Current TSU Projects

One of our current projects is examining the very early events in ALS disease process, specifically those associated with muscle weakness. Muscle weakness occurs because the motor neurons, the cells that no longer function and die in ALS, lose contact with their target muscle. Motor neurons are complicated cells because their cell bodies are in the spinal cord, and they extend processes through the nerves to contact target muscles.

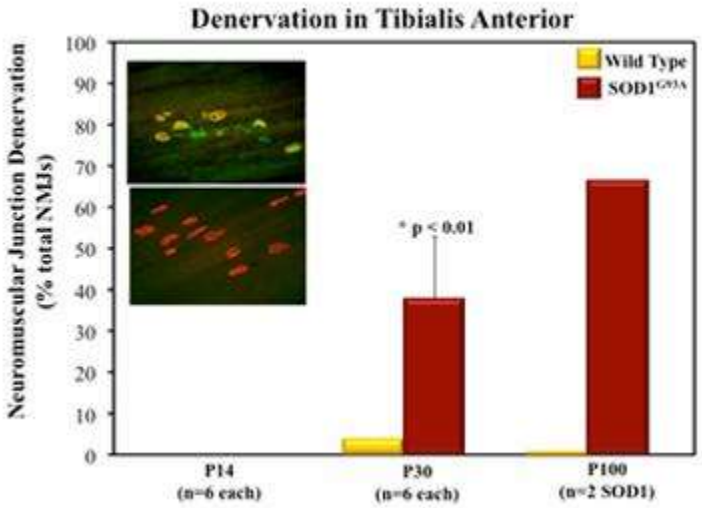
In ALS it is not known if the disease starts in the central nervous system (spinal cord and brain) or in the peripheral nervous system (motor neuron axon and nerve terminal that contacts muscle). Numerous ALS clinical trials have been unsuccessful, perhaps because the treatments are initiated too late in the course of the disease or because the targeted mechanism are too far down the cascade of events that leads to motor neuron death.

Understanding early events may provide new insight into motor neuron biology that may translate to human disease pathogenesis. After identifying the location of early nervous system changes in ALS, we will use this information to propel further studies into disease biomarkers and the development of therapeutic interventions.

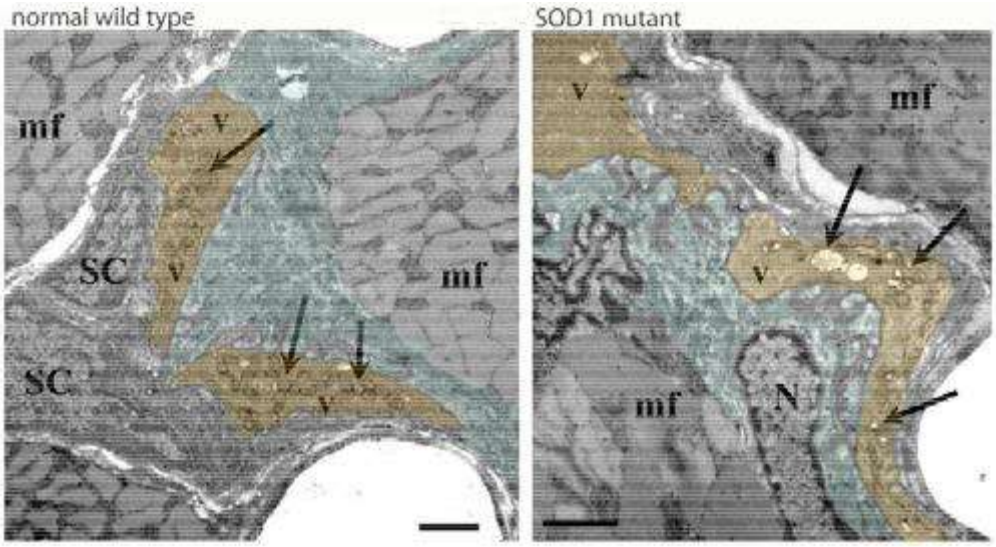
We are using the mutant SOD1G93A mouse model of ALS for this study. This mouse develops muscle weakness, a symptom of ALS, at approximately 90 days of age. We have found that motor neurons lose contact with their target muscles as early as day 25-30 of age, long before overt symptoms are noticed.

This tells us that the disease process begins before clinical signs are noticeable. Furthermore, we now know that the motor neuron appears to be sick before it loses contact with its muscle. We hope that by understanding why the cells are sick, and what can be done to help them, we can prolong the time that the motor neuron maintains contact with muscle and therefore slow, and possibly halt disease progression.

We have started to study the tibialis anterior (TA) muscle in the ALS mouse. This muscle in both human and mouse is responsible for raising the foot. In the mouse we find that the motor neurons lose contact with the muscle between day 14 and 30 of age, as shown in the graph below.



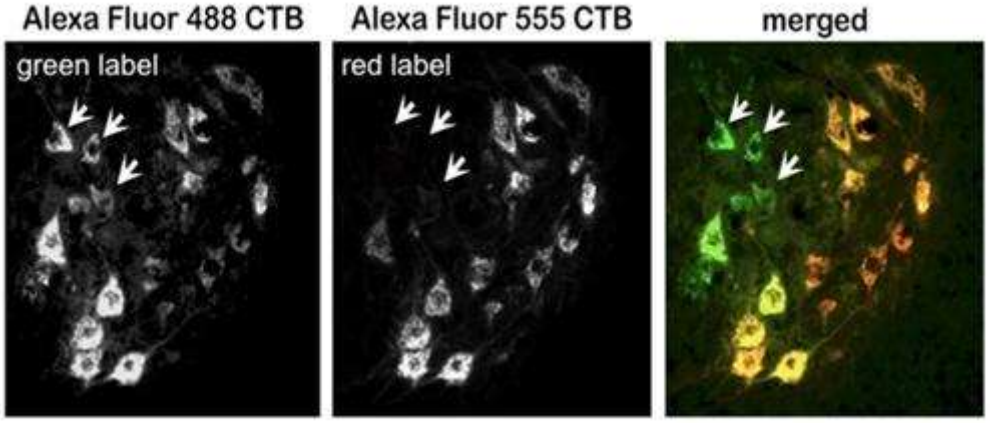
When we examine the area where the nerve comes in contact with the muscle (the neuromuscular junction) at day 14, we can see that even before the denervation occurs, there are abnormalities in the nerve. Below is a picture from the electron microscope. We can see the neuromuscular junction at 10,000 times magnification. The nerve terminal is shaded gold, and the muscle region is green.



The mitochondria in the mutant motor neuron are abnormal and appear to be swollen (arrows). Mitochondria are essential for the cell to have sufficient energy levels.

We are also trying to determine what the motor neurons look like in the spinal cord when they lose contact with the muscle. We have developed a technique that allows us to distinguish which motor neurons have lost contact with the muscle and those that remain in contact. To do this, we make two injections into the TA muscle with a tracer that is taken up by the nerve terminal and transported back to the cell body in the spinal cord.

The first injection is at day 14, when all the motor neurons are in contact with the muscle. These cells appear green in the photo below. The second injection is at day 28, where 40% of the motor neurons have lost contact with the muscle. Only those cells in contact will take up the tracer and will appear red. Cells that contain both green and red are in contact with the muscle, while those that are only green have lost contact (white arrows).



With this type of approach, we can begin to determine specific differences between the motor neurons, helping us to understand why they lose contact with the muscle.