

**CONCEPT PROPOSAL
CIRM BASIC BIOLOGY AWARDS**

The field of stem cell biology is moving at a rapid pace, but despite considerable recent progress, many fundamental issues related to the control of stem cell fate deserve further exploration. CIRM is committed to supporting rigorous and innovative studies that advance our basic understanding of stem cell biology, thereby expanding the knowledge base that fuels clinical advances.

The objective of the CIRM Basic Biology initiative is to provide funding for a strong research portfolio in basic stem cell biology. The intent is to foster cutting-edge stem cell research and to support studies tackling significant, unresolved issues pertinent to understanding the biology of human embryonic stem cells and the control of stem cell fate, with the potential to substantially advance the field. Recently, cellular reprogramming has generated great excitement in the stem cell community, and CIRM intends to support research into understanding the basic molecular mechanisms that drive cell fate changes. Studies on mechanisms of reprogramming include induced pluripotency, induced partial de-differentiation and trans-differentiation. Furthermore, CIRM sees a strong need to support efforts in elucidating the basic molecular and cellular mechanisms underlying self-renewal of human pluripotent stem cells and the control of their differentiation and maturation into metabolically functional cell types. With CIRM's overall mission in mind, funding under this initiative will be limited to studies utilizing human cells, except for groundbreaking reprogramming studies, where necessary use of other mammalian systems may be considered. Specifically, CIRM is seeking proposals in the following areas:

- Mechanisms of cellular reprogramming
 - Molecular basis for induction of multipotency or pluripotency
 - Molecular regulation of induced de-differentiation or trans-differentiation
 - Cellular senescence patterns during reprogramming
- Relationships between reprogramming or self-renewal and oncogenic potential of cultured and transplanted human cells
- Mechanisms that lead to the generation of cancer stem cells in humans
- Genetic, epigenetic and genomic instability of human pluripotent stem cells (hPSC) in long-term cultures, and the effects of such instability on hPSC differentiation and tumorigenicity
- Contributions of epigenetic memory to cellular plasticity
- Role of endogenous microenvironment in stem cell fate regulation
- Molecular mechanisms that enable engineered microenvironments to control stem cell fate
- Identification, isolation and characterization of specific precursor populations at intermediate stages of human stem cell differentiation
- Characterization of molecular determinants of stem cell fate decisions during hPSC differentiation
- Differentiation of hPSCs into fully mature, metabolically functional cell types, tissues and mini-organs
- Molecular basis of hPSC self-renewal
- Human stem cell aging

The CIRM Basic Biology initiative will be open to Principal Investigators (PI) with a Ph.D., M.D. or equivalent degree, at non-profit or for-profit institutions. The PI must be authorized by the applicant institution to conduct the proposed research at the applicant institution 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. Furthermore, the PI must have documented authority from the applicant institution to staff the proposed project and to have access to space and shared resources sufficient to carry out the proposed research. PIs must devote a minimum of 20 percent effort exclusively to research proposed in their application, and higher levels of commitment are encouraged. 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 interest of obtaining the best outcomes for a research project. Institutional proposal limits will be discussed at the Independent Citizen's Oversight Committee meeting.

In anticipation of a large applicant pool, CIRM will release two identical, consecutive RFAs (RFA 08-07 and RFA 09-02), and a PI can only apply to one of these two RFAs. This Basic Biology initiative offers the opportunity to provide further funding for exceptionally successful CIRM SEED projects, but SEED grantees will be judged identically to other applicants to the Basic Biology RFA. Recipients of Comprehensive or New Faculty awards are not eligible to participate in this initiative.

CIRM proposes to fund up to 40 three year awards with justifiable direct project costs of up to \$300,000 per year for a total cost of up to \$60 million for RFAs 08-07 and 09-02 combined.

Provisional timetable

- Release of RFA 08-07 December 2008
 - Applications due April 2009
 - Review June 2009
 - ICOC approval August 2009
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- Release of RFA 09-02 August 2009
 - Applications due Winter (Feb) 2010
 - Review April 2010
 - ICOC approval Summer 2010