**KAP1-lncRNA chromatin regulatory complexes control adult neurogenesis**

Theme: Neuroscience & Mental Health
Reference: MRC19NMHBa Vance

Lead supervisor: Dr Keith Vance, Department of Biology & Biochemistry, University of Bath, email k.w.vance@bath.ac.uk

Co-supervisors: Dr Karim Malik (University of Bristol)

Adult neural stem cells (NSCs), located in the brain ventricular zone-subventricular zone (VZ-SVZ), produce neurons throughout life and can be stimulated by brain injury and neurodegeneration to replace damaged neurons and limit harm. VZ-SVZ NSCs therefore have great potential in regenerative medicine to reduce neuronal damage and functional loss. Yet, the prevalence of age-related neurodegeneration is predicted to rise dramatically over the next few decades with an increase in population age. A greater molecular understanding of the mechanisms controlling adult NSCs self-renewal and neurogenesis is thus required so that new treatment strategies can be developed for brain diseases.

We recently showed that KAP1 (TRIM28) forms a chromatin regulatory complex containing the VZ-SVZ long non-coding RNA (lncRNA) Paupar and that together KAP1-Paupar function as critical regulators of adult neurogenesis in mouse. Kap1 is required for embryonic brain development and adult brain function, whilst lncRNAs have emerged as a new class of gene expression regulators with important functions in adult stem cells. The proposed project will build on these key proof-of-concept experiments to investigate the wider role of KAP1-lncRNA interaction networks in the control of adult neurogenesis. We will use the cutting edge HITS-CLIP method to comprehensively identify the set of lncRNAS that associate with endogenous KAP1 in neurosphere cultures of neural stem cells. Computational genomics will then be performed to prioritise a subset of mouse-human conserved intergenic lncRNAs for functional analysis. CRISPR interference and anti-sense oligonucleotides will be used to deplete the expression of 2-3 orthologous lncRNAs in mouse Neuro-2A and human SHSY5Y neuroblastoma cells and lncRNA loss of function phenotypes characterised. In addition, we will perform chromatin and reporter analysis to dissect conserved mechanisms of KAP1-lncRNA mediated transcription and chromatin regulation. This work will systematically identify important new KAP1-associated lncRNA regulators of neurogenesis with potential to be targeted for the future development of stem cell and neuro-regenerative therapies for the treatment of neurodegeneration and brain injury.

IMPORTANT: In order to apply for this project, you should apply using the DTP's online application form: https://cardiff.onlinesurveys.ac.uk/gw4-biomed-mrc-dtp-student-2019

More information on the application process may be found here:
http://www.gw4biomed.ac.uk/doctoral-students/

APPLICATIONS OPEN ON 24 SEPTEMBER AND CLOSE ON 23 NOVEMBER 2018.

You do NOT need to apply to the University of Bath at this stage – only those applicants who are successful in obtaining an offer of funding from the DTP will be required to submit an application to study at Bath.