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Project title: Assessing efficacy of zinc-finger repressors of prion protein as a therapeutic for prion disease

Project objective: Prion disease is caused by the misfolding of the normal prion protein (PrP) in the brain. Because the disease process requires PrP, an attractive therapeutic approach is to lower the amount of PrP in the brain. The goal of this project was to test a novel set of tools – zinc-finger proteins, or ZFPs – for their ability to lower brain PrP and modify disease in animal models of prion disease.

In theory, there are a few different steps in the production of a protein that could be targeted to lower its levels. One could imagine targeting the protein itself; the RNA molecule that contains the instructions for producing the protein; or the DNA that serves as the template for the RNA. Zinc finger proteins are molecular tools that aim at the DNA. In this project, we studied ZFPs that specifically recognize and target the DNA that encodes the prion protein gene, thereby, in principle, preventing production of the prion protein RNA and ultimately, the prion protein itself.

Summary of accomplishments to date: When we began this project, we had already seen that ZFPs could lower the amount of prion protein in cells in a dish. But lowering the amount of PrP in the complex environment of a living brain is a problem on a different scale. As is consistently the case for brain disease, almost regardless of drug type, the biggest challenge is delivery. ZFPs can't be delivered directly into the brain. Instead, instructions to make the ZFP – in other words, DNA encoding the ZFP – is "packaged" into a delivery vehicle. The goal is for the delivery vehicle to make it into brain cells, where the DNA then persists indefinitely, producing ZFP continuously over the long term. This adds up to an ambitious vision for what conceivably be a one-time therapy.

In this project, we performed experiments in which ZFP DNA was packaged into delivery vehicles that are known to distribute well across the mouse brain. At present, there exists no equivalent human delivery vehicle, but these tools allowed us to do "proof of concept" experiments in both "naïve" (non prion-infected) and prion-infected mice. And we learned that given the right delivery vehicle, ZFPs could significantly lower the amount of PrP in the mouse brain (by about half) and extend the survival of mice infected with prions.

Key findings and implications for the prion disease field: A key implication of this work is that tools exist today that are capable of "turning off" production of the prion protein at it original source – the gene. The key to making the leap from tool to potential medicine will be figuring out how to deliver this "cargo" to most or all of the 100 billion neurons in the adult human brain. While we aren't there yet, many dedicated scientists are working on discovering the human-relevant delivery vehicle that could truly unlock the potential of this kind of therapy, not just for prion disease but for other brain diseases.

Next steps in your work: Our lab continues to focus on facilitating development of PrP-lowering therapies, and developing tools, methods and models that will enable the clinical development of such therapies. Advantageously, many of these tools will be applicable to any potential therapeutic that lowers PrP, even if the exact molecular mechanism and targeting strategy is different.

Thank you to the CJD Foundation for enabling this work!