Title: Molecular Mechanisms of Neuronal Dependent Muscle Plasticity

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Summary:
Two current challenges in the repair of skeletal muscle injury or failure due to degenerative disease, genetic conditions, aging, or trauma are: 1) advancing our understanding of how the mature muscle cell phenotype is maintained, and 2) identification and modification of nerve-dependent processes that are coupled to changes in muscle properties. Meeting these challenges has critical implications for development of therapies directed toward patients with impaired muscle function. The electric fish *Sternopygus macrurus* is a powerful vertebrate model system that can help elucidate cellular and molecular mechanisms that affect different features of the muscle program. In *S. macrurus*, some skeletal muscle fibers fully differentiate only to undergo fusion and subsequent extreme modifications in their morphological and biochemical properties to convert into non-contractile electrogenic cells called electrocytes. Mature electrocytes retain a partial muscle phenotype by continuing to express some, but not all muscle-specific proteins. The suppression of select muscle gene expression in electrocytes is dependent on a continuous, high frequency electrical activation pattern. Further, this deficient muscle phenotype in electrocytes is reversible upon changes in nerve activity patterns. Preliminary data intensified our goal to identify the molecular processes involved in mediating the activity-dependent remodeling of the skeletal muscle program. Specifically, this research tests the hypothesis that the transcriptional mechanisms that mediate neural activity-dependent regulation of muscle genes in skeletal muscle differ in electrocytes of *S. macrurus*.

The specific aims of this research are:

1. determine the transcript profiles in skeletal muscle and electrocytes
2. characterize the role of the calcineurin/NFAT signaling pathway in mediating the neural-dependent regulation of the muscle program in electrocytes
3. identify the genes regulated by myogenic transcription factors in muscle cells versus electrocytes.

To ensure the successful completion of the studies, researchers established the amenability of *S. macrurus* to *in vivo* experimentation using a collection of molecular and cellular tools, and assembled a research team with strong mentorship support and complementary skills and knowledge in neuromuscular biology. This research is expected to enhance understanding of the processes by which neural input controls myogenic gene expression and maintenance of the muscle phenotype – an understanding of muscle function with critical implications to therapeutic approaches for human muscle diseases.