List of research projects available for prospective graduate students

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1.2	**Cardiac Gene Delivery by Enhanced Adeno-associate Virus**
1.3	**Dissection of the Regulatory Pathways for Heart Regeneration and Cardiovascular Disease**
1.4	**Immunology and Nanomedicine in cardiovascular disease**
1.5	**Studying the role of long noncoding RNA in heart disease**
1.6	**Developing Personalized Atrioventricular Heart Valves For Human Implantation: Biomimicry In Design And Testing**
1.7	**The impact of bile acids on vascular function and heart disease**
1.8	**Semaphorin3F in the vascular wall**
1.9	**Modulation of cellular behaviour of ageing cardiomyocytes using amniotic stem cell sesretome**
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2	**Healthy Longevity Translational Research Programme**
2.1	**Longitudinal study of multimodal brain imaging for behavioral prediction in health and neuropsychiatric disease**
2.2	**Mechanisms of Neuronal and Glial Dysfunctions in Aging and Neurodegeneration**
2.3	**Identifying therapeutic targets for skeletal muscle disorders**
2.4	**Elucidating plasticity and cognitive changes in aging and neurodegenerative diseases**
2.5	**Cholinergic mechanisms in different chronic diseased state – divergent roles or a continuum?**
2.6	**Ethics and Regulation of Regenerative Medicine**
2.7	**Task for healthy longevity: Improving aging muscle strength by restoring the communication between the motor neuron and skeletal muscle**
2.8	**Exploring novel RNA-based mitochondrial delivery vectors for mitochondrial targeting of nucleic acids towards mitochondrial gene therapy and for anti-aging**
2.9	**Developing a mitochondrial gene therapy targeting platform – toward mitochondrial gene therapy of LHON**
2.10	**Drug development program: Prenylflavonoids for prevention of menopausal osteoporosis**
2.11	**Integrated Women's Health Program (IWHP): Post-menopausal osteoporosis, fragility fractures and other critical issues facing mid-life Singaporean women**
2.12	**Polycystic ovary syndrome (PCOS)**
2.13	**Neurobehavioral & structural MRI markers for Cognitive Impairment & Dementia**

2.14	**Multimodal MRI-based network breakdown and progression prediction in Cognitive Impairment and Dementia**
2.15	**Retinal markers for Cognitive Impairment and Dementia**
2.16	**Blood markers for Cognitive Impairment and Dementia**
2.17	**The SINgapore GERiatric intervention study to reduce cognitive decline and physical frailty (SINGER) Study**
2.18	**Ionotropic serotonin receptor 5HT3a-R mediated synaptic transmission and plasticity underlying adaptive behaviours.**
2.19	**Investigating the Amygdala – Nucleus Accumbens circuitry mediting motivated behaviours**
2.20	**A role for neutrophin and GABAergic mechanisms in hippocampus in mediation of experimental neuropathic pain?**
2.21	**Sex differences in aging**
2.22	**Mass Up Aging Skeletal Muscle- study of mTORC1 and sarcopenia**
2.23	**Correlating paraspinal muscle mitochondria structure and function change with sagittal spinal alignment**
2.24	**Is ergothioneine a longevity nutrient?**
2.25	**Investigating the potential mechanisms of neuroprotection by the dietary compound, ergothioneine**
2.26	**Influence of genetic, midlife diet and lifestyle factors on successful ageing – The Singapore Chinese Health Study (SCHS)**
2.27	**Conversations between tumours, vasculature and the brain: deciphering mechanisms underlying age-associated elevated mortality risk of stroke among cancer patients**
2.28	**OPTIMIZING NUTRITION FOR LIVING A LONG HEALTHY LIFE**
2.29	**EVALUATING BIOMARKERS OF THE FOOD INTERVENTION STUDY**
2.30	**RE**juvenating **S**enescent **T**raits of **O**lder **A**dults Through **R**egular **E**xercise **(RESTORE)**
2.31	**REBOOT (R**esistance **E**xercise improves Bi**O**l**O**gical age in older adul**T**s**)**
2.32	**BREXINT (BR**east Cancer **EX**ercise **INT**ervention**)**
3	**Human Potential Translational Research Programme**
3.1	**Unravelling inositol's role at the maternal-fetal interface: implications for pregnancy and offspring development**
3.2	**Uncovering the role of CNS in hyperthermia-induced fatigue and potential augmentation strategies to overcome it**
3.3	**Longitudinal study of multimodal brain imaging for behavioral prediction in health and neuropsychiatric disease**
3.4	**Predicting response to mindfulness training**
3.5	**The importance of sleep in the neurobehavioural and psychosocial development of children**

3.6	**Assessing Placental Perfusion and Fetal Growth by Examining Maternal Retina during Pregnancy**
3.7	**Using human in vitro models for studying diabetes disease mechanisms**
3.8	**Myo-Inositol and Fetal Membrane Remodeling and Weakening**
3.9	**Using magnetic resonance imaging and spectroscopy to investigate the role of placental inositol in fetal growth regulation**
3.10	**Investigating the mechanistic role of the placenta in maternal-fetal transmission of mental health risk**
4	**Immunology Translational Research Programme**
4.1	**Harnessing sphingosine-1-phosphate transport for the treatment of inflammatory diseases**
4.2	**The roles of endothelial cell transporter Mfsd7c for CNS vascular health and brain functions**
4.3	**Task for healthy longevity: Improving aging muscle strength by restoring the communication between the motor neuron and skeletal muscle**
4.4	**Molecular pathways of red blood cells invasion during malaria infection**
4.5	**Inactivation of proinflammatory 3emaphori pathways in apoptotic cells**
4.6	**Determining the activation mechanism of the protease caspase-8**
4.7	**mRNA-based engineering of dendritic cells for the cross-priming of broad tumour-killing CD8+ T cells**
4.8	**Mining alarmin adjuvants hidden among the chromatin network**
4.9	**Tilt cancer vaccine-induced immunity in favour of CD8 killer cells**
5	**Infectious Diseases Translational Research Programme**
5.1	**Molecular RNA Virology and Antiviral Strategies (MARVAS)**
5.2	**Achieving Functional Cure of Chronic Hepatitis B**
5.3	**Elucidating capsular polysaccharide biogenesis in Streptococcus pneumoniae**
5.4	**Applying single cell genomics to gain new insights into recurrent urinary tract infection, potentially leading to novel treatment strategies**
5.5	**Developing sexual genetics in E. coli as a new, complimentary engine for synthetic biology applications**
5.6	**Explaining the 2015 GBS yu sheng outbreak in Singapore – and ongoing GBS infections**
5.7	**Development of a versatile, rapidly deployable, one-shot vaccine targeting platform.**

5.8	**Studying viral-host interactions in chronic hepatitis viral infection versus acute viral infection by newly emerged viruses.**
5.9	**Epidemic Ethics during COVID-19**
5.10	**Dynamic gut microbiome modulations to establish colonization resistance against multidrug resistant Klebsiella pneumoniae**
5.11	**Molecular mechanisms of assembly and transmission of viruses causing respiratory tract infections**
6	**Digital Medicine Translational Research Programme Institute for Digital Medicine (WisDM)**
6.1	**Ethics and Governance of AI-driven Health Technologies**
6.2	**Developing red blood cell extracellular vesicles for targeted and functional delivery of therapeutic cargos**
7	**Cancer Translational Research Programme NUS Centre for Cancer Research (N2CR)**
7.1	**Circulating miRNAs That Predict Ovarian Cancer patients' (wild type BRCA1/2) Response to Chemotherapy**
7.2	**To explore a novel Lyn-Rac1-STAT3 axis to tumor immune modulatory pathway in breast and gynecological cancers**
7.3	**Translational Nanomedicine and Theranostics (TNT)**
7.4	**The impact of deregulated homologous recombination proteins on tumour immunogenicity**
7.5-7.7	**7.5 Developing novel therapeutics in cancer for personalized therapy 7.6 Developing new molecular detection methods in cancer 7.7 Discovering new mechanisms in genome maintenance**
7.8	**Investigate the role of NSD2 in m6A RNA methylation in t(4;14) myeloma**
7.9	**Understanding and Targeting the Non-Canonical Oncogenic Function of EZH2 for Therapeutic Intervention in Cancers**
7.10	**Early prediction of radioresistance and distant metastasis through molecular signature-based surveillance strategy**
7.11	**Targeting Cysteine Metabolism in Ovarian Clear Cell Carcinoma**
7.12	**Expression and Functional Analysis of Glycosaminoglycans and Proteoglycans in Breast Cancer**
7.13	**Clinical Molecular Imaging Research for Precision Oncology**
7.14	**Know Thy Neighbour – Spatial Profiling of Intra-tumour Heterogeneity (ITH)**
7.15	**ADAR1 meets NF-kB signaling: Functional role of lncRNA in regulating immune evasion**
7.16	**Investigating the physiological roles of p52-ETS1, a new transcription factor**
7.17	**Alternative UTRs of key cancer genes: Novel regulators and therapeutic targets?**
7.18	**Machine Learning Approach to Cancer and Cardiovascular Risk Prediction**

Updated in Jun 2022

7.19	**Mass spectroscopy biomarker discovery for precision medicine**
7.20	**New digital models of health information implementation**
7.21	**Synthetic Biology of Translational Therapeutics and Large Scale Bioproduction**
7.22	**Noninvasive characterization of endometrosis by circulating, cell-free messenger RNA**
7.23	**Establishing a systematic approach to translate human genetic findings of Coronary Artery Disease into novel biology**
7.24	**Nanomedicine for metabolic diseases**
7.25	**Inflammatory lipid 5emaphori pathways in cancer and neurodegenerative disease.**
7.26	**Ethics and Governance of Precision Medicine**
7.27	**A novel telomere-binding protein**
7.28	**Regulation of the long non-coding RNA TERRA in cancers relying on the Alternative Lengthening of Telomeres (ALT) pathway**
7.29	**Novel Role of Abemaciclib in Activating NK-cell Cytotoxicity against Nasopharyngeal Carcinoma**
7.30	**Targeting transcription factor pathways in cancers**
8	**Synthetic Biology for Clinical & Technological Innovation for Synthetic Biology (SynCTI)**
8.1	**Sustainable Living through Synthetic Biology: Therapeutics, Wellness and Planetary Health**
8.2	**Red Blood Cell Terminal Development**
8.3	**Synthetic Red Blood Cells for RBC Cell Therapy**
8.4	**Engineering and Directed Evolution of Bacteriophage**
9	**Nanomedicine Translational Research Programme**
9.1	**Nanomedicine for cardiovascular disease: atherosclerosis**
9.2	**Nanomedicine for fatty liver disease**
9.3	**Advanced drug delivery in heart disease**
10	**Precision Medicine Translational Research Programme**
10.1	**Novel precision gene editing technologies for treating hemoglobinopathies using humanized mouse models**
10.2	**Novel Precision Technologies to Correct Murations to β-Thalassaemia Using Patient-Specific STEM Cells**
11	**Others**
11.1	**Engineering and characterisation of stem cell extracellular vesicles for improved therapeutic efficacy**
11.2	**Developing novel cell therapies against inherited retinal diseases**

Updated in Jun 2022

11.3	**Elucidating the molecular network underlying vitreous regeneration**
11.4	**Investigating retinal pigment epithelium in the context of age-related retinal degenerative diseases.**
11.5	**Testing methods to improve survival of transplanted RPEs**
11.6	**Development of gene therapy for pediatric liver diseases**
11.7	**3D-Printing of Musculoskeletal Tissues**
11.8	**Development of Novel imaging Based Algorithm for the Screening of Osteoporosis**
11.9	**Role of Type 2 Innate Lymphoid Cells in childhood idiopathic nephrotic syndrome**
11.10	**Single-cell strategies for simultaneous diagnosis of monogenic disorders and screening of chromosomal abnormalities in IVF preimplantation embryos to achieve healthy pregnancies and unaffected livebirths**
11.11	**Heart-Brain Connection: Cognitive Impairment in Heart Failure**
11.12	**Feasibility study to explore heart-brain biomarker correlates of cognitive impairment in atrial fibrillation**
11.13	**Developing a Digital Solution for Salutogenic Brain Health**
11.14	**Independent Living and Future Care for Stroke Patients and Their Caregivers**
11.15	**Addressing Heart-Brain Health Disparities in Women: Music Intervention and Reflective Wisdom for Self-Care**
11.16	**Anto smart pad for Geriatric/Wheelchair users**
11.17	**Late-life depression and help-seeking in primary care**
11.18	**How does multimorbidity affect middle-aged adults? – refinement analysis of a published survey**
11.19	**Prevalence and predictors of chronic treatment guideline adherence among patients attending National University Polyclinics: a Big Data study**
11.20	**BRAIN-EYE-HEALTH AXIS RESEARCH (REALISE)**
11.21	**Inter-disciplinary Nanotechnology in Biomedical Application**

S/N	Principal Investigator	Project Title with brief Description
1	**Cardiovascular Disease Translational Research Programme**	
1.1	**A/Prof Citra NZ Mattar** citramattar@nus.edu.sg Department of Obstetrics & Gynaecology	**Amniotic Fluid Stem Cell Conditioned Medium for Vascular Tissue Regeneration** Amniotic Fluid Stem Cell Conditioned Medium for Vascular Tissue Regeneration Stem cell-derived paracrine effects have emerged as a promising strategy for the reactivation of endogenous mechanisms of repair and regeneration in several diseased models and may aid clinical application and commercialization. Amniotic fluid stem cells (AFSC), obtained via routine transcutaneous amniocentesis, are a promising source with strong application potential in biomedical research and translational medicine. We showed (Kukumberg et al, Sci. Rep 2021) that hypoxia-induced AFSC secretome exhibits a positive effect on human cardiomyocyte proliferation and dramatically lowered myocardial infarct damage in a pilot animal study. Here, we hypothesize that the composition and biological effect of this AFSC conditioned medium generated by hypoxic culture conditions (AFSC-CM) can augment tissue recovery following ischemic injury. We aim to: 1. Evaluate the signaling pathways of human cardiomyocytes and endothelial cells cultured in normoxic and hypoxic conditions under the influence of human AFSC-CM; 2. Evaluate the potential therapeutic application of AFSC-CM in reversing tissue injury in central vasculature ischemia animal model 3. Evaluate the potential therapeutic application of AFSC-CM in reversing tissue injury in peripheral vasculature ischemia animal model This multi-parameter approach will provide a better understanding of the human AFSC-CM influence on cell behavior during ischemia.
1.2	**Dr Jiang Jianming** bchjian@nus.edu.sg Department of Biochemistry	**Cardiac Gene Delivery by Enhanced Adeno-associate Virus** Recently, our group has generated pre-clinical animal models as well as uncovered new gene therapy targets for dilated cardiomyopathy using our established AAV9 gene delivery platform. Although AAV9 is the most tropism to the heart as well as the cargo of U.S. FDA–approved gene therapy for spinal muscular atrophy (SMA), relative high titers of AAV9 based gene therapies targeting heart disease likely induce liver or other tissue toxicity in the clinical trials. Importantly, the manufacturability, efficacy, specificity and safety of gene therapies is still limited by natural vectors, which are not optimized for clinical trials or treatment for heart disease. To solve these problems and realize the full potential of gene

		therapy, we will build enhanced cardiac-specific gene therapy vectors through the AAV capsid engineering. Our approaches include generation of high complexity libraries of AAV variants, random peptide insertion of spike regions and optimization of hotspot regions. Using high-throughput measurement of capsid properties as well as in vivo assessment, we will characterize variant properties important for therapeutic success. Enhanced AAV vectors will be used to target variant cardiac cell types including cardiomyocytes, cardiac fibroblasts, smooth muscle cells and endothelial cells, which will support our cardiovascular program, gene therapy community as well as general cardiovascular research field.
1.3	**Dr Jiang Jianming** bchjian@nus.edu.sg Department of Biochemistry	**Dissection of the Regulatory Pathways for Heart Regeneration and Cardiovascular Disease** Cardiovascular disease is a leading cause of death and disability worldwide. Heart failure (HF) occurs as a consequence of heart muscle damage. However, the adult mammalian heart, including the human heart, has limited potential to generate new muscle following injury and the burden of persisting decreased heart function may eventually lead to HF. Development of regenerative therapeutic strategies to reverse the progression of HF is an urgent and unmet clinical need. Recent research indicates regenerative potential of mammalian heart exists but dissipates shortly after birth. It is generally believed that the potential of heart regeneration is correlated with cardiomyocyte proliferative capacity. Interest in reinstating the generative potential of adult mammalian heart has led to exploration of the mechanisms underlying cardiomyocyte exit from their cell cycle to permanent arrest during the perinatal period. Our research interests focus on identifying and dissecting the regulatory pathways for heart regeneration using cutting-edge and integrated approaches in RNAseq analysis, in vivo gene modulation, stem cell reprograming and high-throughput pharmacological and genetic screening. Our research will not only uncover novel regulators and pathways for reinstating regenerative potential in adult mammalian hearts, but also provide novel targets for drug discovery and lead to better approaches for treatment or prevention of cardiovascular disease.
1.4	**Dr WANG Jiongwei** surwang@nus.edu.sg Department of Surgery	**Immunology and Nanomedicine in cardiovascular disease** Heart failure is predicted the most rapidly increasing cardiovascular disease over the next 20 years. Immune response (inflammation) following heart attack (acute myocardial infarction) is critical to heart injury and repair, and dictates the disease progression towards heart failure. How the immune cells communicate with each other and with heart cells in the disease setting becomes a hot topic and critical step to understand the pathogenic mechanisms underlying heart injury and failure. However, effective pharmacologic treatment is very limited and the currently available drugs for

		cardiovascular disease mostly end up with systemic side effects and/or suboptimal drug targeting to the diseased site. Therefore, our research aims: 1) To discover novel mechanisms of cardiovascular disease with a focus on immunology; 2) To identify novel therapeutic targets using our unique animal models, cell models and cutting-edge technologies including mass spec imaging and advanced flowcytometry; and eventually 3) to develop nanomedicine drug delivery systems for potential therapeutic compounds with advanced nanotechnology. My lab is also working on cardiac hypertrophy, atherosclerosis, cardiac regeneration and cardiac-oncology toxicity. Since my lab has a lot of local and international collaborations, the candidate will work in a multi-disciplinary and dynamic team.
1.5	**Prof Roger Foo** roger.foo@nus.edu.sg Department of Medicine	**Studying the role of long noncoding RNA in heart disease** The RNA world has come into significant spotlight by first-time ever approval of mRNA vaccines, and also FDA approval for the first series of RNA-based therapeutics for human diseases. RNA therapies promise to break the barrier of what were previously undruggable targets that could not be reached by conventional molecules or chemicals. Our lab has been studying the role of regulatory RNA and protein complexes in driving cardiac cell pathophysiology. One of the most interesting set of gene regulatory factors are long noncoding RNA (lncRNA), now found to target systematic cellular changes at a higher-order gene programme level. From single cell RNAseq, we have identified a lncRNA we named VENTHEART indispensable for cardiomyocyte specification. Having proven its crucial role in cardiomyocyte development, we have discovered that the VHRT locus is a significant GWAS and eQTL hit for heart failure. This project therefore proposes (a) to study the molecular 9emaphoring9tion of VHRT, (b) clarify the therapeutic potential using the engineered heart tissue; and (c) map out the VHRT regulatory gene programme. Uncovering the VHRT molecular pathway will open new avenues for therapeutic options.
1.6	**A/Prof Theo Kofidis** surtk@nus.edu.sg Department of Surgery	**Developing Personalized Atrioventricular Heart Valves For Human Implantation: Biomimicry In Design And Testing** The existing prostheses offer an overly simplistic rigid circular implant at the level of the patient's native valve ring and lack all the other atrioventricular valve components. Currently commercially available prostheses, with a rigid and symmetrical shape, lacking cords or connections to the papillary muscles that are prone to serious complications and depend on heavy medications, which may cause serious side-effects. We aim to develop a prosthetic valve which is designed to resemble a patient's natural atrioventricular (mitral and/or tricuspid) valve. Compared to existing valves, the proposed

		prosthetic valve will be prefabricated to the patient's needs. It will serve better than any best available prosthesis, because it will be made precisely fit and function for individual patient, permitting superior hemodynamic performance; it will also allow faster/ better heart recovery after surgery because the annulus of the prosthesis wholly provides freedom of motion to the annulus. This project will not aim to develop off-the-shelf valve prosthesis product as in the current practice; instead the remote diagnosis imaging results are used to manufacture a more closely approximate valve prosthesis for an individual patient. The diagnosis imaging techniques (Echocardiography and CT scan) are able to provide those commonly characterized valve parameters. The individualization of the valvular dimension and geometry is implemented based on the provided imaging data and through a set of algorithm formulae. The individual geometry and dimension will be taken as inputs for engineering drawing software or tools and further used in producing the valvular leaflets and the chords components from a sheet of bovine pericardium. The valvular components are subsequently assembled to form the valve prosthesis exactly fit for the patient's unique anatomy and clinical conditions.
1.7	**Dr Roshni Rebecca Singaraja** mdcrrs@nus.edu.sg Department of Medicine	**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.
1.8	**Dr Roshni Rebecca Singaraja** mdcrrs@nus.edu.sg Department of Medicine	**Semaphorin3F in the vascular wall** 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 large scale human genomic studies and identified several genes associating with CVD, one which is 11emaphoring 3F. To confirm if SEMA3F causes CVD, we administered SEMA3F to mice and found that it was atheroprotective. Using a combination of in vivo, ex vivo and in vitro studies, we found that SEMA3F has beneficial effects on vascular endothelial and smooth muscle cells. In the proposed project, we aim to determine mechanisms underlying SEMA3F's impact on CVD, and to identify pathways to increase SEMA3F as a therapeutic strategy for atheroprotection. 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. Yakala G et al. FURIN Inhibition Reduces Vascular Remodeling and Atherosclerotic Lesion Progression in Mice. Arterioscler Thromb Vasc Biol. 2019;39(3):387-401.
1.9	**Dr Rufaihah Abdul Jalil** surraj@nus.edu.sg Department of Surgery	**Modulation of cellular behaviour of ageing cardiomyocytes using amniotic stem cell sesretome** Hutchinson-Gilford progeria syndrome (HGPS) is a rare disorder of accelerated aging that results in patients dying of myocardial infarction, stroke or other atherosclerotic complications in their teen age. Progerin cumulation disrupts the function of cardiovasacular cells and leads to cardiovascular disease (CVD). Moreover, cumulation of progerin in low levels was observed also in natural aging.

		Cardiomyocyte (CM) signaling between CM and other cell types define crucial cellular processes critical for cardiac function and regeneration. Most of these processes are still not entirely understood. Moreover, the EC-CM signaling changes over time in the process of natural aging. Based on our previous study demonstrating the anti-inflammatory and cardioprotective properties of amniotic fluid stem cell secretome (AFSC-S) on CM in an animal diseased model, we postulate that AFSC-S will positively influence the ageing CM cellular behaviour in an ischemic environment of HGPS patient cells. Furthermore, the characterization of CM secretome will be crucial for a deeper understanding of CM signalling forgoing CVD and informative in understanding cardiac recovery to develop cardioprotective therapy for HGPS patients. Our study focuses on characterization of iPSC-CM secretome, coculture of iPSC-CM with AFSC-S and a pilot study of AFSC-S influence on CM in ischemia/reperfusion injury mouse model.
1.10	**A/Prof Heng Chew Kiat** paehck@nus.edu.sg Department of Paediatrics	**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 (DOI: 10.1371/journal.pone.0237074). 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.
1.11	**A/Prof Heng Chew Kiat** paehck@nus.edu.sg Department of Paediatrics	**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).
2	**Healthy Longevity Translational Research Programme**	
2.1	**A/Prof Juan Helen Zhou** mdczju@nus.edu.sg Department of Medicine	**Longitudinal study of multimodal brain imaging for behavioral prediction in health and neuropsychiatric disease** The project research will be centered around brain network vulnerability hypothesis. The multidisciplinary research program in 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-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 cluster and storage. You are welcomed to check out www.neuroimaginglab.org for more information.
2.2	**A/Prof Ling Shuo-Chien** phsling@nus.edu.sg Department of Physiology	**Mechanisms of Neuronal and Glial Dysfunctions in Aging and Neurodegeneration** Adult-onset neurodegenerative diseases remain the most devastating and crippling diseases without a cure. Our group investigate the mechanisms underlying amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), which affect the motor and cognitive systems, respectively. In particular, we focus on two fundamental questions: (1) why certain types of neurons are vulnerable in particular type of neurodegenerative diseases, and (2) how dysfunctions from glial cells may contribute to neuronal dysfunctions and neurodegeneration. The research in our laboratory uses disease-causing genes in human to understand the normal and pathophysiological process by constructing in vitro and in vivo models followed by an integrated approach combining genomic quantitative analysis, molecular and cellular studies. This arm of our research is to understand the pathogenic

		mechanisms and to identify therapeutic targets for ALS and FTD. late-onset neurodegenerative diseases. The second arm of our recent effort is to identify critical molecules involved in prolonging health- and life-span using the genomic dataset generated in the above-described approaches.
2.3	**Prof Reshma Taneja** phsrt@nus.edu.sg Department of Physiology	**Identifying therapeutic targets for skeletal muscle disorders** De-regulation of epigenetic control is increasingly apparent in many human pathologies including cancer. Small molecule inhibitors to chromatin modifying proteins have shown great promise in preclinical trials validating druggability of epigenetic modulators. In muscle cells, proliferation and differentiation are mutually exclusive events that are regulated by chromatin-associated proteins. Among these, lysine methyltransferases that mediate methylation of histone and non-histone proteins play a central role in maintaining this equilibrium. We have recently shown that G9a and GLP, lysine methyltransferases that mediate histone H3 lysine 9 di-methylation (H3K9me2), inhibit differentiation of skeletal muscle cells. We are currently investigating mechanisms by which they function using RNA-Seq and ChiP-Seq analysis as well as interactome studies using IP-Mass spec to obtain an integrated view by which lysine methylation of histone and non-histone proteins balance growth and differentiation of muscle cells. Our results will help design therapies for muscle disorders that are characterized by a differentiation defect.
2.4	**A/Prof Saji Kumar Sreedharan** phssks@nus.edu.sg Department of Physiology	**Elucidating plasticity and cognitive changes in aging and neurodegenerative diseases** As the percentage of the elderly population continues to rise, aging and the associated neurodegenerative diseases pose a huge burden on the socioeconomics of the society and on the quality of the individuals and caretakers. Aging is thought to play a causal role in the deterioration of cognitive function, but the mechanisms responsible are not yet fully understood. Our lab is interested to decipher the consequences of neuronal dysfunction on plasticity and cognitive function in aging and neurodegenerative diseases such as Alzheimer's disease (AD). We will be using animal models, electrophysiology, molecular biology, and behavioral study to elucidate the impaired functioning of hippocampal neural networks in aging and AD. Delineating the underlying mechanisms would facilitate the development of novel strategies for treating impairments associated with aging and AD. We aim to establish the foundation for translational development of effective therapeutic strategies and for identifying suitable targets for novel drug development.

2.5	**A/Prof Sanjay Khanna** phsks@nus.edu.sg Department of Physiology	**Cholinergic mechanisms in different chronic diseased state – divergent roles or a continuum?** The septo-hippocampal-prefrontal-network is implicated in a variety of functions in young and aged. These include learning and memory, mediation of chronic pain, anxiety and mood disorder. Interestingly, the circuit mechanisms suggested to be involved in the mediation of the foregoing chronic states includes the septal cholinergic neurons. Some hypotheses suggest that the imprint of cholinergic neurons diverges with disease - cholinergic hypoactivity is associated during dementia, while hyperactivity leads to mood disorder (depression). On the other hand, chronic pain, which is associated with cholinergic hyperactivity is also associated with impaired learning and memory, and depression. Most of observations leading to the preceding hypothesis are based on snapshots of cholinergic activity at selected times points. Here we propose, using fluorometric recording with optogenetic techniques, to monitor changes in neuronal activity of septo-hippocampal and septo-prefrontal cholinergic neurons during the disease trajectory to explore the relationship between cholinergic activity and disease development. Furthermore, we will use optogenetic based 'gain of function' and 'loss of function' type experiments to examine causal relationship between cholinergic activities. The chronic neuropathic pain model and its associate comorbidities will the starting point for such investigations. The findings will have implications for promoting healthy lifespan.
2.6	**Dr Tamra Lysaght** tlysaght@nus.edu.sg Centre for Biomedical Ethics	**Ethics and Regulation of Regenerative Medicine** This project broadly the ethics and regulation of translational research and innovation with advanced biomedical technologies. The project aims to generate policy-relevant ethical guidance for researchers and practitioners on translating stem cells and gene-based technologies into regenerative medicine. The project also extends into medical innovation more generally and the experimental use of non-standard interventions in clinical contexts.
2.7	**Dr Tsai, Shih-Yin** phsts@nus.edu.sg Department of Physiology	**Task for healthy longevity: Improving aging muscle strength by restoring the communication between the motor neuron and skeletal muscle** Sarcopenia, defined as an age-associated decline of muscle mass and strength, is a risk factor for mortality and disability in the elderly. Recent clinical trials showed that nutritional supplements had positive effects on muscle mass, but not on muscle strength, demonstrating our limited understanding of the pathophysiological mechanisms of sarcopenia. Since the decline either in motor neuron or skeletal muscle could correspond to sarcopenia, it is difficult to differentiate the sequential molecular events in which part contributing to the initiation of sarcopenia development. The challenge is to have

		a reliable in vitro system to recapitulate the in vivo microenvironment of aging-associated muscle degeneration. The recently developed microfluidic system for the 3D NMJ model , in which both motor neuron and skeletal muscle fibers assess their collective behavior in a 3D microenvironment, could exceed the limitation of 2D co-culture platform. The optogenetic control of motor neuron enables us to measure the muscle strength in the normal physiological condition. This innovative technology will allow us to clarify a cause-effect relationship between motor neuron and skeletal muscle in the development of sarcopenia. The proposed work seeks to identify the regulatory signaling between skeletal muscle and motor neuron in the microfluidic system for the 3D NMJ model. Ultimately, identification of the mechanistic links between skeletal muscle, and motor neuron will provide novel therapeutic strategies for age-induced muscle weakness.
2.8	**Dr Volker Patzel** micvp@nus.edu.sg Department of Microbiology & Immunology	**Exploring novel RNA-based mitochondrial delivery vectors for mitochondrial targeting of nucleic acids towards mitochondrial gene therapy and for anti-aging** Defects of all protein-coding mitochondrial genes have been associated with human, mainly neurodegenerative disorders or with aging. Many mitochondria harbour both, healthy and defect mitochondrial genomes (heteroplasmy) and defects accumulate with aging. Mitochondrial gene therapy could provide cure of mitochondrial disease and dysfunction but is hampered by the lack of an efficient mitochondrial gene delivery system. We developed an efficient novel scalable mitochondrial targeting vector based on RNA subdomains of a long non-coding viral RNA. We demonstrated that this vector system can efficiently target functional recombinant coding (mRNA) or non-coding (antisense) RNA to the mitochondria resulting in mitochondrial gene expression or knockdown of gene expression. The aim of this project is to improve the mitochondrial targeting vectors and to explore them for mitochondrial delivery (i) of 'healthy' gene functions and/or (ii) of the CRISPR/Cas system to selectively destroy defect mitochondrial genomes. The methods cover computational RNA structure design, in vitro techniques including cloning, PCR, and RT-PCR, experiments with tissue culture cells, cybrids, and Rho-zero cells including transfection, nucleofection, reporter gene assays and functional assays, and experiments with mouse models. This project is highly translational and can be explored towards mitochondrial gene therapy of yet incurable human diseases and for anti-aging.
2.9	**Dr Volker Patzel** micvp@nus.edu.sg Department of Microbiology & Immunology	**Developing a mitochondrial gene therapy targeting platform – toward mitochondrial gene therapy of LHON** Defects of all protein-coding mitochondrial genes have been associated with human, mainly neurodegenerative disorders or with aging. Mitochondrial gene therapy could provide therapy or cure but is hampered by the lack of an efficient mitochondrial gene delivery system. We developed a novel

		scalable mitochondrial targeting vector that is based on RNA subdomains of a long non-coding RNA derived from the human cytomegalovirus. We demonstrated that this vector system could efficiently target functional recombinant coding (mRNA) or non-coding (antisense) RNA to the mitochondria resulting in mitochondrial expression of recombinant RNA or knock-down of mitochondrial gene expression. We aim to refine and translate to pre-clinical phase, a novel nucleic acid-based therapeutic platform for the treatment of mitochondrial disease. We will target Leber's Hereditary Optic Neuropathy (LHON), an orphan disease that causes sudden blindness in young adults. The methods cover computational (in silico) RNA structural design, in vitro techniques including cloning, PCR, RT-PCR, the CRISPR/Cas technology, and experiments with tissue culture cells, cybrids, and Rho-zero cells including transfection, nucleofection, reporter gene assays and functional assays, and eventually experiments with a mouse model of LHON. The approach may prevent/restore LHON-associated vision loss and pave the way for mitochondrial gene therapy in general.
2.10	**Prof Yong Eu Leong** obgyel@nus.edu.sg Department of Obstetrics & Gynaecology	**Drug development program: Prenylflavonoids for prevention of menopausal osteoporosis** Screening of bioactive compounds from Traditional Chinese Medicines have resulted in the isolation, characterization, and patenting of novel compounds that activate steroid/nuclear receptors and other TRAF6 signalling pathways to improve osteoblast and osteoclast cellular function. These compounds and their parent extracts have shown potential utility in menopause, bone health, metabolic disease, breast and prostate cancers. We have completed the necessary pre-clinical pharmacokinetic and pharmacodynamic studies in animal models to meet Singapore Health Sciences Authority regulatory requirements for human trials. We have completed Phase 1 pharmacokinetic studies and Phase 2 randomised control trials of the use of Epimedium drug for post-menopausal osteoporosis. Achievement of these planned Phase1/2 human studies will result in pharmaceutical-quality botanical drugs discovered and made in Singapore. The above projects can be individually crafted pursuant to the interests of the motivated and interested student researcher.

2.11	**Prof Yong Eu Leong** obgyel@nus.edu.sg Department of Obstetrics & Gynaecology	**Integrated Women's Health Program (IWHP): Post-menopausal osteoporosis, fragility fractures and other critical issues facing mid-life Singaporean women** The IWHP was initiated to identify and address in a comprehensive fashion, the health care needs of mid-life Singaporean women. This unique program initially focused on menopausal osteoporosis and hip fractures but has since branched out to address other holistic areas of health. This program has two thrusts: firstly, the IWHP cohort itself where women are finely phenotyped, and secondly, the entire Singapore population of mature women available through national healthcare databases. Current work on the IWHP cohort includes a second round of interviews, examinations, and laboratory tests. This will permit an analysis of baseline characteristics as potential risk factors for changes in health outcomes between the first and second round. In addition, we will attempt to develop a population-wide screening strategy for osteoporosis in mid-life Singaporean women based on the first round of data collection and validate the strategy based on the second (follow-up) visit.
2.12	**Prof Yong Eu Leong** obgyel@nus.edu.sg Department of Obstetrics & Gynaecology	**Polycystic ovary syndrome (PCOS)** The androgen-driven PCOS is another focus of our work. In the laboratory, our students has derive the molecular mechanisms for a novel therapeutic derived from nature in an animal model of PCOS. We have proposed a new classification of the PCOS and performed ground-breaking translational studies on the role of sleep, circadian rhythm, melatonin and cortisol in the etiology of PCOS. Using national Swedish databases, we have characterized infertility and depression issues in PCOS.

2.13	**A/Prof Christopher Chen** phccclh@nus.edu.sg Department of Pharmacology	**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 blood-based markers are associated with MBI; d) Interaction between the above mentioned biomarkers influence MBI and NPS.
2.14	**A/Prof Christopher Chen** phccclh@nus.edu.sg Department of Pharmacology	**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-β and p-tau are related to specific brain functional and structural network breakdown leading to cognitive decline and behavioral problems; b) The effect of network changes and atrophy on cognitive performance and behaviour 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.

2.15	**A/Prof Christopher Chen** phccclh@nus.edu.sg Department of Pharmacology	**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), OCT-Angiography) and novel (Doppler OCT, pupilometry, 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.
2.16	**A/Prof Christopher Chen** phccclh@nus.edu.sg Department of Pharmacology	**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-the-art immunoassay platform and assess their relationships with brain integrity and cognition, 3) To compare plasma vs. neural- or endothelial-specific extracellular vesicle measurements to assess the diagnostic and prognostic utility of these biomarkers 4) To develop a combination of multiple biomarkers with high accuracy in predicting longitudinal disease development. We hypothesise that markers involved in the disease pathophysiology, can identify individuals with high disease risk. Specifically, that a) blood-based biomarkers of neurodegeneration and oxidative stress are predictive of incident CeVD in parallel with cognitive decline; b) neural- or endothelial-specific extracellular vesicle biomarkers are more sensitive than neat plasma biomarkers in diagnosing and prognosis for cognitive impairment and CeVD; c) A combination of multiple biomarkers adds value to the diagnostic and prognostic performance of single blood-based biomarkers.

2.17	**A/Prof Christopher Chen** phccclh@nus.edu.sg Department of Pharmacology	**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.
2.18	**Dr Jai Polepalli** jpolepalli@nus.edu.sg Department of Anatomy	**Ionotropic serotonin receptor 5HT3a-R mediated synaptic transmission and plasticity underlying adaptive behaviours** Synapses are the fundamental units of computation in the brain, and normal synaptic function is crucial for normal brain function – consequentially – most neurodegenerative and psychiatric disorders arise from abnormal synaptic function. In the forebrain, fast synaptic transmission is of two types- excitatory and inhibitory, primarily mediated by glutamate and gamma aminobutyric acid (GABA) at glutamatergic and GABAergic synapses respectively. However, in addition to glutamate, the monoamine serotonin also mediates fast excitatory transmission through 5HT3a-Receptors. In the memory and decision-making circuits, fast serotonergic transmission through 5HT3aRs exerts a strong, fast, sub-cortical influence from the neuromodulatory region of the brain- the medial and the dorsal raphe. Although existing literature strongly hinted at the possibility of 5HT3aR serving as a promising therapeutic candidate for neurocognitive disorders, there are no studies to date that directly investigate and dissect the roles of 5HT3aR in cognition- specifically in mediating adaptive behaviours. This project aims to adopt a comprehensive approach to establish and characterize the role of 5HT3aR in mediating adaptive behaviours at multiple levels, ranging from their molecular interactors to their roles in regulating synaptic plasticity, neural circuits and eventually, cognition.

		To achieve the aims of this project, we will use state-of-the-art techniques in mouse genetics, viral mediated gene manipulations, in vitro and in vivo electrophysiology, 2 photon imaging, optogenetics, and rodent behaviour. For more information- www.polepallilab.org
2.19	**Dr Jai Polepalli** jpolepalli@nus.edu.sg Department of Anatomy	**Investigating the Amygdala - Nucleus Accumbens circuitry mediting motivated behaviours** Food, social stimulation and sex are pleasurable and rewarding. The motivation to experience pleasure derived from these pursuits is innate to all mammals and ensures survival. However, motivation to obtain pleasure as a reward has an addictive liability, and pathological 'reward-seeking' manifests as behavioural addiction, often resulting in harmful outcomes such as obesity. Similarly, use of recreational drugs like cocaine and methamphetamine hijacks brain regions that mediate this pleasure response, or 'reward', leading to drug addiction. In healthy individuals however, seeking pleasure through natural rewards has a quenching, or a 'reward-stopping' signal, which acts as a temporary brake on reward seeking. What brain circuitry mediates reward stopping is unknown. The research described in this proposal is intended to describe and delineate the circuitry mediating motivation from the circuitry acting as a brake on motivation, and attempt to identify circuit based therapeutics to treat disorders of the 'reward system'. At the core of the brain's reward circuitry is the nucleus accumbens (NAc), which is involved in the processing of reward signals. This brain region integrates a mix of excitatory, inhibitory and modulatory inputs to optimize motivated behaviours. While inputs to the NAc from the basolateral amygdala (BLA) are thought to facilitate motivation and reward seeking, what brain circuitry mediates reward stopping is unknown. Also, a mechanistic understanding of the synaptic and molecular mechanisms that mediate motivated behaviours is yet to be detailed. Understanding the molecular specifications, synaptic and circuit mechanisms that modulate motivated behaviours underpinning reward-related behaviour is of fundamental interest in neuroscience and behavioural psychology. The primary objective of this proposal is to gain a mechanistic understanding of the synaptic and molecular mechanisms that mediate reward-related behaviours, specifically to identify and characterize neural circuits that underlie the stop signal for reward seeking**.** Defining the synaptic and circuit mechanisms that mediate the brake on reward-seeking, and dissociating those from the adaptations that mediate reward seeking will usher in a better understanding of debilitating human conditions that are caused by either exaggerated reward/pleasure seeking, or the inability to experience pleasure.

		This project will use a range of cutting edge techniques in rodent behaviour, optogenetics, mouse genetics, slice electrophysiology and intersectional genetics. For more information- www.polepallilab.org
2.20	**A/Prof Sanjay Khanna** phsks@nus.edu.sg Department of Physiology	**A role for neutrophin and GABAergic mechanisms in hippocampus in mediation of experimental neuropathic pain?** Chronic pain affects one-fifth of world population. However, there are few effective analgesics, in part because the CNS basis of chronic pain has not been clearly elucidated. Experiments in the our laboratory suggest that experimental neuropathic pain in young rodent is accompanied by decrease in level of TrkA, but not p75 neurotrophin receptors (NTRs) in hippocampus. Notably, TrkA NTRs are implicated in disinhibition, by inhibiting GABAergic inhibition. Indeed, microinjection of bicuculline, a GABAA receptor antagonist, into hippocampus attenuated experimental pain. Thus, we hypothesize that imbalance in hippocampal NTRs leads to a state of chronic pain in young and, perhaps aged rodent, by favoring GABAergic inhibition of hippocampal principal neurons. The project will test this hypothesis by using electrophysiological, cell biology and behavioural techniques. The findings will have implication for drug discovery for chronic pain by identifying NTR in forebrain as novel targets.
2.21	**Dr TSAI, Shih-Yin** phsts@nus.edu.sg Department of Physiology	**Sex differences in aging** Aging-related heathy issues are emerging worldwide. The female advantage in longevity has been observed across years and countries. Many factors have been proposed to attribute to the sex-biased aging difference, including sex hormones, sex differences in adipose tissue and immune system. However, a precise relationship between sex bias and aging is still an enigma. The research interests of my lab explore the underlying mechanism that whether and how sex bias may have a role in aging. We answer this question from a perspective of metabolism and aim to examine metabolic signaling pathways underneath the aging. Specifically, we focus on mTORC1 signaling, as evidenced in our previous studies that the activation of mTORC1 pathway is differentially regulated between males and females. In cells, mTORC1 is a nutritious and energy sensor, and a protein synthesis regulator. Once activated, mTORC1 promotes the phosphorylation of its two substrates: S6K and 4E-BP. mTORC1-mediated phosphorylation activates S6K and inhibits 4E-BP, together leading to initiation of protein translation. Interestingly, while inhibition of mTROC1 has been shown to slow down aging for both females and males, the advantages for each sex seem to result from divergent downstream effectors. Abrogated S6K activities contributed to longer lifespan only for females, whereas males relied more on the protection of activated 4E-BP from aging-induced metabolic declines. Our lab has

		generated a novel mouse model, 4E-BP1 transgenic mice, which provides a unique tool to study how S6K and 4E-BP signaling can be differently regulated in females and males, and how such a different regulation would produce a feedback signaling to instruct sex-biased metabolic phenotypes. Our work will provide a more sophisticated understanding of how mTORC1 pathway is differently regulated between females and males, and will lead to more effective therapies to treat aging-related metabolic disorders.
2.22	**Dr TSAI, Shih-Yin** phsts@nus.edu.sg Department of Physiology	**Mass Up Aging Skeletal Muscle- study of mTORC1 and sarcopenia** Aging is an emerging health issue worldwide. Sarcopenia is commonly related to aging and is a major risk factor for mortality. To date, there is no effective and approved pharmacological intervention to treat sarcopenia. The mechanisms to control skeletal muscle growth during aging is also not well understood. In order to address these questions and discover new therapeutic targets to reverse sarcopenia and strengthen skeletal muscle, my lab is devoted to understand the signaling pathways in skeletal muscle growth. One potential regulator of muscle growth is mechanistic target of rapamycin complex 1. Upon exercise and injury, mTORC1 is acutely activated and induces muscle growth and regeneration. Yet chronic activation of mTORC1 has been documented to be associated with aging-related sarcopenia. This suggests that both the timing and duration control of mTORC1 expression are subject to the strict regulation in muscle cells in order to achieve the maximum benefit for injury-induced repair responses and long-term tissue health. To explore how mTORC1 expression in skeletal cells may contribute to the muscle homeostasis, we utilized genomic approach to analyze which genes are specifically modulating or collaborating with mTORC1 activity in mouse skeletal muscle and how they affected the functional aging. mTORC1 is a crucial regulator of protein homeostasis. Activation of mTORC1 leads to phosphorylation of S6 kinases and 4E-BPs, consequently stimulating translation initiation. This project will use the cutting-edge Ribosome-seq technique to monitor mRNA translation in skeletal muscle and further identify the differentially translated genes regulated by mTORC1 during aging. The candidate genes will be validated in a mouse model of sarcopenia to test therapeutic potential in recovery of the muscle function. A better understanding of mTORC1 pathway would lead to the development of more effective and safe therapies to treat aging-related metabolic diseases, and limiting potential off-target side effects while targeting mTORC1.

2.23	**Dr Hey Hwee Weng Dennis** doshhwd@nus.edu.sg Department of Orthopaedic Surgery	**Correlating paraspinal muscle mitochondria structure and function change with sagittal spinal alignment** Hyperkyphosis of the spine and paraspinal myopathy are age-related phenomena. To keep the human spine upright, paraspinal muscles act as dynamic stabilizers to prevent the forward-hunched posture. The process of aging is thus believed to result from paraspinal muscle dysfunction, leading to accelerated kyphosis of the spine. The current state-of-the-art treatment for paraspinal sarcopenia hinges largely on physical therapy and core muscle strengthening exercise regimes to reverse the process. Unfortunately, these strategies have shown limited efficacy. Multiple clinical and radiological studies have supported the morphological association between paraspinal sarcopenia, spinal degeneration and kyphosis. Few studies have investigated the role of mitochondria abnormality as a mechanism leading to poorer muscle strength. Under high mechanical demand, increase in free radical generation could have enhanced biogenesis of defective mitochondria, resulting in paraspinal dysfunction, thus accelerating the process of spinal kyphosis. This proposed work seeks to further pursue greater understanding in the intergrity of paraspinal muscle mitochondria at lower and upper lumbar spine segments using the novel, accelerated sarcopenic TSC1mKO mice at different stages of kyphosis development. Identification of the mechanistic links between skeletal muscle mitochondria structure and function, and spinal kyphosis will enable novel therapeutic strategies to treat the ageing spine.
2.24	**Prof Barry Halliwell** bchbh@nus.edu.sg Department of Biochemistry	**Is ergothioneine a longevity nutrient?** Our clinical studies have demonstrated that the naturally occurring amino acid, ergothioneine, can accumulate in the body at high concentrations from the diet (especially mushrooms). This avid uptake and retention by the body suggests that ergothioneine may play an important role in health and prevention of disease. We previously demonstrated that blood ergothioneine levels decline with age in elderly individuals greater than 60 years of age. Moreover, significantly lower blood levels of ergothioneine were observed in patients with a range of age-related neurological disorders such as mild cognitive impairment, Parkinson's disease, and dementia (Alzheimer disease and vascular dementia), suggesting that declining ergothioneine levels may be a risk factor for age-related diseases. A recent study also demonstrated that lower levels of ergothioneine are highly associated with elevated markers of frailty in a Japanese population. As such, some have suggested that ergothioneine may be a longevity nutrient, that is, supplementation of ergothioneine may promote healthy ageing and reduce the

		risk of age-related disorders. However, presently little is known about the mechanisms by which ergothioneine may modulate longevity pathways. Using a range of cell culture and molecular techniques, this study will investigate whether ergothioneine interacts with longevity genes to promote healthy longevity. Tapping into an existing cohort we will also investigate the association of ergothioneine levels with various health factors in elderly human subjects.
2.25	**Prof Barry Halliwell** bchbh@nus.edu.sg Department of Biochemistry	**Investigating the potential mechanisms of neuroprotection by the dietary compound, ergothioneine** Numerous studies have demonstrated that blood levels of ergothioneine, a unique dietary amino thiol/thione, are significantly lower in patients with various neurodegenerative disorders such as Parkinson's disease, mild cognitive impairment, and dementia including Alzheimer disease. This suggests that lower ergothioneine levels may play a role in elevating the risk of- or fuel the pathological progress of these neurodegenerative disorders. Supporting this notion, numerous studies in animal models of neurodegeneration have shown that ergothioneine is protective. Studies with cell cultures suggest that ergothioneine may act as an antioxidant and anti-inflammatory agent, however the mechanisms of neuroprotection by ergothioneine remain largely unknown. Using a range of in vitro and in vivo models together with a range of molecular techniques, this study aims to investigate the possible mechanisms of neuroprotection by ergothioneine.
2.26	**Prof KOH Woon Puay** kohwp@nus.edu.sg Dean's Office	**Influence of genetic, midlife diet and lifestyle factors on successful ageing – The Singapore Chinese Health Study (SCHS)** Population ageing is a global problem that poses increasing health, social and economic challenges. The medical, societal and economic burdens of ageing come from increase in the incidence of chronic age-related diseases in the elderly population and gradual loss of bodily functions and independence in activities of daily living. This project will investigate how genetic, midlife factors in diet and lifestyle, as well as subsequent modifications, affect outcomes that define successful ageing measured in the physical, functional and cognitive domains. Findings from this project will provide scientific evidence for direct diet and lifestyle interventions, and inform the development of nutraceutical or functional food for preservation of health and prevention of disease.

2.27	**Dr CRASTA Karen Carmelina** phscras@nus.edu.sg Department of Physiology	**Conversations between tumours, vasculature and the brain: deciphering mechanisms underlying age-associated elevated mortality risk of stroke among cancer patients** Cancer-associated thrombosis is a leading cause of morbidity and mortality in cancer patients, with venous thromboembolism (VTE) being most common. Cancer patients are at four times higher risk than the general population in developing VTE. Advanced age is a risk factor for VTE in cancer patients. As survival rates of cancer patients increase, it becomes crucial to identify older cancer survivors at elevated risk of stroke, especially since mortality risk of stroke increases with time. Unfortunately, molecular mechanisms underlying predisposition of cancer patients to VTE remain scant, highlighting an unmet need. This project proposes to study the mechanistic and clinical systemic impact of the tumour secretome (extracellular vesicles and circulating soluble factors) on vascular/coagulation components. The student will utilise cell biology, biochemistry, functional genomics and clinically-relevant techniques, and will be immersed in an intellectually stimulating lab environment with active interaction with other groups at the Centre for Healthy Longevity. He/she will work closely with our clinical collaborative partners at NUHS (Dr Leonard Yeo and Dr Sia Ching Hui), as well as partners at NUS and A*STAR. Overall, this project will yield better understanding of age-associated cancer coagulome with the intent of helping cancer patients live longer, disease-free lives. www.crastalab.com
2.28	**Dr Elena Sandalova** sanelena@nus.edu.sg Department of Medicine	**OPTIMIZING NUTRITION FOR LIVING A LONG HEALTHY LIFE** Aging is the largest risk factor for age-related diseases and lifestyle choices significantly influence the aging trajectory. Providing lifestyle modifications to maximize health and productivity will prevent chronic diseases in the future. Food is the basis for health and dietary modifications have been linked to a reduction in cardiovascular disease, cancer, diabetes, and mortality. Clinical studies testing the effect of food on health can range broadly from testing specific ingredients or nutrients to testing the effect of defined diets, or dietary guideline adherence on healthy or diseased populations. Randomized control trials (RCTs) are the golden standard for testing nutritional interventions but are challenging since it is hard to control the food that people consume. Ideally, every meal needs to be standardized, measured in terms of caloric intake, macro-, and micronutrient composition, dietary patterns need to be controlled as well as completion of the meal intake.

		The aim of the current project is to develop a meal program based on the latest evidence regarding geroprotective effects of diets, ingredients, and compounds that could improve health outcomes in middle-aged to older individuals. Characterize the meal program's nutritional composition including the presence of bioactive compounds with potential geroprotective effects.
2.29	**Dr Elena Sandalova** sanelena@nus.edu.sg Department of Medicine	**EVALUATING BIOMARKERS OF THE FOOD INTERVENTION STUDY** Aging is the largest risk factor for age-related diseases and lifestyle choices significantly influence the aging trajectory. Providing lifestyle modifications to maximize health and productivity will prevent chronic diseases in the future. Food is the basis for health and dietary modifications have been linked to a reduction in cardiovascular disease, cancer, diabetes, and mortality. Clinical studies testing the effect of food on health can range broadly from testing specific ingredients or nutrients to testing the effect of defined diets, or dietary guideline adherence on healthy or diseased populations. Randomized control trials (RCTs) are the golden standard for testing nutritional interventions, but are challenging, since it is hard to control the food that people consume. Ideally, every meal needs to be standardized, measured in terms of caloric intake, macro-, and micronutrient composition, dietary patterns need to be controlled as well as completion of the meal intake. Biomarkers in response to food have not been established especially in relation to aging. Microbiota or metabolites have been studied but not clearly linked to nutrition's effect on aging. The aim of the study would be to identify biomarkers of aging that respond to standardized meal program intervention.

2.30	**Dr Goh Jorming** jorming@nus.edu.sg Department of Physiology	**RE**juvenating **S**enescent **T**raits of **O**lder Adults Through **R**egular **E**xercise (***RESTORE***) Longitudinal studies have consistently reported improved healthspans in human populations that are physically active, that is, meeting the World Health Organization (WHO)'s recommendations of a minimum of 150 minutes of regular, moderate-intensity physical activity weekly. Unfortunately, most people do not meet even the minimal guidelines. In this project, the goal is to determine whether 3 months of regular physical activity participation will reduce biological age in middle-aged adults. Novel biomarkers of aging, including DNA methylation status, inflammAging markers, and other physiological parameters such as cardiorespiratory fitness and arterial stiffness will be assessed. We will recruit middle-aged adults (40-60 years) that are either healthy or with 1 chronic condition (e.g. hypertension) to undergo a 3 month-long physical activity intervention program. Serial measurements of biomarkers and other secondary outcomes will be conducted from baseline at regular intervals (weeks 0, 6, 12, 18).
2.31	**Dr Goh Jorming** jorming@nus.edu.sg Department of Physiology	**REBOOT** (**R**esistance **E**xercise improves Bi**O**l**O**gical age in older adul**T**s) Skeletal muscle loss usually starts after 40 years of age at a rate of -0.5% per year, and then accelerates rapidly after 60 years. Sarcopenia, a condition typically associated with the geriatric population, is characterized by low skeletal muscle mass and reduced skeletal muscle function or strength. Although the actual prevalence of sarcopenia in Singapore is unknown, recent estimates in a clinical study indicated that ~44% of elderly medical outpatients aged 65 years and above were sarcopenic, and in this cohort, women were far more likely than men to be sarcopenic (58% vs 29%) and frail (68% vs 32%). Elderly women with low muscle strength had an increased mortality risk (OR: 1.65, 95% CI: 1.19-2.30), whereas there was no significant association between muscle mass and mortality, suggesting that the age-related loss of muscle strength is a more important factor in predicting mortality than muscle. In this project, we will investigate the mechanisms through which 6 months of regular strength exercise improves skeletal muscle strength and mass in older (>59 years) adults. Novel biomarkers of aging, including DNA methylation status, inflammAging markers, and other physiological parameters such as cardiorespiratory fitness and arterial stiffness will be assessed.

2.32	**Dr Goh Jorming** jorming@nus.edu.sg Department of Physiology	**BREXINT** (**BR**east Cancer **EX**ercise **INT**ervention) Breast cancer is the most common cancer in Singapore, representing 29.1% of all cancers diagnosed in women, regardless of ethnicity and is the most frequent cause of death (17.3%) amongst Singaporean women with cancer. For women who completed cancer treatment, fatigue is the most reported adverse effect- exacerbated by poor cardiorespiratory fitness and low skeletal muscle strength. Anthracycline-based chemotherapy is also associated with cardiotoxicity, pathological remodeling of the left ventricles, and increased risk of cardiomyopathy or heart failure in breast cancer patients. Hence, cancer and chemotherapy are known to ***accelerate biological aging***. *While exercise training – be it aerobic or strength-based, improves clinical and physiological outcomes in breast cancer survivors,* ***it is not clear whether such interventions also modulate biological aging*****.** Exercise modulates the immune-inflammatory-muscle axis and dampening of the immune response can be improved with physical training, possibly by mediating the i) skeletal muscle secretome, ii) immune cell phenotype, iii) biological age, or all three factors. This project will determine whether 4-months of aerobic and resistance exercise modulates senescence, inflammation and immune expression in women with breast cancer. ***Novel tools*** include applying DNA methylation age, transcriptomic profiling of peripheral blood mononuclear cells (PBMcs) and characterization of exosomal cargo prior to, and after exercise intervention.

3	**Human Potential Translational Research Programme**	
3.1	**A/Prof Chan Shiao-Yng** obgchan@nus.edu.sg Department of Obstetrics & Gynaecology	**Unravelling inositol's role at the maternal-fetal interface: implications for pregnancy and offspring development** Inositol and its derivatives regulate insulin, glucose and lipid signalling and metabolism. Disrupted inositol metabolism is associated with pregnancy complications, and clinical trials of inositol supplementation during preconception and pregnancy demonstrate promising risk reductions in gestational diabetes and preterm birth, which affect ~20% and ~10% of deliveries respectively. Furthermore, elevated maternal glycaemia increases neonatal adiposity, which is attenuated by high placental inositol content. This suggests that inositol mitigates glucose's pro-adipogenic effects in the fetus. However, to develop inositol as an intervention, we must understand how inositol moderates these risks. We hypothesise that inositol modulates lipid transport, metabolism and signalling at the maternal-placental-fetal interface, and hence fetal nutrient transfer and pregnancy progression. Using a range of ex-vivo and in-vitro techniques (including tissue/cell culture, molecular biology, LC-MS lipidomics), we will correlate laboratory findings with multiple maternal and offspring measures (eg. BMI, birthweight) to understand inositol's role at the maternal-fetal interface and its possible consequences for fetal growth and development. In doing so, we may be able to mitigate the long-term negative health implications associated with gestational diabetes, preterm delivery and aberrant fetal growth in the mother and her offspring.

3.2	**Dr Ivan Low Cherh Chiet** phsilcc@nus.edu.sg Department of Physiology	**Uncovering the role of CNS in hyperthermia-induced fatigue and potential augmentation strategies to overcome it.** Exertional hyperthermia is a key factor known to limit human endurance performance. Recent evidence suggests that the CNS may contribute, at least in part, to hyperthermia-induced fatigue. However, the exact physiological mechanisms underlying heat-induced neural perturbations and impairments remains unknown. In this study, we seek to evaluate functional brain changes in human volunteers subjected to exertional hyperthermia using a continuous fNRIS monitoring system. CNS perturbations identified will also be correlated with a host of physiological parameters (eg. heart rate, core temperature, skin temperature, gait variability, electromyography etc) to develop a data model to predict CNS alterations during exertional hypothermia. The understanding of how CNS symptoms develops during exertional hyperthermia is pivotal to our efforts in combating performance deficits during heat stress. Data attained from the continuous monitoring of CNS perturbations throughout the course of exertional hyperthermia may further augment our understanding on the predisposing factors of exertional heat stroke. If successful, insights gained would allow future design of heat mitigation strategies that are efficiently targeted for the abatement of CNS deficits during exertional hyperthermia.
3.3	**A/Prof Juan Helen Zhou** mdczju@nus.edu.sg Department of Medicine	**Longitudinal study of multimodal brain imaging for behavioral prediction in health and neuropsychiatric disease** The project research will be centered around brain network vulnerability hypothesis. The multidisciplinary research program in 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-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 cluster and storage. You are welcomed to check out www.neuroimaginglab.org for more information.
3.4	**Dr Julian Lim** Julian.lim@nus.edu.sg Department of Medicine	**Predicting response to mindfulness training** Mindfulness is a key element in many "third-wave" psychotherapies, and there is now substantial evidence that these are equivalent to some frontline treatments in reducing symptoms of stress, depression and chronic pain. Our laboratory is undertaking a long-term project to understand the predictors and moderators of treatment response to mindfulness training. These predictors include demographic, psychological, and personality data, and fluid and crystallized intelligence. We also acquire structural (T1 volumetric and diffusion-tensor-weighted) and functional (resting-state and task-based) magnetic resonance imaging (MRI) scans, electrophysiological data using high-density EEG recording, and physiological measures such as respiration and heart-rate variability. Graduate students in our lab will contribute to the analysis of this main dataset, which involves constructing a machine-learning algorithm to predict the benefit an individual will receive from mindfulness training, and assess its specificity. As part of this project, we will provide training on MRI connectomics analysis, including methods to use these data for out-of-sample prediction. Opportunities may also be provided to learn analysis of structural MRI, and electrophysiological data. Students may also design and lead side projects to test whether these traits predict the effects of brief mindfulness inductions on perceived stress and other outcome measures
3.5	**Dr June Chi-Yan Lo** mdclocy@nus.edu.sg Department of Medicine	**The importance of sleep in the neurobehavioural and psychosocial development of children** Project 1: Having adequate sleep helps optimize cognitive outcomes in school-aged children. However, the features of sleep macro- and micro-structure that contribute to such benefits are not well established with only a handful of cross-sectional studies linking various stages of sleep with IQ, and sleep stages, slow wave activity, and sleep spindles with executive functioning. To determine the features of sleep that are associated with neurobehavioural and psychosocial development in children, in this longitudinal study, we will track changes in polysomnographically-assessed sleep, cognitive performance, and internalizing and externalizing behaviour in children, aged 7-9 years atbaseline, over a 1-year period.

		Project 2: In this cross-sectional survey, we will uncover factors that determine children's sleep and developmental outcomes. Specifically,we will examine the impact of sleep-related parental involvement and parenting practices on school-age children's sleep, psychosocial, and academic outcomes (objective 1). Moreover, we will investigate the demographic profile of families with suboptimal sleep-related parenting practices in Singapore (objective 2). Data will also be collected from a US sample which will allow cross-cultural comparisons (objective 3).
3.6	**Dr Li Lingjun** obgllj@nus.edu.sg Department of Obstetrics & Gynaecology	**Assessing Placental Perfusion and Fetal Growth by Examining Maternal Retina during Pregnancy** Decreased uterine blood flow may reduce placental perfusion and lead to fetal growth restriction. Evidence has shown changes in the histomorphology of the placental microvessels, leading to the hypothesis that smaller placental size during normal gestation might involve placental vascular and angiogenesis dysfunction, which affects placental transport capacity and blood flow. The eye is a "window" to the human circulation. The retinal blood vessels can now be captured and visualized non-invasively by advances in retinal imaging, which offers an exceptional opportunity for advanced imaging techonology to document, monitor and study human disease. Hence, we hypothesized that maternal retinal vasculature can reflect the placental circulation and fetal growth pattern in very early pregnancy. This prospective cohort will be the first to investigate the association between retinal microvascular parameters and placental perfusion and fetal growth, based on traditional ultrasound imaging and serum bio-markers (e.g. placental growth factor). This study can potentially help researchers better understand the possible morphology of placental microvasculature through retinal vascular imaging, and how changes in maternal microvasculature in vivo may reflect fetal growth (e.g. slow fetal growth) during pregnancy.

3.7	**Dr Teo Kee Keong Adrian** bchtkka@nus.edu.sg ateo@imcb.a-star.edu.sg Department of Biochemistry	**Using human in vitro models for studying diabetes disease mechanisms** Diabetes is a debilitating chronic disease that has spiraled out of control, affecting >400 million people in the world. Often, people with diabetes develop severe complications, leading to an astronomical healthcare burden. In Asia, it is increasingly recognized that the failure in human pancreatic beta cells is the primary culprit for the development of diabetes. Despite so, mechanisms underlying human beta cell failure during the development of diabetes remain unclear. Therefore, we at the Stem Cells and Diabetes Laboratory seek to use human pluripotent stem cells (hPSCs), human islets and human beta cell line to investigate diabetes disease mechanisms. Ph.D. students can expect to be very well-trained in our young and vibrant laboratory (http://www.adrianteolab.com/), be very well-versed in Stem Cells/Diabetes, and be very well-connected with Diabetes Clinicians and Surgeons whom we interact with extensively in the landscape. We seek to place our staff/students in an exciting position of working on translational research that is highly relevant to both our clinician collaborators and our patients. The student is expected to be highly motivated, read the literature extensively, gain in-depth knowledge on the research topic, and master the art of performing research with close guidance and mentorship. Overtime, the student is expected to gain confidence and mature into an independent scientist with excellent knowledge and skills in the areas of Stem Cells and Diabetes.
3.8	**A/Prof Chan Shiao-Yng** obgchan@nus.edu.sg Department of Obstetrics & Gynaecology	**Myo-Inositol and Fetal Membrane Remodeling and Weakening** Preterm premature rupture of the fetal membranes (PPROM) is a pregnancy complication accounting for approximately one third of preterm births, which results in higher risk of infant mortality and morbidity. PPROM is preceded by programmed events that remodels fetal amnio-chorionic membranes, aiding in the weakening and ultimate rupture. Clinical trials of myo-inositol supplementation in pregnancy had reported reductions in preterm birth and PPROM. However, the mechanism involved is unknown. We hypothesise that myo-inositol suppresses premature fetal membrane remodeling and weakening, thereby reducing the risk of PPROM and preterm birth. To investigate this hypothesis, we will culture fetal membranes from term elective caesarean section with different concentrations of myo-inositol. We will subsequently assess the markers of fetal membrane remodeling in the tissue and culture medium using various techniques such as QPCR, western blot, ELISA, gel zymography and senescence assay. In parallel, we will measure the tensile strength of the membranes and associate the biochemical changes induced by myo-inositol treatment with the weakening of the

		membranes. Understanding the role of myo-inositol in regulating the biochemical and biomechanical properties of fetal membrane is essential to substantiate and facilitate the design of future clinical trials investigating the efficacy of myo-inositol prophylaxis against preterm birth.
3.9	**A/Prof Chan Shiao-Yng** obgchan@nus.edu.sg Department of Obstetrics & Gynaecology	**Using magnetic resonance imaging and spectroscopy to investigate the role of placental inositol in fetal growth regulation** Inositol is a highly bioactive carbohydrate involved in signalling, and glucose and lipid metabolism.The placenta is rich in inositols, acts as the gateway regulating supply of nutrients to the fetus and is a major determinant of fetal growth. High placental inositol appears to protect the fetus from the pro-adipogenic effects of maternal hyperglycaemia. Before inositol supplementation can be exploited as a potential intervention in fetal growth disorders, there is a need to understand how placental inositol may regulate fetal growth. This project will use magnetic resonance imaging techniques to quantify and spatially localise inositol isomers within the placentas obtained from pregnancies of babies born small, appropriate, or large for gestational-age. Associations will also be made between placental inositol measures and intrauterine fetal growth and with newborn birthweight. These findings will then be corroborated using data from separate ongoing mother-offspring cohorts, where longer term offspring growth and metabolic data is available. Therefore, this project will clarify the role of placental inositol in fetal growth regulation and will pave the way for development of inositol interventions for fetal growth disorders, which may ultimately mitigate the risk of future cardiometabolic disorders.
3.10	**A/Prof Chan Shiao-Yng** obgchan@nus.edu.sg Department of Obstetrics & Gynaecology	**Investigating the mechanistic role of the placenta in maternal-fetal transmission of mental health risk** Maternal mental health stresses during pregnancy, presenting as anxiety and depression, are associated with later offspring psychopathology, independent of postnatal maternal mental health status. Intrauterine signals of maternal stress received by the fetus via the placenta are thought to program the fetal brain during pregnancy and influence subsequent neurodevelopment. This project aims to identify the key placental pathways involved in maternal-fetal transmission of mental health risk. An integrative bioinformatics approach will be applied to available data (eg. clinical, neurodevelopmental outcomes, placental omics) from ongoing mother-offspring cohorts to determine significant transmission pathways, which can be validated in a separate cohort of samples using a range of laboratory techniques including molecular biology to

		investigate gene expression changes and in vitro cultures for functional analysis and magnetic resonance imaging and spectroscopy to analyse placental structure and measure metabolites respectively. Understanding the precise mechanisms by which the effects of maternal mood are transmitted via the placenta to the fetus will generate novel knowledge critical for designing interventions that can minimise the risk of vertical transmission of mental health vulnerability, and improve long-term neurocognitive and behavioural outcomes of offspring, and ultimately optimising human potential and reducing societal costs of poor mental health.
4	**Immunology Translational Research Programme**	
4.1	**Dr Nguyen Nam Long** bchnnl@nus.edu.sg Department of Biochemistry	**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 source of circulating S1P is yet to be revealed Spns2 and Mfsd2b are the two major S1P exporters (Science 2009; Nature 2017). We are interested in mapping the S1P concentrations in the body. Specifically, we will genetically delete S1P transporters and study the cellular controls for S1P levels in blood and lymphoid tissues. We plan to investigate how S1P gradient will affect the ins and outs of lymphocytes in lymphoid tissues. The knowledge gained can be explored to regulate the traffic of immune cells in treatment of inflammatory conditions.
4.2	**Dr Nguyen Nam Long** bchnnl@nus.edu.sg Department of Biochemistry	**The roles of endothelial cell transporter Mfsd7c for CNS vascular health and brain functions** Several missense mutations of Mfsd7c, an orphan transporter have been reported in 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. These preliminary results indicate MFSD7c is required for the normal growth of CNS blood vessels and ablation of this gene results in microcephaly-associated vasculopathy in mice and humans. 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. A huge gap in knowledge is to understand which nutrient molecules are transported into brain parenchyma. 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 goals are to understand the roles of nutrients for brain development and functions by deorphanizing the ligand(s) for transporters at the blood brain barrier. The broad objective here is to unravel the mechanisms by which Mfsd7c facilitates the delivery of nutrients to the brain and maintains blood vessel functions.
4.3	**Dr Tsai Shih-Yin** phsts@nus.edu.sg Department of Physiology	**Task for healthy longevity: Improving aging muscle strength by restoring the communication between the motor neuron and skeletal muscle** Sarcopenia, defined as an age-associated decline of muscle mass and strength, is a risk factor for mortality and disability in the elderly. Recent clinical trials showed that nutritional supplements had positive effects on muscle mass, but not on muscle strength, demonstrating our limited understanding of the pathophysiological mechanisms of sarcopenia. Since the decline either in motor neuron or skeletal muscle could correspond to sarcopenia, it is difficult to differentiate the sequential molecular events in which part contributing to the initiation of sarcopenia development. The challenge is to have a reliable in vitro system to recapitulate the in vivo microenvironment of aging-associated muscle degeneration. The recently developed microfluidic system for the 3D NMJ model, in which both motor neuron and skeletal muscle fibers assess their collective behavior in a 3D microenvironment, could exceed the limitation of 2D co-culture platform. The optogenetic control of motor neuron enables us to measure the muscle strength in the normal physiological condition. This innovative technology will allow us to clarify a cause-effect relationship between motor neuron and skeletal muscle in the development of sarcopenia. The proposed work seeks to identify the regulatory signaling between skeletal muscle and motor neuron in the microfluidic system for the 3D NMJ model. Ultimately, identification of the mechanistic links between skeletal muscle, and motor neuron will provide novel therapeutic strategies for age-induced muscle weakness.

4.4	**Dr Benoit MALLERET** benoit_malleret@nus.edu.sg Department of Microbiology & Immunology	**Molecular pathways of red blood cells invasion during malaria infection** Malaria, which is caused by Plasmodium parasites through Anopheles mosquito transmission, remains one of the most life-threatening diseases affecting hundreds of millions of people worldwide every year. Zoonotic malaria is a raising public health issue in Southeast Asia and the main goal of this project is to understand the molecular pathways involved in the red blood cell invasion (parasite ligand – host receptor association) in the context of malaria infection. A erythroctyic platform to knock-down the different host-receptor with a CRISPR-Cas9 lentiviral system is already available and well established in vitro culture of different Plasmodium species (Plasmodium falciparum, P. vivax, P. knowlesi) for this project. The characterization of the cell tropism between mature red blood cells (normocytes) and immature red bood cells (reticulocytes) will be also addressed due to different host-receptor repertoires at the surface of the two erythrocyte subsets. We identified already CD98 as a key receptor for Plasmodium vivax with these different tools (Malleret et al. 2021 Nature Microbiology) but a lot of other host-receptors need to be discovered.
4.5	**Dr Chen Kaiwen** Kaiwen.chen@nus.edu.sg Department of Microbiology & Immunology	**Inactivation of proinflammatory signalling pathways in apoptotic cells** Apoptosis is an essential biological process that is required for development and the removal of damaged or superfluous cells. As millions of cells undergo apoptosis daily, there are multiple mechanisms in place to ensure that apoptosis remains immunologically silent. Consequently, defects in apoptotic signalling are associated with a range of inflammatory disease and also susceptibility to infection. The goal of this project is to identify novel mechanisms by which apoptotic signalling inactivates innate immune pathways. This project offers the opportunity to be trained on animal dissection, differentiation and generation of bone marrow-derived macrophages, western blotting, ELISA, microscopy, cloning, retroviral transduction, bacterial infection assays and cell death assays.

4.6	**Dr Chen Kaiwen** Kaiwen.chen@nus.edu.sg Department of Microbiology & Immunology	**Determining the activation mechanism of the protease caspase-8** Caspase-8, the initiator caspase of the extrinisic apoptosis pathway, is best known for its role in triggering cell death. However, recent data in mice and humans demonstrate that caspase-8 deficiency results in severe immunodeficiency, indicating that caspase-8 is required for promoting inflammatory response. However, the mechanisms by which caspase-8 is activated and subsequently 'turned off' is not well understood. The goal of this project is to better understand caspase-8 signalling on a molecular level. This project offers the opportunity to be trained on animal dissection, differentiation and generation of bone marrow-derived macrophages, western blotting, ELISA, microscopy, cloning, retroviral transduction, bacterial infection assays and cell death assays.
4.7	**A/Prof Jinhua Lu** miclujh@nus.edu.sg Department of Microbiology & Immunology	**mRNA-based engineering of dendritic cells for the cross-priming of broad tumour-killing CD8+ T cells** Cancers differ from normal tissues in two major aspects: 1) tumour cells are hyper-proliferative, and 2) tumour cells accumulate genetic mutations. As a result, 1) tumour cells are more susceptible to chemotherapy and radiotherapy than normal cells which disrupt cell growth, and 2) some mutant tumour proteins are targeted by killer CD8 T cells which form the basis of the fast-growing cancer immunotherapies. The challenges are: 1) besides tumour cells, some normal cells, especially the fast-renewing hematopoietic and other tissue progenitor cells, are also damaged by chemo/radiotherapies which limits the dosage/length of such treatments and hence it also limits the therapeutic outcomes; 2) for immunotherapy, a cure is often not achieved because of the cells in most tumours are heterogeneous. The heterogeneity is due to progressive mutational loads when a tumour grows leading to generations of tumour cells with different mutational loads. Immunotherapy is often more effective against some but not other populations which then re-grow the tumour mass in situ or in distant organs. We recently discovered a family of adjuvant peptides suitable for cancer vaccine development (https://medicine.nus.edu.sg/nic/kickstart/projects/). An NMRC OF-IRG grant has been awarded to optimise this in-house platform for developing various cancer vaccines. In this project, CAR-DC will be generated based on this platform for cancer immunotherapy. Basically, monocytes are isolated from patients to introduce two classes of mRNA using our adjuvant peptide (P2M2): 1) the DC1-specific transcription factor DC-SCRIPT which promotes tumour antigen cross-

		presentation to activate CD8+ killer cells, and 2) chimeric antigen receptors (CAR) that target specific nuclear antigens specifically displayed on tumour cells and the tumour-associated vasculature. This engineering strategy is possible because of P2M2 and resultant CAR-DC are expected to home to tumours for antigens and then cross-prime/activate tumour-specific CD8+ killer T cells.
4.8	**A/Prof Jinhua Lu** miclujh@nus.edu.sg Department of Microbiology & Immunology	**Mining alarmin adjuvants hidden among the chromatin network** Self-reactive immunity against the nucleus was first described at the turn of 1950s and it is now known to be a signature of many autoimmune diseases, cancer, and ageing. The antinuclear autoantibodies (ANA) can amplify aberrance in tissue homeostasis to cause or contribute to chronic diseases ans is therefore a routine clinical test in hospitals. What caused these autoantibodies remain poorly defined, but our recent discovery of 3 strong alarmins in the nucleolus has led us to propose that cells contain complex hidden alarmin adjuvants that fuel self-reactive immune responses to nuclear antigens (https://www.nature.com/articles/s41419-021-03766-w). One such alarmins has been translated for cancer vaccine development (https://medicine.nus.edu.sg/nic/kickstart/projects/). In this PhD project, we continue to mine the nucleus for further alarmins for understanding the causes of autoimmune diseases, cancer and accelerated ageing. In addition, some of these alarmins could be applied in vaccine development.
4.9	**A/Prof Jinhua Lu** miclujh@nus.edu.sg Department of Microbiology & Immunology	**Tilt cancer vaccine-induced immunity in favour of CD8 killer cells** A vaccine can induce antibody, CD4 and CD8 mediated immunity. While antibody immunity is highly protective against bacterial, fungal and viral infections, it is predominantly CD8-mediated immunity that is effective against cancers. However, to target an exogenous antigen to MHC class I molecules for CD8 T cell activation is a daunting task. In discovering alarmins hidden among the chromatins, we identified a peptide which brings cancer antigens across the membrane of dendritic cells into the cytoplasm (https://medicine.nus.edu.sg/nic/kickstart/projects/). A cancer vaccine discovery platform has been developed employing this peptide (P2M6), dendritic cells, and T cells. The PhD project focuses on dendritic cell responses to P2M6-linked cancer vaccines and how CD8 T cells are optimally activated to kill tumour cells.

5	Infectious Diseases Translational Research Programme	
5.1	**A/Prof Chu Jang Hann** miccjh@nus.edu.sg Department of Microbiology & Immunology	**Molecular RNA Virology and Antiviral Strategies (MARVAS)** Positive-strand RNA viruses encompass over one-third of all virus genera and include numerous human pathogens, such as dengue virus, West Nile virus, Enterovirus 71, Chikungunya virus, MERS coronavirus and hepatitis C virus. Host factors participate in most, if not all steps of positive-strand RNA virus infection, including entry, viral gene expression, virion assembly and release. Moreover, host factors are targeted by positive-strand RNA viruses to modulate host gene expression and immune defenses. In our current study, human Enterovirus 71, mosquito-borne viruses (Zika and Dengue) as well as SARS CoV-2 are used as the virus models to decipher the interplay of essential host factors with positive-strand RNA viruses. Knowledge gained from these investigations has enabled us to design and develop the formulation of effective vaccine or therapeutic intervention (antivirals) against these medically important virus infections.
5.2	**Prof Lim Seng Gee** mdclimsg@nus.edu.sg Department of Medicine	**Achieving Functional Cure of Chronic Hepatitis B** Background: Chronic Hepatitis B is chronic viral disease affecting the liver and there are over 270million infected patients globally, being the most common cause of liver disease and liver cancer globally. Functional cure (HBsAg loss) is an achievable goal leading to improved survival, lower liver cancer and liver complications. The biology of different stages of Chronic Hepatitis B (CHB) is still not well understood but insights are likely with deep multidimensional phenotyping comprising genomics, transcriptomics, proteomics , microRNA, immunology and virological characterisation, an opportunity we are well placed to explore with our well established cohort of over 2000 Chronic Hepatitis B patients The main focus will be on functional cure of CHB defined as HBsAg loss, not achievable with current therapies. The objectives of our proposal is the understand the virological and immune mechanisms involved in functional cure by examining the liver microenvironment with state of the art technologies such as single cell analysis, genomics, transcriptomics, proteomics, and epigenetics in patients with/without functional cure. As the key to CHB is an indepth analysis of epigenetics of cccDNA, factors found in the HBV TCR to be important in viral replication will be investigated to understand their direct or indirect relationship to HBV. Concurrently, a validated target for HBV will be a particular focus for assay development, computerised modelling, and medicinal library development as possible new classes of antiviral agents. New mechanisms of action, and new antiviral agents can be tested out in the humanised mouse model which is being developed as a model-of-choice for CHB with

		chronic HBV infected hepatocytes and a fully matched immune system. Potential projects for suitable applicants, esp those interested in PhD projects 1. Transcriptome analysis of intrahepatic versus peripheral blood compartment in CHB patients with and without functional cure 2. Functional immunological analysis of intrahepatic compared to peripheral blood in functional cure 3. Innate versus adaptive intrahepatic immune responses in CHB patients with and without functional cure 4. Examination of HBV minichrosome (cccDNA)quantity and function in CHB livers in patients with and without functional cure 5. Dissecting cccDNA silencing mechanisms in patients with and without functional cure of CHB 6. Assay development in novel targets towards HBV 7. Medicinal library construction of potential antiviral agents using novel targets and assays 8. Humanised mice models for Chronic hepatitis B Interested candidates should contact Prof Lim Seng Gee: mdclimsg@nus.edu.sg or Ms Amy Tay: mdctyla@nus.edu.sg
5.3	**Dr Sham Lok To, Chris** miclts@nus.edu.sg Department of Microbiology & Immunology	**Elucidating capsular polysaccharide biogenesis in Streptococcus pneumoniae** Streptococcus pneumoniae is an important respiratory pathogen that causes more than one million deaths worldwide annually. Similar to other pathogenic bacteria, S. pneumoniae encases its cell envelope with capsular polysaccharide (CPS). This layer protects the cell from host insults, such as opsonophagocytosis and mucus clearance. Because of its importance in pathogenesis, all clinically relevant vaccines against S. pneumoniae target the CPS. There are at least 100 serotypes identified and the structural variation of CPS is attributed to the extreme diversity of glycosyltransferases (GTs), flippases, and polymerases at the cps locus. Little is known about the molecular mechanisms governing their specificity, regulation, and function. The long-term goal of this project is investigate the specificity determinants of CPS enzymes based on the wealth of structural information available for pneumococcal CPS. Our approach is enabled by conditional essentiality of the CPS enzymes and the genetic tractability of S. pneumoniae. Understanding how CPSs are synthesized in S. pneumoniae is critical to improve our current antimicrobial and vaccine strategies. Enzyme variants isolated from this work will be valuable tools for synthetic biology and glycoengineering. Besides studying CPS enzymes, we are interested in finding small molecules that inhibit different steps of the CPS pathway as therapeutics.

5.4	**A/Prof Swaine Chen** mdcslc@nus.edu.sg Department of Medicine	**Applying single cell genomics to gain new insights into recurrent urinary tract infection, potentially leading to novel treatment strategies** Urinary tract infections (UTIs) are among the most common infections of humans and a major reason why people take antibiotics. This, in turn, leads to higher antibiotic resistance rates. The primary clinical problem in treating UTI is that for some patients, UTIs recur frequently, despite sometimes prolonged courses of antibiotic therapy. While the majority of bacteria during a UTI are extracellular and present in the urine in the lumen of the bladder (which makes them easy to isolate, monitor, and treat), a subset of intracellular bacteria within the bladder epithelial cells is relatively resistant to antibiotic treatment and host immune defenses. These intracellular bacteria can therefore persist for weeks to months in the bladder (presumably causing no symptoms); upon reactivation, they can cause recurrent UTI. We are applying advances in single cell genomics to understand how UPEC are able to enter and survive in the intracellular niche. Some of our genetic and protein engineering tools are crucial for this work, enabling us to manipulate and visualize clinical strains of UPEC
5.5	**A/Prof Swaine Chen** mdcslc@nus.edu.sg Department of Medicine	**Developing sexual genetics in E. coli as a new, complimentary engine for synthetic biology applications** Genetics has been a cornerstone of biological discovery, leading to understanding, diagnosis, and treatments for numerous human diseases. The history of genetics traces its roots to Gregor Mendel's iconic experiments hybridizing pea plants; a direct line to powerful genetic systems in Drosophila and mice has enabled breakthroughs ranging from congenital disease to cancer. The Chen lab has developed several genetic techniques, in particular focusing on general tools that can be used in wild-type strains of E. coli in addition to the "easier" lab-adapted strains traditionally used for synthetic biology. These tools now, for the first time, enable access to the power of sexual genetics (like that which powers mouse or human genetic studies) combined with high throughput genomics in Escherichia coli, the most well studied bacterium and most important chassis organism for synthetic biology. The marriage of sexual genetics with E. coli enables unprecedented opportunities for research discovery (which requires a robust resource supply chain) and for developing and marketing boutique, purpose-built custom chassis for the broader biotechnology industry.

5.6	**A/Prof Swaine Chen** mdcslc@nus.edu.sg Department of Medicine	**Explaining the 2015 GBS yu sheng outbreak in Singapore - and ongoing GBS infections** The largest reported outbreak of group B Streptococcus (GBS) infections occurred in Singapore in 2015, involving over 300 cases of bloodstream infections. This outbreak was associated with consumption of 魚生 (yu sheng), a dish made from sliced raw fish and served with rice porridge by food stalls. Such foodborne transmission leading to invasive disease had not been reported prior to this outbreak. One clone of GBS, referred to as ST283, was responsible for this outbreak; this strain is almost exclusively found in Southeast Asia in both humans and fish. This project uses genomics, genetics, microbiology, and an animal model of infection to discover why ST283 GBS is so proficient at causing disease in humans and why it is well adapted to aquaculture.
5.7	**A/Prof Sylvie Alonso** micas@nus.edu.sg Department of Microbiology & Immunology	**Development of a versatile, rapidly deployable, one-shot vaccine targeting platform.** The goal of this project is to develop a vaccine platform that has the potential to confer rapid and sustained, protective immunity upon a single shot of small amount of antigen. Conceptually, this vaccine strategy consists of plugging the vaccine antigen candidate to the heavy chains of an anti-Clec9A monoclonal antibody that targets a specific subpopulation of dendritic cells. We have generated proof-of-concept data using two vaccine antigen candidates, namely the universal flu vaccine antigen M2e, and the receptor binding domain (RBD) from SARS-CoV2 Spike protein. We showed that the single administration of Clec9A-M2e and Clec9A-RBD constructs triggers a rapid and prolonged, protective antigen-specific antibody response. However, a number of important aspects remain to be investigated in order to fully evaluate the potential of this vaccine targeting strategy. They include exploring i) the nasal route of administration, ii) the efficacy to prime younger and older immune systems, iii) the ability to trigger a CD8 T cell-mediated protective immune response, and iv) the vaccine efficacy in a diverse genetic background. The multidisciplinary nature of this project will provide students with the opportunity to acquire strong expertise in animal experimentation, ex vivo and in vitro immunology assays, basic virology and cell biology.

5.8	**A/Prof Tan Yee Joo** mictyj@nus.edu.sg Department of Microbiology & Immunology	**Studying viral-host interactions in chronic hepatitis viral infection versus 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 this project, we will use a multidisciplinary approach to identify host factors that are regulated by different viral proteins. The functional significance of novel viral-host interactions identified will be analyzed by using cell culture systems. Identification of novel viral-host interaction therefore offers opportunities for designing new treatments and prevention strategies.
5.9	**Dr Voo Teck Chuan** medvtc@nus.edu.sg Centre for Biomedical Ethics	**Epidemic Ethics during COVID-19** Areas of interest include • ethical and legal issues with COVID-19 vaccination/immunity certificates for international travel • ethical issues with stay-at-home and other confinement orders • family presence for infected patients under medical isolation • vaccinating vulnerable persons without capacity
5.10	**A/Prof Gan Yunn Hwen** bchganyh@nus.edu.sg Department of Biochemistry	**Dynamic gut microbiome modulations to establish colonization resistance against multidrug resistant *Klebsiella pneumoniae*** The aim is to discover the factors that can restore a dysbiotic gut microbiome to a healthy state to effect colonization resistance against multidrug resistant opportunistic pathogens. The project will employ in vitro bioreactor setups and in vivo mouse models to examine various perturbations that can change the microbiome structure and function to establish colonization resistance.

5.11	**Dr Qu Kun** kqu@nus.edu.sg Department of Biochemistry	**Molecular mechanisms of assembly and transmission of viruses causing respiratory tract infections** The broad objective of this project is to dissect the molecular mechanisms of host-pathogen interactions of the most prevalent respiratory viruses which cause the greatest burden on human health and social economy. Past flu pandemics and the ongoing COVID-19 pandemic have sounded the alarm that cross-species pathogen transmission and disease outbreaks will become more and more frequent due to the increasing and inevitable mobility of global population and economy. More measures should be made by governments and health organisations to detect and control the spread of infectious diseases. Closer investigations in virology and microbiology are urgently needed to prepare for the next pandemic. The proposed project will provide multifaceted information in situ of respiratory tract infections caused by SARS-CoV-2 and influenza A virus, from cellular to molecular levels by using combined methods in virology, lipid biology, cryo-electron tomography and subtomogram averaging. At the cellular level, we will expand our understanding of virus-cell interactions, which will potentially lead to discovery of novel targets for broad-spectrum antiviral treatments. At the molecular level, we will elucidate the structural basis of respiratory virus assembly, which will broadly foster new designs of vaccines or novel inhibitors to block the viral replication or maturation.
6	**Digital Medicine Translational Research Programme** **Institute for Digital Medicine (WisDM)**	
6.1	**Dr Tamra Lysaght** tlysaght@nus.edu.sg Centre for Biomedical Ethics	**Ethics and Governance of AI-driven Health Technologies** This project broadly covers the ethical, legal and social issues surrounding the development and introduction of AI-assisted technologies in healthcare. Includes mobile technologies and AI-assisted clinical decision-making platforms.
6.2	**Dr Le Thi Nguyet Minh** phcltnm@nus.edu.sg Department of Pharmacology	**Developing red blood cell extracellular vesicles for targeted and functional delivery of therapeutic cargos** Extracellular vesicles (EVs) are natural carriers of RNAs in intercellular communication. Recently, we have developed a strategy to harness EVs from red blood cells (RBCs) to deliver RNA drugs to cancer cells. RBCEVs are inexpensive to purify in large quantities and can mediate robust delivery of therapeutic RNAs to both leukemia and solid cancer cells for efficient oncogene inhibition. Moreover, this delivery platform is safe as RBCEVs are devoid of DNA, growth factors, and toxic substances. We have also engineered RBCEVs with peptide and antibody conjugation for targeted delivery. Our studies were published in Nature Communications and the

		Journal of Extracellular Vesicles, and the RBCEV technology has been licensed to Carmine Therapeutics. Our goal is to develop RBCEVs into a versatile drug delivery platform with high efficiency, low toxicity, and high specificity. We are currently working on multiple applications of RBCEV-mediated gene therapy for cancer, COVID-19, and other diseases. We are also investigating the potential therapeutic benefits of the natural cargos of RBCEVs; in particular, we hypothesise that the endogenous hemoglobin carried by RBCEVs can protect macrophages from foam cell transformation and thus suppress atherosclerosis progression. Additionally, we seek to elucidate the mechanisms of uptake and intracellular trafficking of RBCEVs. (More information at https://lelabnus.wordpress.com/.)
7	**Cancer Translational Research Programme** **NUS Centre for Cancer Research (N2CR)**	
7.1	**Dr Alan Prem Kumar** apkumar@nus.edu.sg Dean's Office	**Circulating miRNAs That Predict Ovarian Cancer patients' (wild type BRCA1/2) Response to Chemotherapy** Ovarian cancer (OC) is known to be the most lethal gynecological malignancy in women, with approximately 184,799 deaths per year recorded worldwide in 2018. However, the incidence of OC varies from region to region and age annually. Among other sub-types of OC, the most common is serous ovarian cancer (HGSOC and LGSOC), which comprises ~70% of all ovarian cancers. The most practicing treatment of all ovarian carcinomas are surgical removal of tumor tissue terms as debulking. However, for certain patients, early surgery is not desirable as much, thus the chemotherapy is administered before surgery. About 80% OC patients are susceptible to platinum-based medication, mainly cisplatin and carboplatin among others. Here, the function of cisplatin or carboplatin monotherapy is to direct the insertion of platinum into DNA to form crosslinks. During chemotherapy, most patients will relapse and become resistant to platinum (Cisplatin or carboplatin) therapy. Eventually, all patients with HGSOC are resistant to platinum and succumbed to the disease. Our aim is to identify a miRNAs signature set that predicts response to cisplatin or carboplatin chemotherapy in OC patients, who had no alterations in BRCA1/2. The study will first be a retrospective analysis of miRNAs from OC patients' blood plasma and tumor biopsies and correlate expression changes of these miRNAs to chemotherapy response as discovery set. These miRNAs will then be validated in OC cell lines to define their role in chemo-response and elucidation of mechanism. Following which, we would proceed to 2 prospective cohorts to further validate and narrow down the signature set. The ultimate goal is to develop a companion diagnostics kit (blood plasma) for additional clinical testing and eventually into the clinic.

7.2	**Dr Alan Prem Kumar** apkumar@nus.edu.sg Dean's Office	**To explore a novel Lyn-Rac1-STAT3 axis to tumor immune modulatory pathway in breast and gynecological cancers** The Src kinase is the first confirmed oncogene in history and the bona fide target of the SFK inhibitors. Hence, it was once assumed to be the most suitable candidate biomarker to predict the responsiveness of cancer cells to SFK inhibitors. However, such assumptions were soon disproved. Literature has reported there was no correlation between Src kinase activity and SFK inhibitors sensitivity in breast cancer. Hence, despite being a legitimate target of the SFK inhibitors, it is highly likely that Src may not be the most biologically relevant. Interestingly, within Dasatinib-sensitive TNBC cell lines, they discovered that the cell lines are insensitive towards Imatinib and Sunitinib inhibition. Hence, this suggest that the sensitivity of the Dasatinib is indeed brought upon by the targeting of the SFKs and not an off-target effect of Dasatinib. An interesting finding has to come to light that Lyn kinase (a closely related family member of Src kinase) was the top EMT signature gene in microarray analysis of TNBC cell lines and a strong inverse correlation between Lyn expression and overall survival of the breast cancer patients was observed. More compellingly, in their knockdown experiments involving Lyn kinase and Src Kinase, they realized that only the Lyn-knockdown TNBC cell lines closely resemble the Dasatinib-treated TNBC cell lines. Hence, the authors proposed that between Src and Lyn, the latter is likely to be the more clinically and biologically relevant target of the SFK inhibitors. Interestingly, from our Affymetrix Human Gene ST 2.0 Array results using our validated in-house Lyn-specific inhibitor (CHL4), besides the enrichment in gene sets pertinent to EMT, angiogenesis and apoptosis, a number of significant gene sets belonging to the inflammatory pathways were also up regulated. Many of these gene sets belonging to the NF-kB signaling pathway and interferon pathway modulators were enriched upon the treatment of CHL-4. Moreover, through some of our preliminary validation, transient up-regulation of Type I Interferon signaling was observed with Lyn inhibition. Furthermore, in the canonical type I interferon-induced signaling pathway, interferon receptor engagement with the type I interferons is known to activate JAK1 and TYK2. As such, we postulate that the transient up-regulation of Type I Interferon signaling upon Lyn inhibition is likely to be attributed to STAT3. In this study, we will be looking at the IRF3 activity in our breast, cervical, ovarian and endometrial cancer cell models following treatment with CHL-4 or dasatinib as it is a key transcription factor that controls Type I interferon production. Should there be an activation in IRF3, subsequent rescue experiments involving Sting inhibitors and TBK1 inhibitors will

		be performed to see if the inhibition of IRF3 activity can negate the stimulatory effects of CHL-4. At the same time, the ISRE Luciferase Activity assay will be performed to better study the activity of Type I interferon induced JAK/STAT signaling pathway in our female cancer cell models.
7.3	**Prof Chen Xiaoyuan** dnrxc@nus.edu.sg Department of Diagnostic Radiology	**Translational Nanomedicine and Theranostics (TNT)** Our lab specializes in synthesizing molecular imaging probes for positron emission tomography (PET), single-photon emission computed tomography (SPECT), magnetic resonance imaging (MRI), optical imaging (bioluminescence, fluorescence and Raman), contrast-enhanced ultrasound, photoacoustic imaging, and multimodality imaging. The lab aims to develop a molecular imaging toolbox to improve biological understanding, early diagnosis of disease, monitoring of therapeutic responses, and to guide drug discovery/development. LOMIN puts special emphasis on highly sensitive nanosensors for biomarker detection and “theranostic” [thera(peutic) + (diag)nostic] nanomedicine applied to imaging, gene and drug delivery, and monitoring of disease treatment. We are perhaps best known for the development of various forms of theranostics, which integrate in vivo molecular diagnostic tests and imaging with targeted therapeutics that individualize treatment to an individual's specific disease subtype and genetic profile. These can encompass diagnosis followed by stratification based on the likelihood of responses to given treatments, or therapy followed by monitoring of early response to predict treatment efficacy. Sometimes, diagnostic and therapeutic modalities are co-developed (e.g. nanotheranostics, immunotheranostics, magnetotheranostics, optotheranostics, radiothereanostics, etc.). The PI is the founding editor of the journal “Theranostics”.

7.4	**Dr Anand D Jeyasekharan** csiadj@nus.edu.sg Department of Medicine	**The impact of deregulated homologous recombination proteins on tumour immunogenicity** https://www.csi.nus.edu.sg/web/anand-jeyasekharan/ https://www.ncis.com.sg/For-Patients-and-Visitors/Pages/Find-a-Doctor-Details.aspx?docid=Anand_Jeyasekharan Our lab is interested in investigating determinants of tumour immunogenicity after exposure to genotoxic chemotherapy. In other words, the factors that influence how readily a tumour is recognised and subsequently cleared by the immune system after chemotherapy administration. We recently discovered that when a DNA repair protein, RAD51, is overexpressed in epithelial ovarian cancer (EOC), this event is correlated with resistance to platinum chemotherapy. Surprisingly however, RAD51 overexpression did not impact the direct cytotoxicity of platinum chemotherapy, but conferred poor survival due to a tumour microenvironment that is devoid of cytotoxic T-cells. Further details of this research are available in preprint form here: https://www.biorxiv.org/content/10.1101/2020.06.09.137612v1 While DNA repair deficiency has been known to result in altered anti-cancer immunity due to altered neoantigens and cytosolic DNA fragments, this is the first description of the link between overactivity of a DNA repair pathway and altered immunity. We note that RAD51 overexpression in cancer is associated with overexpression of several other proteins involved in homologous recombination (HR), and postulate that this constitutes a state of hyperactive HR. In this project we aim to elucidate the causal link between overexpression of HR proteins and cancer immunogenicity. We plan to systematically analyse how these proteins, either through their HR capabilities or through non-canonical means, regulate important immune pathways in EOC. The project will include the investigation of the impact of HR protein overexpression on repair of distinct genomic regions, and their impact on the activation of immune pathways. Skills that will be gained from this project include fundamental molecular biological techniques, bioinformatic techniques and clinical research methods. In addition, our lab has setup multiplexed immunofluorescence to study these HR proteins and immune pathways in clinically annotated samples. Potential PhD candidates will be expected to design their experiments and drive the project primarily through self -directed learning, with feedback and help from senior members of the laboratory and clinical collaborators.

7.5-7.7	**Dr Cheok Chit Fang** patcfc@nus.edu.sg Department of Pathology	**7.5 Developing novel therapeutics in cancer for personalized therapy** **7.6 Developing new molecular detection methods in cancer** **7.7 Discovering new mechanisms in genome maintenance** My lab focuses on exploiting specific molecular defects in cancer cells for targeted therapy. We are interested in translating the concepts of synthetic lethality to effective cancer treatments. In a broader sense, synthetic lethality describes functional interactions between two pathways/genes/mutations that synergistically reduce fitness and survival. We design CRISPR-based screens to identify synthetic lethal pathways and gene targets that can be manipulated to yield selective targeting of cancer cells. This work has expanded to include synthetic lethal interactions in DNA damage response pathways as part of our interests in deciphering the underlying connections between cancer initiation, progression and genomic instability. Recently, we have also identified new drug targets in metabolic pathways that paved the study for combination therapy with immune checkpoint inhibitors. In collaboration with clinicians and pathologists, our current work continues to espouse new cancer mechanisms in metabolic and DNA repair pathways for therapeutic applications.
7.8	**Prof Chng Wee Joo** mdccwj@nus.edu.sg Department of Medicine	**Investigate the role of NSD2 in m6A RNA methylation in t(4;14) myeloma** Multiple Myeloma (MM), characterized by the uncontrolled proliferation of malignant plasma cells. Recurrent chromosomal translocation t(4;14) is the second-most common and associated with poor prognosis. The Histone Methyltransferase (HMTase) NSD2 is overexpressed in MM due to the t(4;14) translocation. We identified NSD2-interacting proteins in t(4;14) myeloma cells that are enriched in RNA processing. Among these proteins, NSD2 interacts with hnRNPA2B1, a m6A reader. We discovered NSD2 ability to catalyze m6A RNA methylation on single stranded RNA probes in vitro. In this study, we aim to elucidate the role of NSD2 in m6A RNA methylation and its biological significance in t(4;14) myeloma. We hypothesize that the enzymatic SET domain of NSD2 is required for m6A RNA methylation of a specific mRNA subset to regulate their expression. We will perform site directed mutagenesis and introduce point mutations on different NSD2 domains to identify if the SET domain methyltransferase activity is required for RNA methylation. In addition, by using Oxford Nanopore long-reads sequencing technology and m6A-seq, we can pinpoint the genes that are regulated by NSD2 on both the transcription level and m6A abundance level.

7.9	**Prof Chng Wee Joo** mdccwj@nus.edu.sg Department of Medicine	**Understanding and Targeting the Non-Canonical Oncogenic Function of EZH2 for Therapeutic Intervention in Cancers** The dysregulation of euchromatic regions by epigenetic writers such as Polycomb Repressive Complex 2 (PRC2) is a fundamental hallmark of cancers. Overexpression of EZH2, a core catalytic component of PRC2 typically promotes oncogenesis by enzymatic inhibition of tumour suppressor proteins. However, in a group of highly aggressive and refractory cancers such as Natural Killer T-Cell Lymphoma and Triple- Negative Breast Cancer, EZH2 acquires an additional ability to functionally switch from a transcriptional repressor to transcriptional activator of oncoproteins through a mechanism which is independent of its catalytic function. Enzymatic inhibitors of EZH2 are therefore ineffectual in overcoming these malignancies. In this study, we aim to develop CRISPR-Cas9 engineered models of EZH2 in conjunction with a targeted loss-of-function screen to identify and validate transcriptionally activated oncogenic targets of EZH2. This process may also identify a clinically-relevant gene signature. In addition, we hypothesize that targeted degradation of EZH2 will more successfully suppress refractory cancers driven by the non-canonical EZH2 oncogenic signal. Therefore, we intend to generate a novel series of EZH2-PROTAC probes which tag EZH2 for proteasomal-mediated degradation through targeted ubiquitination. Altogether, this study elucidates the molecular mechanisms underlying aggressive non-canonical EZH2 cancer subtypes, with direct applications in diagnostics, therapeutics and prognostication.

7.10	**A/Prof Deng Lih Wen** bchdlw@nus.edu.sg Department of Biochemistry	**Early prediction of radioresistance and distant metastasis through molecular signature-based surveillance strategy** Radiotherapy (RT) has an important role in the multimodality management of cancers and is employed in the neoadjuvant, definitive, or adjuvant setting. Mixed response to RT has been observed in the definitive setting and patients with poor response to RT have higher rate of recurrence and need for further salvage therapy, resulting in higher treatment morbidity. Further, distant metastasis and cancer relapse post-RT is also a major cause of treatment failure. Therefore, a pre-screening strategy to predict response to RT upfront would be valuable in identifying patients with radioresistant tumours as this would impact the treatment strategy at diagnosis. We recently identified a miRNA panel which predicts radioresistance and distant metastasis in cervical cancer through an unbiased microarray and miRNA screening approach. Analysis of public databases validated the prognostic value of the identified signature in determining outcome in cervical cancer. Given similarities in etiology and RT-based treatment strategies for cervical cancer and head and neck squamous cell carcinomas (HNSCC), we interrogated publicly available datasets for HNSCC and found that the identified miRNA signature also predicts poor outcome in HNSCC. The PhD candidate will participate in a multidiscipline research program with basic scientists and clinical scientists to (1) clinically validate the identified miRNA signature and their correlation to radioresistance and distant metastasis; (2) explore the potential of liquid biopsy-based non-invasive molecular surveillance and prediction strategies using identified molecular signatures in CC and HNSCC; (3) understand the mechanistic underpinnings of how candidate miRNAs can mediate the radioresistant and metastatic phenotypes. The work will advance efforts in the development of alternative treatment options to improve the prognosis of patients with resistant/recurrent cervical cancer and head and neck cancer.

7.11	**A/Prof Deng Lih Wen** bchdlw@nus.edu.sg Department of Biochemistry	**Targeting Cysteine Metabolism in Ovarian Clear Cell Carcinoma** The PhD candidate will participate in a multidiscipline research program with basic scientists, and clinical scientists to study the potential of targeting cysteine metabolism in ovarian clear cell carcinomas (OCCC), an aggressive and chemo-resistant tumor subtype comprising approximately 12-16% of epithelial ovarian cancers. Current treatment options for OCCC are limited to combination of platinum-based and other cytotoxic agents to which patients respond poorly due to intrinsic chemoresistance. We have previously reported that OCCC has profound dependence on cysteine for survival in vitro and in vivo, and cysteine-deprived glycolytic OCCC is abolished primarily by oxidative stress-dependent necrosis and ferroptosis. This suggests targeting cysteine metabolism as a novel alternative therapeutic strategy for OCCC. Our pilot study suggests depletion of the extracellular cysteine/cystine pool via pharmacological inhibition and engineered cysteine-degrading enzyme, can re-sensitise cisplatin-resistant cells to the cytotoxic effects of cisplatin. We propose to study the effects of cysteine deprivation and its combinatory effects with cisplatin in 2D cell culture, 3D spheroid and patient-derived organoids and xenograft mouse models. We aim to use pharmacological inhibitors and cysteinase as a mode to systematically deplete extracellular cysteine for therapeutic applications as a cisplatin sensitizer, and to investigate the potential applicability of using novel delivery vehicle to deliver inhibitors or cysteinase to tumour sites for cysteine deprivation locally in in vitro and in vivo models. We will also elucidate molecular mechanism underlying the synergistic anti-cancer effect of cysteine deprivation and cisplatin in OCCC. The knowledge generated from this study will provide proof-of-concept data for the potential translational applications of targeted cysteine deprivation as a cisplatin re-sensitisation strategy for ovarian carcinoma which is the most lethal gynaecological cancer with majority of patients eventually becoming platinum-resistant with subsequent relapses. The PhD candidate will participate in a multidiscipline research program with basic scientists, and clinical scientists to study the potential of targeting cysteine metabolism in ovarian clear cell carcinomas (OCCC), an aggressive and chemo-resistant tumor subtype comprising approximately 12-16% of epithelial ovarian cancers. Current treatment options for OCCC are limited to combination of platinum-based and other cytotoxic agents to which patients respond poorly due to intrinsic chemoresistance. We have previously reported that OCCC has profound dependence on cysteine for survival in vitro and in vivo, and cysteine-deprived glycolytic OCCC is abolished primarily by oxidative stress-dependent necrosis and ferroptosis. This suggests targeting cysteine metabolism as a novel alternative therapeutic strategy for OCCC. Our pilot

		study suggests depletion of the extracellular cysteine/cystine pool via pharmacological inhibition and engineered cysteine-degrading enzyme, can re-sensitise cisplatin-resistant cells to the cytotoxic effects of cisplatin. We propose to study the effects of cysteine deprivation and its combinatory effects with cisplatin in 2D cell culture, 3D spheroid and patient-derived organoids and xenograft mouse models. We aim to use pharmacological inhibitors and cysteinase as a mode to systematically deplete extracellular cysteine for therapeutic applications as a cisplatin sensitizer, and to investigate the potential applicability of using novel delivery vehicle to deliver inhibitors or cysteinase to tumour sites for cysteine deprivation locally in in vitro and in vivo models. We will also elucidate molecular mechanism underlying the synergistic anti-cancer effect of cysteine deprivation and cisplatin in OCCC. The knowledge generated from this study will provide proof-of-concept data for the potential translational applications of targeted cysteine deprivation as a cisplatin re-sensitisation strategy for ovarian carcinoma which is the most lethal gynaecological cancer with majority of patients eventually becoming platinum-resistant with subsequent relapses.
7.12	**A/Prof George Yip** georgeyip@nus.edu.sg Department of Anatomy	**Expression and Functional Analysis of Glycosaminoglycans and Proteoglycans in Breast Cancer** Glycosaminoglycans are highly negatively charged molecules made up of repeating disaccharide subunits consisting of an amino sugar and an uronic acid. They are covalently linked to core protein backbones to form proteoglycans. Besides structural roles, glycosaminoglycans and proteoglycans have important biological functions in regulating cell behaviour through their interactions with growth factors and signalling molecules. They are also involved in microRNA- and exosome-mediated regulation of cancer. In this study, we aim to elucidate the effects of these molecules on cancer cell activities, to investigate their potential clinical use as biomarkers and prognostic indicators, and to utilise them for the development of novel therapeutic targets. A variety of cell and molecular biology techniques will be employed in this project using both in vitro and in vivo models. References: 1. Kumar KS et al (2021). FEBS J;288:486-506. 2. Tan XF et al (2019). Methods Mol Biol;1974:21-30. 3. Lucanus AJ et al (2018). Oncogene;37:833-838. 4. Iravani O et al (2017). Exp Cell Res;350:380-389. 5. Kumar AV et al (2014). Int J Cancer;135:2579-2592. 6. Ibrahim SA et al (2012). Int J Cancer;131:E884-896. 7. Yip GW (2011). Recent Pat Anticancer Drug Discov;6:164-165.

7.13	**Prof Khong Pek Lan** dnrkpl@nus.edu.sg Department of Diagnostic Radiology	**Clinical Molecular Imaging Research for Precision Oncology** Positron Emission Tomography (PET) is a molecular imaging modality that allows visualisation of molecular and metabolic-functional processes by the use of organic molecules and pharmaceuticals labeled with positron-emitting radionuclides (or tracers). These probes provide valuable insights into biochemical, physiological, pathological or pharmacological process in vivo. PET tracers as molecular imaging probes have demonstrated significant clinical utility in oncology impacting on patient management in terms of early diagnosis, identifying histopathology, directing treatment, monitoring therapy response etc. Thus, molecular imaging tools will greatly contribute to the realization of modern precision oncology. The PI, Prof. Khong is the Director of The Clinical Imaging Research Centre (CIRC) of the Yong Loo Ling School of Medicine. CIRC is a core facility that for translational molecular imaging research that provides a platform for development and translation of molecular imaging biomarkers/tracers and theranostics to clinical practice. https://medicine.nus.edu.sg/circ/ Two important novel molecular imaging tracers for oncology will be developed at CIRC; 68Ga-Pentixafor (CXCR4 chemokine receptor) and 68Ga-FAPI (Fibroblast activation protein-α type II inhibitor). Both tracers are highly promising in the evaluation of various cancers using PET imaging, and early experience has found them to be advantageous to the currently used 18F-FDG (fluorodeoxyglucose) in multiple aspects with potential in filling unmet clinical needs. We aim to evaluate its novel role of these tracers in the management of common cancers in Singapore.

7.14	**Prof Ruby Huang Yun-Ju** obgrhy@nus.edu.sg Department of Obstetrics & Gynaecology	**Know Thy Neighbour – Spatial Profiling of Intra-tumour Heterogeneity (ITH)** Personalized medicine has gained much momentum to become the mainstream practice to inform care to cancer patients. The basis of patient stratification relies on the existence of inter-tumoral heterogeneity. This has been extensively documented by The Cancer Genome Atlas (TCGA) projects identifying various molecular subtypes. These molecular subtypes have distinct clinicopathologic outcomes and hence are relevant for therapeutic intervention. However, intra-tumoral heterogeneity (ITH) complicates this approach. Clonal diversity arising from ITH and the clonal evolution of alterations in the spatial and temporal context, results into multiple spatially separated subclones that would acquire distinct aberrations in the same gene, protein complex or signal transduction pathway. Moreover, the existence of heterogeneity is at the multi-omics levels. Therefore, leveraging on novel technologies to address the clonal diversity within ITH has become an urgent need. This project will dive into the spatial biology surrounding ITH to interrogate the tumor immune microenvironment (iTME) and the tumor epithelial-mesenchymal phenotypes (EMP). Cutting-edge technology platforms for high magnitude multiplexing signal detection with high resolution for precise spatial expression will be adopted. The multi-omics landscape from switches along the entire EMP spectrum would be associated with the remodeling of iTME in the selected cancer types and the precursors.
7.15	**Prof Vinay Tergaonkar** bchvt@nus.edu.sg vinayt@imcb.a-star.edu.sg Department of Biochemistry	**ADAR1 meets NF-kB signaling: Functional role of lncRNA in regulating immune evasion** RNA based and RNA targeting theraputics are increasingly becoming useful in clinical applications targeting various disease. Here we are trying to explore the relevance of one such class of RNA in relation to liver cancer. p65 and ADAR1 are also very important for liver homeostasis and have been associated with liver diseases including liver cancer. The proposal addresses an important link of how and what lncRNA are controlled by these 2 important proteins in cells which can be utilised later to target these molecules to treat liver cancer. The student will be able to get a hands on training and skills related to conducting bench work in molecular and cell biology related expirements. By the end of the training he/she will be able to conceptualise resaerch projects and design expirements and analyse the results obtained. Stronger students will also be trained to write papers and present data to others.

7.16	**Prof Vinay Tergaonkar** bchvt@nus.edu.sg vinayt@imcb.a-star.edu.sg Department of Biochemistry	**Investigating the physiological roles of p52-ETS1, a new transcription factor** In this project, a high-throughput screening of small-molecule inhibitors targeting p52-ETS1 interaction will be conducted. We will collaborate with industry partners to help us with the design and synthesis of the inhibitors, and also for further validation of our candidate inhibitors. Successful candidates can be patented and further developed for clinical trials. The student will be able to get a hands on training and skills related to conducting bench work in molecular and cell biology related experiments. By the end of the training he/she will be able to conceptualise research projects and design experiments and analyse the results obtained. Stronger students will also be trained to write papers and present data to others.
7.17	**Dr Yvonne Tay** yvonnetay@nus.edu.sg Department of Biochemistry	**Alternative UTRs of key cancer genes: Novel regulators and therapeutic targets?** Messenger RNAs (mRNAs) comprise central protein-coding regions flanked by 5' and 3' untranslated regions (UTRs) that play important roles in post-transcriptional regulation. UTRs harbor many regulatory sequences and structures which control processes including mRNA stability, localization, export and translation efficiency. Intriguingly, the majority of mammalian genes generate multiple mRNA isoforms that differ in their UTRs. These alternative UTRs are produced by mechanisms including alternative promoter usage, splicing and alternative polyadenylation (APA). Critically, although independent efforts have begun to characterize each facet of UTR processing, little is known about how they converge to determine UTR heterogeneity. As UTRs are frequently subjected to multiple concurrent types of processing, a holistic approach is of key importance to understand how these processes collectively shape the cancer transcriptome and drive carcinogenesis. We anticipate that this work will lead to breakthroughs in our understanding of these diverse facets of RNA processing and their contribution to transcriptome heterogeneity and carcinogenesis, and identify novel regulators of critical cancer genes. Finally, we expect that 3'UTR variants and processing factors that are specifically dysregulated in cancer samples may represent promising new biomarkers for disease stratification, prediction of response to treatment, and/or lead to the development of novel targeted therapies.
7.18	**Dr Chester Drum** mdccld@nus.edu.sg Department of Medicine	**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.
7.19	**Dr Chester Drum** mdccld@nus.edu.sg Department of Medicine	**Mass spectroscopy biomarker discovery for precision medicine** 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.
7.20	**Dr Chester Drum** mdccld@nus.edu.sg Department of Medicine	**New digital models of health information implementation** Technologies such as Blockchain, Digital Identification and Zero Knowledge Proofs are changing the possibilities for usage, study and sharing of medical information. This project is specific to those who want to make a difference in the lives of real patients thorough the application of digital mobility enablers in addition to decentralized (i.e. individually federated) analytics. In short, this project seeks to leverage on the previous work of the PI with World Health Organization, International Standards Organization (ISO) and major global healthcare networks to create a decentralized information sharing and analytics platform for real world data collection.

7.21	**Dr Chester Drum** mdccld@nus.edu.sg Department of Medicine	**Synthetic Biology of Translational Therapeutics and Large Scale Bioproduction** Can biochemical engineering fundamentally change the process of disease treatment and macromolecular creation? In this project you will use a novel form of nanoparticle invented by our lab (Nature Comms, PMID: 29129910) to study 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 nanometer scaled agents for the delivery of active protein substrates and for industrial manufacture of 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 in training. using this technology you will easily produce novel biological therapeutics and bioproduction sequences. Expected outputs for the student will be at least one patent filing and 3-4 publications. You are invited to enquire if interested.
7.22	**A/Prof Citra NZ Mattar** citramattar@nus.edu.sg Department of Obstetrics & Gynaecology	**Noninvasive characterization of endometrosis by circulating, cell-free messenger RNA** The lack of accessible noninvasive tools to examine the molecular alterations occurring in women afflicted with endometrosis limits our understanding of the disease progression, as well as the identification of effective therapeutic strategies. Here, our proposed study is to conduct a comprehensive profiling of circulating, endometrium tissue specific cell-free messenger RNA (cf-mRNA) in plasma of patients with endometrosis against healthy controls of similar age. mRNA (messenger RNA) is the genetic code responsible for directing protein synthesis within the body. While most mRNA is located within cells, a small amount can be found circulating in the bloodstream, known as circulating cell-free mRNA (cf-mRNA). Prior studies shown that tissue specific cf-mRNA found in blood reflects organ function and is a largely unexploited biomarker with great potential. In our proposed work, we will quantify and correlate measurements of endometrium-relevant circulating gene transcripts alongside clinical severity. Data from this study can highlight the potential of cf-mRNA as biomarkers to evaluate endometrosis and female health related alterations; leading to precision healthcare solutions that could improve patient management.

7.23	**Dr Haojie Yu** bchhaoy@nus.edu.sg Department of Biochemistry	**Establishing a systematic approach to translate human genetic findings of Coronary Artery Disease into novel biology** Atherosclerotic coronary artery disease (CAD) represents the leading cause of death worldwide. While human genetic studies have uncovered over 200 loci associated with CAD, a key impediment for translating these genetic findings to clinic practice is the lack of high-throughput functional screening platforms to rapidly ascertain the causal genes linked to cardiovascular phenotypes. Therefore, we seek to combine functional genomics, CRISPR-based high-throughput screens, computational biology and animal models to achieve three fundamental goals: (1) to identify novel causal genes linked to CAD; (2) to discover novel mechanisms regulating atherosclerotic plaque progression and regression; (3) to use the mechanistic insights to develop new therapies for the treatment of CAD.
7.24	**Dr Jiong-Wei Wang** surwang@nus.edu.sg Department of Surgery	**Nanomedicine for metabolic diseases** Nanomedicine is a multi-disciplinary branch of medical science using nanotechnology and biomedical technology to develop diagnosis (nano-diagnostics) and treatment (nano-therapeutics) for diseases. Our lab has set up various unique animal models for metabolic diseases including cardiovascular diseases (atherosclerosis, myocardial infarction and metabolic heart failure) and fatty liver disease as well as a broad range of nanoparticle formulations for drug delivery. In collaboration with both local and international scientists, our lab aims: 1) To identify novel therapeutic targets with special focuses on lipid biology and inflammation/immunology, using our unique animal models, cell models and cutting-edge technologies including mass spec imaging and state-of-the-art flowcytometry; 2) To design and develop nanomedicine drug delivery systems for potential therapeutic compounds with advanced nanotechnology. We welcome talent students from different background including immunology, pharmacy, pharmacology, (bio)chemistry or material science. The candidates will work in a multi-disciplinary and dynamic environment with both local and international collaborators. Good communication skills (team-work), quick learning and independence are required.

7.25	**Prof Ong Wei Yi** antongwy@nus.edu.sg Department of Anatomy And **Dr Deron R. Herr** Department of Anatomy	**Inflammatory lipid signalling pathways in cancer and neurodegenerative disease.** Bioactive lipid mediators affect nearly all cellular and physiological processes and are often dysregulated in disease. Therefore, a better characterization of these signaling lipids will improve our understanding of disease processes and will allow us to develop novel drugs. My lab focuses on how lipid mediators, especially sphingolipids, affect pathological inflammatory processes. Importantly, this fundamental process occurs in blood vessels and promotes the development of cancer, neurodegeneration, and systemic inflammation. We identify specific steps in this process that can be disrupted by drugs, and we use targeted approaches and natural product libraries to develop drug candidates. Using this approach, we have recently identified drug targets for breast cancer, gastrointestinal cancer, inflammatory and neuropathic pain, diabetes, neurodegenerative disease, anxiety, and seizure disorder. The current focus of the lab is to apply these tools to address neurological diseases such as glioblastoma and Alzheimer's disease, and systemic inflammatory processes that occur during coronavirus infections such as COVID-19.
7.26	**Dr Tamra Lysaght** tlysaght@nus.edu.sg Centre for Biomedical Ethics	**Ethics and Governance of Precision Medicine** This project broadly covers the ethical, legal and social issues surrounding the implementation of precision medicine into health systems, including the development of trustworthy oversight mechanisms that account for and are responsive to public values needed to secure the social license to operate in the absence of specific consent.
7.27	**Dr Dennis Kappei** dennis.kappei@nus.edu.sg Department of Biochemistry	**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.
7.28	**Dr Dennis Kappei** dennis.kappei@nus.edu.sg Department of Biochemistry	**Regulation of the long non-coding RNA TERRA in cancers relying on the Alternative Lengthening of Telomeres (ALT) pathway** Telomeres are the molecular caps at the end of chromosomes and consist of hundreds to thousands of repeats with the motif TTAGGG. Due to the end replication problem and active end processing telomeres shorten with every cell division, ultimately leading to cellular senescence. Cancer cells would eventually share this fate. However, they developed two mechanisms to defy telomere shortening: 85% of all tumors reactivate the expression of the reverse transcriptase telomerase which adds telomeric repeats de novo, while the other 15 % use a recombination-based mechanism, termed Alternative Lengthening of Telomeres (ALT). Despite the original believe that telomeres would be transcriptionally silent, their repetitive sequences are actively transcribed into a long non-coding RNA called TERRA. While TERRA has been shown to be important for telomere homeostasis in general, its expression levels are unusually elevated in ALT-positive cancers and these high TERRA levels are thought to contribute to the recombination process of ALT through the formation of R-loops. This project aims to elucidate both the mechanisms behind the elevated TERRA levels as well as their mechanistic consequences. TERRA expression is controlled by an usual promoter structure located within the subtelomeres. Here, three different repeat sequences of different lengths (61bp, 29bp & 37bp) have been previously identified. In particular the 29bp repeat sequence has been shown to activate TERRA transcription. Through DNA-protein interaction studies coupled to quantitative mass spectrometry analysis we aim to identify transcription factors specifically regulating these unusual TERRA promoters. Subsequently, we would examine if and how these transcription factors regulate TERRA levels and ultimately exploit this to manipulate TERRA in the context of ALT cancers. In parallel, we aim to use an innovative in vivo RNA-protein interaction approach to identify novel TERRA-interacting proteins and to decipher how these protein-TERRA interactions translate into changes in telomere homeostasis.

7.29	**A/Prof Sethi Gautam** phcgs@nus.edu.sg Department of Pharmacology	**Novel Role of Abemaciclib in Activating NK-cell Cytotoxicity against Nasopharyngeal Carcinoma** Nasopharyngeal carcinoma (NPC) is among top 10 cancer in males in Singapore. Locally advanced and metastatic disease have high relapse rate and poor prognosis even with best supportive care in combination with radiotherapy and chemotherapy. Attempts to identify novel targeted therapy for NPC are met with limited successes, with poor efficacy and high toxicity in clinical trials so far. From recent published data on genome wide sequencing of NPC patient samples, we identified that G1/S transition is among the top dysregulated pathways in NPC and the availability of FDA approved CDK4/6 inhibitors make this pathway an attractive molecular target in NPC. Through our preliminary data, global proteomic analysis revealed that Abemaciclib, one of CDK4/6 inhibitors, is able to modulate pathways in the innate immune system. In this project, the student will investigate the new Abemaciclib-based combination therapy to activate NK-cell mediated cytotoxicity against NPC. In addition, the precise molecular mechanism will be explored to identify novel treatment strategy in NPC.
7.30	**Prof Daniel Tenen** csidgt@nus.edu.sg Department of Medicine	**Targeting transcription factor pathways in cancers** My laboratory is focusig on transcription factors and gene regulation in cancer. A major effort by my laboratory focuses are listed here: (i) zinc finger protein 143 (ZNF143) is a key regulator in maintenance of progenitor cells integrity. ZNF143 secures essential chromosomal architectures with CTCF to maintain normal liver function, and alteration of such structures leads to hepatocellular carcinoma (HCC) formation. Here we propose to use an in vivo mouse model to demonstrate the importance of ZNF143 in preventing HCC formation. (ii)SALL4 is not expressed in most normal adult tissues and expressed in approximately 30% of cancers. Currently, there are no existing small molecule drugs targeting SALL4. In our laboratory we have discovered novel molecular glues that could degrade SALL4 in cancer cells and show in vivo efficacies. Further pre-clinical studies are needed to improve these chemical modalities. (iii) The human genome comprises of abundant regions that are not translated to proteins but actively transcribe long non-coding RNAs (ncRNAs). We aimed to discover novel lncRNAs that contribute to leukemogenesis in AML and are investigating the functional roles of these lncRNAs.

8	**Synthetic Biology for Clinical & Technological Innovation for Synthetic Biology (SynCTI)**	
8.1	**A/Prof Yew Wen Shan** wenshanyew@nus.edu.sg Department of Biochemistry	**Sustainable Living through Synthetic Biology: Therapeutics, Wellness and Planetary Health** Therapeutics - Many cyclic organic compounds derived naturally from plants, such as cannabinoids and alkaloids, have proven to be of great value for medical use. However, their sophisticated chemical structures often make total chemical synthesis uneconomical or impossible, whereas the mixed nature of plant extracts poses formidable obstacles for downstream enrichment of low-abundance compounds and removal of harmful contaminants. We offer projects that actively addresses these issues by harnessing cutting-edge synthetic enzymology and genetic engineering techniques. So far, we have successfully reconstructed synthetic pathways for several such compounds in model eukaryotic organisms amenable to large-scale bioproduction. Wellness and Planetary Health - Rapid population growth and urbanization has exacerbated demand for materials and require smart cities to produce new products and recycle used ones in a highly efficient and environmentally friendly manner. Meanwhile, modern cities are pressurized to keep pace with the “Digital Revolution” that generates digital data with unprecedented speed and quantity, urging for ever-escalating data storage capacities. We present projects to provide innovative solutions to these challenges. Our current foci are on the development of sustainable processes for biomanufacturing, electronic and plastic waste bioremediation, and de novo enzymatic DNA synthesis.
8.2	**Dr Jiahai SHI** Jh.shi@nus.edu.sg Department of Biochemistry	**Red Blood Cell Terminal Development** Red blood cells (RBCs) account for more than 80% cells in the body. Lack of RBCs lead to anemia affecting one third of world population. RBCs are differenticated from hematopoistic stem cells, followed by colony -forming unit cells (CFU-Es). CFU-Es differenticate into RBCs following a step-wise 4-5 synchonized cell divisions with cell shrinkage, hemoglobinization, nuclear condensation and enucleation, which is called terminal erythropoiesis. Our lab focuses on the mechanistic study of terminal erythropoiesis. The result of our research will pave the road to treat anemia and for large scale RBC production in vitro.
8.3	**Dr Jiahai SHI** Jh.shi@nus.edu.sg Department of Biochemistry	**Synthetic Red Blood Cells for RBC Cell Therapy** RBCs possess many advantages to be an ideal platform to simulate other cells for therapy development. We invented the first generation RBC therapy, leading the NASDAQ listed company, Rubius Therapeutics. After being independent, we invent a second generation RBC therapy, resulting in a spin-off Carcell Biopharma with more than US$ 16 millions venture investment.

8.4	**Dr Julius Fredens** jfredens@nus.edu.sg Department of Biochemistry	**Engineering and Directed Evolution of Bacteriophage** Gene/cell 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, bacteriophage transport much larger DNA and specifically recognise bacteria, making the bacteriophage a promising candidate as a spacious, robust, and genetically inert vehicle. We aim to engineer bacteriophage for DNA delivery to mammalian cells using synthetic genomics and directed evolution.
9	**Nanomedicine Translational Research Programme**	
9.1	**Dr Jiong-Wei Wang** surwang@nus.edu.sg Department of Surgery	**Nanomedicine for cardiovascular disease: atherosclerosis** Nanomedicine is a multi-disciplinary branch of medical science using nanotechnology and biomedical technology to develop diagnosis (nano-diagnostics) and treatment (nano-therapeutics) for diseases. Atherosclerosis is a common cause for a variety of cardiovascular diseases including heart attack and ischemic stroke. Our lab has set up several animal models for atherosclerosis and a broad range of nanoparticle formulations for diagnosis (imaging) and drug delivery. In collaboration with both local and international scientists, our lab aims: 1) To identify novel therapeutic targets with special focuses on lipid biology and inflammation/immunology, using our animal models of atherosclerosis, various cell models and cutting-edge technologies including mass spec imaging and state-of-the-art flowcytometry; 2) To design and develop nanomedicine drug delivery systems (synthetic nanoparticles or extracellular vesicles) for potential therapeutic compounds (or imaging agents) with advanced nanotechnology. We welcome talent students from different background including immunology, pharmacy, pharmacology, (bio)chemistry or material science. Background in cardiovascular research is preferrabe but not a must. The candidates will work in a multi-disciplinary and dynamic environment with both local and international collaborators.

9.2	**Dr Jiong-Wei Wang** surwang@nus.edu.sg Department of Surgery	**Nanomedicine for fatty liver disease** Non-alcoholic fatty liver disease is the most common chronic liver disease, affecting one third of the population in Western societies and even up to 40% of the population in Singapore and Hong Kong. Its prevalence is growing alarmingly and closely associated with other metabolic diseases such as obesity, type 2 diabetes, and cardiovascular disease. Non-alcoholic fatty liver disease may progress to more aggressive nonalcoholic steatohepatitis (NASH) and the lethal cirrhosis that may result in liver cancer and liver failure. There is so far lack of good diagnosis and therapy. In collaboration with hepatologists, chemists, pharmacists and biomedical nanomaterial scientists, we have established a multi-disciplinary team to develop nanomedicine-based diagnosis (nano-diagnostics) and treatment (nano-therapeutics) strategies for the treatment of fatty liver disease. By employing the state-of-the-art animal models and nanotechnology, we aim: 1) To identify novel therapeutic targets; 2) To design and develop nanomedicine drug delivery systems for potential therapeutic compounds (or imaging agents). We welcome talent students from different background including immunology, pharmacy, pharmacology, (bio)chemistry or material science. Good communication skills (team-work), quick learning and independence are required. The candidates will work in a multi-disciplinary and dynamic environment.
9.3	**Dr Jiong-Wei Wang** surwang@nus.edu.sg Department of Surgery	**Advanced drug delivery in heart disease** Myocardial infarction (heart attack) is the main cause of heart failure. Myocardial infarction is mostly caused by blockage of coronary arteries resulting in massive oxidative stress and inflammatory responses followed by cell death and irreversible heart tissue damage. Minimizing cardiac damage while repairing the injured cardiac tissue or regeneration of functional cardiomyocytes to replace the damaged tissue have always been the main challenges in the field. Apart from stenting, however, effective pharmacologic treatment for myocardial infarction remains limited. Furthermore, the currently available drugs for cardiovascular disease mostly end up with systemic side effects and/or suboptimal drug targeting to the diseased site. In this project, we aim to develop clinically viable drug formulations by using advanced nanotechnology to deliver small molecule drugs and nucleic acids (siRNA, microRNA or mRNA) for the treatment of myocardial infarction and related heart injury. Talent students with great passion to explore high risk high rewarding research are highly welcome. The capability of working in a multi-disciplinary and dynamic environment is required.

10	Precision Medicine Translational Research Programme	
10.1	**A/Prof Citra NZ Mattar** citramattar@nus.edu.sg Department of Obstetrics & Gynaecology	**Novel precision gene editing technologies for treating hemoglobinopathies using humanized mouse models** β-hemoglobinopathies are hereditary single gene disorders, with ~ 300 mutations in the human β-globin gene leading to the production of abnormal haemoglobin. Allogeneic haemopoetic stem cell (HSC) transplantation, the current gold standard, is not available for the majority of patients. In contrast, strategies to genetically modify patients' own autologous HSC ex vivo may be beneficial without risking graft rejection, and are employed in current clinical trials of beta-thalassemia using integrating viral vectors. However, this approach is more costly and requires bone marrow conditioning and immunosuppression. Our laboratory investigates in vivo HSC gene modification using non-integrating adeno-associate viral vector and base editing strategies. We will optimise HSC expansion protocols and AAV transduction, and a humanized mouse model to characterise short and long-term effects of in vivo AAV-gene therapy, targeting common β-globin mutations. In vivo gene corrections using AAV delivery of precise base-editing tools will increase the repertoire of gene therapy strategies, making this novel therapy more accessible and less costly.
10.2	**A/Prof Citra NZ Mattar** citramattar@nus.edu.sg Department of Obstetrics & Gynaecology	**Novel Precision Technologies to Correct Murations to β-Thalassaemia Using Patient-Specific STEM Cells** β-Thalassaemia is an inherited blood disorder, which is caused by the mutations in the beta-globin gene leading to the production of abnormal haemoglobin in the neonates. Current treatment includes regular blood transfusions, iron chelation therapy, conditioning therapy and hematopoietic stem cell (HSC) transplantation. Due to complications of myeloablation and donor cell rejection, intrauterine hematopoietic stem cell transplantation (IUHSCT) to the fetuses became a promising stem cell based treatment and currently on clinical trials for alpha-thalassemia. While researchers in this field are still actively seeking novel strategies with which to improve long-term engraftment of donor HSC, the efficiency of gene therapy remains attractive for the beta-thalassemia. Ex-vivo gene therapy using patients own blood cells is challenging and currently on the main focus. In our laboratory, we are generating gene therapy models using induced-pluripotent stem cells (iPSC) generated from patient-derived cells and differentiate them to HSC. Characterization of the differentiated HSC, their behaviour during the culture conditions and genetic manipulation to correct the mutations are the central focus of our project studies. Culturing of stem cells, characterization of the hematopoietic stem cells using flow cytometry, gene

		expression analysis are some of the techniques routinely used in our laboratory.
11	**Others**	
11.1	**Prof James Hoi Po Hui** doshuij@nus.edu.sg Department Orthopaedic Surgery	**Engineering and characterisation of stem cell extracellular vesicles for improved therapeutic efficacy** A large part of the regenerative value of mesenchymal stem cells (MSCs) is attributed to their paracrine secretion of trophic factors, packaged in extracellular vesicles (EVs), that can elicit biological responses in recipient cells such as the regulation of metabolic and inflammatory status. Distinct subpopulations of EVs with unique biophysical properties, proteomic and RNA repertoires, were demonstrated to elicit differential effects on recipient cells, adding to the complexity to the EV biology. Despite the increasing reports on the regenerative efficacy of MSC EV, the mechanism of paracrine action has yet to be fully studied. Increasing evident has shown that MSC paracrine activities can be modulated and enhanced by a wide range of extracellular cues and biophysical treatments. Our group has identified various pre-conditioned and stimulation that are capable of modulating the paracrine function of MSCs for the enhancement of EVs' therapeutic efficacy in cartilage regeneration. Given the distinct biogenesis pathway of EVs' subpopulations, different cellular activation would alter distinct membranous, cytoskeletal and intracellular molecular pathways in MSC. This provides the opportunity for additive engineering of the culture environment to harness MSC paracrine activities from different EV subpopulations for more efficacious MSC paracrine effect. The objective of the study is to (i) investigate the effect of additive enhancement of MSC paracrine activity with combinative treatment/pre-conditioned; (ii) perform in depth characterisation of the MSC EVs for the selected combinative treatment to gain insight to the mechanism of action; and (iii) perform in vivo proof-of-concept study to validate the efficacy of engineered MSC EVs for cartilage regeneration. This project will enable the student to acquire experiences in translational research that involves stem cell and EVs biology, transcriptome, proteomic analysis, and in vivo experiments.

11.2	**Dr Su Xinyi** ophsux@nus.edu.sg Department of Ophthalmology	**Developing novel cell therapies against inherited retinal diseases** Inherited retinal diseases (IRDs) are a group of rare blinding conditions caused by one of more than 250 different genes. Some people living with IRDs experience a gradual loss of vision, eventually leading to complete blindness. Others may be born with or experience vision loss in infancy or early childhood. To better understand the disease pathogenesis, retinal organoids have been generated in the hopes of modeling the human retina featuring very similar cellular composition, layering and functionality. While the organoid technology is a powerful tool in modelling development and diseases, several challenges hinder the further development of the technology for downstream applications. This includes an extensive variability in differentiation efficiency leading to low reproducibility, inferior morphological and/or functional maturity of tissues, thereby limiting their potential for exploring biological complexities. We aim to test synthetic and defined hydrogels to improve the morphological and functional maturation of the retinal organoids. This will be done by studying the effects of the properties of the microenvironment provided by the hydrogel such as stiffness, viscosity, degradability, porosity, protease cleavage sites, ligand type, and ligand density. This information is crucial to generate better models and for enhancing our understanding of retinal tissue development in health and disease conditions, such as IRD.
11.3	**Dr Su Xinyi** ophsux@nus.edu.sg Department of Ophthalmology	**Elucidating the molecular network underlying vitreous regeneration** Endo-tamponade agents are crucial surgical adjuncts for vitreo-retinal surgery. Current gold standard clinical agents provide internal tamponade mainly through buoyancy forces, resulting in drawbacks such as the requirement for prolonged post-operative positioning, temporary loss of vision, raised intraocular pressure, and the need for additional removal surgery, all of which can lead to failure of retinal detachment (RD) repair. There is a clinical need to develop alternative materials to overcome these challenges. We have described a thermogelling tri-component polymer, Vitreogel, as a dual function endo-tamponade with bioactivity in the eye. Vitreogel has successfully prevented failure of RD repair in large animal models, by serving as a long-term endotamponade, providing continual support to the retina thereby preventing subsequent re-detachments. Intriguingly, after Vitreogel undergoes biodegradation, there is in-vivo restoration of a vitreous-like body that obviates the need for a secondary removal surgery. This is the first ever report on the regeneration of vitreous-like body. Mass

		spectrometry (MS)-based proteomics confirmed the presence of major structural components comparable to native vitreous. However, to study how the vitreous is reformed in a temporal manner, and the contribution from surrounding tissues, RNA-sequencing (RNA-Seq) was performed on several eye tissues adjacent to the vitreous cavity. The aim of this project will be to elucidate the molecular mechanisms in temporal fashion from the different tissues that underpin this newly reported phenomenon of vitreous reformation.
11.4	**Dr Su Xinyi** ophsux@nus.edu.sg Department of Ophthalmology	**Investigating retinal pigment epithelium in the context of age-related retinal degenerative diseases.** Age-related macular degeneration (AMD) is one of the leading causes of blindness worldwide. There are existing therapies for early stage 'wet AMD', but once significant cell death and degeneration has occurred, the disease is untreatable. The root cause of AMD is dysfunction of the retinal pigment epithelium (RPE). To develop therapies against RPE dysfunction, we need to gain a deeper understanding of how RPE cells age and become dysregulated in the context of disease. This project will interrogate the dynamics of sub-cellular and molecular changes that occur in aged and diseased RPE, with the aim of identifying novel therapeutic targets.
11.5	**Dr Su Xinyi** ophsux@nus.edu.sg Department of Ophthalmology	**Testing methods to improve survival of transplanted RPEs** Age-related macular degeneration (AMD) is one of the leading causes of blindness worldwide. There are existing therapies for early stage 'wet AMD', but once significant cell death and degeneration has occurred, the disease is untreatable. One potential therapy for late-stage AMD disease is retinal pigment epithelium (RPE) stem-cell transplantation. However, rejection of allografts is a major limitation of cell therapy. It has been reported that overexpression of the immune checkpoint protein programmed death-ligand 1 (PD-L1) protected human islets like organoids and improved the transplantation outcome (Yoshihara et al, Nature volume 586, pages 606–611,2020). The same paper also reported that stimulation with interferon-γ induced PD-L1 expression and restricted T cell activation and graft rejection. This project would explore if similar strategies would help to improve the transplantation outcome of the retinal pigment epithelial cells.

11.6	**Prof Vinay Tergaonkar** bchvt@nus.edu.sg vinayt@imcb.a-star.edu.sg Department of Biochemistry	**Development of gene therapy for pediatric liver diseases** We aim to develop a proof-of-concept for a novel delivery system using an all-in-one vector for genome editing of primary biliary cells. We would then apply for a ground patent for engagement of external stakeholders to level up testing in higher mammals. Because liver transplant is currently the only therapeutic approach for pediatric biliary disorders, our gene therapy may lead to development, transfer and application of new technologies promoting the commercialization of high-value added biotechnology products. We will equip the student with the required skill set to design, conduct and implement pre-clinical research. The overreaching aim of the training is to provide students with an exceptional translational perspective so that at the end of the internship they can clearly detect common needs in healthcare in society and develop the maturity to resolve these issues with the design of products with high commercial value.
11.7	**A/Prof Wilson Wang** doswangw@nus.edu.sg Department of Orthopaedic Surgery	**3D-Printing of Musculoskeletal Tissues** Physical strength and mobility are vital for a healthy living. Musculoskeletal tissues provide physical strength and facilitate functional mobility. Ageing, trauma, disease and birth defects can damage musculoskeletal tissues, affecting functional mobility. Clinically, autografts and allografts are used to treat damaged musculoskeletal tissues. However, their limited supply and associated clinical implications have led to the development of artificial grafts. Recently additive manufacturing/3D-printing technology have garnered research interest, primarily because of their ability to be customized to suit the clinical need. The project focus on the development of bio-ink formulation, that could mimic the native tissue architecture. The graft should be able to facilitate load bearing, load transmission, shock absorption, joint stability, joint lubrication, and joint congruity. The biomechanical properties of these grafts are inherently attributable to its gross anatomy and microarchitecture. In our current project, we will use MRI-assisted 3D-printing technology, where the 3D-printed graft can be custom designed according to MRI scans of animal models. We intend to explore different combinations of polymer materials for this fabrication, and perform in vitro and in vivo tests to assess their biocompatibility and biomechanical efficiency.

11.8	**A/Prof Wilson Wang** doswangw@nus.edu.sg Department of Orthopaedic Surgery	**Development of Novel imaging Based Algorithm for the Screening of Osteoporosis** Osteoporosis is, as defined by the World Health Organisation, a "systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture". The key to the primary prevention of osteoporosis lies in its early screening, diagnosis and treatment. However, despite the advent of accurate screening tools such as dual-energy X-ray absorptiometry (DEXA) scans, osteoporosis still remains extremely under-screened and under-diagnosed, and often remains asymptomatic until complications (fractures) set in. For a screening programme to be effective, screening barriers need to be sufficiently low, and preferably inexpensive, easily administered, and non-invasive. The development of an endto-end automated multi-modal algorithm using dental orthopantomograms (OPGs) fulfils all these key criteria, and is a promising and novel approach for opportunistic osteoporosis screening to improve screening rates. The approach for the study design will be sub-divided into 2 phases. In the 1st phase, retrospective data collection will be performed to build a developmental model of the machine-learning algorithm. In the 2nd phase, this algorithm will be tested on a retrospective cohort of 300 patients.
11.9	**Prof Yap Hui Kim** paeyaphk@nus.edu.sg Department of Paediatrics	**Role of Type 2 Innate Lymphoid Cells in childhood idiopathic nephrotic syndrome** Childhood idiopathic nephrotic syndrome (iNS) is associated with significant morbidity, particularly due to steroid-dependent or steroid-resistant (SD/SR) disease. Existing data implicate a direct Th2 cytokines effects on podocytes in disease pathogenesis. Recent evidence in asthma suggests that Type 2 Innate Lymphoid Cells (ILC2s) are a relatively steroid-resistant source of Th2 cytokines. We hypothesise that ILC2s contribute to the production of Th2 cytokines in iNS relapse and SD/SR disease is mediated by ILC2 steroid-resistance. We aim to (a) compare ILC2 number and Th2 cytokine production in relapse to remission and controls, both in blood and kidney tissue, (b) quantify ILC2 Dexamethasone-sensitivity in vitro and correlate this with clinical SD/SR, and (c) recapitulate iNS through adoptive cell transfer of patient-specific ILC2s into an immunocompromised mouse model. 24 active patients will be recruited and blood sampled in relapse and 1 month after entering remission; their renal biopsy tissue will also be retrieved. ILC2s and Th2 cytokine production, will be studied in peripheral blood following 48h culture with IL-33±Dexamethasone using multi-parameter flow cytometry, or in renal biopsy tissue using Multiplex Immunohistochemistry. For adoptive cell transfer, NSG rats will be injected with ILC2s from patients in relapse, and followed one-month for the development of proteinuria.

11.10	**A/Prof Samuel Chong** paecs@nus.edu.sg Department of Paediatrics	**Single-cell strategies for simultaneous diagnosis of monogenic disorders and screening of chromosomal abnormalities in IVF preimplantation embryos to achieve healthy pregnancies and unaffected livebirths** Preimplantation genetic testing involves the genetic diagnosis of IVF-derived embryos to identify embryos free of specific monogenic disorders or chromosomal abnormalities for subsequent uterine transfer. This procedure ensures that the ensuing pregnancy is unaffected with the monogenic disorder or is chromosomally balanced. Current technology, however, cannot reliably and reproducibly test for both monogenic disorders and chromosomal abnormalities from the limiting genetic material of a preimplantation embryo due to differences in whole genome amplification (WGA) requirements. The ability to identify embryos that are both unaffected with the monogenic disease and chromosomally balanced is crucial to improving implantation and pregnancy rates, and ensuring healthy and unaffected live births. This project aims to develop a generalizable strategy for combined mutation diagnosis (to avoid monogenic disease) and chromosome screening (to exclude chromosomal abnormality) of preimplantation embryos. This aim will be realized through (1) development of a robust, reliable, and reproducible single-cell WGA that is compatible with both monogenic disease diagnostics and chromosomal screening, (2) development of mutation detection and linkage-based diagnostic assays compatible with the WGA protocol, and (3) development of a chromosomal screening strategy compatible with the WGA protocol, and agnostic to the next-generation sequencing platform.
11.11	**Dr Catherine Dong Yanhong** nurdy@nus.edu.sg; mdcdy@nus.edu.sg Department of Medicine	**Heart-Brain Connection: Cognitive Impairment in Heart Failure** The heart and brain are so closely connected that when one is diseased, the other one is also at risk. This is the case for patients with heart failure whose hearts are underperforming, starving the body, especially the brain, of oxygen- and nutrient-rich blood and consequently leading to cognitive problems. However, problems with the brain such as cognition tend to be overlooked. The 2016 European Society of Cardiology guidelines have highlighted the importance of customized management for cognitively-impaired heart failure patients. But data among Asian heart failure populations is scant. Hence we are developing a translational clinical research program on heart-brain connection from mechanistic discovery to interventional trial to address cognitive impairment in HF. Deep machine

		learning will be applied for risk stratification and precision care. We have shown that undiagnosed CI in Asian HF patients is high (44%). HF patients with high levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), a diagnostic HF marker, may be at risk of developing CI. These has been published in a top journal: Dong Y*, et al. (2019). Prevalence, biomarker, and clinical correlates of cognitive impairment and outcomes in Asian patients with heart failure. European Journal of Heart Failure. 21(5): 688-690. (IF: 15.5).
11.12	**Dr Catherine Dong Yanhong** nurdy@nus.edu.sg; mdcdy@nus.edu.sg Department of Medicine	**Feasibility study to explore heart-brain biomarker correlates of cognitive impairment in atrial fibrillation** Atrial fibrillation (AF) is highly prevalent dysrhythmia, associated with a higher risk of cognitive impairment and dementia, with or without a history of clinical stroke. Mild cognitive impairment is common (65%) in high-risk patients hospitalized with chronic AF in the West and leading to poor health outcomes such as poor self-care and treatment compliance, while the prevalence of cognitive impairment in Singaporean and Asia region is unknown. Both AF and dementia share many common risk factors such as older age, vascular risk factors (diabetes, hypertension), vascular disease like heart failure. Many of these shared risk factors are modifiable through early intervention. Greater risk of mortality has been reported in patients with AF and dementia. Therefore, understanding the mechanisms of the association between AF and cognitive impairment is important. However, the mechanism between AF and cognitive impairment is not well established. Therefore, we will explore biomarker correlates of cognitive impairment in AF to unravel aspects of mechanisms accounting for cognitive impairment. To achieve this, we will recruit high-risk AF patients with mild-moderate HF and cardioembolic stroke patients and examine the association between biomarkers such as cardiac, inflammatory and circulating biomarkers, perfusion/hemodynamics and cerebrovascular lesions, and cognitive performance.

11.13	**Dr Catherine Dong Yanhong** nurdy@nus.edu.sg; mdcdy@nus.edu.sg Department of Medicine	**Developing a Digital Solution for Salutogenic Brain Health** The rising ageing population in Singapore demands for a scalable solution such as a digital intervention to address brain health problems upstream, i.e., health promotion and early intervention for the middle-age population at-risk for cognitive decline. However, such digital solution is lacking. We aim to develop a digital solution for salutogenic brain health (DiSaB) and assess the effectiveness of its implementation at primary care setting. We will recruit adults aged 40-55 with chronic conditions e.g., hypertension, hyperlipidemia and diabetes from National University Polyclinics. They are the at-risk population for cognitive decline, as metabolic changes can precede cognitive change, sometimes by as much as a decade. Hence, they are well suited for our DiSaB intervention which is an upstream approach for early detection and intervention. A Micro-randomized controlled trial (RCT) will be conducted to evaluate the feasibility and efficacy of the DiSaB digital intervention. Cognitive tests will be used to evaluate changes in patients at baseline and 6 months. Mixed method design will be employed to identify enablers and barriers using COM-B model for implementation. The Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) framework will be applied to measure implementation effectiveness. Machine learning and micro-randomization will be applied to motivate behavioural changes.
11.14	**Dr Catherine Dong Yanhong** nurdy@nus.edu.sg; mdcdy@nus.edu.sg Department of Medicine	**Independent Living and Future Care for Stroke Patients and Their Caregivers** We are working closely with community service partners in bridging the current service gap in the landscape of stroke care and building a holistic and sustainable translational research in the community. Our innovative service program seeks to improve the brain health of stroke survivors as well as the psychological and emotional well-being of their family members/caregivers. Moreover, we aim to establish a community-based cognitive test to evaluate returning to work, and empower stroke survivors in improving their cognition to maintain functional independence and prevent decline. Similarly, we will empower family caregivers through health education to better support stroke patients in their recovery. Stroke survivors and caregivers will explore the sense of living well and develop future care plan. Early intervention using

		group-based brain training program will be delivered to provide life skills training for stroke survivors and their caregivers to optimise recovery and promote quality of life for independent living. The efficacy of such intervention will be evaluated via the randomised controlled trial. To scale up this brain health program both in Singapore and overseas, we intend to develop a digital solution and apply deep machine learning to optimise stroke recovery.
11.15	**Dr Catherine Dong Yanhong** nurdy@nus.edu.sg; mdcdy@nus.edu.sg Department of Medicine	**Addressing Heart-Brain Health Disparities in Women: Music Intervention and Reflective Wisdom for Self-Care** Women are undertreated and disadvantaged in terms of cardiovascular (CVD) care. Our proposed project aims to address heart-brain health disparities through better self-care practice in women with heart failure (HF) and atrial fibrillation (AF). We aim to recruit a total of adults with HF and comorbid AF consisting of women to men with 1:1 ratio. A mixed method study consisting 2 phases will be adopted. First, we will conduct a qualitative study over individual interviews or 4-5 focus group interviews (3-4 participants/group) music to establish suitable music intervention and reflective self-care practice. Second, a randomised controlled trial to implement the music intervention beneficial for cardiovascular health with reflective self-care practice for patients with HF and AF. The follow-up focus group interviews will be conducted after intervention. The physical, psychological, and cognitive outcomes will be measured at baseline and follow-up. In collaboration with physicists and musicians, we plan to apply basic science (physics and mathematics) to decompose music (sound waveform) of intervention and study the corresponding changes of outcome measures after the intervention. We hope to establish a creative and highly scalable music solution customized to Asian patients, impacting on both heart and brain health through empowering patients' self-care.

11.16	**Dr Catherine Dong Yanhong** nurdy@nus.edu.sg; mdcdy@nus.edu.sg Department of Medicine	**Anto smart pad for Geriatric/Wheelchair users** Anto smart pad is a device developed by our start-up company partner to predict and prevent pressure ulcer and falling risks for people with disability (PwDs). It will reduce the burden of daily frequent monitoring and assessment on PwDs with cerebral palsy, impaired sensory function (e.g., diabetic neuropathy) or cognition (e.g., dementia). Anto smart pad uses proprietary sensors and machine learning to collect data and aid intervention. Its automated monitoring and alert system will empower PwDs and caregivers to detect potential risks of pressure ulcers and falling, initiates self-intervention, prevent deterioration and improve self-care and quality of life. To evaluate Anto smart pad for Geriatric/Wheelchair users, we will recruit approximately 300 PwDs and caregivers from the community. PwDs will undergo a randomized controlled trial (RCT) over 3 months. PwDs and caregivers will receive training. Primary outcome measures include built-in Braden Scale to assess the risk for pressure ulcer development. We use algorithm for predictive modeling and intervention processing. This product will be built with a Neural Network Machine Learning for risk stratification, monitoring and self-intervention. Findings are translatable to residential care, day care, primary care and hospitals.
11.17	**Prof Jose M Valderas** jmvalderas@nus.edu.sg Department of Medicine	**Late-life depression and help-seeking in primary care** Late-life depression is often underdiagnosed and undertreated in primary care, leading to increased frailty and loss of autonomy in many older adults. Primary care plays a crucial role in the early detection and treatment of depression in older adults, whose self-awareness of mental illness tends to be lower than in younger age groups. This gatekeeper role has its own set of challenges in Singapore, given the short consultation times, the country's multi-ethnic population, and the lower depression literacy of older adults. This research programme aims to further our understanding of the barriers to depression detection in older primary care patients and use these findings to devise novel tailored educational interventions. The research programme encompasses several interconnected projects, ranging from a systematic literature review to qualitative and quantitative cross-sectional studies. Students can expect to acquire a diverse skillset in clinical research, such as evidence synthesis, qualitative data collection and analysis, quantitative study design, biostatistics, and scientific writing. Students will need to be

		self-driven and curious about the overall topic. Over time, the aim is to develop an independent researcher who is a critical thinker and can conduct relevant research at the interface of mental health and primary care.
11.18	**Prof Jose M Valderas** jmvalderas@nus.edu.sg Department of Medicine	**How does multimorbidity affect middle-aged adults? – refinement analysis of a published survey** A previous study [https://doi.org/10.1186/s12875-020-01262-2] at a primary care centre in Singapore collected interviewer-administered questionnaires including sociodemographic characteristics, chronic conditions, and Health-related Quality of Life (HrQoL), as measured by EuroQol questionnaire (EQ5D). Multimorbidity (MM; defined as GE3 conditions) was associated with EQ5D scores for pain. The proposed project is a further analysis of the data with the following analysis plan: 1. Multimorbidity: a. Define MM as GE2 conditions, b. Describe MM and associations with Sex and Ethnicity differences adjusting for age, c: describe impact of MM on EQ5D; 2. Comorbidity: a. Describe impact of co-morbidity on EQ5D INDEX, not visual analogue scale, and on specific EQ5D domains, b. Identify most intrinsically comorbid conditions, adjusting for prevalence; 3. Clusters: a. Describe combinations of conditions, b. Conduct exploratory factor analysis to identify non-hierarchical clusters; c. explore the use of discordance metrics. The purpose is to better characterise the population in terms of multimorbidity and comorbidity. The paper would pave the road toward further research projects on the same topic. Students can expect to acquire experience in important clinical research topics such as multimorbidity, chronic diseases, and health-related quality of life, and learn valuable research skills related to data analysis and scientific writing.

11.19	**Prof Jose M Valderas** jmvalderas@nus.edu.sg Department of Medicine	**Prevalence and predictors of chronic treatment guideline adherence among patients attending National University Polyclinics: a Big Data study** National University Polyclinics (NUP), a public primary care organisation provides health services to patients in the Western part of Singapore and plays a key role in chronic disease prevention and management. The provision of this care is hypothesized to have been impacted by COVID-19 pandemic. Management that is not consistent with treatment guidelines has been found to be associated with poorer patient clinical outcomes, higher healthcare costs and utilisation. By exploring NUP Datamart and EPIC records, we aim to discover associations and better understand patterns and trends within the data, providing insights for planning interventions to target nonadherence to treatment guidelines in future research. We hypothesize that older people of lower socioeconomic status (rental blocks), having at least one of diabetes, chronic kidney disease, hypertension or hyperlipidemia, and poorer clinical outcomes based on local guidelines are more likely to have management not consistent with treatment guidelines. We hypothesize that patients seen in NUP during COVID-19 pandemic are more likely to have management not consistent with treatment guidelines than those seen before COVID-19 pandemic. Students can expect to acquire experience and skills in data management, analysis and interpretation of primary care data and scientific writing.
11.20	**Dr Daniel Teh Boon Loong** danielteh@nus.edu.sg Department of Biochemistry	**BRAIN-EYE-HEALTH AXIS RESEARCH (REALISE)** REALISE explores the relationship between eye and the brain. The eye is an extension of the Central Nervous System (CNS), having nerve endings on the retina, and is an important photoreception sensor. The eye is a window into the brain and shares common ageing pathways, immunological and vascular functions. Light-sensing, is a key regulator of the sleep-wake cycle which in turns is vital to the brain function and well-being. We explore the REALISE work in acute and chronic studies to understand how the conditions of the eye affects brain ageing. In local and international collaboration, we will utilize optogenetics and chemogenetics to regulate functions of the eyes and part of the brain in translational pre-clinical mice model and try to elucidate this link to eye-brain health axis. Students will take up a 3 years project to elucidate the effects of eye condition to brain ageing.

11.21	**Dr Daniel Teh Boon Loong** danielteh@nus.edu.sg Department of Biochemistry	**Inter-disciplinary Nanotechnology in Biomedical Application** Nanotechnology offers great versatility and modalities for various biomedical application. It can be used as a delivery tools for genetic and nutrient cargo, at the same time allows live imaging of physiological process. Owings to its versatility to surface modification, we can mix and match the appropriate functional groups to the nanoparticle to change its property and function. This is an inter-disciplinary study applying an array of nanotechnology for its application in biomedical research. We are exploring a wide range of nanoparticle from organic to inorganic to be deploy as 1. Precision tool for targeted load delivery into organs 2. Photonics role for wireless photodynamic therapy in solid cancer Direct visualization of molecular and cellular processes.