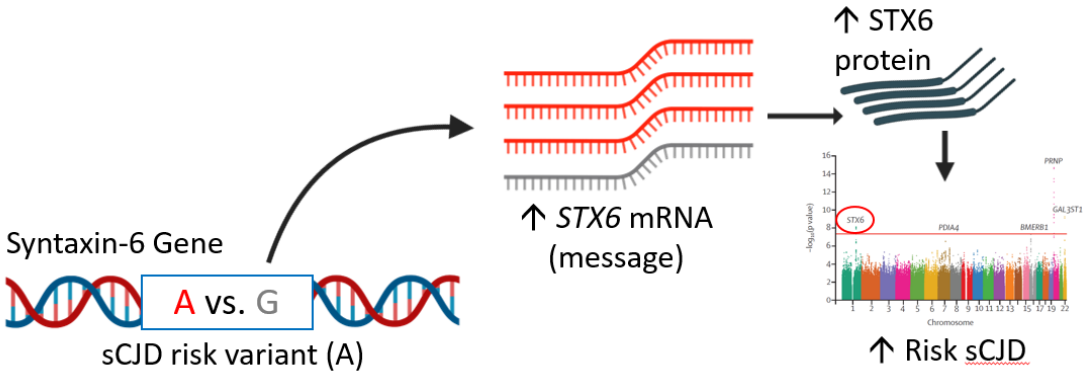
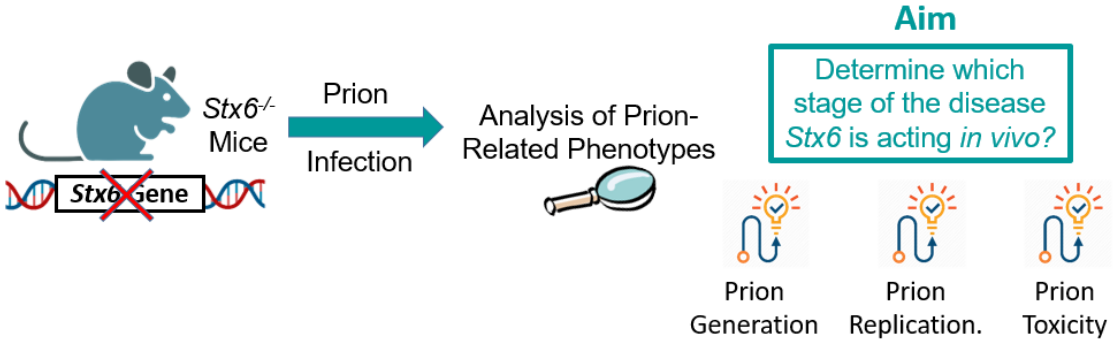
enCurrent Thinking: The Role of Syntaxin-6 in Prion Disease Risk

Genetic variants in the gene, syntaxin-6, increase the risk of developing sporadic Creutzfeldt-Jakob disease (sCJD), the most common human prion disease. These risk variants increase the cell's production of the syntaxin-6 protein, modestly increasing risk in these individuals by about 16%. However, why or how syntaxin-6 contributes to risk of prion disease is not known.



Increased Levels of Syntaxin-6 (STX6) Increase Risk of sCJD. Risk variants in the DNA code at the *STX6* gene increase expression of the gene, which increases susceptibility to developing sCJD.

To investigate the role of syntaxin-6 in physiology and disease, we made genetically engineered mice which do not have syntaxin-6. Remarkably, these mice are healthy with no gross physiological, behavioral or neurological abnormalities. We infected these mice with prions to explore how the absence of syntaxin-6 might affect the disease onset and progression.



Study Objective. Assess prion-related readouts in prion-infected mice with and without syntaxin-6.

In prion disease, the normal form of the prion protein or "PrP" misfolds. When this misfolded form comes into contact with the correctly folded form, it causes the normal protein to misfold, creating a chain reaction, eventually leading to clinical disease. Imagine one domino getting pushed over in a stack, and what this leads to! In mice infected with prions, there is an initial explosive increase in the number of prions, but this stabilises after approximately 10 weeks. When we assessed the levels of prions at multiple times across the disease course, we found no noteworthy difference in prion levels in mice with no syntaxin-6 compared to mice that do have the protein.

When prions have reached maximal levels, it is thought that toxicity then attacks the brain resulting in degeneration. We looked at multiple indicators of toxicity including substances in the blood related to neurodegeneration, by staining brain slices with dyes which stain disease markers, and also

assessing the timing disease develops and progresses. Again, we found no differences in any of these readouts in mice lacking syntaxin-6.

This suggests syntaxin-6 does not affect prion replication nor toxicity in mice infected with prions. However, it is important to remember that syntaxin-6 is implicated in risk of sCJD. Here prions are not introduced by infection; instead the disease appears spontaneously from an unknown cause. In mice infected with prions, we bypass this event where a prion is first generated. Instead we introduce artificial misfolded PrP to kickstart the process. Importantly, this means we are unable to study factors which affect the initial misfolding event using these mice.

The data suggests syntaxin-6 has no therapeutic value for patients with established disease. However, by a process of elimination, it suggests that syntaxin-6 may be involved in the initial generation of a misfolded prion. Indeed, the syntaxin-6 protein seems to interact with PrP which could influence this initial misfolding event. To study this, we would like to pursue generating mice which do not have syntaxin-6, which develop spontaneous prion disease to investigate whether this serves as a protective factor against the disease. If this is shown to be the case, lowering levels of syntaxin-6 in high-risk individuals, may be beneficial to prevent the initial misfolding of PrP and the onset of prion disease, which of course is highly relevant to those individuals with inherited prion diseases.