PATIENT-LED RESEARCH COLLABORATIVE

Patient-Led Research Fund, Award B30
2025 Project Updates

1. C17: An Exploratory, Randomized, Double-Blind Placebo-Controlled Study To Assess The Safety Of An Anti-Sars-Cov-2 Monoclonal Antibody And Response To Treatment In Individuals With Long Covid (OUTSMART-LC) – Dr. Michael Peluso – UCSF

Current status: Ongoing

Summary of work done and next steps: We have completed the clinical trial and performed the primary analysis. We are now finalizing our exploratory analyses which will inform the next round of trials. As part of this, we have formed a collaboration with Invivyd to work toward a larger and more definitive study of next-gen monoclonals in Long COVID.

Published papers:
Preprint is pending. Multiple presentations: 2025 PLRC Virtual Webinar (primary results), 2025 Long COVID Keystone meeting (keynote address), 2025 Australia Long COVID Conference (keynote address), upcoming International Long COVID Conference (Boston) - we will present a secondary analysis that identified markers of treatment response to inform the dosing strategy for a follow up study.

2. C24: Immune repertoire profiling of Long COVID and ME/CFS patients – Dr. Roshan Kumar – HiFiBiO Therapeutics; Dr. Liisa Selin and Dr. Anna Gil – University of Massachusetts Chan Medical School

Current status: Ongoing (experimental portion completed, analysis and writeup ongoing)

Summary of work done and next steps: We have completed the scRNA-Seq and TCR-Seq of our cohort of Long COVID and ME/CFS patients and healthy controls as described in our proposal and are working on completing the analysis of the integrated data and writing up our findings. We have successfully identified disease-associated cell states and are currently focused on classifying networks of disease-associated TCRs for subsequent antigen discovery in a follow-up project.

Published papers: We are working on writing up our findings for submission as a preprint and to a peer-reviewed journal, but have presented our interim findings at several public forums including the 2025 Long COVID and Associated IACIs Keystone Meeting, the 2025 IACFS/ME International Meeting, and webinars sponsored by Renegade Research, Solve ME, and the BWH Long COVID Clinic as well as the private Stanford ME/CFS Working Group Meeting.

3. C14: Microbial metabolites as disease-modifying factors in Long-COVID – Dr. David Esteban – Vassar College

Current status: Ongoing

Summary of work done and next steps: We have collected all samples and participant survey data. Targeted and untargeted metabolomics of stool samples has been completed; this includes new methods development for targeted quantification of stool tryptophan metabolites by a new collaborator at Ohio State University. Sequencing of DNA extracted from stool samples is complete. Laboratory procedures to detect aryl-hydrocarbon receptor agonist activity are nearly complete. We have completed preliminary analysis of survey data and metabolomics data. Microbiome sequencing data analysis is underway. Next steps will be competition of functional aryl hydrocarbon receptor agonist assays and multiomics analysis.

Published papers:

- Poster presented: Esteban,D.J., Das, S., Luong, S, Gold, A., Zhu, J., Diamond, A., Torkelson, E. Altered tryptophan metabolism and aryl-hydrocarbon receptor agonist activity in the gut microbiome of people with Long COVID and ME/CFS. Long Covid International, Boston, MA, Nov 19-20, 2025.

4. C1: Unraveling the pathophysiology of post-exertional malaise in Long COVID and ME/CFS – Prof. Dr. Michele van Vugt – Amsterdam University Medical Centers; Dr. Rob Wüst – Vrije Universiteit Amsterdam; and Dr Brent Appelman – Amsterdam University Medical Centers

Current status: Ongoing

Summary of work done and next steps: all study procedures have been performed on both the Long COVID and ME patients. We have published our initial results in *Nat Comm,* with a second follow-up paper with a comparison to physical inactivity under review. A third paper, investigating ME specifically, is underway.

Published papers:

- Muscle abnormalities worsen after post-exertional malaise in long COVID | Nature Communications
- Skeletal muscle properties in long COVID and ME/CFS differ from those induced by bed rest | medRxiv

5. C15: Characterizing non-restorative sleep in post-viral disease to advance intervention innovations – Drs. Janet Mullington, Robert Thomas, Larissa Engert, Samuel Frank, Monika Haack, Jason Maley, Recep Ozdemir, Haoqi Sun, Alicia Stokes, John Torous, and Brandon M. Westover – Harvard Medical School and the Open Medicine Foundation-Supported Ronald G. Tompkins Harvard ME/CFS Collaboration

Current status: Ongoing

Summary of work done and next steps: We are looking to fill one more control participant slot, in order to complete 15 age and sex matched participants for each of ME/CFS, LC and control groups. We anticipate completing the 2 day in-patient study runs by the end of

November. Assays are underway and sleep EEG is being processed and prepared for biomarker analysis. We have published one paper and have another under review, based on preliminary data analyzed with support from this grant. In addition, these preliminary data have been presented in poster format at the APSS meeting in Seattle (June 6, 2025). We have also had an abstract accepted for a short oral "flash" presentation at the 3rd International Conference on Long COVID to be presented in Boston on the 20th of November, 2025, entitled, "A Candidate Biomarker for Non-restorative, Unrefreshing Sleep in Long COVID".

Dr. Mullington is also planning sessions at the upcoming, "Sleep Regulation and Function" Gordon Research Conference (2026 Sleep Regulation and Function Conference GRC), to be held in Galveston Texas in March, 2026, that are of great relevance for our community. In addition to a session on, "*Post-infectious Disease and Sleep*", there will be sessions on, "The Sleep-Vagal Connection: Implications for Health"; "Sleep and Brain Clearance and Barriers", and, "Using Machine Learning to Look Through the Sleep Window for Disease Biomarker Discovery".

Published papers:

- Haoqi Sun, Rammy Dang, Monika Haack, Kristine Hauser, Jennifer Scott-Sutherland, M Brandon Westover, Sairam Parthasarathy, Susan Redline, Robert J Thomas, Janet M Mullington . Facility-measured nocturnal hypoxemia and sleep among adults with long COVID versus age- and sex-matched healthy adults: a preliminary observational study. Sleep Adv 2025 Mar 22;6(2):zpaf017.

6. C2: A pre- and post-operative study of patients with ME/CFS operated for foraminal stenosis – Prof. Per Sjogren, Dr. Bo Bertilson, Dr. Helena Huhmar, Dr. Lauri Soinne, Dr. Olli Polo, Dr. Jonas Bergquist, and Dr. Bjorn Bragée – Bragee ME Clinic, Stockholm

Current status: Ongoing

Summary of work done and next steps: So far, only 2 patients have completed surgery according to plans, and after an additional ethical permit we have now initiated an expanded recruitment procedure to reach recruitment goals of the study. The two patients so far included have improved considerably post-operatively (for more details see below)

Published papers: No papers published. We presented preliminary findings at the PLRC Webinar 2025. https://www.youtube.com/watch?v=eqV7Me4psr8.

7. C19: Altered T cell responses in Long COVID (PASC) and ME/CFS – Dr. Liisa Selin and Dr. Anna Gil – University of Massachusetts Chan Medical School

Current status: Completed; further investigations ongoing

Summary of work done and next steps: We identified that both Long Covid and ME/CFS patients have dysfunctional CD8 T Cells and severe deficiencies in production of IFNg and TNFa. We tried a treatment with a nebulized antioxidant, anti-pathogen and immune-modulatory agent called Inspiritol. These immune deficiencies and health

improved on treatment. In addition to identification of treatment, we identify a useful new biomarker, CD8 T-cell dysfunction, that assists in diagnosis and tracking response to potential new treatments.

Published papers:

- https://www.sciencedirect.com/science/article/pii/S2666354623001345

8. C27: Systems Biology Approaches to Uncovering Disease Mechanism and Drug Repurposing for Long COVID – Dr. Wenzhong Xiao – Massachusetts General Hospital and the Open Medicine Foundation-Supported Computational Research Center for Complex Diseases

Current status: Completed

Summary of work done and next steps: The work as described in the proposal has been completed. However, the project is continuing to integrate results from new studies and to update the disease models of ME/CFS and long COVID. In addition, we are testing candidate treatments identified by these analyses.

Published papers:

- Hung LY, Wu CS, Chang CJ, Li P, Hicks K, Dibble JJ, Morrison B, Smith CL, Davis RW, Xiao W. A network medicine approach to investigating ME/CFS pathogenesis in severely ill patients: a pilot study. Front Hum Neurosci. 2025 Feb 10;19:1509346. doi: 10.3389/fnhum.2025.1509346.
- Li, G.-H.; Han, F.-F.; Kalafatis, E.; Kong, Q.-P.; Xiao, W. Systems Modeling Reveals Shared Metabolic Dysregulation and Potential Treatments in ME/CFS and Long COVID. Int. J. Mol. Sci. 2025, 26, 6082.doi: 10.3390/ijms26136082.
- Eckey M, Li P, Morrison B, Bergquist J, Davis RW, Xiao W. Patient-reported treatment outcomes in ME/CFS and long COVID. Proc Natl Acad Sci U S A. 2025 Jul 15;122(28):e2426874122. doi: 10.1073/pnas.2426874122.

9. C15: Understanding the relationship between fibrin amyloid microclots and Long COVID – Dr. Caroline Dalton, Dr. Andrew Higham, Prof. Doug Kell, Prof. Resia Pretorius, Prof. David Price – Consortium of UK and South African universities

Current status: Completed

Summary of work done and next steps: We optimised the methodology for assessing microclots and assayed samples from people with Long COVID, ME/CFS and vaccine-injured compared to controls (those who had SARS-CoV infection and some never-infected). We investigated the relationships between microclot counts and characteristics, and symptoms. We have carried out proteomics on a subset of the samples and are currently analysing these data. We have also carried out mitochondrial function assays of the ME/CFS samples using a muscle cell model which will allow us to investigate the relationships between microclots and effects on mitochondria..

Published papers: We presented results at the PLRC webinar 2025. We have published 2 preprints, the first on the microclots will be submitted to a journal when we have added the proteomics data. The second, on the mitochondrial results is under review at the moment.

- https://www.medrxiv.org/content/10.1101/2024.04.04.24305318v1
- https://www.biorxiv.org/content/10.1101/2025.06.03.657595v1.full-text

10. C29: Multi-omic approAches to Solve post-Acute COVID-19/SARS-CoV-2 Syndrome – MOSAICS – Prof. Alain Moreau – Université de Montréal and the Open Medicine Foundation-Supported ME/CFS Collaborative Center at CHU Sainte-Justine/Université de Montréal; Prof. Jonas Bergquist – Uppsala University, Sweden and the Open Medicine Foundation-Supported ME/CFS Collaboration at Uppsala University; Dr. Christopher Armstrong – University of Melbourne and the Open Medicine Foundation-Supported Melbourne ME/CFS Collaboration; Dr. Wenzhong Xiao – Harvard University and the Open Medicine Foundation-Supported Computational Research Center for Complex Diseases; Dr. Dawei Li – Florida Atlantic University; and Dr. Tse Man Sze – Université de Montréal
Current status: Ongoing

Summary of work done and next steps: The MOSAICS project enabled a deep exploration of the biology of Long COVID, leading to two companion studies—"Epigenetic Signatures in Peripheral Blood Mononuclear Cells Correlate with Long COVID Symptom Severity and Clinical Trajectories" and "Saliva DNA Methylation Profiles Reveal Epigenetic Signatures of Long COVID Symptom Persistence and Clinical Trajectory." Both manuscripts were submitted to Nature Communications and conducted in parallel, providing the first combined two-tissue epigenetic analysis of Long COVID. The results show that Long COVID leaves a clear molecular "fingerprint" on both immune cells and saliva, changing how key genes behave without altering DNA itself. These epigenetic patterns explain major symptoms—such as fatigue, brain fog, pain, and autonomic dysfunction—and even predict who will recover or remain ill, a major step toward personalized care. Specifics are retracted from this report (and are available by request), but the study identifies recovery-linked pathways, drugs that can boost these pathways, and identifies a marker of symptom severity. It also confirms at least four key targets and identifies a strong predictor of persistent symptoms. Together, these findings reveal drug-responsive pathways and open the door to more effective, biologically grounded treatments for people still suffering months or years after COVID-19.

Published papers: Both manuscripts described above are In peer review process.