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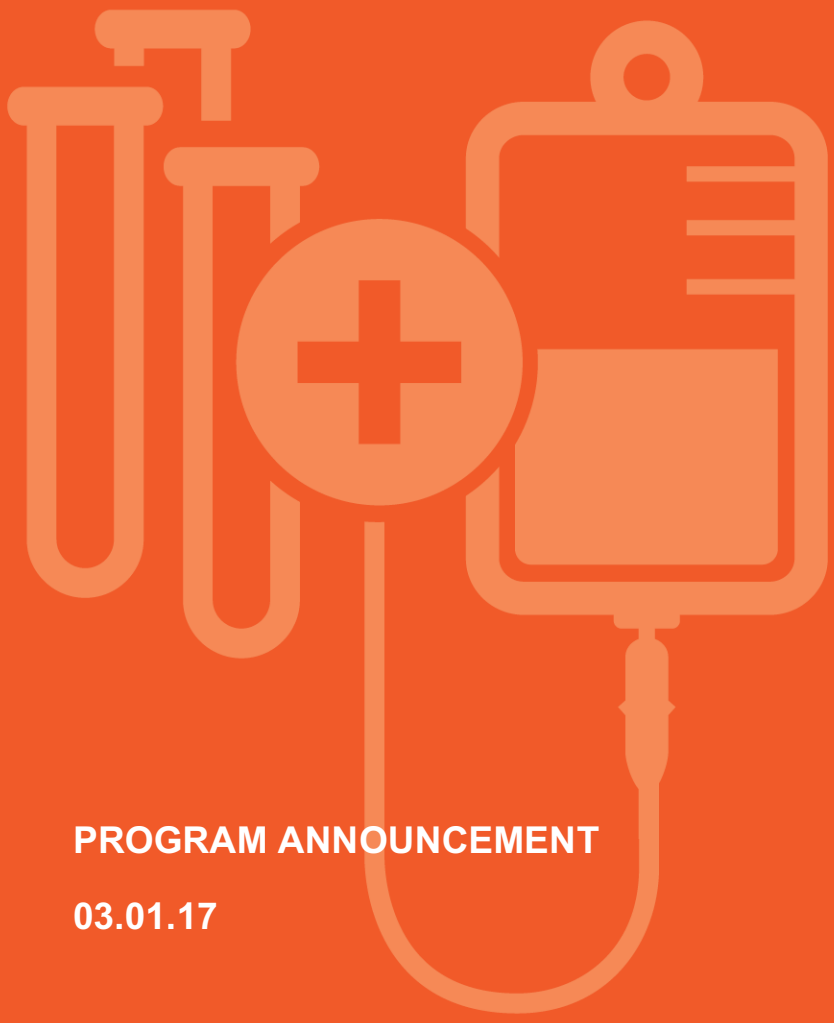
Partnering Opportunity for Translational Research Projects

Program Announcements:

TRAN 1 (Therapeutic)
TRAN 2 (Diagnostic)
TRAN 3 (Medical Device)
TRAN 4 (Tool)



PROGRAM ANNOUNCEMENT

03.01.17

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Partnering Opportunity for Translational Research Projects

TRAN 1: Therapeutic

TRAN 2: Diagnostic

TRAN 3: Medical Device (non-diagnostic)

TRAN 4: Tool

Objective

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

The objective of this initiative is to create a highly competitive opportunity for promising stem cell-based projects that accelerate completion of translational stage activities necessary for advancement to clinical study or broad end use for any one of the following product types:

- ✓ **A.** Stem cell-based ***therapeutic candidate*** (TRAN 1)
- ✓ **B.** ***Diagnostic (including medical imaging agents)*** based on stem cells, or critical for stem cell based therapy development or use (TRAN 2)
- ✓ **C.** ***Medical device*** (non-diagnostic) for a stem cell-based therapy or critical for stem cell based therapy development or use (TRAN 3)
- ✓ **D.** Novel ***tool*** that addresses a critical bottleneck to the discovery or development of stem cell-based therapy (TRAN 4)

Project outcomes, allowable activities, and what qualifies for each of the above product types are described in the corresponding Appendices: A, B, C, and D.

The overall application and review process and general requirements for all product types are described in main document.

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Award Information

How much funding can CIRM provide and for how long?

CIRM awards will cover direct project costs up to the following for each product type:

Product Type	Direct Project Costs, Funding Limit	Time Limit (Months)
Cell Therapy/Biologic	$4M	30
Small Molecule Therapy	$2M	30
Diagnostic	$1.2M	24
Medical Device	$2M	24
Tool	$1M	24

The amount of direct 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. The proposed project period must not exceed the maximum period indicated in the table above.

What activities will CIRM support?

CIRM resources will support all translational activities necessary for advancement to clinical study or end use for a stem cell-based therapy, device, diagnostic or tool. **As each product type has unique characteristics, the specific activities supported under a CIRM award for each product type are described in Appendices A-D.**

The appendices also describe activities that cannot be supported under this award for each product type.

How will funds be awarded?

CIRM will disburse funds pursuant to a Notice of Award. Under the Grants Administration Policy for Discovery, Translation, and Education Projects ("DT&E GAP"), Translational Research Therapeutic awardees (TRAN 1) may elect, upon completion of their award, to treat their award as a loan within the earlier of ten years from the date of the award or ten business days after the acceptance by the Food and Drug Administration of the awardee's application for marketing authorization, as specified in the DT&E GAP. If an awardee does not make this election, the award will be treated as a grant.

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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) 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 the Independent Citizens' Oversight Committee.

Therefore, investigators should only apply when their program has reached the stage where all eligibility criteria are met.

(2) The applicant must propose studies with an eligible therapeutic, device, diagnostic or tool candidate.

The proposed product must meet the specific eligibility criteria described for a therapeutic, diagnostic, device, or tool in Appendices A-D.

(3) The development candidate must be at an appropriate stage of readiness.

The proposed candidate must meet the specific readiness criteria described for a therapeutic, diagnostic, device or tool in Appendices A-D.

(4) The project team must include an experienced Project Manager.

The project team must include a Project Manager who has experience in managing relevant translational programs and who is able to devote at least 35 percent effort to the project. Alternatively, the project manager requirement may be satisfied through a contract with CIRM's Stem Cell Center for project management services.

(5) The applicant must demonstrate appropriate levels of co-funding.

CIRM will require for-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 both 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 only required when project costs are in excess of allowable CIRM award funding. 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).

(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-

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funding and contingency requirements for the term of the project. The determination of solvency will be made at CIRM's sole discretion.

(7) Application must be accurate and complete.

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

(8) Applicant must be a California Organization.

Only California Organizations are eligible to apply. A California Organization is a for-profit or non-profit organization that employs and pays more than 50% of its employees in California, and that directs and controls award activities from California. CIRM may determine, in its sole discretion, whether an applicant is a California organization and whether the project activities are allowable.

(9) Applicant must be in "good standing."

In order to be eligible to apply for CIRM funding an applicant must certify that it is in good standing as follows:

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

(i) The applicant's Chief Executive Officer, Chief Financial Officer, and Principal Investigator must not have been convicted of, nor currently under investigation for, crimes involving fraud/misappropriation; and

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

b. All Applicants:

(i) The Principal Investigator must not be currently under investigation for research misconduct by the applicant institution or a funding agency, and must not be currently debarred by HHS Office of Research Integrity.

How can CIRM funds be spent?

Allowable Project Costs include:

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

Allowable Project Costs do NOT include:

- 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.

The applicant must demonstrate by the application deadline a commitment of funds from other sources for non-allowable project activities that are necessary to achieve the goals of the application.

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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 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.

Schedule and Deadlines

Applications Due*	Approximately the months of April, August, and December of each year Next deadline is April 5th, 2017 at 2pm PST/PDT
Grants Working Group (GWG) Review	Approximately 60 days post submission
ICOC Review and Approval	Approximately 90 days post submission
Award Start	Must start within 90 days of award approval

* It is anticipated that applications under this program announcement will be accepted at approximately four-month intervals. Further information on subsequent offerings can be found at cirm.ca.gov.

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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 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.

If the number of applications received in any given cycle is significantly in excess of the number that the GWG can review in a single session, GWG members will conduct the review in two stages. In the first stage, reviewers will conduct a pre-review of applications to advance a subset of applications to second stage, the full GWG review described below. Those applications that are not advanced to the second stage will not be recommended for funding.

Applications for all product types within a cycle will be reviewed and ranked collectively by the GWG. There are no targeted quotas for funding specific product types.

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

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.

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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 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?

Is the proposed product likely to impact an unmet medical need? Would the product accelerate or increase the likelihood of successfully developing a stem cell technology that significantly improves patient care? Does the proposed product offer a sufficient, impactful, and practical value proposition for patients and/or health care providers?

2. Is the rationale sound?

Is the proposed project based on a sound scientific and/or clinical rationale? Is it supported by the body of available data? Do the data support development of the product?

3. Is the project well planned and designed?

Is the project appropriately planned and designed to achieve meaningful outcomes, to ensure a robust and unbiased approach, as appropriate for the preclinical studies proposed and to complete all activities necessary to support the next stage of development (e.g., Pre-IND or other pre-submission meeting with the FDA for certain therapeutics, diagnostics or devices; advance to manufacturing for commercialization for tools)? 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 proposed milestones and the expected project outcome 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?

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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 translational 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. 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 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.

The main body of the proposal contains the following 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. **Program Summary:** A brief description of the translational project for which partnering is sought and an overview of the overall development program.
3. **Target Product Profile**: Table summary of the candidate development goals – description of the aspirational product not the specific goals of your proposal (template provided).
4. **Statement of Significance and Impact**: Description of the unmet medical need; description of how the proposed product, if successful, would address an unmet need or accelerate or increase the likelihood successfully developing a stem cell treatment(s); and description of the value proposition for your intended product.
5. **Rationale:** Summary of the scientific and/or clinical rationale for developing the intended product as proposed and a summary of the available data that support moving forward with the proposed project at this stage.
6. **Plan and Milestones**: Project plan and milestones (template provided) to achieve the expected project outcome defined for the product proposed.
7. **Timeline**: Activities-based timeline in Gantt chart-like format.
8. **FDA Correspondence**: Relevant FDA correspondence and plan for addressing points raised by FDA.

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9. **Team Organization**: Team structure, leadership, and communications plan, including any CROs or CMOs that will be utilized.

10. **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**.**

11. **Resources and Environment:** A brief description of the resources available to the project and environment.

12. **References.**

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 Discovery, Translation, and Education projects. Generally, project costs for personnel, supplies, travel, equipment, and subcontracts may be claimed. Limits for specific cost categories must be observed.

What are Direct Facilities Costs?

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

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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.

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Award Administration

Issuance of Award

A CIRM award is issued via a Notice of Award, 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, milestones (both technical and financial), success criteria, timelines and budgets prior to issuance of the Notice of Award. CIRM may also review (for compliance with CIRM's policies and regulations) key contracts/agreements (e.g., with Contract Research Organizations or Contract Manufacturing Organizations) that are critical to the success of the project. CIRM reserves the right to review whether an applicant has satisfied the eligibility criteria set forth in this program announcement and, if CIRM determines that an applicant has failed to satisfy one or more criteria, to refrain from issuing a Notice of Award.

Milestones and Payment

Upon execution of the Notice of Award, CIRM will issue the first in a series of milestone-based payments. Continued CIRM funding is based on the achievement of specific Operational Milestones established by CIRM. An "Operational Milestone" is an objective event with defined criteria that is indicative of successful project progress on a "critical path" activity, that if not achieved in a timely manner will inhibit the accomplishment of the expected project outcome in the allowable project period. CIRM establishes Operational Milestones and success criteria at its sole discretion after consultation with the PI based upon information provided in the application.

CIRM will only issue subsequent payments after the Awardee provides CIRM with documentation demonstrating that an Operational Milestone has been accomplished. CIRM expects that the successful applicant will have developed contingency plans that thoughtfully identify risks to the project timeline and budget and provide details for covering such costs, including the source of funding (see "Contingency Plan" under Application Components).

If any Operational Milestone is delayed 6 months or more beyond the scheduled completion date identified in the Notice of Award, CIRM, in its sole discretion, may terminate the award.

Reporting

Grantees will be required to provide periodic written progress and financial reports to CIRM, including notice of achieving Operational Milestones.

CIRM will partner with the Awardee to foster the success of the project through access to both internal experts and the ability to enlist the help of CIRM's external subject matter experts when needed. Awardees will have ongoing communication with the CIRM Program Officer throughout the duration of the award, typically meeting by teleconference and periodically in person.

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Contacts

For information and assistance with this program announcement please contact:

Send email correspondence to Translational@cirm.ca.gov

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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 directs and controls 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 with defined criteria that is indicative of successful project progress on a "critical path" activity, that if not achieved in a timely manner will inhibit the accomplishment of the expected project outcome in the allowable project period

"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.

Appendices

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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Appendix A: Therapeutics

Project Outcome, Activities and Eligibility for Therapeutic Translational Research Projects (TRAN 1)

Project Outcome

Under a Therapeutic Translational Research Project award (TRAN 1), CIRM will enable completion of preclinical development stage activities for a stem cell based therapeutic candidate. Completion of these activities will position the therapeutic candidate for initiation of pivotal Investigational New Drug (IND)-enabling preclinical studies for an IND filing with the FDA.

For projects that are developing a cell-based therapy, a combination product including a cell therapy component, or an eligible biologic regulated by CBER, the **expected outcome** is the conduct of a well prepared pre-IND meeting or equivalent meeting with the FDA resulting in correspondence from the FDA confirming agreement with the IND-enabling preclinical plan. Project proposals must include activities that will result in a complete Pre-IND submission package. Applicants should reference the FDA Guidance on Pre-IND Meetings.

For projects that are developing an eligible small molecule or biologic candidate regulated by CDER, the **expected outcome** is completion of activities that will enable initiation of pivotal IND-enabling preclinical studies for an IND filing with FDA.

What activities will CIRM support to develop a therapeutic?

CIRM funds will support the following activities under TRAN 1 **that enable achievement of the expected outcome** (as described above):

- All activities necessary to ready a single therapeutic candidate for pivotal IND-enabling preclinical studies including:
  - Preparation of cGMP-compliant Master and Working cell banks
  - Assay development and qualification (e.g. in-process and release assays; stability, activity, tumorigenicity and immunogenicity assays)
  - Stability studies
  - GMP-compatible process scale-up/development sufficient to supply Phase 1 trial, and transfer to manufacturing
  - Candidate production to support project
  - Biomarker development
  - Conduct of non-clinical studies including pharmacodynamic, pharmacokinetic (cell biodistribution/fate), immunogenicity, pilot safety and mechanism of action (MOA) studies
  - Studies to select dose, determine regimen and route of administration
  - Selection of indication, development of a clinical plan, including a clinical protocol synopsis and draft protocol, for a Phase 1 trial
  - Preparation for and conduct of a Pre-IND meeting with the FDA

CIRM funds cannot be used to support the following activities under TRAN 1:

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- Studies for therapeutic candidate discovery including lead optimization or allogeneic cell line selection
- Generally, cGMP manufacturing to supply the intended Phase 1 clinical trial
- Clinical trial activities including start-up activities
- Generally, activities covered by CIRM CLIN programs

What therapeutic projects are eligible for funding?

(1) The applicant must propose studies with a single eligible therapeutic candidate that enables achievement of the expected outcome.

CIRM will support preclinical studies that enable readiness to execute on the IND-enabling preclinical plan for a single IND filing with the FDA for a therapeutic candidate that is either:

- A cell therapy where human stem cells[1], progenitor cells[2] or directly reprogrammed cells either compose the therapy or are used to manufacture the therapy (Minimally manipulated bone marrow cells, minimally manipulated cord blood or unmodified hematopoietic stem cells (HSCs), are **not** eligible under this call).
- A small molecule or biologic that meets one of the following criteria:
  - Acts on or is dependent on endogenous human stem/progenitor cells for its therapeutic effect AND is being developed for a rare or unmet need unlikely to receive funding from other sources.
  - Is dependent on targeting human cancer stem cells for its therapeutic effect AND is being developed for a rare or unmet need unlikely to receive funding from other sources.
  - Modifies a human stem cell therapy AND is being developed for a rare or unmet need unlikely to receive funding from other sources.
  - Where a human stem/progenitor cell is necessary to manufacture the therapy AND is being developed for a rare or unmet need unlikely to receive funding from other sources.

(2) The therapeutic candidate must be at an appropriate stage of readiness.

- Reproducible disease modifying activity must have been demonstrated with the proposed human therapeutic candidate in preclinical model(s) relevant to the target indication(s).
- For all projects developing an allogeneic cell therapy:
  - The line proposed for development must have been consented for research and commercial use.
  - Cells must meet the donor eligibility requirements as described in "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (August 2007);" Or, if not: A plan is presented to address donor eligibility requirements.

[1] Under Proposition 71, stem cells are "capable of self-renewal and have broad potential to differentiate into multiple adult cell types."
[2] Under Proposition 71, progenitor cells are "multipotent or precursor cells that are partially differentiated, but retain the ability to divide and give rise to differentiated cells."

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Appendix B: Diagnostics

Project Outcome, Activities and Eligibility for Diagnostic Translational Research Projects (TRAN 2)

Project Outcome

Under a Diagnostic Translational Research Project award (TRAN 2), CIRM will enable completion of development activities for diagnostics for patient screening, risk stratification, diagnosis, treatment selection or monitoring that are based on stem cells or are critical for the development or use of a stem cell based treatment.

For projects that are developing a diagnostic (including medical imaging agents) for multi-site use, the **expected outcome** is the conduct with the FDA of either a well-prepared Pre-Submission meeting or a Pre-IND meeting resulting in correspondence from the FDA indicating adequacy of completed/proposed activities to allow rapid advancement toward clinical studies and subsequent filing for clearance/approval to market. Applicants should consult the FDA Guidance Document on Pre-Submission Meetings.

For projects that are developing a diagnostic for a single commercial reference lab use, the **expected outcome** is the completion of activities to achieve acceptance of a well-prepared analytical validation/verification report and clinical validation plan that meets the requirements under CLIA (Clinical Laboratory Improvement Amendments) to enable diagnostic test launch.

What activities will CIRM support to develop a diagnostic?

CIRM funds will support the following activities under TRAN 2 **that enable achievement of the expected outcome** (as described above):

- Evaluation and verification of unmet medical and user needs
- Implementation of Design Control including initiation and maintenance of Design History File
- Implementation of risk analysis and risk management
- Diagnostic product design development including assay, software development and optimization
- Design verification and validation protocol development and initial testing
- Demonstration of sensitivity, specificity, reproducibility and accuracy adequate for intended use
- Testing with optimized assay of sufficient well characterized clinical samples to confirm performance adequate for intended use
- Activities necessary to ready a single medical imaging agent for pivotal IND-enabling preclinical studies (see Appendix A for representative activities)
- Determination/evaluation of intended use, regulatory path and clinical plan
- Development of clinical (validation/verification) protocols
- Development of a full validation report of test performance characteristics
- Development of manufacturing plan including process verification/validation

- Preparation for and conduct of a Pre-Submission or a Pre-IND meeting with the FDA

CIRM funds cannot be used to support the following activities under TRAN 2:

- Biomarker, technology discovery, candidate test discovery
- Implementation of manufacturing of final diagnostic product design to meet applicable regulatory requirements
- Conduct of final design verification, validation testing
- Conduct of process verification, validation testing
- Clinical studies required for marketing approval

What diagnostic projects are eligible for funding?

(1) The applicant must propose studies with an eligible diagnostic candidate that enable achievement of the expected outcome.

CIRM will support studies on a candidate diagnostic for patient screening, risk stratification, diagnosis, treatment selection or monitoring that will be regulated by the FDA or by the CMS (Centers for Medicare & Medicaid Services (CMS) under CLIA:

- Where human stem, progenitor or directly reprogrammed cells either are a necessary component of the diagnostic or are used to manufacture the diagnostic; OR
- Where the diagnostic is being developed for an intended use with human stem, progenitor or directly reprogrammed cells; OR
- Where the intended use of the diagnostic addresses a critical bottleneck to clinical development or use of human stem cell therapies AND where testing with human stem, progenitor or directly reprogrammed cells confirms the utility of the diagnostic for stem cell based therapy development or use.

(2) The diagnostic candidate must be at an appropriate stage of readiness.

Proof of concept studies with a prototype test (technology, biomarker(s)) or medical imaging agent must have demonstrated that the analyte(s) can be measured at biologically relevant levels for the intended clinical use in sufficient samples to distinguish relevant differences within the target population.

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Appendix C: Medical Devices

Project Outcome, Activities and Eligibility for Medical Device Translational Research Projects (TRAN 3)

Project Outcome

Under a Medical Device Translational Research Project award (TRAN 3), CIRM will enable completion of development activities for a non-diagnostic medical device that is critical for stem cell based therapy development or use and that is subject to FDA regulation for marketing either under a Premarket Notification 510(k), a Premarket Approval (PMA) or within a Biologics License Application (BLA).

For projects that are developing a significant risk medical device that is new or not cleared/approved for a given use where clinical trials are required, the **expected outcome** is the conduct of a well-prepared Pre-Submission meeting with the FDA resulting in correspondence from the FDA indicating, at a minimum, adequacy of the IDE-enabling preclinical plan and preliminary clinical plan for the intended use. Applicants should consult the FDA Guidance Document on Pre-Submission Meetings.

For projects that are developing a non-significant risk or Class II medical device that is new or not cleared/approved for a given use, the **expected outcome** is the conduct of a well-prepared Pre-Submission meeting with the FDA resulting in correspondence from the FDA indicating, at a minimum, adequacy of the preclinical plan, comparison to predicate device (if applicable) and preliminary clinical plan (if applicable) for the intended use to enable filing for clearance/approval to market under a 510(k) or a (PMA). Applicants should consult the FDA Guidance Document on Pre-Submission Meetings.

What activities will CIRM support to develop a device?

CIRM funds will support the following activities under TRAN 3 **that enable achievement of the expected outcome** (as described above):

- Evaluation and verification of unmet medical and user needs
- Implementation of Design Control including initiation and maintenance of Design History File
- Implementation of risk analysis and risk management
- Device product design development including prototype optimization, and testing to demonstrate technical feasibility
- Design verification and validation protocol development and initial testing
- Determination/evaluation of intended use, regulatory path and clinical plan
- Development of clinical (design validation) protocols
- Development of a full validation report of test performance characteristics
- Development of manufacturing plan including process verification/validation
- Preparation for and conduct of Pre-Submission meeting(s) with the FDA

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CIRM funds cannot be used to support the following activities under TRAN 3:

- Technology discovery, device discovery
- Implementation of manufacturing process of locked device design that meets applicable regulatory requirements
- Conduct of final design verification, validation testing
- Conduct of process verification, validation testing
- Manufacturing to supply clinical studies and product launch
- Clinical studies required for marketing approval

What device projects are eligible for funding?

(1) The applicant must propose studies with an eligible device candidate that enable achievement of the expected outcome.

CIRM will support studies on a candidate device intended for use in the cure, mitigation, treatment or prevention of disease that will be regulated by the FDA:

- Where the device is being developed for an intended use with human stem, progenitor or directly reprogrammed cells; OR
- Where the device is being developed for an intended use that addresses a critical bottleneck to translation, clinical development or use of human stem cell therapies AND where testing with human stem, progenitor or directly reprogrammed cells confirms the utility of the device for stem cell based therapy development or use; OR
- Where the therapeutic mechanism of action requires the recruitment or incorporation of an endogenous human stem or progenitor cell.

(2) The device candidate must be at an appropriate stage of readiness.

Proof of concept studies with a prototype device (candidate) must have demonstrated feasibility to meet initial performance criteria in test model(s) relevant to the intended use.

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Appendix D: Tools

Project Outcome, Activities and Eligibility for Tool Translational Research Projects (TRAN 4)

Project Outcome

Under a Tool Translational Research Project award (TRAN 4), CIRM will enable the rapid translation of novel tools for broad use that address critical bottlenecks to the discovery or development of stem cell based therapies and that are **not** subject to regulation by the FDA (Food and Drug Administration) or by the CMS (Centers for Medicare & Medicaid Services (CMS) under CLIA (Clinical Laboratory Improvement Amendments).

The **expected outcome** is to achieve a tool that consistently, robustly and effectively meets performance characteristics required to address the bottleneck as documented in a comprehensive design history file AND that is ready to be transferred to manufacturing for commercialization.

What activities will CIRM support to develop a tool?

CIRM funds will support the following activities under TRAN 4 **that enable achievement of the expected outcome**:

- Evaluation and verification of unmet need (bottleneck) to be addressed by this tool
- Continued evaluation and refinement of criteria that tool must meet to adequately address the unmet need
- Implementation of Design Control or equivalent process including initiation and maintenance of Design History File
- Tool prototype optimization and testing to address criteria
- Determination of "final" tool and testing to show consistent, robust and effective performance against criteria
- Development of manufacturing plan including process verification/validation
- Development of an initial commercialization plan

CIRM funds cannot be used to support the following activities under TRAN 4:

- Technology discovery, tool discovery
- Development and implementation of manufacturing of "final" tool
- Conduct of process verification, validation testing
- Manufacturing to supply product launch
- Preparation for and conduct of clinical studies

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What tool projects are eligible for funding?

(1) The applicant must propose studies with an eligible tool candidate that enable achievement of the expected outcome.

CIRM will support studies on a candidate novel tool for commercialization that addresses a critical bottleneck to the discovery, development or use of stem cell based therapies and that will NOT be regulated by the FDA or by the CMS under CLIA:

- Where human stem, progenitor or directly reprogrammed cells either comprise the tool or are used to manufacture the tool; OR
- Where testing with human stem, progenitor or directly reprogrammed cells confirms the utility of the tool to address a critical bottleneck to the discovery, development or use of human stem cell based therapies.

(2) The tool candidate must be at an appropriate stage of readiness.

Proof of concept studies with a prototype tool (candidate) must have demonstrated feasibility to meet initial performance criteria in test system(s) relevant to addressing the bottleneck.