CALIFORNIA'S STEM CELL AGENCY

Funding Opportunity Concept Plan

CLIN1: LATE-STAGE PRECLINICAL PROJECTS

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 CLIN1 program, CIRM continues to create funding opportunities for the types and stages of clinical 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 late stage preclinical or pivotal IND ~~/IDE~~-enabling 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 CLIN1 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 clinical research projects that are unlikely to receive timely or sufficient funding from other sources.

OBJECTIVE

The objective of this funding opportunity is to support late-stage preclinical studies necessary to file and attain an active IND~~/IDE~~ with the FDA and initiate start-up activities to prepare for a clinical trial for a regenerative medicine therapy (stem cell-based or genetic therapy).

AWARD INFORMATION

What activities will CIRM fund?

CIRM funds will support the following activities under this opportunity:

- All activities necessary for the conduct and completion of IND-enabling activities necessary for the filing of a single IND~~/IDE~~ with the FDA to initiate a clinical trial with a single therapeutic candidate
- Product development activities appropriate to support the IND~~/IDE~~ filing and the resulting clinical trial
- Manufacturing of the therapeutic candidate to support IND ~~/IDE~~-enabling studies or to support the intended clinical trial(s)
- Clinical trial start-up activities

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

- The conduct of a clinical trial beyond start-up activities
- Patient recruitment, screening, or enrollment
- Studies for therapeutic candidate discovery including lead optimization or lead candidate selection

What is the award amount and duration?

CIRM expects projects to advance rapidly and will not accept applications under this program that propose more than 24 months from the award start date (approximately 45 days after the date of ICOC approval) to the planned filing of an IND ~~or IDE~~.

Total Project Costs for a CLIN1 project are limited to:

- $~~6~~7,~~50~~00,000 per award to a non-profit awardee; and
- $~~4~~5,000,000 per award to for-profit awardee

The amount of total 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.

How will funds be awarded?

Funds will be disbursed pursuant to a CIRM Notice of Award. Awardees may elect, upon completion of their award, to treat their award as a loan pursuant to

CIRM's award conversion policy. (See the most recent Grants Administration Policy for Clinical Programs.) Except for the first payment issued upon initiation of an award, payments will be disbursed upon completion of specific operational milestones. Continued funding is contingent upon timely progress, as outlined in the operational milestones 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 45 days of approval

Given the urgency of CIRM's mission, all approved awardees must initiate work on the funded project within 45 days of approval and authorization for funding by the Application Review Subcommittee of the Independent Citizens' Oversight Committee.

Because of the open and ongoing nature of this Program Announcement, investigators should only apply when their program has reached the stage where all eligibility criteria are met.

(2) Must propose studies to support the filing of a single IND ~~or IDE~~ with a single regenerative medicine-based therapeutic ~~or device candidate~~ (stem cell-based or genetic therapy)

CIRM will support preclinical studies that enable an IND filing for a therapeutic candidate that is either:

- 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. Minimally manipulated bone marrow, minimally manipulated cord blood or unmodified hematopoietic stem cells (HSCs), are eligible **only if** being developed as a novel method of addressing a rare or unmet need.
- 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

[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."

[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

function of aged, diseased, damaged, or defective cells, tissues, and/or organs.

- A small molecule or biologic 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).

~~CIRM will support preclinical studies that enable an IDE filing for a medical device candidate (including a diagnostic device) that is:~~

- ~~A device where human stem cells are a necessary component of the device or are used to manufacture the device.~~
- ~~A device intended for clinical use with a genetic therapy or human stem cells where the genetic therapy or stem cell contributes to the therapeutic MOA of the combination product.~~
- ~~A device intended to address a critical bottleneck to clinical development or use of a genetic therapy or stem cell treatment AND where testing with a genetic therapy or human stem cell confirms the clinical safety and efficacy of the device.~~
- ~~A device where the therapeutic MOA requires the recruitment or incorporation of an endogenous stem cell.~~

(3) Must demonstrate appropriate stage of readiness

All projects developing a cell-based therapy, a combination product including a cell therapy component, or an eligible biologic product regulated through the Center for Biologics Evaluation and Research (CBER) must have completed a pre-IND submission and received a written response from the FDA.

~~All projects developing a medical device (including a diagnostic) must have completed a pre-IDE submission and received a written response from the FDA.~~

All projects developing an eligible small molecule or biologic candidate regulated through the Center for Drug Evaluation and Research (CDER) must have selected a lead candidate and have already performed proof of concept studies and have pharmacokinetic/pharmacodynamic (PK/PD) data with that lead candidate. The pre-IND meeting must be completed if a pre-IND meeting is planned.

The proposed IND~~/IDE~~ filing must be no more than 24 months from the project start date.

gene, or introduce new or modified nucleic acids that augment the therapeutic potential of the target cells.

Allogeneic Donor Cell Eligibility

For all projects developing a product candidate that includes allogeneic (donor-derived) cells:

- The cell source (tissue or cell line) proposed for use must have been consented by the donor for intended use and for clinical development and commercial sale
- The cells must meet the Good Tissue Practices (GTP) requirements for donor eligibility (21 CFR 1271 (subpart C)), or there is plan in place to address the GTP requirements

(4) Must include a project manager

The project team must include a Project Manager with experience in managing development programs and able to devote at least 50 percent effort to the project.

(5) Must demonstrate appropriate level of co-funding

CIRM will require for-profit applicants and for-profit partners of non-profit applicants to co-fund at least 20% of the total "Allowable Project Costs". Allowable Project Costs are those costs permitted under CIRM policies and regulations and include direct, facilities and indirect costs. The sum of CIRM funds requested plus the co-funding contribution by the applicant make up the total Allowable Project Cost. Non-profit applicants may provide co-funding but it is not required. The co-funding may come from any funding source arranged by the applicant but may not include "in-kind" or similar types of support. 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). Alternatively, for-profit applicants and for-profit partners of non-profit applicants may elect to fulfill all or a portion of the minimum co-funding requirement by agreeing to issue equity warrants to CIRM. Applicants electing the warrant-based co-funding requirement may request CIRM funding up to the award cap and must issue equity warrants to CIRM in order to cover the portion of the CIRM award amount that corresponds to the co-funding requirement.

(6) 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.

(7) CIRM applicant must be the IND~~/IDE~~ sponsor

The intended IND~~/IDE~~ sponsor (i.e., the entity to be named as the sponsor on the IND ~~or IDE~~ application to the FDA) must be the CIRM applicant organization if an organization-sponsored IND~~/IDE~~ or the CIRM PI if an investigator-sponsored IND~~/IDE~~.

(8) Application must be accurate and complete

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

(9) Applicant must be in "good standing"

Applicants must certify that they are 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.

~~**(10) CIRM/NHLBI Cure Sickle Cell Disease Joint Initiative**~~

~~All applications proposing a therapeutic candidate or medical device for the treatment of sickle cell disease will be considered for funding under the CIRM/NHLBI Cure Sickle Cell Disease Joint Initiative and all application materials will be shared with appropriate NHLBI staff. Under this program, successful applicants are awarded funds from both CIRM and NHLBI. Co-funded projects must adhere to the NHLBI Data Sharing policies and are required to share aggregate data with the Cure Sickle Cell initiative's designated Data Coordinating Center.~~

Who can apply?

California Organizations

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.

Non-California Organization

A Non-California Organization is a for-profit or non-profit organization that employs and pays 50% or less of its employees in California.

For a Non-California Organization, Allowable Project Costs include:

- Cost of non-clinical research activities conducted wholly in California.

Unallowable Costs

For both California Organizations and Non-California Organizations, 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 propose a level of effort on the project consistent with achieving the project's aims and not less than 15% on average over the project period (note: "project" includes both the CIRM-funded and applicant co-funded components). 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

Diversity, Equity, and Inclusion (DEI) in CIRM-Funded Projects

All applicants for the CLIN1 program will be required to include a written plan in the application for outreach and study participation by underserved and disproportionately affected populations. In addition, applicants must provide a statement describing how the research team has considered the influence of race, ethnicity, sex, gender, and age diversity in the development of the proposed therapy or device. Applicants should discuss the limitations, advantages and/or challenges of developing a product or tool that addresses the unmet medical needs of the diverse California population, including underserved racial/ethnic communities. 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 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 also requires 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 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 the generation of knowledge CIRM may publicly share where CIRM-funded data are deposited.

SCHEDULE AND DEADLINES

Applications Due	2:00 pm (PDT/PST) on the last business day of each month (except October)
Grants Working Group (GWG) Review	Approximately 60 days post submission
ICOC Review and Approval	Approximately 90 days post submission
Award Start	Must start within 45 days of award approval (i.e., approximately 135 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 CLIN1 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.