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## **RFA 08-05: CIRM EARLY TRANSLATIONAL RESEARCH AWARDS**

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### **I. PURPOSE**

The purpose of the CIRM Translational Research Initiative is to provide funding to ensure that promising discoveries in stem cell research can be translated to potential stem cell-based cures, therapies and diagnostics for the benefit of patients. Because stem cells possess the unique ability to differentiate into multiple cell types and self-renew, they have great potential to treat or cure chronic diseases and injuries but also present unique challenges for therapeutic development.

The focus of this RFA (“Early Translational Research Awards”) is to support projects that enable the initial stage of translation of basic stem cell-based research toward clinical application. The later stages of translational research will be the subject of a future RFA(s) designed to support preclinical and clinical development activities.

### **II. PROGRAM OBJECTIVES**

The CIRM Early Translational Research Awards are designed to move promising basic research in stem cell science toward the clinic. These awards will support two categories of projects including research that:

- 1) Results in a development candidate that meets an unmet medical need; or
- 2) Addresses a significant bottleneck in the translation of stem cell biology that hinders advancement of effective, novel cell therapies to the clinic.

The first category of projects targeted by the Early Translational Research Awards will support the identification of development candidates. A development candidate is a small molecule, biologic or stem cell-derived cell therapy for which there are compelling data demonstrating reproducible disease-modifying activity in animal models of disease, as well as other supporting data sufficient to consider initiation of IND-enabling activities (see Appendix A).

The second category of projects targeted by this RFA is research directed to resolution of current bottlenecks to translation of novel cell-based therapies. CIRM is particularly interested in proposals addressing bottlenecks to the translation of pluripotent cell-derived therapies.

#### Development Candidates:

CIRM’s mission requires stem cell-derived development candidates to be identified, and then advanced through preclinical and clinical development. Therefore, CIRM will instruct reviewers to prioritize applications focused on the identification of a development candidate, with a goal

of recommending at least 50% of awards to this project category. Examples of development candidates include a stem cell or stem cell-derived progenitor or more differentiated cell, or a small molecule or biologic derived from stem cells or discovered using human stem cell-based assays. For applications to be responsive to this RFA, the use of human stem cells must offer an advantage over other approaches.

The applicant for an award in the development candidate category must present strong supportive evidence of a disease target appropriate for therapeutic intervention and a scientifically justifiable hypothesis for a proposed therapeutic approach. The research plan must detail those activities necessary to achieve a development candidate for consideration for further development. Examples of key activities to achieve a small molecule, biologic or cell therapeutic development candidate are listed in Appendix A.

Investigational New Drug (IND) enabling studies, scale-up and production under Good Manufacturing Practices and IND filing are outside the scope of this RFA. These and other preclinical development activities will be the focus of a future RFA.

#### Bottlenecks:

CIRM is particularly interested in proposals that address bottlenecks to advancement to the clinic of effective, novel cell therapies; particularly cell therapies derived from human pluripotent stem cells. CIRM's priorities for research on such bottlenecks are:

- Development of methods (including animal models) to: 1) monitor the immune response elicited by cell-based therapies; 2) treat rejection of cellular transplants; or 3) induce tolerance to cell-based therapies;
- Development of non-invasive methods to track the migration, integration and/or fate of in vivo transplanted stem cells, including assays to detect early teratomas or other cancers;
- Pre-transplant manipulations of cells to prevent teratoma formation, including methods to efficiently sort undifferentiated pluripotent cells from mixed cell populations;
- Development of cell differentiation, selection and/or purification methods that result in higher and more consistent yield of cells of the desired phenotype, and that are scalable and more cost-effective.

Since inadequate animal models for many diseases constitute a translational bottleneck, CIRM is also interested in proposals that utilize human stem cells for:

- Development of disease models that overcome limitations of current models and are more predictive of therapeutic response in humans.

CIRM will ask reviewers to prioritize applications in this category that address bottlenecks highlighted above. Proposals targeting bottlenecks not highlighted above will require substantial additional justification.

### **III. AWARD INFORMATION**

Under this RFA, CIRM intends to commit up to \$60 million to support up to ten three-year awards with direct project costs of up to \$1.2 million per year. This award will support projects in two categories including research that:

- 1) Results in a development candidate intended to meet an unmet medical need. CIRM will instruct reviewers to prioritize applications that focus on the identification of a development candidate. CIRM will target at least 50% of awards to this category.
- 2) Addresses a significant bottleneck in the translation of stem cell biology that hinders advancement of effective, novel cell therapies to the clinic. Proposals that address bottlenecks to cell therapies derived from human pluripotent stem cells are a priority within this category.

Research utilizing pluripotent stem cells, adult stem cells or progenitor cells will be considered. Particular consideration will be given to proposals that are ineligible for federal funding.

## **IV. ELIGIBILITY INFORMATION**

Applications will only be accepted from Principal Investigators (PIs) who 1) have been officially nominated on a Candidate Nomination Form (CNF, see RFA section VI.A) by their host institution and 2) have submitted a Letter of Intent (LOI, see RFA section VI.B) that was accepted by CIRM.

### **A. Institutional Eligibility**

All CIRM-supported research must be conducted in California. This RFA is open to all academic and non-profit research institutions in the state of California. It is also open to for-profit organizations with established research site(s) in the state of California at the time the application is submitted.

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

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

Non-profit applicant institutions with accredited medical schools will each be eligible to submit up to three applications. Other non-profit institutions and for-profit institutions with 250 employees or more will each be eligible to submit up to two applications. Non-profit and for-profit applicant institutions with fewer than 250 employees may each submit one application. Applicant institutions will be required to certify upon submission of the Candidate Nomination Form that they meet the above criteria.

### **B. Principal Investigator (PI) Eligibility**

Each Principal Investigator (PI) may submit only one application under this RFA. The PI must have an M.D., Ph.D. or equivalent degree, and must be authorized by the applicant institution to conduct the proposed research in California. By the application deadline, the PI must:

- be an independent investigator at a non-profit applicant institution, or have an equivalent position and be an employee of a for-profit applicant institution;

- have documented authority from the applicant institution to staff the proposed project;
- have documented authority from the applicant institution for access to space and shared resources sufficient to carry out the proposed research.

In addition, CIRM, mindful of the urgency of its mission and the scope of these awards, will

- require the PI to commit a minimum of 10% effort. CIRM will instruct reviewers to give added consideration to the PI's qualifications when the PI commits more than 10% effort to the research proposed in his/her application. In extraordinary circumstances, and at the discretion of the President of CIRM, CIRM may allow senior research scientists to commit to a reduced effort in the interests of obtaining the best outcomes for a research project. Such exceptions **must** be requested prior to October 1 to allow the President of CIRM time to review and to approve or deny the request prior to October 15, the deadline for submission of a CNF and LOI.
- require the award to be initiated no later than six months after the date the ICOC approves the application for funding.

**In order to broaden the pool of applicants engaged in moving stem cell research towards clinical application, a PI may apply for either an Early Translational Research Award or a forthcoming Disease Team Research Award, BUT NOT FOR BOTH.** In extraordinary circumstances, and at the discretion of the President of CIRM, a PI may be allowed to apply as PI for both awards. Such exceptions **must** be requested prior to October 1 to allow the President of CIRM time to review and to approve or deny the request prior to October 15, the deadline for submission of a CNF and LOI.

CIRM believes that translational research is often most effectively conducted by a multidisciplinary team. CIRM strongly encourages PIs to form such collaborative teams, including collaborations between non-profit and for-profit entities.

### **C. Collaborative Funding Opportunity with the State of Victoria, Australia**

CIRM has signed a memorandum of understanding (MOU) for **collaborative research funding with the State of Victoria, Australia, pursuant to which research teams comprised of Californian and Victorian scientists may be eligible for additional funding from the Victorian Government for research conducted in Victoria.** Victorian scientists are eligible to participate in CIRM's Early Translational Research Award RFA by partnering with California scientists to form a collaborative team ("CIRM/Victoria teams"). The Victorian Government will provide up to \$5 million to support the Victorian research component for teams that are successful in the CIRM review process and are awarded CIRM funding. Victorian researchers will be required to apply for Victorian government funding and will be subject to its terms and conditions. Victorian scientists interested in further information about this opportunity should contact Roland Diggins, Manager – International Cooperative Initiatives and VISTECH, Tel: +61 3 9651 8102.

For CIRM/Victoria teams, applications are made using the CIRM forms described in this announcement. In addition, those teams must provide further information as required by Victoria relevant to the joint application. The same review panel will review

these applications using the same review criteria (Section V.) that will be used for all other Early Translational Research Award applications. CIRM will only pay for the research performed by the CIRM/Victoria team that is conducted in California. To apply for funding under the CIRM/Victoria MOU, applicants must follow special instructions for collaborative teams in the Research Plan (Section VI.C.9.) and in the Budget (Section VI.C.5).

## V. REVIEW CRITERIA

CIRM intends the Early Translational Research Awards to support research that will lead to development candidates or overcome current bottlenecks to advancement of novel cell therapies to the clinic. CIRM will instruct reviewers to prioritize applications focused on the identification of a development candidate. CIRM will target at least 50% of awards to this category. In the bottleneck category, CIRM will ask the reviewers to prioritize applications that target cell therapy, particularly cell therapies derived from human pluripotent stem cells; or, that utilize stem cells to develop better, more predictive disease models. Applications will be evaluated in four areas: (1) scientific basis, rationale and impact of the proposed research; (2) design and feasibility of the research plan to either identify a development candidate or eliminate a bottleneck; (3) the qualifications and track record of the PI and key team members of the research team; and 4) collaborations, resources and environment.

### A. Scientific Basis, Rationale and Impact

For applications focused on research leading to a development candidate:

- There is strong supportive evidence for the proposed research.
- Human stem cells are necessary or advantageous to the proposed research compared to other approaches.
- The proposed research leads to a development candidate that addresses an unmet medical need.
- The proposed research leads to a development candidate that, if successfully developed and commercialized, would have a significant impact on disease, injury or medical practice.

For applications focused on bottlenecks:

- There is strong supportive evidence for the proposed research.
- The proposed approach to address the bottleneck is based on a scientifically justifiable hypothesis.
- The proposed research addresses a critical bottleneck to the advancement of effective, novel cell therapies to the clinic.
  - CIRM is particularly interested in proposals for research that will overcome bottlenecks to the advancement of human pluripotent cell-derived therapies to the clinic. CIRM will instruct reviewers to give special consideration to such proposals.
- The proposed research utilizes human stem cells to develop better, more predictive disease models to foster the advancement of better candidates to clinical testing.

### B. Design and Feasibility of the Research Plan

For applications focused on a development candidate:

- The target profile for the proposed development candidate is appropriate and is achievable.
- The research plan is well designed to result in a development candidate. The plan adequately addresses all necessary activities to enable a development candidate for subsequent consideration for preclinical development. The plan identifies interim milestones, acknowledges potential problems, and suggests alternative approaches should the proposed primary approaches fail.
- There are preliminary or other supporting data for the proposed development candidate and for successful application of the technologies/methodologies proposed to achieve the development candidate.
- The proposed timeline shows key research activities and highlights interim milestones. The timeline and interim milestones are appropriate, feasible and technically sound. The goal of a development candidate can be reasonably achieved within the proposed period.

For applications addressing a bottleneck:

- Success criteria are established for assessing whether the bottleneck has been overcome. The success criteria are quantitative, well described, meaningful, and scientifically justified.
- The proposed research is carefully designed to give meaningful results and achieve the success criteria.
- Potential difficulties are acknowledged, and alternatives are provided should the proposed primary approaches fail.
- The preliminary data are compelling and supportive of the proposed concepts, hypotheses and approaches.
- The proposed timeline shows key research activities and highlights interim milestones. The timeline and interim milestones are appropriate, feasible and technically sound. The aims of the research and achieving the success criteria can be reasonably met within the allocated period.

### **C. Qualifications of the Principal Investigator and Research Team**

- The PI and key members of the research team have the training and experience to conduct the proposed research.
- The PI has a record of achievement that supports his/her qualifications to conduct and lead the translational research as proposed.
- For those proposals addressing a development candidate, the PI has access to experts or has assembled advisors who can provide expert advice on challenges to achieving a viable development candidate suitable for further development. These may include clinician(s) expert in the disease area of interest, regulatory expert(s), a project manager and/or other consultants
- The PI and key members of the research team are committing sufficient effort to the proposed research to maximize timely achievement of the research goals. CIRM will instruct reviewers to give added consideration to the PI's qualifications where the PI commits effort in excess of 10% to the proposed research.
- The PI has developed a budget that is appropriate for the proposed research.

### **D. Collaborations, Resources and Environment**

- Resources critical to the success of the project are available through: 1) the applicant institution; 2) advisors, consultants or subcontractors; or 3) collaborations including public-private collaborations or collaborative funding opportunities.
- Any proposed collaboration is critical and integral to the success of the research.
- The environment facilitates the interactions that enhance the probability of success of the proposed research.
- There is adequate evidence of institutional support for the PI and for translational research.

## VI. APPLICATION PROCEDURE

Applicant institutions and PIs must follow these instructions for submitting a Candidate Nomination Form, Letter of Intent, and Application for the CIRM Early Translational Research Awards. Applications will only be accepted from PIs who 1) have been officially nominated on a Candidate Nomination Form by their host institution and 2) have submitted a Letter of Intent that was accepted by CIRM.

### A. Candidate Nomination Form (CNF)

Applicant institutions must submit to CIRM a single CNF using the CNF template provided at <http://www.cirm.ca.gov/grants/default.asp>. The CNF must list the name, degree and employment title of each of the PIs the institution wishes to nominate for these awards. CIRM will accept only one CNF from each institution; this form must be signed by an institutional official authorized to nominate candidates on behalf of the entire institution. The signed original CNF must be received by CIRM no later than **5:00 PM (PDT) on October 15, 2008. No exceptions will be made.**

Mail the signed original CNF to:

Early Translational Research Award Candidate Nomination Form  
California Institute for Regenerative Medicine  
210 King Street  
San Francisco, CA 94107

### B. Letter of Intent (LOI)

Each PI nominated by an applicant institution must submit a LOI using the LOI template provided at <http://www.cirm.ca.gov/grants/default.asp>. The LOI should concisely describe the goal of the proposed research and technical approaches that will be used to achieve the goal. **Completed LOIs should be sent as an email attachment to [Early\\_Translational\\_LOI@cirm.ca.gov](mailto:Early_Translational_LOI@cirm.ca.gov). and must be received by CIRM no later than 5:00PM (PST) on October 15, 2008. No exceptions will be made.** Letters of intent are non-binding, but CIRM will not accept an application if the LOI was not received by the stated deadline.

### C. Application Instructions

Application forms will be available online by September 17, 2008. The application for CIRM Early Translational Research Awards consists of four parts:

Part A: Application Information Form (Adobe PDF template provided at <http://www.cirm.ca.gov/grants/default.asp>.)

Part A includes: Abstract, Public Abstract, Statement of Benefit to California, Key Personnel, and Budget (section numbers 1, 2, 3, 4 and 5 below).

Part B: Early Translational Research Award Research Proposal (MS Word template provided at <http://www.cirm.ca.gov/grants/default.asp>.)

Part B includes: Scientific Basis, Rationale and Impact; Project Objective; Specific Aims, Milestones, and Timeline; Research Design and Methods; Preliminary Data and Feasibility; Collaborations, Resources and Environment; and References (section numbers 6-12 below).

Part C: Biographical Sketches for Key Personnel (MS Word template provided at <http://www.cirm.ca.gov/grants/default.asp>) and letters of collaboration.

Part D: Related Business Entities (Adobe PDF template provided at <http://www.cirm.ca.gov/grants/default.asp>.)

In order to comply with the Conflict of Interest policies under which CIRM operates, Part D must be submitted by the applicant organization for any application that, if awarded, would fund a for-profit organization that is either: 1) the applicant organization; 2) a subcontractor; or 3) the employer of a co-investigator, consultant or subcontractor (section number 13 below). This applies whether funding comes from CIRM or from the State of Victoria (under the collaborative funding opportunity).

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 choosing the development candidate or bottleneck, and the scientific context of the research questions and hypotheses being addressed.

B. Unmet Medical Need/Impact: For development candidate projects: Describe the unmet medical need that the project will address in which the use of human stem cells can offer an advantage over other approaches. Summarize the impact that the proposed development candidate would have on the target disease or injury, if it were successfully developed.

For bottleneck projects: Describe the critical research bottleneck to advancing novel, effective cell therapies to the clinic. Summarize how the proposed solution(s) will enable more efficient translation of stem cell based discoveries.

C. Specific Aims: Describe the specific aims of the proposed research.

D. Milestones: Summarize the milestones to be achieved within any given budget year. 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.

2. *Public Abstract (up to 3000 characters in Part A)*

Briefly describe in lay language the proposed research and how it will, directly or indirectly, contribute to the identification of a development candidate or overcome a bottleneck to translation. This Public Abstract will become public information;



therefore, do not include proprietary or confidential information or information that could identify the applicant and/or applicant institution.

3. *Statement of Benefit to California (up to 3000 characters in Part A)*

Describe in a few sentences how the proposed research will benefit the state of California and its citizens. This Statement of Benefit will become public information; therefore, do not include proprietary or confidential information or information that could identify the applicant and/or applicant institution.

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

List all key personnel and their roles on the project. Key personnel are defined as individuals who contribute to the scientific development or execution of the project in a substantive, measurable way, whether or not they receive salaries or compensation under the grant. Key personnel may include any technical staff, trainees, co-investigators (collaborators), or consultants who meet the above definition. For CIRM/Victoria team applications, key personnel sponsored by the Victorian Government must also be listed in this section. A minimum of one percent effort is required for each key person (including key personnel funded by the State of Victoria) except the PI, who must invest a minimum percent effort of 10%. For each key person listed, except for technical staff and students, provide a 2 page biographical sketch using the template provided. The biographical sketch should highlight relevant research and product development experience, including team leadership and/or participation. Include relevant publications, patent applications and regulatory filings.

5. *Budget (included in Part A)*

Provide all budget information requested in the budget section of the Application Information Form. For CIRM/Victoria collaborations, the funding requested from the Victorian Government (total and per year) 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.

Allowable costs for research funded by CIRM are detailed in the CIRM Grants Administration Policy (GAP, see section XI.A. of this RFA). For CIRM/Victoria teams, allowable costs for research funded by Victoria may differ. Guidance will be provided separately by Victoria (see Section X 'Contacts'. 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 work in California. (CIRM is not requesting salaries for individual Victorian key personnel.) The total salary requested by the PI must be based on a full-time, 12-month appointment commensurate with the established salary structure of the applicant's institution. Institutions may request stipend, health insurance and allowable tuition and fees as costs for trainees. Administrative support salaries are expected to be covered exclusively by allowed Indirect Costs.

- **Supplies**

Supply expenses may include specialized reagents, reimbursement costs for human tissue donations, 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 Research Awards are required to attend an annual CIRM-organized meeting 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 XI.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. 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. *Scientific Basis, Rationale and Impact (up to 2 pages in Part B)*

For applications focused on a development candidate, summarize the supportive evidence for disease modifying activity of the proposed development candidate. Supportive evidence includes publications or preliminary data demonstrating the relevance to disease of the target of the proposed development candidate and the relevance of the approach embodied by the development candidate to impact the disease target. Address why human stem cells are necessary or advantageous to the proposed research compared to other approaches. Explain how the proposed research will lead to a development candidate that addresses an unmet medical need. Comment on the significance of the impact on disease, injury or medical practice, if the proposed development candidate were successfully developed and commercialized. State how the proposed concept meets CIRM's primary goal for these Early Translational Research Awards, advancing a stem cell-derived therapy or diagnostic toward the clinic.

For applications focused on a bottleneck, summarize the context and background and the supportive evidence for the proposed research. Justify the underlying hypothesis of the proposed research. Summarize how the proposed research plan overcomes a critical bottleneck to the advancement of effective, novel cell therapies to the clinic. Where relevant, illustrate how the proposed research will utilize human stem cells to develop more predictive disease models to enable the advancement of better candidates into clinical testing.

Within the bottleneck category, CIRM will instruct reviewers to give special consideration to proposals for research on bottlenecks to the development of novel, pluripotent cell-derived therapies.

7. *Project Objective (up to 1 page in Part B)*

For development candidate proposals, provide a target profile for the proposed development candidate. The target profile reflects key features required/desired for

the proposed development candidate. It guides preclinical and clinical development, is continually refined and becomes the product label upon commercialization. Very briefly, address each of the following aspects of a target profile: 1) Description; 2) Indication(s)/Target population; 3) Activity (*in vitro/in vivo*)/Efficacy Endpoint (patients); 4) Safety/Contraindications; 5) Route; and 6) Regimen.

For bottleneck proposals, describe the success criteria that will be used to assess whether the bottleneck has been overcome. Success criteria must be well described, quantitative, meaningful, and scientifically justifiable.

8. *Specific Aims, Milestones, and Timeline (up to 2 pages in Part B)*

Describe the specific aims of the research. Enumerate annual milestones for the project, ideally for each specific aim, which are critical to achieving either a development candidate or the success criteria for overcoming a bottleneck. Milestones should be measurable, scientifically justifiable, feasible, and technically sound. Provide and justify a realistic timeline for completing each specific aim and the related milestone(s) and for achieving the goal of the research (a development candidate or the success criteria for overcoming a bottleneck).

Milestone achievement is an important indicator of progress and a major factor in review of yearly progress reports. Insufficient progress through milestones may result in loss of further funding.

9. *Research Design and Methods (up to 5 pages in Part B)*

Describe concisely, but in sufficient detail to permit evaluation of the merit of the research, the experimental plan to achieve the project objective. The experimental plan for a development candidate must address activities necessary to enable consideration for subsequent preclinical development (see Appendix A). Describe the methods and techniques to be employed to achieve the specific aims and milestones specified in the proposal. Enumerate criteria for determining achievement of milestones and aims. Identify novel or risky aspects of the research, anticipated pitfalls, and provide a description of alternative approaches should the initial approaches fail.

For applications from CIRM/Victoria teams, it is incumbent upon the applicants to clearly delineate the work that will be performed in California and funded by CIRM from the work that will be performed in Victoria and funded by the Victorian Government. This delineation is essential for review of the research plan and the appropriateness of the budget.

10. *Preliminary Data and Feasibility (up to 2 pages in Part B)*

For development candidate proposals, provide preliminary and/or other supporting data that substantiate the relevance to disease of the target of the proposed development candidate and the relevance of the approach embodied by the development candidate to impact the disease target. Provide preliminary data or other supporting data for the proposed development candidate and for successful application of the technologies and methodologies proposed for achieving the development candidate.

For bottleneck proposals, provide preliminary or other supporting data that are compelling and supportive of the proposed concepts, hypotheses and/or approaches leading to the resolution of the bottleneck.

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 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. Provide evidence of institutional support for the PI and for translational research. If applicable, provide evidence for the identification, availability and accessibility of adjunct personnel, beyond the core research team, that may be required for the success of the project. If advisors, consultants or subcontractors will provide expertise or resources critical to the success of the project, summarize their credentials and track record.

When collaborations are part of the research plan, describe the nature of the collaboration and explain why it is critical and integral to the success of the project. For CIRM/Victoria teams, the applicants must clearly describe the unique contribution of the Victorian research component, and how the collaboration enhances or synergizes the research agenda.

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

List all references used in the body of the proposal.

13. *Related Business Entities (Part D)*

Applicants must provide this 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. This applies whether funding comes from CIRM or from the State of Victoria (under the collaborative funding opportunity). Include the following for each such for-profit organization.

- 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).

## **VII. SUBMITTING AN APPLICATION**

Applications will only be accepted from PIs who 1) have been officially nominated on a CNF by their host institution and 2) have submitted a Letter of Intent (LOI) that was accepted by CIRM.

The application for CIRM Early Translational Research Awards consists of four parts:

Part A: Application Information Form (Adobe PDF template provided at <http://www.cirm.ca.gov/grants/default.asp>.)

Part B: Early Translational Research Award Research Proposal (MS Word template provided at <http://www.cirm.ca.gov/grants/default.asp>.)

Part C: Biographical Sketches for Key Personnel (MS Word template provided at <http://www.cirm.ca.gov/grants/default.asp>.) and letters of collaboration.

Part D: Related Business Entities (Adobe PDF template provided at <http://www.cirm.ca.gov/grants/default.asp>.)

All four parts (three parts when Part D is not applicable) of the application for CIRM Early Translational Research Awards (see section VI.C. of this RFA) must be submitted together and received by CIRM no later than **5:00 PM (PST) on November 20, 2008, in both electronic form and in hard copy (a signed original and five copies). No exceptions will be made.** Send electronic copies of all parts of the application as attachments in a single email to [Early\\_Translational\\_Awards@cirm.ca.gov](mailto:Early_Translational_Awards@cirm.ca.gov). In addition to the electronic submission, candidates must submit an original copy of the application (consisting of Parts A-D) signed by both the PI and the institution's Authorized Organizational Official (AOO), plus 5 copies of the full application (preferably double-sided) to:

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

## VIII. SCHEDULE OF RECEIPT AND ANTICIPATED REVIEW

<b>Receipt of Candidate Nomination Forms and Letters of Intent</b>	<b>5:00 PM PDT on October 15, 2008</b>
<b>Receipt of Applications</b>	<b>5:00 PM PST on November 20, 2008</b>
<b>Anticipated Review of Applications by Grants Working Group (GWG)</b>	<b>February, 2009</b>
<b>Anticipated Review and Approval by ICOC</b>	<b>April, 2009</b>
<b>Earliest Funding of Awards</b>	<b>Summer, 2009</b>

## IX. REVIEW AND AWARD PROCESS

The CIRM Scientific and Medical Research Funding Working Group (the Grants Working Group, or GWG) will review applications for the CIRM Early Translational Research Awards. The GWG consists of fifteen basic and clinical scientists from institutions outside California, seven patient advocates who are members of 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 ICOC was established by the California Stem Cell Research and Cures Act (Proposition 71) to oversee CIRM and makes all final funding decisions. The composition of the ICOC can be viewed at <http://www.cirm.ca.gov/faq/pdf/Members.pdf>.

The scientists on the GWG will review the applications and score them according to scientific and technical merit applying the criteria described in Part V.

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

- Appropriate balance between risk and feasibility.
- Appropriate balance between applications addressing development candidates and applications addressing bottlenecks, particularly bottlenecks to translation of cell therapies derived from human pluripotent stem cells.
- Where relevant, the appropriate balance and range of diseases and genetic diversity.
- Other considerations from the perspective of patient advocates.

The GWG's final recommendations for funding will then be forwarded to the ICOC, which makes all final funding decisions.

## **X. CONTACTS**

For information on this RFA:

Rosa Maria Canet-Avilés, Ph.D.  
Scientific Officer  
California Institute for Regenerative Medicine  
Email: [rcanet-aviles@cirm.ca.gov](mailto:rcanet-aviles@cirm.ca.gov)  
Phone: (415) 396-9123

For programmatic information:

Patricia Olson, Ph.D.  
Director of Scientific Activities  
California Institute for Regenerative Medicine  
Email: [polson@cirm.ca.gov](mailto:polson@cirm.ca.gov)  
Phone: (415) 396-9116

For information on CIRM/Victoria teams -  
In California

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## **XI. OTHER REQUIREMENTS**

### **A. CIRM Grants Administration Policy**

CIRM's Grants Administration Policy (GAP) for Academic and Non-Profit Institutions (Non-Profit GAP) and the Interim GAP for For-Profit Institutions (For-Profit GAP) serve as the standard terms and conditions of grant awards issued by CIRM. All research conducted under this award must comply with the stated policy. The Non-Profit GAP can be found on the CIRM website at [http://www.cirm.ca.gov/reg/pdf/reg100500\\_policy.pdf](http://www.cirm.ca.gov/reg/pdf/reg100500_policy.pdf). The Interim For-Profit GAP can be found at <http://www.cirm.ca.gov/policy/policy.asp>. Funding from year to year will depend on scientific progress through the proposed milestones.

### **B. Intellectual Property Regulations**

Non-profit organizations are governed by intellectual property regulations found at [http://www.cirm.ca.gov/reg/pdf/IP\\_Regs\\_100300.pdf](http://www.cirm.ca.gov/reg/pdf/IP_Regs_100300.pdf). For-Profit organizations are governed by intellectual property regulations found at (<http://www.cirm.ca.gov/faq/pdf/ForProfitOrg.pdf>). (Additional requirements will apply to CIRM/Victoria teams. Joint applicants please contact the relevant Californian and Victorian contacts listed above for further details.)

### **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 which can be viewed at: <http://www.cirm.ca.gov/reg/default>. While these regulations prohibit donors of gametes, embryos, somatic cells or human tissue from receiving valuable consideration for their donation, they do allow for reimbursement for permissible expenses as determined by an Institutional Review Board (IRB) (Title 17, California Code of Regulations, section 100080). "Permissible Expenses" means necessary and reasonable costs directly incurred as a result of donor participation in research activities and may include costs such as those associated with travel, housing, child care, medical care, health insurance and actual lost wages. For research activities proposing to obtain gametes, embryos, somatic cell or tissue from human subjects,

CIRM requires the candidate to submit, at the time of application, their reimbursement policy describing how they intend to calculate permissible expenses.

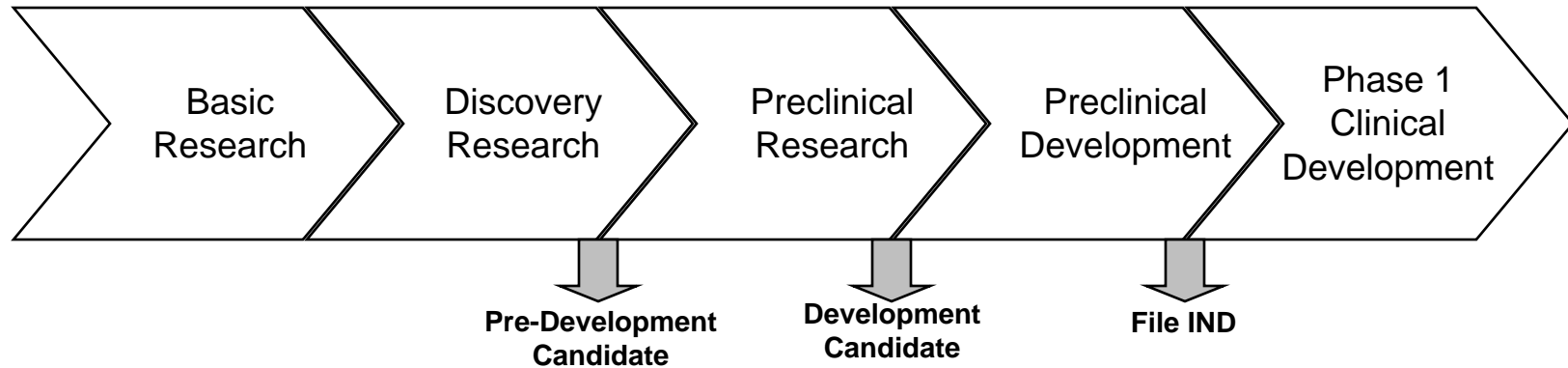


# Appendix A: Representative Activities in Development of a Cell Therapy, a Small Molecule Drug or Biologic (Monoclonal Antibody)



*Examples of activities considered in-scope of the Early Translational RFA*

# Representative Cell Therapy Development Activities

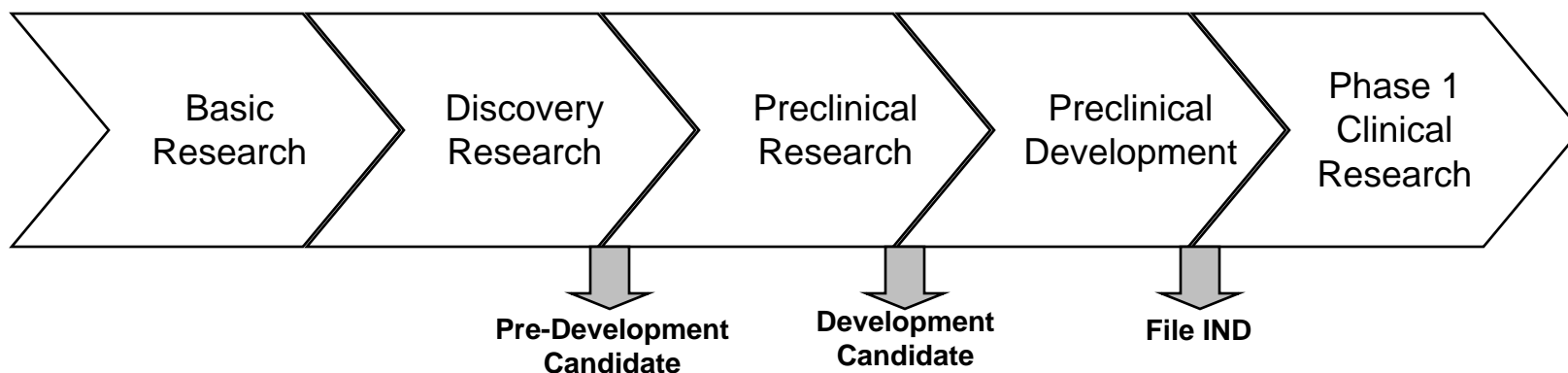


- Target identification
- Target validation/ MOA
- Evidence of disease association, biological validation & therapeutic value

- |   |  |
|---|--|
| <ul style="list-style-type: none"> <li>▪Simplify, standardize and scale stem cell growth</li> <li>▪Develop reproducible methods to differentiate cells, if needed</li> <li>▪Develop parameters to characterize cell populations</li> <li>▪Initial evidence of disease-modifying activity</li> </ul> | <ul style="list-style-type: none"> <li>▪Characterize and define efficacy, potency and safety of cell population</li> <li>▪Reproducible disease modifying activity in relevant models</li> <li>▪Develop methods to deliver cells to target tissues</li> <li>▪Develop GMP Master and Working Cell Banks</li> <li>▪Develop clinical strategy &amp; create development plan</li> </ul> |
|---|--|

- Develop formulation and GMP scalable production methods
- Produce GLP/GMP cells (and reagents)
- Perform IND-supporting pharmacology and PK/ PD
- Perform IND-supporting safety
- Prepare clinical protocol. recruit sites. IRB approvals
- Prepare IND
- Perform pilot safety studies
- Perform dose/ delivery/ regimen studies
- Demonstrate evidence of biological and/or therapeutic effect

# Representative Small Molecule Development Activities



- Target identification
- Target validation/ MOA
- Evidence of disease association, biological validation & therapeutic value
- Screening amenability
- Screening strategy

- Produce reagents & develop assays for HTS and secondary screening
- Perform HTS and secondary screens
- Identify and characterize active compounds
- Evaluate potency, selectivity, & mechanism of action
- Initial evidence of disease-modifying activity

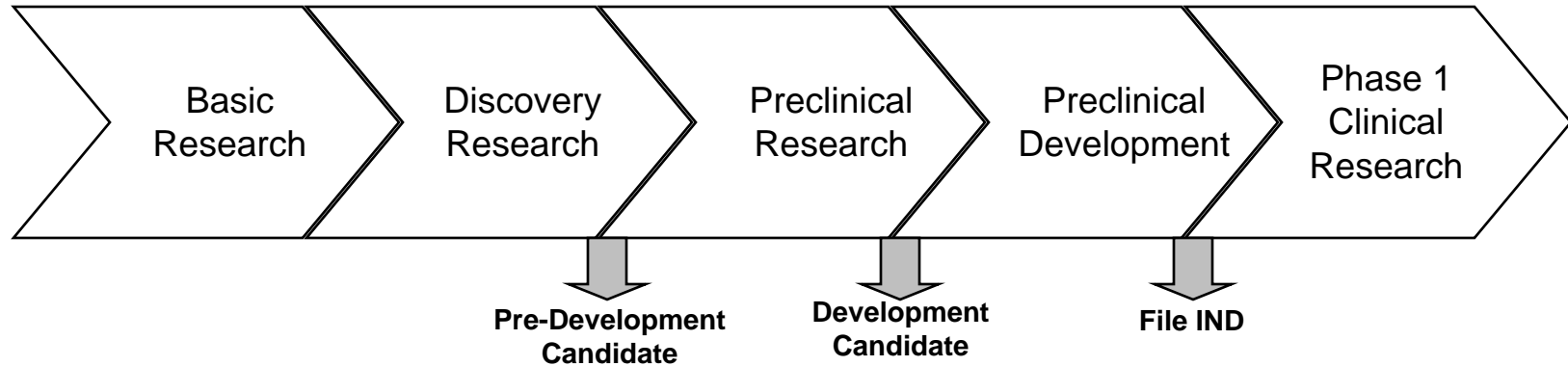
- Conduct lead optimization
- Define in vivo efficacy, potency and safety of lead compound(s)
- Reproducible disease modifying activity in relevant models
- Verify mechanism of action
- Initial tox screen, PK/PD, ADME
- Identify potential drug-drug interactions
- Develop clinical strategy & create development plan

- Develop formulation and scalable GMP production methods
- Produce GLP/GMP drug
- Perform IND-supporting pharmacology and PK/PD, ADME
- Validate human drug-level assays
- Perform IND-supporting safety
- Prepare clinical protocol. recruit sites. IRB approvals

- Perform pilot safety studies
- Perform dose/delivery/ regimen studies
- Demonstrate evidence of biological and/or therapeutic effect

- Prepare IND

# Representative Monoclonal Antibody Development Activities



- Target identification
- Target localization, prevalence, validation
- Evidence of disease association, biological validation & therapeutic value
- Mab generation and screening strategy

- |   |   |
|---|---|
| <ul style="list-style-type: none"> <li>•Develop reagents and screening assays</li> <li>•Generate &amp; screen for candidate Mabs</li> <li>•Identify, produce and characterize candidate Mabs</li> <li>•Evaluate potency, selectivity (tissue &amp; species cross reactivity), and mechanism of action</li> <li>•Initial evidence of disease-modifying activity</li> </ul> | <ul style="list-style-type: none"> <li>•Characterize and define efficacy, potency and safety of candidate MAb</li> <li>•Reproducible disease modifying activity in relevant models</li> <li>•Optimize candidate Mab as required, make GMP producer line</li> <li>• Develop Master and Working Cell Banks</li> <li>•Initial PK/PD</li> <li>•Develop clinical strategy &amp; create development plan</li> </ul> |
|---|---|

- Develop formulation and scalable GMP production methods
- Produce GLP/GMP MAb
- Perform IND-supporting pharmacology and PK/PD
- Perform IND-supporting safety
- Prepare clinical protocol. recruit sites. IRB approvals
- Prepare IND

- Perform pilot safety studies
- Perform dose/delivery/ regimen studies
- Demonstrate evidence of biological and/or therapeutic effect