STUDY THE WHOLE BRAIN

Project ALS Commitment: $1.7M

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Background: For many years, researchers believed that in ALS, motor neurons die through *apoptosis*—programmed cell death—meaning that no other cell types are affected in the disease. However, a 2008 study led by Project ALS researchers Tom Jessell, Hynek Wichterle, and Serge Przedborski showed that brain cells called astrocytes that typically support neuronal function go rogue in ALS, becoming toxic to motor neurons. Since this discovery, scientists have shown that many other brain cell types—including microglia, oligodendrocytes, and interneurons—also experience significant dysfunction in the disease.

Project ALS has assembled a team to understand how cells surrounding motor neurons change in ALS, with an eye toward correcting this dysfunction. One major research focus is on non-neuronal brain cells—including astrocytes, microglia, and oligodendrocytes—that typically support motor neuron function, but become toxic in ALS. Project ALS researchers are using improved stem cell models to observe how these cells, collectively called glia, damage motor neurons in ALS—and to test drugs that might correct their function.

Another Project ALS priority is to map spinal inhibitory interneurons, a cell type that bridges the gap between the brain signaling a movement and a motor neuron enacting it. These crucial brain cells display hallmarks of dying cells relatively early in the ALS disease process, suggesting that their degeneration might contribute to motor neuron death in ALS. As we understand how interneurons and other brain cells affect motor neurons in both healthy and diseased states, we will be able to intervene more effectively to restore normal function in ALS.

Project ALS believes that in order to understand ALS, we must have a better understanding of the healthy brain first. By probing how the brain develops, forms complicated neural circuits, conveys signals, and supports healthy motor neurons, we can more accurately diagnose--and prevent--what goes wrong in ALS.

Summary of Progress: Project ALS studies toward understanding glia in ALS have identified several key pathways of toxicity in ALS—many of which overlap with known changes in the disease, like neuro-inflammation and protein aggregation. Concurrently, researchers in the Jessell laboratory have, for the first time, characterized 57 distinct subtypes of spinal inhibitory interneurons and observed their behavior in healthy stem

cell and animal models. Now, they are conducting the same studies in ALS models to observe differences in how each subtype behaves during the ALS disease progression.

Project ALS has also recruited experts to help us understand how other factors that have been linked to ALS—like innate immunity and the endogenous retrovirus HERV-K—may cause changes in the brain that could trigger the ALS disease process.

Relevant publications:
Astrocytes cause motor neuron toxicity in ALS.
A distinct interneuron subtype modulates locomotor behavior.
Use of stem cell based assays to understand glia in ALS Improved rabies tracer maps neuronal circuits without causing cell death.

Contact us for additional relevant publications or research updates.