

Project Details	
Project Code	MRC22NMHCa Petrik
Title	The role of neural stem cells and neurogenesis in regulating body weight
Research Theme	Neuroscience & Mental Health
Summary	We will investigate the role of neural stem cells and new neurons in the control of body weight. We will determine how diet-induced obesity 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.
Description	<p>We will combine molecular biology and neuroscience to investigate the role of neural stem cells and new neurons in regulation of body weight. To study changes in neural networks, cell dynamics and proliferation, 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). In the UK, 64% of adults and 22% of children are overweight or obese (4). 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 (5-7). 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, called LiPrRP. It reduces weight gain in a mouse model of diet-induced obesity (DIO) (8, 9), it accumulates in the brain, and stimulates appetite-controlling neurons in the hypothalamus (10). In addition, LiPrRP increases survival of new hypothalamic neurons generated from the resident neural stem cells in the process of adult neurogenesis. LiPrRP is scheduled for clinical trials in 2021-22. However, cellular, and molecular mechanisms of action of LiPrRP need to be fully understood. In this project you will receive training in advanced molecular and cellular techniques. You will determine how LiPrRP influences physiology and gene expression of hypothalamic neurons, glia, and stem cells. Using multi-electrode arrays and calcium imaging, you will determine how LiPrRP affects excitability of hypothalamic neuronal networks. To obtain multi-dimensional data on individual cells, you will utilize the cutting-edge patch-seq method (11, 12). This powerful technology allows recording of a cell before its cellular content is collected for subsequent analysis. This data will help determine how LiPrRP affects function and gene expression of individual cells. Finally, you will use time-lapse imaging of neural stem cells to elucidate how LiPrRP influences cell dynamics, self-renewal, and cell proliferation. The supervisory team has shared and complementary expertise in neuroscience and obesity research, notably the biology of Prolactin Releasing Peptide (13) making us ideal mentors for this project. We will combine our expertise in physiology and stem cell biology (14) (Petrik Lab, Cardiff), glia and metabolism (15, 16) (Ellacott Lab, Exeter) and bioinformatics (17)(Zhou Lab, Cardiff) to complement the research</p>

	<p>plan. You will benefit from excellent research support including the Genomic Research Hub and Medicines Discovery Institute (Cardiff) and the Neuroendocrine Research Group, which is part of the ExCEED 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.</p> <p>References 1. Pereira-Miranda et al. 2017 2. Barberio et al. 2019 3. Ferrari et al. 2013 4. NHS Obesity Stats 2019 5. Saunders et al. 2016 6. Aronne 2017 7. Patel and Stanford 2018 8. Maletinska et al. 2015 9. Prazienkova et al. 2017 10. Mikulaskova et al. 2016 11. Picelli et al. 2013 12. Cadwell et al. 2016 13. Ellacott et al. 2002 14. Petrik et al. 2018 15. MacDonald et al. 2020 16. Robb et al. 2020 17. Abdul-Jawad et al. 2021</p>
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Supervisory Team

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