Project Title

Generation of Humanised *STX6* Overexpression Mice to Study Prion Disease Genetic Risk

Project Objective

The goal of this project is to engineer new mouse models with increased levels of Syntaxin-6 (Stx6), a factor which increases risk of developing the most common human prion disease, sporadic Creutzfeldt-Jakob disease (sCJD). We aim to use this novel experimental model to study how increased Stx6 levels affect prion disease to enable a better understanding of pathological disease mechanisms.

Summary of Accomplishments to Date, Next Steps and Implications for the Prion Disease Field

We have successfully generated a mouse model with increased Syntaxin-6 levels in neurons, the brain cells which degenerate in prion disease. We have also initiated work engineering a mouse model with increased Syntaxin-6 levels in oligodendrocytes, which are brain cells which play a supporting role in the brain, as this cell type has the highest increase in Stx6 in individuals with the Stx6 risk genetic variant. To increase the relevance to human, we have also engineered a preparation of the actual human Syntaxin-6 gene which we will also express in mice.

In the coming months, we plan to characterise these mouse models as well as infect them with prions to explore how increased Syntaxin-6 levels affects the disease course. We will assess whether the timing the mice develop the disease, or the amount of animals that develop the disease, differs with altered levels of Syntaxin-6. We will also stain brain slices to analyze known disease markers to see if they are altered.

This work has provided tools to explore the role of a factor which has been proposed to increase the risk of human prion disease. This will provide further supporting evidence for a role of Syntaxin-6 in prion disease and further our understanding on its pathological role. A better understanding of disease processes helps us better understand what has gone wrong, which may facilitate finding new targets for therapy development.