Project Details	
Project Code	NMH27Ca Isles
Title	Investigating placental function and fetal programming in Prader–Willi Syndrome
Research Theme	Neuroscience & Mental Health
Project Type	Wet lab
Summary	By bringing together transcriptomics and cutting edge imaging, and data analysis techniques, this PhD project aims to examine how abnormalities in placental function leads to altered programming of the developing fetal brain in a neurodevelopmental disorder. This interdisciplinary project will provide the student with preclinical lab-based skills, and bioinformatic and data-handling skills that will be applicable to a wide range of career pathways.
Description	The overall aim of this project is to examine placental function and fetal programming using a mouse model for Prader-Willi syndrome. The neurodevelopmental disorder Prader-Willi syndrome (PWS) is caused by loss of paternally-derived gene expression from the imprinted gene interval on chromosome 15q11-q13. PWS is characterised by mild learning difficulties, behavioural problems and, most notably, an insatiable appetite. Recently, it has been suggested that the abnormal feeding-related behaviours characteristic of PWS may be, in part, developmentally programmed in utero via abnormal placental function [1]. This is important as therapies that are being developed targeting gene activity in adult individuals may not be sufficient to rescue the developmental deficits. However, this project may point to additional therapeutic routes in which development in PWS may be enhanced in the immediate postnatal period. Our previous work has shown that homologous PWS-genes are expressed in mouse placenta with marked reduced expression in a PWS mouse model. This leads to a ~25% reduction in Kdr-positive endothelial cells in the labyrinthine zone of the placenta and suggests that placental function and nutrient transfer from mother to fetus may be compromised in PWS. Developmental programming by maternal nutrient provision and/or placental endocrine signalling in utero is recognised to impact offspring brain. Of relevance to PWS, the development of the melanocortin system, which is a key component of the neural control of feeding and energy homeostasis, is particularly sensitive to changes in a multitude of endocrine and nutritional factors [3]. The key hypothesis of this PhD project is that: Changes in the PWS placenta programme abnormal development of the developing hypothalamus The project will explore in detail the changes in PWS placenta and how these affect placental function and fetal hypothalamic development using transcriptomic, structural and functional methods. The key objectives are: 1. Using existing single-cell RNA-seq data, examine which cell-types are enriched for PWS gene expression in human placenta 2. Carry out histological examination of PWS mouse model placenta to characterise endothelial cell phenotype

	3. Examine structural changes of PWS mouse model placenta and fetus using advanced imaging techniques (at the Rosalind Franklin Institute) 4. Perform RNA-seq studies of PWS fetal placenta and developing hypothalamus This project will expose the student to a range of experimental and analysis approaches equipping you with skills in in vivo physiology, advanced imaging and data handling and analysis. At Cardiff, the student will conduct RNA-seq experiments and learn the computational skills to handle these datasets and perform a range of bioinformatic analyses. These include differential gene expression, enrichment of the key genes (the PWS genes and genes involved in key biological functions pathways), and advanced analytical approaches to these data, such as WGCNA (weighted gene correlation network analysis). In addition, the student will use histological approaches including immunostaining and quantification of CD31 and/or vimentin to add granularity to our understanding of the endothelial changes in the PWS mouse placenta. Finally, they will take advantage of advanced research imaging modalities available at the Rosalind Franklin Institute, Diamond Light Source and the Mary Lyon Centre and the necessary sample preparation approaches. Possible imaging modalities that could be explored to understand the structural placental changes include in vivo X-ray CT, synchrotron X-ray CT and cryogenic soft X-ray tomography, depending on the scale of the features of interest. Each of these imaging methods requires sample preparation and data collection optimisation to adapt to mouse tissue samples and cutting-edge deep learning computational approaches for image segmentation and to enable multi-modal correlative imaging approaches. Together, these approaches will enable us to understand how changes in cellular numbers in PWS can affect placental growth, morphology and cellular composition, and in turn affect fetal growth, in particular in the hypothalamus of the brain. This will hugely expand our understanding of how the placenta can programme brain development more generally. Key publications: [1] Brown SSG, Manning KE, Fletcher P, Holland A. In vivo neuroimaging evidence of hypothalamic alteration in Prader-Willi syndrome. Brain Commun. 2022 9;4(5):fcac229 [2] Webberley AE et al. Prader-Willi syndrome genes are expressed in placenta and play a role in function. Disease Models and Mechanism (in press see bioRxiv preprint doi: 10.64898/2026.01.20.692090) [3] Bouret, S.G. (2022) Developmental programming of hypothalamic melanocortin circuits. Exp Mol Med, 54, 403-413
Can be completed part time?	No
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