NUS National University of Singapore | Yong Loo Lin School of Medicine

List of Research Projects Available for Prospective Graduate Students

The list below is grouped by the following 10 Translational Research Programmes (in no particular order):

1	Cardiovascular-Metabolic Disease Translational Research Programme	Projects
2	Healthy Longevity Translational Research Programme	Projects
3	Human Potential Translational Research Programme	Projects
4	Immunology Translational Research Programme	Projects
5	Infectious Diseases Translational Research Programme	Projects
6	Digital Medicine Translational Research Programme / Institute for Digital Medicine (WisDM)	Projects
7	Cancer Translational Research Programme / NUS Centre for Cancer Research (N2CR)	Projects
8	Synthetic Biology for Clinical & Technological Innovation for Synthetic Biology (SynCTI)	Projects
9	Nanomedicine Translational Research Programme	Projects
10	Precision Medicine Translational Research Programme	Projects
11	Others	Projects

List of Research Projects for Prospective Graduate Students (Dec 2024)

1	**Cardiovascular Disease Translational Research Programme**
1.1	Amniotic fluid stem cell conditioned medium for vascular tissue regeneration
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 behavior of ageing cardiomyocytes using amniotic stem sell sesretome
1.10	Investigation of a recently identified ADTRP protein for its role in cardiometabolic diseases
1.11	Genetic epidemiology of cardiometabolic diseases
1.12	Biomarker discovery for precision medicine and patient health using advanced analytics and multiplex mass spectrometry
1.13	Modulation of vascular smooth muscle cell in Type 2 Diabetes
1.14	Exploring the Prospect and Molecular Basis of 3D Spheroid Culture in Vascular Biology and Disease Modelling
1.15	From bench to bedside: Exploring venomous and haematophagous animals for novel therapeutics

2	**Healthy Longevity Translational Research Programme**
2.1	Longitudinal study of multimodal brain imaging for behavioural 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 andneurodegenerative 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 Accumbenscircuitry 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 mechanism of neuroprotection ny 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	SG70 – Towards Healthy Longevity in Singapore
2.28	Conversations between tumours, vasculature and the brain: deciphering mechanisms underlying age- associated elevated mortality risk of stroke among cancer patients
2.29	Rejuvenating Senescent Traits of Older Adults Through Regular Exercise (RESTORE)
2.30	REBOOT (Resistance Exercise improves BiOlOgical age inolder adulTs)
2.31	BREXINT (Breast Cancer Exercise INTervention)
2.32	Improving the validity of ageing clocks in frail older adults
2.33	Current knowledge of Geroscience in health-care professionals
2.34	Current knowledge of Geroscience in community-dwelling middle-aged individuals
2.35	Will Rapamycin turn back time?
2.36	The biological phenotype of the oldest old
2.37	Understanding the association between platelet characteristics of patients with ischemic stroke and the risk of stroke recurrence
2.38	CaV1.3 IQ-domain RNA editing in circadian rhythm

2.39	Cav1.2 Deubiquitinases: implications in cardiovascular diseases
2.40	CaV1.3 IQ-domain RNA editing: implications in mood disorders
2.41	Characterization of a novel NAD+ precursor for muscle and brain health in aging
2.42	Dissecting cellular pathways of aging- and senescence-associated amyloidosis
2.43	Elucidation of common proteotoxic stress response signatures across aging and age-related diseases

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	Longitudinal study of multimodal brain imaging for behavioral prediction in health and neuropsychiatric disease
3.3	Uncovering the role of CNS in hyperthermia-induced fatigue and potential augmentation strategies to overcome it
3.4	The importance of sleep in the neurobehavioural and psychosocial development of children
3.5	Studying the Heterogeneity of Gestational Diabetes Mellitus: Cardio-Metabolic Alteration and Treatment Response in a Multi-Ethnic Population in Singapore (GDM-CARE)
3.6	Harnessing the gut microbiome to combat heat injuries
3.7	Myo-Inositol and Fetal Membrane Remodeling and Weakening
3.8	Using magnetic resonance imaging and spectroscopy to investigate the role of placental inositol in fetal growth regulation
3.9	Investigating the mechanistic role of the placenta in maternal-fetal transmission of mental health risk
3.10	Machine learning of brain MRI to improve mental health and disorder
3.11	Personalizing sleep for better health using large scale device data
3.12	Neurobehavioural functions of school-age children during multiple weeks of sleep restriction and recovery
3.13	Reducing children's screen use for better sleep, mental, and brain health: a personalized approach

3.14	Effects of recurrent short and variable sleep on cognitive performance, brain dynamics, psychological well-being, and glucose metabolism
3.15	Omics, metabolomics and novel risk factors and biomarkers to better understand the etiology and prevention of gestational diabetes mellitus
3.16	Prediction models of gestational diabetes mellitus and unfavorable fetal growth with high-dimensional multi-omics approaches in conjunction with conventional risk factors for improved precision medicine
3.17	Omics for fetal growth- longitudinal and prospective studies to uncover novel risk factors and biomarkers of suboptimal fetal growth: exploring fetal overgrowth or growth restriction
3.18	Long-term health implications of common pregnancy complications and their determinants – a life course perspective
3.19	Nutrition, diet and lifestyle factors and maternal and child heath, and chronic diseases – nutrition/food as the new medicine
3.20	Understanding the pathways to offspring and maternal health through the lens of metabolomics
3.21	Infant Neural Trajectory and EEG (INTr-EEG)

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	Molecular pathways of red blood cells invasion during malaria infection
4.4	Personalized RNA-based Cancer Vaccine for AMLImmunotherapy
4.5	Modelling and evaluating retinal stem cell transplants in humanized immune system
4.6	mRNA-based engineering of dendritic cells for the cross-priming of broad tumour- killing CD8+ T cells
4.7	Mining alarmin adjuvants hidden among the chromatin network

4.8	Tilt cancer vaccine-induced immunity in favour of CD8killer cells
4.9	Generation and characterization of Immunotherapy candidates for surface-displayed Cancer Testes Antigens (CTAs)
4.10	Derivation and characterization of fully human Allo-antibodies in renal transplant rejection
4.11	CELL2VIRUS: a virus-host interaction map at single-cell resolution
4.12	Constructing immune aging atlas through integration of single-cell transcriptomic data
4.13	Spatial meta-transcriptomics for microbiome–host interactions
4.14	Exploration of epigenetic signatures in naïve CD4+ T cells for downstream development of exhaustion across different immunological contexts

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	Development of a versatile, rapidly deployable, one-shot vaccine targeting platform
5.5	Studying viral-host interactions in chronic hepatitis viral infection versus acute viral infection by newly emerged viruses
5.6	Dynamic gut microbiome modulations to establish colonization resistance against multidrug resistant Klebsiella pneumonia
5.7	Virulence regulation of hypervirulent Klebsiella pneumoniae during host infection
5.8	Molecular mechanisms of assembly and transmission of viruses causing respiratory tract infections
5.9	Diabetes mellitus and dysregulated angiogenesis in pulmonary tuberculosis

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
6.3	Single-cell large foundation model for drug discovery
6.4	Develop large language model for subcellular resolution spatial multi-omics

7	Cancer Translational Research Programme / NUS Centre for Cancer Research (N2CR)
7.1	Development of intracellular multi-specific PTK6 antibodies for precision medicine
7.2	LYN kinase in cytoskeletal rearrangements and its effect on tumor immune escape in breast cancer
7.3	Translational Nanomedicine and Theranostics (TNT)
7.4	Interactions between the immune microenvironment and chemotherapy treatment in lymphoma
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 radio resistance and distant metastasis through molecular signature-based surveillance strategy
7.11	Targeting Cysteine metabolism in ovarian clear cell carcinoma
7.12	Anti-tumor effects of electrostimulation in mice with ovarian tumors

7.13	Cancer/Testis Antigen in mitochondria function and potential implications on metastasis and therapy-resistance
7.14	Identify molecular signatures of early prediction of therapy resistance and recurrence to develop surveillance strategies for personalized treatment
7.15	Expression and functional analysis of Glycosaminoglycans and Proteoglycans in breast cancer
7.16	Clinical Molecular Imaging Research for Precision Oncology
7.17	Single centre prospective evaluation of 68Gallium-FAPIPET/MRI in Hepatocellular Carcinoma
7.18	Know thy neighbour – Spatial profiling of Intra-Tumour Heterogeneity (ITH)
7.19	ADAR1 meets NF-kB signaling: Functional role of lncRNAin regulating immune evasion
7.20	Investigating the physiological roles of p52-ETS1, a new transcription factor
7.21	Alternative UTRs of key cancer genes: Novel regulators and therapeutic targets?
7.22	Machine learning approach to cancer and cardiovascular risk prediction
7.23	Mass spectroscopy biomarker discovery for precision medicine
7.24	New digital models of health information implementation
7.25	Synthetic biology of translational therapeutics and large scale bioproduction
7.26	Oral Delivery of Bioorthogonal Catalytic Centres for Treating Gastric Cancer: A Mice Model Study Using Ultra-Stable Thermostable Exoshells
7.27	Non-invasive characterization of endometriosis circulating, cell-free messenger RNA
7.28	Establishing a systematic approach to translate human genetic findings of Coronary Artery Disease into novel biology
7.29	Nanomedicine for metabolic diseases
7.30	Ethics and governance of precision medicine
7.31	A novel Telomere-binding protein

7.32	Regulation of the long non-coding RNA TERRA in cancers relying on the Alternative Lengthening ofTelomeres (ALT) pathway
7.33	Novel role of Abemaciclib in activating NK-cell cytotoxicity against nasopharyngeal carcinoma
7.34	Targeting transcription factor pathways in cancers
7.35	Loss of genomic stability of repetitive sequences as an early epigenetic predictor of leukemia
7.36	Cytoskeletal rearrangements and its effect on tumor immune escape in ovarian cancer
7.37	Uncovering the role of extracellular vesicles enriched FAM3C in promoting NSCLC metastasis
7.38	Targeting chromatin vulnerabilities in cancer
7.39	Identifying epigenetic drivers of therapeutic resistance
7.40	Investigating the role of early-embryonic factor reactivation in cancer cell plasticity
7.41	AI-based protein design and drug discovery
7.42	AI-based protein and RNA structure prediction

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	Next generation DNA delivery to mammalian cells
8.5	Synthetic biology of chemically synthesized macromolecules
8.6	Advancing Genome-Wide Off-Target Detection and AI-Driven Analysis for Safe and Precise CRISPR Therapeutics
8.7	Optimizing Genome Editing Tools through Directed Evolution and Advanced Screening Techniques

9	Nanomedicine Translational Programme
9.1	Nanomedicine for cardiovascular disease: Atherosclerosis
9.2	Nanomedicine for fatty liver disease
9.3	Advanced drug delivery in heart disease
9.4	Development of functional lipid nanoparticles for messenger RNA delivery
9.5	Invention of “3D” messenger RNA to improve intracellular delivery
9.6	Multifunctional nanomaterials to amplify T cell based cancer immunotherapy
9.7	Harnessing artificial intelligence for precision drug delivery
9.8	Development of immune modulator delivery nanomedicne for cancer immunotherapy
9.9	Radioligang Therapy (RLT)
9.10	Development of Individualised Cancer Vaccines
9.11	Translational Nanomedicine
9.12	Development of multimodality molecular imaging probes
9.13	Optimizing Tendon Healing with Functionalized Sutures and Modified Fibrin Gels
9.14	Nanomedicine therapeutic vaccine development

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 mutations to β-Thalassaemia using patient-specific STEM cells
10.3	Next generation sequencing of genetic kidney diseases in Singapore and Asia
10.4	Using human in vitro models for studying diabetes disease mechanisms

10.5	Integrated gene editing platform for inherited retinal diseases
10.6	Computational deep phenotyping for clinical risk prediction
10.7	Machine learning approach to cancer and cardiovascular risk prediction

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
11.3	Investigating retinal pigment epithelium in the context of age-related retinal degenerative diseases
11.4	Study an interesting gene in the development and progression of colorectal cancer via regulating ferroptosis
11.5	Creating isogenic reporter lines to identify regulators of cancer specific promoters
11.6	Development of gene therapy for pediatric liver diseases
11.7	Characterizing hepatocellular carcinoma at spatial resolution
11.8	Identification of SATB2 as biomarker for drug response in CRC
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 applications
11.22	In-depth mechanistic study of neurocognitive dysfunction in patients with systemic lupus erythematosus using multi-modal neuroimaging
11.23	Physiology study of electrolyte changes, CO2 kinetics and their effect on plasma pH under extreme conditions such as during bicarbonate dialysis
11.24	Ethical issues in the development of novel biotechnologies
11.25	Beyond sight - Elucidating the non-visual consequences of ocular diseases
11.26	Handheld pupillometry for a fast detection and diagnosis of ocular diseases
11.27	The Spectral Tuning of Light for MyOPia-control (STOP)
11.28	Understanding the mechanisms and refining the use of bright light for Myopia-control
11.29	Identifying novel eye movement and pupillometric biomarkers for ocular and neurological diseases
11.30	EaRly impAct theraPy with ceftazidime-avibactam via rapID diagnostics versus standard of care antibiotics and diagnostics in patients with bloodstream infection, hospital-acquired pneumonia or ventilator-associated pneumonia due to Pseudomonas aeruginosa or carbapenem non-susceptible Enterobacterales (RAPID)
11.31	Extracellular vesicle (EV) and EV-mimetic therapies for musculoskeletal disorders

1 Cardiovascular-Metabolic Disease Translational Research Programme

S/N	Principal Investigator	Project Title and Abstract
1.1	A/Prof Citra NZ Mattar citramattar@nus.edu.sg Department of Obstetrics & Gynaecology	1.1 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 researchand 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 hypoxicculture conditions (AFSC-CM) can augment tissue recovery following ischemic injury. We aim to: 1. Evaluate the signaling pathways of human cardiomyocytesand endothelial cells cultured in normoxic and hypoxic conditions under the influence of human AFSC-CM; 2. Evaluate the potential therapeutic application of AFSC-CMin reversing tissue injury in central vasculature ischemia animal model 3. Evaluate the potential therapeutic application of AFSC-CMin 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	1.2 Cardiac Gene Delivery by Enhanced Adeno-associate Virus Recently, our group has generated pre-clinical animal modelsas 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	1.3 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	1.4 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	1.5 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 rolein 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 12emaphoring12tion 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	Prof Theodoros Kofidis surtk@nus.edu.sg Department of Surgery	1.6 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, lack 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	1.7 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 associated 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 vascularendothelial 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 theinduction of autophagy. Autophagy. 2022; Jan 11:1-11 3. Monteiro-Cardoso VF et al. Bile Acids: ACommunication 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	1.8 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 14emaphoring 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	1.9 Modulation of cellular 15ehavior 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 ofmyocardial infarction, stroke or other atherosclerotic complications in their teen age. Progerin cumulation disruptsthe 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 stillnot 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 diseasedmodel, we postulate that AFSC-S will positively influence theageing CM cellular 15ehavior in an ischemic environment of HGPS patient cells. Furthermore, the characterization of CMsecretome will be crucial for a deeper understanding of CM 15ehavior15 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/reperfusioninjury mouse model.
1.10	A/Prof Heng Chew Kiat paehck@nus.edu.sg Department of Paediatrics	1.10 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	1.11 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).

1.12	Dr Chester Lee Drum mdccld@nus.edu.sg Department of Medicine	1.12 Biomarker discovery for precision medicine and patient health using advanced analytics and multiplex mass spectrometry Metabolism is at the core of every disease process, in addition to natural mechanisms of oxidative-stress and age- related mitochondrial dysfunction. This project combines deep phenotyping of patients using the technique of mass spectrometry, regression modelling and some basic machine learning algorithms. In particular, we focus on modifiable exogenous analytes which can improve patient outcomes and provide the basis for controlled clinical trial design. One of the most interesting outcomes of this research is the identification of compounds which reduce oxidative stress. 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. Clinical cohorts are sourced from either our own recruitment from Dr. Drum's clinic or through collaborators in Singapore and/or internationally. Clinical findings can be validated via access to the UK Biobank, a resource of over 400,000 clinical records and the MOH National Disease Registry, which covers national outcomes in Singapore. This project is fully funded and open for enrolment.
1.13	A/Prof Vitaly Sorokin sursv@nus.edu.sg Department of Surgery	1.13 Modulation of Vascular Smooth Muscle Cell in Type 2 Diabetes Type 2 Diabetes (T2D) are marked by high blood glucose level and often associated with insulin resistance. Patients suffering from T2D are at much higher risk of cardiovascular- related complications and mortality. Studies have shown that T2D affects the biology of various cell types found in the vasculature, including vascular smooth muscle cells (VSMC). VSMC from T2D patients showed increased proliferation rate, cell migration, and extracellular matrix production. Our laboratory has developed a robust protocol to isolate VSMC from aortic tissues of patients undergoing cardiac surgery. Using these primary cells, we have shown that T2D VSMC exhibited phenotypic characteristics of synthetic VSMC and fibroblast-like cells. A better understanding of how T2D modulates VSMC phenotype would potentially help in the management of T2D- associated cardiovascular complications. Based on our results, the aims of this research project are: 1. To characterize VSMC subpopulation phenotypes in T2D patients using single-cell RNA sequencing technology. 2. To elucidate the molecular pathways leading to the T2D- associated VSMC phenotypic modulation. 3. To identify potential therapeutic targets in T2D VSMC to prevent cardiovascular-related complications.

1.14	A/Prof Vitaly Sorokin sursv@nus.edu.sg Department of Surgery	1.14 Exploring the prospect and molecular basis of 3D spheroid culture in vascular biology and disease modeling 3D culture as a model has been observed in different fields of research, predominantly observed in cancer biology. It has also been widely understood that cells in 3D culture would better mimic specific physiological environment in vivo whereby genes and proteins expressions have been reported to be comparable to the in-vivo conditions. However, in the field of vascular biology, the usage of such 3D modelling has been limited, albeit with recent advancements such as the microfluidic and organ-on-a- chip approaches. Thus, we want to develop a simple and alternative model for studying vascular biology and disease progression using the 3D spheroid culture, with the advantage of less complex setup and high throughput analysis. In our preliminary findings, we have established a 3D spheroid culture aimed at modelling atherosclerosis using patient-derived vascular smooth muscle cells (VSMCs), endothelial cells (ECs) and macrophages. Early findings suggest the potential in these spheroids in exhibiting features of inflammation and having greater response towards oxLDL treatment. Thus, our aim of this project would be: 1. To understand and elucidate the molecular interactions within the spheroid model. 2. To determine the potential of the spheroids in modelling cardiovascular disease progression. 3. To determine the potential of the spheroid in identifying patient- specific therapeutics treatment.
1.15	Dr Koh Cho Yeow choyeow@nus.edu.sg Department of Medicine	1.15 From Bench to Bedside: Exploring Venomous and Haematophagous Animals for Novel Therapeutics Venomous animals, including snakes, spiders, scorpions, bees, cone snails, and sea anemones, as well as hematophagous animals, such as ticks, leeches, mosquitoes, vampire bats, and horseflies, use their venomous or salivary secretions for predation, defence, and feeding. These secretions consist primarily of proteins and peptides, hypothesised to originate from the animals' genomes, and have been recruited and evolved to become specialised toxins. Over the course of millions of years, these toxins have become potent, specific, and stable molecules that target the circulatory system, enabling the incapacitation of prey or extraction of nutrients from hosts. Research into venomous and salivary secretions from animals has led to the discovery and development of life-saving therapeutic related to cardiovascular diseases. For example, captopril, eptifibatide, tirofiban, lepirudin, and bivalirudin are drugs derived from these toxins that are used to treat conditions such as hypertension or thrombosis. Our team has long-standing interest in discovery, design, and development of novel drug candidates like anticoagulants1,2 and natriuretic peptides3,4 from toxins found in venomous and hematophagous animals. Students joining our team will receive comprehensive training and exposure to basic science and translational clinical science research. They will have access to a wide range of techniques, including peptide/protein synthesis, expression, and purification; enzymatic, molecular, and cellular assays; protein/DNA/RNA blotting and cell imaging; high- and medium-throughput screening campaigns; protein structure determinations using x-ray crystallography or cryo-electron microscopy; protein design, engineering, and directed evolution; mass spectrometry- or affinity-based proteomics and RNA sequencing-based transcriptomic studies; animal models in thrombosis, bleeding, myocardial infarction, fibrosis, pulmonary hypertension, nanoparticle drug delivery, and pharmacokinetics (mice, rats, rabbits, pigs); platelet/coagulation assays and biomarker analyses of clinical samples. Our goal is to provide our students and staff with a comprehensive understanding and capability in bench-to- bedside translational research. If you are interested in joining our team or learning more about our research and specific projects, please contact us (choyeow@nus.edu.sg) for further details.

2 Healthy Longevity Translational Research Programme

S/N	Principal Investigator	Project Title and Abstract
2.1	A/Prof Juan Helen Zhou mdczju@nus.edu.sg Department of Medicine	2.1 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 focuses 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 welcome to check out www.neuroimaginglab.org for more information.
2.2	A/Prof Ling Shuo-Chien phsling@nus.edu.sg Department of Physiology	2.2 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 investigates 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 lifespan using the genomic dataset generated in the above-described approaches.

2.3	Prof Reshma Taneja phsrt@nus.edu.sg Department of Physiology	2.3 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	2.4 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 in deciphering 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	2.5 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 include 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 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 cholinergicneurons 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 be the starting point for such investigations. The findings will have implications for promoting a healthy lifespan.

2.6	Dr Tamra Lysaght tlysaght@nus.edu.sg Centre for Biomedical Ethics	2.6 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	2.7 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 contributes 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	2.8 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 22ehavi both, healthy and defect mitochondrial genomes (heteroplasmy) and defects accumulate with aging. Mitochondrial gene therapy could provide cure for 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 along 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	2.9 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	2.10 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 signaling 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	2.11 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	2.12 Polycystic ovary syndrome (PCOS) The androgen-driven PCOS is another focus of our work. In the laboratory, our students have derived 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	2.13 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	2.14 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 25ehavior 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 deeplearning 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	2.15 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, 26ehavior26ize, 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	2.16 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	2.17 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 Worldwide 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	2.18 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 neuro-modulatory 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 molecularinteractors 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 28ehavior. For more information: www.polepallilab.org

2.19	Dr Jai Polepalli jpolepalli@nus.edu.sg Department of Anatomy	2.19 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 behavioursis yet to be detailed. Understanding the molecular specifications, synaptic and circuit mechanisms that modulate motivated behaviours underpinning reward-related 28 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 29 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	2.20 A role for neutrophin and GABAergic mechanisms in hippocampus in mediation of experimental neuropathicpain? Chronic pain affects one-fifth of world population. However, there are few effective analgesics, in part because the CNSbasis of chronic pain has not been clearly elucidated. Experiments in our laboratory suggest that experimental neuropathic pain in young rodents 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 implications 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	2.21 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 signal 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	2.22 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 understanding 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	2.23 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, an 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 integrity 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	2.24 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 maybe 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	2.25 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	2.26 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 an 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	Prof KOH Woon Puay kohwp@nus.edu.sg Dean's Office	2.39 SG70 – Towards Healthy Longevity in Singapore The main objective is to take an integrated and holistic approach to examining the effects of biological, lifestyle and socioeconomic factors that affect multi-dimensional outcomes as Singaporeans transit from health to morbidity around the age of 75 years. A cohort of Singaporeans aged 65-80 years (73 years on average), nested in the prospective cohort of the Singapore Chinese Health Study, will be studied as they develop morbidity beyond these years. Beyond establishing associations, this cohort seeks to: 1. Elucidate the etiologic roles of biological factors in the pathogenesis of health-related ageing outcomes, 2. Identify modifiable factors to promote healthy longevity, 3. Identify risk biomarkers that could be developed for early detection or screening of adverse outcomes in ageing. Findings from the cohort have great potential for contributing towards the scientific basis for developing public health programmes and policies for the promotion of health in multi-dimensional aspects of longevity for all Singaporeans.

2.28	Dr Crasta Karen Carmelina phscras@nus.edu.sg Department of Physiology	2.28 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 33ehavio 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
2.29	Dr Goh Jorming jorming@nus.edu.sg Department of Physiology	2.29 Rejuvenating Senescent Traits of Older Adults Through Regular Exercise (RESTORE) Longitudinal studies have consistently reported improved health spans 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).
2.30	Dr Goh Jorming jorming@nus.edu.sg Department of Physiology	2.30 REBOOT (Resistance Exercise improves BiOlOgical age inolder adulTs) Skeletal muscle loss usually starts after 40 years of age at arate of -0.5% per year, and then accelerates rapidly after 60years. 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.

2.31	Dr Goh Jorming jorming@nus.edu.sg Department of Physiology	2.31 BREXINT (Breast Cancer Exercise INTervention) 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.
2.32	Prof Andrea B. Maier a.maier@nus.edu.sg Department of Medicine	2.32 Improving the validity of ageing clocks in frail older adults Frailty is regarded as an ageing syndrome characterized by functional decline in multiple physiological systems along with increased vulnerability to stress events. Frailty has been associated with a wide range of adverse outcomes such as lower quality of life, disability, falls, fractures, hospitalization, institutionalization and mortality. Biological age-related changes featured as an accumulation of cellular and molecular damage over the life course are considered to be an essential component of driving the development of frailty. Individuals age at the same rate chronologically but not biologically, which explains that those with accelerated biological aging enter a frailty state earlier and have a higher risks of adverse outcomes compared to their peers. A higher biological age determined by a blood biochemistry-based aging clock showed an association with frailty in a prospective cohort of patients admitted to geriatric rehabilitation (RESORT cohort). The aim of this study is to improve this clock using clinical data to tests its capacity to be implemented into clinical care. More projects are available making use of the RESORT cohort.

2.33	Prof Andrea B. Maier a.maier@nus.edu.sg Department of Medicine	2.33 Current knowledge of Geroscience in health-care professionals By 2050 one in six people globally will be over the age of 65 years, compared to one in 11 in 2019. This increase in life expectancy is the result of public health improvements and medical interventions. However, the health span, the period of life absent from age-related diseases, is not improving and the proportion of older adults suffering from multiple chronic diseases simultaneously is expanding. Maintaining health span has therefore become an important topic for modern medicine. The most important risk factor for age-related chronic diseases is ageing. The Geroscience hypothesis posits that delaying the ageing process would delay the onset of these age-related chronic diseases. This notion led to the development of the hallmarks of ageing, nine independent biological factors that interact with each other and drive the aging process. Research into these molecular and cellular mechanisms of ageing has contributed to the development of interventions that increases both lifespan and health span in animal models and humans. Translation of basic science discoveries and human trials into clinical practice are at the edge of implementation. The Geroscience approach aims to change the process of treating diseases in isolation, and instead develop therapeutics that targets fundamental ageing mechanisms and promotes health span. Education is an essential step in the transition from current clinical practice towards the novel Geroscience approach. To date, the current knowledge among healthcare professionals regarding the Geroscience approach is unknown, and this information is highly needed in order to develop educational programs. The aim of the study is to investigate the knowledge about Geroscience among healthcare professionals working in community and hospital settings.
2.34	Prof Andrea B. Maier a.maier@nus.edu.sg Department of Medicine	2.34 Current knowledge of Geroscience in community dwelling middle-aged individuals By 2050 one in six people globally will be over the age of 65 years, compared to one in 11 in 2019. This increase in life expectancy is the result of public health improvements and medical interventions. However, health span, the period of life absent from age-related diseases, is not improving and the proportion of older adults suffering from multiple chronic diseases simultaneously is expanding. Maintaining health span has therefore become an important topic for modern medicine. The most important risk factor for age-related chronic diseases is ageing. The Geroscience hypothesis posits that delaying the ageing process would delay the onset of these age-related chronic diseases. This notion led to the development of the hallmarks of ageing, nine independent biological factors that interact with each other and drives the aging process. Research into these molecular and cellular mechanisms of ageing has contributed to the development of interventions that increases both lifespan and health span in animal models and humans. Translation of basic science discoveries and human trials into clinical practice are at the edge of implementation (the first longevity medicine clinic is to be opened early 2023 at Alexandra Hospital). The Geroscience approach aims to change the process of treating diseases in isolation, and instead develop therapeutics that targets fundamental ageing mechanisms and promotes health span. Education is an essential step in the transition from current clinical practice towards the novel Geroscience approach. To date, the current knowledge among community dwelling middle-aged adults (the end-consumer) regarding the Geroscience approach is unknown, and this information is highly needed in order to develop a public health approach. The aim of the study is to investigate the knowledge about Geroscience among community dwelling middle-aged adults.

2.35	Prof Andrea B. Maier a.maier@nus.edu.sg Department of Medicine	2.35 Will Rapamycin turn back time? Rapamycin (sirolimus) is an inhibitor of the mammalian target of rapamycin (mTOR) and a Food and Drug Administration (FDA) approved drug for immunoprophylaxis. Given intermittently, Rapamycin inhibits the mTOR complex 1 and extends lifespan in animal models in a dose dependent manner by up to 60% and improves measures of health span in middle-aged mice. Therefore, Rapamycin is a potential repurpose drug candidate for geroprotection in humans, however, data of the potential effect in middle aged humans to prevent age-related diseases are currently lacking. LONGER is a double-blinded randomized control trial (RCT)of rapamycin versus placebo for 6 months including 40–60-year-old healthy individuals. This RCT is the first testing if rapamycin can turn back the time in healthy ageing individuals.
2.36	Prof Andrea B. Maier a.maier@nus.edu.sg Department of Medicine	2.36 The biological phenotype of the oldest old The current understanding is that an extended lifespan associates with a relatively young biological phenotype. However, if that is true at extreme ages as nonagenarians and centenarians are partly unknown, specifically which biomarkers are most associated with extreme longevity. TheSG90 cohort includes oldest old individuals which are extremely well phenotyped on clinical and biological level (biomaterial available). The aim is to characterize biological signatures of sustained health in this population of the oldest old to gather a better understanding of successful biological trajectories during the life course. Determinants include epigenetic data, metabolomics, proteomics and lipidodomics. Outcomes include intermediate biological phenotypes next to clinical phenotimes (disease, function and mortality).
2.37	A/Prof Raymond Seet mdcrscs@nus.edu.sg Department of Medicine	2.37 Understanding the association between platelet characteristics of patients with ischemic stroke and the risk of stroke recurrence Stroke is a leading cause of death in many developed and developing countries. Close to 80% of stroke is caused by arterial thrombosis that underpins ischemic stroke. Although platelets play an important role in maintaining hemostasis, overactivation of platelets may lead to platelet aggregation and thrombosis capable of occluding blood vessels. During activation, membrane proteins involved in various pathways of aggregation may be differentially upregulated and expressed. Under these pathological circumstances, platelets of stroke patients may be hyperactivated and increase their expression of membrane proteins. A detailed interrogation of these proteins may be useful to prognosticate stroke outcomes and reveal a newer target for platelet inhibition to prevent stroke recurrence. Hence, the objective of this study is to examine the relationship between platelet surface markers in stroke patients and compare them with those of age-matched controls and long-term stroke outcomes. Flow cytometry and RNAseq would be utilized to study the expression level of these platelet surface markers.

2.38	Prof Soong Tuck Wah phsstw@nus.edu.sg Department of Physiology	2.38 CaV1.3 IQ-domain RNA editing in circadian rhythm RNA editing can diversify protein functions through recoding after adenosine-to-inosine (A-to-I) substitution catalyzed by adenosine deaminases acting on RNA (ADAR) enzymes, which generates various levels of post-transcriptional edited sites in a developmental and spatial-temporal manner. Recoding of exons leads to diversification of protein function in response to various environmental or physiological conditions. CaV1.3 channel is known to undergo RNA editing specifically in the central nervous system. CaV1.3 channel is also found to be the dominant calcium source supporting spontaneous firing of SCN neurons during the day in rodents. Recently the mechanism of decreased current from edited CaV1.3 channel due to a more dominant effect of the reduction of open probability was established with the transgenic knockout mouse model. In this CaV1.3ΔECS knockout mice, disrupted sleep-wake pattern was observed in a gender specific manner. In particular, the KO male animals showed disrupted sleep as they wake up more during the daytime, while this phenotype was not observed in female animals. We hypothesize that deletion of RNA editing may altered the day-firing of SCN neurons and lead to the disrupt sleep in male mice, while there could be compensatory mechanisms in female mice possibly relating to estrogen and estrogen receptors.
2.39	Prof Soong Tuck Wah phsstw@nus.edu.sg Department of Physiology	2.39 Cav1.2 Deubiquitinases: implications in cardiovascular diseases CaV1.2 channel is the major pathway for calcium influx in smooth muscle cells and its dysfunction significantly contributes to cardiovascular disorders. Recently the mechanism of ubiquitin- mediated turnover of CaV1.2 channels by specific E3 ligases has been generally established. In particular, CaV1.2 channels in the absence of CaVβ subunit are recognized by an endoplasmic reticulum (ER)-resident E3 ligase, RFP2 which mediates their polyubiquitination and proteasomal degradation. However, how CaV1.2 channels remain in a dynamic equilibrium between trafficking to plasma membrane and degradation byER-associated degradation (ERAD) complex and how they can be regulated through the removal of polyubiquitination chains by selective deubiquitinases (DUBs) in ER are still unknown. To date, only six DUBs in ERAD, such as USP13, USP25, YOD1, ataxin-3, OTUB1 and VCIP135, have been reported. Among them, USP13 shares about 80% sequence similarity to USP5, only showing the difference on the secondubiquitin-associated domain. Based on these previous findings, we hypothesize that at least one of them may function as the deubiquitinase that reverses CaV1.2 channel polyubiquitination and stabilizes CaV1.2 channel activity.
2.40	Prof Soong Tuck Wah phsstw@nus.edu.sg Department of Physiology	2.40 CaV1.3 IQ-domain RNA editing: implications in mood disorders RNA editing can diversify protein functions through recoding after adenosine-to-inosine (A-to-I) substitution catalyzed by adenosine deaminases acting on RNA (ADAR) enzymes. CaV1.3 channel is known to undergo RNA editing specifically in the central nervous system. Recently the mechanism of decreased current from edited CaV1.3 channel due to a more dominant effect of the reduction of open probability was established with the transgenic knockout mouse model. In thisCaV1.3ΔECS knockout mice, with abolishment of CaV1.3 RNA editing, the male aniamals exhibit anxiety-like behaviours and enhanced fear memory. The mice will be used as a model to investigate the role of CaV1.3 RNA editing in regulating neuronal excitability in amygdala neurons and the connection between amygdala and hippocampus. We will also explore whether there is any gender differences of the anxiety- like behaviour in these animals and whether interventions such as restricted feeding would have beneficial effects on reducing anxiety level. As risk variations in CACNA1D were also associated with major types of psychiatric disorders, we could also explore the potential role of CaV1.3 RNA editing in psychiatric disorders such as BD, SCZ, ADHD, MDD, and ASD.

2.41	Dr Vincenzo Sorrentino vsorrent@nus.edu.sg Department of Biochemistry	2.41 Characterization of a novel NAD+ precursor for muscle and brain health in aging NAD+ is an essential coenzyme for cellular and organismal metabolism. NAD+ levels decline during aging in several tissues, including brain and muscle. Currently, pharma, nutrition and academic entities are heavily pursuing NAD+ boosting strategies in order to ameliorate or treat age-related diseases, however the identification of the best NAD+ precursors and their successful applications are still a major challenge. The current project will be focused on a novel NAD+ booster, trigonelline, discovered in collaboration with Nestle' Research in Switzerland, for its potential benefits on the aging process, through three aims: - characterize the conversion pathway of trigonelline and impact on NAD+ metabolism and aging using neuronal and muscle cellular models and the nematode model of agingC.elegans. - Assess the impact of trigonelline in reducing proteotoxicity and improving mitochondrial function in primary muscle cells derived from aged donors and in neuronal cells and nematode models of Alzheimer's disease. - Test muscle and brain performance, supported by in-depth molecular analyses of these tissues, in aged mice supplemented with trigonelline. This will provide an extensive characterization of trigonelline and of its strong potential for rapid clinical applications for healthy longevity. For Prof. Sorrentino's related articles to this field: 1)DOI: 10.1038/nature25143 2)DOI: 10.1016/j.celrep.2020.108660
2.42	Dr Vincenzo Sorrentino vsorrent@nus.edu.sg Department of Biochemistry	2.42 Dissecting cellular pathways of aging- and senescence- associated amyloidosis Protein homeostasis (proteostasis) includes all processes required to maintain the cellular proteome, from regulation of protein synthesis to aggregation and degradation. Loss of proteostasis occurs in aging and neurodegenerative disorders such as Alzheimer's disease, and in muscle during sarcopenia and inclusion body myositis. Recent published and unpublished work from Sorrentino's research indicates that aging is accompanied by accumulation amyloidogenic aggregates, and this also occurs in senescent cells. However, the major mechanisms and types of protein aggregates occurring in aging and senescence are yet to be defined. This project will focus on unveiling the relationship between aging, proteostasis decline and cellular senescence in the following aims: - Identification of aging-associated amyloid oligomers from brain and muscle tissues of old mice, and from senescent cells generated via several methods, through enrichment and proteomics methodologies. - Mechanistic studies in cells and in the aging model C. elegansto evaluate the role of the identified pro-amyloidogenic proteins on cellular health and on the senescence process via loss- or gain-of- function experiments, followed by molecular characterization. Overall this will unveil mechanisms linked to age- and senescence- associated amyloidosis, and create new opportunities to drug proteostasis in aging. For Prof. Sorrentino's related work: DOI: 10.1016/j.celrep.2020.108660

2.43	Dr Vincenzo Sorrentino vsorrent@nus.edu.sg Department of Biochemistry	2.45 Elucidation of common proteotoxic stress response signatures across aging and age-related diseases While aging and neuromuscular proteinopathies all show features of metabolic and proteostasis dysfunction, the underlying global molecular alterations of these conditions are unknown, and whether there may be shared mechanisms of disease and repair that could be targeted across conditions is unclear. The hypothesis for this project is that proteotoxicity conditions in diseases like Alzheimer's disease, Parkinson's, Hungtington, or during aging itself result in a common cellular adaptation response that can be identified, mapped, and therapeutically targeted. The activities of the project will involve: -Execution and analyses of metabolomics, transcriptomics and proteomics on mammalian cells and nematode models of protein aggregation (e.g. amyloid-beta and Huntingtin), -Cross-reference studies of the datasets obtained with existing datasets of human patients and mice models of aging, and proteotoxic diseases to identify possible common deregulated pathways. -Assessment of the disease relevance of pathways identified by knock-out or overexpression studies in cellular models, and in C.elegans, or by compound-based approaches for known druggable metabolites, lipids or proteins. This will provide a comprehensive view of the effects of proteotoxicity across age-associated diseases and facilitate identification of potential novel disease biomarkers and therapeutics. For Prof. Sorrentino's related work in this field: 1) DOI: 10.1016/j.celrep.2020.108660 2) DOI: 10.1371/journal.pcbi.1007162

3 Human Potential Translational Research Programme

S/N	Principal Investigator	Project Title and Abstract
3.1	A/Prof Chan Shiao-Yng obgchan@nus.edu.sg Department of Obstetrics & Gynaecology	3.1 Unravelling inositol's role at the maternal-fetal interface: implications for pregnancy and offspring development Inositol and its derivatives regulate insulin, glucose and lipid 43ehavior43 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 mitigatesglucose'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 43ehavior43 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	A/Prof Juan Helen Zhou mdczju@nus.edu.sg Department of Medicine	3.2 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 functionalnetworks 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 theinfluence of amyloid-beta, tau, and cerebrovascular pathologyas 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.

3.3	Dr Ivan Low Cherh Chiet phsilcc@nus.edu.sg Department of Physiology	3.3 Uncovering the role of CNS in hyperthermia-inducedfatigue 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 impairmentsremains 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 targetedfor the abatement of CNS deficits during exertional hyperthermia.
3.4	Dr Ivan Low Cherh Chiet phsilcc@nus.edu.sg Department of Physiology	3.4 Harnessing the gut microbiome to combat heat injuries Hyperthermia-induced endotoxemia resulting from elevated gut permeability is amongst the main factors linked to the development of exertional heat stroke. Gastrointestinal ischaemia resulting from elevated heat stress could disrupt the integrity of endothelial tight junctions. The integrity of endothelial tight junctions is heavily influenced by the composition of the intestinal microbiota. Alterations in gut microbiota composition may affect gut permeability and the translocation of substances across the gastrointestinal barrier.While thermal stress is known to disturb gut microbiota function, it remains uncertain if endotoxemia triggered by an acute bout of exertional heat stress can be contributed by perturbations in gut microbiota composition. As such, the impact of gut microbiota modulation on hyperthermia- induced endotoxemia and its associated CNS symptoms is an idea worthy of future investigations. To better understand the changes in human gut microbiota induced by exertional (exercise-induced) heat exposure, this study will profile the gut microbiome before and after a single acute bout of exertional hyperthermia. The microbial community of the stool samples will be characterized (16S- based RNA analysis) to assess the respective impact of exertional and passive heat stress on the gut microbiome. In addition, blood samples will also be collected and analysed for serum endotoxins and gut permeability biomarkers to assess if potential changes in gut microbiome composition is correlated with disrupted gut permeability in individuals subjected to exertional hyperthermia. Successful characterization of post-hyperthermia gut microbiome will not only augment our understanding on the role of gut microbiota composition in mediating hyperthermia-induced endotoxemia,but also allow us to develop nutritional strategies to counter the debilitating effects of exertional heat stress.

3.5	Dr Lo Chi Yan mdclocy@nus.edu.sg Department of Medicine	3.5 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, slowwave 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 45ehavior in children, aged7-9 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-agechildren's sleep, psychosocial, and academic outcomes (objective 1). Moreover, we will investigate the demographicprofile 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 Queenie Li Ling Jun obgllj@nus.edu.sg Department of Obstetrics & Gynaecology	3.6 Studying the Heterogeneity of Gestational Diabetes Mellitus: Cardio-Metabolic Alteration and Treatment Response in a Multi- Ethnic Population in Singapore(GDM- CARE) Gestational diabetes mellitus (GDM) is a transient hyperglycaemic condition identified during pregnancy among pregnant women without history of chronic diabetes. Evidencehas shown that GDM leads to a series of adverse healthoutcomes including pre-term birth, progression to pre-diabetes,and type 2 diabetes after delivery in mothers. Interestingly, GDM is getting more and more prevalent in Asian pregnant women, due to the increasing number of overweight and obesity and genetic susceptibility. Even though there is increasing recognition in GDM, the efficiency and efficacy of treating GDM is poor mostly due to its heterogeneity underlinedby various pathophysiological mechanisms. Therefore, understanding better on GDM heterogeneity can help cliniciansin offering more targeted treatment and follow-up strategy to GDM mothers. This CSAINV proposal aims to define GDM phenotypes in terms of cardio- metabolic profiles in vivo and treatment response during pregnancy, by using a set of uniqueand novel technology applied (i.e. continuous glucose profiling and untargeted metabolites profiling). In this proposed 3-year pregnancy cohort, we will recruit 800 overweight or obese Asian pregnant women in early pregnancy without a history ofdiabetes until delivery. We aim to develop a systematic antenatal and postnatal screening, treatment and intervention guidance in GDM mothers.

3.7	A/Prof Chan Shiao-Yng obgchan@nus.edu.sg Department of Obstetrics & Gynaecology	3.7 Myo-Inositol and Fetal Membrane Remodeling and Weakening Preterm premature rupture of the fetal membranes (PPROM) is a pregnancy complication accounting for approximately onethird 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 senescenceassay. 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.
3.8	A/Prof Chan Shiao-Yng obgchan@nus.edu.sg Department of Obstetrics & Gynaecology	3.8 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 48ehavior48, 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 needto understand how placental inositol may regulate fetal growth. This project will use magnetic resonance imaging techniques to quantify and spatially 48ehavior inositol isomers within the placentas obtained from pregnancies of babies born small, appropriate, or large for gestational-age. Associations will alsobe made between placental inositol measures and intrauterinefetal 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 inositolin 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.

3.9	A/Prof Chan Shiao-Yng obgchan@nus.edu.sg Department of Obstetrics & Gynaecology	3.10 Investigating the mechanistic role of the placenta in maternal-fetal transmission of mental health risk Maternal mental health stresses during pregnancy, presentingas 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 forfunctional 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 fetuswill generate novel knowledge critical for designing interventions that can behaviour the risk of vertical transmission of mental health vulnerability, and improve long-term neurocognitive and behavioural outcomes of offspring, and ultimately behaviour in human potential and reducing societal costs of poor mental health.
3.10	A/Prof Boon Thye Thomas Yeo thomas.yeo@nus.edu.sg Department of Medicine	3.11 Machine learning of brain MRI to improve mental health and disorder We are an interdisciplinary group of neuroscientists and computer scientists seeking to understand the human brain, improve mental health and treat mental disorders. There is a deluge of data across many scientific disciplines. Future scientific breakthroughs will rely on algorithms to explore these massive data. Our group develops and applies machine learning algorithms to generate neuroscientific discoveries from large-scale datasets comprising thousandsof subjects with brain MRI, behavioral, genetic and other physiological measures. For example, we have estimated high-quality functional brain atlases, which are widely used around the world to study healthy brain network organizationand mental disorders. We have also developed machine learning techniques to predict Alzheimer's Disease progression, as well as uncover transdiagnostic mental disorder subtypes. Finally, we are one of the first groups to develop machine learning techniques to "invert" biophysical neural networks, yielding new insights into healthy brain organization and development. We are interested in students with background either in (1) engineering/computer science or (2) neuroscience. For students with neuroscience background, some programming experience is necessary.More information about our group can be found here (https://sites.google.com/view/yeolab/home).

3.11	Prof Chee Wei Liang Michael Michael.chee@nus.edu.sg Department of Medicine	3.12 Personalizing Sleep For Better Health Using Large Scale Device Data Many Asians have poor sleep habits that impact health, wellbeing and productivity. This can be transformed by; 1. Developing and integrating smartphone and wearable based technologies to unobtrusively obtain long-term measurementsof sleep patterns and cognition. 2. Collecting data using the aforementioned platform to characterize sleep patterns acrossthe lifespan and from there uncover their associations with outcome variables relevant to cognition, mood, cardiometabolic health and ageing. 3. Using the above knowledge to personalize age-specific sleep recommendations in a manner relevant to Asians. The student will join a multi-disciplinary team that has experience collecting and analyzing multisensor data in students, working adults and older adults. In the coming years, we will be intensifying efforts in the NUS population, with the goal to characterize and personalize interventions forbetter sleep and wellbeing in this cohort. The student will be involved in the: (1) Development of large-scale data collection pipelines from multiple wearable and e-device streams, Analysis and visualization of intensive longitudinal data; and (2) Design and evaluation of interventions catered to specific groups of individuals.
3.12	Dr Lo Chi Yan mdclocy@nus.edu.sg Department of Medicine	3.13 Neurobehavioural functions of school-age children during multiple weeks of sleep restriction and recovery In school-age children, sleep curtailment is associated with deficits in multiple neurobehavioural domains. Alarmingly, on school days, 64.5% of school-age children in Singapore sleepless than the minimum recommended duration of 8 hours, andthey typically attempt to pay their sleep debt by extending their time in bed during weekends. However, empirical evidence from adolescents and adults suggest that sleep extension for one or two nights may not be sufficient to fully reverse the neurobehavioural impairments caused by repeated sleep restriction on weeknights. To what extent sleep extension on weekends can facilitate the recovery of cognitive functions and mood remains unexplored in children, particularly when sleep restriction is recurrent across weeks. The study aims to investigate the neurobehavioural deficitsand recovery dynamics of two weeks of sleep restriction on weekdays and extension on weekends among school-age children.
3.13	Dr Lo Chi Yan mdclocy@nus.edu.sg Department of Medicine	3.13 Reducing children’s screen use for better sleep, mental,and brain health: a personalised approach Short-sleeping school-age children are at risk for poor mental, cognitive, and brain health. Alarmingly, in Singapore, 64.5% of school-age children sleep less than the minimum recommended duration of 9 hours on school nights. These short-sleeping children, on the other hand, spend on average 2.5 hours per school day on media use for non-academic purposes, revealing the potential of reducing their screen timefor more sleep. The effectiveness of various interventions targeted at reducing media use and/or improving sleep has been studied among school- age children. While these existinginterventions focus on screen use in the evening and before bedtime in view of the physiological effects of light emittance and the cognitively stimulating effects of the media content, they took a one-size-fits-all approach and ignored the individual differences in the duration, type, and purpose of media use throughout the day. In this project, we will use a scalable, personalised approach to curtail media use based on each individual’s need throughout the waking hours so as to (1) advance children’s bedtime and hence, increase their sleep duration, (2) improve their mood, depressive symptoms, and behavioural problems, and (3) enhance their brain and cognitive functions.

3.14	Dr Lo Chi Yan mdclocy@nus.edu.sg Department of Medicine	3.15 Effects of recurrent short and variable sleep on cognitive performance, brain dynamics, psychological well-being, and glucose metabolism Many students and working adults struggle to sleep the recommended amount because of competing wake activities,and thus, face multiple well-established neurobehavioual and metabolic costs associated with sleep loss, e.g. impaired cognitive functions and mood, altered brain activation and network connectivity, reduced glucose tolerance and insulin sensitivity, and higher risk for diabetes. As part of our group's continuous effort to identify alternative short sleep schedules that can attenuate these sub-optimal consequences in the long run while still allowing individuals to meet impending study and work demands, this 16- day laboratory-based studywill investigate whether a variable or a stable sleep schedule will be more effective in minimizing neurobehavioual and metabolic deficits when total sleep opportunity across two weeks is below the recommended sleep duration.
3.15	Prof Cuilin Zhang obgzc@nus.edu.sg Department of Obstetrics & Gynaecology	3.15 Omics, metabolomics and novel risk factors and biomarkers to better understand the etiology and prevention of gestational diabetes mellitus Gestational diabetes mellitus (GDM) is a common pregnancy complication. While established risk factors like obesity and family history of diabetes are recognized, the intricate molecular mechanisms underlying GDM remain largely undefined. Unearthing novel metabolites is pivotal for enhancing our comprehension of GDM's etiology and, for potentially, developing more effective preventative strategies to disrupt the viscious cycle of 'diabetes begetting diabetes'. With these objectives in mind, this study aims to unravel the etiology of GDM by investigating maternal modifiable lifestyle- related factors and novel biomarkers including metabolites. Multiple projects can be undertaken within the overall scope of the study: Examination of modifiable risk factors contributing to GDM, such as nutrition, dietary, and lifestyle factors. Exploration of novel, modifiable biomarkers capable of informing precise prevention strategies for diabetes. These encompass targeted and non-targeted analyses of metabolomics, lipidomics, microbiome profiles, and cardio-metabolic biomarkers. Within the context of established pre-pregnancy and maternal risk factors, an additional research aim is to explore methodological advancements facilitating the identification and utilization of sparse and interpretable metabolite features. This includes enabling mediation analysis with high-dimensional exposures. To achieve these research aims, the study will harness the comprehensive and longitudinal data and biospecimen collected in the NICHD Fetal Growth Study. This dataset comprises 2,802 pregnant women of four races/ethnicities with risk factors and biomarkers data assessed at four timepoints throughout pregnancy.

3.16	Prof Cuilin Zhang obgzc@nus.edu.sg Department of Obstetrics & Gynaecology	3.16 Prediction models of gestational diabetes mellitus and unfavorable fetal growth with high-dimensional multi- omics approaches in conjunction with conventional risk factors for improved precision medicine Prior work from the team have investigated and identified a panel of key biomarkers including fatty acids, amino acids, thyroid function markers, iron status, and HbA1c, associated with the development of GDM. The primary objective of this study is to build upon our prior findings. In this study, we aim to develop a prediction model that integrates conventional risk factors, such as maternal obesity and family history of diabetes, with a comprehensive omics biomarker profile. This model seeks to enable early prediction of GDM, offering a potentially effective and feasible tool for clinical applications. To accomplish this research objective, the project will leverage the comprehensive and longitudinal dataset, along with data derived from biospecimen collected in the NICHD Fetal Growth Study. This dataset comprises 2,802 pregnant women of four race/ethnicity. It provides a wealth of information, including demographics, conventional pre-pregnancy and maternal health-related factors, and rich omics data assessed through blood and urine samples at four key timepoints during pregnancy. This abundant dataset offers a unique opportunity for students to delve into the development and establishment of optimal prediction models for GDM.
3.17	Prof Cuilin Zhang obgzc@nus.edu.sg Department of Obstetrics & Gynaecology	3.17 Omics for fetal growth- longitudinal and prospective studies to uncover novel risk factors and biomarkers of suboptimal fetal growth: exploring fetal overgrowth or growth restriction Within the framework of the well-established developmental origins of health and diseases, addressing suboptimal fetal growth -- whether restricted or excessive -- is pivotal due to its potential impacts on cognitive/physical development, obesity, and cardiometabolic health. The in utero environment significantly influences fetal development. Yet, the association between maternal biomarker profiles and fetal growth remains largely unexplored. The main objective of the study is to investigate maternal biomarker profiles in relation to suboptimal fetal growth. Leveraging longitudinal data collected at various stages of pregnancy, the dataset enables two key analyses: (1) Investigating the associations of maternal biomarker profile with fetal growth at discrete time points; (2) Conducting trajectory analyses to evaluate longitudinal patterns or changes in maternal biomarkers associated with suboptimal fetal growth. This approach provides insights into the dynamic physiological changes in both mother and fetus during pregnancy. To achieve these research aims, the projects will harness comprehensive and longitudinal data, including maternal information, fetal growth data, and biospecimen collected from the NICHD Fetal Growth Study. The NICHD study encompasses 2,802 pregnant women of four races/ethnicities. Fetal growth was assessed by ultrasonogram at four time points over the course of pregnancy. Maternal data on conventional pre-pregnancy and maternal health-related factors, alongside longitudinal omics data obtained from blood and urine samples collected four times during pregnancy, are ready for analysis.

3.18	Prof Cuilin Zhang obgzc@nus.edu.sg Department of Obstetrics & Gynaecology	3.18 Long-term health implications of common pregnancy complications and their determinants – a life course perspective Pregnancy serves as a 'stress test', unveiling underlying cardiometabolic susceptibility (i.e., hypertension during pregnancy, gestational diabetes mellitus [GDM], preterm birth). Women experiencing these complications become high-risk groups for subsequent cardiometabolic disorders (type 2 diabetes, cardiovascular diseases). This project aims to conduct prospective and longitudinal investigations on women with a history of pregnancy-related cardiometabolic complications, including GDM, gestational hypertension, preeclampsia, and preterm birth, to achieve the following objectives: (1) Understand and characterize the etiology of cardiometabolic health profiles following the index pregnancy in these women with a history of these complications; (2) Identify early predictors of mid- to late-life cardiometabolic health profiles and outcomes, including both exogenous (e.g., lifestyle, environmental) and endogenous (e.g., genetics) factors; (3) Investigate long-term cardio-metabolic health for outcomes like type 2 diabetes, cardiovascular diseases, and kidney diseases, among these high-risk women. Data from the Nurses' Health Study II, a prospective longitudinal female cohort of 116,429 U.S. nurses followed for more than 30 years, are ready for use to address these study aims. The NHS II contains rich longitudinal information on health-related characteristics, including diet, physical activity, and reproductive history; they are regularly updated over the follow-up period, enabling time-dependent survival analyses. As part of the Diabetes & Women's Health Study (DWH Study), biosamples measuring cardiometabolic markers and microbiomes were also prospectively collected from the NHS II participants who reported a history of GDM (n=~4500). Genetic data is also available for participants in NHS II and the DWH Study.

3.19	Prof Cuilin Zhang obgzc@nus.edu.sg Department of Obstetrics & Gynaecology	3.19 Nutrition, diet and lifestyle factors and maternal and child heath, and chronic diseases – nutrition/food as the new medicine "Let food be thy Medicine" – a famous quote by Hippocrates, aligns with the growing concept of "food is medicine", endorsed by various health organizations such as the American Heart Association. This idea is supported in numerous studies on chronic diseases including cardiometabolic health, cancer, and brain health, and ageing, suggesting the substantial impacts of diet on one's health status. Such impacts on health also extend for other lifestyle factors, such as physical activity and exercise, alcohol consumption, sleep, and mental well-being. The Global Centre for Asian Women's Health emphasizes the significance of nutrition and lifestyle on women's health, spanning from early- and mid-life to later-life cardiometabolic health. This includes the primary prevention of gestational diabetes, type 2 diabetes, and cardiovascular diseases. Moreover, the Centre is working towards uncovering the intergenerational impacts of these lifestyle factors on offspring. This project aims to understand the relationship between nutrition/diet and lifestyle and women's cardiometabolic health, fetal growth, and their intergenerational impacts from a global perspective. Outcomes of interest focus on gestational diabetes, type 2 diabetes, cardiovascular diseases, fetal growth (restricted or excess fetal growth) throughout pregnancy, and long-term offspring health outcomes. Multiple sources of data covering different geographics and race/ethnicity can be used for this project. Specifically, the Nurses' Health Study II (NHS II), the Diabetes & Women's Health Study, NICHD Fetal Growth Study, and the Growing Up In Singapore Towards healthy Outcomes (GUSTO) Study are ready for use to address the study aim. The NHS II, a prospective longitudinal female cohort of 116,429 U.S. nurses followed for more than 30 years, contains rich longitudinal information on health-related characteristics, including diet, physical activity, and reproductive history; they are regularly updated over the follow- up period, enabling time-dependent survival analyses. As part of the Diabetes & Women's Health Study, biosamples measuring cardiometabolic markers and microbiomes were also prospectively collected from the NHS II participants who reported a history of GDM (n=~4500). Genetic data is also available for participants in NHS II and the DWH Study. The GUSTO Study, a Singapore-based cohort, follows expectant mothers and their children, providing detailed insights into both fetal and maternal health from the antenatal period to the child's first 12 years of life.
3.20	Prof Cuilin Zhang obgzc@nus.edu.sg Department of Obstetrics & Gynaecology	3.20 Understanding the pathways to offspring and maternal health through the lens of metabolomics The concept of the developmental origins of health and disease (DOHaD), posits that several non-communicable diseases (NCDs), such as type II diabetes, have their origins in-utero and in early childhood. It is thus important to examine and identify the critical pathways in pregnancy and early childhood that can have an impact on offspring health and disease. Metabolomics, a comprehensive analysis of small molecules or metabolites, can reveal specific metabolites or metabolic pathways that are involved in the development of diseases. Metabolites act as markers of metabolic changes associated with environmental factors (e.g., diet intake, physical activity, chemical exposure, and stress) which can be used to study the development of various diseases, as well as to inform precise disease-prevention strategies. Harnessing metabolomics data from maternal plasma in pregnancy and cord blood, together with well-characterised basic and clinical data on deeply-phenotyped Singaporean cohorts, the Growing Up in Singapore Towards healthy Outcomes (GUSTO) and Singapore PREconception Study of long-Term maternal and child Outcomes (S-PRESTO) https://www.gusto.sg/ , these are projects that can be undertaken within the overall scope of the study, including: (1) Exploration of maternal/cord blood metabolites contributing to offspring health, including cardiometabolic, musculoskeletal and cognitive health. (2) Identification of novel metabolites linked to maternal health, including pregnancy outcomes (such as gestational diabetes, preeclampsia, fetal growth restriction, small for gestational age, preterm birth), maternal mental health, breastfeeding success and breastmilk composition.

3.21	Dr Evelyn Chung Ning Law paelecn@nus.edu.sg Department of Paediatrics	3.21 Infant Neural Trajectory and EEG (INTr-EEG) Our lab focuses on the biological, social, and environmental determinants of paediatric brain health. Specifically, we examine the influences of socioeconomic status (SES) and contextual factors on the attention and executive functions of children. By carefully dissecting the modifiable determinants, such as early relational health, parental mental health, infant screen use, cognitive and language stimulation, and school readiness, we are designing prevention and treatment programmes for children across the population. In addition, we contribute to the field by unravelling the neural processes via infant brain electroencephalography (EEG). By using EEG, we delineate underlying pathways that contribute to intergenerational transmission of parental psychopathology and cognitive deficits. This lab trains research coordinators on administering cognitive and psychological assessments in multiple cohorts, including the Growing Up in Singapore Towards healthy Outcomes (GUSTO). The data collected are available for analyses to answer research questions pertaining to the above. In particular, we delineate the lifecourse of children with attention and executive functioning deficits from preschool to adolescence. As this interdisplinary lab consists of clinician-scientists, we also have an available clinical population of children with attention-deficit/hyperactivity disorder (ADHD) that helps us understand early life predictors of their outcomes. For more information, please see brainhealthlab.org.

4 Immunology Translational Research Programme

S/N	Principal Investigator	Project Title and Abstract
4.1	A/Prof Nguyen Nam Long bchnnl@nus.edu.sg Department of Biochemistry	4.1 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 celltrafficking 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, wewill genetically delete S1P transporters and study the cellularcontrols 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 cellsin treatment of inflammatory conditions.
4.2	A/Prof Nguyen Nam Long bchnnl@nus.edu.sg Department of Biochemistry	4.2 The roles of endothelial cell transporter Mfsd7c for CNS vascular health and brain functions Several missense mutations of Mfsd7c, an orphan transporterhave 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 cerebralcortical 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 forexchanging 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) forthe 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 facilitatesthe delivery of nutrients to the brain and maintains blood vessel functions.

4.3	Dr Benoit Malleret benoit_malleret@nus.edu.sg Department of Microbiology & immunology	4.3 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. An erythrocytic 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 blood 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.
4.4	A/Prof Liu Haiyan micliuh@nus.edu.sg Department of Microbiology & immunology	4.4 Personalized RNA-based Cancer Vaccine for AML Immunotherapy We hypothesize that personalized RNA-based cancer vaccine, coupled with immune-checkpoint inhibitors delivered in the form of RNA, can be an effective treatment option for AML patients. We will combine the approaches of computing algorithm prediction, T cell activation screening, linker sequence and adaptor protein design, and proof-of-concept validation with both murine leukemia models and patient PBMCs. In this specific project, the student will perform the design, generation, and validation of single-chain variable fragments (scFvs) of anti-PD1 and anti-PD-L1 antibodies. ThescFvs will be cloned and produced in HEK293 cells. Various linker sequences and adaptor proteins to T cells will be incorporated as scFvs' scaffold, and subsequently screened for effective and specific blocking of immune checkpoints during the validation experiments. Furthermore, the anti- leukemia effects of the RNA-based vaccines with/without scFvs will be determined in immune competent murine AML model and humanized mouse models. Survival will be monitored, and antigen-specific T cell responses will be evaluated.
4.5	Dr Su Xinyi ophsux@nus.edu.sg Department of Ophthalmology	4.5 Modelling and evaluating retinal stem cell transplants in humanized immune system There are no effective treatments for end-stage retinal degenerative diseases. In advanced age-related macular degeneration and inherited retinal diseases, there is a profound reduction in the quality of life because of loss of central vision, secondary to an irreversible loss of RPE and photoreceptors cells. Stem cell derived cell/tissue replacement is an emerging therapy, particularly for dry AMD, whereby Phase 1 clinical trials have demonstrated that it is safe, albeit with modest improvements in vision. The lingering and critical question remains whether we can further augment vision recovery via other adjunct mechanisms such as immuno-modulation. The proposed work seeks to address this unmet clinical need, and if successful, will provide novel ways to augment the outcome of retinal cell therapy.

4.6	A/Prof Jinhua Lu miclujh@nus.edu.sg Department of Microbiology & Immunology	4.6 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 limit 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 NMRCOF- IRG grant has been awarded to 57ehavior 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/activatetumour-specific CD8+ killer T cells.
4.7	A/Prof Jinhua Lu miclujh@nus.edu.sg Department of Microbiology & Immunology	4.7 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 and 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.
4.8	A/Prof Jinhua Lu miclujh@nus.edu.sg Department of Microbiology & Immunology	4.8 Tilt cancer vaccine-induced immunity in favour of CD8killer 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.

4.9	A/Prof Paul Anthony MacAry micpam@nus.edu.sg Department of Microbiology & Immunology	4.9 Generation and characterization of Immunotherapy candidates for surface-displayed Cancer Testes Antigens (CTAs) Cancer Testes Antigens (CTAs) are expressed in various types of solid tumors but absent in healthy tissues with the exception of testis and germline-derived cells. My laboratory has identified a number of novel CTAs that are highly upregulated in Breast, Cervical, Lung and Head & Neck tumors and will exploit our expertise in Antibody Engineering to develop new therapeutic/diagnostic candidate antibodies that will be modified into antibody-drug conjugates and CAR-T formulations that can be utilized for future therapy.
4.10	A/Prof Paul Anthony MacAry micpam@nus.edu.sg Department of Microbiology & Immunology	4.10 Derivation and characterization of fully human Allo- antibodies in renal transplant rejection Derivation and characterization of fully human Allo-antibodies in renal transplant rejection. In collaboration with the National University Centre for Organ Transplantation at the National University Hospital we are isolating and characterizing human monoclonal antibodies that target mis- matched HLA molecules-these are the principal determinants of chronic, solid organ rejection.
4.11	A/Prof Jinmiao CHEN micchenj@nus.edu.sg Department of Microbiology & Immunology	4.11 CELL2VIRUS: a virus-host interaction map at single-cell resolution Viral infections continue to pose significant global health challenges, as highlighted by the COVID-19 pandemic. Understanding virus-host interactions at a granular level is crucial for developing effective strategies to combat these infections. The CELL2VIRUS project aims to map virus-host interactions at single-cell resolution using advanced single-cell RNA sequencing and spatial transcriptomic techniques. This project leverages the DISCO database (https://www.immunesinglecell.org/), which comprises over 100,091,857 cells from 16,734 human samples, providing an unprecedented resource for identifying viral transcripts and understanding their impact on host cells. Our research will focus on four key objectives: (1) Identifying viruses and their host cell types across a large-scale dataset, (2) Investigating virus-induced transcriptome reprogramming and its implications for disease development, (3) Exploring the spatial interactions between virus-infected and bystander cells using single-cell spatial transcriptomic data, and (4) Developing a machine learning model to predict virus-infected cells based on gene expression data. By integrating these findings, we will create a comprehensive virus-host interaction map and develop an online resource, CELL2VIRUS, to facilitate the dissemination of our insights and foster further research collaborations. This project has the potential to significantly advance our understanding of virus-host dynamics and contribute to the development of novel therapeutic strategies.

4.12	A/Prof Jinmiao CHEN micchenj@nus.edu.sg Department of Microbiology & Immunology	4.12 Constructing immune aging atlas through integration of single-cell transcriptomic data As global populations age, understanding the underlying mechanisms of immune system aging becomes increasingly critical. The proposed project aims to develop a comprehensive Human Immune Aging Atlas by integrating publicly available single-cell transcriptomic data. This atlas will provide an unprecedented resource for investigating how aging impacts different immune cell types across various tissues, addressing fundamental questions such as whether all cell types age uniformly and how immune aging differs between tissues. Our approach involves creating tissue-specific atlases to identify aging signatures at the cellular level, with a particular emphasis on immune cells. Given the subtle and gradual nature of aging-related changes, larger sample sizes are essential for accurately capturing and analyzing these alterations. By integrating extensive data from diverse populations, we aim to address challenges related to cellular heterogeneity and inter-individual variability. This project also seeks to elucidate the relationship between immune aging and age-related diseases, offering insights that could lead to novel therapeutic strategies for enhancing immune function in the elderly. Ultimately, the Human Immune Aging Atlas will serve as a critical resource for the scientific community, enabling deeper exploration into the aging process and its implications for human health.
4.13	A/Prof Jinmiao CHEN micchenj@nus.edu.sg Department of Microbiology & Immunology	4.13 Spatial meta-transcriptomics for microbiome–host interactions The interactions between host tissues and their resident microbiota play a crucial role in health and disease. However, the spatial context of these interactions remains poorly understood. This project aims to leverage spatial meta-transcriptomics to map and analyze host-microbe interactions at unprecedented resolution. By integrating spatial transcriptomics with microbial RNA profiling, we will create detailed maps that reveal how microbial communities and host cells interact within specific tissue microenvironments. This innovative approach will allow us to explore fundamental questions, such as how microbial populations influence local gene expression in host tissues, and how these interactions contribute to health or disease states. We will apply this technology to various tissue types, providing insights into the spatial dynamics of microbiomes across different physiological contexts. The outcomes of this project will advance our understanding of microbiome-related diseases and open new avenues for therapeutic interventions targeting the spatial organization of host-microbe interactions. This research will generate a valuable resource for the scientific community, enabling further studies into the complex interplay between host and microbiota in a spatially resolved manner.
4.14	Dr Tay Sen Hee Frank mdctays@nus.edu.sg Department of Medicine	4.14 Exploration of epigenetic signatures in naïve CD4+ T cells for downstream development of exhaustion across different immunological contexts We lack an understanding of the epigenetic regulation of T cell exhaustion and research is urgently needed to determine how such an imprint will affect the development of exhaustion. While much has been learned about CD8+ T cell exhaustion in chronic viral infections, there is still a critical gap in our knowledge of this process in CD4+ T cells for immune-mediated diseases (IMD). In our pilot data, 15 healthy controls (62.5%) were exhaustion low (IMD1) and the remaining 9 (37.5%) exhaustion high (IMD2). We hypothesize that T cell exhaustion may be acquired due to a hard-wired program, i.e., propensity to developing CD4+ T cell exhaustion in 37.5% of human healthy controls (IMD2) may be epigenetically determined. In this project, we will perform the following using sorted naïve CD4+ T cells: 1) Induce CD4+ T cell exhaustion using anti-CD3/anti-CD28 in IMD1 and IMD2 2) Differentiation into different subsets CD4+ helper T cells and determining their effector function in IMD1 and IMD2 3) Neutralizing antibodies production to post-primary SARS-CoV-2 vaccination in IMD1 and IMD2 4) Drug and genetic manipulation of DNA methyltransferase inhibitors to rescue the IMD2 phenotype 5) Generation of IMD1-CAR-T and IMD2-CAR-T cells to test their proliferation and anti-tumor efficacy

5 Infectious Diseases Translational Research Programme

S/N	Principal Investigator	Project Title and Abstract
5.1	A/Prof Chu Jang Hann miccjh@nus.edu.sg Department of Microbiology & Immunology	5.1 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 factorswith 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	5.2 Achieving Functional Cure of Chronic Hepatitis B Background: Chronic Hepatitis B is a 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 59ehavior59ize59ng59, 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 are to 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 in-depth 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, 59ehavior59ize 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 59ehavior59 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, especially 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: mdclimsgnus.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	5.3 Elucidating capsular polysaccharide biogenesis in Streptococcus pneumoniae Streptococcus pneumoniae is an important respiratory pathogen that causes more than one million deaths worldwideannually. Similar to other pathogenic bacteria, S. pneumoniaeencases 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 100serotypes 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 to 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. pneumoniaeis 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 Sylvie Alonso micas@nus.edu.sg Department of Microbiology & Immunology	5.4 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.
5.5	A/Prof Tan Yee Joo mictyj@nus.edu.sg Department of Microbiology & Immunology	5.5 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.

5.6-5.7	A/Prof Gan Yunn Hwen bchganyh@nus.edu.sg Department of Biochemistry	5.6 Dynamic gut microbiome modulations to establishcolonization resistance against multidrug resistant Klebsiella pneumonia 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. 5.7 Virulence regulation of hypervirulent Klebsiella pneumoniae during host infection More information can be found at: https://medicine.nus.edu.sg/trp/infectious-diseases/
5.8	Dr Qu Kun kqu@nus.edu.sg Department of Biochemistry	5.12 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 burdenon human health and social economy. Past flu pandemics andthe 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 andinfluenza 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.
5.9	Dr Catherine WM Ong Catherine.ong@nus.edu.sg Department of Medicine	5.13 Diabetes mellitus and dysregulated angiogenesis in pulmonary tuberculosis Uncontrolled diabetes-TB patients are likely to die and remain infectious longer despite effective treatment. Angiogenic factors (AF) are upregulated in TB but the effect of clinically- approved angiogenic inhibitors on survival, and mycobacterial burden in diabetes-TB is unknown. We hypothesise that targeting dysregulated AF from uncontrolled diabetes reduces immunopathology in pulmonary TB. The aims are to determine: 1: the expression of AF in diabetic-TB patients compared to TB patients without diabetes. 2: the regulation of AF in the diabetic-pulmonary TB murine model. 3: the effects of clinically approved anti-AF drugs on immunopathology in the model First, AF will be phenotyped in an existing cohort of diabetic- TB and TB patients. Proteins and gene expression will be analysed by Luminex bead array and single-cell RNA sequencing. Human lung granulomas will be examined for AF expression and 3D granuloma vasculature. Next, AF expression on immune cells will be analysed by flow cytometry in the murine model. 3D granuloma vasculature/intracellular signaling pathways regulating angiogenesis will be examined. Finally, angiogenesis inhibition on TB immunopathology will be examined. Diabetic-TB mice will be administered two angiogenic inhibitors with standard TB drugs. TB drug in murine lung, morphology of granuloma vasculature and hypoxia markers will be assessed. This broad-based PhD project provides immunology training with key BSL3 experience. The results will positively impact the launch of a clinical trial on diabetic-TB patients.

6 Digital Medicine Translational Research Programme / Institute for Digital Medicine (WisDM)

S/N	Principal Investigator	Project Title and Abstract
6.1	Dr Tamra Lysaght tlysaght@nus.edu.sg Centre for Biomedical Ethics	6.1 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	6.2 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 deliverRNA drugs to cancer cells. RBCEVs are inexpensive to purifyin 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/)

6.3	A/Prof Jinmiao CHEN micchenj@nus.edu.sg Department of Microbiology & Immunology	6.3 Single-cell large foundation model for drug discovery In this project, we will develop a novel multi-modal foundational model and pretrain it using a large corpus of publicly available single-cell data (DISCO, CellXGene, HCA). This model aims to learn universal, biologically explainable embeddings of genes, cells, and patients, enabling the capture of interactions across molecular, cellular, and phenotypic levels for a variety of downstream clinically relevant tasks. Next, we will adapt the foundational single-cell model using data from Asian patient cohorts (HCC and NPC) to predict responses to therapies, including immune checkpoint inhibitors, chemotherapy, and combination treatments; identify novel cell type-specific biomarkers for treatment resistance and validate them using experimental approaches. Lastly, we will refine the foundation single-cell model to incorporate generative capabilities, allowing in-silico simulation, spanning a broad spectrum of genetic perturbations and drug treatments, which can accelerate the advancement of personalized therapeutics.
6.4	A/Prof Jinmiao CHEN micchenj@nus.edu.sg Department of Microbiology & Immunology	6.4 Develop large language model for subcellular resolution spatial multi-omics Spatial technology has rapidly advanced, with innovations like CosMx, Stereo-seq, and MERSCOPE achieving sub-cellular resolution and covering thousands of genes or hundreds of proteins. These advancements, coupled with advanced image processing and computer vision techniques, enable precise cell segmentation and spatial analysis of mRNA and protein molecules. Our project will develop SpaLLM, a large language model for subcellular resolution spatial multi-omics, to reconstruct cell-cell interactions and molecule interactions (RNA-RNA, RNA-protein, protein-protein) within individual cells. We will create network graphs where nodes represent cells or molecules and edges denote their spatial adjacency. SpaLLM uses heterogeneous graph attention networks to encode spatial relationships and cross-talks among RNA, proteins, and cells. This approach will reveal latent representations and identify hubs of cells or molecules based on spatial colocalization and expression measurements. By analyzing these hubs across different phenotypic groups, we aim to uncover underlying cellular and molecular mechanisms driving biological differences.

7 Cancer Translational Research Programme/ NUS Centre for Cancer Research (N2CR)

S/N	Principal Investigator	Project Title and Abstract
7.1	Dr Alan Prem Kumar apkumar@nus.edu.sg Dean's Office	7.1 Development of Intracellular Multi-specific PTK6 Antibodies for Precision Medicine Ovarian cancer's 5-year survival rate is a low 43%, primarily due to poor detection, therapy resistance, and relapse. Standard treatments involve surgery and chemotherapy, but about 30% of patients have DNA damage response (DDR) defects, benefiting from PARP inhibitors (PARPi). PARPi combined with immunotherapy has shown promise, yet in the 70% of patients without DDR defects, efficacy is limited, and resistance often develops. Novel therapies are essential. Protein Tyrosine Kinase 6 (PTK6) is overexpressed in ovarian cancer, promoting cisplatin resistance through DNA repair. PTK6 depletion sensitizes cancer cells to chemotherapy and can overcome PARPi resistance. Small-molecule PTK6 inhibitors have failed clinically, but targeting its SH2 and SH3 domains with intracellular antibodies could enhance treatment. Aim 1: Investigate the immunomodulatory effects of PTK6 depletion combined with DNA-damaging therapies. We hypothesize PTK6 depletion could amplify immune responses, boosting immunotherapy effectiveness. Aim 2: Develop PTK6-specific intracellular antibody-drug conjugates (ADCs) targeting all functional PTK6 domains using DotBio's platform. These ADCs, linked to platinum drugs or PARPi, could overcome resistance. Their efficacy will be tested in organ-on-a-chip 3D models and validated in humanized mouse models for future clinical application.
7.2	Dr Alan Prem Kumar apkumar@nus.edu.sg Dean's Office	7.2 LYN Kinase in Cytoskeletal Rearrangements and its Effect on Tumor Immune Escape in Breast Cancer Cancer immune evasion is recognized as a hallmark of breast cancer (BC), especially in aggressive subtypes like triple-negative breast cancer (TNBC), which lacks estrogen, progesterone, and HER2 receptors. TNBC, accounting for 15-20% of BC cases, has the poorest prognosis and highest relapse rate due to its heterogeneity and lack of therapeutic targets. TNBC utilizes various immune evasion mechanisms, including immune cell infiltration inhibition and the production of immunosuppressive molecules. A novel mechanism of immune evasion in TNBC involves actin cytoskeletal remodeling, which alters cellular morphology and motility. This remodeling disrupts the formation of a functional immunological synapse (IS) between TNBC and Natural Killer (NK) cells, hindering NK-mediated tumor-cell elimination. Our group has identified Lyn kinase's role in this process. Their experiments with Lyn-depleted TNBC cells revealed enhanced NK cell cytotoxicity, suggesting Lyn's involvement in immune evasion through cytoskeletal regulation. Lyn inhibition also led to changes in genes associated with immune regulation and cytoskeletal dynamics. The group's hypothesis is that Lyn promotes TNBC invasiveness by preventing effective IS formation. Their research aims to further elucidate Lyn's role in cytoskeletal rearrangements and immune evasion in TNBC.

7.3	Prof Xiaoyuan (Shawn) Chen dnrxc@nus.edu.sg Department of Diagnostic Radiology	7.3 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, diagnosticand 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	7.4 Interactions between the immune microenvironment and chemotherapy treatment in lymphoma https://www.csi.nus.edu.sg/web/anand-jeyasekharan/ https://www.ncis.com.sg/For-Patients-andVisitors/Pages/Find-a-DoctorDetails.aspx?docid=Anand_Jeyasekharan The success of immune checkpoint inhibitors such as anti- PD1/PD- L1 and anti-CTLA-4 antibodies has spurred a broad interest in cancer immunotherapy. How newer immunotherapy agents can be used in conjunction with current chemotherapy remains however an open and important question. Our lab is particularly interested in developing combination chemo-immunotherapies for diffuse large B-cell lymphoma (DLBCL). DLBCL is the most common aggressive lymphoma, affecting both young and elderly adults. Standard-of-care combination treatment through the R-CHOP regimen yields high responses, but relapses occur in a significant proportion of these patients, highlighting the need for better combination strategies based on this chemotherapy backbone. It is becoming increasing clear that the immune microenvironment plays a key role in the prognosis of DLBCL. Importantly, studies have recently discovered that immune stimulation is a consequence of chemotherapy treatment. The mechanism underlying the immune microenvironment's influence on DLBCL prognosis and the contribution of chemotherapy/DNA damage are not well understood. The aim of this project is to decipher how key pathways and effectors, in both the tumour cell and microenvironment, are orchestrated to determine the prognosis of DLBCL upon chemotherapy treatment. The project is multi-modal and will involve a variety of techniques including the application of high- dimensional microscopy and quantitative multiplexed microscopy to patient samples; spatial and bioinformatic analyses on high content data; co-culture validation experiments, in addition to routine molecular biological techniques. 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 forpersonalized therapy 7.6 Developing new molecular detection methods incancer 7.7 Discovering new mechanisms in genomemaintenance 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	7.8 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-readssequencing 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	7.9 Understanding and Targeting the Non-Canonical Oncogenic Function of EZH2 for Therapeutic Interventionin 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	7.10 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 screeningapproach. 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 foundthat 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 miRNAsignature 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 developmentof 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	7.11 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 tointrinsic 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 multi-discipline 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 chemo-resistance. 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 Deng Lih Wen bchdlw@nus.edu.sg Department of Biochemistry	7.12 Anti-tumor effects of electrostimulation in mice with ovarian tumors Ovarian cancer (OC) is the most lethal gynaecologic malignancy, with a 5-year survival rate of <30%. Immunotherapy is ineffective for OC due to an immunosuppressive microenvironment lacking tumor infiltrating leukocytes. Using a syngeneic mouse model, we observe that electrostimulation can inhibits tumor growth possibly through modulation of tumor microenvironment. Thestudy aims to elucidate the underlying the molecular mechanism in a multidisciplinary team including cancer biologist, immunologist, and neurobiologist.
7.13	A/Prof Deng Lih Wen bchdlw@nus.edu.sg Department of Biochemistry	7.13 Cancer/Testis Antigen in mitochondria function and potential implications on metastasis and therapy- resistance. Emerging evidence implicates cancer/testis antigens (CTA) in cancer metabolism via their actions on the mitochondria. Our pilot study suggest CTA expression is involved in the metastatic potential of lung cancer. An increase in CTA in lung cancer brought about a more aggressive cancer phenotype, possibly through alterations in the cells' mitochondria functions. This project aims to establish clinical association of CTA in lung cancer and study the underlying mechanism. The knowledge from this project is to better understand the role of CT antigens in cancer cell energetics and work towards using CTA in biomarker-driven clinical trialsfor mitochondria- or CTA-targeted therapeutics to provide more personalized treatment strategies to improve patient outcomes.
7.14	A/Prof Deng Lih Wen bchdlw@nus.edu.sg Department of Biochemistry	7.14 Identify molecular signatures of early prediction oftherapy resistance and recurrence to develop surveillance strategies for personalized treatment Current treatment for cervical cancer and head and neck cancer includes concurrent chemo-radiotherapy followed by brachytherapy. However, treatment failure characterized by recurrent/metastatic tumours is not uncommon. These tumours are often aggressive and resistant to current therapeutic strategies leaving these patients with little therapeutic options. In a pilot study, 43 first-biopsy samples from patients who were either disease-free (n=23) or recurrent/metastatic (n=20) after standard treatment, were subjected to an unbiased molecular screen and a recurrent/metastatic specific molecular signature was identified. Several candidates in this signature have been suggested to have roles in maintaining the cancer stem cell (CSC) phenotype, which has been associated with disease recurrence/metastasis. However, their specific molecular functions remain to be elucidated and understanding how thissignature affects the CSC population will enable the development of molecularly-targeted therapies for this subset of cells. Identification of our molecular signature from samplesobtained at initial diagnosis suggests the exciting possibility ofusing this signature to predict possible relapse/metastatic disease at point of diagnosis. Together with molecular studies, the candidate is expected to apply this molecular signature to develop a liquid biopsy-based non-invasive molecular surveillance strategy. The long-term goal of this work aims to enable clinicians to predict recurrence/metastasis at initial diagnosis to better-tailor therapeutic regimes and prescribe them in a timelier manner to improve patient outcome. The project is part of a multidiscipline research program with basic scientists, translational researchers and clinical scientists.

7.15	A/Prof George Yip georgeyip@nus.edu.sg Department of Anatomy	7.15 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 74ehavior through their interactions with growth factors and 74ehavior74molecules. 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 74ehavio 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. Bravani 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.
7.16	Prof Khong Pek Lan dnrkpl@nus.edu.sg Department of Diagnostic Radiology	7.16 Clinical Molecular Imaging Research for Precision Oncology Positron Emission Tomography (PET) is a molecular imaging modality that allows 75ehavior75ize75 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.

7.17	Prof Khong Pek Lan dnrkpl@nus.edu.sg Department of Diagnostic Radiology	7.17 Single centre prospective evaluation of 68Gallium-FAPI PET/MRI in Hepatocellular Carcinoma To evaluate the clinical utility of a novel radiotracer, 68Ga- FAPI (Fibroblast activation protein-inhibitor) for PET imaging of Hepatocellular carcinoma (HCC); specifically, in its additional benefit to MRI alone, which is conventionally usedas the imaging modality of choice for HCC, and as a combined hybrid imaging modality of PET/MRI. We aim to study the added value of 68Ga-FAPI PET, combining it with MRI in a single hybrid modality, PET/MRI, inthe context of the current diagnostic pathway in patients with or suspected to have HCC. Specifically, we aim to evaluate its role in (i) lesion detection and characterization prior to surgery (ii) systemic staging after radiological or histological confirmation of HCC (iii) characterization of indeterminate lesions on conventional MRI and (iv) work-up for the detection of HCC in patients with unexplained elevations of serumalpha-fetoprotein (AFP) concentration.
7.18	Prof Ruby Huang Yun-Ju obgrhy@nus.edu.sg Department of Obstetrics & Gynaecology	7.18 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 complexor 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 interrogatethe 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.
7.19	Prof Vinay Tergaonkar bchvt@nus.edu.sg vinayt@imcb.a-star.edu.sg Department of Pathology and Department of Biochemistry	7.19 ADAR1 meets NF-kB signaling: Functional role of lncRNAin regulating immune evasion RNA based and RNA targeting 76ehavior76ize 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 andwhat lncRNA are controlled by these 2 important proteins in cells which can be 76ehavior 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 biologyrelated expirements. By the end of the training he/she will be able to conceptualise 76ehavior projects and design expirements and analyse the results obtained. Stronger students will also be trained to write papers and present data to others.

7.20	Prof Vinay Tergaonkar bchvt@nus.edu.sg vinayt@imcb.a-star.edu.sg Department of Pathology and Department of Biochemistry	7.20 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 candidatescan 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 biologyrelated 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.
7.21	Dr Yvonne Tay yvonnetay@nus.edu.sg Department of Biochemistry	7.21 Alternative UTRs of key cancer genes: Novel regulatorsand 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.
7.22	Dr Chester Lee Drum mdccld@nus.edu.sg Department of Medicine	7.22 Machine Learning Approach to Cancer andCardiovascular Risk Prediction Deep learning is a subset of machine learning which usesvery 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 medicaloutcomes. A robust model of immediate translational value will be created to predict adverse reactions.

7.23	Dr Chester Lee Drum mdccld@nus.edu.sg Department of Medicine	7.23 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 theselection and dosage of anti-oxidant therapies. With success, the impact of this project can reshape the fields of nutrition and pharmaceutical science.
7.24	Dr Chester Lee Drum mdccld@nus.edu.sg Department of Medicine	7.24 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 onthe 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.
7.25	Dr Chester Lee Drum mdccld@nus.edu.sg Department of Medicine	7.25 Synthetic Biology of Translational Therapeutics andLarge 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 ofresearch begun at Massachusetts Institute of Technology andwill create nanometer scaled agents for the delivery of active protein substrates and for industrial manufacture of previouslyunproducable 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.

7.26	Dr Chester Lee Drum mdcccld@nus.edu.sg Department of Medicine	7.26 Oral Delivery of Bioorthogonal Catalytic Centres for Treating Gastric Cancer: A Mice Model Study Using Ultra- Stable Thermostable Exoshells Bioorthogonal catalysis (BC) generates chemical reactions that are absent in normal physiological processes. With in situdrug synthesis, BC holds the promise of site-specific therapy with negligible systemic exposure or side effects. Previously, our lab reported the use of self-assembling, porous thermostable exoshells (tES) to encapsulate and deliver an iron-containing reaction centre for tumor regression in breast cancer mice. When administered with the prodrug indole-3- acetic acid, a natural plant product, the bioactive metabolites produced resulted in apoptosis of cancer cells and complete regression of tumors (Sadeghi et al. ACS Nano, 2022). Giventhe significance of oral delivery as a preferred mode for drug administration, we improved the stability of tES through multiple inter-subunit disulfide linkages. Preliminary studies have shown that ultra-stable tES protected the encapsulated BC against the adverse gastrointestinal environment and exhibited permeabilization through intestinal epithelial cells (Sadeghi et al. IJMS, 2022). Capitalizing on these recent findings, we aim to create a cost-effective oral prodrug therapy to treat an in vivo model of gastric cancer. The therapeutic strategy will couple the oral administration of the reactive BC centre followed by a benign natural substrate for in vivo evaluation together with safety profiling and biodistribution studies.
7.27	A/Prof Citra NZ Mattar citramattar@nus.edu.sg Department of Obstetrics & Gynaecology	7.27 Non-invasive characterization of endometrosis bycirculating, 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 conducta 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 responsiblefor 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 endometrosisand female health related alterations; leading to precision healthcare solutions that could improve patient management.
7.28	Dr Haojie Yu bchhaoy@nus.edu.sg Department of Biochemistry	7.28 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.

7.29	Dr Jiong-Wei Wang surwang@nus.edu.sg Department of Surgery	7.29 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.
7.30	Dr Tamra Lysaght tlysaght@nus.edu.sg Centre for Biomedical Ethics	7.30 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.
7.31	Dr Dennis Kappei dennis.kappei@nus.edu.sg Department of Biochemistry	7.31 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.

7.32	Dr Dennis Kappei dennis.kappei@nus.edu.sg Department of Biochemistry	7.32 Regulation of the long non-coding RNA TERRA in cancers relying on the Alternative Lengthening ofTelomeres (ALT) pathway Telomeres are the molecular caps at the end of chromosomesand 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. WhileTERRA 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 examineif and how these transcription factors regulate TERRA levels and ultimately exploit this to manipulate TERRA in the contextof 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.
7.33	A/Prof Sethi Gautam phcgs@nus.edu.sg Department of Pharmacology	7.33 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 diseasehave 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 dataon 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 proteomicanalysis revealed that Abemaciclib, one of CDK4/6 inhibitors,is able to modulate pathways in the innate immune system. Inthis 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.

7.34	Prof Daniel Tenen csidgt@nus.edu.sg Department of Medicine	7.34 Targeting transcription factor pathways in cancers My laboratory is 83ehavior on transcription factors and gene regulation in cancer. A major effort by my laboratory focuses is listed here: (i) zinc finger protein 143 (ZNF143) is a key regulator in maintenance of progenitor cells integrity. ZNF143secures 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.
7.35	A/Prof Chen Ee Sin bchces@nus.edu.sg Department of Biochemistry	7.35 Loss of genomic stability of repetitive sequences as an early epigenetic predictor of leukemia Approximately half of the human genome is constituted by repetitive sequences, which were once dubbed as ‘junk DNA’. These sequences play essential roles in the maintenance of genomic stability by regulating higher order chromatin organization, silencing of viral transposable, control of faithful chromosome segregation during cell division and heterochromatin formation. How the genomic stability of these repetitive elements is maintained is still unclear but the aberrant loss of transcriptional silencing at many repeats are correlated with carcinogenesis and aggressiveness in various cancers. Inappropriate transcription of these non-coding sequences is detrimental to cell health as it can induce DNA breakage and aberrant repair activation that subsequently result in deletion and fragmentation of the repeat DNA. Fragmented DNA eventually escapes into cytoplasm and blood to activate inflammatory 84 ehavior 84 . A previous work revealed the presence of nuclear JAK2 kinase in several erythroleukemic cell lines, which aberrantly phosphorylate histone H3 tyrosine 41 (H3Y41p) to ectopically derepress oncogenes. Our work on the other hand detected H3Y41p on constitutive heterochromatin to control the transmission of epigenetic silencing of the underlying repeat sequences. We hypothesize that disruption of H3Y41p?dependent maintenance of heterochromatic integrity on repetitive elements can underlie dysregulation of DNA repeats that can induce inflammation and carcinogenesis. Hence identification of repeat maintenance dysregulation and fragmented repeat DNA can constitute possible early predictor of carcinogenesis. This project will study these mechanisms in leukemiconcogenesis. We will interrogate publicly curated acute myeloid leukemic (AML) patient genome databases to uncover mutations in possible epigenetic regulators critical for ensuring repeat stability. The consequences on repetitive DNA sequences and cell 84ehavior due to a certain mutation will be subsequently analysed employing molecular and cellular analyses including animal models. We will establish methodologies to identify circulating DNA fragments in liquid biopsies from AML patients to correlate with mutations of the epigenetic factors. This work is expected to innovate generic technologies that will be applicable to interrogate genomic instability of repetitive DNA sequences as markers to predict oncogenic onset in other cancer models.

7.36	A/Prof Celestial Yap phsyapc@nus.edu.sg Department of Physiology	7.36 Cytoskeletal Rearrangements and its Effect on Tumour Immune Escape in Ovarian Cancer Ovarian cancers account for a significant proportion of gynaecological cancers worldwide, with a majority of patients presenting at advanced stages. Although initial response to treatment may be promising, relapse rates are high and 5- year survival is often poor. Migration and invasion of cancer cells constitute fundamental processes in tumour progression and metastasis and are governed by alterations of various families of cytoskeletal proteins, such as microtubules, actin, and intermediate filaments. These cytoskeletal proteins act in a coordinated manner and mediate numerous cellular and biochemical processes that influence cell shape, structure, division, motility as well as interactions of cells with their extracellular environment. Emerging evidence indicates that cytoskeletal alterations in cancer cells derived from aggressive tumour subtypes render them resistant to killing by cytotoxic immune cells found in the tumour microenvironment. Recent studies have shown that actin-rich structures are associated with increased migration and facilitates epithelial-to-mesenchymal transition in response to increased stiffness of the extracellular tumour microenvironment. However, mechanisms by which cancer cell cytoskeletal rearrangements and its roles in immune evasion are not fullyunderstood. The aim of this project is to examine the cytoskeletal mechanisms influencing ovarian tumour cell behavior, such asalterations in cell shape, cytoskeletal architecture and how these affect the interactions with the cells in the tumour microenvironment, such as immune cells. Analysis will be carried out by assessing the composition of actin fibres, cell- extracellular matrix adhesions, actin-rich migratory structures as well as cytotoxic properties of the relevant immune cells using immunofluorescent imaging, time- lapse microscopy, FACS, modulation of genetic expression of key cytoskeletal proteins, including gelsolin and other actin-binding proteins.
7.37	Prof Goh Boon Cher csigbc@nus.edu.sg Department of Medicine	7.37 Uncovering the role of extracellular vesicles enriched FAM3C in promoting NSCLC metastasis Lung cancer is a leading cause of cancer-related death globally. Metastasis is responsible for as much as 90% of cancer-associated mortality, yet it remains the most poorly understood component of cancer pathogenesis. The precise mechanism of tumor metastasis is still largely unknown. This field of research has garnered renewed interest ever since the discovery of vesicle-based cell-cell communication mediated by exosomes, particularly tumor-derived exosomes. Although multiple factors are known to contribute to cancer metastasis, epithelial-mesenchymal transition (EMT) has been implicated as the critical event initiating cancer invasion, intravasation and extravasation of tumor cells of the metastatic cascade. Therefore, it is crucial to attempt the investigation of EMT driver genes to discover new signaling pathways and druggable targets for treatment of lung cancer, one of the top issues impacting the global health care sector. Based on our preliminary results, FAM3C (ILEI) has been found as a critical driver in the metastatic cascade of advanced lung cancer. Mechanistic experiments further revealed that tumor-derived exosomes enriched FAM3C can activate EMT through Ras pathway effector RalA signaling in NSCLC cells to initiate tumour cell invasiveness and motility. Importantly, we established that RalA, a small GTPase, is a partner protein forFAM3C. These findings imply that targeting FAM3C-RalA interaction may be a feasible strategy to suppress cancer metastasis. In this project, the student will investigate association between FAM3C and Ras pathway effector RalA in driving tumor growth and metastasis of NSCLC. Next, a large-scale drug library screening will be conducted to identify novel and potent inhibitors in treatment of NSCLC through inhibiting FAM3C-RalA interaction. Furthermore, downstream signaling pathway will be investigated to understand FAM3C driven oncogenic mechanisms. Finally, a suitable xenograft mouse model will be used to validate the antimetastatic activity of the shortlisted inhibitors.

7.38	Dr Wee-Wei Tee phstee@nus.edu.sg Department of Physiology	7.38 Targeting chromatin vulnerabilities in cancer Chromatin-associated proteins are emerging as new drug targets for a variety of diseases, especially cancer. Our laboratory is interested to study how chromatin deficiencies underlie human diseases, with a strong focus on therapeutics development. We employ varied experimental approaches such as Next-Generation Sequencing, genome-editing, genetic/chemical screens as well as cancer models (PDXs, tumor organoids, etc.) to address our questions of interest. We recently conducted a systematic investigation of all chromatin regulators in cancer where we overlaid gene expression patterns with clinical data (metastasis, treatment success, and survival) followed by functional studies. This effort enabled us to prioritize candidate factors for downstream therapeutics development. The student will have opportunities to acquire strong expertise in various (epi)genomics and proteomics techniques, perform cancer assays and high-throughput screens, as well as acquire drug development knowledge. The student will also work closely with our clinical collaborators, as well as drug development colleagues at A*STAR EDDC. For more information about the lab, please see: https://medicine.nus.edu.sg/phys/research/research- programs/cancer-programme/tee-wee-wei/
7.39	Dr Wee-Wei Tee phstee@nus.edu.sg Department of Physiology	7.39 Identifying epigenetic drivers of therapeutic resistance Drug resistance, either intrinsic or acquired, represents a major bugbear in precision medicine. It is increasing clear thatepigenetic reprogramming mechanisms contribute to transcriptional plasticity in cancer cells enabling lineage transformation towards a ‘drug-tolerant persister’ (DTP) state.These rare population of DTP cancer cells acquire transcriptomic and epigenetic features resembling that of early embryonic cells that are developmentally plastic. Accordingly, they survive and adapt readily to therapeutic pressures, and over time can re-populate the tumour. Using established commercial cell line and patient-derived xenograftand organoid models of resistance (e.g. Paclitaxel in breast and 2nd/3rd generation TKIs in lung cancers), we propose to isolate and characterize the DTP cancer cells to identify the epigenetic drivers of therapeutic resistance. We intend to alsouse CRISPR-based genetic screens and pharmacologic approaches to identify epigenetic regulators that impede the formation or progression of DTPs, and assess for improved clinical outcomes in combination with standard-of-care treatments. To this end, we have developed epigenetic technologies that are amenable for low input material and ourpreliminary efforts have identified potential candidates for downstream studies. For more information about the lab, please see: https://medicine.nus.edu.sg/phys/research/research- programs/cancer-programme/tee-wee-wei/

7.40	Dr Wee-Wei Tee phstee@nus.edu.sg Department of Physiology	7.40 Investigating a role of early-embryonic factor reactivation in cancer cell plasticity Our lab has a long-standing interest in understanding the epigenetic mechanisms of lineage plasticity in early development (Hu et al., Nature Cell Biology 2020). More recently, we have broadened our investigations to study how cancer cells undergo epigenetic reprogramming to induce phenotypic plasticity. This cross-fertilization strategy has beenrewarding, directing us to uncover conserved players/mechanisms implicated in epigenetic reprogramming and exposing novel cancer vulnerabilities. Indeed cancer cells are known to exhibit certain embryonic features and may co-opt early developmental programs to drive phenotypic plasticity giving rise to disease progression and therapeutic resistance. In ongoing studies, we found that reactivation of select early-embryonic factors can indeed promote cancer cell phenotypic plasticity through epigenetic reprogramming mechanisms, similar to that occurring during early embryogenesis. In this project, the student will combine single-cell RNA sequencing (scRNA-seq), spatial profiling and genetic manipulations to systematically investigate the rolesof early-embryonic factors in tumorigenesis and dissect howtheir heterogenous expressions may correlate to distinct cancer cell states through epigenetic mechanisms. For more information about the lab, please see: https://medicine.nus.edu.sg/phys/research/research- programs/cancer-programme/tee-wee-wei/
7.41	Prof Yang ZHANG zhang@nus.edu.sg Department of Biochemistry	7.41 AI-based protein design and drug discovery Proteins in nature were generated following billions of years of evolution and therefore possess limited structural folds and biological functions. Computational protein design aims to design and engineer new protein sequences with novel structure and function significantly beyond nature proteins. Given their potential to create new function and change cellular pathways, computationally designed proteins and peptides can be used as drugs to treat pharmaceutically important human diseases such as cancer and Alzhelmer's disease. In this project, we will develop new artificial intelligence (AI)- based approaches for high-accuracy de novo protein design. The utilized AI techniques include attention transformer, protein language modeling and diffusion models, which will beintegrated with physics-based and evolutionary profile simulations (e.g., EvoDesign) for accurately designing and engineering new proteins and short peptides. Although the current start-of-the-art methods are successful in designing a variety of functional proteins, there have not yet been a computationally designed protein entering Phase-III clinical trials. Designing the first protein-based clinically effective drug thus represents the 'Holy Grail' of computational protein andpeptide design, which is also the aim of this project.
7.42	Prof Yang ZHANG zhang@nus.edu.sg Department of Biochemistry	7.42 AI-based protein and RNA structure prediction Proteins are the "workhorse" molecules of life and what work proteins do in cells depend on their 3D structure. Protein structure prediction, which aims to determine the spatial location of every atom in proteins from the amino acid sequence by computational simulations, represents one of the most important problems in computational biology. The past five years have witnessed revolutionary progress of the field, due to the introduction of advanced artificial intelligence (AI) and deep machine learning techniques. In this project, you will be developing new AI-based methods for high-resolution structure prediction of proteins and protein- protein interactions under the mentorship of the top leader of the field. The cutting-edge AI techniques will be integrated with cryo- EM density maps and fragment assembly simulations (I-TASSER) for large-size protein complex structure determinations. The methods will also be extended for structure modeling of RNAs which have been increasingly recognized with important biological function and drug design potential, in addition to their canonical roles in transcription and translation. You will be participating in the biennial world-wide CASP experiment, which is called Olympic Games of computational structure biology, to test your protein and RNA structure prediction methods compared to the state of the art of the field.

8 Synthetic Biology for Clinical & Technological Innovation for Synthetic Biology (SynCTI)

S/N	Principal Investigator	Project Title and Abstract
8.1	A/Prof Yew Wen Shan wenshanyew@nus.edu.sg Department of Biochemistry	8.1 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 address 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	8.2 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 differentiated from hematopoisticstem cells, followed by colony -forming unit cells (CFU-Es). CFU-Es differentiate 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 scaleRBC production in-vitro.
8.3	Dr Jiahai SHI Jh.shi@nus.edu.sg Department of Biochemistry	8.3 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 invented a second generation RBC therapy, resulting in a spin-off Carcell Biopharma with more than US$ 16 million venture investment.

8.4	Dr Julius Fredens jfredens@nus.edu.sg Department of Biochemistry	8.4 Next Generation DNA Delivery to Mammalian Cells Gene therapy holds great promises for the future of medicine by enabling precise manipulation of our genetic material. 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. For these revolutionising therapies, DNA is currently delivered using mammalian viruses and lipid nano particles (LNP) with very limited cargo capacity and at high costs. 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. In this project we aim to engineer bacteriophage for DNA delivery to mammalian cells using synthetic genomics and directed evolution.
8.5	Dr Chester Lee Drum mdccld@nus.edu.sg Department of Medicine	8.5 Synthetic Biology of Chemically Synthesized Macromolecules 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 create chemically synthetic functional proteins (Nature Comms, PMID: 34588451). The project is a continuation of research begun at Massachusetts Institute of Technology and has the ability to revolutionize the field of protein engineering. Macromolecular structure prediction will use predictive artificial intelligence from Google AlphaFold in addition to traditional protein engineering principles in our lab. An immediate application will be the world's first chemically synthesized antibody fragment. An interest in deep-tech commercialization and big-idea, blue sky thinking is recommended for applicants to this project. It is fully funded and partnered with ASTAR in addition to a talented NUS team in the lab.
8.6	Dr Jungjoon Kempthorne Lee jjk.lee@nus.edu.sg Department of Biochemistry	8.6 Advancing Genome-Wide Off-Target Detection and AI-Driven Analysis for Safe and Precise CRISPR Therapeutics Unlike conventional therapeutics, CRISPR-based therapies involve irreversible genetic modifications which makes off-targeting a critical safety concern for clinical and commercial use. USFDA guidelines mandate stringent and rigorous safety testing by using methods to predict potential off-targets. Our research focuses on advancing genome-wide off-target detection techniques and strives to develop comprehensive tools for the analysis and validation of CRISPR-based therapeutics. Recent innovations, such as Extru-seq, combine the strengths of both cell-based and in-vitro methods, resulting in high validation accuracy. Another technique, TAPE-seq, utilizes Prime-editor technology to provide superior detection capabilities compared to traditional CRISPR tools. Altogether, these advancements enable a more reliable prognostic evaluation of genome editing. Our lab emphasizes the further development of genome-wide off-target detection techniques, including the integration of high-throughput sequencing technologies and novel molecular assays. We collaborate closely with AI research groups to leverage advanced machine learning models for predicting and prioritizing off-target effects across diverse genomic landscapes. This interdisciplinary approach enhances our ability to design safer and more precise genome-editing tools, with the ultimate goal of translating these technologies into clinically viable solutions.

8.7	Dr Jungjoon Kempthorne Lee jjk.lee@nus.edu.sg Department of Biochemistry	8.7 Optimizing Genome Editing Tools through Directed Evolution and Advanced Screening Techniques The refinement of genome editing tools is essential to ensuring they evolve into best-in-class technologies. To enhance the specificity and efficiency of these tools, directed evolution techniques are employed to identify variants with optimal activity. Our research focuses on the further optimization of genome editing tools by applying advanced screening and molecular techniques. One notable development is the use of Sniper-screen, a tailored screening system used to overcome the usual trade-offs between efficiency and accuracy observed in high-throughput screening systems. This has led to the discovery of Sniper2L, a high fidelity CRISPR-Cas9 variant designed with enhanced specificity and activity. Single-molecule Förster Resonance Energy Transfer (FRET) experiments have confirmed the superior performance of these new variants, paving the way for more precise applications in therapeutic contexts. Beyond variant discovery, our research also aims to expand the functional capabilities of genome editing tools through protein engineering and structure-guided design. Collaborating with experts in computational modeling, we utilize AI-driven simulations to predict mutational effects, further accelerating the evolution of these tools. By integrating experimental and computational approaches, our work seeks to deliver next-generation genome editing technologies tailored for clinical precision and safety.

9 Nanomedicine Translational Research Programme

S/N	Principal Investigator	Project Title and Abstract
9.1	Dr Jiong-Wei Wang surwang@nus.edu.sg Department of Surgery	9.1 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 preferrable 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	9.2 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	9.3 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.
9.4	Dr Ni Qianqian qqian.ni@nus.edu.sg Department of Diagnostic Radiology	9.4 Development of functional lipid nanoparticles for messenger RNA delivery Lipid nanoparticle (LNP) is a well-developed drug delivery system for mRNA delivery which has been widely used in vaccine development during Covid-19 pandemic. However, delivery efficiency remains a challenge for clinical applicationsof mRNA. In our project, we developed a series of functional lipid nanoparticles (LNPs) to enhance biological stability of mRNA and its lysosome escape, and thus yielding high translational capacity of mRNA.
9.5	Dr Ni Qianqian qqian.ni@nus.edu.sg Department of Diagnostic Radiology	9.5 Invention of “3D” messenger RNA to improveintracellular delivery In this project, we developed a novel approach for the construction of “3D” mRNA. Controlled interaction between “3D” mRNA and lipid components could induce polyhedral morphology and adjustable rigidness of delivery vehicle, and finally improve the intracellular delivery of mRNA. We propose to test this mRNA delivery platform technology in multiple diseases models, including mRNA vaccine for cancer immunotherapy, crispr/cas9 mRNA system mediated metabolic disease treatment as well as cardiovascular diseases.
9.6	Dr Ni Qianqian qqian.ni@nus.edu.sg Department of Diagnostic Radiology	9.6 Multifunctional nanomaterials to amplify T cell basedcancer immunotherapy Successful T cell immunotherapy for solid tumors requires that T cell can access tumor tissues effectively, which is difficult to achieve. We developed janus-structured nanoparticles modified with targeting ligands which could guide therapeutic T cells to inflammatory tumor microenvironment. We anticipate that this homing system would robustly improve the infiltration of therapeutic Car-T cells to antigen specific solid tumors. Besides, we propose to develop novel mRNA delivery systems based on our proprietary LNP techniques for in-vivo T cell genetic engineering and cancer immunotherapy.

9.7	Dr Ni Qianqian qqian.ni@nus.edu.sg Department of Diagnostic Radiology	9.7 Harnessing artificial intelligence for precision drugdelivery When equipped with wireless technology and image recognition system, deep learning models have been appliedin clinic endoscopy examination which allows fast and accurate assistant diagnosis of gastrointestinal diseases. We propose to use a multidisciplinary design principle coupling artificial intelligence techniques and robotic drug delivery system to create a technological interface that allows remoteregulation of precision drug delivery. By developing a multitask deep learning algorithm, the endoscopic image information could be analyzed and translated to wireless signal, which will then trigger the ejection of biologic scaffold designed for drug loading to regulate the localization and timing of drug release. We will test this artificial intelligence drug delivery system in multiple gastrointestinal diseases models including bleeding and inflammatory bowel disease.
9.8	Dr Tang Wei wei.tang@nus.edu.sg Department of Diagnostic Radiology	9.8 Development of immune modulator deliverynanomedicne for cancer immunotherapy Cancer is the second leading cause of death in the world. Cancer immunotherapy has brought great hope to cancer patients in recent years, especially with the success in immune checkpoint blockade (ICB) therapy and chimeric antigen receptor (CAR) T-cell therapy. However, their efficacyin solid tumours remains to be improved, which is mainly due to the immunosuppressive tumour microenvironment (TME) that inhibits the infiltration, proliferation, and persistence of cytotoxic T cells. By leveraging advanced nanotechnologies on the delivery of immunomodulators, immunomodulating nanoparticles provide great opportunities to overcome these challenges by switching “cold” tumours to “hot” tumours. Therefore, we seek to integrate chemistry, biomaterials science, nanomedicine, molecular imaging, immuno-engineering, and oncology fundamentals (1) to design novel nanomedicine-based technologies for effective delivery of immunomodulators; (2) to study the cellular interactions in the cancer-immunity cycle; and (3) to develop new therapies for the treatment of solid tumours.
9.9	Dr Jingjing Zhang j.zhang@nus.edu.sg Department of Diagnostic Radiology	9.9 Radioligang Therapy (RLT) Radioligand therapy (RLT) is an emerging drug class uniquely promising for personalized cancer therapy, as both the radionuclides and the carrier molecules (targeting ligands) can be tailored to the individual patient, depending on tumor size and tumor type respectively. The ligand delivers primarilyβ or α radiation derived from nuclear decay, which damages cancer cells in the immediate proximity; the radiation emitted by the radioactive decay causes irreversible ionization of the cells’ DNA, inducing apoptosis. The interest for RLT is rapidly growing, as is the number of experimental and approved drug complexes available for different targets. In parallel to RLT, immune checkpoint blockage (ICB) is recognized as a breakthrough therapy, though with limited efficacy so far due to resistance to immunotherapy often associated with complicated tumor-host-microenvironment interactions. We will take advantage of the immunomodulatory potential of RLTto rationalize the combination of RLT and ICB to improve overall response rate and duration of response.

9.10	Prof Xiaoyuan (Shawn) Chen chen.shawn@nus.edu.sg Department of Diagnostic Radiology	9.10 Development of Individualised Cancer Vaccines Cancer vaccine is a validated and critically important approach in cancer immunotherapy. Our program is focused on continuous innovation in platform technologies in the field of cancer vaccinology. We apply expertise in medicine, gene engineering, chemistry and immunology to gain international competitiveness in cancer vaccine innovation. We will utilize the extensive experience in vaccine development, computational modeling, chemical synthesis, nanomedicine and cellular therapeutics of our researchers, clinical partners, and state-of-the-art research facilities to establish the program of excellence in cancer vaccinology. We aim to develop a pipeline of neoantigen-based vaccine technologies for the treatment of cancer. We will build a high-throughput methodological model to identify alternative neoantigen candidates for the treatment of solid cancer. We will develop robust lipid nanoparticle (LNP) and polymer libraries to enhance delivery of mRNA neoantigens. We will also reprogram dendritic cell nanovesicle (DCNV) vaccines via biomimetic nanotechnology to optimize efficacy, minimize toxicity, and broaden the application of immunotherapies based on DCs.
9.11	Prof Xiaoyuan (Shawn) Chen chen.shawn@nus.edu.sg Department of Diagnostic Radiology	9.11 Translational Nanomedicine Nanoparticles is the logical and encouraging tool for deliveryof medicine in controlled and targeted manner. Nanotherapeutics are expected to provide targeted drug delivery, improve drug solubility, extend drug half-life, improve a drug's therapeutic index, and reduce a drug's immunogenicity, which has the potential to revolutionize the treatment of many diseases. We work on various nanocarriers(e.g. liposome, nanocrystal, virosome, polymer therapeutic, nanoemulsion, and inorganic nanoparticle) for different types of drugs, such as proteins/peptides, chemotherapeutics, RNA therapeutics (e.g. siRNA, mRNA). We tackle key issues related to the clinical development of nanomedicine, including biological challenges, large-scale manufacturing, biocompatibility and safety, government regulations, and overall cost-effectiveness of nanomedicine.
9.12	Prof Xiaoyuan (Shawn) Chen chen.shawn@nus.edu.sg Department of Diagnostic Radiology	9.12 Development of multimodality molecular imaging probes For molecular imaging, particularly, the rise in multimodal instrumentation has sparked hopes for new ways to track multiple molecular targets simultaneously, or to use different imaging methods in combination to more clearly delineate localization and expression of biochemical markers. We apply combined imaging methods and probes to work synergistically to allow high-resolution, high-sensitivity investigation of biological activity. The imaging modalities we have include but not limited to positron emission tomography (PET), single-photon emission computed tomography (SPECT), computed tomography (CT), magnetic resonance imaging (MRI), near- infrared fluorescence (NIF), ultrasound, and photoacoustic. While combining multimodal detectability in the same probe is not necessitated by all applications, there can be advantages to this arrangement. These span the range from small molecules to peptides, proteins, antibodies, and nanoparticulate systems and vary in complexity. We are keen on translating various molecular imaging probes into clinic for disease diagnosis and treatment management.

9.13	Dr Kong Chee Hoe chee_hoe_kong@nuhs.edu.sg Department of Orthopaedic Surgery With Mentor: Dr Dennis Hey	9.13 Optimizing Tendon Healing with Functionalized Suturesand Modified Fibrin Gels Tendon and ligament injuries make up over 50% of all musculoskeletal injuries. Healthcare cost incurred from tendon injuries has been estimated to be valued at 30 billion US dollars per year in USA, and over 115 billion Euros per year in Europe. Surgical repairs are considered for patients with complete ruptures of rotator cuff tendons. However, over50% of these repairs were reported to fail. In addition, re-tearrates of commercially available graft-augmented repairs have been reported to be as high as 90%. In view of these clinical limitations, research in this field is targeted at a combination of factors that influence tendon healing and regeneration. Firstly, the use of non-absorbable sutures are areas of high stress with a higher re-tear rate and can compromise vascular supply by strangulation of tendon tissue that is already known to be relatively avascular. Secondly, most non-absorbable sutures have low bioactivity. The aim of this project is to engineer enhanced suture construct that is functionalized to elute bioactive molecules in a controlled and sustained manner with nanoparticles as a delivery vehicle. The use of fibrin gel as a delivery vehicle for controlled, predictable and sustained release of bioactive molecules will also be investigated.
9.14	Dr Chester Lee Drum mdccld@nus.edu.sg Department of Medicine	9.14 Nanomedicine therapeutic vaccine development We have a patented novel nanotechnology developed at NUSthat is undergoing rapid development and commercialization. It is a thermo-rigid shell (Nature Comms, PMID: 29129910), which encapsulates and folds protein substrates (Nature Comms, PMID: 34588451) and can be used for cancer treatment (ACS Nano, PMID: 35653306), engineered for longhalf-life (Nanomedicine, PMID: 30853651) and even oral administration (Int J Mol Sci, PMID: 36077259) and therapeutic stabilization (Pharmaceutics, PMID: 34834205). This project will use the encapsulation technology for the first time to create a novel RNA based vaccine for either cancer orinfectious disease protection.

10 Precision Medicine Translational Research Programme

S/N	Principal Investigator	Project Title and Abstract
10.1	A/Prof Citra NZ Mattar citramattar@nus.edu.sg Department of Obstetrics & Gynaecology	10.1 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 101ehavior HSC expansion protocols and AAV transduction, and a humanized mouse model to 101ehavior101ize 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	10.2 Novel Precision Technologies to Correct Mutations 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 andcurrently 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 patientsown 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 101ehavior 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, and gene expression analysis are some of the techniques routinely used in our laboratory.

10.3	Prof Yap Hui Kim Prof Ng Kar Hui paenkh@nus.edu.sg Department of Paediatrics	10.3 Next Generation Sequencing of Genetic kidney diseasesin Singapore and Asia Glomerular disease is common cause of chronic kidney disease . About 20-30% of children with SRNS have geneticcauses. Alport syndrome genes are the commonest cause. Genetic testing in glomerular diseases have many clinical impacts, including treatment decisions. However, genetic testing is not routinely performed in Asia due to various reasons. We have set up the first multicenter consortium “Deciphering Diversities: Renal Asian Genetics Network (DRAGoN)” whichnow includes 53 investigators from 23 centres in 8 countries and 651 families. In our first analysis involving 183 samples, we found a genetic diagnosis in 14%. We had also created a bedside predictive clinical scoring tool that allows clinicians topredict which patients are more likely to have a genetic diagnosis. Addition of samples will allow us to create a validation cohort to further validate the predictive score in Asians. This predictive score is particularly relevant to clinicians in budget-conscious countries. Project’s overall aims are to: (1) Perform Next Generation Sequencing in Asian patients suspected to have kidney genetic diseases. (2) Identify reliable clinical predictors of genetic diagnosis in Asians so that clinicians can perform genetic testing in selected patients. (3) Perform health economic analysis of genetic testing in nephrology in Singapore.
10.4	Dr Teo Kee Keong Adrian bchtkka@nus.edu.sg ateo@imcb.a-star.edu.sg Department of Biochemistry	10.4 Using human in vitro models for studying diabetes disease mechanisms Diabetes is a debilitating chronic disease that has spiraled outof 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 youngand 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 withclose 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.

10.5	Dr Su Xinyi ophsux@nus.edu.sg Department of Ophthalmology	10.5 Integrated gene editing platform for inherited retinal diseases Many inherited retinal diseases arise from mutations in genes which are too large to be addressed via the traditional gene- replacement therapy approach. Gene editing is a novel approach to treat such diseases. There are current many approaches to create DNA or RNA editing therapeutics. The aim is to create gene editing platforms and use relevant biological models including patient-derived iPSC cells to assess the safety and efficacy of such therapeutics.
10.6	Dr Chester Lee Drum mdccld@nus.edu.sg Department of Medicine	10.6 Computational Deep Phenotyping for Clinical Risk Prediction Deep phenotyping technologies such as genetic sequencing, RNAseq and mass spectrometry are creating ultra-dense datasets that describe the full biology of our patients. Yet, withthis resource comes a problem: the mass of information requires novel computational techniques to match multidimensional datasets to real-world clinical questions and outcomes. Working with bioinformaticians, clinicians and largehealthcare data sets, you will create novel algorithms to identify at-risk patients across multiple disease types and identify those who will benefit from precision treatments. You will be listed as an official member of the ethics approval and work with patient data to improve medical outcomes. Valuableskills will be a basic understanding of either scripting languages (R, python) or coding skills (Java, etc) and biostatistics. Clinical findings can be validated via access to the UK Biobank, a resource of over 400,000 clinical records and the MOH National Disease Registry, which covers national outcomes in Singapore. This project is fully funded and open for enrolment.
10.7	Dr Chester Lee Drum mdccld@nus.edu.sg Department of Medicine	10.8 Machine Learning Approach to Cancer andCardiovascular 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 medicaloutcomes. A robust model of immediate translational value will be created to predict adverse reactions. Clinical findings can be validated via access to the UK Biobank, a resource of over 400,000 clinical records and the MOH National Disease Registry, which covers national outcomes in Singapore in addition to the NUH medical record. This project is fully funded and open for enrolment.

11 Others

S/N	Principal Investigator	Project Title and Abstract
11.1	Prof James Hoi Po Hui doshuij@nus.edu.sg Department Orthopaedic Surgery	11.1 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 paracrineaction 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 forthe 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	11.2 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	11.3 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.
11.4	Prof Vinay Tergaonkar bchvt@nus.edu.sg vinayt@imcb.a-star.edu.sg Department of Pathology and Department of Biochemistry	11.4 Study an interesting gene in the development and progression of colorectal cancer via regulating ferroptosis Colorectal cancer (CRC) is the third most prevalent cancer and the second leading cause of cancer mortality. Although patients have more treatment options for CRC patients, the prognosis is poor for metastatic CRC patients. Ferroptosis, a newly discovered form of regulated cell death driven by iron- dependent excessive lipid peroxidation, has been implicated in the development and therapeutic responses of various types of tumors. In our project, we mainly focus on elucidatingthe mechanism of ferroptosis in the development and progression of CRC to explore potential therapeutic targets for CRC patients.

11.5	Prof Vinay Tergaonkar bchvt@nus.edu.sg vinayt@imcb.a-star.edu.sg Department of Pathology and Department of Biochemistry	11.5 Creating isogenic reporter lines to identify regulators of cancer specific promoters The project will involve cloning and cell culture methods thatwill help to find specific regulatory gene candidates that the involved in cancer progression.
11.6	Prof Vinay Tergaonkar bchvt@nus.edu.sg vinayt@imcb.a-star.edu.sg Department of Pathology and Department of Biochemistry	11.6 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 onlytherapeutic 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	Prof Vinay Tergaonkar bchvt@nus.edu.sg vinayt@imcb.a-star.edu.sg Department of Pathology and Department of Biochemistry	11.7 Characterizing hepatocellular carcinoma at spatial resolution In this project, we will utilise clinical samples to perform cutting edge single cell and spatial transcriptomic to reconstruct the ecosystem that make up hepatocellular carcinoma.
11.8	Prof Vinay Tergaonkar bchvt@nus.edu.sg vinayt@imcb.a-star.edu.sg Department of Pathology and Department of Biochemistry	11.8 Identification of SATB2 as biomarker for drug response inCRC The mitogen-activated protein kinase (MAPK) signalling pathway plays a fundamental role in the carcinogenesis of colorectal and numerous other neoplasms. The developmentof targeted agents that inhibit MEK 1/2 has created the potential for downstream blockade of the MAPK pathway. Though MEK inhibition has demonstrated clinically significant efficacy in several tumor types, therapeutic success has been limited in colorectal cancer (CRC). Thus, potential rational combination strategies and the investigation into potential predictive biomarkers of response will be in urgent need. In this project, we have identified SATB2, a nuclear matrix- associated transcription factor and epigenetic regulator, which could serve as a promising diagnostic biomarker to predict drug response especially for MEK1/2 inhibitors. Next, we will: a) understand the mechanism by which SATB2 regulates drug response in vitro and in vivo b) explore the role of SATB2 in vivo using genetic engineered CRC mouse model.

11.9	Prof Yap Hui Kim paeyaphk@nus.edu.sg Department of Paediatrics	11.9 Role of Type 2 Innate Lymphoid Cells in childhoodidiopathic nephrotic syndrome Childhood idiopathic nephrotic syndrome (iNS) is associated with significant morbidity, particularly due to steroid- dependent or steroid-resistant (SD/SR) disease. Existing dataimplicate 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 iNSrelapse 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 cytokineproduction, 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	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 Preimplantation genetic testing involves the genetic diagnosisof 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 disorderor 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 compatiblewith 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	11.11 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 cognitiontend 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 ishigh (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	11.12 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 willrecruit 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	11.13 Developing a Digital Solution for Salutogenic BrainHealth 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 andearly 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 toevaluate 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	11.14 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	11.15 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-carepractice 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 reflectiveself-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	11.16 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 theburden of daily frequent monitoring and assessment on PwDswith 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 potentialrisks 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	11.17 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 usethese 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	11.18 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 Qualityof 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 impactof 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	11.19 Prevalence and predictors of chronic treatment guidelineadherence 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 non-adherence 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 Ophthalmology	11.20 BRAIN-EYE-HEALTH AXIS RESEARCH (REALISE) REALISE explores the relationship between the 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 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-year project to elucidate the effects of eye condition to brain ageing.
11.21	Dr Daniel Teh Boon Loong danielteh@nus.edu.sg Department of Ophthalmology	11.21 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 deployed as: (1) Precision tool for targeted load delivery into organs (2) Photonics role for wireless photodynamic therapy in solid cancer (3) Direct visualization of molecular and cellular processes.

11.22	A/Prof Anselm Mak mdcam@nus.edu.sg Department of Medicine	11.22 In-depth mechanistic study of neurocognitive dysfunction in patients with systemic lupus erythematosus using multi-modal neuroimaging Neurocognitive dysfunction (NCD) is prevalent in patients with systemic lupus erythematosus (SLE), impacting physical and psychosocial well-being. The absence of pathology-based NCD assessment has contributed to the rudimentary understanding of the neuropathology of SLE-related NCD, hindering development of cutting-edge diagnostic and therapeutic strategies of SLE-related NCD. Aim 1: To investigate how longitudinal changes of brain structure and function are related to NCD in SLE patients. Hypothesis 1: Brain structural and functional integrity, including grey matter volume, white matter microstructure, functional connectivity and structural-functional alignment, would be compromised and declining longitudinally in SLE patients. Aim 2: To address how blood-brain-barrier (BBB) integrity influences longitudinal structural and functional brain changes, and their relationships with SLE-related NCD. Hypothesis 2: BBB integrity is measured using state-of-the-artdynamic contrast- enhanced magnetic resonance imaging (MRI) and diffusion MRI- based free-water imaging method. Disrupted BBB at baseline would relate to longitudinal declineof structural and functional integrity. Aim 3: To evaluate the relationships between blood biomarkers that indicate BBB disruption, brain structural andfunctional integrity, and SLE-related NCD. Hypothesis 3: BBB integrity would be compromised by neutrophil extracellular traps, imbalance between matrix metalloproteinase 9 and tissue inhibitor of metalloproteinase1, and C5a, enhancing CNS entry of extrathecally-produced neurotoxic autoantibodies.
11.23	Dr Matthew Edward Cove mdcmec@nus.edu.sg Department of Medicine	11.23 Physiology study of electrolyte changes, CO2 kinetics and their effect on plasma pH under extreme conditions such as during bicarbonate dialysis This project will focus on an in-depth physiology study of electrolyte changes, acid-base changes, and CO2 kinetics to build on existing knowledge of this field. The student will learnhow to measure important data such as cardiac output and indirect calorimetry in live animal experiments. Working on this project will train students to understand the and interpret plasma acid base using principle of electroneutrality. The application of this work to provide a better understand of optimal ventilation and dialysis settings and accurately predictthe efficacy of a bicarbonate dialysis in first-in-man studies. This work could be performed stand alone, or as part of a sports or metabolic physiology study.

11.24	Dr G. Owen Schaefer medgos@nus.edu.sg Centre for Biomedical Ethics	11.24 Ethical issues in the development of novel biotechnologies Ethical issues in the development of novel biotechnologies, broadly construed. Examples of specific topics include, but are by no means limited to: (1) Equitable vaccine development (e.g., with regard to future pandemics) (2) Normative justification of regulation and oversight of biomedical research (3) Duties/responsibilities of data subjects (4) Role of public opinion in appropriately shaping biomedical research policy (5) Specifying vague concepts of biomedical oversight(e.g., public interest, equity, risk/benefit ratio) (6) Value and priority of gene editing research (7) Rights to access to novel assisted reproductive technologies (e.g., in vitro gametogenesis, artificial wombs) Prospective students should identify novel approaches or gaps in the existing bioethics literature that can substantially advance our understanding of how to responsibly develop and deploy biomedical innovations. Dr Schaefer is able to serve as primary supervisor on theses that focus on normative/theoretical/philosophical considerations, rather than empirical projects.
11.25	Dr Raymond P. Najjar rpnajjar@nus.edu.sg Department of Ophthalmology	11.25 Beyond Sight - Elucidating the Non-visual Consequences of Ocular Diseases: The eye is not just an extension of the brain. It's a window to neurological health and a complex organ that, through intrinsically photosensitive retinal ganglion cells (ipRGCs), drives and modulates many non-visual cerebral functions such as circadian entrainment, cognition, alertness, sleep and mood. Beyond vision, ocular diseases like glaucoma and diabetic retinopathy can alter the non-visual signalling between the eye and the brain, leading to various impairments in non-visual functions and reducing the patient's quality of life. The successful candidate will have the opportunity to work within a multidisciplinary team of local and international visual-neuroscientists and ophthalmologists, to objectively investigate non-visual (e.g., cognition, alertness, sleep, circadian entrainment, etc.) alterations in different severities of ocular diseases affecting ipRGCs and the outer retina. In this project, the team will also leverage on contemporary findings in non-visual photoreception to improve cognitive performance, alertness, wellbeing, and sleep in patients with ocular diseases, bringing forth a more holistic approach to treating vision impairment.

11.26	Dr Raymond P. Najjar rpnajjar@nus.edu.sg Department of Ophthalmology	11.26 Handheld Pupillometry for a Fast Detection and Diagnosis of Ocular Diseases: The evaluation of the pupillary light response using pupillometry allows for an objective assessment of photoreceptor health in retinal and optic nerve conditions. Ourteam at SERI has recently developed an affordable and easy-to-use handheld chromatic pupillometer (HCP) that relies on contemporary findings in retinal photoreception and artificial intelligence, to allow a fast (1 min), affordable, and accurate detection of ocular diseases. The HCP has recently shown excellent performances for the detection of glaucoma and diabetic retinopathy in a clinical setting. The objectives of this research project are 1/ to improve the diagnostic performance of the HCP prototype by comparing pupillometric signatures across predominant ocular diseases using advanced machine learning strategies and 2/ to evaluate the performance characteristics of the HCP for ocular disease detection in non-ophthalmic settings (polyclinics, community). Through AI-powered, affordable, andeasy-to-use handheld devices like the HCP, our team aims to improve the accuracy of eye disease detection in non-clinical settings and in countries where access to ophthalmic care is limited. Reading material: Najjar et al. 2021 : https://bjo.bmj.com/content/early/2021/11/30/bjophthalmol- 2021-319938 Tan et al. 2022: https://onlinelibrary.wiley.com/doi/abs/10.1111/ceo.14116
11.27	Dr Raymond P. Najjar rpnajjar@nus.edu.sg Department of Ophthalmology	11.27 The Spectral Tuning of Light for MyOPia-control (STOP): Myopia is a highly prevalent refractive error characterized bythe blurred vision of objects when viewed at a distance. Myopia is projected to affect 50% of the world population by2050 and is commonly due to excessive ocular axial growthleading to images being focused in front of the retina. Epidemiological studies have shown that time spent outdoorsis protective against myopia. This can be due to the high intensity and peculiar spectral composition of sunlight. My team is conducting research in animal models and humans tobetter understand the impact of light on ocular growth and identify optimal features (i.e., intensity, pattern and spectrum)of light for better myopia-control. In this project, the candidate will have the opportunity to develop and utilize novel light stimulation, imaging and molecular techniques (e.g., optogenetics), and work within a multidisciplinary local and international team of visual- neuroscientists, ophthalmologists and molecular biologists to elucidate ocular photoreceptoral involvement in the development and prevention of myopia in mammalian models.A better understanding of the impact of light on eye growth would allow the development of effective, passive or active, light-therapy strategies to prevent or delay the onset of myopia in children.

11.28	Dr Raymond P. Najjar rpnajjar@nus.edu.sg Department of Ophthalmology	11.28 Understanding the Mechanisms and Refining the use of Bright Light for Myopia-control Myopia is more than an inconvenience, it's a highly prevalent sight- threatening disease that is projected to affect 50% of theworld population by 2050, becoming the leading cause of irreversible blindness. Epidemiological studies have shown that time spent outdoors is protective against myopia. The protective impact of time outdoors can be due to the high intensity and peculiar spectrum of sunlight. My team is conducting research in animal models and humans to better understand the impact of light on ocular growth and identify optimal features (i.e., intensity, pattern and spectrum) of light for better myopia-control. Our findings highlight a high efficiency of intermittent bright light exposure for myopia- control in chickens and non-human primates. ARVO 2022: https://iovs.arvojournals.org/article.aspx?articleid=2782752 In this research project, the candidate will have the opportunity to learn and utilize novel light stimulation, imagingand molecular techniques (e.g., ophthalmic examinations in large animal models, imaging, ultrasonography, omics, etc.) and work within a multidisciplinary team of visual- neuroscientists, ophthalmologists and molecular biologists to optimize intermittent bright light exposure for myopia-control and elucidate the mechanisms behind its higher efficacy compared to continuous bright light.
11.29	Dr Raymond P. Najjar rpnajjar@nus.edu.sg Department of Ophthalmology	11.29 Identifying novel eye movement and pupillometric biomarkers for ocular and neurological diseases Pupil control and eye movements are subserved by complex neuronal networks, involving a multitude of cortical and sub-cortical brain areas. Dysfunction of these networks may result in abnormalities of pupil-control, ocular movements or ocular fixation. At a motor level, measurements of eye movements allow a direct and simple evaluation of ocular motor dysfunction (e.g. cranial nerve palsies). Conversely, the analysis of eye movements and pupil size allows insight into more complex aspects of human behaviour, such as attention, cognition or consciousness. Neuro-degenerative diseases of the brain or the eye, such as Alzheimer's disease (AD), Parkinson's disease (PD) and glaucoma, may be associated with subtle abnormalities of eye movements and pupil- control. These can be detected only with precise electro-oculography and advanced data processing. The candidate will benefit from a research lab equipped with state- of-the-art pupil and eye trackers, and collaborate with visual neuroscientists, computer scientists, neurologists and neuro- ophthalmologists to investigate gaze and pupillometric alterations in ocular (e.g., glaucoma) and neurological conditions (PD). The ultimate goal of this project is to developdata-driven, AI-powered eye/pupil tracking paradigms for the detection and prediction of ocular and cerebral neurodegeneration.

11.30	Prof David Leslie Paterson uqdpate1@nus.edu.sg Department of Medicine	11.32 EaRly impAct theraPy with ceftazidime-avibactam via rapID diagnostics versus standard of care antibiotics anddiagnostics in patients with bloodstream infection, hospital-acquired pneumonia or ventilator-associated pneumonia due to Pseudomonas aeruginosa or carbapenem non-susceptible Enterobacterales (RAPID) The ADVANcing Clinical Evidence in Infectious Diseases (ADVANCE- ID) Network is established to conduct rapid, cost-effective randomised controlled trials (RCT) to deliver relevantand high-quality evidence to guide clinical practice. ADVANCE-ID is led by Prof David Paterson and Dr Mo Yin, who are experienced in regional and global infectious disease studies, particularly in multidrug-resistant infections. RAPID isthe second multinational clinical trial that is being initiated by ADVANCE-ID, targeting to recruit 1600 patients from 20 hospitals all over the globe. In this trial we hope to integrate rapid diagnostics with early impact antibiotics to determine if this improves patient outcomes. We would like to invite prospective PhD students with ADVANCE- ID, based in National University of Singapore. The programme can be offered full-time or part-time to train keen individuals with innovative multi-disciplinary skills with an aim to support and conduct large-scale randomised controlled trials. The candidate will enjoy opportunities in trial design, implementation and analysis. Highly transferrable skills such as computer programming, Bayesian statistics, in-silico trial simulations, implementation and behavioural science, will be taught. Requirements for applicants include: (1) Basic understanding in clinical applications of statistics (2) Experience in clinical research (3) Work as a productive member of a team Minimum undergraduate or Master's degree
11.31	A/Prof Toh Wei Seong tohws@nus.edu.sg Department of Orthopaedic Surgery	11.31 Extracellular vesicle (EV) and EV-mimetic therapies for musculoskeletal disorders Musculoskeletal disorders are the leading contributor to disability worldwide and place an enormous burden on the health care system in an aging population. Our research program is focused on understanding the mechanisms for degeneration, and developing strategies for regeneration, of tissues of the musculoskeletal system. Our laboratory has set up various animal models for major musculoskeletal disorders including osteoarthritis, intervertebral disc degeneration, and sarcopenia, as well as a broad range of extracellular vesicles (EVs) and EV-mimetics for targeted drug delivery and therapy. We aim 1) to identify novel therapeutic targets using our animal models and cutting-edge technologies such as proteomics, metabolomics, and single cell RNA sequencing; and 2) to design and develop EVs and EV-mimetics based on stem cells and immune cells (e.g., macrophages) for targeted delivery of small molecules, protein/peptides, and RNAs (e.g. miRNA, mRNA).