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

Translational Research Program of PI: Cardiovascular Disease

Department of Dean's Office (Medicine)

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).
Dr Roshni Rebecca Singaraja Email **MDCRRS@nus.edu.sg** Telephone Number **92334856**	**Exosomes as a communication channel in the liver-heart axis** Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in Western countries and affects ~25% of the adult population. Patients with NAFLD are at substantial risk for increased cardiovascular disease. Interactions between fatty liver disease (FLD), central obesity, insulin resistance and cardiovascular disease (CVD) phenotypes are thus far not systematically characterised. Extracellular vesicles (EVs) are nanosized vesicles with a lipid bilayer that are released from different cells, and are considered important mediators of intercellular and extracellular communications. EVs carry a variety of molecules including RNAs, proteins, and lipids. EVs are implicated in the pathogenesis of CVD and MI, and have been shown to reduce vascular dysfunction. We hypothesize that increased CVD in NAFLD is modulated in part via the signalling by liver-derived exosomes on cardiometabolic tissues. As part of a ~$25 million funded project to study the liver-heart axis (Project RESET), we are recruiting 3000 Singaporean subjects who are undergoing deep clinical phenotyping of the liver and cardiovascular system. In addition,

	blood is being collected and banked for exosome isolation. Using exosomes isolated from those with NAFLD alone, those with NAFLD + CVD, and non-diseased controls, we plan to perform microRNA profiling (MiRXES), transcriptomic profiling and metabolomic profiling to identify differentially enriched exosome cargo. As well, we will expose vascular smooth muscle, macrophage and endothelial cells to exosomes and assess CVD phenotypes. The student will gain expertise in human translational studies, OMICs, extracellular vesicles and inter organ communication, as well as gain a deep knowledge of cardiovascular and metabolic diseases. In addition, the student will establish and manage collaborations, including with clinicians and international scientists, attend and present at national/international conferences, and be part of the cardiovascular research institute (CVRI), a vibrant centre with clinicians and scientists.
	The liver-heart axis: Impact of bile acids on cardiovascular disease Cardiovascular diseases are the leading cause of death worldwide, indicating that current therapies are not sufficient to prevent or reduce these devastating diseases. Using "deep DNA sequencing", we identified mutations in a bile acid synthesis gene in humans that reduce LDL cholesterol ("bad cholesterol"), and increases HDL cholesterol ("good cholesterol"). This suggests that cardiovascular disease may be reduced in the mutation carriers. In agreement, in our preliminary data, we find that the altered bile acid profile in these mutation carriers associates with reduced myocardial infarct (heart attacks). These exciting preliminary data suggest that inhibiting this bile acid synthesis gene may be a drug target to protect against cardiovascular diseases in humans. We have also replicated these studies in mice. These findings are unpublished, and would be included in, and form the basis of your PhD thesis, identifying mechanisms by which alterations in bile acids protect against cardiovascular disease, linking liver-derived bile acids with cardiovascular function. The student will gain expertise in human genetics/genomics, mouse models of cardiovascular disease (including microsurgery techniques taught by a clinical cardiovascular surgeon), primary and iPS cell culture, genome editing (CRISPR-Cas9), transcriptomics, as well as in BA, lipid and glucose metabolism. In addition, the student will establish and manage collaborations, including with clinicians and international scientists, attend and present at national/international conferences, and be part of the cardiovascular research institute (CVRI), a vibrant centre with clinicians and scientists. We previously found that humans with mutations in this bile acid

	gene have improved diabetes, and reduced liver fat. This PhD project will add to the protective effects of the altered bile acids also on cardiovascular disease, with its exciting clinical implications.
Dr Sun Zhe Email **HT.SUN@nus.edu.sg** Telephone Number **86155606**	**Understanding environmental impacts on perinatal and childhood cardiovascular health** Maternal and child health constitutes a fundamental pillar in maintaining population and societal stability, while also emblematic of civilisation level of a nation. Recent epidemiological studies start to suggest that maternal environmental exposures can be significantly associated with pregnancy outcomes. For instance, maternal exposure to air pollution (e.g., PM2.5 and ozone) can increase the occurrence risks of adverse pregnancy outcomes and neonatal defects, and even impede long-term child growth and development; conversely, exposure to green and blue environments has demonstrated protective effects. However, these pertinent observational studies still exhibit considerable scope for enhancement in methodological rigour and population coverage, and also are deficient in explorations from pathophysiological and aetiological standpoints. In light of these considerations, our HAITONG (Health Associated Integrated Traverse of Nature and Geoscience) Lab will conduct systematic epidemiological analyses, based on two well-established Singaporean cohorts, as the GUSTO (Growing Up in Singapore Towards Healthy Outcomes) and S-PRESTO (Singapore Preconception Study of Long-Term Maternal and Child Outcomes), in collaboration with parallel cohorts in other countries, such as the ZEBRA (Zhejiang Environmental and Birth Health Research Alliance) maternity cohort with 150,000 participants recruited during 2013-2023. Research will primarily focus on environmental tracking database establishment, real-time personal exposure tracing, maternal exposure tracing and perinatal risk association assessment, epigenetic-level perinatal risk factor screening, biomarker-level perinatal risk factor screening, establishment of an early-stage risk forecasting system and policy guidance. Two main hypotheses will be tested: 1) maternal environmental exposures prior to (preconceptional) and during pregnancy (gestational) can affect maternal metabolism and cardiovascular function, thereby impacting pregnancy outcomes; and 2) maternal environmental exposures can affect foetal intrauterine development, thereby influencing the neonatal congenital health status at birth.
Department of Medicine	

Principal Investigator	Project Title with a brief description
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.
Department of Paediatrics	
Principal Investigator	**Project Title with a brief description**

Assoc Prof Heng Chew Kiat Email **PAEHCK@nus.edu.sg** Telephone Number **67723354**	**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.
Prof Zhang Yang Email **zhang@nus.edu.sg** Telephone Number **66011241**	**AI-based protein design and drug discovery** Proteins in nature are created following hundreds of millions of years of evolution and therefore possess limited structural folds and biological functions. Computational protein design aims to design and engineer new protein sequences with novel structure and function significantly beyond nature proteins. Given their potential to create new function and change cellular pathways, computationally designed proteins and peptides can be used as

	drugs to treat pharmaceutically important human diseases such as cancers and Alzhelmer's diseases. In this project, we will develop new artificial intelligence (AI) and deep machine learning approaches for high-accuracy de novo protein and peptide designs. The utilized AI techniques, including transformer networks, protein language and diffusion models, will be integrated with physics-based and evolutionary profile simulations for accurately designing and engineering new proteins and short peptides. Although the current start-of-the-art methods have been successful in designing a variety of functional proteins, there have not yet been a computationally designed protein entering Phase-III clinical trials. Designing the first protein-based clinically effective drug thus represents the 'Holy Grail' of computational protein and peptide design, which is also the general aim of this project. References: (1) R Pearce, X Huang, D Setiawan, Y Zhang. EvoDesign: Designing protein-protein binding interactions using evolutionary interface profiles in conjunction with an optimized physical energy function. J Mol Biol, 431: 2467-2476 (2019). (2) D Shultis, P Mitra, X Huang, J Johnson, NA Khattak, F Gray, C Piper, J Czajka, L Hansen, B Wan, K Chinnaswamy, L Liu, M Wang, J Pan, J Stuckey, T Cierpicki, CH Borchers, S Wang, M Lei, Y Zhang. Changing the Apoptosis Pathway through Evolutionary Protein Design. J Mol Biol, 431: 825-841 (2019). (3) R Pearce, X Huang, GS Omenn, Y Zhang. De novo protein fold design through sequence-independent fragment assembly simulations. PNAS, 120: e2208275120 (2023).

Department of Dean's Office (Medicine)

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.
Dr Anthony Khong Email **KHONGA@nus.edu.sg** Telephone Number **90850074**	**Dissecting the Role of Mutant DDX3X Persistent Stress Granules in Cancer Biology** Are you fascinated by how molecular mechanisms contribute to cancer? Do you want to be at the forefront of discovering new therapeutic targets? Our lab aims to uncover the enigmatic role of DDX3X mutant stress granules in cancer biology, and we're seeking passionate graduate students to join us! DDX3X is a helicase frequently altered in cancers like leukemia, lymphoma, and breast carcinoma. High expression and mutations in DDX3X drive tumorigenesis and promote persistent stress granules—non-membranous RNA-protein aggregates found in patient biopsies. However, their role in cancer progression remains unclear. I am a new assistant professor at the Cancer Science Institute of Singapore and the Department of Physiology. My previous research has advanced our understanding of stress granules induced by oxidative stress by describing its composition (Khong et al., 2017, Molecular Cell). Our team established that stress granules are RNA aggregates. We now aim to uncover how DDX3X mutations enhance RNA aggregation and stress granule formation, potentially driving cancer hallmarks. By dissecting the assembly and functions of DDX3X stress granules, we hope to reveal new insights into DDX3X-related cancers and develop innovative therapeutic strategies. In our lab, you'll engage in cutting-edge research to elucidate DDX3X stress granules through three key approaches: 1. Blocking Stress Granule Assembly: We'll use a specific inhibitor to study how blocking these granules affects gene expression via RNA sequencing, Ribo-seq, and Timelapse-seq. 2. Analyzing Stress Granule Composition: We'll dissect the transcriptome and proteome of DDX3X stress granules using a FACS-sorting method to understand their molecular makeup. 3. Investigating Tumorigenesis: Through cell-based assays, organoid models, and mouse models, we'll explore how DDX3X stress granules drive tumor development. This is a unique opportunity to dive into cancer biology and contribute to

	groundbreaking discoveries. If you're interested, please reach out to me at khonga@nus.edu.sg. Thank you!
Prof Zhang Yang Email **zhang@nus.edu.sg** Telephone Number **66011241**	**AI-based protein and RNA structure prediction** Protein and RNA are two types of most important molecules in life. While proteins are 'workhorse' molecules carrying out most biological activities of living organisms, RNAs are recently found performing critical cellular functions. Because biological functions of proteins and RNAs are specified by their spatial shape, determination of the 3D structure is essential to annotate their biological functions and to develop new drugs to regulate their functional roles. There are by now 230/31 millions of proteins/RNAs with known sequences; but less than 0.1% of them have structures solved experimentally in the PDB. Therefore, computer-based structure prediction is the only means to alleviate the gap and high demanding of protein/RNA structures by the biomedical community. The past decade has witnessed revolutionary progress of the field due to the introduction of artificial intelligence (AI) and deep learning techniques initiated by the PI and other laboratories. But the advancements occur mainly in single-domain proteins, where state-of-the-art programs, such as AlphaFold and I-TASSER, still have difficulties in multi-domain and multi-chain quaternary protein structure prediction. In this project, we will develop new AI and deep-learning methods for protein and RNA structure predictions. Specifically, cutting-edge AI techniques will be integrated with cryo-EM density maps and I-TASSER folding simulations for large-size protein-protein complex structure determinations. The methods will also be extended for structure modeling of RNAs which have been increasingly recognized with important biological function and drug design potential. The developed methods will be stringently tested in the biennial world-wide CASP experiments, also called Olympic Games of computational structure biology, compared to the state of the art of the field. References: (1) W Zheng et al. Nature Methods, https://doi.org/10.1038/s41592-023-02130-4 (2024). (2) Y Li et al. Nature Communications, 14: 5745 (2023).
Department of Physiology	
Principal Investigator	**Project Title with a brief description**
Dr Tee Wee Wei	**Identifying epigenetic drivers of therapeutic resistance in cancer**

Email **PHSTEE@nus.edu.sg** Telephone Number **65869642**	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 Dean's Office (Medicine)

Principal Investigator	Project Title with a brief description
Assoc Prof Thai Tran Email **PHSTT@nus.edu.sg** Telephone Number **65163663**	**The Academic Respiratory Initiative for Pulmonary Health (TARIPH) – Role of Glucocorticoids in asthma and COPD** This project is funded under the NMRC-Large Collaborative Grant and the potential candidate will be involved in multidisciplinary and collaborative efforts of The Academic Respiratory Initiative for Pulmonary Health (TARIPH). Chronic respiratory disease has unique features in Asians, including inflammatory patterns and corticosteroid resistance (CR). To better understand disease pathogenesis, individual heterogeneity and address precision-based therapeutics, a need for representative, accessible and patient-specific model systems exist. Cutting-edge cell culture techniques have emerged, including organoid technologies and organ-on-chip models that allow the study of lung development, regeneration, and disease. The Global Initiative for Asthma (GINA) Global Burden of Disease Report ranks Singapore as an intermediate risk country for asthma prevalence, however, importantly a high-risk country for asthma-related death, redolent that unique

	endophenotypic features exist in Singaporean asthmatics and potentially across the Asian sub-continent warranting detailed exploration. In a survey of 2,467 asthmatics across 8 Asian countries, including Singapore, 90% reported perceived asthma control, however, 73% experienced one or more exacerbations in the preceding year. Corticosteroid therapy remains first-line for controlling airway inflammation in asthma and preventing exacerbations, and in the majority, remains clinically efficacious. Importantly, up to 10% poorly respond to corticosteroids and are termed' corticosteroid resistant (CR). CR-asthma affects up to 7% of Singaporeans, with a growing number taking large doses of OCS inappropriately, and in some cases, without a doctor's prescription. Various cellular and molecular events underlie CR and, relate to immunologic dysregulation, genetic, and environmental factors, however, a key knowledge gap in explaining the significant burden of CR among Asians remains to be fully understood, especially in the context of Asian genetics, immunology, inflammation and environment. To better understand disease pathogenesis, individual heterogeneity, and precision-based therapeutics, including CR, representative, accessible, and patient-specific model systems are necessary.
Department of Physiology	
Principal Investigator	**Project Title with a brief description**
	Role of CD151 in influenza virus infections 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 Dean's Office (Medicine)	
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

Department of Obstetrics & Gynaecology

Principal Investigator	**Project Title with a brief description**
Assoc Prof Chan Shiao-Yng Email **OBGCHAN@nus.edu.sg** Telephone Number **67722672**	**Investigating the role of vitamins in preventing preterm birth** Preterm prelabour rupture of fetal membranes (PPROM) is a major contributor to approximately one third of all preterm births, which results in higher risk of infant mortality and morbidity. 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.

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.
Department of Dean's Office (Medicine)	
Principal Investigator	**Project Title with a brief description**
Assoc Prof Christopher Chen Li Hsian	**Blood markers for Cognitive Impairment and Dementia**

Email **PHCCCLH@nus.edu.sg** Telephone Number **81253628**	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.
Dr Crasta Karen Carmelina Email **PHSCRAS@nus.edu.sg** Telephone Number **98432749**	**Elucidating mechanisms underlying cancer-related stroke (CRS), an emerging subtype of ischemic stroke in the elderly** One of the Phd Mentor's favourite book is "Consilience" by E.O. Wilson. Consilience describes synthesis of knowledge from different specialized fields of human endeavor. This projects epitomises this and brings the fields of oncology and neurology together. Our lab seeks to understand mechanisms underlying systemic impact of cancer on the human body for disease prevention. This project deals with cancer-related stroke (CRS), an emerging subtype of ischemic stroke with unique pathomechanisms. Notably, Cancer patients are at three times higher risk than the general population in developing stroke! However, knowledge regarding molecular mechanisms underlying cancer-related stroke is scant, highlighting an unmet need. As survival rates of cancer patients increase, it becomes crucial to identify older cancer survivors at elevated risk of stroke. This overarching goal of the project is to determine impact of tumour secretome on vascularisation and coagulation, as well as other novel pathways that engender CRS. The student will utilise an "omics" approach coupled with cutting-edge cell biology tools. He/she will be immersed in an intellectually-stimulating lab environment at the Centre for Healthy Longevity, and will work closely with clinical collaborators at

	NUH (Drs Leonard Yeo, Sia Ching Hui, Andrea Wong), and Prof Han Weping at A*STAR. For more information: crastalab.com
	Membrane damage and inflammation in therapy resistance. Cellular senescence results in a stable cell cycle arrest. Its secretome termed senescence-associated secretory phenotype (SASP), can influence the microenvironment via paracrine action. Senescent cells confer beneficial effects on organismal physiology such as embryogenesis and wound healing. However, the accumulation of senescent cells can contribute to aging and age-related disease. Emerging efforts seek to manipulate senescent cells in a bid improve healthy aging. Our lab has contributed important findings to the field of senescence, with implications for cancer and aging. While senescence can be caused by telomere shortening, dna damage, oncogene activation, chemotherapy etc, plasma membrane damage has recently been identified as a senescence trigger. We will assess whether molecular players that mediate plasma membrane rupture influence phenotypic outcomes of membrane damage-induced senescence. This is a collaboration between Dr. Karen Crasta and Dr. Kaiwen Chen.
	Plasma membrane integrity and senescence in the aging heart Cellular senescence results in a stable cell cycle arrest. Its secretome termed senescence-associated secretory phenotype (SASP), can influence the microenvironment via paracrine action. Senescent cells confer beneficial effects on organismal physiology such as embryogenesis and wound healing. However, the accumulation of senescent cells can contribute to aging and age-related disease. Emerging efforts seek to manipulate senescent cells in a bid improve healthy aging. Our lab has contributed important findings to the field of senescence, with implications for cancer and aging. While senescence can be caused by telomere shortening, dna damage, oncogene activation, chemotherapy etc, plasma membrane damage has recently been identified as a senescene trigger. Membrane damage plays an important role in the pathogenesis of ischemic damage to the myocardium and has implications for cardiac dysfunction. We hypothesise that plasma membrane damage-induced senescence can contribute to cardiac failure. The overarching goal of this project is to elucidate mechanistic pathways, biophysical changes and the cell biology underlying alterations in membrane integrity that can contribute to cardiac dysfunction using cutting-edge tools. This project is in collaboration with Prof Roger Foo, NUS and Prof Keiko Kono

	at OIST, Japan. Opportunity for short-term research internship in Japan available. For more information: crastalab.com
	Role of stress granules in therapy resistance Triple-negative breast cancers lacking targets such as estrogen (ER) and progesterone receptor (PR) expression, and Her2 overexpression, account for the worst prognosis among all breast cancer subtypes. Our lab has shown that therapy-induced senescence (TIS) in TNBCs can lead to chemoresistance. Paradoxically, we have shown that the senescence state alters the tumour secretome to drive migration, invasion and angiogenesis. However, the mechanisms underlying this remains poorly understand. Stress granules are thought to contribute to cell cycle exit. This project aims to examine the role of stress granules and other biomolecular condensates in influencing phenotypic outcomes engendered by TIS. It is a collaboration between Dr. Karen Crasta's lab and Dr. Anthony Khong's lab.
Assoc Prof Saji Kumar Sreedharan Email **PHSSKS@nus.edu.sg** Telephone Number **65165886**	**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
Dr Tsai Shih-Yin Email **PHSTS@nus.edu.sg** Telephone Number **65167617**	**Bioengineering: Identification of translational control in remodeling skeletal muscle microenvironment.** Activation of 4EBP1 in fully differentiated muscle fibers not only retains skeletal muscle functions with age but also cell-nonautonomously increases the number of functional muscle stem cell (MuSCs) and augments neuromuscular synaptic transmission (Ang et al., Nat Commun. 2022). Yet, how a repressor of cap-dependent translation, 4EBP1, preserves muscle functions with age and how 4EBP1-activated myofibers enhance the activities of MuSCs and motor neurons in a cell-

	nonautonomous manner remains unclear. To address the knowledge gap, we will employ 3D muscle-motor neuron-MuSCs co-culture systems to further dissect the action of 4EBP1 in regulating the muscle microenvironment. Our collaborative publication with Prof. Shen Han Ming demonstrated that impaired autophagy leads to an increase in mitochondria secretion, which may activate adaptive immunity (Tan et al., Nat Commun. 2022). In line with this, our preliminary analysis revealed an accumulation of immune cells in the muscle tissue of TSC1mKO mice. Additionally, we will incorporate lymphocytes obtained from various strains of transgenic mice into our research. By using the remodified 3D co-culture systems, we expect to establish mTORC1-4EBP1 as a novel therapeutic target in muscle aging and identify the underlying mechanisms integrated through altered mTORC1-4EBP1 signaling for muscle health. The funding for this part of the project was recently granted by MOE Tier 2 (T2EP30223-0010) in 2024. Another unexpected finding from our in vivo aging study is a sex-dependent change in NMJ remodeling during aging. Male mice that are aging experience a greater level of denervation and fragmentation of AChR compared to their female counterparts. The sex difference in NMJ remodeling will be explored through the use of our newly established 3D culture in the lab and our in vivo aging mouse cohorts.
	Cell Biology: Investigate the regulatory pathways that connect protein synthesis and degradation in skeletal muscle Postmitotic skeletal muscle relies heavily on effective and tightly regulated protein degradation to maintain its proteome stability. Impaired autophagy-lysosomal or ubiquitin-proteasomal protein degradation causes the accumulation of damaged proteins, ultimately accelerating muscle dysfunction with age. Our recent publication revealed that restricting cap-dependent translation through overexpression of the dominant active form of 4EBP1 expands lysosomal-degradation capacity without relieving mTORC1-mediated inhibition of autophagy. Along with its lysosomal-degradation capacity we also finds that activating 4EBP1 in skeletal muscles increases ubiquitin-proteasomal protein degradation. Our goal is to pinpoint the translational targets that control the increased capacity for protein degradation in skeletal muscle.
	Task for healthy longevity: Uncovering the diverging mechanisms responsible for aging in the skeletal and cardiac muscles. During the aging process, skeletal muscle experiences atrophy,

	yet cardiac muscle undergoes reactive hypertrophy in response to a continuous loss of myocytes in the heart. Ultimately, the morphological changes in skeletal and cardiac muscles are both accompanied by reduced contractile function. The uncontrolled proteostasis from mTORC1 hyperactivation have been observed in both aging skeletal and cardiac muscles. Rapamycin treatment alleviated these changes and improved muscle health in both muscle types, indicating that up-regulated mTORC1 signaling drives muscle aging. Together, these data implicate that mTORC1 is indispensable for muscle development, while partial suppression of mTORC1 later in life mitigates muscle aging and preserves muscle health. Yet, the underlying mechanisms of rapamycin-mediated protection from muscle aging remain elusive. It is unclear why mTORC1 hyperactivation leads to an atrophic phenotype in skeletal muscle but a hypertrophic phenotype in cardiac muscle. Our preliminary data show that TSC1mKO mice develop an early onset of cardiac hypertrophy and have a shortened lifespan, confirming the pathophysiological role of constitutive mTORC1 activity in the heart. While it does not prevent mTORC1-induced sarcopenia (Crombie et al., J Cachexia Sarcopenia Muscle. 2022), inactivating muscular S6K1 reduces cardiac hypertrophy in the TSC1mKO mouse background and extends survival. We aim to address the downstream mechanisms by which reduced mTORC1-S6K1 activity promotes healthspan and whether administration of a S6K1 inhibitor can improve muscle functions as a novel treatment for healthy longevity.
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**	**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
Translational Research Program of PI: Immunology	
Department of Biochemistry	
Principal Investigator	**Project Title with a brief description**
Assoc Prof Nguyen Nam Long	**Harnessing sphingosine-1-phosphate transport for the treatment of inflammatory diseases**

Email **BCHNNL@nus.edu.sg** Telephone Number **98238253**	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 Teo Kee Keong Adrian Email **BCHTKKA@nus.edu.sg** Telephone Number **65869641**	**Human in vitro models for studying diabetes disease mechanisms** 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.

Translational Research Program of PI: Nanomedicine

Department of Dean's Office (Medicine)

Principal Investigator	Project Title with a brief description
Dr Ni Qianqian Email **QQIAN.NI@nus.edu.sg**	**Improved Lipid Nanoparticle Technology for mRNA delivery and gene editing** The employment of mRNA and lipid nanoparticle (LNP) technology for systemic delivery of mRNA/gRNA offers

Telephone Number **84395324**	greater flexibility for CRISPR-Cas9 mediated genome editing by averting the drawbacks and potential risks of direct protein or plasmid DNA delivery and allowing for repeated doses. However, there are still some challenges inherent to the mRNA-based approach applied for CRISPR-Cas gene editing: 1) In contrast to mRNA vaccines, where a small amount of mRNA can produce sufficient antigens for body immunization (antigen signals can be effectively amplified via immune systems), CRSPR-Cas9 editing system usually requires hundred fold higher mRNA doses to reach the therapeutic threshold; 2) As liver is the organ of choice when it comes to ease of delivery for lipid nanoparticles, targeting mRNA therapeutics to other solid tissues thus remains a major challenge. To realize the full potential of mRNA technology in CRISPR-Cas9 based gene editing, more advanced in vivo delivery system for precisely targeted delivery especially to extrahepatic tissues, is needed to be developed. Overall, these requirements place greater importance on the efficiency of mRNA delivery to targeted cells and tissues to drive the duration and level of protein expression. This proposal aims to address the current pain in mRNA-based CRISPR-Cas9 gene editing system by 1) enhancing the protein production yield of delivered mRNA, 2) increasing the efficiency of CRISPR-Cas9 based genome editing, and 3) enabling safe and more efficient therapeutic efficacy by precisely targeting extrahepatic tissues.
Dr Zhang JingJing Email **J.ZHANG@nus.edu.sg** Telephone Number **84353534**	**Cancer Theranostics with Molecular Imaging and Targeted Radioligand Therapy in Combination with Immunotherapy in Multiple Types of Cancer** 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 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.