PATIENT-LED RESEARCH COLLABORATIVE

Response to NIAID RFI NOT-AI-24-032
Inviting Comments and Suggestions on NIAID's Strategic Plan

Submitted by the
Patient-Led Research Collaborative
May 24, 2024

Thank you for the opportunity to submit feedback on the National Institute of Allergy and Infectious Diseases' (NIAID) Strategic Plan for the next five years.

We are Patient-Led Research Collaborative (PLRC), a group of patient-researchers with Long COVID and other infection-associated chronic conditions who conducted the first research on Long COVID in May 2020, have continued to conduct influential and landmark research, and have advocated for increased research funding, improved research strategies and design, and better policies for people with these conditions.

As of April 2024, at least 6.9% of adults in the United States and millions more children were experiencing Long COVID, with about one-quarter of people with Long COVID experiencing significant activity limitations. Long COVID impacts all demographics, with disabled people, transgender people, women, and Hispanic/Latino populations being disproportionately impacted.[1] Vaccination does not meaningfully protect against Long COVID,[2] and reinfection increases one's risk of developing it.[3] Of patients sick with Long COVID at 2 months, only 15% were in remission at one year, with one-third of those in remission relapsing later on.[4] People with Long COVID are significantly more likely to experience housing[5] and food[6] insecurity, and economic costs to the US economy are in the trillions of dollars over just the next few years.[7]

NIAID conducts and supports biomedical research to better understand, treat, and prevent infectious and immune-mediated diseases. Infection-associated chronic conditions (IACCs), which include Long COVID, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), postural orthostatic tachycardia syndrome (POTS) and other forms of dysautonomia, chronic Lyme disease, certain cancers and autoimmune diseases, and more, are multisystemic diseases that involve immune system dysregulation triggered by a pathogen. Advancing knowledge on IACC will take a multi-pronged approach across multiple institutes at the National Institutes of Health, but NIAD has the expertise and background necessary to spearhead these efforts and make significant progress in solving these diseases. NIAID's background in studying HIV/AIDS primes the Institute to conduct and fund the type and level of research needed to study infection-associated chronic conditions. In fact, some of the most prominent Long COVID researchers have backgrounds studying HIV/AIDS (e.g. Drs. Steven Deeks, Michael Peluso, and Tim Henrich at UCSF and Dr. Nancy Klimas at the Institute for Neuroimmune Medicine at NSU). We are confident that under Dr. Marrazzo's leadership specifically, who was a RECOVER PI and has extensive infectious disease background relevant to IACCs, NIAID would conduct and fund high-quality research on Long COVID and other IACCs that are of priority to the patient community and could lead to breakthroughs and cures.

When considering NIAID's Strategic Plan for the next five years, we urge you to explicitly include Long COVID and other infection-associated chronic conditions. In President Biden's 2022 Memorandum on Addressing the Long-Term Effects of COVID-19, he promised that his Administration would "harness the full potential of the Federal Government, in coordination with public- and private-sector partners, to mount a full and effective response [against Long COVID]."[8] Through this, NIAID has a mandate to address Long COVID. While the RECOVER Initiative has launched an observational study for Long COVID and a few clinical trials, the program did not have a strong history of biomedical research into infectious-onset conditions, and the trials are primarily on low-quality, non-pharmaceutical treatments. Additional comprehensive pathobiology studies and significantly more clinical trials are sorely needed to properly identify and validate disease mechanisms, biomarkers, and design and screen therapeutics. As Director Dr. Marrazzo has mentioned in a recent discussion with Research!America, there is a clear need to design an integrated, hypothesis-driven strategy for viral-onset syndromes;[9] this is critical to find the pathophysiological commonalities, such as the mechanisms of immune dysregulation after infections, and is crucial to improve clinical care options as quickly as possible. Having NIAID be a key part of this response will ensure that these studies are led by people with a history of solving complex conditions with an infectious onset. This will not only help us in addressing the current COVID pandemic but will help us prepare for future pandemics as well.

We commend NIAID's suggested Research Priorities, and urge you to apply them to Long COVID and other infection-associated chronic conditions when conducting intramural research and issuing a variety of funding opportunities. We request specific mention of Long COVID and/or IACCs in the Research Priorities to ensure that this focus is not lost.

Additionally, we encourage more funding opportunities such as NOFO RFA-NS-24-022 to be applied in the context of Long COVID and IACCs, where Collaborative Research Centers are supported to develop clinical research to discover improved treatments for these conditions. These opportunities should have review boards with expertise in these conditions, which could be drawn from large national collaboratives of IACC experts such as those from PolyBio's Long Covid Research Consortium.

Specifically in regards to the listed Research Priorities, we recommend the following:

Priority 1: Advance foundational research on the immune system, host-pathogen interactions, and pathogen biology.

We recommend the addition of the following bullet points:

- Advance the understanding of the basic mechanisms of Long COVID pathogenesis, including enhancing knowledge of latent and the potential of persistently replicating COVID reservoirs.
- Characterize the hallmarks of aberrant inflammatory and immune responses in Long COVID and other chronic illnesses and conditions triggered by an infectious agent,

including, but not limited to myalgic encephalomyelitis, chronic Lyme disease, post-infectious irritable bowel syndrome (IBS), pediatric acute-onset neuropsychiatric disorders associated with streptococcus (PANDAS), mast cell activation syndrome (MCAS), and dysautonomia.
- Understand acute and post-acute SARS-CoV-2 virus-host interactions related to Long COVID, with particular emphasis on viral persistence.
- Develop and validate tools that allow for identification of viral persistence not only in the bloodstream but in tissue and other locations.
- Understand how chronic viral co-infections (e.g. EBV, CMV, HHV, Lyme) interact with the immuno-pathology of Long COVID and IACCs.

Accumulating evidence demonstrates that SARS-CoV-2 can persist in tissue reservoirs in many locations in the body[10], with replicating capability that may induce and modulate immune response. A recent 2024 paper found 25% of people who had COVID had at least one detectable persisting antigen[11] and a 2024 study out of France found SARS-CoV-2 persistence in megakaryocytes.[12] To characterize the pathophysiology of Long COVID, it is necessary to understand the the biology of SARS-CoV-2 tissue reservoirs, what leads to a reservoir phenotype that may induce chronic disease in the host, and the immune interactions between persistent viral antigens and host immune system. It is also vital to develop and validate the tools that will allow for identification of this persistence, not only in the bloodstream but in the tissue as well[1314].

Priority 2: Apply foundational knowledge of the complex interactions between microbes and the immune system to develop and test medical countermeasures against known infectious diseases (non-HIV/AIDS).

We recommend the addition of “and their long-term sequelae” to each bullet point following “infectious diseases.” Studying the acute phase of an infectious disease is critical for reducing mortality, but NIAID can play a key role in reducing morbidity of these infections as well. Being able to diagnose and develop and evaluate therapies for Long COVID and other IACCs is a crucial aspect to tackling infectious diseases, especially as future pandemics will become more likely with climate change.

Priority 3: Apply knowledge of HIV/AIDS to reduce HIV incidence through the development of safe and effective prevention, treatment, and cure strategies.

We recommend the addition of the following bullet point:
- Advance understanding of the interaction between HIV and Long COVID.

People with HIV are more at risk of developing Long COVID[15]. Additionally, Long COVID can include some exacerbating conditions that people with HIV already may experience, such as reactivated latent infections and immune dysregulation with T cell exhaustion[1617]; it is important to understand the compounding effect of these together and their common immune pathologies.

Priority 4: Apply knowledge of basic immunology to develop and enhance intervention strategies for asthma, allergic and immune-mediated diseases, and transplantation.

We recommend that Long COVID and other IACCs be added directly to Priority 4 by stating "Apply knowledge of basic immunology to develop and enhance intervention strategies for asthma, allergic and immune-mediated diseases, Long COVID and other IACCs, and transplantations."

We also recommend the addition of the following bullet points:

- Advance understanding of why allergies[18] are a risk factor for developing Long COVID.
- Advance the understanding of infection-onset mast cell activation syndrome[1920]
- Advance the understanding of the interaction between the immune system and connective tissue disorders in the context of IACCs[212223]
- Support clinical trials of immunomodulatory agents to treat Long COVID and myalgic encephalomyelitis.*
- Understanding the contribution of infections with pathogens, including SARS-CoV-2, to the development and exacerbation of allergies and asthma in pediatric and adult populations

*In regards to potential clinical trials for Long COVID and ME/CFS, a wide range of potential repurposed drugs have been proposed by experts in the field, including but not limited to: antivirals, anticoagulants, checkpoint inhibitors, BTK inhibitors, JAK-STAT inhibitors, IL-1 blockers, IL-6 antagonists, TNF-alpha inhibitors, poly-IC, immunomodulators including IVIG and immunoadsorption, monoclonal antibodies, prescription mast cell stabilizers, drugs that regulate microglial activation, mitochondrial treatments, DRP-1 inhibitors, drugs used for dysautonomia, and regenerative medicine treatments like stem cells[24252627].

Priority 5: Support innovative research efforts to prepare for and respond to nationally or internationally significant biological incidents affecting public health.

We recommend specifically listing COVID as a priority pathogen and Long COVID as a significant biological incident affecting public health. As of April 2024, 6.9% of the US adult population is currently experiencing Long COVID - similar to the rate of diabetes. With reinfections as a risk factor for Long COVID, this will continue to be a growing public health problem.

Additional Themes

In regards to women's health, we recommend NIAID support research on immunological responses that may drive sex and gender disparities in auto-immune disease and inflammatory chronic conditions such as Long COVID and ME/CFS. Women and gender non-conforming individuals are at higher risk of infection-onset illnesses, and determining why is a major clue into pathophysiology. Regarding DEIA and research inclusion, although Long COVID and ME/CFS disproportionately affect marginalized populations and ethnic and racial minorities,

these populations are underrepresented in biomedical research and clinical trials. We recommend that NIAID implement funding opportunities that target inclusion and representation of marginalized populations, with funding practices committed to epidemiologically representative sampling that ensures equity and inclusion in clinical research[28]. And lastly, an overarching comment that touches on each theme and priority is ensuring the meaningful engagement of patients in research, including patient-driven studies.The impressive community engagement efforts of the Division of AIDS should be applied institute-wide, and can embed lessons learned from our Patient-Led Research Scorecards.[29]

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Thank you again for the opportunity to provide feedback on this comment. We look forward to working alongside NIAID to solve Long COVID and other IACCs, and hope we can count on your explicit inclusion of these conditions in your Strategic Plan for the next five years.

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References

[1] Centers for Disease Control and Prevention. (2024, April 29). Long COVID: Household Pulse Survey. Retrieved from https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm
[2] Al-Aly, Z., Bowe, B. & Xie, Y. Long COVID after breakthrough SARS-CoV-2 infection. Nat Med 28, 1461–1467 (2022). https://doi.org/10.1038/s41591-022-01840-0
[3] Bowe, B., Xie, Y. & Al-Aly, Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. Nat Med 28, 2398–2405 (2022). https://doi.org/10.1038/s41591-022-02051-3
[4] Tran, VT., Porcher, R., Pane, I. et al. Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort. Nat Commun 13, 1812 (2022). https://doi.org/10.1038/s41467-022-29513-z
[5] Packard SE, Susser E. Association of long COVID with housing insecurity in the United States, 2022-2023. SSM Popul Health. 2023 Dec 14;25:101586. doi: 10.1016/j.ssmph.2023.101586. PMID: 38222672; PMCID: PMC10787291.
[6] Urban Institute. (2022, December). Employment and material hardship among adults with long COVID. Retrieved from https://www.urban.org/research/publication/employment-and-material-hardship-among-adults-long-covid-december-2022
[7] Cutler, D. The Economic Cost of Long COVID: An Update. https://scholar.harvard.edu/sites/scholar.harvard.edu/files/cutler/files/long_covid_update_7-22.pdf
[8] White House. (2022, April 5). Memorandum on addressing the long-term effects of COVID-19. Briefing Room: Presidential Actions. https://www.whitehouse.gov/briefing-room/presidential-actions/2022/04/05/memorandum-on-addressing-the-long-term-effects-of-covid-19/
[9] Research!America. (2024, May 22). Research!America Alliance Discussion with Dr. Jeanne Marrazzo, Director of the NIAID [Video]. YouTube. https://www.youtube.com/watch?v=HogNn_nHdrI.
[10] Proal, A.D., VanElzakker, M.B., Aleman, S. et al. SARS-CoV-2 reservoir in post-acute sequelae of COVID-19 (PASC). Nat Immunol 24, 1616–1627 (2023). https://doi.org/10.1038/s41590-023-01601-2
[11] Peluso, M.J., Swank, Z.N., Goldberg, S.A., et al. Plasma-based antigen persistence in the post-acute phase of COVID-19. The Lancet Infectious Diseases 24, E345-E347 (2024). https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(24)00211-1/fulltext

[12] He, F., Huang, B., Cottignis-Calamarte, A., et al. Persistence of SARS-CoV-2 in platelets and megakaryocytes in Post-acute Sequelae of SARS-CoV-2 (Long COVID). Conference of Retroviruses and Opportunistic Infections, March 2024. https://www.croiconference.org/wp-content/uploads/sites/2/posters/2024/347.pdf
[13] Peluso, M.J., Swank, Z.N., Goldberg, S.A., et al. Plasma-based antigen persistence in the post-acute phase of COVID-19. The Lancet Infectious Diseases 24, E345-E347 (2024). https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(24)00211-1/fulltext
[14]PolyBio Research Foundation. (2024, May 19). Dr. Tim Henrich, PolyBio Research Foundation Spring 2024 Symposium Symposium [Video]. YouTube. https://www.youtube.com/watch?time_continue=7450&v=NvAEo2tHn0w
[15] Yang, X., Liu, Z., Zhang, J., et al. Long COVID Between People With and Without HIV: a Statewide Cohort Analysis. Conference on Retroviruses and Opportunistic Infections. March 2024. https://www.croiconference.org/abstract/long-covid-between-people-with-and-without-hiv-a-statewide-cohort-analysis/
[16] Yin, K., Peluso, M.J., Luo, X. et al. Long COVID manifests with T cell dysregulation, inflammation and an uncoordinated adaptive immune response to SARS-CoV-2. Nat Immunol 25, 218–225 (2024). https://doi.org/10.1038/s41590-023-01724-6
[17] Davis, H.E., McCorkell, L., Vogel, J.M. et al. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol 21, 133–146 (2023). https://doi.org/10.1038/s41579-022-00846-2
[18] Merzon, E. et al. Clinical and socio-demographic variables associated with the diagnosis of long COVID syndrome in youth: a population-based study. Int. J. Environ. Res. Public Health 19, 5993 (2022).
[19] Weinstock, L. (2021) *Mast cell activation symptoms are prevalent in long-covid - international journal of infectious diseases*. Available at: https://www.ijidonline.com/article/S1201-9712(21)00751-7/fulltext (Accessed: 24 May 2024).
[20] Theoharides, T.C., Twahir, A. and Kempuraj, D. (2023) 'Mast cells in the autonomic nervous system and potential role in disorders with dysautonomia and neuroinflammation', *Annals of Allergy, Asthma & Immunology*, 132(4), pp. 440–454. doi:10.1016/j.anai.2023.10.032.

[21] Bartlett, M.L., Sova, D. and Jain, M. (2024) *Hereditary connective tissue diseases and risk of post-acute SARS-COV-2*, *MDPI*. Available at: https://www.mdpi.com/1999-4915/16/3/461 (Accessed: 24 May 2024).
[22] Sung Ha Lim, M. (2023) *Autoimmune and autoinflammatory connective tissue disorders following COVID-19*, *JAMA Network Open*. Available at: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2810259 (Accessed: 24 May 2024).
[23] Davis, H.E., McCorkell, L., Vogel, J.M. et al. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol 21, 133–146 (2023). https://doi.org/10.1038/s41579-022-00846-2
[24] Davis, H.E., McCorkell, L., Vogel, J.M. et al. Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol 21, 133–146 (2023). https://doi.org/10.1038/s41579-022-00846-2
[25] Dr. Avi Nath, *ME/CFS Symposium*. (2024). https://videocast.nih.gov/watch=54675
[26] Vij, R. *et al.* Adipose-derived, autologous mesenchymal stem cell therapy for patients with post-COVID-19 syndrome: an intermediate-size expanded access program. *Stem Cell Res. Ther.* **14**, 1–10 (2023).
[27] Hasan, A. *et al.* Mesenchymal stem cells in the treatment of traumatic brain injury. *Front. Neurol.* **8**, 28 (2017).
[28] Centers for Disease Control and Prevention. (2024, April 29). Long COVID: Household Pulse Survey. Retrieved from https://www.cdc.gov/nchs/covid19/pulse/long-covid.htm
[29] Council of Medical Specialty Societies & Patient-Led Research Collaborative. Patient-Led Research Scorecards. Available at https://cmss.org/patient-led-research-integration/.