

## **Proposal for Continuation of the Common Fund Molecular Transducers of Physical Activity (MoTrPAC) Program**

MoTrPAC was established in 2017 with the goal of assembling a comprehensive map of the molecular changes that occur in response to exercise, and when possible, associating these changes with physiologic benefits. The program is the largest of its kind. It encompasses both a large clinical study and parallel studies in animals (rats) to facilitate a mechanistic understanding of the molecular changes.

The program includes 5 initiatives:

- Human Clinical Sites: Assessing changes resulting from endurance training and resistance training in adults and children; individuals who are habitual exercisers will also be analyzed
- Multi'omic Analysis: Including genomic, transcriptomic, epigenomic, metabolomic, proteomic, and lipidomic assays
- BioInformatics Coordination: Coordinating data deposition and analysis; facilitating integrated analysis
- Preclinical Animal Studies: Rat studies designed to parallel the human endurance training in young and older adult animals
- Consortium Coordination – Coordinating all aspects of the consortium

The COVID-19 pandemic had a profound impact on the MoTrPAC Program. The projects have regained their momentum, but mandatory changes in the clinical protocol will extend the time and costs required to complete the study. This concept clearance proposal addresses plans to complete this landmark study.

**Phase 1 Accomplishments:** Prior to the pandemic, a pilot cohort of participants were recruited so that the operating procedures and analytic strategies could be assessed across the consortium. Data from this pre-pandemic cohort are being analyzed. In addition, analysis of 6-month old rats following endurance exercise has been completed, and initial results are available. Over 40,000 molecular changes have been observed, affecting every tissue examined in these animals. Affected molecules cluster into many networks and pathways, with over half of these clusters having different trajectories in males and females. These initial results indicate that MoTrPAC will be an enormous source for discovery and will transform our understanding of the molecular effects of exercise.

### **Phase 2 Concept:**

- Limited competition Funding Opportunity Announcements (FOAs) are proposed for the Clinical Sites, the Multi'Omic Analysis Sites, the BioInformatics Center, and the Consortium Coordinating Center so that the study can continue without disruption. External review of plans and budgets will ensure sound fiscal stewardship.
- In addition, we propose that a Limited Competition FOA be issued to leverage a supplement provided to the rat studies in Phase 1 which enabled a resistance exercise training protocol to be developed. This now provides the opportunity for parallel rat studies of resistance exercise and can thus extend our mechanistic understanding of changes induced by this form of exercise.
- Finally, a concept for mechanistic studies using animal models is proposed to encourage investigators to examine MoTrPAC data and to propose innovative approaches to better understand the extensive changes that result from exercise.

Total estimated costs for these initiatives are \$51M over 4 years.