Human Virome Program

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Program Officer
National Institute of Allergy and Infectious Diseases

September 8, 2022
NIH Council of Councils

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

OSC (Common Fund)

Concept Clearance: New Common Fund Program

TITLE: Human Virome Program

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

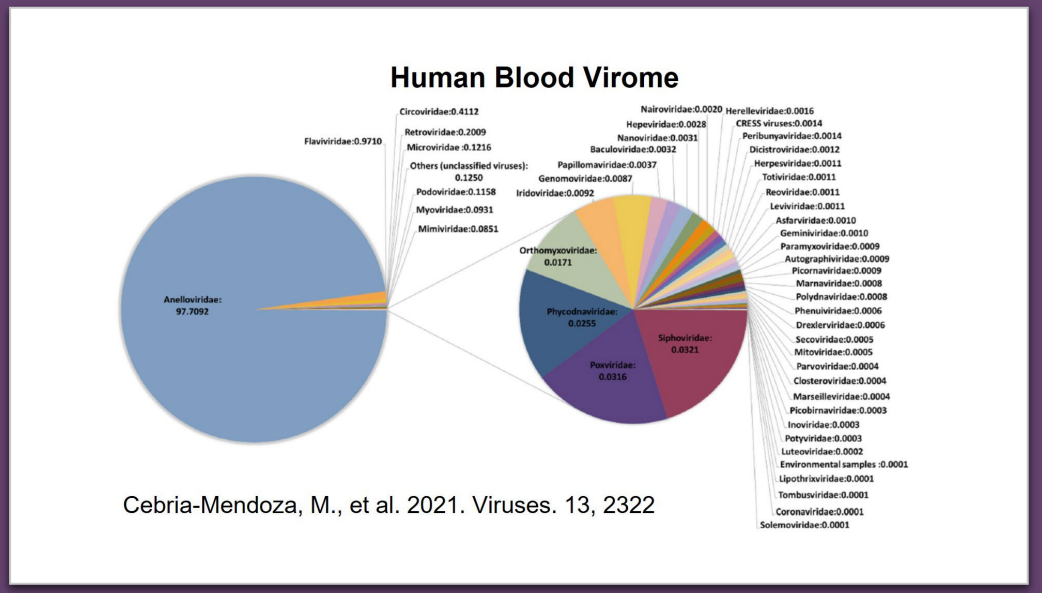
Initiatives:

1. Characterize the human virome in longitudinal, diverse cohorts across the lifespan
2. Develop tools, models, and methods to interrogate and annotate the human virome
3. Elucidate the human host/virome interactome
4. Data analysis and coordinating center

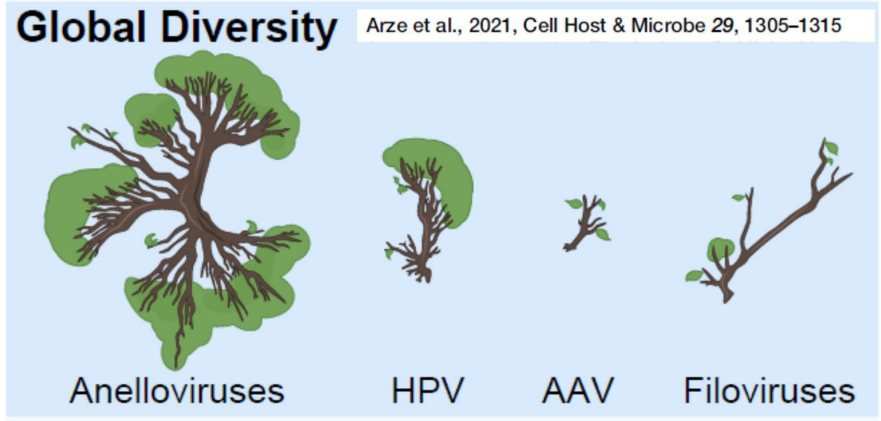
Funds Available: $46M per year (average)
Program Duration: 10 years – 2 phases of 5 years
Council Action: Vote for approval of the concept for Human Virome Program Phase 1

Program Scope

- The primary focus is on the commensal human virome
- Example: Anelloviruses
  - Humans across the globe are infected for their lifetimes
    - What is the source of initial infection?
    - Are they beneficial or do they cause disease?
    - What host cells support Anellovirus replication?

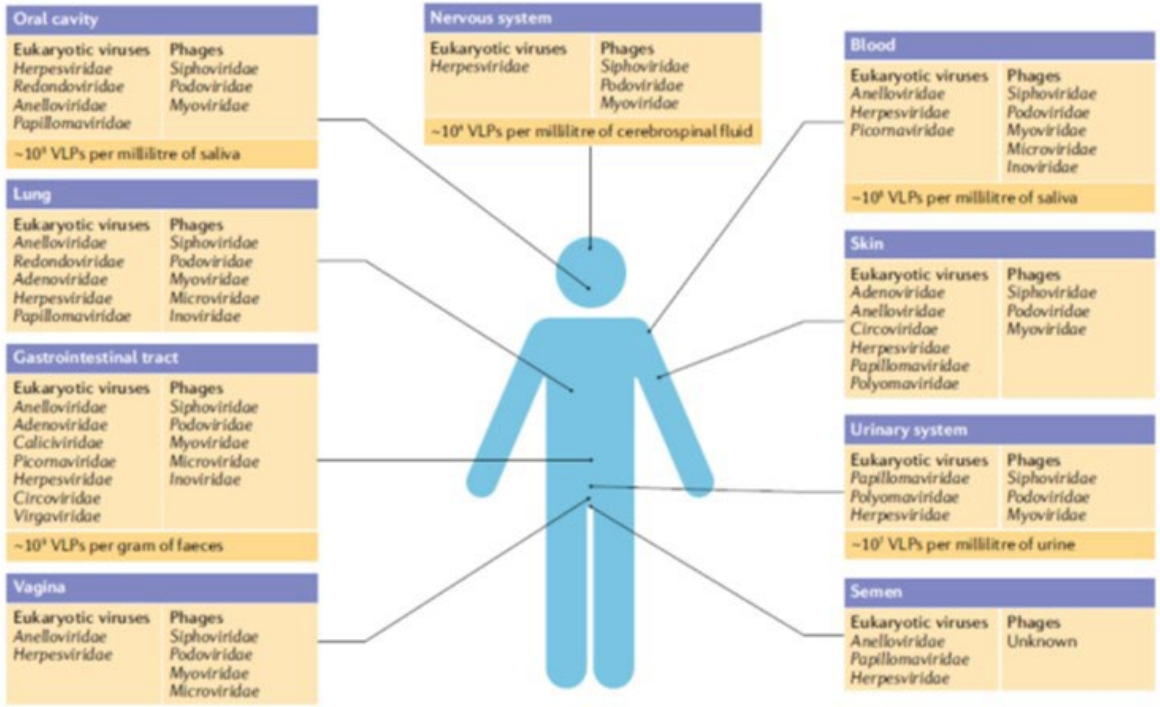


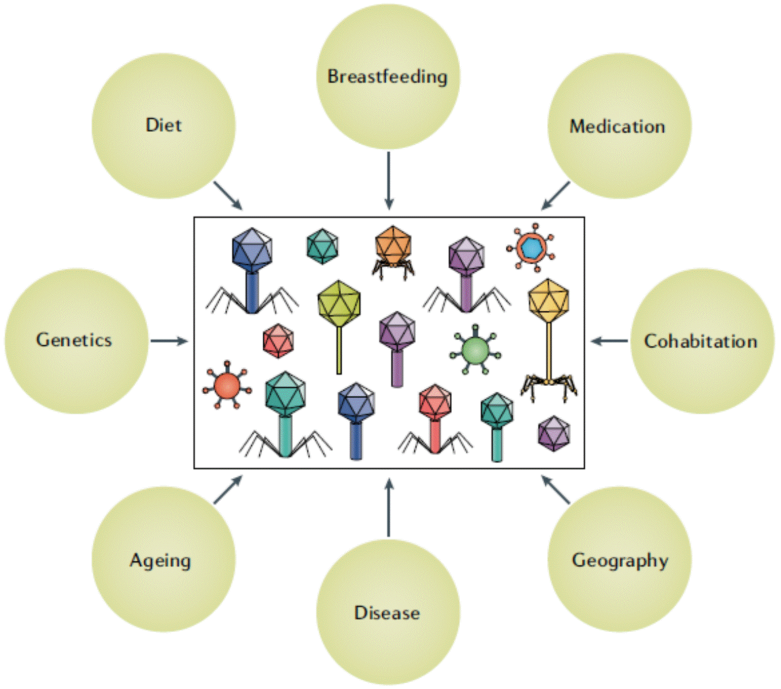
Cebria-Mendoza, M., et al. 2021. Viruses. 13, 2322



Background and 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)

CellPress

Cell Host & Microbe

Resource

Cell Host & Microbe 29, 1014–1029, June 9, 2021

Enteric viruses evoke broad host immune responses resembling those elicited by the bacterial microbiome

Simone Dallari,[1] Thomas Heaney,[1] Adriana Rosas-Villegas,[1] Jessica A. Neil,[1] Serre-Yu Wong,[1,2] Judy J. Brown,[3,4] Kelly Urbanek,[5] Christin Herrmann,[1] Daniel P. Depledge,[6] Terence S. Dermody,[7,8] and Ken Cadwell[8,9,10,*]

Cross-reactivity between tumor MHC class I–restricted antigens and an enterococcal bacteriophage

Fluckiger *et al.*, *Science* 369, 936–942 (2020)

Aurélie Fluckiger[1,2], Romain Daillère[1,2,3], Mohamed Sassi[4], Barbara Susanne Sixt[5,6,7,8,9,10], Peng Liu[6,7,8,9,10], Friedemann Loos[6,7,8,9,10], Corentin Richard[11,12,13], Catherine Rabu[14,15], Maryam Tidjani Alou[1,2,16], Anne-Gaëlle Goubet[1,2], Fabien Lemaitre[1,3], Gladys Ferrere[1,2], Lisa Derosa[1,2,17], Connie P. M. Duong[1,2], Meriem Messaoudene[18], Andréanne Gagné[18], Philippe Joubert[18], Luisa De Sordi[19,20], Laurent Debarbieux[19], Sylvain Simon[14,15], Clara-Maria Scarlata[21], Maha Ayyoub[21], Belinda Palermo[22], Francesco Facciolo[23], Romain Boidot[24], Richard Wheeler[25], Ivo Gomperts Boneca[25], Zsofia Sztupinszki[26], Krisztian Papp[27], Istvan Csabai[27], Edoardo Pasolli[28], Nicola Segata[29], Carlos Lopez-Otin[7,8,9,10,30], Zoltan Szallasi[26,31,32,33], Fabrice Andre[34,35], Valerio Iebba[1,2,36], Valentin Quiniou[37,38], David Klatzmann[37,38], Jacques Boukhalil[16], Saber Khelaifia[16], Didier Raoult[16], Laurence Albiges[1,39], Bernard Escudier[1,39,40], Alexander Eggermont[1,41], Fathia Mami-Chouaib[4,2], Paola Nistico[22,23], François Ghiringhelli[43], Bertrand Routy[18,44], Nathalie Labarrière[14,15], Vincent Cattoir[4,45,46], Guido Kroemer[6,7,8,9,10,47,48,49,50,*], Laurence Zitvogel[1,2,17,49,*]

CellPress
OPEN ACCESS

Cell Host & Microbe

Cell Host & Microbe 30, 110–123, January 12, 2022

Clinical and Translational Report

Enteric virome negatively affects seroconversion following oral rotavirus vaccination in a longitudinally sampled cohort of Ghanaian infants

Andrew HyoungJin Kim,[1,2] George Armah,[5] Francis Dennis,[5] Leran Wang,[2,3] Rachel Rodgers,[2,4] Lindsay Droit,[3] Megan T. Baldridge,[1,2,6] Scott A. Handley,[2,3] and Vanessa C. Harris[7,8,9,*]

Ongoing Human Virome Work

Plasma virome and the risk of blood-borne infection in persons with substance use disorder

Abraham J. Kandathil[1], Andrea L. Cox[1], Kimberly Page[2], David Mohr[3], Roham Razaghi[4], Khalil G. Ghanem[1], Susan A. Tuddenham[1], Yu-Hsiang Hsieh[5], Jennifer L. Evans[6], Kelly E. Coller[7], Winston Timp[1,4], David D. Celentano[8], Stuart C. Ray[1] & David L. Thomas[1]✉

NATURE COMMUNICATIONS | (2021)12:6909 |

Viral dysbiosis in children with new-onset celiac disease

Mohammad El Mouzan[1,2☯], Asaad Assiri[1,2,3☯], Ahmed Al Sarkhy[1,2☯], Mona Alasmi[1,2☯], Anjum Saeed[1,2☯], Abdulrahman Al-Hussaini[4,5☯], Badr AlSaleem[6☯], Mohammad Al Mofarreh[7☯] 2022 PLoS ONE 17(1): e0262108.

Gut dsDNA virome shows diversity and richness alterations associated with childhood obesity and metabolic syndrome

Shirley Bikel,[1,4] Gamaliel López-Leal,[1,4] Fernanda Cornejo-Granados,[1] Luigui Gallardo-Becerra,[1] Rodrigo García-López,[1] Filiberto Sánchez,[1] Edgar Equihua-Medina,[1] Juan Pablo Ochoa-Romo,[1] Blanca Estela López-Contreras,[2] Samuel Canizales-Quinteros,[2] Abigail Hernández-Reyna,[1] Alfredo Mendoza-Vargas,[3] and Adrian Ochoa-Leyva[1,5,*]

iScience 24, 102900, August 20, 2021

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 Program Leaders

- Becky Miller (OSC)
- Lita Proctor (Special Volunteer)

- Beena Akolkar (NIDDK)
- Rudy Alarcon (NIAID)
- Liliana Brown (NIAID)
- Mark Challberg (NIAID)
- Phil Daschner (NCI)
- Alison Deckhut Augustine (NIAID)
- Gerard Lacourciere (NIAID)
- Roger Little (NIDA)
- Dwayne Lunsford (NIDDK)
- Sai Majji (NICHD)
- Aron Marquitz (NIAMS)
- George McKie (NEI)
- Tamara McNealy (NIDCR)
- Amy Palin (NIAID)
- Heiyoung Park (NIAMS)
- Betsy Read-Connole (NCI)
- Mugdha Samant (OD)
- David Spiro (FIC)
- Pothur Srinivas (NCI)
- Shimian Zou (NHLBI)

Working Group Efforts

Request for Information (RFI): Challenges and Opportunities in Elucidating the Human Virome

Notice Number:
NOT-RM-22-010

Key Dates

Release Date:	March 16, 2022
Response Date:	April 29, 2022

NIH Portfolio Analysis

386 NIH Apps → 133 Relevant → 37 Awarded

26 Non-NIH Awards Across 15 Organizations

Human Virome Workshop
April 29, 2022

Goal: To gather information on the current state of knowledge of the human virome and to identify critical gaps

Healthy Human Virome

Definition and characterization of human virome in different tissue compartments in diverse populations across the lifespan

Infant Virome

Establishment of the human virome in the neonatal period, through infancy, and into early childhood

Virome & Disease

Virome/microbiome associations with human disease

Critical Knowledge Gaps Identified

- Diversity and dynamics (across tissues, time, populations, and lifespan)
- Establishment (timing and mechanisms)
- Host immune system interactions
- Functional and multi-omic studies
- Impacts of ‘exposome’
- Isolation, quantification, and propagation
- Animal models
- Standardized protocols
- Reference sequence database
- Annotation and contamination detection tools

Potential Deliverables of Interest to NIH Institutes/Centers

NCI	NEI	NHLBI
NHGRI	NIA	NIAAA
NIAID	NIAMS	NIBIB
NICHD	NIDCD	NIDCR
NIDDK	NIDA	NIEHS
NIGMS	NIMH	NIMHD
NINDS	NINR	NLM
FIC	NCATS	NCCIH

- Discover novel contributors to health and disease
- Novel insights into the development of the immune system and responses to vaccines
- Discover novel biomarkers for disease and/or therapeutic efficacy
- Development of novel viral vectors for gene therapy
- Creation of a human virome reference sequence database/bioinformatic innovation
- Demonstration project for robust data sharing/standardization

Common Fund Criteria

- This program supports the overall NIH mission and fits the criteria for Common Fund programs
- This is an emerging field and consequently, this program requires a broad scope that generally precludes individual IC efforts and requires orchestration and oversight from a central entity
- Program's outcomes/deliverables are of interest to almost all NIH institutes and centers
- Goals are achievable within 10 years
- This program will lay the foundation to enable NIH institutes and centers to pursue their specific research priorities within the context of the human virome

Synergistic Opportunities

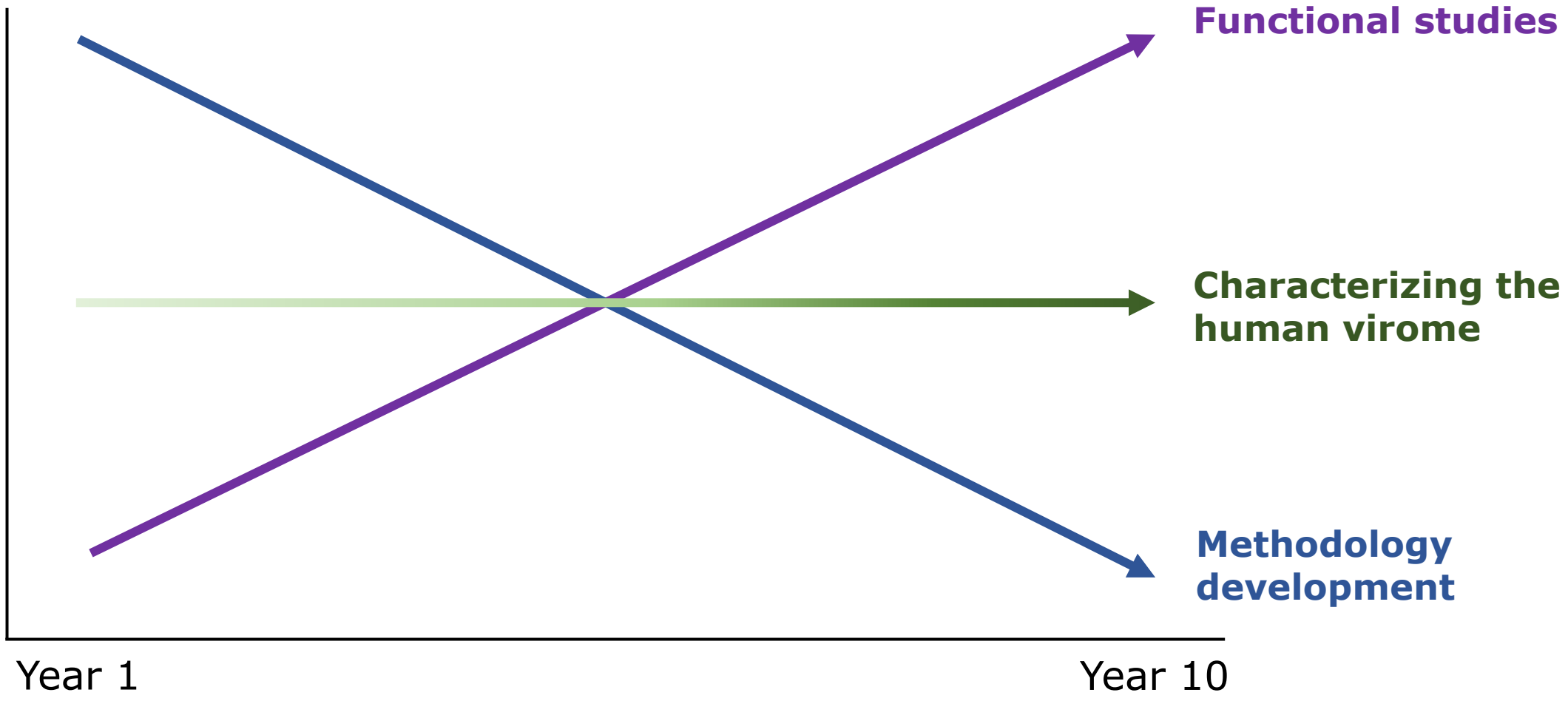
- NIH: Leverage other NIH efforts and Common Fund programs
- NSF: Instrumental and computational tool development for virome research
- DOE (National Microbiome Data Collaborative): “Whole Virome Catalog” partnering with International Committee on Taxonomy of Viruses; viral dynamics of healthy human virome in environments
- Global Virome Project: Global consortium to predict, prevent, and respond to future viral pandemic threats
- ICTV: Viral taxonomy
- American Type Culture Collection: Microbial biorepository
- USDA Animal and Plant Health Inspection Service: Animal and plant viral pathogen research

Human Virome Program Concept

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

1. Characterize the human virome in longitudinal, diverse cohorts across the lifespan
2. Develop tools, models, and methods to interrogate and annotate the human virome
3. Elucidate the human host/virome interactome
4. Data Analysis and Coordinating Center (DACC)

10-Year Program Projection



Human Virome Program Phase 1 Budget

$228.25M over 5 years

	FY24	FY25	FY26	FY27	FY28
Initiative 1 – Virome in diverse cohorts (U01)	$10M	$30M	$30M	$30M	$20M
Initiative 2 – Tools, models, methods (R01)	$4M	$8M	$8M	$8M	$4M
Initiative 3 – Host/virome interactome (R01)	$7.5M	$15M	$15M	$15M	$7.5M
Initiative 4 – DACC (U24)	$3M	$3M	$3M	$3M	$3M
RMS	$250K	$250K	$250K	$250K	$250K
TOTAL	**$24.75M**	**$56.25M**	**$56.25M**	**$56.25M**	**$34.75M**

Council Action:
Vote for approval of the concept for the Human Virome Program

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

Extra Slides

Technical Challenges

PLOS PATHOGENS

PEARLS

5 challenges in understanding the role of the virome in health and disease

David Wang *

Departments of Molecular Microbiology and Pathology and Immunology, Washington University in St. Louis School of Medicine, St. Louis, Missouri, United States of America

Inability to identify all viruses due to the absence of a universal viral sequence: The challenge of viral "dark matter"

Inadequate sampling strategies bias towards DNA viruses and against RNA viruses

Lack of culture systems to propagate components of the virome

The need for experimental animal-infection models

Dichotomy between eukaryotic virus and phage communities

The Human Virome: Dark Matter

Cell Host & Microbe
Review

Bacteriophages of the Human Gut: The "Known Unknown" of the Microbiome

Andrey N. Shkoporov[1,*] and Colin Hill[1]
[1]APC Microbiome Ireland & School of Microbiology, University College Cork, Co. Cork, Ireland
*Correspondence: andrey.shkoporov@ucc.ie
https://doi.org/10.1016/j.chom.2019.01.017

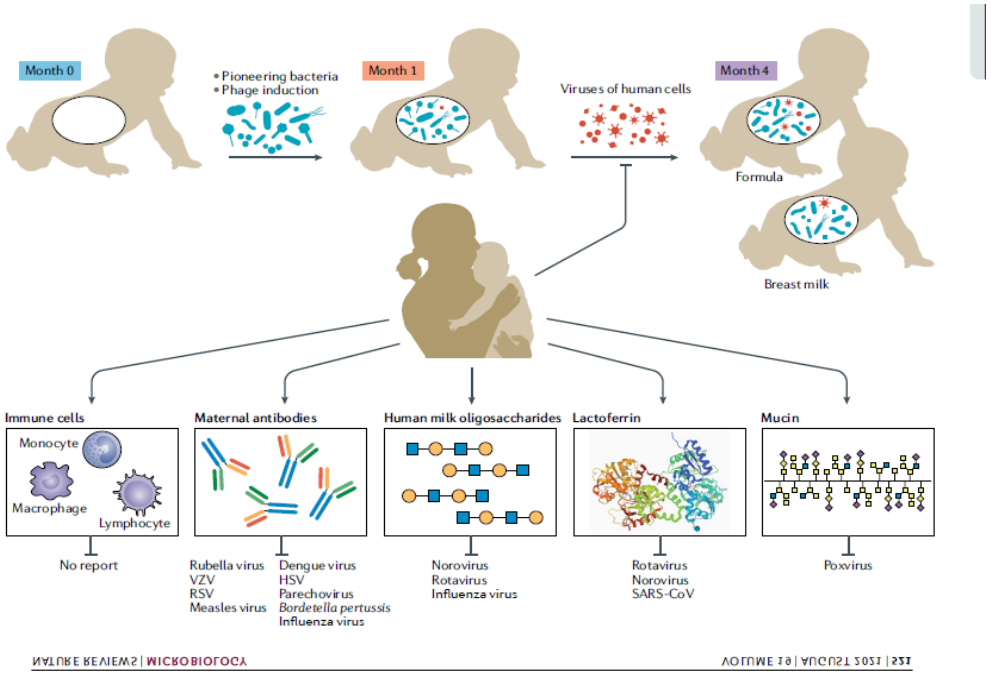
The human gut microbiome is a dense and taxonomically diverse consortium of microorganisms. While the bacterial components of the microbiome have received considerable attention, comparatively little is known about the composition and physiological significance of human gut-associated bacteriophage populations (phageome). By extrapolating our knowledge of phage-host interactions from other environments, one could expect that >10^{12} viruses reside in the human gut, and we can predict that they play important roles in regulating the complex microbial networks operating in this habitat. Before delving into their function, we need to first overcome the challenges associated with studying and characterizing the phageome. In this Review, we summarize the available methods and main findings regarding taxonomic composition, community structure, and population dynamics in the human gut phageome. We also discuss the main challenges in the field and identify promising avenues for future research.

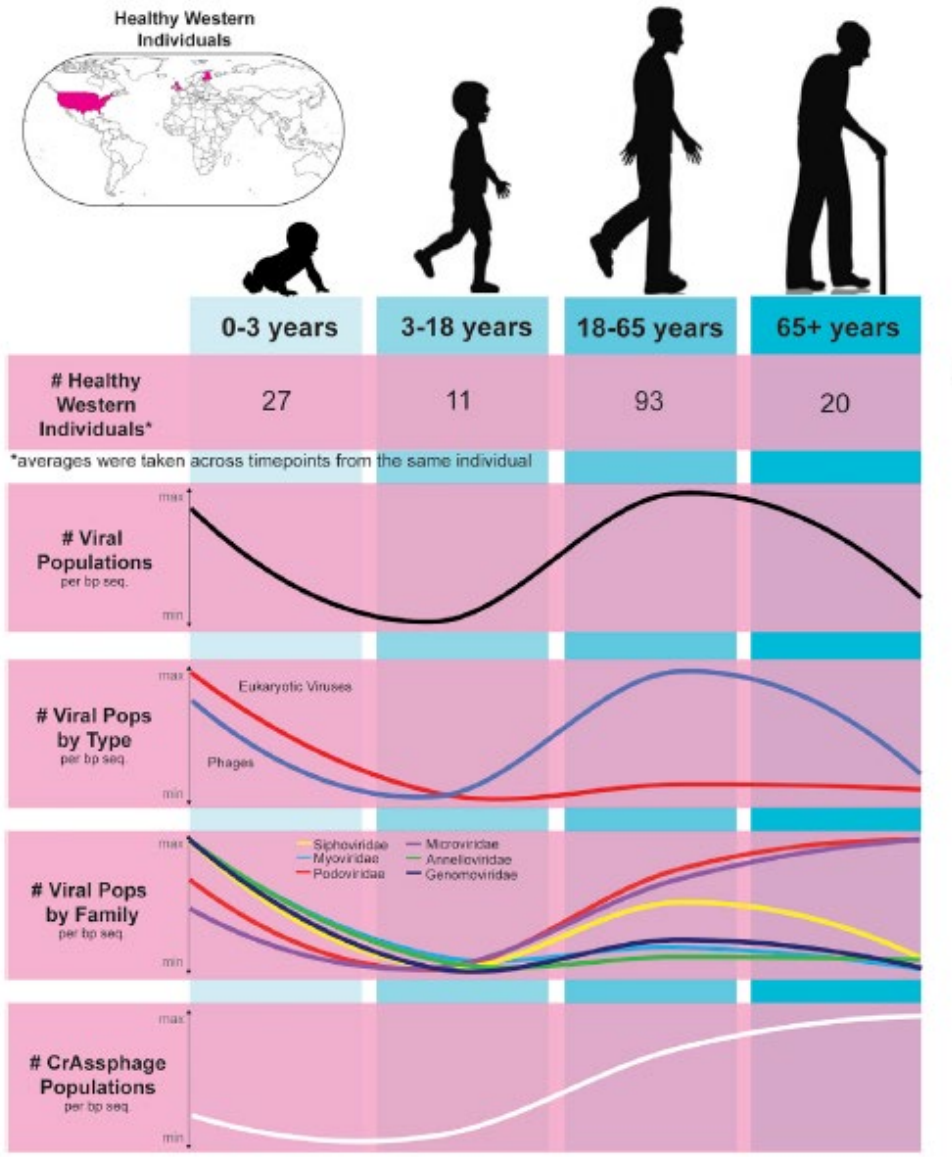
The human virome: assembly, composition and host interactions

Guanxiang Liang ✉ *and Frederic D. Bushman* ✉

Abstract | The human body hosts vast microbial communities, termed the microbiome. Less well known is the fact that the human body also hosts vast numbers of different viruses, collectively termed the 'virome'. Viruses are believed to be the most abundant and diverse biological entities on our planet, with an estimated 10^{31} particles on Earth. The human virome is similarly vast and complex, consisting of approximately 10^{13} particles per human individual, with great heterogeneity. In recent years, studies of the human virome using metagenomic sequencing and other methods have clarified aspects of human virome diversity at different body sites, the relationships to disease states and mechanisms of establishment of the human virome during early life. Despite increasing focus, it remains the case that the majority of sequence data in a typical virome study remain unidentified, highlighting the extent of unexplored viral 'dark matter'. Nevertheless, it is now clear that viral community states can be associated with adverse outcomes for the human host, whereas other states are characteristic of health. In this Review, we provide an overview of research on the human virome and highlight outstanding recent studies that explore the assembly, composition and dynamics of the human virome as well as host–virome interactions in health and disease.

Evolution of the Virome over the Lifespan





The Gut Virome Database Reveals Age-Dependent Patterns of Virome Diversity in the Human Gut

Ann C. Gregory,[1,4,5] Olivier Zablocki,[1,3,4] Ahmed A. Zayed,[1,3] Allison Howell,[1] Benjamin Bolduc,[1,3] and Matthew B. Sullivan[1,2,3,6,*]

Cell Host & Microbe 28, 724–740, November 11, 2020 © 2020 Elsevier Inc.

The Virome's Association with Health and Disease

Gastroenterology 2020;159:1839–1852

BASIC AND TRANSLATIONAL—LIVER

Intestinal Virome Signature Associated With Severity of Nonalcoholic Fatty Liver Disease

Sonja Lang,[1,2,*] **Münevver Demir**,[3,*] Anna Martin,[2] Lu Jiang,[1,4] Xinlian Zhang,[5] Yi Duan,[1,4] Bei Gao,[1] Hilmar Wisplinghoff,[6,7,8] Philipp Kasper,[2] Christoph Roderburg,[3] Frank Tacke,[3] Hans-Michael Steffen,[2] Tobias Goeser,[2] Juan G. Abraldes,[9] Xin M. Tu,[5] Rohit Loomba,[1] Peter Stärkel,[10] David Pride,[1,11,12] Derrick E. Fouts,[13] and Bernd Schnabl[1,4,12]

A catalog of tens of thousands of viruses from human metagenomes reveals hidden associations with chronic diseases

Michael J. Tisza[a] and Christopher B. Buck[a,1]

[a]Laboratory of Cellular Oncology, National Cancer Institute, NIH, Bethesda, MD 20892

The Virome plays a role

Commensal viruses maintain intestinal intraepithelial lymphocytes via noncanonical RIG-I signaling

Lei Liu[1,3], Tao Gong[1,3], Wanyin Tao[1,3], Bolong Lin[1], Cong Li[1], Xuesen Zheng[1], Shu Zhu[1*], Wei Jiang[1*] and Rongbin Zhou[1,2*]

Much attention has focused on commensal bacteria in health and disease, but the role of commensal viruses is understudied. Although metagenomic analysis shows that the intestine of healthy humans and animals harbors various commensal viruses and the dysbiosis of these viruses can be associated with inflammatory diseases, there is still a lack of causal data and underlying mechanisms to understand the physiological role of commensal viruses in intestinal homeostasis. In the present study, we show that commensal viruses are essential for the homeostasis of intestinal intraepithelial lymphocytes (IELs). Mechanistically, the cytosolic viral RNA-sensing receptor RIG-I in antigen-presenting cells can recognize commensal viruses and maintain IELs via a type I interferon–independent, but MAVS-IRF1-IL-15 axis-dependent, manner. The recovery of IELs by interleukin-15 administration reverses the susceptibility of commensal virus-depleted mice to dextran sulfate sodium–induced colitis. Collectively, our results indicate that commensal viruses maintain the IELs and consequently sustain intestinal homeostasis via noncanonical RIG-I signaling.

NATURE IMMUNOLOGY | VOL 20 | DECEMBER 2019 | 1681–1691 | www.nature.com/natureimmunology

Viral complementation of immunodeficiency confers protection against enteric pathogens via interferon-λ

Harshad Ingle[1,6], Sanghyun Lee[2,6], Teresa Ai[1], Anthony Orvedahl[3], Rachel Rodgers[3], Guoyan Zhao[2], Meagan Sullender[1], Stefan T. Peterson[1], Marissa Locke[2], Ta-Chiang Liu[2], Christine C. Yokoyama[2], Bridgett Sharp[4], Stacey Schultz-Cherry[4], Jonathan J. Miner[1,2,5] and Megan T. Baldridge[1,5*]

Commensal microbes profoundly impact host immunity to enteric viral infections[1]. We have shown that the bacterial microbiota and host antiviral cytokine interferon-λ (IFN-λ) determine the persistence of murine norovirus in the gut[2,3]. However, the effects of the virome in modulating enteric infections remain unexplored. Here, we report that murine astrovirus can complement primary immunodeficiency to protect against murine norovirus and rotavirus infections. Protection against infection was horizontally transferable between immunocompromised mouse strains by co-housing and fecal transplantation. Furthermore, protection against enteric pathogens corresponded with the presence of a specific strain of murine astrovirus in the gut, and this complementation of immunodeficiency required IFN-λ signalling in gut epithelial cells. Our study demonstrates that elements of the virome can protect against enteric pathogens in an immunodeficient host.

NATURE MICROBIOLOGY | VOL 4 | JULY 2019 | 1120–1128 | www.nature.com/naturemicrobiology