

**RFA 10-04 CONCEPT PROPOSAL
CIRM BASIC BIOLOGY AWARDS III**

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 require further exploration before the full translational potential of stem cell research can be realized. To capitalize on the existing momentum in the field, CIRM is committed to supporting rigorous and innovative studies that advance our basic understanding of stem cell biology, thereby expanding the knowledge base that both fuels and facilitates clinical advances.

The objective of the CIRM Basic Biology III 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 stem cells and the control of stem cell fate, with the potential to substantially advance the field. CIRM also seeks to explore the potential for stem cell-based approaches to yield novel mechanistic insights into disease processes by supporting innovative, hypothesis-driven research towards understanding the molecular and cellular basis of disease.

CIRM intends to support research applied towards elucidating the fundamental mechanisms that drive cell fate changes. Projects considered in scope with this RFA will include mechanistic studies on cell reprogramming, such as induction of pluripotency, trans-differentiation and induced de-differentiation, as well efforts to unravel the molecular and cellular basis of self-renewal, differentiation, and maturation into lineage intermediates or metabolically functional cell types. With CIRM's overall mission in mind, funding under this initiative will be prioritized towards studies utilizing human cells, except for groundbreaking and highly innovative studies that require the use of other animal systems. Specifically, CIRM is seeking proposals in the following areas:

- Characterization of molecular determinants of stem cell fate decisions during differentiation
 - Molecular characterization of specific precursor populations at intermediate stages of differentiation
 - Molecular basis of lineage specification towards mature adult, metabolically functional cell types, tissues and mini-organs
 - Role of the cellular and extracellular microenvironment in regulation of stem cell fate and behavior
- Molecular basis of human pluripotent stem cell (PSC) self-renewal and expansion.
- Molecular basis of pluripotency or developmental potential of stem cells
- Human stem cell aging and premature senescence
- Mechanisms of cellular reprogramming
 - Molecular basis for induction of multipotency or pluripotency
 - Molecular regulation of induced de-differentiation or trans-differentiation
- Epigenetic and post-translational mechanisms underlying the differentiation potential or plasticity of stem cells and lineage intermediates
- Genetic, epigenetic and genomic instability of PSCs and progenitor cells, and the effects of such instability on differentiation and tumorigenicity

- Molecular mechanisms by which endogenous or engineered multidimensional microenvironments influence stem cell fate and behavior
- Molecular basis of disease: elucidating/validating human disease mechanisms with in vitro, human stem cell-based models

The CIRM Basic Biology III 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.

CIRM proposes to fund up to 30 three-year awards with justifiable direct project costs of up to \$300,000 per year for a total cost of up to \$45 million.

Provisional timetable*

- Release of RFA 10-04 August 2010
- Pre Applications due September 2010
- Applications due December 2010
- Review February 2011
- ICOC approval April 2011

*Assumes a PreApplication process