Research Opportunity Announcement OTA-21-015I:

RECOVER PASC IMMUNOPHENOTYPING CORE LABORATORIES

The NIH is soliciting applications in support of the goals of the Researching COVID to Enhance Recovery (RECOVER) Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) Initiative and Investigator Consortium. This Research Opportunity Announcement focuses on immunophenotyping core laboratory analyses performed in biospecimens collected in the RECOVER adult and pediatric cohorts. The distribution of this research opportunity announcement is limited to sites participating in the RECOVER PASC Consortium.

1. Introduction

Recovery from SARS-CoV-2 infection is extremely variable with many patients recovering quickly and other patients experiencing longer-term important post-acute sequelae. The magnitude of the public health impact of these sequelae is currently unknown but potentially large given the number of individuals across the age spectrum who have been and will be infected with SARS-CoV-2. It is a public health priority that we need to better understand and develop strategies to prevent and treat the post-acute sequelae of SARS-CoV-2 infection (PASC) and that these strategies enable rapid innovation, evolution, and adaptation as more is learned about PASC and its potential impact on public health.

The goal of the trans-NIH RECOVER Initiative is to rapidly improve understanding of recovery after SARS-CoV- 2 infection and to prevent and treat PASC. Toward these ends, the Initiative is designed to address these overarching scientific objectives:

1. Characterize the incidence and prevalence of sequelae of SARS-CoV-2 infection occurring >30 days after index infection.
2. Characterize the spectrum of clinical symptoms, subclinical organ dysfunction, natural history, and distinct phenotypes identified as sequelae of SARS-CoV-2 infection occurring >30 days after index infection.
3. Define the biological mechanisms underlying pathogenesis of the sequelae of SARS-CoV-2 infection occurring >30 days after index infection.

Study of the sequelae of SARS-CoV-2 infection in the RECOVER observational cohorts is potentially confounded by exposure misclassification due to lack of availability of PCR testing at the start of the pandemic, diagnostic performance of available PCR and antigen testing, and asymptomatic infections. Serologic testing for determination of exposure classification is limited by the waning of circulating IgG antibodies to spike and nucleocapsid antigens over time, and the confounding effects of vaccination on spike protein antibodies.

This ROA is not limited to any single cell-type assay. For example, T-cell based assays have been reported to detect evidence of past SARS-CoV-2 exposure in seronegative patients, and may offer an alternative approach for mitigation of misclassification in RECOVER participants

Accordingly, to meet the RECOVER scientific objectives, it is imperative to accurately classify SARS-CoV-2 exposure for all enrolled participants.

2. Objective

With this ROA, NIH is soliciting applications for funding of an immunophenotyping core laboratory to support the scientific goals of the RECOVER Initiative and PASC Investigator Consortium. The specific objective of the RECOVER immunophenotyping core laboratories is:

1) To perform laboratory analyses of existing samples in the RECOVER biorepository to accurately determine the infection status of RECOVER participants who do not have positive

PCR SARS-CoV-2 testing prior to study entry, including participants classified as infected based on WHO criteria without PCR testing, and uninfected controls.

The proposed analytic techniques for determination of SARS-CoV-2 infection status may include serological and/or cell-based assays. Applicants must provide a strong scientific rationale for the proposed analytic approach with inclusion of preliminary data with appropriate positive and negative controls. Pragmatic high-throughput analytic techniques with potential for adaptation to clinical settings are preferred.

Applications should include a budget for 10,967 total samples across the RECOVER adult and pediatric cohorts (see Table at end of this document). All analyses must be completed and entered into the RECOVER REDCap database within 1 year from the start of funding.

Applicants must specify the type and volume of biosamples required for the selected immunophenotyping methods. Please note that all Tier 1 pediatric samples (N=5280) are dried blood spots, so different approaches for each cohort and specimen type can be proposed.

The RECOVER immunophenotyping core laboratory will provide:

- Expertise in and support for development, implementation, and execution of relevant analytic modalities on biospecimens collected in the RECOVER pediatric and adult protocols to identify prior exposure to SARS-CoV-2
- Development of a customized electronic case report form (eCRF) to capture result data in REDCap Central at DRC
- In collaboration with the RECOVER DRC and Biorepository Core:
    - A manual of operations with detailed description of the procedures for biospecimen selection and transfer
- Data management plan
- Quality assurance plan
- Data analysis plan

3. Special Award Terms

The complete terms and conditions of each sub-agreement issued under this ROA are subject to negotiation and will be contained in the Other Transactions Agreement entered between a designated RECOVER Core, on behalf of NIH, and the Awardee. This Special Award Terms section is provided for informational purposes only in order to provide prospective applicants with an understanding of key expectations and terms that may differ from traditional NIH award mechanisms.

Lower Tier Agreements

With mutual consent of the Awardee and the NIH, the designated RECOVER Core will be expected to issue sub-awards to entities identified and approved by the NIH under ROAs associated with the RECOVER initiative.

Negotiation

The NIH reserves the right to:

- Select for negotiation all, some, one, or none of the proposals received in response to this ROA;
- Segregate portions of resulting awards into components and their associated budget and/or milestones that differ from those that have been proposed;
- Accept proposals in their entirety or to select only portions of proposals for award;

- Fund projects in increments and/or with options for continued work at the end of one or more phases, which can consist of more than one milestone;
- Fund projects in increments with options to terminate activities e.g., based on evolving data/needs of the initiative;
- Fund projects of two or more applicant entities as part of a reorganized, consolidated consortium operating under an article of collaboration, teaming arrangement, or other means acceptable to the NIH;
- Fund proposers as sub-awardees of a separate Coordinating Center entity to be established by the NIH;
- Request additional documentation (certifications, etc.); and
- Remove proposers from award consideration should the parties fail to reach a finalized, fully executed agreement, or if the proposer fails to provide requested additional information in a timely manner.

Authority

This Research Opportunity Announcement (ROA) is issued with the goal of establishing an "other transactions" agreement or sub-agreement pursuant to 42 U.S.C. § 285b-3 and 42 U.S.C. § 282(n).

Eligibility

The following entities are eligible to apply under this ROA:

Higher Education

- Public/State Controlled Institutions of Higher Education
- Private Institutions of Higher Education

Nonprofits Other than Institutions of Higher Education

- Nonprofits with 501(c)(3) IRS Status (Other than Institutions of Higher Education)
- Nonprofits without 501(c)(3) IRS Status (Other than Institutions of Higher Education)

For-Profit Organizations

- Small Businesses
- For-Profit Organizations (Other than Small Businesses)

Foreign (non-US based) Institutions

- Public/State Controlled Institutions of Higher Education
- Private Institutions of Higher Education
- Non-profit Institutions
- For-profit Institutions

Proposal Format and Requirements

Each applicant may submit a single application.

The immunophenotyping core laboratory application should clearly and fully demonstrate the proposer's capabilities, knowledge, and experience, and should justify the budget proposed for the estimated number of biospecimens available for analysis of infection status in 10,967 participants over

one year. The actual number of biospecimens may be reduced or eliminated based on interim analyses, recruitment, or other considerations.

The Project Plan shall be limited to a maximum of 3 pages. Requested appendix items and biosketches must be included and are not applied to the 3-page limit. Other appendix items are not permitted.

Proposals for each immunophenotyping core laboratory shall include the following required sections:

- Cover Page
- Project Plan
- Appendix with required appendix items
- Budget and budget justification

Each of these sections will be submitted electronically via the REDCap link provided below.

The Cover Page shall include:

A. The proposal title
B. The applicant's:
    i) Legal entity name
    ii) Address and contact information
    iii) SAM UEI # and expiration date
    iv) DUNS # and expiration date
    v) EIN number
C. The name and contact information for the Awardee's immunophenotyping core laboratory Principal Investigator(s) (maximum 3) and the name and contact information of the RECOVER contact Principal Investigator
D. List of key personnel with titles and affiliations (maximum 10)
E. The name and contact information for the Awardee's Business Official, the person authorized to negotiate and bind the Awardee as a signatory to the Other Transaction agreement.
F. The total cost proposed

The Project Plan (3 pages maximum) must address the following four elements:

A. Technical Approach
The proposal must briefly describe how the work of the proposed immunophenotyping core laboratory will be accomplished. Proposers should describe the type of biospecimen required, the precise analyses planned, and any available information about sensitivity and specificity at varying intervals from infection date. Preliminary data on feasibility is expected. Pre-pandemic negative control data should be available to demonstrate specificity of the proposed assays. The analyses proposed must be able to be run on biospecimens collected according to RECOVER protocols. The applicant is expected to be fully familiar with these protocols. This section should also include a project plan with quarterly milestones and deliverables based on the listed objectives for the one year of support.

B. Key Personnel Experience
Proposers must describe experience of key personnel supporting the planning and implementation of activities described in the ROA. Please provide biosketches describing key personnel in the appendix. Biosketches should conform to the most recent NIH template requirements and do not count towards the page limits.

C. Management/Staffing Plan
Proposals should detail how the proposer will provide the necessary project administration, organization, and staff to ensure quality control, compliance with ROA expectations, and

necessary staffing adjustments. If relevant, proposers must discuss how existing funded project administration, organization, and staff will be leveraged for support of the RECOVER initiative.

D. Past Experience

Proposers should provide examples of prior project experience serving as an applicable immunophenotyping core laboratory as described in this ROA. Each example should include the total funding awarded and dates of award, contact information for a sponsor able to serve as a reference, and a brief description of the project itself, including how the project was analogous to the needs identified in this ROA with respect to the immunophenotyping core laboratory being proposed. Applicants will need to demonstrate prior work with clinical consortia or networks AND competency associated with the analyses being proposed.

Application Appendix

The technical plan must be supported with upload of the following required appendix Items (not counting towards page limits):

1. An existing manual of operations from a prior or ongoing externally funded project serving as an applicable immunophenotyping laboratory described in this ROA
2. Key personnel biosketches

The Budget must address the following:

The Budget section must provide a realistic, fully justified one-year budget and cost proposal for performing the work specified in the ROA with a calculated per sample analysis and reporting cost. The budget and budget justification will be submitted via the REDCap link provided below. Template budget worksheet and budget justification documents must be used. These templates are posted on the Teams site.

The anticipated start date for funding is Jan 15, 2024.

Applicants must provide a clear description of what is included in the immunophenotyping core laboratory costs on separate budget worksheet and budget justification template documents uploaded to the REDCap form. Budget information and any related administrative documentation shall not count toward the total proposal page limit.

The Budget should provide the overall expected total costs for each of the following two budget periods:

1. Start-up total costs (months 1-3)
    - Personnel Costs
        - Key personnel
        - eCRF and MOP development
        - Biospecimen shipping and processing workflow development
    - Other Start-up Costs
        - Local biospecimen processing and storage costs
    - Institutional indirect costs
    - Proposed Cost Share contribution
2. Per sample total cost months 4-12
    - Personnel Costs
        - Key Personnel
        - Data management
        - Immunophenotyping core laboratory analysis and reporting
        - QA/QI and Site Support
    - Other Per Sample Costs months 4-12
        - Biospecimen Transfer costs

        - Biospecimen Storage costs
        - Laboratory supplies costs
        - Laboratory equipment use costs
    - Institutional indirect costs
    - Proposed Cost Share contribution

For the budget worksheet, personnel may be listed in more than one role during the same budget period. For example, the PI may be budgeted in the first 3-month start-up section and in the unit per sample and reporting section. The calendar month effort for both of these activities for each budget period should be reported on their respective lines of the budget worksheet.

The total per sample unit cost is calculated on the budget worksheet as the sum of total per sample costs for first year months 4-12 divided by the projected number of number of samples to be analyzed by the immunophenotyping core laboratory as listed in the table below. Payments for per sample costs may begin during the award period after site training.

The following costs from the budget worksheet will be entered on the REDCap application form:

1. Total Start-Up Costs Months 1-3
2. Total per sample Costs Months 4-12
3. Total Project Costs (Months 1-12)
4. Total per sample unit cost (Total costs months 4-12 divided by projected number of samples)

Review criteria and RECOVER immunophenotyping core laboratory funding

The priority score for each application will be based on:

- Integration of immunophenotyping core laboratory objectives with scientific goals of the RECOVER initiative
- Diagnostic testing characteristics of the proposed analytic approach
- Innovation in efficiency of immunophenotyping core laboratory methods
- Investigator and Institutional environment and record of accomplishment

Application Submission

The required application information must be entered by the PI or their designee on 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 **October 15, 2023, by 5 PM EST**.

REDCap application submission link: Research Opportunity Announcement OTA-21-015I: RECOVER PASC IMMUNOPHENOTYPING CORE LABORATORIES

If you are having difficulty with this link please copy and paste the following text into your browser: **https://redcapedc.rti.org/recover/surveys/?s=E4D47ATL47YW99RK**

Table of number of specimens for Adult & PEDs cohort(s)

ADULT COHORT	Estimated N from adult	+10% QC	Total
Uninfected (negative control)	2680	268	2948
Infected No PCR	750	75	825
Infected PCR + (positive control)	600	60	660

PEDIATRIC COHORT	Estimated N from PEDs	+10% QC	Total
Dried blood spots	5280	528	5808
Whole blood derivatives	660	66	726