RFA 10-05: CIRM Disease Team Therapy Development Awards

This initiative, the Disease Team Therapy Development Awards (previously designated Disease Team II Awards), will support both a Planning Award (Part I) and a Research Award (Part II), each of which will undergo an application, review and approval process. With limited exceptions, receipt of a Part I Planning Award will be a prerequisite for submission of an application for a Part II Research Award. This document provides complete information about applying for a Part I Planning Award, and relevant information about the Part II Research Award. Full details for Part II will be described in a supplement to the RFA, anticipated to be released in summer, 2011. CIRM welcomes applications from qualified for-profit and non-profit organizations.

The Disease Team Therapy Development Award initiative is an expansion of our original Disease Team Award Initiative. CIRM wants to emphasize the importance of developing therapies that could lead to new and more efficacious treatments for patients with debilitating disease or serious injury. The Disease Team Therapy Development Initiative is core to CIRM's mission and as such, the agency will likely seek applications approximately every 2 years as a way to build a strong clinical pipeline for patient therapies and cures.

I. Purpose

Stem cells offer the potential to restore tissues damaged by injury or disease. The rapid expansion of stem cell research over the past few years has led to candidate therapies that are ready for preclinical and clinical development. The purpose of CIRM Disease Team Therapy Development Awards is to enable preclinical and/or early clinical development of novel therapies derived from or targeting stem cells or utilizing direct reprogramming that may offer unique benefit with well-considered risk to persons with disease or serious injury. The Disease Team Therapy Development Awards RFA has two parts: 1) a Part I Planning Award will support up to six months of team assembly, planning and proposal development for the Part II application, and 2) a Part II Research Award will support actively managed teams to conduct milestone-driven translational research to achieve the objective(s) of the RFA.

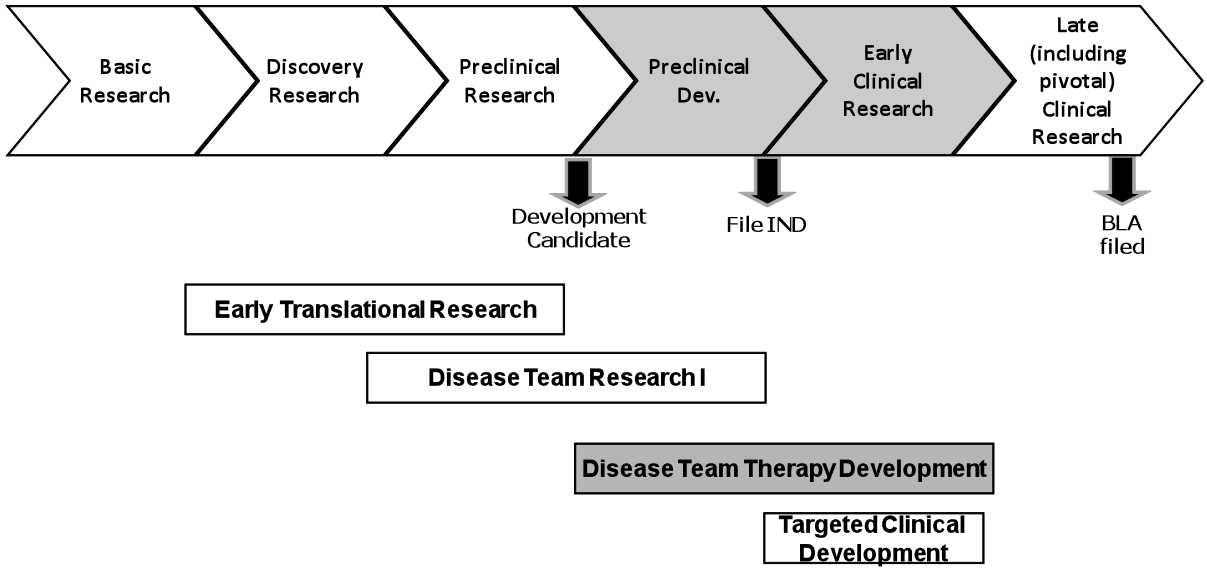
II. Objectives

The key objectives of each Part II Research Award will be to achieve, within 4 years of the Part II Research Award start date, one or more of the following:

1. file a complete and well-supported IND with the Food and Drug Administration (FDA) (and, if desired, other regulatory agencies)
   AND/OR
2. complete a Phase I and/or Phase I/II clinical study that will evaluate preliminary safety and preliminary biological activity/early efficacy in humans
   AND/OR
3. complete a Phase II clinical study that will evaluate efficacy and could lead to more definitive efficacy studies.

For purposes of this RFA, a clinical study is considered complete upon completion of enrollment, database lock and initial assessment of outcomes of the primary and secondary study objectives.

The diagram below shows where the research and activities covered by this RFA fall along the research and therapy development spectrum, and in the context of CIRM's Translational Research Program. These translational RFAs are core to our mission to enable stem cell-based therapies, diagnostics and cures for the benefit of persons with disease and injury.



CIRM seeks novel candidate therapeutics for which there is an unmet medical need, and for which the use of stem cells or directly reprogrammed cells can offer a

significant advantage over current therapies and therapies in pivotal or late-stage development. CIRM will support meritorious therapy development research that is uniquely defined by its mission and that is unlikely to be funded by other agencies.

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

- A cell therapy candidate that is derived from or utilizes hESCs, hiPSCs, neural stem or progenitor cells, directly reprogrammed cells, or any genetically-modified stem cells (where the 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 was characterized or generated through the use of any of the above human cell types.
- A small molecule or biologic candidate that targets cancer stem cells or endogenous stem cells in vivo.
- An engineered functional tissue candidate for implantation in vivo.

Projects using cell types not listed above fall outside the scope of this RFA. Examples include the following:

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

At the time of the Part I Planning Award application deadline, each applicant must have a single development candidate. A development candidate is a candidate therapeutic entity, suitable for use in humans that has completed all the research necessary to initiate the IND-enabling preclinical development activities required for regulatory approval for testing in humans. Projects that are further along in the development pipeline are also eligible. To minimally qualify as a development candidate, a proposed development candidate must meet the following applicable criteria:

- Suitability for use in humans (i.e., not animal cells);
- Compelling, statistically significant, reproducible disease modifying activity with adequate controls in (multiple) relevant in vitro and in vivo models;
- Preliminary assessment of dose, formulation, stability and safety (includes immunogenicity, if applicable) completed;
- Evidence for potential mechanism of action (to inform monitoring);
- Research assays developed to characterize the candidate (e.g., for identity, purity and activity);

- Methods developed for reproducible production of a defined development candidate (including viral vector, if applicable) at yields adequate to conduct research and preclinical research studies;
- Candidate compatible with cGMP (Current Good Manufacturing Practices) (e.g. for a cell therapeutic, derivation and maintenance adequately documented);
- Site, mode and method of delivery selected and/or under development.

A. Part I - Planning Award

Because of the complex nature of preclinical and clinical development projects, CIRM is providing a planning award to help investigators establish teams and collaborations (and appropriate third party agreements, where necessary), identify partners, and support Part II proposal preparation. The planning awards will give investigators access to regulatory, project management and clinical personnel to help prepare necessary supporting documentation required of a preclinical and/or clinical application.

The planning award is designed to:

- Permit early peer review of the scientific and clinical rationale for the preclinical development work and/or the proposed clinical trial
- Permit assessment of the "readiness" of the proposed development candidate for those projects entering IND-enabling preclinical development
- Permit assessment/refinement of the draft Target Product Profile and the clinical competitiveness/impact of the proposed therapeutic
- Permit establishment or reinforcement of collaborations with colleagues within California or one of CIRM's Collaborative Funding Partners jurisdictions
- Support the development of a detailed preclinical and/or clinical development plan in the context of an overall development strategy
- Support Part II application preparation including, for example, development of: a project timeline or Gantt chart, an activity-based budget, a clinical protocol synopsis, manufacturing plan synopsis and long term follow-up plan for trial participants (where warranted).

The output of the Part I Planning Award is submission of a Part II Research Award application, or a summary and justification of activities supported by the Planning Award if an application for Part II is not submitted.

The Part I Planning Award is not designed for the collection of preliminary data or the conduct of pilot studies to support the rationale for a clinical trial or a preclinical development activity. Funding from this award may not be used to pay for any activity prohibited by CIRM's Scientific and Medical Accountability Standards Regulations (17 Cal. Code Regs. §§ 100010 et seq.), or any activity for which SCRO, IRB or IACUC review would be required under those regulations or under any other California or Federal law.

B. Part II - Research Award

The Part II Research Award will support activities commensurate with the objectives of this RFA including but not limited to:

Projects that begin with IND-enabling studies can include all necessary activities to move a development candidate toward clinical studies (first-in-human studies) in compliance with all FDA guidelines. Such activities may include IND-enabling studies including pharmacology, toxicology, analytical assay development, process development and manufacturing, clinical and regulatory strategy development.

Projects that begin with or include clinical studies can include all necessary activities to initiate and complete early clinical trials. 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 that will enable the proposed clinical studies such as cGMP 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 preliminary biological activity/early efficacy studies may employ physiological (which can include imaging), molecular and/or biochemical endpoints as well as the definitive clinical endpoints generally required for market approval. The Part II application should reflect careful thought given to clinical endpoints. Such endpoints could include evaluation of efficacy measure(s) that may be useful in the planning of more definitive efficacy studies.

The proposed clinical trials may include supporting 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 additional 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 supporting studies will specifically inform the trial results and contribute to decision making on continued clinical testing of the proposed cell therapy.

CIRM requires that any clinical trial that is part of the proposed project include at least one clinical trial site in California. CIRM expects clinical trials that it funds to include women and members of minority groups unless a clear and compelling rationale and justification establishes to the satisfaction of CIRM that inclusion is

inappropriate with respect to the health of the subjects or the purpose of the research.

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

- Pivotal clinical efficacy studies designed to be submitted for marketing approval.

- Non-interventional clinical studies (e.g. biomarker discovery; clinical studies that do not involve administration of the proposed cell-based therapy; or studies using samples not from subjects of the proposed clinical studies)

- Process scale-up or production for clinical studies other than those proposed as part of this project.

- Early translational research activities designed to identify a development candidate such as target discovery, early-stage therapeutic discovery activities (such as high-throughput screening), proof-of concept preclinical research, preclinical comparisons of multiple development candidates, all of which are covered in CIRM's Early Translational program.

III. Award Information

A. Part I - Planning Award

Each Part I Planning Award will provide support for up to six months of planning, organization of teams and development of a Part II Research Award proposal. An award will cover project costs of up to $100,000. Indirect costs may not exceed 10% of the total direct project costs, with total costs (direct and indirect) not to exceed $110,000 for each award. CIRM intends to commit up to $3.3 million to support up to 30 Part I Planning awards. CIRM expects to fund approved Part I Planning Award proposals from for-profit and non-profit organizations through grants.

B. Part II - Research Award

Under Part II of this RFA 10-05, CIRM intends to commit up to $240 million to support up to 12 Part II Research Awards. Projects will be funded for up to four years, with justifiable total funds requested (includes direct project costs, direct facilities costs, and indirect costs) up to a maximum of $20 million per project.

CIRM will fund up to $20 million of the total costs of a proposed project for up to four years. CIRM recognizes that budgets for some projects may exceed $20 million. To

meet the needs for funds that exceed the per project maximum $20 million available CIRM funds, applicants will be required to secure additional funds. CIRM's Collaborative Funding Partner Program (Section IV) may be one source for such funds. Additional funds can be used to fund project costs such as activities conducted outside of California and long-term follow-up studies on test subjects. Funding from CIRM, its Collaborative Funding Partners and from other sources is to be reasonably distributed over the award period. Applicants will be expected to address status and sources of any additional funding required for achievement of RFA objectives prior to award issuance during pre-funding administrative review.

C. Part II - Research Award Mechanism

CIRM expects to fund approved Part II Research Award proposals through grants or loans. Sponsorship of the IND will define the applicant organization. Please see Section V for additional information.

The following outlines the applicable Research Award mechanism:

- Loan, if a for-profit organization is the applicant organization. The loan holder will be responsible for the entire Research Award from CIRM, even if a Co-PI is from a non-profit organization. Loan terms are described in Appendix A.

- Grant, if the Principal Investigator (PI) is from a non-profit organization. Grantees will receive funding in quarterly disbursements, and be subject to all terms of CIRM's Intellectual Property and Revenue Sharing Requirements for Non-Profit and For-Profit Grantees (17 Cal. Code Regs. § 100600 et seq.).

Part II Research Award administration and management will be detailed in a supplement to RFA 10-05 available in summer of 2011.

IV. Part II Research Award Collaborative Funding Partners

Three international governmental funding agencies have agreed to participate as collaborative funders of the Part II Research Awards with CIRM: The Cancer Stem Cell Consortium (CSCC) of Canada; the Federal Ministry for Education and Research (BMBF), Germany; and the Andalusian Initiative for Advanced Therapies (Iniciativa Andaluza en Terapias Avanzadas, "IATA"), Spain. If a collaboratively funded Part II Research proposal is approved (a "CIRM/CFP Award"), CIRM will fund all project work done within the State of California and the applicable Collaborative Funding Partner ("CFP") will fund all project work done within its jurisdiction. Through this program, California-based Principal Investigators (PIs) can collaborate with a CFP funded Partner PI to bring important additional resources to the project.

Potential applicants are being informed of the opportunity to collaborate with researchers who are eligible for funding from one of CIRM's participating CFPs to facilitate establishment or reinforcement of collaborations with colleagues from Canada, Germany, or Andalucia having special capacities and resources. The financial parameters of funding available from each CFP in connection with a Part II Research Award and other applicable criteria are set forth in Appendices B (Canada), C (Germany) and D (Andalucia). Contact information, eligibility requirements and application procedures for each of the participating CFPs are provided therein.

California applicants who choose to collaborate with researchers funded by a CFP will be required to specifically identify their proposed research partner and provide other applicable information when submitting their Part II Research Application. Applications for Part I and Part II Awards that include CFP funded researchers will be evaluated by the CIRM Grants Working Group according to the same process and scientific criteria that are applied to all other applications.

The decision to include a CFP funded PI should be guided by the goals of the proposed project, and by the scientific synergies presented by such collaboration. CIRM planning award recipients will be able to use CIRM's Part I planning award funding, including travel funds, to develop collaborative applications for the Part II Research Awards, if they choose to do so.

Special note for German Scientists: Additionally, BMBF, in its sole discretion, may provide supplemental co-funding for the Part I Planning Awards to German scientists who are engaged in planning activities with their California counterparts. The eligibility criteria and other conditions applicable for BMBF funding is set forth in Appendix C.

V. Eligibility Information

This section describes key eligibility requirements for submission and funding of applications for Part I Planning Awards and Part II Research Awards. Some exceptions may be available in extraordinary circumstances; see Section V.B.4 below for details.

A. Part I - Planning Award

Under this RFA, CIRM will not limit the number of Part I Planning Award applications from each eligible institution. However, CIRM will only accept a Letter of Intent (LOI) for a project that meets the following eligibility criteria.

The project must propose a single stem cell-based development candidate that utilizes, is derived from, or targets a stem cell type that is within scope as listed in Section II.

For applications that include an **investigator-sponsored IND**, the investigator-sponsor must be the Principal Investigator (PI) on the Part II Research Award application.

For applications that include an **organization-sponsored IND**, the organization sponsor must be the applicant organization on the Part II Research Award application, and the PI must be an employee of that organization.

1. Part I Institutional Eligibility

At the time of the Part I Planning Award application deadline, the applicant organization must be located in California (that is, the organization must have employees who are conducting business or operations at a location in California). At the time of funding, the applicant organization must be conducting or managing research that is taking place in California. If these requirements are not met, CIRM may terminate all further action on the application.

Both non-profit and for-profit organizations are welcome to 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.

2. Part I Investigator and Planning Leader Eligibility

Principal Investigator
CIRM requires that a single Principal Investigator (PI) and a single applicant institution (the PI’s institution) be designated in each Part I Planning Award application. The PI is the designated point of contact for CIRM and is the person responsible and accountable to CIRM for performance on the Part I Planning Award project. The Part I PI is expected to be the PI on the Part II Research Award application, and is expected to be willing and able to meet the percent effort requirements for the Part II Research Award project. The applicant institution is the designated contact institution for all financial and other administrative considerations.

A Principal Investigator (PI) may submit only one application under this RFA. The PI must have an M.D., Ph.D. or equivalent degree, and must be authorized by the applicant institution to conduct the proposed project. By the Part I Planning Award application deadline for this RFA, the PI:

- must be an independent investigator in California at a non-profit applicant institution, or have an equivalent position and be an employee in California (at least 50-percent time) of a for-profit institution;

- cannot be a PI or Co-PI on an active Disease Team I Award from CIRM;[1]

- must have documented authority from the applicant institution to staff the planning project; and

- must have documented commitment from the applicant institution to provide resources sufficient to carry out the proposed planning activities in California.

Planning Leader

CIRM will allow for a single CIRM-funded Planning Leader. Inclusion of a planning leader is not a requirement, and the PI may also serve as the planning leader.

Both the PI and the Planning Leader must perform their work under the award in California.

3. Part I Percent Effort Requirements

The PI and the Planning Leader must each commit a minimum of 5% effort; and, the sum of the PI % effort + Planning Leader % effort must be greater than or equal to 20%.

B. Part II - Research Award

Only PIs and applicant institutions who receive a Part I Planning Award will be eligible to apply for a Part II Research Award. It is expected that the PI and the applicant institution on the Part I Planning Award will be the same on the Part II Research Award. The Part II Research Award project must propose the same development candidate that was the subject of the successful Part I application.

The proposed Part II project objectives must directly address, within four years: 1) filing a complete and well-supported IND with the FDA (and, if desired, other regulatory agencies); and/or 2) completing a Phase I and/or Phase I/II clinical study that will evaluate preliminary safety and preliminary biological activity/early efficacy in humans; and/or 3) completing a Phase II clinical study that will evaluate efficacy and could lead to more definitive efficacy studies. All activities of the proposed project must address the preclinical or clinical development of a cell-based therapy outlined in Section II.

[1] Though Disease Team I PIs may not apply for Planning Awards, they may be permitted to apply for Research Awards if they have met certain milestones on their Disease Team I projects. See Section V.4 for more information.

CIRM requires that any clinical trial that is part of the proposed project include at least one clinical trial site in California. Applicants should also note the requirements of Section III.C.6.g. of the Grants Administration Policy: “Women and members of minority groups must be included in all CIRM-funded Clinical Research, unless a clear and compelling rationale and justification establishes to the satisfaction of CIRM that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources.”

1. Part II Institutional Eligibility

The Institutional eligibility requirements are the same as for the Part I Planning Award in Section V.A.1, but substituting “Part II Research Award” for “Part I Planning Award”.

2. Part II Principal Investigator, Co-Principal Investigator and Project Manager Eligibility

The following term applies to PIs and Co-PIs on applications for the Part II Research Award.

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. CIRM will not issue a Part II Research Award to any PI or Co-PI who is PI or Co-PI on more than 3 active CIRM awards.

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

<u>Principal Investigator</u>
The Principal Investigator eligibility requirements are the same as for the Part I Planning Award in Section V.A.2, but substituting “Part II Research Award” for “Part I Planning Award”.

<u>Co-Principal Investigator(s)</u>
In order to encourage requisite expertise and experience on the project leadership team, CIRM will allow for a single CIRM-funded Co-Principal Investigator (Co-PI). The Co-PI must have an M.D., Ph.D. or equivalent degree and must be sponsored by the institution at which the Co-PI will conduct the proposed project. By the Part II application deadline, the Co-PI must:

- be an independent investigator in California at the sponsoring non-profit institution, or have an equivalent position and be an employee in California (at least 50-percent time) of the for-profit institution;

- have documented authority from the sponsoring institution to staff the proposed project; and

- have documented commitment from the sponsoring institution to provide appropriate space and resources sufficient to carry out the proposed research.

Designating a Co-PI is not a requirement of this award. The decision of whether to include a Co-PI should be guided by the goals of the project. The Co-PI role is not intended to substitute for any of the responsibilities or effort contributions of the PI. The Co-PI role is most appropriate for leading a discernable portion of the proposed project that is supported by a dedicated budget. All Part II applications will require a leadership plan to be outlined in the Part II supplement. When considering a Co-PI, please be aware that the reviewers will consider the structure and governance of the development team as well as the knowledge, skills and experience of the individual PI and Co-PI. The Co-PI is responsible and accountable to the grantee organization.

Project Manager

CIRM requires that a single project management professional (Project Manager) be designated in each Part II Research 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 Part II project.

3. Part II Percent Effort Requirements

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

4. Extraordinary Exceptions

The President of CIRM has the discretion to permit exceptions to any eligibility requirement specified in this Section V.A.1-3; Section V.B. The President may permit an exception if he determines, in his individual discretion, that the applicant has demonstrated that the exception 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 XIII of this RFA) and the Loan Administration Policy (see Appendix A of this RFA), or they will not be considered. (Note that no exceptions are available for

the scope requirement, in Section II, for a single cell-based therapeutic candidate that utilizes, is derived from, or targets one of the specified cell types.)

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 XII.

Special note for for-profit applicants: CIRM recognizes that the Planning Award may not be suitable for some companies that would otherwise be good candidates for the Research Award. Companies that do not seek or receive Planning Awards may request an exception that would allow them to apply for the Part II Research Award. CIRM would not expect to make more than three such exceptions, so companies should apply for Planning Awards if they are able to do so.

Special note for recipients of Disease Team I awards: Planning Awards are not available for PIs and Co-PIs on Disease Team I awards, but those teams may request an exception that would allow them to apply for the Part II Research Award, subject to the following:

- An exception will only be considered for a team that has completed an IND filing and will be ready to begin early clinical trials by summer of 2012 with the development candidate that is the subject of the Disease Team I award.

- The development candidate must meet all scope requirements detailed in Section II of this RFA.

- Such exemptions **must** be requested prior to October 1, 2011 to allow the President of CIRM adequate time to review and to consider the request well before January 2012, the deadline for submission of a Part II application.

- If the applicant is successful, the Disease Team I Award must be closed out before issuance of an award under this RFA.

VI. Application and Evaluation Process

Submission of an application for the Part I Planning Awards involves a two-step process. Any eligible applicant may submit a Letter of Intent (LOI, see section V for eligibility criteria). Applications will only be accepted from Principal Investigators (PIs) who submitted an LOI that was accepted by CIRM. The PI and the proposed development candidate must be the same as those described in the LOI; otherwise, the application is deemed ineligible.

Part I Planning Award applications and Part II Research Award applications will be independently evaluated by the CIRM Grants Working Group (GWG), which is composed of fifteen scientific experts from outside California, seven patient advocate members of CIRM's Governing Board, and the Chair of the Governing Board. The membership of the GWG can be found at http://www.cirm.ca.gov/workgroups/pdf/GrtWkgGpMbr.pdf. The composition of the Governing Board can be viewed at http://www.cirm.ca.gov/GoverningBoard. The fifteen scientists on the GWG will review the applications and score them for scientific and clinical merit, applying the review criteria described in section VII below. Following the scientific scoring, the full membership of the GWG will then review the entire group of applications, taking into consideration the following criteria:

- Impact of the proposed project on the development of stem cell-based therapies and on regenerative medicine

- Appropriate balance among the RFA objectives (e.g. IND filed, Phase I, I/II or Phase II trial completed)

- Appropriate balance between feasibility, innovation and incremental advances for the treatment of a disease or serious injury

- Appropriate focus in the context of CIRM's development portfolio (composed of funded Disease Team Research Awards, RFA 09-01, Early Translation Research I and II Awards, RFAs 08-05 and 10-01 targeting a development candidate, and Targeted Clinical Development Awards, RFA 10-02 see http://www.cirm.ca.gov/for-researchers/researchfunding) in order to enhance portfolio diversity and reduce risk

- Overlap with other CIRM investments in the translation and clinical portfolio

- Other considerations as appropriate

The GWG will make funding recommendations to the Governing Board, which will make final funding decisions taking into consideration criteria including:

- Appropriate focus in the context of CIRM's development portfolio (comprised of funded Disease Team Research Awards, RFA 09-01, Early Translation Research I and II Awards, RFAs 08-05 and 10-01 targeting a development candidate, and Targeted Clinical Development Awards, RFA 10-02 see http://www.cirm.ca.gov/for-researchers/researchfunding) in order to enhance portfolio diversity and reduce risk

- Overlap with other CIRM investments

Planning and Research Award applications will be evaluated by the CIRM Grants Working Group using the criteria described in the RFA. CIRM's confidentiality and conflict screening rules will apply to everyone who will have access to the applications or attend the review meeting, including CIRM staff, external reviewers, and representatives of Collaborative Funding Partner Agencies. (Disclosure to collaborative funding agencies is protected by inter-governmental agreement, per Gov. Code § 6245.2(e).)

VII. Review Criteria

A. Part I - Planning Award

Applications will be evaluated in three key areas: 1) Significance and Impact; 2) Project Rationale and Feasibility; and 3) Principal Investigator and Planning Leader. The specific criteria for review of applications are based on the standard review criteria described in the CIRM Grants Administration Policy (GAP, see section XIII of this RFA).

1. Significance and Impact

a. Reasonable Draft Target Product Profile: The draft target product profile (TPP) is reasonable and achievable. The intended patient population indicated in the TPP is reflective of the overall unmet medical need.

b. Clinical Competitiveness and Impact: The proposed cell-based therapy, if successfully developed and made available to patients, would have a significant impact on standard of care management of the disease or injury, and would offer advantages over current therapies on the market or in late stage development.

c. Responsiveness: The development candidate proposed is within scope as defined in section II. The draft proposed activities for IND-enabling preclinical, clinical and supporting studies are within the scope of activities defined in section II, and targets and could potentially achieve one or more of the objectives of this RFA.

2. Project Rationale and Feasibility

a. Strong Rationale: There is strong scientific rationale for the proposed therapeutic intervention in the target disease or injury. The therapeutic rationale is justified by preclinical/other evidence.

b. Development Readiness: The data and information presented in the application are supportive of the applicant's assessment of the project status on the Therapeutic Scorecard. The project is sufficiently mature and it's status is such that there is reasonable expectation that the stated project objective(s) can be met (i.e., an IND filing and/or completion of a Phase I, Phase I/II, or Phase II study can be achieved within 4 years of the project start date).

    i. For IND-enabling studies: See section II for list of minimal criteria for a development candidate, some of which are further reiterated here. There is, at a minimum, compelling and reproducible preclinical evidence to begin IND-enabling studies. A single GMP-compatible development candidate has been chosen. Methods have been developed for reproducible production and characterization of a defined candidate (including viral vector if applicable) at yields adequate to conduct the IND-enabling studies. A development stage-appropriate regulatory strategy has been articulated.

    ii. For clinical studies: The applicant has filed an IND and has passed the 30 day period without comment. If on clinical hold, the applicant has identified reasons for the clinical hold and has developed plans to address that are feasible and likely to result in the clinical hold being lifted within a reasonable time frame.

    There is compelling evidence to begin first-in-human clinical studies or to advance to further early clinical studies. cGMP-compatible methods (e.g., for a cell therapeutic derivation and maintenance adequately documented) have been developed for reproducible production of a defined, characterized product (including viral vector if applicable) at yields compatible with the conduct of early stage clinical studies.

c. Feasibility of the Draft Project Plan: The draft project plan and goals are feasible and adequate to meet the objectives of this RFA. The proposed studies will likely result in providing useful information to guide decisions toward future clinical development.

    i. For IND-enabling studies: The IND-enabling studies and activities are focused and adequately address all necessary activities, including IND filing, to enable regulatory approval for the start of clinical trials.

ii. For clinical studies: The clinical studies and activities are focused to provide meaningful data that advances knowledge on the safety and/or activity/efficacy of the candidate cell-based therapy in humans.

3. Principal Investigator (PI) and Planning Leader

Evaluate the Principal Investigator (who will also be the PI on the Part II Research Award) and the Planning Leader against the following criteria. The Principal Investigator may also serve as the Planning Leader.

d. Experienced Principal Investigator: The PI has relevant experience in regulated translational research and therapy development. The PI has demonstrated successful leadership experience. The PI has made specific contributions to the translational and/or clinical research involving the development candidate, and will have a key role in the proposed draft development plan.

e. Experienced Planning Leader: The Planning Leader is appropriately trained and well suited to carry out the planning process (assemble the team, and lead the development of the research plan and supporting documentation). The Planning Leader has relevant experience in regulated translational research and therapy development.

B. Part II – Research Award

Review criteria for the Part II Research Award will be detailed in a supplement to RFA 10-05 available in summer of 2011.

VIII. Application Procedure

A. Part I - Planning Award

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

1. Letter of Intent (LOI)

A PI may submit only a single LOI for this RFA using the LOI template that will be provided by mid-December 2010 at http://www.cirm.ca.gov/RFA_10-05. The LOI should concisely describe the proposed preclinical and/or clinical development

project and explain how it will within four years achieve at least one of the three objectives of the RFA. Applicants must answer the questions included in the LOI template provided. **The completed LOI must be submitted online as instructed on the CIRM web portal (**http://www.cirm.ca.gov/RFA_10-05**) and must be received by CIRM no later than 5:00PM (PST) on January 26th, 2011**. **No exceptions will be made.**

2. Part I Planning Award Application Forms

Application forms and instructions will be available ~~on the CIRM website (http://www.cirm.ca.gov/RFA_10-05)~~ within the CIRM Grants Management Portal (https://grants.cirm.ca.gov) on or around February 1, 2011. The website will be updated with a posting date for the application forms. Only those applicants that submitted an LOI that was accepted by CIRM may submit an application.

The Application for the CIRM Disease Team Therapy Development Part I Planning Awards consists of four parts:

Part A: Application Information Form (~~Adobe PDF template~~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: Disease Team Therapy Development Part I Planning Award Proposal (MS Word template). Part B includes: Draft Proposal Overview, Project Objective and Draft Target Product Profile; Clinical Competitiveness and Impact; Therapeutic Scorecard; Rationale, Status and Supporting Data; PI and Planning Leader (if applicable) Qualifications; and References (section numbers 6-12 below).

Part C: Biographical Sketches for Principal Investigator and Planning Leader (if applicable) (MS Word template).

Part D: Related Business Entities Disclosure Form (Adobe PDF template). In order to comply with the Conflict of Interest policies under which CIRM operates, Part D must be submitted to indicate whether the application would, if awarded, provide funding from CIRM to a for-profit organization that is either: 1) the applicant organization; 2) a subcontractor; or 3) the employer of a co-investigator, consultant or subcontractor (section number 13 below).

The application for a CIRM Disease Team Therapy Development Planning Award includes the following sections:

1. ***Abstract*** *(divided in four parts of up to 3000 characters each in Part A)*
    a. Project Description: Provide a brief description of the proposed project. Describe the scientific and clinical rationale for the

proposed therapy. Address why a human stem cell-based therapy is a preferred approach to achieve the desired therapeutic outcome.

b. Clinical Competitiveness and Impact: Describe the unmet medical need that the proposed therapy will address. Summarize the impact that this therapy would have on the target disease or injury, if it were successfully developed. Describe existing therapies and other therapies currently in late-stage development. Address how the proposed novel therapy could offer a significant improvement in patient care in comparison to existing and candidate therapies.
c. Proposal Overview: Summarize the proposed project plan and describe how it will achieve the objectives of this RFA which are to prepare and file an IND and/or complete of a Phase I, Phase I/II, or Phase II study within 4 years of the Research Award project start date.
d. Milestones: Summarize the high level milestones to be achieved within each year of the four year award period. Include key applicable preclinical, clinical, CMC, regulatory and other milestones ~~milestones~~ for the proposed project.

2. ***Public Abstract*** *(up to 3000 characters in Part A)*
In lay language, briefly describe the proposed research and how the proposed stem cell-derived cell therapy will advance the treatment of disease or serious injury by achieving regulatory approval to begin testing in humans and/or by demonstrating preliminary safety and activity/efficacy 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 institution and, if applicable, the ~~Co-PI~~Planning Leader, and his/her respective applicant institution.

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 the applicant and the applicant institution.

4. ***Key Personnel*** *(included in Parts A and C)*

In the Part I Planning Award Key Personnel section, the PI and the Planning Leader (if applicable) must be named, and must meet the Eligibility Criteria in Section V.A.2. For the PI and the Planning Leader (if applicable) only, provide a two-page biographical sketch using the template provided. The biographical sketch should highlight relevant

research and product development experience, including, for example, team leadership, conduct of clinical studies and/or contribution to regulatory filings for product development. Include relevant publications, patents or patent applications.

For this Part I Planning Award, it is not a requirement that the full development team be formed and named at the time of the Part I application submission.

Additional key personnel will be indentified and additional biosketches will be required in the Part II Research Award application.

5. Budget *(included in Part A)*

Provide all budget information requested in the budget section of the Application Information Form. All allowable costs for research funded by CIRM are detailed in the CIRM Grants Administration Policy (GAP, see section XIII of this RFA).

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

- Salaries for Key Personnel

  Salaries for Key Personnel are limited to the salaries for the Principal Investigator and the Planning Leader, 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 by the PI and Planning Leader must be based on a full-time, 12 month staff appointment or the full time annual salary for employees of a for-profit institution. Administrative support salaries are expected to be covered exclusively by allowed Indirect Costs.

- Consultants/Subcontracts

  Consultant expenses may be requested to pay the costs of engaging seminar speakers or outside experts to provide professional advice or services to assist in planning and application development. Potential collaborators and personnel who are located and employed outside the PI's home institution may request compensation as a consultant in this section. CIRM funds cannot be used for salary support of individuals working outside California.

  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.)

- Travel and Communications
  Travel costs associated with bringing together potential collaborators to work on the Disease Team plan are allowable. Further information about allowable travel costs can be found in the CIRM GAP (see section XIII of this RFA). Communications expenses may be requested to pay for remote conferencing, audio-visual equipment rental, costs of developing meeting materials and if required, conference room leasing.

- Indirect Costs
  Planning Award administration costs will be covered by indirect costs, which will be l limited to no more than 10 percent of allowable direct costs awarded by CIRM. No facilities costs will be provided.

6. Draft Proposal Overview *(up to 2 pages including the high-level timeline, the latter in Gantt chart format or equivalent, in Part B)*
Provide an overview of the proposed project and the objective from Section II the proposal will address (i.e. obtain FDA approval for first-in-human studies and/or to complete a Phase I, I/II, or Phase II trial). Summarize the key activities proposed for funding under Part II of this RFA. Include: IND-enabling and clinical studies, CMC/Manufacturing activities to enable the preclinical development and clinical work that is part of this proposal. List key preclinical, clinical, CMC, regulatory and other milestones. Provide a high-level timeline to obtain FDA approval for first-in-human studies and/or to complete a Phase I, I/II, or Phase II trial.

7. Project Objective and Draft Target Product Profile *(up to 2 pages use template in Part B)*
State the objectives of the proposed project. Provide a Draft Target Product Profile for the proposed therapy in the format provided in the CIRM Target Product Profile table in Part B of the application. For each Profile Component (Description, Rationale, Indication, Activity (in vitro/in vivo) / Efficacy Endpoints (patients), Safety/Contraindications, Dose/Regimen, Dosage form/Route of Delivery, list the target attributes/claims.

8. Clinical Competitiveness and Impact *(up to 1 page in Part B)*
Summarize the current standard of care and competitive landscape for the target disease or serious injury indication. 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.

9. Therapeutic Scorecard *(up to 5 pages use template in Part B)*
Summarize the key preclinical and clinical development milestones using the CIRM Therapeutic Scorecard in Part B of the application. Indicate the appropriate status that best represents the level of supporting data you have

for your proposed development candidate. You may include clarification points within the notes field at the bottom of each section, although please do not include extensive data or descriptions.

10. Rationale, Status, and Supporting Data *(up to 4 pages in Part B).*

a. For projects that begin with IND-enabling studies: Discuss the scientific rationale for initiating preclinical development. Summarize the results of pilot preclinical efficacy and safety studies and other supporting data that support the therapeutic approach. Provide a summary (in tabular form) of the preclinical safety studies and major findings.

b. For projects that begin with or include clinical studies: Discuss the scientific and clinical rationale for testing the proposed cell therapy in the target disease/injury (you may reference appropriate sections of the Investigator Brochure). Summarize the results of preclinical efficacy studies and any clinical studies that support the therapeutic approach. Provide a summary (in tabular form) of the preclinical safety studies and major findings. Summarize the IND status for the proposed cell therapy. Briefly summarize any past clinical hold issues and explain how they were resolved. If currently on clinical hold by FDA, summarize the issues and plans to mitigate.

11.* PI and Planning *Leader Qualifications *(up to 1 pages in Part B)*
List the PI (who is expected to be the PI on the Part II Research Award) and the Planning Leader. The PI may serve as the Planning Leader.

Describe the leadership credentials of the PI. Include: development projects delivered; INDs, Investigational Device Exemptions (IDEs), Biologic License Applications (BLAs), and New Drug Applications (NDAs) filed for which the PI was a lead or contributing investigator; clinical trials for which the PI was a lead or contributing investigator. Describe how the Planning Leader is qualified to lead the development of the proposal and supporting documentation for the project.

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

13. Related Business Entities Disclosure Form
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 ~~E~~ D 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. Part II - Research Award

The application procedure for the Part II Research Award will be detailed in a supplement to RFA 10-05 available in summer of 2011.

IX. Part I Planning Award Application Submission Instructions

Applications will only be accepted from PIs who submitted a Letter of Intent that was accepted by CIRM.

All four parts of the Part I Planning Award application (as outlined in Section VIII.A.2) must be submitted together and received by CIRM no later than 5:00PM PDT on March 22, 2011, in both electronic form (via the CIRM Grants Management Portal at https://grants.cirm.ca.gov) and in hard copy (a signed original and five copies). It is the applicant's responsibility to meet this deadline; no exceptions will be made.

An electronic copy of all four parts of the Part I Planning Award application must be submitted **online** as instructed on the CIRM web portal. In addition, submit an original hard copy of the application (consisting of Parts A-D) plus 5 hard copies (preferably double-sided). The original hard copy must be signed by both the PI and the applicant institution's Authorized Organizational Official (AOO). Send the hard copies via express mail or courier service to:

Disease Team Therapy Development Part I Applications
California Institute for Regenerative Medicine
210 King Street
San Francisco, CA 94107

X. Submission of Supplemental Information

If necessary, the PI may submit limited supplemental materials that provide critical new information related to their planning award proposal after the application deadline but not later than 5:00pm PDT on April 29, 2011. 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 (submit via email to gsambrano@cirm.ca.gov). The body of the letter may not exceed 500 words and should briefly describe the type of information submitted and when the information became available. The following materials qualify for submissions of supplemental materials:

- Within the one-page letter, provide specific citation(s) to journal publications related to the proposed project that were published or accepted for publication since the application submission deadline. You may briefly describe the significance of the publication(s) to the proposal in the letter.

- Within the one-page letter, confirmation of funding secured from other sources or regulatory agency filings or actions (removal of clinical hold) acquired since the application submission deadline.

- Within the one-page letter, 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.

XI. Schedule of Deadlines and Reviews

Part I Planning Award	
Letters of Intent due	5:00 pm (PST), on January 26, 2011
Part I Planning Applications due	5:00 pm (PDT), on March 22, 2011
Anticipated Review of Planning Applications by Grants Working Group (GWG)	Late May 2011

Anticipated Review and Approval by ICOC	August 2011
Funding of Planning Awards	September 2011
Planning Period	September 2011 - February 2012
Part II Research Award	
Part II Research Applications due	January 2012
Anticipated Review of Research Award Applications by GWG	Spring 2012
Anticipated Review and Approval by ICOC	Summer 2012
Earliest Funding of Research awards	Summer 2012

XII. Contacts

For information about this RFA:

Bettina Steffen, MD
Associate Director, Development Activities
Email: bsteffen@cirm.ca.gov
Phone: (415) 396-9120

Patricia Olson, Ph.D.
Executive Director, Scientific Activities
Email: polson@cirm.ca.gov
Phone: (415) 396-9116

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

XIII. CIRM Regulations

Grant or loan 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/cirm-operations/Regulations

A. CIRM Grants and Loan Administration Policies

CIRM's Grants Administration Policy (GAP) for Academic and Non-Profit Institutions (Non-Profit GAP), the Interim GAP for For-Profit Institutions (For-Profit GAP), and the Loan Administration Policy (LAP), including any amendments, serve as the standard terms and conditions of grant and loan awards issued by CIRM. For-Profit applicants should refer to Appendix A for more information about loan terms.

All research conducted under this award must comply with the stated policies, including protections for human subjects. 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 approved timeline.

B. Intellectual Property Regulations

CIRM has adopted intellectual property regulations for non-profit and for-profit organizations. By accepting a CIRM grant or loan, the Grantee agrees to comply with all such applicable regulations.

C. Human Stem Cell Research Regulations

CIRM has adopted medical and ethical standards for human stem cell research (Title 17, California Code of Regulations, sections 100010-100110). All research conducted under this award will be expected to comply with these standards.

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 require awardees to share the results of their studies for the benefit of the field.