Annex A

Research Project	Project details	Faculty (NTU)	Faculty (UoE)
Somatic mutation and regulatory genomic variation in the human brain: relevance to neurodegenerative disease	The aim of this project is to use novel genomic profiling approaches to explore the role of both somatic mutations and regulatory genomic variation in Alzheimer's and Parkinson's disease. We will use a unique collection of human post-mortem brain samples with matched pre-mortem blood samples to explore the accumulation of somatic mutations, epigenomic dysregulation and transcriptional changes in disease-relevant regions of the brain.	A/Prof Foo Jia Nee (NTU) Profile: http://www.lkcmedicine.ntu.edu.sg/aboutus/Faculty-and-Staff/Pages/Foo-Jia-Nee.aspx	Prof Jon Mill (UoE) Profile: https://www.exetermrcsdf.ac.uk/sponsor-profiles/professor-jonathan-mill/
Understanding brain dynamics: merging experiments and models	Healthy brain function is mediated by the coordination of neuronal activity - both locally and across different brain regions - giving rise to large-scale brain dynamics. These dynamics are measured using a variety of techniques, for example magneto-/electro-encephalography or functional MRI in humans, or by fluorescence-based imaging of voltage- or calcium-sensitive indicators in animal models in vivo. Uncovering the nature and mechanisms of large-scale brain dynamics at rest, or during sensory processing, remains a fundamental challenge in neuroscience. In addition to basic insight, improving our understanding of healthy brain dynamics will help us elucidate reasons why abnormal dynamics occur, for example in neurological or neuropsychiatric disorders. This studentship will develop a novel program of interdisciplinary research across in vivo (mouse) experimentation and mathematical modelling. The overall aim is to construct and validate mathematical models of large-scale brain dynamics that are able to explain the spontaneous activity of the rodent brain in vivo. The student will train in optogenetic technologies and in vivo imaging, as well as mathematical model development, multi-variate time series analysis and parameter fitting	Prof George Augustine (NTU) Profile: http://www.lkcmedicine.ntu.edu.sg/aboutus/Faculty-and-Staff/Pages/George-Augustine.aspx	Dr Marc Goodfellow (UoE) Profile: http://emps.exeter.ac.uk/mathematics/staff/mg401

Annex A

	tools, thus placing them at the forefront of interdisciplinary neuroscience. In a first step, targeted optogenetic stimuli will be combined with voltage-sensitive dye imaging in awake mice to probe the response of brain tissue to excitatory and inhibitory afferent stimuli. Neural mass models will be fit to these data, using machine learning approaches. This information will be compiled into a predictive model of cortical dynamics and tested against experimental recordings of spontaneous activity.		
Sensing and imaging synaptic vesicle trafficking and neurotransmitter release - a novel opto-synaptic interface	Whispering Gallery Mode sensors are an advanced optical sensing technology capable of detecting and sizing nanoparticles in the 0.1-500 nm size range. These advanced optical sensing tools have already been utilised for the detection and sizing of Lentiviruses (500 nm) (1), Influenza A virus particles (100 nm) (2), detection of single molecule (1-10 nm) (3) and even single atomic ions (0.1 nm) (4). This doctoral studentship will enable development of WGM sensors as a novel tool for the detection of neuronal synaptic vesicles (SVs) and the direct detection of synaptic activity at the single-molecule level. SVs are a key organelle in brain function, because they store and release the neurotransmitters that are used for inter-neuronal signalling. Imaging individual SVs at the light-microscope level has been a challenge, due to the very small size (approximately 40 nm in diameter) of SVs. The goal is to determine the stoichiometry and structure of SV aggregates and to characterise the role they play in synaptic vesicle trafficking and the transmission of information between nerve cells. SV aggregates for a “reserve pool” of SVs that are mobilised to sustain synaptic transmission during sustained neuronal activity. Thus, being able to sense and visualise these SV clusters in living neurons is important to understand the dynamics of synaptic transmission. It is particularly relevant to clarify	Prof George Augustine (NTU) Profile: http://www.lkcmedicine.ntu.edu.sg/aboutus/Faculty-and-Staff/Pages/George-Augustine.aspx	Prof Frank Vollmer (UoE) Profile: http://emps.exeter.ac.uk/physics-astronomy/staff/fv227

Annex A

	the roles of the SV binding proteins called synapsins. It was previously hypothesized that these proteins control the formation of aggregates during mobilization of reserve vesicles in rapidly-firing neurons (6). Elucidating the interplay of synapsin isoforms in SV aggregation and trafficking has important implication for diseases such as epilepsy, schizophrenia and other brain disorders (7).The relative amounts of synapsin IIA/IB may thereby constitute a novel signal to control the vesicle replenishment and the dynamics of electro-chemical signalling at the synapse.		
The structure basis of the flavivirus replication process	Many members of the mosquito-borne flavivirus are well-known human pathogens such as dengue virus (DENV), Japanese encephalitis virus, West Nile virus, and yellow fever virus and Zika virus. For these RNA viruses, the RNA replication occurs within a replication complex that assembles on the endoplasmatic reticulon of the host cell and comprises both viral proteins and host cofactors. Several proteins of the replication complex constitute validated drug targets because of their crucial functions during viral replication. However, a major impediment in developing drugs targeting the DENV replication complex is that both its structure and composition, the interplay between its molecular constituents as well as the precise molecular mechanisms for viral RNA replication are still elusive. The proposed study aims to reveal the structure of the DENV replication complex to elucidate key protein-protein and protein-RNA interactions within it. This structure will enable the development of novel specific antivirals drugs and better vaccines against the infectious flaviviruses.	A/Prof Luo Dahai (NTU) Profile: http://www.lkcmedicine.ntu.edu.sg/aboutus/Faculty-and-Staff/Pages/Luo-Dahai.aspx	Dr Bertram Daum (UoE) Profile: http://emps.exeter.ac.uk/physics-astronomy/staff/bd309
The effect of age and risk of falling on walking: A holistic	The prevalence of falls among our ageing population presents a huge social and multi-billon dollar challenge to the UK and Singapore. Based on advanced mathematics and human movement science, this thesis will develop and	A/Prof Jia Yi Chow (NTU) Profile:	Dr Genevieve Williams (UoE) Profile:

Annex A

approach to human movement analysis	evaluate novel exercise interventions to provide innovative responses to reducing falls in the elderly.	https://www.nie.edu.sg/profile/chow-jia-yi	https://sshs.exeter.ac.uk/staff/index.php?web_id=Genevieve_Williams
Debugging Lung Disease: Applying mathematical modelling for a precision medicine approach to the Pulmonary Microbiome	Understanding how individual people respond to medical therapy is a key facet of improving the odds ratio that interventions will have a positive impact. Reducing the non-responder rate for an intervention or reducing complications associated with a particular treatment is the next stage of for any medical advance. The Precision Medicine Initiative, launched in January 2015, set the stage for enhanced collaboration between researchers and medical professionals to develop next-generation techniques to aid patient treatment and recovery, and increased the opportunity for impactful pre-emptive care. The microbiome plays a crucial role in health and disease, as it influences endocrinology, physiology, and even neurology, altering the outcome of many disease states, including its ability to augments drug response and tolerance. Therefore, in precision medicine, the focus is on the identification of effective approaches for particular patients based on their genetic, lifestyle and environmental factors. Asian and European phenotypes of respiratory disease and infection are unique and therefore require such precision. While such approaches have been successfully employed to investigate contrasting clinical phenotypes; and by disease trajectories, little is known about 'precision through microbes'. Precision medicine can be applied to the lung microbiome that includes both bacteria and fungi and their associated metabolic states. These 'microbial fingerprints' permit patient stratification and we can identify particular disease phenotypes associated to clinical outcomes potentially amenable to precision and individualised intervention. It is clear that our microbes tell us something about disease, something representing a potential target for clinical intervention.	A/Prof Sanjay Haresh Chotirmall (NTU) http://www.lkcmedicine.ntu.edu.sg/aboutus/Faculty-and-Staff/Pages/Sanjay-Chotirmall.aspx	Prof Krasimira Tsaneva-Atanasova (UoE) http://emps.exeter.ac.uk/mathematics/staff/kt298

Annex A

	Using a well phenotyped and prospectively curated Asian and European dataset across a variety of chronic inflammatory respiratory disease states including severe asthma, chronic obstructive pulmonary disease (COPD) and bronchiectasis, this PhD project aims to perform the following: 1. Prospectively curate novel datasets focused on the Asian microbiome/mycobiome (and their associated metabolomic profiles) in patients with severe asthma, COPD and their associated overlap syndrome states (e.g. asthma-COPD overlap syndrome and bronchiectasis-COPD overlap syndrome). The candidate will gain experience in sequencing, bioinformatics and mass spectrometry. This work will be performed in Singapore. 2. Model mathematically microbiome and mycobiome populations and their interactions across a range of pulmonary disease states: this will utilize computational approaches to identify mathematically significant co-operative and competitive relationships within and between species. There is a scope for spatio-temporal modelling approaches, which would allow us to account for potential differences in anatomical distribution of the microbiome and mycobiome populations within the lung. This work will be performed in Exeter. 3. Apply the developed model systems to clinical settings in diagnosis, prognosis and predicting disease progression across a range of respiratory disease states This work will be performed in Singapore. 4. Finally, the use of microbial metabolomic datasets will further extend the developed models in order to take into account the affected pathways and signalling networks. This will further power our microbial airway interaction models and provide therapeutic and pharmaceutical		

Annex A

	relevance to their in vivo relationships. This work will be performed in Exeter.		