Project Details	
Project Code	MRC21NMHBa Vance
Title	KAP1-long non-coding RNA chromatin regulatory complexes control neurogenesis
Research Theme	Neuroscience & Mental Health
Summary	Adult neural stem cells produce neurons and have great potential in regenerative medicine to limit neuronal damage and functional loss. This project will systematically define novel KAP1-long non-coding RNA chromatin regulatory complexes needed for neuron production that may be targeted to develop new treatments for neurodegenerative disorders.
Description	Adult neural stem cells (NSCs), located in the brain ventricular zone-subventricular zone (VZ-SVZ), produce neurons throughout life. VZ-SVZ NSCs can be stimulated by brain injury and neurodegeneration to replace damaged neurons and limit harm, and have great potential in regenerative medicine to reduce neuronal damage and functional loss. 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 neurogenesis is thus urgently required so that new treatment strategies can be developed for brain diseases. We recently showed that Kap1 and the VZ-SVZ long non-coding RNA (lncRNA) Paupar are critical regulators of adult neurogenesis in mouse. Kap1 is an essential chromatin regulatory protein that is required for embryonic brain development and adult brain function, whilst lncRNAs are a new class of gene expression regulators with important functions in adult stem cells. Our work showed that the Paupar lncRNA binds and modulates KAP1 chromatin regulatory function to control the expression of shared genes important for NSC proliferation and differentiation, and predicted that distinct lncRNA-KAP1 chromatin complexes act genome-wide to regulate adult neurogenesis. The proposed project will build on these important proof-of-concept experiments to investigate the wider role of KAP1-lncRNA interaction networks in the control of NSC self-renewal and neuronal differentiation. We will use the cutting edge HITS-CLIP method to comprehensively identify the genome-wide set of lncRNAS that associate with endogenous KAP1 in neurosphere cultures of VZ-SVZ NSCs isolated from postnatal mice. Computational genomics will be performed to classify KAP1 associated lncRNAs and prioritise a subset of mouse-human conserved intergenic lncRNAs whose genomic loci overlap regulatory elements close to key neuronal genes for functional analysis. CRISPR interference and anti-sense oligonucleotides will be used to deplete the expression of 3-4 orthologous lncRNAs and define conserved functions in mouse Neuro-2A and human SHSY5Y neuroblastoma cells, two widely used neuronal progenitor-like cell types and in vitro models of neural differentiation. Growth curves, flow cytometry, neuronal imaging and RT-qPCR will be performed to define loss-of-function phenotypes and investigate lncRNA gene regulation. In addition, chromatin immunoprecipitation and knockdown experiments will be performed to dissect conserved mechanisms of KAP1-lncRNA mediated transcription and chromatin regulation important for neurogenesis. This project will discover new neuro-developmental regulatory

	mechanisms and identify novel KAP1-associated lncRNA regulators of neurogenesis with potential to be targeted for the development of new therapies to treat neurodegeneration and brain injury.
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