RFA 12-05: CIRM Strategic Partnership I Awards

I. Purpose

The purpose of the Strategic Partnership Awards Initiative ("Initiative") is to attract industry engagement and investment in CIRM funded stem cell research. The intent of the Initiative is to create incentives and processes that will: (i) enhance the likelihood that CIRM funded projects will obtain funding for Phase III clinical trials (e.g. follow-on financing), (ii) provide a source of co-funding in the earlier stages of clinical development, and (iii) enable CIRM funded projects to access expertise within pharmaceutical and large biotechnology partners in the areas of discovery, preclinical, regulatory, clinical trial design and manufacturing process development.

This Initiative requires applicants to show evidence of either having the financial capacity to move the project through development or of being able to attract the capital to do so. This may be evidenced by, for example, (i) significant investment by venture capital firms, large biotechnology or pharmaceutical companies and/or disease foundations; (ii) a licensing and development agreement with a large biotechnology or pharmaceutical company, or a commitment to enter into such an agreement executed prior to the disbursement of CIRM funding; and/or (iii) financial statements evidencing significant liquid assets as described below in Section V, D.

This first call under the Initiative, Strategic Partnership I Awards, is focused on funding projects that are able to complete a clinical trial during the project period. CIRM anticipates releasing two additional RFAs under this Initiative in 2013.

II. Objectives and Scope

The objective of the Strategic Partnership I Award will be to achieve, in 4 years or less, the completion of a clinical trial under an Investigational New Drug (IND) application filed with the Food and Drug Administration (FDA). The proposed clinical trial will evaluate both preliminary safety and preliminary biological activity/early efficacy in humans. CIRM will only fund programs that include a clinical study that can be completed within the project period. In this RFA, a clinical trial will be considered complete upon completion of enrollment, database lock and initial assessment of outcomes of the primary and secondary study objectives.

While all successful applicants are expected to complete a clinical trial within the four years of the award, the project can encompass IND-enabling as well as clinical research. If the proposal begins with a clinical trial, the applicant must have filed a complete IND package with the FDA by the application due date. Projects beginning with IND-enabling studies must include a phase I or I/II clinical trial and must be able to complete the proposed clinical trial within the term of the award.

Priority will be given to eligible proposals aimed at furthering the development of CIRM-funded projects, or having a strong probability of achieving clinical proof of concept, as well as to those that cannot, or are unlikely to, receive timely or sufficient federal funding.

A. Therapeutic Candidate

Each funded Research Award will support a project for a single therapeutic candidate (that is or will be the subject of a single IND filing) that meets any of the following criteria:

- A cell therapy candidate that:
    - is derived from or utilizes (i) pluripotent stem cells or (ii) progenitor/adult tissue-derived stem cells (with the exclusions noted below)
      OR
    - is comprised of adult stem cells that have been modified either pharmacologically or genetically (where the pharmacologic/genetic modification is for the purpose of correction of a disease phenotype or is critical to achieve the therapeutic strategy).

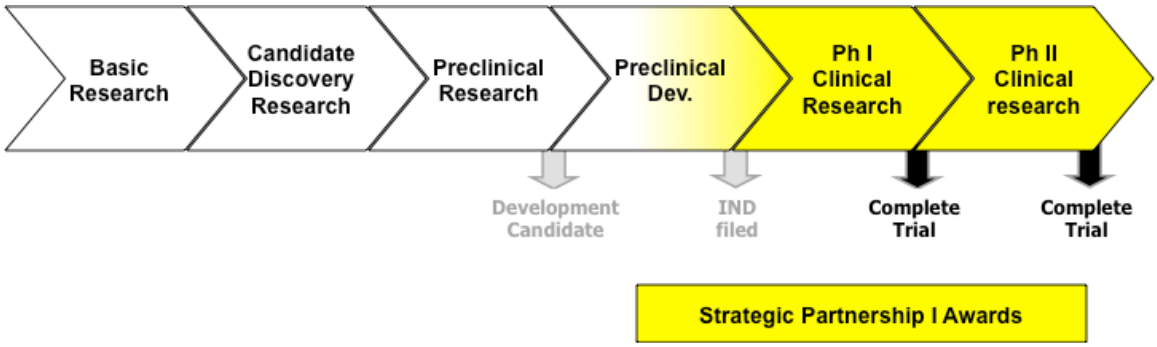
- A small molecule or biologic candidate that (i) mobilizes endogenous stem cells to promote tissue repair/regeneration and for which there is convincing evidence of such activity; or (ii) was identified and characterized using patient-derived induced pluripotent stem cells or their derivatives; or (iii) is specifically targeted to destroy cancer stem cells and for which there is compelling evidence for such activity, based on serial clonal transplantation assays in an in vivo model.

Cell types that fall outside the scope of this RFA include the following:

- minimally manipulated bone marrow cells
- umbilical cord blood stem cells
- adipose-derived stem cells
- unmodified hematopoietic stem cells

B. Research Stage

The scope of this initial call is illustrated in the figure below.



This Research Award will support activities that meet the objective of this RFA, including but not limited to the activities listed below:

- IND-enabling activities necessary to enable a first-in-human clinical study proposed as part of the project. These preclinical activities could include preclinical pharmacology/toxicology studies, assay development, process development, GLP/GMP manufacturing, clinical and regulatory strategy development.

- All activities necessary to initiate and complete an early clinical trial. For this RFA, early clinical trials include Phase I or Phase I/II studies to evaluate preliminary safety and preliminary biologic activity in humans; and Phase II clinical studies conducted to evaluate efficacy of the therapeutic in a particular indication.

- Also included are supporting activities to enable the proposed clinical study such as GMP production, testing and release of candidate therapeutic product for the proposed trial(s) and/or further qualification/validation of relevant assays such as potency assays or specialized clinical assays.

- The proposed clinical trial may include supporting /exploratory studies performed in the context of the clinical trial, designed to provide critical additional data to better inform decisions on continued clinical testing. Examples of such studies include: measurement of pharmacodynamic parameters to improve decisions on dosing; evaluation of relevant biomarkers; use of additional clinical, biological, genomic, immunological, imaging or efficacy measures to enhance/correlate data on the mechanism of action or efficacy of the proposed cell therapy. Applicants will be expected to justify how such studies will specifically inform the trial results and contribute to decision making with respect to continued clinical testing of the proposed cell therapy.

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

- Phase III clinical studies
- Non-interventional clinical studies (e.g. biomarker discovery; clinical studies not involving administration of the proposed therapy; or studies using samples not from subjects of the proposed clinical studies)
- Development and qualification of a medical device for the delivery of a product other than the product proposed for the funded project

CIRM requires any clinical trial in the proposed project to include at least one clinical trial site in California. CIRM expects funded clinical trials to include women and members of minority groups unless a clear and compelling rationale and justification establishes to the satisfaction of CIRM, that such inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.

III. Award Information

A. Amount

Under this Request for Application (RFA), CIRM intends to commit up to $10 million per award to support up to 3 awards under the current funding allocation of $30 million. Any additional funding will be at the discretion of the CIRM Governing Board, the Independent Citizens Oversight Committee (ICOC).

B. Commencement/Other CIRM Awards

Given the urgency of CIRM's mission, all approved applications must be initiated (award start date in issued and signed Notice of Grant or Notice of Loan Award) within 6 months of approval and authorization for funding by the ICOC, unless CIRM's President grants an extension based upon compelling justification of the need for additional time. In the case of awards to applicants that already have a CIRM award such as a Disease Team I award, any funding disbursed to the applicant under this RFA will be for activities not funded by the already existing award.

C. Co-Funding

CIRM will require co-funding from the applicant, which may come from the applicant's own assets, from an industry partner, or from another funding source arranged by the applicant. Applicants must match 100% of the total CIRM funding requested (i.e. one-to-one match) and must use their matching funds (co-funding) to support only direct research project costs. In their application, applicants will be required to address the status and sources of co-funding required for achievement of the RFA objective as well as the longer-term development objective.

D. Budgets and Milestones

For all awards, CIRM reserves the right to negotiate funded project activities, milestones (both technical and financial), success criteria, timelines and budgets prior to issuance of the Notice of Grant Award (NGA) or Notice of Loan Award (NLA), subject to renegotiation annually and/or based on progress. Progress in translational research is important to CIRM. Continued funding is contingent upon timely scientific progress as outlined in the project milestones and timeline established under the NGA or NLA. If milestones are not met, CIRM reserves the right to terminate the project or to negotiate new milestones to refocus/redirect the project.

E. Sub-Contracts

CIRM has the option to review (for compliance with CIRM's policies and regulations and the advancement of its mission) contract/agreements (e.g. with Contract Research Organizations, CROs or Contract Manufacturing Organizations, CMOs) deemed critical to the success of the project. Upon request, the awardee will be required to provide such documentation.

F. Reporting

In addition to annual Progress Reports, as required by the Grants Administration Policy (GAP, see Section XI.A of this program announcement), 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) notification of any serious adverse event related to the therapeutic candidate in a clinical trial, as required by the GAP (see Section XI.A of this RFA) and 4) discussion with CIRM's Clinical Development Advisors at key decision points such as the transition from IND filing to initiation of a clinical trial.

IV. Award Mechanism

CIRM expects to fund approved proposals through grants or loans.

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. Sponsorship of the IND will define the applicant organization (see Section V). Grants are funded through quarterly disbursements 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.) It should be noted that these regulations may change and applicants are encouraged to monitor pending regulatory rulemaking proceedings. Such changes may include an amendment to 17 Cal. Code Regs. section 100608(b) such that it will apply to licensees and sub-licensees of Grantees and Collaborators.

The terms of the Loans are set forth in detail in Appendix A to this RFA. Loan recipients shall be governed by the CIRM Loan Administration Policy that is in effect as of the date of the execution of the Notice of Loan Award. 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. For information on the loan program, consult the CIRM Loan Administration Policy, available at: http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants.

V. Eligibility

For an **investigator-sponsored IND**, the investigator-sponsor must be the Principal Investigator (PI) on the CIRM application.

For an **organization-sponsored IND**, the organization sponsor must be the applicant organization on the CIRM application, and the PI must be an employee of that organization.

An applicant organization may submit up to two applications which must be for two different projects that are the subject of two different IND filings. A Principal Investigator (PI) may submit only one application under this RFA.

A. Project Eligibility

i. The objectives of the proposed project must include the completion, in 4 years or less, of a phase I, phase I/II, or phase II clinical trial under an Investigational New Drug (IND) application filed with the Food and Drug Administration (FDA). The proposed clinical trial(s) will evaluate both preliminary safety and preliminary biological activity/ efficacy in humans.

ii. The proposed therapeutic candidate must meet the criteria described above in Section II.

iii. If the proposal begins with a clinical trial, the applicant must have filed a complete IND package with the FDA by the application due date (June 26th 2012).

iv. In addition, applicants must provide **Evidence of Commercial Validation** (see Section V, D below)

B. Institutional Eligibility

Both non-profit and for-profit organizations may apply. "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 are also referred to as "commercial organizations".

In order to be eligible for this award, at the time of submission of an application, the applicant organization must have secured a location in California from which location they will engage in activities critical to the project, including management of the clinical trial program. The minimum requirements *at the time of funding* include the presence of two or more full time employees in California and a commitment to continued investment in California to support the program as appropriate.

All applicants must provide evidence of commercial validation to be eligible for this award (see Section V, D below).

C. Principal Investigator (PI) Eligibility

CIRM requires that a single Principal Investigator (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. The applicant organization is the designated contact institution for all financial and other administrative considerations.

The PI must have an M.D., Ph.D. or equivalent degree and must be authorized by the applicant organization to conduct the proposed research in California. By the application deadline, the PI must:

- Be an employee of the applicant organization who commits at least 30 percent time working on the project out of the California office of the applicant organization, and have demonstrated expertise in drug development and in managing clinical research programs.
- Have documented authority from the applicant organization to staff the proposed project in California
- Have documented commitment from the applicant organization to provide resources sufficient to carry out the proposed research.

In order to broaden the pool of applicants engaged in stem cell research and to encourage leveraging of CIRM's investment, CIRM is limiting the number of active CIRM research awards in which an investigator may participate as PI or Co-PI. This RFA is not open to investigators who are already a PI or Co-PI on 3 or more active CIRM awards as of June 26th 2012, the deadline for submission of the full application (as further set forth below).

The limit includes all CIRM awards that have been approved but not yet closed out, with the exception of the following CIRM RFAs: Shared Research Labs, Major Facilities, Research Training Awards I & II, Bridges to Stem Cell Research, Disease Team Planning Awards, Disease Team Therapy Development Part I Planning Awards, or Conference Grants.

D. Evidence of Commercial Validation

In order to attract projects having or likely to attract industry investment, including follow-on financing of Phase III clinical trials (which CIRM does not intend to fund), or having adequate self-funding, applicants must provide evidence of commercial validation as part of the submitted application. Such evidence will require submission of supporting documentation both as part of the CIRM LOI submission and with the application, satisfying at least one of the following:

1) Financial Strength and Historical Investment:
   The applicant is a for-profit that has (a) obtained in the past two years, or will obtain concurrent with the issuance of the CIRM award, an equity and/or programmatic investment by venture capital firms, large biotechnology or pharmaceutical companies and/or non-profit foundations, in the amount of at least $15 Million AND (b) at least one year of balance sheet cash (as demonstrated by its most recent financial statements and pro-forma for any concurrent investment) based on the last twelve months (LTM) operating cash burn rate, without taking into account any funds provided by CIRM, AND (c) in the event of a concurrent/pro forma investment, an executed term sheet or letter of intent evidencing satisfaction of paragraph (a) and (b) above, provided that no funds will be disbursed to a successful applicant until it provides a fully executed agreement evidencing satisfaction of the provisions in paragraph (a) and (b) above. For purposes of this RFA, LTM operating cash burn is defined as cash flow from operations, less capital expenditures and any debt service.

AND/OR

2) Collaborative Development Arrangements:
   The applicant is a non-profit or a for-profit that (a) has an existing agreement with a large biotechnology or pharmaceutical company committed to providing financial support for therapeutic development of the proposed project through Phase II and preferably through Phase III if milestones are met (a copy of the agreement shall be provided with the application); AND/OR (b) has an executed term sheet or letter of intent evidencing an intent to enter into such an agreement with a large biotechnology or pharmaceutical company, provided that no funds will be disbursed by CIRM to an approved applicant until it provides a fully executed contract evidencing such agreement.

If CIRM determines that these requirements are not met, it may terminate all further action on the application

E. Project Manager Eligibility

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

F. Extraordinary Exceptions

In extraordinary circumstances, the President has the discretion to permit exceptions to requirements or limitations 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 be consistent with the objectives of this RFA and the requirements of Proposition 71 as well as California state regulations, including the Grants Administration Policy (see Section XI 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 are strongly encouraged to request it 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 X.

VI. Application and Evaluation Process

Submission of an application for a Strategic Partnership I Award 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 that meet all eligibility requirements and have submitted an LOI that was accepted by CIRM.

Applications for the CIRM Strategic Partnership I Awards will be subject to a scientific review and a review of demonstrated commercial validation. The CIRM Grants Working Group (GWG) will conduct a review of the application based on the review criteria outlined in Section VII, A. The IP and Industry Sub-committee of CIRM's Governing Board, the Independent Citizens Oversight Committee (ICOC), will assess the application for evidence of commercial validation as outlined in Section VII, B.

The CIRM Grants Working Group (GWG) is composed of fifteen scientific experts from outside California, seven patient advocate members of CIRM's Governing Board (ICOC), 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 VII, A, below. The GWG (scientists and patient advocates) will then review the entire portfolio of applications, taking into consideration (i) the impact of the proposed project for the development of stem cell-based therapies and on regenerative medicine, (ii) an appropriate balance among applications that address the priorities of this RFA and other meritorious applications, and (iii) other considerations from the perspective of patient advocates.

CIRM's priorities for this RFA include proposals that:

- include a co-funding partnership between an existing CIRM funded project and a biotechnology or pharmaceutical partner;
- include an existing CIRM funded project that has obtained significant venture capital investment for co-funding the project;
- propose to complete a Phase I/II or Phase II clinical study that could demonstrate clinical proof-of-concept if successful;
- cannot, or are unlikely to, receive timely or sufficient federal funding.

The IP and Industry Subcommittee comprises seven members; four of whom were appointed to the Board based on their affiliation with life science commercial entities; one of whom was appointed to the Board based on her position as an executive officer of a UC campus with a medical school; one of whom was appointed to the Board based on his affiliation with a patient advocacy organization; and the Chair of the Governing Board, who is a patient advocate elected by the Board from among candidates nominated by the Governor, the Lieutenant Governor, the Treasurer and the Controller.
The membership list of the subcommittee may be found at http://www.cirm.ca.gov/our-board-meetings/governing-board/icoc/governing-boardicoc-cirm.'

The GWG and the IP and Industry Subcommittee will make funding recommendations to CIRM's Governing Board, the ICOC, which will make final funding decisions.

Project progress for all successful awardees from this RFA will be evaluated by a group of external experts, the Clinical Development Advisors panel, at key milestones and decision points such as the transition from IND filing to initiation of a clinical trial.

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 and external reviewers. (Per Gov. Code §6254.5(e) non-public records may be disclosed to government agencies under confidentiality agreements.)

VII. Review Criteria

Applications will be evaluated for scientific merit by the GWG in five key areas: 1) Significance and Impact; 2) Risk/Benefit; 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 Grants Administration Policy (GAP, see Section XI of this RFA).

The IP and Industry Subcommittee will evaluate the applications in one key area, Evidence of Commercial Validation (see Section VII B, below).

A. Criteria for GWG review

The GWG will be asked to give special consideration to projects aimed at furthering the development of work supported by prior CIRM funding and to projects having a strong probability of achieving clinical proof of concept (based on clinically validated biomarkers or accepted clinical endpoints). For projects that have undergone a due diligence analysis by a pharmaceutical/biotechnology partner resulting in an executed development agreement or a term sheet or letter of intent to enter into a development agreement, reviewers are asked to assess the thoroughness of the diligence analysis with respect to evaluation of Clinical Competiveness and Impact, Risk Benefit, and Design and Feasibility, as set forth below, and to weigh both the scope of the investigation and its conclusions appropriately in their scientific scoring.

1. Significance and Impact

a. Target Product Profile: Evaluate whether 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.

b. Clinical Competitiveness and Impact: Where a due diligence investigation has been conducted in regard to the proposed therapeutic, assess if the investigation was thorough in evaluating the potential for a competitive product. Otherwise, evaluate whether the proposed therapeutic candidate could have a significant impact on the target disease/injury and if it would offer advantages over current therapies on the market or in late stage development. Assess if the proposed project could advance the field of stem cell-

based/regenerative medicine.

c. Responsiveness**:** Evaluate whether the proposed activities are within scope as defined in Section II. Evaluate if this is a project that should receive priority as stated in Sections II and VI. Priority should be given to eligible proposals aimed at furthering the development of CIRM-funded projects, or having a strong probability of achieving clinical proof of concept, as well as to those that cannot, or are unlikely to, receive timely or sufficient federal funding.

2. Risk/Benefit

Where a potential or existing partner has conducted a due diligence investigation on rationale and risk benefit for the proposed therapeutic, assess whether the investigation was thorough. Otherwise, assess if there is strong scientific rationale and a favorable risk/benefit ratio for the proposed therapeutic intervention in the target disease/injury. Based on the preclinical and available clinical data, is there a reasonable expectation that the proposed therapeutic approach will have clinical benefit for patients and are the potential risks to subjects manageable and acceptable in the context of the target patient population?

3. Design and Feasibility

Where a potential or existing partner has conducted a due diligence investigation regarding the proposed project, assess whether the diligence investigation was thorough with respect to consideration of a) through c) below. Otherwise assess the following**:**

a. Development Plan to End-of-Phase II: (End-of-Phase II is here defined as completion of early clinical studies providing sufficient information on safety, efficacy and dose, to enable the transition to phase III. The Project Plan described below may overlap completely with the Development Plan to End-of-Phase II, or may comprise a subset of that plan.)

Evaluate whether the overall Development Plan to End-of-Phase II is well thought out and realizable. Determine if this Development Plan supports achievement of the Target Product Profile.

b. Project Plan: The Project Plan describes the scope of work that will be conducted during the award period and can overlap wholly or in part, with the above Development Plan.

Evaluate the design and feasibility of the Project Plan with respect to the following:

- The proposed project is integral to the Development Plan to End-of-Phase II.

- The Project Plan is feasible and could meet the objective of this RFA, which is to complete a clinical trial within the project period.
- 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.
- The project timeline is realistic and achievable.

c. Key Project Components: Assess the proposed project with respect to the following:

i. Feasibility of the *preclinical plan*: If the IND has not yet been filed, is the IND-enabling plan adequate to enable regulatory approval to advance to a clinical trial, and is the projected timeline for IND filing realistic? If the project contains preclinical studies designed to get off clinical hold, are these adequate to address the clinical hold issue(s) and is the timeline realistic?

ii. Feasibility of the *regulatory path*: A pre-IND meeting has been conducted and major issues raised in those discussions have been addressed.

iii. Feasibility of the *manufacturing strategy*: Assess the feasibility of the manufacturing strategy to supply the proposed clinical trial and to support scale up for future larger trials and commercialization.

iv. Design and Feasibility of the proposed *Clinical Study*:

- The proposed study is well-designed and could achieve the RFA objectives of evaluating both preliminary safety and preliminary biological activity/early efficacy (proof-of-concept) in humans. The trial is designed to test or elucidate mechanism(s) of action of the therapeutic such that, regardless of clinical outcome, information will be gained.
- The choice of patient population is appropriate.
- Enrollment projections are realistic and the study can be completed during the award period.

4. Principal Investigator (PI), Development Team and Leadership Plan

Assess the following:

a. Expertise and Track Record of PI: Assess whether the PI has relevant experience in therapy development, has demonstrated successful leadership experience, and will have a key role in the proposed project.

b. Development Team and Leadership Plan: Evaluate whether an appropriate multidisciplinary team has been assembled to execute the project. Does the team include a Product Development Lead, CMC Lead, Preclinical Lead, Clinical Lead, and a Regulatory Lead in addition to the required Project Manager? Do these team leads have demonstrated expertise in their functional area?

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

c. Clinical Investigators and Clinical Sites: Evaluate if the lead clinical investigators have relevant experience in the target disease area and in conducting clinical studies. Assess whether the clinical sites have staff that are experienced in conducting phase I and phase II trials.

d. Budget: Assess if the proposed budget is appropriate and shows projected costs for key activities (such as IND-enabling activities, CMC activities, clinical trials).

5. Collaborations, Assets, Resources and Environment

Assess the following:

a. Collaborations: Determine whether collaborations (including those with a co-funding partner) needed for the success of the project are in place.

b. Assets: Evaluate the assets, specifically intellectual property and/or licenses that are available to the project. Are Material Transfer Agreements (MTAs) or license agreements that are critical for development of the therapeutic candidate either already in place or at an adequate stage of negotiation to enable the development program? Do the applicants have agreements in place to cross-reference Drug, Device or Facility Master File(s) submitted by the industry partner/collaborator with the appropriate section(s) of the regulatory agency (FDA) (see Parts I and J.)

d. Contract Services: Assess whether the proposed CROs/CMOs/consultants have the experience and expertise to successfully meet expectations, deliverables and timelines and if the development team has appropriate oversight expertise.

f. Resources and Environment: Comment on whether the necessary facilities, major equipment, and services are available for conducting the proposed research.

B. Criteria for IP and Industry Subcommittee review

Evidence of Commercial Validation

The applicant has provided sufficient documentation to establish commercial validation (see Section V, D and Section VIII, 21 for a description of documentation requested) on the basis of “Financial Strength and Historical

Investment" and/or "Collaborative Development Arrangements", and will be assessed as applicable on measures including:

- The amount of historical equity and/or programmatic investment in the applicant organization, with larger amounts being rated more highly
- The number of years of balance sheet cash at the applicant organization as of 3/31/12, and pro forma for any concurrent investment
- The amount of co-funding and future financing committed by the applicant, and if applicable, its partner, for the proposed project and for future development required to achieve FDA approval to market the proposed therapeutic.
- The strength of the commitments by the applicant and, if applicable, any of its partners to fund (a) the project and (b) future development.

VIII. Application Procedure

Applicants must follow these instructions for submission of a Letter of Intent and a Strategic Partnership I Award application. Applications will only be accepted from PIs who submitted a Letter of Intent that was accepted by CIRM. The PI and the project proposed in the application must be the same as those described in the Letter of Intent; otherwise, the application is deemed ineligible.

A. Letter of Intent (LOI)

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 four years achieve the objective of the RFA, which is to complete a clinical trial. Documentation in support of commercial validation may be required as part of the LOI submission. Refer to the LOI instructions and form for the required documentation. **The completed LOI and supporting documentation, if applicable, 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 5:00PM (PDT) on May 16th 2012. No exceptions will be made.**

B. Application Forms

Application forms for this RFA will be available via the Grants Management Portal at https://grants.cirm.ca.gov in May 2012.

The application for this PA consists of up to **twelve parts**:

Part A: Application Information Form (Web-based form) Part A includes: Abstract, Public Abstract, Statement of Benefit to California, Key Personnel, and Budget (section numbers 1- 5 below).

Part B: Strategic Partnership I Award Proposal (MS Word template) Part B includes: Target Product Profile; Clinical Competitiveness and Impact; Risk/Benefit, Development Plan to End-of-Phase II, Project Plan with Milestones and Timeline; IND Status; Clinical Protocol synopsis; Manufacturing Plan synopsis; PI, Development Team and Leadership Plan; Collaborations, Assets, Resources and Environment; Clinical sites; Licenses and Agreements; References (section numbers 6-18 below).

Part C: Biographical Sketches for Key Personnel (including key clinical investigators) (MS Word template) and letters of collaboration and/or institutional support.

Part D: Due Diligence Report. For projects that have undergone a due diligence analysis by a pharmaceutical/biotechnology partner resulting in an executed development agreement or a term sheet or letter of intent to enter into a development agreement, provide a summary and/or checklist of the due diligence investigation(s).

Part E: Activity Based Budget

Part F: FDA correspondence. If you have had discussions/meetings with FDA, copies of regulatory correspondence must be provided.

Part G: Clinical Protocol Required for projects proposing starting with a clinical trial. If final is not available submit draft.

Part H: Investigator Brochure. Required for projects proposing starting with a clinical trial. If final is not available submit draft.

Part I: Copies of authorization for cross reference of Drug, Device or Facility master files.

Part J: Licenses and agreements (MTAs). If you have licenses or MTAs in place, submit copies.

Part K. Evidence of Commercial Validation.

Part L: Related Business Entities Disclosure Form (Adobe PDF template).

The Application includes the following sections:

1. Abstract *(divided in four parts of up to 3000 characters each in Part A)*

P1. Project Description: Briefly describe the proposed therapeutic candidate and summarize the scientific rationale for the proposed intervention in the target disease/injury.

P2. 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

P3. Proposal Overview: Summarize the proposed project plan and describe how it will (a) achieve the overall objectives of the Strategic Partnership Program, which is to leverage CIRM funding and provide follow-on funding to bring therapies through development and (b) achieve the specific objective of this RFA, which is to complete a clinical study within the 4-year project period.

P4. Milestones: Summarize high level milestones to be achieved within the four-year 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 the biopharmaceutical 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 and will be available online; therefore, do not include proprietary or confidential information or information that could identify applicant (e.g., PI name, applicant institution name or location).

4. Key Personnel *(included in Parts 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. For example, list the key lead investigator for each clinical site even though he/she will be compensated as part of a subcontract. It is not necessary to name other clinical site personnel who will be participating in the conduct of the study. Personnel that are not key, such as technical support staff, may be supported by award funds but not named. A minimum of one percent effort is required for each key person with the exception of the PI, who is required to commit a minimum of thirty percent (30%) 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 biographical sketch should highlight relevant experience, in particular, team leadership, conduct of clinical studies and/or contribution to regulatory filings for product development. Include relevant publications, patents or patent applications. Following the biosketch for the PI, provide biosketches for functional area heads and/or members of the development core team (including the individuals responsible for overseeing clinical, clinical operations, regulatory, CMC, data management and translational research activities) and for the lead clinical investigator at each proposed site. Thereafter, include all remaining biosketches in alphabetical order.

5. Budget *(included in Parts A and E)*
Provide all budget information requested in the budget section of Part A and in Part E. Specify and justify costs for subcontracts and consultants in the appropriate section in Part A. In the activities-based budget spreadsheet (Part E), detail activities proposed to be funded by CIRM through this award, funded through another CIRM award, or through co-funding either by self funding or through third parties.
All allowable costs for research funded by CIRM are detailed in the CIRM Grants Administration Policy (GAP, see Section XI.A of this RFA).
Under this RFA, CIRM-funded allowable costs include the following:

- ***Salaries for Key Personnel and other Support Staff***
  Salaries for personnel may include the Principal Investigator and key technical or other 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 for financial administration can be budgeted as direct project costs if adequately justified. All other 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 a CIRM Strategic Partnership I Award are encouraged to attend a CIRM-organized grantee meeting in California and will be required to attend Clinical Development Advisory Panel (CDAP) meetings in San

Francisco at key milestones/decision points. Applicants should budget for one such meeting per year. Travel costs for these meetings should be included 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 XI.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. 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; design of a toxicology study; 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. (Clinical trial execution would include blinding, randomization, patient recruitment, patient treatment, medical monitoring, data collection, clinical site selection/site initiation and IRB activities.)

For any clinical trial that is part of the proposed project, at least one of the clinical sites implementing the protocol must be in California.

•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 for for-profit and non-profit applicants are limited to 20 percent 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. Target Product Profile *(up to 2 pages; use TPP template in Part B; also included as sample A in this RFA.*
Provide a target product profile (TPP) for the proposed therapeutic candidate. The TPP provides the aspirational product attributes 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 Target Product Profile template in Part B, 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). It is worth noting that while this document was developed and issued by the FDA's Center for Drug Evaluation and Research, it contains many guiding principles that apply to developing a TPP for cell therapies and biological products, as well as to CDER-regulated products.

7. Clinical Competitiveness and Impact *(up to 1 page in Part B)*
Summarize the current standard of care and competitive landscape for the target disease/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. Describe the pharmacoeconomic rationale for the proposed therapeutic. Explain how the proposed project will advance the field of stem cell-based or regenerative medicine.

8. Risk/Benefit *(up to 6 pages in Part B)*
Briefly describe the rationale for the proposed therapeutic intervention. Provide a summary (in tabular form) of the key preclinical and clinical (if available) safety and efficacy studies and summarize major outcomes and findings (you may reference appropriate sections of the Investigator Brochure).

Describe the potential benefits and risks of the proposed therapy and explain why the potential benefits outweigh the risks and justify use of the proposed therapeutic intervention in the target disease/injury. The Risk/Benefit analysis is based on the target patient population, other therapeutic options for that population, the scientific rationale, preclinical pharmacology and toxicology studies, and the therapeutic approach.

9. Development Plan to End-of-Phase II *(up to 3 pages in Part B)*
Summarize the development plan to End-of-phase II for the proposed therapeutic candidate and provide a high-level timeline highlighting key preclinical, clinical, CMC, regulatory and other milestones and major decision points, as well as costs to achieve these major milestones. As noted above (Section VII, 3), End-of-Phase II is defined as completion of early clinical studies providing sufficient information on safety, efficacy and dose, to enable the transition to phase III.

10. Project Plan, Milestones, and Timeline *(up to 8 pages plus 1 page for timeline, the latter in Gantt chart format or equivalent, in Part B)*
Describe the project plan and scope of activities proposed for funding under this award. Indicate activities to be conducted by the applicant and/or, if applicable, by the partner.

The Project Plan may overlap wholly with the above Development Plan or may comprise a subset of that plan. Explain how the Project Plan contributes to, and advances, the overall Development Plan to End-of-Phase II.

If the project includes IND-enabling studies, summarize the preclinical IND-enabling plan and describe the objectives of the planned studies.

Provide a timeline for the proposed project that includes key Preclinical, Clinical, CMC, Regulatory, and other critical path activities, and indicate key milestones and go/no go decision points. Milestones should describe precise, quantifiable outcomes of key activities, not simply the work to be conducted.

Identify potential risks to the project and describe the mitigation strategies.

11. IND Status *(up to 2 pages in Part B)*
Summarize any pre-pre-IND discussions and pre-IND meetings with the pertinent section(s) of the regulatory agency regarding the proposed project. Provide copies of any actual FDA correspondence in Part F.
If an IND has not yet been filed, provide a summary with timeline, of the IND-enabling plan, indicating activities already completed and those remaining to be completed.

Summarize the IND status for the proposed therapeutic candidate. Briefly summarize any clinical hold issues and explain how they were/will be resolved. Provide copies of actual FDA correspondence in Part F.

If any amendments to the active IND are planned/required for the proposed project, provide evidence that studies supporting such amendments have been completed.

12. Clinical Protocol Synopsis *(up to 8 pages in Part B Section 3)*
Using the CIRM CLINICAL PROTOCOL SYNOPSIS template, provide a Clinical Protocol Synopsis for each clinical study proposed (up to 8 pages). A copy of this template has been provided as Sample B of this RFA. If the proposed project starts with a clinical trial, provide the full clinical protocol in Part G (submit draft if final is not available).

13. Manufacturing Plan Synopsis for *(up to 6 pages in Part B Section 4)*
Using the CIRM MANUFACTURING PLAN Template, summarize the manufacturing strategy to support the proposed clinical studies. A copy of the template has been provided as Sample C of this RFA.

14. Principal Investigator (PI), Development Team and Leadership Plan *(up to 2 pages in Part B)*
Describe the leadership plan and organizational structure of the development team. List the key members (including consultants) and indicate their roles. Describe the plan for functional area leadership and management (including: Clinical, Clinical Operations, Regulatory, CMC, Translational Research). Indicate who will have responsibility for regulatory and safety filings; data collection and monitoring; and quality control. Describe the plan for oversight of CMOs/CROs. Indicate Applicant and, if applicable, Partner roles and responsibilities; describe the plan for communication, process for project decision making, and plans for resolution of potential issues or conflicts.

15. Collaborations, Assets, Resources and Environment *(up to 3 pages in Part B)*
Provide a list of collaborations (includes development

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

Summarize the assets, knowhow and expertise that the partner 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 brief 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.

16. Clinical Sites *(up to 2 pages in Part B)*
Provide a list of clinical sites for the proposed clinical trial. Provide evidence that the clinical sites have experience in conducting translational early Phase I and II trials. Provide evidence that the clinical sites' projected patient enrollment plan is realistic.

17. Licenses and Agreements *(up to 2 pages in Part B).*
Describe intellectual property assets (patent applications, patents) and any licenses of rights important to development of the therapeutic. If applicable, describe the status of letters authorizing the ability to cross reference Drug, Device or Facility Master File (DMF, FMF). If possible provide copies of authorization letters in Part I.

Provide a brief summary describing the status of Material Transfer Agreements (MTA) or licensing agreements for cell lines or other materials that are critical to the development of the therapeutic candidate and describe the role of those materials in the development of the product. In Part J, provide copies of essential MTA(s), or provide term sheets or letters of intent if an MTA has not yet been entered into. If not possible, please summarize the terms and what stage negotiations are in, including whether there is a term sheet, letter of intent or MTA or licensing agreements.

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

19. Due Diligence Report **(***Part D***)**
If the proposed project has undergone a due diligence analysis by a pharmaceutical/biotechnology partner resulting in an executed development agreement, or term sheet or letter of intent to enter into a development agreement, provide a summary of the scope and extent of the due diligence investigation, including a list of specific assessments, the number and

expertise of personnel involved in conducting the investigation, and a summary of key outcomes.

20. Investigator Brochure *(Part H)*
If the proposed project starts with a clinical trial, provide a copy of the Investigator Brochure for the candidate therapy. If the final is not available submit a draft.

21. Evidence of Commercial Validation *(Part K)*
1) **If the applicant organization is a for-profit** and is seeking to establish commercial validation through demonstration of financial strength and historical investment (see Section V.D.1, above), provide documentation showing that the applicant has:

(a) obtained in the past two years, or will obtain concurrent with the issuance of the CIRM award, an equity and/or programmatic investment by venture capital firms, large biotechnology or pharmaceutical companies and/or non-profit foundations in the amount of at least $15 Million AND
(b) at least one year of balance sheet cash (as demonstrated by its most recent financial statements and pro-forma for any concurrent investment) based on the last twelve months (LTM) operating cash burn rate, without taking into account any funds provided by CIRM, AND
(c) in the event of a concurrent / pro forma investment, an executed term sheet or letter of intent evidencing satisfaction of paragraph (a) and (b) above, provided that no funds will be disbursed to a successful applicant until it provides a fully executed agreement evidencing satisfaction of the provisions in paragraph (a) and (b) above. For purposes of this RFA, LTM operating cash burn is defined as cash flow from operations, less capital expenditures and any debt service.

Specific documents that should be provided are:

- Financial statements prepared in accordance with US GAAP for the quarters ended 3/31/11 and 3/31/12, as well as year ended 12/31/11.
- Documents sufficient to establish the amount invested by venture capital firms, large biotechnology or pharmaceutical companies and/or non-profit foundations, including supporting data such as a capitalization table, to demonstrate $15 million in prior / concurrent investment

AND/OR

2) **If the applicant organization is a non-profit or a for-profit** and is seeking to establish commercial validation by virtue of a collaborative research and development arrangement with a large biotechnology or pharmaceutical company (see Section V.D.2, above), the applicant should submit a fully executed development agreement if such exists. If such an agreement has not yet been entered into, then the applicant must submit an

executed copy of a term sheet and/or letters of intent relating to such agreement.

A fully executed term sheet or letter of intent relating to the agreement shall address the following:

- Levels of co-funding for development for the proposed project which the applicant, with its biopharmaceutical partner, agrees to on an annual basis and the amount it is requesting CIRM to fund annually.
- A general description of the deal structure with the biotechnology or industry partner (e.g. option agreement, licensing agreement with rights of termination, opt-ins, or opt-outs etc)
- For all sources of development funding identified by applicant, all conditions to its and the biotechnology or industry partner's obligations to provide such funding, including but not limited to Go/No Go decision points, opt-ins, opt-outs, rights to terminate and payments associated with a right to terminate/opt-in/opt-out.
- All payments the applicant would receive including upfront payments, any research and development support, full-time equivalent (FTE) support, milestone payments and royalty payments.
- The amount, nature and value of in-kind services, including but not limited to FTEs, that an industry partner will provide without charge, such as regulatory expertise, process development, and clinical development expertise.

22. Related Business Entities *(Part L)*

In order to comply with the Conflict of Interest policies under which CIRM operates, all applicants 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 on Part K and submit 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).

B. Application Submission Instructions

All applicable parts of the Strategic Partnership I Award application must be submitted to CIRM no later than 5:00 PM PDT on June 26th 2012 via the

Grants Management Portal (https://grants.cirm.ca.gov). It is the applicant's responsibility to meet this deadline; no exceptions to this deadline will be made.

C. 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 August 6th PDT 2012. 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 Senior Review Officer 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:

- 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 (e.g., IND, IDE) filings or approvals occurring 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.

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

IX. Schedule of Deadlines and Reviews

LOI due	5:00 pm (PDT), May 16th 2012
Applications due	5:00 pm (PDT), June 26th 2012
Scientific Review of Applications by Grants Working Group (GWG)	September 2012
Review of Evidence of Commercial Validation by the IP and Industry Subcommittee	4th Quarter 2012
Review and Approval by ICOC	October or December 2012.

Earliest Funding of Awards	January 2013

X. Contacts

For information about this RFA:

Ingrid Caras, Ph.D.
Science Officer
California Institute for Regenerative Medicine
Email: icaras@cirm.ca.gov
Phone: (415) 396-9114

For information about the review process:

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

XI. CIRM Regulations

Grant awards made through this RFA 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.

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/files/meetings/pdf/2011/062211_Item_09_SWG_Trials.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. Clinical Trial Registration

CIRM requires that any clinical trial funded under any of its funding programs be listed on http://clinicaltrials.gov/. CIRM will also encourage awardees to share the results, at the completion of their studies, for the benefit of the field.

Sample A: 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 B: CIRM CLINICAL PROTOCOL 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
MAIN INCLUSION/EXCLUSION CRITERIA
Specify the main inclusion/exclusion criteria and explain the rationale.
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
Summarize the study design, including type of study, number of arms, controls or comparators
SUBJECT NUMBER
Provide the total number of study subjects, the number per study arm, and justification
TREATMENT DURATION
Specify the length of the treatment period
DURATION OF FOLLOW UP

Specify the length of the protocol-specified follow up period
DOSE LEVEL (S) AND DOSE JUSTIFICATION
Specify the dose level(s), number of doses, and dosing frequency. Summarize how dosing was determined
ROUTE OF DELIVERY
Specify how the doses will be delivered
DATA and SAFETY MONITORING PLAN (DSMP)
Summarize the Data and Safety Monitoring Plan. Describe measures that will be implemented to minimize risk to study subjects e.g. specific inclusions/exclusions; plans to ensure medical intervention in the case of an adverse event for subjects; plans for surveillance, detection and management of specific adverse events that might or could occur; potential use of an Independent Safety Monitor or Data Safety Monitoring Board (DSMB)
STOPPING RULES
Specify stopping rules
IMMUNE MONITORING & IMMUNOSUPPRESSION
Describe and justify the plan for immunosuppression and immune monitoring (if applicable)
SUPPORTING STUDIES
Summarize supporting studies that are part of this clinical study (e.g. imaging, biomarker analyses, cell phenotyping, genotyping, gene expression analyses), that will provide critical additional data to address the objectives of this RFA or inform decisions on continued clinical testing. Include: *Objectives and rationale* *Sample collections (specify type, frequency)* *Testing methodology* *Data analysis* *Special considerations*
ASSAYS/METHODOLOGIES
Briefly describe any specialized assays or methodologies that will 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
STATISTICAL ANALYSIS PLAN
Summarize the Statistical Analysis Plan or describe how the data will be analyzed
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)
CLINICAL SITES
Indicate the number of clinical sites that will participate in the study. Summarize the criteria for site selection. Provide a list of proposed sites with a brief description of the site's experience and capabilities in the conduct of clinical research.
CLINICAL OPERATIONS PLAN
Summarize the plan for managing the conduct of the clinical study. Describe plans for training clinical investigators and personnel at clinical sites and the plan for oversight and monitoring of clinical sites. Indicate who will be responsible for management and sign off of clinical operations activities.
ENROLLMENT
Describe the enrollment strategy and provide a timeline showing enrollment projections Describe plans for inclusion of women and minorities
LONG TERM FOLLOW UP
Describe requirements and plans for long term follow up and indicate how these will be supported
TIMELINE
Provide a timeline for completion of the study and indicate relevant milestones

Sample C: CIRM MANUFACTURING PLAN SYNOPSIS TEMPLATE

TEST ARTICLE
Describe the Test Article
STARTING CELL
Specify starting cell line or cellular source
MANUFACTURING PROCESS
Provide a brief description of the manufacturing process *Provide a flow diagram of the process from starting cell source to final test article* *Describe the plan for shipment of released lot from the manufacturing facility to clinical sites and describe the steps that will be performed at the clinical site*
PROCESS DURATION
Specify the duration of a manufacturing run and time required to test and release a lot
PRODUCT RELEASE
Provide a list of the product release assays and acceptance criteria
IDENTITY ASSAY
Briefly describe the Identity assay(s)
POTENCY ASSAY
Briefly describe the Potency assay(s)
ADDITIONAL CHARACTERIZATION
Briefly describe any additional characterization assays routinely performed (but not required for lot release)
LOT SIZE
Specify the average lot size (number of doses/treatments)
LOT REQUIREMENTS FOR PROPOSED CLINICAL WORK
Indicate the projected number of lots needed to support the proposed clinical work
LOT FAILURE
Specify the % failure of lot release
GMP MANUFACTURING FACILITY
Indicate where GMP manufacturing of the candidate cell therapy will be performed. Describe the experience and track record of the manufacturing facility
RELEASE TESTING FACILITY
Indicate where Release Testing will be performed. Describe the experience and track record

of the testing facility
DOSE FORMULATION AT CLINICAL SITES
Briefly describe the plan for managing product quality control at clinical sites
CMC ACTIVITIES PROPOSED FOR FUNDING
Specify all CMC-related activities proposed for funding under this RFA and indicate which activities will be funded by CIRM
RISKS
Identify potential risks (e.g. potential for clinical hold, lot failures) and mitigation strategies
TIMELINE
Provide a timeline for the manufacturing runs planned to support the proposed clinical research and indicate relevant milestones
High Level Manufacturing Process Flow Diagram
Include - Material, Unit Operations and Analytical Methods (in process and release tests) and Timeline