RFA 13-03B: CIRM Strategic Partnership III Awards (Track B: Milestone Payment Pathway)

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 future clinical trials (e.g. follow-on financing), (ii) provide a source of co-funding for the earlier stages of clinical development, and (iii) enable CIRM funded projects to access expertise within pharmaceutical and large biotechnology partners in areas such as 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, disease foundations and/or through the public markets; and financial statements evidencing significant liquid assets; or (ii) a collaborative research agreement with a large biotechnology or pharmaceutical company executed by two weeks prior to review by the Application Review subcommittee of CIRM's Governing Board, the Independent Citizen's Oversight Committee (ICOC; Q2, 2014; exact date to be determined). These requirements are described further in Section V.D. The agreement with the large biotechnology or pharmaceutical company need only cover co-funding and collaboration support for the proposed project (and not future development).

CIRM intends to offer repeat calls under this initiative every 6-9 months. The focus, scope and objective may differ with each solicitation.

Award Tracks
Strategic Partnership III will have two possible Award tracks, Track A and Track B, as described below. Under this RFA, a for-profit applicant may apply through either Track A or Track B, but not both. Non-profit applicants may only apply under Track A.

Track A Awards (RFA 13-03A)
A Track A award will provide funding for a single development project for a single therapeutic candidate per applicant over a project period of up to 4 years. Under Track A, a non-profit Principal Investigator (PI) may submit a single application, and a for-profit organization may submit a single application.

Track B Awards (RFA 13-03B: Milestone Payment Pathway)
Track B awards will provide funding for up to five approved development projects per for-profit applicant organization, with funding contingent on successful achievement of the Major Development Milestone for each project, which will be agreed to between CIRM and the applicant in advance of award issuance. Under Track B, a for-profit applicant organization may apply for funding for up to five different development projects, which may be focused on the development of different therapeutic candidates, or the use of a single therapeutic candidate to target distinct, non-overlapping disease indications.

Award Tracks A and B in RFA 13-03 are compared in Table 1:

Table 1: Features of RFA 13-03 Track A and Track B

Award Feature	RFA 13-03A (Track A)	RFA 13-03B (Track B)
Applicant Organization	Not-for-Profit or For-Profit	For-Profit
Maximum Amount of Award Funding	Up to $10M* of **Total** Project Costs (including indirect & facilities costs)	Up to $10M of **Direct** Project Costs per Project
Co-funding Requirement	CIRM : Applicant = 1 to 1	CIRM : Applicant = 1.5 to 1
Number of Applications per Organization	1	Up to 5
Number of Applications per Principal Investigator	1	Up to 3
Readiness	Pre-IND Meeting Required (for Preclinical Stage Projects) or IND Filed (for Clinical Stage Projects) Before Application Deadline (October 21, 2013)	IND Filed Prior to Funding Approval (Q2, 2014)
Award Payment Schedule	Quarterly or Semi-annual Disbursements Throughout 4 Year Period of Award	Only upon Successful Achievement of Major Development Milestone
Commercial Validation Requirements to Demonstrate Financial Strength	Equity and/or Investment of $10M Over Previous 2 Years	Equity and/or Investment of $15M Over Previous 2 Years
Project Scope	IND-enabling Preclinical and Clinical Stage Activities	Clinical Stage Activities (including support activities such as manufacturing costs incurred during the project period)

* In certain extraordinary circumstances, a Track A award may be made up to $15M.

The specific details of RFA 13-03B: TRACK B AWARDS are described below. To apply for a Strategic Partnership Track A Award, refer to RFA 13-03A: TRACK A AWARDS.

RFA 13-03B: TRACK B AWARDS

II. Objectives and Scope

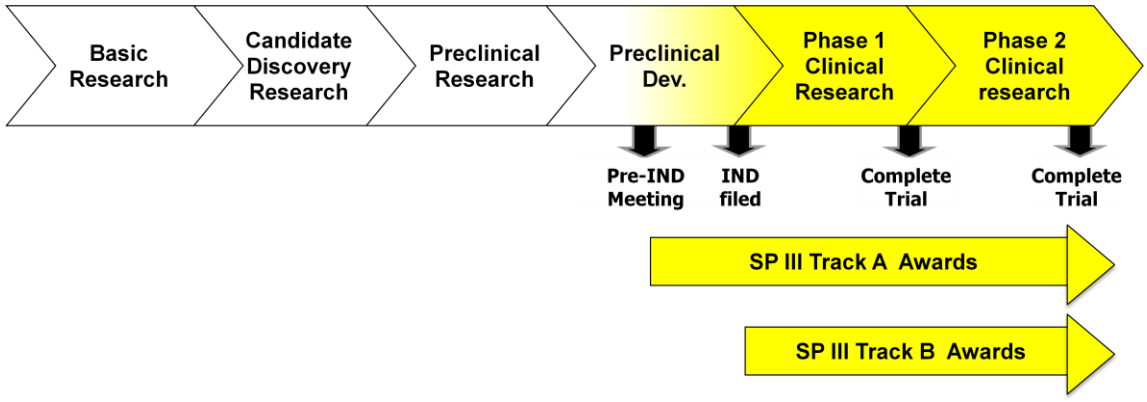
A. Objective

For each project under a Strategic Partnership III Track B award (RFA13-03B), the objective will be to provide, in 4 years or less, evidence of biological activity/efficacy as well as safety in humans by completing a Phase 1 or Phase 2 clinical trial for a stem cell-based therapy. Achievement of this objective is synonymous with achievement of the Major Development Milestone for the project.

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. Evidence of biological activity/efficacy in humans may be established through use of a suitable, *clinically meaningful* biomarker(s) or by using accepted clinical endpoints.

B. Scope

The scope of the Strategic Partnership III Awards (RFA 13-03A and RFA 13-03B) is illustrated in the figure below. RFA 13-03B (Track B) awards will fund clinical stage research only.



The key objective of a Strategic Partnership III Track B award (RFA13-03B) is to achieve the Major Development Milestone, which is to complete a clinical trial that provides evidence of biological activity/efficacy and safety in humans.

Activities eligible for CIRM funding, provided that the Major Development Milestone is met, include, but are not limited to, the activities listed below:

- Any clinical activities necessary for achievement of the Major Development Milestone.

- Supporting activities that enable the relevant clinical study such as cGMP production and/or further qualification/validation of relevant assays.

- Supporting studies performed in the context of the relevant clinical trial that provided critical additional data to better inform decisions on continued clinical testing. Applicants will be expected to justify how such studies specifically informed the trial results.

- Process development activities necessary to enable further development of the therapeutic candidate such as optimization of cGMP production or development and validation of a potency assay.

In general, CIRM funding must be used to support research in California (see Section VIII.B.5 for a more detailed discussion of allowable uses of CIRM funding).

Research activities that fall outside the scope of a RFA13-03B (Track B) award and are not eligible for CIRM funding include the following examples:

- Phase 3 clinical studies

- Early research and translation activities leading up to selection of a therapeutic development candidate

- cGMP production for Phase 3 studies

- Preclinical IND-enabling activities

- Preclinical activities to enable removal of a clinical hold

- 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

C. Priority Areas

With respect to Track B applications, priority for the funding allotted for Strategic Partnership III will be given to eligible proposals that meet one of CIRM's priorities for RFA 13-03B (Track B), listed below:

- Proposals from applicants that have secured a development agreement with a large biotechnology or pharmaceutical company (with a market capitalization of at least $1B) committed to providing financial support for further development of the proposed candidate if milestones are met.

- Proposals that include a Phase 1 or Phase 2 clinical study that could demonstrate clinical proof-of-concept in patients by the end of the project period, based on accepted endpoints of clinical efficacy or an acceptable biomarker relevant to the disease and predictive of clinical efficacy.

III. Award Information

A. Award

Under RFA 13-03, CIRM intends to commit up to $80M to support up to 8 development projects (in total) across both Track A (RFA 13-03A) and Track B (RFA 13-03B). Track B awards will fund up to $10M per project of *direct* project costs for up to five projects per applicant, contingent upon achievement of the Major Development Milestone for that project (justifiable costs *exclude* facilities costs or indirect costs). For all proposals, co-funding is required (see Section III.B). The application must include an activity based budget which identifies activities that CIRM will fund and those that the applicant will fund. For RFA 13-03B awards, the option for a no cost extension will be only at the discretion of the President of CIRM.

B. Co-Funding

Under a RFA 13-03B award, CIRM will require co-funding from the applicant in a 1.5 to 1 ratio (CIRM to applicant). CIRM will fund up to 60% of justifiable ***direct*** project costs (indirect costs and facilities costs will NOT be funded) up to $10M/project. The applicant's co-funding may come from the applicant's own assets, from an industry partner, or from another funding source arranged by the applicant. Applicant co-funding may be provided in the form of capital or justifiable in-kind services.

C. Budgets and Milestones

For all RFA 13-03B awards, CIRM reserves the right to negotiate the success criteria for achievement of the Major Development Milestone for the project prior to issuance of the Notice of Grant Award (NGA) or Notice of Loan Award (NLA).

D. Covered Clinical Trial Costs

CIRM requires any clinical trial proposed for funding to include at least one clinical trial site in California. Only applicants that have demonstrated a sufficient presence in California (as described in Section V.D) are eligible for funding. Expenditures *may* include costs of clinical trials conducted outside of California as part of the funded project; see Section VIII.B.5 for further explanation of permissible expenses. 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.

E. CIRM Oversight

The Grants Administration Policy (GAP; Section XI.A) requires that the grant or loan recipient submit annual Progress Reports to CIRM. At that time, award recipients will be expected to provide periodic documentation (such as copies of IRB approvals) indicating that the research is being conducted in compliance with CIRM's regulations. The GAP requires that award recipients notify CIRM of any serious adverse event related to the therapeutic candidate in a clinical trial. In addition, communication and reporting responsibilities of the grant or loan recipient to CIRM will include providing notification of any clinical hold orders.

F. Award Termination

CIRM reserves the right to terminate an award for one or more projects if a clinical trial is terminated by the applicant for safety or other reasons, or if the IND is placed on an indefinite clinical hold.

G. Commencement/Other CIRM Awards

Given the urgency of CIRM's mission, all approved applications must be initiated (award start date in issued and signed NGA or NLA) within 6 months of approval and authorization for funding by the Application Review Subcommittee of the Independent Citizens' Oversight Committee (ICOC), unless CIRM's President grants an extension based upon compelling justification of the need for additional time. CIRM will only provide funding for activities conducted after, or within 90 days of, issuance of the NGA or NLA.

IV. Award Mechanism

For-profit applicants may choose to accept the award in the form of a grant or a loan. Grants 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 an amendment to 17 Cal. Code Regs. section 100608(b) is currently pending with such proposed amendment available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants.

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. 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. Applicants should be advised that with respect to any and all RFAs, the IP and Industry Subcommittee of CIRM's board may elect to adopt terms other than the guidelines set forth in the LAP. 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. It is anticipated that with respect to RFA 13-03B, the IP and Industry Subcommittee will consider the following loan terms for Track B awards: (i) commencement of the Loan term at the time of disbursement of CIRM funds; (ii) maximum permitted term of five (5) years (iii) specific terms and conditions relating to forgiveness of a Product Backed Loan and (iv) other terms as appropriate.

V. Eligibility

For any project proposed, the applicant organization must be the sponsor of the IND, and the PI must be an employee of the applicant organization.

A. Project Eligibility

A proposal previously reviewed under a prior Strategic Partnership RFA may be submitted provided that the eligibility requirements of RFA 13-03B (Track B) are met.

1. Project Objective: A proposed project must address a serious unmet medical need/injury and the project objective (and Major Development Milestone) will be to provide, within 4 years or less, evidence of safety and biological activity/efficacy in humans by completing a Phase 1 and/or Phase 2 clinical trial under an Investigational New Drug (IND) application filed with the Food and Drug Administration (FDA).

2. Therapeutic Candidate: Each proposed project must be focused on 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 derived from pluripotent stem cells
   - allogeneic tissue-derived stem cells or progenitor cells for repair/regeneration
   - stem cell-engineered functional tissues for implantation in vivo
   - a small molecule or biologic demonstrated to target normal endogenous stem cells in vivo as the primary mechanism of action (MOA), for repair/regeneration

   Therapeutic candidates that fall outside the scope of this RFA include the following:

   - minimally manipulated bone-marrow or minimally manipulated cord-blood
   - genetically or pharmacologically-modified hematopoietic stem cells (HSCs), bone-marrow or cord-blood
   - unmodified HSCs
   - small molecules and biologics, unless specifically targeting normal endogenous stem cells in vivo as primary MOA, for repair/regeneration
   - autologous mesenchymal stem cell (MSC) approaches
   - autologous tissue-derived stem cell approaches

3. Readiness: The Strategic Partnership III RFA 13-03B is designed to capture mature development projects that are at or near an early clinical research stage.
   - An IND for the proposed therapeutic candidate must be filed with the FDA by the date of the Independent Citizens' Oversight Committee (ICOC)/Application Review Subcommittee meeting to approve and authorize funding for Strategic Partnership III awards (Q2, 2014; exact date to be determined).

4. Commercial Validation: In addition, applicants must provide **Evidence of Commercial Validation** (Section V.D).

B. Institutional Eligibility

Applicant organizations must demonstrate a sufficient presence in California (as described in Section V.C) to be eligible for funding. All applicants must also provide evidence of commercial validation to be eligible for this award (Section V.D). Only for-profit organizations may apply for Track B awards under RFA 13-03B.

"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".

Under RFA 13-03B (Track B), an applicant organization may submit up to five applications, each focused on a single distinct development project. Applicant organizations that hold two or more of the following awards: Disease Team, Disease Team Therapy Development, Strategic Partnership I or Strategic Partnership II, as of the application due date, October 21, 2013, are not eligible to apply for this award.

C. California Presence

By the Application Date (October 21, 2013): If the applicant organization does not already have operations located in California, it must have a lease or ownership of a location from which the project will be performed, or a letter of intent or term sheet demonstrating that the applicant is engaged in negotiations to secure a specified location in California from which location it will engage in activities critical to the project.

In addition, the applicant must show the following ties to California:

1. To qualify for any CIRM funding, an applicant organization must have at least 2 full-time equivalent (FTE) non-administrative employees in California during the project period. In addition, the PI is expected to spend at least 30% time in California, working on the approved project. Thus, at a minimum, each applicant organization is required to have at least 2.3 FTEs (0.3 of which represents the PI) located in the state of California during the project period.

2. In addition to the minimum requirement of 2.3 FTEs in California, as described in Section V.C.1, for applicant organizations having greater than 30 employees world-wide, the following requirements apply:

   (i) For applicant organizations which have, within 6 months of the start of the CIRM funded project, at least an additional 5% of the applicant organization's workforce (FTE, up to a maximum of 50 employees) located

in California during the project period, the applicant organization would be eligible to use its approved CIRM funding for clinical trial costs and non-research costs incurred both within and outside the State of California, as permitted by CIRM's regulations and RFA13-03B.

(ii) For applicant organizations which do not satisfy the requirements of subparagraph (i), above, the organization must spend 100% of its approved CIRM funding in California.

Failure to adhere to these requirements will result in a penalty and possible termination of the funding commitment.

D. Evidence of Commercial Validation

In order to attract projects having or likely to attract industry investment, including follow-on financing of Phase 3 clinical trials, 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, 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, an equity and/or programmatic investment through the public markets or by venture capital firms, large biotechnology or pharmaceutical companies (market capitalization of at least $500M), non-profit foundations or government entities, in the amount of at least $15M **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, and the first year of funds for each proposed project, without taking into account any funds provided by CIRM. For purposes of RFA 13-03B, LTM operating cash burn is defined as cash flow from operations, less capital expenditures and any debt service.

AND/OR

2. If the for-profit applicant organization is seeking to establish commercial validation by virtue of a collaborative research agreement with a large biotechnology or pharmaceutical company having a market capitalization of at least $500M to provide the financial and/or in-kind support for the match required by RFA 13-03B, the applicant should submit a fully executed copy of such agreement if one already exists. If such an agreement has not yet been entered into, by the date of the LOI (August 22, 2013) the applicant must provide a letter from the biotechnology or pharmaceutical company indicating its

interest in co-funding the proposed project and that the parties are negotiating the terms of support. The applicant must submit a term sheet and/or letter of intent relating to such agreement, signed by the partner, by the date that Supplemental Information must be filed (January 6, 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 Strategic Partnership III awards (Q2, 2014; exact date to be determined).

See Section VIII.A for specifics of documentation required as part of the LOI and Application. **The agreement with the large biotechnology or pharmaceutical company** need only cover co-funding and collaboration support for the proposed project (and not future development). To that end, the agreement can be in the form of an option, license, funded research collaboration or sponsored research agreement, as long as it provides for a level of co-funding and/or in-kind services sufficient to permit the applicant to meet its co-funding obligations.

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

E. Principal Investigator (PI) Eligibility

CIRM requires that a single PI be designated for each proposed project. A designated PI for RFA 13-03B (Track B) may be PI on no more than three proposed projects. The PI is the assigned point of contact for CIRM for the project 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.

F. Extraordinary Exceptions

In extraordinary circumstances, the President has the discretion to permit exceptions to requirements or limitations in Sections V and VIIIA. 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 (GAP; Section XI.A) and the Loan Administration Policy (LAP; Appendix A), 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 X.

VI. Application and Evaluation Processes

Submission of an application for a Strategic Partnership III Track B (RFA 13-03B) Award involves a two-step process. An eligible applicant organization (see Section V for eligibility criteria) must first submit a Letter of Intent (LOI) for each project proposed under the award. Up to five LOI's may be submitted per applicant organization and each LOI must have a designated PI, who may be PI on no more than three LOI's. Applicants will be notified if an LOI is **NOT** accepted.

In the second step of the process, eligible applicants will submit a full application for each project proposed under the award for which an LOI was accepted (up to five applications per applicant organization). Applications will only be accepted from applicants that meet all eligibility requirements and have submitted an LOI that was accepted by CIRM.

A. Application Review Process

Applications for the CIRM Strategic Partnership III Awards 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 (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. 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 priorities for RFA 13-03B (Track B) include:

- Proposals from applicants that have secured a development agreement with a large biotechnology or pharmaceutical company (with a market capitalization of at least $1B) committed to providing financial support for further development of the proposed candidate if milestones are met.

- Proposals that include a Phase 1 or Phase 2 clinical study that could demonstrate clinical proof-of-concept in patients by the end of the project period, based on accepted endpoints of clinical efficacy or an acceptable biomarker relevant to the disease and predictive of clinical efficacy.

B. Project Evaluation and Milestone Payment

Upon notification by the award recipient that the objective of the project has been achieved, a group of external experts, the Clinical Development Advisory Panel (CDAP), will evaluate the data supporting achievement of the Major Development Milestone and provide advice to CIRM as to whether the Major Development Milestone has been met.

Prior to disbursement of the Milestone Payment, grantees will be expected to provide a final financial report detailing the actual justified project costs incurred during the project period. The amount of the Milestone Payment will be determined as the lesser of: 60% of actual eligible direct project costs incurred during the project period or the award amount approved by the ICOC/Application Review Subcommittee for the project (based on 60% of projected costs), up to a maximum of $10M per project.

CIRM's confidentiality and conflict screening rules will apply to everyone who will have access to applications, or who will attend the review meeting, or who will evaluate the final data, including CIRM staff, external reviewers 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 XII.

VII. Review Criteria

Applications for RFA 13-03B (Track B) will be evaluated for scientific merit by the GWG in five key areas: 1) Significance and Impact; 2) Scientific Rationale and Risk/Benefit; 3) Design and Feasibility; 4) Principal Investigator and Team Leaders and 5) Collaborations and Resources. The specific criteria for review of applications are based on the standard review criteria described in the CIRM GAP (Section XI.A).

The GWG will be asked to give special consideration to CIRM's priorities for this RFA (Section VI).

A. Significance and Impact

1. Target Product Profile: Evaluate whether the target product profile (TPP), which should convey the long term aspirational product attributes and overall intent of the development program, is appropriate and contains metrics for key attributes to enable decision making.

2. Clinical Competitiveness and Impact: 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.

3. Responsiveness**:** Determine if the proposed therapeutic candidate convincingly uses or targets endogenous stem cells. 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.

B. Scientific Rationale and Risk/Benefit

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 data and any 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? Reviewers shall take into account that the Major Development Milestone will require a demonstration of safety and biological activity/efficacy in humans, and that no payment will be required from CIRM unless such milestone is satisfied.

C. Design and Feasibility

1. Major Development Milestone: Evaluate the proposed Major Development Milestone. Assess if it is based on objective and clinically meaningful measures that could provide evidence of clinically relevant biological activity/efficacy as well as safety of the proposed therapy. Assess if there are significant logistical hurdles for realizing the Major Development Milestone (such as manufacturing or enrollment challenges).

2. Development Plan to End-of-Phase 2 and Project Plan: "End-of-Phase 2" is here defined as completion of early clinical studies providing sufficient information on safety, efficacy, dose and dosing regimen, to enable the transition to Phase 3. The Project Plan may overlap completely with the Development Plan to End-of-Phase 2, or may comprise a subset of that plan.

   Under this RFA, proposed projects are expected to include a well thought out development plan to End-of-Phase 2 that is realizable, is designed to enable the transition to Phase 3, and supports achievement of the Target Product Profile. Evaluate if the proposed plan meets these criteria.

3. Proposed Clinical Study: Assess whether the proposed clinical study is well-designed and could achieve the project objective and Major Development Milestone. Assess if the efficacy endpoints or proposed biomarkers of activity are appropriate and provide objective measures of success. Assess if the study design and proposed endpoints are appropriate to inform continued development of the candidate therapy.

   4. 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. Are there steps in the manufacturing process that could adversely impact clinical adoption?

D. Principal Investigator (PI) and Team Leaders

Assess the proposed project with respect to the following:

1. PI and Team Leaders: Do the PI and Team Leaders have the relevant expertise and experience to successfully lead and execute the project?

2. Budget: Is the proposed activities-based budget reasonable and appropriate to support the project?

E. Collaborations and Resources

Assess the proposed project with respect to the following:

1. Clinical Investigators and Clinical Sites: Are the proposed clinical investigators and proposed clinical sites sufficiently likely to enroll patients and complete the trial within the 4 year project period?

2. Contract Services: Do the proposed CROs/CMOs/consultants have the appropriate experience and expertise to successfully meet expectations, timeline and deliverables? Are their contributions necessary for the project to be successful?

3. Assets: Are there sufficient intellectual property (IP) and/or licenses and material transfer agreements (MTAs) available to enable development of the therapeutic candidate?

VIII. Application Procedure

Applicants must follow these instructions for submission of Letters of Intent (LOIs) and applications for Strategic Partnership III Track B awards (RFA 13-03B). An eligible applicant organization may submit up to five applications for five distinct development projects, with no more than three applications having the same PI. Applicants will be notified if a LOI was **NOT** accepted.

Applications will only be accepted for those projects for which a LOI was submitted and accepted by CIRM. The PI and the project proposed in an application must be the same as those described in the corresponding LOI; otherwise, the application is deemed ineligible.

A. Letter of Intent (LOI) and Commercial Validation

An eligible applicant organization may submit up to five LOI's under RFA 13-03B (Track B) using the forms and instructions provided in the Grants Management Portal at https://grants.cirm.ca.gov. Each LOI should concisely describe the proposed project and explain how it will, within four years or less, achieve the Major Development Milestone and objective of RFA 13-03B, which is to complete a clinical trial that provides evidence of safety and biological activity/efficacy in humans for a candidate stem cell-based therapy. Documentation in support of commercial validation is required as part of the LOI submission. See below and refer to the LOI instructions and form.

Commercial Validation

Evidence of Commercial Validation must be provided as part of the LOI submission and consists of the following.

1. If the applicant organization is seeking to establish commercial validation through demonstration of financial strength and historical investment (Section V.D.1), provide documentation showing that the applicant has:
   (a) obtained in the past two years, an equity and/or programmatic investment through the public markets or by venture capital firms, large biotechnology or pharmaceutical companies, non-profit foundations or government entities in the amount of at least $15M **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) For purposes of RFA 13-03B, 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 June 30, 2012 and June 30, 2013, as well as year ended December 31, 2012.
- 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 $15M in prior investment. When available, (even if subsequent to the LOI deadline), applicant will provide financial statements prepared in accordance with US GAAP for the year ended December 31, 2013.

AND/OR

2. If the applicant organization is seeking to establish commercial validation by virtue of an agreement with a large biotechnology or pharmaceutical company having a market capitalization of at least $500M (Section V.D.2) to provide the financial and/or in-kind support for the match required by RFA 13-03B, the applicant should submit a fully executed copy of such agreement if one already exists. If such an agreement has not yet been entered into, by the date of the LOI (August 22, 2013) the applicant must provide a letter from the biotechnology or pharmaceutical company indicating its interest in co-funding the proposed project and that the parties are negotiating the

terms of support. The applicant must submit a term sheet and/or letter of intent relating to such agreement, signed by the partner, by the date that Supplemental Information must be filed (January 6, 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 Strategic Partnership III awards (Q2, 2014; exact date to be determined).

A term sheet or letter of intent relating to the agreement should address the following:

- Levels of co-funding for development for the proposed project (need not include future development) 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 agreement structure with the biotechnology or industry partner (e.g. option agreement, licensing agreement with rights of termination, opt-ins, or opt-outs etc.).
- All payments the applicant would receive including upfront payments, any research and development support, full-time equivalent (FTE) support, and milestone 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 experience in regulatory affairs, process development or clinical development.

The completed LOI and supporting evidence of commercial validation, 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 August 22, 2013. No exceptions will be made.

B. Application Forms

An applicant organization may submit up to 5 applications for RFA 13-03B (Track B), corresponding to the accepted LOIs, using the forms and instructions provided in the Grants Management Portal at https://grants.cirm.ca.gov. Application forms for this RFA will be available in August/September, 2013.

The application for RFA 13-03B (Track B) consists of up to **eight parts**:

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: Strategic Partnership III Track B Award Proposal (MS Word template). Includes Target Product Profile; Clinical Competitiveness and Impact; Scientific Rationale and Risk/Benefit, Major Development Milestone; Development Plan to End-of-Phase 2; Project Plan with Timeline; IND Status; Clinical Protocol Synopsis; Manufacturing Plan Synopsis; PI and Team Leaders; Key Collaborations: Intellectual Property, Licenses and Agreements; References (additional details in sections number 7-20, below).

Part C: Biographical Sketches for Key Personnel (MS Word template). Includes the PI and Team Leaders, as well as the lead clinical investigator for each site and letters of collaboration and/or institutional support.

Part D: Due Diligence Report. [Application Part D is not required for RFA 13-03B (Track B)]

Part E: Activity Based Budget

Part F: FDA Correspondence. [Application Part F is not required for RFA 13-03B (Track B)]

Part G: Clinical Protocol. Required for projects that propose conducting a clinical trial. If final is not available, submit draft.

Part H: Investigator Brochure. Required for projects that propose conducting a clinical trial. If final is not available, submit draft (additional details in section number 21, below).

Part I: Copies of Authorization for Cross Reference of Drug, Device or Facility Master Files. [Application Part I is not required for RFA 13-03B (Track B)]

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

The Application includes the following sections:

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

   Part 1. Project Description: Briefly describe the proposed therapeutic candidate and summarize the scientific rationale for the proposed intervention in the target disease/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 project and describe how it will achieve the Major Development Milestone, which provides, in 4 years or less, evidence of biological safety and activity/efficacy in humans for a candidate therapy that utilizes or targets stem cells.

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 character; 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 the key personnel (such as the PI and Team Leaders) employed by the applicant organization and indicate their roles on the project in the relevant sections of Part A. Key personnel who are not part of the applicant organization (such as the lead investigator for each clinical site) should be listed in the subcontract section of the application.

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 with respect to that person's role on the project. Include relevant publications, patents or patent applications.

5. Budget *(included in Parts A and E)*
Provide the budget information requested in the budget section of Part A and in Part E. Provide an activities-based budget spreadsheet (Part E), indicating key activities and associated costs. Provide a high level budget summary in Part A. All allowable costs for research funded by CIRM are detailed in the CIRM GAP (Section XI.A).

Under RFA 13-03B (Track B), CIRM-funded allowable costs include the following:

- ***Salaries for Key Personnel and other Support Staff***
  Salaries for personnel may include the PI 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 the full time annual salary for employees of a for-profit institution. Administrative support salaries for financial administration can be budgeted as direct project costs if adequately justified. All other administrative support salaries are Indirect costs and are not part of this award.

• 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 III Award are strongly 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 CIRM GAP (Section XI.A).

• 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.)

Except as set forth in Section V.C, 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, cGMP production. (Clinical trial execution would include blinding, randomization, patient recruitment, patient treatment, medical monitoring, data collection, clinical site selection/site initiation and Institutional Review Board (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.

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

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) a consultant. 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).

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

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 A 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). 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 products regulated by the Center for Drug Evaluation and Research (CDER).

8. Clinical Competitiveness and Impact *(up to 3 pages; 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.

9. Scientific Rationale and Risk/Benefit *(up to 10 pages; in Part B)*
Describe the scientific rationale for the proposed therapeutic intervention. Summarize the evidence supporting use of the proposed therapeutic in the target disease and provide key data. 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.

10. Major Development Milestone
State the proposed Major Development Milestone including success criteria; discuss the rationale for it and address why it meets the objective of the RFA which is to provide clinical evidence of biological activity/efficacy as well as safety in humans for a candidate therapy that utilizes or targets stem cells.

11. Development Plan to End-of-Phase 2 *(up to 3 pages; in Part B)*
Summarize the development plan to End-of-Phase 2 for the proposed therapeutic candidate and provide a high-level timeline highlighting key milestones and major decision points. As noted above (Section VII.C.3), "End-of-Phase 2" is defined as completion of early clinical studies providing sufficient information on safety, efficacy and dose, to enable the transition to Phase 3.

12. Project Plan and Timeline *(up to 8 pages including timeline); in Part B)*

Project Plan**:** Describe the project plan and scope of activities proposed under this award. Identify potential risks to the project and describe the mitigation strategies.

Timeline: Provide a timeline showing key activities required to achieve the Major Development Milestone for the proposed project.

13. IND Status *(up to 2 pages; in Part B)*
Summarize the IND status for the proposed therapeutic candidate.
Clinical holds are expected to be resolved prior to the start of funding (see Section V.A.3).

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

15. Manufacturing Plan Synopsis *(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.

16. Principal Investigator (PI) and Team Leaders *(up to 2 pages; in Part B)*
List the key members of the project team (including consultants) and indicate their roles on the project.

17. Clinical Investigators and Clinical Sites *(up to 2 pages; in Part B)*
Provide a list of proposed clinical investigators and clinical sites for the clinical trial.

18. Collaborations and Resources *(up to 3 pages; in Part B)*
Provide a list of key collaborations that will participate in the proposed project (includes consultants/CROs/CMOs), or plans for identification and contracting collaborations. Briefly summarize their specific roles, expertise and experience.

19. Intellectual Property, Licenses and Agreements *(up to 2 pages; in Part B)*
Describe intellectual property assets (patent applications, patents), including any challenges to same and pending litigation relating to same and any licenses of rights important to development of the therapeutic. Identify any potentially blocking intellectual property known to applicant.

Provide a brief summary describing the status of MTAs or licensing agreements for materials that are critical to the development of the therapeutic. In Part J, provide copies of essential MTAs. If not possible, please summarize the terms and what stage negotiations are in.

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

21. 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.

C. Application Submission Instructions

All applicable parts of the Strategic Partnership II Award application must be submitted to CIRM no later than 5:00 PM PDT on October 21, 2013 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.

D. 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 5:00 PM PST on January 6, 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 of supplemental materials 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:

- 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 or lifting of clinical holds 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.
- 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.

E. Opportunity for Clarification of Submitted Information

Critical questions raised by reviewers regarding information submitted in the application will be forwarded to applicants prior to the scientific review meeting. Applicant responses will be in writing and will be made available to the GWG before the review meeting.

IX. Schedule of Deadlines and Reviews

LOI Due	5:00 pm (PDT), August 22, 2013
Applications Due	5:00 pm (PDT), October 21, 2013
Supplemental Information Due	5:00 pm (PST), January 6, 2014
Scientific Review of Applications by Grants Working Group (GWG)	February 5-7, 2014
Review and Approval by ICOC/Application Review Subcommittee	Q2, 2014
Earliest Funding of Awards	Upon Achievement of Major Development Milestone

X. Contacts

For information about this RFA:

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

XI. CIRM Regulations

Grant awards made through RFA 13-03B (Track B) 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) 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. 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. It should be noted that amendments to 17 Cal. Code Regs. are currently pending with such proposed amendment available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants.

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.

F. 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. Applicants should be advised that with respect to any and all RFAs, the IP and Industry Subcommittee of CIRM's board may elect to adopt terms other than the guidelines set forth in the LAP. It is anticipated that with respect to RFA 13-03B, the IP and Industry Subcommittee will consider the following loan terms for Track B awards: (i) commencement of the Loan term at the time of disbursement of CIRM funds; (ii) maximum permitted term of five (5) years (iii) specific terms and conditions relating to forgiveness of a Product Backed Loan and (iv) other terms as appropriate.

XII. 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 which 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: 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

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. The LAP is currently being revised. The new terms, which we expect to be in effect at the time the awards are made, are summarized below. The LAP in effect on the date the Notice of Loan Award is issued will govern the loan.

(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.

Applicants will be informed of the actual costs once finalized.
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