Molecular Transducers of Physical Activity (MoTrPAc)

- Concept for Continuation

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NIH Council of Councils

National Institutes of Health
Office of Strategic Coordination–The Common Fund

OSC (Common Fund)

Concept Clearance: Common Fund Program Continuation

TITLE: Molecular Transducers of Physical Activity (MoTrPAc)

Objectives:

1) To assemble a comprehensive map of the molecular changes that occur in response to exercise, and when possible, relate these to the benefits of physical activity, and
2) To develop a user-friendly data resource that any user can access to develop hypotheses for future studies

Initiatives:

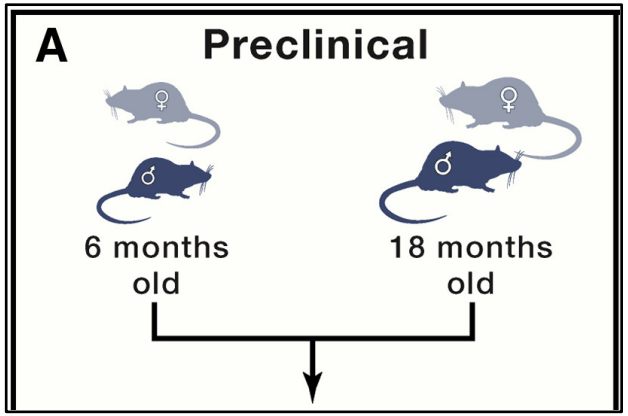
1. Clinical Centers – recruit children and adults into the study
2. Preclinical Animal Studies – explore mechanisms underlying physical activity benefit
3. Multi'omic Analysis Sites – generate multi'omic data from human and rats
4. Bioinformatics Center – coordinate data acquisition, deposition, and analysis; enable access to data by entire community
5. Consortium Coordinating Center (CCC)

Funds Available: $51 M over 4 years
Program Duration: 4 years
Council Action: Vote for approval of the concept for MoTrPAc Continuation

MoTrPAc Questions

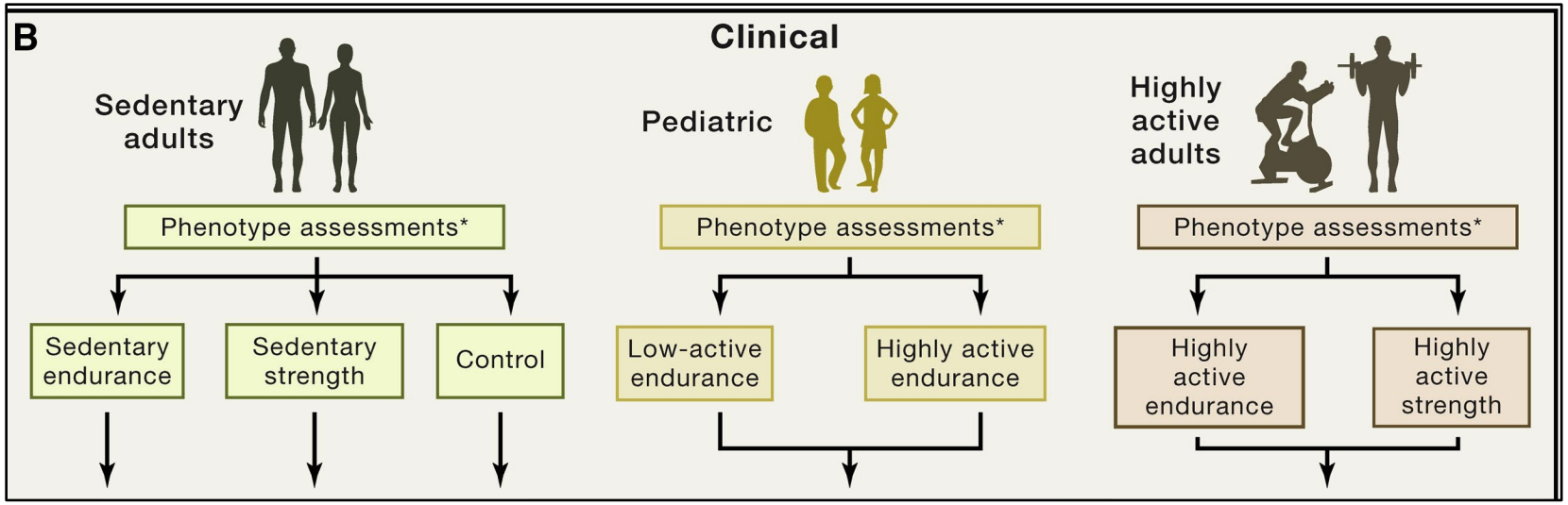
- What are the signals that transmit the health-improving effects of physical activity?
- What are the molecular networks that are triggered by these signals?
- What tissues are affected?
- How are these signals affected by factors like age, sex, genetics, body composition, fitness level, and type of exercise training?
- How do molecular changes correlate with other changes, such as improved mood, better pain management, or better sleep?

MoTrPAc Study Summary



Male/female rats
Young/old adult animals
Up to 19 tissues studied

- Molecular profile before and after a single bout of ENDURANCE exercise?
- Molecular profile before/after training?



Non-exercisers (get trained)

Regular exercisers

- Molecular profile of people who exercise regularly?
- Molecular profile before/after 12 wks of exercise training?
- Molecular profile of low-active/highly-active children?

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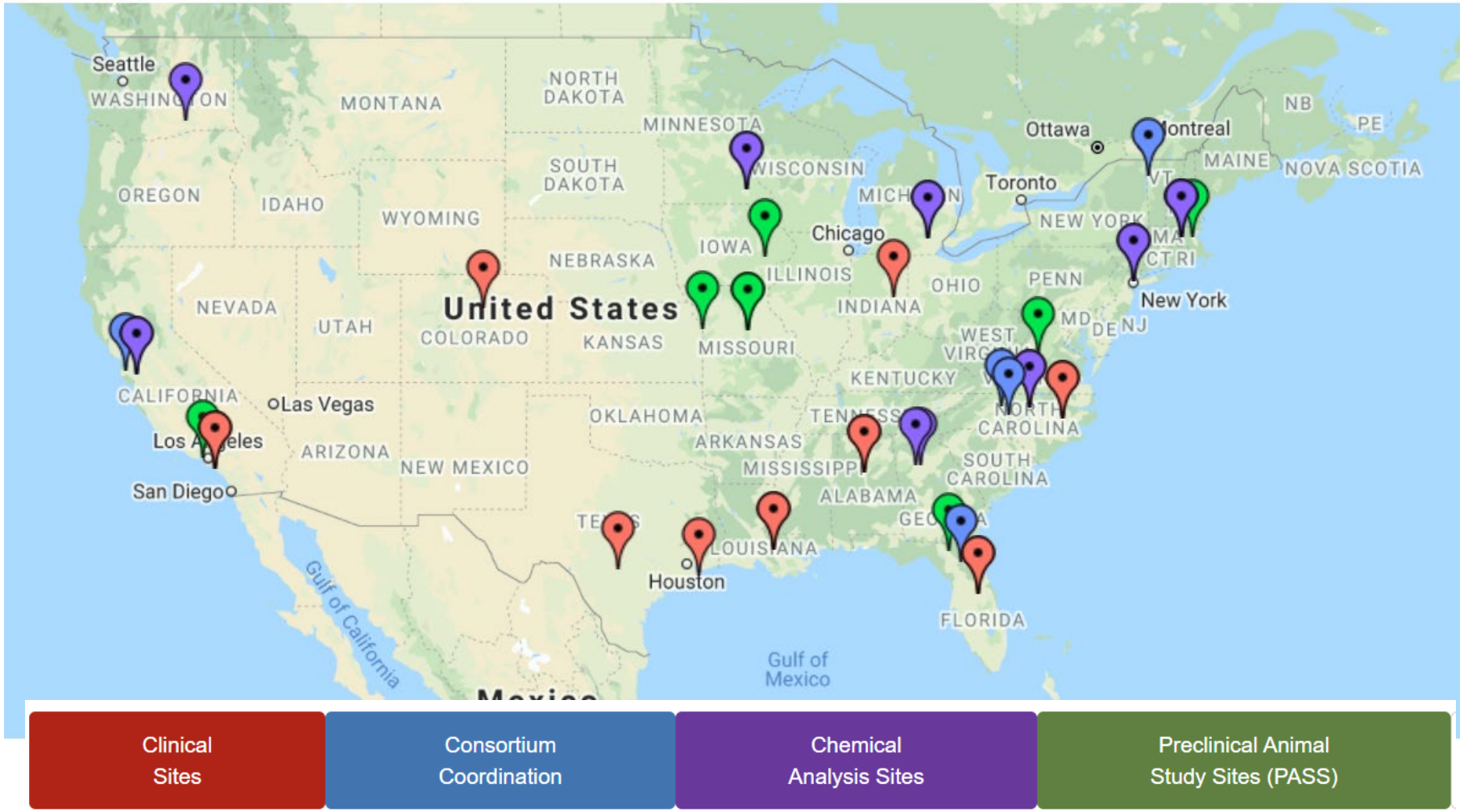
The MoTrPAc Consortium

motrpac.org/aboutUs



- 6 Pre-clinical animal study sites (PASS)
- 7 Clinical Centers (11 recruiting sites)
- 7 Chemical Analyses Sites (CAS)
  - Genes
  - Metabolites
  - Proteins
  - Lipids
  - Vesicles
- Bioinformatics Center (BIC)
- Coordinating Center/Data Monitoring QC/ Biorepository

Update on Clinical Study – Sept 2022

Recruitment for MoTrPAc clinical study began in 2019, and then was suspended by the pandemic

- There is a pre-COVID cohort of participants
  - Multi'omic analysis of these blood, muscle and adipose samples is underway.

Recruitment restarted following discussions with Data Safety Monitoring Board and the Institutional Review Board, led by the Consortium Coordinating Center (CCC).

- As of Sept 2022, all clinical sites are recruiting, under new safety protocols.
- CCC is ensuring rigor and reproducibility of the study and standardized implementation of the protocol

Need for Continuation: Clinical Sites, Analysis Sites, and CCC

- The COVID pandemic had a dramatic effect on MoTrPAc
  - Manual of Procedures had to be modified – increased distancing, PPE
  - IRB approval had to be re-obtained
  - Costs associated with modified protocol increased

- Full enrollment to meet the original objectives for the program will require recruitment through the end of December, 2024
  - Participants will finish the protocol by May, 2025
  - Data generation and analysis will go through September, 2026

- Propose a limited competition renewal of Clinical Sites, Multi'Omic sites, and Consortium Coordinating Center to complete the study
  - Invites peer review to examine details of the study and operations at each site to ensure sound financial stewardship as the program is completed
  - Ensures continuity in implementation of the clinical protocol and analytic strategy

Update and Need for Continuation: Bioinformatics Center (BIC)

Functions of the BIC include:

- Participating and leading bioinformatics-related activities in the MoTrPAC consortium
- Developing and Maintaining the MoTrPAc Data Hub (https://motrpac-data.org/) which provides data deposition and access to MoTrPAc data for internal and external users
- Provide statistical guidance and answer questions about study design
- Developing, running, and maintaining Omics raw data processing pipelines, including RNAseq, ATACseq, RRBS, and proteomics
- Provide data QA/QC for Omics and animal and clinical phenotypic data
- Submit MoTrPAc omics data to public repositories including dbGaP, SRA, Metabolomics Workbench

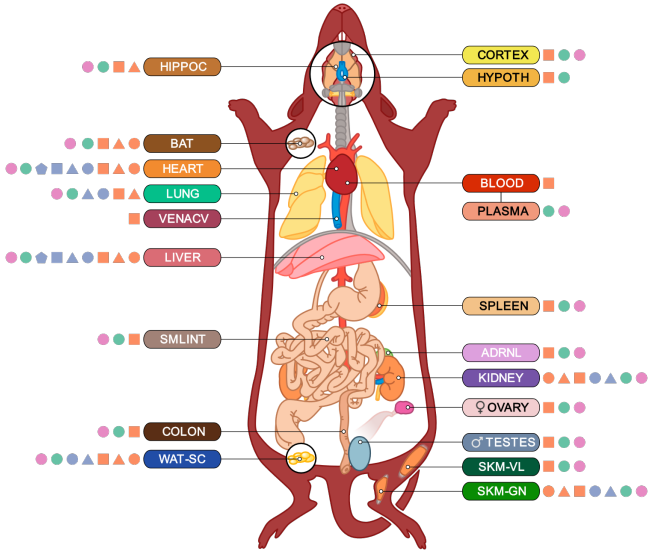
Need for Continuation:

- The BIC provides essential data coordination and data integration functions
- Its continuation is needed through the end of the study to coordinate data analysis and integration and to ensure sustainability of data access
- It is working with the Common Fund Data Ecosystem to ensure sustainability and integration with other CF data
- Propose a limited competition renewal

Update on Animal Studies: Replication of the Human Protocol

Endurance

	6-months	18-months
Acute Exercise	Data analyses in progress	Sample analyses in progress
Progressive Training	COMPLETED; Manuscript in preparation	Sample analyses in progress



Genomics

Epigenomics

- DNA methylation - RRBS (METHYL)
- Chromatin accessibility (ATAC)
- RNA-seq (TRNSCRPT, SPLICE)

Proteomics

- Global protein expression (PROT)

Post-translational modifications

- Phosphorylation (PHOSPHO)
- Acetylation (ACETYL)
- Ubiquitination (UBIQ)

Metabolomics

- Metabolites: named (N-METAB) and unnamed (U-METAB)

Cytokines

- Cytokine immunoassays

Resistance – Ladder Climbing

Figure 1: Training apparatus. A rat is shown climbing a 1.52-m, 20° incline ladder with weight attached to tail. At the top of the ladder a blacked-out housing chamber is where animals rested for 2-min between repetitions.

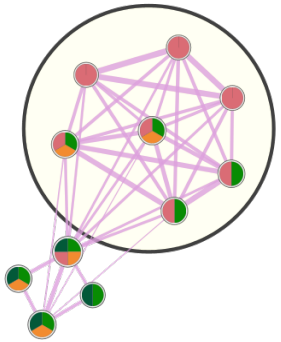
- Supplemental funding allowed the development of a resistance training assay
- Young and older animals are being trained but funds for analysis are limited

Credit for photo:
Dr. Sue Bodine

Preliminary findings from Animal Training Study

Data available at https://motrpac-data.org/analysis/animal

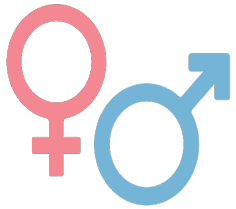
- >40,000 analytes are regulated over the training time course
- Substantial regulation at the transcript, protein, and post-translational modification levels



- Multiomics clustering identifies several major molecular trajectories over the training time course
- Top 10 most enriched pathways are related to metabolism

DNA
↓
RNA
↓
Protein

- Genes regulated by training in multiple tissues are enriched for pathways related to metabolism, inflammation, extra cellular matrix remodeling, and nutrient absorption



- Strong sex-specific response: Half of the multiomics clusters have different trajectories in males and females

Update on Animal Studies: Insights to date

- Sex differences in organ responses are common.
  - Profound sexual dimorphism in rat subcutaneous white fat (scWAT)
  - Despite similar cardiorespiratory improvements, only male rats reduced whole-body adiposity, scWAT adipocyte size, and triglyceride abundance with training.
  - Enrichment of pathways related to insulin signaling, lipid re-esterification, and adipogenesis was seen in females; enrichment of lipid catabolism in males.
- Changes in genetic and epigenetic gene expression across 8 tissues.
  - Genetic associations with training-induced changes in body composition and V02 max.
  - Clusters of tissues (kidney, muscle, heart, lung, liver) have training-induced gene expression changes that associate with physiologic outcomes
  - Other tissues (e.g. hippocampus and brown fat) have training-induced changes that do not associate with physiological outcomes.
- Renal responses to exercise training in both males and females leads to increases in proteins that are anti-inflammatory and ameliorate oxidative stress
- Liver's response to exercise identified novel bile acid and cholesterol biosynthesis responses that could impact digestive health.

Need for Continuation of Animal Studies

Replication of the Human Protocol

- Samples from 18 month endurance exercise animals need to be analyzed
- Resistance training model provides opportunity to replicate resistance portion of human study, but funds for analysis of these samples have been limited
- Propose Limited Competition continuation of these studies to enable investigators to complete these studies

Mechanistic Studies

- Data that will be coming from multi'omic analysis of MoTrPAc Phase 1 (rat and human studies) present tremendous opportunity for discovery
- This data set has been envisioned as stimulatory for investigator-initiated research
- We propose an open competition for a limited number of studies to kick-start a community-wide effort that will continue well past the completion of the MoTrPAc program itself

Proposal for Continuation:

	FY23	FY24	FY25	FY26	Total
Consortium Coordinating Ctr	-	2.5 M	2.5 M	1.3 M	6.3 M
Clinical Sites	0.6 M	13.0 M	7.2 M	-	20.8 M
Multi'omic Analysis Sites	-	0.2	4.6 M	4.7 M	9.5 M
Rat Endurance & Resistance Exercise Study	0.9 M	0.6 M	0.6 M		2.1 M
Mechanistic Studies	-	1.0 M	1.0 M	-	2.0 M
Bioinformatic Center	2.0 M	2.7 M	2.8 M	2.8 M	10.3
TOTAL	**$3.5 M**	**$20 M**	**$18.7 M**	**$8.8 M**	**$51 M**

Note: Many awards from MoTrPAc Phase 1 will have funds to carry over in FY23 and FY24

Acknowledgements

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NIH Program Management Team:

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- Stephanie George, NIAMS
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- Rebecca Lenzi, OSC
- Padma Maruvada, NIDDK
- George Papanicolaou, OSC
- Veronica Taylor, OSC
- John Williams, NIA
- Ashley Xia, NIDDK

MoTrPAc Investigators

MoTrPAc Clinical Study Participants

Council Action:
Vote for approval of the concept for MoTrPAc Continuation

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