Research Opportunity Announcement OTA-21-015E:
Research on Pathobiological Mechanisms Underpinning the Clinical Phenotypes, Symptomatic Manifestations, and Multi-tissue/organ Pathology of Post-Acute Sequelae of SARS-CoV-2 Infection

Purpose

This announcement encourages RECOVER investigators with expertise and insights germane to post-acute sequelae of SARS-CoV-2 infection (PASC) clinical pathobiology to apply for funding that would enable them to apply cross-disciplinary approaches and leverage RECOVER cohort participant enrollment, as well as samples and data collected as part of the RECOVER clinical protocol (under OTA-21-015B) to rapidly advance understanding of the biologic mechanisms underpinning the clinical phenotypes and symptoms of PASC, and the associated multi-tissue/organ pathology.

Background

To further the goals of the National Institutes of Health (NIH) Researching COVID to Enhance Recovery (RECOVER) Initiative, the agency is requesting proposals that address the urgent need to identify the pathobiological mechanisms that characterize the clinical manifestations and multi-organ/system injury resulting from SARS-CoV-2 infection. These effects can include multiple symptoms and multi-tissue/organ injury that persist long past the time that patients have recovered from the initial stages of COVID-19 (often referred to as long COVID) as well as new symptoms that arise after the time of initial infection and may evolve over time (e.g., MIS-C). These effects give rise to multiple, and as yet not well-defined, clinical phenotypes. Symptoms can persist for months and can range from mild to incapacitating. Symptoms can include fatigue, post exertional malaise, shortness of breath, difficulties with concentration and attention ("brain fog"), sleep disorders, fevers, gastrointestinal symptoms, anxiety, depression, headache, a variety of pain syndromes, postural orthostatic tachycardia, and others identified and as yet unidentified. The clinical phenotypes may also represent prodromes to future health threats (i.e., development of autoimmune diseases). While still being defined, these clinical and sub-clinical effects are collectively referred to as post-acute sequelae of SARS-CoV-2 infection (PASC).

Research Objectives

To make rapid progress in understanding the clinical manifestations of PASC and the mechanisms leading to the various symptoms, dysfunction of multiple organs and biologic systems, and phenotypes seen in PASC patients, the NIH encourages the submission of proposals to support these goals.

Examples of possible research to be proposed include but are not limited to the following:

- Studies of SARS-CoV-2 clearance in different tissues after acute infection, with focus on potential persistence of virus and its effects on organ function and chronic immune activation;
- Leveraging biospecimens from well-characterized PASC patient and controls developed within the RECOVER consortium to pursue in-depth characterization of immune response that could shed light on development of autoantibodies;
- Modeling of the interaction between pre-existing organ dysfunction/pathology (e.g., obesity, diabetes, hypertension) and the superimposition of viral infection/injury;
- Host and environmental factors and associated biological pathways (including the microbiome or existing cardiac, respiratory, metabolic, neurologic, or hematologic conditions) that predispose to development of, or resistance to, PASC;

- Time course and features of virus-host interactions leading to PASC, including the impact of SARS-CoV-2 infection on innate and adaptive immune responses;
- Host and environmental factors and the associated biological pathways that mediate the intensity and duration of the neurological, metabolic, immunologic, hematologic, and cardiopulmonary and vascular dimensions of PASC, including long-term host tissue responses, and affect recovery (e.g., modeling of viral infection on inflammation in the brain and CNS dysfunction);
- Biological effects/consequences of the virus-host interaction of SARS-CoV2 infection via ACE2 on modulating tissue/organ function over time including both short-term and long-term sequelae (e.g., mechanistic interplay between the ACE2-expressing neuroepithelial cells, the host-tissue pro-inflammatory milieu, the blood-brain-barrier and alterations in sensory neuron function in the pathogenesis of anosmia in PASC);
- Studies elucidating the pathogenesis of the varied sub-phenotypes of multi-organ dysfunction characteristic of PASC;
- Use of artificial intelligence or machine learning approaches to understand the clinical pathobiology of PASC, its manifestations, and potential prevention strategies;
- Cellular, metabolic, and immune factors as a result of viral infection as a trigger/sustainer of PASC symptoms and clinical phenotypes;
- Dynamics of innate and adaptive immune responses in PASC and implications for screening, diagnostic assay development, and predisposition to develop future immune disfunctions; and
- Using single cell -omics and spatial -omics to systematically (unbiasedly) discover key individual cells and molecular pathways likely responsible for PASC symptoms, organ system dysfunction and sub-phenotypes. Discovery studies such as this may generate innovative hypothesis for future PASC-related studies.

It is envisioned that the applicants for this highly competitive program will propose efficient, cross-disciplinary, and collaborative research teams to address their hypotheses and will have one or more of the following:

- Expertise in clinical assessment of SARS-CoV-2 infection and in elucidating the pathogenesis of the clinical manifestations of PASC;
- Expertise in similar post-infection disorders that share clinical manifestations with PASC and that may have similar protean symptomatology and share common pathobiological mechanisms;
- Expertise in the clinical manifestations of PASC based on experience or expertise in chronic viral infection, immune-autoimmune disorders, germane biological pathways, systems, organs, or diseases;
- Expertise and experience in cross-disciplinary clinical research focusing on tissue/organ/system dysfunction caused by other forms of tissue/organ/system injury relevant to multisystem symptomatology and organ/tissue dysfunction as observed in PASC; and
- Expertise and experience in using tissue and other biospecimens from COVID-19 and/or PASC patients to pursue biomarker discovery, in-depth phenotyping assays (e.g. immunophenotyping; -omics) and *in vitro* studies to gain mechanistic insights.

Supported research is expected to inform the diagnosis, prevention, mitigation, and/or treatment of PASC through elucidating: the pathobiological mechanisms and pathways underpinning post-acute sequelae, the molecular mediators of its protean symptomatology, and the possible multiple clinical clusters/sub-phenotypes. Toward these ends, supported research is expected to leverage and build upon—but should not duplicate—RECOVER cohort enrollment, samples, and data collected during the

protocol implementation. If necessary, additional samples and data previously collected outside the RECOVER study could also be utilized to confirm some of the findings.

Requirements

Proposals should have the potential to lead to rapid delineation of the pathogenesis of PASC clinical symptomatology, multi-organ dysfunction, and patients' sub-phenotypes in order to foster progress in diagnostic, therapeutic, and preventive avenues for PASC. To achieve those goals, applicants must pledge to rapidly share data and biospecimens with the NIH RECOVER (https://recovercovid.org/) data and biospecimen repositories and ultimately with the broader research community. A pledge of rapid submission of results for publication will also be a criterion for application consideration.

Application and Submission Information

Applications should be submitted using the REDCap survey via link provided in the Application Submission section below. All applications submitted in response to OTA-21-015E should include the following:

1. A Cover Page (single page) including the following:
    a. The proposal title. Please ensure to reference the ROA# OTA-21-015E in the title of the proposal to ensure expedited processing.
    b. The applicant's:
        i. Legal entity name
        ii. Address and contact information
        iii. SAM # and expiration date
        iv. DUN # and expiration date
        v. EIN number
    c. The name and contact information for the applicant's Principal Investigator (with eRA Commons account information)
    d. List of key personnel with titles and affiliations
    The name and contact information for the applicant's Business Official, the person authorized to negotiate and bind the applicant as a signatory to the Other Transaction agreement
    e. The total cost proposed for each year
2. Research Strategy section is limited to 6 pages and should include the planned timeline, milestones, and deliverables for the proposed research.
3. Requests are for one year (an additional year could be considered with appropriate justification).
4. Fully justified, itemized budget with attached budget justification.

Proposed budgets should generally not exceed a maximum direct cost of $500,000 per year. In addition, the maximum total costs should generally not exceed $800,000 per year. A higher proposed budget could be considered if appropriately justified. The proposed budget must reflect the actual needs of the proposed project.

Applications nonresponsive to terms of this announcement will not be considered for review.

Review Process

The RECOVER Administrative Coordinating Center will coordinate the review of applications by NIH subject matter experts and external experts. Prioritization and funding decisions will be made by NIH.

Review Criteria

Only the review criteria described below will be considered in the review process:

Budget and Period of Support

NIH anticipates the period of support to be one year for proposals. Applications greater than one year will be reviewed by NIH staff to consider whether the budget and the requested period of support are fully justified and reasonable in relation to the proposed research.

Overall Impact

Given that the aim of these awards is to leverage the RECOVER cohorts to make rapid progress in understanding the mechanisms underpinning the manifestations of PASC, including the mechanisms responsible for the multi-organ/system dysfunction leading to the various symptoms of PASC:

- How might the proposed research increase understanding of the molecular pathways that underlie the long-term effects of SARS CoV-2 infection?
- In what way(s) do the applicants have expertise in understanding the clinical manifestations of PASC and similar post-infection disorders that may share clinical manifestations and mechanistic pathways with PASC?
- How are the applicants' hypotheses clinically relevant regarding the pathobiology of PASC, based on experience or expertise in pertinent biological pathways, systems, organs, or diseases?
- To what extent do the applicants have expertise and experience in cross-disciplinary clinical understanding of tissue/organ/system dysfunction caused by other forms of tissue/organ/system injury relevant to multisystem dysfunction in PASC?
- How do the applicants propose to develop cross-disciplinary and collaborative research?
    - For this particular announcement, note the following: A Multiple PD/PI leadership format is strongly encouraged. The application should include at least one PD/PI with expertise in SARS-CoV-2 clinical science and at least one PD/PI whose primary expertise is in clinically relevant cell biology, physiology, pathophysiology, pathobiology, and/or metabolism. The Multiple PD/PI leadership team might not have previously published together or otherwise have an extensive history of collaboration. The development of the project itself, as reflected in the quality of the preliminary data, the rigor of the approach, and the Multiple PD/PI leadership plan, can provide evidence of a strong and dedicated Multiple PD/PI team.
- In what way does the proposed research have the potential to inform the diagnosis, prevention, mitigation, and/or treatment of PASC through elucidating the clinical pathogenetic mechanisms of PASC and the identification of associated clinical pathways?
- In what way has the proposed research set forth appropriate methodology and feasible project timelines, milestones, and deliverables?
- How do the applicants propose to rapidly share data and results with the broader research community, including, as appropriate, deposition into dbGaP, and how will they rapidly submit results for publication?

Eligibility

The following entities are eligible to receive an award under this ROA:

- *RECOVER Cohort Sites with fully executed contract with the NYU CSC*
- *RECOVER Enrolling Sites operating under a RECOVER hub (hub must have a fully executed contract with the NYU CSC). Applications for Enrolling Sites should indicate the type of RECOVER cohort (adult/pediatric/autopsy/EHR), contact PI and RECOVER hub under which they are operating.*

Application Submission

The required application information must be entered by an authorized administrator with signing authority using the form provided at the REDCap link below. A code will be provided for return access to the REDCap form. The completed proposal form must be submitted by an authorized business official via the REDCap link no later than **January 31, 2022, by 5 PM EST**.

REDCap application submission link: https://redcapedc.rti.org/recover/surveys/?s=T7RDXRLA4TR8XMJ8