Characterisation of a novel cell model for Huntington’s disease: insights into pathogenesis

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Name of Fellow

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Institution
Funder

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Contact information of fellow
Country

United Kingdom

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Characterisation of a novel cell model for Huntington's disease: insights into pathogenesis

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The project/programme is most relevant to:

Huntington's disease

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Research Abstract
Huntington’s disease (HD) is a fatal, autosomal dominant inherited condition caused by a CAG repeat expansion in exon 1 of the gene encoding Huntingtin (Htt) protein. We aim to create a cell model of Huntington’s disease using two different human neural stem cell (hNSC) lines and knocking the mutated exon 1 with various CAG repeat lengths (50, 80 and 120 repeats) into one of the Htt gene alleles to create heterozygous cell lines. This will be achieved using the rAAV vector, which triggers homologous recombination into the native gene locus, thus creating a model that is far more representative of the diseased cell. The two hNSC lines differentiate into dopaminergic and GABA-ergic neurons, a proportion of them specifically forming the medium spiny neurons which are preferentially destroyed in HD. We will then use this model to characterise the effect that the mutated gene has on the phenotype of the neurons. My hypothesis is that mutant HTT will cause CAG length dependent cellular dysfunction in MSNs. This will be tested using LDH and ATP assays, as well as the Cellomics fluorescence based cytotoxicity bioapplication. I will also use electrophysiology and quantitative PCR to assess synaptic function and transcriptional dysregulation, which are known problems in HD. The other hypothesis I wish to test is that wild type and mutant HTT have different cellular trafficking pathways, which impacts on cell function. This will be tested using immunofluorescence and confocal laser microscopy in conjunction with an existing panel of anti-HTT antibodies to different HTT epitopes. I will also use live cell imaging techniques to study the effect of mutant HTT on axonal transport.

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Fellowships

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