PhD Studentship
Developmental Neurobiology

This is a full time, fixed term position for 4 years

Context

The Francis Crick Institute is a partnership between Cancer Research UK, the Medical Research Council, the Wellcome Trust, UCL (University College London), Imperial College London and King’s College London. It is a registered charity whose purpose is to conduct biomedical research into all aspects of human health and disease.

The institute will be a world-leading centre of biomedical research and innovation. It will promote connections between researchers and disciplines and between academic institutions, healthcare organisations and businesses. Dedicated to research excellence, the institute will have the scale, vision and expertise to tackle the most challenging scientific questions underpinning health and disease. It will be world-class with a strong national role—training scientists and developing ideas for public good. Due to open in 2015, the Crick will be located in a new, purpose built research centre in Brill Place, St. Pancras and will house some 1,500 staff.

The position of PhD studentship has been created to address the roles of LATS1/2 kinases in mammalian neuronal development and synaptogenesis. The student will perform experiments using transgenic mice to determine the requirement of LATS1/2 kinases in hippocampal synaptogenesis. For this she/he will use electrophysiology and imaging techniques. She/he will then utilize biochemistry, chemical genetics and mass spectrometry techniques to identify downstream effectors of LATS1/2.

Organisation

The PhD student will be working mainly in the Ultanir lab to conduct her PhD project. He/she will also be a part of our collaboration with Dr. Bram Snijders who heads the Proteomics and Mass Spectrometry Laboratory at Crick, where she/ he will receive mass spectrometry training and perform these experiments.

Objectives

Specific objectives will include, but not be limited to:

- Characterization of Lats1/2 conditional knockout mice by electrophysiology and neuronal dendrite and spine morphology
- Identification of LAT51/2 downstream effectors using chemical genetic methods and mass spectrometry
- Molecular characterization of LATS1/2 and its substrates in cultured neurons.
Person Specification

The post holder should embody and demonstrate our core Crick values: Bold, Imaginative, Open, Dynamic and Collegiate, in addition to the following:

Essential

- Applicants must hold or expect to gain a first/upper second-class honours degree or equivalent in a relevant subject
- Neuroscience knowledge
- Experience in protein biochemistry
- Interest in protein signalling mechanisms
- Motivation in learning techniques including mouse genetics and mass spectrometry

Desirable

- Knowledge of molecular biology
- Knowledge of mass spectrometry

If you would like to apply for this role please follow the application instructions which can be found at [http://www.nimr.mrc.ac.uk/phd/](http://www.nimr.mrc.ac.uk/phd/).

For further details about the PhD programme see [http://www.crick.ac.uk/about-us/phd-programme/](http://www.crick.ac.uk/about-us/phd-programme/).

The closing date for applications is Friday 06 March at 12pm.

Should you have any queries relating to this role, please contact [studentships@nimr.mrc.ac.uk](mailto:studentships@nimr.mrc.ac.uk).

REF 213
Function of LATS kinases in dendrite and dendritic spine development

Dendrites, input receiving regions of neurons, contain actin rich dendritic protrusions called dendritic spines. Spines are sites for more than 90% of excitatory synapses in the brain. Dendrite and spine synapse development is critical for proper wiring of the neural circuitry, as defects in these processes are associated with neurodevelopmental disorders such as autism. Molecular mechanisms regulating these developmental processes are not well-understood.

We are interested in kinase signalling cascades regulating dendrite and spine synapse development. Protein kinases regulate cellular processes by phosphorylating their substrate proteins. There are more than 500 kinases in human genome most of which are expressed in the brain. Functional roles of a majority of these kinases are unknown. We use a powerful chemical method to identify kinase substrates, which is highly effective in uncovering molecular functions of kinases (Hertz et al., 2010; Ultanir et al., 2012; Ultanir et al., 2014). We combine this method with electrophysiology and imaging methods to analyse synaptic function and spine morphology in mouse brain.

Hippo kinase signalling (MST1/2 in mammals) is extensively studied in relation to its roles in cell division, apoptosis and tissue size control. Canonical hippo kinase cascade is well-established in both mammals and flies: MST1/2 phosphorylates to activate Large Tumor Suppressor kinases 1/2 (LATS1/2, warts in flies), which in turn phosphorylates to inactivate the transcription factor YAP. Both hippo and warts are implicated in dendrite maintenance in fly neurons (Emoto et al., 2006). Despite its importance in other tissues and organisms, the role of hippo signalling in developing mammalian neurons is unknown.

This PhD thesis focuses on LATS1/2 kinases in synapse development. LATS2 is highly expressed in mouse hippocampus. PhD student project’s aims are 1) to analyse morphological and physiological development of hippocampal neurons in LATS1/2 conditional knockout mice, 2) to identify LATS1/2 substrates using chemical genetics and mass spectrometry and 3) to establish the downstream mechanisms of LATS1/2 using shRNA knockdown of substrates in neuronal cultures. Identification of substrates is expected to lead to a better understanding of LATS1/2’s role in the brain. Student will have the opportunity to learn methods on cell biology, electrophysiology, transgenic mouse and kinase biochemistry.

We closely collaborate with Dr. Bram Snijders’ group, at the proteomics and mass spectrometry laboratory at London Research Institute. The PhD student will be given a unique opportunity to join both labs and thus learn mass spectrometry and proteomics analysis. With Dr. Snijders’, the student will establish analytical mass spectrometry approaches that will improve the sensitivity and throughput of existing assays.

References

