Final Report 2020 Research Grant

Project Title:

Evaluating prion vaccines in transgenic mouse models of familial prion diseases.

Project Objective:

The main objective of the project was to determine the efficacy of our structure-based prion vaccine in transgenic mouse models of familial prion diseases. We previously developed this prion vaccine based on our knowledge about the structure of the infectious prion, and the vaccine had shown promising prophylactic effects in a transgenic mouse line carrying the P102L GSS mutation. The project allowed us to continue testing the efficacy of the prion vaccine in mice carrying the P102L GSS mutation, and start testing in mice carrying the E200K CJD mutation, as well as the D178N FFI mutation.

Summary of accomplishments to date:

Extensive tests of the vaccine in the TgP101L mouse line, which models the P102L GSS mutation in humans, demonstrated a ~280% extension of health-span, i.e. unimmunized animals started to show disease symptoms at ~177 days of age, while vaccinated animals remained healthy until ~500 days of age. The efficacy trials in the TgE199K mouse line, which models the E200K CJD mutation, are still ongoing. Due to the long duration of the experiment, we still don't have the final numbers on the prophylactic effect of the vaccine, but at current standing we are seeing a ~150% extension of health-span in these mice. More detailed follow-up analyses are need to confirm these results. Efficacy trials in the TgFFI mouse line, which is based on the D178N FFI mutation, were limited in scope and animal numbers. However, these experiments also showed a delayed disease onset in immunized mice.

Key findings and implications for the prion disease field:

The key findings of our project were the substantial delays in disease onset in transgenic mice that received our structure-based prion vaccine versus unimmunized animals. The implications for the prion disease field are that a prophylactic prion vaccine may delay disease onset in genetic prion disease cases, if the animal work translates to human patients. However, as promising as the results are, more work is needed to confirm the results, determine the mechanism of action, and try to improve the delay in disease onset further, before efficacy trials in humans can be attempted.

Next steps in your work:

We are currently applying for funds to study the detailed mechanism that provides the prophylactic effect of the prion vaccine. Initially we suspected the antibody immune response as the main driver behind the delayed disease onset. However, more recent data pointed towards the cellular immune response as key element of the prophylactic effect. This follow-up project should reveal which part of the immune response, e.g. which cell type, is responsible for the protective effect. This knowledge in turn could help to improve the vaccine efficacy, providing more support for a potential trial in mutation carriers.