RFA 12-02: CIRM Tissue Collection for Disease Modeling Awards

I. Purpose

There can be tremendous variability in the course of human diseases, such as the timing of disease onset, its progression, severity of symptoms, and response to therapeutic interventions. Lack of adequate models representing this variability contributes substantially to the high cost of drug development. Variability in disease course stems, at least partially, from genomic heterogeneity in the patient population. While this heterogeneity is not represented in classic rodent genetic models of human diseases, patient-derived human induced pluripotent stem cells (hiPSCs) provide an opportunity to explore human genomic heterogeneity using in vitro systems, or “disease in a dish” models. Particular interest lies in the development of disease in a dish models utilizing previously inaccessible cell types affected in a disease, e.g. neurons. Models are generated via reprogramming to pluripotency of patients’ easily accessible cells, such as those of blood or skin, followed by differentiation to relevant cell types. At the pluripotent stage, cells multiply indefinitely, so that large numbers of cells can be generated for studies designed to link unique aspects of patients’ disease manifestations and drug responses with their complex genetic causes.

Monogenic diseases with known genetic defects and high penetrance were ideal first targets for validating the idea that human disease can be modeled using hiPSC technology. Numerous studies supporting this idea have now been published, and many efforts are ongoing in California and worldwide pursuing this approach. More challenging is the notion of modeling polygenic diseases or diseases with well known single gene defects but low penetrance.

This Request for Applications (RFA) 12-02, CIRM Tissue Collection for Disease Modeling Awards, is one of three RFAs being released as part of the CIRM hiPSC Initiative. The overall goal of the Initiative is to generate and ensure the availability of high quality disease-specific hiPSC resources for disease modeling, target discovery and drug discovery and development for prevalent, genetically complex diseases. This RFA 12-02 will support procurement of the donor tissue samples needed for the establishment of this resource.

II. Objectives

Successful hiPSC-based modeling of genetically complex diseases requires a population-based approach to create a comprehensive collection of cell lines. The RFA 12-02 Awards will fund clinicians and other scientists to identify, recruit and obtain consent from sufficient numbers of affected and unaffected individuals (controls) to represent effectively a given disease's manifestations. These clinicians and scientists ("Tissue Collectors") will then collect tissue samples for hiPSC line generation, along with appropriate demographic, medical and/or diagnostic information.

Tissue samples collected under this RFA will be provided to the recipient of the CIRM RFA 12-03 hiPSC Derivation Award ("Deriver") for the production of hiPSC lines. Once the Deriver has generated, characterized and released the hiPSC lines, the Deriver will ship them to the CIRM human pluripotent stem cell (hPSC[1]) Repository that will be established under RFA 12-04. The Repository will expand, characterize for quality, bank and distribute cell lines to interested investigators. In order to ensure continuity of the hiPSC resource, CIRM will own the hiPSC lines generated pursuant to RFA 12-03 (see section IV). Donor-specific demographic, medical and/or diagnostic information will be associated with each line; it will be compiled by the Tissue Collectors and made available by the Repository. The Repository will distribute the hiPSC lines according to pricing schedules approved by CIRM.

Separate from this set of RFAs, CIRM has partnered with NIH's National Institute for Neurological Disorders and Stroke (NINDS) to fund consortia that develop lines from patients with Huntington's Disease, Parkinson's Disease, and Amyotrophic Lateral Sclerosis (ALS). Thus, to avoid redundancy, this RFA excludes proposals that target these disease indications. In this RFA, CIRM seeks proposals targeting prevalent diseases/conditions with multiple genetic contributions (not monogenic diseases) such as, but not limited to:

- Alzheimer's disease
- Autism spectrum disorders
- Autoimmune diseases
- Bone / Cartilage diseases
- Cardiovascular disease
- Cerebral palsy
- Concussion pathologies
- Diabetes

[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).

- Epilepsy
- Kidney Diseases
- Liver Diseases
- Migraine
- Respiratory diseases
- Schizophrenia

III. Project Requirements

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

Donor Consent: A primary objective of these awards is to make disease-specific hiPSC lines broadly available as tools for disease modeling, study of disease mechanisms and for drug discovery. The protocol for tissue procurement and for collection of demographic, medical and/or diagnostic information should therefore include comprehensive donor informed consent. Comprehensive consent includes, but is not limited to, permission to use donated tissues and derivatives in future research that cannot be determined at this time and in research that may lead to the development of new medical treatments, and thus may have commercial utility (e.g. drug screening), unless the applicant justifies limitations to consent in the application (see section IX.B.10 of this RFA). To ensure broad utility of hiPSC lines derived under this Initiative, CIRM has developed a model consent form designed to be compliant with CIRM regulations and the requirements of this RFA. The model form may be found in Appendix A. Applicants should either use the model consent form or another consent form that supports the goals of this RFA.

Tissue Sample Collection and Shipment: The Tissue Collectors will send the procured tissues/cells to the Deriver. The Deriver will cover shipping costs from the Tissue Collector. To enable the procurement of uniform starting material, Tissue Collectors will use the tissue collection and shipping protocols provided by the Deriver (to be determined). 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 (see section IX.B.11 of this RFA). In that case, the Tissue Collector 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.

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.

In addition to procurement from new donors, samples may also be obtained from existing cell and tissue repositories provided they are 1) preserved in a manner

amenable to hiPSC derivation, 2) associated with appropriate demographic, medical and/or diagnostic information and 3) able to conform to the CIRM consent requirements referenced above. It will be the responsibility of the Tissue Collector to re-consent original tissue donors if indicated, arrange permissions necessary and arrange shipping to the Deriver.

Coding of Private Tissue Donor Information: Tissue Collectors will compile donor-specific demographic, medical and/or diagnostic information from all tissue donors. It will be the responsibility of the Tissue Collectors to code[2] and manage this private tissue donor information in accordance with all applicable rules and regulations including 45 CFR 46 (Common Rule), the Health Insurance Portability and Accountability Act of 1996 ("HIPAA") and the Office of Human Research Protection Guidance on Research Involving Coded Private Information or Biological Specimens http://www.hhs.gov/ohrp/policy/cdebiol.html, while meeting the goals and objectives of this RFA. The Tissue Collectors must also obtain any written patient authorization that may be required under applicable state (including but not limited to California) and federal laws and rules, including, but not limited to, HIPAA. 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.

Re-Contact of Tissue Donors: The ability to re-contact individual tissue donors, as needed to obtain any required additional information or consents and if permissible under the effective Institutional Review Board (IRB) protocol and informed consent document, will remain with the Tissue Collectors' institutions. Tissue Collectors must maintain, in a secure manner, the key to enable re-identification using the codes.

Collection and Transfer of Private Tissue Donor Information: Tissue Collectors will transfer coded private tissue donor information to the Repository. In order to harmonize data collection across the Initiative, the Repository will provide a tool, ideally web- based, for use by the Tissue Collectors in collecting and transferring private tissue donor information. 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

[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.

common to all RFA 12-02 projects across diseases, in order to facilitate the management of this information at the Repository.

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.

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.

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 $4 million to support the collection of tissue samples from 3000 or more individuals (patients and appropriate controls) through approximately three to ten awards. Award funding will be based on justifiable direct project costs for the proposed number of tissue samples to be procured. Projects will be funded for up to two (2) years. Given the urgency of CIRM's mission, and to ensure optimal coordination of activities within the hiPSC Initiative, all approved applications must 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 CIRM's President grants an extension based upon compelling justification of the need for additional time.

For all awards, CIRM has the right to negotiate funded project activities, target numbers for tissue donor enrollment and tissue collection and shipment for each reporting period, timelines and budgets prior to issuance of the NGA, subject to renegotiation semi-annually 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 12-02 awards with those under RFA 12-03 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 approved proposals from non-profit and/or for-profit institutions (separately or in collaborations) through grants. Institutions will receive grant funding through quarterly payments with adjustments semi-annually for actual tissue donor recruitment, tissue collection and shipment. Pre-NGA negotiations with CIRM will establish milestones for an anticipated semi-annual tissue donor recruitment and tissue collection rate that will define a payment schedule, subject to adjustment based on actual and forecast recruitment. Progress on this Initiative is important to CIRM. If the Tissue Collector does not meet the agreed to commitments for tissue donor recruitment and tissue collection, allowing for reasonable delays, 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

CIRM will only accept a Letter of Intent (LOI) for projects that meet the following Eligibility Criteria.

1. The project must use only human cells collected from tissue donors or existing banked human cells.

2. The targeted disease must be genetically complex. Projects to pursue diseases caused by highly penetrant single gene defects (such as spinal muscular atrophy, fragile X syndrome, Marfan syndrome) are NOT in scope for this RFA. If a specific genetic defect is known to impact the targeted disease, it would still be eligible if either (a) other factors significantly contribute to the disease's manifestations and penetrance; or (b) many patients suffering from the same disease lack this mutation, and such patients are included in the study.

3. The targeted disease must be prevalent, i.e. it is NOT a rare disease with a prevalence of fewer than 200,000 affected individuals in the United States.

B. Institutional Eligibility

For this RFA, CIRM is not limiting the number of applications from a single organization. Both non-profit and for-profit organizations are welcome to apply. At the time of the application deadline, the applicant organization must be located in California (that is, the organization must have employees who are conducting business or operations at a location in California). At the time of funding, the applicant organization must be conducting or managing research or clinical activities, or operate a repository of tissue donor biospecimen and/or patient medical data, in California. If these requirements are not met, CIRM may terminate all further action on the 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".

CIRM encourages collaborative endeavors between non-profit and for-profit organizations.

C. Principal Investigator (PI) Eligibility

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

- Be an independent investigator or faculty member in California at a non-profit applicant institution, or have an equivalent position and be an employee in California (at least 50-percent time) of a for-profit applicant institution
- Have authority from the applicant institution to staff the proposed project
- Have commitment from the applicant institution to provide laboratory space and shared resources sufficient to carry out the proposed project.

D. Co-Principal Investigator (Co-PI) Eligibility

This RFA does not allow designation of a Co-Principal Investigator (Co-PI).

E. Percent Effort Requirements

For this RFA, PIs must be willing and able to commit a minimum 5% 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.A 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 PI and disease target described 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 full GWG (scientists and patient advocates) will then review the entire portfolio of applications, taking into consideration the following criteria:

- Appropriate balance of targeted diseases
- Appropriate balance between feasibility, risk and benefit.
- Other considerations from the perspective of patient advocates.

One goal of programmatic review will be to achieve a balance of different disease areas that holds the greatest promise for future impact on disease understanding and mitigation using the banked hiPSC lines. In order to achieve this balance, the GWG may recommend prioritization of a lower scoring application over a higher scoring one.

The GWG will make funding recommendations to the ICOC, which will make final funding decisions.

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) Impact and Significance, 2) Rationale, 3) Quality of the Proposed Protocols 4) Feasibility, 5) Budget, 6) Qualifications of the Principal Investigator (PI) and Team Members, Resources.

1. Impact and Significance.

- The targeted disease is poorly understood at the molecular, cellular and/or genetic levels. Patient-derived hiPSC lines may enable insights into disease mechanism and genetics, leading to new biomarkers, diagnostics and/or therapeutics.
- The targeted disease represents a substantial unmet medical need; if novel therapeutic interventions can be developed using hiPSC-based studies, they have the potential to significantly impact disease in a large patient population.
- Lines derived from patients with the targeted disease will represent a unique resource or will significantly augment other world-wide collection/derivation efforts for this disease.
- The targeted disease is a prevalent, genetically complex disease (see sections II and VI.A).

2. Rationale.

- Important unanswered questions relating to disease mechanism and/or genetic factors contributing to the targeted disease can be addressed using hiPSC lines;

the proposed number of disease and control tissue donors is adequate to address these key questions.
- The rationale for the selection of tissue donors is sound, the proposed tissue donors or existing banked cells adequately represent the genetic and ethnic complexity of the patient population and appropriate controls are included. Female and male donors are, as appropriate, included.
- The targeted disease, as represented by the proposed patient subpopulations, is likely to be amenable to hiPSC-based disease modeling and drug discovery. Cell-based assays can likely be developed for drug screening and development.
- Demographic, medical and/or diagnostic information proposed for collection is appropriate to inform hiPSC-based disease modeling and supports maximal potential utility of the hiPSC lines.

3. Quality of the Proposed Protocols.
- The proposed tissue donor consent and re-contact approach are adequate to support the goals of this RFA, i.e. to generate a hiPSC resource of broad utility and broad availability to investigators at non-profit and for-profit institutions while protecting the rights of tissue donors.
- If limitations are placed on cell use, they are justified, taking their effect on the potential utility of the hiPSC lines into account.
- Private tissue donor information and protected health information is managed and coded in accordance with all relevant state and federal laws and regulations and with CIRM regulations and all patient authorizations are in compliance with applicable state and federal laws to enable the contemplated uses and disclosures.
- Management of tissue inventories and associated demographic, medical and/or diagnostic information, tracking of consent limitations (if applicable) and implementation of tissue/data withdrawal is well thought out.
- If the applicant proposed tissue collection and shipment protocols to avoid collection of blood or skin, their use is justified in the targeted patient population, and the protocols are suitable for hiPSC derivation. (Note, the Deriver will provide the tissue collection and shipping protocols to be used by the Tissue Collectors. The applicants were asked to propose such protocols if blood or skin cannot be reasonably collected from the proposed patient population.)
- If existing banked cells are included, they are preserved in a manner amenable to hiPSC derivation.

4. Feasibility.
- Obtaining institutional review board (IRB) approval(s); identification, recruitment and consenting of tissue donors; collection and shipment of tissues; and acquisition and coding of demographic, medical and/or diagnostic information can all be reasonably achieved for the proposed number of disease and control samples in the proposed time frame.
- The investigator has access to appropriate patient and control populations and/or existing banked cells.
- Tissue collection at sites outside California, if applicable, is appropriately justified.

- The proposal makes adequate use, if applicable, of existing repositories or databanks and their associated demographic, medical and/or diagnostic information.

5. Budget.

- The proposed average costs per tissue donor for the recruitment, consenting and collection of demographic, medical and/or diagnostic information, or for the procurement of existing banked cells/tissues, is justified and reasonable. If the applicant proposes a tissue collection and shipment protocol, to avoid collection of blood or skin, the relevant proposed costs per tissue donor are justified and reasonable.

6. Qualifications of the Principal Investigator (PI) and Team Members, Resources.

- The PI or team members, either individually or collectively, have experience with and/or knowledge of 1) clinical aspects of the targeted disease, 2) the complex genetics of the targeted disease and 3) research using hiPSC to model disease.
- The PI and/or team members have the training and experience to obtain IRB approvals for projects similar to the one proposed, and to carry out the proposed tissue donor recruitment and consenting, and the collection of extensive demographic, medical and/or diagnostic information as applicable to their proposal. (Note, the Repository will provide the data collection tool to be used by the Tissue Collectors. The applicants are asked to provide information about their current data collection approaches/tools to illustrate their experience with medical data compilation).
- The PI and/or team members have experience with management of records, maintaining tissue donor confidentiality while enabling re-contact if indicated and with transferring coded donor-specific data to others.
- The PI and/or team members have experience with executing tissue collection and shipping protocols under standard operating procedures and have appropriate mechanisms for compliance in place.
- The proposed sites are adequate for recruiting the proposed types and numbers of disease and control tissue donors; the resources available to the applicant and team heighten the likelihood of success of the proposed project. The PI and the team have experience in working with patient advocates and disease foundations, as appropriate.

IX. Application Procedure

Applicants must follow these instructions for submission of a Letter of Intent (LOI) and an Application for RFA 12-02, CIRM Tissue Collection for Disease Modeling Awards. 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 PI 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 PI and the disease target must be the same as those described 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 Tissue Collection for Disease Modeling Awards 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. consent form, source document or medical data collection form, letters of collaboration)

The Application includes the following sections:

1. Abstract (up to 1500 characters in Part A)
State the goals of the proposal and explain the rationale for the choice of disease targeted by the proposal and its significance. Summarize the overall plans of the proposed project 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 project and how it will contribute to the application of stem cell biology toward therapeutic and diagnostic innovation. This Public Abstract will become public information; therefore, do not include proprietary or confidential information or information that could identify the applicant (e.g., PI 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., PI 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 technical staff, trainees, 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 PI, who is required to commit a minimum of five percent (5%) 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 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 must be justified in detail, including all subcontracts and consulting fees. Present the costs of this project (for recruitment, consenting, collection of demographic, medical and/or diagnostic information, or for the procurement of existing banked cells/tissues and associated information) on an average per tissue donor basis. Include $100 for blood or skin tissue collection from each donor, assuming these are the tissues more likely to be specified by the Deriver (see sections III and IX.B.11 of this RFA). Should other sources of tissue be more appropriate for collection, include the costs for the execution of those collection protocols in the budget information.

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 Principal Investigator, 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. Institutions may request stipend, health insurance and allowable tuition and fees as costs for trainees. Administrative support salaries should be covered exclusively by allowed Indirect Costs.

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

• Travel
Tissue Collectors (PIs of RFA 12-02 Awards) are 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
Grantees who subcontract CIRM-funded work should note that CIRM-funded activities must generally be conducted in 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. Under this RFA, CIRM may allow increases to these limits for costs associated with tissue collection at sites outside California with appropriate justification. Such activities include tissue donor recruitment, tissue collection and shipping, IRB activities, and acquisition of demographic, medical and/or diagnostic information.

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, tuition and fees 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, tuition and fees, 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. Disease Target (up to 1 page in Part B)

Describe the disease or condition targeted for tissue collection, including its main manifestations, known underlying mechanisms and etiology, and its prevalence in California, the US and worldwide. Explain how the chosen disease, or subcategory of disease, is in scope with the goal of this RFA to target prevalent, genetically complex diseases by referring to the Project Eligibility Criteria listed in section VI.A.

8. Scientific Rationale, Significance and Impact (up to 3 pages in Part B)

Explain how the chosen disease, or subcategory of disease, is likely to be amenable to hiPSC-based disease modeling, what types of assays or approaches you envision can be developed using hiPSC, the relevance of those assays to improving understanding and/or mitigation of disease, and cite or provide relevant data that support these notions. Describe the potential for hiPSC technology, as compared to existing disease models, to impact our understanding of disease mechanism and etiology and for improving the discovery and development of treatment options for large patient populations with significant unmet medical needs.

9. Tissue Donor Selection (up to 2 pages in Part B)

Identify the specific patient population(s) to be recruited for tissue collection and justify their inclusion in this study. Describe any clinical features, genetic or genomic status (e.g. SNP profile), ethnicity and gender, and other relevant

parameters that support the utility of derived hiPSC lines for future disease modeling studies, drug target discovery, and/or drug screening and development. Elaborate on the potential utility of individual cell lines or a cohort as a whole. Describe any features of the proposed patient population that may make the resulting hiPSC lines a unique resource; discuss in the context of other world-wide collection/derivation efforts for this disease. Describe control individuals who will be included and explain why.

Provide a table listing the number of patients, stratified into patient subtypes if applicable, and control individuals who will be included in this study, and justify those numbers. If applicable, list tissue donors' specific genetic defects/risk factors (genes/SNPs) known to be associated with the targeted disease and their penetrance/associated risk increase in the table and indicate whether these individuals have already been identified. CIRM anticipates that proposed projects can vary in size from a few dozen to a few hundred donor individuals, depending on the genetic complexity and phenotypic variability amongst patients suffering from the chosen disease or subcategory of disease.

10. Tissue Donor Recruitment, Consenting and Follow-up/Re-contacting (up to 2 pages in Part B)

Append (in part D) the consent form you are planning to use for this project, pending institutional review board (IRB) approval. A model consent form, developed by CIRM to be compliant with CIRM regulations and the requirements of this RFA, may be found in Appendix A. If your consent approach differs from that of the CIRM model consent, justify the differences. Provide information on your average time to IRB approval. Append (in part D) a letter(s) of support from the IRB(s) that will be responsible for providing approval for the proposed tissue collections, indicating that in principle they are comfortable with broad tissue donor consent as contemplated for this RFA.

Describe the team's access to relevant donor populations, the strategy to be used for tissue donor recruitment (affected individuals and unaffected controls), and comment on typical recruitment failure rates. Describe the planned involvement of patient advocates and patient organizations, if applicable, in the recruitment process. If tissue donors who place restrictions on cell utilization will be included in this project, describe the effect this would have on the utility of the resulting hiPSC lines, and justify their inclusion.

Describe the mechanisms available to you for obtaining demographic, medical and/or diagnostic information, and for tracking tissue donors. Explain whether it will be feasible to re-contact tissue donors to provide information or obtain supplemental consent if necessary for this project or to inform future studies. Describe your experience with donor tracking and/or re-contact.

If existing banked cells/tissues will be used in this project, justify their inclusion, and append the form(s) (in part D) that were used to consent the cell/tissue

donors. If restrictions were placed on cell utilization, explain how re-consenting for broader use will be achieved or, if re-consenting is not intended, describe the effect this will likely have on the utility of the resulting hiPSC lines, and justify their inclusion.

11. Tissue Collection and Shipment (up to 1 page in Part B)

The Deriver will provide protocols/standard operating procedures (SOPs) for tissue collection (likely skin or blood) and shipment; these protocols should be used by all Tissue Collectors unless other tissues/cell types or protocols are required. Describe your experience with implementing tissue collection protocols and with maintaining compliance with SOPs.

If the proposed patient population is not amenable to the collection of either skin or blood samples, explain why and describe concisely, but with enough detail to permit evaluation, the tissue collection and shipment protocols you propose to implement.

12. Demographic, Medical and Diagnostic Information (up to 2 pages in Part B)

Generate a list of all demographic, medical and/or diagnostic information that already exists and/or will be collected from participating tissue donors to be associated with each hiPSC line. Describe how this information will facilitate discovery of disease-related phenotypes and development of drug screening assays in hiPSC-derived cells, or support other possible uses of the hiPSC lines. The Repository will provide a tool, ideally web-based, for Tissue Collectors to use for the compilation of demographic, medical and/or diagnostic information. In order to illustrate your experience with medical data compilation, explain the approach/tool you currently use and append (in Part D) an example of a source document or medical data collection form that you have used in the past for the collection of demographic, medical and/or diagnostic information.

The Tissue Collectors will transfer coded (see footnote in section III of this RFA) private tissue donor information to the Repository. Describe the processes/protocols that will be used to manage and code private tissue donor information in accordance with all applicable rules and regulations including 45 CFR 46 and the Office of Human Research Protection Guidance on Research Involving Coded Private Information or Biological Specimens http://www.hhs.gov/ohrp/policy/cdebiol.html. Furthermore, if the protocol involves the acquisition or development of protected health information (PHI) under the federal Health Insurance Portability and Accountability Act (HIPAA), explain how compliance will be maintained. Note that the Repository will provide the unique ID to be used by the Tissue Collectors. Describe the process for dealing with unintended breaches of tissue donor confidentiality. If existing banked cells will be used, describe the demographic, medical and/or diagnostic information available for those cells and whether additional information will be collected.

13. Data Management (up to 2 pages in Part B)
Describe the informatics tool that will be used to document the tissue/cell inventory and associated demographic, medical and/or diagnostic information. Explain how the security of the information will be maintained, how limits on consent/use of cells will be tracked (if applicable) and how requests for withdrawal of tissue and/or data will be implemented. Describe how the shipping of samples will be tracked. Describe the tools for data export to other entities.

14. Qualifications of the PI and Team (up to 1 page in Part B)
Briefly describe the expertise of the Principal Investigator (PI), team members, collaborators and/or consultants in the following three areas; 1) relevant clinical knowledge of the targeted disease, 2) the complex genetics of the targeted disease and 3) research using hiPSC to model disease. Expertise should also be evident from the Biographical Sketches in Part C.

Describe the experience of the PI and/or team members in obtaining IRB approval for this type of project, requiring broad consent for distribution of cell derivatives, in recruiting and consenting donors for tissue donations comparable to the ones required for this project and in managing and coding private tissue donor information in accordance with all applicable rules and regulations.

15. Collaborations, Assets, Resources and Environment (up to 2 pages in Part B)
List the proposed sites for patient recruitment, provide the rationale for their inclusion, append letters of collaboration acknowledging your access to patients at those sites if not your own, and justify the inclusion of any sites located outside California. Indicate how many tissue donors will be recruited at each proposed site. Include numbers of relevant patients currently treated or typically seen at the proposed sites to support the anticipated volume of donors and timeline. Explain whether, and if so how, you are taking advantage of existing repositories and registries that already have collected relevant patient data that can become part of the demographic, medical and/or diagnostic information associated with each hiPSC line. Describe any other resources available to you that will facilitate achieving the goals of the proposed project.

16. Project Timeline (up to 1 page in Part B)
Provide and justify a realistic timetable for obtaining IRB approval(s), recruiting and consenting the proposed numbers of tissue donors and collecting and shipping tissue samples.

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 PI may submit only a single LOI for this RFA.

All four parts of the CIRM Tissue Collection for Disease Modeling RFA 12-02 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 PI 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 PI 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 collaborations with additional sites for tissue donor recruitment established 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 are not allowed.

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 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.