This webinar is being recorded.

Human Virome Program Technical Webinar

October 16, 2023

commonfund.nih.gov/humanvirome

HumanVirome@od.nih.gov

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

This webinar is being recorded.

Format

- Brief presentations followed by Q&A.
- Submit questions in the “Q&A” box.
- Use chat for technical issues.
- Scientific or situationally specific questions will not be discussed (email us).
- For additional questions, contact us at HumanVirome@od.nih.gov.
- Webinar recording & slides will be posted on website at commonfund.nih.gov/humanvirome.
- For more guidance, see FAQs on website.

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Panelists

Common Fund

- David Bollweg (OD)
- Becky Miller (OD)
- Sonynka Ngosso (OD)

Characterization Centers (RFA-RM-23-019)

- Stacy Carrington-Lawrence (NIA)
- Roberto Flores-Munguia (NIA)
- Katherine Kim (NIA)

Tools & Methods (RFA-RM-23-018)

- Amanda Melillo (NIDCR)

Functional Characterization (RFA-RM-23-017)

- Hye-Sook Kim (NCCIH)

Coordinating Center (RFA-RM-23-016)

- Emmanuel Mongodin (NHLBI)
- Shimian Zou (NHLBI)

The Common Fund Moves the NIH Mission Forward – Faster

Supporting bold scientific programs that **catalyze discovery** across all biomedical and behavioral research

Advances areas of biomedical and behavioral research important to the missions of multiple NIH Institutes and Centers

Spurs subsequent biomedical advances that otherwise would not be possible without an initial strategic investment

Features of Common Fund Programs and How They Catalyze Biomedical Discovery

Making substantial investments in time-limited, goal-driven programs that significantly change the trajectory of biomedical research.

Accelerate emerging science

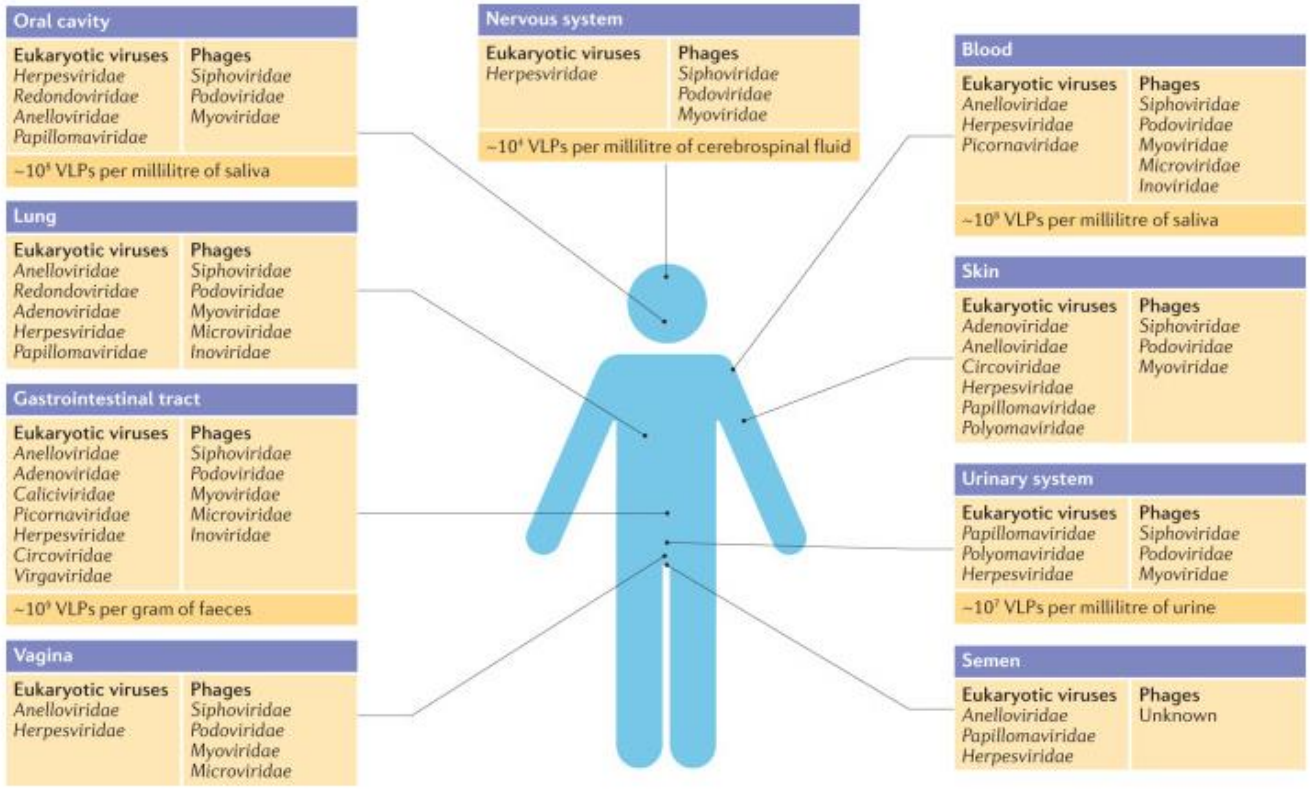
Remove research roadblocks

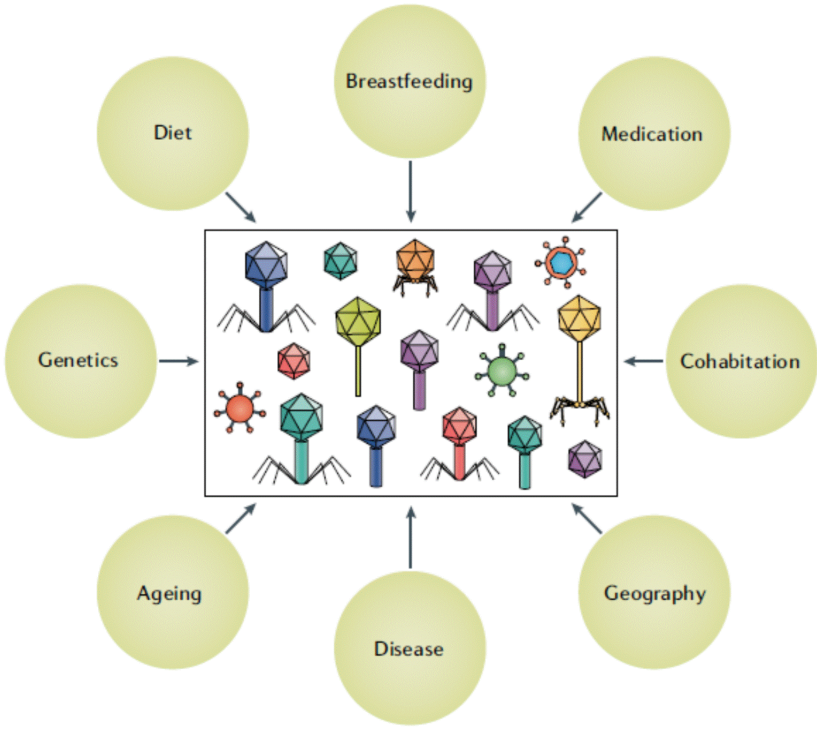
Enhance the research workforce

Support high-risk, high-reward science

Background & Rationale

- The human virome is large and diverse with >10^{13} particles per person
- The commensal virome is largely understudied and its interactions with the human body and long-term impacts on health and disease are unknown





Liang, G., Bushman, F.D. *Nat Rev Microbiol* **19,** 514–527 (2021)

Human Virome Program

Goal: To characterize the human virome and define its role in health and disease

Initiatives:

1. Characterize the human virome in longitudinal, demographically diverse cohorts across the lifespan
2. Develop tools, models, and methods to interrogate and annotate the human virome
3. Study interactions between the virome and the human host and other components of the human microbiome
4. Create a coordination center that will serve as the program organizational hub and that will construct a data portal and human virome reference data set

Consortium Building

- Extensive collaboration required
- Cooperative agreements = substantial NIH involvement
- Overseen by Steering Committee made up of all initiative investigators and NIH staff
- Mandatory meeting attendance & participation
  - Kickoff meeting held three months after awards made
- Abide by developed policies & guidelines
  - Standards, resources, methods, & data
- Deposit developed data, resources, & tools to data portal
- Collaboration projects required
- Plan for Enhancing Diverse Perspectives (PEDP) required

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RFA-RM-23-019 Human Virome Characterization Centers (U54 Clinical Trial Not Allowed)

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

Human Virome Characterization Centers (HVCC)

Goal:

Define the human virome and its dynamics, utilizing longitudinal, diverse human cohorts, across the lifespan by sequencing the viruses that comprise the human virome and provide an accurate estimate of its richness and complexity.

Human Virome Characterization Centers (HVCC)

VCCs Responsibilities

- Identify eukaryotic and prokaryotic viral composition within diverse human populations, across age, ethnicity, sex/gender, and geographic location in people **without evidence of overt disease**.

- Efficiently study the human virome across tissues by planning for the collection and use of biospecimens from at least two anatomical priority sites.
  - Priority sites: blood; respiratory tract; gastrointestinal and urogenital tracts (including urine and stool); oral cavity; central nervous system (sampling cerebrospinal fluid); and skin (including hair follicles). Other biospecimens of interest include tears and breast milk.

Human Virome Characterization Centers (HVCC)

VCCs Responsibilities (Cont.)

- Collect, process, and analyze the virome and human fractions of each sample and determine the relationships between the virome and other components of the host.
- Categorize virus taxonomy (eukaryotic and/or prokaryotic/bacteriophage) and characterize newly identified viruses.
- Determine factors that influence virome composition and its host dynamics.
- Utilize an adequate number of samples to ensure statistical power for hypothesis testing.

Human Virome Characterization Centers (HVCC)

Organization: This NOFO uses the multi-component U54 mechanism.

Each VCC will include five cores:

- Administrative
- Biospecimen Collection
- Biospecimen Analysis
- Data Analysis and Submission
- Ethical, Legal, and Social Implications (ELSI)

Human Virome Characterization Centers (HVCC)

Administrative Core (AC)

- Led by the contact PD/PI of the VCC

- Leadership and decision-making activities of the Center
  - Develop harmonious Standard Operating Practices.
  - Develop metrics for data generation and metadata standards
  - Participate in cross-site studies
  - Engage in cross-training and guide development of data analysis and visualization tools

Other responsibilities include coordinating various components of the VCC, coordination with other VCCs, and facilitating communication and coordination with the HVP CODCC.

Human Virome Characterization Centers (HVCC)

Biospecimen Collection Core (BCC)

Objective: collect and process samples from existing cohorts to be used in isolating and characterizing the human virome according to the standards established by the HVP Consortium, and the Steering Committee of the CODCC.

Biospecimens must comply with the following:

- Sufficient quality along with extensive metadata from individuals with diversity in gender, race, socio-economic status, geography, and other relevant diversity parameters.
- Represent the human lifespan from cohorts with established age ranges (birth-5, 6-12, 13-25, 26-60, 61 and above).
- Absence of overt disease or to be of a certain health status
- Preference will be given to appropriate specimens from longitudinal cohort samples and phenotypic data.

The BCC should develop specific, quantitative annual milestones for collecting, processing, annotating, preserving, and classifying biospecimens.

Human Virome Characterization Centers (HVCC)

Biospecimen Analysis Core (BAC)

Objective: use human biospecimens to identify and provide ***in-depth characterization*** of eukaryotic and prokaryotic viruses (replicating and integrated), viral particles, proviruses, and viral proteins, and to characterize viruses that will contribute to building the human virome database.

Responsibilities:

- Generate high resolution, high content, high-throughput biomolecular data to ***comprehensively*** discover viruses contained within human tissues and biospecimens.
- Establishing and optimizing SOPs for the collection of relevant metadata, including validation and benchmarking of assays, and generating high quality data using multiple assays with metrics for data quality control, reproducibility, and virome variation.
- Work closely with the Data Analysis & Submission Core and CODCC.

Human Virome Characterization Centers (HVCC)

Data Analysis & Submission Core (DASC)

Objective: construct the human virome database produced by the VCC and making it available through publicly-available data repositories.

Responsibilities:

- Data annotation, curation, analysis, and submission to public repositories.
- Building datasets for public repositories including characteristics of the identified viruses, sample preparation, analyses, identification and annotation of cell types and extracellular compartment and demographics of study participants.
- Use of existing software packages and analysis methods (deep analytical capabilities such deep learning, ML) to facilitate data analysis and enhance scientific rigor, reproducibility, and usability.
- Develop and implement Consortium-wide open data and metadata standards, data quality metrics, common data elements, integration of imaging and omics data, and analytical tools for annotation.
- Cross-validation of assays within and across VCCs and interpretation of data generated.
- Design and conduct at least one preliminary study in response to RFA-RM-23-017 to further validate functional characteristics of identified viruses.

Human Virome Characterization Centers (HVCC)

Ethical, Legal, and Social Implications (ELSI) Core

Objective: protect participants, investigators, and NIH staff in matters of privacy, safety, and legality by providing guidance on ELSI and policy issues.

The ELSI core will work closely with the BAC and the DASC on key issues:

- Filtering "human contamination" (i.e., uniquely identifiable genomic sequences belonging to sample donors from processed samples).
- Keeping up to date on technological advances that would make it possible for publicly available data to be traced back to enrolled participants.
- Perform research on potential risks to people, including the potential uses of data and the application of the Genetic Information Nondiscrimination Act (GINA) to HVP data.
- Assist the DASC in the return of results to participants.

Human Virome Characterization Centers (HVCC)

Budget

- NIH Common Fund ***intends to commit*** approx. $20M in FY2024 and $20M in FY2025-2028 for RFA-RM-23-019
- 4-5 awards are anticipated
- Set aside $250,000 in Total funding in project period years 3, 4, and 5 to support multiple collaborative pilot projects **($50,000/year for up to 2 years**).
- Budget should include funds to support travel for PD(s)/PI(s) and pertinent members of the Center to attend HVP Annual Consortium meetings, Consortium activities and workshops.
- NIH may modify budgets on award

Human Virome Characterization Centers (HVCC)

Eligibility

- Foreign institutions **are not** eligible to apply. Non-domestic (non-U.S.) components of U.S. Organizations **are not** eligible to apply. Foreign components **are** allowed.
- For-profit organizations and NIH intramural program **are** eligible to apply.
- Institutions may apply to one or more RFAs for the HVP.

Human Virome Characterization Centers (HVCC)

Administrative Details

- **NIH Involvement**: There will be substantial NIH programmatic involvement in individual projects and Consortium activities.
- **RFAs**: These RFAs are one-off announcements with no revisions or appeals. No late submissions allowed.
- **Review**: Reviews will be in Special Emphasis Panels.
- **FAQs** covering many details are available online:

  https://commonfund.nih.gov/human-virome-frequently-asked-questions

Human Virome Characterization Centers (HVCC)

Important Dates

- Letter of Intent Due Date: **October 17, 2023**
- Earliest Submission Date: **October 17, 2023**
- Application Due Date: **November 17, 2023**
- Peer Review Dates: **March 2024**
- Advisory Council: **May 2024**
- Earliest Start Date: **July 2024**

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RFA-RM-23-018
Human Virome Program: Developing novel and innovative tools to interrogate and annotate the human virome (U01 Clinical Trial Not Allowed)

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

Initiative 2 - Purpose

To address the technological challenges that are currently hindering robust interrogation of the constituents and functionality of the human virome.

This NOFO is focused on two areas:

1) Development of innovative and novel tools, models, and methods to overcome the major challenges in identifying and characterizing human viruses.
2) Development of computational biology and bioinformatics tools to enhance the analysis and visualization of the human virome.

Specific Areas of Research Interest

Examples of application topics of interest include the development of novel or refinement of:

- Tools and/or methods for viral isolation and viral detection, including isolation of replication-competent viruses and simplified methods for nucleic acid sequencing
- Tools and/or methods for viral quantification
- Techniques for *in vitro* viral propagation, replication, infectivity, and/or visualization
- Culture systems with high-throughput capacity
- Enrichment techniques for downstream sequencing
- Laboratory or *in silico* approaches to eliminating environmental background and contaminating sequences
- Approaches for human and animal sample procurement and storage

Specific Areas of Research Interest

Examples of application topics of interest include the development of novel or refinement of:

- *in vitro* assays and animal models for virome dynamics
- Methods and tools for host range prediction from sequence data, viral-viral interaction detection (for example satellites, etc.), ecology-based analysis of viral/host/population dynamics
- *in silico* methods, for example computational, statistical, power analysis, etc., and functional annotation of uncharacterized regions in viral genomes
- *in silico* methods to compare viromes across studies
- Methods to identify sequencing errors leading to false identification of viruses or variants, and lack of matches in current viral databases

PHS 398 Research Plan

- Describe how the tools, technologies or methods will be developed and used to overcome the major challenges in identifying and characterizing viruses.
- In situations where improvement on existing tools/methods/technologies is being proposed, applicants should describe how the proposed new tools will be significantly faster, cheaper, more sensitive, or more robust than existing tools/methods/technologies.
- A description of how the PI(s) plan to work collaboratively with other components of the HVP Consortium to meet program goals.
- **Project Milestones**
  - Milestones are goals that create decision points in the project and should include clear criteria for success.
  - Yearly milestones should provide clear indicators of a project's continued success or emergent difficulties and may be used to evaluate the application not only in peer review but also in consideration of the awarded project for funding of non-competing award years.

Key Dates

Application due date: November 14, 2023
Scientific Review: March 2024
Advisory Council: May 2024
Earliest Start date: July 2024

No late applications will be accepted for this Notice of Funding Opportunity

Budget Information

- The NIH Common Fund intends to commit approximately $4M in FY2024.
- Approximately 8 awards are anticipated, contingent upon availability of funds and receipt of a sufficient number of meritorious applications.
- **Award Budget**
  - Direct costs are limited to a maximum of $350,000 in each year.
- **Award Project Period**
  - The scope of the project should determine the project period. The total award period requested for this funding opportunity may not exceed four years.

This webinar is being recorded.

RFA-RM-23-017
Human Virome Program: Characterization of functional interactions between viruses and human and microbial hosts (U01 Clinical Trial Not Allowed)

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

RFA-RM-23-017 - Purpose

To study functional characterization of human virome interactions within human and microbial hosts.

This NOFO is focused on two areas:

1) Characterize tissue tropism and host reservoirs for all resident viruses.
2) Define and characterize the functional interactions of resident viruses within human host tissues (immune cells, epithelial, endothelial, etc.) and the microbiome.

All commensal viruses that are regularly found in or on humans are acceptable if studies demonstrate new knowledge that will be gained of how virome interactions within human and microbial hosts impact human health.

Specific Areas of Research Interest

Examples of application topics of interest on tissue tropism and host reservoirs include identification and characterization of:

- Host cell and tissue receptors recognized for viral engagement
- Other cell entry factors needed for establishment of infection and persistence
- Host factors important for virus life-cycle maintenance and/or reactivation

Specific Areas of Research Interest

Examples of application topics of interest on virome functional interactions within human and microbial hosts include:

- Virome and immunity (e.g., immune evasion strategies, establishment of innate or adaptive immune responses, or responses to vaccines)
- Host-virome cellular and molecular interactions
- Bacteriophage and microbiome interactions impacting the human host
- Viral dynamics, evolution, emergence, and co-infection
- Comparative studies of viral homologs
- Uncharacterized RNA virus interactions with human or microbial hosts

Non-responsive applications

- Research narrowly focused on pathophysiology of specific viral infection and specific disease states that are not part of a broader application centered on defining and characterizing the human virome
- Research focused solely on interactions between viruses and microbial host independent of the human host
- Primarily translational or product focused research such as developing prevention methods, treatments, reagents, new diagnostic methods, or animal models that are not part of a broader application centered on human virome research

Key Dates

Application submission due date: November 15, 2023
Scientific Review: March 2024
Advisory Council: May 2024
Earliest Start date: July 2024

No late applications will be accepted for this Notice of Funding Opportunity

Budget Information

- The NIH Common Fund intends to commit approximately $12M in FY2024.
- Approximately 10 awards are anticipated, contingent upon availability of funds and receipt of a sufficient number of meritorious applications.
- **Award Budget**
  - Direct costs are limited to a maximum of $750,000 in each year.
  - Set-aside a minimum of $50,000 in direct costs each year for years 3, 4, and 5 for the collaborative pilot projects
- **Award Project Period**
  - The project period is limited to five years.

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Consortium Organization and Data Collaboration Center (CODCC) for the Human Virome Program (HVP) (U24 Clinical Trial Not Allowed)

RFA-RM-23-016

commonfund.nih.gov/humanvirome

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

Responsibilities

- CODCC has two main responsibilities:
  - oversee the organization and management of the HVP Consortium ;
  - coordinate data acquisition, analysis and integration of HVP outputs from various consortium components:
    - creation and up-to-date maintenance of an **HVP Data Portal** that contains the **Human Virome Reference Dataset,** a non-redundant catalog of human viral sequences ;
    - work with a **variety of data types and tools** generated by projects from current (see companion NOFOs) and future HVP funding opportunities ;
    - provide **training**, **documentation**, and technical **support** for end-users within the consortium ;
    - promote **collaboration and communication** among HVP investigators, and coordinate the standardization of protocols to be used in the HVP ;
    - coordinate **outreach activities**.

Purpose

- The HVP CODCC will:
  - serve as an **organizational and cooperation hub** for the HVP Consortium ;
  - serve as the HVP's hub for collecting, storing, curating, and disseminating all data, metadata, analysis and visualization tools, computational models, and aggregate data across the Consortium into a searchable **HVP Data Portal** ;
  - ensure the utility of the database (internally and externally) ;
  - **facilitate collaboration** through HVP Consortium engagement with the research community.

Selected Activities

- **Administration and Management:**
  - Identify **administrator(s)** to dedicate substantial effort to administrative core activities and collaborate closely with the CODCC PD(s)/PI(s), NIH staff, and HVP PD(s)/PI(s);
  - Establish a **Consortium working group(s)** to develop common protocols and standards on specimen collection (including consent language), processing, storage, and analysis;
  - Develop a **virtual repository** of biospecimens, tools, and reagents;
  - Collaborate with NIH staff to organize **HVP scientific meetings**, including the HVP Kick-off Meeting (~3 months after awards are made) and subsequent annual 2-3 day in-person HVP meetings;

Selected Activities

- **Administration and Management (con't)**
  - Arrange/support travel costs of approximately six NIH-appointed External Program Consultants to the annual consortium-wide grantees meeting;
  - Organize and coordinate **HVP governing and advisory bodies**, including the HVP Steering Committee and subcommittees, HVP working groups, and external scientific panels;
  - Facilitate other HVP activities, e.g. small topical workshops, collaborations with outside groups, implementation of HVP developed policies, and consortium opinion and perspective pieces;
  - **Evolve, adapt, and improve** during the project period in response to the needs of the HVP community.

Selected Activities

- **Data management**
  - HVP investigators will be responsible for submitting the data they generate to publicly-accessible repositories (e.g., NCBI)
  - CODCC will **facilitate**, curate, and disseminate data, metadata, analyses and visualization tools, computational models, and completed viral sequences generated by the HVP Consortium, in a manner that ensures interoperability with data from other virome efforts.
- **HVP Data Portal**
  - HVP investigators will also submit their data to CODCC
  - CODCC assembles data into a **searchable Human Virome Reference Dataset** that will be made publicly accessible
  - CODCC ensures common data elements, standards, data requirements, etc.

Selected Activities

- **Open and Controlled HVP Data Access**
  - CODCC will establish appropriate data sharing policies and data access procedures for HVP Consortium to review and approval before implementation
  - CODCC will be responsible for the creation of a robust system that can distinguish between and segregate controlled-access and open-access data
- **Data Analysis and Integration**
  - Ensuring the knowledge base is flexible and extensible to visualize, manage, and integrate multiple types of data (*e.g. genomics, transcriptomics, molecular and cellular imaging, structural data, epidemiological and clinical data*);
  - Facilitating data use by the broader scientific community.

Selected Activities

- **Data Management and Sharing Plan**
  - Effective for due dates on or after January 25, 2023, the Data Management and Sharing Plan will be attached in the Other Plan(s) attachment in FORMS-H application forms packages
  - Nevertheless, include in your main application all sections as outlined under PHS 398 Research Plan
    - Section 1: Overall CODCC Vision and Management
    - Section 2: Administration and Management (Including Consortium Coordination and Outreach)
    - Section 3: Data Analysis and Integration (Including Data Standards, Storage, and Dissemination)

Acknowledgment

Working Group for RFA-RM-23-016 (CODCC):

- Mongodin, Emmanuel (**NIH/NHLBI**)
- Bollweg, David (NIH/OD)
- Brown, Liliana (NIH/NIAID)
- Carrington-Lawrence, Stacy (NIH/NIA/ERP)
- Flores-Munguia, Roberto (NIH/NIA/ERP)
- Kim, Hye-Sook (NIH/NCCIH)
- Little, Roger (NIH/NIDA)
- Melillo, Amanda (NIH/NIDCR)
- Miller, Becky (NIH/OD)
- Ngosso, Sonynka (NIH/OD)
- Novak, Leia (NIH/NIAID)
- Proctor, Lita (NIH/OD)
- Zou, Shimian (**NIH/NHLBI**)

Human Virome Program Working Group

Program Co-Chairs

- Emmeline Edwards (NCCIH)
- Daniel Gallahan (NCI)
- Ronald Kohanski (NIA)

Program Coordinators

- Stacy Carrington-Lawrence (NIA)
- Hye-Sook Kim (NCCIH)
- Amanda Melillo (NIDCR)
- Leia Novak (NIAID)

Common Fund

- Becky Miller
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- David Bollweg
- Lita Proctor (Special Volunteer)

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- Sai Majji (NICHD)
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- Tamara McNealy (NIDCR)
- Emmanuel Mongodin (NHLBI)
- Amy Palin (NIAID)
- Heiyoung Park (NIAMS)
- Betsy Read-Connole (NCI)
- Mark Robien (NIAID)
- Pothur Srinivas (NCI)
- Mukesh Verma (NCI)
- Shimian Zou (NHLBI)

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Q&A

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Extra Slides

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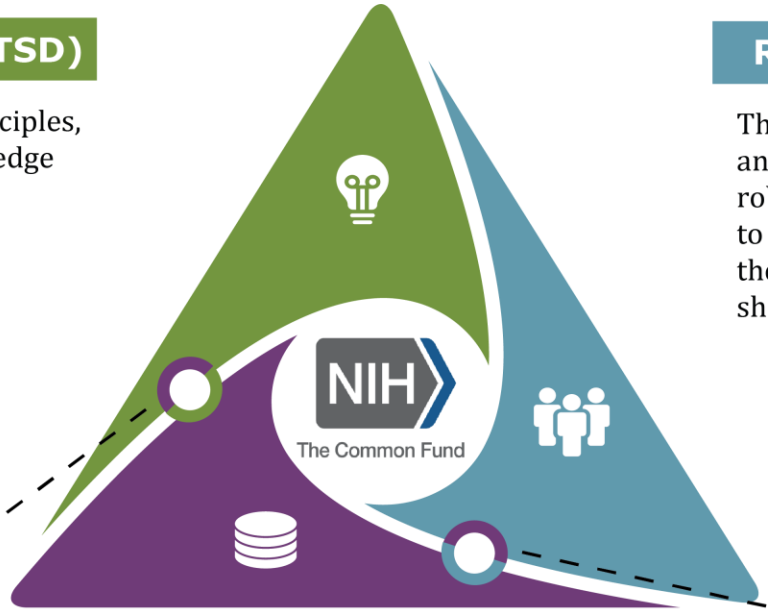
Types of Common Fund Programs

Transformational Science and Discovery (TSD)

These **programs** are designed to establish new scientific principles, models, and research resources to transform scientific knowledge and paths to discovery.

- 4D Nucleome
- A2CPS
- CryoEM
- DS-I Africa
- ExRNA
- Global Health
- Global Health
- HRHR
- Human Virome
- IDG
- MoTrPAC
- NPH
- SMaHT
- SPARC



Re-Engineering the Research Enterprise (RRE)

These **programs** are designed to transform how we do biomedical and behavioral research, how we make the biomedical workforce as robust as possible to ensure new perspectives and ideas contribute to discovery, how we transition that research into prevention and therapies, and how those successful prevention and therapies can be shared broadly.

- ComPASS
- DPC
- FIRST
- Health Comms
- SCGE
- Transformative Research to Address Health Disparities and Advance Health Equity
- UDN

TSD programs that create catalytic data resources

A2CPS • ExRNA • IDG • MoTrPAC
NPH • SenNet • SMaHT • SPARC

RRE program that creates a catalytic data resource

ComPASS

Catalytic Data Resources (CDR)

These **programs** are designed to manage and develop data for scientific discoveries by accelerating research through data resources.

- Bridge2AI
- CFDE
- HuBMAP
- Kids First
- Metabolomics