RFA Concept Proposal: CIRM Program for the Development of New Pluripotent Human Stem Cell Lines

Pluripotent stem cells can play a key role in regenerative medicine and in cell replacement therapies because of their unique ability to self-renew and their developmental potential to form all the cell lineages in the body. To date, only two types of pluripotent human stem cells have been generated successfully – human embryonic stem cells (hESCs) from blastocysts and human embryonic germ cells from the fetal germinal ridge. The genetic background of cell lines acquired by these methods is determined by the donors of the cellular components used for their generation. In order to develop cellular models of heritable disease, it is necessary to derive new cell lines with the genetic background(s) at risk for disease. New, genotype-specific cell lines may be an important tool for understanding differential responses to drugs by patients of different racial backgrounds. CIRM proposes a new program to address these and other needs for new types and sources of human pluripotent stem cell lines.

A variety of alternative methods have been proposed for producing stem cells, many involving the reprogramming of adult somatic cells or of their nuclei. Some approaches such as somatic cell nuclear transfer (SCNT) and selective over-expression of transcription factors have been successful in non-human species. Others, while promising, are still "works in progress" (e.g. the creation of new entities such as through fusion of a somatic cell with an ES cell). Finally, there are numerous efforts to find, document and verify the presence of pluripotent stem cells harvested from adult tissues.

The ability to derive pluripotent stem cells from new sources will enable scientists to generate disease-specific and genotype-specific cells of many phenotypes. Such cells have great value for drug discovery and understanding specific disease mechanisms. Importantly, methods that will not require the donation or use of either human embryos or eggs will significantly reduce the moral and ethical concerns that surround methods currently in use. Finally, new methods of producing pluripotent stem cells will be particularly important because it may be difficult to obtain excess embryos from many racial groups.

This RFA will support the generation of new lines of pluripotent human stem cells including:

- new clinical grade lines of hESCs and other pluripotent human stem cells suitable for future clinical use or other biomedical applications
- new hESC lines generated using improved methods that may be optimal for differentiation along selective lineages or for studies of disease
- disease-specific, pluripotent stem cell lines to support the study of the effects of genetic variation on disease development and response to treatment
- the discovery and implementation of alternative methods for generating pluripotent human cells

CIRM New Cell Lines Awards will be offered to investigators with an MD, PhD or equivalent to conduct their research in California. Awards will be made to support two areas of derivation: the generation of new human lines using excess embryos from in vitro fertilization, and derivations from other sources using new and novel methods. Particular consideration will be given to research applications that cannot be funded by

current federal mechanisms. Each eligible institution may submit up to four applications: two for derivations of hESCs from excess blastocysts, and two applications that propose to use new, alternate methods such as SCNT or reprogramming of adult cells. Each Principal Investigator may submit no more than one application. CIRM proposes to fund up to 16 3-year awards for project costs of up to $300,000 per year at a total cost of $25 million for this round of the program. Eight of the awards will support derivations using excess blastocysts and eight will employ novel, alternate methods.

Provisional Timetable

RFA Release:	Fall 2007
Review of Applications:	Winter 2007-08
ICOC Approval for Funding:	Spring 2008