DISCOVERY

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DISC2: Discovery Stage Research Funding Opportunity for Quest Awards

PROGRAM ANNOUNCEMENT

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DISC2: Discovery Stage Research Funding Opportunity for Quest Awards

Objective

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

This **Quest Awards** Program will promote the discovery of promising new stem cell-based and genetic 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 genetic therapy approach.

Since Proposition 14 dedicates more than a quarter of funds to support research and development of treatments for diseases and conditions of the brain and central nervous system (CNS), **CIRM encourages the submission of proposals developing novel therapeutic or technology candidates to advance the treatment and/or understanding of CNS disorders.**

Contact

For information and assistance with this program announcement please send email correspondence to discovery@cirm.ca.gov.

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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 within 2 years, a novel candidate device, diagnostic test or tool that can immediately progress to translation to enable broad use.

What is the award amount and duration?

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; award duration is up to two years.
- $1,500,000 per award to achieve a candidate that is a therapeutic; award duration is up to three years.

For allogeneic pluripotent stem cell derived therapeutic cell products only, a special supplement of up to $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, all in the context of and for the purpose of final candidate selection. See Appendix for more information on "clinically compatible" cell lines and view CIRM's PSC Webinar for more information on the topic of cell line selection for candidate discovery. If you are requesting this supplement, we strongly encourage you to contact CIRM at discovery@cirm.ca.gov before applying using the subject line "DISC2 Application - PSC Special Supplement."

The amount of direct project costs requested must be adequately justified. The requested amount 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 Independent Citizens' Oversight Committee ("ICOC"). 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.

What activities will CIRM fund?

CIRM encourages the submission of proposals developing novel therapeutic or technology candidates to advance the treatment and/or understanding of CNS disorders.

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CIRM funds <u>will</u> support the following activities under this opportunity:

- ✓ Activities that will lead to selection of a novel candidate therapeutic, diagnostic, medical device, 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(s)
  - ✓ 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 <u>will also</u> support:

- ✓ Activities intended to promote and uphold principles of Diversity, Equity, and Inclusion (DEI) in the conduct of the study
- ✓ Activities associated with sharing data and knowledge from the study

CIRM resources <u>cannot</u> 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
- ✘ Exploratory activities that are not justified as necessary for achieving the expected outcome of the DISC2 program (see next section)
- ✘ 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
- Use of the special supplement funds for purchasing, deriving or testing human cell lines that are not clinically compatible, i.e., lines that will not meet FDA requirements for donor eligibility and/or have not been appropriately consented for clinical development and sale

What is the expected outcome of a Quest Award?

The expected outcome (project deliverable) of a Quest Award is a new candidate therapeutic, medical device, diagnostic or tool that is ready for translational stage activities. Criteria defining readiness for translation for each type of candidate include the following:

Therapeutic:

- A candidate therapeutic identified
- A draft Target Product Profile (see Appendix) developed
- Measures of identity, activity and purity developed
- Demonstration of reproducible disease/injury modifying activity:
    - For candidates composed of or manufactured from stem cells, reproducible disease/injury modifying activity is demonstrated with the candidate in preclinical model(s) relevant to the target indication(s).
        - Autologous candidates, or those derived from an allogeneic source where donor might change, should demonstrate proof of concept with candidate from >1 donor to establish reproducibility
        - Allogeneic candidates must show disease modifying activity with candidate prepared from a clinically compatible stem cell line or source
    - For a genetic therapy candidate that is not a stem cell therapy: disease/injury modifying activity must be demonstrated using a clinically relevant model; and evidence that the genetic therapy candidate will target or have activity on a clinically relevant human cell population must be established.

      CIRM recognizes that for certain types of genetic therapy candidates, it may not be technologically possible to establish evidence of activity in human cell models with the intended candidate. For these rare exceptions, and with justification provided, applicants may propose an alternative set of experiments to generate data supporting the ability of the surrogate candidate to target and/or impact the function of the relevant human cell population.

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- For all other biologic or small molecule candidates (not manufactured from stem cells), disease/injury modifying activity must be demonstrated on or with a clinically relevant human stem/progenitor or cancer stem cell population

- Initial studies performed assessing mechanism of action, pharmacokinetics (PK) (bio-distribution) and early safety
- For any therapeutic candidate containing allogeneic (donor derived) cells[1]:
  - Cells meet the Good Tissue Practices (GTP) requirements for donor eligibility, or there is plan in place to address GTP (donor eligibility requirements are described here https://www.fda.gov/media/73072/download)
  - Cell source (tissue or cell line) has been appropriately consented by donor for intended use and for clinical development and sale

Diagnostic:

- A candidate diagnostic identified
- A draft Target Product Profile (or Product Concept Document, see Appendix) developed
- Demonstration of technical feasibility: tests with diagnostic candidate show that it will be feasible to meet product design requirements
- Demonstration of scientific proof of concept:
  - Testing with the diagnostic candidate demonstrates that analyte can be reproducibly measured at biologically relevant levels for the intended use in sufficient samples to distinguish relevant differences within the target population
  - If the diagnostic is not stem cell based, then testing with a clinically relevant human stem/progenitor or directly reprogrammed cells demonstrates its utility as a diagnostic to address a critical bottleneck to the discovery, development or use of stem cell-based therapies
  - If the diagnostic is intended for use with gene therapy, then testing with a clinically relevant human cell population demonstrates its utility as a diagnostic to address a critical bottleneck to the discovery, development or use of gene therapies
- If diagnostic candidate includes an allogeneic cell, to be competitive for the next stage of CIRM funding (TRAN), the cell source (tissue or cell line) will need to be appropriately consented by donor for intended use, product development and sale

Medical Device:

- A candidate medical device identified

[1] If you are unable to provide this verification, CIRM may require changing from the proposed cell line(s) to one that complies with these requirements. See Appendix for more details.

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- A draft Target Product Profile (or Product Concept Document, see Appendix) developed
- Demonstration of technical feasibility: Tests with device candidate (research prototype) show that it will be feasible to meet product design requirements
- Demonstration of scientific proof of concept:
    - In test model(s) relevant to the intended use, the medical device candidate (research prototype) meets initial performance criteria
    - If the device technology is not stem cell based, then testing with human stem/progenitor or directly reprogrammed cells demonstrates its utility to address a critical bottleneck to the discovery, development or use of stem cell-based therapies
    - If the device technology is intended for use with gene therapy, then testing with a clinically relevant model and, if possible, with a human cell population, demonstrates its utility to address a critical bottleneck to the discovery, development or use of gene therapies
- If device candidate includes an allogeneic cell, to be competitive for the next stage of CIRM funding (TRAN), the cell source (tissue or cell line) will need to be appropriately consented by donor for intended use, product development and sale

Tool:

- A candidate tool identified
- A draft Target Product Profile (or Product Concept Document, see Appendix) developed
- Demonstration of technical feasibility: Tests with tool candidate (research prototype) show that it will be feasible to meet product design requirements
- Demonstration of scientific proof of concept:
    - In test model(s) relevant to the intended use, the tool candidate (research prototype) meets initial performance criteria
    - If the tool/technology is not stem cell based, then
        - Testing with human stem/progenitor or directly reprogrammed cells demonstrates its utility to address a critical bottleneck to the discovery, development or use of stem cell-based therapies OR
        - Testing with relevant human cells demonstrates its utility to address a critical bottleneck to the discovery, development or use of gene therapies
- If the tool/technology candidate includes an allogeneic cell, to be competitive for the next stage of CIRM funding (TRAN), the cell source (tissue or cell line) will need to be appropriately consented by donor for intended use, product development and sale

Eligibility

What types of projects are eligible for funding?

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

(1) The applicant 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 CIRM's governing board, the Independent Citizens' Oversight Committee ("ICOC").

(2) The applicant must propose projects that will achieve the expected outcome, and that are uniquely enabled by human stem cells or uniquely enabling for the advancement of human stem cell-based or genetic therapies as follows:

Eligible Therapeutic Candidates

Discovery research for a novel therapeutic candidate

- That is a cell therapy where human stem or progenitor cells[2] (collectively, "stem cells") either compose the therapy or are used to manufacture the cell therapy.
- That is a genetic therapy[3] 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.
- 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).
- Where human stem cells are uniquely required for candidate identification and testing.

[2] 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.

[3] 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.

Eligible Technology Candidates (Device, Diagnostic, Tool)

- Discovery research for a novel human stem/progenitor cell-based diagnostic, assay or tool candidate that can be used to discover, advance, monitor, or evaluate new therapies, OR
- 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 to achieve the expected outcome, documentation demonstrating the commitment of funds to cover the required additional amount must be provided by the application deadline (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:

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

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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

Unallowable Project Costs 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.
- ✗ 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.

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Application Review Information

What is the process for evaluating an application?

Pre-submission Consultation

In accordance with CIRM's mission, the Agency is committed to helping develop promising stem cell-based technologies by partnering with world-class investigators. Therefore, prospective applicants are encouraged to contact CIRM before applying with questions or to discuss their project's eligibility.

Eligibility Review

CIRM will assess whether the proposed project meets eligibility requirements sought under this program. If CIRM determines, in its sole discretion, that an application does not meet the eligibility requirements of the program or that the submitted application is incomplete or contains false or inaccurate information, CIRM will notify the applicant of its decision and, if CIRM deems it appropriate, allow an opportunity to remedy. If CIRM deems it inappropriate, or if the applicant does not remedy the error in a timely manner, CIRM will terminate all further action on the application.

Scientific Review

The scientific merit of each application will be assessed by the GWG, which is composed of fifteen subject matter experts from outside California, seven patient advocate members of the ICOC, and the Chair of the ICOC. The list of scientific members who may participate in the GWG review can be found at http://www.cirm.ca.gov/WorkingGroup_GrantsReview. The composition of the ICOC can be viewed on the CIRM http://www.cirm.ca.gov/GoverningBoard.

The fifteen participating scientists on the GWG will evaluate the applications and score them according to scientific and technical merit, applying the review criteria described below.

The Application Review Subcommittee of the ICOC will make final funding decisions giving consideration to the GWG recommendations and any recommendations from the CIRM team.

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

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involves assignment to specific reviewers on the panel, a full discussion at review meeting, and scoring 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.

Confidentiality

CIRM's confidentiality and conflict screening rules apply to everyone who will have access to applications or who will attend any review meeting in which confidential information is discussed, including but not limited to CIRM team members, reviewers and members of the ICOC. (Per Gov. Code §6254.5(e), non-public records may be disclosed to government agencies under confidentiality agreements.)

How will the scientific merit of an application be evaluated?

Scientific and patient advocate members of the GWG will evaluate applications and the scientific members will score them based on the following key questions:

1. Does the project hold the necessary significance and potential for impact?

Is the proposed technology likely to result in a candidate that could impact an unmet medical need? Would the expected candidate accelerate or increase the likelihood of successfully developing a stem cell technology or genetic therapy that significantly improves patient care or that address a critical bottleneck to the discovery, development or use of stem cell-based or genetic therapies? Has the applicant presented thoughtful options for progression from successful candidate discovery to translation?

2. Is the rationale sound?

Is the proposed project based on sound scientific rationale? Is the preliminary data compelling and supportive of the proposed project? Is the proposed project uniquely enabled by human stem/progenitor cells or directly reprogrammed cells, or uniquely enabling for the advancement of stem cell-based or genetic therapies?

3. Is the project well planned and designed?

Is the project appropriately planned and designed to achieve the expected outcome, including proof-of-concept data for a product candidate that is ready to advance to translational studies? For candidates that include allogeneic cell components, is the cell source likely to meet donor eligibility requirements and has it been appropriately consented for intended use? Is this a well-constructed, quality project? Are potential pitfalls identified and alternative approaches presented? Do the project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission?

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4. Is the project feasible?

Are the proposed milestones and expected project outcome logical and likely to be achieved within the proposed timeline? Is the proposed team appropriately qualified and staffed? Does the team have access to all the necessary resources to conduct the proposed activities? Is the budget appropriate for the research proposed? If a special budget supplement was requested for acquiring and/or evaluating clinically compatible PSC lines for candidate selection, have these additional activities and costs been adequately considered and justified?

5. Does the project uphold principles of Diversity, Equity, and Inclusion (DEI)?

Does the project plan and design adequately address and account for the influence of race, ethnicity, sex and gender diversity? Would the project outcomes inform the development of a product or tool that serves the unmet medical needs of the diverse California population, including underserved racial/ethnic communities? Does or will the applicant incorporate perspectives and experience from the population that will benefit from the proposed product in the implementation of the research project?

What is the review schedule?

Visit CIRM's Funding Opportunities for Discovery Stage Research page to find the most updated version of this PA and the application submission deadline(s). Applicants learn the final funding decisions approximately 90-120 days post submission. Funded projects must commence within 90 days of final funding decisions.

Schedule and Deadlines

Applications Due	There are generally two cycles per year
Grants Working Group (GWG) Review	Approximately 60-90 days post submission
ICOC Review and Approval	Approximately 90-120 days post submission
Award Start	Must start within 90 days of award approval by the ICOC

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Application Components and Submission

How does one apply?

Applications must be completed and submitted online using the CIRM Grants Management Portal at https://grants.cirm.ca.gov. Any prospective PI must create a login in the system to access application materials and apply. Applications are available in the system only to the PI. A PI may submit only a single Quest Award application in a given review cycle.

What components does an application include?

The Grants Management Portal provides instructions for completing all the necessary components and submitting a final application. The application is designed to collect information necessary to appropriately evaluate the proposal and for CIRM to rapidly initiate an award if approved for funding.

In the online portal, applicants must fill out an eligibility form, indicate key personnel involved in the project, describe how the proposal addresses the objective of the funding opportunity, provide an overview of proposed activities, and prepare and justify an appropriate budget.

The online application also includes the **Positive Selection Preview Page** – a section to be utilized by GWG members to prescreen applications and select a subset to move forward to the second and final stage of review. The Positive Selection Preview Page includes the following subsections:

- Project Summary
- Areas of Impact
- Vision for Progression
- Consideration of diversity, equity and inclusion in project design and execution

What are the contents of the proposal?

The proposal comprises the bulk of detailed information on the project and is central to evaluation by the Grants Working Group if an application is selected for full review. It includes these sections:

1. **Resubmission Statement**: If this application is a resubmission, then the applicant will provide a brief statement on how this application addresses the reviewers' critiques.
2. **Candidate Product Profile**: Table summary describing proposed candidate and usage attributes (template provided).
3. **Statement of Significance and Impact**: Description of how the proposed candidate, if successful, could impact an unmet medical need, and/or accelerate or increase likelihood of successfully developing a stem cell technology or genetic therapy that significantly improves patient care, or how

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it could address a critical bottleneck to the discovery, development, or use of stem cell-based therapies.

4. **Statement of Diversity, Equity and Inclusion (DEI)**: Statement describing how the project will help fulfill the unmet medical needs of the diverse California patient population. See full description below.
5. **Objective and Milestones**: A concise description of the project objective and project milestones (template provided), and criteria for success.
6. **Rationale**: Description of the scientific rationale for the proposed research and the preliminary data.
7. **Research Plan**: A concise but detailed description of methods and techniques to be employed to achieve milestones, and potential pitfalls and alternative approaches.
8. **Summary of Deliverables**: Provide a brief summary of how the research plan will address the Expected Outcomes for the type of candidate to be developed.
9. **Data Sharing Overview**: A description of how raw data, processed data and metadata produced from the project will be made available to the research community consistent with FAIR (Findability, Accessibility, Interoperability, and Reusability) data sharing principles.
10. **Timeline**: Activities-based timeline for achieving project milestones.
11. **Principal Investigator and Team**: A description of the PI and team's expertise and experience.
12. **Resources and Environment**: A brief description of the resources available to the project and environment.
13. **References**

How does one address Diversity, Equity and Inclusion (DEI)?

Applicants must address how the proposed project upholds principles of diversity, equity and inclusion (DEI). In the DEI section of the DISC2 proposal, applicants should describe how the 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. For example, this could be achieved by use of models and tools that account for population diversity (e.g., HLA types, gender, genomics data, cell models – see **CIRM iPSC Repository**, below). Applicants should also address how the research team has or will incorporate diverse and inclusive perspectives and experiences 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.

What is required for the Data Sharing and Management Plan (DSMP)?

The sharing of data and knowledge produced from CIRM-funded projects is key to advancing the field of regenerative medicine and accelerating the discovery, validation and development of treatments for patients. CIRM requires awardees to manage and preserve raw data, processed data, and metadata, and make applicable data and metadata available to the broader scientific community. CIRM also requires applicants to allocate funds in their proposed budget for personnel and/or activities related to managing and sharing data produced from the funded project.

To ensure data processing steps can be replicated and data can be reused by other researchers, CIRM requires sharing of data in accordance with FAIR data principles, using established repositories where possible. CIRM requires that applicants provide a Data Sharing Overview in their proposal, and awardees develop and execute a detailed **Data Sharing and Management Plan (DSMP).** The data repositories selected and other information about deposited data must be reported to CIRM during and after the project period. To promote FAIR data sharing and open science, CIRM may publicly share information about CIRM-funded data, including what types of data were generated and where data are deposited.

Application stage – Data Sharing Overview

A general overview of a plan for sharing data produced in the proposed project (**Data Sharing Overview**) must be included in the application and is subject to evaluation by the 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. For guidelines, please refer to the Data Sharing Budget Justification Guidelines.

Pre-funding administrative review (PFAR) for awarded projects – DSMP

For omics and/or flow cytometry data, a completed DSMP, using templates provided, must be submitted to CIRM as Just in Time (JIT) material during PFAR. CIRM will review DSMPs and work with awardees to optimize the DSMP, including negotiation of milestones and budget. Awardees must agree with CIRM on a DSMP and associated milestones and budget prior to CIRM issuing a Notice of Award. Guidelines and templates to complete the DSMP for Omics / Flow Cytometry Data can be found here. The DSMP consists of 2 documents:

- Part A - DSMP for Omics and Flow Cytometry Data - Data Catalog
- Part B - DSMP for Omics and Flow Cytometry Data - Questionnaire

The templates for these 2 documents must be used when preparing the DSMP for Omics and Flow Cytometry Data as JIT documents during PFAR. For **data from other types of experiments** (e.g., imaging, electrophysiology, etc.), CIRM may work with the awardee to establish data sharing milestones prior to CIRM issuing a Notice of Award.

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Active Award stage

Grantees will report on their data sharing and management activities during regularly scheduled progress reporting and will work with CIRM staff to adjust the DSMP and other data-related milestones as necessary.

Who are Key Personnel?

In the application, we ask you to identify by name pertinent Key Personnel and their specific roles on the project. Key Personnel are defined as (1) the Principal Investigator or Program Director; or (2) any other person, including an independent consultant or an employee of a Subcontractor or Partner, who is expected to contribute to the scientific development or execution of the project in a substantive, measurable way *and* who is expected to: (a) receive or has been promised income, or anything else of value, of $10,000 or more per year for his or her contribution to the project or (b) contribute one percent (1%) or more effort to the proposed project. "Key Personnel" does not include a person who is expected to be involved in the proposed project but who does not satisfy conditions (1) or (2).

Individuals who do not meet the definition of Key Personnel may be supported with CIRM funds, but should not be identified by name in the application. Such unnamed personnel may be referenced indirectly by their role on the project (e.g., technician). The budget includes a line item for requesting support for unnamed personnel.

What should one know before preparing the budget?

Budgets must be justified in detail, including all subcontracts and consulting fees, including, if applicable, any additional costs that would be funded from another source. Allowable Project Costs for research funded by CIRM are detailed in the CIRM Grants Administration Policy for Discovery, Translation and Education Projects. Generally, project costs for personnel, supplies, travel, equipment, data sharing and subcontracts may be claimed. Limits for specific cost categories must be observed.

What are Direct Facilities Costs and how much can an applicant claim?

Direct Facilities Costs are the general operating costs of the grantee's facilities attributable to housing all elements of the CIRM-funded project or activity. Facilities costs for non-profit applicant organizations are limited to the current applicable, federally negotiated rates for the organization as defined by the Office of Management and Budget (OMB) Circular A-21 or A-122. Facilities rates for for-profit applicant organizations are limited to 35% of the direct project costs. Facilities rates are applied to direct project costs exclusive of the costs of equipment, tuition and fees, research patient care costs, as well as the costs of each individual subcontract, consultant, and service agreement in excess of $25,000. The facilities cost rates approved and in place at the time of the application are to be applied to the entire award project period.

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What are indirect costs and how much can an applicant claim?

For-profit organizations cannot claim indirect costs. For non-profit organizations, indirect costs will be limited to 20% of allowable direct research funding costs awarded by CIRM (i.e., project costs and facilities costs), exclusive of the costs of equipment, tuition and fees, research patient care costs, as well as the costs of each individual subcontract, consultant, and service agreement in excess of $25,000. The indirect cost rate budgeted at the time of application is to be applied to the entire award project period.

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Award Administration

Issuance of Award

A CIRM award is issued via a Notice of Award (NOA), which is the formal contract that defines the terms and conditions of an award and documents the commitment of funds from CIRM. CIRM reserves the right to modify or establish funded project activities and the associated budget prior to issuance of the NOA, including optimizing Data Sharing and Management Plans (DSMPs) submitted as Just in Time (JIT) material during pre-funding administrative review (PFAR). CIRM also establishes project milestones, DSMP milestones, success criteria and timelines for milestone achievement at its sole discretion after consultation with the PI and based on information provided in the application and DSMP. CIRM will consult with Data Advisors towards optimizing the DSMP and implementing corresponding milestones as part of the NOA. CIRM may also review key contracts/agreements that are critical to the success of the project for compliance with CIRM's policies and regulations.

Milestones and Payment

Upon execution of the NOA, CIRM will issue an initial payment; subsequent disbursements will be made as outlined in the NOA. Continued CIRM funding is contingent upon timely scientific progress against milestones as outlined in the project milestones, DSMP milestones, and timelines established under the NOA. Where project and/or DSMP milestones are not timely met, CIRM reserves the right to either redirect resources to maximize the project outcome or, at its sole discretion, to suspend payment and/or terminate the project.

Reporting

Grantees will be required to provide periodic written progress and financial reports to CIRM. CIRM will partner with the grantee to foster the success of the project. Grantees will have ongoing communication with the CIRM Science Officer throughout the duration of the award, typically meeting by teleconference and periodically in person.

Upon approval of an award, CIRM will consult with Data Advisors towards optimizing the Data Sharing and Management Plan and implement DSMP milestones as part of the NOA.

No-Cost Extensions

Timely progress on funded projects is of critical importance to CIRM. Therefore, CIRM will consider a one-time, No-Cost Extension (NCE) request of no more than 6 months, submitted at least 30 days before the project end date. Such requests should properly justify how such an extension will advance the project towards its expected outcome, but Grantees should not assume CIRM will approve a NCE request.

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CIRM Regulations

Awards made through this PA will be subject to all applicable CIRM regulations. These regulations can be found on CIRM's website at http://www.cirm.ca.gov/reg/default.asp.

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Contacts and Resources

For more information about this and CIRM's other Discovery stage programs, please visit our Current Funding Opportunities page to access DISC-specific program announcements, webinar materials and FAQs. For scientific questions that are not addressed in the above resources, send email correspondence to discovery@cirm.ca.gov.

For questions related to application review, send email correspondence to review@cirm.ca.gov.

For questions related to budgets or allowable project costs, please consult the Grants Management FAQ on CIRM's website under "For Researchers > Grants > Managing your Grant."

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Definitions

"California organization" means: An entity, regardless of profit status, that has >50% of its employees located in, and paid in, the state of California, and conducts the award activities from the California location.

"For-profit organization" means: a sole-proprietorship, partnership, limited liability company, corporation, or other legal entity that is organized or operated for the profit or financial benefit of its shareholders or other owners. Such organizations also are referred to as "commercial organizations".

"Non-profit organization" means: (1) a governmental entity of the state of California; or (2) a legal entity that is tax exempt under Internal Revenue Code section 501(c)(3) and California Revenue and Taxation Code section 23701d.

"Partner" means an organization that, in exchange for the right to the opportunity for a future financial return, has (1) agreed to provide matching funds for the proposed project or (2) entered into an agreement with the applicant organization relating to the commercialization of the proposed project.

"Subcontractor" means an organization (other than the applicant organization) that is expected to: (a) contribute to the scientific development or execution of the project in a substantive, measurable way *and* (b) receive $25,000 or more through the proposed project. "Subcontractor" does not include suppliers of widely available goods.

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Appendix

Target Product Profile

A Target Product Profile (TPP) is a strategic product development tool for therapeutic development that is the subject of a guidance document released by the FDA (https://wayback.archive-it.org/7993/20190918100706/https://www.fda.gov/media/72566/download).

Diagnostic, medical device and tool product development more typically employs a development tool often designated as the Product Concept Document (typically includes e.g., an assessment of unmet medical, technical and user needs, competitive and IP assessment, intended use, regulatory path to use, design input). For consistency in our Translational Program, we request a TPP, specifically tailored to each candidate type (therapeutic, diagnostic, medical device or tool), which in the case of diagnostic, medical device or tool incorporates elements of the Product Concept Document. A draft TPP template for a candidate that is a therapeutic, a diagnostic, a medical device or a tool may be found within the respective proposal templates for the CIRM Translational Program applications.

Under DISC2, applicants are expected to populate a stage appropriate TPP called the "Candidate Product Profile," which is provided in the proposal template.

Other Resources

CIRM iPSC Repository

As a resource to the regenerative medicine community, CIRM has funded the creation of an Induced Pluripotent Stem Cell Repository, a large, genetically diverse collection of stem cells produced from thousands of individuals representing various diseases of interest and healthy controls. The 2600+ lines were uniformly derived, have undergone rigorous quality control, and include demographic and clinical data. The CIRM Repository is managed by Fujifilm Cellular Dynamics, Inc., who have made the lines available for purchase at https://www.fujifilmcdi.com/cirm-ipsc-products/. SNP data for 2166 CIRM lines and whole genome sequence data for 299 of the CIRM iPSC donors is available at dbGaP. A list of CIRM lines with WGS data can be found here.

Applicants who are interested in using iPSCs to investigate mechanisms of disease, develop novel tools, discover therapeutic targets, or increase diversity in their experimental design are encouraged to explore the CIRM iPSC Repository or request additional information from CIRM Science Officers at discovery@cirm.ca.gov using the subject line "DISC2 application - iPSC Repository."

Please note, cells in the CIRM iPSC Repository are for research use only and are not eligible nor consented for clinical use.

Clinically Compatible PSC Lines

CIRM is working with organizations to provide researchers the opportunity to obtain cell lines that a) comply with the FDA's donor eligibility requirements; and b) are appropriately consented by the donor for intended use and for clinical development and sale. If you are interested in such lines, please visit CIRM's Information for Applicants page, where CIRM provides a list of hPSC lines that, to the best of our

knowledge, could potentially meet the definition of clinically compatible. In addition, several providers of hPSC lines have joined CIRM's Industry Resource Partner Program to provide CIRM researchers with access to their clinically compatible hPSC line(s) under a standard agreement. Please refer to the CIRM Information for Applicants page to contact CIRM for more information on the available lines from CIRM's Industry Resource Partners.

CIRM also recommends viewing CIRM's informational PSC Webinar on the importance of careful cell line selection for developing a translatable therapeutic candidate.

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Revisions

Revision Date	List of Changes
03/15/23	• Corrected technology eligibility information. • Clarified DEI instructions.

02/10/23	• Revised requirement for allogeneic cell therapies:
	  ○ Applicants must demonstrate disease-modifying activity using a candidate prepared from clinically compatible cells
	• Clarified requirements for the Special Supplement for obtaining/sharing clinically compatible lines
	• Added a requirement for complete or proposed outreach, partnership, or educational activities to inform the development of DEI within the research project
	• Revised DSMP requirements and materials:
	  ○ During the application stage, the proposal requires a Data Sharing Overview section.
	  ○ For applications recommended for funding, a detailed DSMP will be required during PFAR.

07/27/21	• Revised candidate eligibility: ○ Gene therapy-related devices, tools, and diagnostics are eligible • Updated expected outcomes for gene therapy projects • Added additional clarification language to requirement for diversity, equity and inclusion in research • Minor edits in gene therapy definition
12/07/21	• Revised expectation for allogeneic (donor-derived) cell therapeutic candidates

06/28/2022	• Updated CIRM's Mission
	• Updated the Objective of the Program Announcement
	• Adjusted maximum award amount and duration for therapeutic applications:
	  ○ Maximum direct project costs were increased to 1,500,000 for a therapeutic; Award duration is 36 months.
	  ○ Additional 200k budget available for specific product types and activities.
	• Replaced the requirement for (i) a statement on addressing underserved needs and (ii) a statement on promoting and upholding principles of DEI with a unified application section on DEI; updated review criterion 5 accordingly
	• Added the Data Sharing and Management Plan as an
	  • updated and separate application component

- Updated names and descriptions of proposal sections

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