RFA 12-04: CIRM hPSC Repository Award

I. Purpose

The CIRM human induced pluripotent stem cell (hiPSC) Initiative has the objective of generating and ensuring the availability of high quality disease-specific hiPSC lines. 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 use in disease modeling, target discovery and drug discovery and development. The Initiative consists of 3 Requests for Applications (RFAs) that will be co-released. RFA 12-02, CIRM Tissue Collection for Disease Modeling Awards, will support investigators ("Tissue Collectors") to collect tissue samples and relevant demographic, medical and/or diagnostic information from suitable patients and control individuals. RFA 12-03, CIRM hiPSC Derivation Award, will fund a single entity ("Driver") to generate hiPSC lines from the collected tissue samples. The potential benefits of these hiPSC lines, as well as other hiPSC and human embryonic stem cell (hESC) lines developed in recent years by California researchers, can be fully realized only if they are readily available to investigators. The purpose of RFA 12-04, the CIRM Human Pluripotent Stem Cell (hPSC[1]) Repository Award, is to fund the creation of a repository for high quality, disease-specific, research grade hPSC lines generated in California to enable their reliable distribution worldwide.

II. Objectives

An hPSC resource will only be effective if the cell 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. These processes are best executed and sustained in the long term by dedicated, professional cell repositories.

[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).

CIRM expects that the CIRM hPSC Repository ("Repository") will become self-sustaining at least in part through the sale of hPSC lines, with discount pricing for investigators in California, the specific terms to be set forth in a Repository Agreement to be entered into by the Repository (see section IV) and CIRM, who will own the hiPSC lines generated pursuant to RFA 12-03.

The impact of the Repository 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, appropriately coded[2] demographic, medical and/or diagnostic information from the tissue donors will be associated with each hiPSC line in order to inform future studies such as disease modeling, target discovery and drug discovery and development. Furthermore, broad use of banked hPSC lines, including use by commercial entities for the development of new medical diagnostics or treatments, will be facilitated through appropriate tissue donors' consents (obtained by the Tissue Collectors).

III. Project Requirements

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

Tool for the Collection and Transfer of Private Tissue Donor Information: In order to harmonize data collection across the Initiative and enable uniform data handling at the Repository, a crucial first responsibility of the Repository will be to develop a new or deploy an existing tool, ideally web-based, for use by the Tissue Collectors for the secure collection of demographic, medical and diagnostic information (private tissue donor information) and its transfer to the Repository. This tool should allow inclusion of data from electronic medical records and additional sources, and may need to be customized to allow acquisition of unique data sets as required by individual RFA 12-02 awards. As early as possible, the Tissue Collectors shall coordinate with the Repository to standardize, to the extent possible, the format and transfer of data elements that are common to all RFA 12-02 projects across diseases, in order to facilitate the management of this information at the Repository.

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[2] For the purpose of this document "coded" means: (1) a code has been used to replace identifying information (such as name, dates related to the tissue donor, certain demographics or social security number) that would enable the investigator (e.g. the Deriver, the Repository and future hiPSC line users) to ascertain the identity of the individual to whom the private information or specimens pertain; and (2) a key to decipher the code is maintained separately in a secure manner, enabling linkage of the identifying information to the private information or specimens. The code may not be derived or related to information about the individual and may not be capable of otherwise being translated.

Handling of Private Tissue Donor Information: The Repository will receive from the Tissue Collectors coded demographic, medical and/or diagnostic information from all tissue donors and will provide potential hiPSC line customers access to that information. It will be the responsibility of the Tissue Collectors to code and manage the private tissue donor information in accordance with all state and federal laws for the protection of research participants and medical information. It will be the responsibility of the Repository to obtain assurance from viewers of coded private tissue donor information that they will refrain from attempting to re-identify tissue donors.

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.

Capacity of Project: CIRM requires inclusion of a minimum of 3000 tissue donors (3 hiPSC lines per tissue donor) in this Initiative, but applicants to RFA 12-03 (hiPSC Derivation) and RFA 12-04 (hPSC Repository) may propose a larger number. 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.

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.

Receipt of Primary Source Cells and hiPSC lines: The Repository will accept from the Deriver all cell preparations from the original tissue samples (primary source cells) and all hiPSC lines derived under RFA 12-03 that meet the quality standards established for the RFA 12-03 award. This includes 3 hiPSC lines each from a minimum of 3000 tissue donors. The Repository will cover shipping costs from the Deriver. It will be the responsibility of the Deriver to ensure that the primary source cells and derived hiPSC lines meet the proposed and, if appropriate, pre-NGA negotiated quality standards established for the RFA 12-03 award so that no quality testing is required at 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.

hPSC Line Banking and Distribution: Expansion, characterization, cryopreservation, storage and worldwide distribution of at least 1 hiPSC line per tissue donor, newly derived under RFA 12-03, from a minimum of 3000 tissue donors and additional

existing hPSC lines generated by California investigators. The Repository must propose to fully process and characterize at least one hiPSC line per tissue sample collected under RFA 12-02 Awards for release for distribution, while storing the remaining two lines as a reserve. The Repository is expected to bank and distribute hiPSC lines generated under this CIRM hiPSC Initiative minimally for an additional 10 years after award closure.

Banking of Primary Source Cells: The Repository will bank the primary source cells from each tissue donor collected under RFA 12-02 Awards and processed by the Deriver (minimally 3000 samples), enabling re-derivation of hiPSC lines if deemed necessary in the future. The Repository is expected to bank and distribute all primary source cells generated under this CIRM hiPSC Initiative minimally for an additional 10 years after award closure.

Tissue Collectors' access to hiPSC lines: The Repository will make the hiPSC lines available to the Tissue Collectors who provided the samples, if requested and at shipping cost. This distribution to each Tissue Collector will be limited to one hiPSC line per tissue sample procured by that Tissue Collector, and it will be subject to an agreement that the use of the hiPSC lines received under this agreement is limited to the laboratory(s) named in the RFA 12-02 Award, and cannot be distributed to third parties by the Tissue Collector.

Re-Contact of Tissue Donors: The ability to re-contact individual tissue donors will remain with the Tissue Collectors' institutions. It will be the responsibility of the Repository to facilitate re-contact of tissue donors if additional or updated demographic, medical and/or diagnostic information is sought by hiPSC line users. This includes appropriate tracking and association of hiPSC lines with the Tissue Collectors and/or their institutions where the tissue and the coded donor information were collected. Tissue Collectors and/or their institutions would bear responsibility for re-contact of donors if permissible under the effective Institutional Review Board (IRB) protocol and informed consent document.

Tissue Donor Privacy: The Repository 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 $10 million total to support one (1) award. The CIRM hPSC Repository will be funded for up to four (4) years for banking primary source cells and three (3) hiPSC lines per tissue donor included under RFA 12-02, i.e. from an anticipated minimum 3000 tissue donors or more if the capacity of the Deriver and the Repository can accommodate a larger number. Funds will also cover costs for banking additional hPSC lines generated by California researchers. 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 lines banked for each reporting period, 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 12-04 Awards with those under RFA 12-02 and RFA 12-03 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 hPSC lines and primary source cells received and banked. Pre-NGA negotiations with CIRM will

establish milestones for an anticipated annual banking rate (hESC lines, hiPSC lines and primary source cells received and processed as proposed) that will define a payment schedule, subject to adjustment based on actual and forecast banking of hPSC lines. Progress on this Initiative is important to CIRM. If the Repository does not meet its agreed to milestones for hPSC banking activities, unless delays are caused by delayed activities on the part of the Tissue Collectors and the Deriver, 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 bank primary source cells and 3 hiPSC lines each (minimally 1 line prepared for distribution and 2 lines stored) from a minimum of 3000 tissue donors within 4 years in California.

B. Institutional Eligibility

For this RFA, CIRM will limit the number of applications from each eligible institution to one. The CIRM hPSC Repository Award RFA (RFA 12-04) is open to non-profit and for-profit applicant organizations. To be eligible for this award, the applicant organization must have been operating a cell repository, not necessarily in California, for at least one year at time of application.

“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 15% time). The Repository has to be present and operated 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/or have relevant experience, and must be authorized by the applicant institution to establish and operate the Repository in California. By the application deadline, the PD must:

- Be an employee at 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 space and resources sufficient to carry out the proposed banking activities in California
- Have experience in operating and overseeing a cell banking facility.

By the time of funding, the PD must:

- Be an employee of the applicant institution and be at its California site (at least 15 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 15% 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 application will be evaluated in four key areas: 1) Quality of the Proposed Repository, 2) Feasibility, 3) Program Director and Team, and 4) Appropriateness of Budget.

1. Quality of the Proposed Repository. The proposed Repository is planned appropriately to achieve its goal of banking the applicant's proposed number of hPSC lines in California and distributing them worldwide.

Facility and Equipment:

- The proposed space (not funded by CIRM beyond Facilities Costs, see section IX.B.5) and equipment are suitable for reliably handling, storing and distributing hiPSC lines from at least 3000 tissue donors and corresponding primary source cell samples or hiPSC lines from a larger number of tissue donors as proposed, as well as additional hPSC lines derived by California investigators. The proposed space and equipment are suitable for reliably handling and storing two reserve hiPSC lines from at least 3000 tissue donors.

Cell Banking Procedures:

- The proposed hPSC banking program will likely result in an efficiently produced, high quality hPSC resource.
- The proposed cell banking procedures, i.e. cell line shipment to the hPSC Repository and to customers, cell line expansion, cryopreservation and storage are suitable for achieving effective and reliable distribution of hPSC lines.
- The hPSC line characterization assays and the minimal release criteria for all assays are appropriate to ensure distribution of high quality hPSC lines. The information contained in the Certificate of Analysis is appropriate for assuring and assessing hPSC line quality.

hPSC derived by California researchers:

- The Repository's acceptance criteria for hPSC lines derived by California researchers, i.e. lines other than those derived pursuant to RFA 12-03, are consistent with broad utility of banked hPSC lines for scientific discovery research and for drug discovery and development.

Quality Control:

- A comprehensive quality control (QC) program is in place to regulate activities and to detect and resolve any emerging QC problems.
- The applicant institution has a record of documentation through Standard Operating Procedures (SOPs), batch records, and master files that ensures appropriate QC and recording of cell production activities. Materials and procedures used to prepare each master cell bank and distribution cell banks are traceable. All data on a particular cell line are collated or referenced in a cell line master file.
- Automated systems are in place for monitoring and protecting the physical integrity of samples and for inventory control.
- Regular audit plans are in place to ensure compliance.

hPSC Line Distribution:

- Access to hPSC lines by future customers worldwide is facilitated by suitable online tools to obtain information.
- The proposed costs per vial are justified.
- The terms of the Material Transfer Agreement (MTA) covering already existing hPSC lines derived by California researchers and accepted into the Repository

are appropriate and do not pose unreasonable barriers to potential interest in the hPSC lines by non-profit or for-profit customers. (The terms of the MTA covering hiPSC lines derived pursuant to RFA 12-03 will be reviewed by CIRM and will NOT be reviewed by the GWG.)

Cell Line and Data Management Systems:

- The proposed tool for the collection of demographic, medical and diagnostic information, to be used by the Tissue Collectors, is well designed to harmonize collection of this information and can be easily implemented at different data collection sites.
- The proposed standards for labeling of individual specimens are appropriate.
- The proposed hardware and software capacity and quality are adequate for tracking hPSC lines and for managing internally and for interrogating externally relevant information associated with hPSC lines.
- If proposed, data and information acquired by future hiPSC users can be effectively collected and added or linked to the online data system.
- An appropriate process is in place to facilitate re-contact of tissue donors by the Tissue Collectors or their institutions, if requested by hiPSC line users and permissible under the effective IRB protocol and informed consent document.
- If proposed, the medical data analysis tool brings novel approaches to data analysis by Repository customers and enables meaningful interrogation of hPSC line-associated demographic, medical and diagnostic information.

Management and Sustainability Plans:

- The proposed management plan is well thought out and is likely to enable effective operation of the Repository.
- The Repository has a reasonable plan to be sustainable at completion of CIRM funding.

2. Feasibility.

- The plan to establish or expand and to operate the proposed Repository in California can be reasonably achieved in a timely fashion.
- The proposed timeline is realistic to establish or expand the Repository facility, to bank the required number of hPSC lines and primary source cells, (from a minimum of 3000 tissue donors or larger numbers as proposed) and to make the coded demographic, medical, and diagnostic information accessible.

3. Program Director (PD) and Team.

Track Record:

- Evidence of prior success and track record supports the qualification of the PD to oversee the establishment and/or expansion and the operation of the proposed Repository.

PD Commitment:

- The PD's level of commitment heightens the probability for success of the Repository.

Appropriate Team:

- The PD and team have appropriate experience and expertise to establish/expand, equip, operate, manage and quality control all components of the proposed Repository.
- The team has experience in production, release and maintenance of master cell banks and distribution cell banks of hESC and/or hiPSC cell lines.
- The team includes individuals with appropriate expertise for creating and maintaining the proposed information infrastructure.

Collaborations:

- Any proposed services from, or collaborations with, subcontractors are critical and integral to the success of the Repository, and there is a reasonable plan to ensure communication amongst collaborators.

5. Appropriateness of Budget.

- The budget for all proposed activities is reasonable and well justified. If not, reviewers will be instructed to lower the score.
- For hiPSC lines derived pursuant to RFA 12-03, the costs for cell banking procedures (shipment, expansion, characterization, cryopreservation and QC) are well delineated on a per tissue donor basis (primary source cells and hiPSC lines, 1 line per sample for distribution and 2 per sample as reserve).

IX. Application Procedure

Applicants must follow these instructions for submission of a Letter of Intent (LOI) and an Application for RFA 12-04, CIRM hPSC Repository 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 hPSC Repository 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. master files, SOPs, letters of collaboration)

The Application includes the following sections:

1. Abstract (up to 1500 characters in Part A)
State the goals of the proposal. Summarize the overall plans for the establishment and operation of the proposed Repository and how these will meet the stated objectives of the RFA.

2. Public Abstract (up to 1500 characters in Part A)
In lay language, briefly describe the proposed Repository 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 Repository 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 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 technical staff, co-directors (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 fifteen percent (15%) effort. Personnel who 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 experience, accomplishments and/or special skills related to the proposed activities. 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, supplies and equipment for all banking activities, i.e. hPSC line handling, quality control and information technology infrastructure, must be justified in detail, including all subcontracts and consulting fees. For hiPSC lines derived pursuant to RFA 12-03, present the costs for cell banking procedures on a per tissue donor basis (primary source cells and 3 hiPSC lines, at least 1 hiPSC line expanded and characterized for release for distribution and up to 2 hiPSC lines less expanded and characterized as a reserve). 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.

If, to achieve the objective of the project described in Part B, the applicant will require funding from sources other than CIRM, then the applicant must specify and justify the added cost and identify funding sources that will enable conduct of the project (in the Part A section "Budget Justification").

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-Directors, 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 PD of the CIRM RFA 12-04 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 setting up the Repository facility at the applicant institution in California should be itemized and justified. Equipment costs should not be included as allowable direct costs in indirect cost calculations.

• Consultants/Subcontracts
Grantees who subcontract CIRM-funded work should note that CIRM-funded activities must generally be conducted in California. The actual Repository must be located in California.

Aside from small consulting contracts, Grantees 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.)

Grantees 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 (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. Facilities, Resources and Collaborations (up to 2 pages in Part B)
Describe the facility/space (not funded by CIRM beyond Facilities Costs, see section IX.B.5) that will house the proposed Repository, and the equipment and other resources needed for the creation of the Repository or for the expansion of an existing cell repository, and how they will accommodate the expected handling and storage capacity necessary for hiPSC lines and corresponding primary source cell samples from at least 3000 tissue donors (or hiPSC lines and primary source cell samples from a larger number of tissue donors as proposed, see section IX.B.9a), as well as additional hPSC lines derived by California investigators. If a new facility is proposed, describe its location in California as well as address the equipment and resources available for the Repository. Indicate how risk of catastrophic facility failure will be minimized. Provide a short description of other resources and assets and the environment available to you that will support the establishment and operation of the proposed Repository. If collaborations are integral to the success of the project, describe their contribution and how they will be managed.

8. Acceptance Criteria (up to 1 page in Part B)
8a. hiPSC generated pursuant to RFA 12-03: It will be the responsibility of the Deriver to ensure that the hiPSC lines (3 per tissue donor) generated under the RFA 12-03 Award and the primary source cells meet proposed and, if appropriate, pre-NGA negotiated specifications. All hiPSC lines generated under that Award and primary source cells that meet those specifications will be accepted into the Repository.

8b. hPSC derived by California researchers: List minimal acceptance criteria for inclusion of an hPSC line in the Repository. The criteria should address
- whether the hPSC line was acceptably derived (see section XII.C of this RFA for relevant regulations); if the hPSC line was derived using CIRM funds, it was acceptably derived.
- appropriate criteria for history, identity and characterization
- extent and quality of associated demographic, medical and/or diagnostic information
- whether informed consent is consistent with the goals of the CIRM hiPSC Initiative to bank hPSC lines with broad availability and broad utility.

CIRM encourages the Repository to accept CIRM-funded hPSC lines under reasonable terms.

9. Cell Banking Procedures (up to 4 pages in Part B)
9a. hPSC banking program:
It will be the Repository's responsibility to accept 3 hiPSC lines per tissue donor, generated by the Deriver, and corresponding primary source cells, into the Repository. Propose and justify a banking approach for this Initiative describing the size of master and distribution cell banks for minimally 3000, or more, hiPSC lines (e.g. at least 1 hiPSC line per tissue donor), and storage of the remaining two hiPSC lines and primary source cells (3000 or more) received from the Deriver. Based on your projected costs for hiPSC line handling, and assuming banking of additional existing hPSC lines generated by California investigators, state and justify the proposed number of tissue donors (primary source cells and 3 hiPSC lines per tissue donor) you will be able to include in your proposed hPSC banking program. In making those calculations, take the projected costs for implementing and operating your proposed "Cell Line and Data Management System" (see section IX.B.11) and "Medical Data Analysis Tool" (see section IX.B.12), if proposed, and other costs into account (as detailed in the Budget Justification, see section IX.B.5).

9b. hPSC line shipment:
Justify and describe concisely, but in sufficient detail to permit evaluation, the shipping methods and conditions for incoming hPSC lines and primary source cells and for distribution of hPSC lines to customers that ensure samples are received and delivered with minimal/no effect on cell line/sample integrity; describe the process for adherence to shipping best practices for hPSC. Append an example of a cell line submission form (in Part D), to be used for hPSC lines from California researchers.

9c. hPSC line expansion and storage:
Justify and describe concisely, but in sufficient detail to permit evaluation, the methods that will be used for the expansion, for the cryopreservation and for the storage of hPSC lines and primary source cells. For hiPSC lines generated by the Deriver and destined for release for distribution (at least one per tissue donor) and for hPSC lines generated by California investigators, describe the approach that will be used for creating a master cell bank for each cell line and for corresponding distribution cell banks and their respective sizes. Describe and justify the minimal release criteria. For hiPSC lines generated by the Deriver and stored as a reserve (up to two per tissue donor), describe the level of expansion and storage. Explain the procedures for back-up storage (in case of facility failure) and inventory procedures for hiPSC lines.

9d. hPSC line characterization, Certificate of Analysis (CoA):
Provide a table listing the assays that will be performed by the Repository to arrive at the CoA for hiPSC lines generated by the Deriver and destined for

release for distribution (at least one per tissue donor) and for hPSC lines generated by California investigators; include the minimal release criteria in the table. Justify and describe concisely, but in sufficient detail to permit evaluation, each assay, and justify the minimal release criteria. List additional cell product characteristics, if applicable, that will be guaranteed with the sale and shipment of each hPSC line. Append (in part D) a sample CoA. For hiPSC lines generated by the Deriver and stored as a reserve (up to two per tissue donor), describe the level of characterization.

10. Repository Documentation and Quality Control (up to 2 pages in Part B)
Describe the quality control (QC) program that will be used to monitor all cell banking procedures, the essential equipment, and batch record systems, raw materials tracking systems and cell line tracking systems. Indicate which assays and procedures used for hPSC banking (see section IX.B.9) have already been or will be standardized using quality-controlled reagents, and explain whether they are or will be qualified or validated. For assays that will not be standardized, qualified or validated, justify why. Provide an example (in Part D) or reference to a master file of an hESC or hiPSC line that your institution/facility has previously produced. Provide a list or link to all Standard Operating Procedures (SOPs) pertaining to hPSC line banking procedures (see section IX.B.9) and all quality management SOPs to be utilized. Provide a Quality Systems design document (in Part D) that describes the underlying mechanisms and management systems related to quality testing and monitoring of personnel and procedures which will provide the basis for high quality cell production and distribution. This will include specifics related to internal and external audits, testing and release criteria, monitoring systems, and corrective action procedures to ensure compliance.

11. Cell Line and Data Management System (up to 3 pages in Part B)
Describe the information technology (IT) infrastructure (hardware and software) and automated systems that will be used to reliably track and monitor hPSC lines to protect their physical integrity, for inventory control from receipt to distribution, and to maintain proper linkage with associated coded demographic, medical and/or diagnostic information.

Tissue Collectors determine which demographic, medical and/or diagnostic data will be collected from tissue donors; this will vary from project to project. However, in order to harmonize data collection across RFA 12-02 projects and enable uniform data handling at the Repository, the Repository will develop a new or deploy an existing tool, ideally web-based, for the collection of this data by the Tissue Collectors. This tool should allow inclusion of data from electronic medical records and additional sources, and may need to be customized to allow acquisition of unique data sets as required by individual RFA 12-02 awards. Describe and/or reference the data collection tool you will develop or deploy for use by the Tissue Collectors, and elaborate on how collection of diverse data sets can be accommodated. Some coordination with Tissue Collectors, prior to

NGA release, may be necessary to harmonize collection of data across all RFA 12-02 projects.

Describe the standards for labeling of individual specimens to be used by the Tissue Collectors. They should include unique IDs for tracking collected tissues/cells, coded private tissue donor information and derived primary source cells and hiPSC lines.

Describe the information infrastructure (hardware and software) that will be used to reliably store and track the coded demographic, medical and/or diagnostic information associated with each hPSC line. Describe web-based tools that will be developed or deployed to enable future customers to obtain all coded information associated with each hPSC line banked under this Initiative, and to trace which hiPSC lines belong to the same cohort, i.e. all lines derived through a given RFA 12-02 Award (same disease, potentially different families, controls) and to specific subgroups within each cohort (as specified in the RFA 12-02 Award, e.g. phenotypic subgroups within given disease). State whether data collected by future hiPSC line users, such as genomic sequence, expression analysis, epigenetic analysis, SNP analysis, publications, or other information will be linked or added to the Repository's hiPSC line information database and made accessible to other hiPSC line users. If so, describe how this will be accomplished.

The ability to re-contact individual tissue donors, if permissible under the effective IRB protocol and informed consent document, will remain with the Tissue Collectors' institutions. Outline how the Repository will facilitate the interaction of hiPSC line users who request to re-contact tissue donors with Tissue Collectors' institutions.

12. OPTIONAL: Medical Data Analysis Tool (up to 2 pages in Part B)

To enhance the utility of the demographic, medical and diagnostic data stored at the Repository, and to facilitate optimal selection of hiPSC lines by potential customers, CIRM encourages the creation of new, or deployment of existing, online tools that enable search-based analyses of medical data within and across different RFA 12-02 projects, such as the ability to search for hiPSC lines from tissue donors who have both diabetes and cardiovascular disease, or for hiPSC lines from female African American donors who carry a specific SNP, irrespective of disease. If you choose to do so, describe those tools. CIRM further welcomes inclusion of additional features in the Repository's information infrastructure that will enable optimal use of the hiPSC lines and the data associated with them.

13. Distribution of hPSC Lines and Associated Tissue Donor Information (up to 1 page in Part B)

Future customers will have access to information associated with each hPSC line through online tools (see IX.B.11, 12), and the cost of hPSC lines for customers will be justified in the sustainability plan (see IX.B.15). Terms of Material Transfer

Agreements between the Repository and future customers are discussed in section IX.B.15.

Describe all additional procedures involved in providing access to hPSC lines and their associated information to potential customers worldwide and append (in Part D) relevant policies and forms, such as the process for obtaining assurance from viewers of coded private tissue donor information to refrain from seeking tissue donor identity and the process by which future customers will submit requests for cell lines.

14. Management Plan (up to 2 pages in Part B)

Describe plans for the development, oversight, management and maintenance of the Repository. Describe the qualifications and responsibilities of the PD and other personnel involved in managing the Repository, including the Information Technology (IT), the QC, the Production and the Characterization Managers. Describe a plan to ensure that use of CIRM funds for the acceptance of hPSC lines into the Repository is limited to those generated by California researchers.

15. Sustainability Plan (up to 2 pages in Part B)

Describe your strategy for ensuring long-term sustainability of the CIRM hPSC Repository at least 10 additional years following completion of CIRM funding through this RFA. Identify the proposed hPSC line fee schedules; it is expected that California researchers will be provided with the most favorable terms. Describe other mechanisms and revenue sources you intend to employ in order to long-term sustain the Repository. Provide information on the history of the applicant institution and the track record of the PD that supports the ability to maintain the Repository for 10 years post award.

The hiPSC lines derived pursuant to RFA 12-03 will be governed by a Repository Agreement between CIRM and the Repository, and the Material Transfer Agreement (MTA) between the Repository and third parties (see section IV and Appendix B). Regarding already existing hPSC lines derived by California researchers and accepted into the Repository, append (in Part D) the Deposit Agreement and the MTAs for non-profit and for-profit customers you currently use and would intend to use. Justify the proposed terms in those agreements.

16. Project Timeline (up to 1 page in Part B)

Provide a realistic timetable for setting up the Repository or expanding an existing repository. Delineate how the anticipated volume of hPSC line banking (hiPSC lines and primary source cell samples from at least 3000 tissue donors or a larger number as proposed, as well as additional hPSC lines derived by California investigators) will be handled. Take into consideration the time it takes to bank an hPSC line from acquisition through expansion, characterization, and preparation of the CoA, to providing information relevant to each hPSC online.

17. 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 hPSC Repository RFA 12-04 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 applicants may submit limited supplemental materials that provide critical new information related to their 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, confirmation of funding secured from other sources acquired since the application submission deadline.

2. Within the one-page letter, additional information acquired since the application submission deadline regarding the space secured by the application deadline to house the Repository.

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.

4. Within the one-page letter, provide specific citation(s) to journal publications related to the proposed Repository 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.

X. Schedule of Deadlines and Reviews

Letters of Intent (LOI) 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 Award	Q2, 2013

XI. Contacts

For information about this RFA:

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For information about the review process:

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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.