Development of Imaging Biomarkers for Stem Cell Transplantation in Amyotrophic Lateral Sclerosis

One of the fundamental limitations in assessing potential efficacy in transplantation of stem cells into the spinal cord or brain is the capacity for monitoring cell survival and migration non-invasively. The brain and spinal cord are particularly challenging, as they are not accessible to biopsy for analyzing cell survival. Another significant challenge to stem cell therapeutics in neurological disease is the availability of a biomarker that can indicate cell-specific effects on the target. We are currently in the process of planning a study of the transplantation of human Glial Restricted Progenitor (GRP) cells into the spinal cords of patients with ALS. Further development of the use of these cells for therapeutic use will rely on the ability to track the cells using imaging methodologies like MRI as well as verification that the transplanted GRPs have disease-relevant activity. We are developing a cell-labeling strategy that would allow for tracking cell survival and migration in ALS patients as well as investigate GRP-specific function relevant to ALS pathology.

Delivering the Growth Factor Neurturin to ALS Patients Using Gene Therapy

Neurturin (NRTN) is a naturally occurring growth factor. Growth factors appear to provide functional and structural benefit to their responsive nerve cells (neurons), no matter how the nerve cells are damaged or impaired.

AAV2-NRTN is an AAV2 viral vector-based gene transfer designed to deliver a modified form of human NRTN to nerve cells.

Because Neurturin is a growth factor, it is believed that its expression in the spinal cord may help to keep motor neurons, and their connections to muscle, alive. It may be used for all types of ALS where motor neurons of the brain and spinal cord are at risk.

This proposal seeks to target the at-risk motor neurons of the cervical spinal cord—a region of the spinal cord that is associated with breathing function as well as arm movement. Motor neurons in this area slowly degenerate, lose their connections to muscles of the arms as well as muscles of breathing (the diaphragm) which results in weakness and breathing difficulties. Because ALS patients ultimately have breathing difficulties, this therapy is specifically designed to target the neurons that control breathing. We believe therefore, that this is a particularly important function to target. We propose that the injection of the compound Neurturin by packaging it with Adeno-associated Virus type 2 (AAV2) will help to deliver NRTN to these at-risk motor neurons and prevent or slow their death.

The Role of Astrocyte Gap Junction Function in ALS Disease Progression

Understanding why disease spread in the majority of ALS patients occurs in adjacent body regions over time is one of the fundamental limitations to designing disease modifying therapies that can be utilized after a diagnosis. Astrocytes have been shown to play a role in disease **propagation** after onset in animal models of ALS. This contiguous anatomic spread has been demonstrated in longitudinal studies of ALS patients as well as cross sectional analyses. There are several theories about how this contiguous spread may take place including transneuronal signaling. However, in other disorders, including epilepsy and stroke, astrocyte communication via gap junctions is also a recognized mode that elicits spread of seizure activity and can promote neuronal loss. The major astrocytic gap junction protein, Cx43, has been shown to be upregulated in some neurodegenerative disorders and, as our preliminary data and another recent publication has shown, upregulated in ALS models. Yet the functional significance of this Cx43 upregulation has not been studied in ALS. We hypothesize that astrocyte Cx43 upregulation in ALS may contribute to nerve cell loss as well as disease spread in ALS.

We have now set our sights on using human induced pluripotent stem cells (iPSC) from ALS patients to understand more about these Cx43 gap junction and hemichannel proteins. We believe that these human iPSC from patients with various forms of ALS (fast progressing, slow progressing, bulbar onset, spinal onset, sporadic ALS, familial ALS) can help us understand how the Cx43 protein may regulate disease progression both anatomically and over time.

NLY01: A GLP-1 Analog for Reducing Neuroinflammation in the Treatment of ALS

Neuroinflammation is a response to nerve cell injury. This results in the release of additional factors in the brain and spinal cord which can cause further nerve cell damage. There is a wealth of evidence in patients as well as animal models of ALS to suggest that neuroinflammation may play a role in the disease by activating cells called microglia and astrocytes. ALS is not the only disease where this occurs. Other neurodegenerative diseases like Parkinson's disease (PD) and Alzheimer's disease (AD) also show this pattern. Therefore, the development of agents, like NLY01, that could selectively reduce microglia and astrocyte overactivation, could have a profound therapeutic potential.

One particular advantage of NLY01 is that because of its long half-life, patients may only need to inject this compound once weekly. This would offer a significant advantage over the currently approved ALS drugs riluzole (taken twice daily and with only a marginal effect) and the more intensive daily intravenous dosing (through a vein in the arm) of the newly approved compound edaravone. We anticipate that because NLY01 is easier to administer, this might improve compliance for patients.

NLY01 activates a receptor on microglial cells thus reducing microglial and astrocyte overactivation. Because NLY01 targets a neuroinflammatory pathways thought to be relevant to ALS as well as other neurodegenerative diseases, it is likely that NLY01 may help to slow disease progression after it begins. It may be used for all types of ALS where neuroinflammation puts motor neurons of the brain and spinal cord at risk.