Project Details	
Project Code	MRCNMH24Ca Petrik
Title	Stem cells and hungry neurons: neuropeptides in energy homeostasis
Research Theme	Neuroscience & Mental Health
Summary	You will investigate the role of neural stem cells and neurons in energy homeostasis. You will determine how neuropeptides and diet affects stem cells, neurons and glia from mouse and human brain. This project will provide advanced training in methods ranging from electrophysiology, calcium imaging, time-lapse live-cell imaging, iPSC technology and single-cell RNA sequencing used in academia and industry.
Description	You will work collaboratively combining molecular biology and neuroscience to investigate the role of neural stem cells and neurons in regulation of body weight and as targets for anti-obesity therapeutics. You will learn cutting-edge technologies, including patch-seq (a combination of patch-clamp electrophysiology and single-cell RNA sequencing, scRNAseq), multi-electrode array recording, calcium imaging, and live cell imaging. Both mouse and human cells will be used in this project. Obesity remains one of the biggest medical and socioeconomic challenges. It increases the risk of depression (1), diabetes and cancer (2). Treatment of obesity requires safe and effective anti-obesity medications. We have developed a lipidized analogue of the neuropeptide Prolactin Releasing Peptide (PrRP), called LiPR. It reduces weight gain in a mouse model of diet-induced obesity (DIO) (3,4) by stimulating appetite-controlling neurons in a part of the brain called the hypothalamus (5). In addition, LiPR increases survival of new hypothalamic neurons generated from the resident neural stem cells in the process of adult neurogenesis and it modulates human neurons derived from induced Pluripotent Stem Cells (iPSCs). LiPR is scheduled for clinical trials in 2024, however, we need to better understand how it works. What genes are downstream of LiPR signalling? What physiological changes does LiPR elicit in hypothalamic mouse and human neurons and stem cells? In this project you will receive training in advanced molecular and cellular techniques to address following objectives: 1) You will determine how LiPR influences physiology and gene expression of both human and mouse neurons, glia, and stem cells; 2) Using multi-electrode arrays and calcium imaging, you will determine how LiPR affects excitability of hypothalamic neuronal networks; 3) To obtain multi-dimensional data on individual cells, you will utilize the cutting-edge patch-seq method (6,7). This powerful technology allows recording of a cell before its cellular content is collected for subsequent analysis. This data will help determine how LiPR affects the function and gene expression of individual cells. Finally, you will use in vitro time-lapse imaging to determine cell dynamics at the clonal level. The supervisory team has shared and complementary expertise in neuroscience and obesity research, notably PrRP (8) making us ideal mentors for this project. We will combine our expertise in physiology and stem cell biology (9) (Petrik Lab, Cardiff), glia and metabolism (10,11) (Ellacott Lab, Exeter), iPSC-derived neurons (Allen Lab, Cardiff) and bioinformatics (12)(Zhou Lab, Cardiff) to complement the research plan. Your interests and preliminary data will allow you to

	steer the project in specific directions. For example, you can emphasize RNAseq over screening of neuronal networks. Or, if you are more interested in human neurons, iPSC-related experiments can be emphasized. You will benefit from excellent research support including the Genomic Research Hub and Medicines Discovery Institute (Cardiff) and the Centre for Excellence in Diabetes Research (Exeter). In addition, we collaborate with Webber Lab (UK Dementia Research Institute, Cardiff) on omics approaches and bioinformatics, with Maletinska Lab (Institute of Organic Chemistry and Biochemistry, Czech Republic) on protein modifications and biochemistry, and with Sierra and Encinas Labs (Achucarro Basque Center for Neuroscience, Spain) on inflammation, microglia, and stem cell biology. References 1. Pereira-Miranda et al. 2017 2. Barberio et al. 2019 3. Maletinska et al. 2015 4. Prazienkova et al. 2017 5. Mikulaskova et al. 2016 6. Picelli et al. 2013 7. Cadwell et al. 2016 8. Lawrence et al., 2002 9. Petrik et al., 2018 10. MacDonald et al., 2020 11. Robb et al., 2020 12. Abdul-Jawad et al., 2021
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