Strategies to Prevent Heart Failure in Diabetes

The prevalence of diabetes is on the rise in Singapore and currently affects 10% of the general population. Patients with diabetes are at increased risk of developing heart failure (HF) and have worse outcomes once HF is established. Studies of Asian populations with HF have identified a lean diabetic phenotype common in Southeast Asia which presents at a younger age and has worse clinical outcomes, but the reasons for this different disease profile are unclear. The leading causes of HF in diabetic patients are acute myocardial infarction and diabetic cardiomyopathy. The overall aim of this research proposal is to understand the pathophysiology and risk factors underlying the development of HF in the Asian lean diabetes phenotype. We hypothesise that understanding the mechanisms underlying the development of HF in lean diabetic patients will identify novel targets and new treatments for preventing the onset and progression of HF. We have four specific aims.

Aim 1: Discovering new treatment targets for protecting the lean and obese diabetic heart from acute myocardial infarction (AMI) and diabetic cardiomyopathy using diabetic mice and human-induced pluripotent stem cell (iPSC) models.

Aim 2: Investigating whether targeting the mitochondrial fusion protein, Mfn2, can prevent cardiac dysfunction in lean and obese diabetic mice and human iPSC models.

Aim 3: Discovering new metabolic treatment targets in lean and obese diabetic AMI patients and diabetic cardiomyopathy using cardiac magnetic resonance imaging, spectroscopy and metabolomics.

Aim 4: Generating a patient risk score that predicts the risk of HF in lean and obese diabetic AMI and diabetic cardiomyopathy patients to guide patient management and improve health outcomes.

We expect to discover novel treatment targets and new treatments for preventing the onset and progression of HF in obese and lean patients with diabetes which have the potential to improve health outcomes.

PROF MARCUS ONG ENG HOCK

Senior Consultant
Department of Emergency Medicine, Singapore General Hospital

Professor and Director
Health Services and Systems Research (HSSR), Duke-NUS Medical School

Director
Prehospital and Emergency Research Center (PERC), Duke-NUS Medical School

Director
Health Services Research Center (HSRC), SingHealth

Future-ready Interventions for Survival after Cardiac Arrest (FRISCA)

Out-of-hospital cardiac arrest (OHCA) occurs when there is sudden cardiovascular collapse. While Singapore has made significant advances in improving outcomes for OHCA, there is considerably more to be done: 1) We need a comprehensive long-term registry and quality of survival data; 2) Community response needs to be enhanced with improved bystander Cardio-Pulmonary Resuscitation (CPR) quality; 3) Ambulance/system response can be optimised further; 4) We need to increase capacity/capability of health systems to deliver quality OHCA care regionally/globally. The overall objective of this STaR application is to increase the number of cardiac arrest survivors with good neurological function by 20%, by implementing a bundle of interventions over 5 years.

We will further develop and expand our internationally established clinical/implementation science research programme in OHCA by 1A: Building a Registry of OHCA Long-term Survivorship and Quality of Life (QoL); 1B: Optimising OHCA Triage and Transport using Artificial Intelligence (AI) Decision Support for Early Risk Stratification; 1C: Modelling the impact of Optimising Transport Policies to Specialised Cardiac Arrest Centres (CACs) using a decision science model; 2: Developing and Implementing Future Ready Smart Community interventions to improve the quality of CPR; 3A: Conducting a Cluster Randomised Controlled Trial (cRCT) on Pre-hospital Targeted Temperature Management using a Novel Cooling Vest; 3B: Conducting a Prospective Cluster Randomised Controlled Trial on Head-Up CPR; 3C: Implementing Transport Policies for CACs in a real-world implementation trial; and 4: Developing an Assessment tool for Developing Pre-Hospital Emergency Care systems in collaboration with the Global Resuscitation Alliance (GRA).

This programme targets a priority disease in Asia and is aligned with the population health, health services research and AI focus areas in Singapore. Evidence from our programme in Singapore will impact the OHCA management not only in Singapore but also in the whole of Asia and globally through the GRA.

PROF PATRICK TAN BOON OOI

Professor
Duke-NUS Medical School

Executive Director
Genome Institute of Singapore, A*STAR

Executive Director
Precision Health Research, Singapore (PRECISE)

Functional Epigenomic Interrogation of Altered Chromatin States in Gastrointestinal Cancer

Epigenetic alterations are fundamental hallmarks of cancer genomes, profoundly influencing foundational features of tumours including aberrant proliferation, chromosomal instability and metastasis. Clinically, cancer epigenetic changes are also associated with patient prognosis, treatment response and drug resistance. Previous work has revealed that epigenetic alterations in cis-acting regulatory elements (CREs; e.g. enhancers and promoters) comprise an essential biolayer, linking hardwired genomic alterations to cancer gene expression and signature phenotypes of malignancy. Our own work on CRE cartographies in gastric cancer (GC), a leading cause of global cancer mortality, has led to multiple senior/co-senior publications in Cell, Nature Genetics, Cancer Cell and Cancer Discovery. Here, we propose to deploy an integrated suite of novel technologies to identify functionally impactful CREs driving molecular and clinical features of GC, and to interrogate how these driver GC-associated CREs are regulated along with their downstream transcriptional programmes.

We seek to a) identify CREs and CRE target genes functionally required for GC malignant phenotypes using clustered, regularly interspaced, short palindromic repeats (CRISPR) interference in bulk populations and at the single-cell level (CROPqtl); b) identify CRE-associated trans-binding complexes regulating expression of GC driver genes via CRISPR-based mass-spectrometry (CRISPR-MS); and c) use icSHAPE to generate genome-wide ribonucleic acid (RNA) structure atlases of GC (an area where knowledge is almost entirely absent) and to link variations in RNA structure to cancer phenotypes and driver molecular alterations. The proposed work, which builds upon an already successful pre-existing translational GC research infrastructure (Singapore Gastric Cancer Consortium) will yield basic insights into the spectrum of epigenomic configurations, transcriptional states and genetic variants contributing to GC development, particularly in non-protein coding genomic regions which occupy 99% of the human genome. Our results will have translational impact by revealing biomarkers linked to GC initiation and progression, and highlight new therapeutic approaches for GC via targeting tissue-specific CREs necessary for maintaining GC cell survival.

PROF STUART COOK

Senior Consultant
Department of Cardiology, National Heart Centre Singapore

Tanoto Foundation Professor of Cardiovascular Medicine
SingHealth Duke-NUS Academic Medical Centre

Distinguished Clinician
Scientist and Senior Consultant, Department of Cardiology, National Heart Centre Singapore

Understanding and Targeting the IL11/LKB1/AMPK/mTOR Axis to Extend Healthspan

We recently discovered that interleukin 11 (IL11) is upregulated in ageing organs, to control key ageing signalling pathways and to underlie cardiometabolic dysfunction in old age. Our preliminary data in old mice shows IL11-stimulated extracellular signal-regulated kinase (ERK) activity to inhibit liver kinase B1 (LKB1)/AMP-activated protein kinase (AMPK) resulting in mTORC1 activation and cell senescence, causing disease. Up till now LKB1 was thought to be constitutively active and it had known role in ageing. Here, under the four aims, we will explore IL11 as an ageing gene and therapeutic target for multi-morbidity while dissecting disease mechanisms and cell-type specific effects:

Aim 1: To perform cardiometabolic phenotyping in mice with germline deletion of IL11. We hypothesise that germline deletion of IL11 in the mouse inhibits critical ageing pathways across tissues and that this preserves organ function and metabolic health in old mice.

Aim 2: To therapeutically target IL11 in mice to prevent and reverse diseases of ageing. We hypothesise that IL11 is an accessible drug target in ageing mouse tissues and that a neutralising IL11 antibody can prevent ageing diseases in old mice, reverse disease in very old mice and extend lifespan.

Aim 3: To identify the cells expressing IL11 in aged kidneys and aorta. We hypothesise that IL11 is upregulated in specific cell types in the kidney and aorta and that autocrine IL11 activity in these cells contributes to age-dependent loss of renal and aortic function.

Aim 4: To establish STK11/LKB1 as a signalling nexus for ageing diseases. We hypothesise that a primary signalling pathway underlying diseases of ageing is mediated via an axis of IL11-regulated ERK/LKB1/AMPK/mTORC1 activity across tissues.

This project explores large new biology with a strong translational focus. If our hypotheses are proven and anti-IL11 therapy translates, the health and economic benefits could be large.

PROF TOH HAN CHONG

Senior Consultant and Deputy Chief Executive Officer (Strategic Partnerships)
Division of Medical Oncology, National Cancer Centre Singapore

Professor
Duke-NUS Medical School

PINNACLE : Precision ImmuNotherapy for Nash And Conquering Liver CancEr

Hepatocellular carcinoma (HCC) typically develops on a background of chronic inflammation, with risk factors including HBV/HCV and increasingly non-alcoholic steatohepatitis (NASH). Indeed, different HCC aetiologies may influence the tumour microenvironment (TME) with implications for immunotherapy response, such as immune checkpoint inhibitor therapy. Emerging evidence suggests a poorer immunotherapy response for NASH-HCC versus viral HCC, yet no therapies exist for NASH and associated liver fibrosis. We have pioneered research into the transcription factor GATA4, the loss of which occurs in ~50% of HCC cases. Our data has highlighted the importance of GATA4 loss in fatty liver and HCC development, suggesting that targeting pathways downstream of GATA4 loss may expand our treatment options and offer early therapeutic intervention. We hypothesise that HCC of different aetiologies or GATA4 status requires differentiated treatments. Therefore, we aim to study GATA4-deficient and NASH-related HCC to characterise the tumour and TME comprehensively, identify pathways and biomarkers of response/resistance, discover and validate therapeutic targets, and assess novel immunotherapy combinations. With our expertise in organoid and mouse models, we will conduct mechanistic and therapeutic studies with preclinical models that accurately recapitulate the biology of GATA4-deficient and NASH-related HCC. In parallel, we also leverage our expertise in performing deep profiling of HCC patient samples to identify clinically relevant targets and biomarkers. Furthermore, we are developing next-generation cell therapies with neoantigen-specific dendritic cell vaccine (in phase 2 trial) and engineered γδ-T cells, based on findings elucidated from preclinical and clinical studies. Our strategy is to position cellular immunotherapies earlier in the adjuvant setting and pre-cancerous NASH/liver fibrosis. With over two decades of experience in translational immuno-oncology and a broad network of academic, clinical and industry collaborations, we are poised to address the unmet need for precision immunotherapies for HCC and NASH to benefit patients locally and beyond.

PROF OOI ENG EONG

Professor
Programme in Emerging Infectious Diseases, Duke-NUS Medical School

Defining How Dengue Virus "Makes Haste Slowly" to Enable a Rational Approach for Engineering New Live Attenuated Vaccine Candidates

Dengue is a mosquito-borne acute viral disease that debilitates an estimated 100 million people each year. It is caused by any one of four dengue viruses (DENV1-4), all of which are expanding their geographic footprint from the tropics to the subtropics. Patchy knowledge of the molecular determinants of clinical and epidemiological fitness of DENV has complicated dengue vaccine development. Studies have shown that clinically fit DENV avoids prematurely activating the innate immune response that limits intrahost infection dissemination. Studies from the applicant's laboratory have found that wild-type DENVs evade immune activation, in part, through slowing its replication rate and "make haste slowly". However, how DENV infection is regulated, especially through virus-host interactions instead of mutations in the viral polymerase, is not understood. The goal of this proposal is to define the DENV-host interactions that regulate virus replication rate. This study will build on our recent findings of two DENV mutants that serve as exquisite tools to interrogate how DENV replication is regulated through virus-host interactions. The first is an attenuating mutation in the prM gene found in DENV2 PDK53—a phase III clinical trial tested vaccine candidate—that has impaired interaction with human high mobility group box 1 (HMGB1) protein that plays critical roles in regulating gene expression. The second is a novel mutation in a conserved region of the DENV NS2B gene. Both mutants show accelerated replication and attenuated infection dissemination compared to their wild-type parents. The specific aims of this study will use these mutants to delve into the mechanisms that operate to regulate DENV replication and hence attenuation. It will also aim to discover new mutations that accelerate DENV replication and use these as well as others to engineer new strains with suitably attenuated phenotype for further development as dengue vaccines.

PROF CHAN KOK YEN JERRY

Senior Consultant
KKIVF Centre, Dept of Reproductive Medicine, KK Women's and Children's Hospital (KKH)

Director
KK Research Centre, KK Women's and Children's Hospital

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SingHealth Duke-NUS Maternal and Child Health Research Institute

Academic Vice Chair
Research – SingHealth Duke-NUS Obstetrics and Gynaecology Academic Clinical Programme (ACP), Duke-NUS Medical School

Preclinical Intrauterine Nanoparticle-based Gene Editing for Genetic Diseases

Inherited monogenic diseases pose a significant clinical and socio-economic burden, many of which cause irreversible damage in-utero, giving rise to an urgent unmet clinical need. Intrauterine gene therapy (IUGT) has shown tremendous promise in providing a cure but is prone to problems with viral toxicity and integration, and the use of a non-physiological promoter. A potential solution would be to perform intrauterine gene editing through nanoparticle (NP)-based delivery. In this proposal which builds on our internationally-recognised success in IUGT and immune ontogeny, we will deliver intrauterine gene editing using advanced NPs. Our long-term objective is to develop the scientific, technical, and safety foundations for the clinical translation of intrauterine gene editing technologies for inherited monogenic diseases using a clinically and ontologically relevant non-human-primate (NHP) model. Our hypothesis is that an NP-based gene editing platform is safe and effective to treat monogenic diseases. Specifically, we will (A) develop and identify the most efficient NP system for messenger ribonucleic acid (mRNA)-based gene-editing tools, (B) demonstrate the efficiency and safety of NP-based intrauterine gene editing targeting PCSK9 and HPD, and (C) map the immune ontogeny and perturbations with NP-based gene editing through high-resolution assays. The goal of this programme is to develop an optimised NP-based intrauterine gene-editing platform of relevance for the treatment of monogenic diseases of significant socio-economic burden. The data derived here, especially from the translationally relevant NHP studies, will inform the development of a clinical protocol, which may apply to almost half of human pathogenic genetic variants, which are caused by point mutations. Concurrent studies of human immune ontogeny funded through NMRC/CIRG/1484/2018 will further identify the ideal time for intervention in tandem with efforts to do the same in the NHP. This proposal brings together a team of internationally-competitive Clinician-Scientists, Scientists and Maternal-Fetal Medicine Specialists to build on the clinical translation of intrauterine gene editing.

CLINICIAN SCIENTIST AWARD (SENIOR INVESTIGATOR) RECIPIENTS

A/PROF CHAN LING LING

Senior Consultant
Department of Diagnostic Radiology, Singapore General Hospital

Associate Professor
Duke-NUS Medical School

Precision Medicine on Head CT to Identify Neurodegeneration through Deep Learning-Based Segmentation Empowered with Brain MR Morphometry (PRECISE)

Neurodegenerative disorders such as dementia, Parkinsonian gait disorders and fall-related traumatic brain injury are a growing public health concern with the ageing population. Radiological assessment of neurodegeneration on screening head computed tomography (CT), heavily utilised for older adult fall-related traumatic head injuries, is subjective and expertise-dependent. Automated quantitative brain volumetry aids detection of neurodegeneration and is increasingly available on brain MRI, but non-existent on CT. However, MRI is expensive and not widely available. Recent deep learning (DL) approaches have shown state-of-the-art performance in complex medical image segmentation tasks, and good results in automating segmentation on head CT.

Using a U-Net convolutional network model and paired CT–MRI big data, we will develop an automated segmentation model on head CT, build normative quantitative brain volumes for the local target population and demonstrate the radiological utility of these measures in radiological head CT reporting.

We hypothesise that DL will automate CT brain segmentation with robust and accurate results, allow the repository of normative quantitative atlas-based volume outputs to be used as reference normative standards, and facilitate radiological detection of neurodegeneration.

Paired head CT—high resolution multi-contrast brain MRI scans from 750 subjects aged 55-85 years (550 healthy and 200 patients clinically diagnosed with Alzheimer's dementia or atypical Parkinsonism)—will be acquired. Quantitative brain segmented volume outputs from the DL model will be validated against the MR volumetric gold standards. Value-add from the quantitative indices derived from automated segmentation on head CT will be assessed.

Harnessing novel AI technologies and good-quality paired CT-MRI big data to automate accurate segmentation tools on head CT holds a promise to provide objective biomarkers to empower precision medicine on head CT as the cheaper and more prevalent clinical neuroimaging alternative with wider scoping and cost-saving impacts on the healthcare of our greying nation.

A/PROF MAHESH CHOOLANI

Associate Professor
Yong Loo Lin School of Medicine, National University of Singapore

Senior Consultant
Department of Obstetrics and Gynaecology, National University Hospital

Non-invasive Prenatal Diagnosis (NIPD) of Genetic Disorders using Massive Parallel Sequencing on Circulating Fetal Nucleated Red Blood Cells (FNRBCs) Isolated from Maternal Blood

There are approximately 7,000 known genetic diseases with >250 new conditions described in medical literature every year. With a worldwide prevalence of ~1%, most genetic diseases are debilitating or even life-threatening. Age-related de novo mutations, especially de novo single nucleotide variants, occur more commonly in paternal as compared to maternal germ cells, and are associated with increased risk of intellectual disability in the offspring. Definitive prenatal diagnoses rely on invasive procedures, which carry a 0.3-2% risk of miscarriage, and remain the most reliable method of prenatal diagnosis of chromosomal aberrations as well as copy number variants. Current first-tier diagnostics have their limitations. Although well established, G-band analysis cannot detect cryptic translocations <3-5Mb. Chromosomal microarray analysis (CMA) has replaced it as the first-tier clinical diagnostic test.

However, CMA is limited by the inability to identify balanced rearrangements and is blind to copy-neutral events. We have known for decades that within the pregnant mother's circulation lies information regarding the wellbeing of her fetus. Whole nucleated fetal cells can be harvested from the maternal circulation non-invasively. However, due to their rarity, fetal cells have to undergo genomic amplification for downstream analysis. Pre-implantation genetic testing has shown the possibility of expanding the genome of a single or a few cell(s) and detecting chromosomal aberrations using next-generation sequencing. We hypothesise that we can determine and detect a range of clinically relevant genetic disorders during pregnancy by interrogating the genome of fetal cells obtained non-invasively. We envision this technology enhancing current prenatal diagnosis strategies. This opens up new avenues/opportunities for individualised therapeutic interventions for condition-specific management that can lead to improved outcomes and quality of life such as genetic counseling/support, future family planning, cascade testing, justifying social and educational services, and connecting to condition-specific support groups. The ultimate goal is to provide autonomy and reproductive choice options to couples worldwide.

PROF TAZEEN HASAN JAFAR

Professor
Health Services & Systems Research Programme, Duke-NUS Medical School

Strategies for Kidney Outcomes Prevention and Evaluation — The SKOPE Study

Chronic kidney disease (CKD) is an enormous global public health problem affecting thousands of Singaporeans. CKD is associated with dialysis-requiring end-stage kidney disease (ESKD), cardiovascular disease (CVD) and death. Building on the success of our NMRC-funded SingHypertension Trial, we propose a pragmatic, randomised controlled trial of a multi-component intervention, "Strategies for Kidney Outcomes Prevention and Evaluation—SKOPE" versus "usual care" over 3 years among 894 adults (447 per arm) with CKD (estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m2) visiting the polyclinics in Singapore. SKOPE components include: 1) nurses trained as health coaches for CKD specific lifestyle counselling using in-person and remote meetings; 2) training physicians in standardised management of CKD; 3) subsidy on SGLT2 inhibitors; and 4) case review meetings. We have a number of specific aims for this project:

Aim 1: Determines whether SKOPE integrated into the primary care system will be more effective than usual care on the primary outcome of preserving kidney function (eGFR slope), and the secondary outcomes of lowering cardiovascular risk and improving health-related quality of life in patients with CKD.

Aim 2: Performs a mediation analysis and estimates the extent to which changes in lifestyle, clinical risk factors, and pharmacologic therapy mediate the benefit of SKOPE versus usual care on preserving kidney function.

Aim 3: Determines the incremental cost-effectiveness of SKOPE compared with usual care on quality-adjusted life years gained from the health system perspective. We will also perform a budget impact analysis.

Aim 4a: Assesses the facilitators and barriers to, and the acceptability of, SKOPE from the key stakeholders' perspectives.

Aim 4b: Explores the impact of a potential or existing pandemic (e.g. COVID-19) on CKD care delivery. If successful, scaling up SKOPE in primary care clinics would prevent death and disability related to ESKD and CVD, and reduce patients' suffering in Singapore and globally.

PROF LEE SOO CHIN

Senior Consultant
Department of Haematology-Oncology, National University Cancer Institute, Singapore

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

Development of Novel Therapeutics and Predictive Biomarkers in Breast Cancer

Devising better treatments represents one important, broad strategy to reduce breast cancer morbidity and mortality. This breast cancer therapeutics and predictive biomarkers programme is centred around therapeutic clinical trials and complemented by a systematic collection of biosamples including tissue and blood, to study drug pharmacokinetics and pharmacodynamics, drug resistance mechanisms and the development of predictive biomarkers. There are three specific aims.

Aim 1: Focused on studying novel therapeutic strategies in breast cancer through clinical trials. Several novel therapeutic trials are planned, some of which represent bench-to-bedside translation of preclinical work done locally, including a trial of lenvatinib + letrozole based on preclinical work in the PI's lab at the Cancer Science Institute, Singapore; a first-in-man autologous antibody-coupled T-cell receptor (ACTR)-T cell trial combined with trastuzumab in HER2+ metastatic breast cancer which is based on work with Dario Campana at the National University of Singapore; using an epigenetic drug, tazemetostat, to induce a tumour-immune gene signature and restore sensitivity to trastuzumab in HER2+ breast cancers based on work with Yu Qiang from the Genome Institute of Singapore; and combining a novel immune-oncology drug, ADG106, an agonistic monoclonal antibody against CD137, with chemotherapy in HER2 negative breast cancer in collaboration with Adagene, USA. Serial tumor biopsies and plasma samples will be collected longitudinally from trial subjects to study the biological effects of drugs and for discovery predictive biomarker work.

Aim 2: Developing a platform for ex-vivo drug sensitivity testing to select rational combinations using patient-derived organoids from breast cancers, aiming for a short turnaround time of 4-6 weeks for real-time guidance of treatment in the clinic.

Aim 3: Explores the use of exosomes as a blood-based biomarker to prognosticate and track treatment progress in advanced breast cancer, starting first with hormone receptor positive/HER2 negative disease then moving on to HER2+ disease if resources and budget permit.

A/PROF RAYMOND SEET

Associate Professor
Yong Loo Lin School of Medicine, National University of Singapore

Senior Consultant
Department of Medicine, National University Hospital

Prognostic Significance of RNA Signatures to Predict Major Complications following Acute Reperfusion Treatment for Ischemic Stroke

Symptomatic intracranial hemorrhage (SICH) and malignant cerebral oedema (MCO) are two dreaded complications of reperfusion treatment in patients with acute ischemic stroke. Using existing resources of the National University Health System (NUHS) Stroke Tissue Repository, we sequenced small and long non-coding RNAs using a RNA sequencing (RNA-Seq) method in whole blood samples of 20 ischemic stroke patients (mean age, 69 years; 50% men) who underwent reperfusion treatment at the National University Hospital, Singapore. These RNAs were subsequently analysed for the development of events (a composite of SICH and MCO). We identified unique RNA expressions that were differentially expressed between these groups. We hypothesise that brain-specific RNAs are released into the circulation following cerebral ischemia, and the detection of these RNAs could signal an increased likelihood of major bleeding and swelling complications following acute stroke therapies. We further hypothesise that the ability to identify these RNAs will allow neurologists and Emergency Room physicians to expeditiously classify patients according to their risk of complications. The overarching objective is to investigate RNA signatures to predict major complications in ischemic stroke patients following reperfusion treatment. Specifically, our aims include:

Aim 1: Deriving an RNA signature of adverse treatment outcomes.

Aim 2: Developing a customised technological platform to profile the derived RNA signature.

Aim 3: Independently validating the performance of the derived panel of RNA signatures to predict adverse events between the customised platform and PCR-based methods.

This study will deliver (1) a validated panel of adverse candidate RNAs associated with major complications; and (2) a customised technological platform to profile these candidate RNAs.

This study builds on compelling preliminary data, creates new knowledge on stroke mechanisms and leverages multidisciplinary expertise to address an important clinical question.

PROF TAI E SHYONG

Professor
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Senior Consultant
Department of Medicine, National University Hospital Scientist, National Heart Centre Singapore

The role of G6PC2 in Glucose Homeostasis and Diabetes in East Asians

Variants at the G6PC2 locus are reproducibly associated with fasting glucose (FG). G6PC2 is specifically expressed in the pancreatic islets and hydrolyses glucose-6-phosphate (G6P) to glucose and inorganic phosphate. However, G6pc2 knockout on insulin secretion in mice lowers fasting glucose and increases insulin secretion at moderate levels of glucose, whereas the glucose-lowering alleles at the G6PC2 locus are associated with lower insulin levels during an oral glucose tolerance test. It has been hypothesised that, in humans, these variants alter the pulsatility of insulin secretion which can improve insulin action and lower glucose despite lower insulin levels. However, this hypothesis has not been tested.

To better understand the role of G6PC2 in humans, we will determine the impact of a variant, rs2232326 (p.S324P) at the G6PC2 locus, on the pulsatility of insulin secretion an and glucose-stimulated insulin secretion (GSIS) in humans. This variant is strongly associated with FG, has been demonstrated to result in low protein expression of G6PC2 in vitro and has a minor allele frequency (MAF) ten times higher in Asians (MAF=4.6%) than in Europeans (MAF=0.17%). We will carry out a recruit by genotype study to examine insulin pulsatility and GSIS using a graded glucose infusion in 48 individuals, half of which will carry the S324P allele. In parallel, we will evaluate the effect of G6PC2 haploinsufficiency, knockout and the S324P variant in human-derived beta-cell models on GSIS and evaluate the mechanisms for any effects. We will further evaluate the hypothesis that the S324P variant or G6PC2 deficiency could increase endoplasmic reticulum stress which in turn could impair beta-cell function. Finally, we will evaluate the interaction between the S324P variant and glucose-lowering drugs that also act on GSIS (GLP-1 agonists) or act on the same pathway as G6PC2 (glucokinase activators) both in vitro and in vivo (human studies).

A/PROF DAVID TAN SHAO PENG

Senior Consultant
Department of Haematology-Oncology, National University Cancer Institute, Singapore

Associate Professor
Yong Loo Lin School of Medicine, National University of Singapore

Development of Novel Therapeutics and Predictive Biomarkers in Gynaecological Cancers

Gynaecological cancers have been rising in incidence amongst Singaporean women. Endometrial, ovarian and cervical cancers now represent the 3rd, 5th and 10th most common cancers amongst women in Singapore respectively. Most of these cancers are treatable at diagnosis with a potential for cure, but the majority of cases presenting at advanced stage will relapse and subsequently develop treatment refractory disease. Hence, there is an urgent need to develop more effective therapeutic options for primary and recurrent gynaecological cancers.

We hypothesise that evaluating the clinical efficacy of novel therapeutic approaches in gynaecological tumours, combined with molecular profiling platforms for therapeutic stratification and in-depth analysis of the tumour microenvironment to identify novel predictive biomarkers, has the potential to result in greater therapeutic gain. Accordingly, we aim to study novel therapeutic strategies in gynaecological cancers through clinical trials; establish a clinical platform to perform comprehensive molecular profiling of gynaecological cancers so as to identify actionable molecular aberrations to match patients to relevant biomarker-driven clinical trials; and develop a spatial immune-profiling platform to identify a) pharmacodynamic changes in the tumour microenvironment; and b) predictive biomarkers for immunotherapeutic strategies in gynaecological cancers.

Our methods involve setting up a gynaecological cancer precision oncology programme involving several early-phase trials of novel therapeutic strategies for patients with recurrent gynaecological cancers, in conjunction with a comprehensive genomic and transcriptomic profiling platform for therapeutic stratification. We will develop a tumour microenvironment-profiling platform using Imaging mass cytometry technology and the GeoMX spatial RNA profiling platform to identify novel predictive biomarkers and new therapeutic targets.

PROF YONG EU LEONG

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

Senior Consultant
Department of Obstetrics and Gynaecology, National University Hospital

Reliable Measurement of Muscle Mass, by a D3-creatine Dilution Assay, to Predict Risk for Osteoporosis and Other Major Health Outcomes as Singaporean Women Age

From 50 years of age, post-menopausal women are at an increased risk of developing sarcopenia and osteoporosis as a result of deterioration of musculoskeletal health. Both disorders increase the risk of falls and fractures. Fat mass and bone mineral density (BMD) can be measured accurately using two specific energies in dual-energy X-ray absorptiometry (DXA) scanning. However, reliable measurement of muscle mass remains elusive, due principally to DXA-determined muscle mass as non-bone, non-fat mass which includes intra-abdominal organs which have the same attenuation signals as muscles. This obviously introduces a measurement error in the estimation of muscle mass. A novel method to measure muscle mass using the stable isotope deuterated-creatine (D3-creatine) has recently been developed. Muscle mass measurement with this method was recently shown to have strong and consistent associations with physical performance and increased risk of adverse outcomes such as injurious falls and mobility problems in older men. No data is currently available for women.

We hypothesise that differences in muscle mass—when measured accurately—can predict trajectories of declines in bone, cardiometabolic, mental health and genital urinary health in ageing women. Accurate measurement of muscle mass, without the use of DXA, would allow us to dissect the relative effects of fat versus muscle on the risk of osteoporosis. The differential effects on women of muscle versus fat mass with respect to the condition known as sarcopenic obesity are unresolved. To understand the effect of muscle mass on women's health, we propose to define thresholds for sarcopenia using muscle mass measured by D3-creatine, that predict increased risk for the following critical and debilitating health conditions: osteoporosis, insulin resistance, diabetes, hypertension, depression, anxiety and urinary incontinence. Achieving our aims will bring novel technology to Singapore in the form of a novel, cost-effective and accurate method to measure muscle mass in mid-life women.

DR YONG WEI PENG

Senior Consultant
Department of Haematology-Oncology, National University Cancer Institute, Singapore

Assistant Professor
Yong Loo Lin School of Medicine, National University of Singapore

Precision Therapy for Gastric and Hepatocellular Cancer

Gastric and hepatocellular cancers represent the 5th and 6th most prevalent and the 4th and 3rd most lethal cancers respectively worldwide. Both cancers have the poorest 5-year survival rate among the most common cancers endemic to Singapore, contributing to a high healthcare burden. The value of precision medicine cannot be over-emphasised, as there is a price to pay when the wrong drug is selected, both by the patient as well as the society at large. Moreover, the administration of futile treatment stretches the already limited healthcare resources.

The research programme focuses on i) precision drug selection; ii) precision drug delivery; and iii) precision drug dosing. In Aim 1, we will conduct prospective studies to assess the value of realtime phenotypic drug screen using patient-derived organoids to predict treatment response. We will incorporate our novel autologous immune cell/cancer organoid co-culture system to screen the response to immune checkpoint inhibitors. Finally, we will evaluate a 5-azacytidine based therapy uncovered by AI-assisted cancer organoid-based drug screen in 'predicted' responders. In Aim 2, we will conduct 2 studies using a minimally-invasive drug delivery system that can deliver drugs into the peritoneal cavity as aerosolised droplets, giving better local tissue penetration and minimising systemic exposure and treatment toxicity. These studies will evaluate the efficacy of pressurised intraperitoneal aerosol chemotherapy (PIPAC) oxaliplatin and IV nivolumab as well as test electrostatic application of PIPAC with paclitaxel in patients with peritoneal metastases. Finally, in Aim 3, we will evaluate the use of AI-base dose decision support tool to personalise drug dosing, with the goal to reduce treatment cost and toxicity.

PROF TINA WONG

Head & Senior Consultant
Glaucoma Department, Singapore National Eye Centre

Professor
Duke-NUS Medical School

Tackling Fibrosis in Glaucoma Surgery

Disordered scarring is at the root of many diseases and conditions, and its pathogenesis remains one of the biggest challenges in modern medicine. Previous approaches based on studies involving fibroblasts as effector cells of scarring in glaucoma surgery have failed to deliver improvements to inhibit scarring despite the generation of much promising data. A new approach to reduce pathological scar formation as the underlying cause of surgical failure is much needed. An emerging concept is that scarring occurs when immune cells stimulate fibroblasts to produce excessive collagen during the repair process. In addition, chronic eyedrops also lead to a profibrotic state of the conjunctiva. This link between immune cells and differential scarring phenotypes in filtration surgery has been alluded to in the past but never fully examined to date.

In this proposal, the scarring phenotype in glaucoma subjects will be investigated. Whole genome exome sequencing of patients undergoing surgery aims to look for major genes and mechanisms underlying the scarring process. A better understanding of the relationship between genetic predisposition and environmental influences on the conjunctival tissues at the surgical site will be explored.

This translational research programme will integrate scientific investigations (genomics, bioinformatics, molecular biology and experimental surgical models) with clinical research to establish a framework for a personalised approach to the identification and management of high risk of scarring for glaucoma patients. We propose to start with a DNA-based approach to stratify patients with the highest risk of scarring. The data generated constitute a resource that will empower the development of a personalised medicine approach to surgical management for the first time.

A/PROF NG SIOK BIAN

Associate Professor
Department of Pathology, Yong Loo Lin School of Medicine, National University of Singapore

Senior Consultant
Department of Pathology, National University Hospital

Senior Consultant
National University Cancer Institute, Singapore

Epstein Barr Virus in ENKTL: Molecular Pathogenesis and Therapeutic Opportunity

Extranodal NK/T-cell lymphoma (ENKTL) is an EBV-associated, aggressive lymphoma prevalent in Asia and shows dismal treatment outcomes. Epstein-Barr virus (EBV) infection is thought to play a crucial role in the pathogenesis of ENKTL, but the precise mechanistic roles of the EBV latent genes and miRNAs in instigating aberrant NK-cell proliferation remain unclear. Defects in DNA damage response (DDR) and replication stress (RS) are established cancer hallmarks and our preliminary data has revealed enrichment of DDR signalling in ENKTL. EBV has been implicated in DDR in solid cancers but it remains unknown how different EBV latent genes/miRNAs may modulate DDR signalling and lead to lymphomagenesis in ENKTL. Meanwhile, accumulating evidence suggests that derailment in global DNA methylation may play a critical role in ENKTL pathogenesis. EBV infection is known to induce genome-wide gene methylation in cancer but it is currently unknown how EBV may modulate DNA methylation in ENKTL, and whether insight into EBV's effect on DNA methylome landscape may be of clinical importance.

For the current study, we aim to (i) unravel the mechanistic link between EBV and fundamental hallmarks of lymphomagenesis that may inform therapeutic directions for ENKTL by perturbing the expressions of specific EBV latent genes and miRNAs in in-vitro ENKTL models; (ii) elucidate the mechanistic association between EBV and DDR by studying DDR gene and protein expression and mutation in ENKTL patient samples, as well as investigate the effects of perturbing EBV latent genes/miRNAs on DDR signalling and DNA replication dynamics in vitro; (iii) investigate the differentially methylated regions of prognostic and therapeutic significance and examine the effect of EBV latent genes/miRNAs on the global methylation pattern of ENKTL. We foresee that an in-depth understanding of EBV's potentially diverse effects in driving lymphomagenesis may lead to more effective treatment options and diagnostic/prognostic modalities for ENKTL.

PROF LIM SENG GEE

Professor
Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore

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Immunological Approaches to Chronic Hepatitis B Functional Cure

Globally, 296 million have Chronic Hepatitis B (CHB), leading to increased deaths and cancer mortality. These can be reduced by 70% if patients achieve HBsAg loss or functional cure (FC). This rarely occurs with current antiviral therapies. Hence, new therapies are needed. These either target the virus or boost immunity to clear the virus. However, the immune mechanisms by which FC occurs are not well understood. High levels of the virus may exhaust immune cells but recovery of immune exhaustion may occur if virus levels decrease (especially HBsAg levels). This is supported by the high rates of FC in CHB on antiviral therapy who stop treatment. Consequently, methods and strategies of how low HBsAg levels can lead to immune recovery and FC are crucial. Preliminary data from our liver biopsy study suggests that HBV-specific CD4 cytotoxic T-cells were increased in patients with FC.

In Theme 1 of our proposal, we will use stored samples from our study of stopping antivirals in CHB patients with low qHBsAg (<100IU/ml), where 9/57 (16%) patients achieved FC to comprehensively (cytokine-chemokine analysis, immune cell phenotyping, HBV specific T cells using pooled peptides, single-cell transcriptomics) characterise immunological changes longitudinally. In our previous grant, we discovered a potent anti-HBV monoclonal antibody (mAb006-11, Singapore patent application:10202107784Y).

In theme 2, we aim to improve its antiviral efficacy by antibody engineering to enhance its half-life and antiviral efficacy to assess its potential. In theme 3, CHB patients with low qHBsAg(<100IU/ml) will be treated with a highly immunogenic HBV-CPG vaccine approved as a prophylactic vaccine(Heplisav-B). This takes place in a randomised control trial (2:1 randomisation, n=74, 80% power for 30% difference) in treated/untreated CHB patients to evaluate FC, and assess the immune mechanism of FC.

This proposal will lead to novel findings that advance the understanding and strategy to achieve FC.

PROF CHENG CHING-YU

Professor
Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore

Senior Clinician Scientist
Glaucoma Department, Singapore National Eye Centre

Transforming Population Eye Health Research (Transformer) Program: From Data and Algorithms to Precision Health

Visual impairment is a major global public health problem, further exacerbated by rapid ageing worldwide. Asia, home to 60% of the world's population, is particularly affected. More effective ways and strategies for detecting and managing diseases are needed. This warrants more 'precise' identification of risk factors and biomarkers of eye diseases to optimise screening and risk-stratification models in the Asian population. In this regard, epidemiological studies provide valuable insights. However, decade-long epidemiological eye cohorts are lacking worldwide. Furthermore, 'traditional statistical modelling' may no longer suffice in unlocking the full potential of population data, and novel approaches are needed. Hence, to transform the population eye health landscape, our program aims to advance precise population eye health through enriching population data and leveraging advanced digital innovations and analytics.

Aim 1: Building on the foundation of the Singapore Epidemiology of Eye Diseases (SEED) study (a multi-ethnic Asian cohort with Malays, Indians and Chinese) and completing its 12-year follow-up.

Aim 2: Establishing, through hybrid federated learning approaches, an integrative data-sharing platform for seamless data analysis across centres, forging wider interdisciplinary collaborations within and beyond Singapore.

Aim 3: Leveraging advanced analytics and big data to develop deep learning algorithms for predicting major blinding eye diseases and refine current models for detecting disease-related visual impairment and visually significant cataracts.

Aim 4: Translate algorithms into deployment for screening and evaluating the performance of the AI model for detecting visual impairment as a clinical decision support tool via a pragmatic randomised controlled trial.

Overall, our program is uniquely positioned to formulate precision health initiatives through granular population data and world-class digital innovations. Collectively, these multipronged action plans will culminate in healthy longevity for our ageing society.

A/PROF IAIN TAN

Senior Consultant
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Associate Professor
Duke-NUS Medical School

Characterising the Immune Microenvironment to Inform Stratified Immunotherapeutic Approaches in MSS Metastatic Colorectal Cancer (MSS-mCRC)

Colorectal cancer (CRC) is the third most common cancer globally. ~95% of mCRC are microsatellite-stable (MSS), MSS-mCRC is refractory to PD1/PDL1 immune checkpoint inhibition with near 0% objective response rates. Current trials generally evaluate 1 combination across all patients with MSS-mCRC, taking it as a single disease entity. MSS-CRC is a heterogeneous disease. In July 2022, we used single cell and bulk omics to update the classification system of CRC, the IMF classification, comprising MSI-H cancers and 4 distinct subsets of MSS-CRC, defined by 2 malignant epithelial cell states and the extent of fibrosis. The 4 molecular subsets of MSS-CRC are characterised by distinct unique molecular features and different component cell types within their TME. Continuing our team's work, the overall objective is to inform stratified immunotherapeutic approaches, tailored to different subsets of MSS-mCRC, through spatial biology, humanised mouse models and histopathological stains. We aim to characterise the cellular composition, spatial organisation and tumour-stromal-immune interactions of different subsets of MSS-CRC and at different metastatic sites. We aim to establish humanised mouse models for pre-clinical evaluation of immunotherapy combinations in different subsets of MSS-CRC. We aim to identify antigen targets that can be further developed into clinical assays.

PROF ECOSSE LAMOUREUX

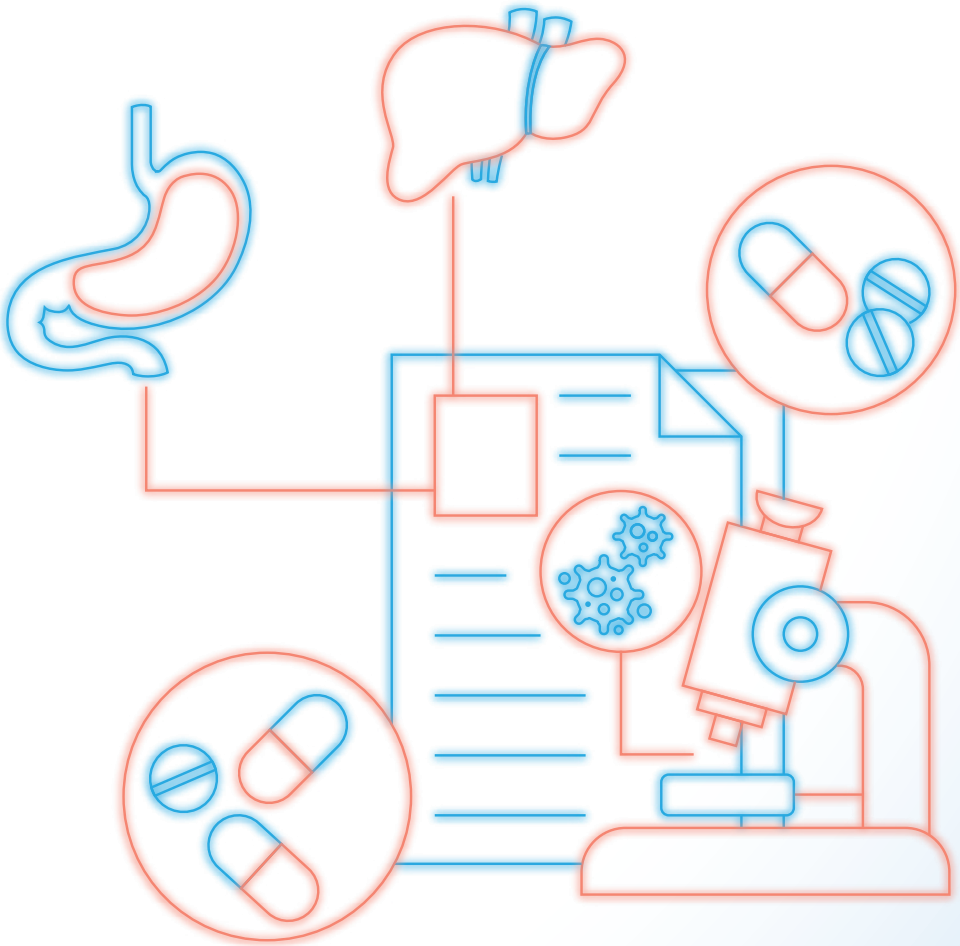
Professor
Health Services Systems Research Department, Duke-NUS Medical School

Director
Population Health and Clinical Epidemiology Platform, Singapore Eye Research Institute

The SenseHealth Research Programme: Untangling the Complex Relationship Between the Severity/Laterality of Age-related Sensory Decline and Frailty in Elderly Singaporeans Through Novel Risk Factors, Non-invasive Biomarkers, Patient-centred Impact, and Potential Intervention Targets to Improve Frailty Outcomes

Age-related vision and hearing impairments (VI and HI) alone, not including combined (dual sensory impairment [DSI]), are potential risk factors of physical frailty in older adults. However, the contribution of the severity and laterality of VI, HI or DSI in the development and progression of frailty remain unclear in elderly individuals at a population-based level. Similarly, prospective data on the factors underpinning the VI/HI/DSI-frailty relationships and the patient-reported impact and economic burden of concomitant frailty and sensory impairments remain scarce, while the effectiveness of sensory treatments to prevent frailty are non-existent. Addressing these knowledge gaps is the focus of this submission through four inter-related objectives.

First, we will recall participants of the PopulatION HEalth and Age-Related SEnsory Decline PRofilE (PIONEER) study, comprising multi-ethnic Singapore residents aged ≥60 years, and evaluate the temporal relationship of the severity and laterality of baseline VI, HI and DSI with frailty at their 4-year follow-up visit to determine their potential as risk factors and susceptibility and prognostic biomarkers. Second, the factors mediating the association between VI/HI/DSI and the incidence/progression of frailty will be investigated in the same population. Third, we will explore the longitudinal impact of concomitant frailty and sensory impairment on several important patient-related outcomes, including falls, loneliness, functioning, quality of life, personal and economic hardships, thereby providing novel in-depth insights into the consequences of combined frailty-sensory losses from the patient's perspective. Finally, we will determine the real-world effectiveness of commonly available sensory treatments for correctable sensory losses in reducing frailty incidence and progression in individuals following sensory treatment gains. Using a mixed-method research design, we aim to identify the barriers and facilitators to the uptake and short- and long-term adherence of these treatments and formulate evidence-based recommendations to improve the uptake and adherence of real world sensory treatments.



CLINICIAN SCIENTIST AWARD (INVESTIGATOR) RECIPIENTS

DR CHAO YINXIA

Junior Principal Investigator
National Neuroscience Institute

Assistant Professor
Duke-NUS Medical School

MicroRNA-mediated Neurodegeneration in Parkinson's Disease

Parkinson's disease (PD) is the most common motor disorder and the second-most prevalent neurodegenerative disease in the ageing population. Owing to many gaps in knowledge about this disease, current treatment methods only provide symptomatic relief and not neuroprotection. Previously, our lab has shown that there is an upregulation of miR-9 and miR-219 in the substantia nigra pars compacta (SNc) in the mouse model of PD 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice. This trend is also similarly observed in the post-mortem SNc of PD patients. We have also demonstrated the neurotoxic effect of miRNA-9 dysregulation in dopaminergic neurons using both in vitro and in vivo animal models, and identifying its target protein V.

In this study, we will 1) screen and compare the plasma levels of miRNAs and their target proteins between PD patients and health controls in 3 PD case-control cohorts; 2) monitor and correlate changes in plasma levels of miRNAs and their target proteins with motor and non-motor symptom progression in PD patients; 3) investigate the toxic effect of miRNA9, miRNA219 and other candidate miRNAs dysregulation on dopaminergic neurons in drosophila; and 4) investigate the functions and mechanisms of miRNA9, miRNA219 and other candidate miRNAs in in vitro PD models and screen their potential proteins.

Utilising 3 case-control cohorts, we aim to document that specific miRNAs (such as miRNA9) are dysregulated in PD patients compared to healthy controls. Abnormal expression of miRNA9 and other candidate miRNAs can lead to DA neuron death potentially through interaction with their target proteins. MiRNAs and their target proteins can be used as biomarkers for PD diagnosis and prognosis. They may also serve as therapeutic targets in PD treatment.

A/PROF SANJAY HARESH CHOTIRMALL

Associate Professor and Provost's Chair in Molecular Medicine
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Indoor Air Microbiomes as a Gateway to Exposome-guided Precision Medicine for Respiratory Disease

In today's world, breathing 22,000 times a day can mean inhaling 11,000 litres of polluted air. This is equivalent to the health risk experienced by a heavy smoker. Air quality remains a key risk factor for ill health in South Asia, reducing life expectancy and contributing to disability. Ambient (outdoor) and household (indoor) air pollution both contribute towards limiting lung capacity and provoking cardiorespiratory and metabolic disease. Indoor air quality influences chronic respiratory disease. Despite this, we know little about microbes inhabiting the urban ecosystem of air. While significant work has focused on outdoor air, limited reports of indoor air exist, and no study has attempted exposome-guided precision medicine by assessing indoor air microbiomes. This proposal addresses this knowledge gap using novel, prospective and integrative approaches. It also employs an experienced interdisciplinary team and multi-centre patient recruitment. While human microbiomes are recognised in health and disease, limited knowledge exists on air microbiome composition, a planetary ecosystem with which our lungs interact with every breath. Our central hypothesis is that air microbiomes, within patients' homes, influence respiratory status and present a novel, unexplored target for intervention.

If proven, the concept of "treating the environment rather than patient" to alter disease represents a global paradigm shift of significant impact. Manipulating "home-exposomes" is a fresh approach to improving airway health. Through metagenomics, bioinformatics and strong preliminary findings, we build on published works that Singaporeans exhibit distinct airway microbiomes reflective of our tropical and urbanised environmental exposures. Our aims include:

Aim 1: Expounding on home-host-environment interactions by determining indoor air (home), airway (host) and device (environment) microbiome composition explicating interactions.

Aim 2: Developing a novel bioinformatics analytical pipeline to integrate clinical and environmental data for precision medicine.

Targeting exposome-associated microbes employs an innovative approach revolutionising the implementation of "microbiomics" into clinical practice.

DR MATTHEW EDWARD COVE

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Assistant Professor
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Design and Testing of a Novel Respiratory Dialysis System to Reduce Lung Injury during Mechanical Ventilation — A Safety and Physiology Study in a Large Animal Model of Hypercapnia

Each year, 20 million patients require mechanical ventilation. Although life-saving, mechanical ventilation causes lung injury that may develop into acute respiratory distress syndrome. Low-tidal volume ventilation reduces lung injury but leads to harmful carbon dioxide (CO2) accumulation. Extracorporeal CO2 removal (ECCO2R) removes excess CO2, facilitating low-tidal volume ventilation. ECCO2R also helps some patients avoid mechanical ventilation, thus eliminating opportunities for ventilator complications to develop. But ECCO2R is complex, expensive and unavailable in most hospitals. We are developing an approach of removing CO2 in the form of bicarbonate using dialysis because dialysis equipment, in contrast to ECCO2R, is readily available in most hospitals.

In previous work funded by an NMRC Transition Award, we demonstrated that removal of bicarbonate using dialysis lowers plasma CO2, but our prototype exposed recipients to excessive dialysis doses. In work funded by an NMRC Clinician Innovator Award, we collaborated with NUS chemists to design a novel buffering molecule that cannot cross dialysis membranes. This allows us to construct dialysates containing almost no bicarbonate while retaining a physiological pH. The overall goal of the current study is to test the hypothesis that CO2 removal with our new dialysate is safe and efficient, and to show that we can minimise electrolyte losses by designing personalising dialysis fluids. We will test this by completing two specific aims.

Aim 1: Showing that dialysates containing our new buffering molecule can be used with conventional dialysis equipment to safely remove clinically meaningful amounts of CO2 in a large animal model.

Aim 2: Measuring CO2 kinetics and electrolyte changes during bicarbonate dialysis, and use these data to develop a method for creating personalised dialysis fluids that minimise electrolyte losses. Successful completion of our proposed work will demonstrate our system is efficient and safe enough for translation into first-in-man studies.

DR SAUMYA SHEKHAR JAMUAR

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SUREFIND-NDD: Singapore Undiagnosed Disease Research Endeavour for Identification of Novel Genetic Discoveries in Neurodevelopmental Disorders

Neurodevelopmental disorders (NDDs) are socially debilitating disorders affecting ~5% of the paediatric population in Singapore, and have considerable overlap with adult neurological disorders. Although there is a strong genetic component to NDD, due to extreme genetic heterogeneity, a cause cannot be identified in the majority of individuals by traditional methods of genetic testing. Recently, the advent of complementary genetic tools such as whole-genome sequencing (WGS), transcriptome sequencing and long-read genomic sequencing have emerged to allow one to comprehensively study genetic variants efficiently and cost-effectively in complex genetic disorders including NDD.

The overarching goal of this research, then, is to use multi-omics analysis to improve our understanding of NDD and use this knowledge to gain insights to identify potential biomarkers and therapeutic targets. Over the past seven years, the applicant and team have recruited over 100 families referred to our genetics clinics across Singapore Health Services (SingHealth), including KK Women's and Children's Hospital, National Neuroscience Institute and National University Hospital for evaluation for NDD, the majority of whom remain undiagnosed despite whole-exome sequencing. This CSA proposal will help the applicant continue to have protected time and fund infrastructure to continue this programme for the recruitment, phenotyping and analysis of patients with undiagnosed diseases. We will apply WGS, blood transcriptome sequencing and long-read sequencing to define high-risk genes within our local population. Bioinformatic algorithms and in-house analytical pipelines will be utilised to identify the causal genes and drive novel gene discoveries.

The use of these complementary technologies will allow us to identify the underlying aetiology for NDDs. Elucidating the genetic causes will allow us to understand molecular pathways and provide insights into potential biomarkers and therapeutic targets. Given the overlap with adult neurological disorders, understanding from these rare disorders can be applied to the commoner adult disorders.

DR ANAND JEYASEKHARAN

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Mechanisms and Therapeutic Relevance of the Interaction between Genotoxic Chemotherapy and Complement Regulators in Lymphoma

Diffuse large B cell lymphoma (DLBCL) is the most common haematological cancer worldwide and in Singapore. Despite good overall responses to the standard first-line regimen of R-CHOP (chemotherapy and an anti-CD20 monoclonal antibody Rituximab), up to 40% of cases will relapse. The majority of these will succumb to the disease despite transient disease reduction with subsequent Rituximab-chemotherapy, highlighting the need for strategies to improve chemotherapy combinations in relapsed DLBCL. Modulating immune clearance of cancer cells after chemotherapy represents a promising approach, as the immune contexture of DLBCL is a critical determinant of relapse-free survival after R-CHOP. We recently discovered that chemotherapy upregulates membrane complement regulatory proteins (mCRPs); which are cell-surface proteins that control the innate immune complement system. We hypothesise that, through the modulation of mCRPs, chemotherapy-induced DNA damage in cancer modifies complement-dependent effects on the immune system—both lytic (innate) and non-lytic (innate/adaptive).

In this proposal, using DLBCL as our model, we intend to identify mechanisms by which DNA damage leads to the upregulation of complement regulators, and its downstream effects in cancer. We will use clinical-grade inhibitors and CRISPR-based genetic screens to decipher signalling pathways involved in chemotherapy-induced mCRP upregulation. We have optimised an in-vitro assay of Rituximab complement dependent cytotoxicity (CDC) as a functional readout for these experiments. We plan to assess the consequence of chemotherapy-induced mCRP upregulation on complement-related phenotypes/immune infiltration using in-vitro co-culture assays and dual-humanised mice with a functional human complement system. Finally, we will study the relationship between mCRPs and the immune microenvironment of DLBCL clinical samples using single-cell RNA sequencing (scRNAseq) and quantitative multiplexed imaging. Chemotherapy-induced changes in mCRPs are hitherto unknown. We expect this project to yield valuable new information on its mechanism and immunomodulatory effect, with the potential for translation to novel therapeutic strategies for relapsed DLBCL.

A/PROF MELVIN CHUA LEE KIANG

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Germline and Somatic Mutational Correlates of Tumour Aggression and Radioresistance in Nasopharyngeal Carcinoma

NPC is a unique Asian-specific head and neck cancer affecting ~200 males in Singapore annually. Survival rates of this cancer have improved in the past decade, driven by advances in precise radiotherapy delivery. In locoregionally-advanced patients, treatment intensification with chemotherapy is recommended. Circulating EBV DNA (as a liquid biopsy) has proven utility in NPC for staging and on-treatment monitoring. However, cfEBV DNA remains a quantitative biomarker and yields limited insights on molecular processes underpinning tumour aggression and radio-/chemo-resistance. To fill this gap, we have performed the germline and somatic mutational profiling of ~900 NPC patients. We discovered a germline variant (rs1131636-T) localised at the RPA1 gene that predicted for inferior survival following radiotherapy. We elucidated that rs1131636-T conferred a radioresistant phenotype through loss of transcriptional downregulation of RPA1 by altering the binding of miR-1253 to the 3'-UTR gene-region. These observations corresponded to an overexpression of RPA1 in post-radiotherapy recurrences as compared to paired pre-radiotherapy tumours. Building on these findings, we now propose to investigate for other germline and somatic correlates of tumour aggression in NPC.

Aim 1: Expanding on our prior discovery and investigating for additional germline and somatic variants that are associated with clinical outcomes.

Aim 2: Exploring our paired genome-transcriptome dataset to characterise the regulatory network of RPA1 and other significant genes (from Aim 1), so as to identify aberrant pathways linked to NPC radioresistance.

Aim 3: Functionally validating these findings using our in-house-derived radioresistant NPC models (RR-C666-1, RR-HK-1). Additionally, we will utilise high-throughput drug screens to derive efficacious drug/drug combinations against radioresistant NPC.

This proposal is poised to enable the discovery of a broad panel of biomarkers to identify NPC patients with radioresistant disease, who may be amendable to novel drug-radiotherapy combinations, which will be conceptualised based on our findings.

DR LI LINGJUN

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National University of Singapore

Studying the Heterogeneity of Gestational Diabetes Mellitus: Cardio-Metabolic Alteration and Treatment Response in a Multi-ethnic Population in Singapore (GDM-CARE)

The transient hyperglycemia first identified during pregnancy is also known as gestational diabetes mellitus (GDM), and it increases risks of adverse pregnancy and neonatal outcomes like pre-eclampsia and macrosomia. With the phenomenal spread of overweight and obesity and genetic susceptibility, GDM is more prevalent in Asian pregnant women (i.e. 2- to 3-fold greater) as compared with European pregnant women, especially ranging from 15% to 30% in Chinese and Indian descendants. Emerging evidence shows that a potential variation in insulin sensitivity, fat deposition and ß-cell activity might underlie across heterogeneous GDM phenotypes, which lead to different pregnancy outcomes and maternal diabetic progression. However, the current clinical treatment and follow-up strategy against GDM is applying a "one-for-all" solution regardless of the variations in GDM pathophysiology. The efficiency and efficacy of the current clinical approach during pregnancy and after delivery, hence, is poor. In this Clinician Scientist Award Investigator (CSA-INV) proposal, our objective is to define GDM heterogeneity in terms of cardio-metabolic profiling in vivo and treatment response during pregnancy, by using a set of unique and novel technologies (i.e. continuous glucose profiling and untargeted metabolites profiling). We hypothesise that understanding GDM phenotypes clinically and molecularly will help in tailoring effective treatment strategies to individuals, and even in predicting and preventing postnatal abnormal glucose metabolism. In this proposed 3-year pregnancy cohort, we will conduct a longitudinal study among 800 overweight (23-24.9 kg/m2) or obese (≥25 kg/m2) singleton pregnant women no later than 12 weeks of gestation—without a history of diabetes and composed of Chinese, Malay and Indian ethnicities—in a Singaporean tertiary hospital (National University Hospital: NUH). All of them will be screened for GDM at 24-28 weeks of gestation and followed through until delivery. Our primary outcome is the GDM phenotype-specific continuous glycemic profiling and cardio-metabolic biomarkers alteration; and our secondary outcome is the GDM phenotype-specific treatment response.

A/PROF LIM SU CHI

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Prospective Study of Biomarkers for Diabetic Kidney Disease Progression in Younger-onset Type 2 Diabetes — from Biology-informed Targeted Proteomics to Trans-omics

Younger-onset type 2 diabetes (YT2D, onset-age≤40) is increasingly prevalent due to childhood and adolescent obesity. We recently reported that YT2D is associated with rapid diabetic kidney disease (DKD) progression. However, the reason for such an aggressive disease-trajectory is unclear. Data from our group and others have suggested the importance of systemic inflammation, vaso-active factors and renal-tubular injury. However, these factors (likely pertinent for YT2D), have not been specifically studied in this high-risk population.

We hypothesise that proteomics targeting the above patho-biology can predict renal-progression among YT2D. We will (i) perform targeted plasma and urine candidate-panel proteomics at baseline and investigate their association with DKD progression prospectively over a ~3 year-period among YT2D (with replication); and (ii) evaluate potential casual-inference using trans-omic (genomics and proteomics) analysis, i.e. Mendelian Randomisation (MR).

From our prospective diabetic cohorts (DN, SMART2D, DORIS, MODY and YOLO combined N~8,000), we have identified 990 YT2D, defined as individuals with non-type 1 diabetes, onset ≤40 years old. We will specifically evaluate the following biomarkers for these DKD progressions: (i) systemic-inflammation with TNF receptors 1 and 2 (sTNFR1 and sTNRF2), haptoglobin; (ii) the vaso-active factors of pigment epithelium-derived factor (PEDF) and Leucine-rich alpha-2-glycoprotein-1 (LRG1) and; (iii) renal-tubular injury: kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL).

For discovery, five selected OLINK multiplex panels with relevant candidate-peptides will be performed in 400 (200-pairs) DKD progressor and non-progressor, defined according to KDIGO's (Kidney Disease–Improving Global Outcomes) criteria. Novel signals will be validated in the remaining ~300 samples. Together with already-available GWAS data, trans-omics analysis using MR causal-inference will be performed. Our data will improve the risk-stratification of DKD, gain insights into its patho-biology and may inform therapeutic targets for YT2D.

DR LIU YU-CHI

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Risk Stratification of Neuropathic Ocular Surface Dysfunction Using Neural Imaging Metrics, Molecular Biomarkers and Artificial Intelligence

Neuropathic ocular surface dysfunction (OSD) is the leading cause of corneal morbidity. The current unmet need and challenge is the early diagnosis and risk stratification of these patients, as patients with early-stage disease are frequently asymptomatic, and current clinical assessments are insensitive to monitor the disease progression precisely. This leads to delayed diagnosis and under-diagnosis, and results in a high economic burden. In the proposal, our central hypothesis is that specific imaging-based features of the corneal nerves, together with specific ocular surface molecular profiles in the neuroinflammatory pathway, are associated with patients' clinical severity of neuropathic OSD.

We first aim to identify the corneal neural imaging and ocular surface molecular biomarkers that are associated with clinical phenotypes of neuropathic OSD (Aims 1 and 2). A total of 515 patients with neuropathic OSD due to either refractive surgery or diabetic mellitus will be recruited. Detailed ocular surface clinical assessment, in-vivo confocal microscopy imaging on corneal nerves, and multi-omic analysis of tear samples, will be performed over an 18-month follow-up period. By incorporating the multimodal longitudinal data, including the clinical characteristics, corneal nerve imaging features and ocular surface multi-omic profiles, we will build a risk stratification algorithm using machine learning techniques (Aim 3). The development of a risk stratification system will allow clinicians to identify those subclinical cases who are at risk of development of OSD, and those cases at risk of progression to moderate and severe OSD. Stratified and strategic management can be delivered, enhancing evidence-based clinical practice and precision medicine.

The study will also provide a novel integrated approach to better understand the pathogenesis of neuropathic OSD. Furthermore, the proteomic and metabolomic markers identified may open new avenues for novel treatment and diagnostic kits for neuropathic OSD.

A/PROF CITRA NURFARAH BINTE ZAINI MATTAR

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Novel Precision Technologies to CorrecT β-Thalassaemia Major: In Vivo AAV-mediated Base-editing of the Commonest Asian IVS1-5(G>C) mutation in Haemopoetic Stem Cells, Utilising Engineered AAV, Personalised Humanised Mouse Models and In Vitro HSC Engineering to Address Critical Translational Questions

Major ß-thalassaemia impacts significantly on medico-economic resources, particularly in populations with high carrier prevalence. This global disease causes 3-4% of early-childhood deaths annually, with severe chronic morbidity arising from progressive disease and inadequate treatment. Gold-standard haemopoetic stem-cell transplantation (HSC-T) is not available to all patients. There is still no universal, affordable and curative treatment for those without a matched haemopoetic stem cells (HSC) donor. Current ex vivo gene therapy trials are extremely costly and risk myeloablation complications. We investigate in-vivo Adeno-associated virus (AAV)-mediated base-editing to correct the commonest single nucleotide variant causing transfusion-dependent thalassaemia (TDT) in a proof-of-concept study utilising personalised humanised mice produced with patient-derived HSC, testing the hypothesis that optimised AAV-mediated delivery of base-editing tools can efficiently correct the IVS1-5(G>C) mutation, the most prevalent across Asian populations.

The long-term aim is to enhance cost-effective precision therapy for major ß-thalassaemia and make it available to all patients. Our short-term aims are to produce an efficient base-editing strategy for in-vivo correction of IVS1-5(G>C) in engineered human HSC, optimise AAV-transduction of HSC in vivo using a humanised mouse model, and assess the safety and efficacy of in vivo AAV-mediated base-edited gene correction in the humanised mouse. We will assess transduction efficacy of several AAV vectors including engineered AAV in vitro, select the most effect AAV for further experiments, acquire TDT patient-derived HSC directly or by fibroblast reprogramming, optimise base editing strategies in-vitro and deliver base editing tools in vivo using a dual AAV strategy to assess long-term safety and efficacy.

This research is highly feasible with the team's collective expertise in gene modification therapies, preclinical models, HSC expansion and engineering, HSC-T in paediatric TDT and perinatal therapy. This novel and innovative study can expedite clinical trials and provide an urgently needed treatment potentially more accessible and cost-effective than current standards, poised to make a substantial global impact.

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Lee Kong Chian School of Medicine

Understanding Tumour Predisposition in Asia (UToPIA) Study: From Patient-centred Research to the Clinic

Cancer is a major focus of the precision medicine initiative. While the clinical validity, utility and actionability of testing at-risk individuals for high penetrance tumour predisposition genes (TPGs) is clear, 40% of individuals who undergo clinical testing today are found to have a genetic variant of unknown significance (VUS). Our proposal seeks to address and understand VUS in TPGs identified in Singaporeans through selecting individuals with VUS for functional evaluation and following up carriers with TPG VUS longitudinally to correlate with clinical outcomes.

Mutations in DNA repair pathway genes are responsible for the majority of tumour susceptibility we see in the clinic and are important targets for precision medicine. We will prioritise VUS in the DNA damage and repair Fanconi anemia (FA) pathway, specifically germline FANCI variants for functional analysis using patient-derived lymphoblastoid cell lines. In parallel, we will also evaluate selected patients with digenic/oligogenic germline variants in the FA pathway to better understand gene-gene interactions clinically. We will prospectively follow up with patients with a TPG VUS for evidence of overt clinical tumour development. All patient material needed for this study is available.

The study team has demonstrated the needed clinical, technical and scientific expertise for the proposed experiments with support from senior members of the study team. Our team has shown that successful classification of a VUS not only directly allows affected patients to receive prompt care; but also aids variant classification efforts globally. Data from this study will further inform on the optimal management of individuals with VUS in TPGs and will be used to guide future health policy decision-making.

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Prognostic Significance of Novel Multimodal Imaging for Diabetic Retinopathy: Can We Improve Diabetic Retinopathy Staging?

Diabetic retinopathy (DR) is one of the leading causes of blindness worldwide. Current DR classification is based on the Early Treatment of Diabetic Retinopathy Study (ETDRS) severity scale which evaluates the risk of progression to proliferative DR (PDR) from colour fundus photography (CFP). In the recommended paradigm of care, patients are managed based on DR severity. Those with referable diabetic retinopathy are referred to specialist clinics, where they are monitored for the development of vision threatening retinopathy (VTDR), which includes PDR and diabetic macular edema (DME) that requires active treatment (e.g. laser, anti-VEGF therapy) to prevent vision loss.

However, fewer than 10% of the referred diabetics require immediate intervention, resulting in a high burden of care, and the current DR classification does not predict the risk of endpoints like DME which has emerged as the main cause of visual impairment. Novel imaging modalities can improve our assessment of DR. Optical coherence tomography angiography (OCTA) allows non-invasive imaging of the retinal vasculature, delineating true capillary non-perfusion and retinal ischemia. Ultrawide field (UWF) imaging captures changes in the peripheral retina not seen on CFP. Imaging features identified on these modalities are associated with the incidence and progression of DR and DME.

Despite the success of these current classification systems, there is a pressing need to improve the current staging and classification of DR in order to better stratify the risk of VTDR, enable early identification and treatment, and facilitate the cost-effective management of DR.

In this proposal, we aim to conduct a long-term prospective study to evaluate the prognostic significant of multimodal imaging biomarkers for diabetic retinopathy progression and develop a novel DR staging algorithm based on these biomarkers to improve the staging for DR. We hypothesise that multimodal DR staging can better predict the risk of development of VTDR compared with ETDRS classification.

A/PROF SNG BAN LEONG

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Integrated Psychological Programme for Management of Postnatal Depression and Persistent Postpartum Pain after Childbirth CODEPAD — II (Collaborative Outcomes of Depression and Pain Associated with Delivery — II)

The childbirth process is associated with the risk of developing postnatal depression (PND) and persistent postpartum pain (PPP), which could contribute to maternal morbidity. There is a lack of routine structured and effective programmes in current practice to monitor and effectively manage PND and PPP. Our pilot study found specific pain and psychological vulnerability factors associated with increased risk of PND after childbirth.

We propose an integrated psychological programmme (IPP) consisting of mindfulness mobile application, music listening, digital health video counselling and mobile electronic survey to effectively prevent, detect, monitor, and treat PND and PPP. The primary aim is to determine whether the use of the IPP will result in lower incidence of PND after childbirth. We will also determine whether the use of the IPP will result in lower postnatal Edinburgh Postnatal Depression Scale (EPDS) scores in a subgroup of labouring women (with outcomes of vaginal or emergency Caesarean delivery) that may have increased risk factors for PND. The interplay of psychological and pain factors during the use of the IPP will also be determined using patient-centric outcomes (mother-child bonding, breastfeeding self-efficacy, quality of life). We will recruit 1,480 women undergoing childbirth at KK Hospital in this randomised controlled trial.

This proposal has the potential to recommend guidelines in community care and to incorporate digital health in the management of PND and PPP. The IPP will also provide patient-centered care tailored to the individual's needs and will have an immediate potential to improve the transition from hospital to community care in postnatal women health.

DR TAN YORK KIAT

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Personalised Rheumatoid Arthritis Therapeutic Strategies Incorporating Dynamic Observation of Joint Changes Using Ultrasound and Thermal Imaging Modalities

Despite therapeutic advances in rheumatoid arthritis (RA), there remain unmet clinical needs for improved disease control within the "window of opportunity" and better selection of Disease-Modifying Anti-Rheumatic Drugs (DMARDs) earlier using a personalised medicine approach. Current clinical practice follows a standard approach, whereby first-line treatment (e.g. methotrexate) is typically given for up to 6 months prior to second-line, more costly, biological DMARDs. Given that the response rate to methotrexate is 40-60%, many patients receive suboptimal treatment from the outset and miss the "window of opportunity", with resultant poorer outcomes.

We aim to utilise dynamic joint changes detected on ultrasound and thermal imaging to differentiate RA patients' responses to first-line treatment after the initial one- or three-month treatment period. If true, patients who may benefit from an earlier step-up to second-line therapy can do so without the need to wait up to 6 months as in current practice.

A clinic-based cohort of 214 RA patients commencing first-line therapy will be recruited and followed up for 6 months. Clinical, ultrasound, and thermal imaging joint assessments will be performed at baseline, 1-month, 3-month, and 6-month time-points. The therapeutic outcomes and whether or not scaling-up therapeutic decision at 6 months will be used as the "gold standard" to assess the prognostic performance of dynamic changes of imaging after the initial 1- or 3-month of first-line treatment (e.g. methotrexate). A prediction model will be built to help select patients who may benefit from an earlier step-up to second-line therapy (e.g. biological DMARDs).

If successful, this potentially paradigm-changing novel management approach will help address unmet clinical needs by improving RA disease control within the "window of opportunity" and allowing better selection of DMARDs earlier through a personalised medicine approach. It is a part of a Comprehensive Bio-Imaging Programme to improve RA/inflammatory arthritis patient care.

A/PROF TEY HONG LIANG

Head of Research and Senior Consultant
National Skin Centre

Associate Professor
Lee Kong Chian School of Medicine

Pathogenesis and Novel Preventive Treatment of Pathological Cutaneous Scarring: Role of SPARC and TH2 Immunological Milieu and Treatment with siRNA-embedded Dissolving Microneedles

Pathological scars, namely keloids and hypertrophic scars, are highly-prevalent conditions arising from the excessive deposition of irregular collagen matrix from the highly-proliferative fibroblasts during wound healing. Keloids are disfiguring, itchy, painful and may restrict mobility. At present, existing treatment options are poor and there is no preventive therapy. Keloid pathogenesis is highly complex, with localised chronic inflammation and accumulation of extracellular matrix components, especially collagen, extending beyond the original wound site. In fibrotic tissues, secreted protein acidic and rich in cysteine (SPARC) is significantly overexpressed and is crucial for incorporating soluble collagen into collagen fibrils. The Th2 immune response (IL-4, IL-5, IL-13) during wound healing also causes fibroblasts to differentiate into apoptosis-resistant myofibroblasts, resulting in persistent SPARC and collagen overexpression. We propose here a three-pronged approach to enhance the understanding of keloid pathogenesis and to deliver a novel preventive treatment for pathological cutaneous scarring. This is through (i) elucidating the roles of SPARC and immunological milieu in keloidal scar specimens and studying the therapeutic effects of dissolving microneedles-delivered small interfering RNA (siRNA) in (ii) rabbits and (iii) humans on scarring.

To understand the keloid immune microenvironment, we propose to use Visium 10x spatial transcriptomics (ST) as an unbiased screening tool, followed by immunohistochemistry for the Th2 immune response and to validate any leads identified from ST. We will then use three-dimensional (3D) volumetric imaging to understand 3D keloid architecture, particularly the spatial interaction of SPARC protein with collagen and fibroblasts. Next, a preclinical trial to test dissolvable microneedle patches containing siSPARC only, and siRNAs targeting SPARC and IL-4Ra will be tested in a rabbit ear hypertrophic scar model. The aim is to test the efficacy of a multi-target approach to prevent scarring. Lastly, a clinical trial will be conducted with microneedles containing siSPARC, with an identified tangible pathway towards product commercialisation.

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Personalising Diabetic Retinopathy Screening Intervals via Risk Stratification Using an Artificial Intelligence-enabled Multi-modal Machine Learning Approach

Nearly 100,000 patients with diabetes are screened annually through the Singapore national DR screening program, the Singapore Integrated DR Programme (SiDRP). With the rising prevalence of diabetes and the aging population, the SiDRP is consistently challenged by the increasing DR screening workload.

DR screening workload can be reduced with two strategies: 1) automated grading; and 2) reduction in screening frequency for persons at low-risk of DR. For strategy 1), we have already developed, and will implement, an AI-based, automated DR screening tool. For strategy 2), we will develop a multi-modal DR predictive algorithm, DR-PREDICT, to identify persons with low-risk of DR incidence/progression within 3 years in this proposal (Aim 1). SiDRP retrospective dataset (2010-2019) consisted of patients' demographic, systemic risk factors and retinal imaging will be the development dataset, split into 80% training and 20% validation. We will use a combination of statistical, machine learning and deep learning techniques. Next, we plan to evaluate the diagnostic performance of DR-PREDICT and workload reduction using SiDRP dataset (2020-2023) for hypothetical modelling, where screening intervals increase from yearly to once every 2 or 3 years for persons with mild NPDR and predicted having low risk of DR progression, or thrice-yearly for those with no DR and predicted having low risk of DR development (Aim 2). We will also evaluate the generalisability of DR-PREDICT to external datasets of international studies (Aim 3). The diagnostic performance (area under the receiver operating characteristic curve, sensitivity, specificity with 95% confidence intervals) of DR-PREDICT will be evaluated against true incidence/progression.

Should DR-PREDICT prove to predict with sufficient precision, DR screening can be personalised based on individuals' DR risks, accompanied with robust monitoring screening attendance, to sustain local and international DR screening programmes for the ever-increasing DR screening demand.

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A Smart Digital Workflow Towards High Precision and Throughput Production for Removable Partial Dentures

Tooth loss, also termed edentulism, is a major dental problem worldwide, particularly among the senior population. A recent study in Singapore found that 69% of adults aged over 65 are wearing dentures. The high prevalence of tooth loss has resulted in high demands of prosthetic replacements, posing challenges to the public dental care system in Singapore. Removable partial dentures (RPDs) are the most commonly-used device to replace missing teeth and restore oral functions. However, the current analogue method to fabricate RPD is a time-consuming, complex, error-prone and expensive process. Due to the inherent inaccuracies in the technique, the fit of the framework and denture base is often undesirable to meet patients' requirements.

We have developed a dedicated "SMART RPD" software to process patient-specific digital intra-oral scan and automatically generate RPD framework designs. These designs can be simply edited and 3D-printed through a sintered laser-melting technique. We hypothesise that this "Smart workflow" is a more precise and efficient process in fabricating RPDs. This proposal seeks to validate this novel workflow through a randomised clinical trial via comparing the RPDs fabricated through the "Smart workflow" against that through the conventional analogue and partial digital workflows. We will evaluate the metal framework and the final RPDs for 1) adaptation of RPD framework; 2) fit of the RPD denture base and patient satisfaction; and 3) cost-minimisation of RPD fabrication process.

The long-term goal of this study is to reduce treatment cost and time, enhance the quality of RPD fabrication, and ultimately improve oral function and the overall quality of life of patients.

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Thermogel Enhanced Retinal Cell Therapy for Age-Related Retinal Degenerative Disease

Vision impairment due to age-related macular degeneration and inherited retinal dystrophies is a major global health issue. Irreversible loss of vision occurs in advanced disease, due to the loss of retinal pigment epithelial and photoreceptor cells. With no current effective clinical treatment, regenerative cell-based therapy represents an intuitive restorative approach to vision recovery.

However, several key challenges remain unaddressed, before retinal cell therapy can be adopted as a clinical standard of care. This includes (i) poor survival and functional integration of cells into the diseased host retinal micro-environment, (ii) sub-optimal surgical techniques for retinal cell transplant and (iii) lack of suitable large animal disease models to assess pre-clinical efficacy. Our patented biodegradable thermogel platform has been shown to function both as a vitreous substitute and an ocular drug delivery platform. We hypothesised that it can be used for the sustained delivery of neuroprotective growth factors to augment the outcome of retinal cell therapy.

In this proposal, we aim to develop an innovative, combinatorial cell and polymer-based neurotrophic factor delivery platform for validation in non-human primate retinal disease models. Specifically, we aim to (i) investigate the use of neurotrophic factors such as Rod-derived Cone Viability Factor to promote cell survival using in vitro iPSC retinal cells, (ii) investigate the use of thermogelling polymer as an intra-operative surgical adjunct for retinal cell transplant and (iii) develop NHP disease models for assessment of thermogelling polymer in vivo.

This proposal builds on the team's established track record in biomaterials, in vitro culture of iPSC-derived retinal cells and cell transplantation into NHP disease models. This represents an unprecedented opportunity to harness the combined promise of advanced biomaterials, iPSC technology and robust pre-clinical validation – to advance the field of regenerative cell therapy and help develop novel therapies for otherwise blinding and incurable retinal degenerative disease.

DR ANGELA SU-MEI KOH

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A Multi-centre Randomised Clinical Trial of Exercise to Retard Cardiovascular Ageing

PROJECT BACKGROUND: Deleterious alterations in cardiovascular (CV) structure and function increase the risks of ageing-related CVD. We found that these CV alterations were associated with circulating serum metabolites linked to tricarboxylic acid (TCA) cycle activity and beta oxidation of fatty acids, suggesting a metabolic basis for CV ageing. Additionally, these CV alterations correlated with exercise levels and changes in metabolite profiles. We hypothesise that modifying these metabolites by intervention, such as exercise, may retard CV alterations and reduce CVD in ageing.

METHODOLOGY/APPROACH: Using a multi-centre clinical trial study design, participants with CV alterations (total N=450) will be stratified based on their serum levels of metabolites (high versus low serum levels of TCA cycle and fatty acid metabolites). Participants from each stratum will be randomised to receive either a 3-month exercise program intervention (2 times per week, 60 minutes each session) or no exercise. Participants will undergo cardiovascular imaging and metabolic profiling at the start and end of the study. We will determine if exercise can reverse high-risk metabolic profiles and improve cardiovascular structure and function. Secondary outcomes include physical skeletal muscle function and frailty scores. Associated factors such as dietary, comorbidities, quality of life and related habits will be tracked simultaneously by questionnaire and proprietary cardiac health mobile application. An explainable artificial intelligence-based cardiac network tool that incorporates medical imaging data, biological/blood measurements and clinical information will be used for data analysis.

SIGNIFICANCE: Without clear mechanisms to explain cardiovascular ageing nor interventions known to retard cardiovascular ageing, our approach will provide much-needed translational evidence to incorporate targeted interventions aimed at reducing cardiovascular disease risk in older populations. This trial would provide more definitive evidence for abnormal metabolism as a driver of cardiovascular ageing and offer a blueprint for measures to prevent and treat ageing-related CVD.

DR CATHERINE ONG

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Diabetes Mellitus and Dysregulated Angiogenesis in Pulmonary Tuberculosis

PROJECT BACKGROUND: Diabetes mellitus (DM) worsens tuberculosis (TB), one of the leading causes of death from an infectious disease. Uncontrolled DM-TB patients are more likely to die and remain infectious longer despite effective treatment. The reasons underlying the worse DM-TB phenotype are unknown. Angiogenic factors (AF) are upregulated in TB patients without DM. The effect of clinically-approved angiogenic inhibitors on survival and Mycobacterium tuberculosis (Mtb) burden in DM-TB has not been determined. We hypothesise that targeting dysregulated angiogenesis from uncontrolled DM reduces immunopathology in pulmonary TB.

SPECIFIC AIMS: Our specific aims are to determine

1) whether the expression of AF is increased in DM-TB patients compared to TB patients without DM;
2) the regulation of AF in the DM-pulmonary TB murine model; and
3) the effects of clinically-approved anti-AF drugs on immunopathology in the DM-pulmonary TB model.

METHODOLOGY/APPROACH: First, AF will be phenotyped in an existing cohort of 60 DM-TB and TB patients recruited in Singapore. AF proteins and gene expression will be analysed using Luminex bead array and single-cell RNA sequencing. Lung granulomas from ten DM-TB and TB patients will be examined for AF expression and 3-dimensional granuloma vasculature. Expression of AF on immune cells will be analysed by flow cytometry in a DM-TB murine model. 3-dimensional granuloma vasculature and intracellular signalling pathways regulating angiogenesis will be examined using chemical inhibitors. Finally, the effects of angiogenesis inhibition on the improvement of TB immunopathology will be examined. Mtb-infected DM mice will be administered two candidate angiogenic inhibitors with standard TB drugs. The effects of TB drug penetration into the murine lung, the morphology of granuloma vasculature and hypoxia markers will be assessed.

SIGNIFICANCE: This project determines if angiogenesis inhibition will improve TB-DM immunopathology. The results will positively impact the launch of the Phase 2 clinical trial to improve the treatment outcomes of DM-TB patients.

DR ADELINE NG

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A Comprehensive Study of NOTCH2NLC-related Neurological Disorders

GC-containing repeat expansions in the NOTCH2NLC gene have been associated with neurological diseases, including neuronal intranuclear inclusion body disease (NIID), essential tremor (ET) and PD. Phenotypic manifestations of NOTCH2NLC GGC expansions are heterogenous, and the prevalence across neurological disorders is unknown. Repeat lengths of >60 to 500 units have been reported pathogenic but the pathophysiological role and prevalence of "intermediate-length" GGC repeats (>40 units) remains unknown. Furthermore, the influence of repeat composition and repeat interruptions on clinical expression requires further investigation. To address these gaps, we aim to comprehensively study NOTCH2NLC-related neurological disorders using a combined approach incorporating long-read sequencing, family studies and genotype-phenotype correlation with imaging and blood-based biomarkers.

Using repeat-primed polymerase chain reaction, we will screen 600 "enriched" cases with neurological disorders and 2000 healthy controls for repeat expansions in NOTCH2NLC. Cases carrying longer repeats (>40 GGC repeats) will undergo further long-read sequencing (LRS) to quantify repeat length and interrogate repeat composition. Suitable cases with longer/pathogenic expansions (>40 units) will undergo detailed clinical phenotyping, family studies, and clinical follow-up with imaging and blood-based biomarkers. LRS performed on these cases will provide more accurate information on repeat composition (e.g., repeat interruptions) that may act as disease modifiers. First-degree relatives will also be screened for the presence of longer GGC repeats to provide important information on the stability of allele size in different generations.

This will be the first comprehensive study investigating the prevalence and role of NOTCH2NLC repeat expansions in neurological disorders. Questions concerning the role of intermediate-length repeat expansions and the influence of repeat composition and repeat interruptions on clinical expression will be addressed in this timely study. Findings from this study will contribute to our understanding of the mechanistic properties underpinning NOTCH2NLC GGC expansions and contribute to improved genotype-phenotype correlation and resolving genetically unexplained cases.

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Testing the Role of Peripheral Scleral and Choroidal Remodelling in Low, High and Pathologic Myopia

High myopia (HM), or extreme near-sightedness, can progress to pathologic myopia (PM), a leading cause of blindness worldwide. PM results from progressive, lifelong and extreme eye elongation with subsequent eye wall (sclera) thinning, allowing for focal outpouchings (staphyloma), which arise concurrently with vision-threatening changes (e.g. myopic macular degeneration, MMD). Only a better understanding of the underlying tissue remodelling changes in PM will allow for preventive therapies.

Both scleral and choroidal remodelling have been suggested to underlie staphyloma formation, chorioretinal damage in MMD and myopic choroidal neovascularisation (mCNV). However, the underlying causal mechanism behind the progression of HM to PM is unknown, and insight is lacking regarding the timing and location of remodelling that drives progression. Specifically, defocus/hyperopia in the mid-periphery has been suggested to drive myopia and lead to the prolate eye shape (and counteracting this defocus may be a potential preventive treatment).

We now have novel imaging modalities: Fourier-domain mode-locked ultrawidefield optical coherence tomography (FDML UWFOCT that can acquire images wider, deeper and 17 times faster than existing clinical systems), ophthalmodynamometry (ODM) coupled with OCT to measure scleral rigidity and a polarisation sensitive OCT (PSOCT) that have all been validated in humans in vivo, and have established a cohort of >1,500 HM and PM subjects seen by the PI over the course of his initial CSA-Inv grant from which to draw. We therefore hypothesise that eye shape changes (a macroscopic, late manifestation of scleral remodelling), scleral collagen anisotropy (a microscopic, early manifestation of scleral remodelling) and choroidal vascular remodelling in the mid-peripheral regions of HM eyes differ from that found in PM eyes, may drive the progression of HM to PM, and progression of myopia in general, and may serve as an imaging biomarker for assessing risk, and direct timing of localised therapeutic and prophylactic treatments.

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Investigation of Drug-induced Toxic Optic Neuropathy Using Human Stem Cell-Derived Retinal Ganglion Cells

Drug-induced toxic neuropathy is a widespread clinical issue faced by neurologists and ophthalmologists alike. Multiple antibiotics and chemotherapeutic agents are the commonest culprits and cause significant morbidity including pain, paraesthesias; and with the optic nerve—blindness.

Retinal ganglion cells (RGC) are highly specialised neurons, similar to central and peripheral neurons, that traverse the optic nerve. They transmit visual signals from the eye to the brain; any dysfunction of these cells results in partial or total blindness. Backed by our clinical neuro-ophthalmology experience in drug-induced optic neuropathy and the fact that we have successfully established a stem cell-derived human retinal ganglion cell model (schRGC) to study optic nerve/ retinal ganglion cell diseases; in this proposal, we intend to address the problem of drug-induced neurotoxicity using this schRGC model.

Together with evidence from previous work in animal models and our own results in schRGC, we now have evidence for the first time that when exposed to toxic drugs like ethambutol, one of the earliest effects of the drug exposure in schRGC is mitochondrial dysfunction. We hypothesise that mitochondrial dysfunction is a key mechanism causing drug-induced toxicity in retinal ganglion cells; interrupting the pathways that result in drug-induced mitochondrial dysfunction will prevent neuronal toxicity.

To investigate this hypothesis and identify key features that diagnose and could prevent or treat drug-induced toxic neuropathy, we intend to use a comprehensive functional, proteomics and genomics approach to develop an in vitro diagnostic assay for drug-induced toxic optic neuropathy, identify key metabolic pathways that can be modified to reduce or prevent drug-induced toxicity in patients where drug cessation is not possible and identify genes that prevent or promote toxicity when modified, with potential for development of future therapeutics for drug-induced toxic neuropathy.

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Evaluation of the Efficacy and Safety of Antibiotic Therapeutic Drug Monitoring in Patients with Difficult-to-Treat Gram-Negative Bacterial (DT-GNB) Infections

Sepsis remains a major cause of morbidity and mortality worldwide in the face of antimicrobial resistance especially in patients with Gram-negative bacteria (GNB) infections. Limited new antibiotics for GNB infections pose a severe threat to clinical management of these patients and thus call for old antibiotics to be repurposed. Dosing regimens of old antibiotics often fail to achieve therapeutic drug concentrations in some septic patients.

Septic patients commonly have significant hemodynamic changes and/or undergo extracorporeal interventions that may increase patients' susceptibility to treatment failure and increase the chance of more resistant bacteria emergence, or toxicity from the antibiotic. Hence, the "one size fits all" dosing principle for antimicrobial treatments of suspect sepsis due to infection by antibiotic-resistant- or less susceptible-GNB [collectively known as "difficult-to-treat" (DT-GNB infections] is no longer viable. This will require therapeutic drug monitoring (TDM) to determine if the dosing is adequate to treat such infections. To this end, we have developed a novel TDM that covers eleven antibiotics for DT-GNB infections with a turnaround time of less than eight hours.

A prospective, open-label, randomised controlled trial will be conducted to evaluate a novel TDM-guided therapy in management of DT-GNB infections. We hypothesise that TDM-guided antibiotic therapy will reduce 14-day all-cause mortality by 6% (absolute risk reduction) in septic and acutely-ill patients with DT-GNB infections, when compared to standard therapy. TDM for 11 antibiotics will be performed for all trial patients although test information will be withheld for the standard therapy arm. The primary aim is to compare the 14-day all-cause mortality rates of novel TDM-guided antibiotic dosing versus standard therapy.

This proposal seeks to provide evidence supporting the application of TDM-guided antibiotic therapy on reducing mortality and morbidity among septic and acutely-ill patients with DT-GNB infections and significant hemodynamic changes, which can potentially shift current practice paradigms.

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Paracrine Factors and Their Inhibitors: A Novel Therapeutic Strategy for Peritoneal Carcinomatosis

Peritoneal carcinomatosis (PC) is a form of localised metastasis arising from any intra-abdominal organ, affecting up to 70% of colorectal cancers and 40% of gastric and ovarian cancers. There is a paucity of efficacious therapeutics and current therapy does not harness tumour biology. This proposal builds upon key findings from my Transition Award project (NMRC/TA/0061/2017) that led to a novel and recently published clinically actionable phenomenon "paracrine addiction", i.e. cancer cells depend on key paracrine factors within the fluid microenvironment for the formation of PC.

We identified plasminogen activator inhibitor-1 (PAI-1) as a key paracrine factor in PC, irrespective of histology, and demonstrated that PAI-1 ligand inhibition lowers tumour burden using unique models of patient-derived ascites-dependent xenografts (PDADXs), which incorporates the PC paracrine microenvironment. Here, we seek to utilise both targeted and unbiased approaches to develop novel PC therapeutics, decipher the mechanism underlying successful PAI-1 inhibition in PC via a CRISPR screen and identify additional druggable paracrine factors shortlisted via our CAPTIVATE platform. We hypothesise that paracrine factors drive PC progression and confer metastatic potential within the peritoneal cavity, and thus inhibition of key paracrine factors via intraperitoneal instillation of therapeutic agents is a novel and efficacious therapy for PC.

This proposal is built upon well-established collaborations and is supported by consortia that the PI has embedded himself within to combat PC. This proposal will generate robust scientific data that would form the foundation and rationale for our translational therapeutics program targeting PAI-1, which will be the critical starting point for the inception of a first-in-human clinical trial to improve survival outcomes of PC patients via PAI-1 ligand inhibition. Further, we will uncover other paracrine factors amenable to paracrine inhibition in PC, paving the way for future research in the development of PC therapeutic strategies and potentially other cancers and disease indications.

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Eradicating Minimal Residual Disease Using "Off The Shelf" Natural Killer Cells for Advanced Nasopharyngeal Carcinoma

NK cells are lymphocytes innately programmed to recognise and eliminate virally infected or mutated cells without the need to engage the class I major histocompatibility complex (MHC) molecule. This property enables them to play a crucial role to eliminate circulating cancer cells, which is essential to prevent carcinogenesis or minimise cancer relapses following definitive cancer treatment. It is therefore unsurprising that both quantities and functions of NK cells are frequently compromised in cancer patients. In locally endemic NPC that is ubiquitously associated with the EBV infection, the presence of detectable post-treatment circulating EBV-DNA has been well-documented to represent minimal residue disease (MRD). MRD portends a high risk of relapse following definitive treatment and thus a worse prognosis.

We hypothesised that infusing adjuvant functional activated NK cells eradicates post-treatment circulating EBV-DNA completely, from currently presenting in 30% of advanced NPC patients to 0%. To this end, our laboratory has developed a robust technique for expanding allogeneic NK cells from peripheral blood mononuclear cells to a nearly 350-fold increase over a 21-day expansion protocol. These expanded, enriched NK cells demonstrated in vitro potent cytotoxic ability against NPC cells. Furthermore, they were proven to be highly effective in vivo in suppressing NPC tumours and exerting an additive tumour suppressive effect when combined with cisplatin chemotherapy in NPC rodent models.

Building on these preliminary data and our previous success in applying autologous NK cell therapy in NPC patients, we propose a phase 1 leading to phase 2 clinical trial to evaluate the safety and preliminary efficacy of adjuvant, allogeneic NK cell treatment for locally advanced NPC patients. If successful, this pre-emptive strike using 'off the shelf' allogeneic NK cells to eliminate MRD among advanced NPC patients will reduce their risk of relapses and invariably improve the survival of these patients.

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Developing Individualised Bacteriophage-Antibiotic Combinations for Difficult-to-treat Bacterial Infections

Carbapenem-resistant Pseudomonas aeruginosa (CRPA), a highly-virulent pathogen, have resulted in debilitating infections despite long-term antibiotics with therapy and repeat surgeries. Phage therapy in combination with antibiotics has demonstrated success clinically for drug-resistant bacteria infections. Upon phage exposure, phage-resistant and antibiotic-susceptible bacterial variants became dominant and replaced the entire bacterial population. These bacterial variants have acquired mutation adaptation to evade phage infection (phage-resistant), resulting in the restoration of antibiotic sensitivities, as illustrated in one drug-resistant PA.

It is unknown if other outbreak CRPA strains behave similarly under phage pressure. In the current phage-antibiotic combination treatment, while the choice of phage is customised according to its effectiveness against the resistant bacteria, the choice of antibiotic remains empirical. Also, phage-antibiotics interactions have not been systematically evaluated. The lack of a scientific rationale in the choices of antibiotics to complement the customised phage therapy, and the limited understanding of phage-antibiotic interactions, greatly restricts the utility of phage-antibiotic combined therapy to treat drug-resistant bacterial infections.

I propose to establish a systematic and individualised approach to recommend appropriate phage-antibiotics combination therapies to achieve the best clinical outcomes through the following study aims.

1) to evaluate whether the hypervirulent outbreak strains of CRPA (phage-sensitive) become phage-resistant and antibiotic-susceptible subpopulation dominant after being exposed to phage, and if so, evaluate the genetic/transcriptomic changes associated with CRPA dominant population changes; and
2) to explore bacteriophages and antibiotics interactions in terms of therapeutic effects on different hypervirulent CRPA strains.

We hypothesise that: 1) After phage exposure, the CRPA population is dominated by phage-resistant subpopulations that are sensitive to antibiotics, confirmed by its genetic or transcriptomic trade-off changes; 2) Phage-antibiotics interactions as to treatment efficacy are bacterial strain-specific. Individualised, the appropriate phage-antibiotic combination is an ideal therapy approach for patients with persistent, drug-resistant bacterial infections, given the escalating crisis of antimicrobial resistance.

DR JACQUELINE CHUA

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Explainable Artificial Intelligence for Glaucoma Detection

Glaucoma is the leading cause of irreversible blindness worldwide. Early detection of glaucoma remains challenging. By the time the current method of visual field testing detects glaucoma, at least 25% of retinal ganglion cells (RGCs) are lost. Optical coherence tomography (OCT) imaging is commonly used to aid glaucoma diagnosis, but its ability for early detection remains inadequate. AI has the potential to provide earlier detection of glaucoma through the discovery of new disease-related patterns. Although AI models in glaucoma have demonstrated performance nearing human levels of accuracy, there is hesitance in adoption as AI models are difficult to interpret and have limited generalisability.

We have pilot data showing that the use of anatomy-based compensation reduced the aspect of ocular peculiarities from OCT data and significantly improved the performance of AI models for glaucoma detection in an independent external dataset of different ethnicity. We propose to use explainable AI methods and anatomically corrected OCT data in AI models to improve their interpretability and generalisability, respectively. The main objective of this proposal is to develop explainable AI methods to improve glaucoma detection and improve the robustness of AI algorithms across ethnicities, which will also provide an additional level of insight into an AI model's decisions. We hypothesise that our novel approach will significantly improve diagnostic performance in the early detection of glaucoma and optimise the role that OCT imaging plays in glaucoma management.

Early glaucoma diagnosis is essential to improving patient outcomes, as earlier treatment can prevent or slow the disease progression and thus preserve patients' visual function. Given that glaucomatous damage irreversibly leads to blindness at late stages, the outcome of this study, a novel method to advance glaucoma diagnosis, will greatly impact the prevention of blindness in Singapore and worldwide.

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Programme for Ocular Inflammation & Infection Translational Research (PROTON)

Intraocular inflammatory diseases account for a significant proportion of visual impairment, decrease in quality of life of patients and substantial economic cost for countries worldwide. Yet, much remains unknown about this heterogeneous disease. Often times, different conditions present with overlapping clinical signs, posing diagnostic challenges. Furthermore, the treatment for idiopathic orbital inflammatory diseases (IOIDs), such as corticosteroids, immunosuppressive agents, or biologics, have therapeutic responses and side effect profiles that vary greatly from patient to patient, making it difficult for ophthalmologists to weigh the risks and benefits for individual patients.

In recent years, a new area of interest known as biomarkers has come into the spotlight. Biomarkers such as proteomes, cytokines and inflammasomes have been increasingly observed to be secreted or activated in specific patterns in different conditions, acting as condition-specific signatures. For example, in the work done so far from the CSA-INV grant on ocular tuberculosis, we have observed differential cytokine and proteomic profile in patients with tubercular uveitis. The Programme for Ocular Inflammation & Infection Translational Research (PROTON) aims to build up on the CSA-INV grant awarded in 2020 and expand the use of uveitis registry to determine the specific clinical phenotypes. This assessment will be based on imaging patterns and biomarkers profile from ocular fluid and peripheral immune cells associated with individual uveitic conditions. By identifying these, we can better predict the likelihood of a specific diagnosis and the probability of treatment response.

The current proposal is a continuation of the prospective multicentre cross-sectional study (CSA-INV grant) and will additionally evaluate inflammasome and specific pathogens through VirScan testing besides clinical-image data collection, cytokine analysis, proteomics study and peripheral blood leukocyte immunophenotyping. These parameters will then be compared between subjects of varying diagnoses and treatment responses. In the future, biomarkers may allow for precision medicine and tailored treatments for individual patients with uveitis, leading to improved patient outcomes.

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The Singapore Platform for Controlled Human Infections with SARS-CoV-2 ('Sing-CoV')

The primary aim of this pilot-controlled human infection study ('Sing-CoV') is to confirm the safety and infectivity of the nasal inoculation of an infectious dose of a SARS-CoV-2 Delta variant in twenty seropositive healthy volunteers with a history of having received mRNA vaccination and Omicron variant infection. Specifically, this study has the following aims.

Aim 1: Establish a SARS-CoV-2 controlled human infection (CHI) model in previously vaccinated and infected seropositive volunteers in Singapore with an infection rate of 50-70%.

Aim 2: Characterise the clinical, virological and immunological responses following controlled inoculation of Delta variant SARS-CoV-2 in Singaporean volunteers.

Aim 3: Identify determinants of breakthrough infection and correlates of protection in individuals with pre-existing immunity.

Aim 4: Explore antigenic imprinting and the effects of pre-existing immunity on response to infection with an immune escape variant.

Aim 5: Examine the time course of the generation of respiratory aerosols containing infectious viruses from inoculation onwards.

We hypothesise that the infective SARS-CoV-2 dose determined in an ongoing study in seropositive individuals in the UK (Development of a SARS-CoV-2 Delta variant human infection challenge model (COVHIC002)) will have an acceptable safety profile as measured by the occurrence of adverse events (AEs) and serious adverse events (SAEs) from the viral challenge (Day 0) up to Day 28 follow up; and that it induces laboratory-confirmed infection in a comparable proportion of participants in a Singapore setting. The key secondary aim of this pilot study is to establish the framework for the safe conduct of CHI studies in Singapore and to build a multi-disciplinary consortium committed to pursuing CHI studies in COVID-19 and other infectious diseases for the development of novel vaccines and treatments in collaboration with local and international academic and industry partners.

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High-dimensional Approach to Understanding Immune Dysregulation in Lupus Towards Novel Therapy

Systemic Lupus Erythematosus (SLE) is a polygenic, systemic autoimmune disease with immune dysfunction driven dually by a lowered activation threshold for immune effector cells and an impaired immunoregulatory axis. Modulated by myriad mechanisms and interactions among varied immune cells, SLE's immunopathogenic complexity results in the marked heterogeneity of lupus clinical manifestations and responses to therapy. Childhood-onset disease is often more severe than adult-onset disease. Current treatments aim mainly to dampen the effector immune responses in which incomplete remission and flares after drug tapering are common.

There is therefore a critical unmet need to interrogate this disease spectrum, systematically and holistically, to identify the mechanism of tolerance loss in SLE such that strategies for the dual targeting of the effector and regulatory immune axes to restore immune homeostasis and achieve sustained remission can be developed. We aim to identify, in childhood and adult-onset SLE, the intracellular signalling milieus that reduce the activation threshold of effector immune cells and mechanisms that drive the defective compensatory immunoregulatory responses by regulatory B (Breg) and T (Treg) cells.

These pathognomonic immune signatures will be validated in a humanised lupus mouse model for follow-on preclinical development with intervention studies. As proof of concept, we have previously observed a reduction of cytotoxic T-lymphocyte-associated protein 4 (CTLA4) expression in the effector CD4+ T cells and an abnormal expansion of Treg-like T cells without the Treg phenotype marker, CD25, in our discovery adult lupus cohort.

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Evidence-based Lifestyle Interventions For The Delay Of Cognitive Decline Among Older Singaporeans: Cohort Study and Randomised Controlled Trial

We propose a study that combines observational and interventional study designs to investigate the relationship between lifestyle factors and cognitive decline among older Singaporeans and assess the feasibility and efficacy of lifestyle interventions in delaying cognitive decline. The cohort component will leverage an existing cohort, the Diet and Healthy Ageing (DaHA) cohort which has recruited over 1,000 participants with comprehensive lifestyle and cognitive data collected.

The intervention component will focus on the promotion of a brain-healthy lifestyle, with special attention paid to common problems among local older adults. The interventions include the promotion of physical, social, and cognitive activities; the control of cigarette smoking and alcohol intake; dietary modification based on local guidelines; increase in consumption of tea, mushrooms and vegetables; better management of hypertension, diabetes, metabolic syndrome and overweight through lifestyle changes; and early detection and management of depression and stress. Interventions will be delivered in two forms, with or without individualisation. In total, 120 older adults aged 60-75 years, who are at risk of dementia will be randomly allocated to one of the two intervention arms and control arm. The primary outcome is a change in processing speed. Secondary outcomes include epigenetic age, systemic chronic inflammation and other health-related measures.

We hypothesise that lifestyle factors are associated with cognitive decline, epigenetic age and systematic chronic inflammation and lifestyle interventions focusing on common problems among the local population. Such interventions delay cognitive decline, slow epigenetic ageing and produce favourable changes in inflammation markers. The study will provide evidence on the role of lifestyles in ageing and the biological changes after lifestyle interventions. The translation of our work into clinical practice could lead to healthier ageing population and reduced incidence of cognitive decline and subsequently result in sizable savings on the direct and indirect cost of dementia care in Singapore.

DR TEO WAN-YEE

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Precision Medicine PDOX (Patient-derived Orthotopic Xenograft) Modelling of Brain Tumor Microenvironment in Craniospinal-metastasising Brain Germinoma Phenotypes for Preclinical Testing (PreCIsionMOdELS 1.0)

PROJECT BACKGROUND: Pediatric brain cancer is the leading cause of death in childhood cancer. Intracranial germ cell tumour is an Asian-centric disease, and the majority (50-70%) are germinomas. No effective molecular inhibitors have been used in this disease—a lack of tumour models impeded preclinical drug development.

SPECIFIC AIMS: The goal of this proposal is to develop Precision PDOX (patient-derived orthotopic xenograft) Mouse Models of metastasising brain germinoma, capable of re-creating patient's sequence of metastases in the craniospinal axis in vivo, to provide biological tumour material from both primary (within the brain) and metastatic sites during the real-time in vivo evaluation of drug efficacy. Specifically, we will evaluate differences in the drug response of two clinical-stage molecular inhibitors, between primary site versus metastatic sites within a single mouse system, and elucidate distinct mechanisms in each site.

HYPOTHESIS: Based on our preliminary data, our working hypothesis is that there exist new secondary targets in the tumour microenvironment promoting metastases, which can be exploited for treatment strategies.

METHODOLOGY/APPROACH: We have successfully repositioned our PDOX Models from static (non-metastasising) to dynamic (metastasising) tumour models in vivo, by changing the macrophage microenvironment. These Models efficiently replicate the metastasising process of tumour cells in patients. Our panel of Precision Models provides an In Vivo Toolbox encompassing a spectrum of 4 new in vivo parameters representing a continuum of patient-relevant clinical features for preclinical testing. This will be an invaluable asset to the neurooncology community and pharmaceutical industry.

IMPORTANCE: 2FDA review of new anti-cancer drugs now includes assessment for substantial relevance to pediatric cancers. Our preclinical data will be crucial for driving FDA approval for molecular inhibitors for germinoma and metastases—currently there are none. Metastases cause 90% of cancer deaths worldwide. Drugs with tumour-killing capabilities may not have an equal ability to control metastatic spread—a significant determinant of survival outcome.

A/PROF ANGELA CHOW

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Different Strokes for Different Folks — Leveraging Community Social Networks for Public Health Education on Antibiotic Use and Antimicrobial Resistance

Antibiotics are the cornerstone of modern medicine. However, the inappropriate use of antibiotics has driven the emergence and increase in antimicrobial resistance (AMR). AMR occurs when the bacteria no longer respond to antibiotics. Infections with antibiotic-resistant bacteria result in excess healthcare costs, morbidity and mortality. Poor knowledge of antibiotic use and AMR are associated with the inappropriate use of antibiotics. "One-size-fits-all" campaigns have little impact on increasing public awareness of AMR and antibiotic use. Whilst healthcare providers are the public's trusted sources of health information, only half of the population have a healthcare encounter annually. To increase accessibility to information on antibiotic use and AMR, community-based non-healthcare influencers should be mobilised.

The proposed research will be conducted over two phases in a neighbourhood comprising 20,000 residents. The Exploratory Phase will involve social network analysis using qualitative and quantitative methods that include in-depth interviews and a questionnaire survey to comprehensively map out the key social networks in the community and identify healthcare and non-healthcare establishments with high degrees of centrality that can be harnessed as health advocates.

Based on findings from the Exploratory Phase, a cohort study will be conducted in the Intervention Phase to evaluate the comparative effectiveness of health education via multimedia online and offline platforms facilitated by non-healthcare establishments and healthcare establishments in increasing Singaporean's knowledge on antibiotic use and AMR, and improving behaviours on antibiotic usage. Harnessing sociometric social network analysis to design and implement antibiotic use and AMR educational interventions is a novel approach yet to be explored internationally. Furthermore, the engagement of highly-accessible non-healthcare advocates in the community for health communication on antibiotic use and AMR has not been trialled. In the long term, the identified influential non-healthcare advocates can be harnessed for other health communication and promotion efforts to augment Singapore's Healthier SG strategy.

A/PROF MONISHA ESTHER NONGPIUR

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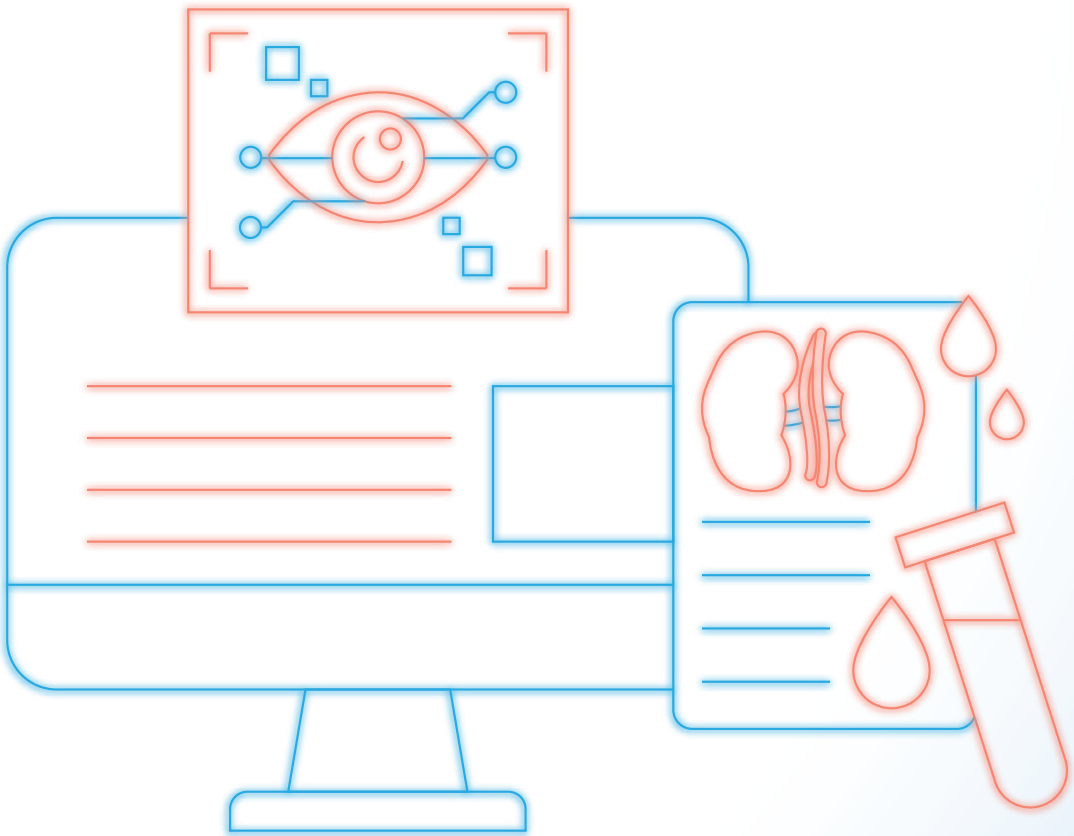
Singapore Primary Angle Closure Evaluation and Diagnostics (SPACED) study

Primary angle closure glaucoma (PACG) is a major form of glaucoma and a cause of irreversible blindness in Singapore and Asia. It is a disease spectrum that starts with primary angle closure suspect (PACS), the earliest disease stage. It then progresses to primary angle closure (PAC), characterised by elevated intraocular pressure (IOP) and culminates with PACG. PACG is potentially preventable by prophylactic intervention such as laser peripheral iridotomy (LPI) if performed in the early disease stage (PACS). Although most PACS eyes are at low risk of converting to PAC/PACG, however, some PACS eyes continue to progress despite a patent iridotomy. Current strategies for patient risk assessment are inadequate to identify those PACS eyes that are likely to develop elevated IOP/PACG and are mainly based on structural features.

In this proposal, we hypothesise that impairment of the aqueous outflow facility, which is the main mechanism for developing elevated IOP in open-angle glaucoma, also occurs in angle closure. This is where PACS eyes with impaired outflow facility are at a higher risk of developing elevated IOP or PACG. To address our hypothesis, we will characterise the outflow facility in angle closure, and evaluate responses to provocative tests and prophylactic interventions (Aim 1). Next, we aim to build a multimodal patient-stratification model using machine-learning approaches to identify earlier those individuals at risk of developing PAC/PACG (Aim 2). Finally, we will build a well-characterised longitudinal cohort of angle closure patients (currently lacking for angle closure) who are treatment-naive at enrolment. This cohort will facilitate the future development of 'precision-medicine' strategies to tailor management strategies that are unique to an individual's characteristics. It is hoped that this project will improve risk stratification of angle closure, and facilitate early administration of prophylactic treatments to those at the greatest risk of developing PACG.



HPHSR CLINICIAN SCIENTIST AWARD (SENIOR INVESTIGATOR) RECIPIENTS

A/PROF WEE HWEE LIN

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Developing a Core Real WOrld Dataset for Economic Evaluations of Oncology Therapies (RODEO)

The treatment landscape in oncology is rapidly evolving, with an increase of over 60% in new drug developments in the past decade. Health technology assessment (HTA) is increasingly being used to inform resource allocation. HTA has traditionally used efficacy data from randomised clinical trials, a study design that minimises bias. However, real-world data (RWD) are increasingly being incorporated in HTA due to a need to increase the representativeness of the data beyond the trial population.

There is a growing use of AI and ML in healthcare but the untapped potential is huge. Electronic medical records (EMR) are an important source of RWD but have been underutilised because of a lack of trained analysts and concerns over data privacy and security. In this proposal, we aim to curate an accurate and valid oncology real-world dataset to facilitate HTA and other health decision-making by (1) cleaning, processing and characterising EMR data and (2) developing use cases to demonstrate the value of this curated oncology real-world dataset. Specifically, we will:

1) Assess data quality by characterising completeness and nature of missing data from real-world sources;
2) Process unstructured data using ML algorithms to facilitate data analyses and achieve standardisation;
3) Demonstrate the use of the core real-world dataset through the following studies;
   a. Determine the comparative effectiveness of selected novel therapies; and
   b. Conduct electronic phenotyping of responders to treatments.

A/PROF KAVITA VENKATARAMAN

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Protecting Feet at Risk in People with Diabetes (PREFERD)

Singapore has a high incidence of diabetes-related lower extremity complications (DRLEC: foot ulcer, infection or gangrene), which contributes to the high rate of amputations. Despite efforts for early identification and improved management of active foot problems, the cost of care remains high, as does the consequent disability and mortality burden. Primary prevention is likely to be cost-saving. However, little is known about the risk and protective factors involved in the development of a first ulcer in people with diabetes, and consequently on effective interventions for primary prevention. This is a critical and unmet healthcare need. Hence, this proposal has the following aims.

Aim 1: Identify patient- and foot-related risk and protective factors for the development of a first ulcer in people with diabetes.

Aim 2: Improve prediction of those at higher risk by combining clinical, patient, foot and footwear data using an AI-based deep learning algorithm.

Aim 3: Pilot interventions for protecting feet at risk to evaluate their feasibility and acceptability.

We will recruit 1,000 participants with diabetes at risk of first DRLEC with follow-up for three years. All participants will undergo detailed assessments at baseline and annually on patient factors (including social support, self-efficacy, self-care, psychological wellbeing and barriers for preventive foot care utilisation), foot status (including thermometry, thermography, plantar pressures, muscle strength and range of motion) and footwear. The new knowledge generated will be combined with available EMR data to build an AI-based prediction algorithm to improve the identification of those at higher risk. Findings will also be used to design and test new interventions for primary prevention. By focusing on primary prevention and interventions in primary care, our proposed work will substantially augment Singapore's capacity to reduce the health and economic burden of DRLECs. The insights on the pathways to the first ulcer and the factors involved will also have substantial international relevance.

A/PROF SHEFALY SHOREY

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Supporting At-risk Mothers Across the Perinatal Period: a Randomized Controlled Trial (SMART)

AIMS: The proposed study aims to develop and evaluate the effectiveness of Supporting At-risk Mothers across the Perinatal Period: A Randomized Controlled Trial (SMART), a mobile-health application (M-Health App) based intervention on maternal depression at 6 months postpartum. It is also aimed that SMART will influence vulnerable mothers' emotional well-being, self-efficacy, help-seeking behaviour (social support), attachment, and interactions with their infants. Lastly, we theorise that emotionally-well mothers will ultimately influence their newborn's physical, social and emotional development.

HYPOTHESES: When compared with those in the control group receiving standard care:
1. Mothers receiving SMART intervention will have better a) emotional well-being (reduced depression and anxiety); b) parenting self-efficacy; c) social support; and d) attachment and interactions with the newborns.

2. Newborns of mothers receiving SMART will have better a) physical development; b) social development; and c) emotional development.

3. It will be more cost-effective to provide SMART than standard care.

METHODOLOGY: A randomised controlled two-group pretest and repeated posttest experimental design will be used. Mothers (n = 200) recruited from a tertiary hospital and polyclinics will be randomly assigned into the two groups. Data will be collected by questionnaire surveys using locally validated and reliable instruments, semi-structured face-to-face interviews, blood samples, videos and telephone interviews. Data will be analysed using SPSS27.0 and thematic analysis.

SIGNIFICANCE OF THE STUDY: This study will identify a clinically useful and potentially effective and cost-effective SMART intervention to improve maternal and newborn outcomes. The widely accessed M-Health App will be used to enhance mother-infant attachment and prevent postpartum depression, one of the debilitating conditions that influence new mothers, their children, and the overall family dynamics. Receiving evidence-based timely support may eventually lead to more positive parenting experiences which may then influence the psychosocial well-being of both mothers and their newborns.

A/PROF TAN KER KAN

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23-hr Laparoscopic Colectomy: From Dream to Reality? A Stepwise Approach

SPECIFIC AIMS:
Aim 1: To examine key stakeholders' perceptions, receptibility, barriers and facilitators towards novel models of next-day discharge post-colectomy in selected patients .

Aim 2: To evaluate clinical, patient-reported, safety and feasibility outcomes by comparing the novel models of next-day discharge with current post-laparoscopic colectomy inpatient care.

Aim 3: To estimate the potential cost-savings between the novel models of next-day discharge with standard care.

HYPOTHESES:
1) Concerns and barriers exist amongst key stakeholders towards next-day discharge following laparoscopic colectomy, which can be addressed prospectively

2) Next-day discharge after laparoscopic colectomy is safe and achieves comparable clinical and patient-reported outcomes as standard care

3) 23-hour colectomy can lead to considerable healthcare cost-savings compared to standard care.

METHODS AND APPROACH: This is a collaborative effort across three public hospitals—NUH, Ng Teng Fong General Hospital (NTFGH), Sengkang General Hospital (SGH)—and the Schools of Medicine and Public Health, National University of Singapore (NUS). Study 1 will examine attitudes, perceived barriers, and facilitators surrounding 23-hour colectomy from the perspectives of eligible patients, caregivers of eligible patients, and healthcare providers. Study 2 will retrospectively examine pre-, intra- and post-operative outcomes in a defined cohort of laparoscopic colectomy patients aged 65 and below in the last five years. Study 3 will pilot a proof-of-concept establishing feasibility, safety, and uptake of this 23-hour colectomy model firstly with patients in NUH, and then with NTFGH and SKH. Lastly, Study 4 will economically evaluate the pilot 23-hour colectomy programme compared to the corresponding cohort of eligible patients who opted instead for standard care.

IMPORTANCE TO SCIENCE AND MEDICINE: This study epitomises NMRC's vision for more self-ownership of health. Through the use of more tailored or targeted health services pathways, in this case for the lowest risk post-operative patients, we seek to free up precious tertiary healthcare resources to cater to more complex cases.

HPHSR CLINICIAN SCIENTIST AWARD (INVESTIGATOR) RECIPIENTS

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EMPOWERing Patients with Type 2 Diabetes Mellitus (T2DM) in Primary Care through App-based Motivational Interviewing PLUS Artificial Intelligence powered Diabetes Management (EMPOWER-PLUS) — A Pragmatic Randomised Controlled Trial

There is an urgent need for better control and prevention of complications in T2DM. Behavioural change is critical, and while literature suggests that motivational interviewing (MI) may be effective in improving glycemic control, no one has explored app-based MI designed specifically for T2DM. The overall objective of this project is to determine the effectiveness of a primary care model combining app-based MI and AI-powered randomised nudges delivered through a mobile application (app) for diabetes management (EMPOWER-PLUS). Our specific aims are to (1) co-design and develop a mobile app-based MI module on our existing EMPOWER app; (2) evaluate the clinical and cost-effectiveness of MI and nudges through EMPOWER-PLUS to deliver diabetes management through a randomised controlled trial (RCT); and (3) evaluate the implementation of the app-based MI. We will achieve this goal by firstly co-designing a mobile app-based MI module with T2DM patients and healthcare practitioners.

After rapid prototyping of the app-based MI, we will conduct a three-arm RCT, with the primary outcome measure being the difference in HbA1c level at week 36 between the intervention and control arms. Secondary outcome measures include cost-effectiveness, quality of life, medication adherence, diet and physical activity. Eligible poorly controlled T2DM patients with T2DM in polyclinics will be randomly assigned to an intervention arm where they will receive the EMPOWER-PLUS app and a smartwatch wearable on top of their usual clinical care. The first control group will have access to nudges delivered through the app and smartwatch wearable in addition to their usual clinical care but will not receive MI. The second control group will receive usual care (no access to MI, nudges and smartwatch wearable).

This study is important for improving T2DM outcomes and reducing healthcare utilisation by providing scientifically evaluated and transformative primary care model. Digital technology and artificial intelligence has a huge potential for the scaling-up of personalised care, behavioural change and patient empowerment.

DR CHETNA MALHOTRA

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Development and Evaluation of ACP-HEART: A Randomised Controlled Trial

Advance care planning (ACP) is a widely discussed intervention for improving the quality of end-of-life care. However, our previous work found that the existing model of ACP is labour-intense, conducted as a one-time rather than a continuous process, and does not facilitate end-of-life care consistent with patient preferences. To address these gaps, we aim to develop and evaluate a novel web-based dynamic ACP intervention (ACP-HEART) among patients with advanced heart failure and a prognosis of less than a year. ACP-HEART will educate patients about their illness and treatment options. It will include a structured approach for patients to think about end-of-life care choices, coach them to communicate preferences with their surrogates and incorporate systems to encourage routine review of preferences.

We will evaluate the intervention through a two-arm randomised controlled trial with 192 eligible patients. Patients in the intervention arm (n=96) will receive the ACP-HEART intervention at least every three months for a period of one year. They will have their ACP document recorded and updated in the National Electronic Health Records by a trained ACP facilitator. Patients in the control arm (n=96) will receive usual care. Between the intervention and control arms, we will compare patients' end-of-life care preferences, ACP documentation, decisional conflict, psychological distress, healthcare costs and receipt of end-of-life care consistent with preferences. We will also assess reach, fidelity and patient satisfaction with the intervention. If found to be effective, ACP-HEART will be the first web-based ACP intervention to systematically implement a dynamic model of web-based ACP among patients with heart failure.

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Refinement and Prospective Validation of a Deep Learning Algorithm for Detecting Chronic Kidney Disease Using Retinal Images (RetiKid)

CKD is a major public health problem associated with significant morbidity and mortality. Screening for CKD is challenging in community and primary care settings, even in high-income countries, because of the need to obtain serum levels of creatinine, or testing urine for protein. The accessibility of the retina to non-invasive imaging and retinal changes has been shown to provide information on systemic vascular and metabolic diseases; we developed and validated an artificial intelligence deep learning algorithm (RetiKid) to detect CKD (corresponding to stage 3-5) from retinal images to complement existing CKD screening strategies. The algorithm showed good performance with area under the curve of 0.91 in internal validation and 0.73 and 0.84 in external test sets. This proof-of-concept study showed the feasibility of using retinal photography as an adjunctive and/or opportunistic screening tool for CKD in community populations.

Building upon this study, in this current proposal, we aim to 1) refine and externally validate RetiKid across several populations using retrospective data as well as in a prospectively-recruited community cohort; 2) to evaluate the incremental cost-savings of extending the annual serum creatinine screening to biannual and triennial for diabetic patients identified as low-risk by RetiKid; and 3) develop a new "early" CKD DLA for screening early CKD (stage 1 and 2), using retinal images from local cohorts and validate it in external cohorts.

If RetiKid is found to be robust and effective, we envision deploying it as a triage tool, i.e. those who tested positive by RetiKid can go for a blood test to confirm CKD status by serum creatinine, and those who tested negative will leave the pathway with a recommendation for an annual screening. This will avoid invasive phlebotomy, shorten the turnaround time considerably and reduce the demand on human resources involved in CKD screening.

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AI-Assisted Visual Impairment Screening Model: Community-based Implementation and Evaluation of Performance, Feasibility and Costs

VI is a major public health problem associated with reduced quality of life. Globally, 600 million people suffer from VI. In Singapore, one-fifth of the elderly aged 60 and over (~180,000) suffer from VI. Among them, half were due to uncorrected refractive error (i.e. can be corrected with spectacles), and the other half were attributed to various eye diseases. With timely detection and intervention, vision can be improved or halted from worsening. Hence, screening for VI is crucial for healthy ageing and productive longevity.

Currently, as part of Project Silver Screen (PSS) which MOH operates, community vision screenings are conducted for elderly nationwide. However, there remain gaps in the current PSS model as it requires two visits, multiple eye tests, substantial manpower and resources. These factors limit the program's screening capacity, efficiency and long-term sustainability to meet the demand for annual screening. A more efficient screening model is needed.

AI technology offers unique opportunities to revolutionise healthcare. We have developed a novel retinal photograph-based AI which can detect disease-related VI. When coupled with a simple vision test, these two tests alone, can detect both refractive error- (e.g. myopia) and disease-related VI (e.g. cataract), forming a new AI-assisted screening model. This game-changing, one-stop solution offers the potential to substantially reduce time, resources and cost.

In this proposed project, using a randomised controlled trial design, we aim to prospectively perform a hybrid effectiveness-implementation study to evaluate and compare the performance, acceptability, operational efficiency and cost differences between the proposed AI-assisted screening model and the current PSS model in a community screening setting.

In line with MOH's long-term focus, this innovation will contribute towards high-value health service delivery (beyond quality to value) and promote better preventive care among Singapore's elderly (beyond healthcare to health).

DR RYAN MAN

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Evaluating the REal-World PAtient-ReporteD and Economic Impact of Combined PHACO-MIGS Surgery (REWARD)

For patients with mild-moderate primary open-angle glaucoma (POAG) and concomitant cataracts, many clinicians now combine phacoemulsification (PHACO) and a new procedure called minimally invasive glaucoma surgery (MIGS) to form PHACO-MIGS. Aside from a slightly greater and longer-lasting intraocular pressure reduction, however, the lack of a clear clinical benefit offered by this combined procedure over PHACO alone means that it is still unclear when PHACO-MIGS should be performed over the latter; or if the patient should instead continue to be treated non-surgically with medication. With the increasing focus on value-based care, assessing the patient-reported and cost-effectiveness of this combined procedure using real-world patient-reported outcome measures (PROMs) can be utilised to inform clinical guidelines and healthcare policy decisions. To date, however, there are very few studies evaluating these outcomes in patients undergoing PHACO-MIGS.

To address these knowledge gaps, my main objective in this HCSA-INV submission is to determine the patient-reported and economic outcomes associated with PHACO-MIGS in comparison with (a) continued topical medication use only; or (b) PHACO alone, in a real-world cohort of patients with mild-moderate POAG and cataracts using sensitive and validated glaucoma-specific PROMs (GlauCATTM and Glau-U) that have been developed by our research group. GlauCATTM is a novel and comprehensive glaucoma-specific scale encompassing multiple patient-identified QoL domains that presents targeted questions to respondents using a type of secure cloud-based artificial intelligence. Glau-U is a preference-based utility measure that has been found to be more sensitive than the widely used EuroQoL 5-Dimension scale in quantifying utility values across the glaucoma severity spectrum. Data from this submission will thus provide a clearer understanding of the patient-reported and economic benefits of PHACO-MIGS over the two traditionally utilised treatment modalities for mild-moderate POAG and concomitant cataracts in a representative clinical population, and aid in informing clinical recommendations for the use of this combined procedure.

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Impact of Machine Learning-based Clinician Decision Support Algorithms in Perioperative Care — A Randomized Control Trial (IMAGINATIVE Trial)

About 17% of patients develop at least one major complication after surgery. Predicting at-risk patients facilitates specific risk and benefit analysis, targeted preoperative optimisation to risks, perioperative management planning, and accurate informed consent. The usage of machine learning (ML) techniques for creating such models is increasing worldwide. However, despite the importance of real-world clinical validation studies for ML algorithms, knowledge of its effectiveness in improving outcomes is lacking. Our team has developed ML models to predict the risk of postoperative mortality and Intensive Care Unit (ICU) admission, called CARES.

We aim to investigate the models' effectiveness for reducing 1-year postoperative mortality and optimising intensive care unit (ICU) bed utilisation as our Specific Aims (SA) 1 and 2, respectively. Our SA 3 is to assess adoption, acceptability, user experience, and concerns regarding ML-based prediction models in clinical use. We will also explore the models' impact on important health service outcomes such as length of hospital stay and operating theatre utilisation rates.

The hybrid type 1 effectiveness-implementation Randomized Controlled Trial study design will be used: patients undergoing surgery are allocated in a 1:1 ratio to CARES-guided (unblinded to risk level) or unguided (blinded to risk level) groups. Patients undergoing elective and emergency surgeries in Singapore General Hospital (SGH) will be eligible for enrollment. We will recruit 4548 participants in each group to detect a reduction in 1-year mortality from 3.5% to 2.5%, with 80% power and a 2-sided 5% alpha.

The success of SA 1 & 2 will provide the case for adopting CARES in other institutions in Singapore and beyond. Most importantly, SA 3 will inform the best path for deployment and uptake of the other ML models. These would include cost-effectiveness, practical barriers to implementation and strategies to improve the buy-in from clinicians.

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Giving the Right Treatment for the Right Patient, Defining Frailty in Elderly Cancer Patients and Understanding Their Preferences for Care

In a population with increasing elderly patients, we are seeing a corresponding increase in cancer incidence. The current definitions for frailty are not accurate especially for those who are in the intermediate or prefrail group. This can lead to over- or under-treatment of patients. This study aims to define frailty in elderly patients more accurately by incorporating biomarkers into the clinical assessment. We also aim to assess the quality of life of patients post treatment under the hypothesis that if elderly cancer patients are correctly stratified as fit, prefrail or frail, the patients would be able to tolerate the treatment offered (curative or palliative or supportive) and their quality of life would be maintained or even improve post treatment. It also assimilates the understanding that QoL generally deteriorates as patient progresses along cancer treatment. We also want to further explore elderly cancer patients' preferences to aid physicians in offering treatment. Shared decision-making has been shown to improve patient satisfaction, treatment adherence, self-rated health, confidence in the decision, patient trust in physicians and healthcare costs.

We aim to recruit 250 newly diagnosed or relapsed acute myeloid leukemia, non Hodgkin lymphoma, multiple myeloma, non small cell lung cancer, and colorectal cancer patients who are planning to undergo chemotherapy. National University Cancer Institute, Singapore (NCIS) sees 3,000 cancer patients yearly and with a study period of 2 years (including 1 year follow up), it is feasible to recruit the patients required.

We aim to increase the quality of the treatment patients received by identifying what local cancer patients value and any discrepancies between preferred and perceived control over decisions. Insights gained from this study will be used to promote shared decision-making, value-centric care and better patient-physician-caregiver communication. Stratifying patients accurately will enable physicians to offer personalised treatment so patients maintain good QoL post treatment.

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Urban Care Farming on Living Well and Productive Engagement of Older Adults

In Singapore, one in five elderly persons aged 75 and above have shown signs of depression, and the proportion who committed suicide rose from 23% in 2,000 to 30% in 2014. This may be contributed by older adults who suffer more severe physical and mental deterioration due to low self-esteem, loss of independence, financial limitation and a lack of social network. These numbers are set to increase in the wake of COVID-19 and its social distancing measures. In line with national efforts, productive ageing in recent years has called upon the need for both efficacious and cost-effective upstream interventions.

This study plans to utilise an urban care farming programme as a viable, productive activity to improve health outcomes and impart practical horticulture skills and knowledge. We will be assessing the cost-effectiveness of this programme using a dynamic Markov micro-simulation from a societal and healthcare provider perspective. In addition, a person-level cost-effectiveness analysis will be carried out to compare outcomes and costs incurred. This study will provide insights into the short-term relationship between urban care farming on mental health, physical health, and healthcare utilisation and cost. In addition to establishing the potential sustainability, our study is expected to impact policy and act as a modelling tool to assess the cost-effectiveness of public health interventions.

In the short term, the programme provides older adults with a better nutritional diet and an opportunity to learn new skills while forming social connections to improve their physical and mental well-being. In the long term, the programme hopes to reduce the disease burden among older adults and slow down hospitalisation rates and nursing home institutionalisation.

CLINICIAN INNOVATOR AWARD (INVESTIGATOR) RECIPIENTS

A/PROF VICTOR KOH TECK CHANG

Head and Consultant
Department of Ophthalmology, National University Hospital

Associate Professor
Department of Ophthalmology, Yong Loo Lin School of Medicine, National University of Singapore

Developing Community-friendly Diagnostics for Glaucoma Monitoring

Glaucoma is one of the most common causes of irreversible blindness in the world and is expected to affect more than 100 million people worldwide by 2040. The global ophthalmic diagnostic market was valued at USD2.6 billion in 2017 and is expected to reach USD3.9 billion by 2025. As a chronic disease, glaucoma requires long-term follow-up investigations that are critical in detecting deterioration in order to provide timely intervention to prevent blindness. The challenge is keeping up the supply of investigations with the demand from an ageing population in which the glaucoma disease burden is expected to increase by close to 50% in the next 20 years. During the COVID-19 pandemic, this supply-demand mismatch is being further exacerbated. There is a pressing need to develop a solution to improve efficiency and decentralise point-of-care for glaucoma investigations.

Current gold-standard ophthalmic investigations limit accessibility due to poor sustainability and scalability—they are bulky, expensive, require a high level of expertise to operate and have poor integration of results for telemedicine. We have developed a suite of glaucoma diagnostic devices which aim to overcome the shortcomings of the corresponding gold standards, enabling community-based follow-up for stable glaucoma patients. Our preliminary studies have shown that each individual device correlates well with their corresponding gold standard. The current study will seek to validate the diagnostic performance of the new devices in routine monitoring of stable glaucoma and the acceptance of these devices by patients. First, we will determine the diagnostic performance of a suite of novel devices including measuring visual acuity, tonometry, and automated perimetry to detect glaucoma progression in 72 glaucoma patients from the National University Hospital over one year. Second, we will compare the adoptability of the new diagnostic devices and their corresponding gold standards by glaucoma patients using administered questionnaires.

DR SHUM CHEUK FAN

Consultant
Surgery, Woodlands Health

Leveraging Artificial Intelligence for Risk Assessment of Renal Masses in Radiologic Images

We aim to develop a software that interprets ultrasound (US) and CT images of kidneys in the Picture Archiving and Communication System (PACS) in the public healthcare sector. Its application in the US will allow polyclinic doctors to prioritise referrals of patients with newly diagnosed renal masses to urologists, while its application in CT will allow urologists to provide more details in patient counselling on treatment options. Over time, the predictive accuracy of this software will continuously improve through machine learning, with the eventual goal of replacing biopsy of renal masses in equivocal cases.

Renal masses range from tiny cysts which are mostly benign to solid tumors with significant risk of malignancy. There are no reliable signs to indicate the presence of kidney masses or to differentiate cancers from benign masses. There are two clinical and logistic hurdles in patient journeys upon finding a renal mass. First, the huge referral loads to the urologists as there are no reliable clinical parameters for triage and polyclinic doctors must consider every case as a possible instance of kidney cancer. Second, patients with equivocal CT features are often reluctant for biopsy due to invasiveness and bleeding risks. These problems prompted the PI to start this project.

Deep neural network (DNN) and semantic segmentation technologies will be used. The DNN will be trained to recognise renal tumors on US and CT images, and predict the likelihood of cancer. These predictions will be based on regression models from clinical databases, prepared by the PI. The project collaborator will develop the software algorithms using these regression models. The accuracy of prediction will be continuously improved as the software refines the models from validation and reading of new cases over time. The software will be an add-on to PACS, so new cases will be fed to it immediately and anonymously.

DR TAY HSIEN TS'UNG

Consultant
Department of Vascular Surgery, Singapore General Hospital

Bringing iGauze, a Prototype AI-vision-based Medical Device from Bench to Bedside, in Order to Prevent Gossipyboma, Reduce Potential Morbidity and Mortality and Improve Patient Safety

BACKGROUND OF THE NEED: Retained surgical gauzes result in patient harm and mandate surgical re-exploration for the removal of said gauzes. The consequences are potential patient anxiety, morbidity and mortality and can culminate in costly lawsuits with damage to hospital reputations. Such occurrences are inevitable even despite the substantial effort invested in preventing such occurrences, and near-misses from count discrepancies can occur in up to 12.8% of cases, although most are caught leading to the published rate of occurrences of only 0.3 to 1.0 per 1,000 cases. Current technologies fail to address the problem well and adoption is poor. Our team comprising a surgical device innovator, clinicians and engineers has designed and trained a prototype system that utilises ML and AI visualization to recognise surgical gauzes and keep a real-time running tally which is constantly displayed back to the surgical team.

AIM AND METHODOLOGY: To reiterate the current prototype into a state ready for field trials and pilot test it in a "live" operating theatre performing complex, prolonged surgery (e.g. oncologic resection), then reiterate it based on stakeholder evaluation and feedback to address specific concerns and constraints while further improving the accuracy of the system, then re-evaluate it in the same setting to ensure all requirements are met.

The downstream impacts are prevention of patient harm from Gossipybomas and surgical reopenings, reduction in requirements for onerous and time-consuming counts and recounts upon gauze count discrepancies occurring, and further adjuncts e.g. on-table X-ray, all of which occur while the patient is kept under GA, or else at the worst case scenario may result in reintubation and re-induction for surgical reopening. Reduction in such overhead for staff will also allow them to divert more attention to other issues pertaining to the operation or logistics surrounding it.

DR ONG CHIAT LING JASMINE

Principal Clinical Pharmacist
Pharmacy-Inpatient, Singapore General Hospital

SMARTRx (Safe Medication management platform augmented by ARTificial intelligence for Prescribers[Rx]) — a Focus on Diabetic Patients

Medication errors can result in prolonged hospitalisation, elevated risk for morbidity and mortality and significant healthcare spending, with an estimated cost of up to USD$40 billion in the United States. Locally, MOH reported medication error as the 5th most common error type between 2002 - 2010 and the 2nd top Serious Reported Event type in 2013.

Diabetes mellitus is a chronic disease fast increasing in global prevalence and is associated with significant morbidity. Oral hypoglycemic agents (OHGAs) and insulins are prescribed in up to 85% of adult diabetic patients but carry a high risk of causing patient injury when used in error. Current strategies adopted by healthcare institutions such as rules-based prescriber order entry (CPOE) and manual pharmacist review of medications were not successful in fully eliminating errors. As COVID-19 accelerated the maturation of digital innovations including AI, we postulate that AI systems can accurately and consistently detect medication errors.

The overall objective of this proposal is to develop, validate and test a multi-modal machine learning AI system to detect diabetes medication errors. Our specific aims include:

1) To develop and validate a novel AI model to detect errors in insulin and OHGA prescriptions in a tertiary hospital setting using a 3-year historical training dataset (2018 – 2021)
2) To prospectively test the performance of the AI model in detecting prescribing errors using an independent 1-year dataset (2022-2023)
3) To simulate a reduction in pharmacist intervention workload and direct healthcare cost savings over 1 year by preventing adverse events that could arise from these prescribing errors.

Historical data of DM patients, together with domain knowledge of endocrinologists and pharmacists, will be utilised for building the AI model. Different classification algorithms will be assessed; we will also utilise deep learning, a novel AI technique, to improve model performance.

DR KAAN HUNG LENG

Consultant
Department of Surgery,
National University Hospital

First-In-Human Feasibility Study for a Colonic Endoscopic Intraluminal Support Structure (CEISS) in Colonic Polypectomy

SPECIFIC AIMS: This project has the following two aims.

1) To develop a safe, stable and robust CEISS working prototype.
2) To deploy the CEISS working prototype into human colons, perform colonic polypectomy and retrieve the CEISS.

HYPOTHESIS: Deploying the CEISS during colonic polypectomy can maintain the gastrointestinal tract lumen without significant visual obstruction to the operating field.

METHODOLOGY/APPROACH: This will be a single-centre, prospective, single-arm feasibility study. We will recruit 5 to 10 healthy human subjects undergoing screening colonoscopy with polypectomy at the National University Hospital. Primary endpoints include a) deployment and complete expansion of the CEISS within the colon in a single attempt and b) retrieval of the CEISS without assistance from endoscopic instruments and damage to the device in a single attempt. Secondary endpoints include a) occurrence and severity of adverse events (e.g. mucosal erosion, bleeding, perforation), b) duration taken to perform polypectomy, c) proportion of polypectomy visualised with deployed CEISS in situ, and d) proportion of polypectomy dissection steps prolonged because of obstruction caused by the deployed CEISS.

FEASIBILITY: Our proposed study is feasible on multiple levels. Firstly, our multidisciplinary research group provides both technical and medical expertise for this hybrid research topic. Secondly, we will collaborate with the National University of Singapore Investigational Medicine Unit for the feasibility trial.

SIGNIFICANCE: This will be the first study to show that our CEISS working prototype can be successfully deployed and retrieved from a human colon during colonic polypectomy. The findings will have important clinical implications and can be potentially practice-changing. If successful, the CEISS can be commercialised to allow procedurists to perform exposed EFTR more easily. In the future, the CEISS can also be adapted for natural orifice transluminal endoscopic surgery and aid in closing iatrogenic perforations, anastomotic leaks and fistulae.

DR YONG JIN

Associate Consultant
Department of Urology,
Singapore General Hospital

Point-of-care Nocturia Evaluation — Improving the Diagnosis and Treatment of Nocturia

AIM: We aim to further establish a previously provisionally patented device to determine urine osmolality through a portable electrical impedance device (SG provisional patent 10202006783R). The main aim of this project is to miniaturise the urine osmolality device so that it can be used as a form of POC test by both patients and physicians to determine and characterise the aetiology of patients who have nocturia.

HYPOTHESIS: Nocturia is a common urinary complaint and is defined by the International Continence Society as the interruption of sleep one or more times to void. Various urological and non-urological conditions can cause nocturia; one cause in particular where the correct diagnosis is crucial for effective therapy is nocturnal polyuria. In a prior study that Goessaert performed, participants with nocturnal polyuria had a significant decrease in night-time urine osmolality as compared to daytime. Hence, our hypothesis is that a POC urine osmolality device could help diagnose a patient with nocturnal polyuria and avail correct treatment.

METHODOLOGY/APPROACH: We have previously performed a proof-of-concept study demonstrating the use of an impendence model to determine urine osmolality (NTUitive gap fund NGF-2020-08-003). This was performed through an impedance model with 96.1 ± 1.8 % accuracy as compared to the results obtained from a standard biochemistry laboratory with a freezing-point osmometer. This technology will be further calibrated and improved, and most importantly miniaturised so that it can fulfil the aims of a palm-sized POC device that is cheap and cost-effective.

FEASIBILITY: With the POC urine osmometer, we would be able to diagnose nocturnal polyuria in an objective fashion, without depending solely on bladder diaries. This would allow urologists to treat more patients with desmopressin (the primary treatment of nocturnal polyuria) and monitor their side effects, hence improving their quality of life.

CLINICIAN INNOVATOR DEVELOPMENT AWARD RECIPIENTS

DR KUAN WIN SEN

Senior Consultant
Department of Emergency Medicine, National University Hospital

Assistant Professor
Department of Surgery, Yong Loo Lin School of Medicine, National University of Singapore

Rapid Immune-profiling Assay for Real-time Stratification of Acute Infections and Sepsis

Acute infections can incite a dysregulated host response and cause organ dysfunction, leading to a syndrome called sepsis. At the centre of this response is the immune system mediated primarily by white blood cells. Paradoxically, the immune system itself may act as a double-edged sword and induce collateral damage to the host through its over-exuberant activity.

The diagnosis of sepsis is often not straightforward clinically due to a myriad of non-specific symptoms and signs patients may present with. Current biomarkers have low diagnostic performance or are laggard, and are thus unable to reflect the actual immune activity in the patient. A delay in diagnosis and implementing evidence-based management may precipitate catastrophic outcomes.

When activated in conditions such as acute infections, white blood cells undergo changes to their count, size, distribution and deformability. We have developed a prototype using deterministic lateral displacement microfluidic technology to directly interrogate these innate biophysical properties. Measurements can be done rapidly at point-of-care in real-time, label-free using very small volumes of unprocessed direct whole blood samples to derive bespoke immune response signatures.

We aim to further develop and optimise the portable integrated automated electronic system, and simultaneously validate the diagnostic performance of immune response signatures on a cohort of patients with different severities of acute infections and sepsis. Our preliminary data support the hypothesis that we can stratify the immune status of patients with acute infections and sepsis in real-time through rapid immune-profiling assay based on white blood cells biophysical properties.

This adjunct to clinical assessment could allow better triage and an appropriate level of care to be rendered quickly to patients via more precise and individualised immune profiling to guide management. The ability to perform repeated sampling at low cost could enable monitoring of patients' response to therapy in inpatients and outpatients, in both urban and rural settings.

DR LIM YINGHAO

Consultant
Department of Cardiology, National University Heart Centre, Singapore

Clinical Assistant Professor
Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore

Non-invasive Right Atrial Pressure Measurement

The estimation of right atrial pressure is a critical step in managing patients suffering from heart failure, pulmonary hypertension or other right-sided heart problems. The gold standard of measurement is by invasive introduction of a pressure transducer through the venous system into the heart chambers and measuring direct pressure through a fluid-filled channel. This is invasive with a small risk of potentially life-threatening complications. Naturally, patient uptake of the above procedure is also limited. Non-invasive estimates of right atrial pressure have been limited in accuracy and temporal resolution.

Our aim is to develop a non-invasive method of estimation of right atrial pressure with high temporal resolution to save patient costs, reduce morbidity, and improve follow-up and titration of therapy.

When a patient is placed in a supine position, the internal jugular vein is at the same level as the right atrium and direct transduction will allow measurement of right atrial pressures.

We have developed a unique sensor consisting of a piezoelectric pressure sensor embedded in a polydimethylsiloxane (PDMS) patch to be applied at the landmarked area of the right internal jugular vein. Early demonstrations have shown excellent correlation against non-invasive blood pressure measurements when transduced against the radial artery. In further testing with an internal jugular vein phantom with simulated patient waveforms, the sensor has also shown good results and correlation. Software processing will account for movement and competing carotid artifacts.

Our intent is to correlate our sensor's results with the gold standard of invasive right atrial pressure measurement, and as such, provide a cheaper and safer way of providing prognostically-significant investigations for better patient outcomes. The eventual direction is industrial collaboration or start-up and push to market with subsequent grants or capital investment.

CL ASST PROF LUKE LOW SHER GUAN

Medical Director
Sengkang Community Hospital

Head
COVID-19 Service, Bright Vision Hospital

Chief Medical Informatics Officer
SingHealth Community Hospitals

Deputy Group Chief Medical Informatics Officer (Continuing Care)
SingHealth

Human-centric Lighting Automated Control System for Light Optimisation at a Singapore Community Hospital

Disruption of the sleep-wake cycle is a known hospital stressor. Besides biological complications, disturbed sleep plays a contributory causal factor in the occurrence of many mental health disorders. These effects extend well beyond the hospitalisation period.

Various interventions have been explored. Environmental factors have consistently shown correlations with sleep quality. In fact, inappropriate lighting has been identified as the sole parameter contributing to poor sleep quality in hospitalised general ward patients upon initial admission.

Human-centric Lighting (HCL) involves not just the elimination of inappropriate lighting to improve sleep quality, but also the duplication and adaptation of natural sunlight to improve sleep quality. However, the circadian rhythm is affected by cumulative light exposure including light sources beyond the HCL intervention. This is of utmost clinical significance for patients who are not in intensive or critical care, and hence not easily confined within the area of the HCL intervention. Furthermore, current HCL interventions do not involve all clinically relevant lighting variables. What is needed is a control system that regulates the network of closed feedback loops for clinically relevant lighting variables.

The overall aim of this study is to achieve Proof-of-Concept (POC) for a prototype Human-Centric Lighting Automated Control System for Light Optimisation (HALO) at a Singapore Community Hospital (CH). This will be achieved through a scoping and design exercise, high-level algorithm development, virtual simulation and scenario testing. There are two specific objectives for this study.

Objective 1: To achieve Technology Readiness Level (TRL) 2 by (1) a scoping and design exercise to gather clinical requirements for HALO; and (2) taking measurements at a typical CH ward.

Objective 2: Will achieve TRL 3 and POC by establishing key performance parameters for HALO, developing a high-level algorithm as well as a virtual simulation for HALO and validating predictions of the above key performance parameters through scenario testing.

A/PROF NGIAM KEE YUAN

Head and Senior Consultant
Division of General Surgery (Endocrine and Thyroid Surgery), Department of Surgery, National University Hospital

Associate Professor
Department of Surgery, Yong Loo Lin School of Medicine, National University of Singapore

Predicting Future Hospital Bed States Using Length-of-Stay Predictor Based on Admission Text

Modern hospitals have to address evolving needs in bed capacity generated by seasonal variations in the demand for healthcare. This creates surges in bed capacity that are often unpredictable, resulting in crowding or long wait times in the emergency department or cancellations of surgeries. Current approaches to address this issue is based on a set of rules that determine the appropriate allocation of beds that often necessitates a trade-off between emergency vs elective bed admissions. However, these rules only account for present bed states and not projected bed states which, in turn, are affected by a multitude of biopsychosocial factors.

The hypothesis is that a text-based, length-of-stay predictor (LOS) predictor would be able to accurately abstract attributes that predict length of stay, in an explainable manner, so as to enable right siting of care and to implement pre-emptive interventions.

This project's primary aim is to train new medical word embeddings using Bidirectional Encoder Representations from Transformers (BERT) on a large local medical text dataset. This pre-trained corpus is then used to train the "Augurium" NLP tool to predict LOS using population level inpatient and emergency department datasets. The supplementary aim of this project is to test the ability of this trained model NLP to detect variation in LOS that might indicate the onset of new complications or unexpected prolonged stays in the hospital. This is achieved using a steady state model with continuous incremental learning (IL).

Given the team's experience in running large-scale neural network workflows on GPUs, it is hoped that the tests would yield a highly tunable and explainable LOS model. In addition, the pre-trained medical word embeddings may be used for other prediction tasks, such as predicting complications, using the same training datasets.

CLINICIAN SCIENTISTS IN THE SPOTLIGHT

Revolutionising Genetic Disease Treatment

SINGAPORE TRANSLATIONAL RESEARCH (STAR) INVESTIGATOR AWARD

Prof Chan Kok Yen Jerry

- Senior Consultant, Department of Reproductive Medicine, KK Women's and Children's Hospital
- Director, KK Research Centre, KK Women's and Children's Hospital
- Director, SingHealth Duke-NUS Maternal and Child Health Research Institute
- Academic Vice Chair, Research – SingHealth Duke-NUS Obstetrics and Gynaecology Academic Clinical Programme, Duke-NUS Medical School

Inherited genetic diseases affect approximately one per cent of the global population, often resulting in irreversible damage to babies before they are even born. Placing a tremendous burden on the healthcare system, economy and society with few remedies in sight, they present a pressing and unmet clinical need. As such, Professor Jerry Chan embarked on groundbreaking research aimed at developing novel therapies using stem cell and gene therapy.

"We are developing new and safer ways to deliver such therapies using nano-particles, which have been successfully used in the mRNA-COVID-19 vaccinations," Prof Chan shares. While such therapies have been carried out successfully in various postnatal applications, his team is exploring the use of nanoparticles to deliver gene therapies directly to affected babies before birth. This cutting-edge approach holds the promise of being a game-changer in the treatment of genetic diseases.

While conventional gene therapies rely on viruses, which can lead to adverse side effects, the use of nanoparticles opens up new possibilities for safer and more targeted treatments. "The current technology has progressed to allow us to readily edit specific areas of the genome," Prof Chan explains.

By rapidly generating new therapeutics and utilising emerging technologies, the team aims to bridge the clinical gaps and drive significant progress in the field. To accomplish this, fostering a multidisciplinary approach is essential, involving chemists, biologists, fetal medicine experts, and immunologists to collaboratively tackle the complex challenges associated with genetic disease treatment.

Nurturing the Next Generation

Prof Chan not only engages in groundbreaking medical research by training the next generation of aspiring professionals. Senior clinician scientists like himself ensure the industry continues to innovate for improved practices and advancements in patient care. "My many research responsibilities synergise with my duties as the Director of MCHRI (SingHealth Duke-NUS Maternal and Child Health Research Institute). They enable me to drive multiple research programmes and networks to address my main goal: the challenges faced in maternal and child health," Prof Chan says. The MCHRI strives to prevent and control diseases at every stage of life, from preconception to adulthood, fostering a healthier population.

When it comes to helping junior clinician scientists flourish, the importance of mentorship and an open-minded approach cannot be overstated. Prof Chan encourages them to identify and address critical gaps in the field by looking at new breakthroughs in the industry. "They need to understand and embrace emerging technologies instead of just working with existing methodologies," he says. By participating in broad-based mentorship programmes, junior clinician scientists shape their thinking in a rapidly evolving world, enabling them to become catalysts for change. As such, the management of programmes and mentoring of new clinician-scientists are essential aspects of a researcher's role, ensuring continued innovation and excellence.

> **"We identify the best opportunities to prevent and control diseases at key stages of life from preconception through pregnancy, infancy, childhood and adolescence to adulthood to ensure a healthier population."**

Treating Heart Failure Linked to Diabetes in Southeast Asia

SINGAPORE TRANSLATIONAL RESEARCH (STAR) INVESTIGATOR AWARD

Prof Derek John Hausenloy

- Professor, Signature Research Program in Cardiovascular & Metabolic Disorders, Duke-NUS Medical School
- Research Director and Senior Consultant, National Heart Research Institute, National Heart Centre Singapore

"There is a high prevalence of diabetes in Singapore and Southeast Asia," explains Professor Derek Hausenloy on his search for new treatments and strategies which prevent the onset of heart failure, especially for Singapore's diabetics. "Heart failure from diabetes in this region is also different from in Europe; the average age of onset in Southeast Asia is around a decade earlier and the condition tends to be more aggressive."

One particularly promising avenue for Prof Hausenloy's project involves targeting mitochondria, the powerhouse of the cell producing energy the heart needs to pump. Mitochondrial dysfunction means that the heart muscle lacks energy and cannot pump effectively, increasing the risk of heart failure. Therefore, new treatment that has the potential to improve mitochondrial function and energy supply to the heart muscle will preserve the pumping function of the heart and prevent the onset of heart failure.

Prof Hausenloy's research is timely here. Only one medicine currently available for lowering blood sugar in adults with type 2 diabetes, SGLT2 inhibitor, has been found to reduce the risk of heart failure in both diabetic and non-diabetic patients. Singapore's multi-ethnic population, as well as its notable incidence of the high morbidity lean diabetic phenotypes, together mean research pathways to more targeted treatments. The data from Singapore's Malay, Indian and Chinese subjects will eventually support the scaling up and extrapolating Prof Hausenloy's research findings to similar ethnicities worldwide.

Bridging the Gulf

"Balancing clinical and lab-based research can be challenging, but also memorable and rewarding," Prof Hausenloy shares. A typical work day, he notes, involves interacting with a diverse range of people in different settings. It can entail the oversight of clinical studies, reviewing the latest research results of fellows, the preparation of grants and papers, as well as meetings with senior management, admin and other research groups.

"Prioritisation, compartmentalisation and passion," Prof Hausenloy readily answers, taking stock of how he maintains a healthy work-life balance despite all these commitments.

"Be prepared for hard work and many challenges," he also advises aspiring clinical scientists, anticipating them needing help with neatly demarcating their time between overlapping clinical or research duties.

"However, the disadvantages of being a clinician scientist are definitely outweighed by the unique advantages, especially for those doing both lab-based and clinical research." Clinician scientists can act as a bridge between the two sides of research, Prof Hausenloy explains, due to their understanding of both lab-based and clinical research. "They are therefore in a unique position to translate research discoveries made in the lab to the clinical setting for patient benefit."

> **"Clinician scientists who undertake both lab-based and clinical research have unique insights into both sides."**

Developing Better Treatments for Lymphoma

CLINICIAN SCIENTIST AWARD (SENIOR INVESTIGATOR)

A/Prof Ng Siok Bian

- Associate Professor, Department of Pathology, Yong Loo Lin School of Medicine, National University of Singapore
- Senior Consultant, Department of Pathology, National University Hospital
- Senior Consultant, National University Cancer Institute, Singapore

Singapore's incidence of lymphoid malignancies is on the rise, and lymphomas are now among the top ten cancers in the country. ENKTL is a particularly aggressive and deadly disease with a high fatality rate, and there is a lack of consensus worldwide about optimal treatment strategies. Together with other EBV-positive lymphomas, ENKTL represents an important global health problem that demands further research and attention.

Investigating the link between EBV and ENKTL could also shed light on the mechanisms by which the virus contributes to cancer development, potentially leading to the development of better treatments for EBV-associated cancers. However, studying ENKTL poses unique challenges due to limited tumour sample availability, and engaging regional and international partners and collaborators is necessary to gain access to patient samples.

"Our long-term goal is to validate the biomarkers and identify molecular subsets of ENKTL of prognostic and clinical importance," shares Associate Professor Ng Siok Bian. Her team hopes that their research can uncover novel therapeutic approaches and identify patients with poor outcome as these patients may require different treatment strategies.

A/Prof Ng's research could significantly impact lymphoma oncology. ENKTL has a poor prognosis with a five-year survival rate of less than 50%. "Studying the link between EBV and ENKTL could provide important insights into the mechanisms of cancer development and the immune response to cancer," she shares. "This could ultimately lead to the development of better treatments for ENKTL and other EBV-associated cancers."

Working Effectively with Others

As a pathologist by training, A/Prof Ng is dedicated to understanding disease biology and discovering novel biomarkers that could impact patient care. On a typical day, the challenges of being a Clinician Scientist (CS) are many, including balancing competing demands between clinical priorities, research, education, and administrative duties, as well as concern about losing clinical competency and maintaining work-life balance. "It requires dedication and passion for both patient care and scientific research, as well as good time management and organisational skills to balance my different responsibilities effectively," A/Prof Ng shares.

And throughout her journey as a clinician-scientist, A/Prof Ng has forged many collaborations and friendships. "Get help if needed," she advises. "Get out of your comfort zone and learn to work with different people while surrounding yourself with those who share similar interests and motivation." Mentors are also crucial: different mentors impart different skill sets and inspiration.

A/Prof Ng's dedication and passion for both patient care and scientific research, as well as her ability to balance different responsibilities effectively, offer hope for progress in understanding and managing ENKTL. With the support of mentors, collaborators, and partners, her team is committed to making a difference in the lives of patients and families affected by this devastating disease. "We will continue to strengthen the ENKTL research roadmap in Singapore and establish ourselves as global leaders in ENKTL research."

> **"Pathology is the study of disease and an important bridge between science and medicine; pathologists play an essential role in the research and advancement of medicine."**

Precise Treatments for Gynaecological Cancer

CLINICIAN SCIENTIST AWARD (SENIOR INVESTIGATOR)

A/Prof David Tan Shao Peng

- Senior Consultant Medical Oncologist, National University Cancer Institute, Singapore
- Development of Novel Therapeutics and Predictive Biomarkers in Gynaecological Cancers

Associate Professor David Tan's CSA-SI-winning work on the NCIS Gynaecological Cancer Precision Oncology Programme centres on improving treatment strategies and molecular profiling for patients with hard-to-treat cancers of the ovary, womb and cervix. It is a focused intervention, especially in its trials for chemotherapy resistant cancers like ovarian clear cell carcinoma (OCCC).

"[OCCC] is quite rare in the West. About 5-10%," explains A/Prof Tan. "But common in Asia; about 25% of patients are diagnosed with it."

"In studying these cancers, we found that they are driven by a pro-angiogenic [substances causing blood vessel formation) pathway," A/Prof Tan elaborates. "What we've also found is that a proportion of these cancers seem quite responsive to immunotherapy."

In the LARA trial, which is run at NCIS as part of the Gynecologic Cancer Group Singapore (GCGS), advanced OCCC patients are treated by combining an anti-angiogenic drug, lenvatinib, and the immunotherapy drug pembrolizumab. Encouragingly, some patients have seen symptomatic improvements and long-term disease control. A/Prof Tan plans to expand this trial to Korea, as part of the wider Asia-Pacific Gynaecologic Oncology Trials Group (APGOT).

Persevering for Patients

Much public debate occurs recently about the cost of cancer care, but beyond the expense of improving cancer outcomes is the incalculable gain from relieving the emotional and financial stresses of caring for and losing a daughter or mother. This is A/Prof Tan's key motivation for his research programme—his motto goes, "if at first you don't succeed, feast, imbibe, bang your head against the wall, be merry, and try, try again".

A/Prof Tan's office door, that said, is always open—especially for discussions on research ideas and patient management. Life in academic oncology, he shares, is "truly a rollercoaster".

"One day you're riding the wave of grants and laboratory experiments being successful, the next day your paper's rejected by a journal, the 3-cm tumour in the patient you just started on a promising new drug trial has doubled in size and she is now in the corridor outside with her hopeful husband and daughter waiting to hear from you about the scan results, and you have three back-to-back meetings lined up from 8 pm to 11 pm to discuss the progress of three clinical trials with investigators from Europe and the US," he says in one uninterrupted breath.

How then does someone navigate working life overall as a hybrid clinician/researcher/lecturer/administrator? And, considering that A/Prof Tan previously received the Transition Award (2012) and the Clinician Scientist Award (2016), while excelling at these jobs too?

"When I got into this business, it was about my patients. So I always see myself primarily as a physician and patient advocate," finishes A/Prof Tan calmly. "And if you go with that as your primary goal, everything else aligns towards that."

> **"Understand what drives the growth and drug-resistant characteristics of each tumour. Then identify an optimal approach to target its Achilles Heel."**

Reversing the Impact of Mechanical Ventilation with Dialysis

CLINICIAN SCIENTIST AWARD (INVESTIGATOR)

Dr Matthew Edward Cove

- Senior Consultant, Department of Medicine, National University Hospital

Senior Consultant Matthew Cove wants to reduce the impact of mechanical ventilation on critically ill patients. These devices are lifesaving in respiratory failure, but reducing the harm caused by them means delivering smaller, less lung-damaging breaths, which in turn causes a toxic accumulation of carbon dioxide in the patients' bloodstream.

Dr Cove's CSA-INV-winning solution? Using dialysis machines to remove carbon dioxide—in the form of bicarbonate—directly from the blood stream.

"Most carbon dioxide is carried in the blood as bicarbonate," Dr Cove explains. "Bicarbonate is very soluble. And it's a small molecule. So it's very dialysable."

What about, however, schools of thought holding that bicarbonate is an essential regulator of the level of acid in blood—how does one prevent the acid level from being too high in patients and causing disorientation and/or fatigue?

"The understanding of the acid base being in the plasma being determined by bicarbonate is a misunderstanding," says Dr Cove. "If you remove bicarbonate but maintain some of the other components of blood within their normal range, you actually have an increase in pH because you're essentially removing carbon dioxide from the system."

Dr Cove and his research team prove this tendency for alkalosis in experiments reviewed within his 2018 American Society for Artificial Internal Organs paper. There, 3 dialysates primed at bicarbonate concentrations of 0, 16 and 32 mmol·L–1 show the pH of blood plasma increasing following bicarbonate removal. The data, too, shows that bicarbonate dialysis is feasible, and that bicarbonate replacements are not needed, so long as the dialysate is designed to maintain the strong ion difference [SID] of blood plasma within acceptable limits.

"Publishing this work has been key in moving the field forwards," says Dr Cove. "It felt like a relief, having reliable reproducible data confirming that our idea works, contrary to conventional teaching."

Creativity and Connecting

An apropos sentiment, considering the challenging and intensive nature of medical research.

"Between scientific research and the arts, there's a lot more overlap than many people realise," advises Dr Cove, for whom the CSA-INV is the latest in a string of research awards.

He cites British comedian John Cleese's talks on creative problem-solving as an inspiration. "When you're doing research, you're innovating. You're creating. Because you're coming across new problems that people might not have experienced before. And you've got to create a solution."

Forging bonds and establishing trust long-term with one's own specialised research community—at conferences and lessons, through timezone-agnostic online meetings, over convivial sessions at the pub—helps here, Dr Cove adds.

"In ICU research, the community is relatively small. So through the other things I'm involved with, because I have academic time, I get to connect with a lot of people I've met with or trained with along the way," he says.

"Some of those people worked in the same labs as me during training. We can talk about the same kind of trials and tribulations, and sometimes recognise that we're thinking the same way and write a paper together," Dr Cove continues. "Being part of a global community, there're always people out there who understand what you're doing. And that keeps it real."

> **"Better to do something less invasive, earlier, to prevent our patients progressing to needing ECMO [Extracorporeal Membrane Oxygenation]."**

Advancing COVID-19 Research Through Human Challenge Studies

CLINICIAN SCIENTIST AWARD (INVESTIGATOR)

A/Prof Barnaby Edward Young

- Senior Consultant, Department of Infectious Diseases, Tan Tock Seng Hospital
- Head, Singapore Infectious Diseases Clinical Research Network, National Centre for Infectious Diseases
- Associate Professor (Clinical), Lee Kong Chian School of Medicine

A controlled human infection (CHI, also known as human challenge) study involves deliberately infecting carefully selected volunteers with a well-characterised infectious agent. While they might sound intimidating, CHI studies have been used for many years to study infections such as malaria, typhoid and influenza. Their importance as models for studying the pathophysiology of infections and for safely and efficiently developing new vaccines and treatments is increasingly recognised.

In 2021, at the height of the pandemic and following months of detailed preparation, the first COVID-19 human challenge study was conducted by Professor Chris Chiu and his team at Imperial College London. They conducted the studies in unvaccinated individuals using an early strain of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). They generated unique immunological, virological and symptom data, precisely mapping out the natural history of SARS-COV-2 infection from inoculation to resolution. Importantly, it also demonstrated the safety of the COVID-19 CHI model, opening the door to future studies with more recent strains.

A CHI study has never before been conducted in Singapore, but Associate Professor Barnaby Edward Young intends to change that with a human challenge study using the SARS-CoV-2 Delta variant. This study will be conducted in individuals who have received COVID-19 vaccinations. It will generate high-quality clinically relevant data, enhancing current understanding of the virology, immunology and transmission dynamics of COVID-19, particularly during the early period while the virus is incubating but before symptoms develop. The availability of effective antivirals and vaccines, with the data from successful COVID-19 challenge studies, will ensure this study is conducted safely for study participants and staff at the quarantine facility.

Instilling Confidence in Future Findings

"The next pandemic is most likely to emerge in Southeast Asia or Asia and it's vital that we are prepared," A/Prof Young says. "Having this capability, closest to where a new pathogen might emerge, will help make sure we are ready and can respond quickly to the benefit of all."

In addition, Asia's biomedical landscape has been rapidly developing: biotech companies in Singapore and across Asia are developing new vaccines and antiviral candidates that need testing in clinical trials to ensure they are safe and effective. CHI studies yield vital biologically relevant data to decide which candidates should progress from pre-clinical and phase 1 studies into later phase efficacy trials—potentially shortening the timeline to them becoming available for clinical use.

One key area of global interest is finding the next generation of COVID-19 vaccines. Ideally, these should offer 'pan-coronavirus' protection and more effectively block virus transmission. This, however, could prove difficult to achieve outside of a human challenge setting when the virus to emerge is unknown. "We don't need to wait and see whether a new vaccine is effective against just what's circulating now," A/Prof Young shares. "We can look and make sure that the vaccine is also effectively protecting against infection from previous variants."

Moving forward, he hopes this study will establish a platform for human challenge studies in Singapore, both for COVID-19 and other infections from dengue and zika to influenza and respiratory syncytial virus. "We want to accelerate bringing the best vaccine and treatment candidates from the research laboratory into later phase trials."

> **"Controlled human infection studies are not easy to conduct and need robust ethical and scientific justification, but in the right setting they can transform bench-to-bedside research."**

Improving Healthcare Outcomes with Data Analytics and Economic Evaluations

HPHSR CLINICIAN SCIENTIST AWARD (SENIOR INVESTIGATOR)

A/Prof Wee Hwee Lin

- Associate Professor, Saw Swee Hock School of Public Health and Department of Pharmacy, National University of Singapore

In today's healthcare system, patients may undergo unnecessary treatments, affecting their finances and using valuable healthcare resources that could be allocated to those who need them more. Cost-effectiveness analyses can evaluate if new health technologies offer value for money to improve resource allocation. However, current approaches rely on clinical trial data that may not reflect the patients who visit clinics. Inefficient processes and lack of data standardisation limit the ability to expand findings from clinical trials.

To address these challenges, Associate Professor Wee Hwee Lin and her team conceptualised an idea four years ago to harness the rich information hidden in patients' clinical notes. They are developing a standing database that allows for a more efficient evaluation of oncology drugs.

"My current work uses text mining to harness information from clinical notes for economic evaluation," A/Prof Wee shares. Subsequently, the team can more accurately identify patients who can benefit from new health technologies, minimise harm to patients who may experience side effects without getting any treatment benefits, and compare the cost-effectiveness of different drugs so the patients and health system are getting value for money.

The team places great emphasis on data privacy and security. They performed distributed data analyses within each hospital using a standard analytical plan so that hospital data are not shared across institutions. Secured virtual machine platforms such as the National University Health System's DISCOVERY AI has been instrumental in allowing academic researchers to access hospital data without compromising security. Data standardisation, such as adopting the Observational Medical Outcomes Partnership (OMOP) standards developed by the Observational Health Data Sciences and Informatics (OHDSI) consortium, is also key.

Assimilating New Team Members and Technologies

When asked how she balances her many responsibilities as a clinician scientist, A/Prof Wee prides herself on being systematic. She recognises that implementing standard operating procedures is imperative to quickly and smoothly assimilate new team members. "The happiness and productivity of my team members translate to my success," A/Prof Wee shares, highlighting the importance of her team members.

Their work is crucial, as patients in routine clinical practice differ from those recruited into clinical trials, resulting in a lack of information relevant to the broader patient population. Their data will be vital to the industry, facilitating the identification of patients suitable for clinical trials and spurring innovation. By providing information that is not readily available, they can demonstrate the efficacy of various treatments by ensuring that patients who are being compared are as similar as possible to reduce bias. It can also highlight new connections, such as how existing drugs may be applied to other conditions they were not developed for.

Through out-of-the-box thinking and data harnessing accomplished with technology, the team's efforts can ultimately lead to better clinical outcomes and reduced costs for patients and the health system. Moving ahead, A/Prof Wee has high hopes for the industry. To make that a reality, she believes it is important for future healthcare professionals to expand their horizons. "This line of work is a multi-disciplinary effort and we need more young people who are willing to step out of their comfort zones of biology and chemistry and venture into machine learning, artificial intelligence and economics."

> **"Being a public health practitioner is not just about focusing on the patients in front of you. It's important to innovate and uplift the industry too."**

Amalgamating Machine Learning and Patient Care

HPHSR CLINICIAN SCIENTIST AWARD (INVESTIGATOR)

A/Prof Hairil Rizal bin Abdullah

- Senior Consultant, Department of Anesthesiology, Singapore General Hospital
- Institutional Value Lead, Singapore General Hospital
- Associate Professor, Duke-NUS Medical School
- Clinical Senior Lecturer, Yong Loo Lin School of Medicine, National University of Singapore

Spurred on by his interest in how technology and healthcare interweave, Associate Professor Hairil Rizal bin Abdullah wanted to observe how recent innovations could address some of the key challenges in Singapore's healthcare system. According to him, rapid advancements in ML and AI in recent years have opened up new possibilities for leveraging such technologies in a patient's medical care journey.

Currently, there is growing interest to develop and adopt such technologies to almost all aspects of our daily life. A/Prof Hairil and his team subsequently set out on a research project centred on creating a decision support tool that utilises ML, which resulted in the development of the Combined Assessment of Risk Encountered in Surgery (CARES) calculator. By analysing available data to provide personalised risk assessments, the tool would empower doctors to make better decisions, in turn improving patient care and optimising hospital resource allocation.

Drawing on statistics from over 100,000 patients, the decision-facilitating capabilities of the CARES calculator have been shown to help clinicians identify high-risk patients and more efficiently allocate the corresponding care and resources needed. The tool has also helped the team derive the first large-scale perioperative data set that considers local characteristics, producing more accurate and individualised results for Singaporeans to improve the overall quality of care provided.

Maintaining the Balancing Act

As someone with administrative, research and clinical duties alongside ongoing PhD studies, A/Prof Hairil knows best the importance of prioritisation. He also greatly appreciates the guidance that his mentors offer, especially when it comes to non-clinical work. Aside from that, resilience is imperative too: A/Prof Hairil advocates staying engaged, asking questions, and being persistent when pursuing knowledge. "Failure and delays are just a normal part of the work. If you're resilient, it doesn't matter if you fail," he adds.

Having already worked on three iterations of the CARES calculator, A/Prof Hairil has high hopes for subsequent ones. The team is adding more outcomes with each iteration, so clinicians will have even more information and predictions about patients as the tool continues to be utilised. Expressing his gratitude for the opportunity to have worked at the forefront of developing innovative solutions that will have a lasting impact on patient care, he shares "I truly believe in the importance of advancing our knowledge in this field, which will make all the effort worth it."

Looking ahead, A/Prof Hairil expects that large language models will be one of the next biggest areas of development in healthcare. As these models would be able to determine surgical risks, complete with a detailed and accurate analysis in plain language, patients may be able to conduct their pre-op and risk assessments at home without having to visit a hospital in the future.

"It's just a matter of waiting for all the technologies to mature together; all the recipes are there."

> **"Healthcare is an area in which ML and AI models carry great potential. Hence, we want to objectively study if these models do actually improve patient outcomes and define the value it brings."**

Providing Better End-Of-Life Care

HPHSR CLINICIAN SCIENTIST AWARD (INVESTIGATOR)

Dr Chetna Malhotra

- Assistant Professor and Deputy Director (Research), Lien Centre for Palliative Care, Duke-NUS Medical School

ACP for the end of life can be time-consuming and emotionally difficult to discuss. But Assistant Professor Chetna Malhotra believes in pushing this field for palliative care forward "so ultimately, these conversations get normalised in society".

Her ACP-HEART project is a web-based tool that empowers patients with heart failure to voice their healthcare needs. "Talking to the caregivers and the doctors gives patients peace of mind. They'll have told their loved ones and their doctor about what matters to them," explains Dr Malhotra.

"It gives them peace of mind as well and avoids that feeling of regret," Dr Malhotra says, noting that the tool also eases the stress and doubt of caregivers. "Everybody around the patient knows what he or she wants. So care can be matched to what's important for the patient."

One novel aspect of ACP-HEART is how it lets patients engage in ACP consistently and easily over time.

"We decide for the future based on our current state of mind. And people's preferences change over time," Dr Malhotra clarifies. "That's why we need to have ACP as a continuous process. Not as a one-time thing."

Motivated to Make a Difference

Balancing medical rigour with communicating to laymen patients during the ups and down of their health journeys is not easy. Here, Dr Malhotra uses short videos to educate patients about their illnesses—and their treatment options. "We simplify a lot of complex information for patients, especially for those who are older and with a lower level of health literacy," Dr Malhotra elaborates.

Dr Malhotra, here, works with a multidisciplinary team of health researchers, palliative care physicians and communication experts. "I feel blessed to receive a lot of input," she says. "It's really a team effort here."

"Some patient representatives work with us to review our tools," adds Dr Malhotra about the iterative and accessible environment for feedback which ACP-HEART fosters. "To see if they can understand everything in a simplified way."

Dr Malhotra's leadership experience on multiple projects about end-of-life care enhances the research design of the ACP-HEART project. And while research is never easy, her advice to aspiring clinician scientists is succinct. "You have to persevere at it," she says. "Keep going. There's going to be lots of ups and downs."

Despite the demanding nature of advanced care planning, Dr Malhotra's dedication remains unwavering. "If I can make some difference in the lives of people and their families, then everything is worth it," she says.

> **"Palliative care has got nothing to do with giving up on lives. It's about living life better."**

Revolutionising Complex Therapeutic Procedures

CLINICIAN INNOVATOR AWARD (INVESTIGATOR)

Dr Kaan Hung Leng

- Consultant, Department of Surgery, Ng Teng Fong General Hospital
- Consultant, Department of Surgery, National University Hospital
- Senior Lecturer, Junior Academic Faculty Scheme, Department of Surgery, National University of Singapore

In recent years, the field of endoscopy has witnessed remarkable advancements in non-invasive procedures, particularly in complex therapeutic interventions. Endoscopists have successfully utilised such interventions for procedures like endoscopic mucosal resection, offering patients shorter recovery times compared to invasive surgeries. However, there remains a glaring clinical gap—endoscopic instruments need to be improved to keep up with potential new interventions.

As such, Dr Kaan Hung Leng devotes her research to improving endoscopy tools to make innovative procedures, which could not be performed with existing technology, possible. "The goal is for non-invasive endoscopic procedures to become an effective alternative for patients who previously required invasive surgical resections," Dr Kaan explains. "Patients who undergo non-invasive endoscopic procedures benefit from shorter hospital stays, reduced operative costs and decreased postoperative pain."

Her research group's efforts are focused on enabling endoscopic full thickness resections, which is a type of minimally invasive procedure. This advancement would expand the range of procedures that can be performed endoscopically, revolutionising the field. However, the challenge lies in the escape of intraluminal air and subsequent reduction of the working space for the endoscope's arms during full thickness resections. To overcome this hurdle, the group has developed innovative devices. They are currently preparing for first-in-human clinical trials to assess the efficacy and safety of their groundbreaking solutions.

Learning as a Lifelong Journey

Dr Kaan possesses a unique combination of surgical expertise and proficiency in non-invasive endoscopic procedures to revitalise the endoscopic field. Innovation also requires multi-disciplinary collaboration, hence necessitating researchers to work closely with professionals hailing from various backgrounds. "The learning curve at the beginning is always going to be difficult regardless of the field you are in or the project you are embarking on," Dr Kaan says. "It's important to familiarise yourself with your collaborators' work."

For her, learning is a never-ending endeavour. In the vast field of medical innovation, there is always something new to discover, and that includes dabbling in patents and healthcare business ideas. It is important for innovative researchers to have a comprehensive understanding of engineering principles, business strategies, and the government and legal requirements pertaining to medical devices.

Dr Kaan also highlights the importance of having pillars of support to rely on when encountering roadblocks, citing family and friends as a great source of encouragement. Additionally, aspiring clinician scientists embarking on their journey should not let their fear of failure or setbacks hinder their progress. "Start with the mentality that you will always fail—that way, if you fail, it's expected; if you succeed, it's a bonus."

> **"My hope is that endoscopists can perform 'mini-surgeries', so that patients do not need to bear the morbidities and mortalities associated with invasive surgical procedures."**

Detecting Kidney Cancers with AI Imaging

CLINICIAN INNOVATOR AWARD (INVESTIGATOR)

Dr Shum Cheuk Fan

- Consultant Urologist, Department of Surgery, Woodlands Health

"When our AI algorithm reaches its diagnostic accuracy of about 85 to 90 per cent, it can provide an alternative for patients," says Dr Shum Cheuk Fan about his project for estimating the risks of kidney cancer from CT scans. "Instead of biopsy. Putting in needles to extract samples from the patient, that runs the risk of bleeding, pain, infections and other more serious injuries and complications."

And this physical pain dissuades people from kidney cancer detection in the first place—why undergo a biopsy when a disease might be non-existent or mild? That inaction can lead to very real yet otherwise avoidable outcomes later on.

"Based on the latest figures from the American Cancer Society, survival at five years from diagnosis is above 90 per cent if it is treated at the early stage. But this drops to a dismal 15 per cent when the cancer has spread to other organs," notes Dr Shum. "Therefore, it is important to identify the risk of cancer in kidney masses found on scans as soon as possible."

Dr Shum's AI-powered algorithm is important here. It is, in this early stage of development, envisioned as non-invasive, pain-free and as accurate as a biopsy. And with the support of Woodlands Health, the National Healthcare Group Centre for Medical Technologies & Innovations (NHG CMTi) and an industrial partner, Dr Shum's research and CSI Award journeys have been—and continue being—bracingly collaborative.

Partners and Priorities

"The project crosses specialty boundaries," says Dr Shum. "It's not just about urology, which is my field. It involves radiology. It also involves pathology because of the imaging and diagnostics."

It also entails working closely with industry stakeholders who have their own key performance indicators and goals in mind.

"They have to." Dr Shum says frankly. "They're a commercial firm. So, dealing with them, we make sure that there's lots of transparency in our communication."

"We make sure that there's a lot of mutual understanding regarding expectations—each other's roles, involvements, the various forms of returns to the various parties," he continues. "And a lot of times all these can be ironed out. It's this mutual understanding that we have that pushes us along and helps us achieve more"

An institutional trial at Woodlands Health is in the project's future. Then, scaling up its scope. Making a mark in America and/or the EU with it is a core objective for Dr Shum.

"The most critical step in research, or an innovation project, is actually your willingness to actualise the idea," muses Dr Shum when asked about being an example for fellow early career researchers. "And there's no wrong way in doing this step. As long as you have the willingness to actualise it, you've taken the most critical step forward. And things will just come in place along your way."

> **"Improving surgical techniques can help one patient at a time. But many more will benefit if I work towards improving diagnostic capabilities."**

TALENT PIPELINE PROGRAMMES

Transition Award (TA)

The TA is designed to help budding clinician scientists who have just completed formal research training. This award provides up to four years of salary and grant support to help recipients build up their research capabilities, facilitating their transition to stable, independent research roles. It will enhance their ability to successfully obtain independent research support in the future.

The long-term goal of the award is to increase the cohort of new and talented NMRC-supported independent CSs in the three CS tracks: TCR, HPHSR or Health Technology.

NMRC Research Training Fellowship (RTF)

The NMRC RTF provides doctors and health science/healthcare professionals with research training to have qualifications and skills to become clinician scientists.

The fellowship provides funding and salary support for formal research training and research attachments at local and overseas institutions. Awardees may also submit a research proposal for seed funding upon completion of the training.

National Outstanding Clinician Scientist (CS Resident Award)

This is a yearly award given to a CS Resident who has excelled at clinical training, and also made significant research contribution(s) with actual or potential translational application to improve clinical care and showed exemplary behaviour during residency. The winner receives a $500 book prize.

TALENT PIPELINE PROGRAMMES AWARD RECIPIENTS

Transition Award (TA)

22 recipients were awarded the TA.

Name	Host Institution	Project Title
Dr Marcus Ang Han Nian	Singapore Eye Research Institute	Widefield and Multi-modal Corneal Imaging to Investigate Corneal Endothelial Cell Loss Following Descemet Membrane Endothelial Keratoplasty (DMEK)
Dr Glenn Kunnath Bonney	National University of Singapore	Interrogating the Proteogenomic Landscape of Pancreatic Cancer for Therapeutic Biomarker Discovery
Dr Jason Chan	National Cancer Centre Singapore	Understanding Therapeutic Resistance in Gastrointestinal Stromal Tumors Beyond Genomics
Dr Rachel Chong Shujuan	Singapore Eye Research Institute	Comparison of Focal Inner and Outer Retina Structure and Function to Accurately Diagnose Glaucoma in High-Myopia Eyes
Dr Saima Hilal	National University of Singapore	Characterising Early Brain Changes in Midlife—A Missing Link to Cognitive Impairment in Old Age?
Dr Oh Choon Chiat	Singapore General Hospital	T-cell Immunity in Persistent Human Papillomavirus (HPV) Skin Infection and Cutaneous Squamous Cell Carcinoma (cSCC) among Organ Transplant Recipients (OTRs)
Dr Troy Puar Hai Kiat	Changi General Hospital	Using 11C-Metomidate PET-CT in Primary Aldosteronism
Dr Raghav Sundar	National University Hospital	Study of Epigenetic Regulators of the Tumor-immune Microenvironment of Gastric Cancer Peritoneal Metastases
Dr Tay Kai Xun Joshua	National University of Singapore	Immuno-Oncology Pathways in Nasopharyngeal Carcinoma for Targeted Treatment
Dr Tay Kae Jack	Singapore General Hospital	Focal Cryotherapy for Prostate Cancer: Does the Radiological-Molecular Landscape Predict Oncological Outcomes?
Dr Tianrong Yeo	National Neuroscience Institute	Gut Microbiome-derived Metabolites Linking the Gut Microbiome to Systemic Inflammation and Neuroinflammation in Asian Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder
Dr Yang Shiwen Valerie	National Cancer Centre Singapore	The Immune Microenvironment in Soft Tissue Sarcomas and Therapeutic Implications for Immunotherapy
Dr Wong Keng Lin Francis	Sengkang General Hospital	The Effect of Mesenchymal Stem Cell (MSC) Exosomes on Enhancing Meniscus Repair: A Translational Study towards Clinical Application
Dr Lim Shir Lynn	National University Hospital	NEUROprotection via optimizINg cerebral blood flow afTer cArdiaC arresT (NEURO-INTACT) study
Dr Chong Shu-Ling	KK Women's and Children's Hospital	A novel approach to identify Serious Bacterial Infections (SBIs) among febrile young infants: the Serious bacterial Infections in Febrile infants Toolkit (SIFT)
Dr Lohendran Baskaran	National Heart Centre Singapore	Improving Obstructive Coronary Artery Disease and Cardiovascular Risk Prediction Using Deep Learning Analysis on Coronary Artery Calcium Imaging
Dr Mo Yin	National University Hospital	Antimicrobial Resistance in Severe Healthcare-associated Infections - Proposal for a Patient Registry

Name	Host Institution	Project Title
Dr Xiao Bin	National Neuroscience Institute	Nanoparticle-assisted Antisense Oligonucleotide Targeting Parkin as Potential Therapeutics for Parkinson's Disease
Dr Ai Peng Tan	National University of Singapore	Precision BRAin COnnectivity Profiling of Learning Difficulties for future therapeutic strategy using network-targeted neurostimulation (BRACO-LD)
Dr Tiew Pei Yee	Singapore General Hospital	Fungal Sensitization as a Potential Contributing Factor to Chronic Obstructive Pulmonary Disease (COPD) Deterioration
Dr Iris Rawtaer	Sengkang General Hospital	Using Sensors to Detect Mild Cognitive Impairment, Early Dementia and Frailty Among Older Adults Living in the Community: A Proactive Approach for Healthy Ageing
Dr Amanda Chee Yun Chan	National University of Singapore	The Role of Novel Auto-Antibodies in Idiopathic Small Fiber Neuropathy

NMRC Research Training Fellowship (RTF)

59 recipients were awarded the NMRC RTF.

Name	Host Institution	Type of Training and Project Title
Dr Ho Wen Teng Vanda	National University Hospital	**Full-time local PhD** Immunosenescence and Mechanisms of Attenuated Vaccine Response to SARS-CoV-2 in Older Adults
Dr Ku Chee Wai	KK Women's and Children's Hospital	**Full-time local PhD** Healthy Early Life Moments in Singapore (HELMS): Metabolic Health and Lifestyle Intervention for Overweight and Obese Women During Preconception and Pregnancy
Dr Lim Hui Jun	Singapore General Hospital	**Full-time overseas PhD** Molecular Characterisation and Biomarkers in Detection of Patients with Increased Risk of Oesophageal Cancer
Dr Oh Lingzhi Bernice	National University of Singapore	**Full-time local PhD** A Novel Cellular Immunotherapy Approach Combining a Compact Anti-GD2 Molecule (IFL-GD2) with Expanded, Activated Natural Killer (NK) Cells and CD16-41BB-CD3zeta T-cells for Childhood Neuroblastoma
Ms Teh Wen Lin	Institute of Mental Health	**Full-time local PhD** Prefrontal Cortical Activity, Impulsivity, and Executive Function in Bipolar Disorder: a Functional Near-infrared Spectroscopy (FNIRS) Study
Dr Chen Hui Lionel Raphael	Singapore General Hospital	**Part-time local PhD** A Study of Epidemiological Trends, Transcriptomic and Immunological Profiles of Early-onset Colorectal Cancer in Singapore
Dr Chen Ziyou David	National University Hospital	**Part-time local PhD** PRIME-IOL: Intraocular PRessure- and Fundus IMage-Exporting IntraOcular Lens for Passive Continuous Monitoring of Age-related Eye Conditions after Cataract Surgery
Dr Chew Linghui Justin	National University Hospital	**Part-time local PhD** Inflammation, Metabolism and Body Composition as Physiological Markers of Homeostatic Capacity in a 'Vitality Index' of Ageing: a Study of the Vitality Domain of Intrinsic Capacity and its Impact on Frailty, Activity Levels and Life-space Mobility
Dr Chiang Jianbang	National Cancer Centre Singapore	**Part-time local PhD** Increasing Uptake of Cascade Testing in Families with Familial Cancer Syndromes: A Randomised Controlled Trial of a Registry-aided Outreach Model
Dr Chua Ser Kenon	Singapore General Hospital	**Part-time local PhD** Wnt Signalling in Fracture Healing and Bone Regeneration

Name	Host Institution	Type of Training and Project Title
Dr Widanalage Sanjay Prasad de Mel	National University Hospital	**Part-time local PhD** Evaluating the Role of Tumor-Associated Macrophages in the Response to Anti-CD38 Monoclonal Antibody Therapy in Multiple Myeloma
Dr Fong Sheng	Singapore General Hospital	**Part-time local PhD** Developing Molecular Biomarkers for Dementia Staging in a Singapore Cohort of Geriatric patient**s**
Dr Han Shuting	National Cancer Centre Singapore	**Part-time local PhD** Neoantigen Screening and Validation Using Engineered Artificial Reporter Cell and Artificial Antigen-presenting Cell (aAPC) Platform in Patients Receiving Adjuvant Dendritic Cell Vaccine and Anti-PD1 Therapy (Nivolumab) Post-resection of Colorectal Cancer with Liver-limited Metastases (CRLM) and Hepatocellular Carcinoma (HCC)
Dr Shirin Kalimuddin	Singapore General Hospital	**Part-time local PhD** Defining a Minimum Threshold of T-cell Immunity for Protection Against Viral Infection: An Experimental Medicine Approach
Dr Koh Hong Xiang Frederick	Sengkang General Hospital	**Part-time local PhD** Identification and Characterisation of the Regulatory Elements of Muscle Stem Cells in Reference to Sarcopenia in Patients with Colorectal Cancer
Dr Lim Yijuan Yvonne	National University Hospital	**Part-time local PhD** Engineering Probiotic to Fight Obesity: Modulating Gut Hormone Level and Increasing Butyrate Production to Reduce Appetite
Dr Loh Ser Pheng John	National University Hospital	**Part-time overseas PhD** A Biodegradable Arterial-Centric Anastomosis Device for Microvascular Surgery
Dr Arun Kumar Narayanaswamy	Singapore Eye Research Institute	**Part-time local PhD** Evaluation of Changes in Post-trabecular Aqueous Outflow Pathways Using High-resolution Multimodal Imaging Platforms
Dr Ng Kok Pin	National Neuroscience Institute	**Part-time local PhD** Genetic Variants of Neurocognitive Diseases in Singapore: From Discovery to Clinical Applications
Dr Ng Tat Ming	Tan Tock Seng Hospital	**Part-time local PhD** Developing betA-lactam pharmacodynamic taRgets in Gram-nEgative bacTeraemia using physiologically-based pharmacokinetic modelling (TARGET)
Dr Oh Choon Chiat	Singapore General Hospital	**Part-time local PhD** Multiomic analysis, Immune Profiling and T-cell Immunity in Persistent Human Papillomavirus (HPV) Skin Infection and Cutaneous Squamous Cell Carcinoma (cSCC) among Immunocompetent Hosts and Organ Transplant Recipients (OTRs)
Dr Saw Pei Li Stephanie	National Cancer Centre Singapore	**Part-time local PhD** Defining Minimal Residual Disease through Major Pathologic Response and Biomarker Discovery in Early Stage EGFR-mutated Non-small-cell Lung Cancer Treated with Neoadjuvant osimErtinib with/without ChemotheRapy (DISCOVER)
Dr Louisa Sun	Alexandra Hospital	**Part-time local PhD** Using Health Technology Assessment to Assess Direct and Indirect Impacts of Life-course Vaccination and Increase Adult Vaccination Compliance in Singapore
Dr Tan Jing Ying Tira	National Cancer Centre Singapore	**Part-time local PhD** Homologous Recombination Deficiency (HRD) in Platinum Sensitive Triple Negative Breast Cancer (TNBC)
Dr Judith Wong Ju Ming	KK Women's and Children's Hospital	**Part-time local PhD** Distilling the Bio-signatures and Mechanisms Underlying Severe Viral Induced Acute Respiratory Distress Syndrome
Dr Wong Meihua Wendy	National University Hospital	**Part-time local PhD** Advancing RNA-based Therapeutics for Inherited Retinal Dystrophies

Name	Host Institution	Type of Training and Project Title
Dr Ang Li'en Yvonne	National University Hospital	**Part-time local Master's Degree** Identifying Exosome Biomarkers of Response in Epidermal Growth Factor Receptor (EGFR) Mutated Lung Cancer
Dr Nicholas Chew	National University Hospital	**Part-time local Master's Degree** Cardiovascular Manifestations and Prognostic Outcomes of Non-Alcoholic Fatty Liver Disease (Master of Clinical Investigation)
Dr Choi Ci-En Ellie	National University Hospital	**Part-time local Master's Degree** Discordant Symptom Burden and Severity Grading in Dermatology, a Mixed-methods Sequential Exploratory Study
Dr Widanalage Sanjay Prasad de Mel	National University Hospital	**Part-time local Master's Degree** Evaluating the Host Microbiome and Cytokine Dysregulation as Predictive factors for Response to Anti CD38 monoclonal antibody-based therapy in Multiple Myeloma
Dr Goh Yihui	National University Hospital	**Part-time local Master's Degree** Sequencing for Pathogens in Patients with Suspected central nervous system infections
Dr Ho Wen Teng Vanda	National University Hospital	**Part-time local Master's Degree** COVID-19 Vaccine Response across the Ages
Dr Jing Mingxue	National University Hospital	**Part-time local Master's Degree** Decoding Ischemic Stroke Mechanisms Through a Detailed Analysis of the Microstructure and Composition of Retrieved Blood Clots
Dr Koh Jean Aan Mark	KK Women's and Children's Hospital	**Part-time local Master's Degree** Duke-NUS Medical School Master of International Translational Medicine Degree
Dr Lee Jie Xin Joycelyn	National Cancer Centre Singapore	**Part-time local Master's Degree** Characterisation of Stool Microbiome in Advanced HCC Patients Receiving Immune Checkpoint Inhibitors
Dr Li Weiquan James	Changi General Hospital	**Part-time local Master's Degree** Real-World Validation of an Artificial Intelligence Characterisation Support (CADx) System for Prediction of Polyp Histology in Colonoscopy: A Prospective Study
Dr Jia Li Low	National University Hospital	**Part-time local Master's Degree** Study of Secondary Squamous Cell Carcinoma of the Head and Neck after Definitive Radiotherapy+/-Chemotherapy for Nasopharyngeal Carcinoma
Dr Mok Chi Wei	Changi General Hospital	**Part-time local Master's Degree** Robotic Mastectomy - A Pilot Study Assessing Surgical Outcomes, Health-Related Quality of Life and Patient Satisfactions
Dr Neo Hui Shan Shirlyn	National Cancer Centre Singapore	**Part-time local Master's Degree** Pilot study of a "Fast Acting Fentanyl Sublingual Tablet (Abstral) for the Prophylactic Treatment of Episodic Activity Induced Dyspnea in Asian Cancer Patients"
Dr Nicholas Ng Beng Hui	National University Hospital	**Part-time local Master's Degree** Neurobiology of Obesity: The Role of the Prefrontal Cortex in Mediating Childhood Obesity Risk Through Changes in Executive Function and Alterations in Eating Behaviours
Dr Roderica Ng	Singapore General Hospital	**Part-time local Master's Degree** Perioperative Preservation of Renal Function in the Non-Cardiac Surgical Population
Dr Kumaran s/o Rasappan	National University Hospital	**Part-time local Master's Degree** Engineered Extracellular Vesicles for Enhanced Bone Regeneration
Dr Shen Jia Yi	National Neuroscience Institute	**Part-time local Master's Degree** Mild Cognitive Impairment in Adult Patients with Epilepsy (PWE): Elucidating the Cognitive Profiles and Clinical Risk Factors of Dementia among Major Epilepsy Subtypes
Dr Tan Chin Kimg	Changi General Hospital	**Part-time local Master's Degree** A Pilot Study on Feasibility and Efficacy of Modified Crohn's Disease Exclusion Diet in Asian Adults with Crohn's Disease

Name	Host Institution	Type of Training and Project Title
Dr Tan Hwee Leong	Singapore General Hospital	**Part-time local Master's Degree** Development of Prognostication Models for Outcomes Following Resection of Hepatocellular Carcinoma Using Multi-modal Healthcare Data.
Dr Tan Li Feng	Alexandra Hospital	**Part-time local Master's Degree** Validation of a Hospital Frailty Risk Score and Association with Clinical Outcomes in Older Adults in Singapore
Dr Tan Shao Ern Timothy	KK Women's and Children's Hospital	**Part-time local Master's Degree** Development of a Multiparametric Magnetic Resonance Imaging Radiomic Signature-based Pre-operative Scoring System for Predicting Risk of Post-operative Cerebellar Mutism Syndrome in Paediatric Medulloblastomas.
Dr Tay Shu Wen	Singapore General Hospital	**Part-time local Master's Degree** The Role of the Faecal Microbiome in Immune Modulation in an Asian Inflammatory Bowel Disease (IBD) Population.
Dr Teh Kim Jun, Kevin	Singapore General Hospital	**Part-time local Master's Degree** The Role of Immune Modulation in Spontaneous Bacterial Peritonitis
Dr Robert John Walsh	National University Hospital	**Part-time local Master's Degree** Single Centre Prospective Evaluation of Gallium-68 FAPI-46 PET/MRI in Hepatocellular Carcinoma Compared to Standard of Care Evaluation
Dr Cheong May Anne	Singapore General Hospital	**Full-time Singapore Biodesign Innovation Fellowship**
Dr Hoon Hui Qing Violet	Tan Tock Seng Hospital	**Full-time Singapore Biodesign Innovation Fellowship**
Dr Liu Zhenghong	Singapore General Hospital	**Full-time Singapore Biodesign Innovation Fellowship**
Dr Wong Tsz Yeung, Emmett	National University Hospital	**Full-time overseas research attachment** Wnt signaling in fracture healing and bone regeneration
Dr Chia Kai Ann, Daryl	National University Hospital	**Full-time overseas research attachment** Evaluating a Novel Locoregional Immune-modulator in an Immune-resistant Mouse Model of Peritoneal Metastasis
Dr Chua Jian Kai Andy	National University Hospital	**Full-time overseas research attachment** Transnasal CNS Delivery of MDM2 and MDMX Dual Inhibitor Using the Minimally Invasive Nasal Depot (MIND) Technique
Dr Lim Pin Miao Fiona	Singapore Eye Research Institute	**Full-time overseas research attachment** A new model for glaucoma screening and management of stable glaucoma patients in the community in Singapore– learning from experience in the UK.
Dr Tan Yijia, Bryan	Woodlands Health Pte Ltd	**Full-time overseas research attachment** Collaborative Model of Care between Orthopaedics and Allied Healthcare Professionals (CONNACT)
Dr Cinnie Yentia Soekojo	National University Hospital	**Full-time overseas research attachment** Wnt signaling in fracture healing and bone regeneration

National Outstanding Clinician Scientist (CS) Resident Award

Three recipients were awarded the National Outstanding CS Resident Award.

Name	Cluster	Clinical Specialty
Dr Paul Tan Hon Sen	Singapore Health Services	Anaesthesiology
Dr Xu Chuanhui	National Healthcare Group	Rheumatology
Dr Clement Wu	Singapore Health Services	Gastroenterology

RESEARCH GRANT PROGRAMMES

(PROJECT-BASED)

FUNDING TRANSLATIONAL AND CLINICAL RESEARCH (TCR)

Funding of TCR is one of the core pillars of NMRC's mandate. In line with this, NMRC offers several grants to support small- to large-scale Singapore-based research initiatives across the biomedical science spectrum. To ensure the best possible use of research funding, all grants are peer-reviewed and awarded competitively.

The active Research Grant Programmes (project-based) in FY2021 and FY2022 are:

- Centre Grant (CG)
- Clinical Trial Grant (CTG)
- Clinician Scientist-Individual Research Grant (CS-IRG)
- Clinician Scientist-Individual Research Grant-New Investigator Grant (CS-IRG-NIG)
- Population Health Research Grant (PHRG)
- Population Health Research Grant-New Investigator Grant (PHRG-NIG)

Open Fund

- Large Collaborative Grant (LCG)
- Individual Research Grant (IRG)
- Young Individual Research Grant (YIRG)

Centre Grant (CG)

The CG aims to support the public healthcare institutions/clusters in building their core research capabilities in terms of common research platforms, shared resources (e.g. equipment) and core manpower; to enhance their collaborative and transdisciplinary research productivity in achieving progress towards the Research, Innovation and Enterprise (RIE) goals of healthcare research. It seeks to capitalise on the institutional research capabilities, and aid in the development of shared resources which can support the public healthcare institutions'/clusters' and/or partnering entities' research in a focused area. The CG encourages collaboration and coordination of research efforts within the institution/cluster or across different healthcare entities focusing on the same area of research to disseminate research findings for the benefits of the community.

Under the RIE2025 CG framework, there are 3 funding categories: Category 1 (Established Centres), Category 2 (Collaborative Centres) and Category 3 (Developing Centres).

Funding Category	Funding Quantum & Duration	Aim
CG Category 1 – Established Centres	Up to $20 million over 4 years	• To support individual Public Healthcare Institutions (PHIs) in strengthening existing research capabilities to meet the CG's objectives • To support individual healthcare clusters in developing/strengthening capabilities in population health research
CG Category 2 – Collaborative Centres	Up to $7 million over 4 years	• To support joint collaborations between two or more PHIs in strengthening existing research capabilities to meet the CG's objectives
CG Category 3 – Developing Centres	Up to $3 million over 4 years	• To support individual PHIs in developing new/existing research capabilities to meet the CG's objectives, under the mentorship or guidance of a named co-partner that can be an entity or an individual

Applicants were required to demonstrate the translational outcomes of their research strategies and alignment with RIE2025 HHP goals[^] in terms of transforming and protecting the health of the nation, through one or more of the following: (i) good healthcare outcomes at sustainable costs; (ii) population health, preventive health, and epidemic preparedness and response; (iii) data-centric healthcare and digital health; and/or (iv) achieving quadruple aims (i.e. improving health outcomes, keeping per capita cost manageable, improving care experiences and keeping providers satisfied).

Specifically for Category 2 (Collaborative Centres), priority consideration was given to applications which focus on at least one of the 7 MOH-prioritised disease domains: (i) Cancers; (ii) Cardiovascular diseases; (iii) Infectious diseases; (iv) Eye; (v) Metabolic and Endocrine; (vi) Neuroscience; and (vii) Mental Health.

Grant Call	Proposals Reviewed	Proposals Awarded	Total Sum Awarded ($ millions)
Apr 2021	40	22	195.00

[^]The RIE2025 HHP goals are to better transform and protect health, advance human potential and create economic value for Singapore.

Clinical Trial Grant (CTG)

The CTG includes two schemes:

1. The **Industry Collaborative Trials (ICT) scheme** supports ICTs, which involve both the clinician and company contributing intellectual inputs and funds to conduct the trial as well as the development of novel or pre-existing drugs/medical devices/interventions for new indications. The prerequisite for application is the PI's ability to obtain industry contribution of at least 70% (cash or in-kind) of the Total Project Costs (TPC). The PI can apply for funding quantum of up to 30% of the TPC (inclusive of 30% indirect costs). Funding quantum for each project is capped at $4.94 million (inclusive of 30% indirect costs) for up to five years. CTG-ICT is a rolling grant call.

FY	Proposals Reviewed	Proposals Awarded	Success Rate	Total Sum Awarded ($ millions)
2021	0	0	NA	0
2022	2	2	100.0%	1.17
Total	**2**	**2**	**100.0%**	**1.17**

2. The **Investigator-Initiated Trials (IIT) scheme** supports IITs of both early and late phases which are initiated and driven by clinicians who are interested to conduct clinical trials on novel or pre-existing drugs/medical devices/interventions for new indications. While there are no requirements for minimum company contributions, applications with industry contributions will be given higher priority. Funding quantum for each project is capped at $1.625 million (inclusive of 30% indirect costs) for up to five years. CTG-IIT grant calls are made twice per year.

Grant Call	Proposals Reviewed	Proposals Awarded	Success Rate	Total Sum Awarded ($ millions)
Jun 2021	8	2	25.0%	2.84
Nov 2021	6	2	34.0%	2.73
Jul 2022	7	2	29.0%	3.21
Total	**21**	**6**	**29.0%**	**8.78**

Clinician Scientist-Individual Research Grant (CS-IRG)

The CS-IRG are provided to clinician scientists to carry out medical research on a specifically defined topic for a period of three to five years in a local public institution. Funding quantum for each project is capped at $1.95 million (inclusive of 30% indirect costs) for up to three years. Projects involving prospective patient/subject recruitment may apply for a funding duration of up to five years. CS-IRG grant calls are made twice per year.

Grant Call	Proposals Reviewed	Proposals Awarded	Success Rate	Total Sum Awarded ($ millions)
Nov 2020*	71	9	12.68%	13.35
Jun 2021	46	9	19.57%	16.99
Nov 2021	31	13	41.94%	21.24
Jul 2022	26	12	46.15%	21.89
Total	**174**	**43**	**24.71%**	**73.47**

*Supported under RIE2020. Funding quantum for each project is capped at $1.8 million (inclusive of 20% indirect costs) for up to three years.

CS-IRG New Investigator Grant (CS-IRG-NIG)

The CS-IRG-NIG is a subcategory of the CS-IRG to cater for new clinical investigators. The CS-IRG-NIG is a step for the new investigator towards winning a first independent national level grant. Applicants with substantial research experience will not be accepted under this category. Funding quantum for each project is capped at $260,000 (inclusive of 30% indirect costs) for up to two years. Projects involving prospective patient/subject recruitment may apply for a funding duration of up to three years, subject to the same funding quantum. CS-IRG-NIG grant calls are made twice per year.

Grant Call	Proposals Reviewed	Proposals Awarded	Success Rate	Total Sum Awarded ($ millions)
Nov 2020*	27	12	44.44%	2.66
Jun 2021	24	7	29.17%	1.73
Nov 2021	27	10	37.04%	2.52
Jul 2022	12	7	58.33%	1.82
Total	**90**	**36**	**40.00%**	**8.73**

*Supported under RIE2020. Funding quantum for each project is capped at $240,000 (inclusive of 20% indirect costs) for up to two years.

Health Services Research Grant (HSRG)

The HSRG promotes the conduct of HSR and enables the translation of HSR findings into policy and practice. The RIE2020 grant scheme held its last grant call in November 2020, and was renamed to PHRG in RIE2025.

Grant Call	Proposals Reviewed	Proposals Awarded	Success Rate	Total Sum Awarded ($ millions)
Nov 2020*	32	10	31.30%	6.85

*Supported under RIE2020.

Health Services Research-New Investigator Grant (HSR-NIG)

The HSR-NIG is a subcategory of the HSRG, launched with the aim of supporting new HSR researchers. The grant scheme was renamed to PHRG-NIG in RIE2025.

Grant Call	Proposals Reviewed	Proposals Awarded	Success Rate	Total Sum Awarded ($ millions)
Nov 2020*	11	7	63.60%	0.82

*Supported under RIE2020.

Population Health Research Grant (PHRG)

As part of MOH's aim to develop an integrated ecosystem that anchors preventive health efforts in primary care and care in the community with good system linkages to support citizens at different life stages, novel strategies and approaches will be needed to drive sustained behavioural modifications for individuals to adopt healthier behaviour and habits. To achieve this, the PHRG will fund research proposals which seek to improve health outcomes through a population health approach under the research areas of Health Promotion and Preventive Health, and Health Services Research. The RIE2025 PHRG comprises two categories:

1. The **Open Category** welcomes applications on all research topics within the Research Areas as articulated above to allow space for researchers to identify emerging areas of need and discover novel ideas that may contribute significantly to health outcomes in the medium- to long-term;
2. The **Thematic Category** supports only proposals with scope falling within the specific Research Themes to specifically address MOH's areas of pressing research needs.

The grant calls for both categories were launched in July 2022.

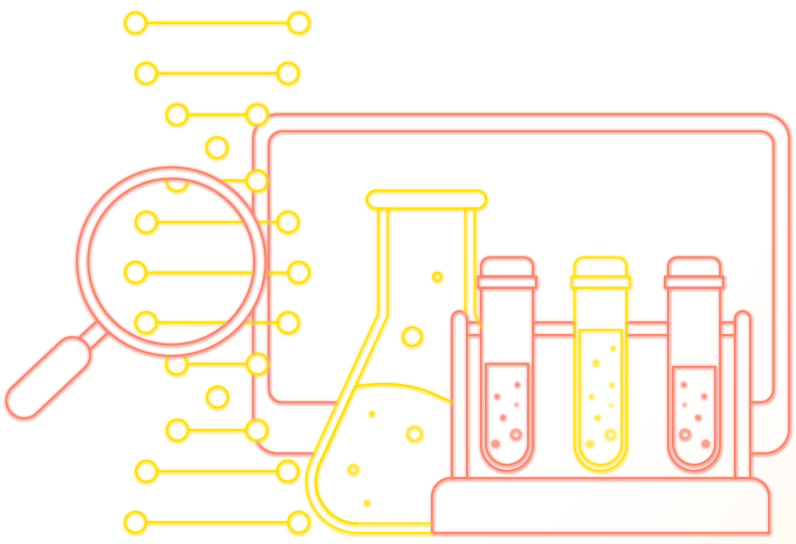
PHRG - Open Category

Grant Call	Proposals Reviewed	Proposals Awarded	Success Rate	Total Sum Awarded ($ millions)
Jul 2022	24	5	20.83%	3.40
Total	**24**	**5**	**20.83%**	**3.40**

Population Health Research Grant – New Investigator Grant (PHRG-NIG)

The PHRG-NIG is a subcategory of the PHRG Open Category as a step for new investigators towards winning their first independent national level grant. Applicants with substantial research experience will not be accepted under this category. The grant call for this subcategory was launched in July 2022.

Grant Call	Proposals Reviewed	Proposals Awarded	Success Rate	Total Sum Awarded ($ millions)
Jul 2022	13	3	23.08%	0.39
Total	**13**	**3**	**23.08%**	**0.39**



OPEN FUND

Large Collaborative Grant (LCG)

The LCG aims to bring together the best teams from public institutions to advance human health and wellness as well as create economic value for Singapore and Singaporeans, through the pursuit of excellence in research and its applications. The purpose of the LCG scheme is to support patient-centric translational research[1], underpinned by basic[2] and/or applied research[3].The scheme will not support pure basic science, pure clinical or pure applied research.

Its key elements include:

- Interdisciplinary collaboration across institutions is preferred and encouraged so as to integrate, coordinate and leverage on the full spectrum of research capabilities in Singapore, from basic science to clinical research.
- LCG programmes should aim to make significant contributions to the advancement of knowledge and help establish Singapore as a global leader in therapeutic areas.
- LCG programmes should facilitate the discovery and application of basic science ideas relevant to the advancement of health, as well as the translation of clinical findings into policy and practice. They should also provide opportunities for international partnerships and/or industry collaborations.
- Pathway(s) to impact should be clearly articulated.

The LCG is open to proposals of the highest quality in all areas, typically involving multidisciplinary teams. To better realise the goals of the HHP domain in Singapore, the following seven areas have been identified as national priorities for research: Cancers and neoplasms, Cardiovascular, Eye, Infection, Mental health, Metabolic and endocrine, and Neurological.

For each grant call, specific therapeutic areas will be selected as the emphasised therapeutic areas which the HHP community is encouraged to address. At the same time, proposals in other areas will also be considered. Similar to the RIE2020 LCG, there are two funding tiers for application, providing funding (inclusive of 30% indirect cost) of up to $10 million and $25 million.

The review process is two-stage. It comprises the Letter of Intent (LOI) and Full Proposal (FP) for shortlisted LOI applications.

For the June 2021 grant call, all seven therapeutic areas were set as the emphasised therapeutic areas. For the May 2022 grant call, there were five emphasised therapeutic areas (Cardiovascular, Infection, Mental health, Metabolic and endocrine, and Neurological).

The following categorisation of research activity is based on UK Health Research Classification System (HRCS):
[1]Translational Research: Prevention, Detection and Diagnosis, Treatment Development and Treatment Evaluation
[2]Basic Research: Underpinning and Aetiology
[3]Applied Research: Disease Management and Health Services

The success rate and details of the awarded programmes for the June 2021 and the May 2022 calls are tabulated in the tables below:

Grant Call	Funding Tier	Letters of Intent Reviewed	Full Proposals Reviewed	Proposals Awarded	Success Rate	Total Sum Awarded ($ millions)
Jun 2021	Tier-1	4	3	1	33.33%	59.92
	Tier-2	5	3	2		
May 2022	Tier-1	4	1	1	42.86%	59.86
	Tier-2	3	3	2		
Total	-	**16**	**10**	**6**	**37.50%**	**119.78**

AWARDED PROGRAMMES:

Programme Title (Funding Tier)	Emphasised Therapeutic Area(s)	Leadership Team (Institution)
An integrated genomic, epidemiological and intervention program for NPC early diagnosis, stratified therapeutics and prevention **(Tier-1)**	Cancers and neoplasms	Corresponding PI: Prof Jianjun Liu (Genome Institute of Singapore: GIS) Theme PIs: Jianjun Liu (GIS), Thomas Loh Kwok Seng (NUS), Melvin Chua (National Cancer Centre Singapore: NCCS)
TAckling & Reducing Glaucoma Blindness with Emerging Technologies (TARGET) **(Tier-2)**	Eye	Corresponding PI: Prof Aung Tin (Singapore Eye Research Institute: SERI) Theme PIs: Aung Tin (SERI), Khor Chiea Chuen (GIS), Cheng Ching Yu (Duke-NUS), Jayant V Iyer (Changi General Hospital: CGH), Leopold Schmetterer (SERI), Michael Girard (SERI), Tina Wong (SERI), Shamira Perera (SERI), Jonathan Crowston (Duke-NUS), Victor Koh (NUH)
Precision Medicine in Liver Cancer across an Asia-Pacific Network 2.0 (PLANet 2.0) **(Tier-2)**	Cancers and neoplasms	Corresponding PI: Prof Pierce Chow (NCCS) Theme PIs: Pierce Chow (NCCS), Patrick Tan (GIS), Vinay Tergaonkar (Institute of Molecular and Cell Biology: IMCB), Toh Han Chong (NCCS), Tam Wai Leong (GIS), Edward Chow Kai-Hua (NUS), Roger Daniel Vaughan (Duke-NUS)
AntiMicrobial resistance Research & Intervention Alliance Singapore (AMRITAS) **(Tier-1)**	Infection	Corresponding PI: A/Prof Hsu Li Yang (NUS) Theme PIs: Hsu Li Yang (NUS), David Paterson (NUS), Mo Yin (NUS), Niranjan Nagarajan (GIS), Gan Yunn Hwen (NUS), Ng Oon Tek (Tan Tock Seng Hospital: TTSH), Sunny Wong Hei (Nanyang Technological University: NTU)
Project RESET: Redirecting immune, lipid and metabolic drivers of early cardiovascular disease **(Tier-2)**	Cardiovascular	Corresponding PI: Prof Roger Foo (NUS) Theme PIs: Roger Foo (NUS), Derek Hausenloy (National Heart Centre Singapore: NHCS), Mark Muthiah (NUH), Josip Car (NTU), Calvin Chin (NHCS), Lohendran Baskaran (NHCS), Mayank Dalakoti (NTFGH), Dennis Wang (Singapore Institute for Clinical Sciences: SICS), Jason Lee (NUS), Jasper Tromp (NUS), Ling Lieng Hsi (NUS), Melvin Leow (TTSH), Chester Drum (NUS), Chrishan Ramachandra (NHCS), Hanwei Hou (NTU), Haojie Yu (NUS), Mark Richards (NUS), Roshni Singaraja (NUS), Torsten Wuestefeld (GIS), Yibin Wang (Duke-NUS), Ringo Moon-Ho Ho (NTU), Sebastian Maurer-Stroh (BII), Yohanes Eko Riyanto (NTU)

Programme Title (Funding Tier)	Emphasised Therapeutic Area(s)	Leadership Team (Institution)
Diabetes StudY in Nephropathy And other Microvascular cOmplications II **(Tier-2)**	Cardiovascular, Eye, Metabolic and endocrine	Corresponding PI: Prof Thomas Coffman (Duke-NUS) Theme PIs: Thomas Coffman (Duke-NUS), Anissa Widjaja (Duke-NUS), Calvin Chin (NHCS), Jean-Paul Kovalik (Duke-NUS), Lim Su Chi (Khoo Teck Puat Hospital: KTPH), Liu Jian Jun (KTPH), Resham Gurung (KTPH), Gavin Tan (SERI), Charumathi Sabayanagam (SERI), Wang Xiaomeng (Duke-NUS), Tai E Shyong (NUS), Adrian Teo (IMCB), Marcus Wenk (NUS), Radoslaw Sobota (IMCB), Sim Xueling (NUS), Enrico Petretto (Duke-NUS), Jacques Behmoaras (Duke-NUS), Nicholas Tolwinski (Yale-NUS), Xia Yun (NTU)

Individual Research Grant (IRG)

The IRG supports research proposals in basic, translational and clinical research relevant to human health and potential, including research that looks at the causes, consequences, diagnosis and treatment of human diseases. Funding quantum for each project is capped at $1.625 million (inclusive of 30% indirect costs) for up to five years.

Grant Call	Proposals Reviewed	Proposals Awarded	Success Rate	Total Sum Awarded ($ millions)
Nov 2020*	129	23	17.8%	31.24
Jun 2021	129	16	12.4%	23.93
Nov 2021	98	18	18.4%	27.14
Jul 2022	80	18	22.5%	27.56
Total	**436**	**75**	**17.2%**	**109.87**

*Supported under RIE2020. Funding quantum for each project is capped at $1.5 million (inclusive of 20% indirect costs) for up to five years.

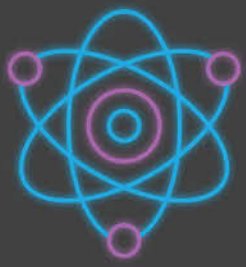
Young Individual Research Grant (YIRG)

The YIRG is a subcategory of IRG and a step for new investigators to their first independent national-level grant. Applicants with substantial research experience will not be accepted under this subcategory. The YIRG is provided to support proposals for basic, translational and clinical research that are relevant to human health and potential, including research that looks at the causes, consequences, diagnosis and treatment of human diseases. Funding quantum for each project is capped at $0.325 million (inclusive of 30% indirect costs) for up to three years.

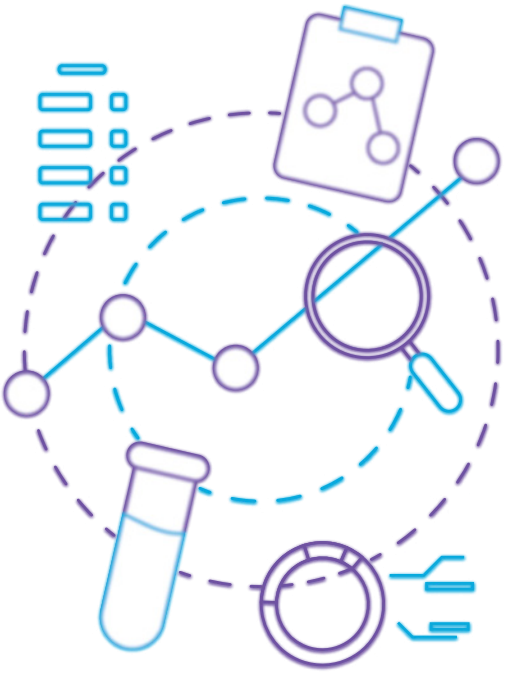
Grant Call	Proposals Reviewed	Proposals Awarded	Success Rate	Total Sum Awarded ($ millions)
Nov 2020*	64	21	32.8%	6.27
Jun 2021	46	14	30.4%	4.54
Nov 2021	45	20	44.4%	6.44
Jul 2022	43	22	51.2%	7.14
Total	**198**	**77**	**38.9%**	**24.39**

*Supported under RIE2020. Funding quantum for each project is capped at $0.3 million (inclusive of 20% indirect costs) for up to three years.

RESEARCH ENABLERS AND INFRASTRUCTURE INITIATIVES



NMRC supports the development, maintenance and enhancement of research enablers and infrastructure initiatives which align with Singapore's focus on strengthening and expanding its capabilities in TCR to drive both health and economic outcomes. NMRC works with other MOH divisions to provide grant administrative support to some of the initiatives, where the MOH divisions serve as deskheads to help the initiatives achieve their national-level objectives and to ensure their strategic alignment with MOH's healthcare research strategy.



The active Research Enablers and Infrastructure Initiatives in FY2021 and FY2022 are:

- Consortium for Clinical Research and Innovation, Singapore (CRIS)
- National Health Innovation Centre Singapore (NHIC)[1]
- National Large Animal Research Facility (NLARF)
- Programme for Research in Epidemic Preparedness And REsponse (PREPARE)

Enablers and Infrastructure Support for Clinical Trials-related Activities

- Bioethics Advisory Committee (BAC)
- Clinical Research Coordinator (CRC)[2]
- Centre for Biomedical Ethics (CBmE)[3]
- Investigational Medicine Unit (IMU)
- Institutional Review Board (IRB)
- Singapore Clinical Research Institute (SCRI)[1]

National Clinical Translational Programmes

- Cardiovascular Disease National Collaborative Enterprise (CADENCE)[1]
- Precision Health Research, Singapore (PRECISE)[1]
- Singapore Translational Cancer Consortium (STCC)[1]

Strategic Datasets and Data-sharing Infrastructure

- National Cohorts Office (NCO)

[1] *CRIS programme*

[2] *Funding for SCRI and clusters in support of CRCs*

[3] *For the Science, Health and Policy-Relevant Ethics in Singapore (SHAPES) programme*

Consortium for Clinical Research and Innovation, Singapore (CRIS)

CRIS is home to six clinical research and translation programmes. They are SCRI, NHIC, STCC, Advanced Cell Therapy and Research Institute, Singapore (ACTRIS), PRECISE, and CADENCE.

The initiatives promulgated by these programmes support clinical trials, including critical trials during crises (SCRI), supporting medtech innovations that bring productivity and improve patient care (NHIC), exploring possibilities to implement preventive healthcare more effectively (STCC, PRECISE and CADENCE), and delivering advanced therapeutic products produced locally (ACTRIS).

The research activities of the programmes in CRIS are in line with MOH's focus on the disease areas with the highest burden for Singapore, and sit at the confluence of advancing and delivering innovations in healthcare, supporting health and biomedical research, and capturing value from the health and biomedical industry in support of MOH's agenda. CRIS provides critical operational and corporate support for IT, HR, Finance, Legal (through MOH Holdings: MOHH), Communications and Strategic Planning for the consortium as a whole.

In addition, CRIS has initiated efforts to integrate business development and forge synergies in clinical research and health economics outcome research for the programmes in the consortium.

National Health Innovation Centre Singapore (NHIC)

The NHIC works with Public Healthcare Clusters (PHCs) across Singapore to identify, develop, commercialise, and adopt beneficial clinical innovations for healthcare and economic impact. NHIC does this by providing strategic funding and project guidance to clinical innovators with the assistance of industry partners and stakeholders.

NHIC collaborates with stakeholders and partners to accelerate the development and implementation of innovative clinical technologies and services in the areas of medtech and biotech, improving the standard of healthcare in Singapore and beyond. In FY2022, NHIC established stronger public-private partnerships through its Clinical Advancement and Development for Research, Entrepreneurship and Enterprise (CADRE[2]) scheme to co-develop healthtech projects and talent at the PHCs from the early stages of the commercialisation journey.

NHIC will continue strengthening its support to the PHCs, in collaboration with industry and international partners, to power the next generation of healthcare innovation.

NHIC is a programme of CRIS.

National Large Animal Research Facility (NLARF)

NLARF is a joint initiative between the SingHealth Duke-NUS and NUHS Academic Medical Centres (AMCs) which serves as a national research support facility for large animal (LA) research. It offers unique capabilities not available elsewhere in Singapore, including the supply of research-quality LAs for HHP research through an in-house breeding programme and importing animals from overseas sources, provision of long-term or temporary housing for overflow LAs from other animal research facilities, supply of animals with special health status, technical support for highly specialised research using LA models and supply of LA bio-resources. NLARF is accredited by AAALAC International[1], demonstrating its commitment to ethical and humane animal care and use.

The SingHealth Experimental Medicine Centre (SEMC) administers the initiative. Further efforts are being undertaken to enhance NLARF's capabilities to support HHP research, including its relocation to the state-of-the-art, purpose-built new NLARF facility in 2024.

[1]Previously known as Association for Assessment and Accreditation of Laboratory Animal Care International.

Programme for Research in Epidemic Preparedness and REsponse (PREPARE)

PREPARE is a national research programme set up by MOH to support and strengthen Singapore's key essential pandemic research capabilities, translational platforms, and expertise to develop tools, methods and products that can be tapped on to detect, respond to, and contain future infectious disease threats.

Infectious disease outbreaks are a continuous threat to Singapore. As an international travel hub with a high population density, Singapore is particularly vulnerable to imported and local transmission of novel infectious diseases and the re-emergence of established ones. Developing cutting-edge research capabilities to prepare for and respond well to future epidemics is thus a crucial national priority.

PREPARE seeks to:

1. Enhance research capabilities for early detection and sense-making to prepare Singapore against future infectious disease threats;
2. Develop and strengthen key enablers in data infrastructure, analytics and behavioural science research to respond to public health crises;
3. Strengthen research capabilities to enhance our national resilience in diagnostics, therapeutics and vaccines; and
4. Develop a strong infectious diseases research collaboration network across countries in our region to respond to epidemics and facilitate multicentre clinical trials.

The initiative is hosted at the National Centre for Infectious Diseases at Tan Tock Seng Hospital.

ENABLERS AND INFRASTRUCTURE SUPPORT FOR CLINICAL TRIALS-RELATED ACTIVITIES

Bioethics Advisory Committee (BAC)

The BAC is an independent national advisory committee which examines ethical, legal and social issues arising from human biomedical science and research, with the aim of protecting the rights and welfare of individuals while allowing the biomedical sciences to develop and realise their full potential for the benefit of mankind. It actively gathers information and views from the international and local community and, after careful deliberation, makes recommendations to the Singapore Government and local research community on the ethical standards for human biomedical research. International engagement and public education are also part of the remit of the BAC.

The Biomedical Ethics Coordinating Office (BECO), Regulatory Policy and Legislation Division, MOH provides policy, administrative and secretariat support to the BAC. Further efforts are being undertaken by the BAC to support the biomedical research landscape in Singapore, and in profiling Singapore as a leading regional and international biomedical research hub with high ethical standards and public trust preserved in local research activities.

Clinical Research Coordinator (CRC)

CRCs are critical manpower in the conduct of clinical trials. They support clinicians by facilitating and coordinating daily clinical trial activities such as identifying suitable potential patients for recruitment. A steady pool of trained CRCs is crucial for enabling rapid patient recruitment and ensuring that clinical trials are completed on time.

The initiative is managed by SCRI, a programme of CRIS. Further efforts are being undertaken to provide continued support to the CRC profession, including the provision of salary support, certification and training programmes to develop and upskill the CRCs.

Centre for Biomedical Ethics (CBmE)

The National University of Singapore (NUS) CBmE's SHAPES initiative supports Singapore's goals in research on HHP through building bioethics capability that supports and facilitates research excellence; working with other enablers to support the development and implementation of policy related to the ethical conduct, governance and translation of clinical research; and developing scholarship and thought leadership related to innovative technologies and therapies.

SHAPES seeks to develop understanding, capacity for good judgement and sound ethical practice in the context of healthcare provision, biomedical science and health-related policy development. Within SHAPES, further efforts are being undertaken to build Singapore's bioethics capabilities and support policy development in key areas such as Clinical Trials and Clinical Research; Clinical Innovation; and Artificial Intelligence and Trust Technologies.

Investigational Medicine Unit (IMU)

The SingHealth and NUHS IMUs provide supporting infrastructure for clinician-investigators, such as a dedicated space and beds for inpatient and outpatient research, computer hardware and software systems for data management and analysis, as well as manpower "infrastructure" such as clinical pharmacologists, clinical research coordinators, specialised research nurses/clinical research nurses and biostatisticians.

The IMUs focus on early phase trials (Phases 1 and 2), preferably first-in-man while also supporting late phase trials, and encourage collaborative efforts across trial units, institutions and clusters in Singapore as well as outside Singapore to develop innovative thought leadership and global competitiveness.

Institutional Review Board (IRB)

The SingHealth Centralised Institutional Review Board (CIRB) and the National Healthcare Group (NHG) Domain Specific Review Board (DSRB) are public-sector IRBs that serve to ensure rigour in ethics review for the protection of human research subjects in biomedical and translational and clinical research. The research ethics reviews conducted by CIRB and DSRB are mutually recognised since 1 October 2014. Further efforts are being undertaken by the IRBs to improve the quality and efficiency of IRB operations to better support clinical research in Singapore.

Singapore Clinical Research Institute (SCRI)

SCRI is the national coordinating body for clinical trials in Singapore. It works with various stakeholders, including the MOH, to implement the national strategy for clinical trials, strengthening Singapore's clinical trials ecosystem.

As the national academic clinical research organisation (ACRO), SCRI is dedicated to enhance clinical research standards. It provides core services such as clinical, biostatistical data, project management expertise and medical informatics solutions as well as infrastructure for late-phase clinical research. The institute actively engages with public agencies and institutions as well as companies and industry to foster public-private collaborations, and also provides thought leadership in the operational and methodological aspects of clinical trials.

Further efforts are being undertaken to strengthen SCRI's capabilities in terms of its coordination abilities and infrastructure to enhance the quality of clinical trials and performance of the local clinical trial ecosystem.

SCRI is a programme of CRIS.

NATIONAL CLINICAL TRANSLATIONAL PROGRAMMES

Cardiovascular Disease National Collaborative Enterprise (CADENCE)

Established in 2023, CADENCE synergises cardiovascular research and translation capabilities across Singapore. The programme aspires to position Singapore as the leading Asian hub for cardiovascular data science research; high-impact multi-site early phase mechanistic cardiovascular clinical trials; and to develop state-of-the-art behavioural interventions for the primary prevention of cardiovascular diseases.

CADENCE focuses on the following three major clinical themes in cardiovascular diseases: cardio-oncology; heart failure; and primary prevention of cardiovascular diseases, given their major contributions to the healthcare and economic burden of cardiovascular diseases in Singapore.

Leveraging the capabilities across its partnering institutions, CADENCE established three joint platforms – Data, Imaging & Tissue Repository; National Cardiovascular Clinical Trials Network; Artificial Intelligence, Digital Health and Human Potential with support from its Business Intelligence and Development unit to achieve its objectives.

CADENCE is a programme of CRIS.

Precision Health Research, Singapore (PRECISE)

PRECISE coordinates a whole-of-government effort to implement Phase 2 of Singapore's National Precision Medicine (NPM) programme. As healthcare needs and the research landscape evolve and become more complex, early intervention and more targeted treatments that produce improved health outcomes are needed. Precision Medicine (PM) is an approach to healthcare that integrates individual and group differences in genes, environment, and lifestyle to predict disease risk, diagnose disease, tailor therapies and reduce clinical complications. In doing so, targeted strategies can be developed for specific individuals and groups to improve outcomes and maximise health spans while mitigating healthcare costs.

The NPM is a three-phase programme which outlines how Singapore should best deploy PM to drive research, clinical innovation, and economic growth. Phase 1 established a Singaporean genome reference database of 10,000 genomes known as SG10K_Health. It is the world's largest multi-ethnic Asian reference database which is currently being used by clinicians and researchers to generate novel insights into the genetics of Asian populations and manage patients with various genetic conditions. Phase 2 will sequence and analyse genomes and phenotypes of about 100,000 consented healthy Singaporeans, forming one of Asia's most deeply phenotyped cohorts, pilot clinical implementation of PM approaches, and establish public-private partnerships as well as data infrastructure to support data-driven innovation. The work of Phase 2 underpins Phase 3, which targets embedding genomics into the Singapore healthcare system to improve population health in a responsible and sustainable manner.

PRECISE is a programme of CRIS.

Singapore Translational Cancer Consortium (STCC)

STCC was established as a nationally coordinated entity to address the need for a cohesive and collaborative national cancer research and translation platform. It aspires to position Singapore as a global leader in research and translational capabilities for selected Asian cancers by advancing Singapore's competitiveness through establishing systems-level frameworks driven by value-based collaborative cancer research use cases.

Under Phase 1, STCC established four joint platforms: Cancer Clinical Trials and Investigational Medicine Units; Cancer Databases and Tissue Banks; Translational Research Integration and Support; and Business Intelligence and Development Unit, which enable collaborative cancer research and translation to achieve health and economic value creation for Singapore.

In Phase 2, it will expand to establish a new joint platform, i.e. Impact and Population Health to enhance the quality of care and lower the long-term cost of cancer care in Singapore through evidence-based recommendations translating research to clinical practices and guidelines.

STCC is a programme of CRIS.

STRATEGIC DATASETS AND DATA-SHARING INFRASTRUCTURE

National Cohorts Office (NCO)

The NCO was set up in 2021 to implement the Strategic Datasets initiative. Its mandate is to advocate and facilitate competency building among cohorts to enhance the long-term biomedical research ecosystem in Singapore. NCO is established with two sub-divisions, NCO (Research) and NCO (Grant Admin). NCO (Research)'s roles include: ecosystem facilitator to connect across cohorts and other stakeholders to build a collaborative ecosystem; cohort advocator to highlight the needs of cohorts at the national level; competency building to establish and encourage best practices; and methodological innovation to promote development, evaluation and dissemination of relevant methods for the cohort research community. NCO (Grant Admin) serves as funding administrator for strategic cohort grant calls. It maintains administrative oversight of the strategic cohorts and is responsible for grant-related administrative and secretariat functions.

The initiative is hosted at the Saw Swee Hock School of Public Health, National University of Singapore. It seeks to support cohorts as critical infrastructural and foundational capabilities that are of strategic value with high potential for long-term impact to major HHP thrusts and Singapore's population health strategies, through grant funding, workshop, training and conference.


EVENTS

NATIONAL MEDICAL EXCELLENCE AWARDS (NMEA) 2021 AND 2022

The NMEA recognise the efforts of outstanding clinicians, clinician scientists and other healthcare professionals for their contributions. It acknowledges their achievements in advancing healthcare, improving the standards of patient safety and driving research and education, which ultimately improve people's lives.

In 2021 and 2022, NMEA recognised nine individuals and four teams for their outstanding contributions.

The following awards were given out:

- National Outstanding Clinician Award
- National Outstanding Clinician Scientist Award
- National Outstanding Clinician Mentor Award
- National Outstanding Clinician Educator Award
- National Clinical Excellence Team Award

NATIONAL OUTSTANDING CLINICIAN AWARD 2021

PROF DALE FISHER

Senior Consultant
Division of Infectious Diseases, Department of Medicine
National University Hospital

Professor
Department of Medicine
Yong Loo Lin School of Medicine
National University of Singapore

Group Chief
Medicine
National University Health System

Professor Dale Fisher is an internationally recognised infectious diseases expert.

Professor Fisher began his career in Singapore during the SARS outbreak in 2003, during which his contributions on the frontline earned him a Courage Medal. He went on to become one of the three founding members, as well as the Head, of NUH's Division of Infectious Diseases. He has held many key positions within the hospital, driving internationally regarded initiatives such as the Outpatient Parenteral Antibiotic Therapy clinic and the Acute Medical Unit. As Chair of the Infection Prevention and Control (IPC) Committee at NUH since 2006, he leads a team which has produced some of Singapore's best clinical outcomes. Notably, he adopted an aggressive stance against Methicillin-Resistant Staphylococcus aureus (MRSA) infection, resulting in a significant decline in MRSA infection rates in NUH and nationally.

As Clinical Lead of the NUHS Infectious Disease Community Pilot Programme, Professor Fisher and his team are making groundbreaking changes to the standards of care in long-term care facilities (LTCFs) with respect to infection prevention and control, antibiotic usage and referral for residents with fever. Based on the promising initial outcomes, there are plans to expand the programme at the national level. In his new appointment as Group Chief of Medicine at the NUHS from 2020, he will spearhead the harmonisation of clinical services across the cluster to improve patient outcomes.

Beyond NUHS and since 2014, Professor Fisher has been the foundation chair of the National Infection Prevention and Control Committee (NIPC), which established national guidelines that are now Singapore's benchmarks.

> **"For his outstanding leadership in advancing key initiatives in the areas of infection prevention and infectious diseases that have shaped and improved patient outcomes in Singapore and globally."**

Being a passionate advocate for improving global patient outcomes, Professor Fisher actively works with international organisations such as the World Health Organization (WHO). He was involved in the Ebola response in Liberia from 2014 to 2015 and has assisted governments in several countries during H1N1 influenza outbreaks for over a decade. Additionally, he has facilitated many training programmes for international outbreak response and IPC globally. Since 2014, he has chaired and participated in many WHO guideline development groups, alongside experts from multiple disciplines to develop WHO guidelines. Since 2018, he has chaired the WHO's Global Outbreak Alert and Response Network (GOARN).

Professor Fisher's expertise came once again to the forefront during the COVID-19 pandemic response, both locally and globally. He was one of 12 international experts selected for the first WHO-China Joint Mission on COVID-19 to China to investigate and advise on interventions to guide the global response. A member of the WHO Health Emergencies Programme (WHE) Experts Advisory Panel he regularly convenes with the WHO and GOARN leadership as well as IPC network leads to discuss global concerns and strategies.

Professor Fisher has also strategically established a national and global media profile to help engender public trust in the pandemic response. Beyond the lay media, he is a well sought-after speaker at academic webinars locally and internationally and is a driving force in the National University of Singapore's COVID-19 update series comprising 36 parts to date. He has also featured in countless other platforms including peer-reviewed journals and even comic strips to enhance Risk Communication and Community Engagement (RCCE). During the COVID-19 outbreak at the foreign worker dormitories in Singapore, Professor Fisher advised on strategies for managing the ground situation and establishing mechanisms for two-way communication. RCCE continues to be developed via a new network of stakeholders he helped establish called "My Brother SG". This initiative has received WHO funding to develop a sustained system to support future COVID-19 needs as well as chronic diseases and mental health issues in foreign workers.

For his outstanding leadership in advancing key initiatives in infection prevention and infectious diseases that have shaped and improved patient outcomes in Singapore and globally, Professor Fisher was awarded the National Outstanding Clinician Award 2021.

NATIONAL OUTSTANDING CLINICIAN SCIENTIST AWARD 2021

"Never give up on a patient, no matter how complicated things may be." This principle has guided Professor Chong Siow Ann since he joined the Institute of Mental Health (IMH), then known as Woodbridge Hospital, in 1989. His dedication to doing the best for his patients has helped many reclaim their lives from mental illness. It also gave him the impetus to advance mental healthcare through research that contributes to a better understanding of mental disorders and improves outcomes and quality of life for individuals with mental illness.

In 2001, Professor Chong spearheaded the development of the Early Psychosis Intervention Programme (EPIP) at IMH. EPIP was the first of its kind in many ways. It focused on shortening the duration of untreated psychosis to achieve better long-term clinical, social and occupational outcomes for young people with psychotic disorders. To this end, it established and drew on an extensive network of community partners, including primary healthcare providers, general practitioners, tertiary institutions and social-service agencies, to enable early detection and intervention. The programme also involved case management in a psychiatric setting for the first time to support patients in their recovery. Professor Chong's outstanding work was recognised with the prestigious WHO's State of Kuwait Prize for Research in Health Promotion in 2006, and the inaugural National Clinical Excellence Team Award by the Ministry of Health in 2008.

In 2007, Professor Chong initiated the first-ever Singapore Mental Health Study, which provided a comprehensive insight into the mental health status of adults aged 18 and above in Singapore. The three-year study established the prevalence of the common mental disorders here, their associated factors, the treatment gap of the disorders as well as the help-seeking behaviour of the local population. He also led the Well-being of the Singapore Elderly (WiSE) Study in 2013 to determine the prevalence of dementia and the extent and nature of caregiver burden; and Mind Matters: A Study of Mental Health Literacy in 2014 to examine the mental health literacy of the local adult population and the extent of stigma associated with mental illness. These national studies led to previously unavailable information, which not only addressed real-world questions relevant to persons with mental illness, their families and healthcare providers, but also guided the formulation of effective national mental health policies.

In the past three decades, Professor Chong has advanced key areas of research in tardive dyskinesia, psychopharmacology, genetics of schizophrenia, early psychosis, epidemiology and health services research. As Chairman of the Subcommittee for Research for the National Mental Health Blueprint, he was instrumental in developing the research strategy to strengthen the mental well-being of Singaporeans. As Vice Chairman of Medical Board (Research) in IMH from 2006 to 2021, he created a vibrant culture of research within the organisation, which led to the establishment of two robust programmes—the Programme for Translational and Clinical Research; and the Programme for Mental Health Policy Research. Under his leadership, IMH has built up an extensive platform for cross-disciplinary collaboration with research centres locally and globally and secured more than $71 million of extramural funding for research since 2000.

In the international arena, Professor Chong led a team of researchers from Singapore, the United States, Australia and Hong Kong, on a cutting-edge five-year Translational Clinical Research in schizophrenia and related psychoses in 2008 to identify the biomarkers for this group of disorders. The findings of this $25-million project provided significant insights into schizophrenia and related psychosis and also placed Singapore on the world map for schizophrenia research.

Professor Chong has contributed peer-reviewed papers, editorials, commentaries as well as book chapters to over 450 publications, and is an associate editor and member of editorial boards of major international journals. He is passionate about engaging the wider community to tackle misconceptions and stigma surrounding mental illness, and has written more than a hundred opinion pieces highlighting psychiatric practices and research as an expert contributor to *The Straits Times*. For his outstanding contributions to mental health research and treatment and changing the perception of mental illness, Professor Chong was awarded the National Outstanding Clinician Scientist Award 2021.

PROF CHONG SIOW ANN

Senior Consultant
Research Division and Department of Psychosis
Institute of Mental Health

Adjunct Professor
Saw Swee Hock School of Public Health
National University of Singapore

> **"For his outstanding contributions to mental health research and treatment, and changing the perception of mental illness."**

NATIONAL OUTSTANDING CLINICIAN MENTOR AWARD 2021

A/PROF WONG KOK SENG

Deputy Chief Executive Officer
Clinical Services
SingHealth Community Hospitals

Senior Consultant
Internal Medicine and Renal Medicine
Singapore General Hospital

Clinical Associate Professor
Duke-NUS Medical School

As the Deputy Chief Executive Officer for Clinical Services at SingHealth Community Hospitals (SCH), Associate Professor Wong Kok Seng plays a pivotal role in providing medical leadership, mentorship and policy oversight to a young SCH team as they strive to establish clinical models and bridge care for the delivery of affordable quality healthcare services in community hospitals.

A firm believer of nurturing the next generation, Associate Professor Wong has knitted countless mentoring relationships with junior doctors. Many are inspired by his perseverance in pursuing the greater good in medicine and his encouragement to forge new grounds as they progress in their careers.

Associate Professor Wong was the Head of Department of Renal Medicine in Singapore General Hospital from 2002 to 2008 and went on to head the Department of Internal Medicine from 2012 to 2018, doubling its strength to meet service needs. In both instances, Associate Professor Wong attracted and retained aspiring talents to join the specialties, ensuring future sustainability for the profession. This could not have been accomplished without the close mentoring relationships forged between him and these talents.

Associate Professor Wong is known for his nurturing mentorship; his mentees often turn to him for his wisdom and advice on facilitating good working relationships with different stakeholders of the healthcare family. His approach to problem-solving inspires many who have worked with him before. He practices to first understand before being understood—he listens, gives his trust and then offers his guidance.

An avid learner and advocate for medical education and mentoring, he collaborated with colleagues from Duke-NUS Medical School and Duke University to organise faculty development courses to equip his senior residents and young consultants to be better teachers and mentors. At the national level, his leadership position in medical education allows him to better align the delivery of education and clinical services with national goals and aspirations.

Associate Professor Wong regards staff development as fundamental in providing adequate care and service to patients. He was instrumental in sending a multidisciplinary SCH team overseas to learn from international clinical experts, and also initiated design thinking workshops, a quality improvement framework and roadmap to upskill the SCH team. The SCH Research & Translational Innovation Office (RTIO) was also established under his leadership and mentorship, opening the doors to more novel and cost-effective care models for the future.

A clear mind, steadfast leadership and nurturing heart are the hallmarks of what make Associate Professor Wong the model collaborative leader and mentor. The highly respected clinician is responsible for building strong teams and nurturing future generations of clinician leaders through his passion in mentoring and education.

For his exemplary contributions and unwavering commitment to being an active role model in guiding and training young clinicians, Associate Professor Wong was awarded the National Outstanding Clinician Mentor Award 2021.

> **“For his exemplary contributions and unwavering commitment to being an active role model in guiding and training young clinicians."**

NATIONAL OUTSTANDING CLINICIAN EDUCATOR AWARD 2021

Professor Tan Hak Koon is a recognised and respected obstetrician who specialises in high-risk obstetric care and maternal foetal medicine. Having dedicated his entire professional life in the public healthcare sector for over 30 years, Professor Tan has contributed significantly to the advancement of obstetrics and gynaecology (O&G) clinical care, research and education at the institutional, national and international levels.

Professor Tan is a compassionate, nurturing and astute clinician leader who adopts a multifaceted approach to healthcare management. To continuously develop and improve patient care, he remains actively engaged on the ground while holding various senior leadership roles. In addition to his clinical and research achievements in O&G, he has also made exemplary contributions towards the advancement of O&G clinical education.

Since the 1990s, Professor Tan has mentored and nurtured numerous young doctors, medical students, clinician scientist residents, nurses and allied health professionals. He constantly engages residents, who are the future anchors of the healthcare system, ensuring that their needs are addressed. As a result of his efforts, Professor Tan has pivoted key changes in O&G graduate medical education. He improved the clinical learning environment for residents and established a "Crisis Management Pathway" in 2018, which provided a structured framework to guide the actions following any signs of distress or coping difficulties in residents, thereby enabling prompt intervention. Additionally, Professor Tan chairs the SingHealth Duke-NUS Obstetrics and Gynaecology Academic Clinical Programme which involves KK Women's and Children's Hospital (KKH) and SGH, improving women's health and well-being through clinical initiatives, education, research and collaborations.

Professor Tan's dedication towards training and education has remained unfettered since the COVID-19 pandemic's onset. The pandemic's impact on residency training was unprecedented; Professor Tan acted swiftly. He worked closely with various stakeholders, mitigating the impact through the implementation of measures especially in areas of curriculum, progression, examination and teaching methodologies. Through these strategies, there were no delays in the progression of the residency training. Final-year residents graduated on time despite the disruption caused by COVID-19.

Professor Tan also continually engaged during COVID-19 through virtual events. He endorsed an online overseas medical education programme that benefited over 900 overseas medical students in 2020.

Beyond SingHealth, Professor Tan has taken on key roles in O&G medical societies in Singapore, formulating educational activities, developing clinical guidelines, planning postgraduate examinations and providing expert opinion to committees in MOH. He currently sits on committees in MOH, overseeing O&G medical education and training which will play a part in policy-making and shaping the future training of O&G specialists in Singapore.

Extending a helping hand to developing countries, Professor Tan has been instrumental in an international voluntary programme to enhance maternal and child health services in government healthcare institutions in 26 districts of India. The programme equipped 200 healthcare workers with skills to manage obstetrics emergencies, and has benefited more than 100,000 mothers and newborns annually, halving the maternal mortality rate of Karnataka state.

For his inspiring dedication and exemplary contributions in advancing O&G clinical education in Singapore and beyond, Professor Tan was awarded the National Outstanding Clinician Educator Award 2021.

PROF TAN HAK KOON

Chairman and Chief of Obstetrics
Division of Obstetrics and Gynaecology
KK Women's and Children's Hospital

Academic Chair
SingHealth Duke-NUS Obstetrics and Gynaecology Academic Clinical Programme

Designated Institutional Official
SingHealth Residency

Associate Dean Residency Education, Office of Academic and Clinical Development & Clinical Professor
Duke-NUS Medical School

> "For his inspiring dedication and exemplary contributions in advancing Obstetrics and Gynaecology clinical education in Singapore and beyond."

NATIONAL CLINICAL EXCELLENCE TEAM AWARD 2021

A/PROF DAVID LYE CHIEN BOON
Senior Consultant
National Centre for Infectious Diseases

Director
Infectious Disease Research and Training Office
National Centre for Infectious Diseases

Associate Professor
Yong Loo Lin School of Medicine
National University of Singapore

Associate Professor
Lee Kong Chian School of Medicine
Nanyang Technological University

PROF LISA NG FONG POH
Executive Director
Biomedical Research Council
Agency for Science, Technology and Research

Executive Director
A*STAR Infectious Diseases Labs (ID Labs)
Agency for Science, Technology and Research

DR BARNABY YOUNG
Consultant
National Centre for Infectious Diseases

Head
Singapore Infectious Disease Clinical Research Network and NCID Research Clinic
Infectious Disease Research and Training Office
National Centre for Infectious Diseases

DR CHIA WAN NI
Research Fellow
Emerging Infectious Diseases Programme
Duke-NUS Medical School

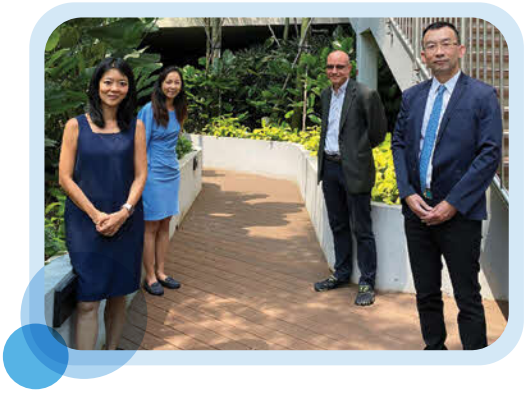
COVID-19 RESEARCH WORKGROUP

The year 2020 presented an unprecedented challenge for healthcare systems across the world. With reported COVID-19 cases rising in Asia, there was an urgent need to understand the novel coronavirus. This led to the establishment of the COVID-19 Research Workgroup (RWG), chaired by Professor Leo Yee Sin, Executive Director, National Centre for Infectious Diseases (NCID) with Associate Professor David Lye, Director, Infectious Disease Research and Training Office, NCID as Deputy Chairman, and advised by Professor Tan Chorh Chuan, Chief Health Scientist, MOH. The RWG convened on 22 January 2020, a day before Singapore reported its first confirmed COVID-19 case, aimed at conducting studies to better understand COVID-19 and its transmission in Singapore.

A critical component of the RWG's research was "PROTECT"—a multi-centre prospective study to detect novel pathogens and characterise emerging infections according to a pre-established outbreak drawer protocol developed in 2012 and coordinated by NCID. This protocol served as a foundation platform covering all public hospitals in Singapore, and enabled the collection of clinical data and biological samples for research. The first PROTECT subject was recruited on 24 January 2020, and as of December 2020 over 600 COVID-19 patients had participated.

The RWG has made significant research contributions in the COVID-19 pandemic, including the development and validation of diagnostic tools, deeper insights and understanding of virus pathogenesis and transmission, biomarkers of disease severity, investigation of COVID-19 clusters in Singapore, characterisation of environmental contamination with the SARS-CoV-2 virus, development and evaluation of potential therapeutic agents, and a greater understanding of the socio-behavioural aspects of the pandemic on healthcare workers and other segments of the community. These research efforts in turn led to improved standards of care, diagnosis, health outcomes and management of COVID-19 patients both locally and globally.

To date, the RWG has contributed to some 212 publications. Notably, 23 of these publications are top-tier scientific journals, including the *New England Journal of Medicine*, *The Lancet*, *JAMA*, *Science*, *Nature* and *Cell*.



Importantly, the RWG's research findings have been translated and incorporated into the investigation of outbreaks, infection control measures and public health policies on quarantine and isolation, as well as the development of diagnosis and treatment methods benefiting patients and the wider community both locally and internationally. Some of the significant diagnostic tools and treatments against COVID-19 include the world's first SARS-CoV-2 neutralisation antibody test (cPassTM) to identify people previously infected with the virus and who subsequently developed an adaptive immune response; the use of remdesivir and baricitinib in the treatment of COVID-19 patients in Singapore, through the RWG's participation in international clinical trials led by the United States' National Institutes of Health and which contributed to national and international treatment guidelines; and the provision of patient samples used to develop the Regeneron monoclonal antibodies, which have since been shown to be effective in treating hospitalised patients with severe COVID-19 in the RECOVERY trial in the United Kingdom.

For their instrumental contributions and significant achievements in COVID-19 research, and management of the pandemic response in Singapore and globally, the COVID-19 RWG was awarded the National Clinical Excellence Team Award 2021.

> "For their instrumental contributions and significant achievements in COVID-19 research, and management of the pandemic response in Singapore and globally."

NATIONAL CLINICAL EXCELLENCE TEAM AWARD 2021

GPFIRST PROGRAMME

The GPFirst Programme was designed to improve the efficiency of Accident & Emergency (A&E) services for better management of patient load, and to optimise the prioritisation of care for patients requiring emergency treatment. The Programme, initiated by Changi General Hospital (CGH) in 2014, aims to encourage patients with mild to moderate conditions to visit a General Practitioner (GP) instead of presenting themselves at the A&E Department at first instance.

In right-siting care, the GPFirst team adopted a multipronged approach, which involved reducing the number of non-emergency cases seen at the A&E; engaging, empowering and collaborating with GPs to enhance their management of mild-to-moderate conditions within the community; and shaping healthcare-seeking behaviours in the community.

A joint study by CGH and the Singapore University of Technology and Design showed that individuals who perceive their medical conditions to be critical were 3.5 times more likely to visit the A&E, even if their condition could be attended to by GPs. Recognising the need for a paradigm shift in mindset, behavioural nudges were incorporated in the data-driven programme to help individuals rethink the level of care needed when they make decisions on where they should seek treatment. Patients referred to the A&E by the participating GPs will be prioritised over minor emergencies and also receive a $50 subsidy to offset their A&E attendance fee.

The GPFirst team also carried out public education campaigns to improve health literacy and empower the community to choose their healthcare providers wisely. Partnerships with the People's Association, Community Centres and Resident Committees were forged to further increase GPFirst's reach through community outreach events.

Through the development of GPFirst, the Programme team established strong collaborations with the network of 305 GP clinics in eastern Singapore. To date, more than 80% of GP clinics in the network have participated in the regional primary care programmes, forming a lively ecosystem to provide accessible, holistic and integrated care with better health outcomes for patients.

GPs in the GPFirst Programme were invited to Continuing Medical Education activities to enhance knowledge-sharing in managing mild-to-moderate conditions within the community and improve the quality of care. The active engagement and collaborations with GPs increase their management of these conditions and contribute to their role as "gate-keepers" to A&E services. GPs are also able to reach out to a CGH A&E consultant via a 24/7 hotline.

The GPFirst Programme has benefited more than 33,000 patients in the East from 2014 to 2019. It also saw a 14% reduction in proportion of attendance at CGH A&E with mild and moderate conditions and a 36.6% reduction in walk-in attendance. Referral appropriateness under GPFirst has maintained at 97% since 2016. The reduction enhances A&Es in streamlining valuable resources to focus on emergency care, thus providing more timely treatment. In a survey of GPFirst's patient-participants, 87.3% rated their overall experience as good or excellent, with 92.3% of them stating that they would recommend family and friends to visit the same GPFirst clinic for mild-to-moderate conditions prior to any A&E visit.

Following the GPFirst Programme in CGH, coupled with the strong support across multi disciplinary teams in the hospital, the GPFirst team worked closely with MOH and other local public hospitals in the sharing of its programme experience to facilitate the expansion of the programme on the national level. GPFirst has since been implemented in other hospitals including Khoo Teck Puat Hospital, National University Hospital, Ng Teng Fong General Hospital, Sengkang General Hospital and Woodlands Health Campus. The GPFirst team continues to be MOH's key partner in facilitating care shifts from the hospital to the community by expanding the Programme to more healthcare institutions.

For their timely contributions in enhancing Accident & Emergency efficiency and shaping a holistic and collaborative healthcare ecosystem with better health outcomes for the community, the GPFirst team was awarded the National Clinical Excellence Team Award 2021.

CLINICAL A/PROF STEVEN LIM HOON CHIN
Senior Consultant
Accident and Emergency
Changi General Hospital

Programme Director
GPFirst
Changi General Hospital

Clinical Associate Professor
Duke-NUS Medical School

CLINICAL A/PROF HOW CHOON HOW
Senior Consultant, Family Physician
Changi General Hospital

Director
Primary Care, SingHealth
Office of Regional Heath
Changi General Hospital

MS PRISCILLA GOH
Manager
Primary Care Integration, GP Engagement
Changi General Hospital

DR OH HONG CHOON
Assistant Director
Health Services Research
Changi General Hospital

Assistant Director
Health Services Research & Evaluation
SingHealth Office of Regional Health

Adjunct Assistant Professor
Duke-NUS Medical School

> "For their timely contributions in enhancing Accident & Emergency efficiencies and shaping a holistic and collaborative healthcare ecosystem with better health outcomes for the community."

NATIONAL OUTSTANDING CLINICIAN AWARD 2022

A/PROF LIM POH LIAN

Senior Consultant
Department of Infectious Diseases
Tan Tock Seng Hospital

Head
Travellers' Health and Vaccination Clinic
Tan Tock Seng Hospital

Director
High Level Isolation Unit
National Centre for Infectious Diseases

Adjunct Associate Professor
Lee Kong Chian School of Medicine
Nanyang Technological University

Clinical Associate Professor
Yong Loo Lin School of Medicine
National University of Singapore

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

Associate Professor Lim Poh Lian joined Tan Tock Seng Hospital (TTSH) in 2003, just three weeks before TTSH became Ground Zero for the Severe Acute Respiratory Syndrome (SARS) outbreak in Singapore. Since then, A/Prof Lim has played instrumental roles within Singapore, as well as the international healthcare landscape; and acquired more than two decades of expertise in managing disease outbreaks: Dengue in 2006, 2013 and 2020; Chikungunya in 2008; H1N1 Influenza in 2009, and demonstrated collective leadership and stewardship in managing the COVID-19 pandemic. For her frontline work during SARS, A/Prof Lim was honoured with the National Day Commendation Medal (2003), and the Courage Star Award (2003).

As Head of the Infectious Diseases department at TTSH (2012 to 2016), A/Prof Lim steered the national preparedness for Middle East Respiratory Syndrome (2012), Ebola (2014), Zika (2016), and yellow fever (2017). She diagnosed the first case of babesiosis in Singapore in 2018 and helped identify Singapore's first case of monkeypox—a rare disease transmitted mainly from animals to humans in Central and West Africa—in 2019.

Today, as Head of the Travellers' Health and Vaccination Clinic at TTSH, A/Prof Lim has provided vaccination expertise and travel medicine care to the government, Singapore Armed Forces and national athletes. She has led innovative vaccination programmes including the Pre-Discharge Vaccination programme at TTSH, delivering over 42,000 doses of Influenza and Pneumococcal Vaccine to hospitalised patients, and the Pioneer Immunisation Programme, for pneumococcal vaccinations in nursing home residents. A/Prof Lim was the Site Director for GeoSentinel in Singapore (2006 to 2018), an international travel medicine surveillance project. A/Prof Lim is also the Senior Consultant at the National Centre for Infectious Diseases and founding Director of its High-Level Isolation Unit, Singapore's specialised bio-containment unit designed to safely manage patients with suspected or confirmed infections that require high level isolation, such as Ebola.

A/Prof Lim serves on the Expert Committee on COVID-19 Vaccination which draws on her understanding of public health policy rollouts, as well as her determined sense of mission in achieving the success of Singapore's COVID-19 vaccine programme—from dealing with logistics hurdles and the sheer number of people to be vaccinated, to communicating scientific and clinical information to help calm public anxiety about COVID-19 vaccines.

In 2008, A/Prof Lim set up the Severe Illness and Death from Possibly Infectious Causes programme, which identifies emerging diseases in Singapore through active surveillance of unexplained deaths and critical illness caused by novel pathogens. As Chair of the National Antimicrobial Resistance Control Committee (NARCC), she established Singapore's national programmes for antimicrobial resistance surveillance and antibiotic stewardship. In 2018, she received the Minister of Health Award for her NARCC contributions. On the global front, A/Prof Lim is the current Chair of the Independent Allocation of Vaccines Group, advising the COVAX Facility on equitable international distribution of COVID-19 vaccines. Her high professional standing is built on her decade of experience as an active member of the World Health Organization's (WHO) Global Outbreak Alert and Response Network Steering Committee, and on the Advisory Group on Reform of WHO's Work in Health Emergencies from 2015 to 2016. She was also appointed to the United Nations Secretary General's Global Health Crises Taskforce in 2016. A/Prof Lim has also chaired WHO's Technical Advisory Group, which addresses health security, bio-threats and deliberate events.

For her outstanding leadership and stewardship in advancing medical excellence in travel medicine, vaccination services, and infectious disease outbreak response and preparedness in Singapore and internationally, A/Prof Lim is awarded the National Outstanding Clinician Award 2022.

> "For her outstanding leadership and stewardship in advancing medical excellence in travel medicine, vaccination services, and infectious disease outbreak response and preparedness in Singapore and internationally."

NATIONAL OUTSTANDING CLINICIAN AWARD 2022

As the first paediatrician in Singapore to practise paediatric emergency medicine, Associate Professor Ng Kee Chong's vision and dedication were pivotal to the establishment of Singapore's first Children's Emergency (CE) at KKH in 1997, and the CE's subsequent transformation to become one of the busiest paediatric emergency departments in the region.

With a strong interest in paediatric disaster response and planning, A/Prof Ng was instrumental in the development of the national guidelines for paediatric mass casualty protocols, including HazMat situations, for civil and national emergencies. He also helped strengthen the Singapore Civil Defence Force's paediatric pre-hospital protocols and care, and continues to teach Advanced Trauma Life Support in the Singapore Armed Forces.

He is currently the Vice-President of the Singapore Resuscitation & First Aid Council and co-chair of the Subcommittee on Emergent Issues under the National Trauma Committee. Globally, he is the first Asian Chair of the Pediatrics Life Support Task Force of the International Liaison Committee on Resuscitation.

To A/Prof Ng, health should never be "medicalised". He believes in a life course approach in advancing the health of the mother, child and the family, starting from the womb, all the way to adulthood, to lay the foundations for transformation of our nation's health, for today and generations to come. This guided the launch of the SingHealth Duke NUS Maternal and Child Health Research Institute in 2021. The Institute serves as the centre of excellence for maternal and child health research and innovation, to support the growth of every woman and child to their fullest potential, to optimise human capital and transform the overall national health.

Recognising the importance of early detection and timely intervention to optimise developmental outcomes of children, A/Prof Ng supported the Department of Child Development to build key collaborations and grow community capabilities. Some of these initiatives include the Early Intervention Programme for Infants and Children, and the Development and Support Programme which subsequently expanded into a nationwide, community-support programme, and was awarded the SingHealth Distinguished Team Award and NMEA National Clinical Excellence Team Award in 2015. He also facilitated the setting up of the KIDS 0-3 programme which has since evolved into the nationwide KidSTART programme. A/Prof Ng was instrumental in the establishment of the KK Human Milk Bank, Singapore's first and only donor human milk bank programme.

A/Prof Ng also led KKH through disease outbreaks like SARS, H1N1 and Zika. During the COVID-19 pandemic, A/Prof Ng assumed the role of Deputy Commander of the KKH Command Centre. He established the Paediatric Emergency Preparedness plan in response to the rapidly evolving COVID-19 pandemic. He led the command team in setting up a tiered isolation facility at KKH—the national centre for managing COVID-19 for women and children in Singapore. This not only enabled the hospital to stagger and reduce risk exposures to patients and healthcare workers during the pandemic, but also allowed KKH to better assess, manage and prepare for other potential disease outbreaks, in conjunction with the hospital and nationwide public health response.

For his unwavering dedication to paediatric emergency medicine, his contributions in advancing clinical education in maternal and child health, and his steadfast leadership in the face of crises, A/Prof Ng is awarded the National Outstanding Clinician Award 2022.

A/PROF NG KEE CHONG

Chairman, Medical Board and Senior Consultant
Department of Emergency Medicine
KK Women's and Children's Hospital

Senior Associate Dean
KKH Campus,
Office of Academic and Clinical Development & Clinical Associate Professor
Duke-NUS Medical School

Clinical Associate Professor
Yong Loo Lin School of Medicine
National University of Singapore

Clinical Associate Professor
Lee Kong Chian School of Medicine
Nanyang Technological University

> **"For his unwavering dedication to paediatric emergency medicine, his contributions in advancing clinical education in maternal and child health, and his steadfast leadership in the face of crises."**

NATIONAL OUTSTANDING CLINICIAN SCIENTIST AWARD 2022

PROF MARCUS ONG ENG HOCK

Senior Consultant and Clinician Scientist
Department of Emergency Medicine
Singapore General Hospital

Professor and Director
Health Services and Systems Research (Signature Research Program)
Duke-NUS Medical School

Clinical Director and Senior Consultant
Unit for Prehospital Emergency Care
Ministry of Health

Professor Marcus Ong is best known both at home and abroad for his research in pre-hospital emergency care. The Singapore General Hospital (SGH) Department of Emergency Medicine's Senior Consultant is one of Singapore's pioneer clinician scientists in this field, dedicating his studies in the last 20 years in areas such as OHCA, and pre-hospital emergency care (PEC). His research has shaped national PEC policy and resulted in lives saved and improved outcomes for OHCA survivors. Prof Ong was recently awarded the prestigious STaR Investigator Award by MOH's NMRC.

To develop cutting-edge data science research to equip healthcare providers and researchers with key skills, Prof Ong started a data science team at SGH and leads a health services and systems research programme at Duke-NUS Medical School and the Health Services Research Centre at SingHealth.

Often working with the Singapore Civil Defence Force, Prof Ong implemented dispatcher-assisted CPR in 2012, heightened awareness of the importance of bystander emergency assistance and doubled the bystander CPR rate from 22% (2011), to 61.8% (2018) for cardiac arrest patients. Prof Ong also implemented the use of high-performance CPR, manual defibrillation, mechanical CPR, drugs such as vasopressin, intraosseous devices, motorcycle paramedics, first responder apps and other innovations. SGH has also seen a 10-fold improvement in the survival rate for OHCA over the last 20 years from 2% in 2001, to 26% in 2019, as a result of efforts from Prof Ong's research team.

Underscoring the importance attached to his studies and the high regard that his name holds, Prof Ong is the PI of more than S$42 million in individual grant funding.

He chairs international multicentre studies on OHCA and is a member and senior opinion leader on OHCA with global scientific bodies. He has received numerous awards including the Minister for Health Award (2018), the NMRC Clinician Scientist Awards (2017, 2013, 2010), the Public Service Medal (Pingat Bakti Masyarakat 2016), the Keith Neely Outstanding Contribution to EMS Award (2015 National Association of EMS Physicians), the inaugural Ian G Jacobs Award for International Group Collaboration to Advance Resuscitation Science (2014) and the Lifetime Achievement Award (Asian EMS Council 2014).

Notably, Prof Ong founded and led multidisciplinary teams in the Pan Asian Resuscitation Outcomes Study (PAROS) clinical research network. PAROS, including clinicians, researchers and policymakers from 14 countries, has enrolled over 200,000 cases. PAROS has had an impact on PEC policy in Asia, including low- and middle-income countries. Prof Ong is also the founding chair of the Singapore-registered Asian Association for Emergency Medical Services, which has members from more than 20 Asian countries. He is also the founding board member of the Global Resuscitation Alliance and a long-time member of the International Liaison Committee on Resuscitation.

Prof Ong has published widely with more than 360 peer-reviewed papers, including in The Lancet and the Journal of the American Medical Association. His research has resulted in significant commercialisation and industry-funding with patents and completed licensing agreements (e.g. Zoll, Global Healthcare), and two start-up companies (Global Healthcare and TIIM SG). His work is frequently featured in local and international media.

For his pioneering research and tireless dedication to prehospital emergency care and systems, which have shaped government policy both locally and regionally, Professor Marcus Ong is awarded the National Outstanding Clinician Scientist Award 2022.

> **"For his pioneering research and tireless dedication to prehospital emergency care and systems, which have shaped government policy both locally and regionally."**

NATIONAL OUTSTANDING CLINICIAN MENTOR AWARD 2022

Associate Professor Daniel Goh is a dedicated academic clinician and visionary leader who has contributed significantly to the field of paediatrics locally, regionally and internationally. He has been a champion for better healthcare for children, and a passionate advocate in mentoring generations of paediatricians for close to 30 years.

A well-respected paediatric pulmonologist in the Asia Pacific region, A/Prof Goh plays a pivotal role in pushing the frontiers in the practice of paediatrics and paediatric pulmonary medicine. He pioneered Singapore's first comprehensive paediatric sleep service and dedicated paediatric fiberoptic bronchoscopy service and was instrumental in developing the paediatric intensive care unit within National University Hospital (NUH). These services have gone on to support many major tertiary clinical programmes including the paediatric liver, kidney and bone marrow transplant programmes, as well as the complex congenital heart programmes in NUH. A/Prof Goh introduced new modalities of therapy and programmes such as the expanded use of non-invasive assisted ventilation, home ventilation and home-care programmes which have changed the outcomes and lives of many children and their families living with complex chronic diseases.

In his role as Head of Department of Paediatrics at the Yong Loo Lin School of Medicine, NUS and Khoo Teck Puat – National University Children's Medical Institute (KTP-NUCMI), NUH from 2007 to 2017, A/Prof Goh nurtured many successful academic paediatricians in their research endeavours with his supportive policies, strategic planning and mentorship. Under his leadership, KTP-NUCMI incorporated the then novel concept of child-friendly and family-centred care into the new paediatric services and facilities in NUH, enhancing patient experience and outcomes.

A/Prof Goh has been actively involved in imparting his knowledge and skills to medical, dental and nursing students, and is an examiner for undergraduate and postgraduate programmes, both locally and overseas. He has also mentored numerous international fellows in paediatric pulmonology and sleep, many of whom are leaders in the field today.

As the longest serving President of the Singapore Paediatric Society from 2003 to 2011, A/Prof Goh spearheaded and streamlined continuing medical education and updates for the paediatric fraternity and developed closely-knit relationships with regional and international organisations.

A firm believer in the collaborative search for knowledge to better care for patients, A/Prof Goh has held several appointments that have allowed him to shape the training of paediatricians in the Asia Pacific region. These include President of the ASEAN Paediatric Federation (2011- 2014), Chairperson of the Asia Pacific Paediatric Sleep Alliance (since 2006), Advisory Board Member of the Asia Pacific Paediatric Association (APPA) (2005 - 2009) and member of the Standing Committee of the APPA (since 2017).

Beyond clinical care and mentoring, A/Prof Goh is a prolific researcher who has published more than 120 high-impact journals and publications. A thought leader in his field, he is a key contributor to numerous industry collaboration and research projects and serves on the editorial board as a reviewer for many regional and international journals. A/Prof Goh is also regularly invited to speak at regional and international conferences.

Throughout his career, A/Prof Goh has received countless nominations and awards for excellence in his field of expertise and dedication in mentoring the next generation of healthcare professionals. He was a recipient of the NUHS-Mochtar Riady Pinnacle Awards for Excellence, National Day Award – Public Administration Medal (Bronze) and Outstanding Asian Paediatrician Award by the Asia Pacific Paediatric Association. A/Prof Goh has also received numerous teaching awards at NUS, including the Faculty Teaching Excellence Award, Special Recognition Award for being the role model to the NUS Medicine Graduating Class and Great Teacher Award.

For his immense dedication, passion, unwavering commitment to patient care and nurturing successive generations of paediatricians, A/Prof Daniel Goh is awarded the National Outstanding Clinician Mentor Award 2022.

A/PROF DANIEL GOH YAM THIAM

Senior Consultant
Department of Paediatrics
Khoo Teck Puat – National University Children's Medical Institute
National University Hospital

Associate Professor
Yong Loo Lin School of Medicine
National University of Singapore

> **"For his immense dedication, passion and unwavering commitment to patient care and nurturing successive generations of paediatricians."**

NATIONAL OUTSTANDING CLINICIAN EDUCATOR AWARD 2022

CLINICAL PROF CHAN CHOONG MENG

Senior Consultant
Department of Renal Medicine
Singapore General Hospital

Group Chief Education Officer
SingHealth

Senior Associate Dean & Co-Director
Academic Medicine Education Institute &
Clinical Professor
Duke-NUS Medical School

Adjunct Professor
Yong Loo Lin School of Medicine
National University of Singapore

Receiving this year's National Outstanding Clinician Educator award aptly caps Clinical Professor Chan Choong Meng's life-long passion in passing on his skills and experience to younger colleagues.

As SingHealth's Group Chief Education Officer, he has overall purview of the academic programmes of the group's various institutions. Looking afar at future healthcare needs, Prof Chan is constantly thinking of the education and training needs necessary to build up medical skills and competencies in future generations of clinicians.

In the past two years when education and training were greatly affected by the COVID-19 pandemic safe management measures, Prof Chan worked to facilitate and ensure safe resumption of essential clinical training for students. He worked closely with the medical schools, Ministry of Health and the Group/Campus Education Directors to optimise clinical training and assessments. Prof Chan embraced gamification and immersive media technologies, working relentlessly with the Graduate Medical Education office, SingHealth Academy and SingHealth Duke-NUS Institute of Medical Simulation to develop resources and infrastructure to support virtual modes of training.

Prof Chan has held several education leadership positions since 2006. He was the Chairman for Undergraduate Teaching Committee for Medicine in NUS Yong Loo Lin School of Medicine (YLLSoM) in 2006, a position he held for six years. In 2012, he was appointed Associate Designated Institutional Official for Singapore General Hospital (SGH) and Academic Vice Chair of Education for Medicine Academic Clinical Programme. In 2014, he was concurrently appointed SGH Campus Education Director and SingHealth Deputy Group Education Director (Undergraduate). From 2015 to 2019, Prof Chan served as the President of the College of Physicians, Singapore.

His passion for teaching is also evident by the number of accolades he has received. In recognition of his contribution to undergraduate education, Prof Chan was awarded the Dean's Teaching Excellence Award from NUS YLLSoM, GCEO (SingHealth) Outstanding Educator award (Special Mention), and NUS Special recognition award for Role Model.

He is a well-respected nephrologist who maintains high standards of care, a quality which he instils in the young doctors who trained with him. For his contribution to Nephrology, he was awarded the Lim Cheng Hong's Award (Nephrology) 2010, the Chapter of Renal Physician Lecture Award (2013) and Singapore Society of Nephrology Sterling Award (2015).

He is also actively involved in teaching medical students, medical officers and residents. Prof Chan served as chief examiner for senior residents' Renal Exit Examination (2015 to 2017). He is also examiner for the prestigious Membership of the Royal Colleges of Physician Practical Assessment for Clinical Examination Skills since 2012, examiner for the Advanced Internal Medicine exit examination and YLLSoM and Duke-NUS examiner. He continues to be an examiner for Renal Medicine exit examination and was Chief Examiner from 2015 to 2018.

Prof Chan is not just a teacher, but also a keen researcher, having published more than 70 articles and received some $600,000 in grant funding. His research interests are in renin-angiotensin system gene polymorphism, acute kidney injury, chronic kidney diseases, diabetic nephropathy and hypertension. He was also frequently invited to chair and present lectures at local and international meetings on renal diseases and medical education.

For his outstanding contributions to the education and training of clinicians and healthcare staff, and exemplary support in developing skills and competencies to uphold high standards of care and treatment, Professor Chan Choong Meng is awarded the National Outstanding Clinician Educator Award 2022.

> "For his outstanding contributions to the education and training of clinicians and healthcare staff, and exemplary support in developing skills and competencies to uphold high standards of care and treatment."

NATIONAL CLINICAL EXCELLENCE TEAM AWARD 2022

CARELINE

CareLine is a 24/7 personal care telephone service pioneered by CGH for vulnerable seniors in need of urgent assistance. It provides health and social support to vulnerable seniors who may be living alone or are frail, and helps them to keep safe and stay healthy at home and within the community settings. Since its launch in 2016, CareLine has cared for close to 19,000 seniors and provided them with assistance to meet both their health and social needs, by tapping on the strong network of community partners across Singapore.

CareLine takes a new and innovative approach for seniors to age well in the community. The strength of CareLine lies in its care relationship model. When seniors enrol into CareLine, CGH CareLine staff conduct an assessment to find out about their needs and preferences. The CareLine team also periodically calls the seniors to check in on their well-being, reminding them of the partnership so that they know that care is just a call away. This allows the CGH CareLine team to gain in-depth understanding of the seniors' psychosocial needs over time.

A technology-enabled client-centred workflow plays a key role in creating a telecare service that enables seniors to be independent, healthy and safe within their communities. Interactions with each senior are tracked closely in the CareLine system. This allows CGH CareLine staff to have a comprehensive view of past call interactions and enables quicker understanding of the seniors' needs, which facilitates seamless communication with the seniors and expedites the delivery of the required assistance.

Since 2016, the CGH CareLine team has responded to over 1,000 urgent calls and addressed the concerns of the seniors, coordinating care as well as linking them to urgent care services, when necessary. While CareLine handles urgent care coordination, the majority of calls received are related to social and community care needs which are essential for our seniors to live well and confidently in the community.

The cornerstone of CareLine's success lies in the strong network and collaborations with the community partners, including grassroots organisations, government agencies, senior activity centres, and voluntary welfare organisations, across Singapore. Under the close partnership that CareLine has with the Silver Generation Office (SGO), the outreach arm of the Agency for Integrated Care, seniors identified as vulnerable or staying alone by SGO are referred to the telecare service. During the initial home visits, Silver Generation Ambassadors will explain about CareLine and facilitate the sign-up by the seniors. When the seniors require assistance or are uncontactable, CareLine is able to activate SGO to provide the necessary response and this could sometimes include conducting a home visit to check on them.

CareLine has transformed health and social care delivery for seniors in a scalable and effective way. In 2019, CareLine was upscaled nation-wide beyond the eastern region of Singapore and it could not have been timelier. During the pandemic period where physical interactions were replaced by digital interactions, CareLine became the catalyst in empowering our seniors to embrace technology. There were 1,500 mobile phones with the CareLine mobile application installed and distributed island-wide to vulnerable seniors so that they could have easy access to the 24/7 CareLine services.

With its focus on proactive and preventive care and its strong collaborations with various community partners, CGH via CareLine has been a forerunner in adopting a population health approach together with the SingHealth Regional Health system. As the Caring General Hospital, CGH has leveraged CareLine as a platform that is accessible 24/7, 365 days a year to empower the seniors to keep well, get well and age well in their communities and homes. CareLine has also strengthened community partnerships by ensuring an integrated health and social care support ecosystem for the seniors.

For their outstanding dedication in establishing an innovative telecare ecosystem to journey with, care for and empower vulnerable seniors so that the seniors can live and age well in the community, the CGH CareLine team is awarded the National Clinical Excellence Team Award 2022.

ADJUNCT A/PROF EUGENE SHUM JIN-WEN
Chief Community Development Officer
Changi General Hospital

Director
Community Partnership, SingHealth Office of Regional Health (SORH)

MS PEARLINE LEE
Deputy Director
Home Care & Safety
Changi General Hospital

MS CLAUDIA MA
Senior Executive
Home Care & Safety
Changi General Hospital

MR ERIC CHEN
Director (Operations)
Silver Generation Office
Agency for Integrated Care

> **"For their outstanding dedication in establishing an innovative telecare ecosystem to journey with, care for and empower vulnerable seniors so that the seniors can live and age well in the community."**

NATIONAL CLINICAL EXCELLENCE TEAM AWARD 2022

A/PROF SWAPNA KAMAL VERMA
Chairman
Medical BoardInstitute of Mental Health

Programme Director
CHAT
Institute of Mental Health

DR CHARMAINE TANG YU ZHENG
Chief
Department of Psychosis
Institute of Mental Health

Deputy Programme Director
CHAT
Institute of Mental Health

MS LEE YI PING
Principal Case Manager
CHAT
Institute of Mental Health

MS CHLOE ANG CHOO ENG
Manager
Department of Psychosis & CHAT
Institute of Mental Health

COMMUNITY HEALTH ASSESSMENT TEAM (CHAT)

"For their instrumental contributions and significant achievements in improving access and delivering quality mental health care to distressed young people and advocating youth mental health literacy."

Adolescence and young adulthood are thought to be particularly tumultuous times for neuropsychological and physical development. Research has shown that one out of every four or five young people in the general population will suffer from at least one mental health condition. The 2016 Singapore Mental Health Study also found that young people in the 18 to 34 age group were more vulnerable to developing mood and anxiety disorders.

The Community Health Assessment Team (CHAT) was set up by IMH in 2009 to address barriers to care experienced by distressed youths aged 16 to 30. These include concerns on stigma, confidentiality, treatment costs and limited local youth-specific mental health services.

CHAT addresses these concerns by providing free and confidential mental health assessments for distressed youths in a conducive environment located at CHAT Hub, *SCAPE, Orchard. Since the onset of COVID-19 in 2020, distressed youths could also receive the assessments virtually. Youths who feel ambivalent towards telephonic and face-to-face sessions are able to access webCHAT, an anonymous, synchronous, text-based online mental health assessment and support option, until they are ready for conventional professional help.

CHAT provides subsidised referrals to hospitals when downstream psychiatric services are needed. For better continuity of care and successful care transition post-assessment, the team ensures young people receive interim case management and interventions until their hospital referrals take place.

CHAT actively partners young people to design outreach projects (e.g. videos, music and theatre forums) to improve youth mental health literacy. This includes recruiting CHAT Ambassadors annually to co-create service improvement projects so as to ensure mental health services stay youth-friendly and relevant. Currently, CHAT has a social media following of over 7,000 on Facebook and 900 on Instagram, further

demonstrating the programme's youth mental health literacy efforts. The number of referrals for CHAT assessment has also increased exponentially, from 51 referrals in 2009 to 2,172 referrals in 2021. The majority of the self-referrals for mental health assessments by youths were by word-of-mouth among friends/colleagues or through webCHAT.

Over the years, CHAT has grown in recognition among local key stakeholders (e.g. young people, Institutes of Higher Learning, Social Service Agencies, government agencies and social enterprises with vested interest in young people and mental health), and is the "go-to" resource for youth mental health information, professional support, training and/or collaboration in advocacy work.

On a national level, CHAT has provided key youth mental health insights and contributed to transformational change discussions on mental health for young people with various partners, including MOH, the Ministry of Social and Family Development, Ministry of Education, Ministry of Culture, Community and Youth, and Ministry of Manpower, as well as National Council of Social Service, and Health Promotion Board at platforms such as the Singapore Youth Action Plan Workgroup Retreat, Youth Mental Well-Being Network and Beyond the Label Youth Alliance. In 2019, CHAT established a five-year partnership with MOH, and Agency for Integrated Care to co-create a new youth service model encompassing the provision of integrated social and mental health services for young people aged 12 to 25.

On an international level, CHAT has actively shared its experiences at International Youth Mental Health Conferences since 2012. The Team has also shared their knowledge with medical and allied health professionals from other countries such as Japan, South Korea, Hong Kong, India, Brunei and Vietnam. In 2019, CHAT was invited to participate in the World Economic Forum, and Special Lancet Commission on Youth Mental Health.

For their instrumental contributions and significant achievements in improving access and delivering quality mental health care to distressed young people and advocating youth mental health literacy, CHAT is awarded the National Clinical Excellence Team Award 2022.

"For their instrumental contributions and significant achievements in improving access and delivering quality mental health care to distressed young people and advocating youth mental health literacy."

NMRC AWARDS CEREMONY AND RESEARCH SYMPOSIUM 2021

The NMRC Awards Ceremony and Research Symposium were held concurrently during a one-day event that attracted clinician scientists, researchers, industry partners and other key players in the biomedical research field. The event was conducted virtually on 6 December 2021, which enabled the participation of overseas attendees. Permanent Secretary (Health) Mr Chan Yeng Kit was the Guest-of-Honour for the event.

The event recognised the achievements of our clinicians and researchers and provided an opportunity for attendees to listen and interact with established local and overseas speakers.

Awards Ceremony

The Awards Ceremony served to recognise awardees under the NMRC Talent Programmes, namely the STaR Investigator Award, the CSA, the TA, the MOH Healthcare Research Scholarship—Master of Clinical Investigation (MCI) and the NMRC Research Training Fellowship.

This was followed by the plenary session where NMRC invited four eminent overseas experts to share their experience and insights in the use of evidence-based research to inform policy decisions and areas in Neurological disorders, Mental Health and Infectious diseases:

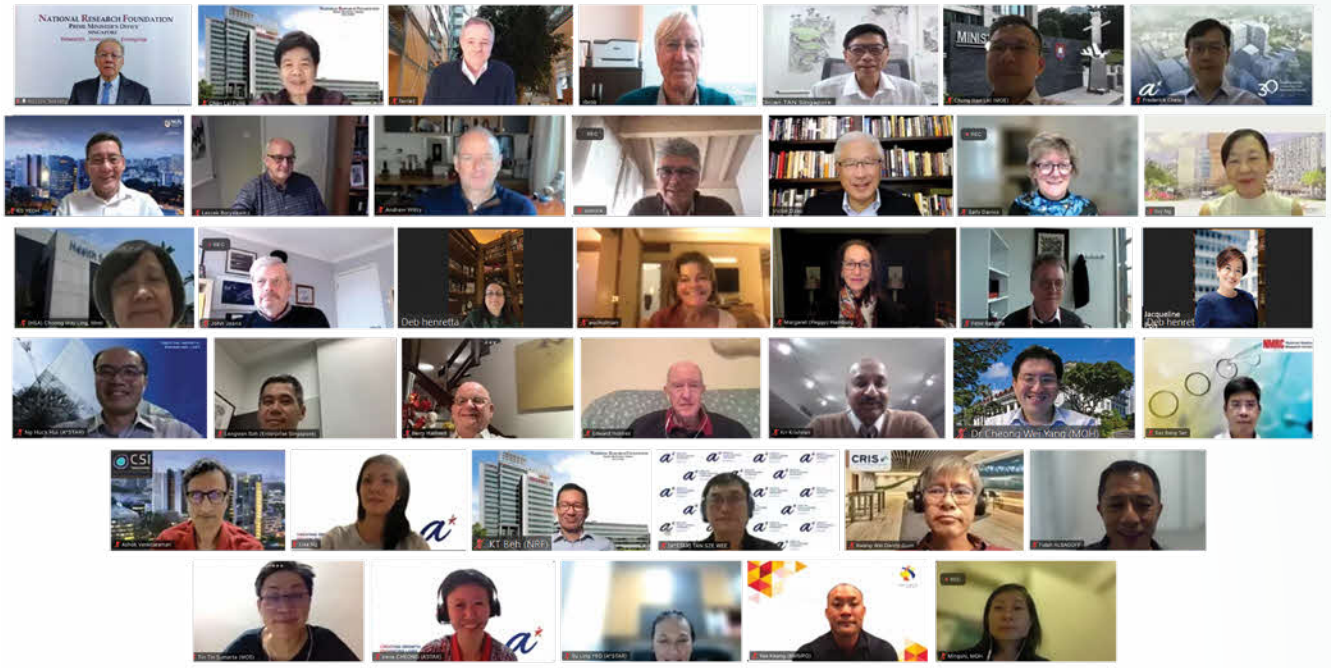
- Professor John Lavis, Professor and Canada Research Chair, Evidence-informed Health Systems;
- Professor Werner Poewe, Emeritus Professor of Neurology, Department of Neurology, Medical University Innsbruckm Austria;
- Professor Patrick McGorry, Executive Director, Orygen, Professor of Youth Mental Health, University of Melbourne; and
- Professor Miles Carroll, Principal Investigator, Wellcome Centre for Human Genetics, University of Oxford and Deputy Director, Head of Research and Development, Public Health England.

Research Symposium

The Research Symposium aims to promote and inculcate the spirit of translational clinical research in Singapore's biomedical research landscape. There were six theme-based concurrent tracks which revolved around MOH's RIE2025 areas of priority of research and the national translational programmes. A total of 24 local and overseas experts were invited to speak at the tracks.

In place of the on-site booth displays of physical events, attendees accessed virtual booths which showcased some of the research enablers and activities in the healthcare clusters and public sector. These included CRIS, SHAPES, NHG, Office of Research Protection Programme (OHRPP), SingHealth Research Integrity, Compliance and Ethics (RICE), NUHS and SingHealth Investigational Medicine Units, College of Clinician Scientists, Singapore Biodesign as well as the CoSTAR-HS, IMPACT and PULSES programmes.

HUMAN HEALTH AND POTENTIAL INTERNATIONAL ADVISORY COUNCIL MEETING 2022



Singapore's 25th Human Health and Potential International Advisory Council (HHP IAC) 2022 meeting was conducted via videoconferencing from 24-25 January 2022. The meeting focused on seeking IAC's guidance on the HHP domain's RIE2025 implementation plans. This meeting also marked the transition of the IAC Chairmanship from Sir Richard Sykes, who had led the IAC since its inception in 2000, to Sir Jeremy Farrar.

The IAC commended the significant progress made on the RIE2025 HHP Strategies, including areas such as health, data and digital health, and pandemic preparedness. The IAC further noted that these strategies remained appropriate for anticipating and responding to the rapid changes in the healthcare landscape and HBMS economic value-creation models in Singapore and globally.

- The IAC emphasised the importance of continued long-term support for basic science research, noting that the incremental accumulation of knowledge over the years, for example in RNA biology, was critical for COVID-19 mRNA vaccines to be deployed successfully today.
- The IAC affirmed the importance of data as a major driver of the HHP RIE2025 strategic framework. They recognised that the strategies to facilitate data sharing were underpinned by the key principles of high trust in data protection and commitment to use data for the benefit of health and society.
- The IAC was strongly supportive of Singapore's efforts to hasten digital adoption across Singapore's healthcare system. They noted that digital health was a green field opportunity area where Singapore had the potential to leverage its strengths and capabilities to position itself as a regional regulatory leader, and differentiate itself in this globally competitive space.
- The IAC was also strongly supportive of PREPARE and commended it for being comprehensive and well thought through. The programme also covered key research areas for pandemic preparedness, and built on Singapore's existing capabilities and unique strengths.

In RIE2025, NMRC will continue to fund and support basic research, and maintain mechanisms to further enable the translation of research outputs into real-world applications and value capture. This will position us well to transform and protect the health of Singaporeans.

OVERVIEW OF FUND COMMITMENT IN FY2021

Research Grant Programmes (Project-based)
$306.22MIL

59%

$2.84 mil	CTG-IIT
$30.34 mil	CS-IRG
$4.39 mil	CS-IRG-NIG
$6.85 mil	HSRG
$0.82 mil	HSR-NIG
$195.00 mil	CG

Open Fund

$55.17 mil	IRG
$10.81 mil	YIRG

Human Capital Awards
$98.44MIL

19%

STaR 6 AWARDEES	$34.46 mil
CSA 26 AWARDEES	$55.41 mil
HCSA 3 AWARDEES	$2.94 mil
CIDA 4 AWARDEES	$0.63 mil
CIA 2 AWARDEES	$0.44 mil
CS/CISSP 22 AWARDEES	$4.56 mil

Research Enablers and Infrastructure Initiatives
$88.33MIL

17%

Talent Pipeline Programmes
$23.09MIL^

5%

TA 12 AWARDEES	$12.08 mil
RTF 28 AWARDEES	$10.43 mil
MCI	$0.58 mil

^Figures include funding for CS resident salary, seed fund and book prizes.

**Figures accurate at the time of print.*
Funding sources: MOH, RIE2020 and RIE2020 White Space, RIE2025 and RIE2025 White Space.

OVERVIEW OF FUND COMMITMENT IN FY2022

Research Grant Programmes (Project-based)
$246.43MIL

46%

$1.17 mil	CTG-ICT
$5.94 mil	CTG-IIT
$43.13 mil	CS-IRG
$4.34 mil	CS-IRG-NIG
$3.40 mil	PHRG
$0.39 mil	PHRG-NIG

Open Fund

$119.78 mil	LCG
$54.70 mil	IRG
$13.58 mil	YIRG

38%

STaR 4 AWARDEES	$21.99 mil
CSA 24 AWARDEES	$44.79 mil
HCSA 9 AWARDEES	$14.77 mil
CIA 4 AWARDEES	$0.88 mil

Human Capital Awards
$82.43MIL

13%

Research Enablers and Infrastructure Initiatives
$307.01MIL

TA 10 AWARDEES	$10.18 mil
RTF 31 AWARDEES	$6.73 mil
MCI	$0.09 mil

3%

Talent Pipeline Programmes
$17.00MIL^

^Figures include funding for CS resident salary, seed fund and book prizes.

**Figures accurate at the time of print.*
Funding sources: MOH, RIE2020 and RIE2020 White Space, RIE2025 and RIE2025 White Space.

NATIONAL MEDICAL
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