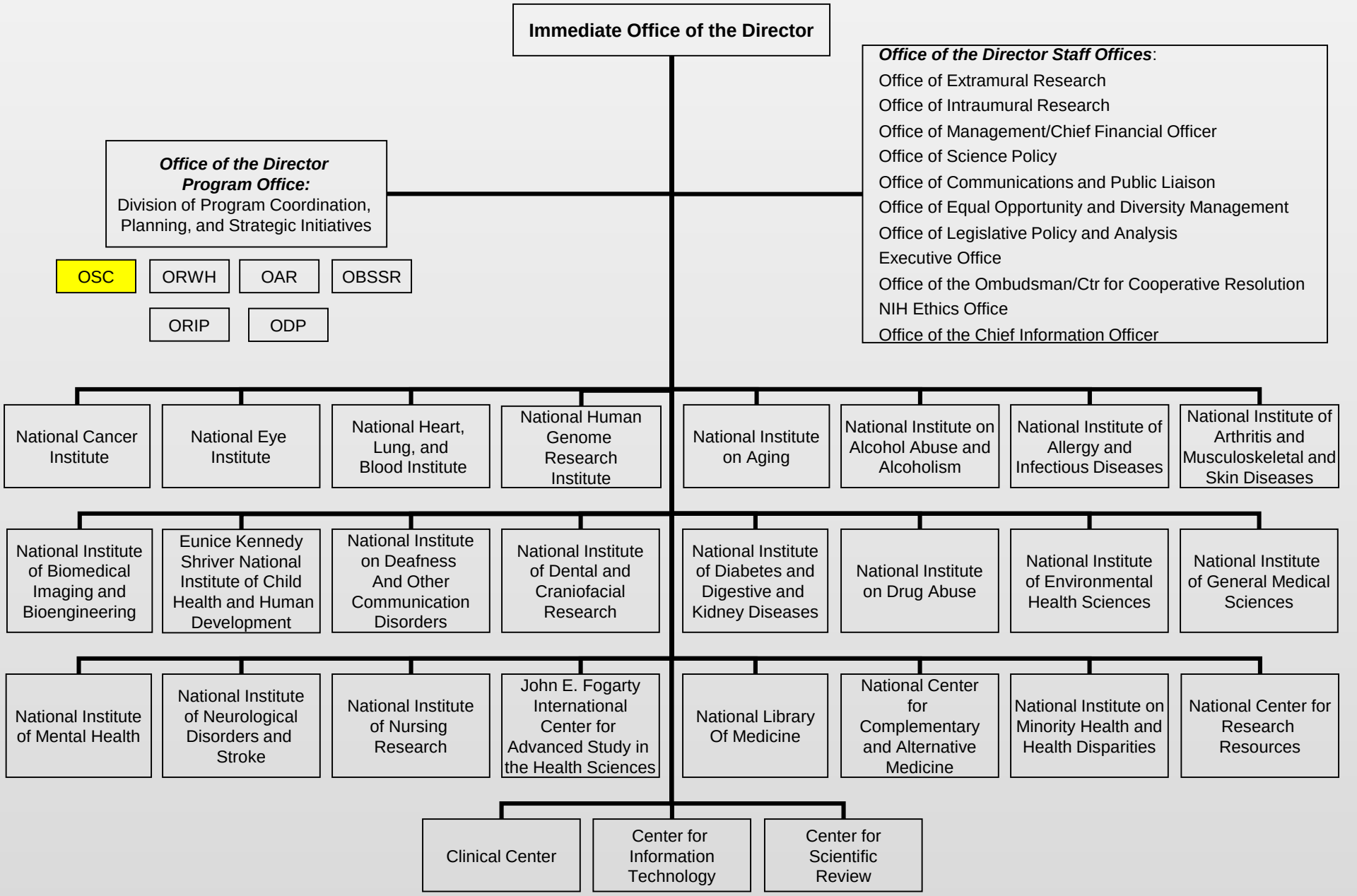
Molecular Transducers of Physical Activity Consortium (MoTrPAC)

Pre-application Webinar - October 22, 2015

2:00 PM	**Welcome, Introductions, and Overview of MoTrPAC**
2:30 PM	**Clinical Centers (RFA-RM-15-015)**
	Clinical Centers Q&A
2:50 PM	**Preclinical Animal Study Sites (RFA-RM-15-013)**
	Preclinical Animal Study Sites Q&A
3:10 PM	**Chemical Analysis Sites (RFA-RM-15-010 and RFA-RM-15-011)**
	Chemical Analysis Sites Q&A
3:30 PM	**Q&A, all MoTrPAC issues**
4:30 PM	**Adjourn**

The NIH Common Fund:
Planning for Transformation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Clinical Center
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Origins of the Common Fund

One Hundred Ninth Congress
of the
United States of America

AT THE SECOND SESSION

Begun and held at the City of Washington on Tuesday, the third day of January, two thousand and six

An Act

To amend title IV of the Public Health Service Act to revise and extend the authorities of the National Institutes of Health, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the "National Institutes of Health Reform Act of 2006".

TITLE I—NIH REFORM

2004: NIH Roadmap is launched

December 9, 2006: Congress unanimously passes a reauthorization bill affirming importance of NIH and its vital role in advancing biomedical research to improve the health of the Nation

Establishes the Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI) within Office of the Director and the NIH Common Fund to provide a dedicated source of funding to enable *trans*-NIH research

Criteria for Common Fund Programs

Transformative: Programs are expected to have **exceptionally high and broadly applicable impact**. They should be relevant to many diseases and many ICs. They should create entirely new approaches to research or clinical care, or establish new biological paradigms.

Catalytic, Short Term and Goal-driven: Programs must achieve - not just work toward - a goal. They have **deliverables** - data sets, tools, technologies, approaches, or fundamental principles of biology, etc – that can be achieved within **5-10 years**. If the deliverable is expected to have ongoing maintenance costs, a vision for transition and sustainment must be articulated.

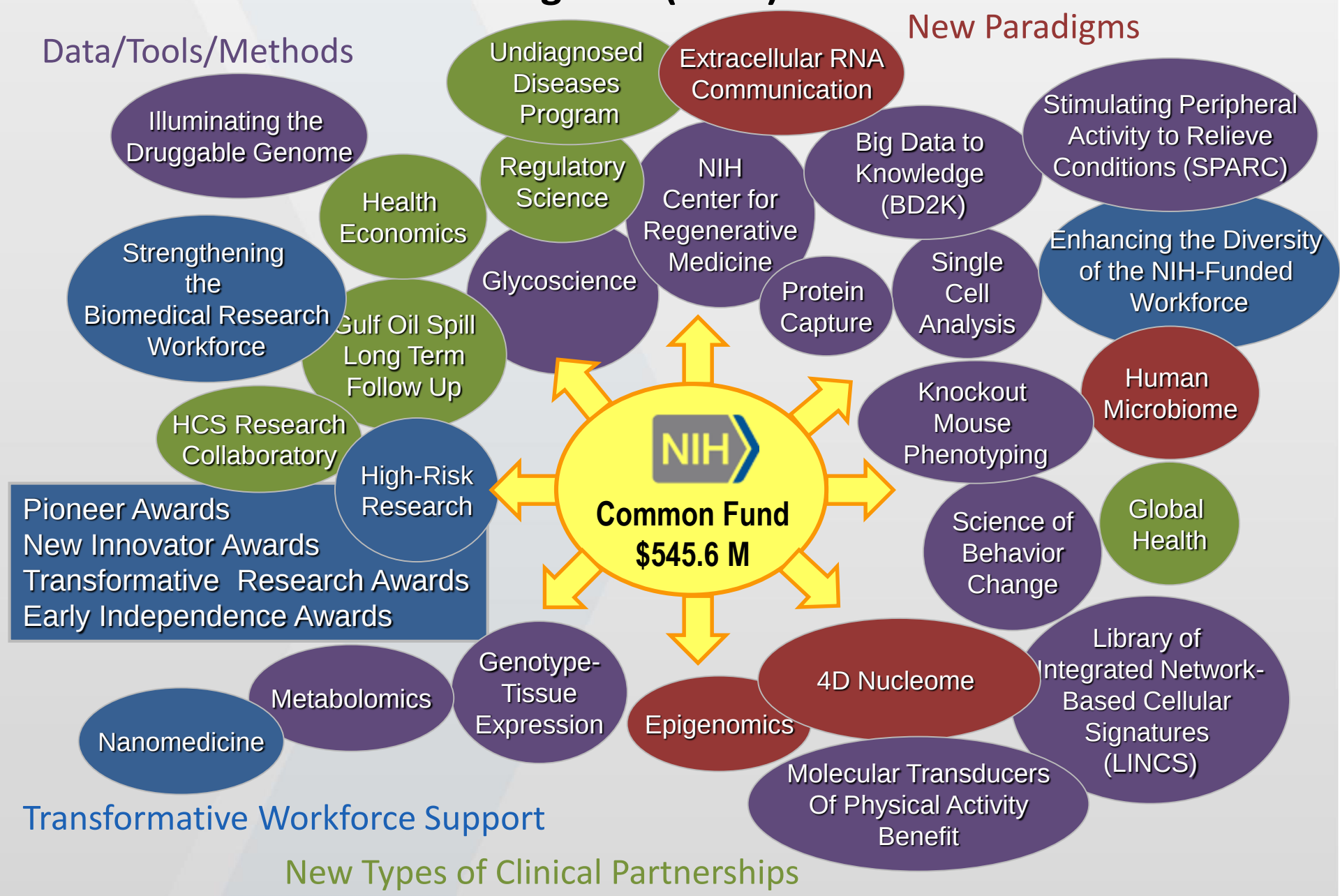
Synergistic /Enabling: Programs should be **value-added to the ICs**, with the output enabling the mission of many ICs.

Requires a High Level of Trans-NIH Coordination: CF programs should address complex issues that require trans-NIH teams, insights and perspectives to design and manage. There must be a **reason why strategic coordination is required**.

Novel: Programs should provide **new solutions to specific challenges**. If similar efforts exist, the CF program should be tightly coordinated to prevent duplication of effort. *Programs should not be something another entity would be likely to support.*

Designed to accomplish goals and deliverables within 5-10 years
Evaluation of program outputs/outcomes is essential

Current Common Fund Programs (FY15)



Why MoTrPAC is "Common Fund-able"

- Common Fund programs are expected to be **transformative** with exceptionally high and broadly applicable impact.
- MoTrPAC data should have **broad impact** by providing data about the molecular response to physical activity and relating it to positive impact to the extent possible
- The complexity of the problem and the program requires **coordination** across many disciplines and between people interested in many diseases/conditions/physiological systems
- MoTrPAC data should **enable** many future IC-supported projects through which data will be analyzed and function/mechanism of candidate transducers will be explored – It will be a significant **community resource**

Molecular Transducers of Physical Activity Consortium (MoTrPAC)

Goal: Assemble a comprehensive map of the molecular changes that occur in response to physical activity.

This map will

- Contain the many molecular signals that transmit the health effects of physical activity.
- Indicate how they are altered by variables such as age, sex, body composition, fitness level, and chronic exposure to exercise.

Product: A user-friendly public data resource that any researcher can access to develop hypotheses regarding the molecular mechanisms through which physical activity can improve or preserve health.

Molecular Transducers of Physical Activity Consortium (MoTrPAC)

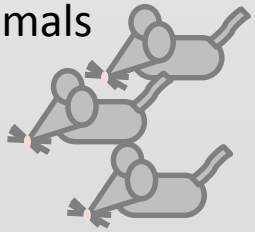
Program Overview

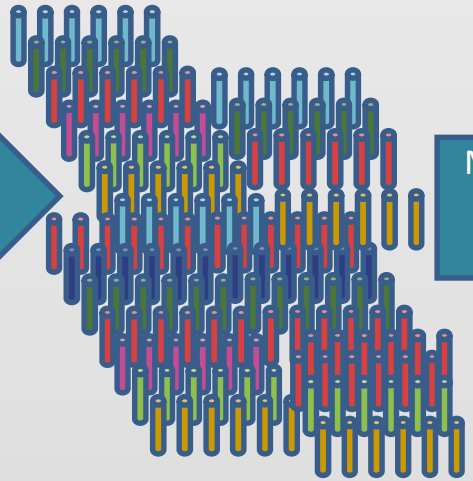
Human volunteers

Participant characteristics
Age, sex, fitness, response to training

Physical activity

Animals





Tissue Samples
Human blood, muscle, adipose
Animal heart, liver, lung, brain

Metabolomics,
transcriptomics,
genomics, etc.

Molecular Transducers of Physical Activity

Participant characteristics
Genes
Proteins
Peptides
Lipids
Sugars
Hormones
Epigenetics
mRNA
ncRNA

Molecular Transducers of Physical Activity Consortium (MoTrPAC)

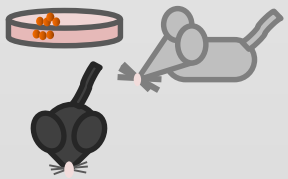
Program Overview (continued)

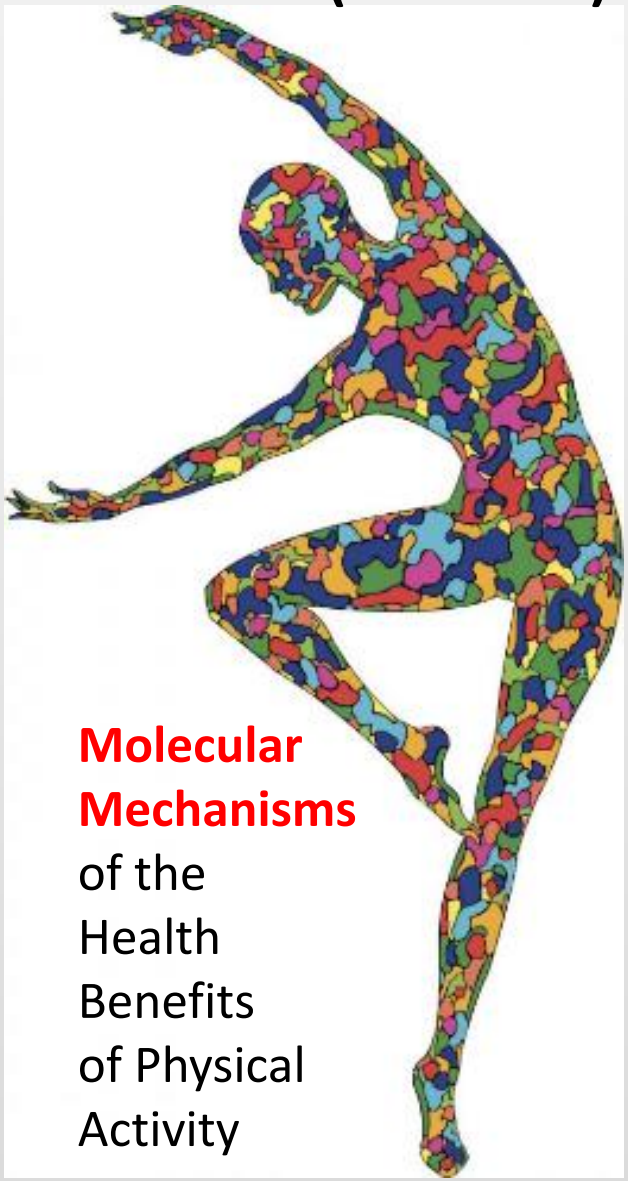
Molecular Transducers of Physical Activity

Participant characteristics
Genes
Proteins
Peptides
Lipids
Sugars
Hormones
Epigenetics
mRNA
ncRNA

Integrated Data Analysis

Mechanistic Studies (cells, animals)





Molecular Mechanisms of the Health Benefits of Physical Activity

MoTrPAC FOAs with total costs for entire 6-year program

Clinical Centers (U01)

6-7 awards, total costs: $43,000,000

Chemical Analysis Sites (U24)

2-4 Metabolomics and Proteomics awards, total costs: $55,000,000

1-2 Genomics, Epigenomics, and Transcriptomics awards, total costs: $31,000,000

Consortium Coordinating Center (U24)

1 award, total costs: $10,000,000

Bioinformatics Center (U24)

1 awards, total costs: $11,000,000

Preclinical Animal Study Sites (U01)

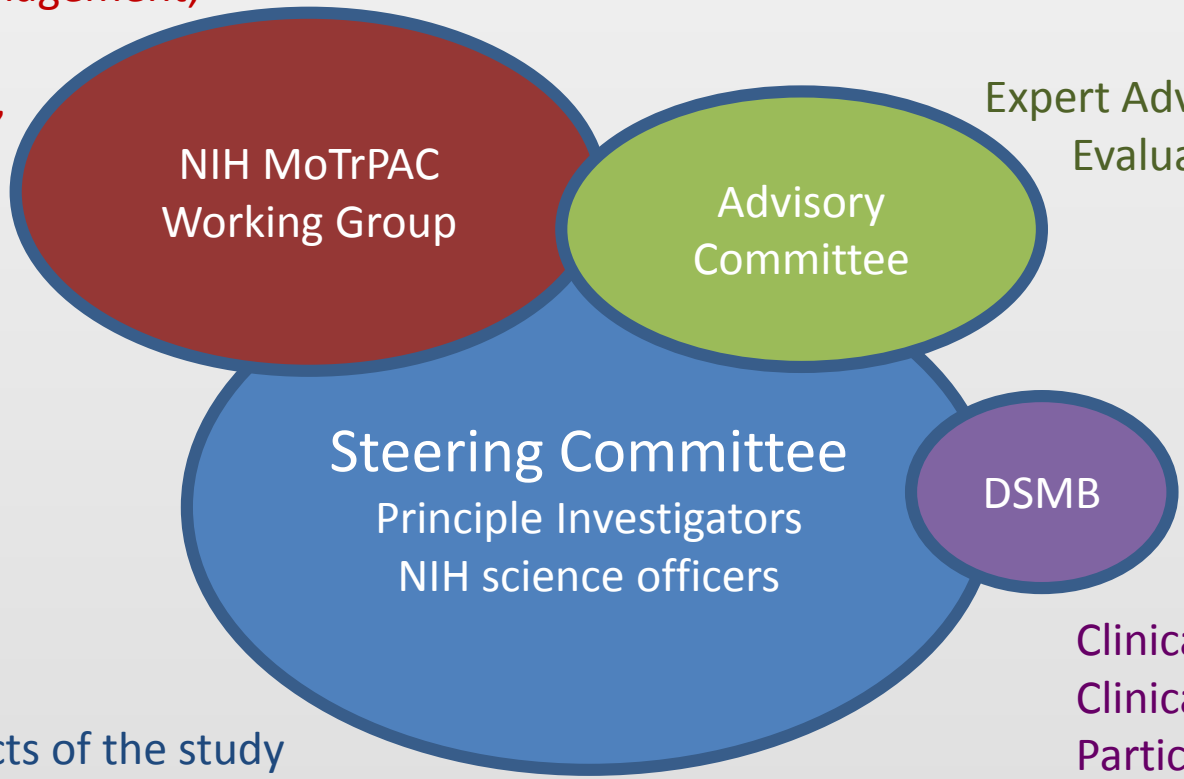
2-3 awards, total costs: $7,000,000

Second set of Preclinical Animal Study Sites (U01)

6-7 four-year awards

MoTrPAC Consortium

Award management,
Oversight,
Evaluation,
Policy



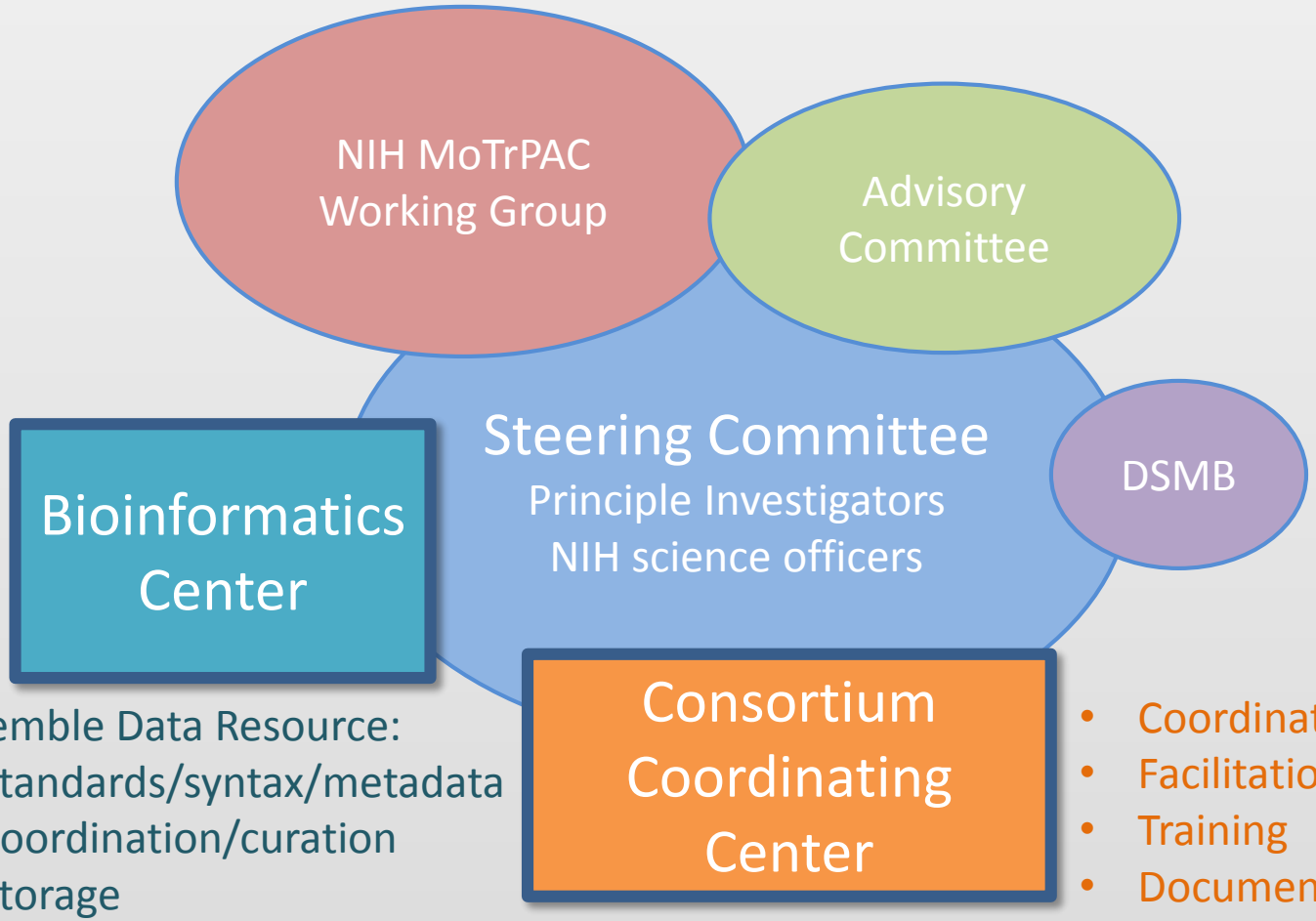
Expert Advice,
Evaluation

Clinical study oversight,
Clinical data quality,
Participant safety

All aspects of the study

- planning
- protocols
- execution
- data
- publication

MoTrPAC Consortium



Assemble Data Resource:

- standards/syntax/metadata
- coordination/curation
- storage
- tools
- analysis

- Coordination
- Facilitation
- Training
- Document management
- Tissue storage/movement
- Opportunity Funds program

Consortium Coordinating Center (RFA-RM-15-014)
For More Information

- **NIH Guide for Grants and Contracts:** http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-15-014.html
- **Scientific/Research Contact:** Dr. Joan A. McGowan, joan_mcgowan@nih.gov
- **Peer Review Contact:** Dr. Richard Ingraham, richard.ingraham@nih.gov
- **Financial/Grants Management Contact:** Ms. Katie Joffee, joffeek@mail.nih.gov
- **NIH Common Fund MoTrPAC website:** https://commonfund.nih.gov/MolecularTransducers

Bioinformatics Center (RFA-RM-15-012)
For More Information

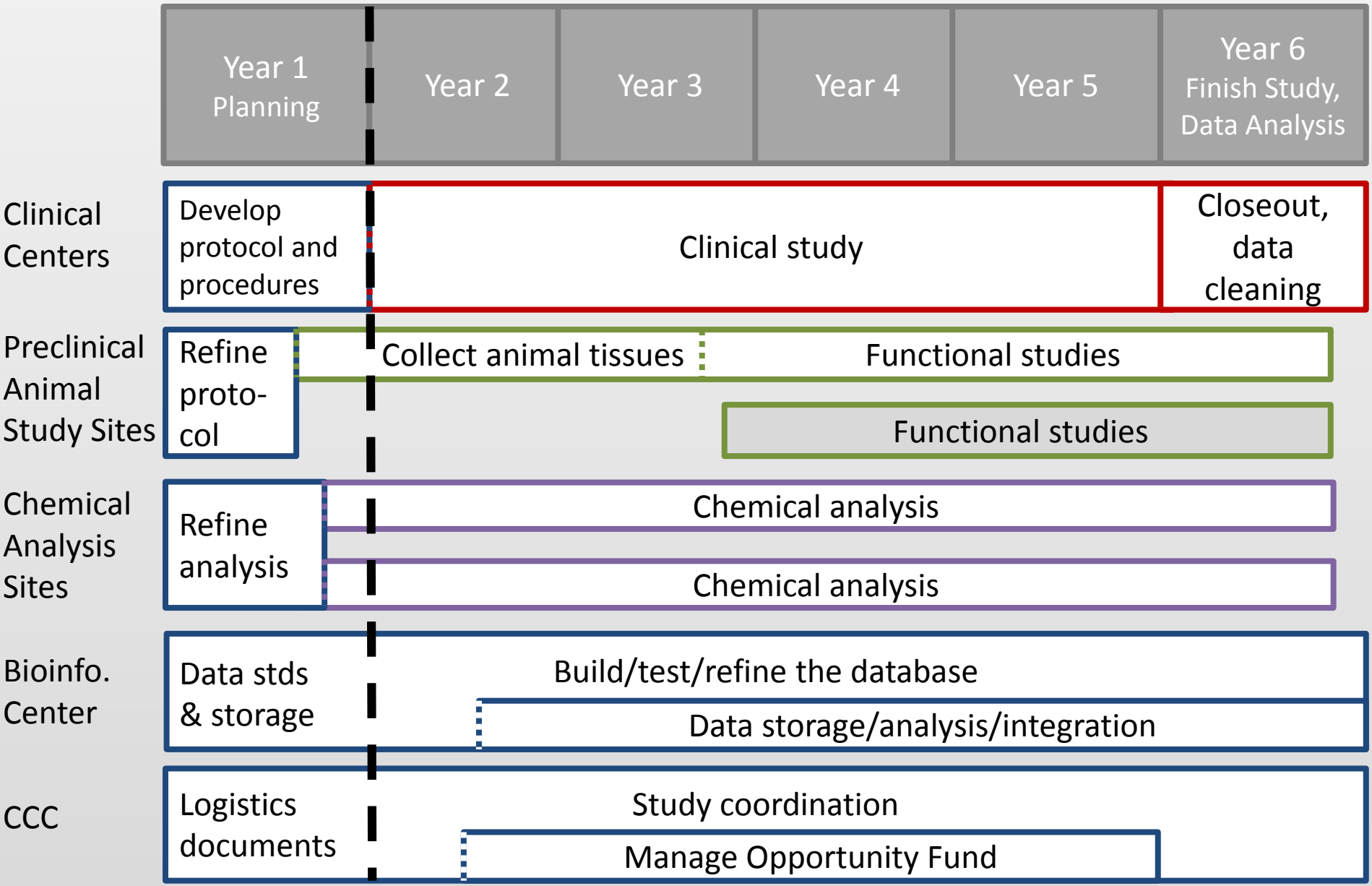
- **NIH Guide for Grants and Contracts:** http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-15-012.html
- **Scientific/Research Contact:** Dr. Vinay M. Pai, vinay.pai@nih.gov
- **Peer Review Contact:** Dr. Richard Ingraham, richard.ingraham@nih.gov
- **Financial/Grants Management Contact:** Ms. Ruthann Rand, randrudy@mail.nih.gov
- **NIH Common Fund MoTrPAC website:** https://commonfund.nih.gov/MolecularTransducers

Responsibilities

All MoTrPAC members will:

- Work together as a consortium
- Help design the overall study
- Use common protocols for clinical and animal physical activity studies
- Follow consortium plans for tissue analysis
- Submit tissues and data to the Consortium Coordinating Center and the Bioinformatics Center
- Participate in data analysis
- Inform mechanistic studies

General Timeline



Clinical Centers (RFA-RM-15-015)
Purpose of Clinical Centers RFA

- **To invite applications for Clinical Centers to conduct multi-center clinical study as part of MoTrPAC, which will:**
  - Enroll and expose participants to physical activity (PA)
  - Collect biospecimens that will facilitate thorough assessment of molecular / biological **responses to physical activity** in line with goals of this project
    - Biospecimen analyses: Extensive assessment using high-throughput technologies at separately funded Chemical Analysis Sites
    - Genomics, transcriptomics, epigenomics, metabolomics, proteomics

Clinical Centers (RFA-RM-15-015)

Overview

- **Clinical Centers are central to overall success of project**
- **Clinical cohort: ~2700 to ~3000 adults and children**
  - Healthy and able to engage in physical activity programs
  - Participants will include: both sexes and wide range of ages, races/ethnicities, and other relevant characteristics
  - Each center will characterize all participants at baseline with respect to age, sex, and objective physiologic, morphometric, and metabolic fitness measures
    - Goals: To fully describe all participants at baseline, to adequately capture covariates that will be used in statistical analyses, to relate the physiologic fitness measures to molecular transducers, and to relate these physiologic measures to existing literature

Clinical Centers (RFA-RM-15-015)

Design Overview

Investigators should propose study design within the following framework

- **Tissue biospecimens will be collected before and at several timepoints after a bout of acute exercise**
- **Acute exercise/biospecimen collection and participant characterization will occur before and after an endurance or resistance exercise training program (e.g., 12 weeks)**
- **Study Participants**
  - Sedentary, randomized to:
    - Non-exercised control – no exercise program
    - Endurance exercise (e.g., 12-week)
    - Resistance exercise (e.g., 12-week)
  - Highly fit, athletic individuals who will not be randomized to exercise training
    - Small comparator group

Clinical Centers (RFA-RM-15-015)

Adult Clinical Centers

- **Clinical Centers (5 or 6): expected to enroll 2400 to 2700 healthy participants ≥18 years of age**
  - Each Clinical Center: capacity to enroll 450 participants
  - Must have demonstrated expertise in:
    - Exposing adults to acute bout of exercise (sufficient to produce changes in purported molecular transducers)
    - Performing objective physiologic, morphometric, and metabolic fitness assessments
    - Enrolling and retaining participants in ~12-week physical activity training programs
    - Collecting biospecimens at baseline and various appropriate time points after single bout of exercise (at start and end of PA program)
      - Blood, skeletal muscle tissue, subcutaneous adipose tissue

Clinical Centers (RFA-RM-15-015)

Children / Adolescent Clinical Center

- **One Clinical Center: expected to enroll ~300 healthy children / adolescents 12 to 18 years of age**
  - Capacity to enroll 300 children / adolescents at various stages of development
  - Participants will be exposed to single acute bout of physical activity → produce changes in purported molecular transducers
    - With appropriate justification, applicants may also propose a short-term (~12-week) exercise training program in sub-sample to assess molecular transducers
  - **Biospecimens**: at baseline and various time points after single bout of exercise (if program proposed, at start and end)
    - Blood required

Clinical Centers (RFA-RM-15-015)

Justification

- **Must specify and provide justification:**
  - Relevant sample size(s)
    - Comparator groups should be smaller in number than training groups (adults)
  - Eligibility criteria
  - Type, intensity, duration of all physical activity exposure(s), including training program
  - Appropriate physiologic, morphometric, and metabolic indicators of fitness
  - Other health-related fitness evaluations
- **May propose to collect additional types of biospecimens:**
  - Specify and justify types of biospecimens and time points for collection
- **Must exhibit feasibility and track record of research team in conducting physical activity exposures**

Final clinical study design and sample size will be developed by Consortium during the study design and planning phase

Clinical Centers (RFA-RM-15-015)
Additional Expectations

- **All Clinical Centers are expected to agree to collaborate with other members of the Consortium**
  - Each Clinical Center will conduct randomized clinical study using common protocol (determined by Steering Committee)
- **Applicants must be prepared to adapt their protocols, sample size, and budgets to accommodate final common clinical study protocol**
- **Clinical Centers are expected to participate and contribute to analyses of data and preparation of publications**

Clinical Centers (RFA-RM-15-015)

Study Phases

- **Phase 1* (Planning phase, ~12 months):**
  - Determine final sample sizes for physical activity and comparator groups
  - Develop common protocol, Manual of Operations, DSMP, other study materials
  - Develop study milestones and various procedures/policies
  - Staff training in common procedures will also occur during this period

**Must support key personnel (in addition to PI) who are critical to fulfilling Phase I objectives*

- **Phase 2 (Recruitment and testing phase, 48 months):**
  - Implement protocol with designated sample size: Collect biospecimens, physiologic assessment data
  - Provide study data to Consortium Coordination Center
- **Phase 3 (Close-out phase, 12 months):**
  - Complete data entry and data cleaning; conduct close-out activities
  - Ship biospecimens for analyses
  - Manuscript writing and dissemination of results

Clinical Centers (RFA-RM-15-015)

Funds Available (Direct Costs)

- **Year 1: $100,000 DC – per clinical center**
- **Adult Centers, years 2–5: $1,000,000 DC (each)**
  - **Year 6: $400,000 DC – per clinical center**
- **Pediatric / adolescent center, years 2–5: $600,000 DC (one center)**
  - **Year 6: $250,000 DC**

Clinical Centers (RFA-RM-15-015)

For More Information

- **To ask a question:** Use the "chat" function in the webinar

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- **NIH Guide for Grants and Contracts:** http://grants.nih.gov/grants/guide/rfa-files/RFA-RM-15-015.html
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Preclinical Animal Study Sites (RFA-RM-15-013)

Overview

This FOA (2016)

- The PASS will serve to
  - Support the collection of tissue samples from one species of exercised animals that complement the data and tissue collection in the human clinical protocol (Phase 1)
  - Conduct initial detailed mechanistic studies to explore the functions, sources, and target tissues of molecules that transduce the effects of physical activity (Phase 2)
- Available funds
  - $67,500 for FY2016, and
  - Approximately $7,000,000 total cost for fiscal years 2017-2021

Second FOA; Additional Phase 2 experiments, beginning in ~2018

- NIH anticipates releasing a second FOA for 5-7 more sites that will conduct additional mechanistic studies.
- ***The second FOA is outside the scope of this webinar.***

Preclinical Animal Study Sites (RFA-RM-15-013)
Investigators

Team and Institutional Environment

Expertise in preclinical exercise modeling and all proposed experimental approaches (Phase 1 and Phase 2 studies)

- Describe any previous experience in multi-center collaborative projects.
- Describe the team's decision-making process.

Extended PI role

- Work with the MoTrPAC Steering Committee to harmonize the preclinical research plan with the full range of the Consortium's efforts.
- Coordinate with Analysis Sites to determine the optimum methods for harvesting, storing, and shipping tissue samples.
- Work with other PASS to conduct Phase 1 physical activity interventions and harvest tissues for analysis, using the animal model chosen by the Steering Committee.

Preclinical Animal Study Sites (RFA-RM-15-013)
Research Strategy

Phase 1 Research Strategy

- Exercise protocol(s) for animals that will parallel human study (RFA-RM-15-015)
- Rationale for the species, strain, number of animals, tissue samples
- Strategy for tissue analysis at the Chemical Analysis Sites (RFA-RM-15-010 and RFA-RM-15-011)
- Timeline: Exercising animals and collecting tissue by the end of year 1

Phase 2 Research Strategy

- Considerations when selecting molecules to be explored
- Plans for animal/cell-based assays
  - Identify source and target tissues of novel signals
  - Identify pathways and cellular processes involving molecular transducers
  - Identify functions of molecular transducers (may need multiple strategies, need not be comprehensive)
- Timeline: Should begin no later than the end of year 3

Preclinical Animal Study Sites (RFA-RM-15-013)
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- **Scientific/Research Contact:** Dr. John P. Williams, williamsj6@mail.nih.gov
- **Peer Review Contact:** Dr. Richard Ingraham, richard.ingraham@nih.gov
- **Financial/Grants Management Contact:** Ms. Katie Ellis, kellis@mail.nih.gov
- **NIH Common Fund MoTrPAC website:** https://commonfund.nih.gov/MolecularTransducers

Molecular Transducers of Physical Activity Genomics, Epigenomics, and Transcriptomics Chemical Analysis Sites (RFA-RM-15-010)

- **Nucleic acid sequencing and other high throughput technologies**
  - DNA sequencing
  - Transcriptional profiling of coding and non-coding RNA
  - Epigenomic analysis
- **One or two sites**
- **Available funds:**
  - $150,000 for FY2016
  - Approximately $31,000,000 for fiscal years 2017-2021

Examples:

- Whole genome sequencing
- Transcriptional and epigenetic changes in relevant tissues
- RNA and DNA analysis of exosomes

Molecular Transducers of Physical Activity Metabolomics and Proteomics Chemical Analysis Sites (RFA-RM-15-011)

- **Metabolomics and/or proteomics approaches**
- **Two to four sites**
- **Available funds:**
  - $150,000 for FY2016
  - Approximately $54,500,000 for fiscal years 2017-2021

Examples:

- Targeted and untargeted metabolomics of plasma & tissues
- Global proteomics analysis
- Targeted plasma proteomics including PTMs
- Protein and metabolite analysis of exosomes

Chemical Analysis Sites (RFA-RM-15-010 and RFA-RM-15-011)
Expectations for Successful Applicants

- **Work with the Steering Committee and other chemical sites to**
  - develop common assay protocols
  - devise plans for the analysis of tissue samples from clinical and animal sites
- **Perform qualitative and/or quantitative assays, generate datasets and perform initial analysis of molecular fingerprints**
- **Track all data and metadata throughout the analysis**
  - from sample receipt
  - to data deposit in an appropriate database
- **Provide all data in a standard format in collaboration with**
  - the Bioinformatics Center and
  - other Chemical Analysis sites

Chemical Analysis Sites (RFA-RM-15-010 and RFA-RM-15-011)

Applicants must propose a Tissue Sample Analysis Plan

For budgeting purposes, assume:

- **Human Participants: ~3000 healthy people**
- **Acute exercise bouts with tissue collection: ~5000**
- **Per acute exercise bout: ~5 blood and 2-3 other tissues**

  Total: ~25,000 human blood,

  ~7500 skeletal muscle, and

  ~7500 adipose tissue samples

- **From exercised animal models:**

  ~5,000 to 10,000 tissue samples

  (e.g., blood, muscle, heart, brain, kidney, liver, white and brown fat)

Chemical Analysis Sites (RFA-RM-15-010 and RFA-RM-15-011)

Components: Project Structure

Administrative Element:

- Led by the PD/PI
- Responsible for the overall management for the works supported and for coordination with the CCC and other MoTrPAC sites.
- A program coordinator assists the PI for overseeing day-to-day operations and manage budgets, travel, and communication with the Consortium.

Bioinformatics Element:

- Expertise to assist in organization, curation and assignment of spectral features to specific molecules, and preliminary analysis of the data from the Chemical Analysis Element(s).
- Work closely with similar staff in the other Chemical Analysis Sites as well as the Bioinformatics Center to assemble, integrate, and analyze data

Chemical Analysis Element(s):

- One or more Chemical Analysis Elements for sample analysis
- Provide expertise in one or more high-throughput discovery chemical analysis approaches.
- Assist the PD/PI in the planning process, the development of standard operating procedures for sample collection, processing, choice of analyses, etc.
- Provide high quality, reproducible analysis of tissue samples collected at the Clinical Centers and PASS

Chemical Analysis Sites (RFA-RM-15-010 and RFA-RM-15-011)

Elements of the application: *Research Strategy section is limited to 30 pages*

- **Description of Project Components**
- **Detailed Tissue Analysis Plan**
  - Methodologies
  - Approaches
- **Preliminary data**
  - Expertise of the staff
  - Resources available in terms of equipment and infrastructure are appropriate for the project.
  - Feasibility of proposed assays, as well as the quality, reliability, and reproducibility of resulting data.
- **Letters of Support with institutional commitment**
- **Resource Sharing Plan:**
  - Resource Sharing Plans
  - Software sharing plans
- **Plan for communication and collaboration with the CCC, Bioinformatics Center, and other Consortium Sites**

Chemical Analysis Sites (RFA-RM-15-010 and RFA-RM-15-011)
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- **Scientific/Research Contact:** Dr. Padma Maruvada, padma.maruvada@nih.gov
- **Peer Review Contact:** Dr. Richard Ingraham, richard.ingraham@nih.gov
- **Financial/Grants Management Contact:** Ms. Sharon Bourque, bourques@extra.niddk.nih.gov
- **NIH Common Fund MoTrPAC website:** https://commonfund.nih.gov/MolecularTransducers

Molecular Transducers of Physical Activity Consortium (MoTrPAC)
General Information

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- **If the webinar ends before we get to your question**
  - Responses will be posted in an FAQ section at https://commonfund.nih.gov/MolecularTransducer
  - Email PhysActMechanisms@mail.nih.gov