A motor neuron connects to a muscle, and the loss of that connection is an early and fateful step in the ALS disease process. New research has shown that maintaining that connection has the potential to improve muscle function in ALS mice, suggesting it may be able to do so in people with ALS as well. That research was the focus of a webinar sponsored by The ALS Association and featuring Stephen Burden, Ph.D., of the New York University Langone Medical Center.

“This research is very exciting,” said Lucie Bruijn, Ph.D., Chief Scientist for The Association. “It brings into focus a part of the disease process we don’t know enough about, and suggests ways to address it therapeutically.”

Dr. Burden explained that a motor neuron stimulates a muscle only at very specific spots, called neuromuscular synapses, or neuromuscular junctions. Here, the tip of the neuron, called an axon, releases a chemical called acetylcholine (uh-SEE-tul-KO-leen), which crosses a tiny gap to the muscle surface, where it interacts with an acetylcholine receptor. When that receptor is stimulated by acetylcholine, it causes the muscle to contract. As a motor neuron begins to undergo the ALS disease process, but still well before it dies, it withdraws its axons, leaving the muscle without stimulation. That causes weakness and ultimately paralysis.

Dr. Burden and others have studied the signals that pass between axon and muscle that control how the synapse forms, and what keeps it intact. That research has shown that the axon sends signals to the muscle to stimulate the formation of the synapse, and the muscle signals back to the axon to keep the axon attached to the muscle. That signaling goes awry in ALS, he said.

The details of the signaling involve a small handful of critical molecules. The axon releases one called agrin. This binds to a muscle molecule called Lrp4. That causes Lrp4 to bind to another muscle molecule called MuSK. When that happens, MuSK causes acetylcholine receptors to cluster together, forming a healthy synapse.

At the same time, the muscle signals back to the axon. MuSK and Lrp4 are both involved on the muscle side, but the receptor on the axon side is still unknown. Dr. Burden has studied this pathway in detail, asking whether he can stabilize the synapse and keep the axon from withdrawing by increasing MuSK/Lrp4 signaling. He has found a “genetic trick” to do so in an ALS mouse model. Using that trick, he has shown that increasing MuSK activity in the SOD1 mouse maintains normal synapses during the early stages of the disease. Not only do they look normal under the microscope, but they work—the mice maintain their strength for longer than mice without the corrective gene treatment.
However, he noted, the treatment doesn’t extend survival significantly—it helps in the early stages of the disease, but doesn’t prevent the final loss of muscle function. He suspects that is because the unknown receptor on the axon is lost as well. If that receptor is lost, no amount of MuSK signaling can keep the axon attached to the muscle. Dr. Burden thinks the problem may stem from inability to get new receptor to the axon. It is made far away in the cell body and must be transported down the length of the axon to reach the synapse. Other researchers have shown that one characteristic of ALS is a defect in axonal transport. Thus, without new receptors coming in, the synapse eventually loses the ability to maintain its receptors.

That problem remains to be solved, but in the meantime, Dr. Burden is working with Genentech, a large biotechnology company, to develop ways to increase MuSK signaling as a therapeutic option in ALS. The strategy they are taking involves antibodies that bind to MuSK, just like Lrp4 does, to stimulate its function. He is engaged in work to characterize these antibodies and to work out details of dosing and timing. “I am very hopeful that this strategy will translate to a human treatment,” he said. The high degree of similarity between mouse and human forms of Lrp4 and other molecules increases that confidence, he said, since it likely means that any result from the mouse will be that much more likely to predict the result in people.

“This type of therapy may lend itself very well to a combination approach to helping the motor neuron survive,” Dr. Bruijn said, with multiple treatment strategies working on multiple different disease mechanisms. “I am also encouraged by the partnership with Genentech, a company that has been very successful in moving their experimental strategies to the clinic.”