RFA 12-03: CIRM hiPSC Derivation Award

I. Purpose

The development of disease in a dish models, using patient-derived human induced pluripotent stem cell (hiPSC) lines, is rapidly gaining momentum. The CIRM hiPSC Initiative has the objective of generating and ensuring the availability of high quality disease-specific hiPSC resources. It specifically targets prevalent, genetically complex diseases for the generation of comprehensive collections of hiPSC lines with significant potential to impact understanding of disease mechanism and improve treatment options through disease modeling, target discovery and drug discovery and development. The Initiative consists of three (3) elements, each funded under a different Request for Applications (RFA). Funds allocated to RFA 12-02, CIRM Tissue Collection for Disease Modeling Awards, will support investigators ("Tissue Collectors") who identify and consent suitable patient populations and collect tissue samples and relevant medical information from them. The recipient of this RFA 12-03 hiPSC Derivation Award ("Deriver") will use the tissue samples collected under RFA 12-02 Awards to derive high quality hiPSC lines. Once characterized and released, the lines will be deposited in CIRM's human pluripotent stem cell (hPSC[1]) Repository, funded under RFA 12-04, thereby enabling rapid distribution to researchers and drug developers worldwide. In order to ensure the continuity of the hiPSC resource, CIRM will own the hiPSC lines generated pursuant to this RFA 12-03 (see section IV).

II. Objectives

The ultimate goal of CIRM's hiPSC Initiative is to provide a resource to the research and drug development community for modeling of prevalent, genetically complex diseases. Successful disease modeling depends on the development of reliable cell-based assays and models that reflect patients' disease phenotypes. The establishment of hiPSC-based models is a complex process with multiple steps, including blood collection or other tissue biopsies, hiPSC derivations, and differentiation into relevant cell types, each prone to introduction of experimental variation that can confound disease phenotype analyses. This is especially pertinent

[1] The CIRM hiPSC Initiative is mainly concerned with the generation and distribution of hiPSC lines. However, the Repository will also be charged with banking additional cell lines generated by California investigators. These may include hiPSC lines and also human embryonic stem cell lines, another type of pluripotent stem cell. Therefore, the name of the Repository refers to human pluripotent stem cells (hPSC).

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, under this RFA 12-03, to provide funds to a single qualified organization that will derive all hiPSC lines proposed in applications funded under RFA 12-02, using a single method for derivation under standard operating procedures.

III. Project Requirements

As part of the CIRM hiPSC Initiative, the Deriver will be expected to address the following issues and engage in the following activities:

Capacity of Project: The applicants to RFA 12-03 will propose a justifiable number of tissue samples from which they will be able to derive high quality hiPSC lines (3 hiPSC lines per tissue donor plus expansion and cryopreservation of primary source cells, if applicable) with the funds provided for this award ($16 million total). CIRM is minimally requiring hiPSC derivations from 3000 tissue donors but applicants may propose a larger number, based on their projected cell handling costs per tissue donor, striking a balance between cost efficiency and hiPSC line quality that meets the goals of the CIRM hiPSC Initiative. The number of tissue donors to be included in this Initiative will need to be aligned with the capacity of the Repository which will receive $10 million total to bank and release for distribution a proposed number of hPSC lines. Thus, during review, the Grants Working Group (GWG) will consider the ability of applicants from each RFA to harmonize and align proposals in order to achieve the goals of this Initiative. The number of RFA 12-02 Awards recommended for funding will be matched so as not to exceed the capacity of the Deriver and the Repository. If an RFA 12-03 applicant Program Director and an RFA 12-04 applicant Program Director, from the same or from different institutions or as part of a joint venture or partnership, wish to coordinate their hiPSC derivation and banking efforts, including coordination of the targeted number of tissue donors (3 hiPSC lines per tissue donor), they may do so by referring to each others' efforts in their applications.

Tissue Sample Collection and Receipt: The Deriver will accept all tissue samples collected under RFA 12-02 Awards. The Deriver will cover shipping costs from the Tissue Collector. To enable the procurement of uniform starting material, the Deriver will propose tissue collection and shipping protocols, likely for blood or skin samples, that should be used by the Tissue Collectors. However, Tissue Collectors may request that the Deriver permit the procurement of a different tissue type or use of a different collection protocol based on the needs of the targeted patient population. In that case, they must work with the Deriver to define protocols for tissue collection and shipping that maximize the probability of deriving high quality lines that can be meaningfully compared for a given targeted patient population.

In case Tissue Collectors include existing banked cells in their project, it will be the responsibility of the Tissue Collectors to arrange all permissions necessary and arrange shipping to the Deriver.

Unique ID: Specimens collected from tissue donors should be labeled with a unique identifying alpha numeric or numeric number (ID) not derived from information about the donor. This ID will be used in tracking collected tissues/cells, coded donor information and derived primary source cells and hiPSC lines. It will be the responsibility of the Repository to establish standards for labeling of individual specimens.

Primary Source cells: The Deriver will expand, if appropriate, and cryopreserve cells from all original tissue samples (primary source cells). CIRM will not own original tissue samples or primary source cells derived from them by the Deriver. Ownership will remain with the Tissue Collector (unless the Tissue Collector and Repository agree otherwise) and the Tissue Collector will permit such materials to be maintained at the Repository.

hiPSC Derivation: The Deriver will derive three (3) high quality hiPSC lines from each tissue/cell sample submitted by the Tissue Collectors, using one derivation method under standard operating procedure.

hiPSC Characterization: It will be the responsibility of the Deriver to ensure that hiPSC lines (3 per tissue donor) meet proposed and, if appropriate, pre-NGA negotiated specifications so that no quality testing is required at the time of receipt at the Repository. The Deriver and the Repository shall agree on the full scope of hiPSC line testing required before the transfer of lines to the Repository.

Cell Transfer to Repository: The Deriver will transfer all hiPSC lines and also primary source cells to the Repository. The Repository will cover shipping costs from the Deriver.

Tissue Donor Privacy: The Deriver will comply with all applicable state (including but not limited to California) and federal laws relating to the privacy and security of individually identifiable health information.

Start-up Meeting: After approval of award funding by CIRM's governing board, CIRM will convene a meeting of the Tissue Collectors, the Deriver and the Repository (Start-up Meeting) to facilitate coordination of activities and processes for transfer of materials, protocols and data, and to develop the hiPSC line nomenclature. Subsequently, CIRM will negotiate with awardees specific activities and deliverables for a given grant, taking into consideration the goals of this RFA and the hiPSC Initiative, inputs from the Grants Working Group review and from other hiPSC Initiative Awardees.

IV. Award Information

Under this RFA, CIRM intends to commit up to $16 million total to support one (1) hiPSC derivation project for up to three (3) years for deriving three hiPSC lines from each of 3000 or more tissue samples (includes control samples). The approved application should be initiated (grant start date in issued and signed Notice of Grant Award (NGA)) within six (6) months of approval and authorization for funding by the Independent Citizen's Oversight Committee (ICOC), CIRM's Governing Board, unless the need for additional time is justified with CIRM approval.

CIRM has the right to negotiate funded project activities, target numbers for hiPSC line derivation, characterization and release of cell lines for each reporting period, success and release criteria, timelines and budgets prior to issuance of the NGA, subject to renegotiation annually and/or based on progress. CIRM may also wish to review in advance of execution (for compliance with CIRM's policies and regulations and consistency with the objectives of this RFA) key contracts/agreements with proposed subcontractors that are critical to the success of the project. Due to the interdependence of activities performed under RFA 12-03 Awards with those under RFA 12-02 and RFA 12-04 Awards, CIRM will oversee and facilitate the coordination of activities by the Tissue Collectors, the Deriver and the Repository. In addition to annual Progress Reports, as required by the Grants Administration Policy (GAP, see section XII.A of this RFA), CIRM will require at least quarterly, succinct progress communications from the Tissue Collectors, the Deriver and the Repository. CIRM will organize meetings amongst hiPSC Initiative grantees to promote the successful execution of the entire hiPSC Initiative.

CIRM will own all hiPSC lines created pursuant to RFA 12-03. The execution of funding contracts (Notice of Grant Awards) and disbursement of funds are predicated on the following: (i) CIRM and the Repository applicant have entered into a Repository Agreement governing all hiPSC lines derived pursuant to RFA 12-03; (ii) CIRM approves template Material Transfer Agreements between the Grantees of each of the awards (RFA 12-02, 12-03 and 12-04) and between the Repository and third parties, which shall have terms substantially similar to those set forth in Appendix B. Appendix B is not intended to be an exhaustive list of all terms of such agreements. CIRM's prior approval shall be required with respect to material modifications of the template agreements.

V. Award Mechanism

CIRM expects to fund one approved proposal from a non-profit or a for-profit institution through a grant. The institution will receive grant funding through quarterly payments with adjustments as required for actual numbers of tissue samples received and three (3) hiPSC lines per tissue sample successfully generated, characterized and released. Pre-NGA negotiations with CIRM will establish milestones for an anticipated annual hiPSC derivation rate that will define a payment schedule, subject to adjustment based on actual and forecasted derivation/release

of hiPSC lines. Progress on this Initiative is important to CIRM. If the Deriver does not meet the agreed to milestones for hiPSC derivation activities, unless delays are caused by delayed activities on the part of the Tissue Collectors, then CIRM has the right to negotiate new milestones if feasible within the timing of the Initiative or to terminate the project.

VI. Eligibility

A. Project Eligibility

In order to be eligible, the project must be a proposal to derive 3 hiPSC lines each from a minimum of 3000 tissue donors within 3 years in California.

B. Institutional Eligibility

For this RFA, CIRM will limit the number of applications from each eligible institution to one. The CIRM hiPSC 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 experience in deriving high quality hiPSC lines and conducting basic characterization under standard operating procedures.

"Non-profit organization" means: (1) a governmental entity of the state of California; or (2) a legal entity that is tax exempt under Internal Revenue Code section 501(c)(3) and California Revenue and Taxation Code section 23701d.
"For-profit organization" means: a sole-proprietorship, partnership, limited liability company, corporation, or other legal entity that is organized or operated for the profit or financial benefit of its shareholders or other owners. Such organizations also are referred to as "commercial organizations".

At the time of application submission, the applicant organization does not have to be located in California. In order to be eligible for this award, at the time of submission of an application, the applicant organization must have secured a location in California from which it will engage in activities critical to the project. At the time of funding, the Program Director has to be present at the California location (at least 25% time). Substantially all of the derivation work must be conducted in California.

C. Program Director (PD) Eligibility

A PD may submit only a single LOI for this RFA. The PD must have an M.D., Ph.D. or equivalent degree, and must be authorized by the applicant institution to conduct the proposed project in California. By the application deadline, the PD must:

- Be an employee of the applicant institution (at least 50-percent time)
- Have authority from the applicant institution to staff the proposed project in California

- Have commitment from the applicant institution to provide laboratory space and resources sufficient to carry out the proposed project in California.

By the time of funding, the PD must:

- Be an employee of the applicant institution and be at its California site (at least 25-percent time).

CIRM is limiting the number of active CIRM research awards in which an investigator may participate as PI (PD) or Co-PI. This RFA is not open to investigators as a PD who are already a PI, PD or a Co-PI on 3 or more active CIRM awards as of September 27, 2012, the deadline for submission of the application.

The limit includes all CIRM awards that have been approved but not yet closed out, with the exception of the following CIRM RFAs/PAs: Shared Research Labs, Major Facilities, Research Training Awards I & II, Bridges to Stem Cell Research, Disease Team Planning Awards, Disease Team Therapy Development Part I Planning Awards, or Conference Grants.

D. Co-Program Director (Co-PD) Eligibility

This RFA does not allow designation of a Co-Program Director (Co-PD).

E. Percent Effort Requirements

For this RFA, the PD must be willing and able to commit a minimum 25% effort exclusively to activities proposed in the application, and higher levels of commitment are encouraged.

F. Extraordinary Exceptions

In extraordinary circumstances, the President of CIRM has the discretion to permit exceptions to requirements or limitations of this section VI. The exercise of such discretion will be only in exceptional cases where the applicant has demonstrated that such an exemption would preserve an important research opportunity or make a critical contribution to one of CIRM's mission objectives. Exceptions must be consistent with the objectives of this RFA and the requirements of Proposition 71 as well as California state regulations, including the Grants Administration Policy (see Section XII of this RFA), or they will not be considered.

If CIRM determines that an application does not meet the eligibility requirements, CIRM may terminate all further action on the application. Applicants who will need an exception are strongly encouraged to request it at least 30 days before the relevant application deadline. To request an exception, or for assistance in determining whether one is necessary, contact the CIRM staff listed in Section XI.

VII. Application and Evaluation Process

Prior to submitting an application, an applicant must submit a Letter of Intent (LOI). Unless notified by CIRM that they do not meet the eligibility criteria (as defined in section VI) based on information provided in the LOI, all applicants who submitted an LOI that was accepted by CIRM may submit an application. The application must have the same PD listed in the LOI, or it will be deemed ineligible.

Applications will be evaluated by the CIRM Grants Working Group (GWG), which is composed of fifteen scientific experts from outside California, seven patient advocate members of CIRM's Governing Board, and the Chair of the Governing Board. The list of scientific members who may participate in the GWG review can be found at http://www.cirm.ca.gov/GrantsWkgGrpMembers. The composition of the ICOC can be viewed at http://www.cirm.ca.gov/GoverningBoard. The fifteen participating scientists on the GWG will review the applications and score them according to scientific and technical merit applying the review criteria described in Section VIII below. The GWG (scientists and patient advocates) will then consider meritorious application(s) for a funding recommendation taking considerations from the perspective of patient advocates into account. One goal of programmatic review will be to make recommendations to the ICOC to harmonize and align the tissue donor numbers between the Deriver and the Repository. The number of RFA 12-02 Awards (Tissue Collection) recommended for funding will be matched so as not to exceed the capacity of the Deriver and Repository. The GWG will make a funding recommendation to the ICOC, which will make the final funding decision.

CIRM's confidentiality and conflict screening rules will apply to everyone who will have access to applications or who will attend the review meeting, including CIRM staff, external reviewers, and representatives of Collaborative Funding Partner Agencies. (Per Gov. Code §6254.5(e), non-public records may be disclosed to government agencies under confidentiality agreements.)

VIII. Review Criteria

The Applications will be evaluated in six key areas: 1) Protocols, 2) Documentation and Quality Control, 3) Feasibility and Resources, 4) Intellectual Property and Other Assets, 5) Program Director (PD) and Team, 6) Budget.

1. Protocols.

Tissue Collection, Shipping and Primary Source Cell Preparation Protocols:

- The preferred tissue source is easy to procure and appropriate for reliable derivation of high quality hiPSC lines. Both affected and unaffected individuals are likely to agree to the collection of the proposed tissue.
- Proposed tissue collection and shipping protocols can be easily adopted by multiple users to provide tissues of suitable and reproducible quality.
- The proposed protocol for the long-term preservation of primary source cells is appropriate.

hiPSC Derivation Protocol:

- The proposed hiPSC derivation protocol has been shown to produce robust hiPSC lines, preferably in the hands of the applicant team.
- The protocol is designed appropriately to enable derivation of large numbers of high quality hiPSC lines suitable for research use.
- The proposed derivation method, preferably genome integration-free, is well justified.
- The proposed minimal success criteria are appropriate.

hiPSC Characterization:

- The proposed hiPSC characterization assays and their minimal release criteria are sufficient and appropriate to establish the quality of newly derived hiPSC lines.

2. Documentation and Quality Control.

- A quality program is in place to regulate activities and to detect and resolve any emerging quality problems. hiPSC derivations and characterizations are performed under appropriate quality standards; the applicant institution has a record of documentation through Standard Operating Procedures (SOPs).
- Appropriate systems are in place for monitoring and protecting the physical integrity of cells and for inventory control.

3. Feasibility and Resources.

- The applicant has the experience, productivity and access to appropriate personnel, space, equipment, sample and data management systems, and technologies (e.g. derivation technology) to reasonably be expected to achieve the goal of derivation and characterization of 3 hiPSC lines per tissue sample from the proposed number of tissue samples (minimum of 3000 tissue samples) in 3 years.
- Evidence of prior success in generating high quality hiPSC lines, using the proposed derivation protocol and as assessed by their utility in subsequent studies, is appropriate.
- The historical hiPSC derivation failure rate is acceptable.

4. Intellectual Property and Other Assets.

- Adequate freedom to operate with respect to derivation and use of the hiPSC lines by academic and commercial entities has been established through patents, patent applications and agreements (including licenses, covenants not to sue etc.).
- Other resources enhance the downstream utility of derived hiPSC lines.

5. Program Director (PD) and Team.

- Evidence of prior success and the track record support the qualification of the PD to oversee the derivation and characterization of high quality hiPSC lines from the proposed number of tissue samples (3 hiPSC lines per tissue sample).
- The PD's level of commitment heightens the probability for success of the hiPSC derivation project.

- The team has appropriate training and experience to carry out the proposed project. The PD or team members have experience in the derivation and characterization of hiPSC lines; this includes hiPSC lines that have been successfully employed by downstream users.
- Any proposed services from, or collaborations with, subcontractors are critical and integral to the success of the hiPSC derivation project, and there is a reasonable plan to ensure communication amongst collaborators.

6. Budget.

- The cell handling costs are well delineated on a per tissue donor basis (primary source cells and 3 hiPSC lines).
- The budget for primary source cell preparation and cryopreservation, and for derivation and characterization of hiPSC lines from the proposed number of tissue samples (3 hiPSC lines per tissue sample) is appropriate and well justified. If not, reviewers will be instructed to lower the score.

IX. Application Procedure

Applicants must follow these instructions for submission of a Letter of Intent (LOI) and an Application for RFA 12-03, CIRM hiPSC Derivation Award. Applications will only be accepted from applicants who submitted an LOI that was accepted by CIRM.

A. Letter of Intent (LOI)

Each applicant must submit an LOI using the forms and instructions provided at http://www.cirm.ca.gov/RFAs. The LOI must be received by CIRM no later than 5:00 pm (PDT) on August 14, 2012. A PD may submit only a single LOI for this RFA.

B. Application Forms

CIRM will only accept Applications from applicants who submitted an LOI that was accepted by CIRM. The PD must be the same as the one named in the LOI; otherwise, the Application is deemed ineligible. Application forms will be available via the Grants Management Portal at https://grants.cirm.ca.gov on August 14, 2012.

The Application for the CIRM hiPSC Derivation Award RFA consists of **four parts**:

Part A: Application Information Form (Web-based form)
Part B: Proposal (MS Word template)
Part C: Biographical Sketches and Letters of Support (MS Word template)
Part D: Supporting Documentation (e.g. sample submission form, protocols, space layout, verification of access to space if applicant organization is located outside of California)

The Application includes the following sections:

1. Abstract (up to 1500 characters in Part A)
State the goals of the proposal. Summarize the overall plan of the proposed project and how it will meet the stated objectives of the RFA. Summarize the rationale for the methods employed to pursue these goals.

2. Public Abstract (up to 1500 characters in Part A)
In lay language, briefly describe the proposed project and how it will contribute to the advancement of stem cell biology and regenerative medicine. This Public Abstract will become public information; therefore, do not include proprietary or confidential information or information that could identify the applicant (e.g., PD name, applicant institution name or location).

3. Statement of Benefit to California (up to 1500 characters in Part A)
Describe in a few sentences how the proposed project will benefit the State of California and its citizens. This Statement of Benefit will become public information; therefore, do not include proprietary or confidential information or information that could identify the applicant (e.g., PD name, applicant institution name or location).

4. Key Personnel (included in Parts A and C)
List all key personnel and their roles on the project. Key personnel are defined as individuals who contribute to the scientific development or execution of the project in a substantive, measurable way, whether or not they receive salaries or compensation under the grant. Key personnel may include any staff, co-investigators, collaborators, or consultants who meet this definition. Key personnel who are not part of the applicant organization should be listed in the subcontract section of the application. A minimum of one percent effort is required for each key person, except the PD, who is required to commit a minimum of twenty five percent (25%) effort. Personnel that are not key, such as technical support staff, may be supported by award funds but not named.

For each key person listed, provide a two-page biographical sketch using the template provided under Part C. The sketch should highlight prior relevant research experience, accomplishments and/or special skills related to the proposed project. Include relevant publications and/or patents or patent applications.

5. Budget (included in Part A)
Provide all budget information requested in the budget section of Part A. Budgets for salaries and supplies for all hiPSC derivation and characterization activities and for quality control must be justified in detail, including all subcontracts and consulting fees. Equipment costs must be justified in detail. Present the cell handling costs on a per tissue donor basis (primary source cells and 3 hiPSC

lines). The total number of tissue donors included in this Initiative may have to be adjusted depending on the capacities of the selected Deriver and Repository.

All allowable costs for research funded by CIRM are detailed in the CIRM Grants Administration Policy (GAP, see Section XII.A of this RFA). Under this RFA, CIRM-funded allowable costs include the following:

• Salaries for Key Personnel
Salaries for Key Personnel may include the Program Director, Co-Investigators, Research Associates, and technical support staff, each of whom must perform the subject work in California, based on percent of full time effort commensurate with the established salary structure of the applicant institution. The total salary requested must be based on a full-time, 12-month staff appointment or the full time annual salary for employees of a for-profit institution. Administrative support salaries should be covered exclusively by allowed Indirect Costs.

• Supplies
Grant funds will support supplies, including specialized reagents and animal costs. Minor equipment purchases (less than $5,000 per item) are considered supplies and may be included as direct costs in the budget.

• Travel
The Deriver (PD of the RFA 12-03 Award) is strongly encouraged to attend the Start-up Meeting and other business meeting(s) for the Tissue Collectors, the Deriver and the Repository (see sections III and IV) as well as a CIRM-organized grantee meeting in California and should include travel costs for these meetings in the budget. Travel costs associated with collaborations necessary to the grant are allowable. Details of allowable travel costs can be found in the GAP (see Section XII.A of this RFA).

• Equipment
Equipment (equal to or more than $5,000 per item) necessary for executing the proposed project at the applicant institution should be itemized and justified. Equipment costs should not be included as allowable direct costs in indirect cost calculations.

• Consultants/Subcontracts
Derivers who subcontract CIRM-funded work should note that CIRM-funded activities must generally be conducted in California. This includes all hiPSC derivation activities funded under this RFA.

Aside from small consulting contracts, Derivers may not use CIRM funds to contract for activities to be performed outside of California. Consulting contracts for out-of-state activities are generally limited to $15,000 per year for

a single contract, and $25,000 per year in aggregate. (CIRM may allow modest increases to these limits in exceptional circumstances.)

Derivers may purchase supplies outside California, but must make a good faith effort to use California suppliers for more than half of their purchases in accordance with CIRM's California Supplier regulation (Cal. Code Regs., tit. 17, § 100502).

• Facilities Costs

Facilities costs for non-profit applicant organizations are limited to the current applicable, federally negotiated rates for the organization as defined by the Office of Management and Budget (OMB) Circular A-21 or A-122. Facilities rates for For-Profit applicant organizations are limited to 35%. Facilities rates are applied to direct project costs exclusive of the costs of equipment and subcontract amounts in excess of $25,000. Applicants may use lower facilities rates. The facilities cost rate budgeted is to be applied to the entire award project period.

• Indirect Costs

Indirect costs for for-profit and non-profit applicants are limited to 20 percent of allowable direct research funding costs awarded by CIRM (i.e., project costs and facilities costs), exclusive of the costs of equipment and subcontract amounts in excess of $25,000. Applicants may use lower indirect cost rates. The indirect cost rate budgeted is to be applied to the entire award project period.

6. Related Business Entities (included in Part A)

All applicants must provide information on related business entities for any application that, if awarded, would fund a for-profit organization either as: 1) the applicant organization; 2) a subcontractor or 3) the employer of a co-investigator, consultant or subcontractor. If the application does not seek funding for any such for-profit organizations, indicate that in this section of Part A. If for-profit funding is sought, include the following for each for-profit organization to be funded:

- A list of any parent organization that owns 50% or more of the for-profit's voting shares;
- A list of all subsidiaries in which the for-profit owns 50% or more of the voting shares; and
- A list of all other related business entities (i.e., entities with which the for-profit shares management and control, or shares a controlling owner).

7. Overview of hiPSC Derivation Program (up to 3 pages in Part B)

Based on your projected costs for primary source cell preparation and derivation and characterization of 3 hiPSC lines per tissue donor (as detailed in the Budget Justification, see section IX.B.5), state and justify the number of tissue donors, minimally 3000, you will be able to include in your proposed hiPSC derivation

program. Provide a work flow diagram from receiving a tissue sample to the release of primary source cells and 3 hiPSC lines for shipment to the Repository. Provide a table listing each step of the proposed hiPSC derivation protocol and the minimal success criteria for each step. Provide another table listing each assay that will be used to assess the quality and pluripotency of the newly derived hiPSC lines and the minimal release criteria for each assay. Specify if a laboratory information management system (LIMS) for real-time tracking of sample processing and data management will be used.

8. Tissue collection and primary source cell preparation protocols (up to 2 pages in Part B)

Identify and justify your preferred tissue as starting material for hiPSC line derivation; comment on ease of procurement from affected and unaffected (control) individuals. Describe concisely, but in sufficient detail to permit evaluation, your preferred tissue collection and shipping protocol that will be transferred to and used by the Tissue Collectors, unless different protocols are negotiated with them. Append (in Part D) an example of a sample submission form and/or provide a description of the tissue collection kit that your laboratory is using to receive tissue samples for hiPSC derivation. Summarize an alternate protocol, utilizing a different tissue type, in case certain targeted patient populations are not amenable to procurement of your preferred tissue type. Comment on ease of adoption of the tissue collection protocols by multiple users. Describe the protocol used for expansion, if indicated, cryopreservation and shipment of primary source cells for long-term storage at the Repository.

9. hiPSC Derivation Method (up to 2 pages in Part B)

Describe concisely, but in sufficient detail to permit evaluation, each step of the protocol that will be used to derive three (3) high quality hiPSC lines per tissue sample, from receipt of the tissue sample (collected and shipped by your preferred method, see section IX.B.8 above) to early passage hiPSC line generation. Justify the derivation method (preferably genome-integration-free), minimal success criteria and other parameters of the protocol where appropriate. Elaborate how the proposed derivation method affects hiPSC line quality. State and explain your historical hiPSC derivation failure rate, especially using the proposed protocol. In case certain targeted patient populations require specific tissue collection protocols (as identified in RFA 12-02 awards), describe how the proposed hiPSC derivation protocol would accommodate use of alternate tissue types as starting material.

10. hiPSC Characterization (up to 3 pages in Part B)

Describe concisely, but in sufficient detail to permit evaluation, each assay that will be used to evaluate the quality of the newly derived hiPSC lines. Provide the rationale for the choice of assays, provide or cite evidence that validates the choice of assay, where appropriate, and justify the minimal release criteria for each assay.

11. Documentation and Quality Control (up to 2 pages in Part B)
Describe the quality program that will be used to monitor all hiPSC derivation and characterization activities and to resolve emerging quality problems. Provide a list or link to Standard Operating Procedures (SOPs) for all key processes and protocols used for tissue collection and shipment, hiPSC derivation and characterization. SOPs for tissue collection and shipment will be transferred to the Tissue Collectors. Explain the systems that will be used to monitor and protect the physical integrity of cells and for inventory control.

12. Supporting Data (up to 2 pages in Part B)
Present supporting data that provide evidence of the PD's and the team's ability to derive and characterize large numbers of high quality hiPSC lines, using the proposed hiPSC derivation and characterization protocols. Provide examples that illustrate the quality and utility of hiPSC lines derived by the applicant team using the proposed protocols, including successful utilization of previously derived hiPSC lines by downstream users.

13. Laboratory Facilities, Capacity and Timeline (up to 2 pages in Part B)
Describe the laboratory space (already existing in California or secured in California) and equipment (existing and purchased under this award) available for this project, and how that relates to the capacity needed for the preparation of primary source cells and for the derivation and characterization of hiPSC lines (3 per tissue sample) from the proposed number of tissue samples (see section IX.B.7) in 3 years. If the applicant institution is located outside of California, append (in Part D) documents showing access to sufficient space in California. Provide and justify a realistic timeline for this project, assuming continuous tissue supply over two years.

14. Intellectual Property and Licenses (up to 1 page in Part B)
Describe all patents, patent applications and agreements (including licenses, covenants not to sue etc.) that demonstrate freedom to operate with respect to derivation and use of the hiPSC lines by academic and commercial entities and append (in Part D) copies of the relevant agreements.

15. Collaborations, Assets, Resources and Environment (up to 2 pages in Part B)
Provide a short description of additional resources, not described above, that will be available to this project. Discuss ways in which the proposed work will benefit from collaborative arrangements where applicable. If collaboration is integral to the success of the project, describe how the collaboration will be managed.

16. References (up to 1 page in Part B)
List all references used in the body of the proposal.

C. Application Submission Instructions

Applications will only be accepted from applicants who submitted an LOI that was accepted by CIRM. A PD may submit only a single LOI for this RFA.

All four parts of the CIRM hiPSC Derivation Award RFA 12-03 Application must be submitted together and received by CIRM no later than 5:00PM PDT on September 27, 2012, via the Grants Management Portal (https://grants.cirm.ca.gov). It is the applicant's responsibility to meet this deadline; no exceptions will be made.

D. Submission of Supplemental Information

If necessary, the PD may submit limited supplemental materials that provide critical new information related to the proposal after the application deadline but not later than 5:00pm PDT on October 31, 2012. Supplementary materials will not be accepted after this deadline. CIRM will accept a one-time-only submission of materials from the PD only if it meets the submission deadline and conforms to the requirements described herein. Accepted submissions will be forwarded to reviewers for their consideration.

The submission should be in the form of a one-page letter addressed to the Senior Review Officer and submitted via email to gsambrano@cirm.ca.gov. The body of the letter may not exceed 500 words and should briefly describe the type of information submitted and when the information became available. The following materials qualify for submissions of supplemental materials:

1. Within the one-page letter, provide specific citation(s) to journal publications related to the proposed project that were published or accepted for publication since the application submission deadline. You may briefly describe the significance of the publication(s) to the proposal in the cover letter.

2. Within the one-page letter, confirmation of funding secured from other sources or, if applicable, additional information confirming the establishment of a California presence since the application submission deadline.

3. Within the one-page letter, notice of patent application(s) filed, notice of allowance received or patent(s) issued, or notice of license(s) to relevant intellectual property (granted or received) since the application submission deadline.

The letter may not be used to describe any additional data or experiments. Changes in scope or in hiPSC derivation and characterization approach are not allowed.

X. Schedule of Deadlines and Reviews

Letters of Intent due	5:00 pm (PDT), August 14, 2012
Applications due	5:00 pm (PDT), September 27, 2012
Review of Applications by Grants Working Group (GWG)	December 2012
Review and Approval by ICOC	Winter 2013.
Earliest Funding of Awards	Q2, 2013

XI. Contacts

For information about this RFA:

Uta Grieshammer, Ph.D.
Science Officer
California Institute for Regenerative Medicine
Email: ugrieshammer@cirm.ca.gov
Phone: (415) 396-9118

For information about the review process:

Gilberto R. Sambrano, Ph.D.
Senior Review Officer
California Institute for Regenerative Medicine
Email: gsambrano@cirm.ca.gov
Phone: (415) 396-9103

XII. CIRM Regulations

Grant awards made through this RFA will be subject to CIRM regulations. These regulations can be found on CIRM's website at http://www.cirm.ca.gov/reg/default.asp.

A. CIRM Grants Administration Policy

CIRM's Grants Administration Policy (GAP) for Academic and Non-Profit Institutions (Non-Profit GAP) and the GAP for For-Profit Institutions (For-Profit GAP) serve as the standard terms and conditions of grant awards issued by CIRM. All research conducted under this award must comply with the stated policy. Progress reports of research, as required by the GAP, are important to CIRM: Funding from year to year will depend on adequate scientific progress as outlined in the grant application timeline. CIRM's GAP is available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants#GAP

B. Interim Regulation Governing CIRM hPSC Repository

CIRM has adopted intellectual property and revenue sharing regulations for non-profit and for-profit organizations. However, these regulations DO NOT apply. Instead, an interim regulation currently being promulgated will govern. By accepting a CIRM Grant, the Grantee agrees to comply with all such applicable regulations. The interim regulations can be found at http://www.cirm.ca.gov/files/Regulations/100620_interim_regulation.pdf

C. Human Subjects and Stem Cell Research Regulations

As reflected in CIRM's GAP, CIRM has adopted medical and ethical standards for human stem cell research (Title 17, California Code of Regulations, sections 100010-100110 available at http://www.cirm.ca.gov/our-funding/our-regulations/stem-cell-regulations-governing-cirm-grants#standards). All research conducted under this award will be expected to comply with these standards including:

Human Subject Research Regulations
All CIRM-funded human subjects research must be performed in accordance with the Common Rule (Title 45 CFR Part 46) and the California Protection of Human Subjects in Medical Experimentation Act (California Health and Safety Code section 24173). CIRM has developed additional disclosure requirements to ensure fully informed consent from tissue donors (see http://www.cirm.ca.gov/files/PDFs/Standards/Reformatted_MES_Regs.pdf). A model consent form, designed to be compliant with the Common Rule and California requirements, may be found in Appendix A.

Payments to Donors of Cells and Tissue
CIRM funds may not be used to pay donors of cells and tissues. Donors may be reimbursed for necessary and reasonable costs directly incurred as a result of donation or participation in research activities. Permissible expenses may include but are not limited to costs associated with travel, housing, childcare, medical care, health insurance and actual lost wages.

D. California Supplier Regulation

CIRM has adopted a regulation to implement the requirement in Proposition 71 that grant recipients make a good faith effort to achieve a goal of purchasing more than 50% of their goods and services from California suppliers (Title 17,California Code of Regulations, section 100502). Grant recipients are required to comply with this standard.