SUPPLEMENT TO RFA 10-05: CIRM DISEASE TEAM THERAPY DEVELOPMENT AWARDS

This initiative, the Disease Team Therapy Development Awards supports both a Planning Award and a Research Award, described in RFA 10-05: CIRM Disease Team Therapy Development Awards (http://www.cirm.ca.gov/RFA_10-05). This document serves as a supplement to RFA 10-05, and provides information about applying for a Research Award. Throughout this document, the terms "Planning Award" and "Research Award" will be used to refer to Awards governed by RFA 10-05, unless otherwise specified.

With limited exceptions (see section V.D-F of this RFA), receipt of a Planning Award is a prerequisite for submission of an application for a Research Award. Planning Award recipients were announced at CIRM's Independent Citizens' Oversight Committee Meeting on August 25, 2011 (http://www.cirm.ca.gov/summaries-review-applications-rfa-10-05-disease-team-therapy-development-awards).

CIRM will conduct a webinar on Friday, September 9, 2011 from 10 AM -12 PM (PST) to review the objectives of the Research Award and the application process. For additional information on this webinar please visit CIRM's website at http://www.cirm.ca.gov/Disease_Team_Webinar.

This RFA Supplement is intended to be a complete description of the requirements for the Research Award. Applicants for the Research Award need not refer back to the original RFA.

I. Purpose

With the rapid expansion of stem cell research over the past few years a number of candidate therapies are ready for preclinical and clinical development. The purpose of CIRM's Disease Team Therapy Development Awards is to advance preclinical and/or early clinical development of novel therapies, derived from or targeting stem cells or utilizing direct reprogramming, potentially offering unique benefit with well-considered risk, to persons with disease or serious injury. The Disease Team Therapy Development Research Award supports actively managed teams to conduct milestone-driven translational and clinical research.

II. Objectives

The key objectives of each Research Award are to achieve, within 4 years of the 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

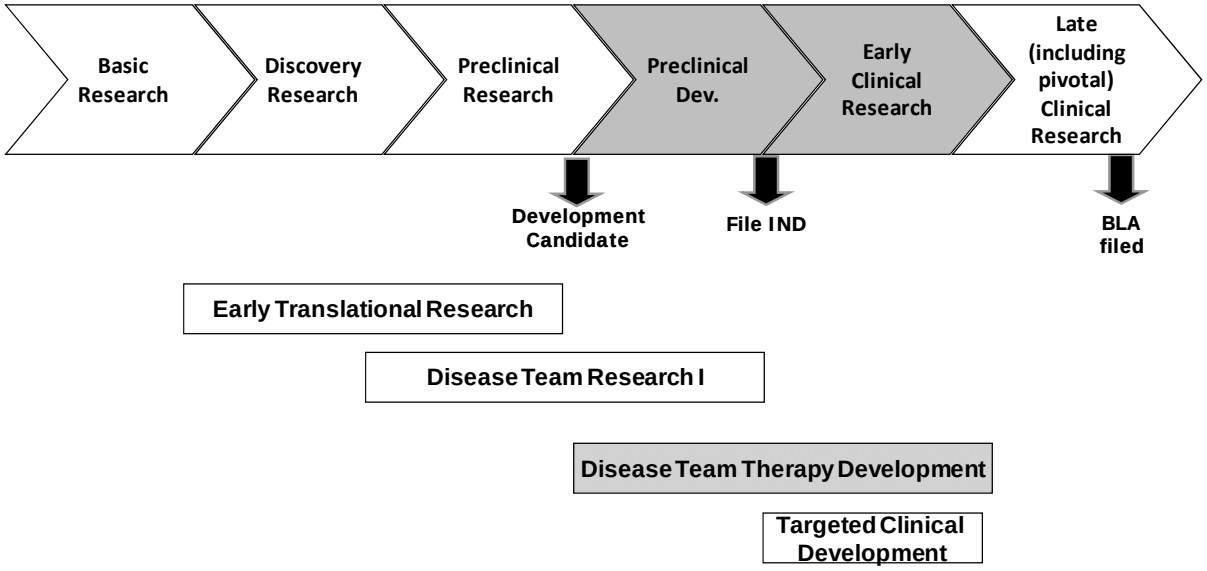
2. Complete a Phase I and/or Phase I/II clinical study evaluating preliminary safety and preliminary biological activity/early efficacy in humans;

   AND/OR

3. Complete a Phase II clinical study evaluating efficacy and potentially leading 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 in the context of CIRM's Translational Research Program. These translational RFAs are core to our mission of advancing development of potential stem cell-based therapies, diagnostics and cures for the benefit of persons with disease and injury.



CIRM seeks novel candidate therapeutics for unmet medical needs, using stem cells or directly reprogrammed cells potentially offering a significant advantage over current therapies, including therapies in pivotal or late-stage development. As CIRM now has a significant translational research portfolio, a project proposing a substantially comparable approach/intervention already represented in CIRM's translational portfolio (see Appendix A) must provide unique and compelling reasons for CIRM support.

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

- A cell therapy candidate derived from or utilizing hESCs, hiPSCs, neural stem cells, neural progenitor cells, directly reprogrammed cells, or any genetically-modified stem cells (where the genetic modification is correcting a disease phenotype or is critical to achieving the therapeutic strategy).

- A small molecule or biologic candidate characterized or generated through using any of the above human cell types.

- A small molecule or biologic candidate targeting cancer stem cells or endogenous stem cells in vivo.

- An engineered functional tissue candidate for transplantation in vivo.

Projects using cell types not listed above fall outside the scope of this RFA. The following are specifically excluded:

- minimally manipulated bone marrow cells

- mesenchymal stem cells

- umbilical cord blood stem cells

- adipose-derived stem cells

- hematopoietic stem cells

A therapeutic candidate is one suitable for use in humans, having completed all the research necessary to initiate IND-enabling preclinical development activities required for regulatory approval for testing in humans. Projects further along in the development pipeline are also eligible. The therapeutic candidate must meet the following applicable criteria:

- Suitable for use in humans (i.e., must use human, 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 potency, dose, formulation, stability and safety (includes immunogenicity, if applicable) completed;

- Evidence for potential mechanism of action;

- Research assays developed to characterize the candidate (e.g., for identity, purity and activity);

- Methods developed for reproducible production of a defined therapeutic candidate (including viral vector, if applicable) at yields adequate to conduct IND enabling 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.

The Research Award will support activities meeting the objectives of this RFA including but not limited to:

- Projects beginning with IND-enabling studies can include all necessary activities to move a therapeutic candidate toward first-in-human clinical studies (within the award period of 4 years) in compliance with FDA guidelines. Activities may include IND-enabling studies including pharmacology, toxicology, analytical assay development, process development and manufacturing, clinical and regulatory strategy development.

- Projects beginning with clinical studies can include all necessary activities to initiate and complete (within the award period of 4 years) early clinical trials. For this RFA, early clinical trials include Phase I or Phase I/II studies to evaluate preliminary safety and preliminary biological activity/efficacy in humans as well as Phase II clinical studies conducted to evaluate preliminary efficacy of the therapeutic in a particular indication.

    - Clinical trial-supporting activities for trials that would be conducted as part of the proposed project, 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 are included.

- 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 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 may 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.

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 such as, biomarker discovery; clinical studies that do not involve administration of the proposed therapeutic candidate; 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 award.

- 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, and preclinical comparisons of multiple development candidates, all of which are covered in CIRM's Early Translational program.

III. Award Information

A. Research Award Information

Under this RFA 10-05, CIRM intends to commit up to $240 million to support up to 12 Research Awards.

CIRM will fund up to $20 million of the total costs (justifiable total funds requested include direct project costs, direct facilities costs, and indirect costs) of a proposed project for up to four years. CIRM recognizes that budgets for some projects may exceed $20 million. Certain funds may be available from CIRM's Collaborative Funding Partner Program (Section IV). Additional funds can be used to fund project costs such as research conducted outside of California and long-term follow-up studies on test subjects. Funding from CIRM, Collaborative Funding Partners and from other sources must be reasonably distributed over the award period.

CIRM highly encourages for-profit applicants who propose clinical trials to secure other sources of funding (at least 50% of the total funds) to leverage CIRM funds. Reviewers will be asked to give preference to the applications that show evidence of securing additional funds for the proposed project. Similarly, non-profit applicants proposing clinical trials are encouraged to engage in partnership(s) with industry to leverage expertise and additional funds for the proposed project. These strategies are intended to leverage CIRM's funds.

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.

B. Research Award Administration and Management

Given the urgency of CIRM's mission, all approved applications must be initiated (award start date in issued and signed Notice of Grant or Notice of Loan Award) within 6 months of approval and authorization for funding by the Independent Citizen's Oversight Committee, unless CIRM's President grants an extension based upon compelling justification of the need for additional time.

For all awards, CIRM reserves the right to negotiate funded project activities, milestones (both technical and financial), success criteria, timelines and budgets prior to issuance of the Notice of Grant Award (NGA) or Notice of Loan Award (NLA), subject to renegotiation annually and/or based on progress. CIRM reserves the right to review (for compliance with CIRM's policies and regulations) key contracts/agreements (e.g. with Contract Research Organizations, CROs or Contract Manufacturing Organizations, CMOs), commitments of additional funds from CFPs and other sources, and "Party IP Agreements" in the context of CFP joint teams, that are critical to the success of the project.

Progress in translational research is important to CIRM. Continued funding is contingent upon timely scientific progress as outlined in the project milestones and timeline established under the NGA or NLA. Where milestones are not met, CIRM reserves the right to terminate the project or to negotiate new milestones to refocus/redirect the project.

In addition to annual Progress Reports, as required by the Grants Administration Policy (GAP, see Section XI.A of this RFA), communication and reporting responsibilities of the grant or loan recipient to CIRM will include: 1) quarterly updates; 2) routine communication by the PI or Project Manager; 3) notification of any serious adverse event for projects with a clinical trial, as required by the GAP (see Section XI.A of this RFA) and 4) discussion with CIRM's Clinical Development Advisory panel (CDAp) approximately once each 12-month project period.

C. Research Award Mechanism

CIRM expects to fund approved proposals from non-profit and for-profit institutions (separately or in collaborations), through grants or loans. Sponsorship of the IND will define the applicant organization (see Section V).

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 B.

- Grant, if the Principal Investigator (PI) is from a non-profit organization.

Grant Terms: Non-profit institutions will receive grant 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.).

Loan Terms: The terms of the Loans are set forth in detail in Appendix B to this RFA. Loan recipients shall be governed by the CIRM Loan Administration Policy that is in effect as of the date of the execution of the Notice of Loan Award, unless both CIRM and the Loan Recipient agree to retroactive application of subsequent amendments, all in accordance with the Loan Administration policy. Approved for-profit applicants who accept a loan will pay for loan administration costs out of indirect costs included in the award.

Loan applicants will be required to submit financial information. For information on the loan program, consult the CIRM Loan Administration Policy (http://www.cirm.ca.gov/files/Regulations/LAP.OAL_.REVIEWED.FINAL_.pdf).

IV. Research Award Collaborative Funding Partners

CIRM has established a program with several other agencies that fund stem cell and regenerative medicine research. Through this Collaborative Funding Partner (CFP) program, California-based Principal Investigators (PIs) can collaborate with a Funding Partner PI ("Partner PI") from a Funding Partner applicant institution ("partner applicant institution") eligible for funding from one of CIRM's CFPs to bring important additional resources to the project. If a collaboratively funded proposal is approved (a "CIRM/CFP Award") CIRM will fund all project research done within the State of California and the CFP will fund all project research done within its jurisdiction. For this RFA, each of the following agencies will participate as a CFP: The Cancer Stem Cell Consortium (CSCC) of Canada; the Federal Ministry for Education and Research (BMBF), Germany; and the Andalucía Initiative for Advanced Therapies (Iniciativa Andaluza en Terapias Avanzadas, "IATA"), Spain.

To apply for a collaboratively funded project involving CIRM and a CFP, applicants must satisfy both the CIRM requirements (Section VIII) and any additional requirements established by the applicable CFP. For more details on these requirements, please see Appendices C, D, or E.

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

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

Both CIRM and the CFP may be involved in the management/oversight of the CIRM/CFP Award, by participating in mutually agreed upon joint award administration activities. These activities may include but are not limited to participation in progress monitoring via progress reports and discussion with a Clinical Development Advisory panel (CDAp).

Disclosure Information

All applicants, including those not applying with a Partner PI are hereby notified that CIRM may share Disease Team Planning Application, Research Award Application and related information submitted by applicants with the CFPs in order to facilitate their participation in this RFA. Information concerning approved

CIRM/CFP Awards may also be shared with CFPs. Before receiving any such material, the CFP will agree in writing to hold the materials in strict confidence and to use them solely for purposes directly related to this RFA.

V. Eligibility

Only PIs and applicant institutions who have received a Planning Award are eligible to apply for this Research Award, with two exceptions: For-profit applicant institutions and recipients of Disease Team I Research Awards (RFA 09-01) may apply for an exemption from the Planning Award requirement, provided that they meet specific criteria. Refer to Section V.E (for-profit applicants) or V.F (Disease Team I applicants) for details.

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

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

It is expected that the PI and the applicant institution on the Planning Award and Research Award will be the same. The Research Award project must propose the same development candidate that was the subject of the successful Planning Award application.

Some Disease Team Planning Awards were subject to conditions that would determine whether CIRM would accept an application for the Research Award. Evidence that each of the specified conditions have been met must be provided in a letter accompanying submission of the Research Award application, and may reference information in the Research Award application.

CIRM requires that any proposed clinical trial include at least one clinical trial site in California. CIRM expects its 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 inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.

A. Institutional Eligibility

Both non-profit and for-profit organizations are welcome to apply. At the time of the Research 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.

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

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

“Non-profit organization” means: (1) a governmental entity of the state of California; or (2) a legal entity that is tax exempt under Internal Revenue Code section 501(c)(3) and California Revenue and Taxation Code section 23701d. “For-profit organization” means: a sole-proprietorship, partnership, limited liability company, corporation, or other legal entity that is organized or operated for the profit or financial benefit of its shareholders or other owners. Such organizations also are referred to as “commercial organizations”.

B. Principal Investigator, Co-Principal Investigator and Project Manager Eligibility

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 Disease Team Therapy Development Research Award to any PI or Co-PI who is PI or Co-PI on more than 3 active CIRM awards at the time of NGA or NLA issuance.

The limit includes all CIRM awards that have been approved but not yet closed out, with the exception of the following CIRM RFAs/PAs: Shared Research Labs, Major Facilities, Research Training Awards I & II, Bridges to Stem Cell Research, Disease Team Planning Awards (RFA 09-01), Disease Team Therapy Development Planning Awards, or Conference Grants.

Principal Investigator

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

A 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 Research Award application deadline for this RFA (January 25, 2012) 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;

- Have documented authority from the applicant institution to staff the proposed project; and must have documented commitment from the applicant institution to provide resources sufficient to carry out the proposed research.

Co-Principal Investigator(s)

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 provide research in support of the proposed project. By the Research Award application deadline (January 25, 2012) 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 scientific goals of the project.

Project Manager

CIRM requires that a single project management professional (Project Manager) be designated as Key Personnel in each 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%) percent effort, in California, to the project.

C. Percent Effort Requirements

CIRM will only fund PIs and Co-PIs who are willing to devote substantial, focused attention to the project. For the Research Award component of this RFA, PIs and

Co-PI must be willing and able to commit following efforts during the duration of the project:

- PIs = minimum of 30%
- Co-PIs = minimum of 20%

D. Extraordinary Exceptions

The President of CIRM has the discretion to permit exceptions to any requirement specified in this Section V. 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 XI of this RFA) and the Loan Administration Policy (see Appendix B), 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 must request it by October 4, 2011. To request an exception, or for assistance in determining whether one is necessary, contact the CIRM staff listed in Section X. Decisions on exceptions will be made by November 15, 2011.

E. For-profit applicants: Special Note

For-profit entities without a funded planning award may request permission to apply for the Research Award. To qualify for consideration, a for-profit applicant must meet the following criteria:

- The therapeutic candidate must meet all scope requirements detailed in Section II of this RFA Supplement and provide evidence that the therapeutic candidate proposed meets the requirement(s) detailed in Section II.
- Evidence is provided that a multidisciplinary team (which may all be employed by the for-profit applicant) containing all appropriate functional groups for the proposed project has been assembled. All necessary partners (Co-PI, Partner PI), and collaborators have been identified and are willing to participate in the project if recommended for funding.

- Proposals seeking CIRM funding for clinical trials are highly encouraged to provide evidence that additional funds (minimum of 50% of the total funds) for the proposed project have been secured or will be secured if recommended for funding.

For-profit entities seeking permission to apply under these terms **must submit: a) an Exception Request Form (Adobe PDF), available on CIRM's web site (http://www.cirm.ca.gov/RFA_10-05) and b) a letter briefly describing the therapeutic candidate, target indication/patient population, proposed preclinical and/or clinical studies and addressing the criteria specified in Section V.E of the RFA.** Letters (not exceeding 5 pages in length) and the completed Exception Request Form should be addressed to the CIRM President, submitted via email to DT2_Exceptions@cirm.ca.gov and **must be received by October 4, 2011.** CIRM will provide a response to the request by November 15, 2011.

F. Special note for recipients of Disease Team I awards

Disease Team Therapy Development Research Awards are generally not available for PIs and Co-PIs on Disease Team I awards, but those teams may request permission to apply for the Research Award, subject to the following:

- Eligibility will only be considered for a Disease Team I award recipient who has completed an IND filing that is ready to begin Phase I clinical trials by summer of 2012 with the therapeutic candidate that is the subject of the Disease Team I award.

- Evidence is provided that a multidisciplinary team containing all appropriate functional groups for the proposed project has been assembled. All necessary partners (Co-PI, Partner PI), and collaborators have been identified and are willing to participate in the project if recommended for funding.

- Proposal seeking CIRM funding for clinical trials are highly encouraged to provide evidence that additional funds (minimum of 50% of the total funds) for the proposed project have been secured or will be secured if recommended for funding.

- The therapeutic candidate must meet all scope requirements detailed in Section II of this RFA and provide evidence that the therapeutic candidate proposed meets the requirement(s) detailed in Section II.

- If the applicant is recommended by the GWG and approved for funding by the ICOC, the Disease Team I Award must be closed out before issuance of an award under this RFA.

Disease Team I applicants seeking permission to apply under these terms **must submit: a) an Exception Request Form (Adobe PDF) available on CIRM's web site (http://www.cirm.ca.gov/RFA_10-05) and b) a letter briefly describing the therapeutic candidate, target indication/patient population, proposed clinical studies and addressing the above criteria.** Letters (not exceeding 5 pages in length) and the completed Exception Request Form should be addressed to the CIRM President, submitted via email to DT2_Exceptions@cirm.ca.gov and **must be received by October 4, 2011**. CIRM will provide a response to the request by November 15, 2011, contingent on these applicants providing evidence to CIRM of an active IND by January 25, 2012, the deadline for submission of a Research Award application.

VI. Application and Evaluation Process

With limited exceptions, receipt of a Planning Award is a prerequisite for submission of an application for a Research Award. **The research project proposed in the Research Award Application should be substantively the same as that described in the successful Planning Award application**. Those PIs who received conditional approval of their Disease Team Planning Awards must provide evidence that the list of conditions specified in the receipt of the award have been addressed. The evidence must be provided in a letter addressed to the Senior Review Officer, (gsambrano@cirm.ca.gov) accompanying submission of the Research Award application (see Part K) and may reference information in the Research Award application.

Research Award applications will be evaluated by the CIRM Grants Working Group (http://www.cirm.ca.gov/GrantsWkgGrpMembers). 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).). The CIRM's GWG is composed of fifteen scientific experts from outside California, seven patient advocate members of CIRM's Governing Board (http://www.cirm.ca.gov/GoverningBoard), and the Chair of the Governing Board.

The fifteen participating scientists on the GWG will review the applications and score them according to scientific and clinical merit applying the review criteria described in Section VII below. The GWG (scientists and patient advocates) will then review the entire portfolio 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 balance in the context of CIRM's translational portfolio (see Appendix A).

- Overlap with other CIRM investments in CIRM's translational portfolio.

- Access to materials and technologies that are critical to the proposed project.

The GWG will make funding recommendations to the Governing Board, who will make final funding decisions.

VII. Review Criteria

Applications will be evaluated in six key areas: 1) Significance and Impact; 2) Rationale; 3) Therapeutic Development Readiness; 4) Feasibility of the Project Plan; 5) Principal Investigator and Development Team; and 6) Collaborations, Resources and Environment. The specific criteria for review of applications are based on the standard review criteria described in the CIRM Grants Administration Policy (GAP, see Section XI of this RFA).

1. Significance and Impact

a. Target Product Profile: The target product profile (TPP) conveys the long term aspirational product attributes and overall intent of the development program. The TPP identifies: 1) the optimal (ideal) profile for the therapeutic candidate, 2) the threshold profile (minimally acceptable to differentiate from current and future competing products) and 3) specific metrics for those attributes addressed by the proposed project to enable key decisions in the development process.

b. Clinical Competitiveness and Impact: The overall development strategy is well considered and reflects thought and commitment to moving the therapeutic candidate through development for the benefit of patients or persons with serious disease or injury. The proposed project is integral to the overall development strategy and supports achievement of the Target Product

Profile. The proposed therapeutic candidate, 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 therapeutic candidate proposed is within scope as defined in section II. The proposed activities for IND-enabling preclinical, clinical and supporting studies are within the scope of activities defined in Section II, and could potentially achieve one or more of the objectives of this RFA. When the project proposes a therapeutic candidate that is substantially comparable to one already represented in CIRM's translational portfolio (see Appendix A), the project must be compelling.

2. Project Rationale

There is strong scientific rationale supported by compelling preclinical studies for the proposed therapeutic intervention in the target disease or injury.

3. Therapeutic Development Readiness

The project is sufficiently mature and its status is such that there is reasonable expectation that the stated project objective(s) (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.

a. Projects beginning with 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 cGMP-compatible therapeutic candidate has been chosen. Processes and 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.

b. Projects beginning with clinical studies: The applicant has filed an IND and has passed the 30 day period without comment. A copy of actual correspondence or a summary of correspondence with the regulatory agency regarding the active IND is provided by the applicant. If the submitted IND was put on clinical hold, the applicant has addressed major issues and the clinical protocol is off the clinical hold at the time of application deadline (January 25, 2012).

i. Preclinical studies required to support the clinical protocol(s) proposed in the application have been completed. Preclinical studies supporting those proposed clinical studies must be complete or clearly defined as to when they will be completed. Evidence of formal meetings with pertinent section of the regulatory agency in the form of actual correspondence or summary of the discussions/meeting are provided and major issues raised in those discussions have been addressed.

ii. 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. A flow diagram is provided for the manufacturing process of the test article from start to finish with indicated stage(s) where samples are withdrawn for in-process and release testing. In addition, a flow diagram showing steps of cell processing, dose formulation, testing and delivery of the test article to the patient at the clinical site (if applicable) is provided.

iii. The manufacturing strategy is feasible. Sufficient product can be prepared and released within the necessary time frame to meet the enrollment requirements. The proposed methodologies are sufficiently qualified/validated to be suitable for intended use. The plan for managing technology transfer and product handling at the clinical sites is adequate to ensure safety and quality of the test article.

If the therapeutic candidate includes a device component, Investigational Device Exemption (IDE)-related issues have been addressed.

4. Feasibility of the Project Plan:

The project plan and goals are feasible and adequate to meet the objectives of this RFA. The project plan proposes studies that address specific metrics (success criteria) defined for attributes of the TPP appropriate for the stage of development. The project milestones describe key activities and deliverables. The project milestones are reliable indicators of the project's progress. The criteria for Go/No Go decisions are adequately defined and provide quantifiable measures of the project's performance. The project timeline is complete, highlights key progress and Go/No Go decision milestones and is realistic.

a. Projects beginning with IND-enabling studies:

i. 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. The manufacturing strategy is feasible. Sufficient product can be prepared and released within the necessary timeframe for the intended clinical trials. Evidence of pre-pre-IND discussion or actual correspondence or summary of the discussions/meeting are provided and major issues raised in those discussions have been addressed.

b. Projects beginning with Clinical studies:

i. The overall study design is feasible and adequate to meet the objectives of the proposed clinical studies. Primary and secondary endpoints for the study and endpoint evaluation criteria are clearly defined.

ii. The choice of patient population is appropriate and enrollment projections are realistic. Conduct and follow-up of the enrolled patients can be completed during the award period. The longer term safety follow-up studies for pluripotent-derived therapeutic candidates, not proposed to be funded by CIRM but required or recommended for regulatory purposes, should be described.

iii. To ensure that adequate safeguards for patients are in place, the proposed Data and Safety Monitoring Plan is adequate to minimize risks to human subjects, and will ensure appropriate oversight and monitoring. The applicant has obtained IRB-approved consent forms. The proposed 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/2011/06_22_11_Agenda%20Item%239_for_6_22-3_11_ICOC_SWG_Resolution_Clinical_Trials_22June2011.pdf).

5. Principal Investigator (PI) and Development Team

a. Expertise and Track Record: 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 therapeutic candidate and will have a key role in the proposed development plan.

b. Development Team and Leadership Plan: An appropriate multidisciplinary team has been assembled to best achieve the project's milestones and objective. The PI has developed a leadership plan that will ensure successful execution of the project. The structure and governance of the team will support status assessment, progress monitoring and project decision-making. The PI together with the Project Manager will foster communication, coordination and collaboration among members of the team, consultants.

   i. Projects beginning with IND-enabling Studies: The team includes a Product Development Lead, CMC Lead, Preclinical Lead, Clinical Lead, Regulatory Lead, and a Project Manager. Leaders have demonstrated expertise in their functional areas.

   ii. Projects beginning with Clinical studies: The team includes a Clinical Lead, CMC Lead, Regulatory Lead, Preclinical Lead, Product Development Lead and a Project Manager. Leaders have demonstrated expertise in their functional areas.

c. Clinical Investigators and Clinical Sites: The lead clinical investigators at participating study sites are recognized opinion leaders or experts in the target disease area, and have relevant experience in conducting clinical studies in the proposed disease area. Clinical sites are staffed with personnel experienced in conducting translational early Phase I and II trials.

   Designated team members responsible for regulatory and safety filings, data collection and monitoring, maintenance of databases, quality control, training and oversight of clinical sites and adherence to the clinical protocol have appropriate expertise in their functional areas. Plans and strategies have been developed for communication and oversight of CROs/CMOs. There is a plan for conflict resolution.

d. Budget: The PI (and Co-PI and Partner PIs, if applicable) have developed a budget that is focused and appropriate for research necessary to achieve the project objective(s).

6. Collaborations, Resources and Environment

a. Resources and Environment: Necessary facilities, major equipment, and services are available for conducting the proposed research.

b. Intellectual Property, Licenses: Relevant assets (i.e. intellectual property, licenses) are available to the project. The applicant has demonstrated that any material transfer agreements (MTAs) or license agreements that are critical for development of the therapeutic candidate are either already in place or at an adequate stage of negotiation to enable the development program. The applicants have agreements in place to cross-reference Drug, Device or Facility Master File(s) submitted by the industry partner/collaborator with the appropriate section(s) of the regulatory agency (FDA). (See Parts H and I).

c. Collaborations: Although not required, collaborations (including, if applicable, those with a Co-PI and Partner PI) are often important to the success of the proposed project, especially if a PI's institution does not have all of the requisite expertise. The applicant has provided evidence that the collaborations are in place (e.g., documented by letters of collaboration in Part C) conveying a commitment to the proposed research and the ability to proceed. If applicable, partnership with industry has been established to accelerate the development program, for example by contributing expertise, technology, and/or assets.

d. Clinical Trials: Considerations will be given to for-profit applicants who propose clinical trials to secure other sources of funding (at least 50% of the total funds) to leverage CIRM funds. Similarly, considerations will be given to non-profit applicants that are engaged in partnership(s) with industry to leverage expertise and additional funds for the proposed project.

e. Contract Services: Consideration will be given as to the plan to use contract research organizations (CROs), contract manufacturing organizations (CMOs), and/or consultants. Specifically, the proposed CROs or consultants have the necessary experience and expertise to successfully meet expectations, deliverables and timelines. Proposed CMOs contracted for manufacture or release testing of the therapeutic candidate have the necessary experience and track record to

successfully produce the clinical supplies needed to support the proposed clinical studies. If such contract services are used, the development team has appropriate oversight expertise.

f. Institutional Support: The applicant institution (including Co-PI sponsoring institution(s), and/or Partner PI applicant institution, if applicable) is committed to supporting translational research, and, if applicable, early phase clinical trials.

VIII. Application Procedure

Applicants must follow these instructions for submission of Research Awards. Eligibility is addressed in Section V.

A. Application Form

Application form will be available via the Grants Management Portal at https://grants.cirm.ca.gov no later than November 1, 2011.

The application for the CIRM Disease Team Therapy Development Research Award consists of **eleven (11) parts** (Parts F and G are applicable to the Clinical Study Applicants only; Part K for Disease Team Planning Award applicants with conditions only):

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

2. Part B: Disease Team Therapy Development Research Award Proposal (MS Word template). Part B includes: Target Product Profile; Overall Development Strategy; Clinical Competitiveness and Impact; Rationale, Status and Supporting Data; Project Plan, Milestones, and Timeline; Leadership Plan; Collaborations, Consultants, CROs/CMOs; Clinical Sites; Assets, Resources and Environment; Licenses and Agreements; References (section numbers 6-18 below). Part B consists of the following sections:
   Part B Section 1– Research Proposal
   Part B Section 2 – CIRM Target Product Profile (TPP) Template
   Part B Section 3 – Summary of Nonclinical Testing
   Part B Section 4 – CIRM Clinical Protocol Synopsis Template
   Part B Section 5 – CIRM Manufacturing Plan Synopsis Template

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

4. Part D: CIRM Activity Based Budget Template

5. Part E: FDA correspondence. If possible and applicable, provide copies of regulatory correspondence.

6. Part F: Clinical Protocol (Clinical Study Applicants Only).

7. Part G: Investigator Brochure (Clinical Study Applicants Only).

8. Part H: Copies of authorization for cross reference of Drug, Device or Facility master files, if applicable.

9. Part I: Licenses and agreements. If possible and applicable, provide copies of those MTAs and contracts that are critical for development of the therapeutic candidate.

10. Part J: Related Business Entities Disclosure Form (Adobe PDF template). In order to comply with the Conflict of Interest policies under which CIRM operates, Part J 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 (See Section XI).

11. Part K: Disease Team planning award applicants with conditions - Evidence that each of the specified conditions have been met must be provided in a letter accompanying submission of the Research Award Application

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

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

P1. 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.

P2. 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.

P3. 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 a Phase I, Phase I/II, or Phase II study of the therapeutic candidate within 4 years of the Research Award project start date.

P4. 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 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, 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)*

List all key personnel and their roles on the project. Key personnel are defined as individuals who contribute to the scientific development or execution of the project in a substantive, measurable way, whether or not they receive salaries or compensation under the grant. Key personnel may include any technical staff, trainees, co-investigators (collaborators), or consultants who meet this definition. Personnel that are not key, such as technical support staff, may be supported by grant funds but not named.

List the key lead investigator for each clinical site in key personnel even though he/she will be compensated as part of a subcontract. It is not necessary to name other clinical site personnel who will be participating in the conduct of the study.

For applications that designate a CIRM-funded Co-PI, key personnel sponsored by the Co-PI must be listed in Part A. For CIRM-funded key personnel, a minimum of one percent effort is required for each key person, except the PI, and Co-PI who are required to commit a minimum of 30% and 20% effort respectively.

For each key personnel listed (except for technical staff and students) 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. Following the biosketches for the PI and, if applicable, the Co-PI, provide biosketches for functional area heads and/or members of the development core team (including the individuals responsible for overseeing clinical, clinical operations, regulatory, CMC, data management and translational research activities) and for the lead clinical investigator at each proposed site. Thereafter, include all remaining biosketches in alphabetical order.

5. Budget *(included in Parts A and D)*

Provide all budget information requested in the budget section of Part A and in Part D. Budgets must be justified in detail, including all subcontracts and consulting fees. All allowable costs for research funded by CIRM are detailed in the CIRM Grants Administration Policy (GAP, see Section XI of this RFA). For CIRM/CFP teams, allowable costs for research funded by the Collaborative Funding Partner may differ. Guidance will be provided separately by the Cancer Stem Cell Consortium (CSCC) of Canada (see Appendix C); the Federal Ministry for Education and Research (BMBF), Germany (see Appendix D); and the Andalucía Initiative for Advanced Therapies (Iniciativa Andaluza en Terapias Avanzadas, "IATA"), Spain (see Appendix E).

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

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

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

- Travel: Recipients (PIs) of CIRM Disease Team Therapy Development Research Award are encouraged to attend a CIRM-organized grantee meeting in California and Clinical Development Advisory Panel (CDAp) in

San Francisco and should include travel costs for these meetings in the budget. Travel costs associated with collaborations necessary to the grant are allowable. Details of allowable travel costs can be found in the GAP (see Section XI.A of this RFA).

- Equipment: Major equipment (more than $5,000 per item) necessary for conducting the proposed research at the applicant institution should be itemized and justified. Equipment costs should not be included as allowable direct costs in indirect cost calculations.

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

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

For activities **other than research**, Grantees may subcontract outside California, but must make a good faith effort to use California suppliers for more than half of their contracts and purchases in accordance with CIRM's California Supplier regulation (Cal. Code Regs., tit. 17, § 100502). Examples of such research support activities include execution of a clinical trial according to a protocol, execution of a toxicology study performed according to an existing protocol, GMP production. (Clinical trial execution would include blinding, randomization, patient recruitment, patient treatment, medical monitoring, data collection, clinical site selection/site initiation and IRB activities).

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

Indirect Costs Indirect costs will be limited to 20 percent of allowable direct research funding costs awarded by CIRM (i.e., project costs and facilities costs), exclusive of the costs of equipment, tuition and fees, and subcontract amounts in excess of $25,000. See Appendices C, D, E for details concerning CFP allowable costs.

6. Target Product Profile *(up to 2 pages use TPP template in Part B, Section 2. Also included as sample A in this RFA)*

Provide a target product profile (TPP) for the proposed therapeutic candidate/intervention. The TPP provides the aspirational product attributes to

help define success and inform the proposed label. A well-designed product discovery effort and development plan starts with a TPP. 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 the pre-specified 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 needs to be annotated as data evolves at appropriate milestones. The TPP should be continually refined and will ultimately become the product label.

Using the CIRM Target Product Profile table in Section 2 of Part B, provide the desired attributes/claims of the therapeutic for the following: indication, target activity, patient profile, efficacy endpoints, safety/contraindications, dose/regimen, dosage form and route of delivery. Specify relevant metrics (success criteria) for attributes to be addressed in the proposed project.

The FDA released the draft guidance document "Guidance for Industry and Review Staff: Target Product Profile – A Strategic Development Process Tool" which may be a helpful resource for developing a TPP. It is available from the FDA's website (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm080593.pdf). *It is worth noting that while this document was developed and issued by the FDA's Center for Drug Evaluation and Research, it contains many guiding principles that apply to developing a TPP for cell therapies and biological products, as well as to CDER-regulated products.*

7. ***Overall Development Strategy*** *(up to 2 pages in Part B)*

Summarize the strategy to develop the candidate therapy in order to bring the therapy to patients, according to the TPP. Provide a high-level timeline of the overall development plan. Include key IND-enabling studies including demonstration of preclinical proof of concept/efficacy, development of a manufacturing process and completion of preclinical safety studies. For clinical studies include key clinical, CMC, regulatory and other milestones.

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. Describe the pharmacoeconomic rationale for the proposed therapeutic.

9. Rationale, Status, and Supporting Data *(up to 8-10 pages in Part B).*

For projects beginning with IND-enabling studies: Discuss the scientific rationale for initiating preclinical development. Provide evidence for the selection of a single therapeutic candidate and development of methods for reproducible production and characterization of the therapeutic candidate. Summarize the results of pilot preclinical efficacy (in appropriate disease model(s)) 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. Summarize any pre-pre-IND discussions or pre-IND meetings with the pertinent section(s) of the regulatory agency regarding the proposed project. If possible provide copies of any actual correspondence with the FDA in Part E.

For projects beginning with clinical studies: Discuss the scientific and clinical rationale for testing the proposed therapeutic candidate in the target disease/injury (you may reference appropriate sections of the Investigator Brochure). Using the CIRM Nonclinical Testing template (Part B, Section 3), summarize the types of in vitro and in vivo studies performed to test the pharmacology and toxicity parameters using the selected therapeutic candidate.

- Describe the potential benefit to patients of the proposed therapy, and the potential risks. Explain why the potential benefits to subjects outweigh the risks and justify testing 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.

- Summarize the IND status for the proposed therapeutic candidate. Briefly summarize any past clinical hold issues and explain how they were resolved. The clinical protocol must be off clinical hold at the time of application deadline (January 25, 2012). Provide, if possible, copies of actual FDA correspondence in Part E.

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

- If the proposed therapeutic candidate is substantially comparable to one already represented in CIRM's current Translational Portfolio, (see Appendix A), justify why the proposed research would be a compelling addition.

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

Describe concisely, but with sufficient detail to permit evaluation of the merit and feasibility of the proposed work, the project plan, including the experimental approaches, methods and techniques proposed for accomplishing the project goals within 4 years. The goals must include one or more objectives from Section II (i.e. obtain FDA approval for first-in-human studies and /or to complete a Phase I, I/II, or Phase II trial). The plan must be based on a clearly stated project timeline that outlines project activities and includes all key milestones, including an estimate of the timing of the go/no go decision milestones. Include a Gantt chart if desired. Milestones describe precise, quantifiable study outcomes of key activities, not simply the work to be conducted.

Describe the product manufacturing strategy and plan to produce and deliver the test article within the necessary timeframe for the intended clinical trial.

For proposals including Co-PIs and/or Partner PIs, clearly indicate activities to be conducted by the applicant PI, Co-PI and/or Partner PI.

- Provide a timeline (in Gantt chart format or equivalent) for the proposed project and include Preclinical, Clinical, CMC, Regulatory, and other critical path activities, milestones and Go/No Go decision points.

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

- Explain how the activities of the proposed project contribute to and advance the overall Development Plan leading to regulatory approval or to become accepted medical practice for the treatment of serious disease/injury.

11. Clinical Protocol Synopsis *(up to 5 pages in Part B Section 4)*

All Applicants: Using the CIRM CLINICAL PROTOCOL SYNOPSIS template provide a Clinical Protocol Synopsis for each study proposed. A copy of this template has also been provided as Sample B of this RFA. (up to 5 pages)

Clinical Study Applicants Only: Provide a copy of the clinical protocol in Part F.

12. Manufacturing Plan Synopsis for Projects that Propose Clinical Studies *(up to 6 pages in Part B Section 5)*

Using the CIRM MANUFACTURING PLAN Synopsis Template summarize the manufacturing strategy to support the proposed clinical studies. This template has also been provided as Sample C of this RFA.

13. Leadership Plan *(up to 2 pages in Part B)*

Provide a detailed leadership and management plan. Describe the organizational structure of the development team. List the key members (including consultants) and indicate their roles. Describe the plan for functional area leadership and management (Include: Clinical, Clinical Operations, Regulatory, CMC and if applicable, Translational Research). Indicate who will have responsibility for regulatory and safety filings; data collection and monitoring; maintenance of databases; product manufacturing; and quality control (If CRO/CMO/contractor function, indicate designated team member responsible for final sign-off). Describe processes for monitoring progress, maintaining team strategy and timelines, and decision-making. Describe the plan for communication with and oversight of CROs (if applicable). Describe plans and strategies for resolution of potential issues or conflicts.

14. Collaborations/Consultants/CROs/CMOs *(up to 3 pages in Part B)*

Provide a list of collaborations/consultants/CROs/CMOs (or plans for identification and contracting) that will participate in the proposed project. Summarize their specific roles, expertise and experience and explain how it is integral to the success of the project. If advisors, consultants or subcontractors will provide expertise or resources critical to the success of the project, summarize their credentials and relevant track records.

15. Clinical Sites *(up to 2 pages in Part B)*

Provide a list of clinical sites for the proposed Phase I, I/II or Phase II clinical trial. Provide evidence that the clinical sites have experience in conducting translational early Phase I and II trials. Provide evidence that the clinical sites' projected patient enrollment plan is realistic.

16. Resources and Environment *(up to 1 page in Part B)*

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

17. Licenses and Agreements *(up to 1 page in Part B).*

Describe intellectual property assets (patent applications, patents). If applicable, describe the status of letters authorizing the ability to cross reference Drug, Device or Facility Master File (DMF, FMF). If possible provide copies of authorization letters in Part H.

Provide a brief summary (up to 1 page) describing the status of Material Transfer Agreements (MTA) or licensing agreements for cell lines or other materials that are critical to the development of the therapeutic candidate and the role of those materials in the product development. If possible provide copies of the essential MTA(s), or any term sheets or letters of intent if an MTA has not yet been entered into, in Part I. If not possible please summarize the terms and what stage negotiations are in including whether there is a term sheet, letter of intent or MTA or licensing agreements.

18. References *(up to 2 pages in Part B)*

List all references used in the body of the proposal.

19. Investigator Brochure *(Part G)*

Provide a copy of the Investigator Brochure for the candidate therapy.

20. Related Business Entities Disclosure Form *(Part J)*

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 J and submit the form. If for-profit funding is sought, include the following for each such for-profit organization to be funded:

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

B. Application Submission Instructions

Disease Team Therapy Development Research Awards applications will only be accepted from applicants who 1) submitted a Disease Team Therapy Development Planning Awards and/or 2) are invited by CIRM to submit a Research Award application, under an Extraordinary Exception, described in section V.D-F.

All applicable parts of the Disease Team Therapy Development Awards application must be submitted and received by CIRM no later than 5:00PM PDT on January 25, 2012 in both electronic form (via the Grants Management Portal) and in hard copy (a signed original plus five copies). It is the applicant's responsibility to meet this deadline; no exceptions will be made. Both the PI and the applicant institution's Authorized Organizational Official (AOO) must sign the original hard copy of the application (consisting of Parts A-K). The original application plus 5 hard copies (preferably double-sided) should be sent via express mail or courier service to:

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

C. Submission of Supplemental Information

If necessary, the PI may submit limited supplemental materials that provide critical new information related to their research proposal after the application deadline but not later than 5:00pm PDT on March 13, 2012. Supplementary materials will not be accepted after this deadline. CIRM will accept a one-time-only submission of materials from the PI only if it meets the submission deadline and conforms to the requirements described herein. Accepted submissions will be forwarded to reviewers for their consideration.

The submission should be in the form of a one-page letter addressed to the Senior Review Officer. 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:

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

2. Within the one-page letter, confirmation of funding secured from other sources or regulatory (e.g., IND, IDE) filings or approvals acquired since the application submission deadline.

3. 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. Changes in scope, experimental approach, or research design are not allowed.

IX. Schedule of Deadlines and Reviews

Application Forms available online	November 1, 2011
Applications due	5:00 pm (PDT), January 25, 2012
Review of Applications by Grants Working Group (GWG)	April, 2012
Earliest Review and Approval by ICOC	June, 2012
Earliest Funding of Awards	August, 2012

X. Contacts

For information about this RFA:

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For information about the review process:

Gilberto R Sambrano, Ph.D.
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California Institute for Regenerative Medicine
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XI. CIRM Regulations

Grant awards made through this RFA will be subject to CIRM regulations. These can be found on CIRM's website under Adopted CIRM Stem Cell Grant Regulations (http://www.cirm.ca.gov/reg/default.asp)

A. CIRM Grants Administration Policy

CIRM's Grants Administration Policy (GAP) for Academic and Non-Profit Institutions (Non-Profit GAP) and the GAP for For-Profit Institutions (For-Profit GAP) serve as the standard terms and conditions of grant awards issued by CIRM. All research conducted under this award must comply with the stated policy. Progress reports of research, as required by the GAP, are important to CIRM: Funding from year to year will depend on adequate scientific progress as

outlined in the grant application timeline. CIRM's GAP is available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants#GAP.

Applicants should 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."

B. Intellectual Property Regulations

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

C. Human Stem Cell Research Regulations

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

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, at the completion of their studies for the benefit of the field.