**MIBTP2 PhD Project Proposal**

The Midlands Integrative Biosciences Training Partnership 2 (MIBTP) is a BBSRC-funded doctoral training partnership between the [University of Warwick](http://www2.warwick.ac.uk), the [University of Birmingham](http://www.birmingham.ac.uk) and the [University of Leicester](http://www.le.ac.uk) recruiting students for four-year studentships starting in Oct 2019. These students would do a year of training and start their PhD research in Oct 2020.

MIBTP2 PhD projects should fit within the Strategic Plan of the BBSRC (<http://www.bbsrc.ac.uk/publications/planning/strategy/strategy-overview.aspx>). In MIBTP2 we are supporting research in the following areas 1) Food security, 2) Bioenergy and industrial biotechnology and 3) Molecules, Cells and Systems. Exploiting New Ways of Working is a cross-cutting theme throughout MIBTP2; in the taught component, mini-projects and the main research component of the programme. MIBTP2 PhD projects should have two academic supervisors, usually in different disciplines, or at least who approach the biological topic from different directions.

**If you would like to offer a PhD project, please complete this form and submit it with the file name format “Smith\_John\_PhD\_Proposal.doc” to Sergio Gonzalez-Sanchez (sgs17@le.ac.uk) by November 5th.**

Please note that while each student is allocated a project budget (max. £4500 pa for consumables, facility use etc.) it is expected that Supervisors will also contribute to the funding of the project and also to training of the PhD students by offering master classes and mini-projects.

If you have any questions regarding this form please contact Jonathan McDearmid (jrm33@leicester.ac.uk).

Principal Supervisor: Professor Ian D Forsythe

Co-supervisor: Dr Joern Steinert

PhD project title: Regulation of neuronal excitability and synaptic transmission by metabolic demand in health and disease.

University of Registration: University of Leicester

**Project outline**

1. Project outline describing the scientific rationale of the project (max 4,000 characters incl. spaces and returns)

The brain uses vast metabolic resources to maintain electrical excitability and to integrate sensory information (Harris et al., 2012).  However, the fundamental mechanisms by which brain activity can influence metabolic rate or how in diseases such as stroke (or dementias), compromised metabolism may influence information transmission are unresolved.  Under physiological conditions, neurons normally adapt to bioenergetic challenges caused by ongoing activity in neuronal circuits; this signalling can induce compensatory expression of proteins to enhance resistance to metabolic, oxidative, excitotoxic, and proteotoxic stresses. During aging these mechanisms may become compromised, resulting in reduced cognitive performance in multiple domains including working and spatial memory and information processing. Similar changes can occur earlier in life during the development of neurological diseases. For instance, changes in nutrient transporter and metabolic enzyme expression levels and/or activities, have been reported in Alzheimer’s disease (AD); for example levels of glucose transporters GLUT1 and GLUT3 are reduced in the brains of AD patients (Simpson et al., 1994; Harr et al., 1995) which is associated with amyloid- signalling (Seixas da Silva et al., 2017) and correlates with diminished brain glucose uptake and subsequent cognitive decline (Landau et al., 2010).

This project will examine how the rates of information transmission (synaptic activity) influence downstream synapses in the brain and will explore the adaptations to ATP depletion and the functional consequences of metabolic limitation.

Our laboratory has extensive experience in the study of synaptic transmission, voltage-gated potassium channels and has ongoing projects concerning the metabolic regulation of neuronal excitability in information transmission. We have recently established that presynaptic ATP depletion during synaptic activity compromises specific steps of synaptic transmission by incorporating computational modelling with physiological measurements (Lucas et al., 2018). We conduct our studies in the auditory brainstem, because this region has a high metabolic rate and we have a well-established *in vitro* brain-slice preparation from which we can conduct *in vitro* electrophysiology, western blotting and immunohistochemistry. Patch recording and imaging methods will be used to monitor presynaptic [ATP] during high rates of synaptic transmission and when metabolic substrates are in limited supply. This novel approach to determine intracellular ATP levels uses a genetically expressed fluorescent indicator to image fluorescence-resonance energy-transfer (FRET). The main focus of the project will relate to metabolic dysfunction in stroke and neurodegenerative conditions as an underlying cause for disease and in relation to ageing.

The successful candidate will join a team of neuroscientists (see web site for further information) studying aspects of neuronal intrinsic plasticity and function, voltage-gated ionic currents and activity-dependent synaptic plasticity (Pilati et al., 2016).

Further information: <http://www2.le.ac.uk/departments/npb/people/professor-ian-forsythe-1>

**References**

Harr SD, Simonian NA, Hyman BT (1995) Functional alterations in Alzheimer's disease: decreased glucose transporter 3 immunoreactivity in the perforant pathway terminal zone. J Neuropathol Exp Neurol 54:38-41.

Harris JJ, Jolivet R, Attwell D (2012) Synaptic energy use and supply. Neuron 75:762-777.

Landau SM, Harvey D, Madison CM, Reiman EM, Foster NL, Aisen PS, Petersen RC, Shaw LM, Trojanowski JQ, Jack CR, Jr., Weiner MW, Jagust WJ, Alzheimer's Disease Neuroimaging I (2010) Comparing predictors of conversion and decline in mild cognitive impairment. Neurology 75:230-238.

Lucas SJ, Michel CB, Marra V, Smalley JL, Hennig MH, Graham BP, Forsythe ID (2018) Glucose and lactate as metabolic constraints on presynaptic transmission at an excitatory synapse. J Physiol 596:1699-1721.

Pilati N, Linley DM, Selvaskandan H, Uchitel O, Hennig MH, Kopp-Scheinpflug C, Forsythe ID (2016) Acoustic trauma slows AMPA receptor-mediated EPSCs in the auditory brainstem, reducing GluA4 subunit expression as a mechanism to rescue binaural function. J Physiol 594:3683-3703.

Seixas da Silva GS, Melo HM, Lourenco MV, Lyra ESNM, de Carvalho MB, Alves-Leon SV, de Souza JM, Klein WL, da-Silva WS, Ferreira ST, De Felice FG (2017) Amyloid-beta oligomers transiently inhibit AMP-activated kinase and cause metabolic defects in hippocampal neurons. J Biol Chem 292:7395-7406.

Simpson IA, Vannucci SJ, Maher F (1994) Glucose transporters in mammalian brain. Biochem Soc Trans 22:671-675.

**Relevance to BBSRC and Approvals**

1. How does this project fit within the remit of the BBSRC? (3-4 lines)

This project integrates fundamental mechanisms of brain function during metabolic compromise with sensory information transmission and computational neuroscience. It gives insights into how the nervous system adapts to ageing, food starvation and the changes triggered by brain ischemic episodes.

2. Select the relevant BBSRC Strategic Research Priority from drop down list:

3. Please select a MIBTP sub-category from drop down list:

4. How does the project comply with BBSRC’s requirement for multidisciplinarity and new ways of working (including use of advanced quantitative skills)? (5 lines)

This project integrates laboratories taking a systems approach to neuronal metabolism, auditory processing with computational neuroscience (collaborations with B Graham, M Hennig, University of Stirling) and disease. Its multidisciplinary nature involves aspects of dementia, cardiovascular disease mechanisms and applications of interdisciplinary methodologies to gain new insides into fundamental questions of physiology and pathology.

5. Please list the techniques that will be undertaken during the project (and how they tie in with q4).

*In vitro* brain slice preparation

Patch clamp recording from neurons

Calcium and ATP imaging

Voltage-clamp

Western blotting

Immunohistochemistry

Computational modeling