Project Details	
Project Code	MRC23NMHCa Petrik
Title	The role of neural stem cells and neurogenesis in molecular mechanisms of anti-obesity therapeutics
Research Theme	Neuroscience and Mental Health
Summary	We will investigate the role of neural stem cells and neurons in energy homeostasis. We will determine how diet affects neural stem cells, neurons and glia in the hypothalamus, a part of the brain which regulates basic physiological functions such as appetite. This project will provide advanced training in methods ranging from electrophysiology, calcium imaging, time-lapse live-cell imaging, and single-cell RNA sequencing used in academia and industry.
Description	We will combine molecular biology and neuroscience to investigate the role of neural stem cells and new neurons in regulation of body weight and anti-obesity therapeutics. You will learn the 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. Obesity remains one of the biggest medical and socioeconomic challenges. It increases the risk of depression (1) and cancer (2) and it is the second leading cause of disability (3). Treatment of obesity should involve anti-obesity drugs; unfortunately, several anti-obesity drugs originally approved for clinical use were later rejected for severe side effects (4-6). There is a clinical need for new safer neuro-active 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) (7, 8) by stimulating appetite-controlling neurons in the hypothalamus (9). In addition, LiPR increases survival of new hypothalamic neurons generated from the resident neural stem cells in the process of adult neurogenesis. LiPR is scheduled for clinical trials in 2022-23. However, its mechanisms of action of LiPR need to be fully understood. The key research question is what genes and physiological processes are downstream of LiPR in hypothalamic cells. In this project you will receive training in advanced molecular and cellular techniques to address following objectives. You will determine how LiPR influences physiology and gene expression of hypothalamic neurons, glia, and stem cells. Using multi-electrode arrays and calcium imaging, you will determine how LiPR affects excitability of hypothalamic neuronal networks. To obtain multi-dimensional data on individual cells, you will utilize the cutting-edge patch-seq method (10, 11). This powerful technology allows recording of a cell before its cellular content is collected for subsequent analysis. This will determine how LiPR affects function and gene expression of individual cells. Finally, you will use time-lapse imaging of neural stem cells to elucidate how LiPR influences cell dynamics. The supervisory team has shared and complementary expertise in neuroscience and obesity research, notably PrRP (12) making us ideal mentors for this project. We will combine our expertise in physiology and stem cell biology (13) (Petrik Lab, Cardiff), glia and metabolism (14, 15) (Ellacott Lab, Exeter) and bioinformatics (16)(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 physiology, the calcium imaging and electrophysiology can be emphasized over RNAseq. You will benefit from excellent research support including the Genomic Research Hub and Medicines Discovery Institute (Cardiff) and the Center 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. Ferrari et al. 2013 4. Saunders et al. 2016 5. Aronne 2017 6. Patel and Stanford 2018 7. Maletinska et al. 2015 8. Prazienkova et al. 2017 9. Mikulaskova et al. 2016 10. Picelli et al. 2013 11. Cadwell et al. 2016 12. Lawrence et al. 2002 13. Petrik et al. 2018 14. MacDonald et al. 2020 15. Robb et al. 2020 16. Abdul-Jawad et al. 2021
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