PROJECT SUMMARY (See instructions):

Skeletal muscle atrophy may result from motor neuron diseases (MNDs), and significantly decreases quality of life or even causes death by disrupting voluntary muscle activities that control essential functions such as speaking, walking, breathing and swallowing. Several MNDs affect only motor neurons, while progressive muscular atrophy indicates that abnormal factors or signals may have been transferred directly from motor neurons into muscles. The underlying mechanisms remain largely unknown, but likely involve the neuromuscular junctions (NMJs). Therefore, discovering the signals released from damaged neurons, and understanding the role of NMJ in transmitting signals from neurons to muscles are essentially important for potential development of novel clinical intervention to prevent or recover from muscular atrophy.

The current proposal is truly interdisciplinary and built on our strong preliminary studies in muscles (Li, UT Health) and motor neurons (Wu, UTMB), which will bridge our expertise perfectly to target the cross-field collaboration in neuron-muscle diseases. We will apply the advanced molecular, cellular and imaging techniques to determine whether muscle atrophy induced by the damaged/degenerated motor neurons requires NMJs to transfer abnormal signals from motor neurons to muscle cells. This is an untested idea (hypothesis), and has a high impact because it revolutionizes the current paradigm of muscle dysfunction or atrophy.

Toward this goal, we will use our established technologies to build a new human cell-based NMJ model, and use it to discover the potential abnormal signals in the damaged or degenerated motor neurons by using genomic screening followed subsequently by qPRC and protein analyses. Several candidates have been investigated in our laboratories that can induce muscle atrophy; we will confirm whether they are released from the damaged motor neurons or through NMJs. We expect that this pilot study will not only invent a novel NMJ-model *in vitro*, but also discover the missed or mismatched signals from the damaged/degenerated neuron to muscles during MND progression. The novel paradigm will be that those discovered candidate genes or trophic factors released from damaged-neuron may serve not only as the biomarkers but also as primary inducers of muscle atrophy. The outcomes should shed light on the future mechanistic studies of MNDs and therapeutic developments.

RELEVANCE (See instructions):

Motor neuron diseases and progressive muscular atrophy are significant health problems that are lack of efficient clinical interventions. Understanding the role of neuromuscular junction in relaying abnormal signals from the damaged motor neurons to muscle cells will advance our knowledge on MND-resulted muscular atrophy and promote the development of novel therapy. This application completely meets the missions of the UT BRAIN Project to promote "new technologies and novel approaches, techniques, and concepts in the earliest stages of development that have the potential for significant impact on neuroscience". Toward this goal, we have built a strong inter-institutional collaborative team that cross boundaries, and contain two PIs with diverse but complementary research strengths and expertise in muscle (Li, UT Health Houston), motor neuron (Wu, UTMB), and stem cells (Li and Wu).