TITLE: Mechanisms and therapy for improving neuromuscular signaling in cancer-cachexia

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RESEARCH PROJECT DESCRIPTION

Up to 80% of cancer patients will develop cachexia, which is a critical factor in the progression of the disease and prognosis of the patient. Cancer cachexia is a destructive, multifactorial syndrome where significant weight loss is observed through progressive atrophy of skeletal muscle and adipose tissue. In affected patients, the development of asthenia reduces physical activity and the ability to breathe and clear airways effectively. Through culmination of these symptoms, cachexia is indirectly responsible for up to 20% of all cancer deaths. To make a significant shift in the management of care for patients with cancer cachexia, we have developed a systematic approach to identify key mechanisms that result in loss of skeletal muscle, respiratory function and physical activity; all contributing to early mortality.

The neuromuscular junction (NMJ) is a critical interface that regulates neurotransmitter signaling, skeletal muscle contractile function and muscle mass. Our preliminary data show significant pathology at the NMJ and within the peripheral nerve. Determining innovative ways to preserve the integrity of the NMJ will improve muscle function in cachectic patients and improve survival outcomes.

Using plasmid DNA or AAV vectors, potential projects include transfection/infection of neuronal and skeletal muscle cultures to characterize and rescue the disease phenotype. This may be complemented by parallel in vivo experiments designed to optimize gene delivery and determine efficacy in models of neuromuscular disease or cancer cachexia.

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