Project Details	
Project Code	MRCNMH25Ex Piers
Title	Development and characterisation of reproducible complex human brain organoids – Bio-engineering and neuronal networks
Research Theme	Neuroscience & Mental Health
Summary	Using induced pluripotent stem cells, we can generate complex multi-cellular 3D human brain tissue models in a dish, termed cerebral organoids. These models provide unique opportunities to study human-centric biological questions about brain function. However, the use of such models is confounded by variability, poor long-term viability, and a limited diversity of cell types. This project will take a multi-disciplinary approach, incorporating 3D bioprinting and novel cell culture techniques to allow us to generate highly reproducible organoids that can be used to study neuronal function in health and disease.
Description	**Background:** The use of human induced pluripotent stem cell (iPSC)-derived tissue models is revolutionising fundamental biology and biomedical research. The development of iPSC-derived cerebral organoids, for example, is providing researchers with the tools to investigate previously impossible neurological questions, something particularly pertinent when investigating human brain disorders with a genetic component. A significant caveat to the use of these models, however, is the inherent variability and lack long term viability, something which is required due to the protracted nature of human brain development. **Project aims:** The project will use human iPSC culture techniques coupled with bio-printing to develop viable and reproducible 3D brain organoids. The student will work with these models and answer the following questions: 1. How do micro-scaffolds react with biological material? 2. What scaffolds provide optimal viability? 3. Does the inclusion of micro-scaffolds lead to increased reproducibility and translational potential? Objectives and learning outcomes for the student: 1. Develop expertise in iPSC culturing to generate complex models 2. Develop 3D bioprinting expertise 3. Develop skills in electrophysiology and super-resolution imaging to assess network excitability **Research Plan** Aim 1: Testing bio-compatibility of printed nano-structures UEx: The student will learn iPSC culture techniques in the lab of primary supervisor TP. They will develop basic 3D organoid cultures and in collaboration with co-supervisor JC, test the biocompatibility of bio-printed scaffolds. This will require stringent optimisation and method development. Readouts will include cell stress markers and cell media testing for secreted factors and biomarker characterisation. Aim 2: Development of guided organoid cultures UEx: The candidate will generate guided cortical organoids that encompass excitatory/inhibitory networks. The student will test novel strategies to develop more reproducible and translatable models including pulse exposure of ventralising and dorsalising factors, for example. There will also be opportunities here to integrate mesodermal

	origin cells including microglia that are normally absent from the organoids. High resolution imaging and subsequent image analysis of the derived organoids will be performed in collaboration with TP's affiliate status at The Living Systems Institute. UB: The candidate will spend time in the lab of co-supervisor DW to learn electro-physiology recordings. They will use this technique to characterise generated organoids and how different guiding strategies and cellular integrations alter neural network excitability. There will also be a focus on characterising the variability within groups. Aim 3: Bio-printing of guided organoids to increase viability UEx: Protocols optimised and developed in aim 2 will be incorporated into bio-printing strategies with the guidance of co-supervisor JC. Initially, the candidate will test the long term viability on bio-printed guided organoids using periodic cell stress readouts. UB: In parallel, the student will validate the models using electrophysiological readouts. **Areas of ownership:** The combinatory strategy will provide the student with opportunities to steer the project in multiple directions depending on their interests, including a focus on the development of micro-scaffold structures for biological systems, complex 3D culture, and electrophysiological assessment of neuronal network activity
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