

Viruses and Chronic Aging: Building a Research Community

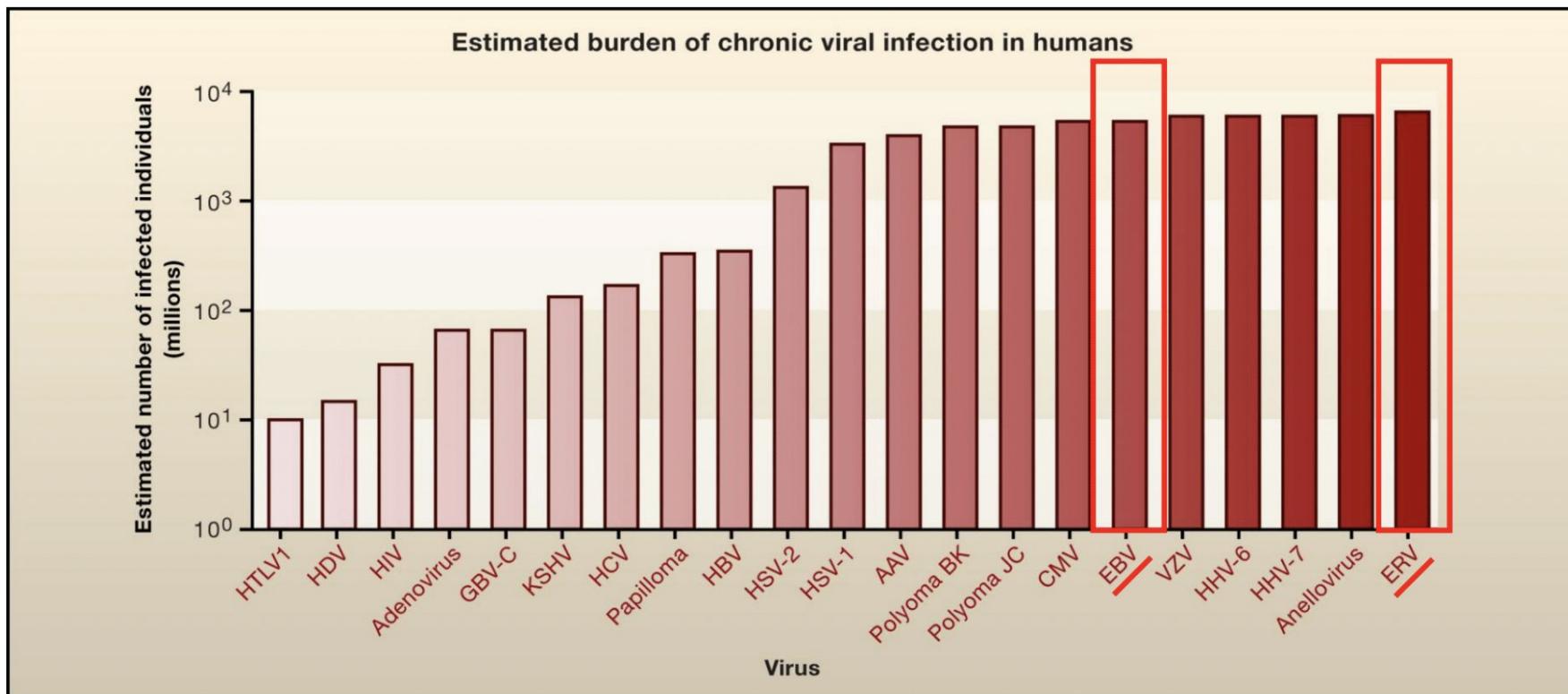
Amy Proal, PhD

PolyBio Research Foundation

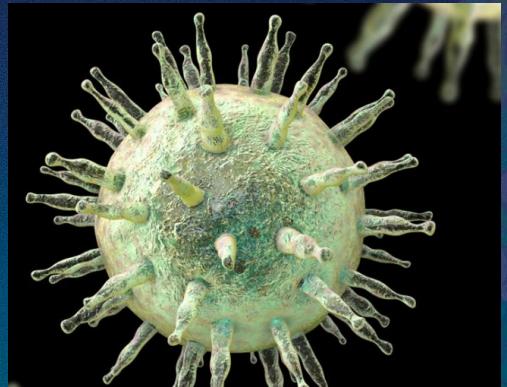
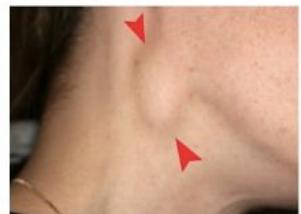
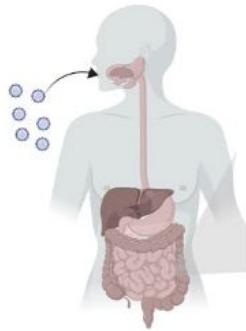
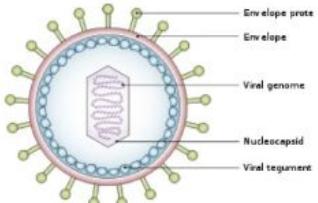
Drivers of aging

- ❑ Mitochondrial dysfunction
- ❑ Inflammaging
- ❑ Cognitive decline

Human Virome



Mononucleosis



Viruses must “hack” our mitochondria to replicate

Review

Pathogens Hijack Host Cell Metabolism: Intracellular Infection as a Driver of the Warburg Effect in Cancer and Other Chronic Inflammatory Conditions

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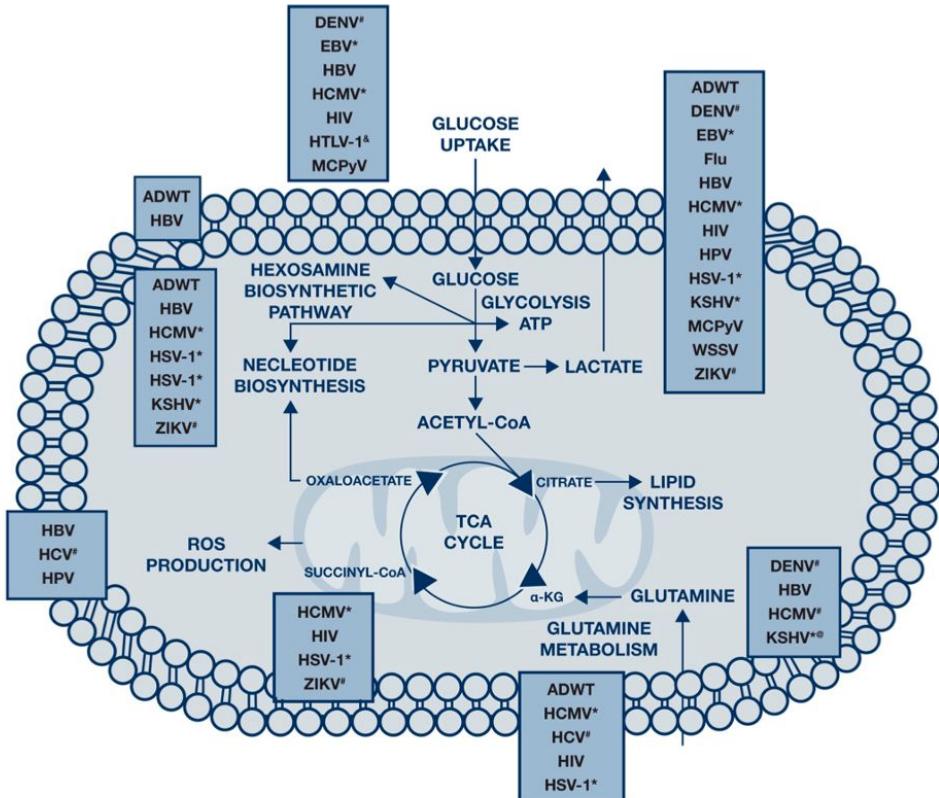
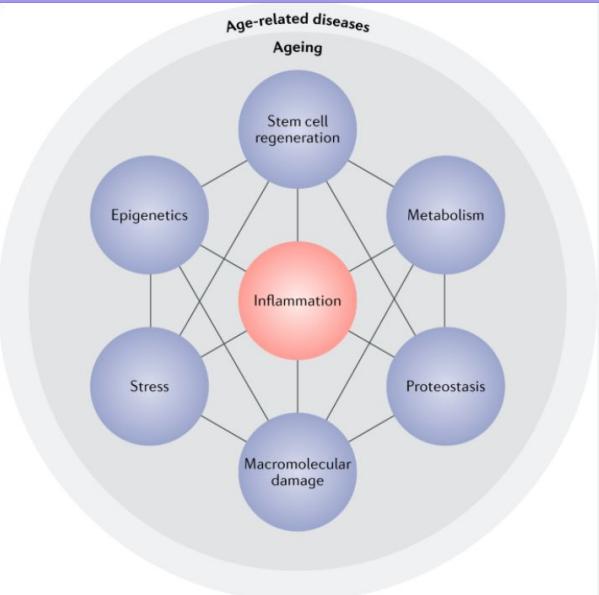


Figure 2. Infection by different viruses alters different metabolic pathways, as demonstrated by alterations in metabolite levels, flux, and tracing. HIV activity is referenced in [76–79]. [®]KSHV downregulates cholesterol synthesis but upregulates lipid synthesis; [#]Flavivirus family; ^{*}Herpesvirus family; ⁺virus downregulates this metabolic activity. Reproduced from [32], an open access article distributed under the Creative Commons Attribution 4.0 International License (<http://creativecommons.org/licenses/by/4.0/>).

Review Article | Published: 25 July 2018

Inflammaging: a new immune–metabolic viewpoint for age-related diseases

[Claudio Franceschi](#), [Paolo Garagnani](#), [Paolo Parini](#), [Cristina Giuliani](#)  & [Aurelia Santoro](#)



[nature](#) > [articles](#) > [article](#)

Article | [Open access](#) | Published: 17 July 2024

Inhibition of IL-11 signalling extends mammalian healthspan and lifespan

[Anissa A. Widjaja](#)✉, [Wei-Wen Lim](#), [Sivakumar Viswanathan](#), [Sonia Chothani](#), [Ben Corden](#), [Cibi Mary Dasan](#), [Joyce Wei Ting Goh](#), [Radiance Lim](#), [Brijesh K. Singh](#), [Jessie Tan](#), [Chee Jian Pua](#), [Sze Yun Lim](#), [Eleonora Adami](#), [Sebastian Schafer](#), [Benjamin L. George](#), [Mark Sweeney](#), [Chen Xie](#), [Madhulika Tripathi](#), [Natalie A. Sims](#), [Norbert Hübner](#), [Enrico Petretto](#), [Dominic J. Withers](#), [Lena Ho](#), [Jesus Gil](#), ... [Stuart A. Cook](#)✉

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doi: [10.1172/JCI118514](https://doi.org/10.1172/JCI118514)

PMCID: PMC507136

PMID: [8613544](#)

Interleukin-11: stimulation in vivo and in vitro by respiratory viruses and induction of airways hyperresponsiveness.

[O Einarsson](#), [G P Geba](#), [Z Zhu](#), [M Landry](#), and [J A Elias](#)

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JOURNAL ARTICLE

Interactomics: Dozens of Viruses, Co-evolving With Humans, Including the Influenza A Virus, may Actively Distort Human Aging

Jérôme Teulière, Charles Bernard, Hugo Bonnefous, Johannes Martens, Philippe Lopez,
Eric Bapteste  Author Notes

Molecular Biology and Evolution, Volume 40, Issue 2, February 2023, msad012,

<https://doi.org/10.1093/molbev/msad012>

Published: 17 January 2023

This network-based analysis uncovered dozens of viruses encoding proteins experimentally demonstrated to interact with proteins from pathways associated with human aging, including cellular senescence, which is a cell's loss of power over division and growth.

Table 1. Top 25 Viruses Able to Interact With Human Cellular Senescence-associated Proteins in the HIVDB.

Virus ^a	Viral family	Viral sequences	Human interactors	Score ^b	Degree ^c
HHV-4	Herpesviridae	35	45	1575	28.8
H1N1	Orthomyxoviridae	11	64	704	24.0
HIV-1	Retroviridae	10	57	570	29.3
HHV-8	Herpesviridae	17	29	493	28.9
HHV-1	Herpesviridae	15	22	330	48.5
HPV16	Papillomaviridae	5	37	185	55.4
HPV18	Papillomaviridae	5	26	130	45.6

“Owing to the considerable number of human viruses, this evolutionary-minded view encourages a reconceptualization of the locus of aging, no longer exclusively focused on our own genetic material but expanded toward a larger set of genetic entities interacting with our species, such as viruses”

Cognitive decline

Neuron

Author Manuscript

HHS Public Access

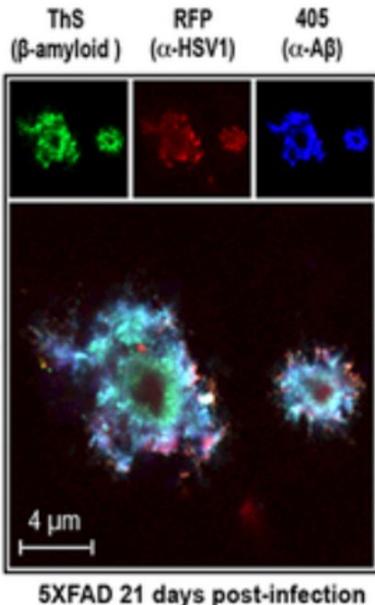
Alzheimer's Disease-Associated β -Amyloid Is Rapidly Seeded by *Herpesviridae* to Protect against Brain Infection

William A. Eimer^{1,2}, Deepak Kumar Vijaya Kumar^{1,2}, Nanda Kumar N. Shanmugam^{1,2}, Alex S. Rodriguez^{1,2}, Teryn Mitchell^{1,2}, Kevin J. Washicosky^{1,2}, Bence György², Xandra O. Breakefield², Rudolph E. Tanzi^{1,2,*}, and Robert D. Moir^{1,2,3,*}

¹Genetics and Aging Research Unit, MassGeneral Institute for Neurodegenerative Disease, Charlestown, MA 02129, USA

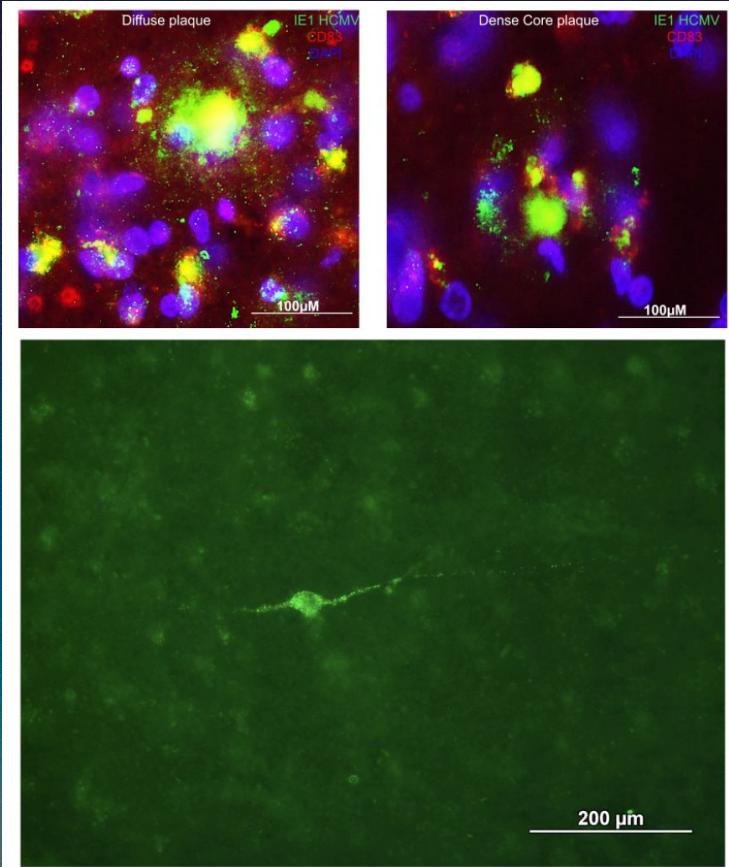
²Department of Neurology, Massachusetts General Hospital and Harvard Medical School, Charlestown, MA 02129, USA

e.



Alzheimer's disease:
Cytomegalovirus concentrated
within microglia around plaques
(top left and top right) as well as
replicating within axons and
dendrites within infected neurons
(bottom)

Image: Ben Readhead PhD, Banner Center for
Neurodegenerative Disease



[Neurotherapeutics](#). 2018 Apr; 15(2): 417–429.

PMCID: PMC5935641

Published online 2018 Feb 27. doi: [10.1007/s13311-018-0611-x](https://doi.org/10.1007/s13311-018-0611-x)

PMID: [29488144](#)

Anti-herpetic Medications and Reduced Risk of Dementia in Patients with Herpes Simplex Virus Infections—a Nationwide, Population-Based Cohort Study in Taiwan

Nian-Sheng Tzeng,^{1,2} Chi-Hsiang Chung,^{3,4,5} Fu-Huang Lin,⁴ Chien-Ping Chiang,⁶ Chin-Bin Yeh,^{1,7} San-Yuan Huang,^{1,7} Ru-Band Lu,^{1,8,9,10,11,12} Hsin-An Chang,^{1,2} Yu-Chen Kao,^{1,13} Hui-Wen Yeh,¹ Wei-Shan Chiang,^{1,14} Yu-Ching Chou,⁴ Chang-Huei Tsao,⁵ Yung-Fu Wu,⁵ and Wu-Chien Chien^{✉^{14,5}}

LongCovid: chronic SARS-CoV-2 infection

nature immunology

Review article

<https://doi.org/10.1038/s41590-023-01601-2>

SARS-CoV-2 reservoir in post-acute sequelae of COVID-19 (PASC)

Received: 30 March 2023

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Published online: 04 September 2023



Check for updates

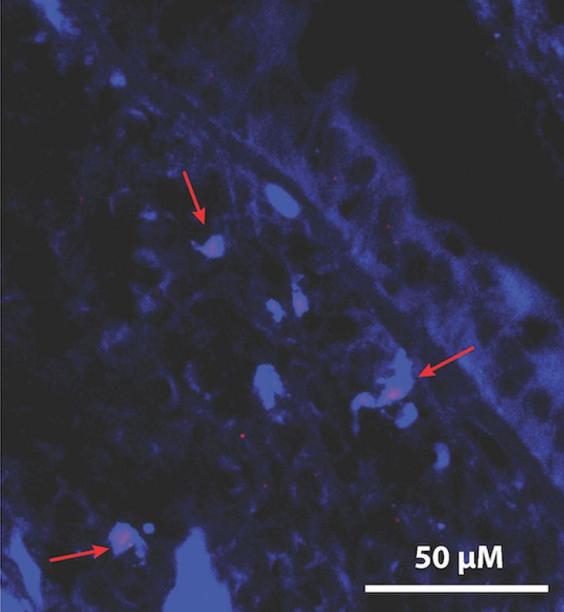
Amy D. Proal , Michael B. VanElzakker^{1,2}, Soo Aleman³, Katie Bach^{1,4}, Brittany P. Boribong ^{5,6,7}, Marcus Buggert ⁸, Sara Cherry ⁹, Daniel S. Chertow ^{10,11}, Helen E. Davies ¹², Christopher L. Dupont ¹³, Steven G. Deeks¹⁴, William Eimer^{7,15,16,17}, E. Wesley Ely¹⁸, Alessio Fasano^{5,6,7}, Marcelo Freire ¹⁹, Linda N. Geng²⁰, Diane E. Griffin²¹, Timothy J. Henrich²², Akiko Iwasaki ^{23,24,25}, David Izquierdo-Garcia^{26,27}, Michela Locci²⁸, Saurabh Mehandru ^{29,30}, Mark M. Painter ³¹, Michael J. Peluso¹⁴, Etheresia Pretorius^{32,33}, David A. Price ^{34,35}, David Putrino³⁶, Richard H. Scheuermann ^{37,38,39}, Gene S. Tan^{13,40}, Rudolph E. Tanzi ^{7,15,16,17}, Henry F. VanBrocklin⁴¹, Lael M. Yonker ^{5,6,7} & E. John Wherry ³¹

Tissue-based T cell activation and viral RNA persist for up to 2 years after SARS-CoV-2 infection

MICHAEL J. PELUSO , DYLAN RYDER , ROBERT R. FLAVELL , YINGBING WANG, JELENA LEVI , BRIAN H. LAFRANCIO , AMANDA M. BUCK , SADIE E. MUNTER, [...], AND TIMOTHY J. HENRICH +25 authors [Authors Info & Affiliations](#)

SCIENCE TRANSLATIONAL MEDICINE • 3 Jul 2024 • Vol 16, Issue 754 • DOI: 10.1126/scitranslmed.adk3295

Pt 16 (442 Days Post COVID-19)



Pt 22 (676 Days Post COVID-19)

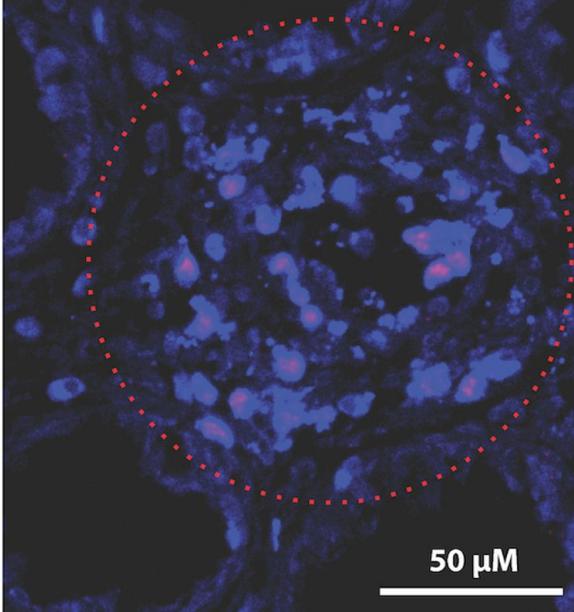


Table 1 | Identification of SARS-CoV-2 RNA and protein after COVID-19

Tissue (biopsy)	RNA Protein	PASC symptoms	Location
Tissue (biopsy)			
Goh et al. ³⁹	✓	S, N	✓ Appendix, skin and breast tissues 163 and 426 d after COVID-19
Zollner et al. ³⁸	✓	N	✓ Gut mucosa/epithelium tissue ~7 months after COVID-19
deMelo et al. ²⁷	✓	N	✓ Olfactory neuroepithelium tissue 110–196 d after COVID-19
Gaebler et al. ³³	✓	N	No Intestinal tissue ~4 months after COVID-19
Cheung et al. ¹¹⁴	✓	S, N	NM Colon, appendix, ileum, hemorrhoid, liver, gallbladder and lymph nodes 9–180 d after COVID-19
Hany et al. ²⁹	NM	N	NM Gastric and gallbladder tissues 274–380 d after COVID-19
Miura et al. ³⁰	✓	N	No Adenoid tonsil, adenoid tissue, nasal cytobrush and nasal wash from children with no documented COVID-19 or upper airway infection in the month before collection
Xu et al. ³⁷	✓	NM	No Child adenoid and tonsil tissue up to 303 d after COVID-19
Peluso et al. ²⁴	✓	NM	✓ Colorectal lamina propria tissue 158–676 d after COVID-19
Yao et al. ²⁵	✓	S,N	✓ Fungiform papillae tongue tissue 6–63 weeks after COVID-19
Tissue (autopsy)			
Stein et al. ³¹	✓	N	NM Dozens of human body and brain tissue types at least 31 d and up to 230 d after COVID-19
Roden et al. ³²	✓	NM	NM Lung tissue up to 174 d after COVID-19
Rendiero et al. ²⁶	NM	S	NM Lung tissue up to 359 d after COVID-19
Stool			
Natarajan et al. ¹¹⁵	✓	NM	✓ Stool up to 230 d after COVID-19
Yonker et al. ⁸⁴	✓	S, N	✓ RNA in stool of children with MIS-C 13–62 d after COVID-19, S and N protein in plasma
Jin et al. ¹¹⁶	✓	S	NM NM Neonatal stool in infants born to mothers whose COVID-19 symptoms resolved more than 10 weeks before delivery
Blood			
Schultheiß et al. ⁴⁰	NM	S1	✓ Plasma at a median time of 8 months after COVID-19
Swank et al. ⁴¹	NM	S, S1, N	✓ Plasma up to 12 months after COVID-19
Peluso et al. ⁴⁴	NM	S1, N	✓ Plasma neuron-derived EVs 35–84 d after COVID-19
Peluso et al. ⁴²	NM	S1, S, N	✓ Plasma up to 16 months after COVID-19
Craddock et al. ⁴⁵	✓	S	✓ Spike linked to EVs in samples obtained at least 8–12 weeks (up to 1 year) after COVID-19
Tejerina et al. ¹¹⁷	✓	NM	✓ Plasma at a median time of 55 d after COVID-19 (also found in stool/urine at the same median time point)

✓, identified; No, not present; NM, not measured; S and S1, spike protein.

Rapamycin: does it improve the immune response to chronic pathogens?

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

INFECTIOUS DISEASE

TORC1 inhibition enhances immune function and reduces infections in the elderly

Joan B. Mannick^{1*†}, Melody Morris¹, Hans-Ulrich P. Hockey², Guglielmo Roma³, Martin Beibel³, Kenneth Kulmatycki¹, Mollie Watkins¹, Tea Shavlakadze¹, Weihua Zhou¹, Dean Quinn⁴, David J. Glass¹, Lloyd B. Klickstein^{1*}

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Inhibition of the mechanistic target of rapamycin (mTOR) protein kinase extends life span and ameliorates aging-related pathologies including declining immune function in model organisms. The objective of this phase 2a randomized, placebo-controlled clinical trial was to determine whether low-dose mTOR inhibitor therapy enhanced immune function and decreased infection rates in 264 elderly subjects given the study drugs for 6 weeks. A low-dose combination of a catalytic (BEZ235) plus an allosteric (RAD001) mTOR inhibitor that selectively inhibits target of rapamycin complex 1 (TORC1) downstream of mTOR was safe and was associated with a significant ($P = 0.001$) decrease in the rate of infections reported by elderly subjects for a year after study drug initiation. In addition, we observed an up-regulation of antiviral gene expression and an improvement in the response to influenza vaccination in this treatment group. Thus, selective TORC1 inhibition has the potential to improve immune function and reduce infections in the elderly.

- ❑ Increased interferon-induced antiviral gene expression
- ❑ Improved response to influenza vaccination
- ❑ Rapamycin participants reported a lower rate of infection for a year
- ❑ Improved T cell exhaustion

Building a community

The Long Covid Research Consortium

A scientific collaboration to rapidly and comprehensively study LongCovid

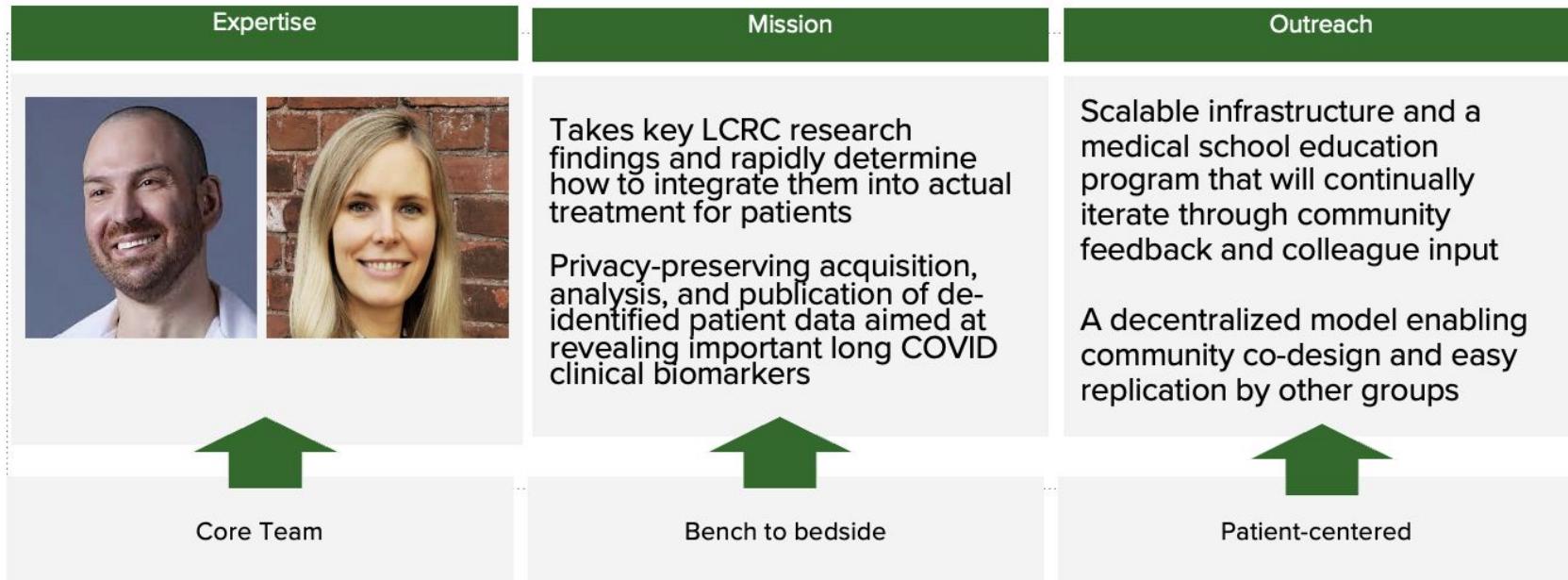


The LongCovid Research Consortium (LCRC) Scientific Team



- ❑ Open science
- ❑ Have a strong hypothesis vision
- ❑ Bet on the best teams
- ❑ Open data sharing
- ❑ Hold regular group brainstorm meetings
- ❑ Do not compromise on methods
- ❑ Create an infrastructure for translation

(CoRE): an open-source long COVID clinic to innovate treatment options and educational programs for long COVID clinicians



Studying viruses across the entire human body

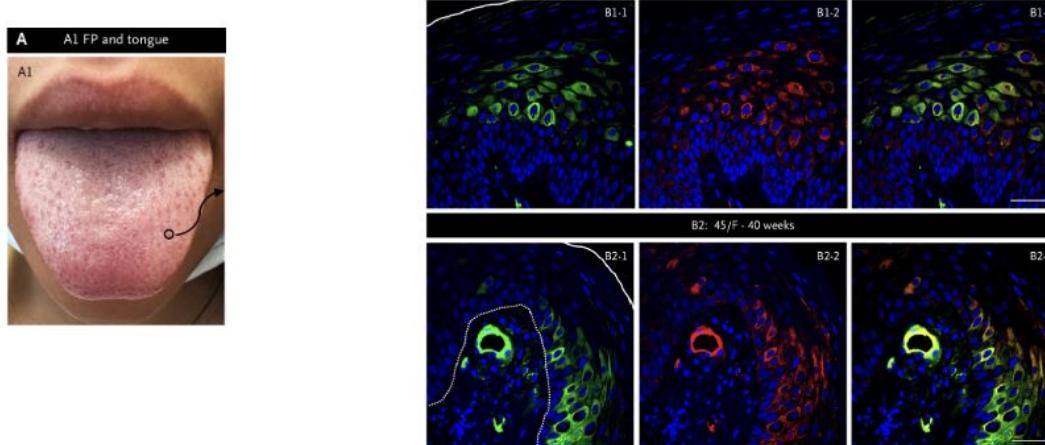
Types of tissue being collected

- Arterial plaque/artery tissue
- Victims of sudden death
- Brain/nerve ganglia
- Gut tissue
- Lymph node tissue
- Small fiber nerve tissue
- Bone marrow
- C2 nerve root
- Craniocervical ligament
- Vagus nerve
- Brain blood clot
- Tonsil/tongue tissue
- Endometriosis

"Don't throw it out!"

Long-Term Dysfunction of Taste Papillae in SARS-CoV-2

Authors: Qin Yao, M.D., Máire E. Doyle, Ph.D., Qing-Rong Liu, Ph.D., Ashley Appleton, B.S., Jennifer F. O'Connell, Ph.D., Nan-ping Weng, M.D., Ph.D., and Josephine M. Egan, M.D. [✉ Author Info & Affiliations](#)



SARS-CoV-2 spike (green) and nucleocapsid (red) proteins measured via immunofluorescence in fungiform papillae epithelium from 2 patients with taste disturbance post-SARS-CoV-2



LEGEND

CONNECTION

Institution

Body Region

Sample Sharing

PROJECT TYPE

Biomarker

Imaging

Model

Therapeutic

Tissue

ME/CFS

Using circulating CD8 T cells as SARS-CoV-2 Reservoir Biosensors

Testing Combinations of Antivirals to Treat Persistent Infection

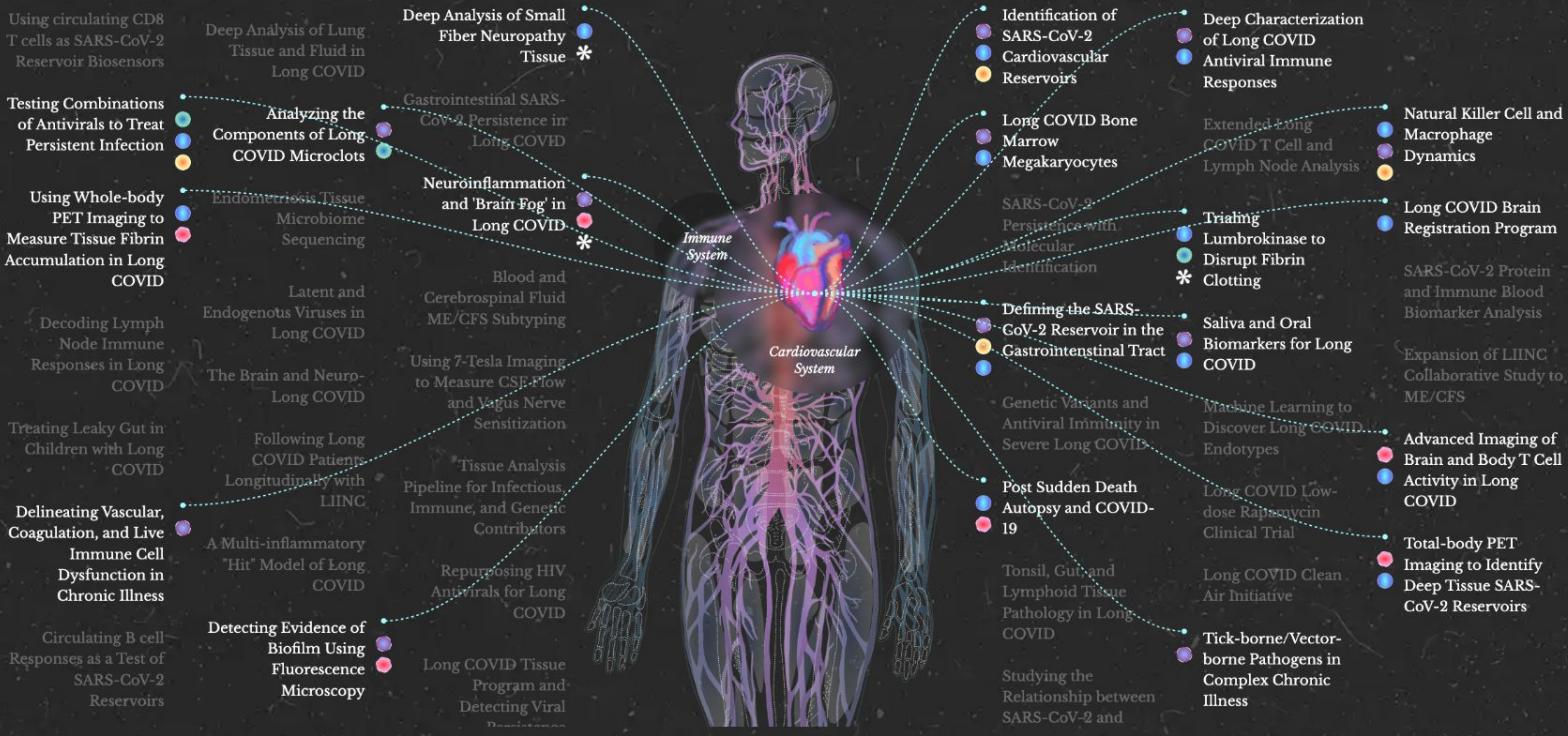
Using Whole-body PET Imaging to Measure Tissue Fibrin Accumulation in Long COVID

Decoding Lymph Node Immune Responses in Long COVID

Treating Leaky Gut in Children with Long COVID

Delineating Vascular, Coagulation, and Live Immune Cell Dysfunction in Chronic Illness

Circulating B cell Responses as a Test of SARS-CoV-2 Reservoirs



INSTITUTIONS

- Cardiff University Georgetown University Harvard Medical School Icahn School of Medicine at Mount Sinai Institut Pasteur France J. Craig Venter Institute
 Johns Hopkins Karolinska Institutet New York University Paris Cité University Stellenbosch University UMass Chan Medical School
 University of California San Francisco University of Colorado Boulder University of Pennsylvania Yale School of Medicine



Thank you!

Amy Proal, PhD

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