Using human stem cells to Identify neuroprotective pathways

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Attempts to identify therapeutic targets to combat neurodegenerative diseases such as Alzheimer’s Disease have largely focussed on unravelling the underlying neurodegenerative process and then to subsequently identify targets that can halt, slow or abrogate neurodegeneration. Thus far, this search has yielded no effective treatments. We are pursuing an alternative approach – we have discovered a gene network that renders neurons resistant to neurodegenerative insults such as β-amyloid. The network comprises more than 1600 differentially expressed genes including around 100 transcription factors organised into several hubs comprising genes associated with regulation of extracellular matrix, growth factor signalling, regulation of inflammation and neuronal differentiation, all processes intimately linked to protection against cell death.

This project will systematically interrogate this transcriptional network to identify those transcription factors, which in isolation or in combination confer neuroprotection. Further, we will use these transcription factors to develop screens to identify novel therapeutic compounds that can drive the transition to a neuroprotective state.

The project will comprise (i) using CRISPR/CAS gene editing of human induced pluripotent stem cells to identify those transcription factors, which in isolation or in combination confer neuroprotection (ii) identification of downstream targets of neuroprotective transcription factors using ChIPseq and RNAseq (iii) development of a high throughput screen to identify small molecules that can induce expression of the neuroprotective network.