RFA 11-03 CONCEPT PROPOSAL:
CIRM BASIC BIOLOGY AWARDS IV

Elucidation of the basic mechanisms that govern human stem cell fate and behavior has the potential to revolutionize the field of medicine. As the engine that fuels biomedical discovery, such studies will not only yield insights that lead to future therapeutic advances, but they will also enable scientists to directly address the technical hurdles and knowledge gaps that are currently hindering the pace of translational medicine. For example, recent advances in cellular reprogramming are providing new opportunities for developing in vitro models of disease, discovering personalized therapies, and generating immune-compatible tissues from a patient's own cells. Nonetheless, many fundamental issues relating to stem cell fate and behavior remain to be explored before the promise of those approaches can be realized. With these challenges in mind, CIRM is committed to supporting rigorous and compelling research that advances 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 IV initiative is to foster cutting-edge research tackling significant, unresolved issues in human stem cell biology. Studies should focus on elucidating basic molecular and cellular mechanisms and should utilize pluripotent stem cells, adult stem cells, and/or their differentiated derivatives. The CIRM Basic Biology Awards IV will support efforts towards characterizing the molecular and cellular basis of self-renewal, differentiation, and maturation into metabolically functional cell types, as well as mechanistic studies on cell reprogramming, such as induction of pluripotency, trans-differentiation and induced de-differentiation. To capitalize on existing momentum in the field, these awards will also support studies utilizing human stem cell-based in vitro models to gain novel insights about disease mechanisms and other medically relevant processes through innovative, hypothesis driven research. Studies addressing the molecular basis of genetic instability or immunogenicity of human stem cells and their derivatives will also fall within scope. 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 approaches that require the use of an animal model system. Specifically, CIRM is seeking proposals in the following areas:

- Cellular and molecular basis of disease or injury: use of *in vitro*, human stem cell-based models to elucidate and/or validate pathological or regenerative mechanisms related to injury or disease; investigators studying 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
- Systems biology approaches using stem cell genomics and phenotype data to elucidate the basis of complex disease and/or inform potential strategies for regeneration.
- Characterization of molecular determinants of human stem cell fate decisions during differentiation
  - 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 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
- Molecular basis of self-renewal and expansion in human pluripotent stem cells (hPSC) or human adult stem cells
- Molecular basis of pluripotency, multipotency, senescence and aging of human stem cells
- Tissue engineering using natural and artificial scaffolds seeded with stem cells and appropriate support cells, growth factors and matrix molecules
- Mechanisms of cellular reprogramming
  - Molecular basis for induction of multipotency or pluripotency
  - Molecular induction of de-differentiation or trans-differentiation of cells for tissue regeneration
- Genomic and epigenetic instability (single cell and related populations) of hPSCs and progenitor cells, and the effects of such instability on differentiation, tumorigenicity or function

The CIRM Basic Biology IV 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. Under 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.

This RFA is open to participating Collaborative Funding Partners.

CIRM proposes to fund up to 25 three-year awards with justifiable direct project costs of up to $300,000 per year for a total cost of up to $35 million.

Provisional timetable*

- RFA Release November 10, 2011
- Pre Applications due January 12, 2012
- Applications due April 25, 2012
- GWG Review June 28-29, 2012
- ICOC approval August 2012

*Assumes a PreApplication process