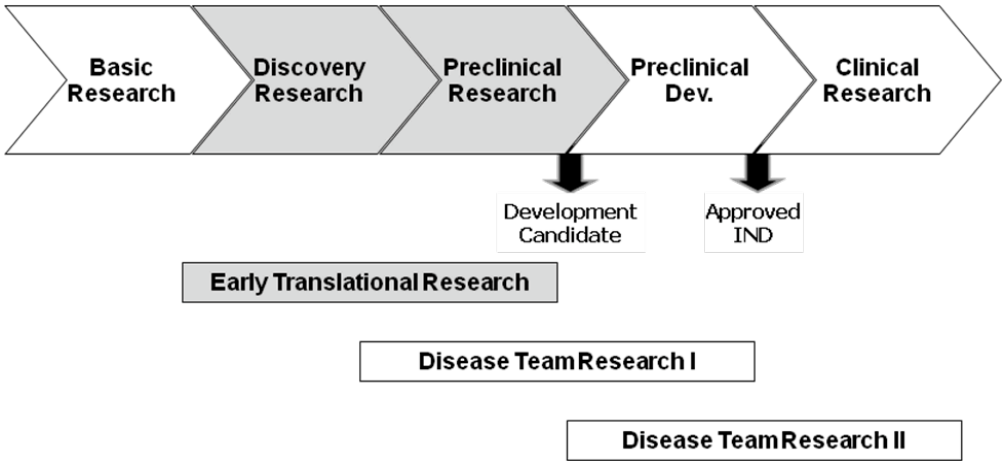
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

RFA 10-01: CIRM EARLY TRANSLATIONAL II RESEARCH AWARDS

I. Purpose

Stem cells offer the unique potential to restore tissues damaged by injury or disease. The rapid expansion of stem cell research over the past few years suggests that there are research discoveries ready for translational research toward the clinic. Translational research encompasses a diverse and potentially challenging series of activities necessary to progress a research stage stem cell discovery towards a potential therapy or diagnostic appropriate for use in humans. The CIRM Translational Research Initiative provides funds to move promising discoveries in stem cell research toward potential stem cell-based therapies and diagnostics. The purpose of this CIRM Early Translational II Research Awards RFA is to support projects that enable the initial stage of this process. The later stages of translational research, including preclinical development and clinical research are supported by other recurring RFAs such as CIRM's Disease Team Research Awards. The diagram below shows the scope of each RFA along the research spectrum. These recurring translational RFAs are core to our mission to enable stem cell-based therapies, diagnostics and cures for the benefit of patients.



II. Objectives

The key objectives of the Early Translational II Research Awards RFA are the conduct of research: 1) that results in a Development Candidate ready for IND-enabling preclinical development or 2) that leads towards a Development Candidate. A therapeutic Development Candidate is a candidate therapeutic entity, suitable for use in humans, that has completed all the necessary research

to enable a decision to initiate preclinical development activities required for regulatory approval for testing in humans. (See Appendix A for research activities typically required to achieve a therapeutic Development Candidate and that therefore fall within the scope of this RFA.) Similarly, a diagnostic Development Candidate is a candidate diagnostic entity (e.g., a test or assay) that has completed necessary research and is ready to initiate preclinical development activities required for regulatory approval for clinical testing.

Two categories of research awards will be made under this RFA:

1) Development Candidate Awards (DC Awards) will support projects intended to result in a novel stem cell-derived development candidate that meets an unmet medical need. By the end of the award period, these projects will have completed all necessary activities to have a development candidate ready to start Investigational New Drug (IND)-enabling preclinical development; and

2) Development Candidate Feasibility Awards (DCF Awards) will support projects that will advance the goal of obtaining a novel stem-cell-derived development candidate but which do not encompass the full scope of activities required to achieve a development candidate. Unlike the above Development Candidate Awards, applicants for these awards need not have completed, by the end of the award period, all of the necessary activities required to start preclinical development for a regulatory filing. Rather, these awards are intended to allow investigators to conduct research to *identify or determine feasibility* of a given potential development candidate. For example, applicants for these awards may wish to identify a lead candidate, reproducibly establish disease-modifying activity or screen multiple candidates against a single, defined disease target.

For applications to be responsive to this RFA: applicants must have already identified a single disease target for therapeutic or diagnostic intervention and have a scientifically justifiable hypothesis for the proposed development candidate; and, human stem cells must be necessary to achieve the outcomes of the proposed research. Examples of responsive research are studies on potential therapeutic development candidates such as stem cell or stem cell-derived progenitor or differentiated cells either genetically modified or not; a biologic derived from stem cells; or a small molecule discovered using human stem cell–based assays.

Among responsive proposals, CIRM will prioritize proposals which:

- Will result in a novel cell therapy development candidate derived from human pluripotent cells (DC Award); or

- Will lead towards a novel cell therapy development candidate derived from human pluripotent cells (DCF Award); or
- Are based on discoveries involving human pluripotent stem cells (e.g., human pluripotent stem cells used for drug or diagnostic discovery); or
- Are ineligible for or unlikely to receive timely or sufficient federal funding.

By the conclusion of the three-year award period for a Development Candidate Award, a successful therapeutic candidate must meet the following applicable criteria:

- Suitability for use in humans (i.e., not murine 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 purified 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 under development.

Comparable relevant criteria must be met at the conclusion of the three-year award period for a Development Candidate Award for a diagnostic candidate. By the conclusion of a Development Candidate Feasibility Award, a subset of the above criteria, defined by the PI, must be met, including suitability for use in humans for a therapeutic candidate (or, with humans for a diagnostic candidate).

This Early Translational II Research award will support research activities that address the above criteria (see also Appendix A).

Research that is <u>outside</u> the scope of these awards includes:

- Target discovery
- IND-enabling preclinical development (e.g. GMP production, GLP toxicology and tumorigenicity studies)
- Clinical studies. Analysis of human subject samples, if directly related to the proposed research, can be funded under this RFA.

Translational research is inherently multidisciplinary, often necessitating collaboration among scientists with diverse expertise in both academic and for-profit institutions. Through this award, CIRM expects to fund approved

proposals from both non-profit and for-profit institutions (separately or in collaborations), through grants or loans. DC Awards may include a co-principal investigator (see section VII.B). To further facilitate collaboration with qualified investigators outside of California, this RFA is offered as part of our Collaborative Funding Partner Program (see section V).

III. Award Information

CIRM intends to commit up to $80 million to this Early Translational II Research Awards program. Of this total, CIRM intends to commit up to $60M towards Development Candidate Awards to support about ten projects. Each of these DC Awards will be funded for up to three years with justifiable total direct project costs of up to $3.5 million over the project period. Direct project costs should be allocated over the project period to best achieve the project goal. CIRM also intends to commit up to $20 million towards Development Candidate Feasibility Awards (DCF Awards) to support about ten projects. Each DCF Award will be funded for up to three years with justifiable total direct project costs of up to $1.15 million over the project period.

For all awards, CIRM reserves the right to negotiate milestones, success criteria, timelines and budgets prior to issuance of the Notice of Grant Award (NGA) or Notice of Loan Award (NLA), subject to renegotiation based on progress. Mindful of the urgency of its mission, CIRM requires that all approved applications be initiated no later than six months after Independent Citizens Oversight Committee (the ”Governing Board”), approval and/or authorization for funding, unless CIRM’s President grants an extension based upon compelling justification of the need for additional time. Progress on the research is important to CIRM. For DC Awards, CIRM will require a written semi-annual progress report in addition to the annual progress report that is required by the CIRM Grants Administration Policy (GAP, section XIII.A). Continued funding is contingent upon timely scientific progress as outlined in the project milestones and timeline established under the NGA or NLA. CIRM plans to release the Early Translational Research Award RFA again in 2011.

IV. Award Mechanism

Approved applicants from non-profit applicant organizations will receive grant funding. Approved applicants from for-profit applicant institutions will receive grants for awards up to $3M and may select either grant *or* loan funding for awards greater than $3M. When submitting the full Application, for-profit applicants for awards greater than $3M must select the type of award mechanism (grant or loan) and, if a loan, the type of loan (see Appendix C).

Grant Terms: Non-profit institutions and for-profits that choose grants 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.).

Loan Terms: The terms of the Loans are set forth in detail in Appendix C to this RFA. Loan recipients shall be governed by the CIRM Loan Administration Policy that is in effect as of the date of the execution of the Notice of Loan Award. Approved 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 Interim CIRM Loan Administration Policy, available at: http://www.cirm.ca.gov/reg/default.asp.

V. Collaborative Funding Partners

CIRM has established a program with several other government agencies that fund stem cell and regenerative medicine research. Through this Collaborative Funding Partner 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 collaborative funding partners to bring important additional resources to proposed projects. If a collaborative funding proposal is approved by both government agencies, (a "CIRM/Funding Partner Award") CIRM will fund all project work done within the State of California and its Funding Partner will fund all project work performed within its jurisdiction. The Collaborative Funding Partner (CFP) participating in this RFA is the German Federal Ministry for Education and Research ("BMBF").

To apply for a collaboratively funded project involving CIRM and BMBF, applicants must satisfy both the CIRM processes and requirements (see below) and any additional requirements put forth by the BMBF. Please see Appendix B for information and requirements of BMBF.

Before funding contracts are signed, successful CIRM/BMBF applicant teams must sign written agreements addressing Intellectual Property (IP) and other issues relating to their collaborative project. Applicants must obtain approval from CIRM and from BMBF of those agreements and must provide CIRM and BMBF with copies. These applicant team Agreements must be consistent with CIRM's applicable IP regulations, with the IP requirements of BMBF and with the provisions of all Agreements between the co-funders.

Before funding contracts are signed, successful CIRM/BMBF applicant teams must obtain all necessary approvals for animal protection, human subject protection, and use of human embryonic stem cells. CIRM and the BMBF will monitor compliance with approval procedures required in their respective jurisdictions.

Both CIRM and BMBF may be involved in the management/oversight of the CIRM/BMBF 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.

VI. Notification Regarding Disclosure Information

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

VII. Eligibility Information

A. Institutional Eligibility

All CIRM-supported research must be conducted in California. Principal Investigators may apply from non-profit and for-profit research organizations that are located in California and are actively conducting or managing research at a site in California at the time of Preliminary Application submission. Non-profit and for-profit institutions sponsoring Co-Principal Investigators (Section VII.B, Co-Principal Investigators) are subject to the same eligibility requirements as applicant institutions.

“Non-profit organization” means: (1) a governmental entity of the state of California; or (2) a legal entity that is tax exempt under Internal Revenue Code section 501(c)(3) and California Revenue and Taxation Code section 23701d.

“For-profit organization” means: a sole-proprietorship, partnership, limited liability company, corporation, or other legal entity that is organized or operated for the profit or financial benefit of its shareholders or other owners. Such organizations are also referred to as “commercial organizations”.

B. Investigator Eligibility

Principal Investigator

CIRM requires that a single Principal Investigator (PI) and a single applicant institution (the PI’s institution) be designated in each application. The PI is the

designated point of contact for CIRM and is the person responsible and accountable to CIRM for scientific performance on the project, including on CIRM/Funding Partner Awards. The applicant institution is the designated contact institution for all financial and other administrative considerations.

An investigator may be a PI on only one Preliminary Application (see section VIII) under this RFA. An investigator who is a PI on a Disease Team Research Award (RFA 09-01) is not eligible to submit a Preliminary Application as PI under this RFA. An investigator who is awarded an Early Translation II Research Award under this RFA will not be eligible to submit a Preliminary Application as PI for Disease Team II Research Awards. The PI must have an M.D., Ph.D. or equivalent degree, and must be authorized by the applicant institution to conduct the proposed research in California. By the Preliminary Application deadline, the PI must:

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

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

- have documented commitment from the applicant institution to provide laboratory space and shared resources sufficient to carry out the proposed research.

Co-Principal Investigator(s)

In order to encourage multidisciplinary team-based research, CIRM will allow for a single CIRM-funded Co-Principal Investigator (Co-PI) **ONLY** for Development Candidate Awards. 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 research in California. By the Preliminary Application deadline, the Co-PI must:

- be an independent investigator at the sponsoring non-profit applicant institution, or have an equivalent position and be an employee (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 laboratory space and shared resources sufficient to carry out the proposed research.

Designating Co-PIs is not a requirement for a Development Candidate Award.

The decision of whether to include Co-PIs (or a Partner PI funded by a CFP, see section V) should be guided by the scientific goals of the project.

C. Percent Effort Requirements

CIRM, mindful of the urgency of its mission, will only fund PIs and Co-PIs who are willing to devote substantial, focused attention to the project. For this RFA, PIs must be willing and able to commit a minimum 20% effort, 15% for Co-PIs.

D. Collaborative Funding Partner Requirements

BMBF's eligibility requirements for Partner PIs are described in Appendix B.

VIII. Application and Evaluation Process

Submission of an application for the CIRM Early Translational II Research Awards RFA involves a two-step process. An eligible PI may submit one Preliminary Application (PreApp). PIs must select the type of award for which they are applying in the PreApp. PIs submitting the most promising, competitive and responsive PreApp proposals will be invited to submit detailed, full Applications. All other applicants will be deferred, with the opportunity to apply in response to a future RFA. CIRM expects to reissue the Early Translational Research Awards in the first half of 2011.

PreApps should emphasize the significance and feasibility of the proposed research and explain how the proposed research will, within three years of the project start date, conduct all necessary activities to achieve or determine the feasibility of achieving a development candidate (DC and DCF Awards, respectively). (See Appendix A for activities to achieve a therapeutic development candidate, see also section II for applicable criteria for a therapeutic development candidate.) For applicants seeking a CIRM/BMBF Funded award, the PreApp should reflect the joint project, which includes those portions of the joint project expected to be performed by BMBF-funded scientists outside the State of California.

PreApps will be evaluated by scientific specialists from outside California who are experts in specific areas of research described in the PreApp and by CIRM scientific staff, based on the scientific review criteria described in section IX below. Applicants whose projects are judged as most promising, competitive, and responsive to the RFA will be invited to submit a full Application.

<u>The PI, (Co-PI and Partner PI, if applicable), the type of award (DC Award or DCF Award) and research project proposed in the full Application must be the same as described in the PreApp; otherwise, the full Application is deemed</u>

ineligible. (If extraordinary circumstances make a substitution of PI or Co-PI necessary, and the President of CIRM concludes that the change improves or does not substantially alter the proposal, the President of CIRM may allow the change. Such requests of the President must be made by June 9, 2010)

Full Applications will be evaluated by the CIRM Grants Working Group (GWG), which is composed of fifteen scientific experts from outside California, seven patient advocate members of CIRM's Governing Board, and the Chair of the Governing Board. The 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/faq/pdf/Members.pdf. The fifteen scientists on the GWG will review the full Applications and score them according to scientific, technical, and potential clinical merit, applying the review criteria described in section IX below. In the case of applications for CIRM/BMBF Funded Awards, the GWG will consider the entire project, including those portions expected to be funded by the BMBF for work performed outside of California.

After the scientific scoring, the full membership of the GWG will then review the entire portfolio of applications, taking into consideration the following criteria:

- Impact of the proposed project for the development of stem cell-based therapies or diagnostics, and on regenerative medicine.
- Appropriate balance of DC and DCF Awards
- Appropriate balance among applications that address the priorities of this RFA and other meritorious applications. CIRM's priorities for this RFA include proposals which:
    - Will result in or lead towards (DC and DCF Awards, respectively) a novel cell therapy development candidate, especially candidates derived from pluripotent stem cells;
    - Are based on discoveries involving human pluripotent stem cells. Human pluripotent stem cells may be used either for discovery or as a candidate for therapy;
    - Are ineligible for or unlikely to receive timely or sufficient federal funding
- Appropriate balance between feasibility, risk and innovation.
- Appropriate balance in the context of CIRM's development portfolio (comprised of funded Disease Team Research Awards, RFA 09-01, and Early Translation Research Awards, RFA 08-05 targeting a development candidate, see http://www.cirm.ca.gov/for-researchers/researchfunding) in order to enhance portfolio diversity and reduce risk.
- Other considerations from the perspective of the patient advocates.

The GWG will make funding recommendations to the Governing Board, which

will make final funding decisions.

CIRM's confidentiality and conflict screening rules will apply to everyone who will have access to applications or who will attend the review meeting, including CIRM staff, external reviewers, and representatives of Collaborative Funding Partner Agencies. (Per Gov. Code §6254.5(e). non-public records may be disclosed to government agencies under confidentiality agreements.)

IX. Review Criteria

CIRM intends the Early Translational II Research Awards to support research that will achieve a development candidate or identify and/or establish the feasibility of a development candidate. As the achievement of development candidates is particularly important to the realization of CIRM's mission, CIRM will ask reviewers to prioritize projects that target achievement of a development candidate. CIRM will also ask the reviewers to give priority to projects which:

- Will result in or lead towards (DC and DCF Awards, respectively) a novel cell therapy development candidate, particularly a candidate derived from human pluripotent stem cells;
- Are based on discoveries involving human stem cells particularly pluripotent stem cells. Pluripotent stem cells may be used either for discovery or as a candidate for therapy;
- Are ineligible for or unlikely to receive timely or sufficient federal funding.

A. Preliminary Application

For both award categories (DC and DCF awards) the PreApp will be evaluated in four key areas: 1) Target Product Profile, Objective and Aims; 2) Rationale and Impact; 3) Research Project Feasibility; 4) Qualifications of the PI (Co-PI, Partner PI) and 5) Responsiveness to the RFA

1) Target Product Profile, Objective and Aims
   The Target Product Profile for the proposed novel development candidate is scientifically and clinically reasonable. The objective and aims of the proposed research to achieve (DC Awards) or lead towards (DCF Awards) the novel development candidate described by the target product profile are focused, complete, logical and achievable in three years.

2) Rationale and Impact
   The scientific rationale is strong for the target for intervention and for the approach to achieve/lead towards a novel development candidate. The proposed development candidate addresses an unmet medical need. The

benefit to patients/persons with disease or injury, if successfully developed and made available, is significant.

3) Research Project Feasibility
The preliminary results and other supportive results are compelling. The preliminary results, in conjunction with the research plan strongly support the feasibility of achieving the objective and aims of the proposed research in three years. The research plan is focused, well designed, and, in conjunction with the preliminary results, addresses all activities necessary to achieve (DC Awards) or lead towards (DCF Awards) a development candidate ready for IND-enabling preclinical development in three years. The research milestones provide quantifiable endpoints and serve as reliable indicators of the project's progress.

4) Qualifications of the PI (Co-PI, Partner PI, if applicable)
The PI (Co-PI, Partner PI, if applicable) has relevant qualifications, including experience leading/conducting translational research, to lead the proposed research project. The Co-PI and/or Partner PI, if applicable, are critical to the proposed research.

5) Responsiveness to the RFA
A target for therapeutic (diagnostic) intervention for disease/injury has been identified and there is a scientifically justifiable hypothesis for the proposed development candidate. Human stem cells are necessary to achieve the outcomes of the proposed research. The proposed research is within the scope defined in the RFA and adequately and appropriately addresses its goals and objectives.

B. Full Application

The full Application will be evaluated in four key areas: 1) Objective, Scientific Rationale and Impact; 2) Feasibility of the Research Plan; 3) Qualifications of the PI (Co-PI and Partner PI, if applicable) and the Research Team and 4) Collaborations, Assets, Resources and Environment. The specific criteria for review of applications are based on the standard review criteria described in the CIRM Grants Administration Policy (GAP, see section XIII.A of this RFA).

1) Objective, Scientific Rationale and Impact

a. <u>Objective:</u> The Target Product Profile describes a novel development candidate. The Target Product Profile for the proposed development candidate is scientifically and clinically reasonable. The objective and aims of the proposed research to achieve (DC Award) or lead toward (DCF Awards) a development candidate that meets the target product profile are focused, complete, logical and achievable in three years.

The proposed success criteria provide scientifically and clinically meaningful measure(s) to determine if the aims and objective of the proposal have been achieved.

b. Scientific Rationale: The therapeutic (diagnostic) target for research that achieves or leads towards a novel development candidate (DC Award and DCF Award, respectively) has been identified. The scientific rationale is strong for the target for intervention. The approach(es) proposed for intervention (e.g. cell therapy) is scientifically compelling.

c. Human Stem Cell Relevance: Human stem cells are necessary to achieve the outcomes of the proposed research compared to other approaches.

d. Impact: The proposed research achieves (DC Award) or leads toward (DCF Award) a novel development candidate that addresses an unmet medical need. The research proposes a development candidate that, if successfully developed and made available to patients, could have a broad and significant impact on disease, injury or medical practice.

2) Feasibility of the Research Plan

a. Preliminary Data
   - The preliminary data are compelling and supportive of the proposed approach to a novel therapeutic (diagnostic) development candidate.
   - The preliminary data are compelling and supportive of successful application of proposed key technologies/methodologies to result in (DC Awards) or lead towards (DCF Awards) a novel development candidate.
   - The PI (Co-PI and Partner PI, if applicable) and other members of the research team have contributed to the preliminary data.

b. Reasonable and Achievable Research Plan
   - The research plan is focused, well designed and will provide clear meaningful results within three years that address the aims and objective(s) of the research to enable achievement of the defined success criteria. For DC Awards, the proposed studies, in conjunction with the preliminary data, address all necessary activities and meet all applicable criteria to achieve a development candidate in three years ready for IND-enabling preclinical development.
   - The research plan identifies and acknowledges potential problems, and suggests alternative approaches should the proposed primary approaches fail.
   - The research plan provides clear project milestones that are critical, quantifiable and reliable indicators of the project's progress, not simply research to be performed.
   - The timeline, which includes the milestones, is feasible. The

objective of achieving a novel development candidate (DC Award) or completing the proposed research leading towards a potential novel development candidate (DCF Award) can be reasonably achieved within the 3-year award period.

3) **Qualifications of the Principal Investigator (Co-PI and Partner PI, if applicable) and Research Team**
   a. Training and Experience: The PI (Co-PI and Partner PI, if applicable) and key members of the research team have the training and experience to conduct the proposed research.
   b. Track Record: The PI (Co-PI and Partner PI, if applicable) has a record of achievement that supports his/her qualifications to conduct and lead the proposed translational research project.
   c. Appropriate Team: The PI has assembled an appropriate multidisciplinary research team to best achieve the project's objective and the research aims.
   d. Team Communication: The PI has a reasonable plan for communication, coordination and collaboration among members of the team.
   e. Commitment: The PI's (Co-PI's and Partner PI's, if applicable) level of commitment to the proposed research increases the probability of successful and timely completion of the project.
   f. Appropriate Budget: The PI (Co-PI and Partner PI's, if applicable) has developed a budget that is focused and appropriate for the research necessary to achieve the project objective(s) and aims. For DC Awards, all activities necessary to achieve a development candidate are addressed in the budget.

4) **Collaborations, Assets, Resources and Environment**
   a. Collaborations: Proposed collaborations (including, if applicable, those with a Co-PI and Partner PI) are critical and integral to the success of the proposed project. These collaborations have been secured and evidence is presented that the collaborator is committed to the proposed research
   b. Relevant Assets: Relevant assets (i.e. intellectual property, licenses) are available to the project.
   c. Resources and Environment: Resources critical to the success of the project, including necessary facilities, major equipment, and services (through advisors, subcontractors) are available for conducting the proposed research. The environment facilitates the interactions that enhance the probability of success of the proposed research.
   d. Institutional Support: The applicant institution is committed to supporting translational research. (Include the Co-PI sponsoring institution(s), and/or Partner PI applicant institution, if applicable)

X. Application Procedure

Applicant institutions and PIs must follow these instructions for submission of a PreApp and, if invited, a full Application for the CIRM Early Translation II Research Award. Full Applications will only be accepted from applicants who 1) submitted a PreApp and 2) are invited by CIRM to submit a full Application.

A. Preliminary Application Forms

Each applicant (see section VII.B for applicant eligibility criteria) must submit a PreApp using the PreApp template provided at http://www.cirm.ca.gov/grants/default.asp. The PreApp should emphasize the rationale for and feasibility of the proposed work and explain how the proposed plan will achieve (DC Award) or lead toward (DCF Award) a novel development candidate within three years of the project start.

The PreApp for the Early Translational II Research Award consists of the following sections:

1) *Cover Page(s)*
   Provide identification information about the PI, and if applicable, about a Co-PI (Development Candidate Awards only) and Institutional Official(s). For CIRM/Funding Partner collaborations, include the name of the Funding Partner, and the name of the Partner PI and the Partner applicant institution.

2) *Title of Proposed Project (limited to 90 characters)*

3) *Target Product Profile, Objective and Impact of Proposed Research (limited to 3000 characters).*
   Provide a target product profile for the proposed novel development candidate. The target product profile reflects key features known and required/desired for the proposed development candidate. The target product profile guides preclinical and clinical research and development, is continually refined and becomes the product label upon commercialization. Briefly address each of the following components of a (therapeutic) target product profile: 1) Description; 2) Scientific rationale for target for intervention and for the approach to achieve/lead towards a novel development candidate; 3) Indications(s)/target; 4) Activity (preclinical in vitro/in vivo/efficacy endpoint (patients); 5) Safety/Contraindications; 6) Route; 7) Regimen. Provide comparable information for a diagnostic candidate. State the objective of the proposed research that will achieve/lead towards a development candidate with above target product profile. Address how human stem cells are

necessary to achieve the outcomes of the proposed research. Discuss the unmet medical need addressed by and the potential impact of the proposed development candidate if successfully developed and made available to patients.

4) *Specific Aims (limited to 1500 characters)*
Summarize the specific aims of the research to meet the objective and will achieve (DC Award) or lead toward (DCF Award) a novel development candidate that has the target product profile.

5) *Project Rationale and Status (limited to 3000 characters)*
Summarize the preliminary results and other supporting (e.g. published) results that support the proposed research to achieve or lead towards a novel development candidate. Indicate results generated by the applicant PI and, if applicable, by a Co-PI (Development Candidate Award only) and/or a Partner PI. Figures or tables cannot be included in the PreApp.

6) *Research Plan and Milestones (limited to 7000 characters)*
Describe concisely the experimental plan to achieve the project objective and aims within three years. For year 1, detail planned activities, experimental design and minimum required outcomes of key activities. Include important details of activities planned for years 2 and 3. Include appropriate milestones and timeline. Milestones should describe precise quantifiable outcomes of key research activities, not simply research to be conducted.

7) *Qualifications of the PI (Co-PI, Partner PI) (limited to 2000 characters)*
Describe the qualifications of the PI and if applicable, the Co-PI or Partner PI, to conduct the proposed research. Highlight translational research leadership and/or team experience. If the project includes participation by a Co-PI or Partner PI, indicate how their participation is critical to the proposed research.

8) *Project Keywords*
Identify keywords appropriate to your proposal. For Disease Category, Approach and Cell Type, select one keyword that most accurately reflects your proposed research. For Specialized Methods, select all keywords that apply to your proposal. If appropriate, provide additional keywords that are central to the proposed project.

In addition to the PreApp form, all applicants must submit a Related Business Entities Disclosure Form (Adobe PDF template provided at http://www.cirm.ca.gov/grants/default.asp). Applicants designating either a PI or Co-PI from a for-profit institution (including institutions to be funded by a

Collaborative Funding Partner) must complete the form by listing all related business entities. Applicants who do not meet these criteria must certify on the form that they do not have any related business entities to declare, and submit the form. The information in this form is required for compliance with the conflict of interest rules under which CIRM operates. The Related Business Entities Disclosure Form should be submitted electronically as a separate attachment along with the PreApp form.

B. Preliminary Application Submission Instructions

A PI may submit only one PreApp for this RFA (see section VII.B. for PI eligibility criteria). The completed PreApp form (less the Official signature) and the Related Business Entities Disclosure Form must be sent as interactive PDF documents (the original document format) as email attachments to ET2PreApp@CIRM.ca.gov.

In addition to the electronic submission of the completed PDF files, a PI must also submit a copy of the PreApp cover page showing the Authorized Organizational Official's signature as a hard copy (via express mail or courier service to Early Translational 2 PreApp, CIRM, 210 King St., San Francisco, CA 94107), *or* as a fax copy (415-396-9142) *or* as a scanned PDF file to ET2PreApp@cirm.ca.gov.

Additionally, applicants whose proposals involve a Collaborative Funding Partner must send a copy of the PreApp to the designated BMBF point of contact listed in Appendix B.

All documents must be received by CIRM no later than 5:00 pm (PDT) on March 18, 2010. No exceptions will be made for late submissions. It is the PI's responsibility to ensure that all required documents are received by the deadline.

C. Full Application Forms

Full Applications for the CIRM Early Translational II Research Awards may be submitted only by applicants who 1) submitted a PreApp (as described above) and 2) are invited by CIRM to submit a full Application. Application forms will be available on the CIRM website (http://www.cirm.ca.gov/grants/default.asp) in mid-May 2010.

The full Application for the CIRM Early Translational II Research Awards consists of

Part A: Application Information Form (Adobe PDF template). Part A includes: Abstract, Public Abstract, Statement of Benefit to California, Key Personnel,

and Budget (section numbers 1- 5 below). Subparts may be included for those applications that include a Co-PI or a Partner PI, respectively.

Part B: Early Translational II Research Proposal (MS Word template). Part B includes: Target Product Profile, Project Objective and Specific Aims; Scientific Basis, Rationale and Impact; Preliminary Data; Research Plan, Milestones, and Timeline; Collaborations, Assets, Resources and Environment; and References (section numbers 6-11 below).

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

Part D: Related Business Entities (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 or (if applicable) from a Collaborative Funding Partner to a for-profit organization that is either: 1) the applicant organization; 2) a subcontractor; or 3) the employer of a Co-Principal Investigator, co-investigator, consultant or subcontractor (section number 12 below).

The application for Early Translational Research Awards includes the following sections:

1) *Abstract (divided in four parts of up to 1500 characters each)*
    a. Project Description: Provide a brief description of the proposed research. Describe the rationale for the target and approach proposed for the potential development candidate. Address why human stem cells are necessary to achieve the outcomes of the proposed research.
    b. Unmet Medical Need/Impact: Describe the unmet medical need that the proposed development candidate will address. Summarize the impact that the proposed research to achieve or lead toward a development candidate would have on the target disease or injury, if it were successfully developed.
    c. Research Plan: Summarize the proposed plan focusing on key research activities to be achieved within any given budget year.
    d. Milestones: Summarize the milestones to be achieved within any given budget year.

2) *Public Abstract (up to 3000 characters in Part A)*
    In lay language, briefly describe the proposed research and how it will, achieve or lead toward a development candidate derived from or based on stem cells. 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, the Partner PI and their respective applicant institutions.

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 and, if applicable, the Co-PI, the Partner PI and their respective applicant institutions.

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 the above definition. For Development Candidate Award applications that designate a CIRM-funded Co-PI, key personnel sponsored by the Co-PI must be listed in Part A. Where the Co-PI is employed by an institution other than the applicant institution, key personnel for the PI can include a project financial administrator. For CIRM/CFP applications, key personnel sponsored by the CFP, their contributions to and percent effort towards the project must also be listed in the corresponding section of Part A.

For CIRM funded key personnel, a minimum of one percent effort is required for each key person on this project except the PI and the Co-PI (if applicable) who are required to commit a minimum of 20% and 15% 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 team leadership and/or research contribution to regulatory filings for product development. Include relevant publications, patents or patent applications. Following biosketches for the PI and, if applicable, the Co-PI and Partner PI, include all remaining biosketches in alphabetical order.

5) *Budget (included in Part A)*

Provide all budget information requested in the budget section of the Application Information Form. Budgets must be justified in detail, including all subcontracts and consulting fees. For CIRM-funded Development Candidate Award applications that designate a Co-PI, the PI and the Co-PI will each be responsible for an individual budget (comprised of CIRM Direct Project Costs, CIRM Direct Facilities Costs and CIRM Indirect Costs) for that portion of the total project performed under their authority. For CIRM/BMBF collaborations, the funding requested from the BMBF (total and per year requested, Part A) must be indicated and justified in sufficient detail (in the Part A section "Budget Justification") for reviewers to assess the appropriateness of the non-California research budget.

If, to achieve the objective of the project described in Part B, the applicant will require funding from sources other than CIRM and, if applicable, it's Funding Partner, then the applicant must specify and justify the added cost and identify funding sources that will enable conduct of the project (in the Part A section "Budget Justification").

All allowable costs for research funded by CIRM are detailed in the CIRM Grants Administration Policy (GAP, see section XIII.A of this RFA). For CIRM/BMBF collaborations, allowable costs for research funded by the BMBF may differ. Guidance will be provided separately by the BMBF (see Appendix B)

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

- Salaries for Key Personnel

Salaries for Key Personnel may include the salaries for the Principal Investigator, Co-Investigators, Research Associates, and technical support staff (all 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 the Co-PI 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. With the exception of the project financial administrator for projects where a Co-PI is at an institution other than that of the PI, administrative support salaries are expected to be covered exclusively by allowed Indirect Costs.

- Supplies

Supply expenses may include 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 Early Translational II Research Awards are strongly encouraged to attend the CIRM-organized grantee meeting held in California and should include travel costs for this meeting in the budget. Travel costs associated with collaborations necessary to the grant are allowable. Details of allowable travel costs can be found in the CIRM GAP (see section XIII.A of this RFA).

- Equipment

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

- 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.

6) *Target Product Profile, Project Objective and Specific Aims (up to 2 pages in Part B)*

Provide a Target Product Profile for the proposed novel development candidate. The target product profile reflects key features known and required/desired for the proposed development candidate. The target product profile guides preclinical and clinical research and development, is continually refined and becomes the product label upon commercialization. Briefly address each of the following aspects of a target product profile: 1) Description; 2) Scientific Rationale; 3) Indication(s)/Target population; 4) Activity (in vitro/in vivo)/Efficacy Endpoint (patients); 5) Safety/Contraindications; 6) Route; and 7) Regimen. Provide comparable information for a diagnostic candidate. State the objective(s) of the proposal and the specific aims to achieve the objective(s) that will achieve (DC Awards) or lead towards (DCF Awards) the novel development candidate described by the target product profile. Provide success criteria that are measures for achievement of the aims and the objective(s) of the research. The

success criteria should be well described, quantitative, meaningful and scientifically justifiable.

7) *Scientific Basis, Rationale and Impact (up to 2 pages in Part B)*
Describe the identified target for the proposed novel development candidate and summarize the scientific basis for its involvement in disease or injury. Summarize the scientific rationale for the proposed approach(es) for intervention as embodied in the proposed development candidate versus other approaches. Address why human stem cells are necessary to achieve the outcomes of the proposed research compared to other approaches. State how the proposed research advances a stem cell-derived therapy or diagnostic toward the clinic. Explain how the proposed research could lead to a novel development candidate that addresses an unmet medical need. Comment on the potential impact on disease, injury or medical practice, if the proposed novel development candidate were successfully developed and made available to patients.

8) *Preliminary Data (up to 3 pages in Part B)*
In this section, indicate which data was generated by the PI and, if applicable, by a Co-PI (Development Candidate Award only) and/or a Partner PI or other members of the research team. Provide preliminary data that support the rationale for and the progress towards the proposed novel development candidate (e.g. for therapeutic - preclinical activity and pilot safety, mechanism and potential biomarkers, assays for characterization and methods for reproducible production and purification, etc.; see also Appendix A). Present preliminary data for successful application of the technologies and methodologies proposed for achieving/leading to the proposed novel development candidate.

9) *Research Plan, Milestones and Timeline (up to 6 pages in Part B)*
For applications from CIRM/Funding Partner teams, applicants must clearly delineate the work that will be performed in California and funded by CIRM from the work that will be performed in the Funding partner's jurisdiction. Similarly, for Development Candidate Award applications that include a Co-PI, please make clear what work will be performed by the PI and his/her team (e.g., key personnel, subcontractors) and which work will be performed by the Co-PI and his/her team. These delineations are essential for review of the research plan and the appropriateness of the budget.

Describe the research plan concisely but in sufficient detail. Include the experimental approaches, methods and techniques proposed to

achieve the research aims and objective(s) within three years. For Year 1, include full details of planned activities and experimental design; include important details of studies and activities planned for years 2-3. Identify novel or risky aspects of the research, anticipated pitfalls, and provide a description of alternative approaches should the initial approaches fail.

Provide annual milestones for the project, ideally for each specific aim, which are critical to achieving the success criteria for achieving or leading toward a novel development candidate. Milestones describe precise, quantifiable outcomes of key research activities, not simply the research to be conducted. Provide and justify a realistic timeline for completing each specific aim and the related milestone(s). Include a Gantt chart if desired. Milestone achievement is an important indicator of progress and a major factor in review of progress reports. Insufficient progress through milestones may result in loss of further funding.

The research plan for a novel development candidate (DC Award) must, in conjunction with the preliminary data, address all activities necessary for the candidate to be ready for subsequent preclinical development within three years and to meet the defined success criteria. (See Appendix A for activities necessary to achieve a therapeutic development candidate; see also section II for criteria for a therapeutic development candidate.) Similarly, the research plan leading towards a development candidate (DCF Award), must, in conjunction with the preliminary data, allow achievement of the success criteria and move the research closer to achieving a development candidate.

10) *Collaborations, Assets, Resources and Environment (up to 2 pages in Part B)*
When collaborations (intra- or inter-institutional including, if applicable, collaborations with a Co-PI or with a Partner PI funded by BMBF) are part of the research plan, describe the nature of the collaboration and explain why it is integral to the success of the project. Successful collaborations are those that bring critical intellectual, technical or infrastructure resources to the project. Discuss how the PI will ensure communication, coordination and collaboration among the team members. If advisors, consultants or subcontractors will provide expertise or resources critical to the success of the project, summarize their credentials and relevant track records.

Discuss relevant assets such as intellectual property (patent applications, patents) and licenses that are available to the project. Intellectual property assets are important for proposed development candidates that must be commercialized to bring benefit to patients.

Provide a short description of the facilities, core services and environment(s) in which the research will be done, and the major equipment and resources available for conducting the proposed research. Discuss ways in which the proposed studies will benefit from unique features of the scientific environment(s).

Provide evidence of institutional support for the PI (the Co-PI and the Partner PI, if applicable) and for translational research.

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

12) *Related Business Entities (Part D)*
All applicants (including, if applicable, a BMBF Funding Partner applicant) 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 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).

D. Full Application Submission Instructions

Full Applications will only be accepted from applicants who 1) submitted a PreApp and 2) are invited by CIRM to submit a full Application.

The full Application consists of four parts:

Part A: Application Information Form (and subparts, if Co-PI or Partner PI), **Part B:** Early Translational II Research Award Proposal, **Part C:** Biographical

Sketches for Key Personnel and letters of collaboration and/or institutional support, **Part D:** Related Business Entities.

All four parts of the full Application for CIRM Early Translational II Research Awards must be submitted and received by CIRM no later than 5:00PM PDT on June 30, 2010, in both electronic form and in hard copy (a signed original and five copies). No exceptions will be made. It is the PI's responsibility to ensure that all required documents are received by the deadline.

Send electronic copies of all parts of the application as attachments in a single email to ET2Awards@cirm.ca.gov. In addition to the electronic submission, candidates must submit an original copy of the full Application (consisting of Parts A-D) plus 5 copies of the full Application (preferably double-sided) to the address below. The original copy must be signed by both the PI and the applicant institution's Authorized Organizational Official (AOO). Applications for a Development Candidate Award designating a Co-PI must also be signed by the Co-PI and the Co-PI's institutional AOO.

Early Translational II Research Awards Application
California Institute for Regenerative Medicine
210 King Street
San Francisco, CA 94107

E. Submission of Supplemental Information

If necessary, the PI may submit limited supplemental materials that provide critical new information related to their research proposal after the application deadline but not later than 5:00pm PDT on August 5, 2010. 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.
Submissions should include a one-page cover letter addressed to the Senior Review Officer. The body of the cover letter may not exceed 500 words and should briefly describe the type of information submitted and when the information became available. The cover page may not be used to describe any additional data or experiments that are not presented in the figure page. The following materials qualify for submissions of supplemental materials:

1) Within the one-page cover 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 cover letter, confirmation of funding secured from other sources or regulatory approvals acquired since the application submission deadline.
3) Up to one single-sided page of preliminary data composed of not more than 2 figures and/or tables with corresponding legends that describe the data and its significance to the proposed project. No additional text or descriptions of additional data are allowed.
4) Up to 2 letters (limited to one single-sided page each) of support for new collaborations related to the proposed research established since the application submission deadline.

The submission of supplementary materials may not be used as an attempt to circumvent any page or character limits specified in the application or RFA. Changes in scope, experimental approach, or research design are not allowed.

XI. Schedule of CIRM Deadlines and Reviews

Preliminary Applications due	5:00 pm (PDT), Thursday, March 18, 2010.
Invitations for Full Applications sent out by CIRM	Mid May, 2010
Full Applications due	5:00 pm (PDT), Wednesday, June 30, 2010
Anticipated Review of Full Applications by Grants Working Group (GWG)	September 2010.
Review and Approval by ICOC	October 2010.
Earliest Funding of Awards	Winter, 2010/2011.

XII. Contacts

For information about this RFA or 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/reg/default.asp.

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 Interim Loan Administration Policy (LAP) serve as the standard terms and conditions of grant and loan awards issued by CIRM. All research conducted under this award must comply with the stated policies. 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).å