# A*STAR and King's College London PhD Studentships October 2021 Entry

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## A*STAR and King's College London PhD Studentships

When choosing a project from this catalogue in the funding section & research proposal section of the online application form, please enter the funding code that corresponds to the theme of your first project choice:

Molecules, Cells and the Basis for Disease: **THEME1_2021**

Neurosciences, Psychiatry and Mental Health: **THEME2_2021**

Imaging and Biomedical Engineering: **THEME3_2021**

Informatics: **THEME4_2021**

**Important dates:**

| Date | Application Stage |
|---|---|
| Deadline for application | Sunday 16th May, midnight |
| Application Outcome | By 28th May 2021 |
| Interviews | Week commencing Monday 14th June 2021 |
| Interview Outcomes | By Friday 18th June 2021 |
| Acceptance of studentship offer | By 2nd of July 2021 |
| Start Date | October 2021 |

The 2020/21 studentships will commence in October 2021. For further information or queries relating to the application process, please contact: doctoralstudies@kcl.ac.uk.

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**Projects listed in this catalogue are subject to amendments, candidates invited to interview will have the opportunity to discuss projects in further detail.**

# THEME1: Molecules, Cells and the Basis for Disease

## 1.1 Capturing the conformational dynamics of G Protein-Coupled Receptors (GPCRs) using an integrative structural approach.

Co-Supervisor 1A: Dr Argyris Politis

Research Division/Department or CAG: NMS, Department of Chemistry

E-mail: argyris.politis@kcl.ac.uk

Website: https://www.kcl.ac.uk/research/politis

Co-Supervisor 1B: Hao Fan

Research Institute: Bioinformatics Institute

Email: fanh@bii.a-star.edu.sg

Website: www.a-star.edu.sg/bii/research/bmad/sldd

**Project Description:**

Membranes are the gateways to the cell, responsible for shaping the structure and function of a wide variety of biomolecules. Integral membrane proteins are embedded within membranes and surrounded by lipids. Lipids provide the medium wherein membrane proteins function. G protein-coupled receptors (GPCRs) is an important class of membrane proteins that constitutes the main target of half of known drug targets. Despite the importance of GPCRs in human health and disease, the molecular level understanding of these biomolecules with ligands and other proteins remain limited. As such, lack of knowledge in the critical ligand-GPCR interface profoundly hinders our understanding of GPCR-related activities and encumbers current efforts for drug development.

The research will deliver a new interdisciplinary strategy to monitor the structural dynamics of complex ligand-GPCR assemblies. We will build a computational-experimental approach that exploits restraints extracted from advanced mass spectrometric technique to generate 3D models of membrane proteins. MS is among the handful of tools that can monitor the conformational dynamics of these assemblies in their native states. This, when coupled with advanced modelling capabilities can provide new insight into the roles of the surrounding environment, their conformational states and even the differential incorporation of small molecules important for their function. This integration is timely; it will push the boundaries towards understanding dynamic GPCR-ligand interactions, unattainable by the individual methods. Overall, the tools developed here will offer a robust technology for making inroads into assisting current efforts for rational drug design and development.

**Two representative publications from supervisors:**

Martens, C.; Shekhar, M.; Borysik, A. J.; Reading, E.; Lau, A. M.; Tajkorshid, E.; Booth, P. J.; **Politis, A.**, Direct protein-lipid interactions shape the conformational landscape of secondary transporters. Nature Communications 2018, 9;4151.

Liu H, Kim HR, Krishna Deepak RNV, Wang L, Chung KY, **Fan H**, Wei ZY, Zhang C. Orthosteric and allosteric action of the C5a receptor antagonists. Nature Structural & Molecular Biology 2018, 25:472.

## 2.1 Investigating conserved endodermal gene regulation.

Co-Supervisor 1A: Dr Fiona Wardle

Research Division/Department or CAG: FoLSM (Randall Centre for Cell & Molecular Biophysics)

E-mail: fiona.wardle@kcl.ac.uk

Website: https://www.kcl.ac.uk/research/wardle-group

Co-Supervisor 1B: Teo Kee Keong Adrian

Research Institute: Institute of Molecular and Cell Biology

Email: ateo@imcb.a-star.edu.sg

Website: https://www.a-star.edu.sg/imcb/imcb-research/scientific-programmes/cell-biology-and-therapies; https://research.a-star.edu.sg/researcher/adrian-teo-kee-keong/

**Project Description:**

This project will address the question of whether regions that control gene expression in the early embryo are conserved in vertebrates. Using expression of Sox17, which is turned on in all endodermal progenitors, this project will set out to identify the regulatory regions that control sox17 in zebrafish and assess whether these regions also control expression in human cells, and vice versa. To carry out this project the student will be trained in genomics techniques, bioinformatics, zebrafish embryology, genome editing and human stem cell culture. In the first year the student will characterise previously identified regulatory control regions in zebrafish, using genome editing, and will use a genomics technique, known as 4C-seq, to identify human regulatory control regions. In the second year the student will move to A*STAR to characterise the regulatory control regions in human stem cells. After 18 months at A*STAR the student will return to KCL to test the activity of these control regions in zebrafish which will answer the question of whether they are conserved in function.

**Two representative publications from supervisors:**

FW: Nelson A. C., Cutty S.J., Gasiunas S.N., Deplae I., Stemple D.L., Wardle F.C. (2017). In vivo regulation of the zebrafish endoderm progenitor niche by T-box transcription factors. Cell Reports, 19:2782-95.

AT: Loo, S.W.L., Soetedjo, A.A.P., Lau, H.H., Ng, H.J.N., Ghosh, S., Nguyen, L., Krishnan, V.G., Choi, H., Roca, X., Hoon, S., and Teo, K.K.A. (2020). BCL-xL/BCL2L1 is a critical anti-apoptotic protein that promotes the survival of differentiating pancreatic cells from human pluripotent stem cells. Cell Death Dis 11, 378.

## 3.1 Programming the brain for obesity

Co-Supervisor 1A: Dr Marika Charalambous

Research Division/Department or CAG: FoLSM, Department of Medical and Molecular Genetics

E-mail: marika.charalambous@kcl.ac.uk

Website: https://www.kcl.ac.uk/people/marika-charalambous

Co-Supervisor 1B: Dr Yu Fu

Research Institute: Institute of Molecular and Cell Biology

Email: fu_yu@sbic.a-star.edu.sg

Website: www.yufulab.com

**Project Description:**

Epidemiological studies provide strong evidence that people who were born small then 'catch up' have a much greater risk of developing metabolic disease as adults. However, the molecular mechanisms that underpin this process are not understood. Leptin is an important metabolic hormone produced by adipose tissue. Levels of circulating leptin report the body's energy reserve and signal to responsive neurons in the hypothalamus to direct the appropriate metabolic outcome. In addition, leptin signalling in early life is required to programme the neuronal circuits that will maintain lifetime responsiveness to this important hormone.

Loss of DLK1 gene function in humans causes Temple Syndrome (TS), where babies are born small with feeding problems, but catch up in early life to develop obesity and metabolic disease. We showed that mice with deleted Dlk1 mimic this disease. Importantly, our mutant mice produce much less leptin in the programming period. We hypothesise that Dlk1-deleted mice and TS patients become obese as adults because they cannot programme their hypothalamus. The project will test this hypothesis by comparing brain development between healthy and Dlk1-deleted mice using a combination of cutting-edge technologies.

**Year 1&2:** Using the mouse model to understand the molecular basis of the failure of leptin production. Performing single-cell RNA sequencing on the hypothalamus to investigate transcriptome of affected neuronal populations.

**Year 3:** Utilising a suite of novel imaging technologies to understand the activity and connectivity of the affected neuronal populations.

**Year 4**: 'curing' the mutant mice by treating them with leptin/other pharmacological agents.

**Two representative publications from supervisors:**

Cleaton MAM, Corish JA, Howard M, Gutteridge I, Takahashi N, Bauer SR, Powell TL, Ferguson-Smith AC, Charalambous M. (2016). Conceptus-derived Delta-like homologue-1 (DLK1) is required for maternal metabolic adaptations to pregnancy and predicts birthweight. Nat Genet, 48(12):1473-1480.

Luo SX*, Huang J*, Li Q*, Mohammad H, Lee CY, Krishna K, Kok AM, Tan YL, Lim JY, Li H, Yeow LY, Sun J, He M, Grandjean J, Sajikumar S, Han W, Fu Y. (2018) Regulation of feeding by somatostatin neurons in the tuberal nucleus. Science, 361(6397):76-81. (* equal contribution).

## 4.1 How are immune cells directed towards sites of infection or inflammation?

Co-Supervisor 1A: Professor Peter McNaughton

Research Division/Department or CAG: IoPPN, Wolfson Centre for Age-Related Diseases

E-mail: peter.mcnaughton@kcl.ac.uk

Website: https://www.kcl.ac.uk/people/peter-mcnaughton

Co-Supervisor 1B: Dr Laiguan Ng

Research Institute: SIgN

Email: Ng_Lai_Guan@immunol.a-star.edu.sg

Website: https://www.a-star.edu.sg/sign/people/principal-investigators/lai-guan-ng

**Project Description:**

**How are immune cells directed towards sites of infection or inflammation?**

Neutrophils and macrophages (leukocytes) are key innate immune effector cells involved in early detection of danger signals that are released by tissue damage and pathogens. Leukocytes move towards these signals to scavenge pathogens, initiate systemic immune responses and trigger injury resolution pathways. How is this vital cascade of events initiated? Recent evidence shows that hydrogen peroxide (H2O2) is released from damaged tissue by specific oxidases and that leukocytes navigate towards the damage up this gradient of H2O2. How is H2O2 detected by leukocytes? Recent work in the McNaughton lab shows that the ion channel TRPM2, which senses both elevated temperature and H2O2, is critical. TRPM2 is expressed in leukocytes and is calcium-permeable, so its activation promotes an influx of calcium into the leading edge of a leukocyte and thus steers it towards its target. At KCL we have established an in vitro system to measure neutrophil/macrophage navigation and to measure intracellular calcium levels. We will investigate the role of TRPM2 in leukocyte motility, using a combination of molecular, bio-informatic, cellular and whole-animal techniques, and using human neutrophils/monocytes and mouse neutrophils/macrophages. We will also conduct in vivo studies with WT and TRPM2 KO mice in which we will monitor neutrophil/macrophage invasion into nerve following injury in vivo.

At A*STAR we will image neutrophil movement in vivo using intravital microscopy. How does block/genetic deletion of TRPM2 in sepsis change leukocyte navigation? Can antagonists for TRPM2 be harnessed to inhibit leukocyte motility and thus aid in combatting life-threatening infection and inflammation?

**Specific skills:** In vitro microscopy and calcium imaging of immune cells. Intravital multi-photon confocal microscopy to track immune cell chemotaxis.

**Generic skills:** Cell biology, pharmacology, immunology, ion channel biology, molecular biology.

**Two representative publications from supervisors:**

H. O. J. Morad, S. Luqman, C.-H. Tan, V. Swann, P. A. McNaughton, TRPM2 ion channels steer neutrophils towards a source of hydrogen peroxide BioRxiv. 2021 (https://doi.org/10.1101/2021.01.06.425587). (Preprint; paper in press).

M. Evrard, I. W.H. Kwok, S. Z. Chong, K. W.W. Teng, E. Becht, J. Chen, J. L. Sieow, H. Leong Penny, C. C. Goh, S. Devi, J. M. Adrover, J. L.Y. Li, K. H. Liong, L. Tan, Z. Poon, S. Foo, J. W. Chua, I. H. Su, K. Balabanian, F. Bachelerie, S. K. Biswas, A. Larbi, W. Y.K. Hwang, V. Madan, H. P. Koeffler, S. C, Wong, E. W. Newell, A. Hidalgo, F. Ginhoux and L. G. Ng. (2018). Developmental analysis of bone marrow neutrophils reveals populations specialized in expansion, trafficking and effector functions. Immunity 48:364.

## 5.1 Force-dependent signalling regulating tissue fibrosis.

Co-Supervisor 1A: Professor Maddy Parsons

Research Division/Department or CAG: FoLSM (Randall Centre for Cell & Molecular Biophysics)

E-mail: maddy.parsons@kcl.ac.uk

Website: https://www.kcl.ac.uk/research/profile/the-parsons-group

Co-Supervisor 1B: Dr Andrea Pavesi

Research Institute: A*STAR IMCB

Email: andreap@imcb.a-star.edu.sg

Website: https://www.a-star.edu.sg/imcb/imcb-research/scientific-programmes/innovative-technologies

**Project Description:**

The ability of cells to make proteins, called extracellular matrix, that build tissues is essential during human development and for maintaining tissues in adults. Failure to properly regulate the production of these proteins leads to diseases such as fibrosis, where a build-up of extracellular matrix leads to loss of function in tissues such as lung, liver and skin. However, it is still unclear how the cells within tissues 'sense' their environment and use this information to regulate how much new extracellular matrix they produce. We believe that understanding this environmental 'sensing' is key to understanding how normal tissues are maintained. To test this, the student will combine skillsets learned from each supervisors laboratory to study how living cells in tissue-like environments respond to changes in their extracellular environment, by altering their gene and protein expression profiles. Ultimately it may be possible to use this knowledge to treat fibrotic diseases.

**Two representative publications from supervisors:**

Pfisterer K, Levitt J, Lawson CD., Marsh RJ, Heddleston JM, Wait E, Ameer-Beg S, Cox S, **Parsons M**. FMNL2 regulates dynamics of fascin in filopodia. J Cell Biol. 2020. 219 (5): e201906111

**Pavesi A,** Tan A, Koh S, Chia A, Colombo M, Antonecchia E, Miccolis C, Ceccarello E, Adriani G, Raimondi MT, Kamm RD, Bertoletti A. A 3D microfluidic model for preclinical evaluation of TCR-engineered T cells against solid tumors. JCI insight 2017. 2 (12)

## 6.1 Platelets: Pivotal players in allergen sensitization

Co-Supervisor 1A: Dr Simon Pitchford

Research Division/Department or CAG: FoLSM (Sackler Institute of Pulmonary Pharmacology, Institute of Pharmaceutical Science)

E-mail: simon.pitchford@kcl.ac.uk

Website: https://www.kcl.ac.uk/people/simon-pitchford

Co-Supervisor 1B: Dr Olaf Rötzschke

Research Institute: Singapore Immunology Network (SIgN)

Email: Olaf_Rotzschke@immunol.a-star.edu.sg

Website: https://www.a-star.edu.sg/sign/people/principal-investigators/olaf-r%C3%B6tzschke

**Project Description:**

Platelets have been recognized for some time to act as inflammatory cells in the defence of the body against infection, performing many functions normally associated with leukocytes. These roles are distinct from platelet function during haemostasis. Interestingly, platelets act as a 'bridge' between the innate and adaptive immune response. Platelets are activated in patients with asthma and are responsible for the misdirected inflammatory response. Recently, we reported that platelets migrate within lung tissue upon allergen sensitization and challenge and associate with lung dendritic cells (DCs), an event that was necessary for inflammatory responses upon subsequent, secondary allergen exposure. We outline a PhD programme to investigate how the process of antigen sensitization affects platelet 'immune signature' and activity and the development of immune memory. Future impact might lead to alternative strategies for 'disease modifying' therapies of allergic disease and provides an excellent basis for understanding host defence of respiratory pathogens in general as a next career step.

This exciting and ambitious project will allow the applicant to work in world-renowned laboratories at KCL and A*Star SIgN to learn in vivo disease models, human immunology, single cell RNA sequencing analysis, and clinical comparisons for relevance with patients with asthma.

Overarching objectives are: 1. Characterize megakaryocyte (MK) and platelet involvement in antigen processing and development of allergen sensitization; 2. To characterise the unique 'immune signatures' of MKs and platelets with relevance to asthma; 3. To probe the importance of this 'immune signature' in allergic inflammation.

**Two representative publications from supervisors:**

**Simon Pitchford, KCL First (Co-) supervisor:** Amison RT, Cleary SJ, Riffo-Vasquez Y, Bajwa M, Page CP, **Pitchford SC.** Platelets play a central role in sensitisation to allergen. *Am J Respir Cell Mol Biol.* 2018; 59: 96-103.

**Olaf Rotzschke, SIgN Second (Co-) supervisor:** Andiappan AK, Puan KJ, Lee B, Yeow PT, Yusof N, Meid SK, Kumar D, Lum J, Foo S, Koh G, Poidinger M, Zolezzi F; eQTLGen Consortium, BIOS consortium, Wang Y, Melén E, **Rotzschke O.** Inversed association of FCER1A allergy variant in monocytes and plasmacytoid dendritic cells. *J Allergy Clin Immunol.* 2020 Nov 5:S0091-6749(20)31562-1.

**Jinmiao Chen, SIgN Third supervisor:** Tran HTN, Ang KS, Chevrier M, Zhang X, Lee NYS, Goh M, **Chen J**. A benchmark of batch-effect correction methods for single-cell RNA sequencing data Genome Biology 2020; 21:12. doi: 10.1186/s13059-019-1850-9.

## 7.1 Using CRISPR/CAS9 screening to identify regulators of vascular calcification in a novel 3D spheroid model of mineralization

Co-Supervisor 1A: Professor Catherine Shanahan

Research Division/Department or CAG: FoLSM, School of Cardiovascular Medicine and Sciences

E-mail: cathy.shanahan@kcl.ac.uk

Website: https://www.kcl.ac.uk/people/catherine-shanahan

Co-Supervisor 1B: Professor Roger Foo

Research Institute: GIS

Email: https://www.a-star.edu.sg/gis/our-people

Website: https://www.a-star.edu.sg/gis/our-people

**Project Description:**

Vascular calcification is the deposition of apatite mineral in the vessel wall and is a well-established risk factor for cardiovascular morbidity and mortality. It is associated with vascular stiffening as well as rupture of atherosclerotic plaques and heart attacks. Vascular calcification is highly prevalent in the ageing population and accelerated in diabetes and chronic kidney disease. It is mediated by vascular smooth muscle cells (VSMCs) which undergo osteogenic differentiation and secrete calcifying exosomes which play a crucial role in initiating mineralization. Despite the current state of knowledge there are currently no treatment options. This project will take an unbiased approach to identify potential therapeutic targets for vascular calcification by performing a comprehensive genetic screen for factors that accelerate or block calcification using in vitro models. Determining the mechanisms via which these targets work and testing them in preclinical models will enable the identification of novel therapeutic targets for the treatment of this detrimental and prevalent pathology.

**Two representative publications from supervisors:**

Müller KH, Hayward R, Rajan R, Whitehead M, Cobb AM, Ahmad S, Sun M, Goldberga I, Li R, Bashtanova U, Puszkarska AM, Reid DG, Brooks RA, Skepper JN, Bordoloi J, Chow WY, Oschkinat H, Groombridge A, Scherman OA, Harrison JA, Verhulst A, D'Haese PC, Neven E, Needham LM, Lee SF, Shanahan CM*, Duer MJ*. (2019) Poly(ADP-Ribose) Links the DNA Damage Response and Biomineralization. Cell Rep. Jun 11;27(11):3124-3138.

Tan, W. L. W., Anene-Nzelu, C. G., Wong, E., Lee, C. J. M., Tan, H. S., Tang, S. J., . . . Foo, R. S. Y. (2020). Epigenomes of human hearts reveal new genetic variants relevant for cardiac disease and phenotype. Circ Res, 127(6), 761-777. doi:10.1161/CIRCRESAHA.120.317254

## 8.1 A Multidisciplinary Approach to Developing Next-Generation Peptide Therapeutics

Co-Supervisor 1A: Dr Martin Ulmschneider

Research Division/Department or CAG: NMS, Department of Chemistry

E-mail: martin.ulmschneider@kcl.ac.uk

Website: https://www.kcl.ac.uk/people/martin-ulmschneider

Co-Supervisor 1B: Peter J. Bond

Research Institute: Bioinformatics Institute (BII) A*STAR

Email: peterjb@bii.a-star.edu.sg

Website: https://www.a-star.edu.sg/bii/research/bmad/msmd

**Project Description:**

The innate immune system serves to recognize and clear a range of microbial pathogens, but its dysfunction during severe infections can lead to sepsis, which kills millions of people annually. This is worsened by the growing crisis of bacterial multidrug resistance, and is also associated with many inflammatory diseases such as arthritis, neurodegenerative disorders, and cancers. Here, we will take a multidisciplinary approach for the rational design and systematic optimization of novel therapeutic peptides with the ability to disrupt innate immune receptors. This will be achieved using a combination of state-of-the-art computational approaches including multiscale molecular simulations and machine learning (ML), in parallel with biophysical and cellular assays. This is a timely project because of the growing utility of therapeutic peptides in a clinical setting, whilst from the methodological standpoint, we have witnessed a revolution in computational power and big data that provides immense opportunities for applying simulation and ML techniques to drug development. In year 1 of this project, training at KCL will be provided in peptide synthesis, cell work, and relevant computational methodologies relevant to molecular design, providing a solid theoretical and practical grounding in the relevant topics and establishing core methodologies and techniques for the remainder of the PhD. In years 2-3, in Singapore, advanced simulation approaches in combination with appropriate ML algorithms will be used to optimize peptide candidates with potential immunomodulatory properties. In the final year, the student will return to KCL to experimentally test and validate lead peptides, towards potential therapeutic application.

**Two representative publications from supervisors:**

Kaur H, Jakob RP, Marzinek JK, Green R, Imai Y, Bolla JR, Agustoni E, Robinson CV, Bond PJ, Lewis K, Maier T, Hiller S. Antibiotic darobactin mimics a b-strand to inhibit outer membrane insertase. Nature. In press (April, 2021).

Chen C, Starr CG, Troendle E, Wiedman G, Wimley WC, Ulmschneider JP, Ulmschneider MB. Simulation-Guided Rational de Novo Design of a Small Pore-Forming Antimicrobial Peptide. JACS (2019)

## 9.1 Regulation of glioblastoma stem cell quiescence

Co-Supervisor 1A: Dr Rita Sousa-Nunes

Research Division/Department or CAG: IoPPN, Centre for Developmental Neurobiology

E-mail: rita.sousa-nunes@kcl.ac.uk

Website: https://devneuro.org/cdn/group-overview.php?groupID=88&height=1254&width=2220&ref=group-leaders; https://www.kcl.ac.uk/people/rita-sousa-nunes

Co-Supervisor 1B: Edward Manser

Research Institute: Institute of Molecular and Cell Biology

Email: ed.manser@imcb.a-star.edu.sg

Website: https://www.a-star.edu.sg/imcb/imcb-research/scientific-programmes/neurometabolism-in-health-diseases

**Project Description:**

Innovative approaches to tackle glioblastoma multiforme (GBM) are greatly needed. GBM is high-grade (IV) glioma, the most common and aggressive of malignant primary brain tumours. GBM patients have an average survival time of 12-15 months post-diagnosis, due to recurrence after treatment.

GBM growth is driven by glioblastoma stem cells (GSCs) so curing GBM requires approaches to eradicate GSCs. This is challenging because a large proportion of GSCs are quiescent.

Quiescence is a cellular state characterised by reversible cell-cycle arrest accompanied by diminished biosynthetic activity. It evolved to protect stem cells from replicative exhaustion and mutations, as well as environmental insults. Quiescent cancer cells are resistant to current therapies. Following therapy-resistance, GSC reactivation from quiescence causes disease relapse.

A major hurdle in studying quiescence is the lack of positive markers for this state. Quiescent stem cells are currently defined by the expression of stem cell-type specific markers, in combination with absence of proliferation markers. The Sousa-Nunes laboratory has found altered nucleocytoplasmic partitioning in quiescent versus active cells, with increased nucleocytoplasmic ratio of polyadenylated transcripts the first positive marker of quiescence. They also found that subcellular compartment transcript bias greatly impacts protein expression. We propose to join complementary expertise to identify molecules and pathways controlling GSC quiescence regulation. In addition to novel insight into a fundamental biological problem, this should yield the first molecular markers of GSC quiescence, which may provide candidates to test for use as clinical biomarkers.

The student will learn cell culture, molecular genetic, cell biological, proteomic and bioinformatic approaches.

**Two representative publications from supervisors:**

**Sousa-Nunes R**, Yee LL, Gould AP. Fat cells reactivate quiescent neuroblasts via TOR and glial Insulin relays in Drosophila. Nature 471(7339):508-12 (2011).

Dong JM, Tay FP, Swa HL, Gunaratne J, Leung T, Burke B, and **Manser E**. Proximity biotinylation provides insight into the molecular composition of focal adhesions at the nanometer scale. Sci Signal. 9(432):rs4 (2016).

# THEME2: Neurosciences, Psychiatry and Mental Health

## 1.2 Motivation to model others' minds: the importance of cognitive motivation for mental state understanding in early adolescence

Co-Supervisor 1A: Dr Caroline Catmur

Research Division/Department or CAG: IoPPN, Department of Psychology

E-mail: caroline.catmur@kcl.ac.uk

Website: https://kclpure.kcl.ac.uk/portal/caroline.catmur.html

Co-Supervisor 1B: Dr Yuen Siang Ang

Research Institute: Social and Cognitive Computing, Institute of High Performance Computing

Email: angys@ihpc.a-star.edu.sg

Website: https://yuensiangang.github.io

**Project Description:**

Understanding others' mental states allows individuals to obtain the social support necessary for mental wellbeing. But some people struggle to understand others. Early adolescence is a period of intense social change, making this a crucial developmental period for mental state understanding. Identification of factors influencing mental state inference during adolescence may lead to improved predictors and treatments for mental ill-health in later life.The factors impacting upon individuals' motivation to engage in mental state understanding are not well understood, and few measures of this motivation exist. This project combines the first supervisor's research into how humans model others' minds, with the second supervisor's expertise in cognitive motivation, to measure motivation to engage in mental state inference. Following development and validation of the 'Motivation to Model Minds' measure (months 1-15, London), the student will assess this ability in the GUSTO cohort of 13-year-old youths (months 16-36, Singapore).

We will capitalise on the exceptionally rich datasets that have been collected from this cohort, allowing us to identify early-life factors which impact on the motivation to model others' minds in adolescence, along with measuring associations during adolescence between the motivation to model minds and other social and cognitive abilities, and mental wellbeing.

Year 4, in London, will focus on writing up the thesis and disseminating the project results.This project involves methodologies from experimental psychology and computational modelling, along with big data analysis techniques. This makes it an exciting opportunity for the student to develop a range of highly transferable skills as part of their studies.

**Two representative publications from supervisors:**

Conway, J. R., Coll, M. P., Cuve, H. C., Koletsi, S., Bronitt, N., **Catmur, C.,** & Bird, G. (2020). Understanding how minds vary relates to skill in inferring mental states, personality, and intelligence.

Journal of Experimental Psychology: General, 149(6), 1032–1047. https://doi.org/10.1037/xge0000704

**Ang Y-S.,** Manohar S., Plant O., Kienast A., Le Heron C., Muhammed K., Hu M., Husain M. (2018). Dopamine modulates option generation for behaviour. Current Biology, 28(10), 1561–1569.

## 2.2 The impact of pubertal transition on trajectories of brain development and onset of depression

Co-Supervisor 1A: Professor Paola Dazzan

Research Division/Department or CAG: IoPPN, Department of Psychological Medicine

E-mail: paola.dazzan@kcl.ac.uk

Website: https://www.kcl.ac.uk/people/paola-dazzan

Co-Supervisor 1B: Michael Meaney

Research Institute: Translational Neuroscience, SICS

Email: michael.meaney@mcgill.ca

Website: https://www.a-star.edu.sg/sics/our-people/our-leaders

**Project Description:**

Psychiatric disorders, like depression and anxiety usually strike at a young age, and the risk for developing these problems is higher in puberty, the time when a child's body begins to change as they become an adult, around age 11 years for girls and 12 years for boys. Still, we do not why puberty is a time of higher risk for developing depression. In particular, we do not know whether the changes that are also happening in the brain around this time can explain why puberty increases chances of having mood problems. Furthermore, we do not know whether other factors, such as growing up in a very supportive family or community environment, may protect some adolescents from experiencing mental health problems in puberty or later on.

This project will evaluate data from two cohorts of school adolescents (age 8-14 years, n=520), recruited in the UK and in Singapore, collected before and after puberty, at three time points (about one year apart). These data include details of puberty, brain structure (obtained with an approach called “magnetic resonance imaging (MRI)”, which provides pictures of the brain), mental health, and social environment.

The study will help us understand when adolescents are most vulnerable to mood problems, when interventions (talking therapy or medications) can reduce risk of adverse mental health outcomes.

The student will develop general skills in psychiatry research and specific skills in MRI data analysis and their integration with biological and social measures.

**Two representative publications from supervisors:**

Brain structure in women at risk of postpartum psychosis: an MRI study.

Fusté M, Pauls A, Worker A, Reinders AATS, Simmons A, Williams SCR, Haro JM, Hazelgrove K, Pawlby S, Conroy S, Vecchio C, Seneviratne G, Pariante CM, Mehta MA, Dazzan P. Transl Psychiatry. 2017 Dec 18;7(12):1286. doi: 10.1038/s41398-017-0003-8. PMID: 29249808

Effects of Antenatal Maternal Depressive Symptoms and Socio-Economic Status on Neonatal Brain Development are Modulated by Genetic Risk.

Qiu A, Shen M, Buss C, Chong YS, Kwek K, Saw SM, Gluckman PD, Wadhwa PD, Entringer S, Styner M, Karnani N, Heim CM, O'Donnell KJ, Holbrook JD, Fortier MV, Meaney MJ; the GUSTO study group. Cereb Cortex. 2017 May 1;27(5):3080-3092. doi: 10.1093/cercor/bhx065.

## 3.2 Cross-cultural analyses of depression and anxiety: the role of genetic and environmental influences

Co-Supervisor 1A: Professor Thalia Eley

Research Division/Department or CAG: IoPPN, Social, Genetic & Developmental Psychiatry Centre

E-mail: thalia.eley@kcl.ac.uk

Website: https://www.kcl.ac.uk/people/thalia-eley

Co-Supervisor 1B: Prof Jianjun Liu

Research Institute: Genome Institute of Singapore

Email: liuj3@gis.a-star.edu.sg

Website: https://research.a-star.edu.sg/researcher/jianjun-liu/

**Project Description:**

This project will expand knowledge of the role of genetic and environmental influences on depression and anxiety, and how these differ in the UK versus Singapore. The student would receive training in developmental psychology, genetics, psychiatric epidemiology and statistics. They would learn advanced longitudinal and genetic association analysis methods, working with large datasets from both the UK and Singapore.

There have been rapid advances in genetic findings regarding depression and anxiety within European ancestries over the last 5 years. However, there is a lack of generalisability to individuals of non-European ancestries. The work within this studentship would help address this.

Alongside expanding knowledge about genetics, understanding of the importance of the role of the environment, and interplay between genetic and environmental factors has grown. This project will allow the student to explore effects of lifelong family, home, social and peer related environmental factors on depression and anxiety outcomes in the late twenties.

Additionally, the student will be able to choose an approach to exploring gene-environment interplay. They can either examine the extent to which genetic factors operate through the environment (gene-environment correlation), or the way in which genetic factors influence sensitivity to the environment (gene-environment interaction).

All questions will initially be addressed within UK samples, then time and datasets allowing, in Singapore samples in order to make cross-cultural comparisons.

The overarching year objectives are:

Year 1. Environmental analyses.
Year 2. Genetic analyses.
Year 3. Transfer to Singapore. Gene-environment interplay analyses.
Year 4. Cross-cultural analyses. Return to UK. Completion/submission of thesis.

**Two representative publications from supervisors:**

Purves, K., Coleman, J., Meier, S., Rayner, C., Davis, K., Cheesman, R., Bækvad-Hansen, M., Børglum, A., Wan Cho, S., Deckert, J., Gaspar, H., Bybjerg-Grauholm, J., Hettema, J., Hotopf, M., Hougaard, D., Hübel, C., Kan, C., McIntosh, M., Mors, O., Mortensen, P., Nordentoft, M., Werge, T., Nicodemus, K., Mattheisen, M., Breen., G.*, & Eley, T.C.* (2020) A major role for common genetic variation in anxiety disorders. Molecular Psychiatry, 25, 3292–3303. doi: 10.1038/s41380-019-0559-1

Lam, M., C.Y. Chen, Z. Li, A.R. Martin, J. Bryois, X. Ma, H. Gaspar, M. Ikeda, B. Benyamin, B.C. Brown, R. Liu, W. Zhou, L. Guan, Y. Kamatani, S.W. Kim, M. Kubo, A. Kusumawardhani, C.M. Liu, H. Ma, S. Periyasamy, A. Takahashi, Z. Xu, H. Yu, F. Zhu, C. Schizophrenia Working Group of the Psychiatric Genomics, C. Indonesia Schizophrenia, R.o.s.n.-C. Genetic, N. the, W.J. Chen, S. Faraone, S.J. Glatt, L. He, S.E. Hyman, H.G. Hwu, S.A. McCarroll, B.M. Neale, P. Sklar, D.B. Wildenauer, X. Yu, D. Zhang, B.J. Mowry, J. Lee, P. Holmans, S. Xu, P.F. Sullivan, S. Ripke, M.C. O'Donovan, M.J. Daly, S. Qin, P. Sham, N. Iwata, K.S. Hong, S.G. Schwab, W. Yue*, M. Tsuang*, J. Liu*, X. Ma*, R.S. Kahn*, Y. Shi*, & H. Huang* (2019) Comparative genetic architectures of schizophrenia in East Asian and European populations. Nature Genetics, 51, 1670-1678. doi: 10.1038/s41588-019-0512-x.

## 4.2 The intergenerational transmission of neurodevelopmental risk in middle childhood following maternal depression in pregnancy: Longitudinal evidence from clinical and population-based studies in the UK and Singapore.

Co-Supervisor 1A: Dr Vaheshta Sethna

Research Division/Department or CAG: IoPPN, Department of Forensic and Neurodevelopmental Sciences

E-mail: vaheshta.sethna@kcl.ac.uk

Website: https://kclpure.kcl.ac.uk/portal/vaheshta.sethna.html

Co-Supervisor 1B: Dr Michael Meaney

Research Institute: Singapore Institute for Clinical Sciences (SICS)

Email: michael.meaney@mcgill.ca

Website: https://www.a-star.edu.sg/sics/About-Us/Our-Investigators/Michael-Meanley

**Project Description:**

The influence of maternal depression on child outcomesis well studied. Children born to women who experience depression in pregnancy are at increased risk for depression and other forms of psychopathology; yet others are resilient with respect to mental health outcomes. In contrast, our understanding of why and how children are at risk or remain resilient, is limited. This project aims to identify pathways to developmental outcomes, in 7–9- year-old children, of mothers who are depressed in pregnancy. Understanding these pathways is crucial in developing early preventative and treatment strategies. Access to both the Psychiatry Research and Motherhood (PRAM) study (UK) and the Singapore based Growing Up in Singapore Towards Healthy Outcomes (GUSTO) study, will enable a cross-cultural investigation of how multiple risk factors and potential contributory processes work together when they co-occur. The study will offer data management skills and training in sophisticated statistical analyses of large datasets. Training in observational parenting data, and exposure to a wide knowledge base from perinatal mental health, bio-psychosocial and environmental factors, to behaviour and cognition in child development, will be offered. A thesis incorporating publications will be a suggested approach. Year 1 will comprise experience of working with families (KCL), year 2 and the first 6 months of year 3 (Singapore) will comprise training in statistical techniques, analysis and manuscript write-up for data collected across both studies. The last six months of year 3 and year 4 (UK) will be dedicated to working out processes of risk transmission and thesis completion.

**Two representative publications from supervisors:**

**Sethna, V.**, Pote, I., Wang, S., Gudbrandsen, M., Blasi, A., McCusker, C., … McAlonan, G. M. (2017). Mother-infant interactions and regional brain volumes in infancy: An MRI study. Brain Structure and Function, 222(5), 2379–2388. doi:10.1007/s00429-016-1347-1.

**Meaney MJ** (2018) Perinatal maternal depression as a population health issue. American Journal of Psychiatry. 175: 1084-1093.

## 5.2 Using virtual reality and brain-computer interface technology to investigate sense of body ownership, movement and agency in patients with functional neurological disorder and schizophrenia.

Co-Supervisor 1A: Dr Paul Shotbolt and Dr Sukhi Shergill

Research Division/Department or CAG: IoPPN, Academic Psychiatry/Psychosis

E-mail: paul.shotbolt@kcl.ac.uk and sukhi.shergill@kcl.ac.uk

Website: https://kclpure.kcl.ac.uk/portal/sukhi.shergill.html

Co-Supervisor 1B: Professor Kai Keng Ang

Research Institute: Institute for Infocomm Research

Email: kkang@i2r.a-star.edu.sg

Website: https://www.a-star.edu.sg/i2r

**Project Description:**

Functional Neurological Disorder (FND) is the second commonest diagnosis in neurology clinics and causes significant disability (Carson & Stone, 2015). Motor FND symptoms are subjectively reported by patients as involuntary (Edwards, 2012). This may be mediated by altered sense of body ownership and agency, also found in schizophrenia (Shergill 2014).

Previous studies of these constructs, using experimental paradigms such as the rubber hand illusion, have led to conflicting results. In this project, novel VR environments will be used. We anticipate that their immersive nature plus the ease of manipulation to change experimental conditions will allow more valid investigation.

The hypotheses are that, compared to controls, patients with FND and schizophrenia will; 1. be more susceptible to manipulation of sense of body ownership. 2. show reduced agency over the movements of an avatar. 25 individuals diagnosed with FND, 25 with schizophrenia and 25 healthy controls recruited. Body ownership and agency assessed in two VR environments; a 'virtual mirror' avatar (participants see an avatar in front of them that follows their movements), and a 'virtual body illusion' (participants see a projected true image of their body from the back).

The thesis will also include proof of concept development of BCI for use in FMD patients. We anticipate this technology has potential to be an effective treatment in FMD.

**Skills Training**

1. Assessment of FND/schizophrenia patients (Year 1,2);
2. VR design (Year 1,2);
3. BCI development (Year 3,4);
4. all aspects of relevant research methods and data analysis, publication and dissemination of results (Years 1-4).

**Two representative publications from supervisors:**

Functional magnetic resonance imaging of impaired sensory prediction in schizophrenia.

Shergill SS, White TP, Joyce DW, Bays PM, Wolpert DM, Frith CD. JAMA Psychiatry 2014 Jan;71(1):28-35.

Brain-Computer Interface-Based Soft Robotic Glove Rehabilitation for Stroke.

Nicholas Cheng , Kok Soon Phua, Hwa Sen Lai , Pui Kit Tam, Ka Yin Tang , Kai Kei Cheng, Raye Chen-Hua Yeow, Kai Keng Ang, Cuntai Guan, Jeong Hoon Lim. IEEE Transactions on Biomedical Engineering, Vol. 67, No. 12, December 2020.

# THEME3: Imaging and Biomedical Engineering

## 1.3 Cardiac blood flow simulation for patients with heart failure and atrial fibrillation HF-AF

Co-Supervisor 1A: Professor Steve Niederer

Research Division/Department or CAG: FoLSM, Department of Biomedical Engineering

E-mail: steven.niederer@kcl.ac.uk

Website: https://kclpure.kcl.ac.uk/portal/steven.niederer.html

Co-Supervisor 1B: Dr Cui Fangsen

Research Institute: Institute of High Performance Computing

Email: cuifs@ihpc.a-star.edu.sg

**Project Description:**

Heart failure and atrial fibrillation are two common cardiovascular disease that commonly co[1]exist. However, there are many aspects of treating atrial fibrillation in the presence of heart failure that are still unknown. One of these aspects is the effect of the two commonly atrial fibrillation used treatments. i.e., rate control and rhythm control on the blood pumped by the heart during each heartbeat. During this project, the student will learn how to simulate the blood flow in the heart undergoing rate and rhythm control treatments. The simulation results will be used to determine the favourable and adverse effects of each treatment on heart performance. We will test if these simulations can be used to predict patient outcomes. We will use a high[1]performance computation to predict the results and then validate them against the patients' data.

By working on this project, the student will learn how to define a research question, collect and analyse patient-specific data, use a multidisciplinary approach to model the phenomenon mathematically, computationally simulate the blood flow, and translate the results in a medically relevant guideline. Besides the technical skills, the student will be trained to communicate clearly with the scientific community, think critically, identify current challenges and find research opportunities in their field of interest. The prospective student will benefit from the world class computational facilities and mentoring by prominent scientists during this international collaboration between KCL and A*STAR.

**Two representative publications from supervisors:**

De Vecchi, A., Marlevi, D., Nordsletten, D.A., Ntalas, I., Leipsic, J., Bapat, V., Rajani, R. and **Niederer, S.A.**, 2018. Left ventricular outflow obstruction predicts increase in systolic pressure gradients and blood residence time after transcatheter mitral valve replacement. Scientific reports, 8(1), pp.1-11.

Kumar G. P., Kabinejadian F., Liu J. F., Leo H. L., Ho P., **Cui F.**, 2017. Simulated bench testing to evaluate the mechanical performance of new carotid stents, Artificial Organs, 41(3), pp267-272.

## 2.3 Development of multimodal imaging tools for monitoring Immunotherapy response in cancer

Co-Supervisor 1A: Dr Graeme Stasiuk

Research Division/Department or CAG: FoLSM, School of Biomedical Engineering and Imaging Sciences

E-mail: graeme.stasiuk@kcl.ac.uk

Website: https://www.kcl.ac.uk/people/graeme-stasiuk

Co-Supervisor 1B: Edward George Robins

Research Institute: Singapore Bioimaging Consortium (SBIC)

Email: Edward_Robins@sbic.a-star.edu.sg

Website: https://www.a-star.edu.sg/sbic/research/overview/pet-chemistry-group

**Project Description:**

Immunotherapy is a new treatment for cancer, it uses our own immune system to fight the spread of and reduce the size of cancer in the body. Used throughout the world it is very expensive and does not always work. This project sets out to make imaging tools that can be used in any medical scanner in a hospital to monitor immunotherapy treatment. Currently this is done with tools that go to highly active parts of the body and not specifically to the cancer. These multimodal tools will be for magnetic resonance imaging (MRI), and positron emission tomography (PET) so we can use the high resolution of MRI with the high sensitivity of PET. Targeting two parts of the cancer that immunotherapy effects, firstly Granzyme B and secondly reactive oxygen species (ROS), both of which are found in very high levels within cancers. Therefore, these tools will tell us where the tumour is and if immunotherapy is working.

The PhD student will firstly spend 18 months in King's College London learning chemical synthesis of the tools, how to develop nanoparticles for loading the MRI, PET and targeting agents. They will learn how to handle radioisotopes (68Ga, 89Zr and 18F).

The student will then go to A*STAR in Singapore for 2 years. Initially, the emphasis will be to establish the radiolabelling chemistries developed at KCL in A*STAR laboratories and to studying the tools and methods required to develop cancer models both in cell lines and preclinical models using MRI and PET.

**Two representative publications from supervisors:**

"A single pot template reaction towards a manganese based T1 contrast agent", S. Anbu, S,H. L. Hoffmann, F. Carniato, L. Kenning, T.W. Price, T. J. Prior, M. Botta, A. F. Martins, **G.J. Stasiuk**, Angewandte Chem. Intl. Ed. 2021, Accepted. https://doi.org/10.1002/anie.202100885

**Goggi JL,** Hartimath SV, Hwang Y, Tan YX, Khanapur S, Ramasamy B, Jiang L, Yong FF, Cheng P, Tan PW, Husaini MAR, Yuen TY, Jieu B, Chacko AM, Larbi A, Renia L, Johannes C, **Robins EG** (2020) Examining immunotherapy response using multiple radiotracers. Mol Imaging Biol **22**:993–1002 https://pubmed.ncbi.nlm.nih.gov/32006204/

# THEME4: Informatics

## 1.4 Delineating Microbial and Drug Interactions through Data Science

Co-Supervisor 1A: Dr Sophia Tsoka

Research Division/Department or CAG: NMS, Department of Informatics

E-mail: sophia.tsoka@kcl.ac.uk

Website: https://kclpure.kcl.ac.uk/portal/sophia.tsoka.html

Co-Supervisor 1B: Dr Min Wu

Research Institute: Institute for Infocomm Research (I2R)

Email: wumin@i2r.a-star.edu.sg

**Project Description:**

Complex networks can be used to describe a wide variety of systems of high technological and intellectual importance. In the analysis of biomedical data, analysis of disease-related networks, microbe-host or microbe-drug interactions are particularly critical in delineating complex physiological mechanisms, including immunity. Computational methods and data analytics, through network analysis and machine learning methods, aim to model individual pairwise interactions between biological entities in a holistic manner, so that the properties of the entire system dynamics, such as self[1]organisation or adaptiveness, can be revealed.

In the study of medically important systems, community structure detection provides a topological perspective of interactions at system-level and can lead to critical insights into the functional organisation of the underlying molecular processes. Additionally, methodologies with predictive potential, such as classification or regression, can link observations to specific phenotypic outcomes. In this project we will apply state-of-the-art computational methodologies that span data representation and integration through knowledge graphs, combinatorial optimisation for community detection in multi-layer graphs, graph neural networks to model microbe-host and drug-target interactionsin a predictive framework and graph convolutional networks for microbe-drug associations. Overall, this project provides training into popular data science strategies for Bioinformatics and Systems Biology and will contribute to novel mechanistic insights in the context of microbial interactions and drug discovery.

**Two representative publications from supervisors:**

N. Fyhrquist, G. Muirhead, S. Prast-Nielsen, M. Jeanmougin, P. Olah, T. Skoog, G. Jules-Clement, M. Feld, M. Barrientos-Somarribas, E. van den Bogaard, P. Zeeuwen, G. Ricken, J. Schalkwijk, T. Ederveen, W. Daubener, S. K. Eller, H. Alexander, D. Pennino, S. Suomela, I. Tessas, E. Lybeck, A. M. Baran, H. Darban, R. S. Gangwar, U. Gerstel, K. Jahn, P. Karisola, L. Yan, B. Hansmann, S. Katayama, S. Meller, M. Bylesjö, P. Hupé, F. Levi-Schaffer, D. Greco, A. Ranki, J. M. Schröder, J. Barker, J. Kere, S. Tsoka, A. Lauerma, V. Soumelis, F. O. Nestle, B. Homey, B. Andersson, H. Alenius, “Microbe-host interplay in atopic dermatitis and psoriasis”, Nature Communications, 10, 4703, 2019.

Long, Y., Wu, M., Kwoh, C. K., Luo, J., & Li, X. “Predicting human microbe–drug associations via graph convolutional network with conditional random field”, Bioinformatics, 36(19), 4918-4927, 2020.