Research Opportunity Announcement

OTA-19-007 for Cure Sickle Cell

CURE SICKLE CELL INITIATIVE

Analytical and/or Clinical Validation of Candidate Biomarkers for Curative Therapies in Sickle Cell Disease

Introduction

In September 2018, the National Heart, Lung, and Blood Institute (NHLBI) launched the Cure Sickle Cell Initiative (CureSCi), a national initiative that supports technologies and treatments that accelerate the implementation of accessible cures for sickle cell disease (SCD).

This effort will bring together the necessary stakeholders to seize opportunities and address challenges faced by the patient community to access clinical trials and potential curative treatments. Likewise, the initiative intends to address challenges faced by the medical research community and biomedical industry to bring therapies and treatments to market. NHLBI's initiative will play a critical role in bringing together government agencies and the private sector to improve on processes that will help accelerate the implementation of curative therapies.

The vision of CureSCi is to accelerate the development of treatments aimed at a genetic-based cure for sickle cell disease. To this end, CureSCi intends to assist investigators as they move meritorious, peer-reviewed projects through IND enabling studies and into clinical trials. CureSCi will not replace NHLBI funding of sickle cell disease-focused science through traditional mechanisms. NHLBI will continue to fund meritorious investigator-initiated grants related to sickle cell disease. CureSCi also intends to support meritorious, peer-reviewed projects intended to support the clinical evaluation of novel gene therapy and gene editing.

Authority

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

Objectives

The NHLBI is soliciting applications to develop and validate assays necessary for the assessment of hematological outcomes and other measures of disease modification following transplantation of an autologous, gene modified (gene therapy or gene edited) hematopoietic cell graft conducted with the intent to provide a single treatment resulting in alleviation or 'cure' of sickle cell disease. Priority is given to assays that can be validated in both manufacturing processes and in clinical trials deployed in clinical laboratories at the treatment sites.

Key Dates

Proposal Due Date: July 31, 2019 by 5:00 PM local time of applicant organization.

ROA expiration Date: August 1, 2019

Project Duration
Applicants should propose studies that can be conducted within a 2-year timeframe.

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 overarching purpose of this Research Opportunity Announcement (ROA) is to promote the validation of strong candidate biomarkers and endpoints for sickle cell disease that can be used to facilitate the development of curative genetic therapeutics from Phase I through Phase II/III clinical trials and in post approval studies. Specifically, the focus of this ROA is on advanced analytical and clinical validation of hematological and sickle cell disease modification biomarkers, biomarker signatures, and/or endpoints using retrospective and/or prospective methods. It is assumed that: 1) a candidate biomarker has already been identified, and 2) assay technology has already been developed although it is understood that further optimization may occur. Research supported by this ROA will ultimately demonstrate that biomarker or endpoint change is reliably correlated with variables such as clinical outcome, and hematological changes. The goal of this ROA is to facilitate the advancement of robust and reliable biomarkers, biomarker signatures and endpoints necessary for the assessment of hematological outcomes and other measures of disease modification following transplantation of an autologous, gene modified (gene therapy or gene edited) hematopoietic cell graft conducted with the intent to provide a single treatment resulting in alleviation or 'cure' of sickle cell disease.

Use of the BEST (Biomarkers, EndpointS, and Other Tools Resource) standardized biomarker definitions (https://www.ncbi.nlm.nih.gov/books/NBK338448/) is required for all studies.

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

- Develop and validate assays to quantitatively determine cellular distribution and semi-quantitative cellular expression of fetal, adult and/or sickle hemoglobin
- Develop and validate assays to assess biomarkers of red blood cell hemolysis
- Develop and validate assays to assess red blood cell rheology, including microfluidics and imaging flow cytometry sickling assays

- Develop and validate assays to assess biomarkers of inflammation related to vascular injury in sickle cell disease
- Validation of biomarker(s), using retrospective and/or prospective methods, with the intended use as primary and/or secondary outcome endpoints in evaluation of curative genetic strategies for sickle cell disease

Examples of studies that are NOT responsive to the ROA. NIH/NHLBI will continue to fund science in the areas listed below through other NHLBI-funding mechanisms, but not through this specific CureSCi ROA.

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

- Development of patient reported outcomes for sickle cell disease
- Development of measures for neurocognitive changes related to sickle cell disease
- Development of measures that do not have a strong rationale for use in the evaluation of primary and/or secondary outcome endpoints in curative genetic strategies for sickle cell disease
- Natural history studies aimed only at exploring disease pathophysiology, genetic or epigenetic mechanisms rather than focused on biomarker, biomarker signature or endpoint development for use in the development of curative therapeutic options for sickle cell disease
- Applications that propose animal studies
- Studies focused on biomarker identification and discovery
- Applications that solely focus on creating or maintaining patient registries
- Therapeutic target identification
- Development or clinical testing of candidate therapeutics
- Clinical intervention studies other than those necessary to validate biomarkers

Special Award Terms

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 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 an Operational Milestone, 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 Cure Sickle Cell 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 advantageous and provide the best value to the NHLBI toward achieving the goals of the Cure Sickle Cell initiative 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;
- 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. A 'proposer' who does not receive an award may be invited to participate in the larger Cure Sickle Cell initiative and remains eligible for subsequent submission to Cure Sickle Cell ROAs or collaborative activities.

Proposal Process

Submission in response to this ROA occurs in two stages. Stage 1 requires submitting a preliminary study overview; Stage 2 requires submitting a full proposal. All proposals will require a NHLBI staff consultation after completion of the preliminary review and prior to approval to submit a full proposal.

The preliminary study overview and full proposal application is submitted using the on-line application system available at https://secure.emmes.com/scl/resources/login.jsp. The application system is accessed via the Cure Sickle Cell website once the applicant has completed the registration process. The application system allows the applicant to move between the sections of the proposal and save any data entered. Applicants can access the application system at any time. The applicant will be able to view, complete and/or submit their proposal as appropriate.

The Preliminary Application Form includes requests for information in the following broad categories:

- Investigator information (Biosketch, CV, etc.)
- Alignment with Cure Sickle Cell Initiative ROA programmatic scope
- Funding Level
- Proposal overview
- Institutional/Organizational contact information

NHLBI CureSCi Initial Eligibility and Preliminary Review
The on-line application system allows preliminary review to be conducted using information provided by the applicant in the first section. The applicant is strongly encouraged to complete and submit this section of the application in a timely manner to initiate the eligibility and preliminary review process.

Based on this preliminary review, the NHLBI may reject the application or propose one of the following two options:

Full Proposal Submission
If upon review of the Preliminary Application, the proposal is determined to be in scope and an applicant receives permission, the applicant will be invited to submit the full proposal application as described in this ROA. The full proposal will undergo a quality check to ensure the requested information has been provided, followed by a scheduled full review by a selection committee convened by the NHLBI. The full proposal must be submitted by the proposal due date of July 31, 2019. 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 Cure Sickle Cell ROA program and eligibility criteria will be rejected.

90 Day Conceptualization Award
If upon review of the Preliminary Application, the proposal is determined to be in scope, and would benefit from further conceptualization and/or development, the applicant will be invited to submit an abbreviated application as described in this ROA. If determined by NHLBI to be scientifically meritorious the NHLBI may elect to award funding for an initial 90-day period in which the applicant will develop the comprehensive full proposal specified in this ROA, including the detailed Research Plan. The full proposal must be submitted within 60 days of award for consideration for additional funding based on the review and approval of the NHLBI.

Full Proposal Application Contents and Format

The full proposal application form includes requests for 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 technical proposal must not exceed 12 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 work and, in particular, on the phase of clinical research activities being contemplated. The Project Plan must include the following elements for both full submission and abbreviated proposal submission:

1. Project Summary: Description of the project.
2. Study Objectives: State the specific objectives of the efforts. Briefly provide the context for the proposed set of studies, with an emphasis on the biological research rationale for the biomarker or endpoint, along with a cogent argument outlining its importance and unmet need. In addition, the major objectives of the proposed study should be stated, including the technical questions to be answered to validate the biomarker or endpoint relative to the intended Context of Use.
3. Research Plan: The Research plan narrative must include in following sections. Each section should address the requested information.

    - *Rationale and Unmet Need*
        - Define the unmet need for the proposed biomarker or assay's intended use in clinical trials for curative therapies in sickle cell disease.
        - Provide a strong biological rationale that supports and justifies the biomarker, biomarker signature, or endpoint, along with the proposed analytical and clinical validation scheme.
        - Describe the method of detection for the biomarker, biomarker signature or endpoints and address the feasibility of this method of detection for eventual use in Phase I and Phase II/III clinical trials across multiple clinical testing sites.
        - Provide information on characteristics of the sample (i.e., specimen, image, physiological endpoint) to be used for the measurement and how the measurement result will be used.
        - If applicable, provide a comparison to other available biomarker or endpoint approaches discussing the advantages of the proposed biomarker approach and addressing the unmet need for a biomarker.
    - *Supporting Data*
        - Provide a clear outline of the data supporting an argument that the biomarker has been identified along with the existing evidence that it measures the clinical concept of interest.
        - Provide preliminary validation data demonstrating that the candidate biomarker identifies, measures or predicts the concept of interest.
        - Provide information about the types of specimens that the assay or detection method utilizes.
        - Summarize any data supporting the feasibility of the biomarkers use in a clinical setting.
        - Discuss whether any analytical validation metrics have been analyzed or completed; if so, provide the metrics.
        - Describe the current status of biomarker clinical validation relative to clinical validation metrics, if applicable.
    - *Approach and Detailed Plan*

    For abbreviated applications for the 90 day conceptualization award the Approach section is limited to No more than 2 page summary of plans to further refine the scientific understanding of the biomarker (its association with sickle cell disease, clinical outcome or therapeutic target), its

assay or method of detection, and its performance (dose response/specificity and sensitivity of response and temporal relationship of response to magnitude of biomarker change.

Full submission proposal must provide the following detailed plan in the Approach section.

- Plan to assure standardized and representative clinical sample and data collection
- Carefully detailed plan to complete analytical validation of the assay or method of detection, or evidence that this has already been completed
- Plan for evaluation of (i) Accuracy, (ii) Precision, (iii) Analytical sensitivity, (iv) Analytical specificity including interfering substances, (v) Reportable range of test results for the test system, (vi) Reference intervals (normal values) with controls and calibrators, (vii) Harmonization of analytical performance if the assay is to be performed in multiple laboratories, (viii) Establishment of appropriate quality control and improvement procedures, (ix) Any other performance characteristic required for test performance with determination of calibration and control procedures
- Plan for further optimization and analytical validation of the biomarker detection method, including establishing threshold or cut-off for assay
- Feasibility and readiness of the methods for measuring biomarkers for implementation and clinical testing across multiple sites
- Plan to systematically extend the understanding of the association between the biomarker and the disease, clinical outcome or therapeutic target using retrospective and/or prospective multi-site clinical designs
- If biomarker identification and initial proof of concept are based on animal data, outline the approach for translation to human pathophysiology, target engagement or prediction of response to an intervention, across multiple sites
- Plan to evaluate the performance of the biomarker in a clinical setting (sensitivity and specificity of biomarker response, quantitative nature of biomarker response relative to dose, time of intervention or progression of disease, etc.) across multiple sites
- Plan to validate the performance of the biomarker against an established measurement
- The statistical design and analysis plans for validation activities, including plans to ensure that the study is scientifically rigorous, adequately powered for multi-site designs, appropriate randomization plans are in place to minimize bias, and that reporting is transparent
- Plans to address regulatory requirements needed to get the biomarker and its assay into clinical trials within its intended clinical context
- If FDA qualification of the biomarker is under consideration, plans for FDA interactions should be described
- Documented evidence that the applicant has obtained all of the required approvals and certifications necessary to proceed with work planned

4. Letters of Support

5. Operational Milestone Based Plan: The plan should describe all proposed Operational Milestones. Milestones are quantitative goals that can be used for go/no-go decision making as the project advances. A list of activities planned for each phase are not considered milestones because they do not provide decision-making goals. Milestones will provide clear indicators of a project's continued success or emergent difficulties. Progress toward achievement of milestones will be

evaluated by NHLBI Staff, and funding for the project may be discontinued if milestones are not met. Each Operational Milestone should include objective completion criteria and an anticipated completion date, as well as a timeline showing each milestone in a Gantt chart like format. Pricing for each milestone should be separately identified in the Budget.

6. Protection of Human Subjects Research: As required by federal regulations (45 CFR 46) and NIH policy, applications that propose to involve human subjects must address: 1. the risk to subjects 2. the adequacy of protections against risk 3. potential benefits of the research to subjects and others 4. the importance of the knowledge to be gained 5. for clinical trials, a data and safety monitoring plan.
7. Commercial Development Plan: Describe any planned commercial development activities, if applicable.
8. Team Organization: Team structure, leadership and communications plan, including biosketches of individuals identified as the principal investigator and all key personnel
9. Resources and Environment: Resources available to the project and environment in which the activities will be performed.
10. 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. 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.

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

Proposals may be submitted immediately and will be considered until 31 July 2019. This final submission date may be extended at the discretion of the NHLBI and is subject to the availability of funds.

If selected for final award negotiation, the terms, scope, and budget of the NHLBI OT Agreement will be shared with the applicant. As a cursory administrative matter, the applicant will also be given special instructions for how to submit the full application into the NIH eRA ASSIST application, which allows the NHLBI to obligate funds and issue payments to the Awardee. If the applicant does not have an eRA commons account, the applicant should proceed with obtaining this account as soon as possible to avoid award delays. Applicants are reminded that award is not final until an OT Agreement has been executed between the NHLBI and the Awardee.

Financial and administrative questions should be addressed to the NHLBI Agreements Officer at NHLBI_OTA@mail.nih.gov.

Technical and scientific questions should be addressed to Traci Mondoro, PhD, NHLBI Project Officer at mondorot@nhlbi.nih.gov.