

## **PUBLIC ABSTRACT**

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease that attacks the motor neurons of the brain and spinal cord of healthy adults. The disease progresses rapidly and is always fatal, leaving patients paralyzed and unable to breathe. There is still no known cause for the majority of cases and no effective treatment or cure.

One of the major pathological features of ALS is the accumulation of large protein aggregates inside degenerating neurons. Surprisingly, very few studies have examined the effects of aggregation in ALS. This is likely because the role of aggregation remains controversial, with researchers implicating them either as neurotoxic, with harmful effects on normal cellular function, or as neuroprotective, presumably by acting to sequester harmful proteins. We believe that by studying the role of aggregates during stress and/or disease, we may gain valuable insight into the cause and propagation of ALS, with significant impact for the development of new therapies. The research that we propose, here, is based on our own recent data and from a growing pool of research indicating that large aggregations form as a natural protective mechanism against disease. We believe that this protective response comes too late in disease to have any significant impact on motor neuron survival and we therefore propose to provide these aggregates as early as possible to treat the disease.

From our previous work, we have shown that the formation of aggregates can be related to changes in a process known as alternative splicing, whereby a single gene is capable of producing a number of diverse proteins called isoforms. We have found that certain genes undergo splicing to create isoforms capable of self-aggregation. Interestingly, some of these isoforms are found associated with large aggregates in ALS. The protein peripherin is part of a large family of structural support genes known as intermediate filaments and is considered important in neuroregeneration. Peripherin's exact role is unknown, however, it may play a key role in protecting motor neurons because mutations or errors in its expression can be associated with the development of motor neuron disease. Interestingly, an aggregating peripherin isoform, known as Per-28, is specifically increased in ALS patients. Because cells normally dispose of disease-causing proteins and other harmful byproducts by isolating and degrading them, producing isoforms that aggregate and sequester toxic proteins may represent an attempt by the cell to save itself when overwhelmed by disease; we believe that increased Per-28 expression represents such a mechanism for motor neurons in ALS.

We have identified a unique opportunity to generate and deliver large synthetic aggregates to degenerating motor neuron populations of the spinal cord in commonly used animal models of ALS. Using safe viral vectors to deliver Per-28 before or after the first clinical signs of motor neuron disease, we hope to significantly slow disease progression. Because detection of ALS prior to symptom onset is not possible given the current lack of reliable biomarkers, we are particularly interested in whether this treatment will work once symptoms have appeared, which is more realistic in terms of treating ALS patients. Our ultimate goal is to be able to provide a minimally invasive and effective treatment for all ALS patients based on the enhancement of an already natural protective response. It is important to note, however, that while the majority of research indicates that these intracellular aggregates are protective, there is the possibility that delivery of synthetic aggregates may worsen the disease in mice. Regardless of this outcome, however, we have designed an unprecedented experiment that will allow us to gain significant knowledge about which disease mechanisms require targeting. As such, our work will either provide a new treatment for ALS or generate new ideas about the underlying disease pathology and help accelerate drug discovery.