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Translational Stage Funding Opportunity

TRAN1 Therapeutic
TRAN2 Clinical Diagnostic
TRAN3 Medical Device
TRAN4 Tool

PROGRAM ANNOUNCEMENT
06.10.22

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TRAN1 Therapeutic
TRAN2 Diagnostic
TRAN3 Medical Device
TRAN4 Tool

Objective

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

The objective of this initiative is to support promising regenerative medicine (stem cell-based or genetic therapy) 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:

- ✓ **TRAN1:** Stem cell-based or genetic therapy **therapeutic candidate** (Appendix A)
- ✓ **TRAN2: Diagnostic** (including medical imaging agents) based on stem cells, or critical for stem cell-based or genetic therapy development or use (Appendix B)
- ✓ **TRAN3: Medical device** (non-diagnostic) for a stem cell-based therapy or critical for stem cell-based or genetic therapy development or use (Appendix C)
- ✓ **TRAN4: Novel tool** that addresses a critical bottleneck to the discovery or development of stem cell-based or genetic therapy (Appendix D)

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.

Contact

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

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Award Information

What is the award amount and duration?

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, Genetic 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 from the award start date (approximately 90 days after the date of ICOC approval) indicated in the table above.

How will funds be awarded?

Funds will be disbursed pursuant to a CIRM Notice of Award. Under the Grants Administration Policy for Discovery and Translation Projects "D&T GAP"), Translation Research Therapeutic awardees (TRAN 1) may, upon completion of the award, elect to treat their award as a loan pursuant to the Loan Election Option in the Grants Administration Policy for Clinical Stage Projects. If an awardee does not make this election, the award will be treated as a grant. (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.

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.**

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

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Eligibility

What types of projects are eligible for funding?

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

(1) The applicant must be ready to initiate work on the funded project within 90 days of approval.

Given the urgency of CIRM's mission, all approved awardees must initiate work on the funded project within 90 days of approval and authorization for funding by the Application Review Subcommittee of 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 with experience in managing relevant translational programs and able to devote at least 50 percent effort to the project. Visit (https://www.cirm.ca.gov/sites/default/files/Guidance_for_Translational_Stage_Project_Manager_Qualifications.pdf) to download CIRM Guidance on Qualifications for Translational Stage Project Manager.

(5) The applicant must demonstrate appropriate level 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 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 in "good standing."

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

- The applicant's Chief Executive Officer, Chief Financial Officer, and Principal Investigator must not have been convicted of, or currently under investigation for, crimes involving fraud/misappropriation;
- The applicant must have accounting systems in place that are capable of tracking CIRM funds; and
  The Principal Investigator or key personnel named in the application must not be currently under investigation for research misconduct by the applicant institution or a funding agency and must not be currently debarred by HHS Office of Research Integrity.

Who can apply?

Only California Organizations are eligible to apply for this opportunity.

A California Organization is a for-profit or non-profit organization that employs and pays more than 50% of its employees in California and that directs and controls the award activities from California.

For a California Organization, Allowable Project Costs include:

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

Unallowable Costs

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 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.
- Must **not** currently have another application that is substantially similar or has overlapping activities pending review or approval under any CIRM opportunity.

Schedule and Deadlines

Applications Due*	There are generally two cycles per year.
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

*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 strongly encouraged to contact CIRM before applying with questions or to discuss their project's eligibility and proposed activities.

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 and nurse 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. The ICOC patient advocate and nurse members participating on the GWG will evaluate the applications on Diversity, Equity and Inclusion.

CIRM does not expect the application volume for Translation Stage Awards to exceed the capacity of a Grants Working Group review session; however, when it does, CIRM will make use of the two-stage streamlined process for high volume application review. When the number of applications received in a cycle is significantly in excess of the number that can be reviewed by the GWG panel, the GWG members conduct the review in two stages. In the first stage, GWG members (including scientific members and patient advocate and nurse members of the Governing Board) will conduct a pre-review of applications (called "Positive Selection") to identify applications that the panel believes are most responsive to the funding opportunity and hold the most potential for impact. Applications that are not selected are examined by the CIRM scientific team and CIRM President to determine whether any additional applications merit a full GWG review. The remaining non-selected applications are deemed to be denied. Since the selection process is focused on quickly identifying promising proposals rather than identifying deficiencies in applications, no reviewer comments are collected at this stage. Positively selected applications advance to the second stage of review, which involves assignment to

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specific reviewers on the panel, a full discussion at review meeting, and scoring by the GWG. 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.

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

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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?

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

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

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:

Resubmission Statement: *For revised and resubmitted applications,* an overview statement on how the applicant has addressed reviewers' prior requests and concerns.

Project Summary: High-level summary of the project.

Target Product Profile: Template-based product label containing base case and optimal product specifications for the proposed product.

Value Proposition: Description of the unmet medical need and the product's potential value to patients, healthcare providers and caregivers.

Diversity, Equity, and Inclusion (DEI): Statement describing how the project helps fulfill the unmet medical needs of the diverse California patient population. See full description below.

Scientific Rationale: Explanation of how published and preliminary research findings support the continued translation of the proposed product

Project Plan and Milestones: Description of all proposed activities detailing how the objective of the Program Announcement will be met.

Allogeneic Cell Derivation: *For proposed products that use allogeneic cells,* a description of how the cells were derived.

Gantt-Format Timeline: Timeline for all proposed activities.

FDA Correspondence: Template-based tabular summary of regulatory requests and proposed action plans.

Team Organization: Qualifications of the proposed team and plans for team collaboration.

Risk Mitigation & Financial Contingency Plan: Potential risks, mitigation strategies, associated costs, and non-CIRM sources of contingency funding.

Resources & Environment: Institutional offerings that will benefit the project.

References

Diversity, Equity, and Inclusion (DEI)

All applicants for the TRAN program will be required to provide a statement describing how their overall study plan and design has considered the influence of race, ethnicity, sex, gender, and age diversity. Applicants should discuss the limitations, advantages and/or challenges of their research proposal in developing a product or tool that addresses the unmet medical needs of the diverse California population, including underserved racial/ethnic communities. Examples include use of models and tools that account for population diversity (e.g. HLA types, gender, genomics data, cell models). Applicants should also address how perspectives and experience from the population that will benefit from the proposed product have been or will be incorporated in the implementation of the research project, including, for example, developing partnerships with patient organizations, acquiring training in cultural sensitivity and/or DEI, utilizing institutional resources for DEI, and allocating funds and/or personnel to address DEI.

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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 and Management 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 and Management 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 and Management 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.

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 and how much can an applicant claim?

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.

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

Indirect Costs are administrative costs of the awardee incurred for common or joint objectives, which cannot be readily and specifically identified with a particular project. 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.

To that end, upon approval of an award CIRM may appoint a Translation Advisory Panel (TAP) to partner with the awardee. The TAP will be composed of at least one

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

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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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.

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Appendices

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 regenerative medicine-based therapeutic candidate (stem cell-based or genetic therapy). 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 genetic therapy, a combination product including a cell or genetic therapy component, or an eligible biologic regulated by CBER, the **expected outcome** at the conclusion of a TRAN award 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 (https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/small-business-and-industry-assistance-frequently-asked-questions-pre-investigational-new-drug-ind).

For projects that are developing an eligible small molecule or biologic candidate regulated by CDER, the **expected outcome** at the conclusion of a TRAN1 award 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 human 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
- ✓ Activities intended to promote and uphold principles of Diversity, Equity, and Inclusion (DEI) in the conduct of the study

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

- ✘ Studies for therapeutic candidate discovery including lead optimization
- ✘ 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 human therapeutic candidate that enable achievement of the expected outcome at the conclusion of the TRAN award. 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 human 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 cells, 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 function of aged, diseased, damaged, or defective cells, tissues, and/or organs.

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[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." Progenitor cells may include directly reprogrammed cells if they meet the criteria in the above definition.

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

- 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).

(2) The therapeutic candidate must be at an appropriate stage of readiness to initiate a TRAN award. The application must provide data demonstrating that reproducible disease-modifying activity was achieved under the following conditions:

- Activity was demonstrated in preclinical model(s) relevant to the target clinical indication(s); Recognizing that for certain genetic therapies no relevant preclinical model may exist, a proposal for such a genetic therapy shall provide an explanation regarding the lack of a relevant preclinical model and alternative data showing relevance to the target clinical indication.
- If the product is intended to be manufactured from a single cell source (e.g., an established cell line or monoclonal antibody), then the human therapeutic candidate proposed for clinical translation is identical to the test article that was used to demonstrate disease modifying activity.
- If the product is intended to be manufactured from multiple cell sources (e.g., an autologous therapy or personalized allogeneic therapy), then disease-modifying activity must have been demonstrated with test articles that were generated using comparable manufacturing processes from at least two donor sources or cell lines.

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) https://www.ecfr.gov/current/title-21/chapter-I/subchapter-L/part-1271/subpart-C), or there is plan in place to address the GTP requirements
- For detailed guidance on donor eligibility see “Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (August 2007)” (https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091345.pdf)

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Appendix B: Clinical Diagnostics

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

Project Outcome

For TRAN2 projects, CIRM will support completion of development activities for diagnostics for patient screening, risk stratification, diagnosis, treatment selection or monitoring that are based on human stem cells or are critical for the development or use of a human stem cell-based or genetic therapy treatment.

For projects that are developing a diagnostic (including medical imaging agents) for multi-site use, the **expected outcome** at the conclusion of a TRAN2 award 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: https://www.fda.gov/media/114034/download

For projects that are developing a diagnostic for a single commercial reference lab use, the **expected outcome** at the conclusion of a TRAN award 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 (https://www.fda.gov/media/114034/download) or a Pre-IND meeting with the FDA
- ✓ Activities intended to promote and uphold principles of Diversity, Equity, and Inclusion (DEI) in the conduct of the study

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 or progenitor cells[3] (collectively "stem 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 a genetic therapy[4] approach or human stem cells **OR**
- Where the intended use of the diagnostic addresses a critical bottleneck to clinical development or use of human stem cell or genetic therapies **AND** where testing with human stem cells or relevant genetic therapy-targeted

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[3] Under Proposition 14, progenitor cells are "multipotent or precursor cells that are partially differentiated, but retain the ability to divide and give rise to differentiated cells." Progenitor cells may include directly reprogrammed cells if they meet the criteria in the above definition.

[4] For the scope of this solicitation, CIRM considers genetic therapy to mean a human therapeutic intervention that: 1) alters the genomic sequence of cells or 2) introduces or directly manipulates nucleic acids (such as mRNAs, antisense oligonucleotides) in cells. The intervention may include strategies to repair a disease-causing gene sequence, remove or inactivate a disease-causing gene, or introduce new or modified nucleic acids that augment the therapeutic potential of the target cells.

cells confirms the utility of the diagnostic for stem cell-based or genetic 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.

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) https://www.ecfr.gov/current/title-21/chapter-I/subchapter-L/part-1271/subpart-C), or there is plan in place to address the GTP requirements
- For detailed guidance on donor eligibility see "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (August 2007)" (https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091345.pdf)

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Appendix C: Medical Devices

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

Project Outcome

For TRAN3 projects, CIRM will enable completion of development activities for a non-diagnostic medical device that is critical for development or use of a human genetic or stem cell-based therapy 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** at the conclusion of a TRAN3 award 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: https://www.fda.gov/media/114034/download

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** at the conclusion of a TRAN3 award 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 (https://www.fda.gov/media/114034/download)
- ✓ Activities intended to promote and uphold principles of Diversity, Equity, and Inclusion (DEI) in the conduct of the study

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 human stem or progenitor cells[5] (collectively, "stem cells") are a necessary component of the device or are used to manufacture the device **OR**
- Where the device is being developed for an intended use with human stem cells or a genetic therapy[6] **OR**
- Where the device is being developed for an intended use that addresses a critical bottleneck to translation, clinical development, or use of human genetic or stem cell therapies **AND** where testing with human stem or relevant genetic therapy-targeted cells confirms the utility of the device for genetic or stem cell-based therapy development or use **OR**

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[5] Under Proposition 14, progenitor cells are "multipotent or precursor cells that are partially differentiated, but retain the ability to divide and give rise to differentiated cells." Progenitor cells may include directly reprogrammed cells if they meet the criteria in the above definition.

[6] For the scope of this solicitation, CIRM considers genetic therapy to mean a human therapeutic intervention that: 1) alters the genomic sequence of cells or 2) introduces or directly manipulates nucleic acids (such as mRNAs, antisense oligonucleotides) in cells. The intervention may include strategies to repair a disease-causing gene sequence, remove or inactivate a disease-causing gene, or introduce new or modified nucleic acids that augment the therapeutic potential of the target cells.

- Where the therapeutic mechanism of action requires the recruitment or incorporation of an endogenous human stem 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 in humans.

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) https://www.ecfr.gov/current/title-21/chapter-I/subchapter-L/part-1271/subpart-C), or there is plan in place to address the GTP requirements
- For detailed guidance on donor eligibility see “Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (August 2007)” (https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091345.pdf)

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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 human genetic or 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** at the conclusion of a TRAN4 award 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
- ✓ Activities intended to promote and uphold principles of Diversity, Equity, and Inclusion (DEI) in the conduct of the study

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

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 human genetic or stem cell-based therapies and that will NOT be regulated by the FDA or by the CMS under CLIA:

- Where human stem or progenitor cells[7] (collectively, "stem cells") either comprise the tool or are used to manufacture the tool **OR**
- Where testing with human stem or relevant genetic therapy[8]-targeted cells confirms the utility of the tool to address a critical bottleneck to the discovery, development, or use of human genetic or 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.

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[7] Under Proposition 14, progenitor cells are "multipotent or precursor cells that are partially differentiated, but retain the ability to divide and give rise to differentiated cells." Progenitor cells may include directly reprogrammed cells if they meet the criteria in the above definition.

[8] For the scope of this solicitation, CIRM considers genetic therapy to mean a human therapeutic intervention that: 1) alters the genomic sequence of cells or 2) introduces or directly manipulates nucleic acids (such as mRNAs, antisense oligonucleotides) in cells. The intervention may include strategies to repair a disease-causing gene sequence, remove or inactivate a disease-causing gene, or introduce new or modified nucleic acids that augment the therapeutic potential of the target cells.

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Recent Document Revisions

Revision Date	List of Changes
6/10/22	• Updated CIRM's Mission • Updated the Objective of the Program Announcement • Replaced the requirement for (i) a statement on addressing underserved needs and (ii) a statement on promoting and upholding principles of DEI with a unified application section on DEI; updated review criterion 5 accordingly • Updated names and descriptions of Proposal sections

07/01/21	• Project Manager revised to minimum 50% effort
	• Revised candidate eligibility:
	  ○ Small molecule and biologic candidates eligible
	  ○ Removed requirement for gene therapy, small molecule, and biologic candidates to be developed for a rare or unmet need unlikely to receive funding from other sources

01/01/21	• Added requirement for statement on addressing the underserved:
	  ○ Applicants must provide a statement regarding how their study plan and design has considered the influence of race, ethnicity, sex and gender diversity.
	• Clarified therapeutic candidate eligibility:
	  ○ Gene therapy projects do not require a "vital research opportunity" vote by GWG under Prop 14.
	• Added Data Sharing Plan Requirement.
	• Updated Prop 14 definitions.