

CSC-NZ CRCC Joint Funding Programme 2019-20

Summary of NCD research proposals and supervisors

Reference	Proposal title	Supervisor(s)
University of Auckland		
NCD, 2020-01	In silico modelling for fatty livers	Dr Harvey Ho harvey.ho@auckland.ac.nz Dr Chris Bradley
NCD, 2020-02	Mechanisms of heart disease in diabetes	Dr Kim Mellor k.mellor@auckland.ac.nz
NCD, 2020-03	Precision medicine for type 2 diabetes	A/Prof Rinki Murphy r.murphy@auckland.ac.nz
NCD, 2020-04	Application of Machine Learning to Aid Cardiac Diagnosis and Treatment	Dr Jichao Zhao j.zhao@auckland.ac.nz
NCD, 2020-05	Ionic basis of cardiac arrhythmogenesis in metabolic syndrome: A computer modelling analysis	Dr Jichao Zhao j.zhao@auckland.ac.nz
NCD, 2020-06	The roles of traditional Chinese medicine (TCM) practitioners and their patients in enhancing safety monitoring for TCMs in New Zealand	A/Prof Jo Barnes j.barnes@auckland.ac.nz
NCD, 2020-07	An overlooked opportunity in treating cardiovascular disease by restoring heart rate variability	Dr June Chiew Han j.han@auckland.ac.nz Dr Kenneth Tran k.tran@auckland.ac.nz A/Prof Andrew Taberner a.taberner@auckland.ac.nz
NCD, 2020-08	Using big data to estimate the prevalence of dementia in New Zealand	Dr Sarah Cullum sarah.cullum@auckland.ac.nz

Auckland University of Technology		
NCD, 2020-09	Novel Approach for Her2×Her3 Bispecific Antibody-Drug Conjugate Targeting Breast Cancer	A/Prof Jun Lu jun.lu@aut.ac.nz
NCD, 2020-10	New Zealand Surf Clam extracts for the prevention and control of diabetes and its joint pain complication	A/Prof Jun Lu jun.lu@aut.ac.nz
University of Otago		
NCD, 2020-11	Finding neural biomarkers of depression through machine-learning big EEG data	A/Prof Zhiyi Huang hzy@cs.otago.ac.nz
NCD, 2020-12	Stress responses in the diabetic heart: Effects of exercise training and glycemic control	Dr. J. Chris Baldi chris.baldi@otago.ac.nz
NCD, 2020-13	Development of synthetic miRNAs that target PAX2 for cancer therapy	Professor Michael Eccles michael.eccles@otago.ac.nz
NCD, 2020-14	Non-Pharmacological Modulation of the Autonomic Nervous System and the Neuroendocrine System to Complement Inflammation and Healing	A/Prof Steve Tumilty steve.tumilty@otago.ac.nz Professor G David Baxter Dr Lizhou Liu
NCD, 2020-15	Traditional Chinese Medicine based powder for lung diseases	Dr Shyamal Das shyamal.das@otago.ac.nz
NCD, 2020-16	Tumour-Targeted Bioorthogonal Prodrug Activation	Dr Allan Gamble allan.gamble@otago.ac.nz Professor Sarah Hook
NCD, 2020-17	Nanomedicines for oral delivery of <i>Sonchus oleraceus</i> antioxidants	A/Prof Arlene McDowell arlene.mcdowell@otago.ac.nz
NCD, 2020-18	Chemical tools to study cannabinoid receptors	Dr Andrea Vernall andrea.vernall@otago.ac.nz
NCD, 2020-19	Trans-ancestral dissection of genetic architecture of abdominal aortic aneurysm AAA	Dr Wen-Hua WEI wenhua.wei@otago.ac.nz Professor Greg JONES greg.jones@otago.ac.nz Professor Jie DU
NCD, 2020-20	Arginine metabolism and Alzheimer's disease and psychosis	A/Prof Ping Liu ping.liu@otago.ac.nz
NCD, 2020-21	Develop genetic epidemiology biomarkers to enhance early identification of children at risk of reading disabilities	Dr Wen-Hua WEI wenhua.wei@otago.ac.nz Dr Hunter HATFIELD hunter.hatfield@otago.ac.nz Professor Ranran SONG

2020-01: In silico modelling for fatty livers 脂肪肝的电脑模拟

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Project outline	<p>Non-alcoholic fatty liver disease (NAFLD) affects 25-30% of the population in developed countries. Marked by excess triglyceride deposits in hepatocytes, NAFLD and its severe inflammatory subtype non-alcoholic steatohepatitis (NASH) are associated with diabetes, leading to cirrhosis and carcinoma. The epidemic increase of NAFLD requires a deeper understanding of the regulatory mechanisms controlling the response of liver metabolism to nutritional challenges and medical drugs. Evidences from imaging data show that the distribution of lipids in fatty livers is uneven in liver lobules, the functioning units of the liver. A recent Nature letter details the proteomic difference in hepatocytes located at the peri-portal and peri-central regions of liver lobules [1]. Since in vivo studies of human liver metabolism are encumbered with ethical and technical issues, in silico approaches, including the one recently published in Nature Communications [2], use computational/mathematical modelling to simulate the central liver metabolism including the regulation of enzyme activities and their spatial heterogeneity.</p> <p>The aim of this study is to analyse these recent developments in NAFLD research, and to utilise the computational tools available from the Auckland Bioengineering Institute (OpenCMISS, CellML, etc) to curate, simulate the spatial distribution of lipids in lobules and the whole liver, and their treatment.</p>
References	<p>[1] K. B. Halpern <i>et al.</i>, "Single-cell spatial reconstruction reveals global division of labour in the mammalian liver," <i>Nature</i>, vol. 542, no. 7641, pp. 352–356, Feb. 2017.</p> <p>[2] N. Berndt <i>et al.</i>, "HEPATOKIN1 is a biochemistry-based model of liver metabolism for applications in medicine and pharmacology," <i>Nat Commun</i>, vol. 9, no. 1, pp. 1–12, Jun. 2018.</p>
NCD CRCC priority area	Diabetes and obesity

2020-02: Mechanisms of heart disease in diabetes

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Project outline	<p>More than 80% of diabetic patients have heart failure, and it is clear that heart abnormalities in diabetic patients are distinctive from those observed in non-diabetes – and a specific treatment is urgently required. Our studies suggest that disturbed metabolism of sugars (glucose and fructose) may be a key instigator of heart damage in diabetes. The goal of this project is to fully characterize the metabolic disturbance related to diabetes-induced heart injury and test novel interventions to rescue heart dysfunction in diabetes.</p> <p>The successful candidate will learn state-of-the-art techniques in molecular biology, in vivo cardiac function and in vitro characterisation of metabolic pathways.</p>
References	<ul style="list-style-type: none"> • Molecular mechanisms of cardiac pathology in diabetes - Experimental insights. Varma U, Koutsifeli P, Benson VL, Mellor KM, Delbridge LMD. Biochim Biophys Acta Mol Basis Dis. 2018 May;1864(5 Pt B):1949-1959. • Diabetic Cardiomyopathy: The Case for a Role of Fructose in Disease Etiology. Delbridge LM, Benson VL, Ritchie RH, Mellor KM. Diabetes. 2016 Dec;65(12):3521-3528. • Myocardial stress and autophagy: mechanisms and potential therapies. Delbridge LMD, Mellor KM, Taylor DJ, Gottlieb RA. Nat Rev Cardiol. 2017 Jul;14(7):412-425. <p>Myocardial glycogen dynamics: new perspectives on disease mechanisms. Chandramouli C, Varma U, Stevens EM, Xiao RP, Stapleton DI, Mellor KM, Delbridge LM. Clin Exp Pharmacol Physiol. 2015 Apr;42(4):415-25.</p>
NCD CRCC priority area	<p>Cardiovascular diseases</p> <p>Diabetes & obesity</p>

2020-03: Precision medicine for type 2 diabetes

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Project outline	<p>This study hopes to identify precision medicine approaches for type 2 diabetes (T2D) in the NZ population. We will use a retrospective study design using a cohort of 1000 people with diabetes who have already had genetic analysis and consented for their medical records to be used for the purposes of investigating how their diabetes medication response links with their genetics and other clinical characteristics such as lipids, age, gender. We will also use a prospective study design where we will recruit another 200 people with prediabetes or diet-controlled T2D. After a baseline evaluation, we will ask them to take 3 different oral diabetes medications (single dose or for 3 days) followed by an oral glucose tolerance in turn, to see whether the glucose lowering responses to each of these medications differs by genetics, body composition, lipids, age and gender. Genetic variants will include CREBRF gene which is of particular relevance to those of Pacific ancestry.</p> <p>Potential research partner in China is with Prof Guang Ning at Ruijin Hospital</p>
References	https://link.springer.com/article/10.1007/s00125-018-4623-1 https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=376427
NCD CRCC priority area	Diabetes, obesity, gene-environment interactions and big data

2020-04: Application of Machine Learning to Aid Cardiac Diagnosis and Treatment

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Project outline	<p>Atrial fibrillation (AF) is the most common sustained heart rhythm disturbance (arrhythmia). At present, 25% of the world population aged 40 and above will experience AF in their lifetime. Furthermore, as a result of the aging population and the increasing incidence of heart failure, the prevalence of AF is projected to more than double in the following few decades, becoming a global epidemic. AF leads to a multi-fold increased risk of heart failure and stroke and is a primary cause of hospitalizations. However, the current treatment of AF remains suboptimal.</p> <p>Our team at Auckland Bioengineering Institute (ABI) aims to improve our understanding of AF, and to investigate effective strategies for AF treatment by combining novel computational approaches (signal/structural analysis, computer models and machine learning) with structural imaging, experimental mapping and clinical studies.</p> <p>The specific research that I want to bring to your attention is our recent collaboration with Dr Haojie Li (李浩杰) in Beijing Fuwai Hospital, China. Beijing Fuwai Hospital is a first-class hospital in China, specializing in cardiovascular diseases. They treat ~100, 000 patients with heart rhythm diseases annually. Dr. Li, a cardiology consultant in Fuwai Hospital will provide access to the precious clinical data from his hospital, as well as his clinical expertise. Dr Zhao's team at ABI has extensive expertise and experience in machine learning and big data analysis. The large-scale clinical dataset including patient characteristics, 3D CT and information on drug treatment and outcomes will provide an ideal testing ground for a novel clinical diagnosis and treatment stratification. The PhD or postdoc will work on this very exciting project.</p>
References	https://www.researchgate.net/profile/Jichao_Zhao
NCD CRCC priority area	cardiovascular and cerebrovascular diseases

2020-05: Ionic basis of cardiac arrhythmogenesis in metabolic syndrome: A computer modelling analysis

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Project outline	Metabolic syndrome (MetS), closely linked to sedentary lifestyles and excessive caloric intake, is defined as a cluster of multiple risk factors for cardiovascular disease: obesity, hypertension, insulin resistance, high serum triglycerides, and low high-density lipoprotein. MetS is a global epidemic and a major public health burden affecting ~35% of the adult population and ~3.3% of children/adolescents. Furthermore, MetS increases the risk of subsequent cardiovascular disease by 2- to 3-fold and diabetes by 5-fold. Individual components of MetS, such as obesity and diabetes, are closely associated with a higher prevalence of atrial fibrillation (AF), the most common heart rhythm disturbance. In a clinical study with >15,000 participants, a stepwise increase in AF risk was observed in patients with an increasing number of components of MetS. The risk of developing new-onset AF is 2-fold greater in patients with MetS. Importantly, Prof. Prash Sanders at The Royal Adelaide Hospital has demonstrated that a 5-fold lower AF recurrence is achieved by aggressive risk factor management of all MetS components. However, the precise mechanisms underlying the increased AF risk in MetS remain unclear, thereby impeding the development of effective treatment strategies for AF patients with MetS. The PhD student or Postdoc will use computer models as powerful tools to investigate this complex causal relationship between AF and MetS.
References	https://www.researchgate.net/profile/Jichao_Zhao
NCD CRCC priority area	cardiovascular and cerebrovascular diseases; diabetes and obesity

2020-06: The roles of traditional Chinese medicine (TCM) practitioners and their patients in enhancing safety monitoring for TCMs in New Zealand

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Project outline	<p>In recent years, the use and safety of traditional Chinese medicines (TCMs), has attracted attention globally.¹ Key organisations concerned with the safety of medicines (e.g. World Health Organisation, International Society of Pharmacovigilance) have emphasized the need to enhance safety monitoring systems for TCMs.^{2,3} TCM has a long history of traditional use in China, and its proper practice incorporates approaches to reduce the toxicity of TCM preparations.⁴⁻⁷ To modernise TCM practice, TCM needs to develop and adopt safety monitoring and reporting systems both within and outside China.^{2,8} In Western countries, including New Zealand (NZ), TCM sits outside mainstream healthcare; still, many people in NZ, particularly in Auckland, are of Chinese origin and these people (and others) use TCM as a key healthcare approach. However, TCM practitioners and their patients in NZ are unlikely to be aware of national pharmacovigilance systems, or to report safety concerns (i.e. side-effects) to them. This programme aims to investigate ways of enhancing safety monitoring for TCMs. The first phase will explore the experiences, views, practices and knowledge of TCM practitioners and their patients in NZ on the safety of TCMs, and on identifying and reporting safety concerns associated with their use. This work will involve both qualitative (e.g. interviews, focus groups) and quantitative (e.g. questionnaires/surveys) methods involving both TCM practitioners and patients. The second phase involves developing an educational/awareness intervention on TCM safety/pharmacovigilance for TCM practitioners, and then conducting a randomized controlled trial to assess its effects on TCM practitioners' identification and reporting of safety concerns associated with TCMs. This work involves developing collaborations with TCM practitioners in NZ. Existing collaborations with the NZ Pharmacovigilance Centre, and Prof Li Zhang, Dongfang Hospital and Beijing University of Chinese Medicine, China, and Dr Lida Teng, Japan, will be important in this project.</p>
References	<p>References: 1. Barnes J, McLachlan AJ, Sherwin CT, Enioutina EY. Herbal medicines: challenges in the modern world. Part 1: Australia and New Zealand. <i>Expert Rev Clinical Pharmacology</i> 2016;9(7):905-15; 2. Barnes J. Pharmacovigilance of herbal medicines. <i>Drug Safety</i> 2003;26(12):829-851; 3. Rodrigues E, Barnes J. Pharmacovigilance of herbal medicines: the potential contributions of ethnobotanical and ethnopharmacological studies. <i>Drug Safety</i> 2013;36:1-12; 4. Teng L, Shaw D, Barnes J. Traditional Chinese herbal medicine. <i>Pharm J</i> 2006;276:361-363; 5. Barnes J, Teng L, Shaw D. TCM: balancing choice and risk. <i>Pharm J</i> 2004;273:342; 6. Teng L, Shaw D, Barnes J. Characteristics and practices of Traditional Chinese Medicine retail shops in London: A</p>

	<p>cross-sectional study using an observational approach. <i>J Ethnopharmacology</i> 2015;173:318-329; 7. Teng L, Shaw D, Barnes J. Practice of traditional Chinese herbal medicine shops in central London. <i>Phytochemistry Letters</i> 2008;1(2):94-98; 8. Zhang L, Yan J, Liu X, Ye Z, Yang X, Meyboom R, Chan K, Shaw D, Duez P. Pharmacovigilance practice and risk control of Traditional Chinese Medicine drugs in China: Current status and future perspective. <i>Journal of Ethnopharmacology</i> 2012;140:519-525. Further reading: Heinrich M, Barnes J, Gibbons S, Prieto J, Williamson EM. Fundamentals of Pharmacognosy & Phytotherapy (3rd ed). Edinburgh: Elsevier, 2018; Barnes J, Anderson LA, Phillipson JD. Herbal Medicines (3rd ed). London: Pharmaceutical Press, 2007 (710 pages); Barnes J. Adverse drug reactions and pharmacovigilance of herbal medicines. In: Talbot J, Aronson J. Stephens' Detection and Evaluation of Adverse Drug Reactions (6th edition). Chichester: Wiley, 2012: 645-683; Teng L, Shaw D, Barnes J. Traditional Chinese veterinary medicine. In: Katerere DR, Luseba D (editors). Ethnoveterinary botanical medicine: herbal medicines for animal health. Boca Raton: Taylor & Francis, 2010: 353-372</p>
NCD CRCC priority area	Modernisation of traditional Chinese medicine

2020-07: An overlooked opportunity in treating cardiovascular disease by restoring heart rate variability

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Project outline	<p>In Chinese medicine, pulse diagnosis is a very helpful tool used to assess the health of all major organ systems of the body. The diagnostic information is based on the rhythm of the heart, assessed at the radial pulse felt next to the wrist. Between one heart beat and the next, there are naturally-occurring time differences. This physiological phenomenon, coined 'heart rate variability (HRV)', is prominent at birth, and it reflects a sign of good health. Low HRV indicates reduced ability for physiological and psychological resiliency, and is associated with a higher risk of death in patients with heart disease and in elderly subjects. The utility of HRV extends to the monitoring of healthy aging and longevity, as well as in Tai Chi.</p> <p>Despite its importance in our everyday life challenges and its clinical utility, HRV has not yet shown to have a cardiac therapeutic value. Standard pacemakers pace the heart at fixed rates and do not incorporate HRV. The detrimental effect and the non-optimal cardiac output have been reported to be associated with fixed-rate pacing. Given that HRV is decreased in cardiovascular diseases, one might logically assume that reinstating HRV to a diseased heart would improve cardiac function. Remarkably, this has not been tested. To begin testing the therapeutic opportunity from re-instating HRV, we have collected pilot data testing the effects of HRV on cardiac function. Our pilot data show that muscle force production from rat heart muscle tissue samples increased when electrically stimulated to contract under an HRV protocol (with stimulation varying sinusoidally between two frequencies). In contrast, muscles that were exposed to a fixed-frequency stimulation (mimicking the complete absence of HRV), declined in force production. Based on these exciting pilot data, we propose that re-instating HRV will have a therapeutic potential for health benefit and hence can be utilised to maximise restoration of heart function in disease.</p> <p>Techniques used will be calorimetric measurement of force and heat output of cardiac tissue samples, and RNA transcriptomic sequencing. Collected data will be used to parameterise and refine our mathematical model to provide insightful mechanistic interpretation.</p>
References	<p>Liu et al. (2018) The effects of Tai Chi on heart rate variability in older Chinese individuals with depression. <i>Int J Environ Res Public Health</i>, 15(12): 2771.</p> <p>Sessa et al. (2018) Heart rate variability as predictive factor for sudden cardiac death. <i>Aging</i>, 10(2): 166-177.</p> <p>Han et al. (2018) Left-ventricular energetics in pulmonary arterial hypertension-induced right-ventricular hypertrophic failure. <i>Front Physiol</i>, 8(1115): 1-12.</p>
NCD CRCC priority area	Cardiovascular diseases

2020-08: Using big data to estimate the prevalence of dementia in New Zealand

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Project outline	<p>In New Zealand (NZ) the prevalence of dementia is anticipated to triple in the next 30 years, the greatest increase being amongst the rapidly ageing Asian (Chinese and Indian) population living in NZ. We do not have accurate data about the extent and impact of dementia in NZ as there is no national dementia registry and there has never been a dementia prevalence study. We suspect that dementia is greatly underdiagnosed in Asian populations due to cultural stigma and under utilization of services. We wish to explore the utility of data linkage of routinely collected health and social care data as an alternative method to predict and identify dementia. Data linkage might provide a cost-effective process to assess and monitor the extent of dementia and the impact of baseline characteristics and interventions on routinely collected outcomes such as hospital admission, utilization of state-funded home care services, care home placement and mortality.</p> <p>The aim of our study is to conduct a dementia prevalence study that also measures the psychological and economic impact of dementia on carers in European and Asian populations living in South Auckland. We will compare our findings with a dataset constructed from routinely collected health and social care for the same population. We will assess the sensitivity and positive predictive value of the routinely collected dataset against the population-based 'gold standard' in both European and Asian subgroups to demonstrate the potential range of results.</p> <p>Our findings will allow us to explore cost-effective methods of predicting and/or identifying people who may be living dementia, which will facilitate culturally appropriate targeted care for non-English speaking populations. We can use these linked data to estimate the current and future economic burden of dementia in NZ, which will inform policy and practice.</p>
References	<p>Xu, Junfang & Wang, Jian, Wimo, Anders, Fratiglioni, Laura & Qiu, Chengxuan (2017). The economic burden of dementia in China, 1990-2030: Implications for health policy. Bulletin of the World Health Organization. 95. 18-26.</p> <p>Jia L, Quan M et al (2019). Dementia in China: epidemiology, clinical management, and research advances. The Lancet Neurology, 2019.</p> <p>http://www.sciencedirect.com/science/article/pii/S147444221930290X</p>
NCD CRCC priority area	neuropsychiatric disorders and age-related diseases; big data.

2020-09: Novel Approach for Her2×Her3 Bispecific Antibody-Drug Conjugate Targeting Breast Cancer

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Project outline	<p>Bispecific antibody–drug conjugates (bsADC) is a targeted anti-tumour drug with coupling cytotoxic drug and bispecific antibody. It is predicted that bsADC will play an important role in the development of targeted therapeutics against cancer in the coming years.</p> <p>A novel approach for bispecific antibody-drug conjugate will be developed in this proposed project. Bispecific antibody with natural antibody structure or five amino acids left in hinge region can be produced in our collaborative research facility. We will use the advantages of the "BAPTS"(Bispecific Antibody by Protein Trans-Splicing) technology platform to design sites for conjugation in the hinge region to conjugate the bispecific antibody and cytotoxic drugs. Site-specific conjugation will be applied for bsADCs design. BsADCs with high homogeneity will be produced by this study. This novel synthesis method of bispecific antibody–drug conjugates will provide promising biopharmaceutics for future clinical drug discovery and development. We will design Her2×Her3 bsADC targeting breast cancer in particular those with multi-drug resistance. This research will also provide reliable theoretical and technical support for the further research of bispecific antibody–drug conjugates.</p>
References	<ol style="list-style-type: none"> 1. Comer F, Gao C, Coats S. Bispecific and Biparatopic Antibody Drug Conjugates, Damelin M, editor, Innovations for Next-Generation Antibody-Drug Conjugates, Cham: Springer International Publishing, 2018: 267-280. 2. Nasiri H, Valedkarimi Z, Aghebati-Maleki L, Majidi J. Antibody-drug conjugates: promising and efficient tools for targeted cancer therapy. Cell Physiol. 2018 Jan 10. doi: 10.1002/jcp.26435. 3. Sau S, Alsaab H O, Kashaw S K, et al. Advances in antibody-drug conjugates: a new era of targeted cancer therapy. Drug Discovery Today. 2017, 22(10):1547-1556. 4. Junutula J R, Raab H, Clark S, et al. Site-specific conjugation of a cytotoxic drug to an antibody improves the therapeutic index. Nature Biotechnology. 2008, 26(8): 925-932. 5. Thusspatience P C, Shah M A, Ohtsu A, et al. Trastuzumab emtansine versus taxane use for previously treated HER2-positive locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma (GATSBY): an international randomised, open-label, adaptive, phase 2/3 study. Lancet Oncology. 2017, 18(5): 640-653. 6. Li J, Perry S, Muniz-Medina V, et al. A Biparatopic HER2-Targeting Antibody-Drug Conjugate Induces Tumor Regression in Primary Models Refractory to or Ineligible for HER2-Targeted Therapy. Cancer Cell. 2016, 29(1): 117-129. 7. Andreev J, Thambi N, Bay A E P, et al. Bispecific Antibodies and Antibody–Drug Conjugates (ADCs) Bridging HER2 and Prolactin Receptor Improve Efficacy of HER2 ADCs. Molecular Cancer Therapeutics. 2017, 16(4): 681-693. 8. Mishra R, Patel H, Alanazi S, et al. HER3 signaling and targeted therapy in cancer. Oncology Review. 2018, 12(1):355. doi: 10.4081/oncol.2018.355.

	<p>9. Pohlmann P R, Mayer I A, Mernaugh R. Resistance to Trastuzumab in Breast Cancer. Clinical Cancer Research. 2009, 15(24): 7479-7491.</p> <p>10. Narayan M, Wilken J A, Harris L, et al. Trastuzumab-Induced HER Reprogramming in “Resistant” Breast Carcinoma Cells. Cancer Research. 2009, 69(6): 2191-2194.</p>
NCD CRCC priority area	Cancer

2020-10: New Zealand Surf Clam extracts for the prevention and control of diabetes and its joint pain complication

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Project outline	<p>Natural marine products are characterized by structural diversity and biological diversity, and are one of the important sources of new drug discovery. At present, the medicinal active ingredients of the marine molluscs are mainly biological toxins, polysaccharides, glycoproteins and unsaturated fatty acids in terms of their chemical compositions. Their pharmacological effects are manifested in anti-tumour, anti-inflammatory, anti-viral, and human immunity.</p> <p>We hypothesise that New Zealand surf clams have a prevention and protective effect on type 2 diabetes and its joint pain complications, which is mediated by inflammation. Those conditions may be improved by certain clam extracts. The aim of this project is to isolate active components of New Zealand surf clams, study their anti-inflammatory bioactivities and their effects in glycemic control as well as on management and relief of joint pain, which is intensified by the diabetes condition.</p>
References	<p>Chakraborty, K., Thilakan, B., & Kizhakkekalam, V. K. (2018). Antibacterial aryl-crowned polyketide from <i>Bacillus subtilis</i> associated with seaweed <i>Anthophycus longifolius</i>. <i>J Appl Microbiol</i>, 124(1), 108-125.</p> <p>-Conroy, A. M., Smith, P. J., Michael, K. P., & Stotter, D. R. (2010). Identification and recruitment patterns of juvenile surf clams, <i>Macra discors</i> and <i>M. murchisoni</i> from central New Zealand. <i>New Zealand Journal of Marine and Freshwater Research</i>, 27(3), 279-285.</p> <p>-Cranfield, H. J., & Michael, K. P. (2001). Growth rates of five species of surf clams on a southern North Island beach, New Zealand. <i>New Zealand Journal of Marine and Freshwater Research</i>, 35(5), 909-924.</p> <p>-Joy, M., & Chakraborty, K. (2017). Biogenic antioxidative and anti-inflammatory aryl polyketides from the venerid bivalve clam <i>Paphia malabarica</i>. <i>Food Chem</i>, 237, 169-180.</p> <p>-Maldonado-Aguayo, W., Lafarga-De la Cruz, F., & Gallardo-Escarate, C. (2015). Identification and expression of antioxidant and immune defense genes in the surf clam <i>Mesodesma donacium</i> challenged with <i>Vibrio anguillarum</i>. <i>Mar Genomics</i>, 19, 65-73.</p> <p>-Maneesh, A., & Chakraborty, K. (2017). Unprecedented antioxidative and anti-inflammatory aryl polyketides from the brown seaweed <i>Sargassum wightii</i>. <i>Food Res Int</i>, 100(Pt 1), 640-9.</p> <p>-Odeleye, T., Li, Y., White, W. L., Nie, S., Chen, S., Wang, J., & Lu, J. (2016). The antioxidant potential of the New Zealand surf clams. <i>Food Chem</i>, 204, 141-149.</p> <p>-Santiago, C., Sun, L., Munro, M. H., & Santhanam, J. (2014). Polyketide and benzopyran compounds of an endophytic fungus isolated from <i>Cinnamomum mollissimum</i>: biological activity and structure. <i>Asian Pac J Trop Biomed</i>, 4, 627-32.</p> <p>-Tinu Odeleye, J. L., William Lindsey White. (2019). Bioactives from marine molluscs – extraction techniques and potential health applications. <i>Food and Function</i>, 10, 2278-89.</p> <p>-Yu, J. H., Song, J. H., Choi, M. C., & Park, S. W. (2009). Effects of water temperature change on immune function in surf clams, <i>Macra veneriformis</i> (Bivalvia: Mactridae). <i>J Invertebr Pathol</i>, 102(1), 30-35.</p>
NCD CRCC priority area	Diabetes

2019-11: Finding neural biomarkers of depression through machine-learning big EEG data

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Project outline	<p>Work days lost to mental disorders are double other health issues. Anxiety and depression are particularly disabling. The key problem is that their biological causes are unknown. So, psychiatry has only superficial symptom checklists that deliver diagnoses equivalent to “fever”; with poor treatment-targeting, high health costs, and major societal impact. In reaction, the National Institute of Mental Health has called for diagnosis via “biomarkers” of causes, not symptoms.</p> <p>The immense power of machine learning offers a springboard. It can already use EEG to distinguish depression from health. But, a biomarker must measure ongoing depressivity (i.e., a personality trait) not classify momentary depression as a categorical temporary state. This is much harder than, e.g., face classification. We have recently developed a machine learning system that uses EEG to predict ($p < 0.001$) depressivity scores in people not included in its original training.</p> <p>Unfortunately, recognition of “depression” will not, alone, deliver a biomarker. We need measures that are interpretable; and, as New Scientist notes, “A deep-learning neural network is a black box. If it works, great. If it doesn’t, you’re screwed.” Worse, with “depression” we must distinguish between different, at present unknown, causes of different depressive disorders.</p> <p>Our unique combination of world-class neuropsychological, clinical, machine learning, and parallel algorithm expertise will allow us to progressively deconstruct both the computational black box of our machine learning solutions with big EEG data and, ultimately, the biological black box of “depression” itself. Uniquely, our neuropsychology-machine learning interactions will help sieve EEG biomarkers from a “depression EEG” pool of unknown aetiology. Like blood tests of specific infections sieved from a “fever” pool, our biomarkers will define new specific types of depressive disorder. We hope to break new ground with a general paradigm that should be immediately applicable to the search for biomarkers of other mental disorders; and so provide a potent impetus to psychiatry more generally.</p> <p>We have an agreement of collecting EEG data from healthy and depressed participants with The Second Xiangya Hospital. We also have collaboration with a Chinese EEG company called EEGSmart. In the area of parallel computing and big data analysis, we have a long-term collaboration with Shanghai Jiao Tong University.</p>
References	Wang, Y, Huang, Z, McCane, B, & Neo, PS-H, EmotioNet: A 3-D Convolutional Neural Network for EEG-based Emotion Recognition. IEEE International Joint Conference on Neural Networks, 2018: in press.

	Wang, Y, McCane, B, McNaughton, N, Huang, Z, Shadli, S, & Neo, P, AnxietyDecoder: An EEG-based Anxiety Predictor using a 3-D Convolutional Neural Network, in 2019 IEEE International Joint Conference on Neural Networks (IJCNN). 2019.
NCD CRCC priority area	neuropsychiatric disorders

2020-12: Stress responses in the diabetic heart: Effects of exercise training and glycemic control

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Project outline	<p>The diabetic heart, even before developing disease, is often characterized by slowed relaxation and reduced contractility. These changes limit the work capacity of the heart (maximal cardiac output) and limit the functional capacity of people with diabetes. Calcium 'triggers' the heart to contract in a dose-dependent manner. Our recent research has determined that the calcium-stimulated force produced by diabetic hearts (Langendorff preparation) and isolated skinned cardiomyocytes is reduced in human heart samples (left ventricle and right atrial appendage) and diabetic rat models. This reduction in calcium sensitivity prevents the diabetic heart from responding well to stress or exercise, and may contribute to the high rates of heart failure in people with diabetes. The first aim of our current work is to determine how diabetes-associated post-translational phosphorylation and O-GlcNAcylation of myofilament proteins (e.g. cTnI, myosin binding protein C) affects the cardiomyocyte calcium sensitivity of force production.</p> <p>The second aim of our research is to determine whether exercise training and/or pharmacological interventions (e.g. cardiac calcium sensitizers, CAMK2 inhibitors) can reverse diabetic cardiac dysfunction. These experiments will examine the effects of chronic exercise training and pharmaceutical interventions on heart function from whole organ to single skinned cardiomyocytes and combine these studies with state-of-the-art biochemical techniques. We are seeking motivated students with an interest in cardiovascular/exercise physiology and/or pharmacology to join our lab and examine how diabetes impairs cardiovascular function.</p>
NCD CRCC priority area	Cardiovascular and cerebrovascular disease and Diabetes and Obesity

2020-13: Development of synthetic miRNAs that target PAX2 for cancer therapy

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Project outline	<p>RNA interference (RNAi) is a widespread mechanism responsible for the regulation of gene expression in eukaryotes. Key elements of the RNAi machinery are small regulatory RNAs, which serve as 20–30 nucleotide probes targeting multi-enzymatic protein complexes associated with the expression of specific transcripts and genes. Among them, microRNAs (miRNAs) and small interfering RNAs (siRNAs) are found to be the most important for post-transcriptional gene silencing. The miRNAs (also called miRs) are represented by small non-coding RNAs consisting of 19–25 nucleotides. The <i>PAX</i> genes are an example of genes regulated by naturally occurring endogenous miRNAs, and are frequently aberrantly expressed in human cancer tissue, contributing to the tumour phenotype. Paired box (<i>PAX</i>) transcription factors are critical regulators of normal embryogenesis, but have been found to promote oncogenic properties when aberrantly expressed. The aberrant re-expression of <i>PAX</i> proteins is observed in a variety of cancers, including leukaemia, breast, prostate, kidney and bladder carcinoma. As a result, <i>PAX</i> proteins are known to be frequently expressed in a number of malignant cell types, as well as being required for cell proliferation or survival, suggesting that they might be potential therapeutic targets for cancer gene therapy. <i>PAX2</i> is thus a potentially relevant and unique target for therapy in several cancer types. However, to date no clinically translatable methods for specifically inhibiting the activity of <i>PAX2</i> or its function <i>in vivo</i> have successfully been developed. In this project, the overall aim will be to design novel synthetic miRNAs that target <i>PAX2</i> mRNA, and thereby reduce the level of <i>PAX2</i> protein in cancer cells <i>in vitro</i> and <i>in vivo</i>. The project therefore involves the design of synthetic miRNAs to silence <i>PAX2</i> expression, and demonstration that these novel synthetic miRNAs significantly inhibit <i>PAX2</i> mRNA and protein expression in cancer cells, both <i>in vitro</i> and <i>in vivo</i> in model systems.</p>
References	<ol style="list-style-type: none"> 1. T.A. Farazi, J.I. Hoell, P. Morozov and T. Tuschl, MicroRNAs in human cancer, <i>Adv. Exp. Med Biol</i> 774 (2013) 1-20. 2. A. Muratovska, C. Zhou, S. He, P. Goodyer, M.R. Eccles, Paired-box genes are frequently expressed in cancer and often required for cancer cell survival, <i>Oncogene</i> 22 (2003) 7989–7997. 3. E.J. Robson, S.J. He, M.R. Eccles, A PANorama of <i>PAX</i> genes in cancer and development, <i>Nat. Rev. Cancer</i> 6 (2006) 52–62.
NCD CRCC priority area	Cancer

2020-14: Non-Pharmacological Modulation of the Autonomic Nervous System and the Neuroendocrine System to Complement Inflammation and Healing

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Project outline	Degenerative musculoskeletal diseases are common health problems in New Zealand and China, and are expected to increase in prevalence with aging populations. The autonomic nervous system and hypothalamic-pituitary-adrenal axis have been shown to be dysfunctional in a number of disorders, such as osteoarthritis, and tendinopathy. When an individual is presented with pain, the hypothalamus coordinates the stress response by activation of the neuro-endocrine system or stress axis. Further, the end products of the stress axis activation have been shown to modulate several immune parameters, thereby playing an important role in inflammation and tissue healing. The trend towards individualized medicine and issues around polypharmacy as well as pain medication issues has led towards an increasing popularity of drug free interventions such as acupuncture and spinal manipulation (Tuina) to restore the autonomic system balance and subsequently have an effect on pain and healing via modulation of endocrine and physiological processes. The student will study the mechanisms of effects of acupuncture and tuina using physiological measures such as blood flow and salivary hormone analysis, as well as clinical measures of pain and function to gain a better understanding of the systemic effects and clinical effectiveness of these interventions. This study will be a pragmatic observational trial investigating the use of acupuncture, tuina, and acupuncture with tuina on a degenerative musculoskeletal disorder, with one-year observational period. Historical contexts, literature reviews and consultation with Chinese clinical professions will guide the research design and methodology of this study.
NCD CRCC priority area	Modernisation of traditional Chinese medicine Age related Diseases

2020-15: Traditional Chinese Medicine based powder for lung diseases

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Project outline	<p>Respiratory diseases such as asthma, chronic obstructive lung diseases (COPD) and lung cancer are prevalent in China. For example, in 2016, there were 80 million COPD patients and >32 million asthma patients. Traditional Chinese Medicine (TCM) has been used as nebulization in Chinese hospital in last two decades to treat respiratory diseases, but no products in the form of a dry powder inhaler (DPI) have been developed yet. Drugs remain as a powder in DPIs, which are dispensed by DPI devices. TCM based powders can be generated from Chinese material medica extracts by different particle engineering techniques such as spray drying, mixing, milling, or coating etc. The processing techniques can influence powder bulk and surface properties such as particle size and size distribution, surface area and porosity, morphology, flowability, moisture content, surface energy and surface composition. The surface properties can influence ultimate product functionality.</p> <p>The project is to develop a TCM based powder platform for treating lung diseases such as COPD or Lung cancer. This specific objectives are-</p> <ul style="list-style-type: none"> i) The influence of different powder engineering techniques on bulk and particle properties (surface and solid state) of TCM based powder ii) The optimization of lung delivery efficiency. iii) The influence of relative humidity and temperatures on the storage stability of the powders iv) The in vitro safety of the powders. v) Pharmacokinetic study of the powder (if time/collaboration available) <p>(I am also interested to develop a quick release tablet based on TCM based powders. This will investigate</p> <ul style="list-style-type: none"> i) The influence of different powder engineering techniques on bulk and surface properties of TCM based powder ii) The influence of powder properties on tablet quality such as disintegration and dissolution. iii) The influence of different (modified) excipients on tablet properties.)
References	<p>Eedara, B.B., Tucker, I. and Das, S.C.* (2019) In vitro dissolution testing of respirable size anti-tubercular drug particles using a small volume dissolution apparatus, <i>International Journal of Pharmaceutics</i>, 559, 235-244.</p> <p>Momin, M.M.A., Tucker, I.G., and Das, S.C.* (2019) The influence of storage relative humidity on aerosolization of co-spray dried powders of hygroscopic Kanamycin with the hydrophobic drug Rifampicin. <i>Drug Development and Industrial Pharmacy</i>, 45 (7), 1205-1213.</p>

	<p>Momin, M.M.A., Tucker, I.G., Doyle, C., Sinha, S. and Das, S.C.* (2018) Co-spray drying of hygroscopic kanamycin with the hydrophobic drug rifampicin to improve the aerosolization of kanamycin powder for treating respiratory infections, <i>International Journal of Pharmaceutics</i>, 541, 26–36.</p> <p>Momin, M.M.A., Sinha, S., Tucker, I.G., Doyle, C. and Das, S.C.* (2017) Dry powder formulation of kanamycin with enhanced aerosolization efficiency for drug-resistant tuberculosis, <i>International Journal of Pharmaceutics</i>, 528, 107–117.</p> <p>Momin, M.M.A., Thien, S. J., Krittaphol, W. and Das, S.C.* (2017) Simultaneous quantification of PA-824, moxifloxacin and pyrazinamide in pharmaceuticals using RP-HPLC: Method development, validation and application in inhaler formulation for drug-resistant tuberculosis, <i>Journal of Pharmaceutical and Biomedical Analysis</i>, 135, 133–139.</p>
NCD CRCC priority area	Chronic obstructive pulmonary disease and modernisation of traditional medicine

2020-16: Tumour-Targeted Bioorthogonal Prodrug Activation

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Project outline	<p>One potential way to improve the outcome of targeted prodrug therapies is the use of bioorthogonal chemical reactions.¹ While most research in the field has focused on chemical biology and bioconjugation applications; i.e. tracking biomolecules and cells in living systems, more recently, these bioorthogonal chemical reactions have been reported to click-and-release drugs and probes; i.e. to selectively target and activate prodrugs and pro-probes.² The Gamble group have been investigating a bioorthogonal prodrug activation strategy based on the 1,3-dipolar cycloaddition of an azide and <i>trans</i>-cyclooctene (TCO).^{3,4}</p> <p>While the proof-of-concept for prodrug activation is established,^{3,4} there is a need to selectively target the activation group (TCO) to the tumour, and improve reaction rates and concentrations of drug released at the targeted site via modifications to the linker and the TCO-ligand conjugate.</p> <p>Stage One of this project will involve the design and synthesis of novel linkers and TCO molecules that react faster than the current linkers and TCO's in use. These strategies alone, or in combination, are expected to provide superior <i>in vivo</i> drug activation. We are interested in incorporating new drug molecules, perhaps those related to traditional medicines into our prodrugs, and examine their activation in cancer cell culture.</p> <p>Stage Two of this project will then look at synthesizing TCO-ligand conjugates that enable targeted activation of the best prodrug (determined in Stage 1) using <i>in vitro</i> and <i>in vivo</i> ligand targeting studies.</p>
References	<ol style="list-style-type: none"> 1. Sletten, E. M. and Bertozzi, C. R. (2009) <i>Bioorthogonal chemistry: Fishing for selectivity in a sea of functionality</i>. Angew. Chem. Int. Ed. 48, 6974-6998. 2. Li, J.; Chen, P. R. <i>Development and application of bond cleavage reactions in biorthogonal chemistry</i>. Nature Chemical Biology 2016, 12, 129-137. 3. Matikonda, S. S., Orsi, D. L., Staudacher, V., Jenkins, I. A., Fiedler, F., Chen, J., and Gamble, A. B. (2015) <i>Bioorthogonal prodrug activation driven by a strain-promoted 1,3-dipolar cycloaddition</i>. Chem. Sci. 6, 1212-1218. 4. Matikonda, S. S.; Fairhall, J. M.; Fiedler, F.; Sanhajariya, S.; Tucker, R. A. J.; Hook, S.; Garden, A. L.; Gamble, A. B. <i>Mechanistic Evaluation of Bioorthogonal Decaging with trans-Cyclooctene: The Effect of Fluorine Substituents on Aryl Azide Reactivity and Decaging from the 1,2,3-Triazoline</i>. Bioconjugate Chem. 2018, 29, 324-334.
NCD CRCC priority area	Cancer and Modernization of Traditional Medicine

2020-17: Nanomedicines for oral delivery of *Sonchus oleraceus* antioxidants

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Project outline	<p>Antioxidants mediate oxidative damage to lipids, proteins and DNA that occurs when there is an excess of reactive oxygen species in the body. The consumption of plant-derived antioxidants has been associated with the prevention of diseases, including cancer and neurodegenerative disorders, caused by oxidative stress.</p> <p>The puha thistle (<i>Sonchus</i> sp.) is an abundant New Zealand resource and a significant part of the traditional Māori diet. Leaves of the puha plant (<i>Sonchus oleraceus</i>) are rich in antioxidants that have the potential to be formulated into a supplement product.</p> <p>Whilst a number of biochemical assays exist for estimating the antioxidant activity of plant extracts, the assessment of antioxidant activity in biological systems is an area of research that is in its infancy still. We have previously shown that <i>S. oleraceus</i> antioxidants are absorbed into cells <i>in vitro</i> and can exert an antioxidant effect. Can this effect be maintained following <i>in vivo</i> administration? Many health claims have been made about the benefits of consuming antioxidants, however there is a need to verify these claims with data on biological activity. Delivery of antioxidants using nanoparticle formulations will be investigated <i>in vivo</i> using zebrafish embryos, an exciting new model of human disease in which to study oxidative stress.</p> <p>Aim: To investigate the oral delivery of antioxidant phytochemicals using nanoparticle formulations</p>
References	<p>Ou Z-Q, Schmierer D, Rades T, Larson L, McDowell A. Application of an online post-column derivatization HPLC-DPPH assay to detect compounds responsible for antioxidant activity in <i>Sonchus oleraceus</i> L. leaf extracts. <i>Journal of Pharmacy and Pharmacology</i> 2012; 65:271-9</p> <p>Ou Z-Q, Rades T, McDowell A. Anti-ageing effects of <i>Sonchus oleraceus</i> L. (puha) leaf extracts on H₂O₂ induced cell senescence. <i>Molecules</i> 2015; 20:4548-64.</p> <p>Yang H-M, Ham, Y-M, Yoon W-J, Roh SW, Jeon Y-J, Oda T, Kang S-M, Kang M-C, Kim E-A, Kim D and Kim K-N. Quercitrin protects against ultraviolet B-induced cell death <i>in vitro</i> and in an <i>in vivo</i> zebrafish model. <i>Journal of Phytochemistry and Photobiology B: Biology</i> 2012; 114:126-131</p>
NCD CRCC priority area	Age-related diseases and modernisation of traditional medicine

2020-18: Chemical tools to study cannabinoid receptors

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Project outline	<p>The cannabinoid receptor (CBR) is a Class A GPCR that plays an important role in many human pathophysiological conditions such as cancer, pain neurological and metabolic disorders. As such, there is a requirement to develop tools to better understand the role of CBR in these disease pathologies. Globally, cannabinoid type 1 receptor (CB1R) is very topical because of the increasing number of countries legalising cannabis that contains, among other chemical constituents, CB1R agonists. Cannabinoid type 2 receptor (CB2R) is also of great interest, in particular its mediation of signalling in the immune system. There are a variety of existing tools available for studying CBR such as fluorescent antibodies, radioligands, covalent ligands and selective small molecule ligands, however each of these have limitations. This aim of this PhD project is to design and synthesise new chemical tools for CBR that will allow exquisite examination of CBR, leading to improved and more efficacious drug interventions targeting CBR.</p>
NCD CRCC priority area	Cancer, diabetes and obesity, neuropsychiatric disorders and age-related diseases.

2020-19: Trans-ancestral dissection of genetic architecture of abdominal aortic aneurysm AAA

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Project outline	<p>Abdominal aortic aneurysm (AAA) is a life-threatening disease causing substantial mortality. The only medical treatment for AAA is surgical repair. AAA is highly inheritable where genetics contributes as high as 70% of the AAA risk. The prevalence of AAA differs substantially across ethnic groups, e.g. 1.2% in European and 0.11% in Chinese populations, but the disease pathogenesis remains largely obscure. Most genetic studies of AAA are based on samples with European ancestry and have identified only a dozen of associated loci that jointly could explain a small proportion of the risk. Epidemiology studies suggest that old age (i.e. > 65), smoking and male gender are major environmental risk factors but provide little clues of possible interactions with genetic variants in AAA aetiology.</p> <p>This project aims to enhance dissection of the genetic architecture of AAA by leveraging trans-ancestral approaches that can: a) analyse European and Chinese samples together to increase power of detection of novel loci, b) identify risk variants either shared across ethnic groups or ancestry-specific to inform prognosis, c) prioritise candidate casual variants by integrating evolutionary and regulatory information. This project is also well positioned to characterise roles of gene-gene and gene-environment interactions in regulating AAA.</p> <p>The supervisors form a strong multidisciplinary team that has been proactive in developing the collaboration important to both countries where the number of AAA patients is big particularly in China given it's world largest population. Findings from this project will improve risk prediction and help develop early intervention of AAA.</p>
References	Pinard et al. (2019) <i>Circulation Research</i> 124:588-606 Jones et al. (2017) <i>Circulation Research</i> 120:341-353 Li et al. (2017) <i>Circulation</i> 135(21):2041-57 Wei et al. (2014) <i>Nature Reviews Genetics</i> 15(11):722-33
NCD CRCC priority area	cardiovascular and age-related diseases, gene-environment interactions and big data

2020-20: Arginine metabolism and Alzheimer's disease and psychosis

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Project outline	<p>L-arginine is a semi-essential amino acid with a number of bioactive metabolites. Nitric oxide, for example, is a gaseous signalling molecule that plays an important role in synaptic plasticity and learning and memory, and is a key factor for the stabilization and regulation of the vascular microenvironment. Polyamines are essential for cells to grow and to function in an optimal manner. Agmatine, decarboxylated arginine, regulates the production of nitric oxide and polyamines, and participates directly in learning and memory processes.</p> <p>Accumulating evidence (including our own) implicates altered arginine metabolism in the pathogenesis of Alzheimer's disease and schizophrenia, and indicates the potential of using blood biomarkers centered on arginine metabolism for clinical diagnosis and prognosis of both diseases. Professor Jijun Wang's research team at Shanghai Mental Health Center has been carrying out an international leading longitudinal study involving a large cohort of adolescents and young adults at clinical high-risk for psychosis. We have recently been awarded a 2019 Shanghai government to government international cooperation project (NZ and Shanghai joint project) on biomarker identification and validation for Alzheimer's disease and clinical high-risk syndrome of psychosis from the Shanghai Science and Technology Commission.</p>
References	<p>-Bergin DH, Jing Y, Mockett BG, Zhang H, Abraham WC, Liu P. (2018) Altered plasma arginine metabolome precedes behavioural and brain arginine metabolomic profile changes in the APPswe/PS1ΔE9 mouse model of Alzheimer's disease. <i>Translational Psychiatry</i>, 8:108.</p> <p>-Liu P, Jing Y, Collie ND, Dean B, Bilkey DK, Zhang H. (2016). Altered brain arginine metabolism in schizophrenia. <i>Translational Psychiatry</i>, 6:e871.</p> <p>-Liu P, Fleete MS, Jing Y, Collie ND, Curtis MA, Waldvogel HJ, Faull RLM, Abraham WC, Zhang H. (2014). Altered arginine metabolism in Alzheimer's disease brain. <i>Neurobiology of Aging</i>, 35:1992-2003.</p>
NCD CRCC priority area	Neuropsychiatric disorders and age-related diseases

2020-21: Develop genetic epidemiology biomarkers to enhance early identification of children at risk of reading disabilities

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Project outline	<p>Reading disabilities (RD) are complex neuropsychological disorders affecting millions of children worldwide. While the underlying causal mechanisms are largely obscure, early identification of children at risk of RD is critical to allow timely interventions before mental suffering and reading impairment take place. Furthermore, early identification can improve genetic epidemiology studies currently limited by substantial heterogeneity in phenotyping and language-specific aetiology. For example, the prevalence of dyslexia – a common form of RD, is ~10% and ~4% in English-speaking and Mandarin-speaking populations respectively.</p> <p>The Chinese language is a unique medium for studying RD because of a) the morpheme-based logographic system where each character is based on meaning rather than phonology, b) the impact of Confucianism motivated learning and social settings on RD trajectories, c) likely different genetic background and functional neurology associated with reading. However, public awareness of RD in China is relatively low and dedicated research is much needed particularly in the area of early identification. Our recent collaborations reinforce the hypothesis of distinct aetiology of RD in Mainland China and the role of Pinyin (an alphabetic coding system mapping Mandarin sounds to characters) in early screening for RD.</p> <p>Leveraging recent advances in studying brain developmental disorders and in early screening for RD in the English-speaking communities, this project aims to develop novel biomarkers to enhance early identification of children at risk of RD. A set of new objective measures will be also used to generate additional data of eye movement, sleep and movement patterns in study cohorts.</p>
References	Peterson and Pennington (2015) <i>Annu Rev Clin Psychol</i> 11:283–307 DeMille et al. (2018) <i>PNAS</i> 115(19): 4951–6 Liu et al. (2019) <i>Am J Med Genet B Neuropsychiatr Genet</i> 180:488–95 McBridge et al. (2018) <i>Current Developmental Disorders Reports</i> 5:217-25
NCD CRCC priority area	neuropsychiatric disorders, gene-environment interactions, big data