RFA 14-02: Preclinical Development I Awards

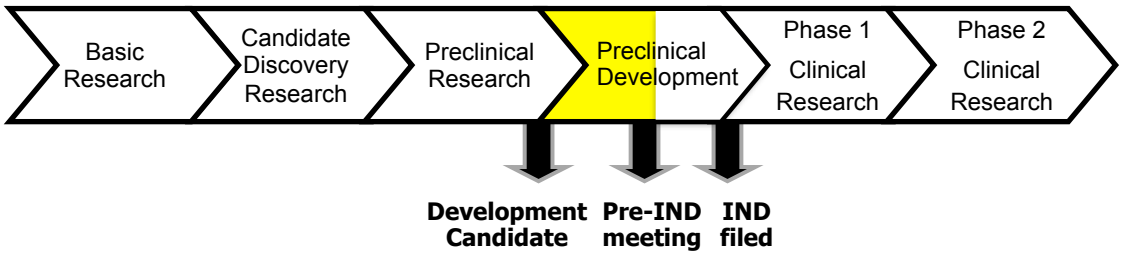
I. Purpose

In keeping with its mission to advance stem cell research and regenerative medicine for the discovery and development of cures and therapies for treatment of chronic disease or injury, CIRM has invested substantially in preclinical research projects to identify Development Candidates derived from or targeting stem cells, and in development projects to advance projects through to early phase clinical trials. This initiative specifically addresses a gap in funding between preclinical research and the activities essential to advance on a development pathway to a product. The purpose of the CIRM Preclinical Development Awards initiative is to fund early preclinical development activities for Development Candidates (DCs) derived from or targeting stem cells that have compelling and reproducible efficacy in preclinical models of disease or injury, and that are sufficiently well characterized to be ready for the transition from preclinical research to preclinical development. Funding will be provided for the most promising, competitive and successful Development Candidates that CIRM has already invested in at the preclinical research stage, as well as for compelling new projects that are co-funded with matching funds. Competitive projects will have the potential to address unmet medical needs or to significantly improve upon existing therapeutic options for persons with disease or injury. Recipients of these awards will carry out the preclinical activities needed to inform and support the conduct of a well-prepared pre-IND meeting with the Food and Drug Administration (FDA), in which readiness to initiate IND-enabling pivotal studies should be demonstrated. Projects that successfully complete the early development activities funded by this initiative, including the conduct of a pre-IND FDA meeting to obtain regulatory agency advice, will be better positioned to obtain further development funding for pivotal IND-enabling studies and Phase 1 clinical trials.

II. Objectives and Scope

The objective of a Preclinical Development I award will be to carry out all activities needed to conduct, within 30 months, a well-prepared pre-IND meeting with the FDA in which readiness to initiate pivotal IND-enabling safety studies using the product manufactured according to current Good Manufacturing Practice (cGMP) is demonstrated. In preparation for their meeting with the FDA, awardees will prepare a pre-IND meeting briefing package describing preclinical efficacy and safety studies,

the GMP manufacturing protocol and associated assays, as well as a draft synopsis of the proposed Phase 1 clinical trial protocol. At the end of the award period, the awardee successfully utilizing these funds, based on the completed activities and the interactions with the FDA, including the pre-IND meeting and formal minutes thereof, should have the proposed Development Candidate that is ready for pivotal IND-enabling studies. The scope of the award is illustrated in the figure below:



The award will fund activities including, but not limited to:

- If applicable, generation of Master Cell Bank and Working Cell Banks compliant with cGMP.
- Development and qualification of a cGMP-compliant manufacturing process at a scale to effectively support manufacture of the DC for pivotal IND-enabling studies and Phase 1 trials.
- Development and qualification of in-process and release assays for identity, purity, immunogenicity (where applicable), stability and activity (potency) of the DC.
- Development of assays for monitoring therapeutic activity in the clinic (i.e., biomarker assays).
- Optimization of effective dose range, dosing regimen and route of administration in appropriate animal models.
- Completion of non-clinical studies (excluding pivotal IND enabling non-clinical studies) to further assess pharmacology, product fate/distribution or pharmacokinetics, safety (immunogenicity) and mechanism-of-action.
- Finalization of target indication and development of a clinical plan, including a clinical protocol synopsis and draft protocol, for a Phase 1 trial.
- Preparation of a draft Development Plan through End-of Phase 2.
- Preparation for and conduct of key regulatory meetings including pre-pre-IND and a pre-IND meeting with the FDA.

Activities that fall outside of the scope of this RFA include the following examples:

- Early research and translation activities focused on selection of a Development Candidate.
- Pivotal IND-enabling Good Laboratory Practice (GLP) safety and tumorigenicity studies.
- cGMP production for clinical studies.
- Clinical studies.
- Development and qualification of a medical device for the delivery of a

product other than the product proposed for the funded project.

Priority will be given to eligible proposals that:

- Propose cell therapies, especially cell therapies that are differentiated derivatives of pluripotent stem cells or directly reprogrammed cells.
- Address potentially transformative, rather than incremental, regenerative approaches to unmet medical needs.
- Have at least 25% co-funding from any source of funding external to CIRM *and* are projects in which the Development Candidate was identified using prior CIRM funding.
- Have the required one to one matching co-funding from industry, where the Development Candidate was not identified using prior CIRM funding.

III. Award Information

A. Award

Under this Request for Applications (RFA), CIRM intends to commit up to $40 million for the support of about five to eight awards. Projects will be funded for up to 30 months, with total project costs of $5 - $8 million. Justifiable costs include direct project costs, facilities costs and indirect costs. In exceptional circumstances, there is the potential to increase the award up to $10 million per application, if fully justified and if the Grants Working Group agrees that it is warranted. All applications must include a fully justified, detailed, activity-based budget.

B. Co-Funding

For projects in which the proposed Development Candidate was not identified with support of prior CIRM funding, CIRM will require that matching funding be provided by the applicant. Applicants must match 100% of the total CIRM funding requested (i.e. one to one match). The matching funds may come from the applicant, from an industry partner, or from another funding source arranged by the applicant, and may be provided in the form of capital or justifiable in-kind services. CIRM will prioritize projects where the matching co-funding comes from industry. In their proposal, applicants will be required to address the status and sources of co-funding, and in the activity-based budget, identify those activities that CIRM will fund and those that the applicant will fund.

CIRM also encourages matching co-funding for projects in which the proposed Development Candidate was identified with prior CIRM funding. Because the ability to recruit external funding is an indicator that a project may be particularly promising, CIRM will prioritize projects that have received prior CIRM funding and which are able to demonstrate co-funding equivalent to at least 25% of the amount requested from CIRM.

C. Budgets, Milestones and CIRM Oversight

For all RFA14-02 awards, CIRM reserves the right to negotiate funded project activities, milestones (both scientific and financial), success criteria, timelines and budgets prior to issuance of the Notice of Grant Award (NGA) or Notice of Loan Award (NLA). In addition, CIRM will work with the Principal Investigator (PI) to ensure that the team includes the necessary project management expertise, and reserves the right to approve the selection of a project manager. Progress in translational research is important to CIRM. Continued funding is contingent upon timely progress, as outlined in the project milestones and timeline established under the NGA or NLA, and, when applicable, the on-going ability of the applicant to fund its operations and to satisfy its co-funding commitment; continued funding decisions will also take into consideration competitiveness of the candidate therapy and the feasibility of subsequent development. In the event that either agreed-to milestones are not achieved or there are significant changes in the competitive landscape or feasibility of the development program, CIRM reserves the right to terminate the project or to negotiate new milestones to refocus or redirect the project.

The Grants Administration Policy (GAP; see Section XII.A) requires that the grant or loan recipient submit annual Progress Reports to CIRM. In addition, communication and reporting responsibilities of the grant or loan recipient to CIRM will include: 1) quarterly updates; 2) routine communication by the PI or Project Manager; 3) discussion with CIRM's Clinical Development Advisory Panel (CDAP) at key decision points; 4) receipt of key regulatory documentation such as the pre-pre-IND and pre-IND briefing packages, informal correspondence and formal minutes from agency meetings or other key agency correspondence and 5) participation of CIRM representatives as observers in key regulatory meetings.

D. Contracts

For compliance with CIRM's policies and regulations and the advancement of its mission, CIRM has the option to review contracts and agreements that it deems critical to the success of the project, including, but not limited to, those with Contract Research Organizations (CROs) or Contract Manufacturing Organizations (CMOs). Upon request, the awardee will be required to provide such documentation.

E. Commencement/Closure/Other CIRM Awards

Given the urgency of CIRM's mission, all approved applications must be initiated (grant start date in issued and signed Notice of Grant Award) within 6 months of approval and authorization for funding by the Application Review Subcommittee of the ICOC, unless CIRM's President grants an extension based upon compelling justification of the need for additional time. Similarly, as timely progress on funded projects is important to CIRM, CIRM will not automatically approve requests for No-Cost Extensions (NCE). Requests for a NCE must be well justified in order to be approved. In the case of awards to applicants that already have a CIRM award, any

funding disbursed to the applicant under this RFA will be for activities not funded by the already existing award.

IV. Award Mechanism

CIRM expects to fund approved proposals through grants or loans. RFA 14-02 awards to non-profit organizations will be in the form of a grant. For-profit applicants may choose to accept the award in the form of a grant or a loan.

Grants under this RFA are funded through quarterly or semi-annual disbursements (at CIRM's option) and are subject to the revenue sharing provisions in CIRM's regulations (Intellectual Property and Revenue Sharing Requirements for Non-Profit and For-Profit Grantees (17 Cal. Code Regs. § 100600 et seq.)

Loan recipients shall be governed by the CIRM Loan Administration Policy (LAP) that is in effect as of the date of the execution of the NLA (17 Cal. Code Regs. § 100800 et seq.). Approved applicants who accept a loan will pay for loan administration costs and the costs of CIRM's due diligence review out of funds included in the award. Loan applicants will be required to submit financial information in connection with CIRM's due diligence.

The terms of the Loan are set forth in detail in Appendix A. For additional information on the loan program, consult the CIRM LAP, available at: http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants.

V. Eligibility

A. Project Eligibility

1. Funding: The Development Candidate that is the subject of the proposal may have been identified in prior CIRM-funded research (e.g., from a CIRM Early Translational Research Award), or may have been identified using non-CIRM funding. For projects in which the Development Candidate was identified with non-CIRM funding, CIRM will require matching (one to one) co-funding for the current proposal; matching funding from industry gives priority status. For projects in which the Development Candidate was identified with CIRM funding, co-funding at any level is encouraged and co-funding of at least 25% the amount requested from CIRM gives priority status.

2. Development Candidate: All projects must be focused on a single, defined Development Candidate derived from or targeting stem cells. The following types of candidates are eligible for this award:
   - A cell therapy derived from pluripotent stem cells or directly reprogrammed cells (autologous or allogeneic).

- Allogeneic tissue-derived stem or progenitor cells for repair or regeneration.
- Autologous tissue-derived stem or progenitor cells for repair or regeneration, excluding unmodified hematopoietic stem cells (HSC). Mesenchymal Stem (or Stromal) Cells (MSC) must be genetically modified or be part of a therapeutic device to be eligible.
- Engineered tissues with a cellular component derived from stem cells for transplantation.
- Genetically or pharmacologically modified stem cells (includes autologous or allogeneic approaches).
- A small molecule or biologic convincingly demonstrated to target normal endogenous stem cells *in vivo* as the primary mechanism of action (MOA) for repair or regeneration.
- A small molecule or biologic convincingly demonstrated to target cancer stem cells *in vivo* as the primary mechanism of action (MOA). *Development Candidates in this category must have been identified as part of a prior CIRM-funded project*.

Development Candidates that fall outside the scope of this RFA include the following:

- Unmodified HSCs.
- Autologous MSC that aren't genetically modified or part of a therapeutic device.
- Small molecules or biologics identified using stem or progenitor cells (e.g. using iPSC-derived cells), but which do not target a stem or progenitor cell population either ex vivo or *in vivo*.
- New indications for Development Candidates that have already received preclinical or clinical development funding from CIRM (e.g. from Disease Team or Strategic Partnership RFAs).
- Modifications of therapeutic candidates already funded by CIRM Disease Team or Strategic Partnership Awards.
- Minimally manipulated bone marrow or minimally manipulated cord blood.

3. Readiness: This Initiative is intended to fund projects in which a single Development Candidate has been identified. The Development Candidate must meet the following criteria:
   - For cell therapeutic candidates, compatibility with applicable regulatory requirements (e.g. Good Tissue Practice (GTP) and GMP) to allow rapid progression into preclinical development. (For example, for a cell therapeutic, the cell line may need to meet donor eligibility requirements (http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm073964.htm) and the reagents used in its development and maintenance should be appropriately sourced and adequately documented).

- Convincing, reproducible disease modifying activity has been demonstrated with applicable controls in one or more disease-relevant preclinical model(s), and/or clinically with an analogous product.
- Preliminary preclinical assessments to evaluate dose and safety (e.g. overt toxicity, immunogenicity and/or genomic integrity, if applicable) have been conducted.
- Preliminary mechanism of action studies have been conducted.
- Research assays have been developed to characterize the candidate (e.g., for identity, purity and activity).
- Methods have been developed for reproducible and scalable research grade production of the candidate (including viral vector, if applicable) at purity, yields and scale adequate to support preclinical research studies.
- Drug administration mode and method of delivery has been selected or is under development.

B. Institutional Eligibility

Both non-profit and for-profit organizations may apply. At the time of the letter of intent (LOI) deadline, the applicant organization must be located in California (that is, the organization must have employees who are conducting business or operations at a location in California). At the time of funding, the applicant organization must be conducting or managing research that is taking place in California. If these requirements are not met, CIRM may terminate all further action on the application.

Non-profit and for-profit institutions sponsoring Co-Principal Investigators (Section VII.B, Co-Principal Investigators) are subject to the same eligibility requirements as applicant institutions.

“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.
“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”.

CIRM encourages collaborative endeavors between non-profit and for-profit organizations.

C. Principal Investigator (PI) and Co-Principal Investigator (Co-PI) Eligibility

CIRM requires that a single PI and a single applicant organization (the PI’s organization) be designated in each application. The PI is the designated point of contact for CIRM and is the person responsible and accountable to CIRM for scientific performance on the project. A PI may submit only one application under

this RFA. The applicant organization is the designated contact institution for all financial and other administrative considerations.

CIRM recognizes that when a project moves from research into development, the expertise to lead the development project may not be the same expertise that successfully led the research project. For this reason, CIRM does not require that the PI who led the translational research to identify the Development Candidate also be the PI for the Preclinical Development project. However, CIRM does expect that the research project PI will be part of the Preclinical Development project team.

In order to encourage multidisciplinary team-based research, CIRM will allow for a single CIRM-funded Co-Principal Investigator (Co-PI) to be designated. However, designating a Co-PI is not a requirement. The decision of whether to include a Co-PI (or a Partner PI funded by a CFP, see Section VI) should be guided by the scientific goals of the project. The Co-PI role is most appropriate for leading a substantive and critical portion of the proposed project that is supported by a dedicated budget. All applications will require a leadership plan. When considering a Co-PI, please be aware that the reviewers will consider the structure and governance of the development team as well as the knowledge, skills and experience of the individual PI and Co-PI.

The PI (and Co-PI or Partner PI, when applicable) must each have an M.D., Ph.D. or equivalent degree, and must be authorized by the applicant institution to conduct the proposed research in California. By the LOI deadline, the PI and Co-PI must each:

- Be an independent investigator in California at a non-profit applicant institution, or have an equivalent position and be an employee in California (at least 50-percent time) of a for-profit applicant institution.
- Have documented authority from the applicant institution to staff the proposed project.
- Have documented commitment from the applicant institution to provide laboratory space and shared resources sufficient to carry out the proposed research.

In order to ensure effective leadership of this development stage program, an investigator may participate as a PI or a Co-PI on no more than two active CIRM Preclinical Development, Disease Team, Disease Team Therapy Development, Strategic Partnership, or Early Translational Development Candidate awards as of the funding start date for a Preclinical Development Award I.

In addition, this RFA is not open to investigators as a PI or Co-PI who are already a PI or Co-PI on three or more active CIRM awards as of November 3, 2014, the deadline for submission of the full application. The limit includes all CIRM awards that have been approved but not yet closed out, with the exception of the following CIRM RFAs/PAs: Shared Research Labs, Major Facilities, Research Training Awards II, Bridges to Stem Cell Research, Tissue Collection for Disease Modeling Awards, hiPSC Derivation Award, hPSC Repository Award or Conference Grants.

D. Project Manager Eligibility

CIRM requires a project management professional (Project Manager) be designated in each RFA 14-02 Award application. The Project Manager must have relevant experience in managing preclinical development programs and must be able to devote an appropriate (≥50%) percentage effort, in California, to the project.

E. Percent Effort Requirements

CIRM, mindful of the urgency of its mission, will only fund PIs and Co-PIs who are willing to devote substantial, focused attention to the project. For this RFA, PIs must be willing and able to commit a minimum 30% effort, 20% for Co-PIs.

F. Extraordinary Exceptions

In extraordinary circumstances, the President has the discretion to permit exceptions to requirements or limitations in Section V of this RFA. The exercise of such discretion will be only in exceptional cases where the applicant has demonstrated that such an exemption would preserve an important research opportunity or make a critical contribution to one of CIRM's mission objectives. Exceptions must further the objectives of this RFA and must comply with the requirements of Proposition 71 and all applicable California state regulations, including the Grants Administration Policy (see Section XII.A of this RFA) and the Loan Administration Policy (see Appendix A of this RFA), or they will not be considered.

If CIRM determines that an application does not meet the eligibility requirements, CIRM may terminate all further action on the application. Applicants who will need an exception must request it at least 14 days before the LOI deadline or at least 30 days before the relevant application deadline. To request an exception, or for assistance in determining whether one is necessary, contact the CIRM staff listed in Section XI.

VI. Collaborative Funding Partners

CIRM has established a program with other agencies that fund stem cell and regenerative medicine research. Through this Collaborative Funding Partner (CFP) program, California-based Principal Investigators (PIs) can collaborate with a Funding Partner PI ("Partner PI") from a Funding Partner applicant institution ("partner applicant institution") eligible for funding from one of CIRM's CFPs to bring important additional resources to the project. If a collaboratively funded proposal is approved (a "CIRM/CFP Award") CIRM will fund all project work done within the State of California and the CFP will fund all project work within its jurisdiction.

For projects in which the proposed Development Candidate was identified with support of prior funding from CIRM and a Collaborative Funding Partner, CIRM will

work with the CFP to determine whether collaborative funding can be made available for preclinical development. Please contact CIRM before the LOI deadline (June 5, 2014) to discuss funding for established collaborations.

To apply for a collaboratively funded project involving CIRM and a CFP, applicants must satisfy both the CIRM requirements and any additional requirements established by the CFP.

Before funding contracts are signed, successful CIRM/CFP applicant teams must have a signed written agreement adequately addressing Intellectual Property (IP) issues relating to the collaborative project and must provide copies to CIRM and the CFP. These IP Agreements will be reviewed by both CIRM and the CFP to ensure that they are consistent with applicable regulations of CIRM and the CFP and with the Agreement between the co-funders.

Before funding contracts are signed, successful CIRM/CFP applicant teams must obtain all necessary approvals for animal protection, human subject protection, and use of human embryonic stem cells, unless the approval is not required to initiate the award. CIRM and the CFP will monitor compliance with approval procedures required in their respective jurisdictions.

Both CIRM and the CFP may be involved in the management/oversight of the CIRM/CFP Award, by participating in mutually agreed upon joint award administration activities. These activities may include but are not limited to participation in progress monitoring via progress reports and discussion with a Clinical Development Advisory Panel (CDAP) prior to, and in preparation for, the pre-IND meeting with the FDA.

Disclosure Information

All applicants, including those not applying with a Partner PI, are hereby notified that CIRM may share Preliminary Applications, full Applications and related information submitted by applicants with a CFP in order to facilitate their participation in this RFA. Information concerning approved CIRM/CFP Awards may also be shared with a CFP. Before receiving any such material, the CFP will agree in writing to hold the materials in strict confidence and to use them solely for purposes directly related to this RFA.

VII. Application and Evaluation Process

Submission of an application for a Preclinical Development Award I involves a two-step process. An eligible applicant (see Section V for eligibility criteria) must first submit a Letter of Intent (LOI). In the second step of the process, eligible applicants will submit a full application. Applications will only be accepted from applicants who meet all eligibility requirements and have submitted an LOI that was accepted by CIRM. Applicants will be notified by June 17, 2014 if their LOI is NOT accepted. **The**

research project, PI and Co-PI (if applicable) proposed in the full Application must be the same as that described in the LOI.

Full Applications will be evaluated by the CIRM Grants Working Group (GWG), which is composed of fifteen scientific experts from outside California, seven patient advocate members of CIRM's Governing Board, and the Chair of the Governing Board. The list of scientific members who may participate in the GWG review can be found at http://www.cirm.ca.gov/WorkingGroup_GrantsReview. The composition of the ICOC can be viewed at http://www.cirm.ca.gov/GoverningBoard.

The fifteen participating scientists on the GWG will review the applications and score them according to scientific and technical merit applying the review criteria described in Section VIII below. The entire GWG will make funding recommendations based on scientific merit. The Board's Application Review Subcommittee will make funding decisions based on the GWG recommendations, any staff recommendations and a programmatic review.

CIRM's confidentiality and conflict screening rules will apply to everyone who will have access to applications or who will attend the review meeting, including CIRM staff, external reviewers, representatives of Collaborative Funding Partner Agencies and members of the CDAP. (Per Gov. Code §6254.5(e), non-public records may be disclosed to government agencies under confidentiality agreements.) The policies, procedures and laws that address confidentiality of records submitted to CIRM are described in Section XIII.

VIII. Review Criteria

Full applications for RFA 14-02 will be evaluated for scientific merit by the GWG in five key areas: 1) Significance and Impact; 2) Scientific Rationale and Preclinical Development Readiness; 3) Design and Feasibility; 4) Principal Investigator, Development Team and Leadership Plan; and 5) Quality of Collaborations, Assets, Resources and Environment. The specific criteria for review of applications are based on the standard review criteria described in the CIRM GAP: http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants#GAP.

The GWG will be asked to give special consideration to CIRM's priorities for this RFA, which are the following:

- Cell therapies, especially cell therapies that are differentiated derivatives of pluripotent stem cells or directly reprogrammed cells.
- Potentially transformative, rather than incremental, regenerative approaches to unmet medical needs.
- Have at least 25% co-funding from any source of funding external to CIRM *and* are projects in which the Development Candidate was identified using prior CIRM funding.

- Have the required one to one matching co-funding from industry, where the Development Candidate was not identified using prior CIRM funding.

Reviewers will evaluate the applications for the following criteria:

A. Significance and Impact

1. Target Product Profile: The target product profile (TPP) conveys the long-term aspirational product attributes and overall intent of the development program and contains metrics for key attributes to enable decision-making.

2. Competitiveness and Impact: The proposed therapeutic candidate could have a significant impact on standard-of-care management of the target disease or injury and it could offer advantages over current therapies on the market or in late stage development. The proposed project could significantly advance the field of stem cell-based regenerative medicine.

3. Responsiveness: The project is relevant to stem cell-based regenerative medicine; the evidence that the therapeutic has a stem cell connection is strong and compelling. The proposed activities are within scope as defined in Section II. The proposed project meets the priority criteria described above.

B. Scientific Rationale and Preclinical Development Readiness

1. Scientific Rationale: There is a strong scientific rationale for the proposed therapeutic intervention in the target disease or injury. Based on the preclinical data, there is a reasonable expectation that the proposed therapeutic approach could have a meaningful clinical benefit for patients.

2. Readiness: The data presented are sufficient and compelling enough to indicate that the proposed Development Candidate is ready to enter preclinical development, based on the following criteria (see Section V.A.3 for more detail):

    - Compatible with GTP and GMP regulatory requirements (for cell therapeutic candidates).
    - Convincing, reproducible disease modifying activity in preclinical models and/or clinically with an analogous product.
    - Preliminary data assessing overt toxicity, tumorigenicity and immunogenicity (where applicable).
    - Preliminary data assessing mechanism of action.
    - Research grade assays developed to characterize the candidate (identity, purity, activity).
    - Methods developed for reproducible and scalable research grade production of the candidate.

- Drug administration mode and method of delivery selected or under development.

C. Design and Feasibility

1. Design and Feasibility of the Project Plan and Timeline: The Project Plan describes the scope of work that will be conducted during the award period and includes all activities necessary to prepare for pivotal IND-enabling studies using the GMP manufactured product, including conduct of a pre-IND meeting and receipt of formal minutes from the FDA (see Section II for a description of in-scope activities). It is feasible to conduct the proposed activities as described and the project timeline is realistic and achievable.

2. Regulatory status: If a pre-pre-IND meeting has already been held, the major issues raised during the meeting have been or are being addressed.

3. Draft Clinical Trial Synopsis: The draft of the proposed study is reasonable and could achieve the objective of evaluating both preliminary safety and assessing measures of biological activity and efficacy in humans. The trial is designed to test or elucidate mechanism(s) of action of the therapeutic such that, regardless of clinical outcome, meaningful information will be gained. The choice of patient population is appropriate

4. Milestones: The project milestones capture key activities and are reliable indicators of the project's progress. The criteria for Go/No Go decisions are adequately defined and provide quantifiable measures of the project's performance.

5. Budget: The proposed budget, both overall and for key activities, is focused, adequate to cover the cost of the project and well justified. For applications that include co-funding, the activities that CIRM will fund and those that the applicant and/or its partner will fund are clearly identified. There is supportive evidence that the funds will be available to the project.

D. Principal Investigator, Development Team and Leadership Plan

Reviewers will assess the proposed project with respect to the following:

1. Expertise and Track Record of PI (Co-PI and Partner PI, if applicable): The PI has relevant experience in preclinical development, has demonstrated successful leadership experience, and will play a key role in the proposed project.

2. Expertise and Track Record of Project Manager: The Project Manager has demonstrated project management experience in preclinical development studies.

3. Development Team and Leadership Plan: An appropriate multidisciplinary team has been assembled to execute the project, including leads for key project functional areas (e.g. CMC, Preclinical, Regulatory and Clinical leads) in addition to the required Project Manager. The team leads have demonstrated expertise in their functional area. If CRO/CMOs are utilized, there is experience on the team at successfully managing these contracted activities.

   The PI has developed a leadership and communication plan that will ensure successful execution of the project. The plan includes methods for progress monitoring, project decision-making and conflict resolution.

E. Collaborations, Assets, Resources and Environment

1. Collaborations: Collaborations that are critical and integral to the success of the project are in place (including those with a Partner-PI and/or other co-funding partner, if applicable). Evidence is provided that the collaborator is committed to the proposed research

2. Assets: Critical assets (e.g. patent applications, patents, Material Transfer Agreements, or license agreements) that are necessary to enable development of the therapeutic candidate are either already in place or at an adequate stage of negotiation to enable and justify investment in the development and future clinical testing and commercialization of the proposed product (see Section IX.B.13).

3. Contract Services: The proposed CROs/CMOs/consultants have the experience and expertise necessary to successfully meet expectations, deliverables and timelines.

4. Resources and Environment: The necessary facilities, major equipment, and services are available for conducting the proposed research. The applicant institution (and Co-PI, sponsoring institution(s), and/or Partner PI applicant institutions, if applicable), are committed to supporting preclinical development work.

IX. Application Procedure

Applicants must follow these instructions for submission of a Letter of Intent (LOI), and a full Application for the Preclinical Development I Awards (RFA 14-02). Full applications will only be accepted from PIs who submit a Letter of Intent that is accepted by CIRM. Applicants will be notified if their LOI is NOT accepted. The PI and the project proposed in the application must be the same as those described in the LOI; otherwise, the application is deemed ineligible.

A. Letters of Intent

A PI may submit only a single LOI for this RFA using the forms and instructions provided in the Grants Management Portal at https://grants.cirm.ca.gov. The LOI should concisely describe the proposed project and explain how it will, within 30 months, achieve the objective of the RFA 14-02, which is to carry out all activities needed to conduct a well-prepared pre-IND meeting with the FDA in which readiness to initiate IND-enabling pivotal studies using the GMP manufactured product is demonstrated. In addition, applicants will be required to submit evidence that appropriate experiments have been done to demonstrate that the proposed Development Candidate meets the eligibility criteria described in Section V.A. Applicants who propose a project that is new to the CIRM pipeline must submit evidence that matching (one to one) co-funding has been or will be secured for the project. By the due date of the Letter of Intent, the applicant shall provide either (i) one or a combination of existing co-funding agreement(s) providing evidence for funding sufficient to meet the matching requirements, or (ii) in the event that such agreement(s) have not yet been entered into at the time of the LOI, then the applicant shall provide a letter or letters from the prospective co-funder(s) that indicate(s) that the parties are in process of negotiating an agreement in which the co-funder(s) will provide funding and/or in-kind services sufficient to match CIRM funding for the proposed project. CIRM's Application Review Subcommittee will not consider for funding any recommended applications unless funding agreements necessary to meet the applicant's matching requirements are executed prior to the Subcommittee's consideration of the Grants Working Group's recommendations.

The completed LOI must be submitted online using the CIRM Grants Management Portal at https://grants.cirm.ca.gov and must be received by CIRM no later than 5:00 PM (PDT) on June 05, 2014. No exceptions will be made.

B. Full Application Forms

Application forms will be available via the Grants Management Portal at https://grants.cirm.ca.gov in early June 2014.

The application for the CIRM Preclinical Development I Awards consists of up to six parts:

Application Part	Description	Required?
A	Application Information Form	Yes
B	Proposal	Yes
C	Biographical Sketches	Yes
D	Activity Based Budget	Yes
E	Licenses, Co-Funding and Material Transfer Agreements	Yes, if applicable
F	Regulatory Correspondence	Yes, if applicable

Part A: Application Information Form (Web-based form). Includes Abstract, Public Abstract, Statement of Benefit to California, Key Personnel, Budget, Budget Justification and Related Business Entities Disclosure (additional details in sections number 1- 6, below).

Part B: Preclinical Development I Awards Proposal (MS Word template) Includes Target Product Profile; Clinical Competitiveness and Impact; Scientific Rationale and Preclinical Development Readiness; Project Plan with Milestones and Timeline; a Draft Clinical Trial Synopsis; PI, Development Team and Leadership Plan; Collaborations, Assets, Resources and Environment; Intellectual Property, Licenses and Agreements; References (additional details in sections number 7-14, below).

Part C: Biographical Sketches for Key Personnel (MS Word template) **and letters of collaboration and/or institutional support**

Part D: Activity Based Budget (MS Excel template)

Part E: Licenses, Co-Funding Agreements and Material Transfer Agreements (MTAs).

Part F: Regulatory correspondence. Copies of any relevant regulatory correspondence, such as pre-pre-IND package and nonbinding comments from a pre-pre-IND meeting with the FDA, must be provided.

The full Application includes the following sections:

1. Abstract *(In four parts of up to 3000 characters in Part A)*
Part 1. Project Description: Describe the proposed Development Candidate and summarize the scientific rationale for the proposed intervention in the target disease or injury.

Part 2. Clinical Competitiveness and Impact: Describe the unmet medical need that the proposed therapy will address and explain how the proposed therapy

could improve patient care compared to other therapies either available or in development.

Part 3. Proposal Overview: Summarize the proposed preclinical development activities and how these will meet the stated the objective of the RFA, to complete preclinical development activities necessary to conduct a well-prepared pre-IND meeting with the FDA.

Part 4. Milestones: Summarize high-level milestones to be achieved within the 30-month award period.

2. Public Abstract *(up to 3000 characters in Part A)*
In lay language, briefly describe the proposed project and explain how the proposed stem cell-derived therapy will advance the treatment of disease or serious injury in humans. This Public Abstract will become public information and will be available online; do not include proprietary or confidential information or information that could identify the applicant and applicant organization or, if applicable, a co-funding partner.

3. Statement of Benefit to California *(up to 3000 characters in Part A)*
Describe in a few sentences how the proposed research will benefit the State of California and its citizens. This Statement of Benefit will become public information will be available online; therefore, do not include proprietary or confidential information or information that could identify applicant and/or partner (e.g., PI name, applicant institution name or location).

4. Key Personnel *(included in Part A and C)*
List all key personnel and their roles on the project in the relevant sections of Part A. Key personnel are defined as individuals who contribute to the scientific development or execution of the project in a substantive way, whether or not they receive salaries or compensation under the grant. Key personnel may include any staff, collaborators or consultants who meet this definition. Key personnel who are not part of the applicant organization should be listed in the subcontract section of the application. Personnel that are not key, such as technical support staff, may be supported by award funds but need not be named. A minimum of one percent effort is required for each key person, except the PI, who is required to commit a minimum of thirty percent (30%) effort, a Co-PI, if applicable, who is required to commit a minimum of twenty percent (20%) effort and the Project Manager, who is required to commit a minimum of fifty percent (50%) effort.

For each key person listed, provide a two-page biographical sketch using the template provided under Part C. The sketch should highlight prior relevant experience, accomplishments and/or special skills related to the proposed activities. Include relevant publications and/or patents or patent applications. The biosketches for the PI (and Co-PI and partner PI, where applicable) should

be provided first, followed by the biosketch of the Project Manager. Thereafter include all remaining biosketches in alphabetical order.

5. Budget *(included in Parts A and D)*
Provide all budget information requested in the budget section of Part A and in Part D. Specify and provide well-justified budgets for subcontracts and consultants in the appropriate section in Part A. In the activities-based budget spreadsheet (Part D), detail key activities and associated costs. Include costs proposed to be funded by CIRM through this award or through co-funding either by self-funding or through third parties. Clearly identify those activities that CIRM will fund and those that the applicant will fund. Proposed budgets should align with the sequence of when the activities will be conducted and must be well justified in the appropriate section of Part A.

For applications that designate a Co-PI, the PI and the Co-PI will each be responsible for an individual budget (comprised of CIRM Direct Project Costs, CIRM Direct Facilities Costs and CIRM Indirect Costs) for that portion of the total project performed under their authority. For CIRM/CFP collaborations, the funding requested from the CFP (total and per year requested, Part A) must be indicated and justified in sufficient detail (in the Part A section "Budget Justification") for reviewers to assess the appropriateness of the non-California research budget. For applications that include co-funding, address the status and sources of co-funding, and provide supportive evidence of commitment from the co-funder within the timelines set forth in Section IX.B (Part E)

All allowable costs for research funded by CIRM are detailed in the CIRM GAP (Section XII.A). For CIRM/CFP teams, allowable costs for research funded by the Collaborative Funding Partner may differ. Guidance will be provided separately by the individual CFP at such time as an eligible CFP has notified CIRM of their interest in participating.

Under this RFA, CIRM-funded allowable costs include the following:

- ***Salaries for Key Personnel and other Support Staff***
  Salaries for Key Personnel may include the Principal Investigator, co-Principal Investigator or Partner Investigator, Co-Investigators, Research Associates, and technical support staff, each of whom must perform the subject work in California, based on percent of full time effort commensurate with the established salary structure of the applicant institution. The total salary requested must be based on a full-time, 12-month staff appointment or the full time annual salary for employees of a for-profit institution. Institutions may request stipend, health insurance and allowable tuition and fees as costs for trainees. Administrative support salaries should be covered exclusively by allowed indirect costs.

- ***Supplies***

Grant funds will support supplies, including specialized reagents and animal costs. Minor equipment purchases (less than $5,000 per item) are considered supplies and may be included as direct costs in the budget.

• Travel
Recipients (PIs) of CIRM Preclinical Development I Award are encouraged to attend a CIRM-organized grantee meeting in California and will be required to attend at least one Clinical Development Advisory Panel (CDAP) meeting in San Francisco prior to the pre-IND meeting. Applicants should budget for one such meeting per year and include travel costs for this meeting in the budget. Travel costs associated with collaborations necessary to the grant are allowable. Details of allowable travel costs can be found in the GAP (see Section XII.A of this RFA).

• Equipment
Major equipment (more than $5,000 per item) necessary for conducting the proposed research at the applicant institution should be itemized and justified. Under this RFA, no more than 5% of total direct project costs can be used for equipment. Under special circumstances, with sufficient rationale, CIRM may allow a higher percentage of direct project costs for equipment. Equipment costs should not be included as allowable direct costs in indirect cost calculations.

• Consultants/Subcontracts
Grantees that subcontract CIRM-funded work should note that CIRM-funded research must generally be conducted in California. Examples of such research include study design; clinical protocol development; development of a GMP manufacturing process and qualified assays; analysis and interpretation of data; development of new methods.

Aside from small consulting contracts, Grantees may not use CIRM funds to contract for research to be performed outside of California. Consulting contracts for out-of-state research are limited to $15,000 per year for a single contract, and $25,000 per year in aggregate. (CIRM may allow modest increases to these limits in exceptional circumstances.)

For activities **other than research**, Grantees may subcontract outside California, but must make a good faith effort to use California suppliers for more than half of their contracts and purchases in accordance with CIRM's California Supplier regulation (Cal. Code Regs., tit. 17, § 100502). Examples of such activities include execution of a clinical trial according to a protocol, execution of a toxicology study performed according to an existing protocol, GMP production.

• Facilities Costs

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%. Facilities rates are applied to direct project costs exclusive of the costs of equipment, tuition and fees and subcontract amounts in excess of $25,000. Applicants may use lower Facilities rates, and use up to 100% of the awarded funds for direct research purposes. The Facilities cost rate budgeted is to be applied to the entire award project period.

• Indirect Costs

Indirect costs will be limited to ten percent for for-profit applicants, and to fifteen percent for non-profit applicants, 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, and subcontract amounts in excess of $25,000. Applicants may use lower indirect cost rates and use up to 100% of the awarded funds for direct research purposes. The Indirect cost rate budgeted is to be applied to the entire award project period.

6. Related Business Entities *(included in Part A)*

In order to comply with the Conflict of Interest policies under which CIRM operates, all applicants (including, if applicable, a Co-PI, a Funding Partner applicant institution, e.g., Partner PI and/or a co-funding company) must provide information on related business entities for any application that, if awarded, would fund a for-profit organization either as: 1) the applicant organization; 2) a subcontractor or 3) the employer of a Co-Investigator, consultant or subcontractor. If the application does not seek funding for any such for-profit organizations, indicate that in this section of the form. If for-profit funding is sought, include the following for each such for-profit organization to be funded:

- A list of any parent organization that owns 50% or more of the for-profit's voting shares;
- A list of all subsidiaries in which the for-profit owns 50% or more of the voting shares; and
- A list of all other related business entities (i.e., entities with which the for-profit shares management and control, or shares a controlling owner).

7. Target Product Profile *(up to 2 pages; use TPP template in Part B; also included as Sample B)*

Provide a target product profile (TPP) for the proposed therapeutic candidate. The TPP provides the aspirational attributes of the product to help define success and inform the proposed label. The TPP should articulate the overall intent of the therapeutic development program, and the studies proposed within this research proposal should be designed to collect data that will support the TPP. The TPP should provide the optimal profile (ideal) and the threshold profile (minimally acceptable to differentiate from current and future competing

products), and identify criteria (metrics) for key decisions in the development process. It is a comprehensive outline of product specifications with respect to safety, effectiveness, quality, clinical evaluation, non-clinical evaluation, regulatory requirements and commercial factors e.g., market advantage and target differentiation. The TPP is a dynamic document that should be continually refined as data evolves and will ultimately become the product label.

Using the CIRM TPP template in Part B of the application (see Sample B for the template), provide the desired attributes/claims of the therapeutic for the following: indication, target activity, patient profile, efficacy endpoints, safety/contraindications, dose/regimen, dosage form and route of delivery. The FDA released the draft guidance document "Guidance for Industry and Review Staff: Target Product Profile – A Strategic Development Process Tool" which may be a helpful resource for developing a TPP. It is available from the FDA's website (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080593.pdf). While this document was developed and issued by the FDA's Center for Drug Evaluation and Research (CDER), it contains many guiding principles that apply to developing a TPP for cell therapies and biological products, as well as to products regulated by CDER.

8. Clinical Competitiveness and Impact *(up to 1 page; in Part B)*
Describe the target patient population and summarize the current standard of care and competitive landscape for the target disease or injury. Describe how the proposed novel therapy could lead to a significant improvement in patient care compared to existing therapies or to other therapies currently in late-stage development. Explain how the proposed project will advance the field of stem cell-based or regenerative medicine.

9. Scientific Rationale and Preclinical Development Readiness *(up to 10 pages including the Summary Table; in Part B)*
Describe the scientific rationale for the proposed therapeutic intervention and the overall relevance of the project to stem cell based regenerative medicine. Summarize the body of evidence that the therapeutic candidate has a strong and compelling stem cell connection. Summarize the evidence demonstrating strong and reproducible efficacy of the therapeutic candidate in animal models of the target disease or related diseases, and provide key data. In addition, include a Preclinical Studies Summary Table (see Sample C) of all relevant preclinical (and where available, clinical) efficacy and safety studies carried out with the Development Candidate (*in vitro* and *in vivo*) and summarize major outcomes and findings.

Describe the potential benefits and risks of the proposed therapy and explain why the potential benefits outweigh the risks for treatment of the target disease or injury. Provide key data from preliminary pharmacology and safety studies listed in the Summary Table.

10. Project Plan, Milestones, and Timeline *(up to 8 pages plus 2 pages for milestones using provided template and 1 page for timeline, the latter in Gantt chart format or equivalent; in Part B)*

Project Plan**:** Describe the project plan and scope of activities proposed for funding under this award. Indicate activities to be conducted by the PI and, if applicable, by the Co-PI, Partner PI or a co-funding partner if contributing in-kind resources. Identify potential risks to the project and describe the mitigation strategies.

Milestones: Using the Milestone template provided in Part B of the application list the major project milestones by project year. Indicate Progress Milestones versus Go/No Go Milestones and include target completion dates and success criteria (an example of a milestone template is provided in Sample A). Milestones should include key tasks to be performed and success criteria with precise, quantifiable and objective measures of success.

Timeline: Provide a timeline for the proposed project that includes key Pre-Clinical, CMC, Regulatory and other critical path activities, as well as major milestones.

11. Draft Clinical Trial Synopsis *(up to 4 pages in Part B, using provided template)*

Use the Clinical Trial Synopsis Template to provide a draft synopsis for the Phase 1 study. A copy of this template is provided as Sample D of this RFA.

12. Principal Investigator (PI), Development Team and Leadership Plan *(up to 2 pages; in Part B)*

Summarize the relevant leadership and preclinical development experience of the PI and the Project Manager in preclinical development and leadership. List the key members of the team, their expertise and their roles. Describe the plan for oversight of CMOs/CROs. Indicate PI and, if applicable, Co-PI and Partner PI roles and responsibilities. Describe the leadership and communication plan including methods for progress monitoring, project decision-making and conflict resolution.

13. Collaborations, Assets, Resources and Environment *(up to 3 pages; in Part B)*

Provide a list of collaborations that will participate in the proposed project (includes development partner/consultants/CROs/CMOs), or plans for identification and contracting collaborations. Summarize their specific roles, expertise and experience and explain how their participation is integral to the success of the project.

Summarize the assets, know-how and expertise that the partner (Partner PI or Co-funder) will provide (if applicable). If consultants or subcontractors will provide

expertise or resources critical to the success of the project, summarize their credentials and relevant track records.

Provide a description of the facilities, environment(s), core services, and resources available for conducting the proposed project and discuss how the proposed project will benefit from unique features of these resources. Include a description of resources available for data storage and data management.

14. Intellectual Property, Licenses and Agreements (Parts B and E).
Describe intellectual property assets (patent applications, patents), including any challenges and pending litigation relating to same and any licenses or rights important to development of the therapeutic. Identify any intellectual property known to applicant that may restrict the applicant's freedom to operate.

Provide a brief summary describing the status of Material Transfer Agreements (MTAs) or licensing agreements for cell lines or other materials that are critical to the development of the therapeutic candidate and describing the role of those materials in the development of the product. In Part E, provide copies of relevant MTAs. If no MTAs or licensing agreements have been executed, provide term sheets or letters of intent. If that is not possible, summarize your progress to date in obtaining MTAs or licensing agreements.

For previously CIRM-funded projects that intend to have co-funding for this award, or for a project that has not been previously funded by CIRM and is subject to the co-funding requirement, the applicant shall provide the following if they did not provide a co-funding agreement at the time of the LOI:

i. A co-funding agreement, if available.
ii. If a co-funding agreement is not available as of the application due date (November 3, 2014), the applicant may submit a term sheet and/or letter of intent outlining terms of the co-funder(s) support, signed by the co-funder(s) which demonstrates the applicant's ability to meet the required co-funding under the terms of the agreement(s).
iii. If a term sheet and/or letter of intent is not available as of the application due date (November 3, 2014), the applicant must provide a letter from the co-funder(s) indicating continued interest in co-funding the proposed project and expected time frame for completing a term sheet.
iv. Applicants must submit a term sheet and/or letter of intent outlining terms of the co-funder(s) support, signed by the co-funder(s) a by the date that Supplemental Information must be filed (December 22, 2014) and a fully executed agreement must be provided by two weeks prior to the date of the ICOC/Application Review Subcommittee meeting to approve and authorize funding for the Preclinical Development projects under this RFA (Q1, 2015; exact date to be determined).

15. References *(up to 2 pages, in Part B)*
List all references used in the body of the proposal.

D. Full Application Submission Instructions

All applicable parts of the Preclinical Development I Awards application must be submitted together and received by CIRM no later than 5:00PM PDT on November 3, 2014 via the Grants Management Portal https://grants.cirm.ca.gov. It is the applicant's responsibility to meet this deadline; no exceptions will be made.

E. Submission of Supplemental Information

If necessary, the PI may submit limited supplemental materials that provide critical new information related to their research proposal after the application deadline but not later than 5:00pm PDT on December 22, 2014. Supplementary materials will not be accepted after this deadline. CIRM will accept a one-time-only submission of materials from the PI only if it meets the submission deadline and conforms to the requirements described herein. Accepted submissions will be forwarded to reviewers for their consideration.

The submission should be in the form of a one-page letter addressed to the Associate Director of Review and submitted via email to gsambrano@cirm.ca.gov. The body of the letter may not exceed 500 words and should briefly describe the type of information submitted and when the information became available. The following materials qualify for submissions of supplemental materials:

Within the one-page letter:

- Provide specific citation(s) to journal publications related to the proposed project that were published or accepted for publication since the application submission deadline. You may briefly describe the significance of the publication(s) to the proposal in the cover letter.
- Confirmation of funding secured from other sources.
- Regulatory meetings (e.g. pre-pre-IND) since the application submission deadline.
- Notice of patent application(s) filed, notice of allowance received or patent(s) issued, or notice of license(s) to relevant intellectual property (granted or received) since the application submission deadline.
- Identification of any challenges to relevant patents; updates to and pending litigation or newly initiated litigation.

The letter may not be used to describe any additional data or experiments. Changes in scope, experimental approach, or research design are not allowed.

X. Schedule of Deadlines and Reviews

Letters of Intent due	5:00 pm (PDT), Thursday, June 5,

	2014
Full Applications due	5:00 pm (PST), Monday, November 3, 2014
Review of full Applications by Grants Working Group (GWG)	Q1, 2015
Review and Approval by Application Review Subcommittee	Q2, 2015
Earliest Funding of Awards	Q2/Q3, 2015

XI. Contacts

For information about this RFA:

Lisa Kadyk, Ph.D.
Science Officer
California Institute for Regenerative Medicine
Email: lkadyk@cirm.ca.gov
Phone: (415) 396-9304

For information about the review process:

Gilberto R. Sambrano, Ph.D.
Associate Director, Review
California Institute for Regenerative Medicine
Email: gsambrano@cirm.ca.gov
Phone: (415) 396-9103

For information about Collaborative Funding Partnerships:

Ian K. Sweedler
Senior Counsel for International Programs
California Institute for Regenerative Medicine
Email: isweedler@cirm.ca.gov
Phone: (415) 396-9122

XII. CIRM Regulations

Grant awards made through RFA 14-02 will be subject to CIRM regulations. These regulations can be found on CIRM's website at http://www.cirm.ca.gov/reg/default.asp.

A. CIRM Grants Administration Policy

CIRM's Grants Administration Policy (GAP) for Academic and Non-Profit Institutions (Non-Profit GAP) and the GAP for For-Profit Institutions (For-Profit GAP) serve as

the standard terms and conditions of grant awards issued by CIRM. All research conducted under this award must comply with the stated policy. Progress reports of research, as required by the GAP, are important to CIRM: Funding from year to year will depend on adequate scientific progress as outlined in the grant application timeline. CIRM's GAP is available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants#GAP.

B. Intellectual Property Regulations

CIRM has adopted intellectual property and revenue sharing regulations for non-profit and for-profit organizations. By accepting a CIRM Grant, the Grantee agrees to comply with all such applicable regulations. See http://www.cirm.ca.gov/sites/default/files/files/funding_page/Reg100600_100611_27_January_2014.pdf

C. Human Stem Cell Research Regulations

As reflected in CIRM's GAP, CIRM has adopted medical and ethical standards for human stem cell research (Title 17, California Code of Regulations, sections 100010-100110 available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants#standards). All research conducted under this award will be expected to comply with these standards. This information can be found on the CIRM website.

CIRM expects that clinical trials will be conducted in accordance with all applicable State and Federal regulations and in accordance with CIRM's Medical and Ethical Standards: http://www.cirm.ca.gov/sites/default/files/files/funding_page/Reformatted_MES_Regs.pdf

D. California Supplier Regulation

CIRM has adopted a regulation to implement the requirement in Proposition 71 that grant and loan recipients make a good faith effort to achieve a goal of purchasing more than 50% of their goods and services from California suppliers (Title 17,California Code of Regulations, section 100502). Grant and loan recipients are required to comply with this standard.

E. Loan Administration Policy

In the event that the applicant chooses to receive an award in the form of a loan rather than a grant, the Loan Administration Policy (LAP) will apply and is available at: http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants and is summarized in Appendix A.

XIII. Confidentiality of Submissions to CIRM

CIRM protects the confidential information it receives from applicants and grantees to the maximum extent permitted by law. That protection is embodied in a number of laws and policies, described below, and applies to the confidential information submitted by all applicants and grantees. CIRM does not enter into separate non-disclosure agreements with individual applicants or grantees.

A. CIRM Employees

CIRM employees are subject to the confidentiality requirements identified in a CIRM policy known as the "Incompatible Activities Statement." By law (Cal. Gov. Code § 19990) state employees are prohibited from engaging in activity identified by their employing agencies' Incompatible Activities Statements. CIRM employees are also subject to the confidentiality provision in the CIRM Employee Handbook. All employees sign statements acknowledging receipt of the Incompatible Activities Statement and the CIRM Employee Handbook.

Excerpt from Incompatible Activities Statement:

No employee shall utilize his or her status as a CIRM employee to acquire access to confidential information other than on behalf of the CIRM.

Additionally, no employee shall use such information for private gain or advantage or provide confidential information to persons to whom issuance of this information has not been authorized.

Excerpt from Employee Handbook:

All records and information relating to CIRM and its activities are confidential and employees must, therefore, treat all matters accordingly. No CIRM or CIRM related information, including without limitation, documents, notes, files, records, oral information, computer files or similar materials (except in the ordinary course of performing duties on behalf of CIRM) may be removed from CIRM without the President's authorization. Additionally, the contents of CIRM's records or information otherwise obtained in regard to CIRM activities may not be disclosed to anyone, except where required for an official purpose or by law. Employees must not disclose any confidential information, purposefully or inadvertently through casual conversation, to any unauthorized person inside or outside CIRM. Employees who are unsure about the confidential nature of specific information must ask their supervisor for clarification. Employees will be subject to appropriate disciplinary action, up to and including dismissal, for purposefully or accidentally, revealing information of a confidential nature.

B. Clinical Development Advisory Panel

Members of CIRM's Clinical Development Advisory Panel (CDAP) sign contracts that include the following provision:

Advisor shall keep confidential any information provided by CIRM or any information conveyed orally to Advisor by CIRM with oral notification of its confidentiality (the "Confidential Information"). Advisor agrees to maintain the secrecy of CIRM's Confidential Information and agrees not to use it except in performing the Services under this Agreement and not to disclose it to anyone outside CIRM or anyone within CIRM's organization who does not have a need to know it to perform under this Agreement. This non-disclosure provision shall not apply to any of the following:

1. Information that Advisor can demonstrate by written records was known to him or her prior to the effective date of this Agreement;
2. Is currently in, or in the future enters, the public domain other than through a breach of this Agreement or through other acts or omissions of Advisor; or
3. Is obtained lawfully from a third party.

C. Grants Working Group

The Grants Working Group (GWG) reviews grant applications. All members sign statements guaranteeing confidentiality, at the time of their appointment, and again prior to accessing application materials for each grant round.

D. Public Records Act

As a state agency, CIRM is required to allow public access to certain categories of documents held by the agency. The Public Records Act (California Government Code section 6250 et seq.) exempts certain categories of documents from public disclosure. As relevant here, agencies are not required to release trade secrets, as defined by section 3426.1(d) of the Civil Code:

"Trade secret" means information, including a formula, pattern, compilation, program, device, method, technique, or process, that (1) Derives independent economic value, actual or potential, from not being generally known to the public or to other persons who can obtain economic value from its disclosure or use; and (2) Is the subject of efforts that are reasonable under the circumstances to maintain its secrecy. In addition, CIRM operates under special Public Records Act exemptions included in Proposition 71, the ballot initiative that created CIRM. Proposition 71 (Health & Safety Code, sec. 125290.30(e)(2)(B)-(C)) exempts from disclosure:

1. Records containing or reflecting confidential intellectual property or work product, whether patentable or not, including, but not limited to, any formula, plan, pattern, process, tool, mechanism, compound, procedure, production data, or compilation of information, which is not patented, which is known only to certain individuals who are using it to fabricate, produce, or compound an article of trade or a service having commercial value and which gives its user

an opportunity to obtain a business advantage over competitors who do not know it or use it.

2. Prepublication scientific working papers or research data.

Sample A: PRECLINICAL DEVELOPMENT AWARD MILESTONES TEMPLATE

The text below shows an example milestone with tasks and success criteria. To fill out the template, delete the example text and type in your own project milestones, tasks and quantifiable, objective success criteria. Reviewers will use these draft milestones to evaluate your overall project plan. However, please note that milestones will be subject to further review and refinement during the CIRM Pre-Funding Administrative Review Process.

PI INFORMATION
Give name of Principal Investigator and his/her Institution
CIRM AWARD NUMBER
Give CIRM Award Number (XXY-0zzzz)
TITLE OF CIRM AWARD
Preclinical Development of a GMP Manufacturing Process for iPSC-derived Cells for Treatment of a Disease
MILESTONE 1 TITLE AND TIMELINE
Development of cGMP Master and Working Cell Banks of iPSC-derived intermediate cell type LMN (Y1Q1-Y1Q2)
MILESTONE 1 TASKS
1) Establish a MCB using cGMP Methods, containing 50 vials of 1x10^6 cells.
2) Establish a WCB using cGMP Methods, containing 200 vials of 1x10^6 cells.
3) Initiate Stability Assays on cGMP cells, for assessment of viability every 6 months.
MILESTONE 1 SUCCESS CRITERIA
1) Cells in MCB and WCB must be at least 99% XYZ+ and ABC+.
2) Cell viability prior to freezing must be at least 98% and after thaw must be at least 95%.
3) Passage # of MCB must be ≤ P5; Passage # of WCB must be ≤ P10.
4) Karyotype analyses look normal in 20/20 spreads for each cell bank.
MILESTONE 2 TITLE AND TIMELINE
Development of cGMP method to differentiate from LMN intermediate progenitor to OPQ differentiated cell.
MILESTONE 2 TASKS
MILESTONE 2 SUCCESS CRITERIA

Sample B: CIRM TARGET PRODUCT PROFILE (TPP) TEMPLATE

TARGET PRODUCT PROFILE for	
<Delete this text and type Name of your Product/Therapy here>	
INDICATION: ***Disease or condition for which your product/therapy will be indicated***	
Optimal indication and decision criteria < Delete and type your text here>	***Minimally acceptable indication and criteria*** < Delete and type your text here>
BIOLOGICAL ACTIVITY: ***Biological activity of your product/therapy***	
Optimal biological activity and decision criteria < Delete and type your text here>	***Minimally acceptable biological activity and criteria*** < Delete and type your text here>
EFFICACY: ***Proposed efficacy endpoints for your product/therapy***	
Optimal efficacy endpoints and decision criteria < Delete and type your text here>	***Minimally acceptable efficacy endpoints and criteria*** < Delete and type your text here>
SAFETY/CONTRAINDICATIONS*:* ***Potential safety risks associated with your product/therapy***	
Optimal safety profile and decision criteria <Delete and type your text here>	***Minimally acceptable safety profile and decision criteria*** <Delete and type your text here>
DOSE/REGIMEN: ***Briefly describe the proposed dose and dosing regimen of your product/therapy.***	
Optimal dose and dosing regimen and decision criteria <Delete and type your text here>	***Minimally acceptable dose and dosing regimen and decision criteria*** <Delete and type your text here>
DOSAGE FORM/ROUTE OF DELIVERY: ***Briefly describe the proposed dosage form and route of delivery for your product/therapy.***	
Optimal dosage form and route of delivery and decision criteria <Delete and type your text here>	***Minimally acceptable dosage form and route of delivery and decision criteria*** <Delete and type your text here>

Sample C: CIRM PRECLINICAL STUDIES SUMMARY TEMPLATE

This table is meant to be a comprehensive summary of all safety and efficacy experiments done to evaluate the Development Candidate or closely related therapeutic candidate, and should be provided with the Letter of Intent (to help gauge eligibility) as well as with the full Application (to help reviewers assess Scientific Rationale and Preclinical Development Readiness). At the full Application stage, it also will be necessary to provide the most critical efficacy and safety data demonstrating preclinical development readiness.

To fill out the table, remove example text and type in your own study descriptions.

Product Description: *(Example: Gene-modified human iPSC-derived cardiomyocytes: iCM)*

Study Purpose and Title	**Study Objective(s)**	**Test Article**	**Animal model**	**Key outcome(s)**
Efficacy and Safety: Implantation of iCM into mouse AMI model, two doses	*Assess left ventricular function, extent of scar formation, retention of human cells, arrhythmias, other overt toxicity*	*Human iCM (Development Candidate)*	*Mouse with LAD ligation to induce AMI*	*Electrical coupling of human CM with mouse CM. Reduced scar size, trend toward improved LVEF.*
Safety: Tumorigenicity of iCM	*Assess tumorigenicity of iCM in immune-deficient mice*	*Human iCM (Development Candidate)*	*NSG mice, implanted subcutaneously with two doses iCM*	*No tumors in 20/20 mice tested, at 250,000 and 500,000 cells/animal.*

Sample D: CIRM CLINICAL TRIAL SYNOPSIS TEMPLATE

STUDY TITLE
Provide full title of the study
CLINICAL PHASE
Specify clinical phase (1, 2a)
STUDY OBJECTIVES
Provide a brief description of the study objectives e.g., why is the study being done, what is the intent? E.g., safety, feasibility ***Primary Objectives:*** ***Secondary Objectives:*** ***Exploratory Objectives:***
STUDY RATIONALE
Summarize the rationale for testing the proposed therapy
STUDY POPULATION
Briefly describe the study population and explain the rationale for choosing this population
PRIMARY ENDPOINT (S)
Describe the Primary Endpoint(s) and the set of measurements used to address the objectives
SECONDARY & EXPLORATORY ENDPOINTS
Describe the Secondary & Exploratory Endpoint(s) and measures that will address them
STUDY DESIGN
Outline the proposed study design, including type of study, number of arms, controls or comparators
ROUTE OF DELIVERY
Specify how the doses will be delivered
IMMUNE MONITORING & IMMUNOSUPPRESSION
Describe and justify the plan for immunosuppression and immune monitoring (if applicable)
ASSAYS/METHODOLOGIES
Briefly describe any specialized assays or methodologies that may be used in this clinical study or supporting study/studies. (Provide a more detailed summary of assay

methods and summarize assay qualification/validation in Part D). Indicate where specialized testing will be conducted
OUTCOME CRITERIA
Describe criteria that would define whether you would or would not move forward with the subsequent development plan, based upon primary and designated secondary objectives
RISKS
Identify potential risks and mitigation strategies (e.g. need for and risks associated with long term immunosuppression)
TIMELINE
Provide a high-level timeline for completion of the study and indicate anticipated milestones

Appendix A: LOAN INFORMATION

Loan Terms: As stated within the body of this Request for Application, a successful applicant may choose to accept the award in the form of a grant or a loan. If the award is in the form of a Loan, the CIRM and the successful applicant will enter into a loan agreement and the Loan Administration Policy (LAP) will govern. Terms of the loan are summarized below –see http://www.cirm.ca.gov/sites/default/files/files/funding_page/2012_MAY_Loan%20Administration%20Policy%20incorporated%20by%20regulation%20100800.pdf for actual regulations.

(i) Two types of Loans, Company-Backed Loans and Product-Backed Loans, are available. Company-Backed Loans are subject to repayment regardless of the success of the project, whereas a loan forgiveness mechanism is available for Product Backed Loans. No personal guarantees or collateral are required.
(ii) Term: The term of the loan will be 5 years, subject to extensions as set forth in the LAP.
(iii) Payments: All principal and interest will be due and payable at the end of the loan term, unless the repayment obligation has been forgiven or accelerated. Loans that are extended require periodic payments of interest accrued.
(iv) Interest Rate: The interest rate for the initial term of the loan shall be LIBOR plus 2%.
(v) Warrants: Loan recipients will be required to provide CIRM with warrants; the amount of such warrant coverage will depend on the type of loan requested and satisfaction of certain criteria as outlined in the LAP.
(vi) Extension of Term: Loan Recipient may extend the initial term in one year increments (provided it is in compliance with the Notice of Loan Award and LAP), subject to (a) payment of 25% of unpaid and accrued interest and (b) an interest rate increase in the amount of 1% over the rate in effect the prior year.
(vii) Loan Administration Costs: Approved for-profit applicants who accept a loan will pay for loan administration costs out of the award. If the term of the loan is extended beyond year 5, the loan recipient must pay any additional loan administration costs.

Loan applicants will be required to submit financial information. For additional information about the loan program, consult the CIRM LAP, available at: http://www.cirm.ca.gov/reg/default.asp.