Rationale & Hypothesis: Huntington’s disease (HD) is a monogenic, dominantly-inherited, progressive neurodegenerative disorder. It is caused by a trinucleotide expansion in the huntingtin gene. Although the genetics of HD are simple, the pathology is complex and is yet to be fully understood. Mitochondrial dysfunction and epigenetic-driven transcriptional dysregulation are major factors in the pathology of the disease. Histone de-acetylase (HDAC) inhibitors have shown promising disease-modifying effects in HD. We therefore propose that the mitochondrial dysfunction in two cell models of HD may be ameliorated by HDAC inhibitors.

Objectives: To determine mitochondrial function and morphology in HD mutant fibroblasts and PC12 cells expressing a mutant huntingtin fragment (mtHTT PC12). To investigate the effect of HDAC inhibitor treatment on mitochondrial function.

Methodology: Mitochondrial dysfunction will be analysed using a luciferase assay for cellular ATP levels and tetramethylrhodamine methyl ester (TMRM) to measure mitochondrial membrane potential. The mitochondria will be stained with rhodamine123 fluorescent stain and their morphology analysed using the InCell2000. The effect of a selection of HDAC inhibitors on mitochondrial function and morphology will be assessed.

Findings: ATP levels and the mitochondrial membrane potential are reduced in fibroblasts from a patient with Huntington’s disease. Assessment of the mitochondrial function in mtHTT PC12 cells and the pharmacological rescue experiments with HDAC inhibitors are still on-going, but will reveal whether the observed mitochondrial impairment may at least partially be due to epigenetic mechanisms.