CALIFORNIA'S STEM CELL AGENCY

Funding Opportunity Concept Plan

TRANSLATIONAL STAGE FUNDING OPPORTUNITY for

TRAN1: Therapeutic
TRAN2: Diagnostic
TRAN3: Medical device
TRAN4: Tool

BACKGROUND

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

Through the Translational Research program, CIRM continues to create funding opportunities for the types and stages of research that otherwise do not exist or are of limited scope and focus to advance the field of regenerative medicine. Existing federal funding opportunities for translational activities are primarily driven by the internal priorities and interests of the administering body and, therefore, are unpredictable and limited in both scope and focus. The Translational Research program is a part of CIRM's core product development programs that unlike other funding sources, provide reliable and predictable funding throughout the award period, and bring expert CIRM staff and advice to support accelerated outcomes and advancement of projects along key stages of the product development pathway. CIRM therefore provides this unique opportunity to California scientists to support stages in the development of translational research projects that are unlikely to receive timely or sufficient funding from other sources.

OBJECTIVE

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
- TRAN2: Diagnostic (including medical imaging agents) based on stem cells, or critical for stem cell-based or genetic therapy development or use
- TRAN3: Medical device (non-diagnostic) for a stem cell-based therapy or critical for stem cell-based or genetic therapy development or use
- TRAN4: Novel tool that addresses a critical bottleneck to the discovery or development of stem cell-based or genetic therapy

AWARD INFORMATION

What activities will CIRM fund?

CIRM resources will support all translational activities necessary for advancement to clinical study or end use for regenerative medicine-based (stem cell-based or genetic therapy) products including a therapeutic, medical device, diagnostic, or tool. As each product type has unique characteristics, the specific activities supported under a CIRM award for each product type are briefly summarized below.

TRAN1

For TRAN1 projects, CIRM will support all activities necessary to ready a single human therapeutic candidate for pivotal IND-enabling preclinical studies.

- 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 the Center for Biologics Evaluation and Research (CBER), the expected outcome at the conclusion of a TRAN1 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.
- For projects that are developing an eligible small molecule or biologic candidate regulated by the Center for Drugs Evaluation and Research (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.

TRAN2

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.
- For projects that are developing a diagnostic for a single commercial reference lab use, the expected outcome at the conclusion of a TRAN2 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.

TRAN3

For TRAN3 projects, CIRM will support 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.
- 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.

TRAN4

For a TRAN4 project, CIRM will support 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 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.

ELIGIBILITY

What types of projects are eligible for funding?

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

(1) Must be ready to initiate work on the funded project within 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.

(2) Must propose studies with a single regenerative medicine-based product candidate (stem cell-based or genetic therapy) **that enables achievement of the expected outcome at the conclusion of the TRAN award**

Therapeutic (TRAN1) Candidates

- 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.

[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.

- 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.
- 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).

Diagnostic (TRAN2) Candidates

- Where human stem cells either are a necessary component of the diagnostic or are used to manufacture the diagnostic
- Where the diagnostic is being developed for an intended use with a genetic therapy approach or human stem cells
- 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 cells confirms the utility of the diagnostic for stem cell-based or genetic therapy development or use

Medical Device (TRAN3) Candidates

- Where human stem cells are a necessary component of the device or are used to manufacture the device.
- Where the device is being developed for an intended use with human stem cells or a genetic therapy
- 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
- Where the therapeutic mechanism of action requires the recruitment or incorporation of an endogenous human stem cell

Tool (TRAN4) Candidates

[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.

- Where human stem cells either comprise the tool or are used to manufacture the tool; OR
- Where testing with human stem or relevant genetic therapy-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.

(3) Must demonstrate appropriate stage of readiness

Therapeutic (TRAN1) Candidates

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)
- 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.

Diagnostic (TRAN2) Candidates

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.

Medical Device (TRAN3) Candidates

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.

Tool (TRAN4) Candidates

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.

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

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

(4) Must include a project manager

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

(5) Must demonstrate appropriate level of co-funding

CIRM will require for-profit applicants and for-profit partners of non-profit applicants to co-fund at least 20% of the total "Allowable Project Costs". Allowable Project Costs are those costs permitted under CIRM policies and regulations and include direct, facilities and indirect costs. The sum of CIRM funds requested plus the co-funding contribution by the applicant make up the total Allowable Project Cost. Non-profit applicants may provide co-funding but it is 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). Alternatively, for-profit applicants and for-profit partners of non-profit applicants may elect to fulfill all or a portion of the minimum co-funding requirement by agreeing to issue equity warrants to CIRM. Applicants electing the warrant-based co-funding requirement may request CIRM funding up to the award limit and must issue equity warrants to CIRM in order to cover the portion of the CIRM award amount that corresponds to the co-funding requirement.

(6) For-profit organizations must demonstrate solvency

For-profit organizations must provide documentation that shows 180 days cash on hand from date of application submission and the financial ability to meet the co-funding and contingency requirements for the term of the project. The determination of solvency will be made at CIRM's sole discretion.

(7) 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:

a. The applicant's Chief Executive Officer, Chief Financial Officer, and Principal Investigator must not have been convicted of, or currently under investigation for, crimes involving fraud/misappropriation;

b. The applicant must have accounting systems in place that are capable of tracking CIRM funds; and

c. The Principal Investigator or key personnel named in the application must not be currently under investigation for research misconduct by the applicant institution or a funding agency and must not be currently debarred by HHS Office of Research Integrity.

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.

ADDITIONAL REQUIREMENTS

Positive Selection

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

Diversity, Equity and Inclusion in CIRM-Funded Projects

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 the research team has or will incorporate diverse and inclusive perspectives and experience in the implementation of the research project, including, for example, developing partnerships with patient organizations, acquiring training in cultural competence and/or DEI, utilizing institutional resources for DEI, and allocating funds and/or personnel to address DEI.

The GWG and CIRM's governing board will evaluate these statements as a review criterion in making funding recommendations. Priority will be given to projects with the highest quality plans in this regard.

Data Sharing Plan

The sharing of data and knowledge produced from CIRM-funded projects is key to advancing the field of regenerative medicine and accelerating treatments to patients. CIRM requires its awardees to develop and execute a Data Sharing Plan that includes management and preservation of data and making applicable data available to the broader scientific community. CIRM also requires sharing of data in accordance with FAIR data principles through established repositories including, but not limited to, specialized NIH-supported repositories, generalist repositories, cloud platforms and institutional repositories. The Data Sharing Plan must be included in the application and the plan is subject to evaluation by the Grants Working Group. Applicants are required to allocate funds in their proposed budget for personnel and/or activities related to managing and sharing data produced from the funded project. The repository selected and summary of the data shared must be reported to CIRM during and after the project period. To promote the generation of knowledge CIRM may publicly share where CIRM-funded data are deposited.

SCHEDULE AND DEADLINES

Frequency of Opportunity	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 (i.e., approximately 150 days post submission)

REQUESTED FUNDING ALLOCATION

On an annual basis, CIRM will present for the Board's consideration a calendar-year budget for each of its on-going research programs, including the TRAN program. The indirect cost rate will be set at 20% for non-profit applicant organizations. CIRM will not fund indirect costs for for-profit applicant organizations.

REQUESTED DELEGATION OF BOARD AUTHORITY

To streamline the processes for high volume application review and to enable timely calls to highly specific opportunities or challenges, CIRM requests the Governing Board delegate to the President or his designee the authority to examine those applications that are not selected for a full review and to make the final determination whether to submit such applications to the GWG for a full review or to deny funding.