CALIFORNIA'S STEM CELL AGENCY

Funding Opportunity Concept Plan

DISC2: DISCOVERY STAGE RESEARCH FUNDING OPPORTUNITY for QUEST AWARDS

BACKGROUND

The mission of CIRM is to accelerate world class science to deliver transformative regenerative medicine treatments in an equitable manner to a diverse California and world.

Through the Discovery Quest program, CIRM continues to create funding opportunities for the types and stages of research that otherwise do not exist or are of limited scope and focus to advance the field of regenerative medicine. Existing federal funding opportunities for discovery stage activities are primarily driven by the internal priorities and interests of the administering body and, therefore, are unpredictable and limited in both scope and focus. The Discovery Quest program is a part of CIRM's core product development programs that unlike other funding sources, provide reliable and predictable funding throughout the award period, and bring expert CIRM staff and advice to support accelerated outcomes and advancement of projects along key stages of the product development pathway. CIRM therefore provides this unique opportunity to California scientists to support stages in the development of discovery research projects that are unlikely to receive timely or sufficient funding from other sources.

OBJECTIVE

The objective of this funding opportunity is to:

1) Promote the discovery of promising new **stem cell-based and genetic ~~therapy~~therapeutic candidates~~technologies~~** that ~~could~~ can be translated for clinical~~to enable broad~~ use ~~and ultimately, improve patient care~~;

OR

2) Promote the discovery of promising new **biomarker candidates** that can be translated for clinical use.

Projects funded through the Quest Awards must~~should~~ propose a therapeutic or biomarker candidate~~technology~~ that is uniquely enabled by human stem/progenitor cells or directly reprogrammed cells, or uniquely enabling for the advancement of stem cell-based therapies or ~~aimed at developing a~~ genetic therapies.~~therapy approach.~~

AWARD INFORMATION

The Expected Outcome of a Quest Award is to produce, within 3 years, a project deliverable that is a novel candidate therapeutic; OR ~~or within 2 years,~~ a novel candidate biomarker,~~device, diagnostic test or tool~~ that can immediately progress to translational activities necessary for approval for clinical~~translation to enable broad~~ use.

What activities will CIRM fund?

CIRM funds will support the following activities under this opportunity:

- Activities that will lead to the selection of a novel candidate therapeutic that is~~, device, diagnostic test or tool~~ ready for translation ~~to enable broad use and ultimately, improve patient care~~ including:
    - Studies necessary~~Developing and implementing assays~~ to identify/test/characterize candidate ~~(or prototype)~~ therapeutic. ~~, device, diagnostic test, tool/technology~~
    - Feasibility and initial reproducibility assessment.
    - Optimization of candidate(s) including testing of cell lines, gene therapy vectors, and identifying structure-activity relationships.~~Characterization/optimization of candidate(s)~~
    - Proof- of concept studies with candidate; for non-stem cell-based candidates (e.g., small molecules, biologics~~certain devices, diagnostic tests, tools~~), proof of concept testing with human stem, progenitor, directly reprogrammed cells, or relevant human somatic cells targeted by a genetic therapy.

  - Developing Target Product Profile. ~~(Product Concept Document) for candidate therapeutic, device, diagnostic test or tool~~
  - Preparation for and conduct of stage appropriate regulatory meetings (e.g., for stem cell-based cell therapeutic candidates – an INTERACT meeting).

- Activities that will lead to the selection of a novel candidate biomarker with a specified clinical Context-of-Use that is ready for translation including:
  - Studies conducted to identify/specify/characterize candidate biomarker.
  - Studies necessary to refine or specify Context-of-Use.
  - Testing and characterization of analytical methods for biomarker assessment.
  - Initial proof of concept studies using appropriate clinical samples/data.
  - Preparation and completion of stage appropriate regulatory meeting/submission (e.g., Letter of Intent submission to FDA's Biomarker Qualification Program).

CIRM funds cannot be used to support the following activities under this opportunity:

- ~~For stem cell projects, research lacking a strong rationale for the unique necessity of human stem/progenitor cells or directly reprogrammed cells to achieve the project deliverable OR research uniquely enabling for the advancement of stem cell-based therapies that does not include testing with human stem/progenitor cells or directly reprogrammed cells to achieve the project deliverable~~
- Translational activities to develop either a Good Manufacturing Process (GMP) ~~-) -~~ compliant process~~,~~ or a Clinical Laboratory Improvement Amendments (CLIA) ~~-) -~~ compliant process.
- Translational activities to implement Design Control including initiation and maintenance of Design History File.
- Translational activities to develop a process for commercialization. ~~for a tool or technology~~
- Translational activities necessary for the filing of a well-supported IND, 510(k) or IDE with the FDA~~,~~ for validation testing under CLIA or for commercialization.
- Preparation for and conduct of clinical trials.
- Clinical validation studies of candidate biomarker necessary for regulatory acceptance.

What is the award amount and duration?

CIRM will fund direct project costs of up to:

- $1,750,000 per award to achieve a therapeutic candidate; award duration is up to three years.
- $1,000500500,000 per award to achieve a biomarker candidate; award that is a diagnostic test, a device or a tool; Award duration is up to two three years.
- $2,0001,500,000 per award to achieve a candidate that is a therapeutic candidate; award; Award duration is up to three years.
    - Up to an additional $200,000 per award may be requested for activities related to obtaining and/or sharing clinically compatible pluripotent stem cell lines; testing multiple lines for selecting the final candidate to be translated; or for addressing scientific diversity. Budget request must be strongly justified on a per line basis.

The amount of direct project costs requested must be adequately justified and is subject to adjustments prior to issuance of an award based upon assessments of the Grants Working Group (GWG), the CIRM team, or by the Application Review Subcommittee of CIRM's Governing Board. The proposed project period must not exceed the maximum period from the award start date (approximately 90 days after the date of ICOC approval) indicated above.

How will funds be awarded?

Awards will be made in the form of a grant. Funds will be disbursed pursuant to a CIRM Notice of Award. The first payment will be issued upon initiation of an award and subsequent payments will be disbursed on a regular interval at CIRM's option. Continued funding is contingent upon timely progress, as outlined in the project milestones and timeline established under the Notice of Award, and, when applicable, the ongoing ability of the applicant to fund its operations and to satisfy its co-funding commitment.

ELIGIBILITY

What types of projects are eligible for funding?

To be eligible, the proposed project must satisfy the following requirements:

(1) Must be ready to initiate work on the funded project within 90 days of approval

Given the urgency of CIRM's mission, all approved awardees must initiate work on the funded project within 90 days of approval and authorization for funding by the Application Review Subcommittee of the Independent Citizens' Oversight Committee.

(2) The applicant must propose studies leading to~~for~~ a novel candidate therapeutic or biomarker~~new technology~~ that will achieve the Expected Outcome, and that is uniquely enabled by human stem cells or uniquely enabling for the advancement of human stem cell-based therapies or genetic therapies as follows:

- Discovery research for a novel therapeutic candidate:
  - A. That is a cell therapy where human stem or progenitor cells[1] (collectively, "stem cells") either compose the therapy or are used to manufacture the cell therapy.
  - B. That is a genetic therapy[2] approach (**i**) that targets a human somatic cell for its therapeutic effect, AND (**ii**) is intended to replace, regenerate, or repair the function of aged, diseased, damaged, or defective cells, tissues, and/or organs.
  - C. That acts on or is dependent on endogenous human stem cells for its therapeutic effect, that is dependent on targeting human cancer stem cells for its therapeutic effect, that modifies a stem cell therapy, OR where a human stem cell is necessary to manufacture the therapy (e.g., extracellular vesicles).
  - D. Where human stem cells are uniquely required for candidate identification and testing.
- Discovery research for a novel biomarker~~human stem cell-based diagnostic test, assay or tool~~ candidate: ~~that can be used to discover, advance, monitor, or evaluate new therapies, OR~~
  - That supports the development or clinical use of any ~~research or investigational~~ therapeutic~~s~~ of the modalities ~~types targeted by DISC2,~~ defined above in bullets A-C.
  - For which human stem/progenitor cells are uniquely enabling for identification, testing, validation or assessment.

[1] Under Proposition 14, progenitor cells are "multipotent or precursor cells that are partially differentiated, but retain the ability to divide and give rise to differentiated cells." Progenitor cells may include directly reprogrammed cells if they meet the criteria in the above definition.

[2] For the scope of this solicitation, CIRM considers genetic therapy to mean a human therapeutic intervention that: 1) alters the genomic sequence of cells or 2) introduces or directly manipulates nucleic acids (such as mRNAs, antisense oligonucleotides) in cells. The intervention may include strategies to repair a disease-causing gene sequence, remove or inactivate a disease-causing gene, or introduce new or modified nucleic acids that augment the therapeutic potential of the target cells.

- ~~Discovery research for a novel technology candidate (a medical device, diagnostic test, tool) that addresses a critical bottleneck to the discovery, development, or use of stem cell-based or genetic therapies, where the proposed activities include proof of concept testing with human stem cells or relevant human somatic cells targeted by a genetic therapy.~~

(3) Co-funding is not required

If the project requires funding over and above that which CIRM provides, documentation demonstrating the commitment of funds to cover the proposed co-funding amount must be provided at the time of application submission (e.g., copy of executed term sheet showing amount of co-funding, conditions, and source).

(4) For-profit organizations must demonstrate solvency

For-profit organizations must provide documentation that shows 180 days cash on hand from date of application submission and the financial ability to meet the co-funding and contingency requirements for the term of the project. The determination of solvency will be made at CIRM's sole discretion.

(5) Application must be accurate and complete

All required components of the application must be completed and may not contain false or inaccurate information.

(6) Applicant must be in "good standing"

In order to be eligible to apply for CIRM funding, an applicant must certify that it is in good standing, as follows:

a. The applicant's Chief Executive Officer, Chief Financial Officer, and Principal Investigator must not have been convicted of, or currently under investigation for, crimes involving fraud/misappropriation;

b. The applicant must have accounting systems in place that are capable of tracking CIRM funds; and

c. The Principal Investigator or key personnel named in the application must not be currently under investigation for research misconduct by the applicant institution or a funding agency and must not be currently debarred by HHS Office of Research Integrity.

Who can apply?

Only California Organizations are eligible to apply for this opportunity.

A California Organization is a for-profit or non-profit organization that employs and pays more than 50% of its employees in California and that directs and controls the award activities from California.

For a California Organization, Allowable Project Costs include:

- Costs for research activities conducted wholly in California; and
- Costs for research activities conducted outside of California, provided that the California Organization exercises direction and control over the activities.

Unallowable Costs

Allowable Project Costs do NOT include the costs of activities performed by a separate out-of-state organization that retains intellectual property or independent publication rights in any intellectual property (e.g., invention, technology, data) arising out of the CIRM funded project. Unallowable costs also include project costs incurred before the date the ICOC approves the application for funding, which can be as early as 90 days post application submission.

Who can serve as the Principal Investigator (PI)?

To be eligible, the PI must satisfy the following requirements:

- Must be an employee of the applicant organization or be accountable for the conduct of the proposed project to the applicant organization through a formal contract.
- Must commit at least 20 percent effort to working on the project. Any effort for which salary from CIRM is claimed must be expended in California.
- Must be authorized by the applicant organization to conduct the research and assume the responsibilities of the PI.
- Must not currently have another application pending review or approval under this funding opportunity.
- Must not currently have another application that is substantially similar or has overlapping activities pending review or approval under any CIRM opportunity.

ADDITIONAL REQUIREMENTS

Positive Selection

CIRM anticipates that the number of applications submitted will be very high for this competition. When the number of applications received in a cycle is significantly in excess of the number that can be reviewed by the GWG panel, the GWG members conduct the review in two stages. In the first stage, GWG members (including scientific members and patient advocate and nurse members of the Governing Board) will conduct a pre-review of applications (called "Positive Selection") to identify applications that the panel believes are most responsive to the funding opportunity and hold the most potential for impact. Applications that are not selected are examined by the CIRM scientific team and CIRM President to determine whether any additional applications merit a full GWG review. The remaining non-selected applications are deemed to be denied. Since the selection process is focused on quickly identifying promising proposals rather than identifying deficiencies in applications, no reviewer comments are collected at this stage. Positively selected applications advance to the second stage of review, which involves assignment to specific reviewers on the panel, a full discussion at review meeting, and scoring by the GWG.

Diversity, Equity and Inclusion in CIRM-Funded Projects

All applicants for the DISC2 program will be required to provide a statement describing how their overall study plan and design has considered the influence of race, ethnicity, sex, gender, and age diversity. Applicants should discuss the limitations, advantages and/or challenges of their research proposal in developing a product ~~or tool~~ that addresses the unmet medical needs of the diverse California population, including underserved racial/ethnic communities. Examples include use of models and tools that account for population diversity (e.g. HLA types, gender, genomics data, cell models). Applicants should also address how the research team has or will incorporate diverse and inclusive perspectives and experience in the implementation of the research project, including, for example, developing partnerships with patient organizations, acquiring training in cultural competence and/or DEI, utilizing institutional resources for DEI, and allocating funds and/or personnel to address DEI.

The GWG and CIRM's governing board will evaluate these statements as a review criterion in making funding recommendations. Priority will be given to projects with the highest quality plans in this regard.

Data Sharing and Management Plan

The sharing of data and knowledge produced from CIRM-funded projects is key to advancing the field of regenerative medicine and accelerating treatments to patients. A general overview (Data Sharing Overview) of a plan for sharing data produced in the proposed project must be included in the application and is subject to evaluation by the Grants Working Group (GWG). Applicants must allocate funds in their proposed budget for personnel and/or activities related to managing and sharing data produced from the funded project. CIRM requires~~CIRM requires its~~ awardees to develop and execute a Data Sharing Plan that includes management and preservation of raw data, processed data and metadata~~data~~ and making applicable data and metadata available to the broader scientific community. To ensure data processing steps can be replicated and data can be reused by other researchers, CIRM ~~also~~ requires sharing of data in accordance with FAIR~~FAIR~~ data principles (Findability, Accessibility, Interoperability and Reusability) through established repositories where possible. The data~~including, but not limited to, specialized NIH-supported~~ repositories~~, generalist repositories, cloud platforms and institutional repositories. The Data Sharing Plan must be included in the application and the plan is subject to evaluation by the Grants Working Group. Applicants are required to allocate funds in their proposed budget for personnel and/or activities related to managing and sharing data produced from the funded project. The repository~~ selected, and summary of the data shared must be reported to CIRM during and after the project period. To promote FAIR data sharing and open science,~~the generation of knowledge~~ CIRM may publicly share information about ~~where~~ CIRM-funded data, including what types of data were generated and where data are deposited.

Data Coordination and Management Center

Subject to board approval, CIRM has preliminary plans to fund the ~~creation~~development and implementation of a Data Coordination and Management Center (DCMC) through a separate funding opportunity. At such time, CIRM will require awarded teams to coordinate activities with the DCMC.

SCHEDULE AND DEADLINES

Frequency of Opportunity	One or ~~T~~two ~~Two~~ cycles per year
Grants Working Group (GWG) Review	Approximately 90 days post submission
ICOC Review and Approval	Approximately 120 days post submission

Award Start	Must start within 90 days of award approval (i.e., approximately 210 days post submission)

REQUESTED FUNDING ALLOCATION

On an annual basis, CIRM will present for the Board's consideration a calendar-year budget for each of its on-going research programs, including the DISC2 program. The indirect cost rate will be set at 20% for non-profit applicant organizations. CIRM will not fund indirect costs for for-profit applicant organizations.

REQUESTED DELEGATION OF BOARD AUTHORITY

To streamline the processes for high volume application review and to enable timely calls to highly specific opportunities or challenges, CIRM requests the Governing Board delegate to the President or his designee the authority to examine those applications that are not selected for a full review and to make the final determination whether to submit such applications to the GWG for a full review or to deny funding.