Accelerating and Advancing the Discovery of Novel Stem Cell and Regenerative Medicine Therapies~~Treatments~~ and Applications: Discovery Stage Programs

The mission of CIRM is to accelerate the development of stem cell therapies to patients with unmet medical needs. To better serve this mission, CIRM is proposing a new paradigm for promoting the discovery of promising new regenerative medicine ~~stem cell~~ technologies (stem cell-based and gene therapy) and driving their rapid translation towards improving patient care. Through this program, CIRM will provide funding opportunities that:

- Are predictable and recur regularly
- Support exploration of new ideas
- Are responsive to emerging concepts, key bottlenecks or downstream needs
- Support stem cell discoveries that could lead to therapies, tools, diagnostic tests, and devices
- Incent progression of stem cell discoveries towards impacting patients ("passing the baton")
- Provide linkages to downstream funding opportunities
- Provide supplemental funding to enrich the experience of graduate students and postdoctoral and clinical fellows

To accomplish these goals, CIRM will establish calls for three complementary types of proposal and will accept applications on a recurring basis. This concept plan further describes the three proposed Discovery Stage Research Program Announcements listed below.

- DISC 1: Funding Opportunity for Inception Awards
- DISC 2: Funding Opportunity for Quest Awards
- DISC 3: Funding Opportunities for Challenge Awards

This concept document provides the general terms and conditions as established by CIRM for issuing a funding opportunity, subject to approval by CIRM's Governing Board.

ELIGIBILITY REVIEW

CIRM has the sole discretion to determine whether an applicant has satisfied the eligibility criteria for a program. CIRM may exercise its authority at any time before an award is executed. To the extent that CIRM exercises this authority after the Application Review Subcommittee has approved an award, CIRM will notify the Application Review Subcommittee and the public of its action by including an action item regarding the decision on the agenda for the next meeting of the Application Review Subcommittee.

DISC 2: DISCOVERY STAGE RESEARCH FUNDING OPPORTUNITY for QUEST AWARDS

OBJECTIVE

The objective of this funding opportunity is to promote the discovery of promising new stem cell-based and gene therapy technologies that could be translated to enable broad use and ultimately, improve patient care. Projects funded through the Quest Awards should propose 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 gene therapy approach.

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 brings 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.

PROGRAM FEATURES

Promoting Discovery and Accelerating Translation

The goal of a Quest Award is to produce, within 2 years, a project deliverable that is a novel candidate therapeutic, device, diagnostic test or tool that can immediately progress to translation to enable broad use.

AWARD INFORMATION

What is the CIRM funding allocation, project funding and project term?

- CIRM will fund direct project costs of up to
  - $500,000 per award to achieve a candidate that is a diagnostic test, a device or a tool
  - $900,000 per award to achieve a candidate that is a therapeutic

What activities will CIRM support?

CIRM funds will support the following activities under this opportunity:

- Activities that will lead to selection of a novel candidate therapeutic, device, diagnostic test or tool ready for translation to enable broad use and ultimately, improve patient care including:

    - Developing and implementing assays to identify/test/characterize candidate (or prototype) therapeutic, device, diagnostic test, tool/technology
    - Feasibility and initial reproducibility assessment
    - Characterization/optimization of candidate(s)
    - Proof- of concept studies with candidate; for non-stem cell-based candidates (e.g. certain devices, diagnostic tests, tools), proof of concept testing with human stem, progenitor, ~~or~~ directly reprogrammed cells, or relevant human somatic cells targeted by a gene 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)

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

How will applications be reviewed?

- In anticipation of high demand, members of the Grants Working Group (GWG) will review Quest Award applications in two stages. In the first stage, GWG members will conduct a pre-review of applications (called "Positive Selection", see Appendix) to advance a subset of applications to the second stage, which will involve a full review by the GWG.

Consideration of Past CIRM Award Information (If Applicable):

- The GWG may consider information from a previously funded and related CIRM award as

part of its review. CIRM will provide the GWG with objective information regarding a related award that CIRM, in its sole discretion, deems relevant, including but not limited to achievement of specific milestones, data, and outcomes for a related CIRM award or awards.

- A "related CIRM award" includes: (1) an award for which the applicant PI served as the PI, a co-PI, a co-investigator, or otherwise substantially participated in the conduct of the award; (2) an award involving the same research project or product; or (3) an award that includes overlapping team members.

Addressing the Needs of Underserved Communities 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 and gender 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.

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 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. CIRM requires its awardees to develop and execute a Data Sharing Plan that includes management and preservation of data and making applicable data available to the broader scientific community. CIRM strongly encourages sharing of data in accordance with FAIR data principles through established repositories 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 encouraged 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 the generation of knowledge CIRM may publicly share where CIRM-funded data are deposited.

How will funds be awarded?

- Awards to successful applicants will be in the form of a grant.
- CIRM will disburse funds pursuant to a 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 (see below).

ELIGIBILITY

What types of projects are eligible for funding?

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

(1) The applicant must propose discovery research for a new technology that is uniquely enabled by human stem cells or uniquely enabling for the advancement of human stem cell based therapies or ~~aimed at developing a~~ gene therapies~~y~~ ~~approach~~ including

- Discovery research for a novel therapeutic candidate:
    - where human stem, progenitor, or directly reprogrammed cells either compose the therapy or are used to manufacture the therapy
    - that stimulates, recruits or targets endogenous stem cells or cancer stem cells
    - where human stem, progenitor or directly reprogrammed cells are uniquely required for candidate identification and testing
    - that is a gene therapy[1] approach intended to replace, regenerate or repair the function of aged, diseased, damaged, or defective cells, tissues, and/or organs
- Discovery research for a novel human stem cell-based diagnostic test, assay or tool that can be used to discover, advance, monitor, or evaluate new therapies, OR
- Discovery research for novel technologies (a medical device, diagnostic test, tool) that addresses a critical bottleneck to the discovery, development or use of stem cell-based or gene therapies and that propose proof of concept testing with human stem/progenitor cells or relevant human somatic cells targeted by a gene therapy ~~and that addresses a critical bottleneck to the discovery, development or use of stem cell-based therapies~~

(2) The applicant must be ready to initiate work on the funded project within 60 days of approval

Given the urgency of CIRM's mission, all approved awardees must initiate work on the funded project within 60 days of approval and authorization for funding by the Application Review Subcommittee of CIRM's governing board, the Independent Citizens' Oversight Committee ("ICOC").

(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

[1] For the scope of this solicitation, CIRM considers gene therapy to mean a human therapeutic intervention intended to: 1) alter the genomic sequence of cells or 2) alter the cellular lineage or function via gene delivery (i.e., direct lineage reprogramming). The intervention may include strategies to repair a disease-causing gene sequence, remove or inactivate a disease-causing gene, or introduce new or modified genes that augment the therapeutic potential of the target cells.

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. For-Profit and Non-Profit (in existence for less than five years):

(i) 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; and

(ii) The applicant must have accounting systems in place that are capable of tracking CIRM funds.

b. All Applicants:

The Principal Investigator 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 and on what activities may funds be spent?

Only California Organizations are eligible to apply. A California Organization is a for-profit or non-profit organization that employs and pays more than 50% of its employees in California.

Allowable project costs include:

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

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

SCHEDULE AND DEADLINES

Applications Due	Specific dates and times will be posted on the CIRM website.
Grants Working Group (GWG) Review	Approximately 2-3 months post submission
ICOC Review and Approval	Approximately 3-4 months post submission
Award Start	Must start within 2 months of award approval

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 DISC program. That allocation will describe the amounts provided for the Inception, Quest and Challenge. 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 is proposing process changes further described in specific programs below, that require delegation of Board Authority.

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.

- ~~To issue periodic Challenge Question Announcements that define a specific question(s) and specific award terms unique to that question under the umbrella of the Challenge Awards Program Announcement~~