The ALS Center for Cell Therapy and Regeneration Research at Johns Hopkins

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Prospects in ALS Therapy for 2018

A Gene Therapy Strategy to Deliver Nerve Growth Factors to ALS Patients

The last year in the ALS Center for Cell Therapy and Regeneration Research at Johns Hopkins has been marked by several translationally relevant milestones for the ALS Center for Cell Therapy and Regeneration Research. Our work with a gene therapy designed to deliver a nerve growth factor, recently underwent Pre-IND review at the FDA with excellent feedback and a clear path towards our planned IND filing in the first quarter of 2019 after our preclinical work is complete. This means that this gene therapy could potentially be used in an early phase ALS clinical trial in 2019.

Modulating Neuroinflammatory Cascades to Prevent Motor Neuron Dysfunction

The ALS Center for Cell Therapy and Regeneration Research also has a new collaborative project working with a compound, NLY-01, that has already undergone Pre-IND evaluation with the FDA for another neurological disease. In the upcoming year, we will examine whether this novel compound is effective in our ALS animal models and ALS stem cell models. Because this compound has an extensively studied pharmacokinetic and pharmacodynamic profile and has already undergone an initial review by the FDA, we anticipate that if we can establish efficacy in ALS, this drug compound also could be transitioned to the clinic quickly.

Using Human Induced Pluripotent Stem Cells (iPSC) to Model ALS in a Dish

We continue to invest heavily in induced pluripotent stem cell (iPSC) technologies in an effort to reflect the heterogeneous presentation of ALS, understand disease mechanisms, and screen for targeted ALS therapeutics. These precision medicine strategies have seen great success in other diseases and we believe the same for ALS. These precision medicine strategies are being utilized across all of our projects.

Johns Hopkins Medicine is on the forefront of precision medicine in ALS…

Johns Hopkins has been a leading center for patients with neuromuscular disease for over four decades. The Johns Hopkins Multidisciplinary Amyotrophic Lateral Sclerosis (ALS) Clinic, one of the busiest in the country, recorded 364 new patient and >600 follow-up patient visits per year. In addition to providing state-of-the-art care, the center has a comprehensive bench to bedside mission, having carried out over 25 clinical trials, and is closely linked with the Packard Center for ALS Research and the ALS Center for Cell Therapy and Regeneration Research at Johns Hopkins.

We are now combining our understanding of ALS in our patients with a large library of induced pluripotent stem cells (iPSC) from these individuals. We can make these iPSC from patients with familial ALS (FALS), normal people (Control),

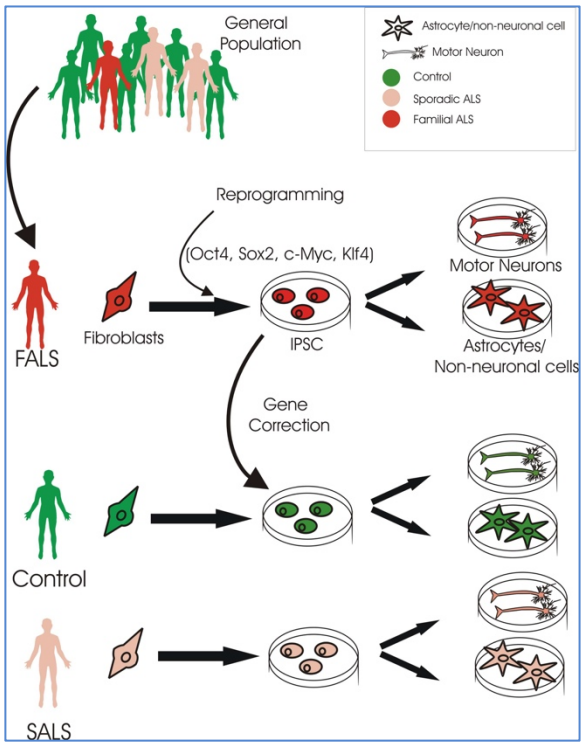

Figure 1. Precision Medicine in ALS using human induced pluripotent stem cells.

and patients with sporadic ALS (SALS). Once we make these cells, we can keep them forever and make them into motor neurons, astrocytes, or other cells relevant to ALS (**Figure 1**).

As **Figure 2** illustrates, we are now able to use these cells to **A.** Understand more about ALS-specific pathology by growing motor neurons from these patients in a dish. **B.** Record from individual ALS motor neurons from patients to see if they are hyperexcitable. **C**. See if motor neurons from certain ALS patients are particularly susceptible to cell stress. **D.** Understand how ALS cells interact with normal cells in the brain. **E**. Use large numbers of iPSC from many ALS patients to begin screening drugs that will be beneficial to our patients.

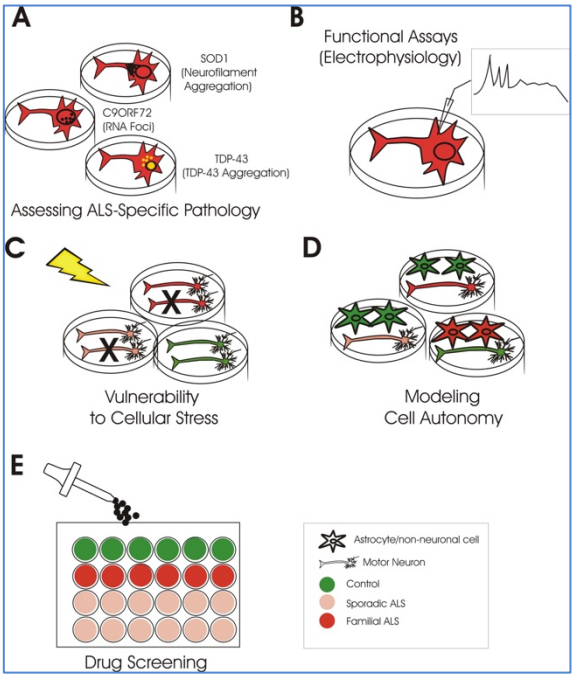

Figure 2: Human iPSC-derived motor neurons and astrocytes can help us model ALS in a dish and screen drugs that may be tailored to individual forms of ALS

Our Progress…

We are using our expertise in the differentiation of iPSC from ALS patients to create a platform that will allow us to study how ALS iPSC-astrocytes influence the electrical activity of iPSC-neurons. As seen below, we now have the capability to perform electrophysiological recordings, in real time, from large numbers of cells in a dish (microelectrode array). We believe this platform will allow us to screen drugs that can modulate the influences of iPSC-astrocytes on neurons. We have already begun to study a drug, tonabersat, that can influence astrocyte-mediated activity on neurons.

Halting the Spread of ALS in the Body by Modulating Cell-Cell Communication

Our effort to understand how ALS spreads from one region of the body to another has found footing in our identification of the astrocyte connexin protein (connexin 43). We believe that this protein may mediate how ALS astrocytes induce motor neuron death and also lead to disease spread. Excitingly, this last year we have identified a compound which may block this effect. We are particularly enthusiastic because this drug has already been used in patients and has an excellent safety profile. Therefore, it could be quickly transitioned to early phase ALS clinical trials if we find it is effective in our ALS models.