Developing a scaffold-based model of neurodegeneration for high throughput screening

The success rate for drug approval to treat Alzheimer's disease (AD) was less than 1% in 2014, and the number of people suffering with AD is expected to increase until at least 2050. A major component of the failure to bring novel drugs for AD to market is the translational gap between *in vitro*, animal and human studies. This is the result of an unmet need for more physiologically relevant *in vitro* systems for drug screening. 2D cultures have been utilised as the main screening system for decades, providing an easy and cost effective first stage assessment; however, 2D systems lack the biophysical properties which have been found in 3D cultures to improve *in vitro* to *in vivo* translation. Currently, most published 3D systems are organoids. Whilst these are insightful and replicate aspects of neuronal architecture within the brain, the diffusion dynamics, high heterogeneity, and labour-intensive development can be disadvantageous.

Using the novel technology of 3D bio-printing, this project aims to develop a scaffold-based 3D quad-culture model of AD for drug screening using human induced pluripotent stem cells (iPSCs). Protocols to differentiate human neural progenitor cells into cortical neurons, astrocytes and oligodendrocytes have been established from AD mutation lines and healthy controls. These cell types, alongside iPSC-derived microglia, form the quad-culture of cells within the model. The quad-culture is suspended in a hydrogel of extracellular matrix proteins, which has been modulated to mimic brain biomechanics. The cell-hydrogel suspension is "printed" onto 96- and 394-well plates using a 3D bioprinter, which uses drop-on-demand technology to allow high resolution placement of the cells. Consequently, this model will exercise the benefits of a 3D model, including extracellular deposition of amyloid-β plaques, while maintaining the benefits of 2D systems, including reproducibility, reliability, and suitability for high throughput screening.