REDUCE INFLAMMATION

Project ALS Commitment: $2.2M

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Background: For many years, researchers have noted that neuro-inflammation is a hallmark of neurodegenerative diseases including ALS, Alzheimer's, and Parkinson's. However, the many complicated pathways that feed inflammation have not been sufficiently characterized in these diseases to point to clear therapeutic targets that will effectively halt the negative effects of neuro-inflammation. In the past three years, Project ALS has undertaken an aggressive effort to elucidate the causes and mechanisms of neuro-inflammation in ALS.

Summary of Progress: Project ALS is currently supporting studies that deal with distinct pathways of neuro-inflammation, each with a unique therapeutic target:

-DP1: Using the *ALS in a Dish* stem cell model pioneered in partnership with Project ALS, the laboratory of Kevin Eggan noticed that brain cells called *glia*, which normally help neurons function, become toxic to motor neurons in ALS. By blocking a specific mechanism of neuro-inflammation called the DP1 pathway, they successfully rescued ALS motor neurons and extended their life significantly. Now, Project ALS and Eggan are partnering with an industry partner with drugs to block DP1 in humans for pre-clinical trials.

-PDE4: A hallmark of neurodegenerative disease is the accumulation of misfolded proteins, which form plaques or tangles in affected brain cells and prevent them from functioning properly. Normally, a cell structure called the *proteasome* is responsible for preventing the accumulation of these misfolded proteins—but in ALS, the proteasome is impaired. In early stages of this project, Fred Goldberg, a foremost expert on proteasome function, has shown in initial studies that Rolipram, a first-generation antidepressant, shows efficacy in boosting proteasome function—and blocking protein tangles—in ALS. Now, with collaborators at Columbia University and University of Massachusetts, Goldberg's team is exploring Rolipram and related PDE4 inhibitors in pre-clinical models of ALS.

-TBK1

-p62/Optineurin

Relevant Publications:

DP1 Receptor Mediates Glial Toxicity
Goldberg Defines the Proteasome
Rolipram Improves Proteasome Function in AD

Contact us for additional relevant publications or research updates.