## GENERAL AUDIENCE SUMMARY

| APPLICANT NAME | DATE SUBMITTED |
|---|---|
| Kolarcik, Christi L | 2/1/2016 2:02:38 PM |

TITLE OF PROJECT *(Titles exceeding 81 characters, including spaces and punctuation, will be truncated.)*

Motor system connectivity influences in amyotrophic lateral sclerosis

This General Audience Summary will become public information; therefore, do not include proprietary/confidential information.

Communication between neurons and muscles occurs at synaptic connections which are often compromised in neuromuscular disease. Multiple hypotheses on where connections breakdown exist for amyotrophic lateral sclerosis (ALS). Do the earliest changes occur at the spinal motor neuron or the cortical level? How do disruptions in axonal transport contribute? Underlying these potential mechanisms is the neural circuitry which ultimately mediates the pathological process. This proposal will unravel the synaptic connections to motor neurons innervating affected muscles and determine how these change in ALS. Our hypothesis is that synaptic inputs to muscles affected in ALS will change with disease progression; these inputs will enable us to predict disease spread through the motor system. First, we will map the neural circuitry that controls the motor neurons innervating two hindlimb muscles in the mouse using transneuronal viral tracers. Both fast- and slow-twitch muscles will be included to identify muscle fiber/motor neuron-type specific changes. By defining the direct and more elaborate multi-synaptic pathways, we can determine how and when synaptic connections are affected as ALS progresses. We will investigate pre-symptomatic, denervation, symptom onset and end-stage disease phases. The time course of synaptic connectivity changes and transport deficits will be elucidated, providing insights into mechanisms underlying degeneration and leading to targeted therapeutic options.

## SCIENTIFIC ABSTRACT

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Motor system connectivity influences in amyotrophic lateral sclerosis

This Scientific Abstract will become public information; therefore, do not include proprietary/confidential information.

Amyotrophic lateral sclerosis (ALS) is a progressive, fatal motor neuron disease involving both corticospinal/corticobulbar and spinal/bulbar motor neurons. Although it is regarded as a “system degeneration disorder”, an understanding of how the neural circuitry to affected muscles is affected in the disease has not been thoroughly investigated. Our objective is to define the neural connections to particular muscles and to provide a description of how and when these connections change over the course of ALS. We hypothesize that synaptic inputs to muscles affected in ALS will change with disease progression and that these inputs will enable us to predict the spread of the disease throughout the motor system. To address this hypothesis, we propose two specific aims. First, we will utilize transneuronal viral tracers to develop an atlas of neuronal connections to both slow- and fast-twitch muscles in control mice. Once this comprehensive analysis is completed, we will evaluate alterations in both connectivity and transneuronal transport in the G93A SOD1 mouse model of ALS at pre-symptomatic, denervation, symptom onset and end-stage disease phases. This will allow us to delineate the time course of transport deficits implicated in ALS disease pathogenesis and provide unique insights into the mechanisms that underlie motor neuron degeneration. Although the proposed studies will be performed in a model of ALS, we expect our findings will extend to other neuromuscular diseases. More specifically, communication between neurons and muscles requires a synaptic connection, and these connections are often compromised in neuromuscular disease. Changes at the neuromuscular junction directly impact both the neural circuitry and cellular transport which underlie the degenerative process. Similarly, the work proposed will compare different muscle types (i.e., fast-twitch versus slow-twitch) enabling conclusions about motor neuron dysfunction to be both muscle fiber and motor neuron-type specific. In addition, our studies represent a unique approach for studying the contribution of disruptions in axonal transport. These changes could alter transneuronal transport (i.e., the exchange of material between neurons) OR provide an avenue for the transfer of a prion-like material that promotes degeneration. Finally, while the mouse does not fully recapitulate the human motor system and therefore human neuromuscular diseases, lessons regarding the impact of the underlying neural circuitry in mice will lay the groundwork for investigations in humans and mouse models of numerous other neuromuscular diseases. We anticipate that our multi-level, multi-disciplinary perspective will yield insights into these conditions and positively impact patients via the identification of targeted therapies.