MoTrPAC: Molecular Transducers of Physical Activity

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On behalf of the MoTrPAC Program Management Team

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

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
    - 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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CellPress

Cell
Leading Edge

Perspective

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

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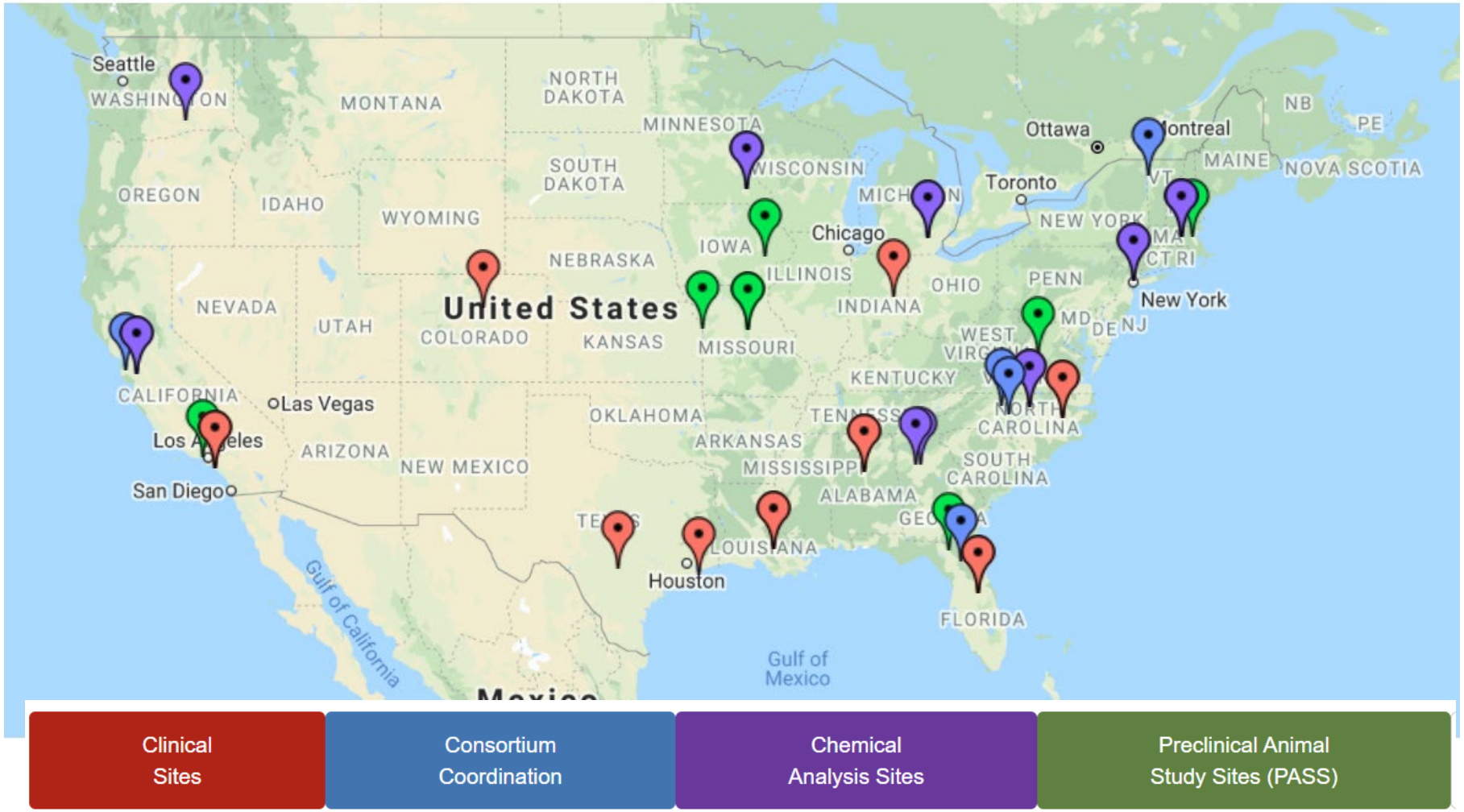
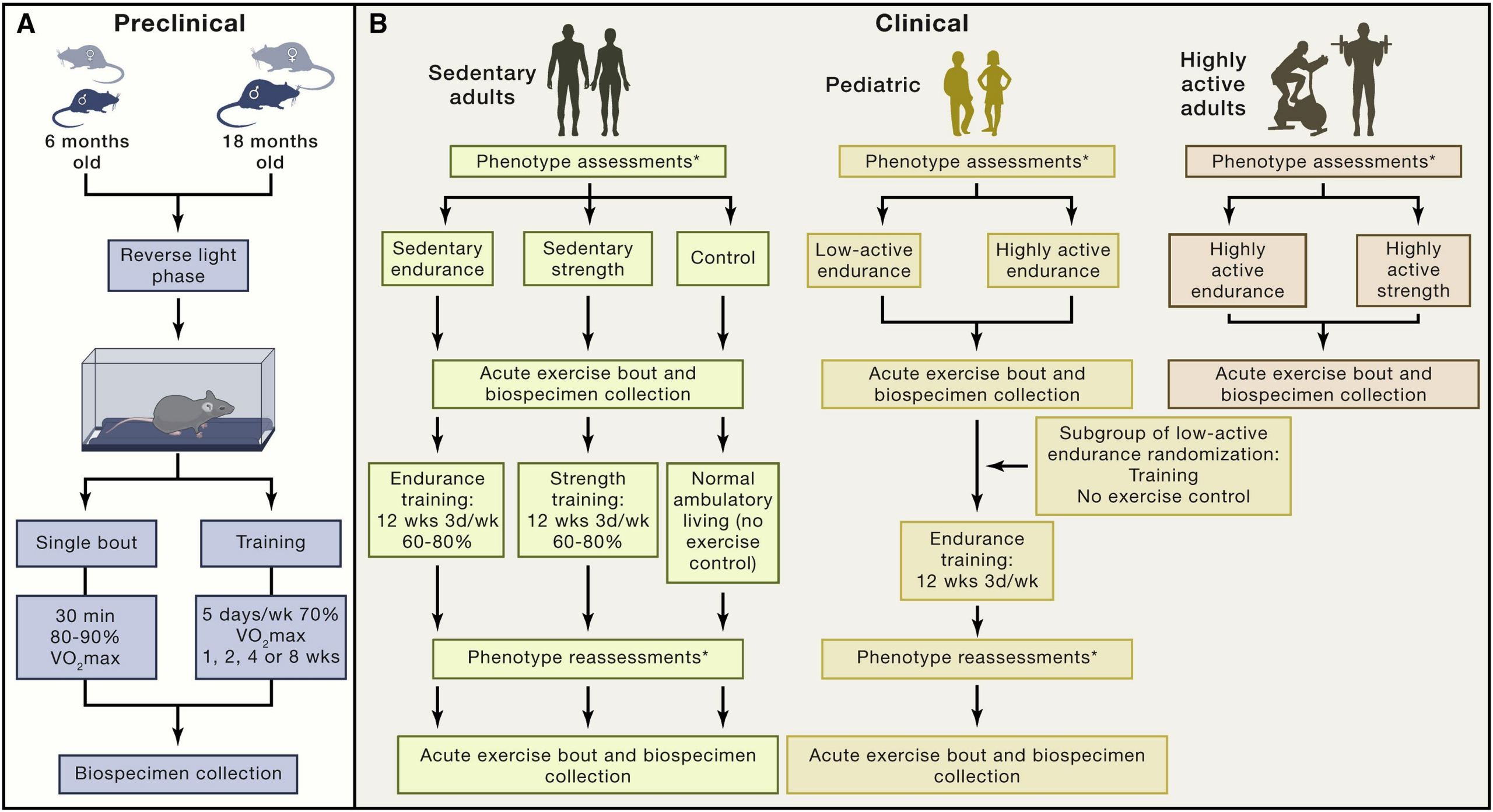
The MoTrPAC Consortium

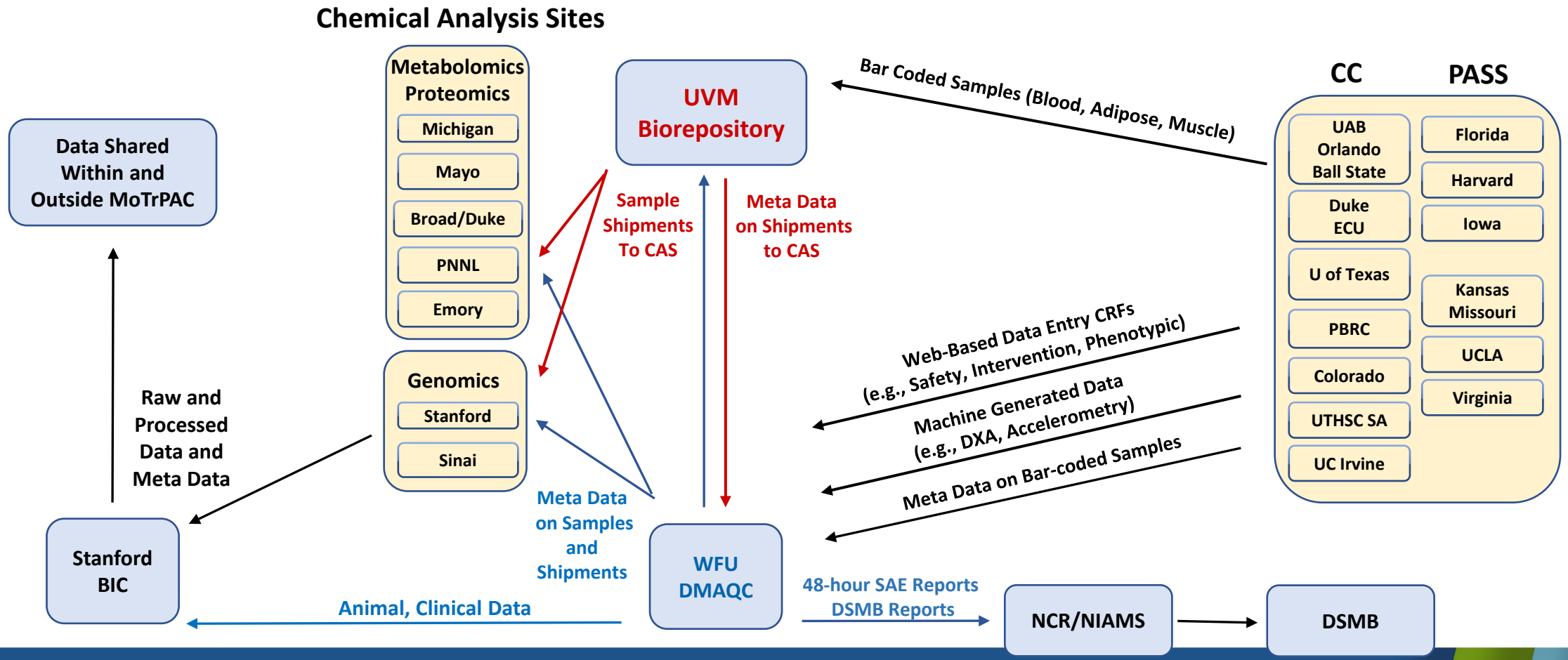
motrpac.org/aboutUs



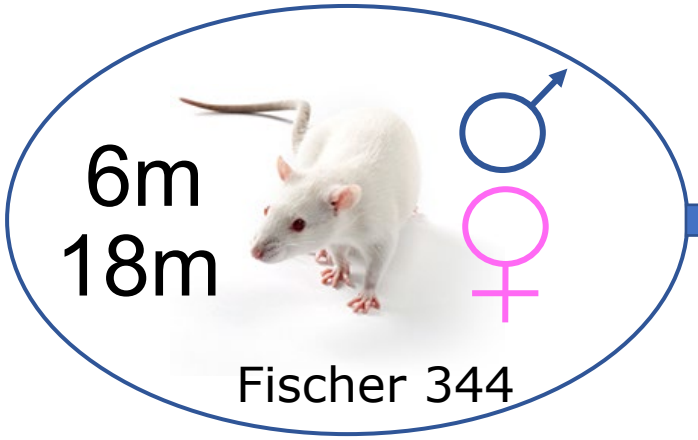
- 6 Pre-clinical animal study sites (PASS)
- 7 Clinical Centers (11 recruiting sites)
- 7 Chemical Analyses Sites (CAS)
- Bioinformatics Center (BIC)
- Coordinating Center/Data Monitoring QC/ Biorepository


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
Subgroup of low-active endurance randomization: Training No exercise control
Endurance training: 12 wks 3d/wk
Phenotype reassessments*
Acute exercise bout and biospecimen collection
Highly active adults
Phenotype assessments*
Highly active endurance
Highly active strength
Acute exercise bout and biospecimen collection

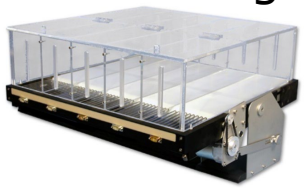
Sample and Data Flows

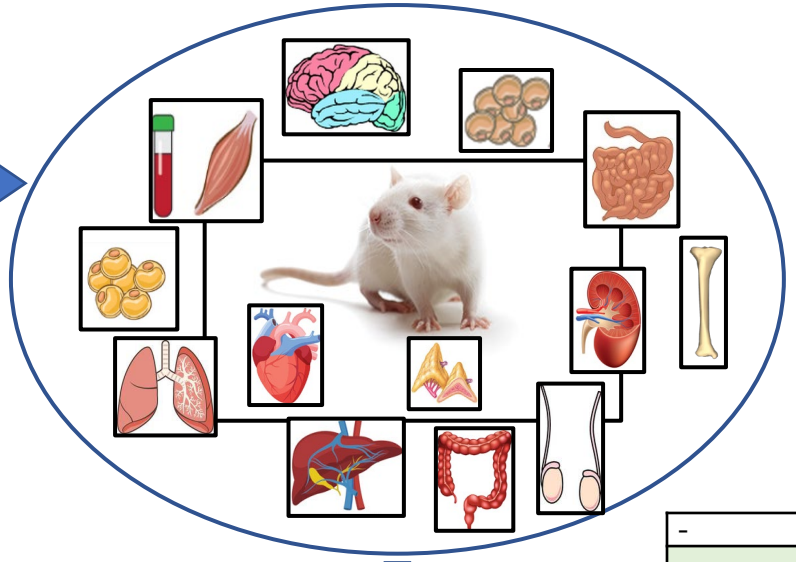


Pre-clinical Animal Studies, Phase 1 (PASS Phase 1)

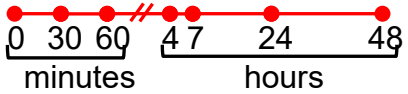


Reverse Light-Cycle



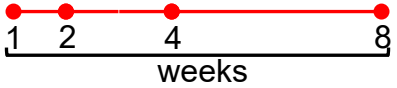


Acute Exercise
30 minutes, ~80% VO_2max



+

Chronic Progressive Training
~70% VO_2max



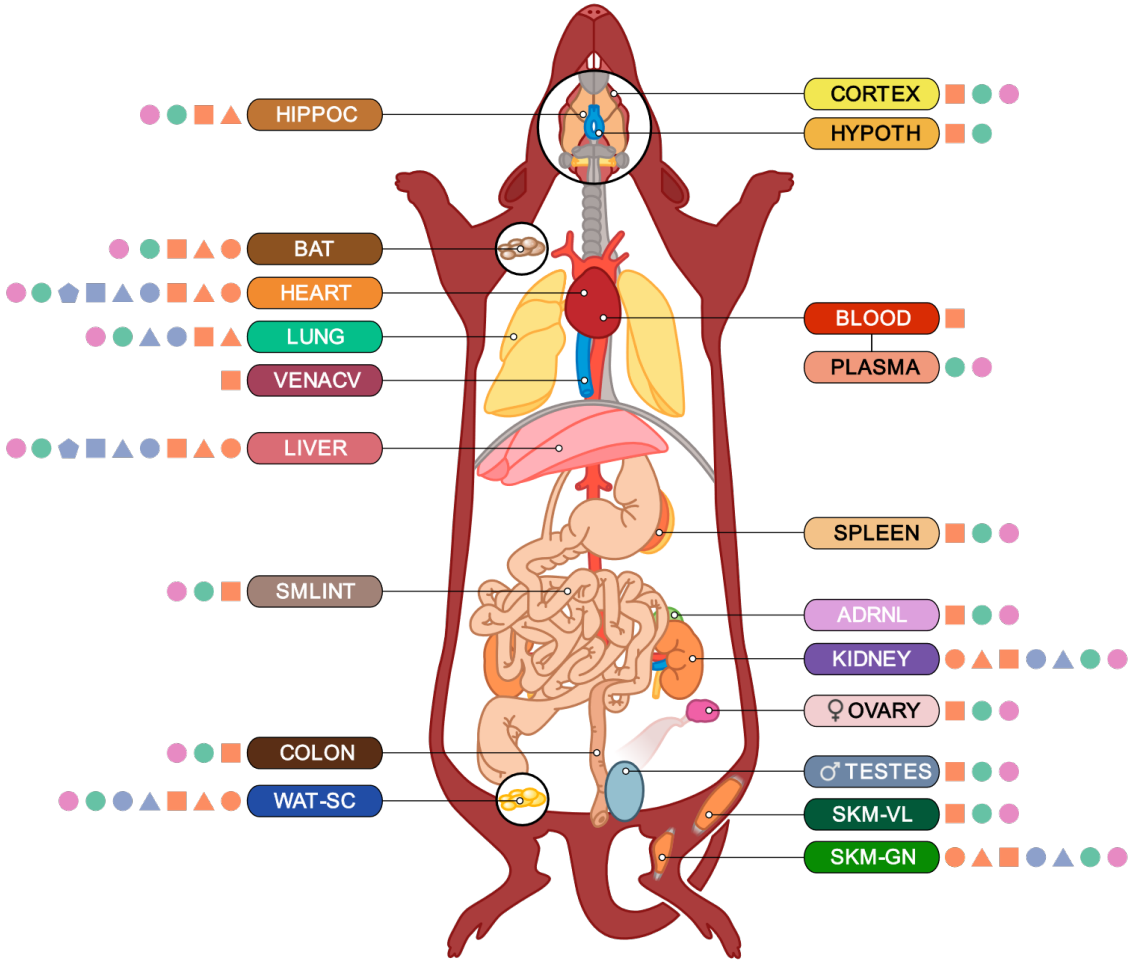
Chemical Analysis Sites
Data generation for
Multi-omics analysis

-	6-month	18-month
Acute Exercise	Samples being analyzed	To be analyzed
Progressive Training	COMPLETED; Manuscript in preparation	To be analyzed

Chronic Progressive Training in 6-month animals (PASS 1B-06)

- Phenotypes Measured: Body Weight; Body Composition (by NMR); Maximum Oxygen Uptake (VO_2 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

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

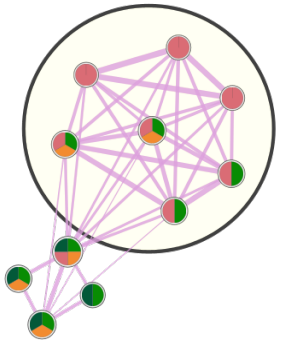
- Metabolites: named (N-METAB) and unnamed (U-METAB)

Cytokines

- Cytokine immunoassays

Preliminary findings from PASS Training Study (1B-06)

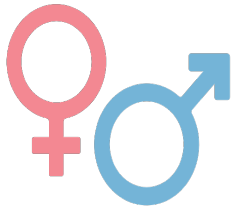
- >40,000 analytes are regulated over the training time course
- Substantial regulation at the transcript, protein, and PTM levels



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

DNA
↓
RNA
↓
Protein

- 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

Screening and Phenotyping* (~2 months)	Randomized to:	Pre-intervention Testing (~3 weeks)			Intervention (~12 weeks)			Post-intervention Testing (~2 weeks)			
		Familiarization, washout**	Acute exercise test	Biospecimen collection+	Endurance exercise	Resistance exercise	Physical activity monitoring	Phenotyping*	Washout**	Acute exercise test	Biospecimen collection+
~990 women aged 18+ yr	EE, n=~840	X	X	X	X		X	X	X	X	X
~990 men aged 18+ yr	RE, n=~840	X	X	X		X	X	X	X	X	X
Meet eligibility criteria	Control, n=~300	X		X			X	X	X		X

* 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

Screening (~2 months)	Enrollment	Testing (~2 weeks)			
		Phenotyping*	Familiarization, washout**	Acute exercise test	Biospecimen collection+
	HAEE, n=~150	X	X	X	X
	HARE, n=~150	X	X	X	X

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

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

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

Group	CPET Cycling	1-RM CP, LP, LE	Isometric Knee Ext	Grip Strength	EE Acute Test	RE Acute Test	Progressive EE Training	Progressive RE Training
HAEE	X		X	X	Cycling 40 min 65% VO_2max			
HARE	X	X	X	X		5 upper body 3 lower body 3 sets, 10-RM		
SED EE	X		X	X	Cycling 40 min 65% VO_2max		25-30 min CE 25-30 min TM 60-80% HRR	
SED RE	X	X	X	X		5 upper body 3 lower body 3 sets, 10-RM		5 upper body 3 lower body 3 sets, 10-RM
SED CON	X		X	X				

MoTrPAC Clinical Study-Pediatrics

Table 1. Pediatric MoTrPAC Overview

Screening for eligibility	Cross-Sectional Phase Enrollment	Health and Fitness Phenotyping and Acute Exercise Challenge (~3 weeks)	Intervention Phase Enrollment (EE or Control, ~12 weeks)	Post Intervention Health and Fitness Assessments (~2 weeks)
	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		60 Low Activity EE males	
	25 High Activity EE females		25 control females	
	25 High Activity EE males		25 control males	

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 Oxylipins

Adipose-

- Gen/Epi/Transcr
- Proteomics
- Broad Nontargeted Metab
- GA Tech Lipidomics
- UM Untargeted Metab
- Duke Targeted Metab
- Mayo Targeted Metab
- Emory Oxylipins

GET MSSM; Stanford				
Tissues	RNA-seq	ATAC-Seq	Methylation	WGS
Blood	X	X	X	X
Sk. Muscle	X	X	X	
White adipose	X	X	X	

Broad	
Tissues	HILIC Positive
Blood	X
Sk. Muscle	X
White adipose	X

UMICH	
	$IP^+; R^+; RP^-$
Blood	X
Sk. Muscle	X
White adipose	X

Emory	
Tissues	Lipidomics
Plasma	X
Sk. Muscle	X
White adipose	X

Proteomics at PNNL			Proteomics at Broad	
Tissues	Proteome		Tissues	Proteome
Sk. Muscle	X		X	X
White adipose	X			

Proteomics at Broad Olink	
Blood	X

Oxylipins - Georgia Tech	
Tissues	Lipidomics
Plasma	X
Sk. Muscle	X
White adipose	X

Targeted - Duke				
Tissues	Acyl-CoAs	Nucleotides	BCAA-derived	Clinical analytes
Blood			X	X
Sk. Muscle	X	X	X	
White adipose	X	X	X	

Targeted - Mayo				
Tissues	Amines	Acylcarnitines	Ceramides	TCA (organic acids)
Blood	X	X	X	X
Sk. Muscle	X	X	X	X
White adipose	X	X	X	X

MoTrPAC and COVID-19

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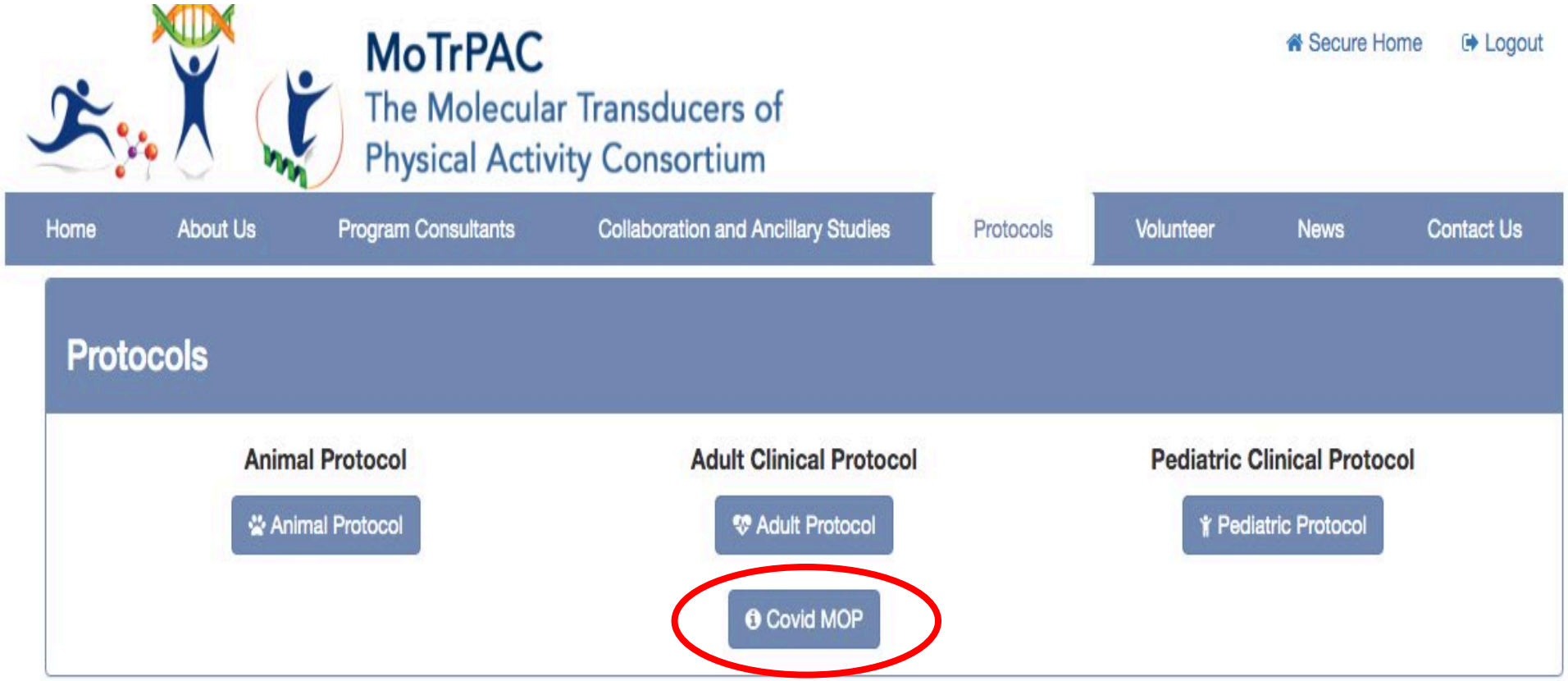

MoTrPAC and COVID-19

ELSEVIER

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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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Acknowledgements

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MoTrPAC Investigators

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