INTRODUCTION: Mutations within DJ1 give rise to an early onset recessive form of Parkinson's Disease (PD) but it remains unclear how mutation of DJ1 leads to PD. To decipher the pathways within which DJ1 function and how they might contribute to disease pathogenesis, we conducted a high throughput and high content screen against known DJ1 interactors to determine how they may affect DJ1 function and phenotypes associated with PD.

Aim: Identify modulators of DJ1 function

Method: We developed two assays to monitor the biological function of DJ1:

1) A high throughput cell viability assay as loss of DJ1 increases the sensitivity of the cell to environmental stress and toxins

2) A high content assay to monitor the translocation of DJ1 from the cytoplasm to the mitochondria which occurs upon exposure of cells to stress.

Wild type and DJ1 knockdown SH-SY5Y neuroblastomas were infected with shRNA lentivirus targeting known DJ1 interactors. Cells were subsequently exposed to environmental toxins and the effect observed in the above assays.

Results: Several genes (e.g. PSF, PPP2R2C) were identified that were able to rescue the effect of DJ1 loss with regard to cell viability as well as genes which were able to enhance the loss of DJ1 such as 4E-BP. We also identified metallotheins as important for the translocation of DJ1 to the mitochondria.

Conclusion: Using this approach we have been able to construct a detailed molecular pathway of the proteins that are involved in the function of DJ1 and identify potential therapeutic targets.