MoTrPAC: Molecular Transducers of Physical Activity

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Program Leader, OSC

On behalf of the MoTrPAC Program Management Team
MoTrPAC Program Goals

• Assemble a comprehensive map of the molecular changes that occur in response to exercise and when possible relate these changes to the benefits of physical activity
  
  o This map will contain the many molecular signals that transmit the health-improving effects of physical activity, and indicate how signals are altered by variables such as age, sex, body composition, fitness level, and exposure to exercise training.

• Develop a user-friendly database that any researcher can access to develop hypotheses for additional studies regarding the mechanisms whereby physical activity improves and/or preserves health
Consortium organization and Study design

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**Perspective**

**Molecular Transducers of Physical Activity Consortium (MoTrPAC): Mapping the Dynamic Responses to Exercise**

The MoTrPAC Consortium

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

6 months old

18 months old

Reverse light phase

Single bout

Training

30 min 80-90% VO₂max
5 days/wk 70% VO₂max 1, 2, 4 or 8 wks

Biospecimen collection

(B) Clinical

Sedentary adults

Phenotype assessments*

Sedentary endurance
Sedentary strength
Control

Acute exercise bout and biospecimen collection

Endurance training: 12 wks 3d/wk 60-80%
Strength training: 12 wks 3d/wk 60-80%
Normal ambulatory living (no exercise control)

Phenotype reassessments*

Acute exercise bout and biospecimen collection

Pediatric

Phenotype assessments*

Low-active endurance
Highly active endurance

Acute exercise bout and biospecimen collection

Endurance training: 12 wks 3d/wk

Phenotype reassessments*

Highly active adults

Phenotype assessments*

Highly active endurance
Highly active strength

Acute exercise bout and biospecimen collection

Subgroup of low-active endurance randomization: Training
No exercise control
Pre-clinical Animal Studies, Phase 1 (PASS Phase 1)

- **Fischer 344**
  - 6m
  - 18m

-Chronic Progressive Training
  - ~70% VO\textsubscript{2}max
  - 1 2 4 8 weeks

Acute Exercise
  - 30 minutes, ~80% VO\textsubscript{2}max
  - 0 30 60 minutes
  - 0 4 7 24 49 hours

Reverse Light-Cycle

Chemical Analysis Sites
  - Data generation for Multi-omics analysis

<table>
<thead>
<tr>
<th></th>
<th>6-month</th>
<th>18-month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Exercise</td>
<td>Samples being analyzed</td>
<td>To be analyzed</td>
</tr>
<tr>
<td>Progressive Training</td>
<td>COMPLETED; Manuscript in preparation</td>
<td>To be analyzed</td>
</tr>
</tbody>
</table>
Chronic Progressive Training in 6-month animals (PASS 1B-06)

6m Animals

- 1 wk
- 2 wk
- 4 wk
- 8 wk
- Controls

**Phenotypes Measured:** Body Weight; Body Composition (by NMR); Maximum Oxygen Uptake (VO₂ max); Maximum Running Speed; Muscle Weight; Muscle Histology

- Metabolic adaptations to the exercise training protocol differed by sex.
- The effect of treadmill exercise on body composition varied between males and females.
  - Adult **males** lose fat mass
- Treadmill training induced a shift in muscle fiber type composition
- There is a robust cardiovascular response to chronic treadmill exercise at 6 months of age, in both sexes.
- MoTrPAC’s Tissue Repository has stored tissues for additional ancillary studies.
High-dimensional molecular profiling of the training response

Genomics
- DNA methylation - RRBS (METHYL)
- Chromatin accessibility (ATAC)
- RNA-seq (TRANSCRIPT, 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
Preliminary findings from PASS Training Study (1B-06)

- >40,000 analytes are regulated over the training time course
- Substantial regulation at the transcript, protein, and PTM levels
- Multiomics clustering identifies several major molecular trajectories over the training time course
- Top 10 most enriched pathways are related to metabolism
- Genes regulated by training in multiple tissues are enriched for pathways related to metabolism, inflammation, ECM remodeling, and nutrient absorption
- Strong sex-specific response: Half of the multiomics clusters have different trajectories in males and females
Next steps: PASS

- Multi-omic and multi-tissue analyses of samples from Acute Exercise of 6-month-old animals (PASS 1A-06)

- Analyses of samples from 18-month-old animals: Training (PASS 1B-18) and Acute Exercise (PASS 1A-18)

- Comparison of responses between 6- and 18-month animals

- Mechanistic studies (PASS Phase 2) are ongoing

- Data release planned in 2022
MoTrPAC Clinical Study - Adults

**Sedentary (SED) Participants**

<table>
<thead>
<tr>
<th>Screening and Phenotyping* (~2 months)</th>
<th>Randomized to:</th>
<th>Pre-intervention Testing (~3 weeks)</th>
<th>Intervention (~12 weeks)</th>
<th>Post-intervention Testing (~2 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>~990 women aged 18+ yr</td>
<td>EE, n=840</td>
<td>X X X</td>
<td>X</td>
<td>X X X</td>
</tr>
<tr>
<td>~990 men aged 18+ yr</td>
<td>RE, n=840</td>
<td>X X X</td>
<td>X</td>
<td>X X X</td>
</tr>
<tr>
<td>Meet eligibility criteria</td>
<td>Control, n=300</td>
<td>X X</td>
<td></td>
<td>X X</td>
</tr>
</tbody>
</table>

- Familiarization, washout*
- Acute exercise test
- Biospecimen collection*
- Endurance exercise
- Resistance exercise
- Physical activity monitoring
- Phenotyping*
- Washout*
- Acute exercise test
- Biospecimen collection*

* Phenotyping includes assessments of aerobic fitness, muscle strength, body composition, physical activity; some pre-intervention phenotyping visits occur before randomization

** Washout (no exercise or testing) before acute exercise test, biospecimen collection

**Highly Active (HA) Participants**

<table>
<thead>
<tr>
<th>Screening (~2 months)</th>
<th>Enrollment</th>
<th>Testing (~2 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control, n=300</td>
<td>HAEE, n=150</td>
<td>X X X X X</td>
</tr>
<tr>
<td>Control, n=300</td>
<td>HARE, n=150</td>
<td>X X X X</td>
</tr>
</tbody>
</table>

- Phenotyping*
- Familiarization, washout**
- Acute exercise test
- Biospecimen collection

* Phenotyping includes assessments of aerobic fitness, muscle strength, body composition, physical activity

** Washout (no exercise or testing) before acute exercise test and biospecimen collection

NIH National Institutes of Health
Office of Strategic Coordination – The Common Fund
Eligibility Criteria – Physical Activity Levels

**Highly Active, Endurance Exercise (HAEE)**
- 240+ minutes/week of EE for 1+ years (increased heart rate, rapid breathing, sweating)
- Must include cycling at least 2 days/week
- Limited RE in past year
- No performance enhancing drugs in last 6 months

**Highly Active, Resistance Exercise (HARE)**
- 3+ upper body and 3+ lower body RE, 2+ days/week for 1+ years (high intensity)
- Limited to no more than 90 minutes/week of moderate EE
- No performance enhancing drugs in last 6 months

**Sedentary (SED)**
- No more than 1 day/week or 60 minutes/week of regular EE that results in increased heart rate, rapid breathing, and/or sweating in past year
### Exercise Testing and Training

<table>
<thead>
<tr>
<th>Group</th>
<th>CPET Cycling</th>
<th>1-RM CP, LP, LE</th>
<th>Isometric Knee Ext</th>
<th>Grip Strength</th>
<th>EE Acute Test</th>
<th>RE Acute Test</th>
<th>Progressive EE Training</th>
<th>Progressive RE Training</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAEE</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>Cycling 40 min 65% VO₂max</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HARE</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>5 upper body 3 lower body 3 sets, 10-RM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SED EE</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>Cycling 40 min 65% VO₂max</td>
<td>25-30 min CE 25-30 min TM 60-80% HRR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SED RE</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>5 upper body 3 lower body 3 sets, 10-RM</td>
<td>5 upper body 3 lower body 3 sets, 10-RM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SED CON</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
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MoTrPAC Clinical Study - Pediatrics

### Table 1. Pediatric MoTrPAC Overview

<table>
<thead>
<tr>
<th>Screening for eligibility</th>
<th>Cross-Sectional Phase Enrollment</th>
<th>Health and Fitness Phenotyping and Acute Exercise Challenge (~3 weeks)</th>
<th>Intervention Phase Enrollment (EE or Control, ~12 weeks)</th>
<th>Post Intervention Health and Fitness Assessments (~2 weeks)</th>
</tr>
</thead>
</table>
| 135 Low Activity EE females | • Aerobic fitness  
• Muscle strength  
• Habitual physical activity  
• Dietary and behavioral questionnaires  
• Preparation and Familiarization with EE challenge  
• Washout EE Challenge with blood sampling | 60 Low Activity EE females | • Aerobic fitness  
• Muscle strength  
• Habitual physical activity  
• Dietary and behavioral questionnaires  
• Preparation for EE challenge  
• Washout EE Challenge with blood sampling |
| 135 Low Activity EE males | • Aerobic fitness  
• Muscle strength  
• Habitual physical activity  
• Dietary and behavioral questionnaires  
• Preparation and Familiarization with EE challenge  
• Washout EE Challenge with blood sampling | 60 Low Activity EE males | • Aerobic fitness  
• Muscle strength  
• Habitual physical activity  
• Dietary and behavioral questionnaires  
• Preparation for EE challenge  
• Washout EE Challenge with blood sampling |
| 25 High Activity EE females | • Aerobic fitness  
• Muscle strength  
• Habitual physical activity  
• Dietary and behavioral questionnaires  
• Preparation and Familiarization with EE challenge  
• Washout EE Challenge with blood sampling | 25 control females | • Preparation for EE challenge  
• Washout EE Challenge with blood sampling |
| 25 High Activity EE males | • Aerobic fitness  
• Muscle strength  
• Habitual physical activity  
• Dietary and behavioral questionnaires  
• Preparation and Familiarization with EE challenge  
• Washout EE Challenge with blood sampling | 25 control males | • Preparation for EE challenge  
• Washout EE Challenge with blood sampling |

**Pediatrics Study:**
- Pediatric participants are classified by Tanner Stage
- Protocol mirrors the adult protocol, but fewer children are entered in training phase
- Training is endurance exercise only
- Only blood samples are collected
- Recruitment is at a single clinical site
Prioritization
Blood – no prioritization
Skeletal muscle
• Gen/Epi/Transcr
• Proteomics
• Broad Nontargeted Metab
• UM Untargeted Metab
• GA Tech Lipidomics
• Duke Targeted Metab
• Mayo Targeted Metab
• Emory Oxylinps
Adipose-
• Gen/Epi/Transcr
• Proteomics
• Broad Nontargeted Metab
• GA Tech Lipidomics
• UM Untargeted Metab
• Duke Targeted Metab
• Mayo Targeted Metab
• Emory Oxylinps
MoTrPAC and COVID-19

motrpac.org
MoTrPAC and COVID-19

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Rapid report

Rapid report on using data to make standardized decisions about enrollment during the COVID-19 pandemic: perspectives from the MoTrPAC study

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• Lyndon Joseph, NIA
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  • Betsy Wilder, OSC

MoTrPAC Investigators

MoTrPAC Clinical Study Participants