Research Opportunity Announcement

OTA-20-011

Host-targeting Therapies for COVID19

Introduction

Given the remarkable variations in severity of SARS-CoV-2 infection among different groups and the striking contributions of lung, cardiac, vascular, and hematologic dysfunction to COVID-19 morbidity and mortality, it is clear that host- and community-related factors are important modulators of COVID-19. It is therefore imperative to test not only antiviral therapies, but also host-targeting treatments that seek to ameliorate tissue injury, enhance reparative responses, and improve health outcomes related to heart, lung, and vasculature by targeting pathobiological processes with organ system or risk group specificity. Examples of such treatments include, but are not limited to, immunomodulators and as well drugs and biologics that target particular pathways such as mTOR, IL-system, coagulation, or the renin-angiotensin systems. Host-targeting interventions may be repurposed or novel agents or devices, used alone or in combination, or may involve strategies of medical care.

The urgency of the COVID crisis transcends what any single entity can accomplish acting in isolation and calls for rapid and efficient mobilization and coordination of clinical trial infrastructure. Toward this end, the purpose of this initiative is to establish and quickly launch an innovative and integrated clinical trial platform spanning multiple networks and infrastructure and capable of rapid and efficient execution of robust clinical trial testing of promising host-directed interventions for COVID-19. Building upon extant clinical trial capacity, this collective "network of networks" will be aimed at rapid and rigorous testing of mechanistically diverse COVID-19 host-directed interventions that target critical points along the clinical spectrum, from exposure through development of mild symptoms, development of symptoms requiring hospitalization, and extending through convalescence and recovery. The overall goal is to establish a sound evidence base for clinical practice and development of safe and effective interventions and implementation strategies.

This solicitation:

1. Invites Data and Clinical Coordinating Centers that have appropriate expertise in clinical trial design and implementation, as well as existing relationships with a network/consortium of Clinical Centers, to propose inpatient or outpatient trials of host-targeting interventions in patients infected with SARS-CoV-2, designed appropriately for the population and intervention being studied. Although the primary focus of this program is on adaptive design-based testing of interventions in phase II or III drug or therapeutic trials, it is strongly encouraged that proposed studies also include complementary aims such as collecting data, images, and biospecimens; identifying

predictive biomarkers; and/or clarifying the pathobiology or the distinctive organ-/individual-specificity of this disease.

2. Invites Data and Clinical Coordinating Centers with appropriate expertise and capacity to submit a proposal to serve as the Administrative Coordinating Center for the Network of Networks Platform, outlining the functions, roles, and responsibilities of such a Coordinating Center in ensuring the efficient and effective operations of this COVID-19 Master Clinical Trials Platform and to assist NHLBI in identifying most critical strategic opportunities and to assist in enhancing the likelihood that all funded trials are successful in achieving their scientific goals.

Authority

This Research Opportunity Announcement (ROA) is issued with the goal of establishing an "Other Transactions" (OT) agreement pursuant to 42 U.S.C. § 285b-3.

Objectives

- The NHLBI is soliciting applications for multicentered phase 2 and 3 randomized, controlled clinical trials of host-targeting strategies to prevent and treat SARS-CoV-2 disease. Although the primary focus of this program is on adaptive-design-based clinical testing of interventions, it is strongly encouraged that proposed studies also include aims such as identification of prognostic biomarkers, developing or refining activities that improve the safety or efficacy of the clinical care of COVID-19 patients and/or that slow or prevent the progression of COVID-19. Taken together, these studies should establish a sound evidence base for clinical practice and development of safe and effective interventions.
- The NHLBI is also soliciting applications from experienced Data and Clinical Coordinating Centers with an established network or consortium of Clinical Centers to serve as the Administrative Coordinating Center for the Network of Networks Platform. This overarching administrative coordinating center will be established to coordinate the development and implementation of the master protocols across the range of COVID-19 populations described above and provide logistics, administrative support, for the network of networks and support independent oversight of trial progress. This may include in the future the need to develop and support peer review of protocols. This initiative is open to experienced Data and Clinical Coordinating Centers with an established network or consortium of Clinical Centers with heart, lung, and blood expertise. Organizations or institutions submitting applications are required to propose trials of a host-targeting intervention(s), but changes in the intervention(s) or trial design may be negotiated with NHLBI. The rationale for trials should be based on thorough evaluation of other ongoing trials and networks. The development and implementation of master protocols for adaptive trials for: 1) in-hospital (including ICU) patients, 2) high risk infected outpatients, or 3) convalescing and recovered patients is expected. The overall goal is to establish an inter-connected, centrally coordinated structure with clinical centers executing master protocols for adaptive platform trials to increase the clinical trial bandwidth across the country and rapidly scale up and maximize the number of host-directed trials that are conducted and which complement other ongoing trials.

- Proposals with the following characteristics are strongly encouraged :
  - Submitted as a collaborative effort by two or more clinical trial networks/consortia.
  - Trial designs implemented using the master protocols for adaptive platform approaches supporting rapid adaptive sequential and/or combination testing of multiple interventions. Proposals should address adaptive approaches to randomization, monitoring for safety, futility and efficacy, and sample size adjustment. Also, where appropriate, seamless transition from phase 2 to phase 3.
  - High feasibility to launch trials within the next one to two months and likely to complete in no more than 9 to 12 months.
  - Trial designs in which the test and control interventions are in the context of and additive to usual care.
  - Trial designs and plans capable of facile adaptation to the rapidly evolving clinical landscape with consideration of the possible different evolutions of the pandemic as reflected in the diverse models of the rate of disease in the United States in the future.
  - Proposals should address adaptive approaches to changes in usual care and incorporation of emerging promising interventions into the master platform protocols.
  - Strategies for leveraging a common comparison group for two or more interventions being tested in a participant population of interest, including implications for masking.
  - Consent processes that address e-consent, use of legally authorized representatives, and other alternative consent processes, as well as utilization and sharing of EHR data, as appropriate
  - Data, image, and biospecimen collection plans that enable a deeper understanding of the pathobiology and patient stratification and which include, for example, extensive phenotyping and genotyping of patients and identification of biomarkers
  - Plans for data harmonization that include adoption of COVID-19 common data elements (CDEs) and for rapid data, image, and biospecimen sharing
  - Recruitment strategies to ensure inclusion of appropriate participant populations to enhance generalizability of research findings
  - Collaborations with industry to gain access to leading-edge technologies and novel therapeutic agents capable of selectively modulating the immune system and other host-directed biological systems to ameliorate the course of COVID-19.
  - Collaborations with other trial networks in the United States which may have other sources of funding.

Eligibility

Organizations

The following entities are eligible to apply under this ROA:

Higher Education Institutions

• 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)

Scope

The goal of this ROA is to forge a Network of Networks capable of conducting multiple, multicenter randomized, controlled clinical trials of promising host-targeting interventions aimed at mitigating and ameliorating the tissue injury/enhancing repair responses in the lung, heart, and vasculature and improving clinical outcomes for the prevention or treatment of COVID-19 disease. Host-targeting interventions should encompass the range of organ systems affected during COVID-19 and may be used in combination with anti-viral interventions. Proposed projects should be for focused, adaptive design-based phase II/III efficacy trials to treat or prevent the cardiovascular, pulmonary and hematologic manifestations of COVID-19 disease. This ROA is not intended to replace traditional NIH research funding mechanisms (e.g., R01, P01, R34, U01, UG3).

Examples of research areas of interest include, but are not limited to:

- Host-targeting therapies known to have immunomodulatory or anti-inflammatory effects such as Interferon-beta 1, alpha and lambda, IL6 receptor blockade with monoclonal antibodies (e.g., tocilizumab), IL1 receptor antagonist, anakinra, steroids and other immunotherapies.
- The Renin-Angiotensin-Aldosterone (RAAS) pathway and angiotensin converting enzyme (ACE) pathway targets such as ARBs, ACE inhibitors, combination RAAS drugs, (moexipril), monoclonal antibodies, recombinant human ACE2 (rhACE2), or Ang1-7.
- Treatments targeting alternative biologically plausible mechanisms/pathways (e.g., mTOR, platelet hyper-activation, autoimmune vasculitis).
- Treatment trials of convalescent plasma, hyperimmune globulins, and other blood-derived therapeutics.
- Treatment trials of GM-CSF and other chemokines.

- Use of immunoadjuvants to prevent progression of COVID-19.
- Testing of immunomodulating intervention (e.g. BCG vaccination) to prevent viral infection in healthcare or nursing home settings.
- Virus-targeting agents such as remdesivir, Kaletra (lopinavir/ritonavir), and the anti-malarial, hydroxychloroquine, used in combination with a host-targeting intervention.
- Combination therapies of multiple agents listed above or others as appropriate.
- Combinations of new agents and changes in way that care is delivered.

What is NOT eligible for funding under this ROA?

Examples include (but are not limited to) the following:

- Development of animal models
- Pre-clinical studies
- Phase I/IIa studies
- Single-center studies
- Observational studies

Regulatory Approvals for Clinical Trials

All applicants for clinical trials must have all necessary regulatory approvals, such as an IND authorization or IDE approval before award (i.e., pre-IND conversations documented at the time of submission and INDs/IDEs before award). Given the urgency to test promising interventions, the applicant may provide, in lieu of an IND, communication from FDA indicating it is safe to proceed with the proposed clinical protocol if proposing a new trial under an open IND/IDE or compassionate use.

Special Award Terms

The complete terms and conditions of each Other Transaction award issued under this ROA are subject to negotiation and will be contained in the OT Agreement entered between the NHLBI 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 NHLBI, successful Data and Clinical Coordinating Centers will be expected to issue sub-awards to entities identified and approved by the NHLBI as a result of this or future ROAs that solicit ideas for new and novel agents targeting understudied areas or interventions. The Awardee will therefore need to dedicate a sufficient level of qualified professional services to develop and implement the systems, processes, and

management techniques to effectively and efficiently execute and manage clinical sub-awards at the direction of the NHLBI. As a future extension to this capability and with the mutual consent of the Awardee, the NHLBI may require the successful Data and Clinical Coordinating Centers to develop and maintain an internal proposal solicitation, receipt, and peer review function.

Milestone-Based Payment Schedule

NHLBI funds issued under the OT Agreement will be disbursed based upon achievement of specific Operational Milestones, as proposed by the Awardee in its application and subsequently approved by NHLBI.

An "Operational Milestone" is an objective, measurable event that is indicative of project progress occurring as proposed in the application. NHLBI establishes Operational Milestones in the OT Agreement based upon information provided in the application. Except for the first payment issued upon the execution of the OT Agreement, payments will be obligated and disbursed upon completion of specific Operational Milestones.

With mutual consent of the Awardee and the NHLBI, adjustments may be made to the timeline for inclusion in the OT Agreement to ensure that funds are appropriately dispersed across Operational Milestones. If NHLBI determines, in its sole discretion, that an awardee has failed to satisfy one or more Operational Milestone(s), NHLBI may terminate the OT Agreement.

Award Criteria and Selection Information

Awardees will be selected through an objective review process. Multiple awards are anticipated. The level of funding for awards made under this ROA has not been predetermined but will depend on (1) the objectives proposed by the applicant and how well they fit with the goals of the host targeting therapies initiative, (2) quality of the proposals received, and (3) availability of funds. Agreements for all awards will be negotiated with eligible entities whose proposals are determined to be the most meritorious and provide the best value to the NHLBI toward achieving the goals of the host targeting therapies initiative and in accordance with the NHLBI priorities.

The NHLBI 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 proposals 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 proposals 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 NHLBI;

- Fund proposers as sub-awardees of a separate Coordinating Center entity to be established by the NHLBI;
- Request additional documentation (certifications, etc.); and
- Remove proposers from award consideration should the parties fail to reach a finalized, fully executed agreement, or the proposer fails to provide requested additional information in a timely manner.

Proposal Process

Submission in response to this ROA occurs in two stages. Stage 1 requires submitting a Letter of Request; if approved to proceed by NHLBI (see >$500k process on NHLBI web site), proceed to Stage 2, which requires submitting a full proposal using eRA ASSIST. In its sole discretion, NHLBI may invite applicants to skip Stage 1 and proceed to Stage 2 directly, if deemed ready to submit a full proposal.

STAGE 1 - NHLBI Host-targeting Therapies Initial Eligibility and Preliminary Review

NHLBI will review and determine whether the applicant should proceed with completing the full proposal submission. The NHLBI may request additional information be provided by the applicant to complete their initial eligibility and preliminary review. These requests will be sent to the applicant via email. Applicants are strongly encouraged to provide the requested information in a timely manner to prevent any potential delays in the review process. Proposals that do not meet the initial Host Targeting Therapies ROA program and eligibility criteria will be rejected.

Stage 1 will be patterned after the NHLBI >$500K process (https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/applications-with-direct-costs-of-500000-or-more-in-any-one-year) that includes a Letter of Request addressed to the appropriate NHLBI division (heart, lung or blood) outlining major elements of research, budget, feasibility, and specific elements related to COVID-19 studies (see process on NHLBI website, https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/applications-with-direct-costs-of-500000-or-more-in-any-one-year).

In order for the NHLBI to make an informed decision about whether to accept a proposed application for review, the Letter of Request (see https://www.nhlbi.nih.gov/grants-and-training/policies-and-guidelines/applications-with-direct-costs-of-500000-or-more-in-any-one-year) should not exceed 5 pages and should include:

- The proposed project title
- The anticipated solicitation (Funding Opportunity Announcement/Research Opportunity Announcement
- The anticipated application receipt date
- The expected start date to launch the study
- The status of regulatory consultation and any requisite regulatory approvals (e.g., IND authorization or IDE approval as appropriate and IRB review) or communications from

the FDA related to the agent being tested. This approval will be needed at the time of award

- The key personnel (the eRA Commons *userid* must be included for the PI or contact PI)
- The submitting organization or institution
- Demonstrated ability of the group or history of the investigators in conducting clinical research
- Succinct summary of the specific research question(s) to be addressed
- Brief description of the rationale for and importance of the research question(s), particularly from a public health perspective, describing what the study will contribute to advancing the diagnosis, consequences, treatment, and/or prevention of COVID-19 and COVID-19 related conditions and how the proposed study will complement other ongoing trials
- Summary of the study -- sample size, methods, primary and secondary outcomes, description of interventions, key measurements to be obtained, duration of study, very brief description of statistical methods, very brief description of power focusing on the primary question or major hypotheses, and impact of different feasible projections of future disease rates
- Brief description of any preliminary work, including pilot testing of interventions
- Brief summary of the safety profile, evidence for efficacy, drug availability now and on a large scale in the future, drug administration, storage, and dosing requirements of intervention(s)
- Evidence for the appropriateness of the trial design, equipoise among the trial arms, and how the trial interventions compare to usual or standard care; briefly address how the trial will address and adapt to a very dynamic clinical landscape in which "usual care" is rapidly evolving; and whether co-enrollment of research participants in other clinical trials is permissible
- Brief description of commitment to and experience with development and implementation of a master protocol for an adaptive platform trial
- Flexibility to adapt to changing environment, including for example, evolution of standard of care and treatment modalities
- Efforts to standardize and collaborate with other studies including utilization, as appropriate, of COVID-19 CDEs, harmonized endpoints and outcome measures, and leveraging multiple existing networks, cohorts, or other relevant infrastructure and studies
- Brief summary of evidence in support of ability to meet accrual targets
- Planned organizational structure for the study, including the sites and coordinating center; include brief information about key investigators
- Description of the planned demographics of study participants, including plans to comply with:
    - NHLBI Policy for Inclusion of Women and Minorities as Subjects in Clinical Research
    - NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research

    - NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects
    - NIH Policy and Guidelines on the Inclusion of Individuals Across the Lifespan as Participants in Research Involving Human Subjects
- Monitoring plan for clinical studies, including a Data and Safety Monitoring Board/Observational Study Monitoring Board, if required
- Direct and total costs by year, and for the entire duration of the study – generally a one-paragraph description of major sources of costs in the study using one of the two tables provided via the following link: https://www.nhlbi.nih.gov/files/docs/500K%20Budget%20Tables_2018-09-17.xlsx . Specify (1) any funding provided by other entities (federal agencies, foundations, companies), and (2) any goods or services (and their value) provided by any of these parties, including drugs/placebo, equipment, procedures, etc.
- A description of any anticipated agreements with third-parties relevant to the proposed project, including details about any provisions or restrictions related to intellectual property, publication, data and specimen sharing, and dissemination of results
- Given the context of current COVID-19 public health emergency:
    - Plan for expedited data, images and biospecimen sharing and facilitating data and biospecimen sharing through: usage of COVID-19 CDEs; plans for the use and sharing of EHR data as applicable; plans, including timelines, for making data and biospecimens available rapidly through NHLBI-designated repositories; and sharing data and biospecimens, as available, with public health agencies
    - Plan for interim analyses and rapidly disseminating the results for clinical or public health practice, including a brief description of the intended audience, approaches designed to reach that audience, and a timeline
- Brief description of the consent process and justification, if applicable, for Waiver of Informed Consent (WIC) or Exception from Informed Consent (EFIC), with plans for community consultation in the case of EFIC

STAGE 2 - Full Proposal

If upon review of the Letter of Request the NHLBI determines the proposed research to be in scope and hold significant promise for achieving the objectives of this ROA, the applicant will be invited to submit a full proposal. The full proposal will be submitted via eRA ASSIST following instructions that will be provided to the applicant.

The full proposal should include information in the following areas:

• Additional administrative information about the applicant and institution or organization (name, address, entity and Principal Investigator NIH Commons Registration information), including SAM information and DUN and Bradstreet number, human and animal assurance approvals as appropriate.

• Project Plan uploaded as searchable PDF format in a font size of 11 or 12 point and font type of Arial or Times New Romans. Margins must be 1-inch wide (top, bottom, left, and right). The project plan must not exceed 50 pages in length. Biosketches must not exceed 4 pages in length

and are not counted in the page limit. Also excluded from the page limitation are cover sheets, letters from collaborators and consultants, and representation and certification documents.

• Budget reflecting the proposed milestone-based payment schedule and total cost proposed, accounting for cost share amounts offered by the applicant. (If proposing F&A include a negotiated federal rate approval.)

Project Plan

The precise contents of the Project Plan will depend on the nature of the proposed clinical trial. The Project Plan should generally include the following elements:

- Project Summary: Description of the project.
- How the proposed intervention will improve patient outcomes and/or quality of life. Discussion of the scientific rationale and data, including the therapeutic candidate, that support its use in COVID19 disease and in the patient population in which testing will occur.
- Risk/Benefit Profile: Risk/benefit profile and draft of the Investigator's Brochure (IB), if available.
- Operational Milestone Based Plan: The plan should describe all proposed Operational Milestones. Each Operational Milestone should include objective completion criteria and an anticipated completion date, as well as a 9-12 month timeline showing each milestone in a Gantt chart like format. Pricing for each milestone should be separately identified in the Budget.
- Food and Drug Administration (FDA) Correspondence: Relevant FDA comments and plan for addressing any issues raised by FDA and official FDA meeting minutes and/or FDA correspondence relevant to the proposed project.
- Adaptive-design clinical protocols synopsis and draft of clinical protocols in the framework of a master protocol for an adaptive platform trial.
- Data and Safety Monitoring Information: The proposal should include a description of how clinical trial research activities will be monitored consistent with the NIH Policy for Data and Safety Monitoring. A Data and Safety Monitoring Plan should be submitted as part of a proposal. The NHLBI reserves the right to establish an NHLBI Data and Safety Monitoring Board (DSMB) for any clinical trial project funded under this ROA.
- Financial Contingency Plan: Potential risks, mitigation strategies, and associated costs, including a description of a viable source to cover these costs (other than NHLBI and not including co-funding). The plan must address how obligations to patients, including ethical ones, will be financed by the applicant, should milestones not be met and/or upon termination of the award due to lack of progress.
- Team Organization: Team structure, leadership and communications plan, including biosketches of individuals identified as the principal investigator and all key personnel.

- Resources and Environment: Resources available to the project and environment in which the activities will be performed.
- References

Budget

The Budget section of the application must provide a realistic, fully justified budget and cost proposal for performing the work over a specified period of performance needed to accomplish project objectives. In particular, the budget must include a proposed Operational Milestone-based payment schedule, including objective completion criteria and anticipated completion date for each Operational Milestone. Except for the first payment issued upon the execution of the OT Agreement, payments will be obligated and disbursed upon completion of specific Operational Milestones subject to the availability of funds. Costs resulting from a delay or failure to meet an Operational Milestone will be the sole responsibility of the Awardee. Successful applicants will therefore have thoughtfully accounted for foreseeable project risks and developed contingency plans that do not involve the need for additional funding from NHLBI. (see "Financial Contingency Plan" under Project Plan elements).

Provide the overall expected cost for each of the following categories:

- Personnel
- Equipment
- Travel
- Subawards/subcontracts/consultants
- Other direct costs
- Total cost (with indirect costs included)
- Proposed Cost Share contribution

Submission and Contact Information

For best consideration, initial Stage 1 Letters of Request should be submitted via email by **Friday, May 15, 2020, by 5 PM EDT** to NHLBI_OTA@mail.nih.gov. Additional letters of request will be considered on a monthly basis (June 15, July 15, August 15). Letters from each of these submission dates may be batched to evaluate multiple proposals together. This mailbox will also be used to answer questions. If invited to submit a Stage 2 full proposal, the applicant will be provided specific instructions for how to submit via eRA ASSIST.

Financial and administrative questions should be addressed to Benjamin Sakovich, NHLBI Agreements Officer.

Technical questions should be addressed to the NHLBI Division that best aligns with the study: James Kiley, Division of Lung Diseases, David Goff, Division of Heart and Vascular Diseases and Keith Hoots, Division of Blood Diseases and Resources.

A note about eRA Registration

NHLBI uses the eRA Commons system to administer OT awards. If you are invited to submit a full proposal in eRA ASSIST, you will need to be registered in eRA Commons, which can take some time to complete – as many as several weeks in some cases. Therefore, if you are considering submitting a proposal and are not yet registered in eRA, it is highly recommended that you begin the process of registering your organization, Program Director/Principal Investigator (PD/PI) and Signing Official (SO) in eRA Commons as soon as possible to avoid possible award processing delays. To register, please follow the instructions via this website: https://public.era.nih.gov/commons/public/registration/registrationInstructions.jsp.

1. Complete the online Institution Registration Form and click Submit.

2. The NIH database will send you an email with the link to confirm your email address.

3. Once your email address is verified, the NIH will review your request and let you know of the result via email.

4. If your request is denied, you will get an email notifying you of the reason.

5. If your request is approved, you will get an email with your Commons User ID and temporary password.

6. Log into Commons with the temporary password and the system will prompt you to change temporary password to a permanent one. Your SO will be prompted to electronically sign your registration request. (Please review your registration information carefully.)

7. Once your SO has electronically signed the request, your organization will be active in Commons and you may create and maintain additional accounts for your institution staff.

To complete the registration above, you may need to register for the following if you haven't done so already:

Dun & Bradstreet Number (DUNS) - https://fedgov.dnb.com/webform/

Employer Identification Number (EIN)- https://www.irs.gov/businesses/small-businesses-self-employed/apply-for-an-employer-identification-number-ein-online

Small Business Administration (SBA) - https://www.sbir.gov/registration

System for Award Management (SAM) - https://www.sam.gov/SAM/