Long COVID Update

Briefing for the Advisory Committee to the Director (ACD)

June 14, 2024

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Principal Deputy Director, NIAID

Walter J. Koroshetz, MD
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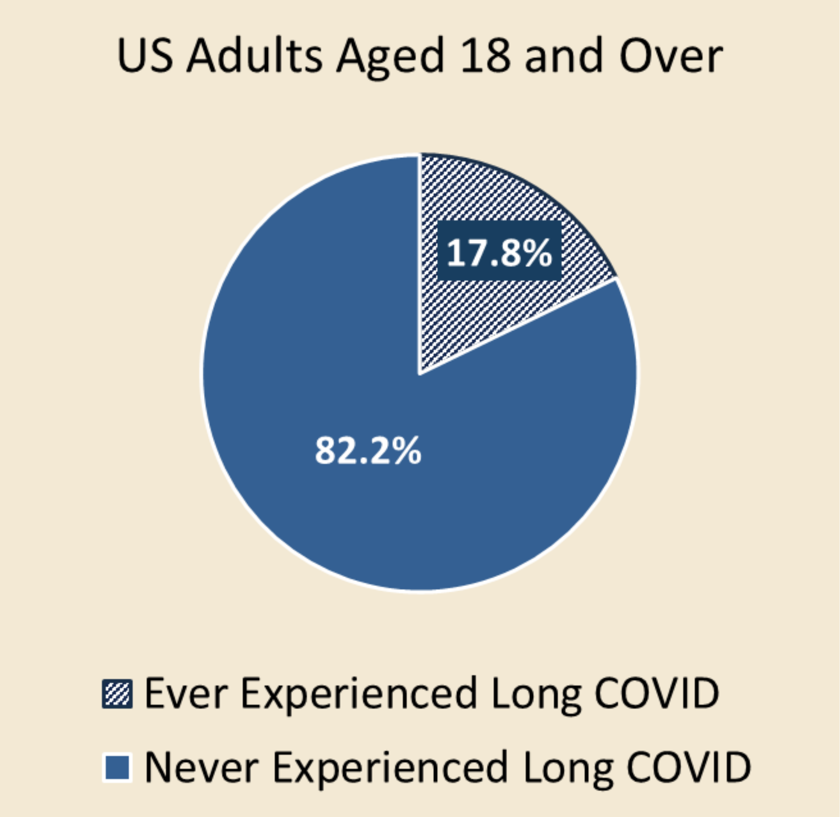
RECOVER
Researching COVID to Enhance Recovery

NIH National Institutes of Health
Researching COVID to Enhance Recovery

Introduction



- Approximately **17%** of adults aged 18 and over have EVER experienced post-COVID conditions (Long COVID). These adults had COVID and had some symptoms that lasted three months or longer.
- The Researching COVID to Enhance Recovery (RECOVER) Initiative – launched in 2021 – is an initial investment in research towards understanding Long COVID and other long-term, chronic illnesses that may appear post infection.

Source: U.S. Census Bureau, Household Pulse Survey, 2022-2024. Phase 4.1, April 2 – 29, 2024. https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm

NIH's RECOVER Initiative Objectives

Rapidly improve our **understanding** of and ability to **predict, treat, and prevent** PASC

KEY SCIENTIFIC AIMS

1. Understand clinical spectrum/biology underlying recovery over time
2. Define risk factors, incidence/prevalence, and distinct PASC sub-phenotypes
3. Study pathogenesis over time and possible relation to other organ dysfunction/disorders
4. Identify interventions to treat and prevent PASC

GUIDING PRINCIPLES

- **Patient-centered,** participants as partners
- **National Scale with inclusive**, **diverse** participation & community engagement
- **Platform protocols,** standardized methodologies, and common data elements
- **Adaptive** approaches based on emerging science

RECOVER's National Scope

With observational research sites across the country, the RECOVER Cohort is enrolling adults, children and their caregivers, and pregnant participants and their newborn infants.

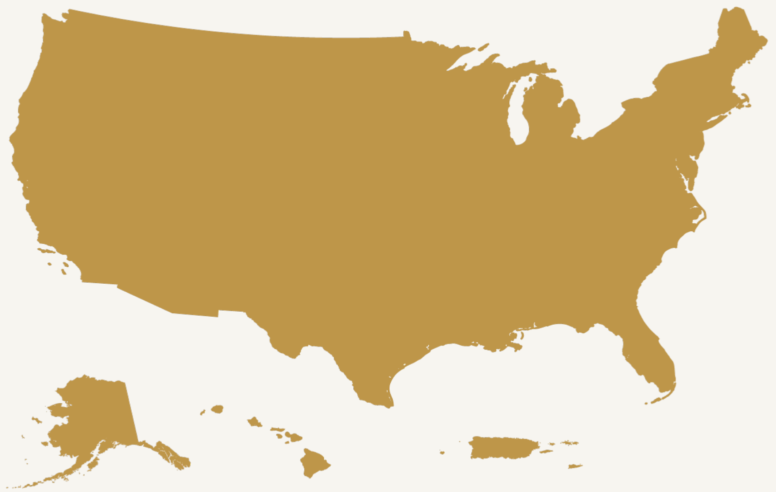
Adult and Pediatric enrollment takes place at over **30+ Hubs**

EHR, Adult, and Pediatric Studies include **60,000,000+ patient records**

Enrollment sites are active at **155+ locations** across the Nation

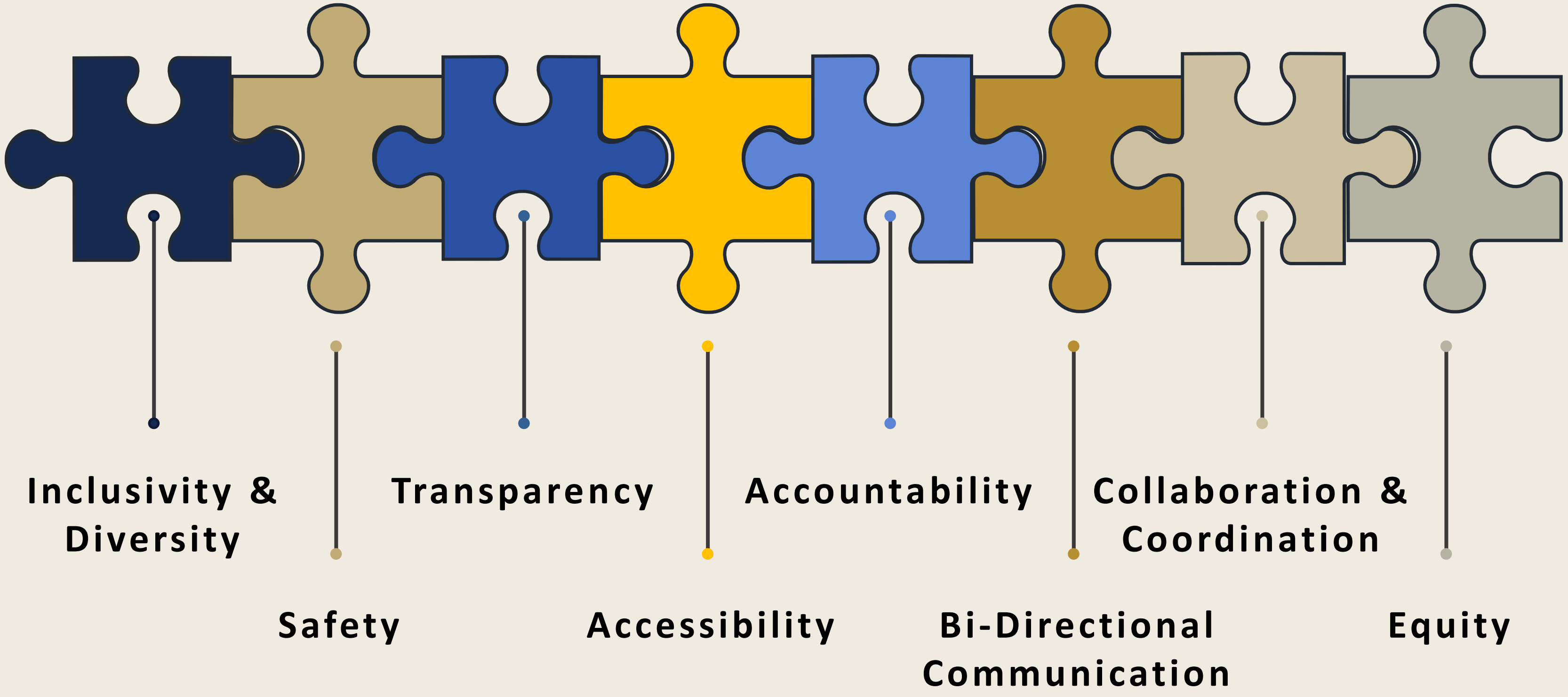
- **Adult**
- **Pregnancy**
- **Pediatric**
- **Autopsy**
- **EHR**

Enrollment Sites National Scope



Principles for Patient & Community Representative Engagement

RECOVER's Eight Principles of Engagement



RECOVER's Representative Engagement Definition

The process of working collaboratively with groups of people who are affiliated by geographic proximity, special interests, or similar situations with respect to the issues affecting their well-being.

(Informed by the definition of community engagement developed that federal agencies developed in the Principles of Community Engagement).

RECOVER's Representative Engagement Approach & Frameworks

Representative Engagement Approach

- Patient and community members are **involved in every phase of RECOVER research** and **coalesce in NCEG** at the center of RECOVER (e.g., planning, conducting, disseminating).
- Major RECOVER Initiative **decisions are made in partnership with patient and community Representatives**, and with broader input from patients and communities.
- Patient and community **members who are not Representatives are able to share ideas, concerns, hopes, and needs.**

Frameworks Leveraged

- **PCORI Engagement Rubric:**

  Emphasizes patients as partners in planning, conducting, and disseminating research.

- **Meaningful Involvement of Patient Advocates (Spieldenner, et al, 2022):**

  Emphasizes the voice of community members in decision-making and leadership.

- **Trauma-Informed Community Engagement:**

  Engages people with histories of trauma, recognizes the presence of trauma symptoms, and acknowledges the role that this plays in their lives.

Clinical characterization findings from the RECOVER observational cohorts

RECOVER
Researching COVID to Enhance Recovery

RECOVER: Helping Long COVID Patients by Informing Diagnosis, Care, and Treatment

RECOVER Key Scientific Aims

Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-phenotypes	Pathogenesis	Interventions

RECOVER Findings (Examples from 50+ publications)

- Symptom-based definition of Long COVID in adults and children (proposed)
  - Major step toward working case definition for diagnosis and patient monitoring
- Symptoms and conditions specifically associated with Long COVID in children (e.g. circulatory and respiratory)
- Vaccination significantly decreases risk of Long COVID
- Higher risk of new cardiovascular, neurologic, endocrine, GI symptoms in Black and Hispanic patients
- Distinguishing immune features of Long COVID identified

Patient Relevance

- Improved Diagnosis, Monitoring, and Care
- Better Preventative Care
- Better Diagnosis, Monitoring, Care, and Targeted Treatments

Findings from Long COVID Pathobiology Studies

RECOVER
Researching COVID to Enhance Recovery

The Post-Acute Sequelae of COVID-19: Symptom clusters overlap with ME/CFS

Fatigue in almost 90% of those with PASC. Prevalence of post-exertional malaise maybe as high as well.

Neurologic

- Memory/Word finding difficulties*
- Concentration difficulties/“brain fog”*
- Executive function difficulties*
- Sleep disorders*
- Pain syndromes- muscle, joint*
- Abnormal sensations- tingling*
- Headache*
- Postural Orthostatic Tachycardia*
- Abnormal smell/taste
- Visual abnormalities
- Dizziness/balance problems

CardioPulmonary

- Shortness of breath
- Dry cough
- Chest pain
- Exercise intolerance*
- Postural Orthostatic Tachycardia*
- Palpitations/Fast heart rate*
- Myocarditis
- Pulmonary fibrosis

Mental Health

- Post traumatic stress disorder
- Anxiety
- Depression

Gastrointestinal*

- Diarrhea
- Decreased appetite
- Nausea
- Abdominal pain

Other

- Abnormal temperature regulation*
- Chills, flushing sweats
- Sore throat
- Extreme thirst
- Skin changes
- Menstrual changes

**** Common symptom of ME/CFS***

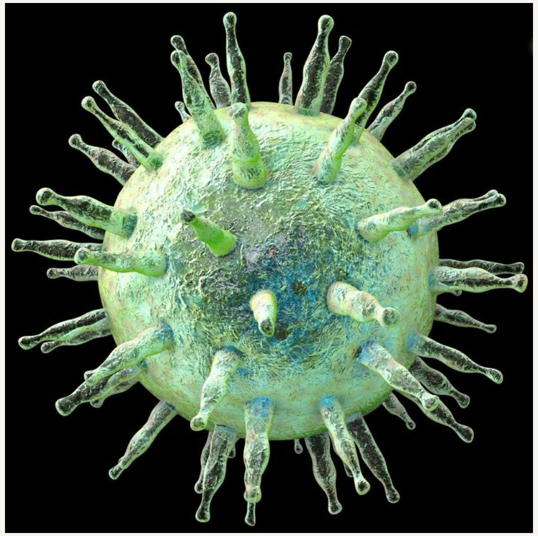
See Davis HE et. al. (2021) Characterizing Long Covid in an International Cohort: **7 months** of symptoms and their impact. medRxiv preprint https://www.medrxiv.org/content/10.1101/2020.12.24.20248802v2

Pathogenesis of Long-COVID

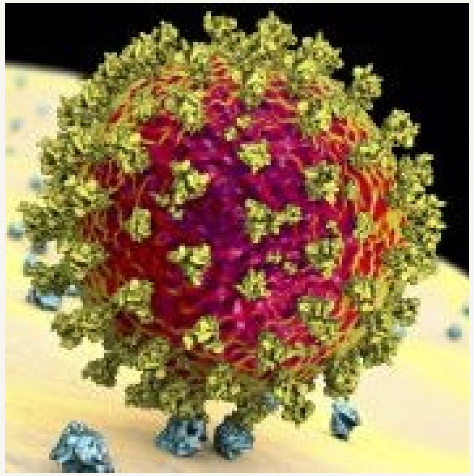
Viral reactivation

Persistent viral infection

Immune dysregulation

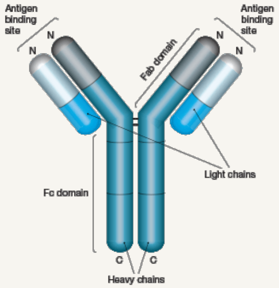


EBV



SARS-CoV-2 antigen

Macrophages



Antibodies

Is there autoimmunity in PASC?

> Viruses. 2022 Jun 28;14(7):1415. doi: 10.3390/v14071415.

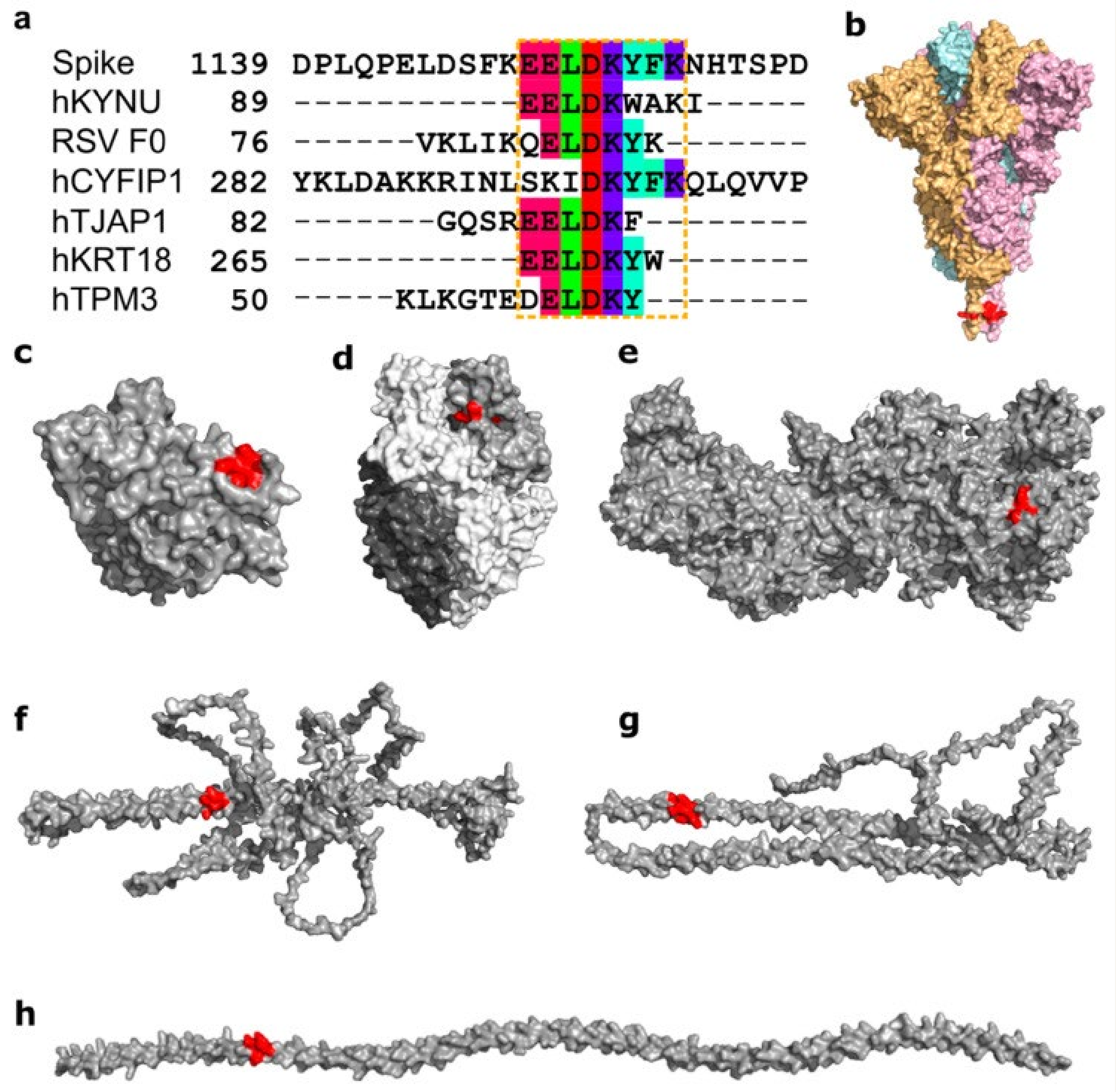
Potential Autoimmunity Resulting from Molecular Mimicry between SARS-CoV-2 Spike and Human Proteins

Janelle Nunez-Castilla [1], Vitalii Stebliankin [2], Prabin Baral [3], Christian A Balbin [1], Masrur Sobhan [4], Trevor Cickovski [2], Ananda Mohan Mondal [2 4 5], Giri Narasimhan [2 5], Prem Chapagain [3 5], Kalai Mathee [5 6], Jessica Siltberg-Liberles [1 5]

Affiliations + expand

PMID: 35891400 PMCID: PMC9318917 DOI: 10.3390/v14071415

- PASC symptoms might result from cross-reacting antibodies between viral antigens and host proteins.
- Computational investigations reveals molecular mimicry between the SARS-CoV-2 spike protein and known epitopes.
- The figure on the right shows a spike motif that is shared in multiple human proteins linked to known COVID-19 complications such as blood-clotting disorders and cardiac disease.



Nunez-Castilla. *Viruses,* June 2022.

Potential role for autoimmunity in PASC

Auto antibodies to multiple self antigens are observed during acute COVID-19 infection. 10.1038/d41586-021-00149-1

A number of small studies suggesting autoimmunity in some persons with PASC.

- Dysregulated autoantibodies targeting vaso and immunoregulatory receptors in Post COVID Syndrome correlate with symptom severity. DOI: 10.3389/fimmu.2022.981532
- Autoimmune Effect of Antibodies against the SARS-CoV-2 Nucleoprotein. DOI: 10.3390/v14061141
- Reaction of Human Monoclonal Antibodies to SARS-CoV-2 Proteins With Tissue Antigens: Implications for Autoimmune Diseases DOI: 10.3389/fimmu.2020.617089
- Autoimmunity is a hallmark of post-COVID syndrome. DOI: 10.1186/s12967-022-03328-4
- Persistent Autoimmune Activation and Proinflammatory State in Post-Coronavirus Disease 2019 Syndrome. DOI: 10.1093/infdis/jiac017
- Persistent IgG anticardiolipin autoantibodies are associated with post-COVID syndrome. DOI: 10.1016/j.ijid.2021.09.079

Is there persistence of viral material?

Article

Evolution of antibody immunity to SARS-CoV-2

https://doi.org/10.1038/s41586-021-03207-w

Received: 3 November 2020

Accepted: 6 January 2021

Published online: 18 January 2021

Check for updates

Christian Gaebler[1,11], Zijun Wang[1,11], Julio C. C. Lorenzi[1,11], Frauke Muecksch[2,11], Shlomo Finkin[1,11], Minami Tokuyama[3,11], Alice Cho[1,11], Mila Jankovic[1,11], Dennis Schaefer-Babajew[1,11], Thiago Y. Oliveira[1,11], Melissa Cipolla[1,11], Charlotte Viant[1], Christopher O. Barnes[4], Yaron Bram[5], Gaëlle Breton[1], Thomas Hägglöf[1], Pilar Mendoza[1], Arlene Hurley[6], Martina Turroja[1], Kristie Gordon[1], Katrina G. Millard[1], Victor Ramos[1], Fabian Schmidt[2], Yiska Weisblum[2], Divya Jha[3], Michael Tankelevich[3], Gustavo Martinez-Delgado[3], Jim Yee[7], Roshni Patel[1], Juan Dizon[1], Cecille Unson-O'Brien[1], Irina Shimeliovich[1], Davide F. Robbiani[8], Zhen Zhao[7], Anna Gazumyan[1], Robert E. Schwartz[5,9], Theodora Hatziioannou[2], Pamela J. Bjorkman[4], Saurabh Mehandru[3] ✉, Paul D. Bieniasz[2,10] ✉, Marina Caskey[1] ✉ & Michel C. Nussenzweig[1,10] ✉

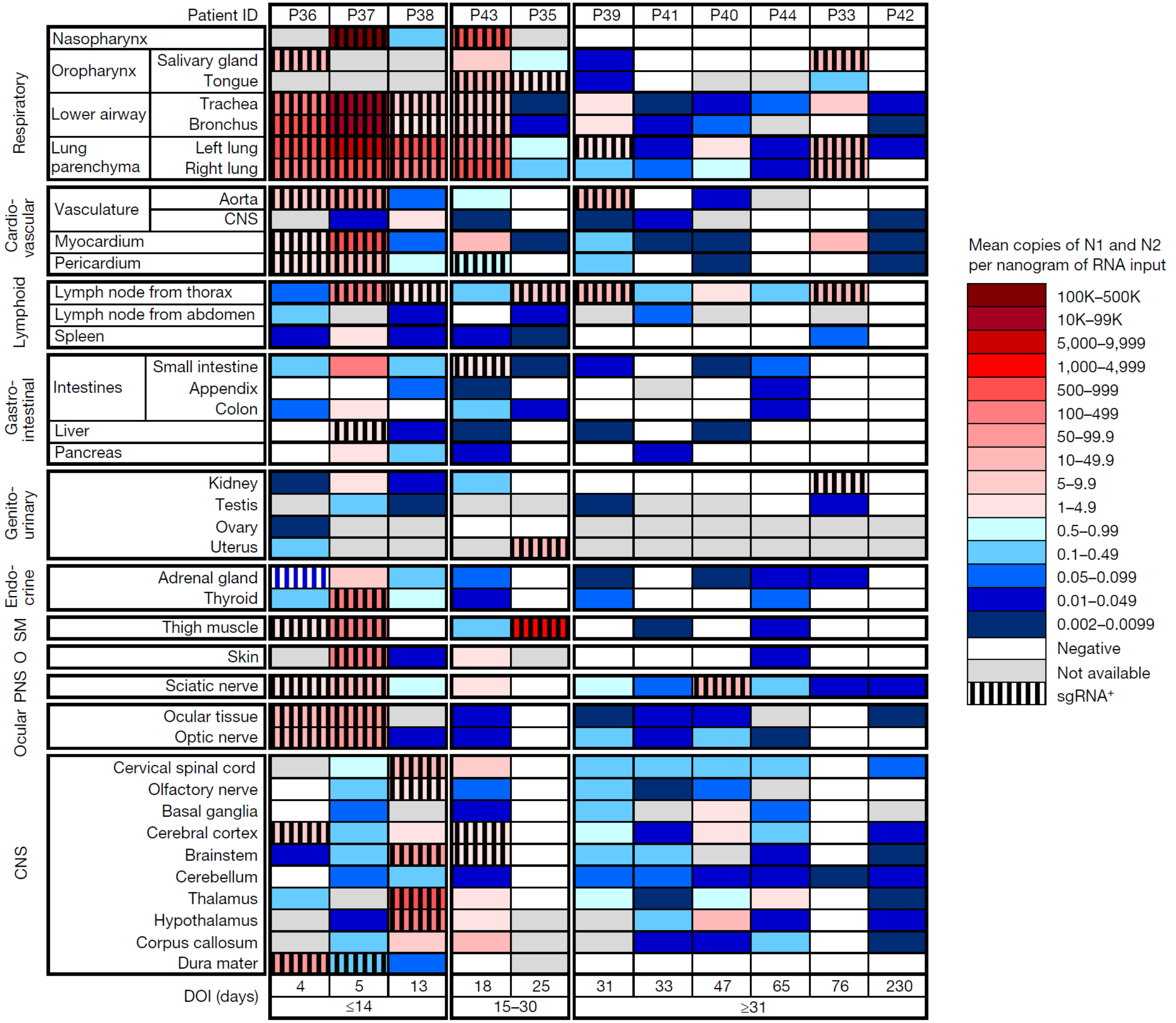
- Intestinal biopsies obtained from asymptomatic individuals at 4 months after the onset of coronavirus disease 2019 (COVID-19) revealed the persistence of SARS-CoV-2 nucleic acids and immunoreactivity in the small bowel of 7 out of 14 individuals.
- We conclude that the memory B cell response to SARS-CoV-2 evolves between 1.3 and 6.2 months after infection in a manner that is consistent with antigen persistence.

SARS-CoV-2 infection and persistence in the human body and brain at autopsy

Sydney R. Stein[1,2], Sabrina C. Ramelli[3], Alison Grazioli[4], Joon-Yong Chung[5], Manmeet Singh[6], Claude Kwe Yinda[6], Clayton W. Winkler[7], Junfeng Sun[3], James M. Dickey[1,2], Kris Ylaya[5], Sung Hee Ko[8], Andrew P. Platt[1,2], Peter D. Burbelo[9], Martha Quezado[5], Stefania Pittaluga[5], Madeleine Purcell[10], Vincent J. Munster[6], Frida Belinky[8], Marcos J. Ramos-Benitez[1,2,11], Eli A. Boritz[8], Izabella A. Lach[1,2], Daniel L. Herr[12], Joseph Rabin[13], Kapil K. Saharia[14,15], Ronson J. Madathil[16], Ali Tabatabai[17], Shahabuddin Soherwardi[18], Michael T. McCurdy[17,19], NIH COVID-19 Autopsy Consortium*, Karin E. Peterson[7], Jeffrey I. Cohen[20], Emmie de Wit[6], Kevin M. Vannella[1,2], Stephen M. Hewitt[5], David E. Kleiner[5] & Daniel S. Chertow[1,2]✉

Autopsies on 44 COVID-19 patients from acute infection through over 7 months following symptom onset.

- SARS-CoV-2 is **widely distributed** even in patients who died with asymptomatic or mild infection
- **Virus replication is present** in multiple pulmonary and extrapulmonary tissues early in infection
- **RNA in multiple anatomic sites**, including brain, **for up to 230 days after symptom onset.**
- **Paucity of inflammation** or viral cytopathology outside the lung



The persistence of SARS-CoV-2 in tissues and its association with long COVID symptoms: a cross-sectional cohort study in China

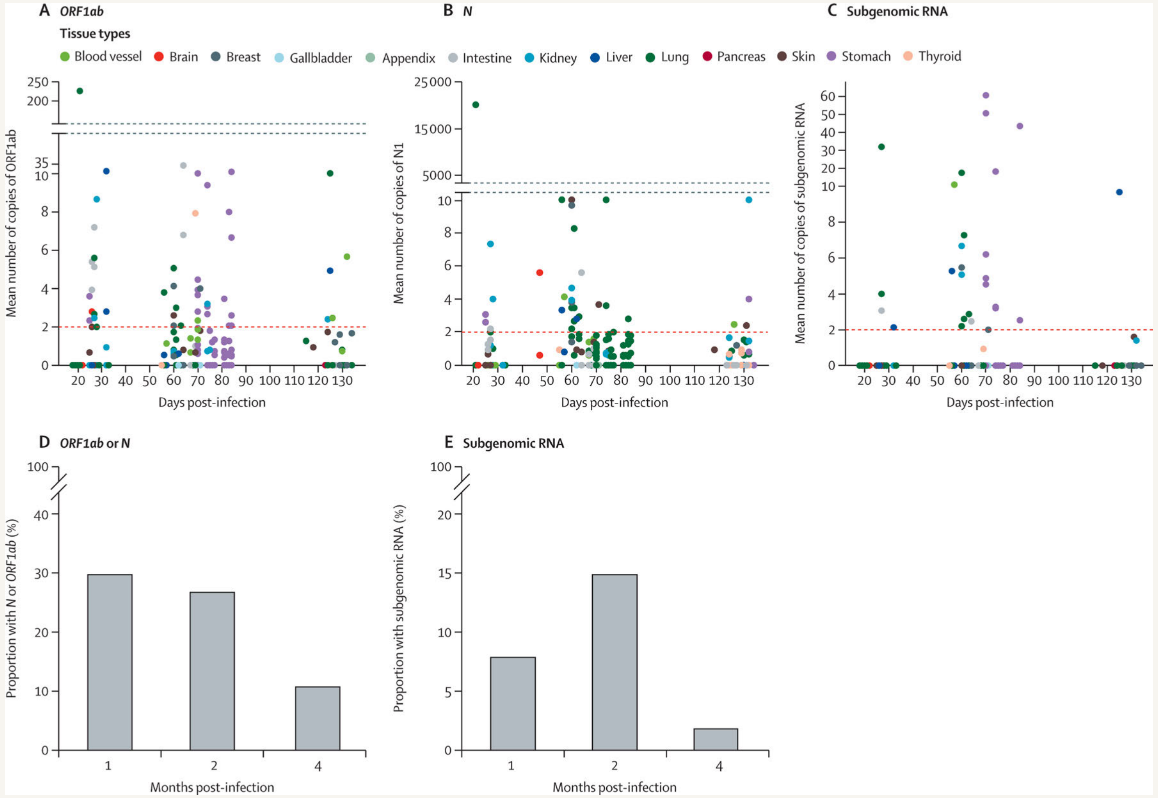

ARTICLES | ONLINE FIRST

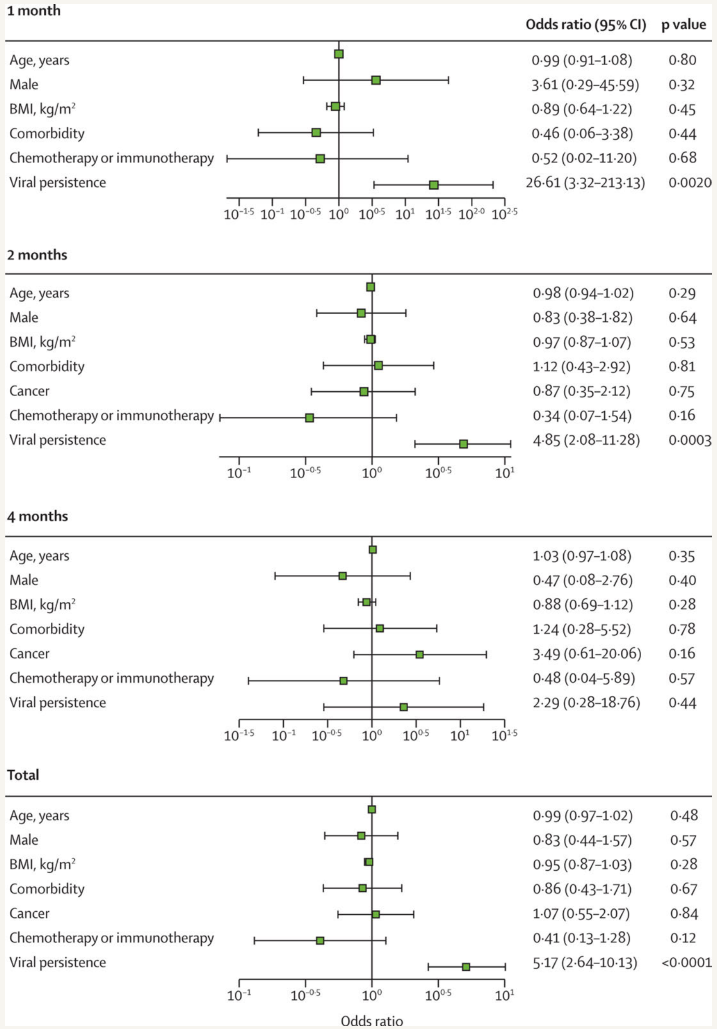
The persistence of SARS-CoV-2 in tissues and its association with long COVID symptoms: a cross-sectional cohort study in China

Wenting Zuo, MD † • Di He, MD † • Prof Chaoyang Liang, MD † • Prof Shiyu Du, MD • Prof Zhan Hua, MD • Qiangqiang Nie, MD • Prof Xiaofeng Zhou, MD • Prof Meng Yang, MD • Prof Haidong Tan, MD • Jiuyang Xu, MD • Prof Yanbing Yu, MD • Prof Yuliang Zhan, MD • Ying Zhang, MD • Xiaoying Gu, PhD • Weijie Zhu, MD • Hui Zhang, MD • Hongyan Li, PhD • Weiliang Sun, PhD • Mingzhi Sun, PhD • Prof Xiaolei Liu, MD • Prof Liguo Liu, MD • Chuanzhen Cao, MD • Rui Li, MD • Prof Jing Li, PhD • Yun Zhang, PhD • Yuting Zhang, PhD • Jing Guo, PhD • Prof Ling Zhao, MD • Chuan-Peng Zhang, MD • Hongyu Liu, MD • Shiyao Wang, MD • Prof Fei Xiao, MD • Yeming Wang, MD • Prof Zai Wang, PhD • Haibo Li • Prof Bin Cao, MD • Show less •

Show footnotes

Published: April 22, 2024 • DOI: https://doi.org/10.1016/S1473-3099(24)00171-3 • Check for updates





www.thelancet.com/infection Published online April 22, 2024
https://doi.org/10.1016/S1473-3099(24)00171-3

Is PASC a result of immune dysfunction?

Letter | Published: 13 January 2022

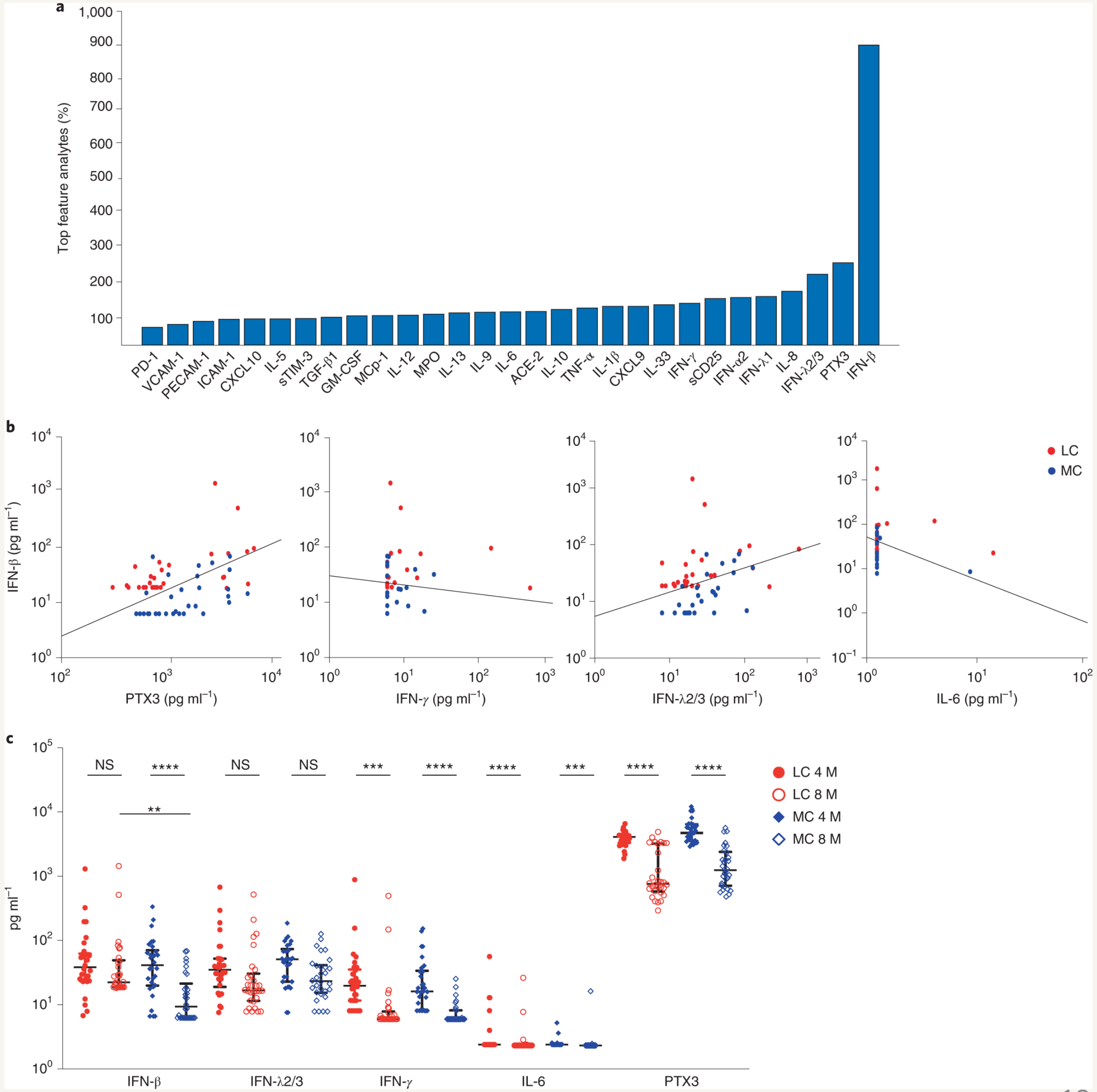
Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection

Chansavath Phetsouphanh, David R. Darley, Daniel B. Wilson, Annett Howe, C. Mee Ling Munier, Sheila K. Patel, Jennifer A. Juno, Louise M. Burrell, Stephen J. Kent, Gregory J. Dore, Anthony D. Kelleher & Gail V. Matthews

Nature Immunology **23**, 210–216 (2022) | Cite this article

- Log linear classification models reveal the inflammatory mediator IFN-β as the most important feature to distinguish patients with PASC from matched controls.
- Combinations of IFN-β, PTX3, IFN-γ, IFN-λ2/3 and IL-6 associated PASC with 78.5–81.6% accuracy.

Phetsouphanh et al. *Nature Immunology*, January 2022



Long COVID manifests with T cell dysregulation, inflammation and an uncoordinated adaptive immune response to SARS-CoV-2

nature immunology

Letter

https://doi.org/10.1038/s41590-023-01724-6

Long COVID manifests with T cell dysregulation, inflammation and an uncoordinated adaptive immune response to SARS-CoV-2

Received: 9 February 2023

Accepted: 29 November 2023

Published online: 11 January 2024

Check for updates

Kailin Yin[1,2,9], Michael J. Peluso[3,9], Xiaoyu Luo[1,2], Reuben Thomas[1], Min-Gyoung Shin[1], Jason Neidleman[1,2], Alicer Andrew[1,2], Kyrlia C. Young[1,2], Tongcui Ma[1,2], Rebecca Hoh[3], Khamal Anglin[3], Beatrice Huang[3], Urania Argueta[3], Monica Lopez[3], Daisy Valdivieso[3], Kofi Asare[3], Tyler-Marie Deveau[4], Sadie E. Munter[4], Rania Ibrahim[3], Ludger Ständker[5], Scott Lu[6], Sarah A. Goldberg[6], Sulggi A. Lee[7], Kara L. Lynch[8], J. Daniel Kelly[6], Jeffrey N. Martin[6], Jan Münch[5], Steven G. Deeks[3], Timothy J. Henrich[4] & Nadia R. Roan[1,2]

- Global differences in T cell subset distribution implying ongoing immune response
- Sex-specific perturbations in cytolytic subsets.
- Increased frequencies of $CD4^+$ T cells poised to migrate to inflamed tissues and exhausted SARS-CoV-2-specific $CD8^+$ T cells
- Higher levels of SARS-CoV-2 antibodies and a
- Mis-coordination between their SARS-CoV-2-specific T and B cell responses.
- Analysis suggested an improper crosstalk between the cellular and humoral adaptive immunity in LC

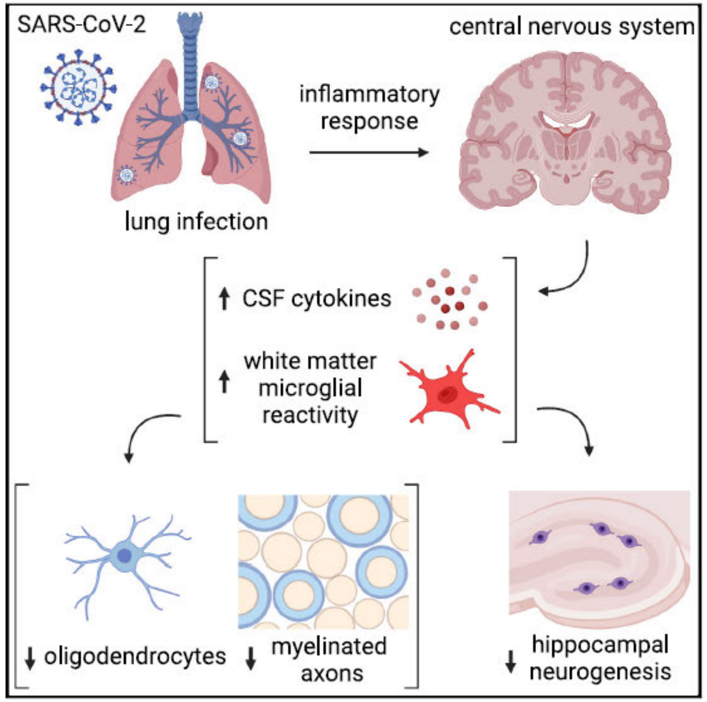
Is PASC a result of immune dysfunction?

Cell

Article

Mild respiratory COVID can cause multi-lineage neural cell and myelin dysregulation

Graphical abstract



Authors

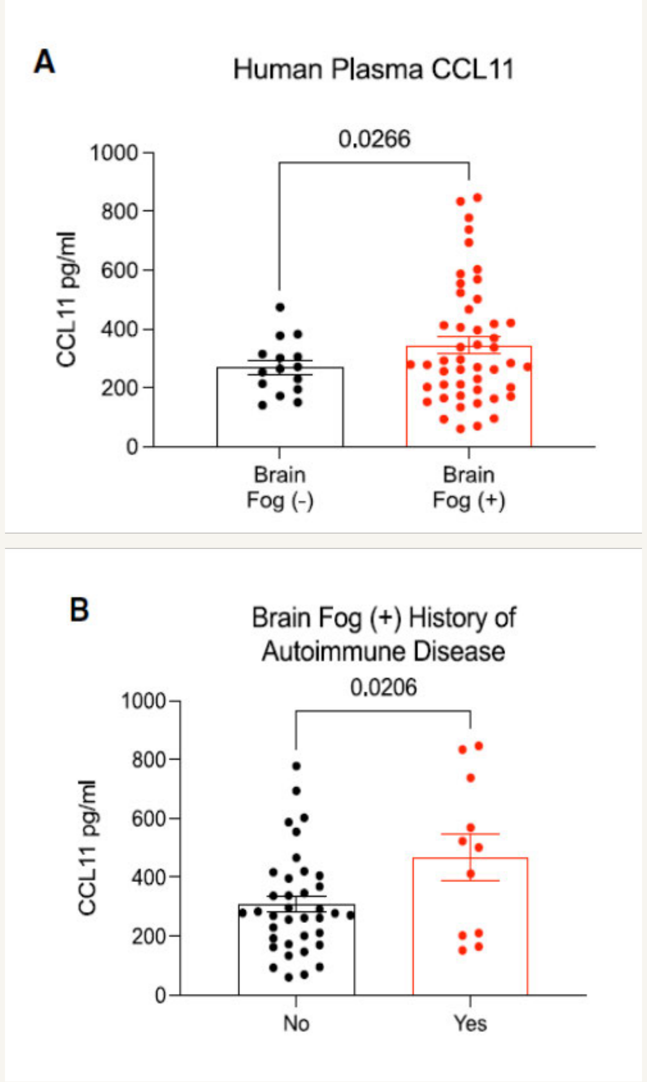
Anthony Fernández-Castañeda, Peiwen Lu, Anna C. Geraghty, ..., Avindra Nath, Akiko Iwasaki, Michelle Monje

Correspondence

akiko.iwasaki@yale.edu (A.I.), mmonje@stanford.edu (M.M.)

In brief

Mild respiratory COVID causes neuroinflammation and multi-lineage cellular dysregulation in the central nervous system, a phenomenon mirroring cancer-therapy-related cognitive impairment.



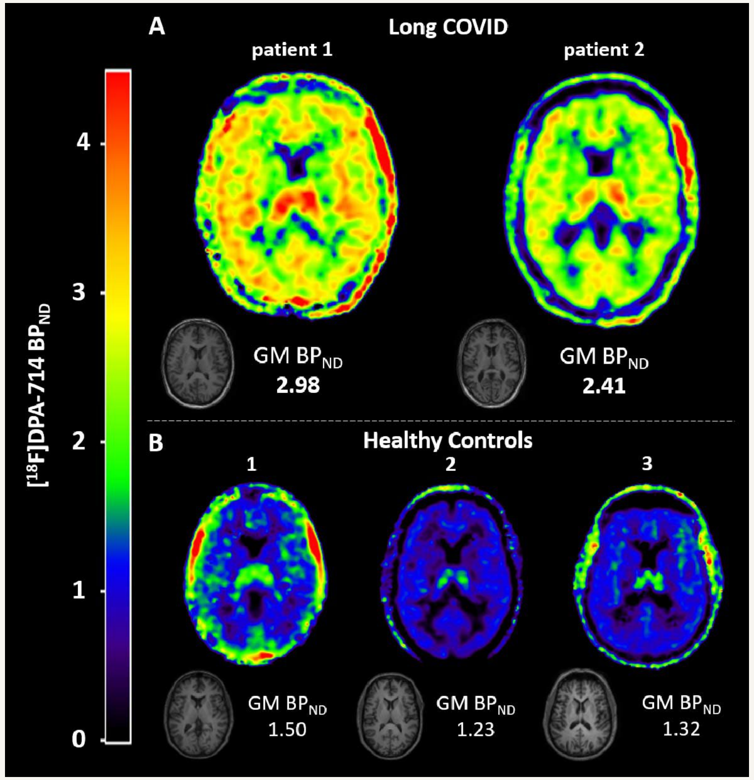
- People experiencing long COVID with cognitive symptoms had elevated CCL11 cytokine levels in their plasma
- CCL11 activates hippocampal microglia and impairs neurogenesis
- Also, mild respiratory COVID causes persistent loss of myelinating oligodendrocytes

Fernández-Castañeda et al. *Cell*, July 2022

PET imaging suggestive of brain inflammation

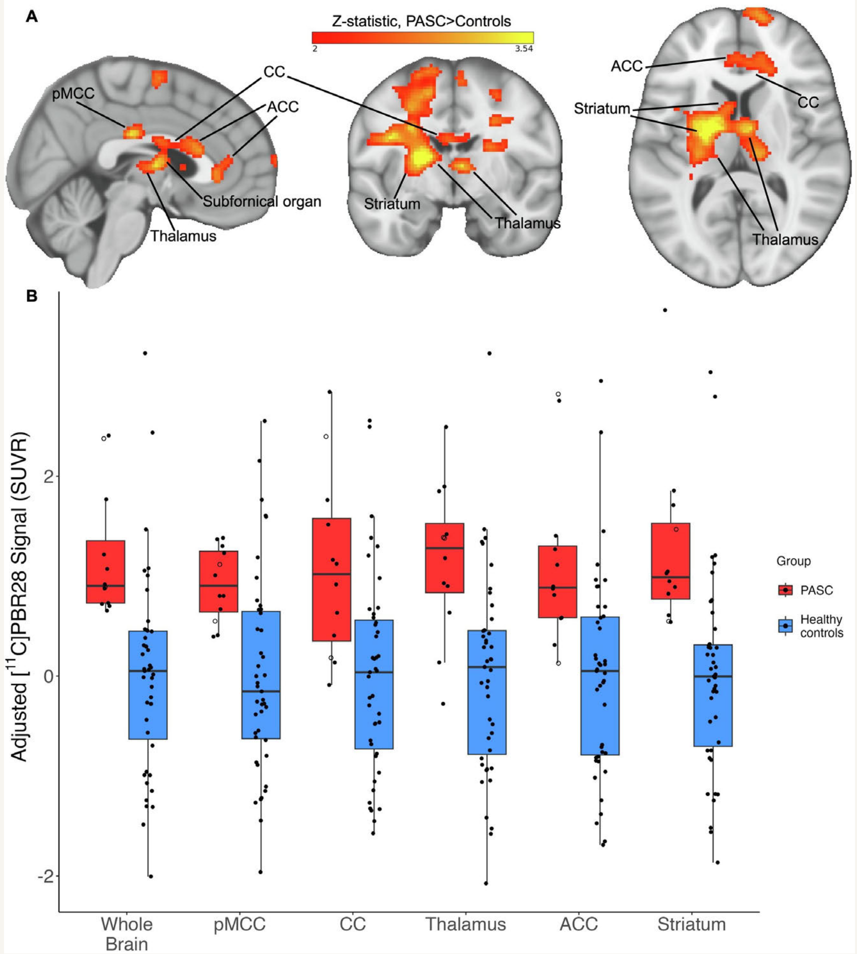
Long COVID is associated with extensive *in-vivo* neuroinflammation on [18F]DPA-714 PET

Denise Visser[1], Sandeep S.V. Golla[1], Sander C.J. Verfaillie[2], Emma M. Coomans[1], Roos M. Rikken[1], Elsmarieke M. van de Giessen[1], Marijke E. den Hollander[1], Anouk Verveen[2], Maqsood Yaqub[1], Frederik Barkhof[1,3], Janneke Horn[4], Bart Koopman[5], Patrick Schober[6], Dook W. Koch[2], Robert C. Schuit[1], Albert D. Windhorst[1], Michael Kassiou[7], Ronald Boellaard[1], Michele van Vugt[8], Hans Knoop[2], Nelleke Tolboom[9], Bart N.M. van Berckel[1]



Neuroinflammation in post-acute sequelae of COVID-19 (PASC) as assessed by [11C]PBR28 PET correlates with vascular disease measures

Michael B. VanElzakker,[1,5,*] Hannah F. Bues,[1] Ludovica Brusaferri,[2,3] Minhae Kim,[2] Deena Saadi,[1] Eva-Maria Ratai,[2] Darin D. Dougherty,[1] and Marco L. Loggia[2,4]



Blood brain barrier dysfunction

nature neuroscience

Article https://doi.org/10.1038/s41593-024-01576-9

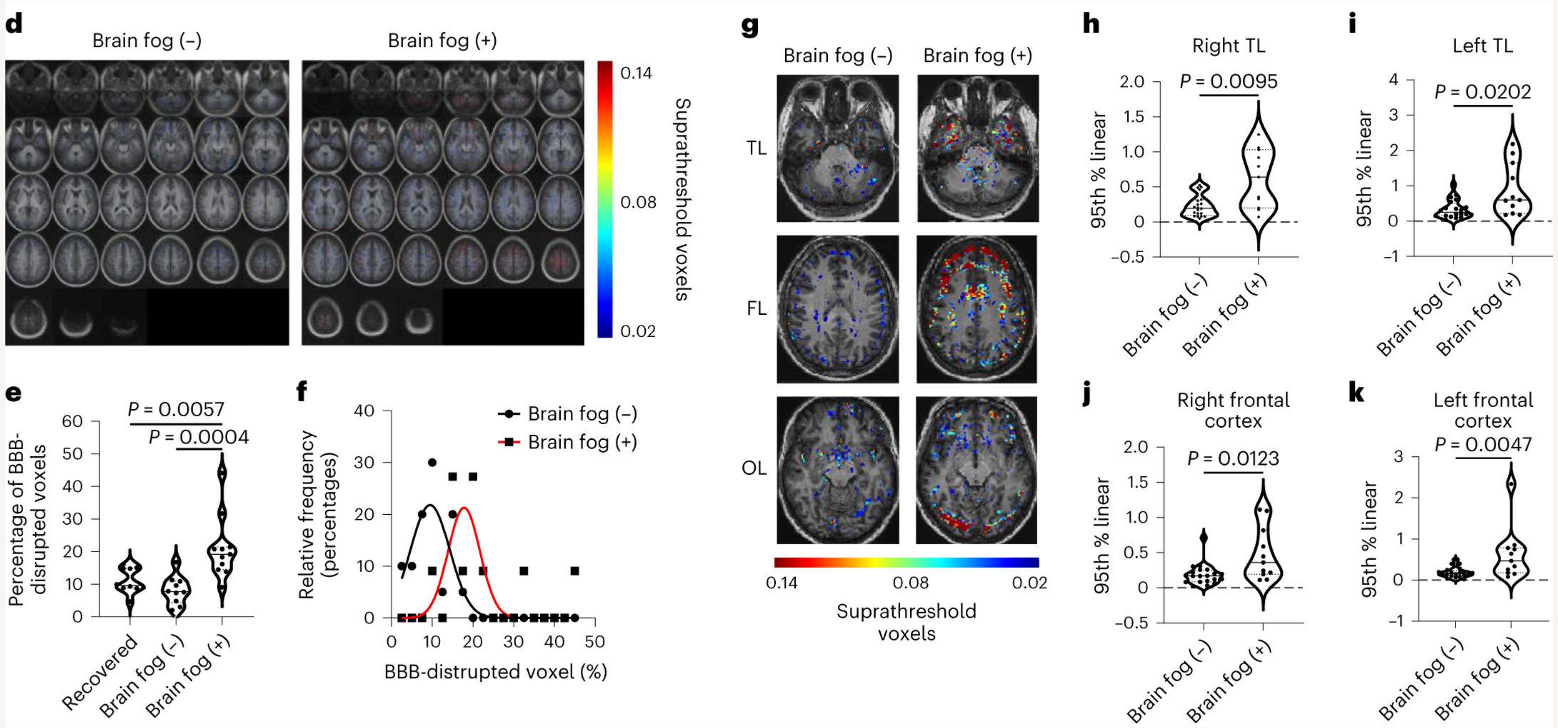
Blood–brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment

Received: 16 November 2022

Accepted: 9 January 2024

Published online: 22 February 2024

Chris Greene[1], Ruairi Connolly[2], Declan Brennan[2], Aoife Laffan[2], Eoin O'Keeffe[1], Lilia Zaporojan[2], Jeffrey O'Callaghan[1], Bennett Thomson[1], Emma Connolly[3], Ruth Argue[4], Ignacio Martin-Loeches[5], Aideen Long[6], Cliona Ni Cheallaigh[6,7], Niall Conlon[7,8], Colin P. Doherty[2,9,10] & Matthew Campbell[1,10]



Clinical Trials Progress to Date

Development of RECOVER Clinical Trials Portfolio

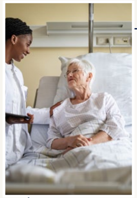
Clinical Spectrum	Risk Factors	Incidence/ Prevalence	Sub-phenotypes	Pathogenesis	**Interventions**

Critical inputs from patients, clinicians, and other perspectives shaped clinical trial priorities and design

Sources & Inputs

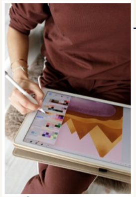
- Landscape Analysis
- Concept Proposals (ROA)
- Clinician Input
- **Patient Input**
- EHR Data
- Inventory of Interventions & Outcomes
- Industry Collaboration
- Federal Agency Partners

Patient Input:

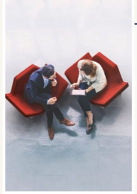


- Input on master protocol development

- Focus groups and interviews to learn patient perspectives



- Survey data from RECOVER and non-RECOVER patients



- Insights from National Community Engagement Group

Design Stages

- Identify symptom clusters
- Prioritize interventions
- Define outcome measures

RECOVER Clinical Trials Portfolio part 1

Enrolling

Platform	Symptom Cluster
VITAL	Viral Persistence & Immune Dysregulation
NEURO	Neurologic/Cognitive Dysfunction (“Brain Fog”)
AUTONOMIC	Autonomic Dysfunction (Racing heart, dizziness, fatigue)
SLEEP	Sleep Disorders (Excessive sleepiness, disrupted sleep)
ENERGIZE	Exercise Intolerance/Fatigue

5 adaptive platforms with 8 clinical trials collectively testing 13 active interventions

Shared clinical endpoints, approach to patient screening, and regulatory framework:

➡ **improved diagnosis/monitoring/care and paves the way for future treatments**

RECOVER Clinical Trials Portfolio part 2

Platform	Symptom Cluster	Trials	Interventions
VITAL	Viral Persistence & Immune Dysregulation	Viral Persistence	• Paxlovid 15 days • Paxlovid 25 days
NEURO	Neurologic/Cognitive Dysfunction	Cognitive Dysfunction	• Trans-cranial DC stim • Brain HQ • PASC Core
AUTONOMIC	Autonomic Dysfunction	Severe POTS	• IVIG, Coordinated Care
		Moderate POTS	• Ivabradine, Coordinated Care
SLEEP	Sleep Disorders	Hypersomnia	• Solriamfetol • Modafinil
		Complex Sleep Disturbances	• Melatonin • Light Therapy
ENERGIZE	Exercise Intolerance/Fatigue	Exercise Intolerance	• Cardiopulm Rehab
		Post-exertional Malaise	• Structured Pacing

5 adaptive master protocol platforms with 8 clinical trials collectively testing 13 active interventions

RECOVER by the Numbers

Observational

60 Million
Electronic Health Records

30,000
Enrolled in Clinical Cohorts

60,000
Participants in Community-based Cohorts

Pathobiology

>40
Studies of Pathogenesis

197
Autopsies Performed

Clinical Trials

>200
Candidate Interventions Evaluated for Inclusion

8 trials
13 Interventions

5
Adaptive Platform Master Protocols Across Multi-therapeutic Domains

Patient and Community Engagement

>1,000
Patients included in Protocol Design, Trial Application Review, and/or Symptom Survey Development

31
Public Seminars on Long COVID/RECOVER

>500
Diverse and Multi-disciplinary Investigators and Patients in RECOVER Consortium

Findings

- **54** Scientific Reports Published/Accepted
- **16** Scientific Reports Under Journal Review
- **77** Scientific Reports In Preparation

Long COVID Research Path Forward in 2024 and beyond

RECOVER
Researching COVID to Enhance Recovery

Collaborative Discovery: Deidentified data now available to researchers

BioData CATALYST

- **Secure data** from >**14,000 adults** now **available to authorized researchers** through the cloud-based ecosystem **BioData Catalyst®** (BDC)
- Goal to spur scientific **innovation**, **collaboration**, and **discovery**
- Provides platform for **sharing data** and **validating results**
- Facilitates Long COVID connections to benefit from or **inform future studies**.

This is just the beginning: Additional adult, pediatric, and autopsy cohort data from RECOVER will be released on an ongoing basis.

RECOVER

Researching COVID to Enhance Recovery

An Initiative Funded by the National Institutes of Health

recoverCOVID.org