King’s Bioscience Institute

Projects 2015

Neuroscience
Contents

Neurogenesis in the ageing brain: connecting the systemic milieu to brain structure and function .......... 3
Study of the effect of novel oral anticoagulants on the performance of the blood-brain barrier .................. 4
Investigating the function of an autism-associated chromatin remodelling factor in brain development ...... 6
Functional analysis of neural networks in zebrafish models of epilepsy .................................................. 7
Investigating the pathophysiological mechanisms linking depression and type 2 diabetes ...................... 8
Effect of autoantibodies in fetal brain development .................................................................................. 9
Development of biomarkers to distinguish pseudoprogression and progression in glioblastoma .......... 11
Awakening the brain with dopaminergic therapy in Parkinson’s disease. Why do some patients respond
while others do not? A resting-OFF and turning-ON fMRI study ............................................................... 13
Developing a translational stem cell model of autism .............................................................................. 14
Identifying biomarkers and causal mechanisms of chemotherapy-induced painful peripheral neuropathies
.................................................................................................................................................................. 15
Exploring mitochondrial retrograde signalling as a novel treatment target in neurodegenerative disease.. 17
A zebrafish model of EPG5-related multisystem disorders associated with defective autophagy .......... 18
The endoplasmic reticulum-mitochondria axis in Alzheimer’s disease and dementia ......................... 19
Repurposing of drugs for treatment of psychiatric conditions ............................................................... 20
RBM3 – Potential hypothermia-independent neuroprotection ............................................................... 21
Neurogenesis in the ageing brain: connecting the systemic milieu to brain structure and function

Theme: Neuroscience
Supervisor 1 & Collaborating Clinician: Dr Michael O’Sullivan, MD, PhD
Research Division or CAG: Neuroscience Division and Clinical Neurosciences CAG
E-mail: mike.osullivan@kcl.ac.uk

Supervisor 2: Dr Sandrine Thuret, PhD
Research Division or CAG: Neuroscience Division
E-mail: sandrine.1.thuret@kcl.ac.uk
Website: http://www.kcl.ac.uk/ioppn/depts/neuroscience/research/centres/ccbb/groups/nnmh/about.aspx

Project description:

Neurogenesis – the production of newborn neurones – is now known to occur throughout adult life in specific locations. One example is the hippocampus, where new neurones are crucial to the acquisition of certain types of memory. In previous work, the Thuret lab developed an in vitro model of the maturation of hippocampal progenitor cells and showed that serum derived from blood samples of older individuals adversely affects neuronal differentiation and maturation. Separately, the O’Sullivan group has shown that integrity of the main output pathway of the hippocampus – the fornix – is central to subtle deterioration in memory in ageing.

The objective of this PhD will be to unite these cellular and systems perspectives of hippocampal circuitry and explore their relationships to ageing. In individuals, in vitro markers of the systemic environment for neurogenesis will be correlated with structure and function of hippocampal circuits, probed by advanced imaging. Structure will be explored with diffusion tensor MRI and tractography; function through resting blood flow and fMRI with specific cognitive tasks (e.g. pattern separation).

Year 1 - Structure. Analysis of existing data combining in vitro assays (Thuret lab), 3T MRI including fornix reconstructions and cognition (O’Sullivan lab, n=30).
Year 2 - Function. Resting and task fMRI in an existing and new sample, to investigate the relationships between systemic milieu and hippocampal function (e.g. fMRI of pattern separation)
Year 3 - Intervention. Adapt existing imaging assays of hippocampal plasticity and test whether longitudinal changes with learning can be predicted by in vitro assays.

Two representative publications:


Study of the effect of novel oral anticoagulants on the performance of the blood-brain barrier

Theme: Neuroscience
Supervisor 1: Dr Sarah Ann Thomas (Reader in Physiology)
Research Division or CAG: Department of Physiology/Institute of Pharmaceutical Sciences
E-mail: sarah.thomas@kcl.ac.uk
Website: http://www.kcl.ac.uk/lsm/research/divisions/ips/about/people/Thomas/index.aspx

Supervisor 2: Dr Jignesh Patel (Honorary Consultant Pharmacist in Anticoagulation / Clinical Senior Lecturer)
Research Division or CAG: Department of Haematological Medicine, King’s College Hospital / Institute of Pharmaceutical Science
E-mail: jig.patel@kcl.ac.uk
Website: http://www.kcl.ac.uk/lsm/research/divisions/ips/about/people/Patel/Patel.aspx

Collaborating Clinician: Professor Roopen Arya (Consultant Haematologist and Director of King’s Thrombosis Centre)
E-mail: roopen.arya@nhs.net
Website: http://www.kingsthrombosiscentre.org.uk/index.php/staff/10-doctors/3-dr-roopen-arya
Summary of role: Head of the King’s Thrombosis Centre. The King’s Thrombosis Centre research group meet monthly to discuss on-going research studies within the group and to provide appropriate support for all research fellows. The student will be expected to attend and contribute to these meetings plus relevant national and international conferences.

Project description:
Intracranial haemorrhage is a devastating consequence of oral anticoagulation, with a reported incidence of 0.2 to 0.5% per year. The novel oral anticoagulants (NOACs), dabigatran and rivaroxaban have both demonstrated significantly lower rates of intracranial haemorrhage (ICH) compared to the current standard of warfarin therapy. Both dabigatran etexilate and rivaroxaban are substrates for the intestinal transmembrane efflux protein, P-glycoprotein, which is highly expressed on the luminal membrane of the blood-brain barrier (BBB). The BBB protects the brain from harmful substances and it could be that P-glycoprotein and other efflux proteins are protecting against ICH.

This study aims to investigate the specific P-glycoprotein binding of rivaroxaban and dabigatran within the BBB in comparison to warfarin, identify which other blood-brain barrier transport proteins the NOACs interact with and explore what implications this might have for clinical practice.

Our objectives will be to:

• YEAR 1:i) examine the integrity of human brain endothelial cell membranes on exposure of the luminal and abluminal surfaces to clinically relevant concentrations of dabigatran, rivaroxaban, and warfarin and ii) quantify the cellular accumulation of these drugs in an in vitro human BBB model.

• YEARS 2 and 3:iii) identify transporters involved in the accumulation of dabigatran, rivaroxaban, and warfarin using chemical inhibition methods and Western blotting,

• YEAR 4:iv) use whole animal methods to quantify delivery of each drug across the BBB in vivo and v) compare and contrast real world and clinical trial ICH outcome data for dabigatran, rivaroxaban and warfarin, to the laboratory findings, so specific recommendations for clinical practice can be made.
Two representative publications:

1) Dentali et al., Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. Circulation 2012; 126:2381-2391

Investigating the function of an autism-associated chromatin remodelling factor in brain development

Theme: Neuroscience
Supervisor 1: Dr. M. Albert Basson
Research Division or CAG: Craniofacial Development and Stem Cell Biology
E-mail: albert.basson@kcl.ac.uk
Website: http://www.kcl.ac.uk/dentistry/research/researchlabs/bassonlab.aspx

Supervisor 2: Dr. Cathy Fernandes
Research Division or CAG: Institute of Psychiatry
E-mail: catherine.fernandes@kcl.ac.uk
Website: http://www.iop.kcl.ac.uk/staff/profile/default.aspx?go=10093

Collaborating Clinician: Professor Patrick F. Bolton
Research Division or CAG: Institute of Psychiatry
Email: patrick.bolton@kcl.ac.uk
Website: http://www.iop.kcl.ac.uk/staff/profile/default.aspx?go=10618

Summary of role: To provide expertise in the genetics and clinical manifestations of autism spectrum disorder (ASD), organise observations of the assessment, ASD diagnosis and treatment of children by the National Specialist multi disciplinary team I lead.

Project description:
Autism-spectrum disorders (ASDs) affect more than 1/110 individuals in the population, yet the aetiology of ASDs is not understood. The recent identification of loss-of-functions mutations in the CHD8 gene, which encodes a chromatin remodelling enzyme, in patients with autism, provide us with a unique opportunity to investigate the developmental mechanisms that underlie autism.

We have generated a new conditional mouse line that will allow the investigation of CHD8 functions in neural progenitors from specific brain regions. In addition, we have developed new tools to identify CHD8-regulated regulatory elements in neural progenitors using Chromatin Immunoprecipitation (ChIP) assays.

The aim of this project will be to identify the functions of CHD8 in brain development and to identify the molecular genetic pathways deregulated upon the loss of CHD8 in neuronal progenitors.

To achieve this goal, the student will:

1) delete CHD8 specifically from the embryonic neocortex and analyse the effects on brain development and behaviour, using in situ hybridisation and immunohistochemistry;
2) quantitative PCR and chromatin immunoprecipitation approaches to identify the genes and signalling pathways affected by CHD8 loss and the gene promoters and regulatory elements to which CHD8 is recruited in neuronal progenitors.

The student will join a multi-disciplinary group at King's with strong international collaborations. The student will gain experience in state-of-the-art mouse genetics, quantitative chromatin and RNA techniques, the analysis of signalling in neural development and have the opportunity to interact with leaders in the areas of child psychiatry, epigenetics and neural development.

Two representative publications:
Functional analysis of neural networks in zebrafish models of epilepsy

Theme: Neuroscience
Supervisor 1: Dr Martin Meyer, Senior Lecturer
Research Division or CAG: MRC Centre for Developmental Neurobiology
E-mail: martin.meyer@kcl.ac.uk
Website: www.kcl.ac.uk/ioppn/depts/devneo/index.aspx

Supervisor 2 & Collaborating Clinician: Prof Deb K PAL, Professor of Paediatric Epilepsy, IOPPN
Research Division or CAG: Basic & Clinical Neuroscience
E-mail: deb.pal@kcl.ac.uk
Website: www.childhood-epilepsy.org

Project description:
Children with severe epilepsies often have difficult to treat seizures and may suffer devastating consequences for their development. Causative gene mutations for a handful of severe childhood epilepsies are known including in GRIN2A. However, it is not known precisely how mutations in these genes cause seizures or how they disrupt the normal development of neural networks. To address these questions requires detailed and dynamic functional analysis of neural circuits. The size, inaccessibility and number of neurons in the mouse brain means that, in current mouse models of epilepsy, the number of neurons that can be analysed in this way, as a fraction of the total, is tiny. The larval zebrafish brain on the other hand is small, containing only ~100,000 neurons, and at larval stages zebrafish are translucent allowing imaging of the entire and intact brain.

The aim of the thesis will be
1. Use TALEN and Crisp/Cas9 genome editing techniques to generate new (stxbp1), and analyse existing (scn1a, grin2a) zebrafish mutant models in a background of transgenic zebrafish that express a genetically encoded reporter of neural activity (GCaMP) throughout the brain.
2. Use in vivo functional imaging using high-speed, light sheet microscopy to image the zebrafish brain with cellular resolution to build functional maps of the mutant brain.
3. Use automated, high throughput analysis of seizure and locomotor behaviours in the above mutants to study developmental progression of disease phenotypes and as a medium throughput screen of known antiepileptic drugs and novel compounds.

Prof Pal will guide the student on the phenotypic features and human neural correlates of mutations; Dr Meyer will supervise all zebrafish work including generation of new mutants, imaging, image analysis and behavioural analyses.

Rotation project: Will involve using behavioural analysis (medium throughput tracking of locomotor behaviours) to detect spontaneous seizures in larval zebrafish mutants and/or increased susceptibility to pharmacologically induced seizures.

Two representative publications:

Investigating the pathophysiological mechanisms linking depression and type 2 diabetes

Theme: Neuroscience
Supervisor 1: Paul Caton
Research Division or CAG: Diabetes and Nutritional Sciences
E-mail: paul.w.caton@kcl.ac.uk
Website: http://www.kcl.ac.uk/lsm/research/divisions/dns/about/people/Profiles/Dr-Paul-Caton.aspx

Supervisor 2 & Collaborating Clinician: Khalida Ismail
Research Division or CAG: Department of Psychological Medicine
E-mail: Khalida.2.ismail@kcl.ac.uk
Website: http://www.kcl.ac.uk/ioppn/depts/pm/people/acaprof/khalidaismail.aspx

Project description:
Type 2 diabetes (T2D) is a major risk factor for development of cognitive disorders, such as depression and dementia. Neuroimaging analysis has revealed that brains of individuals with T2D display reduced brain volume, as well as distinct regional defects including atrophy within the hippocampus. The mechanisms linking neurological disorders and T2D are unclear. However, neuro-inflammation has been postulated as a mediator of depression/cognitive impairment, whilst chronic inflammation is a common finding in T2D, suggesting inflammation to be a plausible mechanism linking pathogenesis of the two conditions.

Objectives
This project will aim to elucidate novel links between T2D and depression, with particular focus on the role of inflammation in both conditions. We are particular interested in understanding the role of two poorly characterised inflammatory proteins, eNAMPT and LCN2, in T2D and depression.

Year 1 – 2: Identification of novel biomarkers linking depression, cognitive impairment and T2D. This part of the study will utilise the South London Diabetes Study (SOUL-d) of 1790 newly diagnosed T2D patients, as well as an 8-year follow-up of this cohort. Clinical information detailing depressive symptoms in this cohort has already been collected (Khalida Ismail)
Year 3 – 4: Characterisation of the functional impact of novel biomarkers (identified in years 1 and 2), using in vitro and in vivo model systems of type 2 diabetes, depression and cognitive impairment.
(Paul Caton)

Skills: ELISAs, cell culture and mouse models of T2D and cognitive impairment, imaging/microscopy, gene and protein expression analysis, statistics, analysis of large clinical data sets.

Two representative publications:
1) Laake et al., (2014) The Association Between Depressive Symptoms and Systemic Inflammation in People With Type 2 Diabetes: Findings From the South London Diabetes Study; Diabetes Care, 37; 2186 – 2192
Effect of autoantibodies in fetal brain development

Theme: Neuroscience
Supervisor 1: Prof Guillermina Girardi
Research Division or CAG: Women’s Health
E-mail: guillermina.girardi@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/guillermina.girardi.html

Supervisor 2 & Collaborating Clinician: Prof A. David Edwards
Research Division or CAG: Perinatal Imaging & Health
E-mail: ad.edwards@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/ad.edwards.html

Summary of role: Prof Edwards will give input on fetal brain neurodevelopment in humans and will provide his expert advice on translational studies. The student will learn from Prof Edwards about the Developing Human Connectome Project, in which one of the aims is to investigate if there is a correlation between maternal autoantibodies and abnormal fetal brain neurodevelopment in humans.

Project description:
A large number of patients with autoimmune diseases experience neuropsychiatric symptoms. There is growing evidence about the trans-placental passage of maternal autoantibodies and a spectrum of brain abnormalities and cognitive impairment has been described in infants born to mothers affected by autoimmune diseases. This suggests that exposure to autoantibodies in the uterus affects foetal brain development and induces behavioural and cognitive problems later on in life. However, little is known about the molecular aspects of the pathogenicity of these autoantibodies in the CNS.

The aim of the project would be to understand the effects of in utero exposure to autoantibodies on foetal brain development in mice and long-term consequences (neuropsychiatric disorders) in the offspring. Autoantibodies might affect fetal neurodevelopment by different mechanisms.

We will investigate the following:
- direct binding
- by inducing placental insufficiency and thus compromising the transport of oxygen and crucial nutrients for fetal development.
- by the release of inflammatory mediators in maternal circulation (interleukins, TNF, complement components)

Techniques to be used:
- Affinity purification of autoantibodies using magnetic beads and sepharose columns
- Radiolabelling of autoantibodies
- Animal handling – we will work in a mouse model to evaluate pregnancy and fetal outcomes
- Imaging techniques (MRI, SPECT/CT and 1HMRS) will be used to evaluate antibody binding and fetal metabolism/damage.
- Isolations of different subsets of brain cells: cortical cells, oligodendrocytes, astrocytes and neural stem cells using MAC separation
- We will also evaluate potential therapies to prevent placental/fetal damage in the in vivo model.
Two representative publications:


Development of biomarkers to distinguish pseudoprogression and progression in glioblastoma

Theme: Neuroscience
Supervisor 1: Prof Gareth J Barker
Research Division or CAG: Institute of Psychiatry
E-mail: gareth.barker@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/gareth.barker.html
See also: http://www.kcl.ac.uk/study/pg/services/SupervisoryExcellenceAwards.aspx

Supervisor 2 & Collaborating Clinician: Dr Thomas Booth
Research Division or CAG: Neuroscience
E-mail: thomasbooth@nhs.net
Website: https://www.kch.nhs.uk/profiles/49716/thomas-booth

Project description:
Glioblastoma, the most aggressive type of brain tumour has one of the poorest prognoses of all cancers. Typically treatment involves surgical removal combined with radiotherapy and concomitant and adjuvant temozolomide chemotherapy. (1) This treatment is associated with pseudoprogression, the false appearance of progressive disease manifesting as an increase in size of the contrast-enhancing lesion on conventional follow-up MRI. (2) This confounds response assessment and may affect clinical management. Advanced MR imaging studies show promise in distinguishing pseudoprogression from true disease progression. (3-9)

This interdisciplinary project aims to determine the accuracy in distinguishing pseudoprogression from progression using advanced quantitative MRI techniques (e.g. dynamic susceptibility contrast (DSC) and dynamic contrast enhanced (DCE)), clinical (e.g. Karnofsky performance status) and pathological tissue biomarkers (e.g. IDH, MGMT, Ki67, CD34, GFAP). Optimisation of a combined biomarker protocol will be performed using multivariate and support vector machine analyses for multi-site (i) retrospective data (year 1-2) (ii) prospective phantom-based, healthy control and patient data (year 2-4).

Along with generic and transferable skills training, the student will learn specific medical image processing (http://www.olea-medical.com/) and analysis techniques including segmentation (http://www.cbica.upenn.edu/sbia/software/) for identifying neuroanatomical and pathological image features; metrics of image heterogeneity; statistical and machine learning. The student will determine how individual biomarker results can be presented at a multi-disciplinary neuro-oncology meeting (year 3-4); and how clinical management and patient outcomes are affected.

The project will provide prospective pilot data to inform a potential future National NIHR study, which would be implemented by the National Cancer Research Institute Brain Tumour Imaging Subgroup.

(6) Suh CH, Kim HS, Choi YJ, Kim N, Kim SJ. Prediction of Pseudoprogression in Patients with Glioblastomas Using the Initial and Final Area Under the Curves Ratio Derived from Dynamic


Two representative publications:


Awakening the brain with dopaminergic therapy in Parkinson’s disease. Why do some patients respond while others do not? A resting-OFF and turning-ON fMRI study

Theme: Neuroscience
Supervisor 1 & Collaborating Clinician: Dr. Marios Politis
Research Division or CAG: Neuroscience
E-mail: marios.politis@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/marios.politis.html

Supervisor 2: Dr. Anthony Vernon
Research Division or CAG: Neuroscience
E-mail: anthony.vernon@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/anthony.vernon.html

Project description:
Parkinson’s disease (PD) is a chronic neurodegenerative disorder primarily characterised by the motor symptoms of bradykinesia, rigidity, and tremor, and by the loss of dopaminergic neurons in the basal ganglia. One of the major issues with managing patients with PD in the clinic is their fluctuating response to dopaminergic treatment. Whilst some patients exhibit excellent (>50% improvement measured with specialised clinical PD scales) and fast (<30min) response following oral administration of levodopa, others do not respond as well (<20% improvement) and show delay (>45 min) or no response following levodopa. It is currently unknown which are the brain mechanisms underlying the difference between levodopa responsive vs. non-responsive PD. Previous experimental studies using electrophysiology and studies with transcranial magnetic stimulation in humans indicate that PD animals and patients who not respond to levodopa fail to induce electric responses within the basal ganglia networks. State-of-the-art functional MRI (fMRI) techniques can give insight into brain activation in both humans and rodent models through measuring Brain Oxygen-Level-Dependent (BOLD) signal changes following a pharmacological challenge, at a voxel level, in the brain in vivo.

In this PhD project, the student will use resting- and active-state (motor task) fMRI, and study two groups of PD patients (16 PD patients with good vs 16 PD patients with poor levodopa response) following a challenge with levodopa. Animal work on the effects of L-dopa on brain networks will be carried out in to parallel the clinical study to link imaging findings to cellular changes.

Objectives:
To assess changes of default-mode and executive-control resting-state brain networks following a levodopa challenge in good vs poor levodopa PD responders
To assess brain activation during motor control in brain networks following a levodopa challenge in good vs poor levodopa PD responders
To determine the correlation between resting and levodopa-induced brain activation functional networks in good vs poor levodopa PD responders
To establish a resting state brain network signature in a well-validated rodent model of Levodopa dyskinesia to link imaging changes to cellular level events and provide a translational assay for screening novel antidyskinetic treatment strategies

Two representative publications:

Developing a translational stem cell model of autism

Theme: Neuroscience
Supervisor 1: Jack Price
Research Division or CAG: Neuroscience
E-mail: jack.price@kcl.ac.uk
Website: http://www.kcl.ac.uk/ioppn/depts/neuroscience/research/centres/ccbb/groups/nsc/about.aspx

Supervisor 2: Eva Loth
Research Division or CAG: Behavioural and Developmental Psychiatry
E-mail: eva.loth@kcl.ac.uk
Website: http://www.eu-aims.eu/the-group/consortium/king-s-college-london/
See also: https://kclpure.kcl.ac.uk/portal/en/persons/eva-loth(1e95ad45-1e73-4383-a1ee-c71aa094bcc1)/publications.html

Collaborating Clinician: Declan Murphy
Research Division or CAG: Sackler Institute and the Behavioural and Developmental CAG
E-mail: declan.murphy@kcl.ac.uk
Website: http://www.kcl.ac.uk/ioppn/depts/fans/people/index.aspx

Summary of role: Professor Murphy is director of the Sackler Institute, head of the department of Forensic and Neurodevelopmental Sciences, and Director of the Behavioural and Developmental CAG

Project description:
Autism is the highest cost neurodevelopmental disorder in the world. Its cause is unknown but new evidence suggests a crucial role of neuroinflammatory factors. If a mother has influenza during her first trimester, her child has a three-fold increased risk of having autism.

This project will, for the first time, examine the pathophysiology of this risk; and determine if it can be rescued. Using an integrated translational approach, we will investigate the mechanisms by which inflammation impacts brain development at the cellular, molecular, and brain systems levels, as well as clinical outcome.

We have generated induced pluripotent stem cells (iPSCs) from autistic patients and controls1. Neural differentiation of these iPSCs reproduces in tissue culture the events from gastrulation through neuronal maturation in the human embryo. We can use this model to ask: what changes in neuronal development following exposure to neuro-inflammatory stimuli provoked by influenza? Can we identify molecular mechanisms that drive these changes? Do these disturbances correlate with the clinical and neuroimaging phenotypes of patients? Finally, can we2 identify novel therapeutic targets?

This project sits at the interface of lab-based neuroscience and clinical research. It provides training in stem cell technologies (tissue culture; immunohistochemistry; high-content imaging), molecular analysis (transcriptomics; DNA methylation; microRNA analysis), neuroimaging (e.g. inflammatory pathways and brain function) and clinical phenotyping. To investigate the role of peri-natal neuroinflammatory risk factors in brain, we will capitalise on a large multi-modal data set (>500 participants) collected as part of the multi-centre EU-AIMS Longitudinal European Autism Project.

Two representative publications:

Identifying biomarkers and causal mechanisms of chemotherapy-induced painful peripheral neuropathies

Theme: Neuroscience
Supervisor 1: Dr. Sarah Flatters
Research Division: Wolfson Centre for Age-Related Diseases
E-mail: sarah.flatters@kcl.ac.uk
Website: https://www.kcl.ac.uk/ioppn/depts/wolfson/about/people/staff/flatterssarah.aspx

Supervisor 2: Prof. Stephen McMahon
Research Division or CAG: Wolfson Centre for Age-Related Diseases
E-mail: stephen.mcmahon@kcl.ac.uk
Website: https://www.kcl.ac.uk/ioppn/depts/wolfson/about/people/staff/mcmahonsteve.aspx

Collaborating Clinician: Dr. Mark Harries
Research Division or CAG: Cancer CAG
E-mail: Mark.Harries@gstt.nhs.uk

Summary of role: Dr. Harries will provide samples from patients with chemotherapy-induced neuropathies for laboratory analysis and valuable insight into the patient presentation of CIPN

Project description:
Chemotherapy-induced painful peripheral neuropathy (CIPPN) is the major dose-limiting side effect of several first-line chemotherapeutics. 30-70% of patients will develop CIPPN, which often persists following chemotherapy. Currently there is no treatment to prevent or treat CIPPN. Prevention of CIPPN would be greatly aided with a blood biomarker to identify patients susceptible to CIPPN accompanied with knowledge of the causal mechanisms to develop novel targeted pharmacotherapy.

Using a rat model which accurately mimics clinical CIPPN presentation, an increase in atypical neuronal mitochondria of rats was observed. Mitochondria are major sources of reactive oxygen species (ROS) and we have demonstrated that ROS is causal to CIPPN in vivo. These publications and ongoing lab studies indicate that mitochondrial dysfunction is causal to CIPPN and mtDNA content in blood is altered during CIPPN. This project will involve a multi-faceted experimental approach using ex vivo cells/tissues from translational rodent models of CIPPN and human blood samples from CIPPN patients. Thereby linking cellular mechanisms and whole animal behaviour through to clinical CIPPN.

- Year 1/MRes: Behavioural assessment in rat models of CIPPN. Quantification of mitochondria/mtDNA in rat blood and tissues.
- Year 2: Measure oxidative phosphorylation and glycolysis in rat sensory neurones using state-of-the-art technology. Quantification of mitochondria/mtDNA in human blood samples.

Training: Diverse range of in vivo and ex vivo experimental techniques, data analysis, presentation skills, project organisation and time management. Seminars, workshops, journal clubs through both department and London Pain Consortium.
Two representative publications:

1) Flatters SJL and Bennett GJ (2006) Studies of peripheral sensory nerves in paclitaxel-induced painful peripheral neuropathy: Evidence for mitochondrial dysfunction. *Pain* 122(3): 245-257  [This was the first study to demonstrate a potential role of mitochondria in CIPPN pathology in the absence of neurodegeneration.]

2) Fidanboylu M, Griffiths LA and Flatters SJL (2011) Global inhibition of reactive oxygen species (ROS) inhibits paclitaxel-induced painful peripheral neuropathy. *PLoS ONE* 6(9):e25212  [The first author of this paper completed his experimental contribution to this paper during a 3-month MRes rotation project in my lab.]
Exploring mitochondrial retrograde signalling as a novel treatment target in neurodegenerative disease

Theme: Neuroscience
Supervisor 1: Dr Joseph Bateman, PhD
Research Division or CAG: Wolfson Centre for Age-Related Diseases
E-mail: joseph_matthew.bateman@kcl.ac.uk
Website: http://openwetware.org/wiki/Bateman

Supervisor 2: Prof Clive Ballard, MB ChB, MRC Psych, M.Med.Sci., MD
Research Division or CAG: Wolfson Centre for Age-Related Diseases
E-mail: clive.ballard@kcl.ac.uk
Website: http://www.kcl.ac.uk/biohealth/research/divisions/wolfson/research/drugdiscunit/staff/ballardclive.aspx

Project description:
Mitochondrial dysfunction is increasingly considered to be a critical factor in the development of neurodegenerative disease. Mitochondria play vital roles in the generation of cellular energy, apoptosis, calcium buffering and the generation of reactive oxygen species. Mitochondrial dysfunction plays a clear role in Parkinson’s disease and has been linked to Alzheimer’s disease (AD). Mitochondrial retrograde signalling is the regulation of nuclear gene expression by mitochondria\(^1\). The neuroprotective potential of manipulation of the retrograde response remains untested in neurodegenerative disease and is an important opportunity to identify novel treatment targets\(^1\). The aim of this collaborative project is to investigate mitochondrial retrograde signalling in AD\(^2\) and Parkinson’s disease dementia (PDD) and potential strategies for reversal. This will be achieved through an interdisciplinary translational approach combining analysis of a Drosophila (fruit fly) model of mitochondrial dysfunction (Bateman lab) and models of neurodegeneration of mammalian neurons (Ballard lab). The overall aims of the PhD are:

Aim 1: Identification of conserved retrograde signalling genes and genetic analysis in Drosophila.
Aim 2: Genetic strategies for reversal of mitochondrial dysfunction phenotypes in Drosophila and mammalian neurons.
Aim 3: Identification and analysis of compounds targeting mitochondrial retrograde signalling as potential therapeutic agents preventing neurodegeneration in mammalian neurons.

The project will lead to the identification of new factors associated with neurodegenerative disease that can be developed as novel therapeutic targets.

Two representative publications:
A zebrafish model of EPG5-related multisystem disorders associated with defective autophagy

Theme: Neuroscience
Supervisor 1: Dr Yaniv Hinits
Research Division or CAG: Randall Division for Cell and Molecular Biophysics
E-mail: yaniv.hinits@kcl.ac.uk
Website: http://www.kcl.ac.uk/lsm/research/divisions/randall/research/sections/signalling/hinits

Supervisor 2: Prof. Corinne Houart
Research Division or CAG: MRC Centre for Developmental Neurobiology
E-mail: corinne.houart@kcl.ac.uk
Website https://kclpure.kcl.ac.uk/portal/corinne.houart.html

Collaborating Clinician: Dr Heinz Jungbluth
Research Division or CAG: Department of Basic and Clinical Neuroscience, IoPPN
E-mail: Heinz.1.Jungbluth@kcl.ac.uk
Website: https://kclpure.kcl.ac.uk/portal/heinz.1.jungbluth.html

Summary of role: Dr Jungbluth is the leading expert in EPG5-related human multisystem disorders and with his team was the first to identify recessive EPG5 mutations as the cause of Vici syndrome. He initiated the EPG5 diagnostic service at Guy’s Hospital and leads ‘Vici syndrome and related disorders due to defective autophagy’ on the GeCIP Genomics England project.

Project description:
Autophagy is a highly conserved intracellular pathway with the ultimate aim of delivering proteins and organelles targeted for degradation to the lysosome. Primary disorders of autophagy have been recently recognized as an emerging group of human disorders involving a fundamental intracellular mechanism potentially amenable to pharmacological manipulation.

EPG5-related Vici syndrome (VS) is the most extensive of these disorders and affects virtually all tissues, including skeletal and cardiac muscles, neurons and the immune system. Congenital and acquired defects concerning the same organ are frequently seen, emphasizing the crucial role of autophagy in both cell development and maintenance.

The value of zebrafish (Danio rerio) as a model to study the role of autophagy in development and degeneration has been recently demonstrated, but there is currently no zebrafish model of EPG5-related Vici syndrome. The proposed research will utilize zebrafish epg5 null mutants made by genome editing methods and GFP transgenics, to provide a proof-of-principle that zebrafish faithfully replicates the manifestations of a human multisystem disorder associated with a primary autophagy disorder. The project will provide the foundation for developing a library of zebrafish models of primary human autophagy defects, as a basis for high-throughput large-scale chemical screening in partnership with industry.

Throughout this project the student will develop fundamental skills for working with a commonly used model organisms in a translational context for the investigation of heart development, neurodevelopment and neurodegeneration, and for the advancement of therapeutic options for common human diseases.

Two representative publications:

2) Hinits, Y. et al. Zebrafish Mef2ca and Mef2cb are essential for both first and second heart field cardiomyocyte differentiation. Dev Biol 369, 199-210 (2012)
**The endoplasmic reticulum-mitochondria axis in Alzheimer’s disease and dementia**

Theme: Neuroscience  
Supervisor 1: Professor Chris Miller  
Research Division or CAG: Department of Basic and Clinical Neuroscience, Neuroscience  
E-mail: chris.miller@kcl.ac.uk  
Website: http://www.kcl.ac.uk/iop/depts/neuroscience/research/Groups/Miller/Index.aspx

Supervisor 2: Dr Wendy Noble  
Research Division or CAG: Department of Basic and Clinical Neuroscience, Neuroscience  
E-mail: Wendy.Noble@kcl.ac.uk  
Website: http://www.kcl.ac.uk/iop/depts/neuroscience/research/Groups/Noble/Index.aspx

Collaborating Clinician: Professor Chris Shaw  
Research Division or CAG: Department of Basic and Clinical Neuroscience, Neuroscience  
E-mail: chris.shaw@kcl.ac.uk  
Website: https://kclpure.kcl.ac.uk/portal/chris.shaw.html  
Summary of role: Access to clinical populations, liaison with clinical services, translational development.

Project description:  
Mitochondria and the endoplasmic reticulum (ER) form close physical associations that regulate a number of fundamental physiological processes. Recently, we demonstrated that these associations are mediated by binding of the outer mitochondrial membrane protein PTPIP51 to the integral ER protein VAPB which together form a “molecular scaffold” that acts to tether the two organelles. Many of the functions regulated by ER-mitochondria associations are disrupted in Alzheimer’s disease and related dementias, and we have demonstrated that ER-mitochondria interactions are disrupted in these diseases. Moreover, we have shown that this disruption is linked to changes in binding of VAPB to PTPIP51 and activation of glycogen synthase kinase-3 (GSK3), a kinase strongly implicated in dementia. Thus, we have identified a new pathogenic mechanism for dementia. The hypothesis that underlies this project is that some dementia-linked insults induce GSK-3 phosphorylation of VAPB and/or PTPIP51 to disrupt their binding and perturb ER-mitochondria associations.

The primary objectives are:  
1. To identify phosphorylation sites in VAPB and PTPIP51, and to determine whether these are GSK-3 sites using mass spectrometry; we already have data to support this notion (Yr1).  
2. To determine whether GSK-3 phosphorylation of VAPB and/or PTPIP51 regulates their binding. This will be achieved by mutating identified VAPB/PTPIP51 phosphorylation sites and by manipulating GSK-3 activity in transfected cells, and then assaying binding of VAPB to PTPIP51 (Yr 1/2).  
3. To determine whether phosphorylation of VAPB and/or PTPIP51 regulates ER-mitochondria associations by use of advanced microscopy (Yr3).  
4. To determine whether GSK-3 inhibitors and other novel drugs we have identified can correct defective ER-mitochondria associations and linked functions that are induced by dementia insults (Yr3).

The project will involve training in molecular/cellular neurosciences, proteomics, signal transduction and advanced microscopy techniques.

Two representative publications:  

Repurposing of drugs for treatment of psychiatric conditions

Theme: Neuroscience
Supervisor 1: David Barlow
Research Division or CAG: Institute of Pharmaceutical Science (IPS)
E-mail: dave.barlow@kcl.ac.uk
Website: http://www.kcl.ac.uk/lsm/research/divisions/ips/research/pharmabio/Staff/Barlow/index.aspx

Supervisor 2: David Taylor
Research Division or CAG: Pharmaceutical Sciences CAG (and IPS)
E-mail: david.taylor@slam.nhs.uk
Website: https://www.kcl.ac.uk/lsm/research/divisions/ips/research/clinicalprac/staff/Taylor.aspx

Collaborating Clinician: Fiona Gaughran
Research Division or CAG: Psychosis, Institute of Psychiatry
Email: fiona.p.gaughran@kcl.ac.uk
Website: https://www.national.slam.nhs.uk/about-us/our-experts/fionagaughran/
Summary of role: Lead Consultant in the Psychosis Service at SLAM and Honorary Senior Lecturer in the Institute of Psychiatry. Responsible for implementing new, evidence-based approaches relating to people with psychotic illnesses that have been resistant to treatment.

Project description:
Recent clinical trials have shown that the oral antibiotic minocycline affords significant benefits in early schizophrenia. The potential for repurposing minocycline, therefore, to provide adjuvant treatment of schizophrenia has - in this instance - been signalled through retrospective consideration of its pharmacological activity profile. Such repurposing of drugs is now widely used within the Pharmaceutical industry as a means to feed the drug discovery pipeline. Computational tools that can be used in virtual screening of chemical libraries, in search of specific patterns of pharmacological activity, offer the potential to facilitate this task.

The research proposed here will comprise two distinct but interrelated studies: the first, a focussed study (using Clinical Practice Research Database medication histories), to test the hypothesis that use of oral minocycline by adolescents (to treat severe acne) has a beneficial effect resulting in improved prognosis for individuals with schizophrenia; the second, a comprehensive cheminformatics study, to develop and validate Random Forest models to classify small molecule compounds based on their known activities against a range of pharmacological targets, and the application of these models to determine whether such in-silico screening would identify minocycline as a candidate for repurposing for treatment of schizophrenia. The two studies are connected through the overarching aim to explore the off-target effects of small molecule synthetic compounds as a means to identify marketed drugs that exhibit potential for re-purposing to new indications and to alert of possible adverse side effects elicited by prospective new chemical entities early in the drug discovery programme.

Two representative publications:
1) Chaudhry, B. et al. (2012) J. Psychopharmacol. 26, 1185-1193
RBM3 – Potential hypothermia-independent neuroprotection

Theme: Neuroscience
Supervisor 1: Dr Claire Thornton
Research Division or CAG: Perinatal Imaging and Health
E-mail: claire.thornton@kcl.ac.uk

Supervisor 2 & Clinical Collaborator: Prof Henrik Hagberg
Research Division or CAG: Perinatal Imaging and Health
E-mail: henrik.hagberg@kcl.ac.uk

Project description:
Moderate to severe hypoxic-ischaemic encephalopathy (HIE), caused by a lack of oxygen or blood flow to the brain in term or near-term babies, affects 1-2 in every 1000 live births in the UK and far more in the developing world. Currently, therapeutic hypothermia is the only therapy available for term HIE, doubling the chance of survival and improving long term motor and cognitive outcome. However, hypothermia is only successful in 1 in every 7 babies and further interventions are urgently required.

Recently, (RBM)3 was identified as mediating the neuroprotective effects of cooling by regulating structural plasticity. In animal models of adult neurodegeneration, this regeneration of synapses was lost but restored on RBM3 overexpression. Interestingly, RBM3 was able to promote synaptic reformation independently of cooling. RBM3 is highly expressed in immature brain declining into adulthood. Therefore the aim of the project is to determine whether RBM3 is neuroprotective in neonatal HIE.

During the rotation the student will characterise the neuroprotective effects of RBM3 in response to oxygen-glucose deprivation ± cooling. During Yr 1&2, we will use animal models of HI and modulate RBM3, its upstream regulation and its downstream targets, to determine neuroprotection. We will also analyse whether this protection offers synergy with hypothermia or if it represents a standalone therapy. In addition, we will determine whether perinatal inflammation modulates RBM3 expression, an insult known to abrogate the neuroprotective effects of hypothermia. Finally, in Yr3 we will identify novel/repurposed compounds to modulate the pathway in vivo in order to generate preclinical data.

Two representative publications: