RFA 13-02: CIRM Basic Biology Awards V

I. Purpose

Investigations of the basic mechanisms underlying stem cell biology, cellular plasticity, and cellular differentiation form the foundation of future translational and clinical advances. Despite considerable recent progress, many fundamental issues related to the control of stem cell fate and cellular reprogramming, especially with regard to human cells, remain to be resolved. The purpose of the CIRM Basic Biology Initiative is to support basic research that enables the realization of the full potential of human stem cells and reprogrammed cells for therapies and for biomedical innovation.

II. Objectives

The objective of the Basic Biology Awards V RFA is to foster cutting-edge research tackling significant, unresolved issues in human stem cell biology, with emphasis on unraveling the key molecular and cellular mechanisms that dictate cell fate. Due to the urgency and breadth of CIRM's mission, the Basic Biology Awards V will comprise two categories of research, each with a unique potential to advance the stem cell field. The first category, or "track", is highly similar to previous iterations of the CIRM Basic Biology Awards and will target rigorous investigations using human pluripotent stem cells, adult stem cells, reprogrammed cells and/or their differentiated derivatives to elucidate fundamental molecular and cellular mechanisms pertinent to stem cell biology and/or regenerative medicine. Studies utilizing disease- or patient-specific human stem (or reprogrammed) cells as in vitro models to gain novel insights about disease mechanisms and other medically relevant processes will also be supported through this track. The second category of awards will target concise, exploratory research projects aimed at testing highly novel hypotheses that if proven, have the potential to dramatically and rapidly advance the stem cell field. Through this second track, CIRM seeks to enable transformative discoveries by fostering a scientific environment that nurtures high risk, high gain pursuits.

A. Award Tracks

Under this RFA , an applicant investigator may apply through one of two possible tracks**:**

Track 1) The **Fundamental Mechanisms Awards** will target rigorous studies elucidating basic molecular and cellular mechanisms underlying key human stem cell properties and behaviors. These awards will also support studies utilizing human stem cell- or reprogrammed cell-based in vitro models to gain novel insights about disease mechanisms and other medically relevant processes.

Track 2) **The Exploratory Concepts Awards** will target stem cell or reprogrammed cell studies testing highly novel hypotheses that if proven, would challenge dogma and result in a transformative discovery for the stem cell field.

B. Project Scope

While both types of Basic Biology Awards support basic research into stem cell biology and related science, the scope and priorities differ between the tracks.

For applications to be responsive to this RFA, the following criteria must be met:

Track 1) Fundamental Mechanisms Awards

- Studies must utilize human stem cells, reprogrammed cells or their derivatives, and these cells must be necessary to achieve the outcomes of the proposed research
- Studies must target key cellular and molecular mechanisms with relevance to stem cell and/or related biology
- For those studies proposing to elucidate disease mechanisms using in vitro stem cell or reprogrammed cell models, the following criteria must be met:
    i. The human stem cell lines or reprogrammed cells to be utilized in the study have already been derived and are ready for testing; and
    ii. A relevant phenotype has been identified and validated in these lines (published reference or documentation in the form of preliminary data).
- Supportive preliminary data have been generated

Track 2) Exploratory Concepts Awards

- Stem cells, reprogrammed cells or their derivatives are necessary to achieve the outcomes of the proposed research
- Studies may utilize human cell models and/or vertebrate animal model systems, with compelling justification for the use of vertebrate animal model systems
- Studies must propose feasible approaches for testing highly novel concepts related to stem cell biology, direct reprogramming or determination of cell fate and identity that if proven, would challenge current dogma or answer longstanding questions in basic human stem cell biology
- Preliminary data need not have been generated but may prove helpful

It is the responsibility of the applicant Principal Investigator to determine which of the two tracks is most relevant for the proposed research, as only one preliminary application may be submitted per Principal Investigator.

Research that is **outside the scope** of the Basic Biology Awards and therefore **unresponsive** includes, but is not limited to:

- Developing new methodologies for generating induced pluripotent stem cells (iPSC) or making them more efficiently
- Deriving new iPSC lines (or reprogrammed cells) from patient cells and performing descriptive studies (e.g. differentiation assays, profiling experiments) in order to identify a phenotype
- Screening chemical or biological libraries for the purpose of identifying/optimizing therapeutic compounds
- Translational Research, i.e. determining feasibility of cell populations, drugs or biologics for therapeutic efficacy; studying animal models of disease to identify therapeutics
- Studies using non-vertebrate model systems

Inclusion of such out-of scope activities **may result in a project being deemed ineligible.**

C. Priorities/Areas of Focus

Fundamental Mechanisms Awards

CIRM is seeking and will prioritize proposals submitted through the Fundamental Mechanisms track in the following areas of focus:

- Characterization of molecular determinants of human stem (or reprogrammed) cell fate decisions during differentiation, including:

  − Cellular and molecular characterization of specific cell populations that emerge during differentiation, from precursors and lineage intermediates to mature, terminally differentiated cell types

  − Molecular basis of lineage specification towards mature adult, metabolically functional cell types, tissues and mini-organs

  − Role of the endogenous and/or engineered microenvironment in the regulation of stem cell fate, behavior, and the properties of stem cell derivatives

  − Mechanisms underlying cellular diversity in stem cell-derived populations

- Cellular and molecular basis of disease or injury: use of **existing/established in vitro** human stem (or reprogrammed) cell based models **with validated**

phenotypes to elucidate pathological or regenerative mechanisms related to injury or disease (***Note: See Section B for details on responsiveness criteria for this area of focus)***; investigators using such systems to study childhood-related neurological disorders are particularly encouraged to apply

- Studies to understand and address immunogenicity of human stem cell derivatives in transplantation; mechanisms by which immune suppression and tolerance approaches affect human stem cells and their derivatives in vitro or in vivo

- Molecular mechanisms relating to stem cell properties, e.g. self-renewal, developmental potential, aging, genomic/genetic/epigenetic instability, and tumorigenicity in human pluripotent stem cells (hPSC) or human adult stem cells

Exploratory Concepts Awards

Hypotheses to be tested through the Exploratory Concepts Awards must be directly related to stem cell biology, direct reprogramming or determination of cell fate and identity. Rather than specifying areas of focus, CIRM expects the Principal Investigator to provide compelling arguments for the novelty and transformative potential of the anticipated outcomes.

III. Award Information

Under this Request for Applications (RFA), CIRM intends to commit up to $40 million to support up to 30 awards, each having been submitted through either the 1) Fundamental Mechanisms track or 2) Exploratory Concepts track.

1) Fundamental Mechanisms Awards will be funded for up to 3 years, with justifiable direct project costs of up to $250,000 per year. CIRM anticipates that approximately 2/3 of all Basic Biology Awards V will be issued through the Fundamental Mechanisms track.

2) Exploratory Concepts Awards will be funded for up to 2 years, with justifiable direct project costs of up to $200,000 per year. For these awards, no-cost extensions will not be permitted. CIRM anticipates that approximately 1/3 of all Basic Biology Awards V will be issued through the Exploratory Concepts track.

A summary of key differences between the tracks is presented below in **Table I**.

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

Progress on these awards is important to CIRM. Continued funding is contingent upon timely progress as outlined in the project plan and timeline established under the Notice of Grant Award (NGA). For all awards, CIRM reserves the right to negotiate funded project activities, prior to issuance of the Notice of Grant Award (NGA), subject to renegotiation annually and/or based on progress. CIRM may also wish to review for compliance with CIRM's policies and regulations key contract/agreements that are critical to the success of the project.

Table I. Distinguishing Features of the Basic Biology Awards V by Track

Track	1. Fundamental Mechanisms	2. Exploratory Concepts
Project Goals	Elucidating cellular and molecular mechanisms	Exploring novel ideas with transformative potential
Cell Use	Human cells	Human cells and/or nonhuman vertebrate models, with compelling justification
Preliminary Data	Required	Not required, but helpful
Award Details	3 years, $250,000/yr (direct)	2 years, $200,000/yr (direct)
Scope/Priorities	See Section IIB,C	See Section IIB,C

IV. Award Mechanism

CIRM expects to fund approved proposals from non-profit and for-profit institutions (separately or in collaborations), through grants. Institutions will be subject to all terms of CIRM's Intellectual Property and Revenue Sharing Requirements for Non-Profit and For-Profit Grantees (17 Cal. Code Regs. § 100600 et seq.).

V. Eligibility

A. Institutional Eligibility

Both non-profit and for-profit organizations are welcome to apply. At the time of the Preliminary Application (PreApp) deadline, the applicant organization must be located in California (that is, the organization must have employees who are conducting business or operations at a location in California). At the time of funding, the applicant organization must be conducting or managing research that is taking place in California. If these requirements are not met, CIRM may terminate all further action on the application.

"Non-profit 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".

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

B. Principal Investigator (PI) Eligibility

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 PreApp deadline, the PI must:

- Be an independent investigator in California at a Non-profit applicant institution, or have an equivalent position and be an employee in California (at least 50-percent time) of a For-profit applicant institution
- Have documented authority from the applicant institution to staff the proposed project
- Have documented commitment from the applicant institution to provide laboratory space and shared resources sufficient to carry out the proposed research.

In order to broaden the pool of applicants engaged in stem cell research and to encourage leveraging of CIRM's investment, CIRM is limiting the number of active CIRM research awards in which an investigator may participate as PI or Co-PI. This RFA is **not open** to investigators as a PI who is already a PI or Co-PI on 3 or more active or awarded CIRM awards as of June 27, 2013, the deadline for submission of the full application. This limit includes all CIRM awards that have been approved or are active and have not yet closed out, with the exception of the following CIRM RFAs/PAs: Shared Research Labs; Major Facilities; Research Training Awards I & II; Bridges to Stem Cell Research; Disease Team Planning Awards; Disease Team Therapy Development Part I Planning Awards; and Tissue Collection for Disease Modeling Awards or Conference Grants.

C. Co-Principal Investigator (Co-PI) Eligibility

This RFA does not allow designation of a Co-Principal Investigator (Co-PI).

D. Percent Effort Requirements

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

E. Project Eligibility

Projects that are out of scope or include activities defined as unresponsive in section II.B. may be considered ineligible for consideration under the Basic Biology Awards V RFA.

F. Extraordinary Exceptions

The President of CIRM has the discretion to permit exceptions to any eligibility requirement specified in this Section V. The President may permit an exception if he determines, in his individual discretion, that the applicant has demonstrated that the exception would preserve an important research opportunity or make a critical contribution to one of CIRM's mission objectives. Exceptions must further the objectives of this RFA and comply with the requirements of Proposition 71 as well as California state regulations, including the Grants Administration Policy (see Section XIII of this RFA).

If CIRM determines that an application does not meet the eligibility requirements, CIRM may terminate all further action on the application. Applicants who will need an exception are strongly encouraged to request it at least 30 days before the relevant application deadline. To request an exception, or for assistance in determining whether one is necessary, contact the CIRM staff listed in Section XII.

VI. Collaborative Funding Partners

CIRM has established a program with several other agencies that fund stem cell and regenerative medicine research. Through this Collaborative Funding Partner (CFP) program, California-based Principal Investigators (PIs) can collaborate with a Funding Partner PI ("Partner PI") from a Funding Partner applicant institution ("partner applicant institution") eligible for funding from one of CIRM's CFPs to bring important additional resources to the project. If a collaboratively funded proposal is approved (a "CIRM/CFP Award") CIRM will fund all project work done within the State of California and the CFP will fund all project work within its jurisdiction. For this RFA, the Chinese Ministry of Science and Technology (MOST), Institute for Stem Cell Biology and Regenerative Medicine, India (inSTEM) and the United States National Institute of Health (NIH) are each participating as a CFP.

To apply for a collaboratively funded project involving CIRM and a CFP, applicants must satisfy both the CIRM requirements and any additional requirements put forth by the CFP. For more details on these requirements, please see Appendices A, B and C.

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

Before funding contracts are signed, successful CIRM/CFP applicant teams must obtain all necessary approvals for animal protection, human subject protection, and use of human embryonic stem cells, unless the approval is not required to initiate the

award. CIRM and the CFP will monitor compliance with approval procedures required in their respective jurisdictions.

Both CIRM and the CFP may be involved in the management/oversight of the CIRM/CFP Award, by participating in mutually agreed upon joint award administration activities. These activities may include but are not limited to participation in progress monitoring via progress reports.

VII. Notification Regarding Disclosure of Information

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

VIII. Application and Evaluation Process

Submission of an application for this RFA involves a two-step process. Any qualified applicant PI may **submit a single brief Preliminary Application (PreApp) through either** the **Fundamental Mechanisms track or** the **Exploratory Concepts track, but not both.** Applicants submitting the most promising, competitive and responsive PreApp proposals will be invited to submit a detailed, full Application. All other applicants will be deferred with the opportunity to apply in response to a future RFA. CIRM expects to reissue a Basic Biology Awards RFA within the next 12-15 months.

PreApps should emphasize the overall impact of the proposed work and address the review criteria for the PreApp described in Section IX. PreApps will be evaluated by scientific specialists from outside California who are experts in specific areas of research described in the PreApp and by CIRM scientific staff, based on the scientific review criteria described in Section IX below. **The research project and Principal Investigator (and Partner PI, if applicable) proposed in the full Application must be the same as those described in the PreApp**.

Full Applications will be evaluated by the CIRM Grants Working Group (GWG), which is composed of fifteen scientific experts from outside California, seven patient advocate members of CIRM's governing board, and the Chair of the governing board. The list of scientific members who may participate in the GWG review can be found at http://www.cirm.ca.gov/GrantsWkgGrpMembers. The composition of the ICOC can be viewed at http://www.cirm.ca.gov/GoverningBoard.

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

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

IX. Review Criteria

A. Preliminary Application

The goal of the PreApp review process is to identify the most promising, competitive, and responsive proposals. PreApps will be evaluated in several key areas according to award track, as indicated below.

A.1 PreApp Review Criteria: Fundamental Mechanisms Awards (For Exploratory Concepts Awards, see section IX.A.2)

PreApps submitted through the Fundamental Mechanisms track will be evaluated in three key areas: 1) Significance and Innovation; 2) Feasibility and Experimental Design; and 3) Responsiveness to the RFA. The quality of appropriate preliminary results is an important factor in assessing feasibility of the proposals.

1. Significance and Innovation
    - Major Unsolved Problem: The project addresses a major unsolved problem in stem cell biology or regenerative medicine (see priorities/areas of focus for this Track in section II.B.1).
    - Innovative Project: The research explores novel mechanisms, pathways or cellular events with potential to significantly advance the field. The applicant employs innovative or creative approaches.
    - Focus on Mechanism: The project is focused on elucidating basic molecular or cellular mechanisms.
    - Logical Rationale: The rationale is logical and scientifically sound.
    - Major Impact: If successful, the project would have a major impact on potential applications of stem cell research and regenerative medicine, rather than incrementally advancing the field.

2. Feasibility and Experimental Design
    - Sound Approach: The overall experimental approach is sound and likely to produce meaningful results.
    - Logical and Achievable Aims: The specific aims are logical and well organized with achievable milestones or timeline provided for the 3-year timeframe.

- Compelling Preliminary Results: The scientific evidence and preliminary results (as summarized by the applicant) are well understood, substantive, compelling and supportive of the proposed concepts, hypotheses, and approaches.

3. Responsiveness to the RFA
   - Studies utilize human stem cells, reprogrammed cells or their derivatives, and these cells are necessary to achieve the outcomes of the proposed research (Use of animal models as an *assay* to test or evaluate human cells is considered within scope of this RFA).
   - Studies target key cellular and molecular mechanisms with relevance to stem cell and/or related biology (section IIB, C)
   - Stem cell or reprogrammed cell lines that are to be used for in vitro studies of disease/injury mechanisms have already been derived and a phenotype has been described (citation or preliminary data)

A.2 PreApp Review Criteria: **Exploratory Concepts Awards** (For Fundamental Mechanisms Awards, see section IX.A.1)

PreApps submitted through the Exploratory Concepts track will be evaluated in three key areas: 1) Novelty and Transformative Potential; 2) Feasibility and Experimental Design; and 3) Responsiveness to the RFA. Preliminary data are not required but may prove helpful for supporting rationale or feasibility.

1. Novelty and Transformative Potential
   - Novel Hypothesis: The project tests a highly creative or novel hypothesis.
   - Logical Rationale: The proposed hypothesis is based on solid reasoning or a logical premise.
   - Transformative Potential: A successful outcome would challenge dogma or resolve a critical bottleneck in the field of basic stem cell biology.

2. Feasibility and Experimental Design
   - Sound Design: The experimental approach will allow the proposed hypothesis to be successfully tested and enable meaningful conclusions to be drawn.
   - Logical and Achievable Aims: The experimental design includes logical aims or milestones that can be achieved within two years.

3. Responsiveness to the RFA
   - The proposed research is directly related to stem cell biology, direct reprogramming or determination of cell fate and identity.

- The proposed research utilizes human and/or vertebrate model cells/systems. Any use of nonhuman vertebrate models is compellingly justified as necessary and translatable to the human system.

B. Full Application

Review criteria for full Applications are dictated by the track through which the Application was submitted, as indicated below.

B.1 Review Criteria: Fundamental Mechanisms Awards (for Exploratory Concepts Awards, see section IX.B.2)

The full application will be evaluated in four key areas: 1) Significance and Innovation; 2) Feasibility and Experimental Design; 3) Qualifications of the Principal Investigator and Research Team; and 4) Responsiveness to the RFA. A key component for assessing feasibility will be the quality of the preliminary data. The specific criteria for review of applications (below) are elaborated from the standard review criteria described in the CIRM Grants Administration Policy (GAP, see section XIII.A of this RFA).

1. Significance and Innovation
   - Major Unsolved Problem: The project addresses a major unsolved problem in stem cell biology or regenerative medicine (see focus areas for this Track in section II.B.1).
   - Innovative Project: The research explores novel mechanisms, pathways or cellular events with potential to significantly advance the field. The applicant employs innovative or creative approaches.
   - Focus on Mechanism: The project is focused on elucidating basic molecular or cellular mechanisms.
   - Logical Rationale: The rationale is logical and scientifically sound.
   - Major Impact: If successful, the project would have a major impact on potential applications of stem cell research and regenerative medicine, rather than incrementally advancing the field.

2. Feasibility and Experimental Design
   - Sound Approach: The proposed research is carefully designed to give meaningful results.
   - Logical and Achievable Aims: The specific aims are logical and the research proposal well organized with achievable milestones and timeline provided over the 3-year timeframe.
   - Alternative Plans: Potential difficulties are acknowledged, and alternative plans are provided should the proposed strategies fail.
   - Research Facilities & Environment: Appropriate facilities are available to conduct the proposed research. The scientific environment is beneficial and conducive to project success.

- Compelling Preliminary Data: The scientific evidence and preliminary data are well understood, substantive, compelling and supportive of the proposed concepts, hypotheses, and approaches.

3. Principal Investigator (PI) and Research Team
   - Track Record: Evidence of prior success and track record supports the qualification of the PI to conduct the proposed research.
   - PI Commitment: The PI's level of commitment heightens the probability for success of the project.
   - Appropriate Team: The research team has appropriate expertise to conduct the proposed research. Any proposed collaboration(s) is critical and integral to the success of the research, and there is a reasonable plan to ensure communication amongst collaborators.

4. Responsiveness to the RFA
   - Studies utilize human stem cells, reprogrammed cells or their derivatives, and these cells are necessary to achieve the outcomes of the proposed research (Use of animal models as an *assay* to test or evaluate human cells is considered within scope of this RFA).
   - Studies target key cellular and molecular mechanisms with relevance to stem cell and/or related biology (section IIB, C)
   - Stem cell or reprogrammed cell lines that are to be used for in vitro studies of disease/injury mechanisms have already been derived and a phenotype has been described (citation or preliminary data)

B.2 Review Criteria: Exploratory Concepts Awards (for Fundamental Mechanisms Awards, see section IX.B.1)

The full application will be evaluated in four key areas: 1) Novelty and Transformative Potential; 2) Feasibility and Experimental Design; 3) Qualifications of the Principal Investigator and Research Team; and 4) Responsiveness to the RFA. Preliminary data are not required but may be helpful for supporting rationale or feasibility.

1. Novelty and Transformative Potential
   - Novel Hypothesis: The project tests a highly creative or novel hypothesis.
   - Logical Rationale: The proposed hypothesis is based on solid reasoning or a logical premise.
   - Transformative Potential: A successful outcome would challenge dogma or resolve a critical bottleneck in the field of basic stem cell biology.

2. Feasibility and Experimental Design

- Sound Design: The experimental approach will address the proposed hypothesis and enable meaningful conclusions to be drawn.
- Logical and Achievable Aims: The experimental design includes logical aims or milestones that can be achieved within two years.
- Research Facilities & Environment: Appropriate facilities are available to conduct the proposed research. The scientific environment is beneficial and conducive to project success.

3. Principal Investigator (PI) and Research Team
   - Track Record: Evidence of prior success and track record supports the qualification of the PI to conduct the proposed research.
   - PI Commitment: The PI's level of commitment heightens the probability for success of the project.
   - Appropriate Team: The research team has appropriate expertise to conduct the proposed research. Any proposed collaboration(s) is critical and integral to the success of the research, and there is a reasonable plan to ensure communication amongst collaborators.

4. Responsiveness to the RFA
   - The proposed research is directly related to stem cell biology, direct reprogramming or determination of cell fate and identity.
   - The proposed research utilizes human and/or vertebrate model cells/systems. Any use of nonhuman vertebrate models is compellingly justified as necessary and translatable to the human system.

X. Application Procedure

Applicants must follow these instructions for submission of a PreApp and, if invited, a full Application for the Basic Biology Awards V. Full applications will only be accepted from applicants who 1) submitted a PreApp and 2) are invited by CIRM to submit a full application.

A. Preliminary Application Forms

Each applicant must submit a PreApp using the forms and instructions provided in the Grants Management Portal at https://grants.cirm.ca.gov. **The correct PreApp form is determined by the track through which the proposal will be submitted. Instructions for Fundamental Mechanisms PreApps are described below in subsection A.1; Instructions for Exploratory Concepts PreApps follow in subsection A.2**.

A.1 Fundamental Mechanisms PreApp Instructions

The PreApp for the Fundamental Mechanisms track consists of the following sections:

1. Principal Investigator
Identification information about the PI and Authorized Organizational Official. For CIRM/CFP collaborations, include the name of the Partner PI and the Partner applicant institution.

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

3. Specific Aims of Proposed Research (limited to 1500 characters)
Describe concisely the goal and specific aims to be achieved by the proposed project.

4. Preliminary Results (limited to 3500 characters)
Summarize concisely the preliminary data that support the proposed study. Figures or Tables cannot be included in the PreApp.

5. Experimental Approach and Design (limited to 3500 characters)
Describe concisely the experimental approaches proposed for accomplishing the project goals within 3 years including appropriate milestones or timeline. Highlight novelty or creative use of approaches and methods. For proposals including a Partner PI, clearly indicate proposed activities to be conducted by the applicant PI and by the Partner PI.

6. Significance of Proposed Research (limited to 3000 characters)
Describe the importance of the proposed research for stem cell biology and regenerative medicine. Identify the major unsolved problem addressed by the proposed research and, most importantly, describe how proposed experiments will overcome existing hurdles and significantly advance the field.

7. Project Keywords
Select one keyword in each category (from the list provided) that best describes the proposed research. If appropriate, supply additional keywords that are central to the proposed project.

8. Project Eligibility Section
Complete this section to certify that proposed research meets project eligibility requirements for this RFA.

9. Related Business Entities Disclosure
Applicants must complete the Related Business Entities Disclosure section, when applicable (see instructions at https://grants.cirm.ca.gov). Applicants (PIs) from a for-profit institution (including Partner PIs from a for-profit institution to be funded by the Funding Partner) must complete the disclosure by listing all related business entities. The information in this form is required for

compliance with the Conflict of Interest policy under which CIRM operates.

A.2 Exploratory Concepts PreApp Instructions

The PreApp for the Exploratory Concepts track consists of the following sections:

1. Principal Investigator
Identification information about the PI and Authorized Organizational Official. For CIRM/CFP collaborations, include the name of the Partner PI and the Partner applicant institution.

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

3. Hypothesis (limited to 500 characters)
State the novel hypothesis to be tested through the proposed research.

4. Impact and Transformative Potential (limited to 1500 characters)
Succinctly describe how the field of stem cell biology or regenerative medicine would be transformed if the proposed hypothesis were proven to be true. Describe in direct, specific terms and avoid generalizations such as “increased knowledge”.

5. Novelty (limited to 500 characters)
Differentiate the concepts to be explored in this proposal from what is already known or expected in the field of stem cell biology.

6. Rationale (limited to 2500 characters)
Describe the scientific rationale behind the novel hypothesis to be explored. If applicable, concisely describe any preliminary data supporting the proposed study (optional). Figures or Tables cannot be included in the PreApp.

7. Experimental Approach and Design (limited to 2500 characters)
Describe the experimental approaches proposed for achieving project goals including appropriate aims/milestones or timeline. Explain how the overall experimental design will ensure that the proposed hypothesis is successfully tested within two years.

8. Project Keywords
Select one keyword in each category (from the list provided) that best describes the proposed research. If appropriate, supply additional keywords that are central to the proposed project.

9. Project Eligibility Section
Complete this section to certify that proposed research meets project eligibility requirements for this RFA.

10. Related Business Entities Disclosure
Applicants must complete the Related Business Entities Disclosure section, when applicable (see instructions at https://grants.cirm.ca.gov). Applicants (PIs) from a for-profit institution (including Partner PIs from a for-profit institution to be funded by the Funding Partner) must complete the disclosure by listing all related business entities. The information in this form is required for compliance with the Conflict of Interest policy under which CIRM operates.

B. Preliminary Application Submission Instructions

PreApps must be submitted online using the CIRM Grants Management Portal at https://grants.cirm.ca.gov. A PI may submit only a single PreApp for this RFA, which must be received by CIRM no later than 5:00 pm (PDT) on March 11, 2013.

C. Full Application Forms

Full Applications for this RFA 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 via the Grants Management Portal at https://grants.cirm.ca.gov on May 24, 2013.

The application for the Basic Biology Awards V consists of **three parts**:

Part A: Application Information Form (Web-based form, now includes related Business Entities)
Part B: Proposal (MS Word template)
Part C: Biographical Sketches and Letters of Support (MS Word template)

The full Application includes the following sections:

1. Abstract (up to 1500 characters in Part A)
State the goals of the proposal. Summarize the overall plans of the proposed research and how these will meet the stated objectives of the RFA. Summarize the rationale for the studies and techniques employed to pursue these goals.

2. Public Abstract (up to 1500 characters in Part A)
In lay language, briefly describe the proposed research and how it will contribute to the advancement of stem cell biology and regenerative medicine. This Public Abstract will become public information and will be posted on the CIRM website. Therefore, do not include proprietary or confidential information or information that could identify the applicant (e.g., PI name, applicant institution name or location).

3. Statement of Benefit to California (up to 1500 characters in Part A)

Describe in a few sentences how the proposed research will benefit the State of California and its citizens. This Statement of Benefit will become public information and posted on the CIRM website. Therefore, do not include proprietary or confidential information or information that could identify applicant (e.g., PI name, applicant institution name or location).

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. Key personnel who are not part of the applicant organization should be listed in the subcontract section of the application. Personnel that are not key, such as technical support staff, may be supported by grant funds but not named.

A minimum of one percent effort is required for each key person, except the PI, who is required to commit a minimum of twenty percent (20%) effort.

For each key person listed, provide a two-page biographical sketch using the template provided under Part C. The sketch should highlight prior relevant research experience, accomplishments and/or special skills related to the proposed research. Include relevant publications and/or patents or patent applications. Following biographical sketches for the PI and, if applicable, the Co-PI(s), include all remaining biographical sketches in alphabetical order.

5. Budget (included in Part A)

Provide all budget information requested in the budget section of Part A. Budgets must be justified in detail, including all subcontracts and consulting fees. For CIRM/CFP collaborations, the funding requested from the CFP (total and per year requested, Part A) must be indicated and justified in sufficient detail (in the Part A section "Budget Justification") for reviewers to assess the appropriateness of the non-California research budget.

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

All allowable costs for research funded by CIRM are detailed in the CIRM Grants Administration Policy (GAP, see Section XIII.A of this RFA). For CIRM/CFP teams, allowable costs for research funded by the Collaborative Funding Partner may differ. Guidance will be provided separately by MOST (China), inSTEM (India) and NIH (US) in Appendices A-C, respectively.

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

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

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

• Travel
Recipients (PIs) of CIRM Basic Biology Awards V are encouraged to attend a CIRM-organized grantee 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 GAP (see Section XIII.A of this RFA).

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

• Consultants/Subcontracts
Grantees that subcontract CIRM-funded work should note that CIRM-funded **research** must generally be conducted in California.

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

For activities **other than research**, Grantees may subcontract outside California, but must make a good faith effort to use California suppliers for more than half of their contracts and purchases in accordance with CIRM's California Supplier regulation (Cal. Code Regs., tit. 17, § 100502).

•Facilities Costs

Facilities costs for non-profit applicant organizations are limited to the current applicable, federally negotiated rates for the organization as defined by the Office of Management and Budget (OMB) Circular A-21 or A-122. Facilities rates for For-Profit applicant organizations are limited to 35%. Facilities rates are applied to direct project costs exclusive of the costs of equipment, tuition and fees and subcontract amounts in excess of $25,000. Applicants may use lower Facilities rates, and use up to 100% of the awarded funds for direct research purposes. The Facilities cost rate budgeted is to be applied to the entire award project period.

• 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. Applicants may use lower Indirect cost rates and use up to 100% of the awarded funds for direct research purposes. The Indirect cost rate budgeted is to be applied to the entire award project period.

See Appendices A-C for details concerning CFP allowable costs.

6. Related Business Entities (included in Part A)

All applicants (including, if applicable, a Funding Partner applicant institution) must provide information on related business entities for any application that, if awarded, would fund a for-profit organization either as: 1) the applicant organization; 2) a subcontractor or 3) the employer of a Partner PI, co-investigator, consultant or subcontractor. 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).

7. Rationale and Significance (up to 1 page in Part B)

For Track 1 Fundamental Mechanisms Applications:

Summarize the context and background of the application and the specific rationale for the work proposed. Specifically identify the gaps in the current knowledge base that the project is intended to fill. If the aims of the application are achieved, state how the findings will make a critical contribution to the field of stem cell biology or regenerative medicine.

For Track 2 Exploratory Concepts Applications:
State the novel hypothesis to be tested and its underlying rationale. Differentiate the concepts to be explored in this proposal from what is already known or expected in the field. Describe how a successful outcome would lead to a transformative discovery, i.e. challenge dogma or resolve a critical bottleneck in the field of stem cell biology or regenerative medicine.

8. Specific Aims (up to 1 page in Part B)
Explain the goal of the specific research proposed. Identify and enumerate each specific aim of the proposal in a concise and step-wise fashion, and describe how each aim will support the goal of this research.

9. Preliminary Data (up to 4 pages in Part B)
This section is optional for the Exploratory Concepts track, but mandatory for the Fundamental Mechanisms track. Provide preliminary data to support the concepts, hypotheses and/or approaches proposed in the application. Clearly indicate data generated by the applicant PI and, if applicable, by the Partner PI.

10. Research Design and Methods (up to 4 pages in Part B)
Describe concisely, but in sufficient detail to permit evaluation of the merit of the research, the experimental design, methods and techniques to be employed to achieve the goals specified in the proposal. Use clear and consistent terminology to identify the species of origin for various cell types that may be employed throughout the project. Identify the new or risky aspects of the research, anticipated pitfalls, and plans to overcome or circumvent difficulties that may arise. Describe the methods of analysis of results. Describe specific criteria for success including meaningful quantitative measures to determine if the objective of the proposed studies has been achieved.

For applications from CIRM/CFP teams, the proposed research must be presented as an integrated project. However, applicants must clearly delineate the research that will be performed in California and funded by CIRM from the research that will be funded by the CFP. This delineation is essential for review of the research plan and the appropriateness of the budget.

11. Project Timeline (up to 1/2 page in Part B)
Provide a realistic timetable for completing each proposed specific aim of the project; where appropriate, provide specific milestones for evaluating the achievement of each specific aim.

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

13. Collaboration and Environment, Including Laboratory Facilities and Major Equipment (up to 1 page in Part B)

Provide a short description of the facilities and environment in which the work 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 or employ useful collaborative arrangements where applicable. If collaboration (including CIRM/CFP collaborations) is integral to the success of the project, describe how the collaboration will be managed.

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.

All three parts of the Basic Biology Awards V application must be submitted together and received by CIRM no later than 5:00 PM PDT on June 27, 2013 via the Grants Management Portal (https://grants.cirm.ca.gov). It is the applicant's responsibility to meet this deadline; no exceptions will be made.

E. Submission of Supplemental Information

If necessary, the PI may submit limited supplemental materials that provide critical new information related to their research proposal after the application deadline but not later than 5:00pm PDT on August 21, 2013. Supplementary materials will not be accepted after this deadline. CIRM will accept a one-time-only submission of materials from the PI only if it meets the submission deadline and conforms to the requirements described herein. Accepted submissions will be forwarded to reviewers for their consideration.

The submission should be in the form of a one-page letter addressed to the Senior Review Officer and submitted via email to gsambrano@cirm.ca.gov. The body of the letter may not exceed 500 words and should briefly describe the type of information submitted and when the information became available. The following materials qualify for submissions of supplemental materials.

Within the one-page letter:

- Provide specific citation(s) to journal publications related to the proposed project that were published or accepted for publication since the application submission deadline. You may briefly describe the significance of the publication(s) to the proposal in the cover letter.
- Confirmation of funding secured from other sources
- Regulatory (e.g., IND, IDE) filings or approvals acquired since the application submission deadline.
- Notice of patent application(s) filed, notice of allowance received or patent(s) issued, or notice of license(s) to relevant intellectual property (granted or received) since the application submission deadline.

The letter may not be used to describe any additional data or experiments. Changes in scope, experimental approach, or research design are not allowed.

XI. Schedule of Deadlines and Reviews

Pre-Applications due	5:00 pm (PDT), Mar 11, 2013
Invitations for full Applications sent out by CIRM	May 24, 2013
Full Applications due	5:00 pm (PDT), June 27, 2013
Review of full Applications by Grants Working Group (GWG)	October, 2013
Review and Approval by ICOC	January, 2014
Earliest Funding of Awards	March, 2014

XII. Contacts

For information about this RFA or the review process:

Gilberto R. Sambrano, Ph.D.
Associate Director, Review
California Institute for Regenerative Medicine
Email: gsambrano@cirm.ca.gov
Phone: (415) 396-9103

XIII. 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 Administration Policy

CIRM's Grants Administration Policy (GAP) for Academic and Non-Profit Institutions (Non-Profit GAP) and the GAP for For-Profit Institutions (For-Profit GAP) serve as the standard terms and conditions of grant awards issued by CIRM. All research conducted under this award must comply with the stated policy. Progress reports of research, as required by the GAP, are important to CIRM: Funding from year to year will depend on adequate scientific progress as outlined in the grant application timeline. CIRM's GAP is available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants#GAP

B. Intellectual Property Regulations

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

C. Human Stem Cell Research Regulations

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

D. California Supplier Regulation

CIRM has adopted a regulation to implement the requirement in Proposition 71 that grant and loan recipients make a good faith effort to achieve a goal of purchasing more than 50% of their goods and services from California suppliers (Title 17,California Code of Regulations, section 100502). Grant and loan recipients are required to comply with this standard.