

## CJD Foundation Grant Progress Report

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**Title:** The RAP approach for effective prevention and treatment of prion diseases

**Project objective:** We aim to develop an effective gene therapy treatment and prevention strategy against human prion diseases through simultaneously knocking down the key mediator for prion toxicity, suppressing the replication of the prion agents, and protecting brain cells from prion-induced toxicity and damages.

**Summary of accomplishments to date:** We have successfully developed a couple of plasmid DNA vectors that can be used to knock down expression of the gene for prion protein (PrP), the essential mediator for prion toxicity. We have also developed a plasmid vector to express a secreted form of a neuroprotective peptide that can protect neuronal cells from prion toxicity and other cellular stresses. The first experiments in transgenic mouse models for common human prion diseases using these plasmid vectors assisted by novel nanoparticles are near completion. In addition, we also found evidence that the neuroprotective peptide also has direct anti-prion replication activity in vitro, which should make the neuroprotective peptide more effective in vivo.

**Key findings and implications for the prion disease field:** Both plasmid vectors we developed appear to be safe for gene therapy treatment in animals inoculated with human CJD prions, which fulfills the safety requirement for clinical applications. Their effectiveness for prion treatment awaits the conclusion of the current experiments as well as further animal experiments with viral vectors. However, the plasmid vectors in their current forms seem to express the cargo genes only briefly in vivo, which may limit their effectiveness.

**Next steps and related prion research:** We will create high titer viral vectors from these plasmid vectors, inject the viral vectors into CJD-inoculated transgenic mouse models, and examine their effectiveness in terms of enhanced survival and attenuated pathology in the brain.

We will also start similar experiments in a transgenic mouse model that develops spontaneous prion disease, making it a better model for sporadic and inheritable prion diseases in humans. The mice will be treated at various preclinical and clinical stages with our plasmid or viral vectors to assess the effectiveness in prevention and treatment of spontaneous prion diseases.

In addition, we will start optimizing the plasmid vectors so as to allow for sustained cargo gene expression from naked plasmid vectors without the need for conversion into viral vectors that are much more expensive and carry other major caveats.