CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

RFA 09-01: CIRM DISEASE TEAM RESEARCH AWARD

I. Purpose

Stem cells will play an increasing role in the treatment of acute and chronic disease and serious injury. The application of pluripotent stem cell research to clinical problems is in its infancy, and though few stem cell-based therapies have progressed into clinical testing and practice to date, preclinical data suggest that many new stem cell therapies are ready for translation. The purpose of the California Institute for Regenerative Medicine (CIRM) Disease Team Research Awards is to accelerate potential therapies based on stem cell research toward clinical testing. To facilitate this goal, CIRM intends to support actively managed multidisciplinary teams engaged in milestone-driven translational research. The mission of these teams will be to conduct the necessary research and regulatory activities to prepare and file a complete, well supported Investigational New Drug Application (IND) with the Food and Drug Administration (FDA) (and, if desired, other regulatory agencies), to enable Phase I clinical testing.

Translational research is an inherently multidisciplinary process, requiring the combined strengths of basic research institutions, medical centers, and biotechnology and pharmaceutical companies. Collaborative arrangements between industry and academic institutions are likely to be needed in order to assemble teams with the requisite complementary expertise to successfully translate promising basic findings into viable therapeutics. CIRM expects to fund both non-profit institutions and for-profit companies (separately or in collaborations) through grants or loans, with opportunities for awards to multiple co-principal investigators to ensure that the most qualified people in the organizations are intimately involved in the research. The Disease Team Research Award is core to CIRM's mission and as such, the agency will likely seek applications every twelve to eighteen months as a way to build a strong clinical pipeline for patient therapies and cures.

II. Objectives

The key objective of the Disease Team Research Awards is to file an IND within 4 years of the start of the award. Projects targeted by this RFA will support the preclinical research and development activities necessary to achieve a development candidate and file an IND (see Appendix A). Project activities may include but are not limited to: all *in vitro* and *in vivo* assays for characterization, including determination of purity, biological activity, mechanism and/or disease/injury modifying activity; preclinical pharmacology; pharmacokinetic, toxicology, or immunomodulation studies; candidate production including process

optimization, source material verification, and scale up; and regulatory and clinical strategy tasks to meet FDA guidelines for IND filing.

This program is specifically directed at projects that include therapeutic candidates with demonstrated activity against a disease target. Projects of suitable scientific maturity for this award will have demonstrated, at a minimum, reproducible evidence of disease- (or injury-) modifying activity; however, projects further along in preclinical research or preclinical development are also suitable for this award. Examples of candidates include a stem cell, stem cell-derived progenitor or stem-cell derived differentiated cell, or a small molecule or biologic derived from stem cells or discovered using human stem cell-based assays. This program does not support target discovery, early-stage therapeutic discovery activities (such as high-throughput screening), and also excludes projects already in clinical trials.

CIRM intends to support projects targeting a broad range of diseases and injuries. CIRM seeks potential therapeutics for which there is an unmet medical need, and for which the use of stem cells can offer a significant advantage over current therapies and therapies in development. CIRM will support novel product development research across the full spectrum of experimental approaches and stem cell types including: pluripotent (particularly embryonic stem cells), multipotent, progenitor and cancer stem cells, and will prioritize research that is unlikely to be funded by other agencies. This initiative will consider multiple roles for human stem cells in the development of therapies, including but not limited to: cell transplantation and integration, mobilization of endogenous cells, modification of the immune system, stem cells as delivery vehicles, and stem cell-based disease models for drug screening and development (in cases in which no clinically relevant screening model exists), but not diagnostics.

This program will support multidisciplinary teams staffed by professionals with diverse expertise. Importantly, both a team leader (Principal Investigator, PI) and a project management professional (Project Manager) will be required in the staffing plan. These two individuals will be responsible for: developing and maintaining team strategy and energy, keeping the team focused, achieving expectations and milestones, and providing ongoing communication with CIRM. The team leader provides vision, strategy, and overall project direction, has scientific and financial accountability, and should be a practicing professional with a record of effective scientific leadership. The Project Manager will oversee project operations and ensure that the team activities progress smoothly. In addition to these two key individuals, Disease Teams might include members with the following expertise, either as full time or advisory members: basic research including but not limited to stem cell biology and immunology, animal models, specialization in the pathophysiology and treatment of a particular disease, transplantation; assay development, pharmacology, toxicology, project management, process development, manufacturing and scale-up, quality control and assurance, biostatistics, ethics, regulation of biomedical products, and the design and conduct of clinical trials. Team composition is likely to be dynamic, and staffing needs will evolve as projects progress toward the clinic. As projects move through development, basic researchers might decrease their involvement and translational experts or advisors (e.g. process development, regulatory and clinical trial design) would become more actively engaged.

III. Award Information

Under this RFA 09-01, CIRM intends to commit up to $210 million to support up to 12 awards. Projects will be funded for up to four years, with justifiable total funds requested (includes direct project costs, direct facilities costs, and indirect costs) of $3 million to a maximum of $20 million per project. Continued funding is contingent upon achievement of agreed-to milestones and "Go" decisions at key decision points (see Section V.A). Because of the magnitude of these awards, CIRM reserves the right to negotiate and revise project budgets before issuance of the Notice of Grant Award (NGA) or Notice of Loan Award (NLA). The urgency of CIRM's mission necessitates that all approved applications must be initiated (NGA/NLA, issued and signed) within 6 months of the Independent Citizens Oversight Committee (ICOC) approval and authorization for funding. Another similar Disease Team Research Award RFA (II) is expected to be offered again in late 2010 or early 2011.

A. Mechanism of Award

CIRM will offer grant funding for approved non-profit applicant organizations, and loan funding for approved for-profit applicant institutions. Non-profit applicants with Co-PIs at for-profit organizations may also apply for loan funding. Loans will be administered over a six- or ten-year term. The interest on six year loans will be prime plus 300 basis points; the interest on ten year loans will be prime plus 500 basis points. The prime rate will be that on the date the ICOC authorizes funding of the loan. For eligibility information and loan terms, consult the Interim CIRM Loan Administration Policy, available at: http://www.cirm.ca.gov/reg/default.asp.

B. Collaborative Funding Partners

CIRM has established a program with several agencies that fund stem cell and regenerative medicine research. Through this Collaborative Funding Partner program, California-based Principal Investigators (PIs) can collaborate with researchers eligible for funding from one of CIRM's collaborative funding partners, bringing additional resources to the project. If a collaborative funding proposal is approved (a "CIRM/Funding Partner Award") CIRM will fund all project work done within the State of California (up to the $20 M budget limit) and its Funding Partner will fund all project work within its jurisdiction. Collaborative funding partners participating in this RFA include the Cancer Stem Cell Consortium (CSCC) of Canada; the Medical Research Council (MRC), United Kingdom; and the Spanish Ministry of Science and Innovation (MICINN). For this round of Disease Team Research Awards, an applicant may designate no more than one Collaborative Funding Partner.

To apply for a collaboratively-funded project, applicants must complete both the CIRM requirements (Section VIII below) and any additional requirements put forth by the Funding Partner (see Appendices B-D). The CIRM application forms (Section VIII), approved procedures (Section VI), review criteria (Section VII) and review panel will be the same for all Disease Team applicants, independent of whether a Collaborative Funding Partner is designated in the application. Applicants must follow special instructions for collaboratively-funded teams in the Statement of Benefit (Section VIII.C.3), the Key Personnel (Section VIII.C.4), the Budget (Section VIII.C.5), the Research Plan (Section VIII.C.9), the Leadership Plan (Section VIII.C.12), and the Institutional Commitment (Section VIII.C.13) sections of the

CIRM full application; and in the Project Objective (Section VIII.A.3) and Research Team Leadership (Section VIII.A.5) sections of the Preliminary Application.

C. Supplemental Funding

Supplemental funding may be available to successful applicants from disease-specific private foundations. Please refer to Appendix E for details.

IV. Eligibility

Unlike most previous RFAs released by CIRM, CIRM will not limit the number of submissions from each California applicant institution. Instead, CIRM has introduced a new process in which any qualified PI may submit a brief Preliminary Application (Pre-Application, PreApp) for consideration. Applicants who submit the most promising, competitive, and responsive pre-application proposals will be invited to submit a full application. Details of the application process are provided in Section VI below.

The following provisions (Sections IV.A, and IV.B) apply to all applicants seeking CIRM funds. CIRM/Funding Partner teams are referred to Section IV.C for additional information.

A. Institutional Eligibility

All CIRM-supported research must be conducted in California. PIs may apply from non-profit and for-profit research organizations that are located in California and actively conducting or managing research at a site in California at the time of Pre-Application submission. Non-profit and for-profit institutions sponsoring Co-Principal Investigators (Section IV.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

In order to support multidisciplinary team-based research, CIRM will allow for a single CIRM-funded Principal Investigator (PI) and up to two additional CIRM-funded Co-Principal Investigators (Co-PIs) on each award. The following investigator eligibility requirements apply to CIRM-funded PIs or Co-PIs, unless otherwise stated.

Principal Investigator

CIRM requires that a single PI and a single institution (that PI's institution, or "applicant 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 CIRM/Funding Partner Awards. The applicant institution is the designated contact institution for all financial and other administrative considerations.

The PI must have an M.D., Ph.D. or equivalent, and must be authorized by the applicant institution to conduct the proposed research in California. By the Pre-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)

Each Co-PI must have an M.D., Ph.D. or equivalent, and must be sponsored by the institution at which the Co-PI will conduct the proposed research in California. By the Pre-Application deadline, the 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 of this award. The decision of whether to include Co-PIs should be guided by the scientific goals of the project. All applications will require a leadership plan as outlined below (Section VIII.C.12). When considering Co-PIs, please be aware that the reviewers will consider the structure and governance of the research team as well as the knowledge, skills and experience of the individual PI and Co-PIs.

PI and Co-PI Commitment

In order to broaden the pool of applicants engaged in translational stem cell research, an investigator may submit one preliminary application (PreApp, See Section VI) as either a PI or a Co-PI; and, the same investigator may be a Co-PI on up to one additional preliminary application. An investigator who applied as a PI on CIRM RFA 08-05 "Early Translational Research Award" is not eligible to apply as a PI, but may apply as a Co-PI on this award.

Mindful of the urgency of CIRM's mission and the scope of these awards, CIRM will require PIs to commit a minimum 30% effort to this project, and Co-PIs to commit a minimum 20% effort. During review of the full application, CIRM will instruct reviewers to give added weight to the PI's (or Co-PI's) qualifications when the PI commits more than 30% effort to the

proposed research, and when the Co-PI commits more than 20% effort to the proposed research. CIRM is seeking leaders for these awards who are fully committed to the goals and success of the project.

In extraordinary circumstances, and at the discretion of the President of CIRM, a senior research scientist may be permitted to apply as a PI with a commitment of less than 30% effort (or as a Co-PI with a commitment of less than 20% effort), if s/he convincingly demonstrates that doing so is optimal for the research project. Such exceptions **must** be requested prior to June 22, 2009 (see contact information below) to allow the President of CIRM adequate time to review and to consider the request prior to July 16, 2009, the deadline for submission of a full application.

C. Collaborative Funding Partner Principal Investigator Designation

In addition to the CIRM-funded PI and Co-PI positions described above, CIRM/Funding Partner teams may designate a Funding Partner PI ("Partner PI") and a Funding Partner applicant institution ("Partner applicant institution"). The role(s) and responsibilities of the Partner PI should be addressed in the Leadership Plan (Section VIII.C.12). The Partner PI is subject to the eligibility and minimum effort requirements of the Funding Partner, described in the Appendices.

V. Award Administration and Project Management

A. CIRM Award Administration and Project Management

CIRM's Grants Administration Policy (GAP) for Academic and Non-Profit Institutions (Non-Profit GAP), supplemented by the GAP for For-Profit Institutions (For-Profit GAP) and 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: continued funding will depend on adequate scientific progress as outlined in the project timeline.

Because of the magnitude of these awards, CIRM, the PI, and the Project Manager will be involved in the active management of these projects. A Project Manager must be included in every team proposal and budget, and must be named and engaged by the time of execution of the NGA or NLA. In addition to annual Progress Reports, 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; and 3) participation in Evaluation Meetings. CIRM responsibilities will include: progress monitoring via written reports and teleconferences, establishing oversight advisory committees, and the conduct of the Evaluation Meetings.

Evaluation Meetings occur at the key decision points in development projects, at which time go / no go decisions are made. These decision points occur:

- between the preclinical research and preclinical development phases, where a significant step-up in funding is required, and the decision is made whether to initiate IND-enabling activities; and
- upon completion of critical IND-enabling studies, and the team is moving towards a regulatory filing for first-in-man studies.

Evaluation Meetings will be chaired by CIRM's Chief Scientific Officer (CSO), and include members of an oversight advisory committee, CIRM staff, and project representatives. Project PI, Co-PIs and relevant project personnel will present their project data including progress against the project milestones, an updated Budget (Section VIII.C.5), and updated Project Objective / Target Profile (Section VIII.C.6), an updated Preclinical Research and Development Plan (Section VIII.C.9), and recommendation for action. Possible outcomes of an Evaluation Meeting include: continuation of successful projects, redirection if appropriate, or project discontinuation. Go / no go determinations will be made by the CIRM President based on recommendations by the oversight advisory committee in consultation with the CIRM CSO and staff.

Review criteria for the full application (Section VII.B) will form the basis of the evaluation. In addition, the oversight advisory committee will consider:

1. Performance: The project team has achieved the agreed-to milestones, and has presented quantifiable study outcomes. The team has achieved the milestones within budget.
2. Readiness: The project team has adequately addressed the key product characterization and product production tasks appropriate to the phase of development (Appendix A).
3. Therapeutic Candidate Competitiveness and Impact: The data presented and the updated Target Profile indicate a therapeutic candidate that will offer an advantage over other therapies in practice or in the development pipeline. Results achieved to date demonstrate a trend toward clinically significant efficacy and that no limiting toxicities have surfaced.
4. Feasibility and Next Steps: Feasible strategies and key issues in all areas critical to the successful achievement of the next phase of the project (i.e. science/biology, analytical development, pharmacology, toxicology and immunomodulation, process development and manufacturing, clinical, and regulatory) are defined and addressed in the updated Research and Development Plan.

B. CIRM/Funding Partner Award Administration and Project Management

In addition to Section V.A above, the following terms apply to CIRM/Funding Partner Awards.

Additional Documentation Requirements for CIRM/Funding Partner Teams

Before funding contracts are signed, successful CIRM/Partner applicant teams must have a full written agreement addressing Intellectual Property (IP) issues relating to the collaborative project and must provide CIRM and Funding Partner with copies. Agreements must be consistent with CIRM IP Regulations and with the Agreement between the co-funders.

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

Collaborative Project Management
Both the Partner PI and the Funding Partner may be involved in the active management of the CIRM/Funding Partner Award, by participating in mutually agreed upon joint award administration activities. These activities may include but are not limited to participation in: the Evaluation Meeting(s), and progress monitoring via annual progress reports, quarterly updates and teleconferences. Further information will be available before CIRM issues the NGA/NLA for any CIRM/Funding Partner Award.

VI. Application and Evaluation Process

Submission of an application for the CIRM Disease Team Research RFA involves a two-step process. Any qualified PI may submit one brief Preliminary Application (PreApp). Applicants submitting the most promising, competitive and responsive proposals will be invited to submit a detailed, full application. All other applicants will be deferred. Both the Early Translational and the Disease Team Research Awards are core CIRM research programs that CIRM expects to reissue in a 12-18 month cycle (2010 and Winter 2011, respectively). Applicants whose proposals are deferred will have the opportunity to reapply in a subsequent cycle of either the Early Translational II or the Disease Team Research II Awards.

PreApps should emphasize the significance and feasibility of the proposed work and explain how the proposed plan for therapy development will result in an IND filing within four years of the project start. 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 VII below. Applicants whose projects are judged as most promising, competitive, and responsive to the RFA will be invited to submit a full application. The PI, (and if applicable the Co-PI(s)) and research project proposed in the full application must be the same as those described in the PreApp; otherwise, the full application is deemed 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 merit of the proposal, the President of CIRM may allow the change.)

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, the Independent Citizen's Oversight committee (ICOC), and the Chair of the ICOC. The membership of the GWG can be found at http://www.cirm.ca.gov/workgroups/pdf/GrtWkgGpMbr.pdf. The composition of the ICOC can be viewed at http://www.cirm.ca.gov/faq/pdf/Members.pdf. The fifteen scientists on the GWG will review the applications and score them according to scientific, technical, and clinical merit, applying the review criteria described in section VII below. The full membership of the GWG will then review the entire portfolio of applications, taking into consideration the following criteria:

- Impact of the potential project on the development of stem cell-based therapies, and on regenerative medicine.

- Appropriate balance between feasibility and innovation.

- CIRM's (and its Funding Partners', if applicable) unique ability to support the research.

The GWG will make funding recommendations to the ICOC, which will make final funding decisions.

Loan Applications

In addition to the other application requirements in this RFA, loan applicants will be required, as part of the full application, to indicate a preference between available loan terms: recourse or non-recourse, and six- or ten-year loans. Note that if a proposal seeks recourse loan funding for a project with scientific merit, the ICOC may deny the application if the applicant does not meet the credit standards for recourse loans. Accordingly, applicants that prefer recourse loans must indicate whether they would accept non-recourse loan funding as an alternative. Loan applicants will be required to submit loan information. If a loan applicant is a non-profit organization, the loan information must be submitted by the for-profit organization sponsoring the Co-PI.

VII. Review Criteria

A. Preliminary Application

The goal of the PreApp review process is to identify the most promising, competitive, and responsive proposals. The PreApp will be evaluated in four key areas: Project Objective, Rationale, and Significance; Scientific Maturity; Feasibility of the Preclinical Research and Development Plan; and Qualifications of the PI and Research Team Leadership.

1. Project Objective, Rationale, and Significance

   The project objective (target profile) for the proposed therapeutic is appropriate and achievable. The scientific rationale is strong for the proposed therapeutic approach. The proposed therapeutic addresses an unmet medical need. The use of human stem cells is necessary or significantly advantageous to the proposed research compared to other approaches. The proposed therapeutic will offer an advantage over other therapies in practice or in the development pipeline.

2. Scientific Maturity

   Compelling and reproducible evidence (particularly from research conducted by the PI, Co-PI(s) or Partner PI) demonstrates that the proposed therapeutic has disease- (or injury-) modifying activity. The project is sufficiently mature, such that

there is reasonable expectation that an IND filing can be achieved within 4 years of the project start date (late 2013 or early 2014).

3. Feasibility of the Preclinical Research and Development Plan

   The preclinical research and development plan(s) are well designed, focused and adequately address all necessary activities, including IND filing, to enable regulatory approval for the start of clinical trials. The research milestones will provide quantifiable endpoints and serve as reliable indicators of the project's progress.

4. Qualifications of the PI and Research Team Leadership

   Evaluate the research team leadership (PI, and if applicable the Co-PIs) against the following criteria. For CIRM/Funding Partner applications, include the Partner PI in the assessment. The team leaders have relevant experience in translational research and therapy development. The team leaders have demonstrated successful leadership experience. The team leaders have made specific contributions to the scientific underpinnings of the proposed therapeutic candidate and the proposed development plan. The PI, Co-PIs, and Partner PI have critical roles in the proposed research and development project.

B. Full Application

The full application will be evaluated in four key areas described below. 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.A of this RFA).

1. Scientific Rationale and Significance
   a. Achievable Objective: The project objective (target profile) for the proposed therapeutic is appropriate and achievable.
   b. Scientific Rationale: There is strong supportive evidence for the proposed therapeutic approach
   c. Use of Human Stem Cells: The use of human stem cells is necessary or strongly advantageous to the proposed research and development plan compared to other approaches.
   d. Unmet Medical Need: The proposed project addresses a critical clinical problem or an unmet medical need.
   e. Clinical Competitiveness: The proposed therapeutic will offer an advantage(s) over other therapies in practice or in the development pipeline.
   f. Impact for Patients: The proposed therapeutic has the potential, if successfully commercialized, to have a significant impact on disease, injury or medical practice.

2. Feasibility of the Preclinical Research and Development Plan
    a. Preliminary Data and Maturity: The preliminary data are compelling and supportive of the proposed therapeutic. Compelling and reproducible evidence demonstrates that the proposed therapeutic approach has disease- (or injury-) modifying activity. The project is sufficiently mature such that there is reasonable expectation that an IND can be filed within 4 years of the project start date, enabling a timely start to clinical trials.
    b. Logical and Achievable Plan: The preclinical research and development plan(s) are well designed to achieve the target profile. The plan is focused, and adequately addresses all necessary activities for IND filing. Necessary resources, technologies and services are identified and accessible. Feasible strategies and key issues in all areas critical to the successful achievement of the project (i.e. science/biology, analytical development, pharmacology, toxicology, immunomodulation, process development and manufacturing, clinical, and regulatory) are identified and addressed.
    c. Meaningful Milestones and Feasible Timeline: The project milestones will provide quantifiable endpoints and reliable indicators of the project's successful progress. The timeline, which highlights milestones, timing of go/no go decision milestones, and IND filing, is feasible.

3. Principal Investigator (PI) and Research Team Leadership

    Evaluate the research team leadership (PI, and if applicable the Co-PIs) against the following criteria. For CIRM/Funding Partner applications, include the Partner PI in the assessment.

    a. Expertise and Track Record: The team leaders have the appropriate expertise to conduct the proposed work. Evidence of prior success and track record supports the qualification of the PI (and Partner PI and/or Co-PIs, if applicable) to successfully lead and execute the plan for therapy development.
    b. Commitment: The PI's, Co-PIs', and Partner PI's levels of commitment increase the probability of success of the project.
    c. Research Team: The team leaders have assembled an appropriate research team, including a Project Manager. The structure of the team reflects the changing needs of the project as it progresses through preclinical research and development.
    d. Budget: The team leaders have developed a budget that is focused and appropriate for activities to achieve IND filing.
    e. Leadership Plan: The PI has developed a leadership plan that will motivate and create efficient operations for the team. The structure and governance of the team will support status assessment, progress monitoring, and project decision-making. The approach to resolution of potential issues or conflict,

including disputes over authorship, inventorship, performance and scientific direction, is thoughtful and complete. The PI will foster communication, coordination and collaboration among members of the team.

4. Collaborations, Resources, and Environment
    a. Resources and Environment: Necessary facilities, major equipment, and services are available for conducting the proposed research.
    b. Relevant Assets: Relevant assets (i.e. intellectual property, licenses) are available to the project.
    c. Adjunct Personnel: The PI has identified and has access to adjunct personnel who may be required for the evolution and success of the project.
    d. Collaborations: Proposed collaborations are critical and integral to the success of the proposed project. The collaboration(s) enriches and synergizes the research plan. These collaborations have been secured and evidence is presented that the collaborator is committed to the proposed research.
    e. Institutional Support: The applicant institution is committed to supporting translational research. (Include the Co-PI sponsoring institution(s), and/or Partner applicant institution, if applicable)

VIII. Application Procedure

Applicants must follow these instructions for submission of a PreApp and, if invited, a full application for the CIRM Disease Team 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

Pre-Application

Each applicant must submit a Pre-Application (PreApp) using the PreApp template provided at http://www.cirm.ca.gov/grants/default.asp. The PreApp should emphasize the significance and feasibility of the proposed work and explain how the proposed plan for therapy development will lead to an IND filing within four years of the project start.

The PreApp for the Disease Team Research Award consists of the following sections:

1. *Cover Page*
   Provide identification information about the PI, Co-PIs (if applicable) and Institutional Official. For each PI and Co-PI, include their name and institution. For CIRM/Funding Partner collaborations, include the Funding Partner, and the name of the Partner PI and the Partner applicant institution.

2. *Title of Proposed Project (limited to 100 characters)*

3. *Project Objective (target profile) and Status (limited to 6000 characters; 2 pages)*

    a. Project Objective: Provide a target profile for the proposed therapeutic. The target profile reflects desired key attributes of the proposed therapeutic candidate. The target profile guides preclinical and clinical development, is continually refined and becomes the product label upon commercialization. Briefly, address each of the following aspects of a target profile: 1) Description; 2) Scientific Rationale; 3) Indication(s) / Target; 4) Activity (in vitro/in vivo) / Efficacy Endpoint (patients); 5) Safety / Contraindications; 6) Route; 7) Regimen; 8) Risk versus Benefit; and 9) Clinical Competitiveness. For allogenic cell therapy candidates, immune tolerance or immunosuppression strategies should be addressed above.

    b. Status: Summarize the preliminary data and other supporting data for the project including disease- (or injury-) modifying activity of the proposed therapeutic. Indicate the data that were generated by the applicant PI and Co-PIs, and Partner PI, if applicable.

4. *Preclinical Research and Development Plan and Milestones (limited to 9000 characters; 3 pages)*
   Include an overall plan for therapy development, including the experimental approaches, methods and techniques proposed for accomplishing the project goals within 4 years. The goals must include preparing and filing an IND. 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. Milestones describe precise, quantifiable study outcomes for key project activities, not simply the work to be conducted. Include FDA interactions in the milestones.

   For Year 1, summarize planned activities and experimental design. For example, include rationale for choice of *in vitro* or *in vivo* models, parameters to be tested, study design and outcomes analysis. State the success criteria. Include important details for years 2-4.

5. *Research Team Leadership (limited to 3000 characters; 1 page)*
   List the PI and Co-PIs (if applicable) of the research team. For each PI or Co-PI include: name and a brief description of their role on the project (i.e. describe which studies listed in #4 above they will supervise or execute). Describe the leadership credentials of the PI. Describe the qualifications of the PI and Co-PIs to lead their component of the project. Include: development projects delivered; INDs, Investigational Device Exemptions (IDEs), Biologic License Applications (BLAs), and New Drug Applications (NDAs) filed where the PI or Co-PI was a lead or contributing investigator; clinical trials where the PI or Co-PI was a lead or contributing investigator. For CIRM/Funding Partner teams, include the above required information for the Partner PI.

6. *Project Keywords*

Select keywords (from each category of the list provided) that apply to the proposed research. If appropriate, supply additional keywords that are central to the proposed project.

Related Business Entities Disclosure Form

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 policy 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

Each applicant may submit only a single PreApp as PI for either this RFA or for the Early Translational RFA (RFA 08-05), not both. The completed PreApp form and the Related Business Entities Disclosure Form must be sent as interactive pdf documents (the original document format) as email attachments to DiseaseTeamPreApp@CIRM.ca.gov and must be received by CIRM no later than 5:00 pm (PDT) on March 26, 2009. Additionally, a hard copy of the cover (first) page of the PreApp, signed by an institutional official authorized to sign on behalf of the applicant's organization, must be received by CIRM no later than 5:00 pm (PDT), on March 26, 2009. **No exceptions for late PreApps will be made.** CIRM/Funding Partner teams must also copy the designated Partner point-of-contact listed in the Appendices (Submission Requirements Table) on the electronic submission.

Send the signed cover page of the PreApp to:

Disease Team Research Award PreApp
California Institute for Regenerative Medicine
210 King Street
San Francisco, CA 94107

C. Full Application Forms

Full applications for the CIRM Disease Team 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) by mid May 2009.

The full application for the Disease Team Research Award consists of five parts:

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).

Part B: Disease Team Award Research Proposal (MS Word template). Part B includes: Project Objective/Target Profile; Scientific Basis, Rationale, and Impact; Preliminary Results; Preclinical Research and Development Plan, Milestones, and Timeline; References; Collaborations, Resources and Environment; and Leadership Plan (section numbers 6-12 below).

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

Part D: Institutional Letter(s) of Commitment and other letters of commitment or agreement (no template provided; section number 13).

Part E: Related Business Entities (Adobe PDF template). In order to comply with the Conflict of Interest policies under which CIRM operates, Part E must be submitted to indicate whether the application would, if awarded, provide funding from CIRM or a Collaborative Funding Partner to a for-profit organization that is either: 1) the applicant organization; 2) Co-PI sponsor institution; 3) a subcontractor; or 4) the employer of a co-investigator, consultant or subcontractor (section number 14 below).

The application for Disease Team Research Awards includes the following sections:

1. *Abstract (up to 3000 characters in Part A)*
    a. Project Description: Provide a brief description of the proposed project. Describe the rationale for choosing the therapeutic candidate and the clinical context of the research questions and hypotheses being addressed.
    b. Unmet Medical Need / Impact: Describe the unmet medical need that the project will address in which use of human stem cells offers an advantage over other approaches. Summarize the impact that the proposed therapeutic candidate would have on the target disease or injury, and medical practice, if it were successfully developed.
    c. Research and Development Plan: Summarize the overall proposed plan, focusing on important activities to be accomplished 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)*
Briefly describe in lay language the proposed research and how it will lead to the filing of an IND for a stem cell-based therapeutic. This Public Abstract will become public information; therefore, do not include proprietary or confidential information or information that could identify the PI, the applicant institution, the

Co-PI(s) and his/her institution(s), or the Partner PI and his/her Partner applicant institution.

3. *Statement of Benefit to California (up to 3000 characters in Part A)*
   Describe how the proposed research will benefit the State of California and its citizens. This Statement of Benefit will become public information; therefore, do not include proprietary or confidential information or information that could identify the PI, the applicant institution, or the Co-PI(s) and his/her institution(s). For CIRM/Funding Partner applications, the form will contain a space for a Statement of Benefit to its citizens.

4. *Key Personnel (included in Part 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, and must include the Project Manager. For applications that designate a CIRM-funded Co-PI who is employed by an institution other than the applicant institution, key personnel can include a financial project administrator. For CIRM/Funding Partner team applications, key personnel sponsored by the Funding Partner must also be listed in this section.

   A minimum of one percent effort is required for each key person, except the PI and Co-PIs, who are required to commit a minimum effort of thirty percent (30%) and twenty percent (20%), respectively. For each key person (except for technical staff and students) listed, provide a two-page biographical sketch using the template provided. The sketch should highlight prior relevant research and product development experience, including team leadership or team participation. Specify development projects delivered; INDs/IDEs and/or BLAs/NDAs filed where the PI or Co-PI was a lead or contributing investigator; clinical trials where the PI or Co-PI was a lead or contributing investigator. Include relevant publications and/or patents or patent applications.

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. All allowable costs for research grants are detailed in the CIRM Grants Administration Policy (GAP, see section XI.A of this RFA). For all CIRM-funded applications that designate one or more Co-PIs, the PI and each Co-PI will be responsible for an individual budget (comprised of the Direct Project Costs, the CIRM Facilities Costs, and the CIRM Indirect Costs) for the portion of the total project performed under their authority. CIRM 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.

For CIRM/Funding Partner collaborations, the funding requested from the Funding Partner must be indicated (in the Part A section "Partner Proposed Budget") for reviewers to assess the appropriateness of the non-California project budget.

6. *Project Objective / Target Profile (up to 2 pages in Part B)*
   Provide a target profile for the proposed therapeutic. The target profile reflects desired key features of the proposed therapeutic candidate. The target profile guides preclinical and clinical development, is continually refined and becomes the product label upon commercialization. Briefly, address each of the following aspects of a target profile: 1) Description; 2) Scientific Rationale; 3) Indication(s) / Target; 4) Activity (in vitro/in vivo) / Efficacy Endpoint (patients); 5) Safety / Contraindications; 6) Route; 7) Regimen; 8) Risk versus Benefit; and 9) Clinical Competitiveness. For allogenic cell therapy candidates, immune tolerance or immunosuppression strategies should be addressed above.

7. *Scientific Basis, Rationale, and Impact (up to 2 pages in Part B)*
   Describe the disease or serious injury target, and summarize the scientific basis and rationale for the therapeutic candidate. Address why human stem cells are necessary or advantageous to the proposed research compared to other approaches. Explain how the proposed research will result in a therapeutic candidate that meets an unmet medical need. Comment on the impact of the therapy on disease, injury or medical practice, if the proposed therapeutic were successfully developed and commercialized.

8. *Preliminary Results (up to 4 pages in Part B)*
   Provide preliminary data or other supporting data for the proposed therapeutic and for successful application of the technologies and methodologies proposed for achieving the IND application. Include statistical approaches and power analyses, where appropriate.

9. *Preclinical Research and Development Plan, Milestones, and Timeline (up to 8 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. This delineation is essential for review of the research plan and the appropriateness of the budget.

   Include an overall plan for therapy development, including the experimental approaches, methods and techniques proposed for accomplishing the project goals within 4 years. The goals must include preparing and filing an IND. 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. Include planned FDA meetings in the milestones. Milestone achievement is an important indicator of progress and is a major factor

in review of yearly progress reports. Insufficient progress through milestones may result in loss of further funding.

Describe concisely, but in sufficient detail to permit evaluation of the merit of the research, the preclinical research and development plan to achieve the project objective. The preclinical research and development plan must address activities necessary to enable consideration for subsequent clinical studies (first-in-man studies), and must comply with all FDA guidelines. Include IND-enabling studies including pharmacology, toxicology, and strategies to address analytical development, process development and manufacturing, clinical and regulatory issues.

For Year 1, include full details of planned activities and experimental design. For example, include rationale for choice of *in vitro* or i*n vivo* models, parameters to be tested, study design and outcomes analysis. State success criteria. Describe proposed assays for candidate therapy development including potency assays. Potency assays should reliably address mechanism(s) of action hypothesized to underlie a therapeutic effect. Include important details of studies and activities planned for years 2-4.

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

11. *Collaborations, Resources and Environment (up to 2 pages in Part B)*
    Provide a short description of the facilities, core services and environment in which the work will be done, and the major equipment and resources available for conducting and enabling the proposed research. Discuss relevant intellectual property and licenses that are available to the project. Discuss ways in which the proposed studies will benefit from unique features of the scientific environment in which they are conducted. When collaborations 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 or infrastructure resources to the project. If applicable, identify adjunct personnel, beyond the core research team, who may be required for the success of the project, and provide evidence for their availability and accessibility. If advisors, consultants or subcontractors will provide expertise or resources critical to the success of the project, summarize their credentials and relevant track records.

12. *Leadership Plan (up to 2 pages in Part B)*
    Provide a detailed leadership and management plan. For CIRM/Funding Partner teams, this plan must address operations not only within the CIRM-funded Californian team, but among all investigators. Describe the organizational structure and governance of the team. Describe the role(s) and responsibilities of the PI, the Project Manager, Co-PI(s), and the Partner PI, if applicable. Include the management approach and processes that will be employed, including a communication plan. Describe methods and processes that will maintain team strategy, energy and focus; monitor progress; and enable scientific decision-making. Describe an approach for resolution of potential issues or conflict, including disputes over authorship, inventorship, performance and scientific

direction. Summarize the oversight of adjunct personnel, advisors, consultants, and collaborators.

13. *Institutional Commitment (up to 2 pages each per PI, Co-PI(s), and Collaborative Funding Partner in Part D).*
    The applicant institution (and, if different from the applicant institution, the institution of each Co-PI(s)) and the Partner applicant institution must provide a letter of support, signed by a senior organizational official who has the authority, or who has been delegated the authority, to commit the institution(s) to support the proposed program. These letters should document in specific terms the nature of the institution's current and future commitment to the proposed program during the period of the award and should include a description of facilities and resources available to the program. A discussion of the institution's track record and future plans for supporting translational research and preclinical development should also be included.

14. *Related Business Entities (Part E)*
    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) Co-PI sponsor institution; 3) a subcontractor or 4) the employer of a co-investigator, consultant or subcontractor. If the application does not seek funding for any such for-profit organizations, indicate that on Part E and submit the form. If for-profit funding is sought, include the following for each 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 five parts: Part A: Application Information Form, Part B: Disease Team Research Awards Proposal, Part C: Biographical Sketches for Key Personnel, Part D: Institutional Letter(s) of Commitment, and Part E: Related Business Entities. **All five parts of the full application for CIRM Disease Team Research Awards must be submitted together and received by CIRM no later than 5:00 pm (PDT) on July 16, 2009, in both electronic form and in hard copy (a signed original and five copies)**. **No exceptions for late applications will be made.** Send electronic copies of all parts of the application as attachments in a single email to DiseaseTeamResearchAwards@cirm.ca.gov. CIRM/Funding Partner teams must also copy the designated Partner point-of-contact listed in the Appendices (Submission Requirements Table) on the electronic submission.

In addition to the electronic submission, candidates must submit an original copy of the application (consisting of Parts A-E) plus 5 copies of the full application (preferably double-

sided) to the mailing address below. The original copy must be signed by both the PI and the applicant institution's Authorized Organizational Official (AOO). Applications designating a Co-PI(s) must also be signed by the Co-PI and the Co-PI's institutional AOO.

Disease Team Research Awards Application
California Institute for Regenerative Medicine
210 King Street
San Francisco, CA 94107

IX. Schedule of Deadlines and Reviews

Pre-Applications due	5:00 pm (PDT), March 26, 2009
Invitations for full applications sent out by CIRM	Mid May 2009
Full Applications due	5:00 pm (PDT), July 16, 2009
Review of full applications by Grants Working Group (GWG)	September 2009
Review and Approval by ICOC	Fall 2009
Earliest Funding of Awards	December 2009

X. 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

XI. CIRM Regulations

Grant awards made through this RFA will be subject to CIRM regulations. These regulations can be found on CIRM's website at http://www.cirm.ca.gov/reg/default.asp

A. CIRM Grants and Loan Administration Policies

CIRM's Grants Administration Policy (GAP) for Academic and Non-Profit Institutions (Non-Profit GAP), supplemented by the GAP for For-Profit Institutions (For-Profit GAP) and 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 grant application timeline.

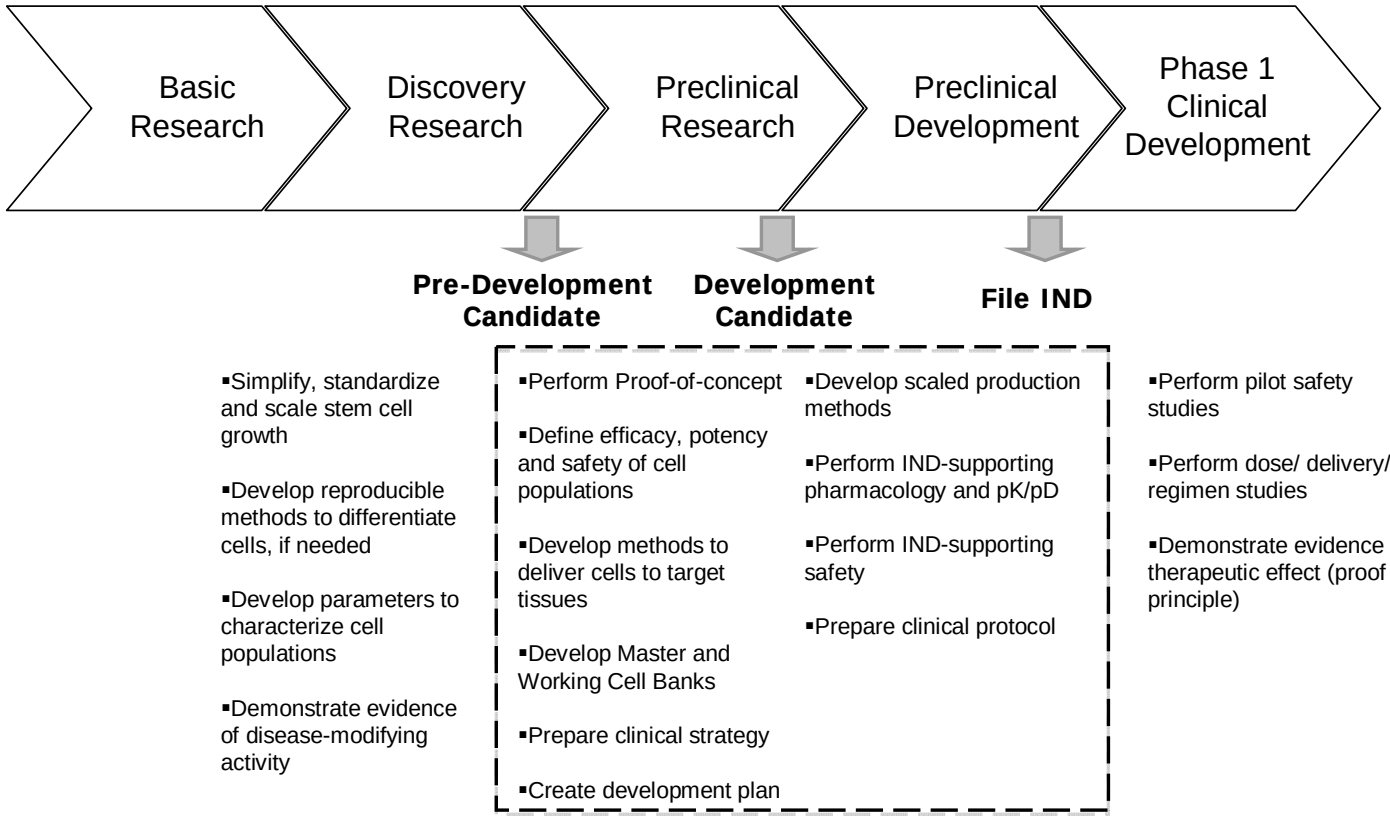
B. Intellectual Property Regulations

CIRM has adopted intellectual property regulations for non-profit and for-profit organizations.

C. Human Stem Cell Research Regulations

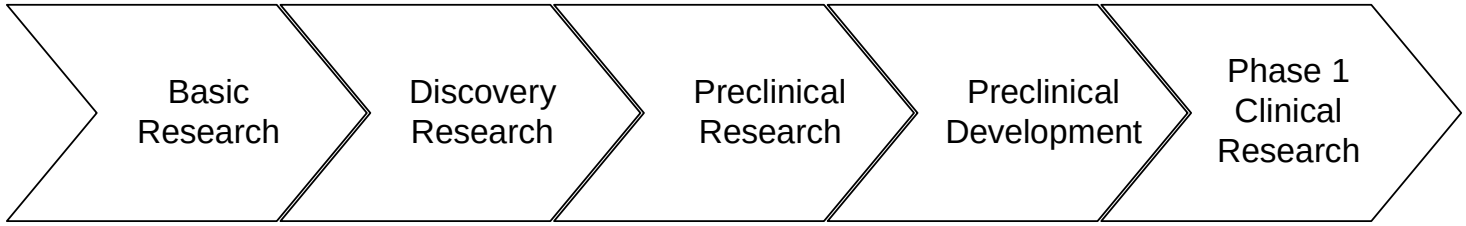
CIRM has adopted medical and ethical standards for human stem cell research (Title 17, California Code of Regulations, sections 100010-100110). All research conducted under this award will be expected to comply with these standards.

Cell Therapy Development Activities



Examples of activities considered in-scope of the Disease Team RFA

Small Molecule Development Activities



Pre-Development Candidate

- Target identification
- Evidence of disease association/biological validation & therapeutic value
- Target validation/MOA
- Screening amenability
- Screening strategy plan
- Develop cell-based assays for in vitro evaluation of activity — HTS

- Demonstrate evidence of disease-modifying activity
- Perform HTS
- Identify and characterize active compounds
- Evaluate potency, selectivity, reversibility and mechanism of action

Development Candidate

- Perform Proof-of-concept
- Conduct lead optimization
- Define efficacy, potency and safety of lead compound
- Verify mechanism of action
- Create PKDM profile
- Identify potential drug-drug interactions
- Prepare clinical strategy
- Create development plan

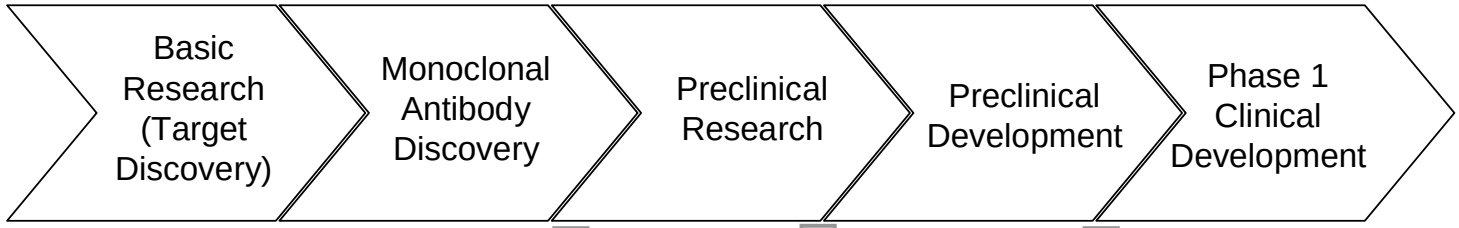
File IND

- Develop formulation and scaled production methods
- Perform IND-supporting pharmacology and PK/PD
- Validate human drug-level assays
- Identify clinical toxicity-monitoring parameters
- Perform IND-supporting safety
- Prepare clinical protocol

- Perform pilot safety studies
- Perform dose/ delivery/ regimen studies
- Demonstrate evidence of therapeutic effect (proof of principle)

Examples of activities considered in-scope of the Disease Team RFA

Monoclonal Antibody (MAB) Development Activities



Pre-Development Candidate | **Development Candidate** | **File IND**

- Identify target
- Perform target validation
- Perform expression prevalence in tissue versus normal; RNA; protein (immunohistochemistry)
- Demonstrate function of target

Target Development
- Identify immunogens
- Determine specificity
- Develop validation reagents and screening assays (secondary, tertiary)

MAB Generation (HTS)
- Conduct immunization
- Test alternate Mab generation methods
- Perform screening

MAB Evaluation (HTL)
- Perform in vivo pharmacology
- Perform affinity and epitope characterization
- Create candidate supply
- Generate initial cell line

Pre Development
- Perform in vivo pharmacology
- Complete antibody engineering
- Create candidate supply
- Develop cell lines
- Perform early process development
- Perform pilot safety
- Prepare clinical strategy

IND Enabling
- Produce GLP drug supply
- Develop GMP process
- Produce GMP drug supply
- Perform IND enabling toxicology/
- safety/pK
- Prepare clinical protocol

Examples of activities considered in-scope of the Disease Team RFA

APPENDIX B: COLLABORATIVE FUNDING PARTNER OVERVIEW AND CONTACT INFORMATION: CANCER STEM CELL CONSORTIUM, CANADA

THE FOLLOWING MATERIAL IN APPENDIX B WAS PREPARED BY THE CANCER STEM CELL CONSORTIUM:

I. PURPOSE

The purpose of this funding opportunity is to support the research of multi-disciplinary teams of scientists, co-led by Canadian and Californian Principal Investigators (PIs) that will result in a cancer stem cell based therapy or a therapy derived from cancer stem cell assays with the specific aim of improving cancer treatment.

II. FUNDS AVAILABLE

Under this RFA 09-01, the CSCC intends to commit up to CDN$40 million to support the Canadian component of up to two (2) projects funded through the Collaborative Funding Partner Program. Projects will be funded for up to four (4) years, with justifiable total Canadian project costs of up to CDN$20 million per project, conditional upon CIRM funding up to US$20 million per project to support the Californian component.

Teams invited to submit full applications at the Preliminary Application stage may be eligible to request development grants from CSCC. Details will be provided to the applicants during the PreApp stage.

III. BACKGROUND

Cancer stem cells represent an exciting and promising new avenue for cancer research as their presence, in many malignancies studied so far, may explain the ability of tumours to proliferate, metastasize and survive traditional chemotherapy and radiation treatments. The ability to extract, culture and expand cancer stem or progenitor cell populations is central to advancing research and to enabling a rigorous investigation of the potential of cancer stem cells as targets for new, more specific, therapeutics. The importance of this research has been recognized worldwide. In 2006, the Canada-California Strategic Innovation Partnership (CCSIP), (an initiative establishing a bilateral public/private partnership between Canada and California), identified research on cancer stem cells as a strategic theme area for collaboration between the two jurisdictions.

In 2007, building on the momentum created by the CCSIP and the leadership of Canadian and Californian scientists in the cancer stem cell field, several of Canada's major research funding agencies established the Cancer Stem Cell Consortium (CSCC) (http://www.cancerstemcellconsortium.ca/). The CSCC is a not-for-profit corporation committed to:

i) Developing and implementing an international strategy for cancer stem cell research, technology development, clinical translation activities, and commercialization opportunities to allow the biomedical community to move quickly and effectively from discoveries to application in the clinic;

ii) Establishing partnerships among organizations in Canada, California, and other jurisdictions; and
iii) Securing investments to fund the activities of the CSCC.

Current members of the CSCC include the Canada Foundation for Innovation (CFI), Genome Canada, the Canadian Institutes of Health Research (CIHR), the Ontario Institute for Cancer Research (OICR) and the Stem Cell Network of Centres of Excellence (SCN). CSCC is dedicated to identifying and developing partnerships with other Canadian funding organizations and stakeholders to enhance the availability of funding for cancer stem cell research. As additional partnerships for this initiative are identified, the relevant information will be posted on the CSCC website (http://www.cancerstemcellconsortium.ca/).

In June 2008 the CSCC established a formal partnership with California through the signing of a Memorandum of Understanding (MOU) with the California Institute for Regenerative Medicine (CIRM) to explore possible collaborative funding of cancer stem cell research projects undertaken by Canadian and Californian research teams. The first opportunity for CSCC and CIRM collaborative funding of cancer stem cell research arising in the context of this MOU is CIRM's RFA 09-01 Disease Teams Research Awards Competition. Fully integrated applications submitted to the CIRM Disease Team Research Awards Competition from Canadian and Californian researchers working on cancer stem cells are eligible for funding through CIRM's Collaborative Funding Partner Program. Successful cancer stem cell projects, co-led by Canadian and Californian scientists, will be co-funded by the CSCC and CIRM, with Canadian scientists funded by the CSCC and Californian scientists funded by CIRM. Collaborations with scientists outside of California and Canada are not eligible for funding through this initiative.

IV. AWARD INFORMATION

Teams of Canadian and Californian scientists submitting applications through CIRM's Collaborative Funding Partner Program must complete both the CIRM requirements (Section VIII of RFA 09-01) and any additional requirements put forth by the CSCC. A number of the CSCC requirements are outlined in this document, with additional requirements to be provided at a later date. CIRM application forms (Section VIII), approved procedures (Section VI), review criteria (Section VII) and review panel will be used by applicants submitting a CIRM-CSCC collaborative project. In addition, applicants must follow special instructions for collaboratively-funded teams in the Statement of Benefit (Section VIII.C.3), the Key Personnel (Section VIII.C.4), the Budget (Section VIII.C.5), the Research Plan (Section VIII.C.9), the Leadership Plan (Section VIII.C.12), and the Institutional Commitment (Section VIII.C.13) sections of the CIRM full application and in the Project Objective (Section VIII.A.3.) and Team Leadership (Section VIII.A.5) sections of the Preliminary Application.

CSCC requests that teams of Canadian and Californian scientists designate a Californian PI ("CIRM PI") (responsible for communicating to CIRM for the Team) and a Canadian PI ("CSCC PI"). All communications about successfully funded grants should cite both PIs.

A. General Guidelines

The general guidelines of each of the participating partner agencies must be followed. At this time, funding is available from Genome Canada and the Canadian Institutes of Health

Research (CIHR). In addition, the Ontario Institute for Cancer Research (OICR) will consider requests to support translation activities proposed by scientists from Ontario. As additional partners join the consortium, CSCC will notify the community of additional funding opportunities.

Relevant general guidelines for each of the individual funding organizations are outlined below:

Genome Canada: http://www.genomecanada.ca/en/portfolio

CIHR: http://www.cihr-irsc.gc.ca/e/805.html

OICR: http://www.oicr.on.ca/Grants/November2008PolicyGuidelines.pdf

B. Canadian Investigator Eligibility

To submit a proposal, Canadian investigators must be eligible to receive grant funding from the participating funding agencies relevant to the RFA.

Participation in this RFA is NOT limited to scientists who registered their intent to submit an application to the Disease Team Research Awards Competition.

In general, eligible lead applicants include Canadian researchers, scholars and health professionals affiliated with the following institutions and organizations:

- Canadian post-secondary institutions and their affiliated institutions including hospitals and research institutes;
- Canadian non-governmental, not-for-profit organizations (including community or charitable organizations) with an explicit research or knowledge translation mandate;
- Canadian non-federal government departments or agencies, including regional health authorities, when specific programs of those departments or agencies do not fund the activity that forms the subject matter of the grant.

In addition, the following special conditions apply:

i. Members of the team may pursue other avenues of research in addition to their commitment to the *Disease Team Research Award*; however, each individual investigator must contribute sufficient time to this project to ensure the achievement of its research objectives. The CSCC PI must commit a minimum of thirty percent (30%) effort to the project.

ii. Members of a team may be located in one or more departments, faculties or eligible institutions in Canada and California. As well, teams may include international, private sector (for-profit organizations), or federal laboratory scientists. However, CSCC funding is restricted to work performed within CSCC-eligible institutions, i.e., the CSCC will not support research to be undertaken outside Canada, in for-profit organizations or in federal laboratories, except where second order transfer/inter-institutional agreements are in place.

iii. The CSCC will require funded teams of Canadian and Californian scientists engage in information exchange within the Consortium, adhere to all Consortium policies and

principles and participate in other CSCC-wide annual activities and events, including annual meetings, networking activities and training programs.

iv. The applicants must have documented commitment from the host institution to provide laboratory space and shared resources sufficient to carry out the proposed research.

C. Eligible Costs

Support for Canadian scientists will primarily be for operating funds, but may include reasonable requests for minor equipment essential for the proposed research. However, funds will not be available for major equipment, infrastructure, renovation, or facilities.

Guidelines for eligible use of funds from specific agencies can be found on their web-sites at the links below:

Genome Canada: http://www.genomecanada.ca/en/portfolio/

CIHR: http://www.nserc-crsng.gc.ca/Professors-Professeurs/TFAGindex-GAFTindex_eng.asp

OICR: http://www.oicr.on.ca/Grants/November2008PolicyGuidelines.pdf

V. APPLICATION PROCEDURE

Applicants to the CSCC-CIRM Collaborative Funding Partner Program must submit a single integrated Pre Application and full application to CIRM by the deadlines stated in the RFA 09-01. In addition, applicants must satisfy CSCC specific requirements, which are described below. This includes submission of the following documents to the CSCC in electronic format by the specified dates: i) a Notification of Intent to Submit; ii) a copy of the Pre Application; iii) a detailed budget for the Canadian component; and iv) a copy of the full application (refer to the table in Section F).

A. Notification of Intent to Submit Pre Application

The CSCC PIs must notify the CSCC of their intent to submit a Pre Application by **February 25, 2009**. The notice must include the names, affiliations and contact information for the CSCC PI, the CIRM PI, and Co-PIs, as well as the title of the proposal.

B. Budget Form

Canadian scientists will provide budget information on the CSCC budget form (to be made available to applicants invited to submit a full application) and on the CIRM budget form. Each CSCC member organization has specific objects of expenditure that it can support within a project. When developing a budget plan and completing the CSCC budget form, applicants must specify from which CSCC member organization they are requesting funding for each budget item. Guidance from the CSCC secretariat will be provided to applicants in constructing budgets to ensure that the eligibility rules for each funding agency are adhered to. The CSCC budget form must be submitted by **June 25, 2009** to allow time for review of

eligibility by the CSCC members. Applicants will then be required to transfer the relevant information to the CIRM budget form to be submitted July 16, 2009.

C. Statement of Benefit to Canada

In Part A of the full application Form (see Section VIII, C) applicants must describe how the proposed research will benefit Canada and its citizens. This Statement of Benefit will become public information; therefore, do not include proprietary or confidential information or information that could identify the PI(s), the applicant institution(s), or the Co-PI(s) and his/her home institution(s).

D. Value Added by the Collaborative Funding Partner Program

While the research proposed in the application must be meritorious, it is also essential that applicants demonstrate that, when compared to funding the proposal through a series of stand-alone grants from individual organizations, the team structure of the Disease Team Research Awards Competition and the opportunities provided by the Collaborative Funding Partner Program provide added value in terms of the speed and efficiency with which new knowledge will be generated or translated into better cancer treatment, improved cancer prevention and outcomes, and/or new services, products and technologies. This requirement should be addressed in the Collaborations, Resources and Environment section of the Full Application Form (see Section VIII, C).

E. Intellectual Property Requirements

- Intellectual property generated in the course of the Collaborative Funding Partner Program through CSCC funding will be owned in accordance with CSCC Funded Researcher(s)' institutional policies, and CSCC Funded Researchers, or their institutions (as applicable) will have the right to manage and exploit the intellectual property, subject to specific arrangements as to Joint Intellectual Property to be entered into with California CIRM Grantees in compliance with CIRM IP Regulations.

- CSCC Funded Researchers will be bound by the specified CIRM IP Regulations in relation to activities within the State of California. CSCC Funded Researchers would also be required to comply with CIRM IP Regulations for joint inventions and technology (Joint Intellectual Property) when these resulted from CIRM Funded Research or Technology.

- In agreement with CIRM, CSCC will reserve march-in rights to ensure that IP generated during the course of the project using CSCC funding can be fully exploited for the national benefit.

- A further condition of award will be that CIRM or other funded partners agree to provide free access to the Canadian research community to all Publication Related Biomedical Materials generated during the course of the project, to provide consistency with the CIRM requirements for California.

F. Submission Requirements

The following table summarizes the submission requirements for applications to the CSCC-CIRM Collaborative Funding Partner Program.

CSCC Submission Requirements					
Form	Purpose	Submitted by	Submit-ted to	Submis-sion Date	Contact Info (for questions regarding the application process)
Notification of Intent to submit a Pre Application	*This document is to inform the CSCC of your intent to submit a PreApp.*	Applicants submitting a Collaborative PreApp to CSCC and CIRM	CSCC	Feb 25, 2009	Cindy Bell Email: cscc@genomecanada.ca Phone: (613) 751-4460 ext 118
Electronic submission (e-mail) of a copy of the complete Pre Application (PreApp) submitted to CIRM	*This document is based on a template (Adobe pdf). This document is an abbreviated narrative of project overview, the preclinical research and development plan; and the research team.*	Applicants submitting a Collaborative PreApp to CSCC and CIRM	CSCC	March 26, 2009	Cindy Bell Email: cscc@genomecanada.ca Phone: (613) 751-4460 ext 118
CSCC Budget Form	*This form provides detailed budget information, including the source of the funds requested from the participating Canadian agencies*	Invited Canadian Applicants to CSCC and CIRM Collaborative Partner Funding Program	CSCC	June 25, 2009	Cindy Bell Email: cscc@genomecanada.ca Phone: (613) 751-4460 ext 118
Electronic submission (e-mail) of a copy of the complete set of documents submitted to CIRM during the application process	*Detailed information about the proposed project*	Invited Applicants to CSCC and CIRM Collaborative Partner Funding Program	CSCC	July 16, 2009	Cindy Bell Email: cscc@genomecanada.ca Phone: (613) 751-4460 ext 118

VI. CSCC CONTACT

Please submit required documents and requests for information about the CSCC-CIRM Collaborative Funding Partner Program to:

Cindy L. Bell, Ph.D.
Interim Executive Director, CSCC
Email: cscc@genomecanada.ca
Phone: (613) 751-4460 ext 118

APPENDIX C: COLLABORATIVE FUNDING PARTNER OVERVIEW AND CONTACT INFORMATION: MEDICAL RESEARCH COUNCIL (MRC), UNITED KINGDOM

THE FOLLOWING MATERIAL IN APPENDIX C WAS PREPARED BY THE MEDICAL RESEARCH COUNCIL, UK:

Funding available

- MRC has made £5m available to support UK participation in the CIRM Disease Team RFA.
- It is anticipated that this will fund the participation of UK groups in one or two of the top-ranked fundable proposals involving a UK team.

Who can apply

- Proposals must involve UK activity that is either itself at the preclinical stage or that is critical to the progression of the collaborative proposal towards clinical testing.
- Applicants must have strong collaborative links with Californian PIs.
- MRC support will be provided to fund the UK component of competitive proposals where the UK team leader has the status of Co-PI and is fully involved in the project's leadership plan.
- Commercial links can be accommodated under UK state-aid rules, but funding will be provided through the UK academic partner.
- The normal MRC eligibility rules apply; please see the applicants' handbook and the Research Council UK website.
- All UK applicants must have first discussed their proposal with MRC Head Office.

How to apply

- UK participants will submit a joint pre-application with Californian partners using the CIRM PreApp form, as specified in the RFA text.
- The resource request associated with the UK component need not be specified at this stage. For invited full applications, the funding to be requested from MRC must i) be indicated and justified in sufficient detail on the CIRM application form, and ii) be further detailed in a separate annex so that the breakdown of costs is provided under standard MRC headings.
- At the Full Application stage UK participants will also need to submit the same information as required of Californian applicants, including bio-sketch(es) and Letters of Institutional Commitment.

How will funding be provided to the UK partner

- UK participation will be funded as an MRC award to the eligible UK organisation under standard arrangements. Funding will be provided at 80% FEC.

Terms and Conditions of the MRC award

- Standard MRC terms and conditions will apply to the UK component of a collaborative disease team award. These are specified in the applicants' handbook, and encompass:
  i) the core Research Councils UK terms and conditions
  ii) the additional MRC-specific terms and conditions relating to medical research
  iii) the MRC supplementary terms and conditions for research grants involving human stem cells.

Specific terms of the CIRM-MRC collaborative award

- A condition of any MRC award will be that CIRM or other funded partners on the award agree to abide by the Code of Practice for the UK Stem Cell Bank and for the Use of Stem Cell Lines. This includes the requirement to deposit any hESC line derived using MRC funds in the UK Stem Cell Bank, and to seek approval from the Steering Committee for the UK Stem Cell Bank for the import, export or use of any hESC lines in the UK.
- A further condition of award will be that researchers funded by CIRM or other funding partners agree to provide free access to the UK research community to all tangible research material of biomedical relevance jointly generated by participating UK groups and such other researchers during the course of the project, to provide consistency with the CIRM requirements for access to "Publication-Related Biomedical Materials" by Californian researchers.

Intellectual property

- Intellectual property generated in the course of the collaborative project through MRC funding will be owned by the host UK institution, who will have the right to manage and exploit the project intellectual property.
- Participating UK groups will be bound by the specified CIRM IP provisions in relation to commercial exploitation activities within the State of California. UK partners will only be required to comply with such CIRM IP provisions when commercialising inventions or technology jointly generated with CIRM-funded researchers.
- MRC wishes to assure itself that the funded UK institutions are able to manage and exploit effectively the intellectual property generated from the MRC-funded research. In agreement with the CIRM position, MRC will reserve march-in rights to ensure that IP generated during the course of the project using MRC funding can be fully exploited for the national benefit and that of the Research Organisation involved.

Consortium agreement

- The terms of collaboration must be determined early in a proposal's development and relevant agreements put in place by the start of the collaboration. Collaboration arrangements should ensure transparency in the project design and in the analysis and publication of results (including if these are negative). Consideration should also

be given to issues such as: relative responsibilities, governance arrangements, indemnity, intellectual property rights, reporting and access to data and samples.
- MRC funding will not be released until an appropriate consortium agreement has been agreed and signed by all collaborative partners, and approved by MRC and CIRM (and any other collaborative funding partner).

Monitoring Performance of Collaborative Projects

- For funded collaborative projects, both MRC and CIRM will have access to all grantee-generated progress and financial reports across the full scope of the project's work.
- MRC and CIRM will meet periodically to review the progress of the collaboratively funded projects, and funding may be cancelled should there be a failure in making satisfactory progress.

Further information

- Available from Dr Catriona Crombie, MRC Programme Manager for Stem Cells and Developmental Biology (catriona.crombie@headoffice.mrc.ac.uk)

APPENDIX D: COLLABORATIVE FUNDING PARTNER OVERVIEW AND CONTACT INFORMATION: SPANISH MINISTRY OF SCIENCE AND INNOVATION (MICINN), SPAIN

THE FOLLOWING MATERIAL IN APPENDIX D WAS PREPARED BY THE SPANISH MINISTRY OF SCIENCE AND INNOVATION:

The following table summarizes the submission requirements for Spanish applicants. For further details, please refer to the web site of MICINN: (http://web.micinn.es/contenido.asp?menu1=4&menu2=3&menu3=&dir=05_Investigacion/032CoopIntern/03@Cooperacion/00-PgsInts).

MICINN Submission Requirements					
Document	Purpose	Submitted by	Submitted to	Submission Date	Contact Info
Electronic submission (e-mail) of a copy of the complete pre-application submitted to CIRM (pdf format)	Project overview	Applicants submitting a collaborative pre-application to MICINN and CIRM	MICINN	March 26, 2009	Bibian García Ministerio de Ciencia e Innovación Postal address: Albacete 5, 5ª planta – sur, 28027 Madrid, Spain Phone: +34 / 916038385 E-mail: b.garcia@micinn.es
Curriculum vitae of research group leaders	Information about scientific background and qualification of participating scientists	Applicants submitting a collaborative pre-application to MICINN and CIRM	MICINN	March 26, 2009	
Preliminary overview on Spanish project budget	Budget overview	Applicants submitting a collaborative pre-application to MICINN and CIRM	MICINN	March 26, 2009	
Electronic submission (e-mail) of a copy of the complete set of documents submitted to CIRM during the application process (pdf format)	Detailed information about the proposed project	Applicants invited to submit a full proposal to MICINN and CIRM	MICINN	July 16, 2009	Bibian García Ministerio de Ciencia e Innovación Postal address: Albacete 5, 5ª planta – sur, 28027 Madrid, Spain Phone: +34 / 916038385 E-mail: b.garcia@micinn.es
Detailed justification of funding requested from MICINN	Detailed budget information	Applicants invited to submit a full proposal to MICINN and CIRM	MICINN	July 16, 2009	

APPENDIX E: SUPPLEMENTAL FUNDING OPPORTUNITY AND CONTACT INFORMATION

THE FOLLOWING MATERIAL IN APPENDIX E WAS PREPARED BY THE JUVENILE DIABETES RESEARCH FOUNDATION INTERNATIONAL:

I. The Juvenile Diabetes Research Foundation International

Successful applicants whose projects would accelerate the development of cellular therapy for Type 1 Diabetes are encouraged to contact The Juvenile Diabetes Research Foundation International (http://www.jdrf.org/), which may provide funding for collaborative projects that depend on work outside the State of California. Contact: Adrianne L. Wong, Ph.D. awong@jdrf.org +1 212-479-7642.