Accelerating and Advancing the Translation of Novel Stem Cell Treatments and Applications

The mission of CIRM is to accelerate the development of stem cell treatments to patients with unmet medical needs. To better serve this mission, CIRM is proposing a new paradigm for driving the rapid translation of promising new stem cell technologies towards improving patient care. Through this program, CIRM will provide funding opportunities that:

- Are predictable and recur regularly.
- Provide multiple translational pathways for advancement of stem cell discoveries
- Link to downstream CIRM clinical funding opportunities

This concept plan further describes the four proposed Translation Stage Program Announcements listed below.

- TRAN 1: Partnering Opportunity for Translational Research Projects: Therapeutic
- TRAN 2: Partnering Opportunity for Translational Research Projects: Diagnostic
- TRAN 3: Partnering Opportunity for Translational Research Projects: Medical Device
- TRAN 4: Partnering Opportunity for Translational Research Projects: Tool

ELIGIBILITY REVIEW

CIRM has the sole discretion to determine whether an applicant has satisfied the eligibility criteria for a program. CIRM may exercise its authority at any time before an award is executed. To the extent that CIRM exercises this authority after the Application Review Subcommittee has approved an award, CIRM will notify the Application Review Subcommittee and the public of its action by including an action item regarding the decision on the agenda for the next meeting of the Application Review Subcommittee.

TRAN 1: TRANSLATION STAGE PARTNERING OPPORTUNITY for THERAPEUTICS

OBJECTIVE

The objective of this funding opportunity is to enable completion of early preclinical development stage activities for a stem cell or gene therapy based therapeutic candidate. Completion of these activities will position the therapeutic candidate for initiation of pivotal IND-enabling preclinical studies for an IND filing with the FDA. CIRM expects projects under this program to advance rapidly and to be accomplished within 30 months and must be adequately justified.

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 **objective** is to conduct 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.

For projects that are developing an eligible small molecule or biologic candidate regulated by CDER, the **objective** is to complete activities that will enable initiation of pivotal IND-enabling preclinical studies for an IND filing with the FDA. Note that small molecules and biologics (except gene therapy) projects are only eligible if advancing a therapeutic candidate produced under a previous CIRM award.

AWARD INFORMATION

What is the CIRM project funding and project term?

- CIRM will fund direct project costs of up to $4M per award for projects where the therapeutic candidate includes a cell therapy or a biologic, or direct project costs up to $2M where the therapeutic candidate is a small molecule. Project costs must be well justified.
- The project period is up to 30 months and must be adequately justified.

What activities will CIRM support?

CIRM funds will support the following activities under this opportunity:

- 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- compliant process scale-up/development and transfer to manufacturing

- Candidate production to support translational studies
- Biomarker development
- Conduct of non-clinical studies including pharmacodynamic, pharmacokinetic (cell biodistribution/fate), immunogenicity 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 this opportunity:

- Generally, cGMP manufacturing to supply the intended Phase 1 clinical trial
- Clinical trial activities including start-up activities
- Studies for therapeutic candidate discovery including lead optimization

How will applications be reviewed?

Should the demand for TRAN Awards exceed the capacity of a Grants Working Group (GWG) review session, members of the GWG will review applications in two stages. In the first stage, GWG members will conduct a pre-review of applications (called "Positive Selection", see Appendix) to advance a subset of applications to the second stage, which will involve a full review by the GWG.

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.

Addressing the Needs of Underserved Communities 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 and gender 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).

The GWG and CIRM's governing board will consider these statements in their evaluations and 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 strongly encourages 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 encouraged 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.

How will funds be awarded?

CIRM will disburse funds pursuant to a 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. Except for the first payment issued upon initiation of an award, payments will be disbursed semi-annually or at CIRM's option. Continued funding is contingent upon timely progress, as outlined in the project milestones and timeline 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 (see below).

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~~60 days of approval.

Given the urgency of CIRM's mission, all approved awardees must initiate work on the funded project within ~~90~~60 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 a single eligible therapeutic candidate.

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, progenitor cells 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 gene therapy[1] approach (**i**) that targets a stem cell for its therapeutic effect, OR any other somatic cell ~~if deemed a "vital research opportunity" by the CIRM Grants Working Group~~; AND (**ii**) is intended to replace, regenerate, or repair the function of aged, diseased, damaged, or defective cells, tissues, and/or organs; AND (**iii**) is being developed for a rare or unmet medical need unlikely to receive funding from other sources.
- A small molecule or biologic that (**i**) 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/progenitor cell is necessary to manufacture the therapy; AND (**ii**) is being developed for a rare or unmet need unlikely to receive funding from other sources; AND **(iii)** is a therapeutic candidate produced under a previous CIRM award.

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

- Reproducible disease modifying activity must have been demonstrated with the therapeutic candidate in preclinical model(s) relevant to the target indication(s)
- All projects developing an allogeneic cell therapy:
    - The line proposed for development must have been consented for research and commercial use
    - Cells 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)" http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091345.pdf OR, IF NOT:
    - A plan is proposed to address the donor eligibility requirements

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

[1] For the scope of this solicitation, CIRM considers gene therapy to mean a human therapeutic intervention intended to: 1) alter the genomic sequence of cells or 2) alter the cellular lineage via gene delivery (i.e., direct lineage reprogramming). The intervention may include strategies to repair a disease-causing gene sequence, remove or inactivate a disease-causing gene, introduce new or modified genes that augment the therapeutic potential of the target cells.

The project team must include a Project Manager who has experience in managing development programs and who is able to devote at least 35 percent effort to the project. This 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 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-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.

(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, or 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:

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.

On what activities can 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.

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	Specific dates and times will be posted on the CIRM website
Grants Working Group (GWG) Review	Approximately 2-3 months post submission
ICOC Review and Approval	Approximately 3-4 months post submission
Award Start	Must start within ~~3~~2 months of award approval

TRAN 2: TRANSLATION STAGE PARTNERING OPPORTUNITY for DIAGNOSTICS

OBJECTIVE

The objective of this funding opportunity is to enable completion of early stage development activities for diagnostics for patient screening, risk stratification, diagnosis, treatment selection or monitoring that are based on stem cells or critical for stem cell based therapy development or use. CIRM expects projects under this program to advance rapidly and to be accomplished within 24 months and must be adequately justified.

For projects that are developing a diagnostic (including medical imaging agents) for multi-site use, the **expected outcome** is to conduct a well-prepared Pre-Investigational Device Exemption (Pre-IDE) or comparable Pre- Submission meeting* or a Pre-IND meeting resulting in correspondence from the FDA indicating agreement with 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** is to complete activities to achieve acceptance of a well-prepared analytical validation/verification report and clinical validation plan that meets requirements under CLIA (Clinical Laboratory Improvement Amendments) to enable diagnostic test launch.

*(http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf)

AWARD INFORMATION

What is the CIRM project funding and project term?

- CIRM will fund direct project costs of up to $1.2M per award. Project costs must be well justified.
- The project period is up to 24 months and must be adequately justified.

What activities will CIRM support?

CIRM funds will support the following activities under this opportunity:

- 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

- Development of design verification and validation protocols and 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 Pre-IDE (or other Pre-Submission) or a Pre-IND meeting(s) with the FDA (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf)

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

- 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
- Biomarker, technology discovery, candidate test discovery

How will applications be reviewed?

Should the demand for TRAN Awards exceed the capacity of a Grants Working Group (GWG) review session, members of the GWG will review applications in two stages. In the first stage, GWG members will conduct a pre-review of applications (called "Positive Selection", see Appendix) to advance a subset of applications to the second stage, which will involve a full review by the GWG.

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.

Addressing the Needs of Underserved Communities 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 and gender 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).

The GWG and CIRM's governing board will consider these statements in their evaluations and 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 strongly encourages 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 encouraged 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.

How will funds be awarded?

CIRM will disburse funds pursuant to a Notice of Award. Except for the first payment issued upon initiation of an award, payments will be disbursed semi-annually or at CIRM's option. Continued funding is contingent upon timely progress, as outlined in the project milestones and timeline established under the Notice of Award, and, when applicable, the on-going ability of the applicant to fund its operations and to satisfy its co-funding commitment (see below).

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 candidate.

CIRM will support studies on a candidate diagnostic test 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) under CLIA:

- Where human stem, progenitor or directly reprogrammed cells either are a necessary component of the test or are used to manufacture the test OR
- Where the diagnostic test 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 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 diagnostic for stem cell based therapy development or use.

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

Proof of concept studies with a prototype test (technology, biomarker(s)) 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.

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

The project team must include a Project Manager who has experience in managing development programs and who is able to devote at least 35 percent effort to the project. This 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 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-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.

(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, or 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:

   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.

<u>On what activities can funds be spent?</u>

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.

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	Specific dates and times will be posted on the CIRM website
Grants Working Group (GWG) Review	Approximately 2-3 months post submission
ICOC Review and Approval	Approximately 3-4 months post submission
Award Start	Must start within ~~3~~2 months of award approval

TRAN 3: TRANSLATION STAGE PARTNERING OPPORTUNITY for MEDICAL DEVICES

OBJECTIVE

The objective of this funding opportunity is to 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 and approval for marketing either under a Premarket Notification 510(k), a Premarket Approval (PMA) or within a Biologics License Application (BLA). CIRM expects projects under this program to advance rapidly and to be accomplished within 24 months and must be adequately justified.

For projects that are developing a significant risk medical device that is new or not approved for a given use where clinical trials are required, the **expected outcome** is the conduct a well-prepared Pre-Investigational Device Exemption (Pre-IDE) meeting with the FDA resulting in correspondence from the FDA confirming agreement with the IDE-enabling preclinical plan.

For projects that are developing a non-significant risk or Class II medical device that is new or not approved for a given use, the **expected outcome** is the conduct a well-prepared Pre-Submission* meeting with the FDA resulting in correspondence from the FDA indicating agreement on the Clinical Plan and Intended Use to enable filing for clearance/approval to market under a 510(k) or a PMA.

*(http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf)

AWARD INFORMATION

What is the CIRM project funding and project term?

- CIRM will fund direct project costs of up to $2M per award. Project costs must be well justified.
- The project period is up to 24 months and must be adequately justified.

What activities will CIRM support?

CIRM funds will support the following activities under this opportunity:

- 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
- Development of design verification and validation protocols and testing
- 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 Pre-IDE (or other Pre-Submission) meeting(s) with the FDA (http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf)

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

- 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
- Technology discovery, device discovery

How will applications be reviewed?

Should the demand for TRAN Awards exceed the capacity of a Grants Working Group (GWG) review session, members of the GWG will review applications in two stages. In the first stage, GWG members will conduct a pre-review of applications (called "Positive Selection", see Appendix) to advance a subset of applications to the second stage, which will involve a full review by the GWG.

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.

Addressing the Needs of Underserved Communities 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 and gender 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).

The GWG and CIRM's governing board will consider these statements in their evaluations and 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 strongly encourages 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 encouraged 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.

How will funds be awarded?

CIRM will disburse funds pursuant to a Notice of Award. Except for the first payment issued upon initiation of an award, payments will be disbursed semi-annually or at CIRM's option. Continued funding is contingent upon timely progress, as outlined in the project milestones and timeline established under the Notice of Award, and, when applicable, the on-going ability of the applicant to fund its operations and to satisfy its co-funding commitment (see below).

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 candidate.

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;
- 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 MOA requires the recruitment or incorporation of an endogenous human stem or progenitor cell.

(3) The 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.

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

The project team must include a Project Manager who has experience in managing development programs and who is able to devote at least 35 percent effort to the project. This 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 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-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.

(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, or 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:

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.

<u>On what activities can funds be spent?</u>

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.

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	Specific dates and times will be posted on the CIRM website
Grants Working Group (GWG) Review	Approximately 2-3 months post submission
ICOC Review and Approval	Approximately 3-4 months post submission
Award Start	Must start within ~~3~~2 months of award approval

TRAN 4: TRANSLATION STAGE FUNDING OPPORTUNITY for TOOL EARLY DEVELOPMENT AWARDS

OBJECTIVE

The objective of this funding opportunity is to drive 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). CIRM expects projects under this program to advance rapidly and to be accomplished within 24 months and must be adequately justified.

For projects that are developing a novel tool for commercialization, the **expected outcome** is to achieve a tool that consistently, robustly and effectively meets performance characteristics required to address the bottleneck and that is ready to be transferred to manufacturing.

AWARD INFORMATION

What is the CIRM project funding and project term?

- CIRM will fund direct project costs of up to $1M per award. Project costs must be well justified.
- The project period is up to 24 months and must be adequately justified.

What activities will CIRM support?

CIRM funds will support the following activities under this opportunity:

- 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
- 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

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

- 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
- Technology discovery, tool discovery

How will applications be reviewed?

Should the demand for TRAN Awards exceed the capacity of a Grants Working Group (GWG) review session, members of the GWG will review applications in two stages. In the first stage, GWG members will conduct a pre-review of applications (called "Positive Selection", see Appendix) to advance a subset of applications to the second stage, which will involve a full review by the GWG.

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.

Addressing the Needs of Underserved Communities 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 and gender 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).

The GWG and CIRM's governing board will consider these statements in their evaluations and 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 strongly encourages 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 encouraged 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.

How will funds be awarded?

CIRM will disburse funds pursuant to a Notice of Award. Except for the first payment issued upon initiation of an award, payments will be disbursed semi-annually or at CIRM's option. Continued funding is contingent upon timely progress, as outlined in the project milestones and timeline established under the Notice of Award, and, when applicable, the on-going ability of the applicant to fund its operations and to satisfy its co-funding commitment (see below).

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 candidate.

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 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.

(3) The 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.

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

The project team must include a Project Manager who has experience in managing development programs and who is able to devote at least 35 percent effort to the project.

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

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REQUESTED FUNDING ALLOCATION

CIRM will request funding for this program from the Board on an annual basis as part of the Board's consideration of CIRM's annual research budget.

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

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 proposes making use of the two stage streamlined process for high volume application review proposed for Discovery Stage Awards programs (see Appendix). This process requires delegation of Board Authority.

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.