

Research Opportunity Announcement

OTA-19-005 for Cure Sickle Cell

CURE SICKLE CELL INITIATIVE

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.

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 for preclinical and clinical projects focused on curative strategies for sickle cell disease in the areas of gene therapy (replacement) and gene editing. Proposed projects may also be focused on developing or refining activities that improve the safety or efficacy of the clinical protocol for gene therapy or gene edited autologous hematopoietic transplantation (e.g. improved bone marrow conditioning regimens, maximizing stem cell mobilization and harvesting).

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)

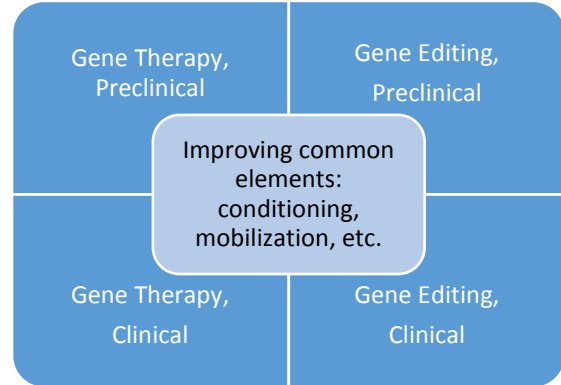
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For-Profit Organizations

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

Scope

The graphic depicts a simplified landscape of the type of projects that are eligible for funding through CureSCi. This ROA is not intended to replace traditional NIH research funding mechanisms (i.e. R01, R21). Proposed projects should be focused on the gene therapy and gene editing strategies for cures for sickle cell disease on the path from pre-IND to IND Phase I to Phase I/II to Phase II studies. The goal of this ROA is to support multiple research projects that when integrated sustain a unifying research strategy using genetic engineering technologies to achieve a long-term cure for sickle cell disease. *Ex vivo* and *in vivo* gene modification approaches are allowed.



Examples of research of interests include, but are not limited to:

- Gene modification or gene addition strategies to increase fetal hemoglobin expression in patients with sickle cell disease;
- Gene addition strategies to express anti-sickling beta globin and increase the amount of adult hemoglobin (HgbA) in patients with sickle cell disease;
- Gene modification strategies to correct the gene mutation that leads to SCD;
- Methods to enhance transplantation and engraftment, or minimize rejection, of modified cells as part of a genetic engineering for sickle cell disease curative transplantation strategy. For example, this could include strategies to improve *in vivo* expansion, selection, persistence, or distribution of modified cells;
- Small scale proof-of-concept clinical trials (feasibility, safety, or efficacy);
- IND-enabling studies in animals (safety and/or toxicology).

What is NOT eligible for funding under this CureSCi 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 animal models
- Normal red cell biology
- Pain in sickle cell disease
- Allogeneic transplants for sickle cell disease
- Stroke, acute chest syndrome, neurological issues, or end organ damage in sickle cell disease
- In utero gene therapy
- Late phase (III/IV) clinical trials
- Early stage product/technology development

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Regulatory Approvals for Clinical Trials Applicants

All applicants for Clinical Trials must have an active IND or IDE for the proposed candidate in the proposed indication before applying (i.e., the IND/IDE has been filed with FDA for >30 days and has approval to proceed with the proposed clinical protocol). The applicant must provide communication from FDA indicating it is safe to proceed with the proposed clinical protocol if proposing a new trial under an open IND/IDE. Phase 2 trial applicants must have Phase 1 safety data obtained with the proposed treatment in an appropriate indication unless agreement to proceed with the Phase 2 protocol is otherwise indicated by the FDA.

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;

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- 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 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.

Proposals are 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. 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 Cure Sickle Cell ROA program and eligibility criteria will be rejected.

California Institute for Regenerative Medicine (CIRM) Co-Funding

Applications that meet the eligibility requirements of this ROA and the program announcement for CIRM [CLIN1: Late Stage Preclinical Projects](#) or [CLIN2: Clinical Trial Stage Projects](#) may be eligible for co-funding from both the NHLBI and CIRM, which are partnering to maximize resources available for projects of mutual interest. At the time of Initial Eligibility and Preliminary Review, NHLBI may recommend that applicants develop and submit an identical proposal to both CIRM and to the NHLBI to be considered for

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such co-funding opportunities. Applications submitted for co-funding will be considered jointly by NHLBI CureSci and CIRM and as such will require the sharing of scientific review summary reports and other information necessary to coordinate pre-award and post-award management activities.

NHLBI CureSci Staff Consultation

Prior to approval to submit a full proposal, a NHLBI staff consultation meeting is required for all proposals that meet initial eligibility and preliminary review and prior to approval to submit a full proposal. Applicants will be sent a notice via email requesting their participation in a meeting to discuss the proposed research project with NHLBI CureSci staff via an in-person meeting or a conference call (i.e., staff consultation).

Full Proposal Submission

If upon review of the Preliminary Application form, the proposal is determined to be in scope and an applicant receives permission, the applicant is invited to submit the full proposal. The full proposal will undergo a quality check to ensure the requested information has been provided, followed by a scheduled full review by the Scientific Review Committee. Applicants who are applying for co-funding with CIRM are requested to submit their CIRM application in lieu of the application format described below.

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 25 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. Subject to guidance received from the NHLBI CureSci Staff Consultation, the Project Plan should generally include the following elements:

1. Project Summary: Description of the project.
2. Target Product Profile: Description of the aspirational goals of the commercialized product that outlines the base case and optimal product profile that describes a medical and commercial value proposition that supports adoption by patients and health care providers.
3. Value Proposition & Clinical Development Plan: Description of the indication and unmet medical need that will be addressed with the product. Description of the current standard of care and how

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the proposed product will improve patient outcomes and/or quality of life. Description of the value created by this product that supports its adoption by patients and healthcare providers. Description of next steps in clinical development of the proposed product.

4. Rationale: Discussion of the scientific rationale and data, including with the therapeutic candidate, that supports its use in the target disease and for the patient population in which testing will occur and the intended treatment population.
5. Completed IND-Enabling Studies Summary: Tabular summary of completed IND-enabling studies and description of study outcomes.
6. Preclinical Studies Summary: Tabular summary of completed preclinical studies (or planned preclinical studies).
7. Previous Clinical Experience Summary: Tabular summary of clinical data with the proposed or related product, if the proposed product has been previously tested or utilized in patients
8. Risk/Benefit Profile: Risk/benefit profile and draft of the Investigator's Brochure (IB), if available.
9. 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 timeline showing each milestone in a Gantt chart like format. Pricing for each milestone should be separately identified in the Budget.
10. 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.
11. Manufacturing Summary: Manufacturing plan synopsis.
12. Clinical Protocol: Clinical protocol synopsis and draft of the full clinical protocol, if available.
13. 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](#). If available, 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.
14. Operational Plan: Clinical operations plan for the subsequent or proposed clinical trial, if clinical trial initiation activities are proposed.
15. Commercial Development Plan: Describe any planned commercial development activities.
16. 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). For clinical trials applications, the plan must address how ethical obligations to patients will be financed by the applicant, should milestones not be met and/or upon termination of the award due to lack of progress.
17. Team Organization: Team structure, leadership and communications plan, including biosketches of individuals identified as the principal investigator and all key personnel.
18. Resources and Environment: Resources available to the project and environment in which the activities will be performed.
19. References

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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. (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

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

Financial and administrative questions should be addressed to 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.