California Institute for Regenerative Medicine

Concept Plan

Proposed to the Independent Citizens Oversight Committee's Science Subcommittee

December 8, 2014

Accelerating the Development of Stem Cell Treatments: Clinical 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 an overhaul in the manner in which it does business, referred to as "CIRM 2.0" in previous communications with the Independent Citizens Oversight Committee (ICOC). CIRM intends to implement a more streamlined process for awarding and administering grants that will include frequent and predictable submission opportunities followed by rapid review, quick funding decisions, streamlined contracting and the prompt initiation of research. Post-award, CIRM intends to become a more active partner with its recipients to further increase the probability of timely success.

CIRM ultimately intends to use this basic approach for all three stages of stem cell development activities – Discovery, Translational, and Clinical. This first concept plan addresses Clinical Stage programs, with the other stages to be proposed in the near future.

CIRM intends to expedite support for the clinical stage candidate stem cell therapies that demonstrate scientific excellence. Under this initiative CIRM will provide funding for eligible projects that are completing late stage preclinical development through any stage of clinical trial activity.

To accomplish this, CIRM will establish an open call for proposals and will accept applications on a monthly basis for three complementary award types. This concept plan further describes the three proposed Program Announcements listed below.

- **PA 15-01:** Funding Opportunity for Late Stage Preclinical Projects
- **PA 15-02:** Funding Opportunity for Clinical Trial Stage Projects
- **PA 15-03:** Funding Opportunities for Supplemental Accelerating Activities

Given the open opportunity to apply and amend rejected applications, requests to appeal the outcome of a GWG review will be limited to demonstrable conflicts of interest as defined in the CIRM Grants Administration Policy.

REQUESTED FUNDING ALLOCATION

CIRM requests up to $50M to cover issuance of awards across these three Program Announcements during the remainder of the 2014/2015 fiscal year. The Indirect Cost rate will be set at 10%. There is no preset cap for individual awards. Instead each application will undergo a thorough independent budget review prior to review by the GWG.

PA 15-01: FUNDING OPPORTUNITY for LATE STAGE PRECLINICAL PROJECTS

OBJECTIVE

The objective of this funding opportunity is to complete late stage preclinical studies necessary to attain an active IND with the FDA and initiate start-up activities to prepare for a clinical trial for a stem cell-based 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 preclinical studies that will enable the filing of a well-supported IND with the FDA for a clinical trial with a single therapeutic candidate
- Assay development
- Process development
- IND-enabling preclinical safety, efficacy, and toxicology studies
- Manufacturing to support IND-enabling studies
- cGMP manufacturing to supply the intended Phase I clinical trial
- 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

How will funds be awarded?

Awards to non-profit applicants will be in the form of a grant. For-profit applicants may choose to accept the award in the form of a grant or a loan. Except for the first payment issued upon initiation of an award, payments will be disbursed upon completion of specific operational milestones. CIRM expects projects to advance rapidly and will not accept applications under this PA that propose more than two years of funding.

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 with a single stem cell-based therapeutic candidate

CIRM will support preclinical studies that enable a well-supported IND for a therapeutic candidate that is either:

- A cell therapy where stem or progenitor cells either comprise the therapy or are used to manufacture the 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 unlikely to receive funding from other sources.
- A small molecule or biologic that (**i**) stimulates/recruits endogenous stem cells as the primary MOA for repair/regeneration OR specifically targets cancer stem cells as the primary MOA, and (**ii**) is being developed for a rare or unmet need unlikely to receive funding from other sources.

(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 must have completed a pre-IND meeting with the FDA and have correspondence from the FDA confirming agreement with the IND-enabling preclinical plan.

All projects developing an eligible small molecule candidate must have selected a lead molecule and have already performed proof of concept studies and have pharmacokinetic/pharmacodynamic (PK/PD) data with that lead.

All projects, regardless of type, must be within 24 months of filing an IND with the FDA.

(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) Co-funding requirements

CIRM will require for-profit applicants to co-fund at least 20% of the total allowable costs of the project. 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. Documentation demonstrating the commitment of funds to cover the proposed co-funding amount must be provided by the application deadline (e.g., copy of executed term sheet showing amount of co-funding, conditions, and source).

(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.

Who can apply?

California Research Organizations

California Organizations (for-profit and non-profit) may use CIRM funds for eligible project costs incurred both in California and outside California. To qualify as a California organization, the organization must have >50% of its employees located in, and paid in, the state of California, and conduct the award activities from the California location.

Non-California Research Organizations

Non-California organizations may also apply; however, CIRM funding can be used only for allowable expenditures incurred within California. The applicant must demonstrate by the application deadline a commitment of funds from other sources for project activities outside of California.

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
- Must commit at least 30 percent effort to working on the project (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

SCHEDULE AND DEADLINES

Applications Due	5:00 pm (PDT/PST) on the last business day of each month
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 130 days post submission)

PA 15-02: FUNDING OPPORTUNITY for CLINICAL TRIAL STAGE PROJECTS

OBJECTIVE

The objective of this funding opportunity is to complete a clinical trial for a stem cell-based therapy that addresses an unmet medical need.

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 a Phase 1, Phase 2, or Phase 3 clinical trial with a single therapeutic candidate
- Manufacturing of product to supply the proposed clinical trial
- Exploratory biomarker testing of samples from the clinical trial
- Assay development (e.g. potency assay)

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

- Early research and translation for candidate discovery/selection
- Formal comparability studies
- Manufacturing or process development activities to support clinical trials other than the trial proposed in the application
- Studies to remove a clinical hold by the FDA

How will funds be awarded?

Awards to non-profit applicants will be in the form of a grant. For-profit applicants may choose to accept the award in the form of a grant or a loan. Except for the first payment issued upon initiation of an award, payments will be disbursed upon completion of specific operational milestones.

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 a single clinical trial using a stem cell-based therapy

CIRM will support the completion of a single Phase 1, Phase 2, or Phase 3 trial per award. The trial must test the safety and/or efficacy of a therapeutic candidate that is either:

- A cell therapy where stem or progenitor cells either comprise the therapy or are used to manufacture the 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 unlikely to receive funding from other sources.
- A small molecule or biologic that (**i**) stimulates/recruits endogenous stem cells as the primary MOA for repair/regeneration OR specifically targets cancer stem cells as the primary MOA, and (**ii**) is being developed for a rare or unmet need unlikely to receive funding from other sources.

(3) Must have regulatory approval to proceed with proposed trial

- ***All applicants*** must have an active IND for the proposed candidate in the proposed indication before applying (i.e. the IND has been filed with FDA for >30 days and is not on clinical hold).
- ***Phase 2 trial applicants*** must have Phase 1 safety data supporting progression to Phase 2, obtained with the proposed candidate in an appropriate indication.
- ***Phase 3 trial applicants*** must have compelling Phase 2 data for the same indications, completed an End-of-Phase 2 meeting, and obtained FDA agreement on the trial design for Phase 3.

(4) Must include a project manager

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

(5) Co-funding requirements

CIRM will require co-funding from the applicant as indicated below. The co-funding may come from any funding source arranged by the applicant. Applicants must commit at least the percentage of total project costs indicated below. Documentation demonstrating the commitment of funds to cover the proposed co-funding amount must be provided by the application deadline (e.g., copy of executed term sheet showing amount of co-funding, conditions, and source).

Minimum Percentage of Total Project Costs the Applicant Must Provide

Applicant Type	Phase 1	Phase 2	Phase 3
Non-profit	None	40%	50% with CIRM contribution not to exceed $20M
For-profit	30%	40%	50% with CIRM contribution not to exceed $20M

(6) Must adhere to requirements for clinical trial sites in California

Applicant organizations located outside of California must have at least one clinical site in California and CIRM funding can only be used for costs incurred within the State.

California applicant organizations are expected to have clinical trial sites in California and must provide justification for inclusion of any sites located outside the State.

(7) For-profit organizations must demonstrate solvency

For-profit organizations must provide documentation that shows 180 days cash on hand from date of application submission.

Who can apply?

California Research Organizations

California Organizations (for-profit and non-profit) may use CIRM funds for eligible project costs incurred both in California and outside California. To qualify as a California organization, the organization must have >50% of its employees located in, and paid in, the state of California, and conduct the award activities from the California location.

Non-California Research Organizations

Non-California organizations may also apply; however, CIRM funding can be used only for allowable expenditures incurred within California. The applicant is expected to

demonstrate by the application deadline a commitment of funds from other sources for project activities outside of California.

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
- Must commit at least 30 percent effort to working on the project (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

SCHEDULE AND DEADLINES

Applications Due	5:00 pm (PDT/PST) on the last business day of each month
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 130 days post submission)

PA 15-03: FUNDING OPPORTUNITY for SUPPLEMENTAL ACCELERATING ACTIVITIES

OBJECTIVE

The objective of this funding opportunity is to support new activities on active CIRM-funded development projects that will significantly accelerate or increase the likelihood of success of the proposed therapy.

AWARD INFORMATION

What activities will CIRM fund?

CIRM funds will support the following activities under this opportunity:

- Activities to accelerate an ongoing clinical trial that is currently funded by CIRM – NOTE: the application will only be considered for activities resulting in the trial being completed sooner than proposed under the original parent award.
- Manufacturing improvements and optimization, or scale up to support later stage development
- Nonclinical bridging studies to demonstrate comparability of product produced with an improved manufacturing process
- Exploratory biomarker validation
- Assay development (e.g. potency assay)

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

- The conduct of a new clinical trial
- Studies for therapeutic candidate discovery
- Activities approved for funding under the parent award

How will funds be awarded?

Awards to non-profit applicants will be in the form of a grant. For-profit applicants may choose to accept the award in the form of a grant or a loan. Except for the first payment issued upon initiation of an award, payments will be disbursed upon completion of specific operational milestones.

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 new activities within 45 days of approval

Given the urgency of CIRM's mission, all approved awardees must initiate work on the funded new activities within 45 days of approval and authorization for funding by 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 supplement an active, development, CIRM-funded project

The applicant must currently have an active CIRM-funded development award (such as a Disease Team Award, Strategic Partnership Award, Late Stage Preclinical Award [PA 15-01], or Clinical Trial Stage Award [PA 15-02]).

(3) Must use the same therapeutic candidate as the parent CIRM-funded project

The new activities proposed must use the same therapeutic candidate as in the parent award and any process development or product improvements must be under the same IND.

(4) Co-funding requirements

CIRM will require all applicants to co-fund at least 40% of the total costs of the proposed new activities. The co-funding may come from any funding source arranged by the applicant. Documentation demonstrating the commitment of funds to cover the proposed co-funding amount must be provided by the application deadline (e.g., copy of executed term sheet showing amount of co-funding, conditions, and source).

Who can apply?

Only CIRM grantees with an active CIRM-funded development award (such as a Disease Team Award, Strategic Partnership Award, Late Stage Preclinical Award [PA 15-01], or Clinical Trial Stage Award [PA 15-02]) can apply.

California Research Organizations

California Organizations (for-profit and non-profit) may use CIRM funds for eligible project costs incurred both in California and outside California. To qualify as a California

organization, the organization must have >50% of its employees located in, and paid in, the state of California, and conduct the award activities from the California location.

Non-California Research Organizations

For non-California organizations, CIRM funding can be used only for allowable expenditures incurred within California. The applicant is expected to demonstrate by the application deadline a commitment of funds from other sources for project activities outside of California.

Who can serve as the Principal Investigator (PI)?

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

- Must be the same PI as the parent award
- Must not currently have another application pending review or approval under this funding opportunity

SCHEDULE AND DEADLINES

Applications Due	5:00 pm (PDT/PST) on the last business day of each month
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