Progress Report: Blazeman Foundation – April 1, 2014

Project Title: Administration of Hsp70 maintains muscle innervation in the SOD1 mouse- a new therapeutic approach?

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Project Description and Summary of Progress:

While MN degeneration is a late stage event in ALS, muscle denervation occurs significantly earlier in the disease and is presumably the cause of muscle weakness, a prominent clinical symptom. Strategies to prevent denervation may improve quality of life by maintaining muscle control and slowing disease progression. We reported that administration of recombinant human Heat Shock Protein 70 (rhHSP70) delayed symptom onset and increased lifespan in SOD1G93A mice. rhHsp70 was localized to the muscle and not CNS suggesting it modulates peripheral pathophysiology. In a second study rhHSP70 may be a therapeutic strategy for ALS. rhHsp70 has be granted orphan drug status by the FDA. However, current commercially available recombinant protein is prohibitively expensive and of variable stability and function. Further investigation of rhHSP70 therapeutic potential is not possible until we can efficiently produce a pure and active protein. The goal of this proposal is to develop the protocols for protein production and develop GMP large-scale production strategies that will facilitate IND application and clinical trials.

We are continuing to make progress and remain on schedule as originally predicted. During the first six months of the project we generated several clones of the full-length protein and the substrate binding domain derivative. Initial small-batch purification has begun and as shown below the preliminary purification process has produced good yields of the full-length protein and its derivative. Since the submission of the last progress report (October 2013) we have made great strides in the production protocol.

In the next six months we will finalize our standard operating procedure for the full-length Hsp70 protein production. This will include quality control procedures to increase purity, assure function of the full-length protein and produce additional derivatives. We should have sufficient protein to begin initial test for effectiveness to prevent or delay initial muscle denervation in the SOD1 mice. We also continue to work on the Hsp70 derivatives. Importantly, we will be having discussions with the Innovations group at Wake Forest for advice on moving to GMP production and FDA approval. We will also be discussing with different GMP facilities, how our protocols best fit with GMP production.