CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

# Proposal for a CIRM Human Pluripotent Stem Cell (hPSC) Initiative

The success of drug development depends to a large extent on our understanding of disease mechanisms and on the availability of relevant screening assays and disease models that facilitate the identification and development of therapeutic approaches. The advent of human induced pluripotent stem cell (hiPSC) technology provides an unprecedented opportunity to impact these aspects of the drug development pipeline by enabling the generation of disease in a dish models that consist of relevant cell types with authentic patient genotypes. These models may reflect a disease phenotype more accurately than previous cellular models or animal models, and have the potential to make drug discovery faster, more efficient and more personalized to individual patients.

In pursuit of its mission to advance the development of therapies and cures based on stem cell science, CIRM proposes a comprehensive initiative to support the generation of high quality human pluripotent stem cell (hPSC)-based tools for in vitro use by the research and drug development community. CIRM convened two meetings of its Medical Accountability Standards Working Group in spring 2010 and 2011, respectively, to consider ethical and policy issues related to an hPSC initiative. Furthermore, to assess the value and best approaches of an hPSC generation and banking effort, CIRM held a scientific workshop in November 2010.[1] Two specific needs that are likely to have an important impact on scientific discovery and the drug development process were identified: the derivation of hiPSC lines and the establishment of an hPSC bank. These will be pursued through three RFAs, and through a collaboration with the National Institute of Neurological Disorders and Stroke (NINDS) of the National Institutes of Health (NIH). In parallel, CIRM is exploring a genomics initiative that can provide additional disease analysis tools and thus enhance the potential impact of the proposed hPSC effort.

The proposed CIRM hPSC initiative consists of four elements; the
1. CIRM – NINDS/NIH collaboration on neurodegenerative diseases, the
2. CIRM hiPSC Disease Lines Awards RFA (RFA 12-02, Disease Lines Awards), the
3. CIRM Core hiPSC Derivation Award RFA (RFA 12-03, Derivation Award), and the
4. CIRM hPSC Bank Award RFA (RFA 12-04, hPSC Bank Award).

What follows is a brief description of the CIRM - NINDS/NIH collaboration and the concept proposals for the three CIRM RFAs.

[1] The reports for these three meetings can be found at http://www.cirm.ca.gov/for-researchers/publications-cirm-meetings-and-workshop.

## 1. CIRM – NINDS/NIH collaboration on neurodegenerative diseases

In June 2011, the ICOC approved CIRM becoming a member of the public private partnership initiative sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) at the NIH to develop and bank well characterized hiPSC lines for neurodegenerative diseases, and to make them publicly available. CIRM is contributing funds to a consortium that develops lines from patients with Huntington's Disease, Parkinson's Disease, and Amyotrophic Lateral Sclerosis (ALS). As a member of this collaboration with NINDS, CIRM will have a seat on the External Scientific Board and on the Oversight Board that will focus on evaluating and assuring adequate progress of the project.

## 2. CIRM hiPSC Disease Lines Awards
## RFA 12-02 Concept Proposal

There can be tremendous individual heterogeneity in the course of many human diseases, such as the timing of disease onset, its progression, severity of symptoms, and response to therapeutic interventions. Lack of adequate models representing this heterogeneity contributes substantially to the high cost of drug development. Evidence suggests that this variability stems, at least partially, from genomic heterogeneity in the patient population. While rodent genetic models do not represent the heterogeneity of human diseases, patient-derived hiPSC provide an opportunity to sample human genomic heterogeneity in disease in a dish models. To create such models, previously inaccessible cell types affected in a disease, e.g. neurons, are generated from patients' easily accessible cells, such as those of blood or skin, via reprogramming to pluripotency, followed by differentiation to the relevant cell types. While at the pluripotent stage, cells multiply indefinitely, so that large numbers of cells can be generated for extensive studies that link unique aspects of patients' disease manifestations and drug responses with their complex genetic causes.

Monogenic diseases with known genetic defects and high penetrance were ideal first targets for validating the idea that human disease can be modeled using hiPSC technology. Several studies supporting this idea have now been published, and many efforts are ongoing worldwide, many in California including some with CIRM support, to pursue this approach. More challenging is the notion of modeling polygenic diseases, where little to nothing is known of the underlying defects, or modeling diseases with well known single gene defects but low penetrance. Successful hiPSC-based modeling of such diseases will depend on the availability of comprehensive sets of cell lines, representing affected and unaffected individuals from multiple families, that must be accompanied by detailed medical records of the cell donors as a basis for formulating hypotheses about phenotypes in a dish. To ensure the highest possible standards for hiPSC line derivations and to minimize experimental variability, CIRM seeks to fund a single Core hiPSC Derivation Award through RFA 12-03, dedicated to the derivation and basic

characterization of all hiPSC lines proposed in funded Disease Lines Awards (RFA 12- 02), using standard operating procedures and a single method of derivation.

The objective of the Disease Lines Awards (RFA 12-02) is to enable hiPSC-based modeling of prevalent, genetically complex diseases with significant potential for impacting our understanding of disease mechanism and for improving the discovery and development of treatment options for such patient populations. These awards will fund stem cell scientists and clinicians who will collaborate to identify, recruit and consent large enough numbers of patients and control individuals, including women and members of minority groups as appropriate, to effectively represent a given disease's manifestations, collect comprehensive medical records and provide tissue samples to the recipient of the Derivation Award (RFA 12-03) for the production and basic characterization of hiPSC lines. Once derived, characterized and released, the hiPSC lines will be made available, at no cost, to the PIs of the corresponding Disease Lines Awards (RFA 12-02) and will be deposited in the hPSC Bank (RFA 12-04) for distribution (along with the original sample) to interested investigators in California and worldwide for stem cell research.

In a public-private partnership with NIH's NINDS, CIRM is contributing funds to a consortium that develops lines from patients with Huntington's Disease, Parkinson's Disease, and Amyotrophic Lateral Sclerosis (ALS). Thus, to avoid redundancy, CIRM will not seek proposals in these disease indications. Specifically, CIRM will prioritize the following disease areas in this RFA:

- Alzheimer's disease
- Autism spectrum disorders
- Autoimmune diseases
- Cardiovascular diseases
- Cerebral palsy
- Diabetes (type I & type II)
- Respiratory diseases

The Disease Lines Awards RFA (RFA 12-02) will be open to Principal Investigators (PI) with a Ph.D., M.D. or equivalent degree, at non-profit and 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. The PI must devote a minimum of 5 percent effort exclusively to research proposed in the application, and higher levels of commitment are encouraged.

CIRM proposes the funding should support the collection of samples for hiPSC line derivation from approximately 1200 individuals (patients and appropriate controls) through 3-10 two-year awards. Justifiable direct project costs will be commensurate with the number of patients and control individuals included in the proposed projects for a total cost for this RFA of up to $4 million.

## 3. CIRM Core Human Induced Pluripotent Stem Cell (hiPSC) Derivation Award RFA 12-03 Concept Proposal

Successful in vitro disease modeling depends on the development of reliable cell-based assays that reflect patients' disease phenotypes. The establishment of hiPSC-based models is a complex process with multiple steps, including tissue biopsies, hiPSC derivations, and differentiation into relevant cell types, each prone to introduction of experimental variation that can confound disease phenotype analysis. This is especially pertinent for modeling diseases which themselves display much phenotypic variability. In order to ensure as much experimental consistency as possible across derived hiPSC lines, CIRM intends to provide funds to a single qualified organization that will derive all hiPSC lines proposed in applications funded under the Disease Lines Awards (RFA 12-02) using a single method for derivation under standard operating procedures. Once derived, subjected to basic characterization for pluripotency, genomic integrity, etc. and released, the lines will be deposited in CIRM's hPSC Bank (RFA 12-04), thereby enabling rapid distribution to researchers and drug developers.

The Derivation Award RFA (RFA 12-03) is open to non-profit and for-profit applicant organizations able to derive large numbers of hiPSC lines in California. The applicant organization must have documented experience in deriving high quality hiPSC lines and conducting basic characterization under standard operating procedures, and have the capacity to derive hiPSC lines from up to 1200 individuals in three years.

CIRM proposes to fund 1 three-year award for a total cost of up to $16 million. This funding is expected to allow derivation and basic characterization of hiPSC lines (3/individual) from approximately 1200 patients and controls.

## 4. CIRM Human Pluripotent Stem Cell (hPSC) Bank Award RFA 12-04 Concept Proposal

California researchers have already generated many disease-specific human induced pluripotent stem cell (hiPSC) and human embryonic stem cell (hESC) lines, many with CIRM funds. For the potential benefits of these human pluripotent stem cell (hPSC) lines to be fully realized, they must be readily available to the many users who would utilize them for drug development efforts and as tools of scientific discovery. An hPSC resource will only be effective if the lines

provided are adequately documented and of a high consistent quality. This can be assured if rigorous methods of quality control are applied throughout supply chain management from cell line procurement, expansion and storage to distribution. Equally important is the verification of cell identity, purity, viability and sterility. As these processes are best executed and sustained in the long term by professional cell banks, CIRM intends to provide funds for the establishment of an hPSC repository located in California that will bank and distribute high quality, disease-specific hiPSC and hESC lines generated in California for research use.

The impact of the CIRM hPSC Bank will depend on the utility of the hPSC lines and their widespread use by investigators and drug developers worldwide. In order to maximize the value of the banked hPSC lines, especially disease-specific hiPSC lines, they should be accompanied by comprehensive medical records from the cell donors to inform future studies such as phenotype discovery and assay development. Thus the bank must have appropriate technology in place to maintain the privacy and confidentiality of patient records. Furthermore, broad use of banked hPSC lines, including commercial use, will be facilitated through appropriate cell donors' consents and by developing suitable licensing terms. Finally, the bank's business plan must enable it to become self-sustaining.

The hPSC Bank Award RFA (RFA 12-04) is open to non-profit and for-profit applicant organizations able to establish a cell banking facility in California by the start of funding or that have a cell banking facility that already exists in California. The applicant organization must have documented experience in operating a cell banking facility, including overseeing and executing the banking activities as well as associated business activities. Funds will be provided for one-time costs for equipment/instrumentation and for setting up the informatics infrastructure. In addition, applicants may request funds for a 3 year period to cover normal allowable costs, as well as hPSC line handling costs.

CIRM proposes to fund 1 three-year award with justifiable total costs of up to $10 million to bank hPSC lines derived from up to 1500 individuals.

## Provisional timetable for RFAs 12-02, 12-03, and 12-04

- Concept proposals - December 2011
- Release of RFAs - May 2012
- Letters of Intent due – June 2012
- Applications due - August 2012
- GWG Review - November 2012
- ICOC approval – January / February 2013