List of Potential Thesis Advisors and Projects available for Laboratory Rotation – January 2024 intake

Translational Research Program of PI: Cardiovascular Disease

Department of Medicine

Principal Investigator	Project Title with a brief description
Dr Chester Lee Drum Email **MDCCLD@nus.edu.sg** Telephone Number **83183106**	**Machine Learning Approach to Cancer and Cardiovascular Risk Prediction** Deep learning is a subset of machine learning which uses very deep neural networks to learn complex relationship between input variables and final output in very large datasets. In a process called supervised learning, an algorithm is trained iteratively on a high-quality annotated dataset. Each iteration culminates with a hypothetical/predicted output which is compared against the real output and the error is used intelligently to adjust the weight associated with each input parameter for the next iteration and the process is continued till the predicted output matches the real output. Finally, the trained model is used to predict the outcome for a new set of inputs. Working with bioinformaticians, clinicians and large healthcare data sets, you will create novel algorithms to identify patients at risk of drug adverse effects and who will benefit from precision treatments. You will be listed as an official member of the ethics approval and work with patient data to improve medical outcomes. A robust model of immediate translational value will be created to predict adverse reactions.
Dr Koh Cho Yeow Email **MDCKOHC@nus.edu.sg** Telephone Number **97231897**	**From Toxins to Therapeutics** 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 research. Please email (choyeow@nus.edu.sg) for more details.

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The impact of bile acids on vascular function and heart disease

Cardiovascular diseases (CVD) are the leading cause of death worldwide, indicating that current therapeutic options are inadequate. To identify novel markers of CVD, we performed a human genetic screen and identified several genes associating with CVD. One of these encodes a bile acid synthesis gene. We have found that the absence of this gene increases the circulatory levels of chenodeoxycholic acid (CDCA), a bile acid synthesized in the liver. To confirm this finding, we administered CDCA to mice with susceptibility to CVD and found decreased vessel blockage (atherosclerotic plaques). However, how the increase in CDCA decreases CVD is unclear. Using primary human vascular cells (endothelial, smooth muscle and macrophage) in vitro and studies in mouse models, in this programme, we aim to identify the mechanisms by which CDCA protects against CVD, and validate CDCA as a therapeutic target for CVD. Highly motivated PhD students will work on exciting translational research, and gain expertise in cardiovascular diseases and atherosclerosis, bile acids, mouse models, primary human and mouse cells, and a variety of molecular biology, protein biochemistry and immunohistological methods. Students will also manage national and international collaborations including with clinicians and scientists, present at international meetings and author publications. References: 1. Rattanasopa C et al.

Semaphorin3F reduces vascular endothelial and smooth muscle cell PI3K activation and decreases neointimal plaque formation. https://doi.org/10.1101/2022.03.22.485288 2. Tripathi M et al. Caffeine prevents restenosis and inhibits vascular smooth muscle cell proliferation through the induction of autophagy. Autophagy. 2022; Jan 11:1-11 3. Monteiro-Cardoso VF et al. Bile Acids: A Communication Channel in the Gut-Brain Axis. Neuromolecular Med. 2021;23(1):99-117

Department of Paediatrics

Principal Investigator	Project Title with a brief description
Assoc Prof Heng Chew Kiat Email **PAEHCK@nus.edu.sg** Telephone Number **67723354**	**Genetic epidemiology of cardiometabolic diseases** 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). **Investigation of a recently identified ADTRP protein for its role in cardiometabolic diseases** 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.

Translational Research Program of PI: Cancer

Department of Biochemistry

Principal Investigator	Project Title with a brief description
Assoc Prof Deng Lih Wen Email **BCHDLW@nus.edu.sg** Telephone Number **65161239**	**Identify molecular signatures of early prediction of therapy resistance and recurrence to develop surveillance strategies and targeted therapy for personalized treatment** 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 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. **Investigate the impact of electroacupuncture on tumor growth and tumor microenvironment** 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-? 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.

Targeting Cysteine Metabolism in Ovarian Clear Cell Carcinoma

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 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.

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A novel telomere-binding protein

Telomeres are nucleoprotein structures at the end of chromosomes and are essential for both the end replication problem as well as for preventing chromosomal fusions due to recognition of the tips of linear chromosomes by the DNA repair machinery. While the end replication problem limits the proliferative capacity of normal cells and contributes to the human aging process, ultimately all cancer cells need to bypass this proliferative limit for their indefinite expansion. Likewise, deprotected telomeres may fuse with each other, subsequently leading to breakage-fusion-bridge cycles and in consequence ever increasing genome instability. Therefore, a precise understanding of these two key aspects of telomere homeostasis is essential for our understanding of cancer development and progression. We have recently identified a completely uncharacterized gene (0 Pubmed entries) as a novel direct telomere-binding protein. Furthermore, we have already identified that this factor regulates the telomeric chromatin composition and subsequently telomere-mediated genome stability. As part of this project we will aim at understanding the precise molecular mechanism of this novel telomere regulator, study extra-telomeric roles in gene regulation and characterize a recently established KO mouse model. These biological questions will be paired with cutting-edge technology, among others spanning ChIP-seq, RNA-seq and quantitative mass spectrometry (MS) with a particular emphasis on ChIP-MS approaches applied to our in vivo mouse model.

Department of Pharmacology

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.

Department of Physiology

Principal Investigator	Project Title with a brief description
Dr Anthony Khong Email **KHONGA@nus.edu.sg** Telephone Number **90850074**	**Are stress granules, a model RNA-protein biomolecular condensate, enhancing signal transduction pathways?** Stress granules are cytosolic protein-RNA biomolecular condensates that form during acute cellular stresses such as hypoxia, oxidative stress, virus infection, and chemotherapeutics. Their cellular function is to provide stress resistance, but the molecular mechanism of how remains unclear. This is relevant in cancer biology because tumors may have usurped stress granules to survive chemotherapeutics and the tumor microenvironment. This project will test the idea that

stress granules enhance signal transduction pathways relevant to cell survival. Preliminary data indicate stress granules are concentrating kinases and enhancing MAPK signaling. The approach is to look for differences in signal transduction pathways between wildtype and stress granule deficient cells by proteomics and signaling arrays. This work will be done in collaboration with the proteomics core facility at the Cancer Science Institute.

Are subdiffraction G3BP biomolecular condensates stabilizing mRNAs and promoting tumorigenesis?

G3BP are genes involved in multiple aspects of RNA biology ranging from translation, RNA stability, and assembly of stress granules. High expression of G3BP in tumors correlates with poor patient prognosis for many cancers, including breast, lung, and gastric. Recent super-resolution studies indicate G3BP proteins can form subdiffraction condensates without stress. The assembly and functions of the subdiffraction condensates need to be clarified. Moreover, G3BP is known to be involved in contradictory molecular processes: RNA stability and RNA decay. My laboratory hypothesizes G3BP is involved in RNA stability when it forms subdiffraction condensates. We predict G3BP's ability to create the condensates depends on its interaction with Caprin1, which is antagonized by another protein USP10 because G3BP1-Caprin1 interaction is also vital for the large biomolecular condensate stress granules. We will test this idea by disrupting G3BP-CAPRIN1 interaction with a short peptide and determine if G3BP subdiffraction condensates (by expansion microscopy) and RNA stability are reduced. The anticipated outcome will provide molecular insight into the role of G3BP proteins in RNA and cancer biology.

Determine the composition of stress granules in cancer cells and tumors

Stress granules are cytosolic protein-RNA biomolecular condensates that form during acute cellular stresses such as hypoxia, oxidative stress, virus infection, and chemotherapeutics. Their cellular function is to provide stress resistance, but the molecular mechanisms are unclear. This is relevant to cancer biology because tumors may have usurped stress granules for various cancer processes. In this project, we will determine the protein and RNA composition of stress granules in cancer cells. The data collected will explain how stress granules are involved in cancer biology. We will use a newly developed technique called HyPro to investigate stress granules' protein and RNA composition. The approach enables labeling interactors and spatial neighbors of RNAs of interest by

biotinylation, which can be subsequently identified by streptavidin pulldown, followed by mass spectrometry and deep sequencing. We will use RNAs known to be highly enriched in stress granules to biotinylate proteins and RNAs in stress granules (Khong et al. 2017, Mol Cell). We anticipate discovering new components of stress granule RNAs, and proteins will allow us to formulate hypotheses on how stress granules are involved in cancer biology.

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Identifying epigenetic drivers of therapeutic resistance in cancer

Drug resistance, either intrinsic or acquired, represents a major bugbear in precision medicine. It is increasing clear that epigenetic reprogramming mechanisms contribute to transcriptional plasticity in cancer cells enabling lineage transformation towards a 'drug-tolerant persister' (DTP) state. These rare population of DTP cancer cells acquire transcriptomic and epigenetic features resembling that of early embryonic cells that are developmentally plastic. Accordingly, they survive and adapt readily to therapeutic pressures, and over time can re-populate the tumour. Using established commercial cell line and patient-derived xenograft and organoid models of resistance (e.g. Paclitaxel in breast and 2nd/3rd generation TKIs in lung cancers), we propose to isolate and characterize the DTP cancer cells to identify the epigenetic drivers of therapeutic resistance. To this end, we have developed epigenetic technologies that are amenable for low input material. We intend to also use pharmacologic approaches to identify epigenetic drugs that impede the formation or progression of DTPs, and assess for improved clinical outcomes in combination with standard-of-care treatments. Close collaboration with clinicians is an integral part of our research process, ensuring a multidisciplinary approach that bridges the gap between laboratory findings and clinical applications. The student will undergo comprehensive training in various advanced -omics techniques, including but not limited to ChIP-seq, ATAC-seq, HiChIP and Proximity labeling proteomics. Representative publications from the lab: 1. Hu et al., Nature Cell Biology 2020 (PMID:31932739) 2. Zhang et al., Nature Communications 2023 (PMID:37117180)

Targeting embryonic priming factors in cancer cell plasticity

Cellular plasticity plays a crucial role in (re)programming cell states during embryonic development, but it can also contribute to the susceptibility of tissues to oncogenic transformation. In our laboratory, we are specifically interested in investigating the epigenetic mechanisms that govern this cellular plasticity.

Recently, we published a study demonstrating the involvement of an early-embryonic factor, NELFA, in promoting the epigenetic reprogramming of pluripotent embryonic stem cells (ESCs) into a highly plastic totipotent-like state (Hu et al., Nature Cell Biology 2020; PMID:31932739). Additionally, our research has revealed that NELFA is overexpressed in cancer and plays a role in driving various aspects of cancer cell plasticity, including epithelial-mesenchymal transition (EMT), stemness, and therapeutic resistance (Zhang et al., Nature Communications 2023; PMID:31932739). These findings underscore how cancer cells exploit early developmental programs to facilitate phenotypic plasticity and highlight the significance of embryonic factors in this process. Based on these observations, we hypothesize that the reactivation of select early-embryonic factors could induce remodeling of the epigenome in cancer cells, akin to the developmental reprogramming observed in early embryos. This remodeling process is likely to contribute to tumor heterogeneity and confer therapeutic resistance. As an extension of our study, we have performed an unbiased pan-cancer transcriptomic analysis and identified numerous early-embryonic genes that are re-activated in cancer, many of which remain uncharacterised, in cancer. Building upon these insights, our proposed research aims to address three main objectives: (1) Elucidate the mechanisms that govern the reactivation of these early-embryonic factors in cancer cells. (2) Investigate the precise molecular mechanisms through which these factors exert their effects. (3) Identify potential therapeutic approaches that can selectively target these factors and impede their pathological influence. Close collaboration with clinicians is an integral part of our research and student will receive training in various -omics technology.

Translational Research Program of PI: Digital Medicine

Department of Ophthalmology

Principal Investigator	Project Title with a brief description
Prof Cheng Ching-Yu Email **CYCHENG@nus.edu.sg** Telephone Number **65767277**	**Digital and Precision Community Screening Platform for Ageing Diseases: Vision, Metabolism and Heart** 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 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

New Technologies to Identify Undiagnosed Glaucoma in the Community

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.

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

Visual impairment is a major global public health problem, further exacerbated 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 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.

Department of Physiology

Principal Investigator	Project Title with a brief description
Assoc Prof Mathuru, Sriram Ajay Email **YNCSAM@nus.edu.sg** Telephone Number **66015312**	**Modeling human brain disorders in animals using a neurogenetics approach.** 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 Chrnb4 genes; and oxytocin receptors OXTR, and OXRTL. More examples can be found at https://mathurulab.com/publications/

Nicotinic acetylcholine receptors in the development of nicotine addiction and comorbid disorders

Nicotine dependence is often comorbid with susceptibility to multi-substance addiction and psychiatric ailments such as 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 a3 and a5 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.

Translational Research Program of PI: Infectious Diseases

Department of Biochemistry

Principal Investigator	Project Title with a brief description
Dr Qu Kun Email **KQU@nus.edu.sg** Telephone Number **66018154**	**Structure-guided design of vaccines against emerging infectious diseases** Vaccine development was typically measured in decades. However, structure-based antigen design, computational biology, protein engineering, gene synthesis, and improved manufacturing platforms revolutionised vaccine design and production with unprecedented speed and precision. It can't be denied that the structure-based design of SARS-CoV-2 spike proteins with two or more stabilizing mutations is a potent and critical approach for the prompt development of viral vector and mRNA vaccines in 2020. Structure-guided immunogen design

for infectious diseases is an increasingly viable approach. The use of cryo-electron microscopy and tomography (cryo-EM and cryo-ET) has been widely applied to understand the structure of antigens and antibodies. Structural determination and morphological characterisation are emerging as precision models or templates to aid in the design of vaccine immunogens and platforms. The future trend in structure-guided design will be integrated tightly into biochemistry and immunology, animal models and clinical trials, deep learning, and bioinformatics. In this PhD project, the candidate will take advantage of structural virology and synthetic biology to design new types of vaccines.

Department of Microbiology & Immunology

Principal Investigator	Project Title with a brief description
Assoc Prof Tan Yee Joo Email **MICTYJ@nus.edu.sg** Telephone Number **65163692**	**Understanding viral-host interactions in chronic hepatitis viral infection and acute viral infection by newly emerged viruses** Approximately 2 billion people have been infected by two viruses, hepatitis B virus (HBV) and hepatitis C virus (HCV), which primarily attack the liver. Although HCV and HBV are completely different viruses, both of them preferentially infect hepatocytes and are able to subvert the innate and adaptive immunity, leading to chronic infection. In contrast, acute infection happens for many newly emerged viruses, like influenza A virus and coronavirus, after zoonotic transmission. For all these viruses, the complex interplay between viral proteins and host cell machineries contributes to viral replication and/or pathogenesis. However, the exact manner by which each virus participates in this complex process is not completely understood. In our laboratory, we are using multidisciplinary approaches to identify host factors that are regulated by different viral proteins to drive viral replication. The functional significance of novel viral-host interactions identified will then be analyzed by using cell culture systems including protein interaction assays, gene knockdown and infectious clones. Identification and in-depth characterization of novel viral-host interactions offer new opportunities for drug screening, designing new treatments and prevention strategies.

Department of Physiology

Principal Investigator	Project Title with a brief description
Assoc Prof Thai Tran	**Role of CD151 in influenza virus infections**

Email **PHSTT@nus.edu.sg** Telephone Number **65163663**	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.

Translational Research Program of PI: Human Potential

Department of Medicine

Principal Investigator	Project Title with a brief description
Assoc Prof Zhou Juan Email **MDCZJU@nus.edu.sg** Telephone Number **66014918**	**A longitudinal study of multimodal brain structure and function in health and neuropsychiatric disorders** The project research will be centered around the brain network vulnerability hypothesis. The multidisciplinary research program focus on large-scale brain structural and functional networks in healthy developing and aging brain and symptoms-related changes in diseases such as neurodegenerative disorders and psychosis. Statistical, computational, and machine learning methods are developed to fuse multimodal neuroimaging data and build predictive models. Our current lines of research include the following: 1) detecting early brain network changes in preclinical and clinical neuropsychiatric disorders such as Alzheimer's disease and psychosis; 2) understanding the neurophysiological signatures and behavioral relevance of time-varying brain functional connectivity; 3) examining the longitudinal brain network changes and its associations with cognitive and mental problems in the developing and aging brain; 4) investigating the underlying neural mechanism of brain-computer interface-based intervention; 5) examining the influence of amyloid-beta, tau, and cerebrovascular pathology as well as other risk factors on brain integrity and cognition in aging; 6) developing machine learning and statistical methods for big data analysis, brain decoding, brain-behavior associations, and disease prognosis. Lab members have access to research-dedicated Siemens 3T MRI scanners, MR-compatible EEG, eye-tracking devices, and high-performance computing clusters and storage. You are welcome to check out www.neuroimaginglab.org for more information.

Department of Obstetrics & Gynaecology

Principal Investigator	Project Title with a brief description

Assoc Prof Chan Shiao-Yng	**Investigating the role of vitamins in preventing preterm birth**
Email **OBGCHAN@nus.edu.sg** Telephone Number **67722672**	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. PPROM 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 PPROM 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.

Department of Paediatrics

Principal Investigator	**Project Title with a brief description**
Prof Lee Yung Seng	**the role of early life factors in growth, cardiometabolic health, and mental health during puberty**
Email **PAELEEYS@nus.edu.sg** Telephone Number **67723356**	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

Translational Research Program of PI: Healthy Longevity

Department of Biochemistry

Principal Investigator	Project Title with a brief description
Prof Barry Halliwell Email **bchbh@nus.edu.sg** Telephone Number **96320963**	**Elucidating the neuroprotective mechanisms of ergothioneine.** Ergothioneine is a natural dietary thiol/thione that is avidly taken up by the human body (via a specific transporter, OCTN1) and accumulates in tissues including the brain (crossing the blood brain barrier). However, our group has shown that individuals with neurological disorders such as mild cognitive impairment, dementia, and Parkinson's disease have significantly lower plasma levels of ergothioneine compared with healthy age-matched subjects. A broad range of studies reveal that ergothioneine may be neuroprotective in a range of neurodegenerative animal models and against a range of neurotoxins. Taken together this suggests that ergothioneine may be important for the brain in maintaining homeostasis and for the prevention of neuronal dysfunction or may even have therapeutic value in the treatment of neurodegenerative disorders. However, despite numerous studies demonstrating preservation of neurons and neuronal function by ergothioneine, the reasons for its accumulation in the brain and the exact mechanisms of neuroprotection are not well understood. This project will utilize a range of techniques including transcriptomics, metabolomics, and other techniques to identify the cellular interactions and impact of ergothioneine in neurons and thereby shed light on the possible role(s) of ergothioneine in prevention of neurological disorders. **Establishing plasma levels of ergothioneine in the population and the associations of low ergothioneine levels with age-related diseases.**

Our preliminary studies have shown that plasma levels of a dietary compound, ergothioneine, are significantly lower in individuals with a wide range of age-related disorders including, mild cognitive impairment, dementia, Parkinson's disease, age-related macular degeneration, and diabetic retinopathy. Other groups have made similar associations to cardiovascular diseases and frailty. However, as yet there are no indications as to what constitutes "normal healthy" levels of plasma ergothioneine in the population, nor has a lower threshold of unhealthy or "at risk" (whereby lower ergothioneine may predispose an individual to high risk of age-related disease) levels of plasma ergothioneine been established. The project will analyse ergothioneine and related metabolites in plasma samples (using liquid chromatography mass spectrometry) from a broad range of individuals from the population to establish guidelines for these levels and also aim to identify possible reasons for declining levels with age and disease in the population.

Protection against ocular diseases by the dietary compound, ergothioneine.

Age-related macular degeneration (AMD) is one of the leading causes of irreversible blindness and vision impairment. Numerous pathological processes are believed to be involved including oxidative damage, abnormal lipid and protein metabolism, mitochondrial dysfunction, immune dysregulation, and irregularities in extracellular matrix, leading to damage of the retinal pigmented epithelium and photoreceptors. At present no cure for AMD exists. Ergothioneine a natural diet-derived thiol compound has been shown to accumulate in the body, with especially high levels detected in the certain regions of the eye. We recently demonstrated that patients with AMD had lower plasma levels of ergothioneine, with indications of decreased levels also in the ocular fluids. However, the role of ergothioneine in the eye is not well understood. This project will further investigate the potential protective and therapeutic effect of ergothioneine in the eye and its possible mechanisms of action using stem-cell derived retinal epithelium and animal models of light-induced eye damage. These mechanistic studies form the basis for future clinical application of ergothioneine in the treatment and prevention of ocular disorders such as AMD.

Dr Vincenzo Sorrentino

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Dissecting cellular pathways of aging- and senescence-associated protein aggregation

Protein homeostasis (proteostasis) includes all processes required to maintain the cellular proteome, from regulation of protein synthesis to aggregation and degradation. Loss of

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proteostasis occurs in aging and neurodegenerative disorders such as Alzheimer's disease, and in muscle during sarcopenia and inclusion body myositis. Recent published and unpublished work from Sorrentino's research indicates that aging is accompanied by accumulation amyloidogenic aggregates, and this also occurs in senescent cells. However, the major mechanisms and types of protein aggregates occurring in aging and senescence are yet to be defined. This project will focus on unveiling the relationship between aging, proteostasis decline and cellular senescence in the following aims: - Identification of aging-associated amyloid oligomers and other proteostasis alterations from senescent cells generated via several methods, through enrichment and proteomics methodologies. - Mechanistic studies in senescent cells and in the aging model C. elegans to evaluate the role of the identified pro-aggregation proteins on cellular health and on the senescence process via loss- or gain-of-function experiments, followed by molecular characterization. Overall this will unveil mechanisms linked to age- and senescence-associated proteostasis collapse, and create new opportunities to drug proteostasis in aging. For Prof. Sorrentino's related work: DOI: 10.1016/j.celrep.2020.108660

Elucidation of common proteotoxic stress response signatures across aging and age-related diseases

While aging and neuromuscular proteinopathies all show features of metabolic and proteostasis dysfunction, the underlying global molecular alterations of these conditions are unknown, and whether there may be shared mechanisms of disease and repair that could be targeted across conditions is unclear. The hypothesis for this project is that proteotoxicity conditions in diseases like Alzheimer's disease, Parkinson's, Hungtington, or during aging itself result in a common cellular adaptation response that can be identified, mapped, and therapeutically targeted. The activities of the project will involve: - Access and analyze existing datasets of human patients and mice or lower organism models of aging, and proteotoxic diseases to identify possible common deregulated pathways (bioinformatics/data analysis). - Execution and analyses of molecular studies, and if relevant, metabolomics, transcriptomics and proteomics on models of protein aggregation (e.g. aged primary cell lines or aged C. elegans nematodes, amyloid-beta and Huntingtin, aged mouse tissues) - Assessment of the disease relevance of pathways identified by knock-out or overexpression studies in cellular models, and in nematode C. elegans, or by compound-based approaches for known druggable metabolites, lipids or proteins. This will provide a comprehensive view of the effects of proteotoxicity across age-associated diseases, and facilitate identification of potential novel disease biomarkers and therapeutics. For Prof.

Sorrentino's related work to this field: 1)DOI: 10.1016/j.celrep.2020.108660 2) doi.org/10.1371/journal.pcbi.1007162

Department of Dean's Office (Medicine)

Principal Investigator	Project Title with a brief description
Prof Koh Woon Puay Email **KOHWP@nus.edu.sg** Telephone Number **94521466**	**Multi-dimensional frailty in community-dwelling elderly – The Singapore Chinese Health Study** The main objective is to take an integrated and holistic approach to examining the effects of biological, lifestyle and socioeconomic factors that affect multi-dimensional outcomes as Singaporeans transit from health to morbidity around the age of 75 years. A cohort of Singaporeans aged 65-80 years (73 years on average), nested in the prospective cohort of the Singapore Chinese Health Study, will be studied as they develop morbidity beyond these years. Beyond establishing associations, this cohort seeks to: 1. elucidate the etiologic roles of biological factors in the pathogenesis of health-related ageing outcomes, 2. identify modifiable factors to promote healthy longevity, 3. identify risk biomarkers that could be developed for early detection or screening of adverse outcomes in ageing. Findings from the cohort have great potential for contributing towards the scientific basis for developing public health programmes and policies for the promotion of health in multi-dimensional aspects of longevity for all Singaporeans.

Department of Obstetrics & Gynaecology

Principal Investigator	Project Title with a brief description
Prof Yong Eu Leong Email **OBGYEL@nus.edu.sg** Telephone Number **81125777**	**Integrated Women's Health Program: a unique program designed to explore and address women's health care concerns from menopause to healthful long life.** 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 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

Department of Pharmacology

Principal Investigator	**Project Title with a brief description**
Assoc Prof Christopher Chen Li Hsian Email **PHCCCLH@nus.edu.sg** Telephone Number **81253628**	**Blood markers for Cognitive Impairment and Dementia** 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-theart 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.

Multimodal MRI-based network breakdown and progression prediction in Cognitive Impairment and Dementia

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-ß 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.

Retinal markers for Cognitive Impairment and Dementia

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.

The SINgapore GERiatric intervention study to reduce cognitive decline and physical frailty (SINGER) Study

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.

Department of Physiology

Principal Investigator	**Project Title with a brief description**
Assoc Prof Mathuru, Sriram Ajay Email **YNCSAM@nus.edu.sg** Telephone Number **66015312**	**Oxytocin signaling in social and non-social behaviors.** 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)
Prof Reshma Taneja Email **PHSHEAD@nus.edu.sg** Telephone Number **65163236**	**Interrogating relapse mechanisms in rhabdomyosarcoma** 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. **Investigating the role of BRD4 isoforms in rhabdomyosarcoma** 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 ERMS

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Unraveling the Mechanisms of Cognitive Decline in Aging and Neurodegenerative Diseases

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

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Task for healthy longevity: Targeting muscular protein homeostasis to improve muscle function for healthspan extension.

Life expectancy has increased, yet it was due to decreased mortality rather than reduced years of disability worldwide. The gains in the number of years living with a disability substantially impact the economic and social systems. Physical disability is highly associated with the progressive decline in muscle functions. This proposal aims to explore the therapeutic potential of intervening mTORC1-S6K1 signaling to promote muscle health and prolong the healthy lifespan in the elderly. mTORC1-S6K1 is an evolutionarily conserved signal transduction pathway promoting cell growth and metabolism. Although counterintuitive, emerging evidence shows that hyperactive mTORC1-S6K1 accelerates muscle aging,

	suppressing it attenuates the process. This proposed work seeks to evaluate the role of mTORC1-S6K1 in the diet-, age-, and genetic-induced muscle dysfunction. The mouse-based studies will enable us to (1) gain insight into the mechanisms via which mTORC1-S6K1 inhibition improves muscle health and (2) define the role that skeletal and cardiac muscles specific changes in responding to modulation of mTORC1-S6K1 signaling. Collectively, the outcomes of this project are expected to establish mTORC1-S6K1 as a novel therapeutic target in muscle aging and identify the underlying mechanisms integrated through alternations in mTORC1-S6K1 signaling for muscle growth and health.

Translational Research Program of PI: Synthetic Biology

Department of Biochemistry

Principal Investigator	Project Title with a brief description
Assoc Prof Chang, Matthew Wook Email **BCHCMW@nus.edu.sg** Telephone Number **66017929**	**Innovative solutions powered by synthetic biology** The Chang Lab is leveraging synthetic biology to develop innovative solutions to societal problems. Its research arms include: 1) sustainable bioproduction, 2) synthetic genomics, and 3) therapeutics. Sustainable bioproduction: By harnessing natural biocatalysts, industrially valuable products can be synthesized from renewable feedstocks. At the Chang Lab, we aim to develop sustainable bioproduction processes by engineering microbial hosts, enzymes, or pathways, and repurposing novel microbial strains. Synthetic genomics: Though it sounds like science fiction, organisms can be customized by redesigning their genomes. Called synthetic genomics, these techniques allow researchers to better understand biological functions and design biological systems. Currently, we are part of an international initiative to assemble the first eukaryotic synthetic genome. Future projects will expand these efforts by applying synthetic genomics to complex mammalian cells. Therapeutics: Found within our bodies is a delicate microbial ecosystem, with disruptions linked to disease. To prevent and treat these conditions, we are developing novel techniques that rewire our interactions with our bodies' resident microbes. Ongoing projects include producing live biotherapeutics targeted against specific diseases and engineering genetic systems for diagnostics.
Dr Julius Fredens Email	**Engineering and evolution of bacteriophages for DNA delivery**

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Gene therapy holds great promises for the future of medicine by enabling precise manipulation of the genetic material in patients and cells. Besides correcting defective genes, new functionalities can be introduced to (i) reprogramme immune cells against cancer (CAR-T therapy), (ii) create immunity through DNA/RNA-based vaccines, and (iii) counteract natural processes such as ageing. These revolutionising therapies depend on efficient, targeted delivery of custom DNA. Mammalian viruses and lipid nano particles (LNP) are the dominant vehicles for DNA delivery despite their inability to carry more than 10 kb of DNA. This size limitation is becoming a bottleneck as more elaborate constructs and gene circuits are required for the field to unlock its full potential. Unlike mammalian viruses and LNPs, bacteriophages transport much larger DNA and specifically recognise their host, making phages promising candidates as spacious, robust, and genetically inert vehicles. We have recently established techniques to i) efficiently engineer large phage genomes in vivo or cell-free, and ii) control phage packaging of custom DNA. In this project we will engineer the phage tail fibres in an attempt to programme the phage to target a specific cell. This will allow programmable DNA delivery to specific bacteria, and serve as the first important step towards targeting specific human cells for gene therapy.

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Engineering Red Blood Cells as therapeutic cargos.

Red blood cells (RBC) possess many advantages to being ideal cargos for a wide range of payloads. We developed the first-generation RBC therapy using hematopoietic stem cells (HSC). This technology leads to a publicly listed company on NASDAQ. Then we develop the second-generation RBC therapy using mature RBCs. The engineering RBCs could carry different therapeutic proteins on the surface against different diseases. Here we will engineer RBCs for cancer therapy. Particularly, we will engineer RBCs to carry 41BBL, IL12, IL15, and other ligands belonging to the TNF family. The engineered RBCs should simulate the activation and proliferation of T cells, NK cells, and other immune cells in vivo for cancer therapy. Moreover, we will engineer RBCs with MHC-1 complex with tumor-specific antigen, and other T cell simulation cytokines. These engineered RBCs will simulate the activation and proliferation of T cells with tumor-specificity. Our engineered RBC platform will be the off-the-shelf and allogeneic cell therapy against cancers.

Principal Investigator	Project Title with a brief description
Dr Chester Lee Drum Email **MDCCLD@nus.edu.sg** Telephone Number **83183106**	**Synthetic Biology of Translational Therapeutics: Chemical synthesis of complex biologicals** This project will include a select graduate in a paradigm changing project, which will create new therapeutic biologicals from synthetic chemistry. The opportunities are endless and the project is supported by 2 new grants from ASTAR and the NMRC. This project will give the student a chance to not only learn the science, but also interact with multiple pharmaceutical and cultured meat industrial partners for implementation of the project discoveries. You will join a team using a novel form of nanoparticle invented at NUS (Nature Comms, PMID: 29129910) to create protein folding dynamics and novel cellular uptake mechanisms for drug delivery. The project is a continuation of research begun at Massachusetts Institute of Technology and will create previously unproducable therapeutic solutions. Prof. Drum was clinically trained at BWH, Harvard Med School and the team is composed of enthusiastic and highly talented scientists with deep experience in commercialization and technology development. Expected outputs for the student will be at least one patent filing and 3-4 publications and you can expect to work closely with world experts in the field.

Translational Research Program of PI: Immunology

Department of Biochemistry

Principal Investigator	Project Title with a brief description
Assoc Prof Nguyen Nam Long Email **BCHNNL@nus.edu.sg** Telephone Number **98238253**	**Harnessing sphingosine-1-phosphate transport for the treatment of inflammatory diseases** 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.

Mechanistic transports of lysolipids in the lysosomes

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 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 recyles 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.

The roles of the blood brain barrier Mfsd7c for CNS vascular health and brain functions

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 MFDS7C 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.

Department of Physiology

Principal Investigator	**Project Title with a brief description**
Assoc Prof Lim Hsiu Kim, Lina Email **PHSLHKL@nus.edu.sg** Telephone Number **91915100**	**Regulation of DNA sensing and recognition in cancer through cGas/STING and Annexin-A1** 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. **Vaccination and preexposure to COVID19 and susceptibility to influenza** 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 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.

Translational Research Program of PI: Precision Medicine

Department of Biochemistry

Principal Investigator	Project Title with a brief description
Dr Federico Tesio Torta Email **BCHFDTT@nus.edu.sg** Telephone Number **91807912**	**Human plasma lipidomics** The student, during a 3 weeks rotation project, will first learn the fundamentals of mass spectrometry lipidomics through reading literature, attending presentations and meetings with current members of the lab. In her second and third week the student will analysed under supervision aliquots of commercial samples and perform data analysis to understand where the differences in the lipid content of the samples might be and what could be the reasons. This will cover the student's data interpretation skills and will give a flavour of what the daily activity in our lab might be.

Dr Teo Kee Keong Adrian	**Human in vitro models for studying diabetes disease mechanisms**
Email **BCHTKKA@nus.edu.sg** Telephone Number **65869641**	This project involves the use of human pluripotent stem cells (hPSCs), human islets and human beta cell line to investigate diabetes disease mechanisms. The student can expect to be exposed to methods/skills such as hPSC/human islet/human beta cell cultures, gene knock down and overexpression, manipulation of signalling pathways and numerous other modern molecular techniques. The student is expected to be highly motivated, read the literature extensively, gain in-depth knowledge on the research topic, master basic molecular biology techniques quickly and carry out experiments with guidance/mentorship. It will be ideal if the student has had some prior research experience. A major focus of my laboratory is the appropriate and dedicated mentoring of trainees in the laboratory. This pertains to a considerable amount of one-to-one time each week, direct hands on training in the laboratory on one or more research projects and intensive scientific communication through monthly journal clubs and weekly laboratory meetings. PhD students can expect to be extremely well-versed in the field of Stem Cells and Diabetes as long as he/she takes advantage of the training environment painstakingly developed by myself for the student. The student is also encouraged to read up on the Stem Cells and Diabetes Laboratory (http://www.adrianteolab.com/) to find out more about our research.

Department of Medicine

Principal Investigator	**Project Title with a brief description**
Dr Chester Lee Drum Email **MDCCLD@nus.edu.sg** Telephone Number **83183106**	**Biomarker discovery for precision medicine and patient health using advanced analytics and multiplex mass spectrometry.** Redox chemistry is involved in literally every reaction that transfers an electron. The term oxidative-stress, refers to an imbalance in reductive potential for reactions that have a relevance to human biology and clinical outcomes. Despite the near universal acceptance that oxidative stress plays a fundamental role in aging, carcinogenesis and cardiovascular disease, a clinically actionable marker of oxidative stress remains to be discovered. We use mass spectrometry of known pathways, oxidatively modified substrates and precursor - product ratios to determine personalized signatures of oxidative stress in our collected patient cohorts. The goal of the project is to discover and characterize a biomarker that can be monitored in clinical use that guides the selection and dosage of anti-

oxidant therapies. With success, the impact of this project can reshape the fields of nutrition and pharmaceutical science. This project has already resulted in multiple small molecules that are entering clinical trials to improve clinical care. The combination of patient information, high precision mass spectrometry and basic informatics is a superby training environment for graduate work and a high impact thesis.

Computational Deep Phenotyping for Clinical Risk Prediction and Discovery for New Uses of Old Drugs

Deep phenotyping technologies such as genetic sequencing, RNAseq and mass spectrometry are creating ultra-dense datasets that describe the full biology of our patients. Yet, with this resource comes a problem: the mass of information requires novel computational techniques to match multidimensional datasets to real-world clinical questions and outcomes. Working with bioinformaticians, clinicians and large healthcare data sets, you will create novel algorithms to identify at-risk patients across multiple disease types and identify those who will benefit from precision treatments. You will be listed as an official member of the ethics approval and work with patient data to improve medical outcomes. Valuable skills will be a basic understanding of either scripting languages (R, python) or coding skills (Java, etc) and biostatistics. A particular focus of this project is the development of novel techniques to phenotype drug response in patients adn create a new algirthm to guide prescription of common outpatient medicines.

Translational Research Program of PI: Nanomedicine

Department of Diagnostic Radiology

Principal Investigator	Project Title with a brief description
Dr Ni Qianqian Email **QQIAN.NI@nus.edu.sg** Telephone Number **84395324**	**Coordinated mRNA-Mn2+ nanovaccine for STING-mediated cancer immunotherapy** Specific aims: Emerging evidence has demonstrated the potential of mRNA for the treatment of infectious diseases as well as cancers. While promising, the clinical translation of mRNA cancer vaccines encounters a few challenges including limited therapeutic efficacy. In our project, we propose to elaborate the reliability of combination of mRNA vaccine with manganese ion (Mn2+) which serves as novel STING agonist to potentiate the antigen-specific personalized cancer immunotherapy. Overall, our project proposes a new immunotherapeutic strategy by generating mRNA-Mn2+

hybrids based nanovaccine and will improve the understanding of structural optimizations of mRNA and the potential of combination of mRNA vaccine with Mn2+ mediated metalloimmunology. Hypothesis: We hypothesize that mRNA encoding protein/peptide cancer vaccines combined with metalloimmunology through coordination of mRNA with Mn2+ will offer a new cancer immunotherapy strategy. In preliminary studies, mRNA-Mn2+ self-assembled particles significantly enhanced mRNA translation which is presumably due to the reduced formation of ds-mRNA, indicating that the coordinated mRNA-Mn2+ nanoparticles will overcome the current challenges of ds-mRNA contaminant that hinders effective translation of mRNA delivered. A library of ionizable lipids will be constructed to screen the appropriate LNP components to improve binding affinity of mRNA-Mn2+ to LNPs and augment STING-activation properties. Methodology and approach: We propose to develop mRNA-Mn2+ coordinated nanoparticles that are encapsulated inside LNPs with tunable ionizable lipids to achieve robust anti-tumoral immunity. Briefly, the coordination of mRNA and Mn2+ will be conducted followed by characterizations. Then, we will screen various ionizable lipids to construct mRNA-Mn2+ LNP nanoformulas. Binding affinity and translation efficiency will be evaluated to optimize the most suitable formulas. Using model antigens, therapeutic efficacy of mRNA-Mn2+ nanovaccine and the underlying mechanisms involved in immune regulation will be performed.

Design of nucleic acid immune agonist delivery platform technology to elicit potent and safe anti-tumor immunity

The past decades have witnessed rapid and exciting progress in immune-oncology. Nucleic acids (CpG, dsRNA, cGAS etc) represent a key family of immune agonists in pattern recognition receptors (PRRs) mediated cancer immunotherapy. However, clinical translation of nucleic acid immune agonists is hampered by the suboptimal therapeutic efficacy, inefficient delivery to dendritic cells (DCs) and limited biostability. In this proposal, a novel nucleic acid delivery platform will be developed to improve Toll like receptor 9 (TLR9) agonist cancer immunotherapy, spanning TLR9 agonist screening, self-assembly DNA nanotechnology for DC targeted delivery and combining TLR9 agonist with radiation therapy for synergistic cancer therapy. The central hypothesis of this proposal is that the immune agonist delivery platform will enable potent and safe anti-tumor immunity and synergistically sensitize cancer radiation therapy. Specific aim 1: To develop a nucleic acid nanoplatform for targeted TLR9 agonist delivery Hypothesis: Structure optimization and surface modification of DNA delivery system will improve the potency of TLR9 agonist. In our preliminary study, a tailor designed nanoplatform was

developed with higher stability and improved DNA delivery over unmodified DNAs. The current proposal aims to continue this effort and develop a novel and highly viable platform technology to screen new and high-quality immune agonists and construct a safer and more effective platform for precise DC targeted delivery. Specific aim 2: To evaluate the safety, efficacy, and mechanism of synergy between TLR9 agonist and radiation therapy Hypothesis: The combination of immune agonist with radiation therapy will enable synergistic effect by improving the immunogenicity and reshaping immunosuppressive microenvironment. We anticipate that nucleic acid delivery system will enhance the potency of TLR9 agonists and synergize with conventional radiation therapy. The synergy between TLR9 agonist and radiation therapy will be a novel therapeutic strategy in cancer therapy and enhance the clinical translational relevance of the proposed studies.

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Radiotheranostics

Radiotheranostics is the combination of disease-specific molecular imaging followed by radionuclide therapy. Radionuclide theranostics for precision oncology is being driven by rapid advances in novel diagnostics and therapeutic interventions, with dramatically expanded radiopharmaceuticals toolbox over the last few years. The obvious benefits and medical demand naturally drive its further development, supported by the breakthroughs in cancer biology discovery; the technological advances associated with e.g., PET and SPECT molecular imaging; the more widely distributed production of diagnostic and therapeutic isotopes; and a more robust production and regulation system for radiopharmaceuticals. Prostate-specific membrane antigen (PSMA) and somatostatin receptor (SSTR) targeting radiopharmaceuticals for prostate cancer and neuroendocrine cancers, respectively, are well-known cancer targets, and promising new targets like the prolyl peptidase fibroblast activation protein (FAP) expressed in the tumor microenvironment in various tumor types, have also gained attraction. One of our project aims to explore a theranostic pair of 68Ga radiolabeled FAP-targeted PET/CT or PET/MRI imaging, followed by the beta-particle emitter 177Lu and alpha-particle emitter 225Ac labeled FAP-binding derivatives for targeted radionuclide therapy, as well as the combination with immunotherapy, to explore a precise and individualized FAP-targeted radionuclide theranostic system in various cancer types. Altogether, the ecology of radiotheranostics continues to expand, making it possible for researchers to exploit new isotopes, search for new targets, conceptualize and design new drugs; other potential strategies include but are not limited to radiosensitization by inhibition of DNA repair, targeted alpha therapy, combining radioligand

	therapy and immune checkpoint inhibitors, combining radioligand therapy and other systemic therapies.

Translational Research Program of PI: Do not belong to any TRP

Department of Obstetrics & Gynaecology

Principal Investigator	Project Title with a brief description
Assoc Prof Citra Nurfarah Zaini Mattar Email **OBGCNZM@nus.edu.sg** Telephone Number **91184294**	**Novel precision gene editing technologies for treating hemoglobinopathies using humanized mouse models** ß-hemoglobinopathies are hereditary single gene disorders, with ~ 300 mutations in the human ß-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 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 ß-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)

Department of Orthopaedic Surgery

Principal Investigator	Project Title with a brief description
Assoc Prof Toh Wei Seong Email **TOHWS@nus.edu.sg**	**Development of cell membrane nanotherapeutics for osteoarthritis** Osteoarthritis (OA) is a chronic degenerative joint disorder associated with pain and inflammation and is the leading cause

Telephone Number **67723327**	of disability worldwide. Owing to the complexity of OA inflammation driven by a plethora of inflammatory cytokines, current specific anti-cytokine therapies have not been successful. In our preliminary studies, we used cell membranes derived from macrophages to coat nanoparticles and presented these nanosized entities to an OA inflammatory microenvironment. We demonstrated their use as viable and effective broad-spectrum anti-inflammatory agents. Specifically, we generated nanoparticles coated with membranes derived from different macrophage subsets, namely naïve (M0), pro-inflammatory (M1) and anti-inflammatory (M2) macrophages. Amongst all, M2 macrophage membrane-coated nanoparticles had the highest potency in binding inflammatory cytokines, IL1ß and TNFa, and suppressing IL1ß-induced nitric oxide production and matrix degradation in chondrocytes and cartilage explants. As the onset of inflammation in OA is preceded by the activation of innate immune cells, deciphering the profile of innate immune cells and their activities during OA would allow us to rationally design immune cell membrane nanoparticles for effective OA treatment. It is therefore hypothesized that by deciphering the cell membrane profile of innate immune cells activated during OA, immune cell membrane coated nanoparticles can be rationally designed and engineered for broad spectral capture of inflammatory mediators to reduce OA inflammation and promote joint repair. In this project, student will learn to design immune cell membrane-coated nanoparticles and hybrids based on the profile of innate immune cells activated during OA, and characterize their physicochemical and functional properties, towards developing optimal cell membrane therapeutic for osteoarthritis.

Department of Paediatrics

Principal Investigator	**Project Title with a brief description**
Prof Yap Hui Kim Email **PAEYAPHK@nus.edu.sg** Telephone Number **96751552**	**Advanced interpretation of variants of unknown significance in genetic kidney diseases using innovative functional studies** 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 PrecIsion 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 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.

Genetic variant landscape and kidney disease risks in the Singaporean population

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 severe 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.