Emma Wilson, Postdoc - 'High Throughput CRISPR/Cas9 Screening investigating novel modulators of Mitochondria ER Contact sites within neurodegenerative diseases'

Alzheimer's disease (AD) and Parkinson's disease (PD) and two of the most common neurodegenerative diseases With an ageing population, AD and PD are becoming increasingly prevalent, with cases of AD set to increase to 75.6million by 2030. Unfortunately, many drugs are ineffective treatments for AD and PD therefore it is important that we investigate the underlying causes with the aim to highlight novel drug targets. Genes associated with familial AD, amyloid precursor protein, Presenilin-1 and Presenilin-2 are enriched at Mitochondria ER Contact Sites (MERCS) and mutations in these genes can result in increased MERCS proximity and enhanced lipid metabolism. While Mutations in α Synuclein, can causes a reduction in MERCS, Ca2+ flux and ATP production and PINK1 and Parkin, genes associated with familial PD have been shown to localise to MERCS upon mitophagy induction.

We hypothesise that MERCS dysfunction contributes to neurodegeneration however the exact mechanism is unknown. To further understand the role of MERCS in neurodegenerative diseases we conducted a high throughput pooled genome-wide CRISPR/Cas9 knockout screen to identify novel modulators of MERCS using split mVenus reporter HeLa cell line. Here we generated two gene lists which were enriched in cell populations with an increase or decrease in fluorescence intensity of MERCS. We plan to use arrayed screening techniques in 3 cellular ER-Mito reporter models to validate this list. The top hits from these screens will be examined for effects on MERCS functions including calcium flux, autophagy, mitochondrial quality control and lipid metabolism.