

List of Potential Thesis Advisors and Projects available for Laboratory Rotation – January 2025 intake

Translational Research Program of PI: Cardiovascular Disease

Department of Medicine

Principal Investigator	Project Title with a brief description
<p>Dr Koh Cho Yeow</p> <p>Email MDCKOHC@nus.edu.sg</p> <p>Telephone Number 97231897</p>	<p>From Toxins to Therapeutics</p> <p>Venomous animals, including snakes, spiders, scorpions, bees, cone snails, and sea anemones, as well as hematophagous animals, such as ticks, leeches, mosquitoes, vampire bats, and horseflies, use their venomous or salivary secretions for predation, defence, and feeding. These secretions consist primarily of proteins and peptides, hypothesised to originate from the animals’ genomes, and have been recruited and evolved to become specialised toxins. Over the course of millions of years, these toxins have become potent, specific, and stable molecules that target the circulatory system, enabling the incapacitation of preys or the extraction of nutrients from hosts. Research into venomous and salivary secretions from animals has led to the discovery and development of life-saving therapeutic related to cardiovascular diseases. For example, captopril, eptifibatide, tirofiban, lepirudin, and bivalirudin are drugs derived from these toxins that are used to treat conditions such as hypertension or thrombosis. Our team has long-standing interest in discovery, design, and development of novel drug candidates like anticoagulants and natriuretic peptides from toxins found in venomous and hematophagous animals. Students joining our team will receive comprehensive training and exposure to basic science and translational clinical science research. They will have access to a wide range of techniques, including peptide/protein synthesis, expression, and purification; enzymatic, molecular, and cellular assays; protein/DNA/RNA blotting and cell imaging; high- and medium-throughput screening campaigns; protein structure determinations using x-ray crystallography or cryo-electron microscopy; protein design, engineering, and directed evolution; mass spectrometry- or affinity-based proteomics and RNA sequencing-based transcriptomic studies; animal models in thrombosis, bleeding, myocardial infarction, fibrosis, pulmonary hypertension, nanoparticle drug delivery, and pharmacokinetics (mice, rats, rabbits, pigs); platelet/coagulation assays and biomarker analyses of clinical samples. Our goal is to provide our students and staff with a comprehensive understanding and capability in bench-to-bedside translational</p>

	research. Please email (choyeow@nus.edu.sg) for more details.
<p>Dr Roshni Rebecca Singaraja</p> <p>Email MDCRRS@nus.edu.sg</p> <p>Telephone Number 92334856</p>	<p>Exosomes as a communication channel in the liver-heart axis</p> <p>Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in Western countries and affects ~25% of the adult population. Patients with NAFLD are at substantial risk for increased cardiovascular disease. Interactions between fatty liver disease (FLD), central obesity, insulin resistance and cardiovascular disease (CVD) phenotypes are thus far not systematically characterised. Extracellular vesicles (EVs) are nanosized vesicles with a lipid bilayer that are released from different cells, and are considered important mediators of intercellular and extracellular communications. EVs carry a variety of molecules including RNAs, proteins, and lipids. EVs are implicated in the pathogenesis of CVD and MI, and have been shown to reduce vascular dysfunction. We hypothesize that increased CVD in NAFLD is modulated in part via the signalling by liver-derived exosomes on cardiometabolic tissues. As part of a ~\$25 million funded project to study the liver-heart axis (Project RESET), we are recruiting 3000 Singaporean subjects who are undergoing deep clinical phenotyping of the liver and cardiovascular system. In addition, blood is being collected and banked for exosome isolation. Using exosomes isolated from those with NAFLD alone, those with NAFLD + CVD, and non-diseased controls, we plan to perform microRNA profiling (MiRXES), transcriptomic profiling and metabolomic profiling to identify differentially enriched exosome cargo. As well, we will expose vascular smooth muscle, macrophage and endothelial cells to exosomes and assess CVD phenotypes. The student will gain expertise in human translational studies, OMICs, extracellular vesicles and inter organ communication, as well as gain a deep knowledge of cardiovascular and metabolic diseases. In addition, the student will establish and manage collaborations, including with clinicians and international scientists, attend and present at national/international conferences, and be part of the cardiovascular research institute (CVRI), a vibrant centre with clinicians and scientists.</p>
	<p>The liver-heart axis: Impact of bile acids on cardiovascular disease</p> <p>Cardiovascular diseases are the leading cause of death worldwide, indicating that current therapies are not sufficient to prevent or reduce these devastating diseases. Using “deep DNA sequencing”, we identified mutations in a bile acid synthesis gene in humans that reduce LDL cholesterol (“bad</p>

	<p>cholesterol”), and increases HDL cholesterol (“good cholesterol”). This suggests that cardiovascular disease may be reduced in the mutation carriers. In agreement, in our preliminary data, we find that the altered bile acid profile in these mutation carriers associates with reduced myocardial infarct (heart attacks). These exciting preliminary data suggest that inhibiting this bile acid synthesis gene may be a drug target to protect against cardiovascular diseases in humans. We have also replicated these studies in mice. These findings are unpublished, and would be included in, and form the basis of your PhD thesis, identifying mechanisms by which alterations in bile acids protect against cardiovascular disease, linking liver-derived bile acids with cardiovascular function. The student will gain expertise in human genetics/genomics, mouse models of cardiovascular disease (including microsurgery techniques taught by a clinical cardiovascular surgeon), primary and iPS cell culture, genome editing (CRISPR-Cas9), transcriptomics, as well as in BA, lipid and glucose metabolism. In addition, the student will establish and manage collaborations, including with clinicians and international scientists, attend and present at national/international conferences, and be part of the cardiovascular research institute (CVRI), a vibrant centre with clinicians and scientists. We previously found that humans with mutations in this bile acid gene have improved diabetes, and reduced liver fat. This PhD project will add to the protective effects of the altered bile acids also on cardiovascular disease, with its exciting clinical implications.</p>
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Department of Paediatrics

Principal Investigator	Project Title with a brief description
<p>Assoc Prof Heng Chew Kiat</p> <p>Email PAEHCK@nus.edu.sg</p> <p>Telephone Number 67723354</p>	<p>Genetic epidemiology of cardiometabolic diseases</p> <p>We have genomic and well characterized phenotypic data from large longitudinal cohorts of >20,000 participants above 45 years old from Singapore who were recruited in the 1990s. They have all been genotyped with genome-wide arrays. Based on follow-up of hospital records and the death registry, more than 2000 of them have either developed cardiometabolic diseases or/and have died of the diseases. Along with >3000 coronary artery disease cases recruited from the National University Heart Centre, these provide powerful means to investigate association of risk factors with diseases and gene x environment interactions. Numerous high impact publications have arisen from our genetic epidemiological studies (https://pubmed.ncbi.nlm.nih.gov/?term=heng+CK&sort=date).</p>

	<p>Investigation of a recently identified ADTRP protein for its role in cardiometabolic diseases</p> <p>Androgen-dependent Tissue Factor Pathway Inhibitor Regulatory Protein (ADTRP) was recently identified. Although its gene has been shown to be associated with coronary artery disease (CAD), its role in the disease's pathogenesis is still poorly understood. Our study has found, for the first time, that CAD patients have significantly lower levels of this novel protein in the blood circulation than controls. Our findings from in vitro investigations have also suggested this protein to be a cardio-protective factor. The novel protein is an enigmatic one that we have shown to have potentially great impact on cardiometabolic health, possibly as a biomarker for assessing CAD risk and as a therapeutic target. As it is a recently discovered protein, very little is known about its characteristics. This provides ample scope for investigations.</p>
<p>Dr Sun Zhe</p> <p>Email HT.SUN@nus.edu.sg</p> <p>Telephone Number 86155606</p>	<p>Understanding environmental impacts on perinatal and childhood cardiovascular health</p> <p>Maternal and child health constitutes a fundamental pillar in maintaining population and societal stability, while also emblematic of civilisation level of a nation. Recent epidemiological studies start to suggest that maternal environmental exposures can be significantly associated with pregnancy outcomes. For instance, maternal exposure to air pollution (e.g., PM2.5 and ozone) can increase the occurrence risks of adverse pregnancy outcomes and neonatal defects, and even impede long-term child growth and development; conversely, exposure to green and blue environments has demonstrated protective effects. However, these pertinent observational studies still exhibit considerable scope for enhancement in methodological rigour and population coverage, and also are deficient in explorations from pathophysiological and aetiological standpoints. In light of these considerations, our HAITONG (Health Associated Integrated Traverse of Nature and Geoscience) Lab will conduct systematic epidemiological analyses, based on two well-established Singaporean cohorts, as the GUSTO (Growing Up in Singapore Towards Healthy Outcomes) and S-PRESTO (Singapore Preconception Study of Long-Term Maternal and Child Outcomes), in collaboration with parallel cohorts in other countries, such as the ZEBRA (Zhejiang Environmental and Birth Health Research Alliance) maternity cohort with 150,000 participants recruited during 2013-2023. Research will primarily focus on environmental tracking database establishment, real-time personal exposure tracing, maternal exposure tracing and perinatal risk association assessment,</p>

	<p>epigenetic-level perinatal risk factor screening, biomarker-level perinatal risk factor screening, establishment of an early-stage risk forecasting system and policy guidance. Two main hypotheses will be tested: 1) maternal environmental exposures prior to (preconceptional) and during pregnancy (gestational) can affect maternal metabolism and cardiovascular function, thereby impacting pregnancy outcomes; and 2) maternal environmental exposures can affect foetal intrauterine development, thereby influencing the neonatal congenital health status at birth.</p>
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Translational Research Program of PI: Cancer

Department of Biochemistry

Principal Investigator	Project Title with a brief description
<p>Assoc Prof Deng Lih Wen</p> <p>Email BCHDLW@nus.edu.sg</p> <p>Telephone Number 65161239</p>	<p>Identify molecular signatures of early prediction of therapy resistance and recurrence to develop surveillance strategies and targeted therapy for personalized treatment</p> <p>Radiotherapy (RT) plays a crucial role in the management of cancer, being used in neoadjuvant, definitive, or adjuvant settings. However, the response to RT can vary among patients, and those with poor response have higher rates of recurrence and require additional salvage therapy, leading to increased treatment morbidity. Treatment failure is often attributed to distant metastasis and cancer relapse after RT. Therefore, a pre-screening strategy to predict upfront response to RT would be valuable in identifying patients with radioresistant tumors, enabling tailored treatment strategies at the time of diagnosis. We have recently identified a specific molecular signature associated with radioresistance and recurrent/metastatic tumors through an unbiased molecular screen. In addition to clinically validating this molecular signature and its correlation with radioresistance and recurrence/metastasis, we aim to elucidate the underlying mechanisms. Several candidates in this signature have been implicated in maintaining cancer stem cell (CSC) and anoikis resistance phenotypes, which are associated with disease recurrence/metastasis. Understanding the molecular functions of this signature and its impact on the CSC population will facilitate the development of targeted therapies for this subset of cells. The identification of this molecular signature from samples obtained at initial diagnosis holds the exciting potential for predicting relapse/metastatic disease at the point of diagnosis. Alongside molecular studies, the candidate will apply this molecular signature to develop a non-invasive liquid</p>

	<p>biopsy-based molecular surveillance strategy. The ultimate goal of this research is to enable clinicians to predict recurrence/metastasis at the time of diagnosis, leading to more tailored therapeutic regimens and improved patient outcomes.</p>
	<p>Investigate the impact of electroacupuncture on tumor growth and tumor microenvironment</p> <p>Acupuncture, an ancient Chinese therapeutic strategy, is widely used in the clinical treatment of various acute and chronic diseases, including cancer. Recent studies suggest that electroacupuncture, an alternative form of acupuncture, can inhibit or delay tumor growth in breast cancer and osteosarcoma in mice. It also affects the distribution of paclitaxel in lung cancer mice, promoting its accumulation by modifying the tumor microvasculature and microenvironment. Emerging evidence suggests that electroacupuncture has the ability to regulate tumor immunoactivity by increasing NK cell activity and peripheral IFN-γ levels, leading to reduced tumor sizes in patients with cervical squamous carcinoma. However, the mechanism underlying NK cell activation by electroacupuncture remains unclear. Some studies suggest that electroacupuncture induces beta-endorphin release, a possible mediator of NK cell induction, although this theory has been challenged by the suppressive effects of morphine administration on NK cell activity. Additionally, the endocannabinoid receptor can activate NK cell activity. Previous research has shown that electroacupuncture can activate the endocannabinoid system, and further exploration of its role in electroacupuncture-induced NK cell activity is warranted. The effects of electroacupuncture on cytotoxic CD8⁺ T cell activation, which play a crucial role in cancer immunotherapy, remain undefined. Therefore, this study aims to evaluate the impact of electroacupuncture on tumor immunogenicity using the murine ID8 ovarian cancer cell model. The study will focus on examining the effect of electroacupuncture on immune cell recruitment in ovarian cancer growth, studying differential gene expression crucial for tumor reduction upon electroacupuncture, and characterizing the possible roles of catecholamines in electroacupuncture-induced tumor regression.</p>
	<p>Targeting Cysteine Metabolism in Ovarian Clear Cell Carcinoma</p> <p>Ovarian clear cell carcinomas (OCCC) are aggressive and chemo-resistant tumors, representing approximately 13% of epithelial ovarian cancers. Standard treatments for OCCC using platinum-based and cytotoxic agents have limited success due</p>

	<p>to inherent resistance. However, recent findings indicate that OCCC cells rely heavily on cysteine for survival, both in vitro and in vivo. Depriving these cells of cysteine disrupts glycolytic function, leading to necrosis and ferroptosis caused by oxidative stress. Targeting cysteine metabolism emerges as a promising therapeutic approach for OCCC. One mechanism behind the resistance of OCCC cells to cisplatin, a commonly used platinum-based drug, is the increased efflux of the drug facilitated by its conjugation with glutathione (GSH) and subsequent extrusion through cellular transporters. Cysteine is a critical component in intracellular GSH synthesis, which is essential for compound detoxification and redox balance. Restoring cisplatin sensitivity in resistant OCCC cells can be achieved by depleting the extracellular cysteine/cystine pool through pharmacological inhibition or the use of cysteinase. Our study aims to investigate the effects of cysteine deprivation alone and in combination with cisplatin using 3D tumor spheroids and mouse models. We will explore the use of cysteinase to deplete extracellular cysteine, enhancing OCCC cell sensitivity to cisplatin. Additionally, we will explore novel delivery methods for localized cysteinase delivery in vitro and in vivo. Patient-derived OCCC organoids and organoid xenograft models will be employed to evaluate the anti-cancer effects of cysteine deprivation and investigate the underlying molecular mechanisms contributing to the synergy between cysteine deprivation and cisplatin. The findings of our study will provide proof-of-concept data supporting targeted cysteine deprivation as a strategy to restore sensitivity to cisplatin treatment in ovarian carcinoma, the most lethal gynecological cancer. Since resistance to platinum-based therapies is common among ovarian cancer patients, our research holds particular relevance in addressing this clinical challenge.</p>
<p>Prof Zhang Yang</p> <p>Email zhang@nus.edu.sg</p> <p>Telephone Number 66011241</p>	<p>AI-based protein and RNA structure prediction</p> <p>Protein and RNA are two types of most important molecules in life. While proteins are ‘workhorse’ molecules carrying out most biological activities of living organisms, RNAs are recently found performing critical cellular functions. Because biological functions of proteins and RNAs are specified by their spatial shape, determination of the 3D structure is essential to annotate their biological functions and to develop new drugs to regulate their functional roles. There are by now 230/31 millions of proteins/RNAs with known sequences; but less than 0.1% of them have structures solved experimentally in the PDB. Therefore, computer-based structure prediction is the only means to alleviate the gap and high demanding of protein/RNA structures by the biomedical community. The past decade has witnessed revolutionary progress of the field due to the</p>

	<p>introduction of artificial intelligence (AI) and deep learning techniques initiated by the PI and other laboratories. But the advancements occur mainly in single-domain proteins, where state-of-the-art programs, such as AlphaFold and I-TASSER, still have difficulties in multi-domain and multi-chain quaternary protein structure prediction. In this project, we will develop new AI and deep-learning methods for protein and RNA structure predictions. Specifically, cutting-edge AI techniques will be integrated with cryo-EM density maps and I-TASSER folding simulations for large-size protein-protein complex structure determinations. The methods will also be extended for structure modeling of RNAs which have been increasingly recognized with important biological function and drug design potential. The developed methods will be stringently tested in the biennial world-wide CASP experiments, also called Olympic Games of computational structure biology, compared to the state of the art of the field. References: (1) W Zheng et al. Nature Methods, https://doi.org/10.1038/s41592-023-02130-4 (2024). (2) Y Li et al. Nature Communications, 14: 5745 (2023).</p>
	<p>AI-based protein design and drug discovery</p> <p>Proteins in nature are created following hundreds of millions of years of evolution and therefore possess limited structural folds and biological functions. Computational protein design aims to design and engineer new protein sequences with novel structure and function significantly beyond nature proteins. Given their potential to create new function and change cellular pathways, computationally designed proteins and peptides can be used as drugs to treat pharmaceutically important human diseases such as cancers and Alzheimer's diseases. In this project, we will develop new artificial intelligence (AI) and deep machine learning approaches for high-accuracy de novo protein and peptide designs. The utilized AI techniques, including transformer networks, protein language and diffusion models, will be integrated with physics-based and evolutionary profile simulations for accurately designing and engineering new proteins and short peptides. Although the current start-of-the-art methods have been successful in designing a variety of functional proteins, there have not yet been a computationally designed protein entering Phase-III clinical trials. Designing the first protein-based clinically effective drug thus represents the 'Holy Grail' of computational protein and peptide design, which is also the general aim of this project. References: (1) R Pearce, X Huang, D Setiawan, Y Zhang. EvoDesign: Designing protein-protein binding interactions using evolutionary interface profiles in conjunction with an optimized physical energy function. J Mol Biol, 431: 2467-2476 (2019). (2) D Shultis, P</p>

	Mitra, X Huang, J Johnson, NA Khattak, F Gray, C Piper, J Czajka, L Hansen, B Wan, K Chinnaswamy, L Liu, M Wang, J Pan, J Stuckey, T Cierpicki, CH Borchers, S Wang, M Lei, Y Zhang. Changing the Apoptosis Pathway through Evolutionary Protein Design. <i>J Mol Biol</i> , 431: 825-841 (2019). (3) R Pearce, X Huang, GS Omenn, Y Zhang. De novo protein fold design through sequence-independent fragment assembly simulations. <i>PNAS</i> , 120: e2208275120 (2023).
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Department of Dean's Office (Medicine)

Principal Investigator	Project Title with a brief description
<p>Assoc Prof Ng Siok Bian</p> <p>Email PATNSB@nus.edu.sg</p> <p>Telephone Number 90105242</p>	<p>Epstein-Barr Virus and Lymphomagenesis: Deciphering the Role of viral microRNA BART19-3p in Extranodal NK/T-cell Lymphoma</p> <p>Epstein-Barr virus (EBV)-associated extranodal NK/T-cell lymphoma (ENKTL) is a rare and aggressive malignancy predominantly affecting populations in Asia and Latin America. Among the EBV microRNAs (EBV-miRNAs), miR-BART19-3p has emerged as a highly expressed potential oncomir in ENKTL. Currently, we are investigating the functional role of miR-BART19-3p in ENKTL pathogenesis, focusing on its impact on the EP300-interacting inhibitor of differentiation 1 (EID1), a transcriptional corepressor with significant tumor-suppressive properties. miR-BART19-3p transfection significantly increased colony formation, indicating its role in promoting tumor proliferation and miRNA-mRNA pull-down assays identified EID1 as a direct target of miR-BART19-3p. Subsequent analyses revealed a marked reduction in EID1 protein expression following miR-BART19-3p transfection, suggesting that the downregulation of EID1 is a critical event in ENKTL tumorigenesis. Our data suggests that EID1 likely serves as a pivotal mediator of tumor-suppressive mechanisms in ENKTL. The suppression of EID1 by miR-BART19-3p underscores its potential as a therapeutic target. This study highlights miR-BART19-3p as a key driver of ENKTL pathogenesis through its interaction with EID1. Future investigations will aim to delineate the downstream pathways modulated by EID1 and explore the therapeutic potential of targeting the miR-BART19-3p/EID1 axis in ENKTL. Emerging data from our current study further reinforces the essential roles which EBV BART miRNAs play in ENKTL oncogenesis. This thus provides a strong basis to investigate other EBV-encoded miRNAs which may be potential contributors to ENKTL oncogenesis. Students working on this project will gain valuable experimental skill sets including western blotting and RNA interference (RNAi) strategies such as transfection with</p>

siRNA (small interfering RNA). They will also learn how to integrate data obtained from experimental work and those derived from bioinformatic analysis following sequencing of knocked-down samples to obtain a comprehensive overview of the interactions between EBV miRNAs and human mRNAs.

Unraveling the Tumor Immune Microenvironment in ENKTL: Insights from Spatial Proteomics and Transcriptomics

Extranodal natural killer/T-cell lymphoma (ENKTL) is an aggressive non-Hodgkin lymphoma with poor outcomes, particularly in advanced stages, and limited treatment options. While immune checkpoint inhibitors have shown promise in relapsed or refractory cases, a deeper understanding of the tumor immune microenvironment (TIME) is essential for developing effective therapies. Recent advancements in spatial profiling technologies have revealed significant heterogeneity in tumor-associated macrophages (TAMs) within ENKTL. Utilizing Nanostring's GeoMx Digital Spatial Profiling (DSP) platform, we identified two macrophage clusters within the TIME of ENKTL, with Cluster 2 demonstrating enriched immune response pathways, antigen presentation, and associations with better overall survival compared to Cluster 1. Further analysis of immune checkpoint markers, including B7H3, PD-1, and CD163, provided additional prognostic insights. To enhance our understanding of these macrophage clusters and their role in ENKTL progression, we are employing advanced spatial platforms such as Stereosequencing and Xenium Analyzer 5K-plex to achieve robust cross-validation and improved resolution of gene and protein targets. These approaches aim to provide a comprehensive pipeline for understanding the crosstalk between tumour and immune cells, as well as identifying novel therapeutic targets and biomarkers. By integrating transcriptomic and proteomic insights with cutting-edge spatial technologies, our study seeks to bridge the gap between discovery and clinical application, ultimately expediting the development of effective treatments for advanced-stage ENKTL patients. By participating in this project, students will be able to learn about how the various spatial platforms available serve as useful tools to characterize and study the landscape of the tumour and immune microenvironment. Students will also learn to apply various bioinformatic strategies to analyze the data obtained from these platforms, and in so doing, obtain meaningful biological conclusions from them.

Principal Investigator	Project Title with a brief description
Dr Alan Prem Kumar Email APKUMAR@nus.edu.sg Telephone Number 65165456	Targeting Lyn Kinase Overcomes Cytoskeletal Driven Immune Evasion in Triple Negative Breast Cancer Emerging evidence indicates that cytoskeletal alterations in breast cancer cells derived from aggressive tumour subtypes render them resistant to killing by cytotoxic immune cells found in the tumour microenvironment. Moreover, these breast cancer cells commonly upregulate expression of the SRC-family kinase, LYN, an important signalling intermediary modulating proliferation, invasion, migration, and immune regulation. Recent studies have shown that LYN kinase promotes formation of actin-rich structures associated with increased migration and facilitates epithelial-to-mesenchymal transition in response to increased stiffness of the extracellular tumour microenvironment. However, mechanisms by which LYN kinase promotes cancer cell cytoskeletal rearrangements and its roles in immune evasion are not explored. The aim of this project is to examine the mechanisms by which LYN kinase signalling influences alterations in cell shape, cytoskeletal architecture and interactions with cytotoxic immune cells. Analysis will be carried out by assessing the composition of actin fibres, cell-extracellular matrix adhesions, actin-rich migratory structures as well as cytotoxic properties of the relevant immune cells using immunofluorescent imaging, time-lapse microscopy, FACS and LYN-specific inhibition or genetic knockdown. Findings from these studies will form the basis for development of novel therapeutic modalities for difficult to treat aggressive breast cancer.
<u>Department of Physiology</u>	
Principal Investigator	Project Title with a brief description
Dr Anthony Khong Email KHONGA@nus.edu.sg Telephone Number 90850074	Dissecting the Role of Mutant DDX3X Persistent Stress Granules in Cancer Biology Are you fascinated by how molecular mechanisms contribute to cancer? Do you want to be at the forefront of discovering new therapeutic targets? Our lab aims to uncover the enigmatic role of DDX3X mutant stress granules in cancer biology, and we're seeking passionate graduate students to join us! DDX3X is a helicase frequently altered in cancers like leukemia, lymphoma, and breast carcinoma. High expression and mutations in DDX3X drive tumorigenesis and promote persistent stress granules—non-membranous RNA-protein aggregates found in patient biopsies. However, their role in cancer progression remains unclear. I am a new assistant professor at the Cancer

	<p>Science Institute of Singapore and the Department of Physiology. My previous research has advanced our understanding of stress granules induced by oxidative stress by describing its composition (Khong et al., 2017, Molecular Cell). Our team established that stress granules are RNA aggregates. We now aim to uncover how DDX3X mutations enhance RNA aggregation and stress granule formation, potentially driving cancer hallmarks. By dissecting the assembly and functions of DDX3X stress granules, we hope to reveal new insights into DDX3X-related cancers and develop innovative therapeutic strategies. In our lab, you'll engage in cutting-edge research to elucidate DDX3X stress granules through three key approaches:</p> <ol style="list-style-type: none"> 1. Blocking Stress Granule Assembly: We'll use a specific inhibitor to study how blocking these granules affects gene expression via RNA sequencing, Ribo-seq, and Timelapse-seq. 2. Analyzing Stress Granule Composition: We'll dissect the transcriptome and proteome of DDX3X stress granules using a FACS-sorting method to understand their molecular makeup. 3. Investigating Tumorigenesis: Through cell-based assays, organoid models, and mouse models, we'll explore how DDX3X stress granules drive tumor development. This is a unique opportunity to dive into cancer biology and contribute to groundbreaking discoveries. If you're interested, please reach out to me at khonga@nus.edu.sg. Thank you!
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Translational Research Program of PI: Digital Medicine

Department of Ophthalmology

Principal Investigator	Project Title with a brief description
<p>Prof Cheng Ching-Yu</p> <p>Email CYCHENG@nus.edu.sg</p> <p>Telephone Number 65767277</p>	<p>Digital and Precision Community Screening Platform for Ageing Diseases: Vision, Metabolism and Heart</p> <p>Cardiovascular diseases (CVD), diabetes and vision impairment are among the top 10 leading causes of disease burden in Singapore. As population ages, the prevalence of these medical conditions and the number of people with multiple chronic diseases are rapidly increasing. The rise in the burden of these aging diseases also augments the growth of market in digital healthcare technology, as both healthcare providers and patients desire to have a more effective way to identify and manage preventable or treatable diseases. The pandemic of COVID-19 further makes digital healthcare 'in-demand' in Singapore and worldwide, and in turn boost the demand and expansion for digital health solutions in the industry. Primary prevention or efficient screening of these prevalent diseases in communities</p>

	<p>represents the most cost-effective, affordable and sustainable course of action in the long run. In this programme, we propose to develop cutting-edge digital and analytic technologies that will transform the ways we screen and auto-triage these three major medical conditions (vision loss, CVD and diabetes), based on simple, low cost, and non-invasive retinal photography. Our general hypothesis is that artificial intelligence (AI) technology is able to fully harness the richness of retinal photos, and thus is able to uncover the hidden features of retinal photos and diseases, providing new approaches to detect people with poor vision and/or identify those at higher risk of CVD and diabetes</p>
	<p>New Technologies to Identify Undiagnosed Glaucoma in the Community</p> <p>Due to the irreversible nature of glaucoma, early case detection is crucial for timely treatment to halt or slow down the progression of the disease in early stages, thus preventing further vision loss and blindness. However, glaucoma screening in the general population has been challenging, mainly due to the lack of simple, cost-effective, and sustainable screening tools. We therefore are conducting this project to establish a sustainable and effective national case detection program, by using novel screening vehicles with an added incorporation of AI-assisted technologies to allow utility by non-specialists, thus scaling up community-based screening.</p>
	<p>Transforming Population Eye Health Research (Transformer) Program: From Data and Algorithms to Precision Health</p> <p>Visual impairment is a major global public health problem, further exacerbated with rapid aging worldwide. Asia, home to 60% of the world population is particularly affected. New ways to more effectively detect, risk-stratify, and manage eye diseases are needed. Population-based studies provide valuable insights to facilitate this. However, long-term epidemiological eye cohorts are lacking worldwide. Hence, our program aims to advance precise population eye health through enriching population data and leveraging on advanced digital innovations and analytics. The Singapore Epidemiology of Eye Diseases Study, a multi-ethnic population cohort encompassing the three main ethnicities in Singapore, is one of the very few landmark eye cohorts. We will continue strengthening its 12-year follow-up. Furthermore, we will build up an integrative data-sharing and analytics platform, forging wider interdisciplinary collaborations within and beyond Singapore. We will also develop and apply state-of-the-art big data analytics and</p>

	<p>artificial intelligence (AI) to better detect and risk-stratify eye diseases, leveraging on the vast clinical, imaging and genomic data. Finally, to further translate our AI algorithms into deployment, we will adopt and test them as clinical decision support tools in real-world screening program. Overall, these approaches would advance precision eye health through granular population data and digital innovations.</p>
<p>Department of Physiology</p>	
<p>Principal Investigator</p>	<p>Project Title with a brief description</p>
<p>Assoc Prof Mathuru, Sriram Ajay</p> <p>Email YNCSAM@nus.edu.sg</p> <p>Telephone Number 66015312</p>	<p>Modeling human brain disorders in animals using a neurogenetics approach.</p> <p>My lab studies neural mechanisms underlying natural behavior motivated by rewards and risks. Our research focuses on applying the insights gained from such studies to model phenotypes associated with human brain disorders including substance dependence, depression, anxiety disorders, neurodegeneration, and dementia. Towards this end, a substantial portion of the work in our lab in the past few years has revolved around developing resources and the appropriate methodology to perform quantitative behavioral analyses using the zebrafish. In 2022, we discovered a novel function for the gene CCSER1. In addition to its known function in the cell cycle, acting as a tumor suppressor, it also has a role in reward processing behavior that changes preference for alcohol in self-administration assays in genetic mutants. (See, FM Nathan, C Kibat, T Goel, J Stewart, A Claridge-Chang, AS Mathuru* Contingent stimulus delivery assay for zebrafish reveals a role for CCSER1 in alcohol preference. Addiction Biology DOI: https://doi.org/10.1111/adb.13126). Transcriptomic analyses of the mutant fish suggest that neurodevelopmental processes may be compromised. We are now moving towards examining brain development, synapse, neuronal maturation, and multi-omics to understand the molecular functions of the gene CCSER1 in normalcy and disease. Other major projects in the lab focus on the functions of nicotinic acetylcholine receptors Chrna3, Chrna5, and Chrn4 genes; and oxytocin receptors OXTR, and OXRTL. More examples can be found at https://mathurulab.com/publications/</p>
	<p>Nicotinic acetylcholine receptors in the development of nicotine addiction and comorbid disorders</p> <p>Nicotine dependence is often comorbid with susceptibility to multi-substance addiction and psychiatric ailments such as</p>

	<p>anxiety disorders and clinical depression. This points towards potential common genetic players and neural circuits. Here, we show that zebrafish are powerful systems to uncover the underlying neurobiology. Human genetic studies have associated chrna3 and chrna5 genes that code for the $\alpha 3$ and $\alpha 5$ nicotinic acetylcholine receptor (nAChR) subunits with nicotine dependence, alcohol dependence, anxiety disorders, and neuroticism. We generated zebrafish homozygous mutant lines in both these genes using the CRISPR/Cas-9 technique. We developed a two-choice Self-Administration Zebrafish Assay (SAZA) to quantify voluntary preference for nicotine and alcohol. Our results show that in nAChR mutants there is not only a change in the preference to administer aversive substances like nicotine and alcohol, but other behaviors like anxiety-like behaviors, appetite, and bouts of sleep also change. They are accompanied by changes in gene expression profiles in the brain that can be extensive or minimal depending on the mutant gene. This suggests that these genes may be critical players in the development of comorbid mental disorders. The next phase of our project is aimed at gaining mechanistic insights into individual variability leading to susceptibility, or resilience by employing neural activity imaging, single nuclei and spatial transcriptomics, and structural and epigenetic changes in mutants.</p>
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Translational Research Program of PI: Infectious Diseases

Department of Microbiology & Immunology

Principal Investigator	Project Title with a brief description
<p>Dr Sham Lok To Email MICLTS@nus.edu.sg Telephone Number 66016356</p>	<p>Ligation of capsular polysaccharides to peptidoglycan in <i>Streptococcus pneumoniae</i></p> <p><i>Streptococcus pneumoniae</i> is a human respiratory pathogen that kills nearly a million people worldwide annually. One of the key virulence factors in pneumococcus is the capsular polysaccharide (CPS). To produce the CPS, sugar residues and other constituents are added to the lipid carrier undecaprenyl phosphate. The completed lipid-linked precursors are transported to the outer leaflet of the cell membrane, polymerized, and conjugated to the cell wall peptidoglycan. Effective conjugation to peptidoglycan is essential for the CPS to remain attached to the cell surface. While most of the enzymes responsible for capsule synthesis were identified, how the finished polymer is ligated to peptidoglycan remains elusive. One candidate of the potential ligase is Cps2A, a</p>

	<p>conserved protein found in most capsule types. Cps2A belongs to the LCP (LytR/Cps2A/Psr) family, which has been implicated in ligating teichoic acids to peptidoglycan. Yet, cells with cps2A inactivated produce an indistinguishable amount of CPS that remains attached to the cell wall. We hypothesize that LytR may compensate for the function of Cps2A. This project aims to investigate whether LytR can substitute for the CPS ligase function using genetic approaches. The findings will be complemented by biochemical approaches to confirm the enzymatic activities of these enzymes. Understanding CPS synthesis is important because all clinically relevant vaccines against pneumococcus target CPS.</p>
<p><u>Department of Physiology</u></p>	
<p>Principal Investigator</p>	<p>Project Title with a brief description</p>
<p>Assoc Prof Thai Tran</p> <p>Email PHSTT@nus.edu.sg</p> <p>Telephone Number 65163663</p>	<p>Role of CD151 in influenza virus infections</p> <p>The project examines the role of CD151 in influenza virus infections using in vitro, ex vivo and in vivo models and spatial transcriptomic analysis to identify the molecular mechanisms and contribution of CD151 in this disease process.</p>
	<p>The Academic Respiratory Initiative for Pulmonary Health (TARIPH) – Role of Glucocorticoids in asthma and COPD</p> <p>This project is funded under the NMRC-Large Collaborative Grant and the potential candidate will be involved in multidisciplinary and collaborative efforts of The Academic Respiratory Initiative for Pulmonary Health (TARIPH). Chronic respiratory disease has unique features in Asians, including inflammatory patterns and corticosteroid resistance (CR). To better understand disease pathogenesis, individual heterogeneity and address precision-based therapeutics, a need for representative, accessible and patient-specific model systems exist. Cutting-edge cell culture techniques have emerged, including organoid technologies and organ-on-chip models that allow the study of lung development, regeneration, and disease. The Global Initiative for Asthma (GINA) Global Burden of Disease Report ranks Singapore as an intermediate risk country for asthma prevalence, however, importantly a high-risk country for asthma-related death, redolent that unique endophenotypic features exist in Singaporean asthmatics and potentially across the Asian sub-continent warranting detailed exploration. In a survey of 2,467 asthmatics across 8 Asian countries, including Singapore, 90% reported perceived asthma</p>

	<p>control, however, 73% experienced one or more exacerbations in the preceding year. Corticosteroid therapy remains first-line for controlling airway inflammation in asthma and preventing exacerbations, and in the majority, remains clinically efficacious. Importantly, up to 10% poorly respond to corticosteroids and are termed 'corticosteroid resistant (CR). CR-asthma affects up to 7% of Singaporeans, with a growing number taking large doses of OCS inappropriately, and in some cases, without a doctor's prescription. Various cellular and molecular events underlie CR and, relate to immunologic dysregulation, genetic, and environmental factors, however, a key knowledge gap in explaining the significant burden of CR among Asians remains to be fully understood, especially in the context of Asian genetics, immunology, inflammation and environment. To better understand disease pathogenesis, individual heterogeneity, and precision-based therapeutics, including CR, representative, accessible, and patient-specific model systems are necessary.</p>
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Translational Research Program of PI: Human Potential

Department of Dean's Office (Medicine)

Principal Investigator	Project Title with a brief description
<p>Dr Ong Yi Ying</p> <p>Email YY.ONG@nus.edu.sg</p> <p>Telephone Number 67723405</p>	<p>The role of early life factors in growth, cardiometabolic health, and mental health during puberty</p> <p>The Growing up in Singapore Towards Healthy Outcomes (GUSTO) study is a comprehensive birth cohort study which started 15 years ago, which aims to examine how pregnancy and early life influences shape the future health of the offspring. The concept of developmental origins of health and disease (DOHaD) and developmental programming is the scientific basis for this study and its research aims. the DOHaD concept proposes that in-utero and early life experiences (termed the first 1000 days) will have long lasting effect on the subsequent health and development of the offspring. The areas of focus include growth and adiposity, metabolic health, neurocognitive development, mental health, dental health, and allergy. more than 1200 mothers were recruited at early pregnancy, and more than 900 children and their mothers are still be followed up today. The children are now entering puberty and there are opportunities to study how the first 1000 days influence development and various health outcomes</p>

Department of Obstetrics & Gynaecology

Principal Investigator	Project Title with a brief description
Assoc Prof Chan Shiao-Yng Email OBGCHAN@nus.edu.sg Telephone Number 67722672	Investigating the role of vitamins in preventing preterm birth Preterm prelabour rupture of fetal membranes (PPROM) is a major contributor to approximately one third of all preterm births, which results in higher risk of infant mortality and morbidity. PPRM is preceded by programmed events that remodels fetal amnio-chorionic membranes, leading to the weakening and ultimate rupture. A healthy maternal diet high in vegetables, fruits and nuts in preconception and during pregnancy is associated with better outcomes in fetal growth and development and in reducing risk of preterm births. However, the underlying mechanisms involved are diverse and poorly understood. We hypothesise that specific vitamins alter fetal membrane remodeling and its signalling to the myometrium, and can prevent premature membrane weakening as well as suppress untimely myometrial contractility, thereby reducing the risk of PPRM and preterm birth. To investigate this hypothesis, we will assess changes in the tensile strength of fetal membranes and muscle contractility of myometrial tissue following pre-culture with various combinations and concentrations of vitamins in vitro. Furthermore, we will explore underlying mechanisms in greater depth by investigating markers of inflammation and oxidative stress pathways using techniques such as qPCR, immunoblotting and ELISA; transcriptomics by RNAseq; and lipidomics by LCMS in the tissue and culture medium. Additionally, experimental findings can be corroborated using datasets from multiple ongoing local and international mother-offspring cohorts. Understanding the role of vitamins in regulating the biochemical and biomechanical properties of fetal membranes and myometrial contractility is essential to substantiate and facilitate the design of nutritional interventions as prophylaxis against preterm birth.

Translational Research Program of PI: Healthy Longevity

Department of Dean's Office (Medicine)

Principal Investigator	Project Title with a brief description
Prof Dheen, Shaikali Thameem	Multi-omics approach to understand mechanisms of microglia-mediated neuroprotection in ageing brain and

<p>Email ANTSTD@nus.edu.sg</p> <p>Telephone Number 65163217</p>	<p>associated neurodegenerative diseases</p> <p>Microglia are resident immune cells of the brain playing important roles in neuroinflammation, and synaptic plasticity through regulation of brain-derived neurotrophic factor. In the ageing brain, microglia are dystrophic with iron accumulation, associated with neurodegenerative diseases such as Alzheimer's. Studies show iron alters lipidomic and epigenomic profiles, and affects transcription and cellular functions. We aim to evaluate the lipidomic, transcriptomic and epigenomic profiles of iron-treated microglia (dystrophic microglia model) to gain better insights into role of dystrophic microglia in age-associated neurodegenerative diseases. This study will identify molecular targets useful for improving the neuroprotection in the ageing brain. This study will employ high-throughput, next-gen omics techniques (Ref: https://doi.org/10.1101/2024.08.08.607139)</p>
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Department of Obstetrics & Gynaecology

Principal Investigator	Project Title with a brief description
<p>Prof Yong Eu Leong</p> <p>Email OBGYEL@nus.edu.sg</p> <p>Telephone Number 81125777</p>	<p>Integrated Women's Health Program: a unique program designed to explore and address women's health care concerns from menopause to healthful long life.</p> <p>Prof Yong's research oeuvre encompass basic laboratory research, genetic diagnostic testing, cohort epidemiological studies, lead compound discovery and development of botanical drugs, and randomised control trials for new interventions that benefit Singaporean women and their children. In 2014, Prof Yong started the Integrated Women's Health Programme (IWHP), which is a unique well-funded cohort focused on the key health concerns of mid-life Singaporean women. For the first time, the size and scope of women-specific health issues, such as menopausal symptoms, osteoporosis, anxiety, depression, insulin resistance, diabetes, urinary incontinence, poor sleep, sexual dysfunction, muscle weakness and sarcopenia have been scientifically characterised and published. Hip fractures incidence and causes of mortality A 7-year follow-up of the IWHP cohort has been completed in 2023. New parameters ready for epidemiological analyses include menopausal "Brain Fog", arthralgia, cognitive decline and dementia, cardiovascular health including carotid intimal thickness scans and new methods to determine sarcopenia including urinary D3-creatine dilution assays and MRI scans. With this knowledge of the health needs of mature women, innovative interventions to improve MUSCLE strength and reduce sarcopenia adapted to the needs Singaporean mid-life</p>

	<p>women will be conducted. SKILLSETS to be acquired: Study design, Conduct and analyses of RCT, Program Development, Regulatory compliance, Epidemiological Analytics, Biostatistics, Scientific writing, Development of novel assessment tools, Health care advocacy. Scholars interested in Epidemiology of Women's Health and role of MUSCLE in health and disease should look for further details below: • https://medicine.nus.edu.sg/researchers/yong-eu-leong/ • https://medicine.nus.edu.sg/obgyn/research/reproductive-development-biology-research-program/iwhp.html • https://medicine.nus.edu.sg/obgyn/research/reproductive-development-biology-research-program/nuclear-receptor-biology-and-drug-discovery.html</p>
Department of Pharmacology	
Principal Investigator	Project Title with a brief description
<p>Assoc Prof Christopher Chen Li Hsian</p> <p>Email PHCCCLH@nus.edu.sg</p> <p>Telephone Number 81253628</p>	<p>Blood markers for Cognitive Impairment and Dementia</p> <p>The specific aims of this project funded by a Singapore Translational Research (STAR) Investigator Award are : 1) 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. 2) To examine novel blood-based biomarkers of neurodegeneration and oxidative stress using a state-of-the-art immunoassay platform and assess their relationships with brain integrity and cognition, 3) To compare plasma vs. neural- or endothelial-specific extracellular vesicle measurements to assess the diagnostic and prognostic utility of these biomarkers 4) To develop a combination of multiple biomarkers with high accuracy in predicting longitudinal disease development. We hypothesise that markers involved in the disease pathophysiology, can identify individuals with high disease risk. Specifically, that a) blood-based biomarkers of neurodegeneration and oxidative stress are predictive of incident CeVD in parallel with cognitive decline; b) neural- or endothelial-specific extracellular vesicle biomarkers are more sensitive than neat plasma biomarkers in diagnosing and prognosis for cognitive impairment and CeVD; c) A combination of multiple biomarkers adds value to the diagnostic and prognostic performance of single blood-based biomarkers.</p>
	<p>Multimodal MRI-based network breakdown and progression prediction in Cognitive Impairment and Dementia</p>

The specific aims of this project funded by a Singapore Translational Research (STAR) Investigator Award are : 1) To examine longitudinal brain network and microstructural changes using multimodal MR imaging and evaluate their interactions with AD & CeVD and cognitive and behavioural decline in patients with NCI, MCI and dementia. The hypotheses are : a) Plasma amyloid- β and p-tau are related to specific brain functional and structural network breakdown leading to cognitive decline and behavioral problems; b) The effect of network changes and atrophy on cognitive performance and behavior is network-specific and disease stage-dependent and modulated by CeVD markers c) Individuals with both CeVD and AD would have an accelerated trajectory of neurodegeneration and cognitive decline. 2) To build a large international longitudinal database comprising local and international imaging and neurobehavioural data to develop AI algorithms for predicting dementia risk and progression. We hypothesize (a) that deep learning can be used to harmonize imaging and neurobehavioural data across multiple sites; b) By pooling harmonized data across multiple sites, the larger sample size will dramatically improve prediction of future cognitive decline and clinical outcomes.

Neurobehavioral & structural MRI markers for Cognitive Impairment & Dementia

The specific aims of this project funded by a Singapore Translational Research (STAR) Investigator Award are : 1)To study, in a cohort of 700 subjects with up to 5 years longitudinal follow up, the independent and joint associations of MRI, retinal imaging, blood and neurobehavioural markers with risk of cognitive decline & vascular events. We hypothesise that a) Longitudinal MRI, retinal as well as blood-based and neurobehavioural markers are associated with poorer cognitive performance and incidence of dementia and vascular events. B) Both baseline and serial change in, one or more of these biomarkers, will add additional predictive information on progression of cognitive decline and incident events beyond the utility of currently used predictors. 2)To examine how Mild Behavioural Impairment (MBI) is influenced by the independent and interactive effects of MRI, retinal and blood biomarkers. We hypothesise that : a) Severity of CeVD and neurodegeneration, structural and functional disruptions and reduced perfusion on MRI are associated with MBI; b) Retinal markers are associated with MBI; c) Altered levels of bloodbased markers are associated with MBI; d) Interaction between the above mentioned biomarkers influence MBI and NPS.

	<p>Retinal markers for Cognitive Impairment and Dementia</p> <p>The specific aims of this project funded by a Singapore Translational Research (STAR) Investigator Award are : 1) To determine the relationship of existing (retinal vasculature, Optical Coherence Tomography (OCT), OCTAngiography) and novel (Doppler OCT, 24ehavior24ize, hyperspectral OCT) retinal imaging measures over time to progression and development of vascular cognitive impairment and other imaging markers of dementia, with a goal to determine the potential diagnostic and prognostic value of retinal imaging. We hypothesise that as multiple cross-sectional studies have consistently demonstrated the association of retinal imaging biomarkers and dementia, retinal imaging biomarkers will be predictive of the incidence and progression of dementia. 2) The creation of an international big data consortium, AIDA (Artificial Intelligence for Dementia Assessment) to evaluate retinal imaging markers of dementia. Using datasets from multiple institutions around the world and through the integration of deep learning, we hypothesize that we will be able to further improve the sensitivity and specificity of retinal imaging biomarkers to detect dementia.</p>
	<p>The SINGapore GERiatric intervention study to reduce cognitive decline and physical frailty (SINGER) Study</p> <p>The specific aims of this project funded by a Large Collaborative Grant are : 1) To investigate novel interventions for vascular cognitive impairment (VCI). We propose to conduct a large community based innovative trial as part of the World Wide FINGERS interdisciplinary network for the prevention of cognitive impairment or dementia The trial will recruit 1200 subjects at high risk to develop cognitive impairment and dementia. The main goal is to determine the efficacy and safety of multimodal lifestyle interventions together with intensive blood pressure lowering. We hypothesize that these interventions will reduce cognitive decline and severity of cerebrovascular disease (CeVD) and other VCI biomarkers. 2) To examine how CeVD, tau, and amyloid impact longitudinal brain integrity and cognitive decline in elderly at risk for cognitive decline or dementia. We hypothesize that CeVD and AD have distinct influence on brain, retina and blood markers of neurodegeneration and cerebrovascular burden. Further, we hypothesize that these multimodal measures at baseline coupled with polygenic scores could identify high risk individuals and predict future disease progression or response to intervention.</p>

Department of Physiology

Principal Investigator

Project Title with a brief description

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Elucidating mechanisms underlying cancer-related stroke (CRS), an emerging subtype of ischemic stroke in the elderly

One of the Phd Mentor's favourite book is "Consilience" by E.O. Wilson. Consilience describes synthesis of knowledge from different specialized fields of human endeavor. This projects epitomises this and brings the fields of oncology and neurology together. Our lab seeks to understand mechanisms underlying systemic impact of cancer on the human body for disease prevention. This project deals with cancer-related stroke (CRS), an emerging subtype of ischemic stroke with unique pathomechanisms. Notably, Cancer patients are at three times higher risk than the general population in developing stroke! However, knowledge regarding molecular mechanisms underlying cancer-related stroke is scant, highlighting an unmet need. As survival rates of cancer patients increase, it becomes crucial to identify older cancer survivors at elevated risk of stroke. This overarching goal of the project is to determine impact of tumour secretome on vascularisation and coagulation, as well as other novel pathways that engender CRS. The student will utilise an "omics" approach coupled with cutting-edge cell biology tools. He/she will be immersed in an intellectually-stimulating lab environment at the Centre for Healthy Longevity, and will work closely with clinical collaborators at NUH (Drs Leonard Yeo, Sia Ching Hui, Andrea Wong), and Prof Han Weping at A*STAR. For more information: crastalab.com

Membrane damage and inflammation in therapy resistance.

Cellular senescence results in a stable cell cycle arrest. Its secretome termed senescence-associated secretory phenotype (SASP), can influence the microenvironment via paracrine action. Senescent cells confer beneficial effects on organismal physiology such as embryogenesis and wound healing. However, the accumulation of senescent cells can contribute to aging and age-related disease. Emerging efforts seek to manipulate senescent cells in a bid improve healthy aging. Our lab has contributed important findings to the field of senescence, with implications for cancer and aging. While senescence can be caused by telomere shortening, dna damage, oncogene activation, chemotherapy etc, plasma membrane damage has recently been identified as a senescence trigger. We will assess whether molecular players that mediate plasma

	<p>membrane rupture influence phenotypic outcomes of membrane damage-induced senescence. This is a collaboration between Dr. Karen Crasta and Dr. Kaiwen Chen.</p>
	<p>Plasma membrane integrity and senescence in the aging heart</p> <p>Cellular senescence results in a stable cell cycle arrest. Its secretome termed senescence-associated secretory phenotype (SASP), can influence the microenvironment via paracrine action. Senescent cells confer beneficial effects on organismal physiology such as embryogenesis and wound healing. However, the accumulation of senescent cells can contribute to aging and age-related disease. Emerging efforts seek to manipulate senescent cells in a bid improve healthy aging. Our lab has contributed important findings to the field of senescence, with implications for cancer and aging. While senescence can be caused by telomere shortening, dna damage, oncogene activation, chemotherapy etc, plasma membrane damage has recently been identified as a senescence trigger. Membrane damage plays an important role in the pathogenesis of ischemic damage to the myocardium and has implications for cardiac dysfunction. We hypothesise that plasma membrane damage-induced senescence can contribute to cardiac failure. The overarching goal of this project is to elucidate mechanistic pathways, biophysical changes and the cell biology underlying alterations in membrane integrity that can contribute to cardiac dysfunction using cutting-edge tools. This project is in collaboration with Prof Roger Foo, NUS and Prof Keiko Kono at OIST, Japan. Opportunity for short-term research internship in Japan available. For more information: crastalab.com</p>
	<p>Role of stress granules in therapy resistance</p> <p>Triple-negative breast cancers lacking targets such as estrogen (ER) and progesterone receptor (PR) expression, and Her2 overexpression, account for the worst prognosis among all breast cancer subtypes. Our lab has shown that therapy-induced senescence (TIS) in TNBCs can lead to chemoresistance. Paradoxically, we have shown that the senescence state alters the tumour secretome to drive migration, invasion and angiogenesis. However, the mechanisms underlying this remains poorly understand. Stress granules are thought to contribute to cell cycle exit. This project aims to examine the role of stress granules and other biomolecular condensates in influencing phenotypic outcomes engendered by TIS. It is a collaboration between Dr. Karen Crasta's lab and Dr. Anthony Khong's lab.</p>

<p>Assoc Prof Mathuru, Sriram Ajay</p> <p>Email YNCSAM@nus.edu.sg</p> <p>Telephone Number 66015312</p>	<p>Oxytocin signaling in social and non-social behaviors.</p> <p>Zebrafish are freshwater fish that live in small shoals in the wild. We have found that social partners are highly effective in alleviating fear in fish. We are now interested in understanding the neural mechanisms underlying this social buffering in fish. More broadly we are also interested in understanding the social cognitive abilities of zebrafish, the brain regions involved, and the molecular players participating in these behaviors, specifically using the oxytocin receptor mutant lines that we have generated recently. (Ref A Gemmer, K Mirkes, L Anneser, T Eilers, C Kibat, AS Mathuru, S Ryu, E Schuman Oxytocin receptors influence the development and maintenance of social behavior in zebrafish (Danio rerio). Sci Rep 12, 4322. https://doi.org/10.1038/s41598-022-07990-y)</p>
<p>Prof Reshma Taneja</p> <p>Email PHSHEAD@nus.edu.sg</p> <p>Telephone Number 65163236</p>	<p>Interrogating relapse mechanisms in rhabdomyosarcoma</p> <p>Patients with high risk RMS have poor prognosis. In this proposal, we investigate the basis of relapse by analysing cancer cell states in response to chemotherapy. The proposal involves an interdisciplinary approach, integrating the most cutting-edge experimental approaches including single-cell and spatial transcriptomics applied to patient samples and experimental models of tumorigenesis amenable to perturbation. We will perform advanced computational analyses and test regulators of cell state as novel therapeutics for therapy resistant disease.</p>
	<p>Investigating the role of BRD4 isoforms in rhabdomyosarcoma</p> <p>The goal of this project is to understand the role of BRD4 as an epigenetic vulnerability in embryonal rhabdomyosarcoma (ERMS). BRD4, is a bromodomain and extraterminal (BET) protein. It has two main isoforms BRD4S and BRD4L. BRD4 is deregulated in multiple cancers and has surfaced as a promising drug target. However, the function of the two main isoforms (BRD4L and BRD4S) has not been analyzed in most cancers. This complicates determining therapeutic efficacy of pan-BET inhibitors. Using functional and transcriptomic analysis of isoform-specific knockdown cells, we found that BRD4L likely has an oncogenic role and inhibits differentiation. Depletion of BRD4L impairs tumor progression but does not impact metastasis. On the other hand, depletion of Brd4S has no significant impact on tumor growth, but unexpectedly promotes metastasis. Since the two isoforms play distinct roles, it is paramount to elucidate the roles of BRD4L and BRD4S and examine the therapeutic efficacy of pan-BRD4 targeting in</p>

	ERMS
<p>Assoc Prof Saji Kumar Sreedharan</p> <p>Email PHSSKS@nus.edu.sg</p> <p>Telephone Number 65165886</p>	<p>Unraveling the Mechanisms of Cognitive Decline in Aging and Neurodegenerative Diseases</p> <p>Our laboratory employs cutting-edge techniques such as long-term electrophysiology, patch-clamp techniques, optogenetics, chemogenetics, and behavioral studies to investigate plasticity and cognitive changes in aging and neurodegenerative diseases. As the elderly population increases, aging and associated neurodegenerative diseases pose socio-economic burdens and affect quality of life. We aim to understand the mechanisms underlying cognitive decline in aging and diseases like Alzheimer's. By studying hippocampal neural networks using animal models, we seek to uncover the impaired functioning and identify novel therapeutic strategies and drug targets. For more information, please refer to our publications. For more information regarding our publications, please refer to: https://pubmed.ncbi.nlm.nih.gov/?term=sajikumar+s&sort=date</p>
<p>Dr Tsai Shih-Yin</p> <p>Email PHSTS@nus.edu.sg</p> <p>Telephone Number 65167617</p>	<p>Bioengineering: Identification of translational control in remodeling skeletal muscle microenvironment.</p> <p>Activation of 4EBP1 in fully differentiated muscle fibers not only retains skeletal muscle functions with age but also cell-nonautonomously increases the number of functional muscle stem cell (MuSCs) and augments neuromuscular synaptic transmission (Ang et al., Nat Commun. 2022). Yet, how a repressor of cap-dependent translation, 4EBP1, preserves muscle functions with age and how 4EBP1-activated myofibers enhance the activities of MuSCs and motor neurons in a cell-nonautonomous manner remains unclear. To address the knowledge gap, we will employ 3D muscle-motor neuron-MuSCs co-culture systems to further dissect the action of 4EBP1 in regulating the muscle microenvironment. Our collaborative publication with Prof. Shen Han Ming demonstrated that impaired autophagy leads to an increase in mitochondria secretion, which may activate adaptive immunity (Tan et al., Nat Commun. 2022). In line with this, our preliminary analysis revealed an accumulation of immune cells in the muscle tissue of TSC1mKO mice. Additionally, we will incorporate lymphocytes obtained from various strains of transgenic mice into our research. By using the remodified 3D co-culture systems, we expect to establish mTORC1-4EBP1 as a novel therapeutic target in muscle aging and identify the underlying mechanisms integrated through altered mTORC1-4EBP1 signaling for muscle health. The funding for this part of the project was recently granted by MOE Tier 2 (T2EP30223-0010) in 2024. Another unexpected finding from our in vivo</p>

	<p>aging study is a sex-dependent change in NMJ remodeling during aging. Male mice that are aging experience a greater level of denervation and fragmentation of AChR compared to their female counterparts. The sex difference in NMJ remodeling will be explored through the use of our newly established 3D culture in the lab and our in vivo aging mouse cohorts.</p>
	<p>Cell Biology: Investigate the regulatory pathways that connect protein synthesis and degradation in skeletal muscle</p> <p>Postmitotic skeletal muscle relies heavily on effective and tightly regulated protein degradation to maintain its proteome stability. Impaired autophagy-lysosomal or ubiquitin-proteasomal protein degradation causes the accumulation of damaged proteins, ultimately accelerating muscle dysfunction with age. Our recent publication revealed that restricting cap-dependent translation through overexpression of the dominant active form of 4EBP1 expands lysosomal-degradation capacity without relieving mTORC1-mediated inhibition of autophagy. Along with its lysosomal-degradation capacity we also finds that activating 4EBP1 in skeletal muscles increases ubiquitin-proteasomal protein degradation. Our goal is to pinpoint the translational targets that control the increased capacity for protein degradation in skeletal muscle.</p>
	<p>Task for healthy longevity: Uncovering the diverging mechanisms responsible for aging in the skeletal and cardiac muscles.</p> <p>During the aging process, skeletal muscle experiences atrophy, yet cardiac muscle undergoes reactive hypertrophy in response to a continuous loss of myocytes in the heart. Ultimately, the morphological changes in skeletal and cardiac muscles are both accompanied by reduced contractile function. The uncontrolled proteostasis from mTORC1 hyperactivation have been observed in both aging skeletal and cardiac muscles. Rapamycin treatment alleviated these changes and improved muscle health in both muscle types, indicating that up-regulated mTORC1 signaling drives muscle aging. Together, these data implicate that mTORC1 is indispensable for muscle development, while partial suppression of mTORC1 later in life mitigates muscle aging and preserves muscle health. Yet, the underlying mechanisms of rapamycin-mediated protection from muscle aging remain elusive. It is unclear why mTORC1 hyperactivation leads to an atrophic phenotype in skeletal muscle but a hypertrophic phenotype in cardiac muscle. Our preliminary data show that TSC1mKO mice develop an early onset of cardiac hypertrophy and have a shortened lifespan,</p>

	<p>confirming the pathophysiological role of constitutive mTORC1 activity in the heart. While it does not prevent mTORC1-induced sarcopenia (Crombie et al., J Cachexia Sarcopenia Muscle. 2022), inactivating muscular S6K1 reduces cardiac hypertrophy in the TSC1mKO mouse background and extends survival. We aim to address the downstream mechanisms by which reduced mTORC1-S6K1 activity promotes healthspan and whether administration of a S6K1 inhibitor can improve muscle functions as a novel treatment for healthy longevity.</p>
<p>Department of Psychological Medicine</p>	
<p>Principal Investigator</p>	<p>Project Title with a brief description</p>
<p>Dr Feng Lei Email PCMFL@nus.edu.sg Telephone Number 97867090</p>	<p>Evidence-based lifestyle interventions for the delay of cognitive decline among older Singaporeans: cohort study and randomized controlled trial</p> <p>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 on an existing cohort, the Diet and Healthy Ageing (DaHA) cohort which have 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 paying 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 individualization. 120 older adults age 60-75 years, who are at risk of dementia will be randomly allocated to one of the two intervention arms and control arm. Primary outcome is change in processing speed. Secondary outcomes include epigenetic age, systemic chronic inflammation and other health-related measures. We hypothesize that lifestyle factors are associated with cognitive decline, epigenetic age and systematic chronic inflammation and lifestyle interventions focusing on common problems among local population can delay cognitive decline, slow epigenetic ageing and produce favorable changes on inflammation markers. The study will provide evidence on the role of lifestyles in ageing and the biological changes after</p>

	<p>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.</p>
<p>Translational Research Program of PI: Immunology</p>	
<p>Department of Biochemistry</p>	
<p>Principal Investigator</p>	<p>Project Title with a brief description</p>
<p>Assoc Prof Nguyen Nam Long</p> <p>Email BCHNNL@nus.edu.sg</p> <p>Telephone Number 98238253</p>	<p>Harnessing sphingosine-1-phosphate transport for the treatment of inflammatory diseases</p> <p>Sphingosine-1-phosphate (S1P) is the signaling lipid that plays numerous functions including regulation of immune cell trafficking and blood vessel integrity by activating 5 different S1P receptors (S1PR1-5). The sources of circulating S1P for signaling are yet to be entirely understood. Spns2 and Mfsd2b were recently discovered as the two major S1P exporters (Science 2009; Nature 2017). Interestingly, Spns2 and Mfsd2b provide S1P for different functions. We focus on dissecting the roles of S1P from Spns2 as this transporter provides essential sources of S1P for the immune cell trafficking. Deletion of Spns2 in the whole body prevents neuroinflammatory diseases. Targeting Spns2 in the endothelial cells is also sufficient to block immune cell infiltration for triggering inflammation. In this project, we investigate the roles of S1P-Spns2 axis in the gut. Answering the physiological roles of Spns2 in triggering gut inflammations and the availability of atomic structures of Spns2 will enable generation of therapeutic approaches for treatment of the inflammatory diseases in the gut.</p>
	<p>Mechanistic transports of lysolipids in the lysosomes</p> <p>It has been well documented that a defect in the remodelling of lipids such as sphingolipids and phospholipids often leads to the ectopic accumulation of lipids in the lysosomes in the lysosomal storage diseases (LSD). These diseases including Gaucher, Sandhoff, Fabry, Tay-Sachs, and Niemann-Pick type C are inherited metabolic diseases characterized by defective lysosomal functions. We identified Spns1 as a potential gene candidate that we hypothesized is involved in the recycling of lysolipids in the cells. Spns1 shares 54% identities with Spns2, which is a sphingosine-1-phosphate transporter. Our preliminary data show that Spns1 is a lysosomal protein. Lack</p>

	<p>of this protein results in severely delayed development in mice. Sphingolipids and phospholipids are accumulated in the tissues of Spns1 knockout mice and Spns1 deficient cells. In this project, we will pursue these specific aims: 1) Generation of tissue specific knockout of Spns1. 2) Determination of the physiological functions of Spns1 using the conditional knockout mice. 3) Determination of molecular mechanisms by which Spns1 recycles lipids from lysosomes for regulation of cell behaviors. Collectively, we aim to reveal the important roles of lipid recycling from the lysosomes regulated by Spns1 for the cell and tissue functions.</p>
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	<p>The roles of the blood brain barrier Mfsd7c for CNS vascular health and brain functions</p> <p>Several missense mutations of Mfsd7c, an orphan transporter have been reported in the Fowler syndrome. Affected subjects exhibit signs of severe neurological defects. We recently reported the characterizations of Mfsd7c knockout (KO) mice and compare it to phenotypic findings in human mutations (JCI 2020). Mfsd7c is a transporter that is specifically expressed in blood vessels. Global KO of Mfsd7c in mice resulted in late gestation lethality, due to central nervous system (CNS) phenotypes. We found that the angiogenic growth of CNS blood vessels in the brain of Mfsd7c KO embryos was inhibited in cortical ventricular zones and ganglionic eminences. Vascular tips are dilated and fused resulting in glomeruloid vessels. Both embryos and humans with bi-allelic MFSD7C mutations exhibited reduced cerebral cortical layers, enlargement of the cerebral ventricles, and microcephaly in mice and humans. These preliminary results indicate MFSD7c is required for the normal growth of CNS blood vessels and the brain. The blood brain barrier is the critical barrier that partitions blood from neurons. It is equipped with multiple transport systems that are essential for exchanging nutrients, ions, and wastes between blood and neuronal cells. Guided by these preliminary data, we hypothesize that Mfsd7c transports an essential nutrient(s) for the brain development and functions. Mfsd7c and its ligands are also required for blood vessel functions. The overarching aims of this project are to identify the nutrients transported by Mfsd7c and characterize the physiological roles of these nutrients for the brain growth. The broad objective here is to identify micro-nutrients that are required for brain functions and apply this knowledge for treatment of brain-related diseases.</p>
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Department of Physiology

Principal Investigator	Project Title with a brief description
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<p>Assoc Prof Lim Hsiu Kim, Lina</p> <p>Email PHSLHKL@nus.edu.sg</p> <p>Telephone Number 91915100</p>	<p>Regulation of DNA sensing and recognition in cancer through cGas/STING and Annexin-A1</p> <p>The host immune system recognizes regions of viral and self RNA via specific receptors that activate host immune responses. Annexin-A1 is an immune response protein which has anti-viral properties. We and others believe that cancer cells express cytosolic DNA which can be sensed by immune cells and cancer cells themselves. Why the immune system does not react to these abundant DNAs/RNAs are unclear. We predict that expression levels of ANXA1 can positively regulate sensitivity of the immune cells and cancer cells to DNA. In fact, our published results show that RNA and DNA stimulation of cancer cells induces cancer cell death, which is dependent on ANXA1. We therefore, plan to determine that ANXA1 enhances DNA and RNA sensing in immune cells and cancer cells in vitro and in vivo. We believe that the DNA can be released from tumor cells and this can activate innate immune cells in the tumor microenvironment, and this may not be sensed by the immune system due to lowered ANXA1 levels. Knowing these mechanisms of how cancers evade immune recognition will bring us closer to finding treatments for cancer.</p>
	<p>Vaccination and preexposure to COVID19 and susceptibility to influenza</p> <p>The coronavirus disease 2019 (COVID-19) epidemic represents one of the most devastating pandemics in modern history. SARS-CoV-2, the etiologic agent of COVID19 has now spread across the planet to 188 countries and devastated the global economy. In the response to the pandemic, countries have taken extreme measures to thwart the spread of the disease and multiple countries, (including Singapore) have closed their borders, created mask mandates and social distancing measures. Although retrospective analyses will no doubt assess the efficacy of various countries' response to this unprecedented event, one potential advantage of Singapore's approach to pandemic management has been the 'knock-on' effect it has had on other common respiratory pathogens such as influenza viruses. Influenza viruses infect millions of people each year and can result in severe or even fatal complications including pneumonia and respiratory distress syndrome. The Singapore Ministry of Health started influenza monitoring 40 years ago to monitor for possible outbreaks and to track influenza strains, and it is the first time since the start of the monitoring that there have been no cases of flu reported through the surveillance system for almost a year. In January 2020, 652 flu-like cases were sent in for analysis and 320 were flu positive (50%). In comparison, in January 2021, 200 flu-like cases were sent in</p>

	and 0 were flu-positive. This project will study the interaction between influenza and coronaviruses with even subclinical infection by coronaviruses preventing influenza infection These questions are critically important as influenza pandemics have historically had far more devastating impact than the current coronavirus pandemic especially among younger people. It is thus key to our understanding of current and future pandemics to determine if and how the influenza virus is going to reappear to cause the next pandemic.
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Translational Research Program of PI: Nanomedicine

Department of Diagnostic Radiology

Principal Investigator	Project Title with a brief description
<p>Dr Ni Qianqian</p> <p>Email QQIAN.NI@nus.edu.sg</p> <p>Telephone Number 84395324</p>	<p>Improved Lipid Nanoparticle Technology for mRNA delivery and gene editing</p> <p>The employment of mRNA and lipid nanoparticle (LNP) technology for systemic delivery of mRNA/gRNA offers greater flexibility for CRISPR-Cas9 mediated genome editing by averting the drawbacks and potential risks of direct protein or plasmid DNA delivery and allowing for repeated doses. However, there are still some challenges inherent to the mRNA-based approach applied for CRISPR-Cas gene editing: 1) In contrast to mRNA vaccines, where a small amount of mRNA can produce sufficient antigens for body immunization (antigen signals can be effectively amplified via immune systems), CRISPR-Cas9 editing system usually requires hundred fold higher mRNA doses to reach the therapeutic threshold; 2) As liver is the organ of choice when it comes to ease of delivery for lipid nanoparticles, targeting mRNA therapeutics to other solid tissues thus remains a major challenge. To realize the full potential of mRNA technology in CRISPR-Cas9 based gene editing, more advanced in vivo delivery system for precisely targeted delivery especially to extrahepatic tissues, is needed to be developed. Overall, these requirements place greater importance on the efficiency of mRNA delivery to targeted cells and tissues to drive the duration and level of protein expression. This proposal aims to address the current pain in mRNA-based CRISPR-Cas9 gene editing system by 1) enhancing the protein production yield of delivered mRNA, 2) increasing the efficiency of CRISPR-Cas9 based genome editing, and 3) enabling safe and more efficient therapeutic efficacy by precisely targeting extrahepatic tissues.</p>

<p>Dr Zhang JingJing</p> <p>Email J.ZHANG@nus.edu.sg</p> <p>Telephone Number 84353534</p>	<p>Cancer Theranostics with Molecular Imaging and Targeted Radioligand Therapy in Combination with Immunotherapy in Multiple Types of Cancer</p> <p>Cancer theranostics with multi-modality molecular imaging and molecular targeted radioligand therapy represents a promising advancement in both cancer diagnosis and treatment. Molecular imaging reveals disease processes at a cellular level, enabling early diagnosis and real-time monitoring of therapeutic responses. Radioligand therapy targets specific membrane proteins receptors or antigens overexpressed in malignancies, delivering radionuclides directly to cancer cells and making it highly effective for cancer treatment. Our Theranostics Centre of Excellence (TCE) advances theranostics through pioneering innovative research and technology, translating discoveries into transformative clinical solutions, and fostering interdisciplinary partnerships. The centre boasts a well-equipped research facility with an integrated imaging platform, including nanoSPECT/CT, nanoPET/MRI, microPET/CT, second near-infrared bioimaging (NIR-II), IVIS spectrum in vivo imaging system, and ultrasound/photoacoustic imaging (PAI). It is also a leading platform for radiopharmaceutical development, featuring a chemical synthesis unit, a radiolabelling hot lab (radio-HPLC, radio-iTLC, gamma counter), a tissue culture room, and an animal holding room. Our lab is deeply engaged in studying molecular and cellular biology to uncover the intricate mechanisms underlying cancer development and progression, exploring the genetic and epigenetic alterations that drive tumor initiation, growth, and metastasis. We investigate the complex interactions between cancer cells and their microenvironment. At the forefront of nanomedicine and material sciences, we develop and apply nanomaterials like nanoparticles, nanoprobes, and nanozymes to enhance cancer treatment precision and efficacy. By integrating radiomics and texture analysis to extract quantitative features from PET/CT and MRI images, bioinformatics and systematic analysis to identify prognostic biomarkers, single-cell RNA sequencing to explore tumor heterogeneity, and nanotechnology for high-quality imaging and targeted drug delivery, we aim to uncover the molecular and cellular mechanisms driving cancer progression and resistance. These approaches help develop more effective diagnostic tools, identify novel therapeutic targets, and create personalized treatment strategies to improve patient outcomes.</p>
<p>Translational Research Program of PI: Do not belong to any TRP</p>	
<p><u>Department of Diagnostic Radiology</u></p>	

Principal Investigator	Project Title with a brief description
<p>Dr Choi Yoon Seong</p> <p>Email YOON.C@nus.edu.sg</p> <p>Telephone Number 87818084</p>	<p>Quantitative Neuroimaging Markers for Phenotyping and Prognosis Prediction of Cognitive Decline with a Focus on the Alzheimer's Disease Spectrum</p> <p>This research project aims to develop and validate quantitative neuroimaging markers for phenotyping and prognosis prediction of cognitive decline in elderly patients and normal individuals, with a focus on the Alzheimer's disease spectrum. The project will utilize a variety of advanced imaging techniques, including structural and advanced MRI (e.g., DTI, SWI), multimodal PET markers to quantify neurodegeneration, glymphatic function, and other relevant biomarkers. The goal is to identify optimized imaging markers that can be integrated into clinical settings for phenotyping and prognostic prediction of cognitive decline by evaluating these markers in a clinical context alongside non-imaging findings such as demographics, genetic profiles, and plasma markers. You will handle imaging data with variable quantitative analyses, including conventional statistics, machine learning, and deep learning. Our lab has several research-ready datasets that have led to publications, which is being expanded by integrating further initiative/consortium datasets, the UK Biobank, and clinical patient data from collaborations with institutions in Singapore and Korea. As part of the project, you will be listed as an official member of the ethics approval and work with imaging data to improve medical outcomes. You will use coding skills in R and Python and apply biostatistical methods. In addition, you will learn and apply various image analysis methods and validate imaging findings in diverse datasets, including different ethnicities and clinical versus initiative data.</p>

Department of Obstetrics & Gynaecology

Principal Investigator	Project Title with a brief description
<p>Assoc Prof Citra Nurfarah Zaini Mattar</p> <p>Email OBGCNZM@nus.edu.sg</p> <p>Telephone Number 91184294</p>	<p>Novel precision gene editing technologies for treating hemoglobinopathies using humanized mouse models</p> <p>β-hemoglobinopathies are hereditary single gene disorders, with ~ 300 mutations in the human β-globin gene leading to the production of abnormal haemoglobin. Allogeneic haemopoetic stem cell (HSC) transplantation, the current gold standard, is not available for the majority of patients. In contrast, strategies to genetically modify patients' own autologous HSC ex vivo may be beneficial without risking graft rejection, and are employed in current clinical trials of beta-thalassemia using integrating viral vectors. However, this approach is more costly</p>

	<p>and requires bone marrow conditioning and immunosuppression. Our laboratory investigates in vivo HSC gene modification using non-integrating adeno-associate viral vector and base editing strategies. We will optimise HSC expansion protocols and AAV transduction, and a humanized mouse model to characterise short and long-term effects of in vivo AAV-gene therapy, targeting common β-globin mutations. In vivo gene corrections using AAV delivery of precise base-editing tools will increase the repertoire of gene therapy strategies, making this novel therapy more accessible and less costly. In this project, we focus on: 1. In vitro and in vivo gene editing (base editing) of haemopoetic stem cells 2. In vivo gene editing using Humanized mouse models 3. Induced Pluripotent Stem Cells and reprogramming to HSC to examine an alternative strategy of gene editing 4. Developing tools for HSC gene editing (viral and non-viral vectors)</p>
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Department of Paediatrics

Principal Investigator	Project Title with a brief description
<p>Prof Yap Hui Kim</p> <p>Email PAEYAPHK@nus.edu.sg</p> <p>Telephone Number 96751552</p>	<p>Advanced interpretation of variants of unknown significance in genetic kidney diseases using innovative functional studies</p> <p>Supervisor: Prof Yap Hui Kim Co-Supervisor: A/Prof Ng Kar Hui About 20-30% of adults and children with chronic kidney disease have an underlying genetic disorder. We have set up the first multicenter consortium “Deciphering Diversities: Renal Asian Genetics Network (DRAGoN)”, which now includes 53 investigators from 23 centres in 8 countries and 651 families, in order to characterise the genetic landscape of paediatric renal disease in Asia (Lu et al., 2022). We have also set up a multi-centre study in Singapore (Renal Alliance in PrecIision Diagnosis in Singapore: RAPIDS) to clinically implement genetic testing in nephrology in a scalable, sustainable and cost-effective manner. Through these consortiums, we have identified several variants in known genes (e.g. COL4A5, PKD1) which have uncertain clinical significance. This implies there is inadequate scientific knowledge to determine the pathogenicity of these genetic variants. Patients with such genetic variants have inconclusive genetic results. We have also identified genetic variants in poorly understood (VPS33B) or novel genes (KCNT1) in patients. This project aims to construct and validate a translational pipeline for the functional characterisation of such uncertain genetic variants in renal tubular or cystic genes. The work will involve generating renal tubuloid cultures (Schutgens et al., 2019) from patient urine samples and performing downstream experiments including</p>

	<p>gene expression analysis, cell trafficking studies using a high throughput flow cytometry assay, as well as ion uptake experiments and patch clamp electrophysiology. Overall, this project will equip the candidate with a wide range of common and unique cellular and molecular biology techniques, and provide the candidate with an opportunity to work with a multidisciplinary team in one of the few translational nephrology laboratories in Asia. In addition, this work can create results that may be potentially be directly impactful on the patients' clinical diagnosis and management.</p>
	<p>Genetic variant landscape and kidney disease risks in the Singaporean population</p> <p>Supervisor: Prof Yap Hui Kim Co-Supervisor: A/Prof Ng Kar Hui; A/Prof Lee Guat Lay, Caroline Genomics is increasingly an integral part of mainstream medicine and has the potential to revolutionize healthcare delivery globally. With the advent of next generation sequencing, our understanding of genetic kidney diseases has been redefined. Based on large international and European cohorts, 81-100% and 44% of patients with congenital and infantile nephrotic syndrome (NS) have genetic diagnosis respectively, and 25-30% of steroid-resistant NS have been shown to be genetic etiologies. Patients with genetic nephropathies generally do not respond well to immunosuppression and progress more rapidly to kidney failure. A critical enabler of precision medicine is the availability of genomic variation data from both patients and the general population, to identify genetic disorders prevalent in the population. Comprising nearly 60% of the global population, Asian genomes, especially Southeast Asians, are severely under-represented. The genetic spectrum for Asian patients appears to be different compared to the other populations, and this is most evidently shown by the lower NPHS2 mutational rates in Asians compared to Caucasians and Middle East patients. This study aims to profile the population prevalence estimates of presumed pathogenic genetic variants in major kidney genes in Singapore through analysis of SG10K data. The prevalence of variants associated with autosomal dominant kidney anomaly and carrier burden of variants associated with autosomal and X-linked recessive conditions will be systematically compared between the three major ethnic groups (Chinese, Malay and Indian), as well as with other populations in the open accessed genomics databases (eg. UK Biobank). The findings of this study will provide insights into genetic kidney disease risk and to address knowledge gaps for populations across East Asia, South Asia, and a major proportion of Austronesian-speaking Southeast Asian group represented by Malays.</p>