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
  - What are the signals that transmit the health-improving effects of physical activity?
  - How are these signals affected by factors like age, sex, 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?
- Develop a user-friendly database that any researcher can access to develop hypotheses for additional studies

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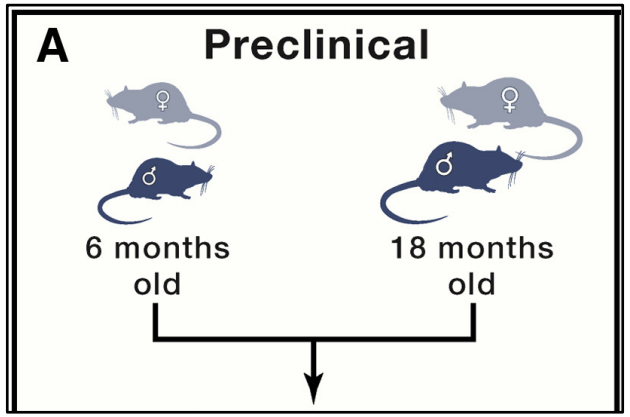
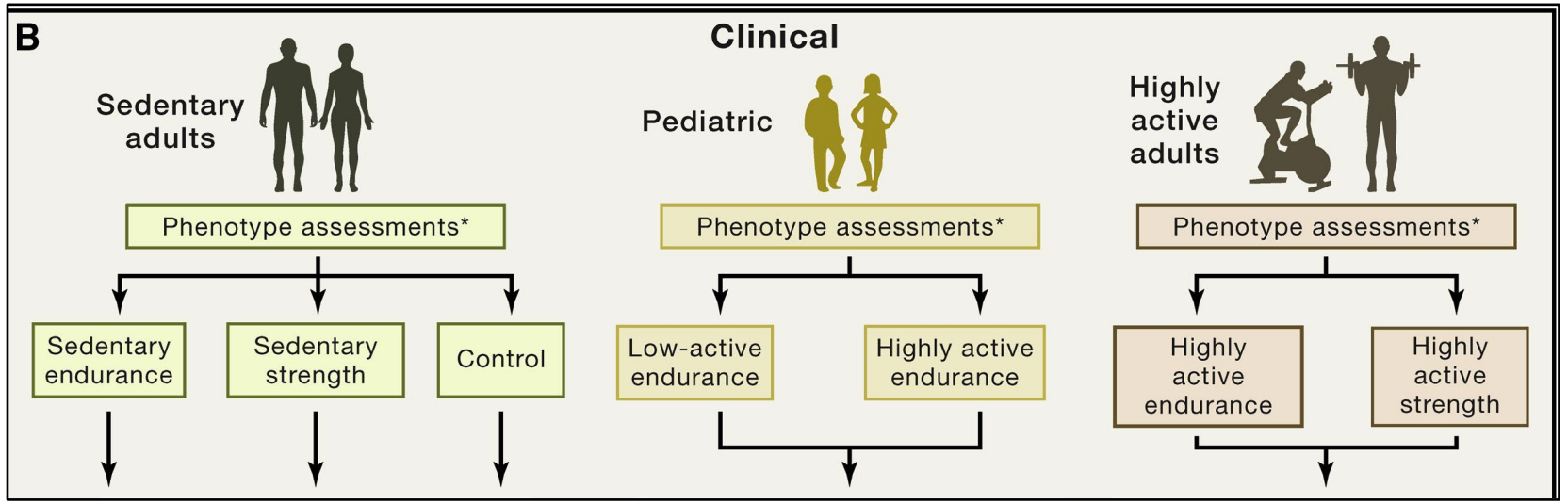


Male/female rats
Young/old adult animals
Up to 19 tissues studied

- What does the molecular profile look like before/after a single bout of exercise?
- What does the molecular profile look like before/after 8 wks of training?
- Are there differences between sexes?
- Are there differences with age?



Non-exercisers (get trained)

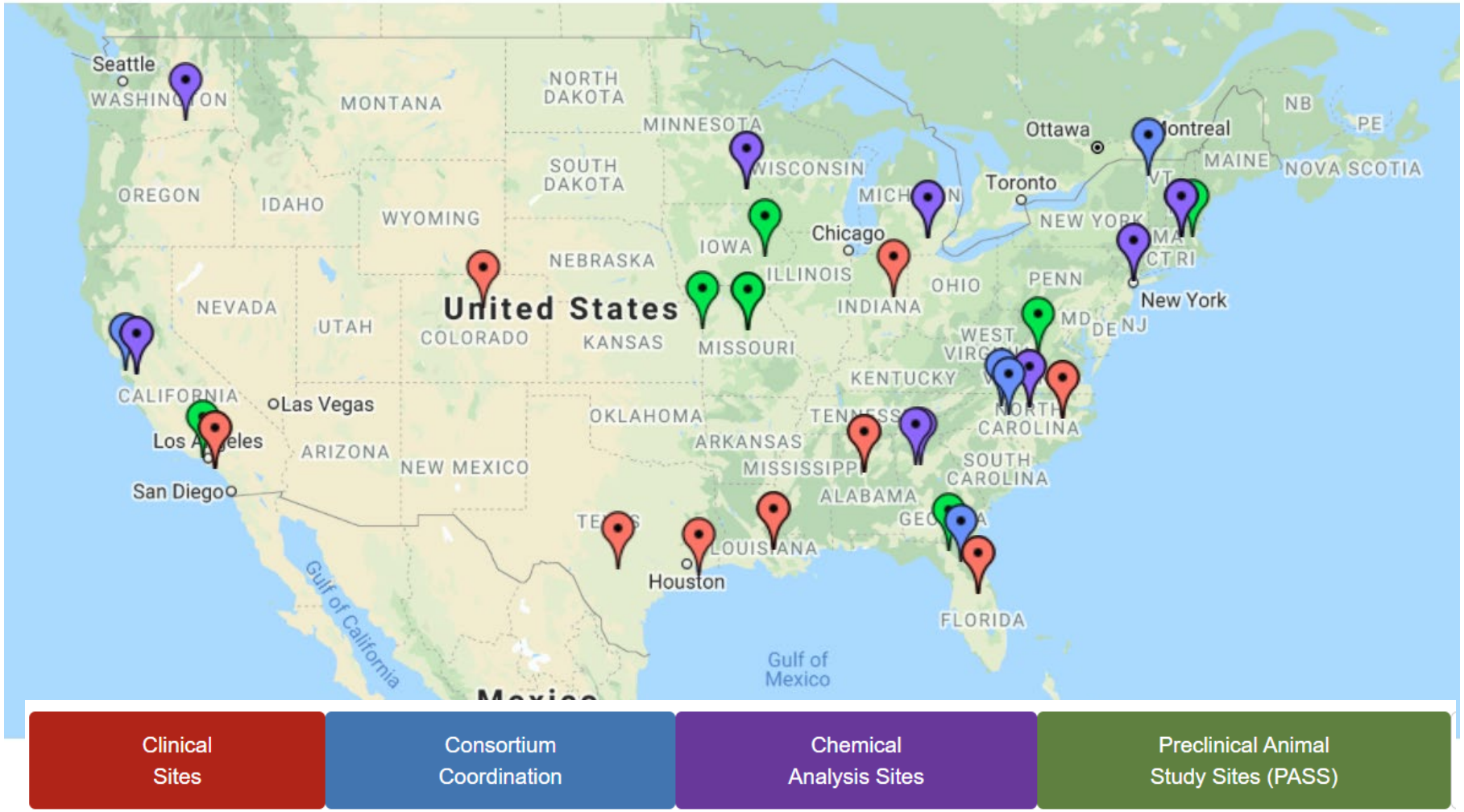
Regular exercisers

- What is the molecular profile of people who exercise regularly?
- What is the molecular profile of people before/after 12 wks of exercise training?
- Understanding the variability of the human response:
  - to endurance/strength training?
  - by age
  - by sex

- What is the molecular profile of low-active/highly-active children?

The MoTrPAC Consortium

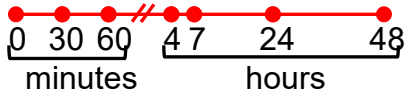
motrpac.org/aboutUs



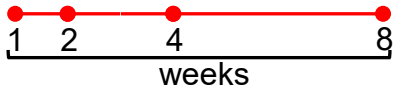
- 6 Pre-clinical animal study sites (PASS)
- 7 Clinical Centers (11 recruiting sites)
- 7 Chemical Analyses Sites (CAS)
  - Genes
  - Metabolites
  - Proteins
  - Lipids
  - Vesicles
- Bioinformatics Center (BIC)
- Coordinating Center/Data Monitoring QC/ Biorepository

Update on Animal Studies – May 2022

Acute Exercise
30 minutes, ~80% VO_2max

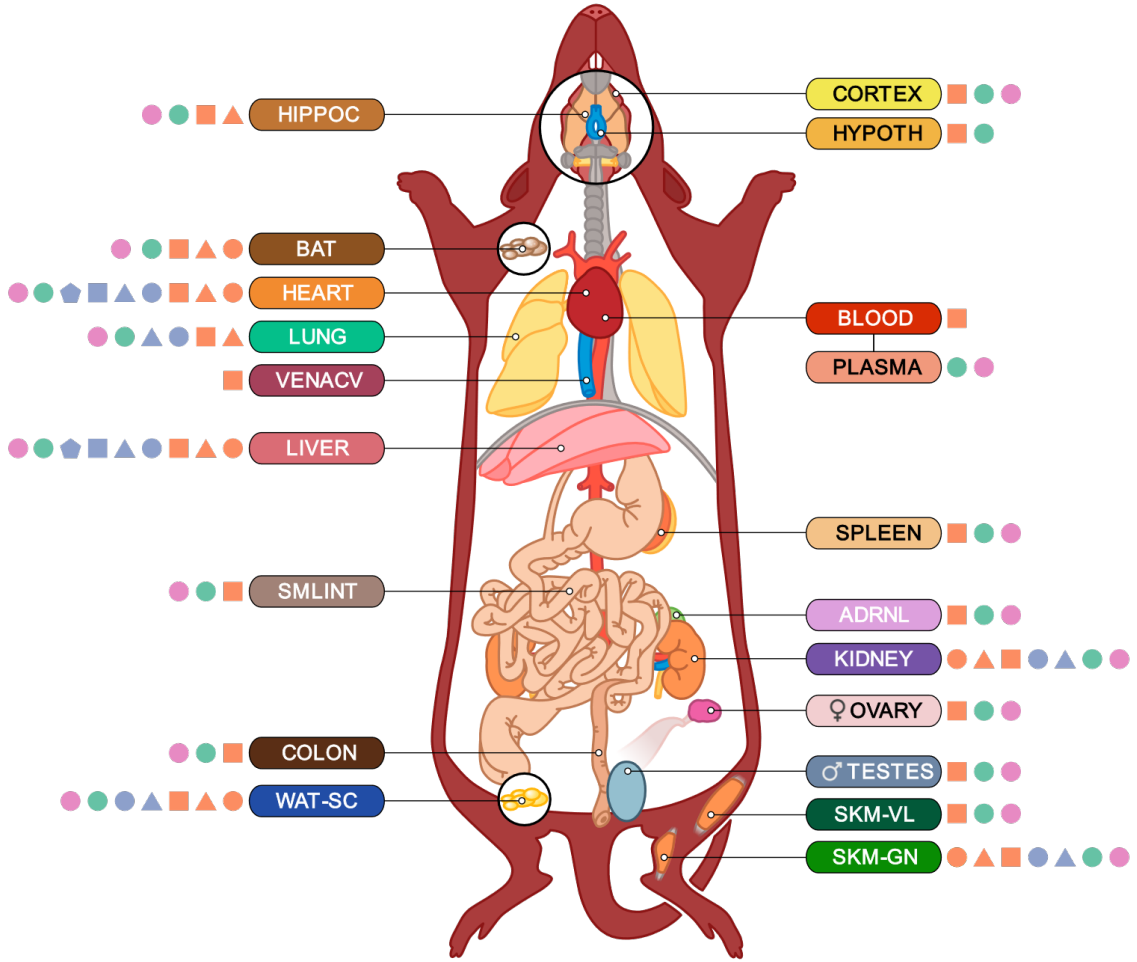


Chronic Progressive Training
~70% VO_2max



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

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)

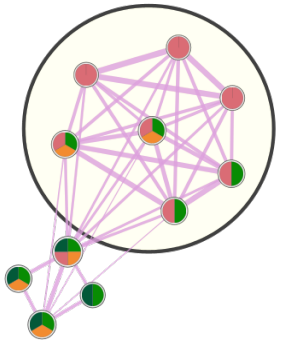
Cytokines

- Cytokine immunoassays

Preliminary findings from Animal Training Study

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

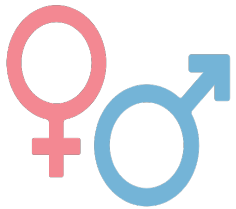
- >40,000 analytes are regulated over the training time course
- Substantial regulation at the transcript, protein, and post-translational modification levels



- 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

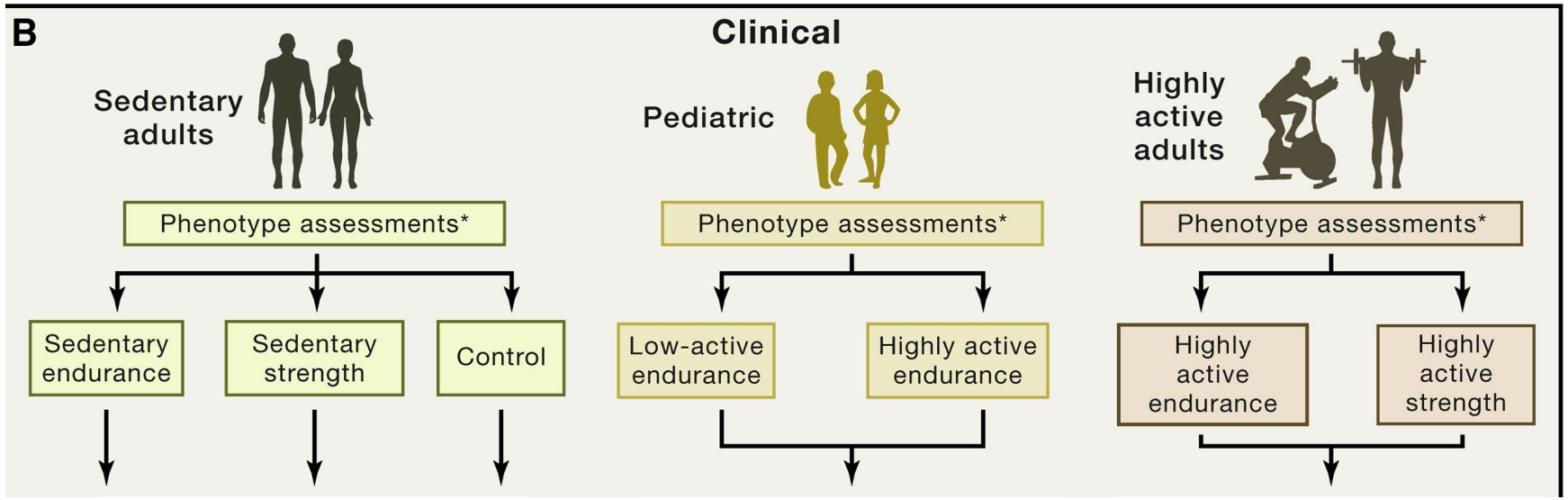


- Strong sex-specific response: Half of the multiomics clusters have different trajectories in males and females

Next steps: Animal Studies

- 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 are ongoing
- Data release planned in 2022

Update on Clinical Study – May 2022



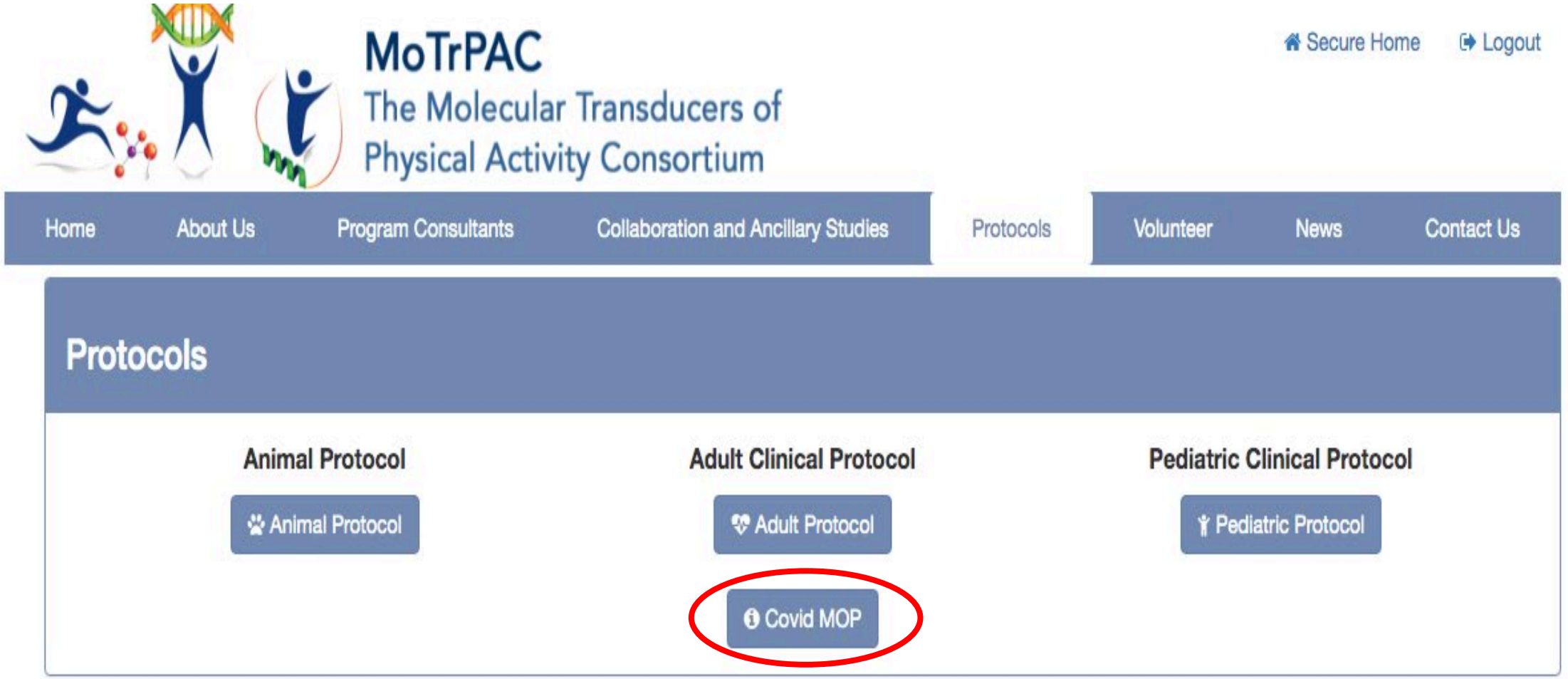
Recruitment for MoTrPAC clinical study began in 2019, and then was suspended by the pandemic: There is a pre-COVID cohort of participants

Analysis of these blood, muscle and adipose samples is underway.

Recruitment restarted following discussions with DSMB and IRB. As of May 2022, all clinical sites are recruiting, under new safety protocols

MoTrPAC and COVID-19

motrpac.org



Plan for multi-omics analyses of Human Samples

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

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

Leveraging MoTrPAC

- Lidocaine safety study
- Tracking free-living physical activity
- Effect of exercise on cellular composition of muscle and adipose (MoTrHisto)
- Mitochondrial response to exercise training (MoTrMito)
- Exercise effect on sleep and growth in children

Interactions with other research studies or programs

MoTrPAC Ancillary Studies Policy is at motrpac.org

Acknowledgements

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MoTrPAC Investigators

MoTrPAC Clinical Study Participants