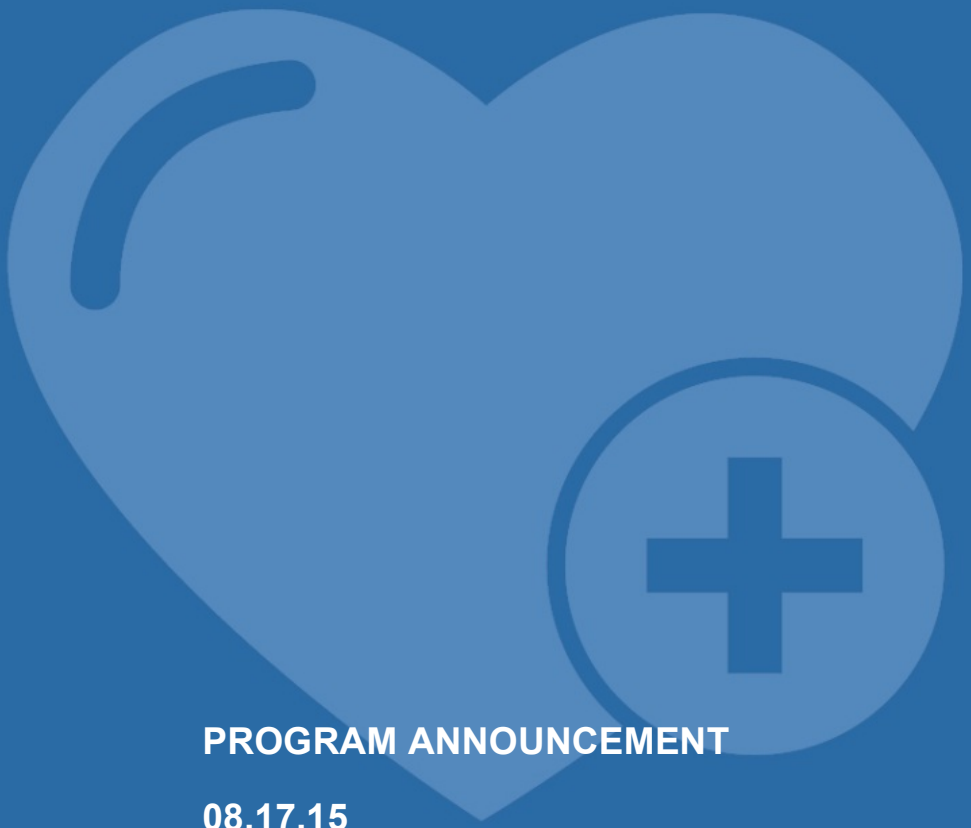
CLINICAL

Partnering Opportunity For Supplemental Accelerating Activities

CLIN 3



PROGRAM ANNOUNCEMENT

08.17.15

CLINICAL

Partnering Opportunity For Supplemental Accelerating Activities

CLIN 3

Objective

The mission of California Institute for Regenerative Medicine (CIRM) is to accelerate stem cell therapies to patients with unmet medical needs.

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

Under this program, CIRM will act not only as a funding agency, but will also devote significant internal resources and leverage its external team of world-class subject matter experts to actively advance the project. The result of a successful application will be the formation of a true partnership that both accelerates the program and gives it the greatest opportunity for success.

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Award Information

What activities will CIRM support?

CIRM resources 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 resources 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
- ✗ Construction or renovation of physical infrastructure

How will funds be awarded?

CIRM will disburse funds pursuant to an amendment to the Notice of Award. Under the Grants Administration Policy for Clinical Stage Projects, awardees may elect to treat their award as a loan within the earlier of seven years or the submission of an application to the Food and Drug Administration for marketing authorization. (See GAP, sec. IV.) If an awardee does not make this election, the award will be treated as a grant. Except for the first payment issued upon initiation of an award, payments will be disbursed upon completion of specific Operational Milestones. **Costs resulting from a delay or failure to meet an Operational Milestone will be the sole responsibility of the recipient.** Successful applicants will have thoughtfully accounted for foreseeable project risks and developed contingency plans that **do not** involve additional funding from CIRM (see "Contingency Plan" under application components).

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Eligibility

What types of projects are eligible for partnering?

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

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. **Applications submitted prior to the completion of all necessary prerequisites may be subject to refusal for subsequent consideration from CIRM.**

(2) Must supplement an active CIRM-funded development 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 [CLIN 1], or Clinical Trial Stage Award [CLIN 2]).

All activities proposed in an application must be directly related to a single project objective. This objective may include multiple sub-activities that are related and necessary to achieve the proposed objective. For example, a proposal to escalate the dose of a therapeutic in a trial might involve manufacturing activities to produce additional material and clinical trial activities to administer the new dose. Activities unrelated to the dose escalation objective would not be allowed within the same application.

(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 the proposed new activities with at least the percentage of the total "Allowable Project Costs" indicated in the table below. Allowable Project Costs are those costs permitted under CIRM policies and regulations and include both direct, facilities, and indirect costs. The sum of CIRM funds requested plus co-funding contribution by the applicant make up the total Allowable Project Costs. 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). Only funds that will be spent concurrently with CIRM funds (e.g. no sooner than ICOC

approval and no later than completion of the final Operational Milestone) will qualify toward this co-funding requirement.

Minimum Percentage of the Total Allowable Project Costs the Applicant Must Provide

Applicant Type	Preclinical	Phase 1	Phase 2	Phase 3
Non-profit	None	None	40%	50%
For-profit	20%	30%	40%	50%

Who can apply?

Only CIRM awardees with an active CIRM-funded development award (such as a Disease Team Award, Strategic Partnership Award, Late Stage Preclinical Award [CLIN 1], or Clinical Trial Stage Award [CLIN 2]) can apply.

California Based 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 manage the award activities from the California location.

Non-California Based 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 partnering opportunity
- Any effort for which salary from CIRM is claimed must be expended in California

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Schedule And Deadlines

Applications Due	2:00 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)

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 may 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, allow an opportunity to remedy, and if not timely remedied, terminate all further action on the application.

Budget Review

An external team of budget professionals will review the proposed budget to provide information to CIRM regarding how the proposed costs compare with established market rates for similar activities (or how well the costs are justified when market rates are not established). When a proposed budget differs significantly from market rates, adjustments to the budget will be required by CIRM prior to further review of the application. Applicants will be notified of the specific discrepancies and applications will not be forwarded for scientific review until an amended budget has been submitted and approved by CIRM. Additionally, project budgets may be subject to further adjustments prior to issuance of an award based upon assessments of the GWG, the CIRM team, or by the Application Review Subcommittee of the ICOC.

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Scientific Review

Scientific merit will be assessed by the CIRM Grants Working Group (GWG), which is composed of fifteen scientific experts from outside California, seven patient advocate members of CIRM's Governing Board (ICOC), and the Chair of the Governing Board. 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 at 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 GWG will score each application and make one of the following specific recommendations to the ICOC's Application Review Subcommittee: 1) fund the project based on the proposal's exceptional merit; 2) do not fund the project but allow for resubmission; or 3) do not fund the project and do not allow resubmission. In the event the GWG recommends amendment and resubmission, the applicant may elect, prior to the ICOC's final funding decision, to amend and resubmit the application for reevaluation by the GWG.

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

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).

Appeals

All decisions of CIRM and the ICOC are final. Given the open opportunity to amend and re-submit rejected applications, requests to appeal the outcome of a GWG review will be limited to demonstrable conflicts of interest as defined in CIRM's Conflict of Interest Policy for Scientific Members of the GWG (http://www.cirm.ca.gov/files/files/funding_page/Reg100003_Conflict_of_Interest_0.pdf).

How will the scientific merit of an application be evaluated?

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

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

Do the proposed activities add value to the parent award? Will the conduct of these activities accelerate completion of the parent project, accelerate development of the therapy to patients, or increase the likelihood of successful development of the therapeutic candidate?

2. Is the rationale sound?

Are the proposed activities justified and integral to the core objective of the parent award? Is there evidence that pursuing these activities is necessary and appropriate at this time?

3. Is the project well planned and designed?

Is the project appropriately planned and designed to meet the objective of the program announcement and achieve meaningful outcomes to support further development of the therapeutic candidate? Is this a well-constructed, quality program? Do the project plan and timeline demonstrate an urgency that is commensurate with CIRM's mission?

4. Is the project feasible?

Are the intended objectives 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? Does the team have a viable contingency plan to manage risks and delay?

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 application in a given review cycle and may not submit additional applications during the review period.

Applications are due by 2:00pm (Pacific Time) on the last business day of each month. Applications received after the deadline will be deferred to the next monthly 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. Applicants are required to indicate key personnel involved in the project, describe how the proposal addresses the objective of the partnering opportunity, provide a detailed plan of proposed activities, complete a detailed activity-based budget, and provide reference materials, such as FDA correspondence that confirms the status of the project. Applicants will also be required to provide a financial contingency plan that addresses how the applicant will cover possible funding shortfalls.

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The main body of the proposal contains the following sections:

1. **Program Summary:** A brief description of the overall development program and the project for which partnering is sought and a summary of parent award activities.
2. **Target Product Profile**: Tabular summary of the drug development goals – description of the aspirational product not the specific goals of your proposal (template provided).
3. **Statement of Significance and Impact**: Description of the value that proposed activities add to the parent award in terms of accelerating development or increasing the likelihood of successful development of the therapeutic candidate to provide an improvement over the standard of care for the patient population.
4. **Rationale:** Rationale justifying why the proposed activities are necessary at this time and how they will accelerate delivery of the proposed therapeutic to patients and/or increase the likelihood of program success.
5. **Plan**: Project plan to achieve the objective of the program announcement.
6. **Timeline**: Activities-based timeline in Gantt chart-like format current for the parent award and describing the parent award with proposed accelerating activities incorporated.
7. **FDA correspondence**: Relevant FDA correspondence and plan for addressing any issues raised by FDA related to accelerating activities.
8. **Manufacturing Summary**: Manufacturing plan synopsis (template provided) if you are proposing manufacturing activities.
9. **Clinical Protocol**: Clinical protocol synopsis (template provided) and final or draft clinical protocol and a graph of monthly or quarterly enrollment projections if you are proposing additional activities for a clinical trial.
10. **Team Organization**: Team structure, leadership, and communications plan, including any CROs or CMOs that will be utilized.
11. **Operational Plan**: Clinical operations plan (template provided) if you are proposing additional activities for a clinical trial.
12. **Contingency Plan**: Summary of potential risks, costs associated with those risks, and mitigation strategies, **together with a financial contingency plan outlining viable funding sources in the event that costs exceed the amount of funding disbursement.**
13. **Resources and Environment:** A brief description of the resources available to the project and environment.
14. **References**

Note: Reviewers may request and will be provided material relating to the parent award and progress on the parent award.

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?

A specific and well-justified activities-based budget must be provided that clearly outlines the total costs of the project, including those costs not proposed to be funded by CIRM. The corresponding budget justification should provide enough detail to allow budget professionals to determine the appropriateness of the costs in relation to the activities being performed. Allowable Project Costs for research funded by CIRM are detailed in the CIRM Grants Administration Policy for Clinical Stage Programs. Generally, project costs for personnel, supplies, travel, equipment, and subcontracts may be claimed. Limits for specific cost categories must be observed.

What are the rules for spending CIRM funds outside of California?

California Based Organizations

California organizations (for-profit and non-profit) may use CIRM funds for Allowable Project Activities conducted both in California and outside of California. "Allowable Project Activities" means those activities that are conducted in California, and for activities outside of California, those activities over which the California organization exercises direction, supervision and control, including activities performed by a wholly owned subsidiary of the California organization outside of California. It does not include activities undertaken by a separate organization outside of California that retains intellectual property or publication rights in connection with the performance of those activities, including a research collaboration in which the research is conducted outside of California.

Non-California Based Organizations

Non-California organizations cannot use CIRM funds for any costs incurred outside California.

What are Direct Facilities Costs?

Direct Facilities Costs are the general operating costs of the awardee'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.

How much can an applicant claim for indirect costs?

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.

Award Administration

Issuance of Award

A CIRM award is issued via a Notice of Award Agreement, which is the formal contract that defines the terms and conditions of an award and documents the commitment of funds from CIRM.

Operational Milestones and Payment

CIRM funds under the award will be disbursed based on achievement of specific Operational Milestones established by CIRM. An "Operational Milestone" is an objective event that is indicative of project progress occurring as proposed in the application. CIRM establishes Operational Milestones for inclusion in the Grant or Loan Agreement based upon information provided in the Application. Upon issuance of the award, funds budgeted to achieve the initial Operational Milestone will be disbursed. Upon the successful completion of the initial Operational Milestone and each successive milestone, additional funds will be disbursed. If funds allocated to a specific Operational Milestone (including both CIRM funds and the required applicant co-funds) are exhausted prior to achievement of that milestone, the Awardee will be responsible for covering any remaining costs. CIRM expects that the applicant's contingency plan will identify project timeline and budget risks and will provide details for covering such costs, including the source of funding. CIRM reserves the right to make adjustments to the timeline for inclusion in the Grant or Loan Agreement to ensure that funds are appropriately dispersed across Operational Milestones.

Suspension Events

CIRM reserves the right to hold or terminate disbursements if CIRM determines, in its sole discretion, that a Suspension Event has occurred. A "Suspension Event" means a pre-defined condition that triggers a hold of CIRM funding until the suspension event has been resolved, if resolvable. Following a Suspension Event, the Awardee is expected to provide CIRM with a plan to resolve the issue that triggered the Suspension Event. CIRM establishes Suspension Events for inclusion in the Grant or Loan Agreement based on information provided in the Application.

Reporting

Awardees will be required to provide periodic written progress and financial reports to CIRM.

Upon approval of an award, CIRM will appoint a Clinical Advisory Panel (CAP) to partner with the Awardee. The CAP will be composed of at least one CIRM science

officer, one external advisor, and a patient representative and will provide guidance and advice to foster success of the project. CAPs have the ability to enlist the help of CIRM's external subject matter experts when needed. Awardees will have ongoing communication with the CAP throughout the duration of the award, typically meeting by teleconference on a quarterly basis and in person once a year.

Other Requirements

Clinical trials funded by CIRM must be listed on http://clinicaltrials.gov/ and awardees must submit the administrative and scientific results of the trial to the clinicaltrials.gov results database within one year of completion of the studies (in compliance with FDAAA801), for the benefit of the field.

Contacts

For information about this program announcement or the review process:

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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.

"Operational Milestone" means an objective event that is indicative of project progress occurring as proposed in the application.

"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.

"Suspension Event" means a pre-defined condition that triggers a hold of CIRM funding until the suspension event has been resolved, if resolvable.

Appendix

CIRM Regulations

Grant or Loan awards made through this program announcement 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.