Connectome 2019
Birmingham, UK

THEME BREAKOUT SESSION INFORMATION

1. NEUROINFLAMMATION: iPSC-Derived Microglia from Protocols to Function *with Hugh Perry (UK DRI)*

Talks and discussion featuring Siddarthan Chandran, Renzo Mancuso, Soyon Hong, David Klenerman, and Phil Taylor.

The ability to derive microglia-like cells from iPSCs offers many opportunities and there are high expectations. However, working with iPSC-derived cells there is a need to be clear: What cell type we are really dealing with and how do we characterise them? Do we have appropriate and relevant functional assays? What are the key questions we wish to address? How do we share our expertise across the UK DRI?

In this session we will hear how we can learn lessons from the study of iPSC-derived neurons, consider the molecular and functional phenotyping of iPSC-derived microglia in vivo and in vitro and hear about novel approaches to assay function.

2. VASCULAR ROLE IN NDG: Establishing a Cross-Centre Theme *with Joanna Wardlaw (UK DRI at Edinburgh)*

The UK DRI is establishing a Cross-Centre Theme in vascular contributions to neurodegeneration.

Why? There is strong evidence that vascular risk factors and cerebrovascular disease are major contributors to neurodegeneration, and of vascular dysfunction in the early stages of Alzheimer's disease. However, many aspects of how vascular dysfunction affects the brain are poorly understood and therapies are limited.

What? The purpose of this theme is to establish a community of researchers, under the umbrella of the UK DRI, whose research is relevant or potentially relevant to advancing understanding interactions between vessels and the brain. It aims to establish greater synergies across UK DRI Centres, and with other relevant groups, to deliver the UK DRI mission.

How? It will increase awareness of the role of vascular dysfunction in neurodegeneration, increase information exchange, foster cross-centre collaboration, enhance career progression of young researchers, advance technologies, and initiate new programmes of research leading to clinical trials.

Please join this session if you are interested in being part of this cross-centre theme, participating in workshops and promoting vascular disease awareness in the UK DRI.

3. GENETIC THERAPIES: Current and Future Technologies and Facilitating Collaboration across the UK DRI *with Chris Shaw (UK DRI at Kings) & Nick Fox (UK DRI at UCL)*

Gene therapies for neurodegenerative disorders are coming of age with the extraordinary success of Spinraza™ and Zolgensma™ for Type 1 Spinal Muscular Atrophy. A number of UK DRI clinicians are leading trials of antisense oligonucleotide (ASO) and adenoviral associated viral (AAV) gene therapies for patients with neurodegenerative disorders. The UK DRI is already investing in preclinical Gene Therapy programmes at KCL and UCL and after Connectome 2019, they will be offering significant new funding for themes that generate new ideas and cross-centre collaborations.

With that in mind we have put together a programme that seeks to inform attendees about current and future gene therapy technologies and their application. Speakers include Professor Sarah Tabrizi on the latest results from ASOs in Huntington's disease. Adrian Isaacs on gene therapy strategies for C9orf72 FTD/ALS, Dr Younbok Lee on cassette design to enhance gene and micro-RNA expression, and Dr Natalia Arias on the route of administration for viral vectors. We will finish with an overview of KCL's AAV vector platform and UCL's genetic therapy Centre and a panel discussion about how we might engage with other interested researchers across the DRI and facilitate collaboration.

4. MULTI-'OMICS BRAIN ATLAS: Project Overview and Future Plans *with Paul Matthews (UK DRI at Imperial)*

Molecular neuropathology using multiple 'omics methods, many of which can be applied at a single cell level, are bringing fundamentally important new insights to dementia research. The purpose of this session is to bring together researchers from across the UK DRI who are involved in (or could benefit from) multi-'omics interrogations of human brain cell or tissue pathology. With an initial focus on Alzheimer's Disease, we describe how we are working with researchers across different UK DRI Centres to create a first multi-'omics brain atlas (mapping) project. The session will review current plans with the intention both of informing Connectome participants and of seeking advice from them. We will discuss key challenges for the human brain multi-'omics field including access to tissue, data reproducibility, quality control of the tissue and approaches to integration of the large datasets. Outcomes of the meeting include identification of new potential stakeholders (collaborators or data users) and opportunities, from which working groups will be formed to enhance involvement and accelerate progress of this UK DRI-wide effort.

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5. BIOINFORMATICS: Advanced Approaches in iPSC Modelling

with Caleb Webber & Valentia Escott-Price (UK DRI at Cardiff)

Induced pluripotent stem cells promise human models of the inaccessible brain cells across all the UK DRI disorders. Key session questions include model selection, the significant experimental variability and detecting and investigating cellular phenotypes, with short talks followed by longer discussion. In the first part of this session, we will discuss experimental design challenges with short talks from Valentina Escott-Price (Cardiff) on which UK DRI disorders would benefit from the polygenic risk models only human models can deliver, and from Caleb Webber (Cardiff) on addressing experimental variation and reproducibility. In the second half, we will discuss how we can use these models to understand cellular dysfunction with short talks from Adrian Isaacs (UCL) on identifying cellular phenotypes and dysfunction, and from Manos Metzakopian (Cambridge) on genome-wide CRISPR screens.

6. ANIMAL MODELS: Behavioural Phenotyping, iPSC – Mouse Chimeras, and New Mouse Lines of Interest *with Frances Wiseman (UK DRI at UCL) and Maksym Kopanitsa (UK DRI at Imperial)*

Talks and open discussion featuring Sara Wells, Sriram Balusu, and others.

Goal: Development of capacity in mouse models of dementia and tool models for the UK DRI.

Vision: *Long-term* (5-10 years) to complement anticipated developments in alternative preclinical models. *Collaborative* resource sharing (within UK DRI and externally via EMMA) to maximise impact. *Robust* genetics, husbandry and experimental design to produce generalizable data.

Dementia is caused by brain pathology leading to changes in cognition and behaviour. The brain is composed of a significant number of different cell types (subtypes of neurons, astrocytes, oligodendrocytes and microglia) and also interacts with the vascular and sensory systems. Genetic and epidemiological data indicate that the immune system, metabolic state and particularly cardiovascular health impact on dementia development. Thus physiology “below the neck” has a key role in disease. The UK DRI Animal Models programme will develop preclinical models to study this complexity for hypothesis-driven basic research. To complement future advances in organoid technology the programme will focus on:

i) **cell type diversity** (regional and cell-type vulnerability)
ii) interaction of the brain with **vasculature, sensory systems and whole organism physiology**
iii) **and the phenotyping of changes in cognitive and behaviour**

This will include the development of novel models of disease, tool development for hypothesis-driven research and increasing phenotyping capability (with an emphasis on novel home-cage tasks, sensory, cardiovascular and metabolisms tests). The UK DRI has awarded funds for the development of novel genetic models and for the central phenotyping of these and other commonly used animal models, at MRC Harwell (by open competition and independent review).

The themed session at Connectome will focus on the following topics –

Phenotyping Capability: opportunities for cross-site collaboration

i) Sensory system: hearing and sight
ii) Home-cage phenotyping: quantification of natural behaviours and touch-screens tasks
iii) Whole organism physiology: telemetry (blood pressure/glucose), blood biochemistry etc.
iv) In vivo electrophysiology and imaging

iPSC and Mouse Models: understanding cell diversity

i) Chimeric models: postnatal engraftment and blastocyst complementation (capacity development)

Cell-type Identification: Cres and Tags

i) Development or central import: which models are needed? (e.g. genetic hits, transcriptional hubs, neuronal subtypes, synaptic compartment)
ii) Central validation of commonly used lines: which lines are predominately used? (genetics of line and/or developmental expression pattern)

7. CENTRE MANAGERS: TBC *with UK DRI HQ*

TBC