Catalogue of available PhD projects offered by Fellows of the College of Clinician Scientists Singapore

May 2022

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Foreword

The mission of the College of Clinician Scientists is to promote excellence in translational and clinical research. Key pillars are nurturing the next generation of Clinician-Scientists and to foster national and international research to advance the boundaries of science. To strengthen the pillars, this catalogue compiles available PhD projects offered by Fellows of the College of Clinician Scientists which are open for application to both local and overseas candidates. While projects are categorised in their traditional specialty realms, it is recognised that many projects are cross-disciplinary, and so projects may appear in more than one category.

Prospective PhD candidates are highly encouraged to contact the Main Supervisor to discuss the details including project funding, salary support, integration of clinical training and related matters. While PhD studies for Clinician-Scientists are generally commenced during and beyond Senior Residency training, the College recognises that formal research training needs to be tailored to the individual. In the spirit of lifelong learning, the College warmly invites candidates across all clinical grades considering an academic career to reach out.

Geriatric Medicine

Title	**Neurobehavioral & structural MRI markers for Cognitive Impairment & Dementia**	
Main Supervisor	A/Prof Christopher Chen	
Email	phccclh@nus.edu.sg	
Conferring Institution	National University of Singapore	
Co-Supervisor(s)/ Institution	Dr Saima Hilal (Saw Swee Hock School of Public Health, NUS)	
Abstract	The Memory Aging and Cognition Centre (MACC) is a multi-disciplinary research programme with extensive Singaporean and global collaborations. It aims to investigate and provide novel insights into the risk factors and biomarkers for cognitive decline and dementia that may lead to potential therapies. We imagine a future where cognitive decline and dementia can be prevented and treated. It is our mission to translate our research into productive interventions which promote healthy memory and healthy ageing in Singapore. More details on our projects are available on http://www.macc.sg/MACC-Projects-Clinical-Studies-Memory-Clinical-Trials 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 changes in structural and functional MRI, retinal vascular and retinal neuronal markers as well as blood-based vascular and neurodegenerative markers, and neurobehavioural markers are associated with poorer cognitive performance on follow-up visits 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 above and beyond the utility of currently used predictors. 2. To examine how the syndrome of Mild Behavioural Impairment (MBI) is influenced by the independent and interactive effects of MRI, retinal and blood biomarkers. We hypothesise that : a) Severity of cerebrovascular disease and neurodegeneration, structural and functional connectivity disruptions and reduced cerebral perfusion on MRI are associated with MBI; b) Retinal vascular and neuronal markers are associated with MBI; c) Altered levels of blood-based vascular and neuro-degenerative markers (for example, higher levels of cytokines, p-tau and β-amyloid) are associated with MBI; d) Interaction between the above mentioned biomarkers influence MBI and NPS	
Skillsets to be acquired	Experience of conducting a large longitudinal study focusing on biomarkers for cognitive impairment and dementia. Understanding and analysis of a) cognitive and neurobehavioural data, b) structural and functional MRI, c) retinal imaging, d) blood biomarkers.	
Project details (check all that apply)	☒Patient contact required ☐Clinical Trial ☐Overseas attachment ☐Biosafety/Biocontainment required ☐Animal experiments	☒Laboratory work ☐Product development ☒Others (specify): Neuropsychology. MRI analysis

Title	**Multimodal MRI-based network breakdown and progression prediction in Cognitive Impairment and Dementia**
Main Supervisor	A/Prof Christopher Chen
Email	phccclh@nus.edu.sg
Conferring Institution	National University of Singapore
Co-Supervisor(s)/ Institution	A/Prof J Zhou (Centre for Translational MR Research, NUS) A/Prof T Yeo (Centre for Translational MR Research, NUS)
Abstract	The Memory Aging and Cognition Centre (MACC) is a multi-disciplinary research programme with extensive Singaporean and global collaborations. It aims to investigate and provide novel insights into the risk factors and biomarkers for cognitive decline and dementia that may lead to potential therapies. We imagine a future where cognitive decline and dementia can be prevented and treated. It is our mission to translate our research into productive interventions which promote healthy memory and healthy ageing in Singapore. More details on our projects are available on http://www.macc.sg/MACC-Projects-Clinical-Studies-Memory-Clinical-Trials The specific aims of this project funded by a Singapore Translational Research (STAR) Investigator Award are : 1. To examine longitudinal brain network breakdown and microstructural changes using multimodal MR imaging and evaluate their interactions with Alzheimer's Disease (AD) & cerebrovascular disease (CeVD) pathology and contribution to cognitive and behavioural decline in patients with no, mild cognitive impairment (MCI) and dementia. The hypotheses are : a) Plasma amyloid-β and tau are related to specific brain functional and structural network breakdown leading to cognitive decline and behavioral problems; b) The effect of structural/functional network changes and atrophy on cognitive performance and behavioural problems is network-specific and disease stage-dependent and modulated by CeVD markers c) MCI with CeVD would have less typical AD-type brain structural and functional connectivity changes compared to MCI without CeVD. Furthermore, with both CeVD and AD pathology, individuals with no or mild cognitive impairment would have an accelerated trajectory of downstream neurodegeneration and cognitive decline. 2. To build a large international longitudinal database comprising local and international imaging neurobehavioural data to develop AI algorithms for predicting dementia risk and progression. The hypotheses are : a) We hypothesize that deep learning can be used to harmonize imaging and neurobehavioural data across multiple sites; b) By pooling harmonized data across multiple sites, the larger sample size will dramatically improve prediction of future cognitive decline and clinical outcomes.
Skillsets to be acquired	Experience of conducting a large longitudinal study focusing on biomarkers for cognitive impairment and dementia. Understanding and analysis of a) cognitive and neurobehavioural data, b) quantitative and functional MRI, c) Artificial Intelligence, d) international collaborations
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Title	**Retinal markers for Cognitive Impairment and Dementia**
Main Supervisor	A/Prof Christopher Chen
Email	phccclh@nus.edu.sg
Conferring Institution	National University of Singapore
Co-Supervisor(s)/ Institution	Prof L Schmetterer, Prof TY Wong, Prof D Milea and Dr J Chua (Singapore Eye Research Institute), A.Prof Carol Cheung (Chinese University of Hong Kong)
Abstract	The Memory Aging and Cognition Centre (MACC) is a multi-disciplinary research programme with extensive Singaporean and global collaborations. It aims to investigate and provide novel insights into the risk factors and biomarkers for cognitive decline and dementia that may lead to potential therapies. We imagine a future where cognitive decline and dementia can be prevented and treated. It is our mission to translate our research into productive interventions which promote healthy memory and healthy ageing in Singapore. More details on our projects are available on http://www.macc.sg/MACC-Projects-Clinical-Studies-Memory-Clinical-Trials The specific aims of this project funded by a Singapore Translational Research (STAR) Investigator Award are : 1. To determine the relationship of existing (retinal vasculature, Optical Coherence Tomography (OCT), OCT-Angiography) and novel (Doppler OCT, pupilometry, hyperspectral OCT) retinal imaging measures over time to progression and development of vascular cognitive impairment and other imaging markers of dementia, with a goal to determine the potential diagnostic and prognostic value of retinal imaging. We hypothesise that as multiple cross-sectional studies have consistently demonstrated the association of retinal imaging biomarkers and dementia, retinal imaging biomarkers will be predictive of the incidence and progression of dementia. 2. The creation of an international big data consortium, AIDA (Artificial Intelligence for Dementia Assessment) to evaluate retinal imaging markers of dementia. Using datasets from multiple institutions around the world and through the integration of deep learning, we hypothesize that we will be able to further improve the sensitivity and specificity of retinal imaging biomarkers to detect dementia.
Skillsets to be acquired	Experience of conducting a large longitudinal study focusing on biomarkers for cognitive impairment and dementia. Understanding and analysis of a) cognitive and neurobehavioural data, b) retinal and brain imaging, c) Artificial Intelligence, d) international collaborations
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Title	**Blood markers for Cognitive Impairment and Dementia**
Main Supervisor	A/Prof Christopher Chen
Email	phccclh@nus.edu.sg
Conferring Institution	National University of Singapore
Co-Supervisor(s)/ Institution	Dr Mitchell Lai, Dr C Drum, Prof B Kennedy, Prof B Halliwell (NUS)
Abstract	The Memory Aging and Cognition Centre (MACC) is a multi-disciplinary research programme with extensive Singaporean and global collaborations. It aims to investigate and provide novel insights into the risk factors and biomarkers for cognitive decline and dementia that may lead to potential therapies. We imagine a future where cognitive decline and dementia can be prevented and treated. It is our mission to translate our research into productive interventions which promote healthy memory and healthy ageing in Singapore. More details on our projects are available on http://www.macc.sg/MACC-Projects-Clinical-Studies-Memory-Clinical-Trials 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, including oxidative stress, vascular disease and neurodegeneration, could identify individuals with high disease risk. Specifically, that a) blood-based biomarkers of neurodegeneration and oxidative stress are predictive of incident development of cerebrovascular disease in parallel with cognitive decline; b) While providing additional information on the tissue origins and thus a more direct link to the brain pathology, neural- or endothelial-specific extracellular vesicle biomarkers are more sensitive than neat plasma biomarkers in diagnosing and prognosing for cognitive impairment and CeVD; c) A combination of multiple biomarkers affiliated to the different pathophysiological pathways adds value to the diagnostic and prognostic performance of single blood-based biomarkers and predict future disease progression of cognitive impairment and CeVD.
Skillsets to be acquired	Experience of conducting a large longitudinal study focusing on biomarkers for cognitive impairment and dementia. Understanding and analysis of a) cognitive and neurobehavioural data, b) brain imaging, c) blood biomarkers d) international collaborations
Project details (check all that apply)	☒Patient contact required ☐Clinical Trial ☐Overseas attachment ☐Biosafety/Biocontainment required ☐Animal experiments ☒Laboratory work ☐Product development ☒Others (specify): Neuropsychology. MRI analysis

Title	**The SINgapore GERiatric intervention study to reduce cognitive decline and physical frailty (SINGER) Study**
Main Supervisor	A/Prof Christopher Chen
Email	phccclh@nus.edu.sg
Conferring Institution	National University of Singapore
Co-Supervisor(s)/ Institution	Prof A Maier (NUS) , A/Prof J Zhou (NUS), Dr M Lai (NUS)
Abstract	The Memory Aging and Cognition Centre (MACC) is a multi-disciplinary research programme with extensive Singaporean and global collaborations. It aims to investigate and provide novel insights into the risk factors and biomarkers for cognitive decline and dementia that may lead to potential therapies. We imagine a future where cognitive decline and dementia can be prevented and treated. It is our mission to translate our research into productive interventions which promote healthy memory and healthy ageing in Singapore. More details on our projects are available on http://www.macc.sg/MACC-Projects-Clinical-Studies-Memory-Clinical-Trials The specific aims of this project funded by a Large Collaborative Grant are : 1. To investigate novel interventions for vascular cognitive impairment (VCI). The WHO Guidelines on risk reduction of cognitive decline and dementia provide evidence-based recommendations on lifestyle behaviours and interventions to delay or prevent cognitive decline and dementia. However, how best to implement such interventions and importantly whether a multi domain lifestyle intervention is effective, safe and globally feasible remain important research topics. Hence we propose to conduct a large community-based innovative trial as part of the World Wide FINGERS interdisciplinary network for the prevention of cognitive impairment or dementia The trial will recruit 1200 subjects at high risk to develop cognitive impairment and dementia. The main goal is to determine the efficacy and safety of multimodal lifestyle interventions together with intensive blood pressure lowering. We hypothesize that these interventions will reduce cognitive decline and severity of cerebrovascular disease (CeVD) and other VCI biomarkers. 2. To examine how CeVD, tau, and amyloid impact longitudinal brain structural and functional 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, reflecting complex underlying disease interactions that will be revealed in a longitudinal study. 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.
Skillsets to be acquired	Experience of conducting a large clinical trual focusing on biomarkers for cognitive impairment and dementia. Understanding and analysis of a) cognitive and neurobehavioural data, b) structural and functional MRI, c) retinal imaging, d) blood biomarkers.
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Haematology

Title	***In vivo* Adeno-Associated Viral vector-mediated Base-Editing of Haemopoetic Stem Cells to correct β-Thalassaemia Major**	
Main Supervisor	AP Citra NZ Mattar (Dept O&G)	
Email	citramattar@nus.edu.sg	
Conferring Institution	NUS Medicine, Department of O&G	
Co-Supervisor(s)/ Institution	Dr Rufaihah Abdul Jalil NUS Medicine, Department of Surgery	
Abstract	Major β-thalassaemia impacts significantly on medico-economic resources particularly in populations with high carrier prevalence. This global disease causes 3-4% of early-childhood deaths annually, with severe chronic morbidity arising from progressive disease and inadequate treatment. There is still no universal, affordable and curative treatment for those without a matched HSC donor. Current ex-vivo gene therapy trials are extremely costly and risk myeloablation complications. We investigate in-vivo AAV-mediated base-editing to correct the commonest single nucleotide variant causing transfusion-dependent thalassaemia (TDT) in a proof-of-concept study utilizing personalised humanized mice produced with patient-derived HSC, testing the hypothesis that optimized AAV-mediated delivery of base-editing tools can efficiently correct the IVS1-5(G>C) mutation, the most prevalent in Asian populations. The specific aims of this project are: **(1)** produce an efficient base-editing strategy for *in vivo* correction of the IVS1-5 (G>C) mutation in engineered human HSC, **(2)** optimise AAV-transduction of human HSC in vitro and *in vivo* using a humanised mouse model, and **(3)** assess phenotype correction, safety and efficacy of *in vivo* AAV-mediated base-edited gene correction in a humanized mouse model for β-thalassaemia. **Potential Application:** In this era of precision and personalized medicine, gene modification therapies work where conventional HSCT does not, but the current ex vivo approaches employed in clinical trials are extremely costly and impose a high medical burden (e.g. complications of myeloablation). Base editing can be adapted readily to correct individual single nucleotide variants causing the majority of β-thalassaemias, and with a safer optimized AAV-mediated delivery, a single-dose in vivo treatment strategy can be planned which will circumvent the obstacles of ex vivo gene therapies. This novel and innovative study can expedite clinical trials and provide an urgently-needed treatment potentially more accessible and cost-effective than current standards, poised to make substantial global impact.	
Skillsets to be acquired	1. Haemopoetic stem cell culture, expansion and transduction with AAV 2. Optimisation of HSC transduction with clinical AAV vectors 3. Design base editing strategies using AAV to deliver gRNA and DNA template 4. Targeted deep sequencing to assess correct editing, off-target mutations, indels 5. Haemopoetic programming of iPSC 6. In vivo base editing proof of principal experiments in humanised mouse models using patient-derived HSC 7. Assessment of genotoxicity, cellular toxicity and immunotoxicity of in vivo AAV-mediated base editing in a humanised mouse model	
Project details (check all that apply)	☒Patient contact required ☐Clinical Trial ☐Overseas attachment ☒Biosafety/Biocontainment required ☒Animal experiments	☒Laboratory work ☐Product development ☐Others (specify):

Neurology and Neuroscience

Title	**Neurobehavioral & structural MRI markers for Cognitive Impairment & Dementia**	
Main Supervisor	A/Prof Christopher Chen	
Email	phccclh@nus.edu.sg	
Conferring Institution	National University of Singapore	
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Main Supervisor	A/Prof Christopher Chen	
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Title	**The SINgapore GERiatric intervention study to reduce cognitive decline and physical frailty (SINGER) Study**	
Main Supervisor	A/Prof Christopher Chen	
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Conferring Institution	National University of Singapore	
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Obstetrics and Gynaecology

Title	**Integrated Women's Health Program (IWHP): Post-menopausal osteoporosis, fragility fractures and other critical issues facing mid-life Singaporean women.**
Main Supervisor	**Prof Yong Eu Leong** MBBS, FRCOG, PhD, Emeritus Consultant Department of Obstetrics & Gynaecology, National University of Singapore
Email & website	obgyel@nus.edu.sg • https://medicine.nus.edu.sg/researchers/yong-eu-leong/ • https://medicine.nus.edu.sg/obgyn/research/reproductive-development-biology-research-program/iwhp.html
Conferring Institution	NUS
Co-Supervisor(s)/ Institution	A/Prof Susan Logan, Obstetrics and Gynaecology, NUS Prof Michael Kramer, McGill University, Canada Prof Jane Cauley, University of Pittsburgh, USA Prof Inger Sundstrom, Uppsala University, Sweden
Abstract	**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, physical examinations, laboratory tests, and cutting-edge technologies and new measurement tools to probe and measure accurately the risk factors that affect the health of mid-life women. Data from this second round follow up 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. The final objective of IWHP is to pioneer innovative laboratory tests and novel assessments tools to probe and understand determinants and risk factors for adverse health, and devise strategies for healthful ageing in Singaporean women.
Skillsets to be acquired	Study design, Program Development, Regulatory compliance, Epidemiological Analytics, Biostatistics, Scientific writing, Development of novel assessment tools, Health care advocacy.
Project details (check all that apply)	☒Patient contact required ☐Clinical Trial ☒Overseas attachment ☐Biosafety/Biocontainment required ☐Animal experiments ☒Laboratory work ☒Product development ☐Others (specify):

Title	**Drug development program: Randomised control trials of the novel drug, *Epimedium*, for menopausal osteoporosis.**
Main Supervisor	**Prof Yong Eu Leong** MBBS, FRCOG, PhD, Emeritus Consultant Department of Obstetrics & Gynaecology, National University of Singapore
Email & website	obgyel@nus.edu.sg • https://medicine.nus.edu.sg/researchers/yong-eu-leong/ • https://medicine.nus.edu.sg/obgyn/research/reproductive-development-biology-research-program/nuclear-receptor-biology-and-drug-discovery.html
Conferring Institution	NUS
Co-Supervisor(s)/ Institution	A/Prof Susan Logan, Obstetrics and Gynaecology, NUS Dr. Tai Bee Choo, Biostatistics and Clinical trials, NUS
Abstract	Screening of bioactive compounds from Traditional Chinese Medicines have resulted in the isolation, characterization, and patenting of novel compounds that activate steroid/nuclear receptors and other TRAF6 signalling pathways to improve osteoblast and osteoclast cellular function. These compounds and their parent extracts have shown potential utility in menopause, bone health, metabolic disease, breast and prostate cancers. We have completed the necessary pre-clinical pharmacokinetic and pharmacodynamic studies in animal models to meet Singapore Health Sciences Authority regulatory requirements for human trials. We have completed Phase 1 pharmacokinetic studies and Phase 2 randomised control trials of the use of Epimedium drug for post-menopausal osteoporosis. Achievement of these planned Phase1/2 human studies set the stage for Phase 3 RCT to prove the efficacy fo the drug for menopausal osteoporosis. These studies will for the first time 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.
Skillsets to be acquired	Drug Development, GMP-production and quality controls; Clinical trial design, PK-PD analytics; patient recruitment and management, RCT execution and Regulatory compliance; Safety monitoring; Scientific writing, Working with drug companies, Product commercialization, sales planning and entrepreneurship.
Project details (check all that apply)	☒Patient contact required ☒Clinical Trial ☒Overseas attachment ☐Biosafety/Biocontainment required ☐Animal experiments ☒Laboratory work ☒Product development ☐Others (specify):

Title	**Myo-Inositol and Fetal Membrane Remodeling and Weakening**	
Main Supervisor	A/Prof Chan Shiao-Yng	
Email	obgchan@nus.edu.sg	
Conferring Institution	National University of Singapore	
Co-Supervisor(s)/ Institution	A/Prof Leo Hwa Liang, NUS Dr Oliver Watkins, NUS Dr Hannah Yong, A*STAR SICS	
Abstract	Preterm premature rupture of the fetal membranes (PPROM) is a pregnancy complication accounting for approximately one third of preterm births, which results in higher risk of infant mortality and morbidity. PPROM is preceded by programmed events that remodels fetal amnio-chorionic membranes, aiding in the weakening and ultimate rupture. This includes collagen modifications, apoptosis, inflammation, oxidative stress and senescence. Clinical trials of myo-inositol supplementation in pregnancy had reported reductions in preterm birth and PPROM. However, the mechanism involved is unknown. We hypothesised 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 – obtained from uncomplicated singleton pregnancies at term elective caesarean section – with different concentrations of myo-inositol. We will subsequently assess the markers of fetal membrane remodeling in the tissue and culture medium using various techniques such as QPCR, western blot, ELISA, gel zymography and senescence assay. In parallel, we will measure the tensile strength of the membranes and associate the biochemical changes induced by myo-inositol treatment with the weakening of the membranes. Additionally, to study the rescuing effect of myo-inositol, we will precondition fetal membranes with myo-inositol followed by treatment with known inducers of PPROM (i.e. tumor necrosis factor-α, thrombin and lipopolysaccharide) and perform similar assessment of remodeling markers and tensile strength. 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.	
Skillsets to be acquired	- Technical: Molecular biology, tissue culture, biomechanics, statistical analysis - Non-technical: Problem-solving, critical thinking, written and oral communication, project management	
Project details (check all that apply)	☐Patient contact required ☐Clinical Trial ☐Overseas attachment ☒Biosafety/Biocontainment required ☐Animal experiments	☒Laboratory work ☐Product development ☐Others (specify):

Title	**Using magnetic resonance imaging and spectroscopy to investigate the role of placental inositol in fetal growth regulation**	
Main Supervisor	A/Prof Chan Shiao-Yng	
Email	obgchan@nus.edu.sg	
Conferring Institution	National University of Singapore	
Co-Supervisor(s)/ Institution	Dr Sendhil Valan, A*STAR SICS Dr Oliver Watkins, NUS	
Abstract	Inositol is a highly bioactive carbohydrate involved in signalling, and glucose and lipid metabolism. The placenta is rich in inositols and acts as the gateway regulating supply of nutrients to the fetus. Hence placental function is a major determinant of fetal growth. Fetal growth disorders are associated with increased risks of later cardiometabolic disorders in offspring such as obesity and diabetes. Urinary inositol is increased in both large and small for gestational-age human newborns and in intrauterine growth restricted (IUGR) piglets. High placental inositol appears to protect the fetus from the pro-adipogenic effects of maternal glycaemia. Before inositol supplementation can be exploited as a potential intervention in fetal growth disorders, there is a need to understand how placental inositol may regulate fetal growth. Different inositol isomers and their highly diverse array of derivatives are known to have quite different bioactivities and some may also inhibit the bioactive effects of others. This project will use magnetic resonance imaging techniques to quantify and spatially localise inositol isomers and other metabolites within the whole placental organ, and within smaller biopsies of placenta and umbilical cord tissue. Results will be compared between placenta obtained from pregnancies of babies born small, normal, or large for gestational-age. Associations will also be made between placental inositol measures and in-utero fetal growth and with newborn birthweight. This will allow the unravelling of the metabolic networks involved in how inositols may impact placental function and fetal growth. These findings will then be corroborated using data from separate ongoing mother-offspring cohorts, where longer term offspring growth and metabolic data is available. In conclusion, this project will clarify the role of placental inositol in fetal growth regulation and will pave the way for development of inositol interventions for fetal growth disorders, which may ultimately mitigate the risk of future cardiovascular disorders.	
Skillsets to be acquired	- Technical: MRI, tissue handling, bioinformatics, statistical analysis - Non-technical: Problem-solving, critical thinking, written and oral communication, project management	
Project details (check all that apply)	☐Patient contact required ☐Clinical Trial ☐Overseas attachment ☒Biosafety/Biocontainment required ☐Animal experiments	☒Laboratory work ☐Product development ☐Others (specify):

Title	**Investigating the mechanistic role of the placenta in maternal-fetal transmission of mental health risk**	
Main Supervisor	A/Prof Chan Shiao-Yng	
Email	obgchan@nus.edu.sg	
Conferring Institution	National University of Singapore	
Co-Supervisor(s)/ Institution	Dr Hannah Yong, A*STAR SICS	
Abstract	Maternal mental health stresses during pregnancy, presenting as anxiety and depression, are associated with later offspring psychopathology, independent of postnatal maternal mental health status. Studies of Singaporean children demonstrate strong links between maternal antenatal depressive symptoms and differential brain microstructure around birth and childhood, which is associated with behavioural issues during infancy and increased vulnerability to conditions such as major depressive disorder in later life. 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, *in vitro* cultures for functional analysis and magnetic resonance imaging and spectroscopy to analyse placental structure and measure metabolites respectively. Understanding the precise mechanisms by which the effects of maternal mood are transmitted via the placenta to the fetus will generate novel knowledge critical for designing interventions that can minimise the risk of vertical transmission of mental health vulnerability, and improve long-term neurocognitive and behavioural outcomes of offspring, and ultimately optimising human potential and reducing societal costs of poor mental health.	
Skillsets to be acquired	- Technical: Molecular biology, cell/tissue culture, bioinformatics, statistical analysis - Non-technical: Problem-solving, critical thinking, written and oral communication, project management	
Project details (check all that apply)	☐Patient contact required ☐Clinical Trial ☐Overseas attachment ☒Biosafety/Biocontainment required ☐Animal experiments	☒Laboratory work ☐Product development ☐Others (specify):

Title	**Preconception health of couples – a paradigm shift to improving maternal and child health at the general population level**	
Main Supervisor	A/Prof Chan Shiao-Yng	
Email	obgchan@nus.edu.sg	
Conferring Institution	National University of Singapore	
Co-Supervisor(s)/ Institution	Dr Huang Zhongwei NUHS/IMCB	
Abstract	Singapore is facing the perennial challenge of low total fertility rates with year-on-year decline to the lowest in 2021 at 1.10. This is also attributable to lower fecundity and poorer reproductive outcomes in women of advancing maternal age. Furthermore, rising rates of obesity and suboptimal metabolic health in mothers are impacting adversely on the short- and long-term health of their children, contributing to the increasing prevalence of medical conditions such as diabetes and cardiovascular disease. The majority of couples planning pregnancy in Singapore are not aware of this and many do not perceived themselves to have risk factors for any adverse reproductive outcomes. Thus, a novel model of integrated and multidisciplinary care for all couples planning pregnancy commencing from preconception stage and seamlessly progressing into prenatal, antenatal, and postpartum care in addition to the creation and maintenance of a large, curated database capturing longitudinal health outcomes of women and children can be set on a path for continuous improvement of health services to enhance health outcomes. This will result in the development of a fully-integrated mobile application customised to local women planning pregnancy, facilitate research into the refinement and benefits of preconception care for short and long term maternal and offspring outcomes, as well as research into the health economics of care, efficacy, and cost-effectiveness to develop new evidence-based recommendations for improved preconception care to optimize maternal and child health. The proposed PhD will set out to evaluate the development, utility, acceptability, and effectiveness of this novel model of care in the real-world setting using established methods in implementation research.	
Skillsets to be acquired	Health Services Research Large data management and analytics Epidemiological principles and concepts Reproductive Biology and Fertility Sciences Health Education Public Health Translational Research in Clinical Sciences Clinical Study Design Clinical Trial Design	
Project details (check all that apply)	☒Patient contact required ☒Clinical Trial ☐Overseas attachment ☐Biosafety/Biocontainment required ☐Animal experiments	☒Laboratory work ☐Product development ☒Others (specify): Surveys/Questionnaires design Large data management and analytics

Oncology

Title	**The Epigenetic differentiation of viral and non-viral hepatocellular carcinoma**	
Main Supervisor	Professor Pierce Chow	
Email	Pierce.chow@duke-nus.edu.sg	
Conferring Institution	PhD Program in Clinical and Translational Science, Duke-NUS Medical School Singapore	
Co-Supervisor(s)/ Institution	N.A	
Abstract	While viral-related HCC (hepatis B and hepatitis C related) is dominant, the rapid increase in the prevalence of metabolic liver disease has brought about a significant increase in the number of non-viral related HCC. Our current research conducted under the aegis of the NMRC Translational-Clinical Research (TCR) Program in Liver Cancer has shown that the metabolome of viral-related and non-viral related HCC differ significantly. Epigenetic examination of patient-derived tissue samples carried out in our program (High-C, ChpSeq) suggest that the main drivers of HCC and especially non-viral HCC may be epigenetic in origin.	
Skillsets to be acquired	Wet bench skills pertaining to the preparation of samples and the precipitation of histones. Interpretation of epigenomics data. Experience in the management of a clinical cohort study including patient selection, enrolment and follow-up.	
Project details (check all that apply)	☒Patient contact required ☐Clinical Trial ☐Overseas attachment ☒Biosafety/Biocontainment required ☐Animal experiments	☒Laboratory work ☐Product development ☒Others (specify): clinical research

Oncology

Title	**Understanding Tumour Predisposition in Asia**
Main Supervisor	Joanne Ngeow
Email	Joanne.ngeow@ntu.edu.sg
Conferring Institution	LKC Medicine
Co-Supervisor(s)/ Institution	Depends on the project specifics
Abstract	The optimal manner of achieving seamless translational cancer research is on a single platform of research, clinical care and education. One such platform can be characterized as clinical cancer genetics translational research, which involves the utilization of nucleic acid-based technologies to identify, characterize and understand genes which cause susceptibility to traditional and complex heritable cancer syndromes, to determine their role in sporadic carcinogenesis and to perform molecular epidemiologic analyses as they might relate to future clinical applications. . Our program focuses on understanding tumor predisposition in Asia. At present, we have characterized the germline mutation spectrum in Singapore for breast, ovarian and endometrial cancers as well as for sarcomas. This information has been used to guide clinical guidelines and policy. We are particularly interested in systematically drawing out genomic and biological similarities and parallels amongst various disease processes. Thus, commonalities of processes and fundamental understanding from cancer research can be utilized and extended to other diseases beyond heritable cancer syndromes. Ongoing available PhD projects include : 1) Genetics of childhood cancers 2) Genetics of sarcomas and other rare cancers 3) Genetics of endocrine-related cancers 4) Implementation of genomic medicine into routine clinical care 5) Health economics of genetic testing in the Singapore context 6) Understanding genetic testing decision-making in Asia 7) Genetics of telomere biology disorders and early aging 8) Genetics of polyposis 9) Others : non-cancer genomic medicine projects – email to discuss
Skillsets to be acquired	Broadly, the student will learn Genomic Medicine and Next generation sequencing Our research program span translational, clinical and health services research. Skillsets to be acquired will depend on the specifics of the project and is usually tailored to the student's interest. Some students will elect to do a project that is based at the bench while others may choose a more clinically oriented project and learn qualitative research skills. Research focus for the team include : (1) Functional genomics, (2) Cancer epidemiology, (3) Genetic epidemiology, (4) Health Services Research – qualitative studies and economic evaluation, (5) Clinical trials. Students will be expected to spend time with the clinical team weekly case discussions.
Project details (check all that apply)	☒Patient contact required ☒Clinical Trial ☒Overseas attachment ☐Biosafety/Biocontainment required ☐Animal experiments ☒Laboratory work ☐Product development ☐Others (specify):

Ophthalmology

Title	**Retinal markers for Cognitive Impairment and Dementia**	
Main Supervisor	A/Prof Christopher Chen	
Email	phccclh@nus.edu.sg	
Conferring Institution	National University of Singapore	
Co-Supervisor(s)/ Institution	Prof L Schmetterer, Prof TY Wong, Prof D Milea and Dr J Chua (Singapore Eye Research Institute), A.Prof Carol Cheung (Chinese University of Hong Kong)	
Abstract	The Memory Aging and Cognition Centre (MACC) is a multi-disciplinary research programme with extensive Singaporean and global collaborations. It aims to investigate and provide novel insights into the risk factors and biomarkers for cognitive decline and dementia that may lead to potential therapies. We imagine a future where cognitive decline and dementia can be prevented and treated. It is our mission to translate our research into productive interventions which promote healthy memory and healthy ageing in Singapore. More details on our projects are available on http://www.macc.sg/MACC-Projects-Clinical-Studies-Memory-Clinical-Trials The specific aims of this project funded by a Singapore Translational Research (STAR) Investigator Award are : 1. To determine the relationship of existing (retinal vasculature, Optical Coherence Tomography (OCT), OCT-Angiography) and novel (Doppler OCT, pupilometry, hyperspectral OCT) retinal imaging measures over time to progression and development of vascular cognitive impairment and other imaging markers of dementia, with a goal to determine the potential diagnostic and prognostic value of retinal imaging. We hypothesise that as multiple cross-sectional studies have consistently demonstrated the association of retinal imaging biomarkers and dementia, retinal imaging biomarkers will be predictive of the incidence and progression of dementia. 2. The creation of an international big data consortium, AIDA (Artificial Intelligence for Dementia Assessment) to evaluate retinal imaging markers of dementia. Using datasets from multiple institutions around the world and through the integration of deep learning, we hypothesize that we will be able to further improve the sensitivity and specificity of retinal imaging biomarkers to detect dementia.	
Skillsets to be acquired	Experience of conducting a large longitudinal study focusing on biomarkers for cognitive impairment and dementia. Understanding and analysis of a) cognitive and neurobehavioural data, b) retinal and brain imaging, c) Artificial Intelligence, d) international collaborations	
Project details (check all that apply)	☒Patient contact required ☐Clinical Trial ☐Overseas attachment ☐Biosafety/Biocontainment required ☐Animal experiments	☒Laboratory work ☐Product development ☒Others (specify): Neuropsychology. MRI analysis

Pathology

Title	**Blood markers for Cognitive Impairment and Dementia**	
Main Supervisor	A/Prof Christopher Chen	
Email	phccclh@nus.edu.sg	
Conferring Institution	National University of Singapore	
Co-Supervisor(s)/ Institution	Dr Mitchell Lai, Dr C Drum, Prof B Kennedy, Prof B Halliwell (NUS)	
Abstract	The Memory Aging and Cognition Centre (MACC) is a multi-disciplinary research programme with extensive Singaporean and global collaborations. It aims to investigate and provide novel insights into the risk factors and biomarkers for cognitive decline and dementia that may lead to potential therapies. We imagine a future where cognitive decline and dementia can be prevented and treated. It is our mission to translate our research into productive interventions which promote healthy memory and healthy ageing in Singapore. More details on our projects are available on http://www.macc.sg/MACC-Projects-Clinical-Studies-Memory-Clinical-Trials 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, including oxidative stress, vascular disease and neurodegeneration, could identify individuals with high disease risk. Specifically, that a) blood-based biomarkers of neurodegeneration and oxidative stress are predictive of incident development of cerebrovascular disease in parallel with cognitive decline; b) While providing additional information on the tissue origins and thus a more direct link to the brain pathology, neural- or endothelial-specific extracellular vesicle biomarkers are more sensitive than neat plasma biomarkers in diagnosing and prognosing for cognitive impairment and CeVD; c) A combination of multiple biomarkers affiliated to the different pathophysiological pathways adds value to the diagnostic and prognostic performance of single blood-based biomarkers and predict future disease progression of cognitive impairment and CeVD.	
Skillsets to be acquired	Experience of conducting a large longitudinal study focusing on biomarkers for cognitive impairment and dementia. Understanding and analysis of a) cognitive and neurobehavioural data, b) brain imaging, c) blood biomarkers d) international collaborations	
Project details (check all that apply)	☒Patient contact required ☐Clinical Trial ☐Overseas attachment ☐Biosafety/Biocontainment required ☐Animal experiments	☒Laboratory work ☐Product development ☒Others (specify): Neuropsychology. MRI analysis

Psychiatry

Title	**Investigating the mechanistic role of the placenta in maternal-fetal transmission of mental health risk**	
Main Supervisor	A/Prof Chan Shiao-Yng	
Email	obgchan@nus.edu.sg	
Conferring Institution	National University of Singapore	
Co-Supervisor(s)/ Institution	Dr Hannah Yong, A*STAR SICS	
Abstract	Maternal mental health stresses during pregnancy, presenting as anxiety and depression, are associated with later offspring psychopathology, independent of postnatal maternal mental health status. Studies of Singaporean children demonstrate strong links between maternal antenatal depressive symptoms and differential brain microstructure around birth and childhood, which is associated with behavioural issues during infancy and increased vulnerability to conditions such as major depressive disorder in later life. 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, *in vitro* cultures for functional analysis and magnetic resonance imaging and spectroscopy to analyse placental structure and measure metabolites respectively. Understanding the precise mechanisms by which the effects of maternal mood are transmitted via the placenta to the fetus will generate novel knowledge critical for designing interventions that can minimise the risk of vertical transmission of mental health vulnerability, and improve long-term neurocognitive and behavioural outcomes of offspring, and ultimately optimising human potential and reducing societal costs of poor mental health.	
Skillsets to be acquired	• Technical: Molecular biology, cell/tissue culture, bioinformatics, statistical analysis • Non-technical: Problem-solving, critical thinking, written and oral communication, project management	
Project details (check all that apply)	☐Patient contact required ☐Clinical Trial ☐Overseas attachment ☒Biosafety/Biocontainment required ☐Animal experiments	☒Laboratory work ☐Product development ☐Others (specify):

Radiology

Title	**Neurobehavioral & structural MRI markers for Cognitive Impairment & Dementia**	
Main Supervisor	A/Prof Christopher Chen	
Email	phccclh@nus.edu.sg	
Conferring Institution	National University of Singapore	
Co-Supervisor(s)/ Institution	Dr Saima Hilal (Saw Swee Hock School of Public Health, NUS)	
Abstract	The Memory Aging and Cognition Centre (MACC) is a multi-disciplinary research programme with extensive Singaporean and global collaborations. It aims to investigate and provide novel insights into the risk factors and biomarkers for cognitive decline and dementia that may lead to potential therapies. We imagine a future where cognitive decline and dementia can be prevented and treated. It is our mission to translate our research into productive interventions which promote healthy memory and healthy ageing in Singapore. More details on our projects are available on http://www.macc.sg/MACC-Projects-Clinical-Studies-Memory-Clinical-Trials 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 changes in structural and functional MRI, retinal vascular and retinal neuronal markers as well as blood-based vascular and neurodegenerative markers, and neurobehavioural markers are associated with poorer cognitive performance on follow-up visits 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 above and beyond the utility of currently used predictors. 2. To examine how the syndrome of Mild Behavioural Impairment (MBI) is influenced by the independent and interactive effects of MRI, retinal and blood biomarkers. We hypothesise that : a) Severity of cerebrovascular disease and neurodegeneration, structural and functional connectivity disruptions and reduced cerebral perfusion on MRI are associated with MBI; b) Retinal vascular and neuronal markers are associated with MBI; c) Altered levels of blood-based vascular and neuro-degenerative markers (for example, higher levels of cytokines, p-tau and β-amyloid) are associated with MBI; d) Interaction between the above mentioned biomarkers influence MBI and NPS.	
Skillsets to be acquired	Experience of conducting a large longitudinal study focusing on biomarkers for cognitive impairment and dementia. Understanding and analysis of a) cognitive and neurobehavioural data, b) structural and functional MRI, c) retinal imaging, d) blood biomarkers.	
Project details (check all that apply)	☒Patient contact required ☐Clinical Trial ☐Overseas attachment ☐Biosafety/Biocontainment required ☐Animal experiments	☒Laboratory work ☐Product development ☒Others (specify): Neuropsychology. MRI analysis

Title	**Multimodal MRI-based network breakdown and progression prediction in Cognitive Impairment and Dementia**	
Main Supervisor	A/Prof Christopher Chen	
Email	phccclh@nus.edu.sg	
Conferring Institution	National University of Singapore	
Co-Supervisor(s)/ Institution	A/Prof J Zhou (Centre for Translational MR Research, NUS) A/Prof T Yeo (Centre for Translational MR Research, NUS)	
Abstract	The Memory Aging and Cognition Centre (MACC) is a multi-disciplinary research programme with extensive Singaporean and global collaborations. It aims to investigate and provide novel insights into the risk factors and biomarkers for cognitive decline and dementia that may lead to potential therapies. We imagine a future where cognitive decline and dementia can be prevented and treated. It is our mission to translate our research into productive interventions which promote healthy memory and healthy ageing in Singapore. More details on our projects are available on http://www.macc.sg/MACC-Projects-Clinical-Studies-Memory-Clinical-Trials The specific aims of this project funded by a Singapore Translational Research (STAR) Investigator Award are : 1. To examine longitudinal brain network breakdown and microstructural changes using multimodal MR imaging and evaluate their interactions with Alzheimer's Disease (AD) & cerebrovascular disease (CeVD) pathology and contribution to cognitive and behavioural decline in patients with no, mild cognitive impairment (MCI) and dementia. The hypotheses are : a) Plasma amyloid-β and tau are related to specific brain functional and structural network breakdown leading to cognitive decline and behavioral problems; b) The effect of structural/functional network changes and atrophy on cognitive performance and behavioural problems is network-specific and disease stage-dependent and modulated by CeVD markers c) MCI with CeVD would have less typical AD-type brain structural and functional connectivity changes compared to MCI without CeVD. Furthermore, with both CeVD and AD pathology, individuals with no or mild cognitive impairment would have an accelerated trajectory of downstream neurodegeneration and cognitive decline. 2. To build a large international longitudinal database comprising local and international imaging neurobehavioural data to develop AI algorithms for predicting dementia risk and progression. The hypotheses are : a) We hypothesize that deep learning can be used to harmonize imaging and neurobehavioural data across multiple sites; b) By pooling harmonized data across multiple sites, the larger sample size will dramatically improve prediction of future cognitive decline and clinical outcomes.	
Skillsets to be acquired	Experience of conducting a large longitudinal study focusing on biomarkers for cognitive impairment and dementia. Understanding and analysis of a) cognitive and neurobehavioural data, b) quantitative and functional MRI, c) Artificial Intelligence, d) international collaborations	
Project details (check all that apply)	☒Patient contact required ☐Clinical Trial ☐Overseas attachment ☐Biosafety/Biocontainment required ☐Animal experiments	☒Laboratory work ☐Product development ☒Others (specify): Neuropsychology. MRI analysis

Title	**The SINgapore GERiatric intervention study to reduce cognitive decline and physical frailty (SINGER) Study**	
Main Supervisor	A/Prof Christopher Chen	
Email	phccclh@nus.edu.sg	
Conferring Institution	National University of Singapore	
Co-Supervisor(s)/ Institution	Prof A Maier (NUS) , A/Prof J Zhou (NUS), Dr M Lai (NUS)	
Abstract	The Memory Aging and Cognition Centre (MACC) is a multi-disciplinary research programme with extensive Singaporean and global collaborations. It aims to investigate and provide novel insights into the risk factors and biomarkers for cognitive decline and dementia that may lead to potential therapies. We imagine a future where cognitive decline and dementia can be prevented and treated. It is our mission to translate our research into productive interventions which promote healthy memory and healthy ageing in Singapore. More details on our projects are available on http://www.macc.sg/MACC-Projects-Clinical-Studies-Memory-Clinical-Trials The specific aims of this project funded by a Large Collaborative Grant are : 1. To investigate novel interventions for vascular cognitive impairment (VCI). The WHO Guidelines on risk reduction of cognitive decline and dementia provide evidence-based recommendations on lifestyle behaviours and interventions to delay or prevent cognitive decline and dementia. However, how best to implement such interventions and importantly whether a multi domain lifestyle intervention is effective, safe and globally feasible remain important research topics. Hence we propose to conduct a large community-based innovative trial as part of the World Wide FINGERS interdisciplinary network for the prevention of cognitive impairment or dementia The trial will recruit 1200 subjects at high risk to develop cognitive impairment and dementia. The main goal is to determine the efficacy and safety of multimodal lifestyle interventions together with intensive blood pressure lowering. We hypothesize that these interventions will reduce cognitive decline and severity of cerebrovascular disease (CeVD) and other VCI biomarkers. 2. To examine how CeVD, tau, and amyloid impact longitudinal brain structural and functional 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, reflecting complex underlying disease interactions that will be revealed in a longitudinal study. 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.	
Skillsets to be acquired	Experience of conducting a large clinical trual focusing on biomarkers for cognitive impairment and dementia. Understanding and analysis of a) cognitive and neurobehavioural data, b) structural and functional MRI, c) retinal imaging, d) blood biomarkers.	
Project details (check all that apply)	☒Patient contact required ☒Clinical Trial ☐Overseas attachment ☐Biosafety/Biocontainment required ☐Animal experiments	☒Laboratory work ☐Product development ☒Others (specify): Neuropsychology. MRI analysis

Title	**Using magnetic resonance imaging and spectroscopy to investigate the role of placental inositol in fetal growth regulation**	
Main Supervisor	A/Prof Chan Shiao-Yng	
Email	obgchan@nus.edu.sg	
Conferring Institution	National University of Singapore	
Co-Supervisor(s)/ Institution	Dr Sendhil Valan, A*STAR SICS Dr Oliver Watkins, NUS	
Abstract	Inositol is a highly bioactive carbohydrate involved in signalling, and glucose and lipid metabolism. The placenta is rich in inositols and acts as the gateway regulating supply of nutrients to the fetus. Hence placental function is a major determinant of fetal growth. Fetal growth disorders are associated with increased risks of later cardiometabolic disorders in offspring such as obesity and diabetes. Urinary inositol is increased in both large and small for gestational-age human newborns and in intrauterine growth restricted (IUGR) piglets. High placental inositol appears to protect the fetus from the pro-adipogenic effects of maternal glycaemia. Before inositol supplementation can be exploited as a potential intervention in fetal growth disorders, there is a need to understand how placental inositol may regulate fetal growth. Different inositol isomers and their highly diverse array of derivatives are known to have quite different bioactivities and some may also inhibit the bioactive effects of others. This project will use magnetic resonance imaging techniques to quantify and spatially localise inositol isomers and other metabolites within the whole placental organ, and within smaller biopsies of placenta and umbilical cord tissue. Results will be compared between placenta obtained from pregnancies of babies born small, normal, or large for gestational-age. Associations will also be made between placental inositol measures and in-utero fetal growth and with newborn birthweight. This will allow the unravelling of the metabolic networks involved in how inositols may impact placental function and fetal growth. These findings will then be corroborated using data from separate ongoing mother-offspring cohorts, where longer term offspring growth and metabolic data is available. In conclusion, this project will clarify the role of placental inositol in fetal growth regulation and will pave the way for development of inositol interventions for fetal growth disorders, which may ultimately mitigate the risk of future cardiovascular disorders.	
Skillsets to be acquired	• Technical: MRI, tissue handling, bioinformatics, statistical analysis • Non-technical: Problem-solving, critical thinking, written and oral communication, project management	
Project details (check all that apply)	☐Patient contact required ☐Clinical Trial ☐Overseas attachment ☒Biosafety/Biocontainment required ☐Animal experiments	☒Laboratory work ☐Product development ☐Others (specify):

Cross-Discipline

Cross-Discipline

Title	***In vivo* Adeno-Associated Viral vector-mediated Base-Editing of Haemopoetic Stem Cells to correct β-Thalassaemia Major**
Main Supervisor	AP Citra NZ Mattar (Dept O&G)
Email	citramattar@nus.edu.sg
Conferring Institution	NUS Medicine, Department of O&G
Co-Supervisor(s)/ Institution	Dr Rufaihah Abdul Jalil NUS Medicine, Department of Surgery
Abstract	Major β-thalassaemia impacts significantly on medico-economic resources particularly in populations with high carrier prevalence. This global disease causes 3-4% of early-childhood deaths annually, with severe chronic morbidity arising from progressive disease and inadequate treatment. There is still no universal, affordable and curative treatment for those without a matched HSC donor. Current ex-vivo gene therapy trials are extremely costly and risk myeloablation complications. We investigate in-vivo AAV-mediated base-editing to correct the commonest single nucleotide variant causing transfusion-dependent thalassaemia (TDT) in a proof-of-concept study utilizing personalised humanized mice produced with patient-derived HSC, testing the hypothesis that optimized AAV-mediated delivery of base-editing tools can efficiently correct the IVS1-5(G>C) mutation, the most prevalent in Asian populations. The specific aims of this project are: **(1)** produce an efficient base-editing strategy for *in vivo* correction of the IVS1-5 (G>C) mutation in engineered human HSC, **(2)** optimise AAV-transduction of human HSC in vitro and *in vivo* using a humanised mouse model, and **(3)** assess phenotype correction, safety and efficacy of *in vivo* AAV-mediated base-edited gene correction in a humanized mouse model for β-thalassaemia. **Potential Application:** In this era of precision and personalized medicine, gene modification therapies work where conventional HSCT does not, but the current ex vivo approaches employed in clinical trials are extremely costly and impose a high medical burden (e.g. complications of myeloablation). Base editing can be adapted readily to correct individual single nucleotide variants causing the majority of β-thalassaemias, and with a safer optimized AAV-mediated delivery, a single-dose in vivo treatment strategy can be planned which will circumvent the obstacles of ex vivo gene therapies. This novel and innovative study can expedite clinical trials and provide an urgently-needed treatment potentially more accessible and cost-effective than current standards, poised to make substantial global impact.
Skillsets to be acquired	8. Haemopoetic stem cell culture, expansion and transduction with AAV 9. Optimisation of HSC transduction with clinical AAV vectors 10. Design base editing strategies using AAV to deliver gRNA and DNA template 11. Targeted deep sequencing to assess correct editing, off-target mutations, indels 12. Haemopoetic programming of iPSC 13. In vivo base editing proof of principal experiments in humanised mouse models using patient-derived HSC 14. Assessment of genotoxicity, cellular toxicity and immunotoxicity of in vivo AAV-mediated base editing in a humanised mouse model
Project details (check all that apply)	☒Patient contact required ☐Clinical Trial ☐Overseas attachment ☒Biosafety/Biocontainment required ☒Animal experiments ☒Laboratory work ☐Product development ☐Others (specify):

Cross-Discipline

Title	**Understanding Tumour Predisposition in Asia**
Main Supervisor	Joanne Ngeow
Email	Joanne.ngeow@ntu.edu.sg
Conferring Institution	LKC Medicine
Co-Supervisor(s)/ Institution	Depends on the project specifics
Abstract	The optimal manner of achieving seamless translational cancer research is on a single platform of research, clinical care and education. One such platform can be characterized as clinical cancer genetics translational research, which involves the utilization of nucleic acid-based technologies to identify, characterize and understand genes which cause susceptibility to traditional and complex heritable cancer syndromes, to determine their role in sporadic carcinogenesis and to perform molecular epidemiologic analyses as they might relate to future clinical applications. . Our program focuses on understanding tumor predisposition in Asia. At present, we have characterized the germline mutation spectrum in Singapore for breast, ovarian and endometrial cancers as well as for sarcomas. This information has been used to guide clinical guidelines and policy. We are particularly interested in systematically drawing out genomic and biological similarities and parallels amongst various disease processes. Thus, commonalities of processes and fundamental understanding from cancer research can be utilized and extended to other diseases beyond heritable cancer syndromes. Ongoing available PhD projects include : 1) Genetics of childhood cancers 2) Genetics of sarcomas and other rare cancers 3) Genetics of endocrine-related cancers 4) Implementation of genomic medicine into routine clinical care 5) Health economics of genetic testing in the Singapore context 6) Understanding genetic testing decision-making in Asia 7) Genetics of telomere biology disorders and early aging 8) Genetics of polyposis 9) Others : non-cancer genomic medicine projects – email to discuss
Skillsets to be acquired	Broadly, the student will learn Genomic Medicine and Next generation sequencing Our research program span translational, clinical and health services research. Skillsets to be acquired will depend on the specifics of the project and is usually tailored to the student's interest. Some students will elect to do a project that is based at the bench while others may choose a more clinically oriented project and learn qualitative research skills. Research focus for the team include : (1) Functional genomics, (2) Cancer epidemiology, (3) Genetic epidemiology, (4) Health Services Research – qualitative studies and economic evaluation, (5) Clinical trials. Students will be expected to spend time with the clinical team weekly case discussions.
Project details (check all that apply)	☒Patient contact required ☒Clinical Trial ☒Overseas attachment ☐Biosafety/Biocontainment required ☐Animal experiments ☒Laboratory work ☐Product development ☐Others (specify):

End