Summary

This proposal will address the **PRD RISK** of impaired performance due to reduced muscle mass, strength and endurance. Our proposed computational model ("MASS") will help to fill the following **IRP Gaps**: M24 (Characterize the time course of changes in muscle protein turnover, muscle mass and function during long duration space flight), M2 (Characterize in-flight and post-flight muscle performance), and M7 (Develop the most efficient exercise program for the maintenance of muscle fitness).

Prolonged space flight profoundly affects the structure and function of both slow and fast fibers in human skeletal muscle. In a recent study by Fitts et al. (*J Physiol*, 588: 3567-92, 2010), muscle biopsies obtained from nine ISS crewmembers about 45 days pre- and on landing day post-flight showed that prolonged exposure to microgravity induces significant fiber atrophy (~20% in the soleus type I fibers). Moreover, these effects appear to depend on muscle and muscle fiber type (e.g. soleus type I >> gastrocnemius type II). Importantly, the percent decreases in fiber diameter correlated directly with the initial pre-flight fiber size and inversely with the amount of treadmill running, demonstrating that the initial state of the muscle and the extent of exercise both impacted the extent of muscle atrophy. Similar effects were seen at the macro-scale: muscles that had larger overall muscle volume initially showed a higher degree of atrophy as compared to muscles with lower overall muscle volume. This and many other similar studies underscore the importance of being able to predict how exercise regimens will affect individual muscle groups in microgravity and to use these predictions to design data-driven exercise programs that effectively preserve fiber cross-sectional area and muscle force during long-duration flights.

The goal of this proposal is to develop a Muscle Adaptation in Space-flight Simulator ("MASS") that is capable of predicting long-term muscle adaptation in space flight, given a predetermined amount of time in space and a prescribed exercise regimen. This framework will provide researchers, trainers, and astronauts with a novel, useful, and predictive tool to guide the design of exercise regimens that effectively mitigate muscle loss during long-duration LDEMs. Once the combined simulation framework has been validated by comparison with existing bed-rest and space-flight data, we will use the model to make predictions of changes in muscle protein turnover, mass, strength, and function during long-term space flight to Mars, which will enable several key to be addressed:

1. *What is the time course of lower limb muscle loss during space flight?*
2. *How does exercise influence the time course of lower limb muscle loss?*
3. *What exercise intervention will mitigate the lower limb muscle loss over a long-term space flight such that astronauts are functional prior to landing on Mars?*
4. *How do factors in addition to unloading influence muscle atrophy during space flight and how can those be mitigated during long-term space flight?*
5. *How might pharmacologic interventions influence the time course of lower limb muscle loss?*