Rustbelt Center for AIDS Research

Case Western Reserve University and the University of Pittsburgh

Introductory Meeting for the Pitt HIV Community

June 24, 2022

The Centers for AIDS Research

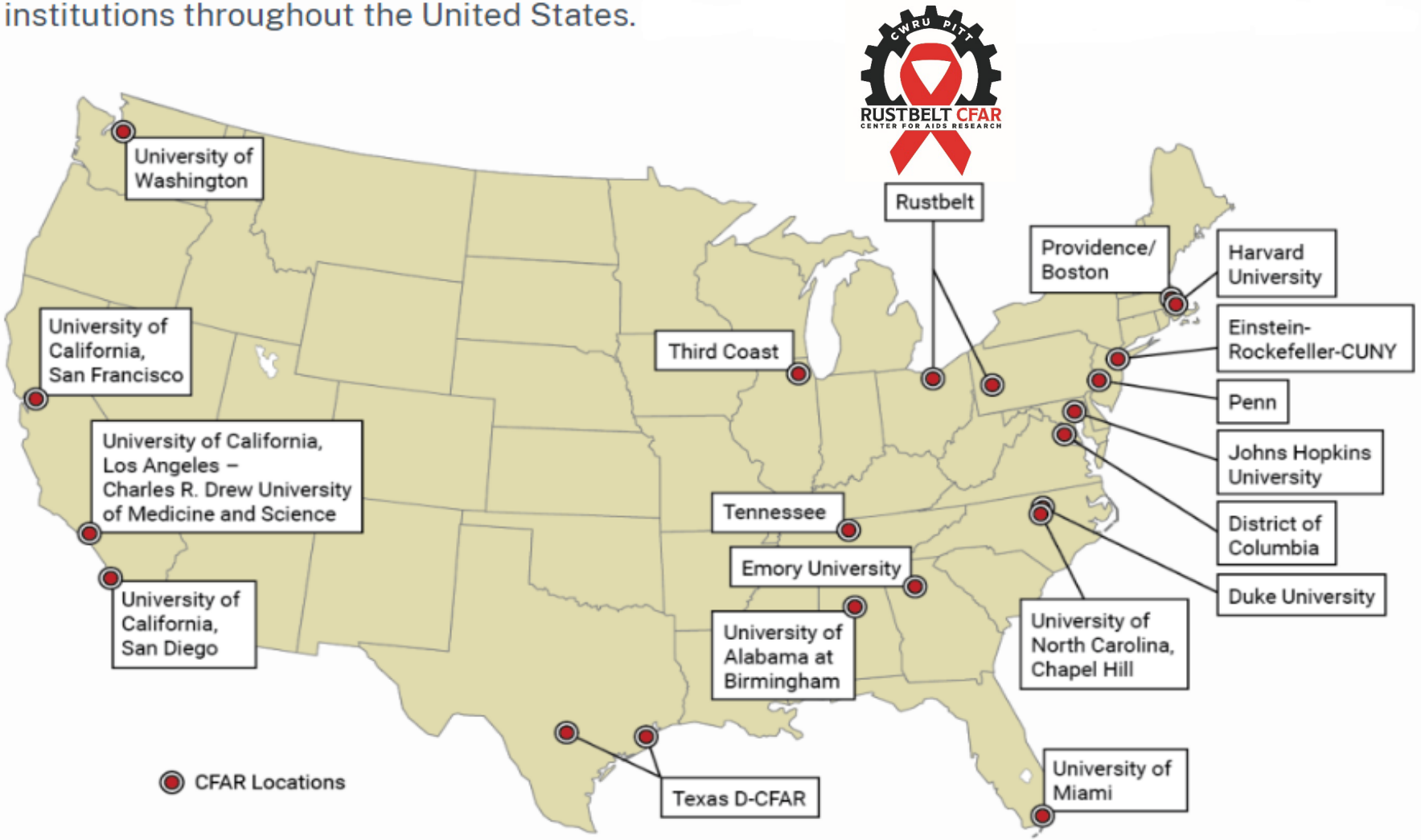
- This program was initiated by the NIAID Division of AIDS in 1988 and is co-funded by eleven NIH Institutes.
- **The CFAR Program**
  - Administrative management: the CFAR team within the Basic Science Program in the Division of AIDS at NIAID
  - Scientific management: CFAR Steering Committee, comprised of representatives from the co-funding institutes and centers as well FIC and the Office of AIDS Research
- **Objective:** To provide administrative and shared research support to synergistically enhance and coordinate high quality AIDS research projects through support of core facilities that provide expertise, resources, and services not otherwise readily obtained through more traditional funding mechanisms.
- The CFAR program emphasizes the importance of interdisciplinary research, and collaboration, especially between basic and clinical investigators, translational research and emphasis upon inclusion of minorities and inclusion of prevention and behavioral change research.

Timeline for Forging the Pitt-CWRU Alliance

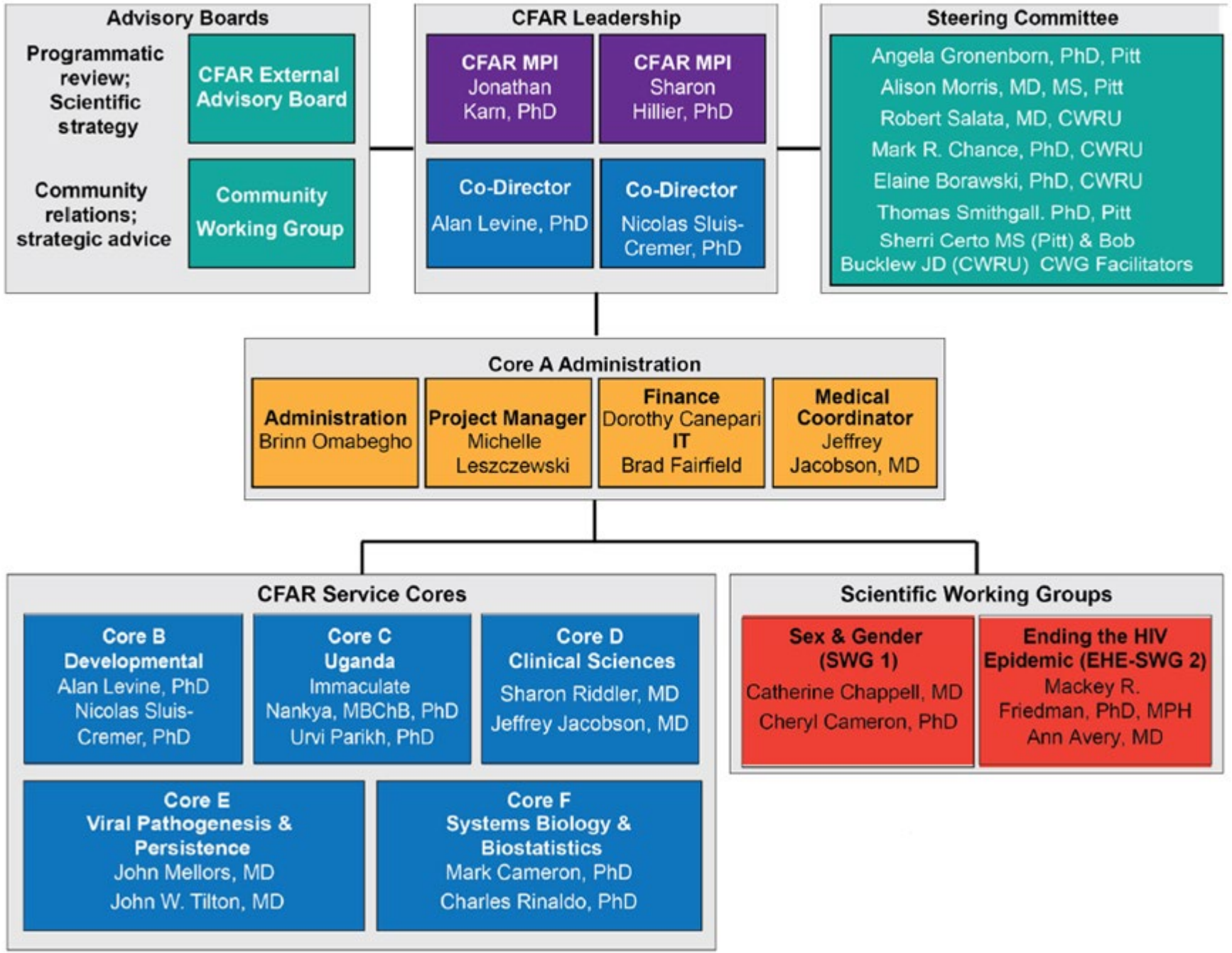
- Nov 2016: First discussed by Mellors and Karn
- Apr 2017: First joint planning meeting at CWRU
- Dec 2017: First joint Catalytic and Developmental RFAs
- Aug 2018: Joint Rustbelt CFAR Symposium
- Apr 2019: Joint Developmental award Mini-Symposium
- Dec 2019: Joint Developmental award Mini-Symposium
- Mar 2020: Joint Rustbelt CFAR Symposium
- Two years experience running joint SWGs
- Regular Zoom leadership meetings
- Funded May 2022 after three attempts!!

Centers for AIDS Research Sites

There are 19 Centers for AIDS Research (CFARs) located at academic and research institutions throughout the United States.



Organizational Structure of the Rustbelt CFAR



Rustbelt Center for AIDS Research

Case Western Reserve University/University Hospitals Cleveland Medical Center
University of Pittsburgh

Administrative Core A

Directors: Sharon Hillier (Pitt); Jon Karn (CWRU)

Aims:

1. **To provide joint leadership and administrative support for the RUSTBELT CFAR.** Core A will work with CFAR members and the External Advisory Committee to set priorities, allocate budgets and coordinate all activities across the Cores and SWGs. The laboratory Cores will be expected to show 40% to 60% utilization by each institution.
2. **To coordinate a rigorous annual review and scientific planning process and implement the plan through enhancement of Core services, recruitment, and stimulation of new research.** Emphasis is placed on driving interdisciplinary and inter-institutional collaboration, especially between basic and clinical investigators.
3. **Ensure improve communication and coordination across the CFAR.** A **RUSTBELT CFAR** Community Working Group comprised of representatives of the Community Advisory Groups (CABs) related to HIV research across Pitt and CWRU will be facilitated through Core A. Other key coordinating functions include Regulatory Coordination, the CFAR website and use of the iLab financial control system to facilitate access to Core services.
4. **To stimulate training and developmental activities throughout the CFAR.**

Developmental Core B

Directors: Alan Levine (CWRU); Nicolas Sluis-Cremer (Pitt)

Aims:

1. **Conduct responsive Mentored Scientist Pilot Grant and Catalytic Fund programs that accelerate junior faculty development.**
   - ❑ One-year pilot grants of $50,000 will be awarded on a competitive basis to junior faculty at both sites who have not previously received independent federal research grants. Senior investigators new to HIV research also eligible
   - ❑ The Catalytic Fund fosters collaboration by supporting teams that include outstanding researchers from both institutions.
   - ❑ CFAR Core Awards, which allow investigators of all ranks to apply for credit of up to $7,500 for defined services offered by **Cores C, D, E and F**.
2. **Identify, mentor, and support the next generation of HIV investigators.**
   - ❑ Developmental grant potential applicants, applicants, and awardees are required to enter into a formal mentoring relationship with appropriate CFAR-designated mentors.
3. **To provide Minority Training Programs**

Rustbelt Center for AIDS Research
Case Western Reserve University/University Hospitals Cleveland Medical Center
10900 Euclid Avenue, Cleveland, Ohio 44106-4960
Phone (216) 368-3915

University of Pittsburgh
204 Craft Avenue, Pittsburgh, PA 15213-3005
Phone (412) 641-6435

Principal Investigators	Co-Directors
Jonathan Karn, PhD	Alan Levine, PhD
Sharon Hillier, PhD	Nicolas Sluis-Cremer, PhD

Solicitation for HIV/AIDS-Related Developmental Project Grants

The **RUSTBELT CFAR** is inviting applications for developmental project grants focused on HIV/AIDS research in the following areas:

1. Novel approaches to prevent HIV infection
2. HIV persistence and viral latency
3. NeuroAIDS including substance use
4. Antiretroviral therapy and drug resistance
5. Basic science focused on viral pathogenesis, host-protein interactions and drug discovery

We encourage applications that investigate sex and gender differences in HIV/AIDS

Application Criteria:

- Early career investigators (Senior Research Associates, Instructors, Assistant Professors)
- Established investigators new to HIV/AIDS research
- Investigators in Uganda
- All applications must propose use of at least one RUSTBELT CFAR Core

Budget and Project Period: 5 awards of **$50,000** (total costs; no indirect cost recovery) will be funded for 1 year.

Key Dates:
Application Due Date: -------**, 2022**
Peer Review: ------ **2022**
Notification of Award Date: ------**, 2022**
Anticipated Start Date: **Jan 3, 2023**

Required Application Components and Application Format:

- Face Page (NIH PHS 398)
- Budget and Budget Justification (Funds are for research supplies and staff salary support)
- NIH biosketches for key personnel
- Proposal Narrative (sections **A** – **C**, 3-page total)
  - **A**. Specific Aim(s)
  - **B**. Significance & Innovation
  - **C**. Research Design and Methods
  - **D**. Plans for future funding (1/2 page)
  - **E**. References Cited (not included in page limit)

Submission: All proposals must be submitted electronically via email, **as a single PDF file**, to ….

Questions: Please contact Dr. Alan Levine (alan.levine@case.edu) at Case Western Reserve University or Dr. Nicolas Sluis-Cremer (nps2@pitt.edu) at the University of Pittsburgh with any questions.

- RFA will be released within the next 3-4 weeks
- Please encourage young investigators to apply
- Have to take advantage of CFAR cores
- Contact me with any questions

Uganda Core C


Directors: Immaculate Nankya (CWRU, Kampala); Urvi Parikh (Pitt)

Aims:

1. **Facilitate scientific exchange and project coordination between CFAR investigators in Uganda, Cleveland and Pittsburgh**
   Examples of collaborative projects:
   - ❑ Role of gender on HIV infection and HIV-related complications
   - ❑ Role of hormonal contraception on the size of the HIV reservoir
   - ❑ Sensitive drug resistance evaluations for antiretroviral therapy and pre-exposure prophylaxis in diverse sample types
2. **Support a state-of-the-art lab in Uganda through ongoing technology transfer**
   - ❑ Enable Pitt investigators to use testing and research services in Uganda to avoid shipping samples to the US for routine or specialized assays (e.g., HIV viral load, next-generation sequencing)
   - ❑ Share Ugandan samples with Pitt investigators for studies using non-subtype B HIV
3. **Provide mentorship and training in international research for new investigators in Uganda and in the Rustbelt CFAR**

Core C Assay Catalog – Uganda and Pitt

HIV Infection Confirmation

- ❑ Viral load (Panther Hologic, GeneXpert)
- ❑ Immunoassays (EIA, Geenius)

Genotyping

- ❑ HIV Sanger, Illumina platform NGS, UMI-barcoding NGS
- ❑ Somatic mutation analysis

HIV Pre-Clinical Testing and Phenotyping

- ❑ Patient-derived recombinant virus cloning
- ❑ site directed mutagenesis
- ❑ ART/PrEP resistance determination
- ❑ Novel inhibitor efficacy evaluation
- ❑ Ex-vivo challenge tissue studies (rectal, cervical)

HIV Basic Research in Uganda

- ❑ Methylation assays for aging
- ❑ EDITS assay (measures inducible cells)
- ❑ qPCR for quantifying size of reservoir

Kerri Penrose
kjp43@pitt.edu
Research Manager, Pitt

- ❑ Assays can be tech transferred to Uganda as needed by specific projects
- ❑ Pitt can offer support for cross-validation of assays that use field-collected specimens such as dried blood spots or genital track swabs

- ❑ **Rustbelt CFAR Core C is available to help you expand your international research!**

Clinical Sciences Core D


Directors: Jeffrey Jacobson (CWRU); Sharon Riddler (Pitt)

Aims:

1. **Provide clinical information and biologic samples from PWH and uninfected individuals for CFAR investigators.**

2. **Coordinate acquisition of fresh biologic samples from PWH and uninfected individuals for CFAR investigators.**

3. **Provide clinical support to CFAR investigators for the design, implementation, and analysis of clinical and translational studies focusing on HIV care and prevention.**

Major Resources of Core D

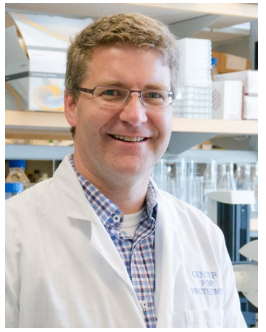
Site	Program	Available sample types	
		Repository	Fresh
CWRU	PCRD (CFAR) >5000 patients in database	Plasma, PBMC, cell pellets, serum >200,000 aliquots in repository	Plasma, PBMC, routinely. For specific projects: Leukopak, serum, LN biopsy, CSF, distal rectal biopsy specimens, semen, CVL
Pitt	Clinical Research Site		Plasma, PBMC, Leukopak, serum, rectal tissue, cervical tissue, vaginal tissue, semen
Kampala	Joint Clinical Research Centre (**Core C)**	Plasma, serum, PBMC	Plasma, serum, PBMC, lymph node

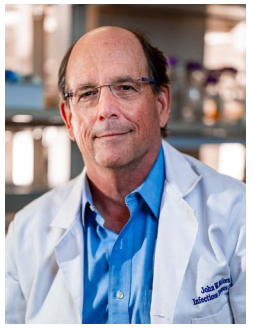
- Guidance for study design, statistical considerations, data management, regulatory submissions available
- Linkages to collaborators, study populations, CFAR Cores, Institutional resources, clinical trial networks

Rustbelt Center for AIDS Research

Case Western Reserve University/University Hospitals Cleveland Medical Center
University of Pittsburgh

Viral Pathogenesis & Persistence - Core E





Directors: John “Chip” Tilton (CWRU); John Mellors (Pitt)

Aims:

1. **Support applied research toward an HIV cure by providing:**

- ❑ Accurate quantification of HIV Reservoirs
- ❑ Primary cell models of latent HIV infection
- ❑ Simplified analysis of HIV integration sites
- ❑ Analysis of individual proviral transcription

2. **Support basic research into HIV biology, transmission, and pathogenesis.**

- ❑ HIV single genome sequencing (SGS)
- ❑ High-resolution visualization of HIV transcription

3. **Support applied research to enhance HIV prevention and treatment efforts.**

- ❑ Quantification of drug-resistant variant frequency for current and new antiretroviral agents in development

Core E Assay Catalog

Virology Services

General

1. Lentivirus and Lentiviral Vector Production
2. Site-directed mutagenesis, env mutants and pseudovirus generation
3. Access to the shRNA library
4. Nanoscale flow cytometry (NFC) training and expertise

Reservoir Quantification and Characterization

1. Automated Plasma Single Copy Assay (autoSCA) on ≥5mL of plasma
2. Manual SCA on very low sample volumes (1-5mL)
3. Automated HIV-1 DNA and Cell-Associated HIV-1 RNA (CARD)
4. Total and Intact HIV-1 DNA ddPCR
5. Quantitative or Fully Autologous Viral Outgrowth Assay (QVOA or FAVIO)
6. Autologous Latency Clearance Assay (AulClear)
7. Cell-associated DNA and RNA Single Genome Sequencing (CARD-SGS)
8. Next Generation Sequencing (NGS) including UMI-NGS
9. Near Full Length Proviral Amplification and Sequencing
10. Integration Site Analyses and Bioinformatics
11. Envelope Detection by Induced Transcription-based Sequencing (EDITS)

Primary Cells

1. Polarized Th17 and microglial models
2. Human Lymphoid Aggregate Culture (HLAC)
3. Polarized Explant Models

Kerri Penrose
kjp43@pitt.edu
Research Manager, Pitt

Josh Cyktor
jcc114@pitt.edu
Asst Professor, Pitt

Core E Access Information

1. Current: email Kerri Penrose with inquiries
2. Future: iLab Core Facility Management System

Rustbelt Center for AIDS Research

Case Western Reserve University/University Hospitals Cleveland Medical Center
University of Pittsburgh

Systems Biology & Biostatistics Core F


Directors: Mark Cameron (CWRU); Charles Rinaldo (Pitt)

Aims:

1. **Support transcriptomic and microbiome studies of HIV immunology and pathogenesis.**

- ❑ Provides a robust technological platform for transcriptional analysis by RNA-seq and deep sequencing in clinical and animal models of HIV infection.
- ❑ Innovative services to characterize the microbiome in HIV transmission, gender research, and pathogenesis including advanced technological platforms for complex molecular analysis of proteins and microbiome pathways.

2. **Support functional immunology studies of HIV.**

- ❑ Centralized access to current immunologic technologies, protocols, and training for the isolation, manipulation, culturing, and expansion of primary immune cells from blood and tissues, and immune modeling to advance basic immunologic research and translational studies in development of novel immunotherapeutic approaches toward a functional cure of HIV infection.

3. **Provide bioinformatics and data management support for multi-omics.**

- ❑ Facilitate all aspects of systems biology studies, i.e., centralized data acquisition, management, and reporting structure for all cohorts and ‘omics.
- ❑ Utilize high-capacity assay, analysis workflows, and publicly available ‘omic data to build publications and databases.

4. **Provide biostatistical support.**

- ❑ Biostatistical design and analysis to identify key drivers of protective immune responses, assist in designing validation strategies and writing of manuscripts, and provides the metadata and data standardization pipelines for upload of results to public databases.

Rustbelt CFAR Special Services: Systems Biology & Biostatistics Core F

Core F Microbiome: Adam Brugener, PhD (CWRU)

- ❑ Characterize the microbiome, proteome, and metabolome in HIV.
- ❑ Mass spectrometry and computational data on in vivo bacterial community structure, functional pathways, and metabolic processes.

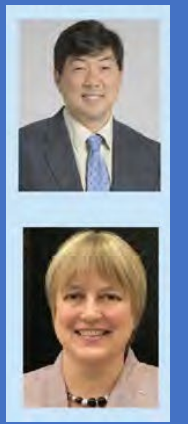
Core F Translational Immunology: Alok Joglekar, PhD (Pitt) ; Robbie Mailliard, PhD (Pitt)

- ❑ Adaptome studies; T cell TCR and B cell analyses.
- ❑ 6-way cell sorting with up to 50 parameters under BSL2+ containment.

Core F Bioinformatics/Systems Biology: Jishnu Das, PhD (Pitt); Liangliang Zhang, PhD (CWRU)

- ❑ Network analysis and systems biology to define complex molecular phenotypes that underpin host immunity to HIV.
- ❑ Big data analyses and protocols for multi-color flow cytometry, transcriptomics, microbiome, and proteomics.

Core F Biostatistics: Curtis Tatsuoka PhD (CWRU/Pitt); Leslie Meyn, PhD (Pitt) in support of Core D



- ❑ Project planning and experimental design; developing statistically analyzable hypotheses with appropriate statistical methodology; sample size projections with power analyses.

Rustbelt Center for AIDS Research

Case Western Reserve University/University Hospitals Cleveland Medical Center
University of Pittsburgh

Sex and Gender Scientific Working Group (SWG)


Directors: Catherine Chappell (Pitt); Cheryl Cameron (CWRU)

Aims:

1. **To engage CFAR members in research involving sex and gender differences in HIV.**
   - ❑ Monthly meetings increasing knowledge base on sex and gender, catalyzing new research, integrating sex/gender in existing research with community stakeholder input and involvement
   - ❑ Focus on 5 opportunities areas already identified: (i) The impact of sex and obesity on HIV persistence and pathogenesis; (ii) Sex and gender disparities in HIV-associated immune activation; (iii) The interaction between antiretroviral medication and exogenous sex hormones; (iv) Understanding the multiple social and behavioral factors that impede successful treatment and prevention for cis- and transgender women; and (v) Sex differences in latency reversal and viral persistence.
2. **To facilitate incorporation of sex and gender differences in HIV research**
   - ❑ Develop in vitro gender-specific primary cell models of HIV latency for gender-based cell and molecular biology studies
   - ❑ Large repository of samples from cross-sectional studies and longitudinal cohorts that will be characterized by sex, gender, and hormonal (endogenous or exogenous) status
3. **To coordinate junior mentorship program**
   - ❑ Scientific teams (junior and senior members) will be created with focus on sex and gender

Rustbelt Center for AIDS Research

Case Western Reserve University/University Hospitals Cleveland Medical Center
University of Pittsburgh

Ending the HIV Epidemic Strategic Working Group


Directors: Ann Avery (CWRU); Mackey R. Friedman (Pitt)

Aims:

1. **Expand academic/community/practitioner partnerships to develop research programs that identify gaps across EHE pillars in Cleveland and Pittsburgh.**

- ❑ The EHE SWG will identify the gaps in the HIV pillars driving the local epidemic, specifically: (i) diagnosis, (ii) treatment, (iii) prevention, and (iv) response.
- ❑ The SWG will provide opportunities for its members to engage productively with community stakeholders, practitioners, and policymakers to develop collaborations and research proposals designed to address the specific gaps within each pillar.

2. Facilitate new EHE implementation research projects that align with the pillars of the NIH HIV strategy in communities disproportionately impacted by HIV.

- ❑ EHE SWG will develop productive interactions with RUSTBELT CFAR Cores, Sex & Gender SWG1, and the Inter-CFAR Implementation Science Working Group to develop grant proposals for a robust EHE research and practice.
- ❑ EHE SWG will leverage the expertise of the Inter-CFAR Implementation Science Working Group and the respective strengths of Pitt and CWRU to establish an inter-institutional HIV prevention and implementation research training structure linking junior investigators with senior investigators in the field of EHE.
- ❑ The EHE SWG will provide opportunities for its members to engage productively with community stakeholders, practitioners, and policymakers to develop collaborations and research proposals designed to address the specific gaps within each pillar.

Ending the HIV Epidemic Strategic Working Group (continued)

Action Items

1. Enhance RUSTBELT CFAR investigator participation and training to develop a **rapid assessment of current HIV epidemiological trends** across the geographical hotspots in Cuyahoga and Allegheny Counties.
2. Leverage the relationships of the RUSTBELT CFAR with community programs and health departments to establish an **implementation strategy to reduce new HIV infections** in Cuyahoga County.
3. Initiate effective and innovative **community prevention research programs** to EHE high-priority sites in Cuyahoga County.
4. Establish an inter-institutional HIV prevention **and implementation research training structure** linking junior investigators with senior investigators.

Thank you for your time!

If you are interested in getting involved and/or learning more about our core services, the developmental award program, and our scientific working groups, please contact:

Michelle Leszczewski
leszczewskimn@upmc.edu