Summary and Recommendations of the CIRM Human iPS Cell Banking Workshop

San Francisco, November 17-18 2010

EXECUTIVE SUMMARY

The California Institute for Regenerative Medicine (CIRM) is charged with supporting the development of cures and therapies based on stem cell science. CIRM has created a nimble portfolio of funding mechanisms to advance its therapy-centered goals in the face of continuous scientific breakthroughs in the field. Significant efforts have been made to include induced pluripotent stem cells (iPS cells) in this portfolio given the blossoming research in this area. In November of 2010, CIRM organized a workshop to assess the value of supporting more formal iPS cell banking efforts. The focus of an iPS cell bank would be to increase the number and quality of human cell lines available for therapeutic development activities such as *in vitro* disease modeling and high-throughput screening, although not cell therapy at this stage. Participants were asked for practical advice on the elements that would increase the impact of such a bank on the development of cures and therapies for human disease.

Workshop participants were enthusiastic about the concept of CIRM increasing its support of cell banking efforts in California. Although research and biobanking organizations have begun to offer iPS cell banking services, none of these banks have focused on optimizing the therapeutic value of these cells. Two independent banking needs were identified:

I. A banking repository to retain the iPS cell resources generated by the research community in California. This repository would increase the therapeutic value of each line by increasing the availability, quality, and comprehensive analysis of these cells.
II. A more comprehensive effort to generate iPS cells for disease modeling in areas of CIRM priorities. Cell banking centers, potentially linked to deep genomics screening efforts, would be involved in *in vitro* screening of disease population samples with the goal of identifying new candidate therapeutics.

Discussion centered on practical issues that would maximize the impact of iPS cell banking efforts, including performing experiments and collecting patient-related information that would increase the value of these lines. The consensus was that generation of iPS cell lines for therapeutic purposes would benefit from multidisciplinary input from stem cell scientists, geneticists, clinicians working with patients, and bioethicists and professionals with experience coordinating issues of patient consent and intellectual property. CIRM was seen as instrumental to facilitating these efforts through its funding and its leadership in this area.

BACKGROUND

Recent breakthroughs in the ability to generate human induced pluripotent stem cells (iPS cells) by reprogramming of somatic cells are having a dramatic impact on biomedical research. iPS cell lines are being generated from patients with a host of intractable diseases, from autism to heart disease to diabetes. These valuable pluripotent cell lines can be differentiated into cells that were previously inaccessible to researchers, such as human brain and heart cells, that carry the same genetic background as a patient with a specific disorder. iPS cells and their derivatives can be used to understand the biological properties of human cells, to generate *in vitro* models of human diseases, and to develop high-throughput screens to identify potential therapeutics or drug toxicities. The great promise offered by iPS cells is that studying human cells, which may reflect a disease phenotype more accurately than previous cellular models or animal models, will make therapeutic drug discovery faster, more efficient, and eventually, customizable to individual patients.

Several practical issues must be addressed to increase the impact of these stem cells on disease-based research. High quality iPS cell lines must be systematically generated from a diverse patient population and from appropriate control individuals for each disorder, and these lines must be made broadly available to the research community. In addition, careful documentation of iPS cell lines must be maintained in order to track biological characteristics such as cell and patient phenotypes, technical issues such as the method used to generate a line or the number of times the line has been passaged in culture, and legal aspects such as the degree of patient consent for the use of each line. Since iPS cell technologies are still in their infancy, different aspects of the process will need to be optimized before iPS cells can become reliable tools for therapeutic drug development. Reprogramming protocols need to be systematically compared; storage, culturing and expansion procedures need to be streamlined; and cellular characterization must be standardized. Rigorous and dynamic attention to these details, possibly through a centralized resource such as an iPS cell banking facility, could prove an invaluable asset for furthering the therapeutic potential of iPS cells.

WORKSHOP OUTCOMES

CIRM's iPS Cell Banking Workshop took place on November 17 and 18, 2010 in San Francisco. Participants comprised a diverse group of individuals engaged in different aspects of stem cell research, administration, and tissue banking (see Appendix I for the Agenda and participant list). The sessions were loosely organized by speaker expertise and included topics as diverse as methods of iPS cell derivation, the role of human cells in modeling diseases, genetic and epigenetic analysis of stem cells and their derivatives, and cell distribution and banking approaches. Participants were invited to comment on the need for iPS cell banks, and to give opinions about the organization and composition of such a bank. They addressed issues that would optimize the value of an iPS cell bank, challenges that might be faced in organizing and maintaining such a facility, and organizational models for the bank that would further CIRM's goal of promoting the therapeutic potential of stem cells.

I. Value of iPS Cell Banking in California

Many scientists with an interest in disease modeling, including California researchers funded by CIRM, are generating iPS cell lines from diverse groups of patients using a variety of different reprogramming methods. Investigators at academic research centers and in the biotechnology sector, however, do not have the resources to extensively characterize each of these lines and make them generally available to the biomedical community once their primary research objectives are completed. In addition, scientists who are interested in using human cells do not always have the clinical contacts to recruit adequate patients and controls, and clinicians with access to patients might not have the expertise or the resources necessary to create iPS cells. Given these challenges, workshop participants indicated that increased support of iPS cell generation and banking would be of potential benefit to the community for the following reasons:

1. iPS cell lines generated in research laboratories could be preserved and made more readily available if the burden of quality control, storage, expansion and distribution were shifted to a dedicated facility. A bank could collect disease lines generated in research laboratories, characterize these lines and optimize their growth conditions, and make them available to the research community.

2. A central facility could add value to an iPS cell line by collecting background information and making it available in a searchable database. For instance, a bank could collect clinical information about the patient from whom each line was derived; it could maintain detailed, comparable records of how each line was generated, propagated, and stored; and it could negotiate and record issues of intellectual property and patient consent for each line. This information could impact disease modeling, selection criteria for drug development purposes, or other therapeutic applications.
3. Similarly, a bank could collect cellular or biological characteristics for each line, such as HLA haplotype, genotyping information, or co-morbid patient phenotypes that might impact the interpretation of research on these cells.
4. Extensive characterization of iPS cell lines could be done in a more rigorous and economical way by a centralized facility. For instance, a cell bank could negotiate lower prices for assays such as HLA haplotyping, disease genotyping, or genomic and epigenomic analyses. Characterizing iPS cell lines using some or all of these assays might be financially unfeasible for researchers in small independent laboratories.
5. A cell bank could dedicate resources towards developing more consistent cell lines. For example, by evaluating different methods of reprogramming, a cell bank could select the best methods of reprogramming and appropriate controls for a particular research application, and develop standard operating procedure (SOPs) for the derivation and characterization of iPS cells.
6. A cell bank could dedicate resources to creating new iPS cell lines from an appropriate sample size of patients that could more usefully represent the heterogeneity of the human disease than any other approach, using a particular reprogramming method, even when those lines have been generated previously using different methods. Re-deriving iPS cells using a better reprogramming method might not be a viable project for a research laboratory or biotechnology company.
7. A bank could target particular diseases as priorities for iPS cell research, facilitate the generation of new iPS cell lines and control lines to study these diseases, and make these lines available to researchers who do not have the capability to recruit patients or to generate iPS cells themselves. Making iPS cells available to a broader base of researchers would strongly enhance CIRM's goal of supporting the development of cures and stem cell therapies through a more thorough understanding of the nature of disease, and by increasing our ability to identify patient types who will respond appropriately to the therapeutics that are developed.

In conclusion, this workshop identified two iPS cell banking activities that would benefit from increased CIRM support. First, CIRM could facilitate the commercial banking of iPS cell lines that are already being generated in research laboratories throughout California. The purpose of this effort would be to make existing iPS cell lines more available to the research community, and to standardize the information available for each line. Second, CIRM could help nucleate the generation of high-quality, comparable cell lines available for the study of particular diseases that are not being adequately served through existing research efforts. Here, efforts should be focused on generating iPS cells using optimal reprogramming methods from the most clinically relevant patients in a way that maximizes the use of these lines for research and screening purposes. These banking efforts will require thoughtful and meaningful collaborations between clinicians and researchers working on a particular disorder.

Increased availability of high quality iPS cell lines from patients with many different disorders would dramatically impact research on human disease, particularly if information about the genetic background and medical history of each patient were available for each line. Furthermore, if cell banks appropriately selected their patients and optimized their methods for

generating iPS cell lines, large-scale screens or clinically relevant diagnostic tools could be developed using patient-derived stem cells. By promoting and funding the development of iPS cell banking, CIRM could dramatically impact the therapeutic use of human iPS cells. It would also leave an indelible mark upon the research environment in California.

II. Factors to Consider in Establishing an iPS Cell Bank in California

Workshop participants discussed multiple aspects of cell banking, with an eye towards optimizing its value to the research community and increasing the clinical relevance of iPS cell lines. The factors that were considered most relevant to designing a successful bank were:

A. Determining the diseases and patients to be targeted
B. Establishing stringent inclusion criteria for iPS cells that optimize the quality and translational potential of these lines. The utility of a cell line will be affected by issues such as its scientific quality, the availability of adequate controls, the constraints on use of that cell line as dictated by ethical and consent issues, and by the accompanying patient information available for each line
C. Establishing the "scorecard" of assays that will be used to characterize each line
D. Developing a searchable database of characteristics for each line
E. Developing a flexible and reliable approach towards adopting inevitable technical advances in the field
F. A strategic plan that integrates the bank's approach to each of these issues, develops reliable procedures to make useful cell lines available to the research community, and leverages additional resources to enhance impact and potential to become self sustaining once CIRM funding is no longer available

These six points are discussed in greater detail below.

A. Choosing which patients/diseases will be included in the bank:

Reprogramming human somatic cells has become relatively straightforward. In principle iPS cells could be used to elucidate the cellular causes of disease susceptibility and the consequences of the tremendous genetic variability that we are discovering among humans, and could inform our understanding of the biological differences between individuals. However, creating iPS cell lines is expensive and resource intensive, so a more reasonable short-term goal is to target specific disorders and patient populations that would benefit from iPS cell modeling. The first decisions to be made in establishing a cell bank must therefore be to select the patients and diseases to be targeted, and to determine how many lines need to be maintained in the bank.

Disease selection could be based on the potential impact of iPS cells on therapeutic development for a particular disease, on the prevalence of that disease in California, or on the availability of clinicians with an adequate patient base and researchers with expertise in the field. There was significant disagreement among workshop participants about the diseases that should be targeted by an iPS cell bank, with some researchers promoting the value that iPS cells would bring to their particular field. There was consensus, however, that the optimal diseases to target could vary over time. A significant proportion of the current disease research using iPS cells is being conducted on highly penetrant monogenic disorders, for instance. The next advance might be to target disorders with a straightforward genetic etiology whose penetrance is affected by changes in the patient's environmental history or genetic background;

disorders with highly complex etiology might be more appropriately targeted in the future as the technology evolves. In any case, workshop participants agreed that a bank should develop a plan for identifying the diseases that it will prioritize, as this decision has practical implications as discussed below.

Once a bank settles on a particular disorder or group of disorders, it will need to determine the number of individuals necessary to adequately model this disorder *in vitro*, and to define the clinical profile of patients to be targeted. These characteristics will vary depending on the disease selected, but a bank should have a thoughtful plan for patient selection before it begins collecting patient samples. Furthermore, the number of iPS cell lines a bank can support will be determined by the resources available to the bank and by the in-house effort required to generate and maintain each line. An iPS cell bank could choose to generate its own iPS cell lines using a standard procedure and make these available to the biomedical community, which would maximize the comparative value of each iPS cell but would be very expensive. Alternatively, the bank could leverage the intensive research in this area and import iPS cell lines that are being generated in research laboratories. These lines would be valuable assets if the bank could ensure that each cell line was a high quality pluripotent cell line collected with appropriate patient consent and generated in an acceptable fashion. In this case, the bank would need to develop stringent inclusion criteria for each line, and might even require that iPS cell lines be submitted in conjunction with a sample of the tissue of origin so that each line could be re-derived if necessary.

Several workshop participants recommended that the bank recruit existing lines that meet a stringent set of entry criteria, where appropriate. Including lines generated by researchers outside of the bank could dramatically increase the number of quality lines available to the community with relatively little additional cost. The bank might also choose to use these lines to compare the effect of different reprogramming methods on cellular phenotypes from cells derived from iPS cell lines, which could be of scientific value to the field.

B. Inclusion criteria:

A cell bank should develop stringent criteria for including an iPS cell line, in order to maintain quality control. Scientific factors, issues related to donor history and controls, and the ethical or legal status of an iPS cell line would impact the value of that line for creating disease models or other therapeutic development. Issues to consider in developing inclusion criteria for iPS cells in a bank include:

1. Scientific factors
    a. Somatic cell of origin: The cell of origin might be an important factor to consider in generating iPS cells for specific applications. For instance, there is evidence that iPS cells can retain epigenetic memory of their cell of origin after reprogramming. In some cases, it might be important to consider the eventual application of an iPS cell line *before* choosing the donor cell type. Moreover, certain types of cells, notably immune cells, undergo genetic recombination and this additional variance might make these blood cells inappropriate starting material for many research applications.
    b. Method of reprogramming: There is evidence that some methods are more efficient than others in achieving complete reprogramming. In addition, some methods alter the genome of a cell through insertion of vector constructs and DNA deletions or rearrangements. The reprogramming method used to generate iPS cells should be carefully evaluated, and recorded.

c. Number of lines: There is some biological variability even among lines reprogrammed using similar methods from the same donor in the same lab. Most researchers have noted that this variability is relatively small, and workshop participants agreed that generating three independent lines from each donor is probably sufficient to control for line variability.
d. Number of patients: There will be additional biological variability among iPS cells generated from different individuals with the same disease. iPS cell lines from patients with diseases that have a single genetic contributor, such as spinal muscular atrophy (SMA), might be less variable than lines from patients with diseases of a more complex etiology, such as autism spectrum disorders (ASDs). For each disease, the bank should carefully consider how many individuals are necessary to ensure that the disease variability is appropriately represented in the bank.
e. Controls: An essential aspect to designing disease models using iPS cells is the availability of adequate controls. Individual-to-individual variability is one key factor that will determine how many controls are needed. As discussed below, donor features such as age, gender, or relatedness to the patient donor could impact the appropriateness of a control line. In addition, control and patient donors might need to be handled similarly, from collection through derivation, as an iPS cell line's history could impact its cellular phenotype. Finally, it might be necessary to develop more refined control lines for certain applications. For diseases with a single genetic contributor, for instance, it might be possible to genetically manipulate an iPS cell line in order to correct the genetic defect. The bank might want to consider ways of creating these lines, where appropriate.

2. Donor information
   a. Donor features: factors such as age, blood type or gender could be important for developing iPS cell-based models of a disease.
   b. Donor medical history: disease history, family history and other genetic information, therapeutic regimen, and other medical factors that could be relevant for grouping patients together, should be documented.
   c. Controls: the availability of donors that are related in age, gender, or genetic background, and the clinical history of the donor, could impact the value of an iPS cell line. Banks should consider what controls are needed for each disease and iPS cell line.

3. Ethical and legal considerations
   a. Licensing status of a line: licensing information, if applicable, will make it easier to determine whether a line can be used commercially.
   b. Patient consent: the degree of patient consent, and whether the donor consented to make the lines available for translational research applications, will impact the value of an iPS cell line.
   c. Ability to re-contact patient: for some research projects, it will be of great value to be able to contact patients for additional medical information, family history, or to recruit patients to clinical trials.
   d. Other ethical issues: as scientists begin to use human cells from donors for therapeutic development, new ethical issues will present themselves. The bank should develop a methodology to address ethical issues as they arise.

Since these are still early days in the field of somatic cell reprogramming, the optimal conditions for creating a valuable iPS cell line are unknown. Workshop participants recommended that a bank document as much information about a line as possible at the time of its generation or acceptance into the bank. In addition, they recommended that the bank develop standard

consent forms and ethical models that would maximize the use of a cell line for as many applications as possible.

C. Cell characterization and scorecard:

Participants indicated that biological characterization of each iPS cell line should be an essential goal of an iPS cell bank for several reasons. First, scoring cells against a standard panel of assays is an important factor in establishing good quality control for each line. This is particularly important for iPS cell lines, which are at risk of accumulating genetic or epigenetic insults throughout the reprogramming process as well as during subsequent culturing steps. Second, monitoring of cells against a standard panel of assays will be important for optimizing culture conditions for cell maintenance and differentiation. Finally, extensive cell characterization can provide opportunities to systematically compare variables across different cell lines. Participants recommended developing a quality "scorecard" for each cell line and maintaining it in a searchable database that could be made available to scientists interested in purchasing iPS cell lines.

The assays to be included in this scorecard were an issue of debate at this workshop. Standard methods of assessing pluripotency, including immunocytochemical analysis of pluripotency markers and the ability to differentiate into cells from all three germ layers, were obviously considered essential. Cell culture issues, such as optimal culturing conditions and monitoring for cell culture artifacts, were also highlighted. Most researchers agreed, however, that specialized assays such as teratoma formation might not be necessary for each line. Similarly, it was agreed that the characteristics of cells differentiated from each line could be determined by the researchers who use these cell lines and not by the bank itself.

Many participants indicated that the bank should perform genetic and epigenetic assays on both the cell-of-origin and on the iPS cell line to establish that appropriate reprogramming has occurred and that no detrimental genetic changes were introduced in the process. The workshop participants were divided on whether complete DNA sequencing and epigenetic mapping would be necessary as a part of the scorecard, but all agreed that this information might make the lines a more valuable tool for the research community. There was general agreement that the cellular assays that comprised an iPS cell's scorecard would need to be periodically re-evaluated in order to maintain scientific relevance. A successful bank would have a plan for evaluating and integrating new assays into this scorecard as necessary.

D. Searchable database:

An iPS cell line's history is one of its most valuable attributes. As indicated in the discussion above, a successful iPS cell bank would standardize the information collected for each cell line and maintain this information in a searchable database. The database should include the following information:

1. All cell handling variables (details such as the donor tissue, reprogramming method, media and feeder cells used, and the number of passages that a cell line underwent before freezing)
2. Donor information (such as patient medical record, age, gender, ethnicity, genomic information and family history)
3. Scorecard (including the results of assays to measure pluripotency, cell growth, and differentiation characteristics)
4. Published research for each line (including links to research on each line and related lines)

5. Ethical and consent issues (including patient consent for utilization of the information gained from translational research using his/her cells, and consent to re-contact the patient for additional information)
6. Legal and intellectual property issues

E. Technical optimization:

Reprogramming technology is in its infancy, and methods for working with iPS cells are still being optimized. For instance, the most efficient method of generating iPS cells at the moment involves using integrating viruses carrying four independent transcription factors (generally c-Myc, OCT-3/4, SOX2, and Klf4). However, new less invasive methods of reprogramming using non-integrating episomal vectors, chemical compounds or transduction using synthetic mRNAs for these factors are being developed. It is possible that technical advances will make a currently preferred method of reprogramming obsolete, or that the optimal techniques for generating iPS cells might depend upon the particular application for which the iPS cell line is intended. Individuals involved in existing banking efforts for different tissues and cells stressed the importance of maximizing dynamic, flexible procedures into the bank's operation. For instance, participants recommended that the bank maintain fibroblasts or other cells-of-origin for each iPS cell line, so that it could re-derive lines from this source using new methods should it become necessary.

To begin with, however, the bank must decide whether it will target a single method of iPS cell generation, which can be dynamically modified as the field evolves; or whether it will accept cells generated through any method and focus on the quality of the lines once they have been generated. In either case, it was recommended that a bank establish inclusion criteria and technical methods based on the current state of the art, and maintain meticulous documentation of the reprogramming method used to generate each line.

F. Other banking issues

Participants indicated that general issues such as the size of the bank, the inclusion criteria for iPS cell lines, the assays to be included in a cell's quality control "scorecard," and standard operating procedures (SOPs) for handling cells should be established before creating a bank. If the focus is on increasing the availability and therapeutic utility of high quality iPS cell lines for research on human diseases, particular thought should be given to issues of patient consent, ethics, and intellectual property that could impact the use of these cells for commercial development. Speakers indicated that an iPS cell facility would be most successful if it could guarantee rapid adoption of new methods, reagents, and cell lines. Finally, the facility should leverage its location and therapeutic mission when integrating into the global banking environment, as this will help ensure its continued success once CIRM support is not longer available. The bank should develop a strategic/business plan that considers issues such as:

1. What is the bank's budget? How many cell lines can be maintained in the bank for this budget? What funding sources are available to support this budget?
2. Will specific diseases be targeted? If so, what are the inclusion criteria for a disease?
3. How many patients will be targeted per condition? How does genetic variability factor into this decision?
4. How many iPS cell lines will be stored per patient?
5. How will patients be recruited or cell lines collected? What inclusion criteria need to be met for lines to be admitted into the bank?

6. How will cells be prepared for distribution and how actively will lines be maintained? If there is no demand for a particular iPS cell line, will the line still be made or will it be kept as a primary tissue/cell until a cell line is requested from that tissue?
7. Will the bank be involved in evaluating the effect of different reprogramming methods on iPS cells?
8. What will the bank establish as the "gold standard" characterization panel (the iPS cell scorecard)?
9. What information will be included in the searchable database?
10. How will the bank integrate new methods into its procedures? Who will determine when to methods need to be updated?
11. How will the bank fit into the international space? What sort of agreements will it establish with other banks, research organizations, patient organizations and commercial entities?
12. How will the bank ensure that it is not replicating content in the NIH bank, the UK stem cell bank, or other banks in existence?
13. What will its intellectual policy be? How will the bank handle licensing issues?
14. How will ethical policy be set? How will the bank handle ethical/consent issues with patients?
15. Is this bank commercially viable in the long-term, once CIRM funding is no longer available? What is the business model?

These six areas of consideration emerged as central to designing a strong iPS cell bank that would survive CIRM and provide a valuable asset to both the people of California and the global biomedical research community.

III. iPS Cell Bank Models

In discussing an iPS cell bank, workshop participants identified two distinct banking needs: an iPS cell bank as a repository and distribution mechanism for cell lines generated by investigators in the field, and an iPS cell facility that would recruit patients and generate cell lines for certain targeted disorders.

Basic iPS cell repository. A central facility that would collect, store, characterize, and distribute iPS cell lines generated by other investigators. The bank would establish stringent inclusion criteria for accepting iPS cell lines (for instance, lines must be fully consented and accompanied by a patient medical record; they must have been cultured for only a certain number of passages; they must be accompanied by a sample of the donor tissue). The bank would be responsible for basic quality control, and could perform some value-added tests such as genotyping, but would not be involved in research to optimize iPS cell generation methods. This model is based on similar cell banks managed by Coriell and American Type Culture Collection (ATCC) that provide a service to investigators who wish to make their cell lines available to the community. CIRM funding would be made available to investigators who wish to prepare iPS cell lines for inclusion into one of these banks.

iPS cell generation facility. This type of bank would identify understudied target diseases, generate iPS cell lines from selected donors, and promote the use of these lines for disease-related research. Through collaborations with clinicians, the facility would collect tissue and medical information from selected donors. iPS cell lines would be reprogrammed in-house and/or by other researchers under contract, and the facility would be fully responsible for characterizing each line. To avoid obsolescence, the bank would develop standard operating procedures that would be periodically updated through careful evaluation. Substantial funding

would be required both to conduct research activities on site, and to retain a core of stem cell technicians, ethicists, law experts, and other professionals required support the activities of the bank.

An iPS cell generation facility could expand its scope by accepting iPS cell lines already created by researchers and characterizing them in similar ways as cells generated in-house. This would leverage the work of researchers throughout California who are generating iPS cell lines, and add value to these existing lines by providing extensive characterization. Since the facility would be generating new lines as well, it could be involved in limited research activities such as comparing iPS cells from different labs that were reprogrammed using different methods.

In conclusion, participants were enthusiastic about increasing CIRM support of iPS banking but cautioned that the details discussed above would determine the impact and success of these efforts.

CIRM RESPONSE TO RECOMMENDATIONS

The workshop resulted in a recommendation that CIRM support iPS cell banking activities that promote the use of human iPS cells for developing disease models and other therapeutic research activities. These banks would be of great value to the scientific community and to the people of California, and would advance CIRM's core mission. CIRM therefore proposes to release the following funding mechanisms:

A. iPS cell repository for existing cell lines

iPS cell banking involves cell culture, expansion and cryopreservation of cells, and the development of a database to track patient characteristics and cell line history. Biobanking organizations such as Coriell and ATCC have years of experience banking and distributing cells for research, so they are natural allies in the effort to bank the hundreds of iPS cells that are being generated in California. Representatives from these organizations indicated that they would be able to customize their banking services to CIRM's requirements.

To establish a banking repository, CIRM would publish a Request for Proposals (RFP) inviting biobanking organizations to submit proposals to provide banking and accessory services identified above. Given that most of the leading biobanking organizations are outside of California, CIRM will explore the option of opening this RFP to organizations throughout the world, although preference will be given to organizations willing to establish a branch in the state. CIRM would structure the contract with a biobanking organization to cover basic cell quality assays, cryopreservation, the collection of accessory information such as patient medical records, and the cost of distribution. Once the bank was established, CIRM would be involved in periodically re-evaluating the facility, and it could negotiate amendments to its contract to accommodate changes. Under a separate funding mechanism, CIRM would make funds available to researchers in California interested in optimizing their lines for submission to the biobank.

B. iPS cell generation banks for target diseases

To nucleate the generation of a comprehensive group of iPS cell lines for the study of particular diseases, CIRM would release a Request for Applications (RFA) to fund a small number of pilot banks. The Grants Working Group (GWG) would evaluate these proposals based on the scientific validity of the approach, the strength of clinical and research collaborations, the quality of their "scorecard," the bank's strategic plan, the rationale for

developing iPS cells for the disorders being targeted, and on other items discussed in Section II. Target disorders for which significant banking efforts are underway using other funding would be deprioritized.

Developing a strategic plan for an iPS cell bank is a complex administrative procedure that requires coordination of a multidisciplinary team. The RFA would require that these multidisciplinary teams include stem cell scientists with appropriate expertise in deriving and handling iPS cells, disease modeling expertise, and/or experience in high throughput screening; clinicians able to manage patient recruitment and selection as well as contribute to the research design; genomics, epigenomics, and bioinformatics scientists to perform genetic analyses of the donors and the derived cell lines; bioethicists and personnel familiar with patient consent and intellectual property issues; and possibly a biobanking partner to bank and distribute the cells for research. To help applicants build appropriate teams, CIRM will consider releasing a two-part RFA. Part one would award planning grants to individuals interested in developing a proposal to submit to the iPS cell banking RFA. The planning grants would provide funding for team building and application planning activities. Part two would award a small number of pilot banks to those applications deemed most competitive by the GWG and the CIRM Independent Citizens' Oversight Committee (ICOC) Governing Board.

CIRM has developed a portfolio of flexible funding mechanisms that are actively advancing therapeutic development. The institute recognizes the tremendous therapeutic potential of induced pluripotent stem cells, and is proposing to support a comprehensive iPS cell banking effort that will increase the availability of high quality iPS cell lines available for research on human disease.

CIRM iPS Cell Banking Workshop Agenda

Purpose

- Solicit perspectives from leaders in the field of stem cell research and regenerative medicine on the CIRM iPS Cell Banking Proposal
- Provide an opportunity for leaders in the field to exchange ideas
- Provide recommendations on execution of a CIRM RFA or RFP

November 17, 2010	
7:30 am	**Breakfast**
	CONFERENCE OPENING
8:30 am	**Introduction – Sohel Talib, PhD –Science Officer CIRM** **Welcome – Alan Trounson, PhD – President, CIRM** CIRM iPS Cell Banking Presentation
Session 1. Global iPSC Banking Efforts **15 minute talks / 20 minute discussion**	
Chair	**John O'Shea, MD** Scientific Director of the Molecular and Immunology and Inflammation Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) Intramural Research Program, The National Institutes of Health (NIH)
8:45 am	John O'Shea, MD – Scientific Director of the Molecular and Immunology and Inflammation Branch, NIAMS Intramural Research Program, NIH *Title - TBD*
9:00 am	Roger Pedersen, MD – Professor, Department of Surgery, Laboratory for Regenerative Medicine and Cambridge Stem Cell Initiative, University of Cambridge *Title –TBD*
9:15 am	Bernat Soria, MD, PhD – Director of the Cell Therapy and Regenerative Medicine Program (former Minister of Health) *Andalusian strategy in stem cell banking and advanced therapies*
9:30 am	Haruhisa Inoue, MD, PhD – Associate Professor, Center for iPS Cell Research and Application, Kyoto University *iPS cell banking facilitating disease-specific iPSC research*
9:45 am	**Discussion**
Questions to consider for presenters and discussion • How does CIRM's iPS cell banking proposal complement or duplicate these efforts? • How can we coordinate with other institutions and organizations? • What would make a CIRM banking initiative a unique resource? • How can CIRM leverage efforts underway at other institutions?	
10:05 am	**Coffee Break**

Session 2a. Haplotype & Patient Diversity **15 minute talks / 25 minute discussion**	
Chair	**Roger Pedersen, MD** Professor, Department of Surgery, Laboratory for Regenerative Medicine and Cambridge Stem Cell Initiative, University of Cambridge
10:20 am	Dennis L. Confer, MD – Chief Medical Officer, The National Marrow Donor Program *Assessing HLA haplotype frequency and diversity in the Be The Match registry of unrelated bone marrow donors*
10:35 am	Jeanne Loring, PhD – Professor of Chemical Physiology, The Scripps Research Institute *Building an ethnically diverse iPSC bank for predicting drug toxicity*
10:50 am	**Discussion**
Questions to consider for presenters and discussion • What are the key issues to consider in haplotype diversity? • What are the key issues to consider in patient diversity?	
Session 2b. Patient Recruitment – A Clinical Perspective **15 minute talks / 25 minute discussion**	
Chair	**Roger Pedersen, MD** Professor, Department of Surgery, Laboratory for Regenerative Medicine and Cambridge Stem Cell Initiative, University of Cambridge
11:15 am	Richard Wade-Martins, MA, DPhil – Director, Oxford Parkinson's Disease Centre *Developing new stem-cell based neuronal models to study Parkinson's disease*
11:30 pm	Anne Rosser, PhD, FRCP – Director, The Brain Repair Group and Professor of Clinical Neurosciences, Cardiff University Schools of Medicine and Biosciences *Clinical considerations with reference to the European Huntington's disease cohorts*
11:45 pm	**Discussion**
Questions to consider for presenters and discussion • What selection criteria should be considered in patient recruitment? • How many patients will be needed in different types of diseases? • What should be the key concerns with informed consents? • What clinical data/contact information should be collected?	
12:10 pm	**Lunch**
Session 3. Disease & Patient Cohort Considerations Part 1 **15 minute talks/25 minute discussion**	
Chair	**Irving L. Weissman, MD** Director, Institute for Stem Cell Biology and Regenerative Medicine and the Virginia and D.K. Ludwig Professor for Clinical Investigation and Cancer Research, Stanford University
1:10 pm	Irving L. Weissman, MD – Director, Institute for Stem Cell Biology and Regenerative Medicine and the Virginia and D.K. Ludwig Professor for Clinical Investigation and Cancer Research, Stanford University *iPS and ES cells: Barriers to their use in understanding disease pathogenesis and in therapeutic transplantation*
1:25 pm	Bruce R. Conklin, MD – Senior Investigator, Gladstone Institute of Cardiovascular Disease *Banking iPS cell lines from sudden death syndromes*

1:40 pm	Ira J. Fox, MD – Director of the Center for Innovative Pediatric Regenerative Therapies, University of Pittsburgh, Children's Hospital of Pittsburgh of UPMC, and McGowan Institute for Regenerative Medicine *iPS cells in the liver, adult and pediatric liver disease, genetics and toxicology*
1:55 pm	John E. Wagner, MD – Director, Division of Hematology-Oncology and Blood and Marrow Transplantation, Department of Pediatrics and Co-Director, Center for Translational Medicine, University of Minnesota *Identification of candidate hematopoietic and non-hematopoietic genetic diseases of childhood for iPS cell banking*
2:10 pm	**Discussion**

Questions to consider for presenters and for discussion

- How many diseases should be included in the bank for this to be a broadly useful tool for the community?
- Which diseases should be included in the bank?
- How many samples will be needed to represent disease variability? How will this vary between diseases?
- How will samples be used for disease in a dish, toxicity in a dish, or research purposes?
- What type of control samples should be collected? How many control samples will be necessary?
- What type of information should be attached to each sample?

Session 4. Neurological Disease & Patient Cohort Considerations Part 2
15 minute talks / 25 minute discussion

Chair	**Clive Svendsen, PhD** Director, Cedars-Sinai Regenerative Medicine Institute
2:35 pm	Clive Svendsen, PhD – Director, Cedars-Sinai Regenerative Medicine Institute *Spinal Muscular Atrophy and Huntington's disease: Model disorders for iPS generation.*
2:50 pm	James Ellis, PhD – Senior Scientist, SickKids; Co-Director, Ontario Human iPSC Facility *Reprogramming autism spectrum disorders at the Ontario Human iPSC Facility*
3:05 pm	David H. Rowitch, MD, PhD – Professor of Pediatrics & Neurosurgery, Howard Hughes Medical Institute Investigator, Chief of Neonatology, UCSF Benioff Children's Hospital *Models of cerebral palsy and newborn brain injuries using iPS Cells*
3:20 pm	Uta Francke, MD – Professor of Genetics and Pediatrics, Stanford University *Perspectives from pediatric genetic neurological and behavioral disorders*
3:35 pm	**Discussion**

Questions to consider for presenters and for discussion

- What are the most appropriate neurological diseases to include in the bank?
- How many samples will be needed to represent disease variability? How will this vary between neurological diseases?
- What are the challenges for late onset neurological disorders or for diseases where the phenotype might be difficult to observe? What other challenges might impact banking and patient and disease selection?
- What type of control samples should be collected? How many control samples will be necessary? How will this differ between diseases?

4:00 pm	**Coffee Break**

Session 5. Genomics 15 minute talks / 30 minute discussion	
Chair	**Joseph R. Ecker, PhD** Professor, The Salk Institute for Biological Studies Plant Biology/Genomic Analysis Laboratories
4:15 pm	Vanessa Hayes, PhD – Professor of Genomic Medicine, J. Craig Venter Institute *Genomics meets iPS cell banking*
4:30 pm	Kelly A. Frazer, PhD – Professor of Pediatrics and Chief, Division of Genome Information Sciences, Moores UCSD Cancer Center *The role of genomics in stem cell research*
4:45 pm	Joseph R. Ecker, PhD – Professor, The Salk Institute for Biological Studies Plant Biology/Genomic Analysis Laboratories *Sequencing and comparison of epigenomes from human ES and IPS cells*
5:00 pm	**Discussion**

Questions to consider for presenters and for discussion

- Should a genomic sequencing element be incorporated?
- Should an epigenetic sequencing element be incorporated
- How would you determine the number of patients from each disease and how can genetics inform this issue?

November 18, 2010	
7:30 am	**Breakfast**
Session 6. iPSC Derivation: Cell Source, Method of Derivation, & Characterization (Scorecard) **15 minute talks / 25 minute discussion**	
Chair	**James Ellis, PhD** Senior Scientist, SickKids; Co-Director, Ontario Human iPS Cell Facility
8:30 am	Joseph Wu, MD, PhD – Associate Professor of Medicine, Stanford University School of Medicine *Clinical hurdles of iPS cell therapy*
8:45 am	Peter Tonge, PhD – Postdoctoral Fellow, Andras Nagy laboratory, Mount Sinai Hospital *Transposon mediated reprogramming*
9:00 am	Derrick J. Rossi, PhD – Assistant Professor, Harvard Medical School; Member, Immune Disease Institute *Directing cell fate with modified-mRNA*
9:15 am	Sheng Ding, PhD – Associate Professor of Chemistry, The Scripps Research Institute *Small molecules for reprogramming*
9:30 am	Emile Nuwaysir, PhD – Vice President and Chief Operating Officer, Cellular Dynamics International *Industrial-Scale Episomal Reprogramming*
9:45 am	Berta Strulovici, PhD – VP Research and CTO, iPierian, Inc. *iPS cells at iPierian: Shortening the road from academic breakthrough to industrial drug discovery*
10:00 am	**Discussion**
Questions to consider for presenters and for discussion • What should be considered when choosing the cells source? What is the best cell source? • What should be considered when selecting a derivation method? Which derivation method should be used? • What should be included in the Certificate of Analysis?	
10:25 am	**Coffee Break**
Session 7. Banking, Distribution, & Data Management **15 minute talks/20 minute discussion**	
Chair	**Sohel Talib, PhD** Science Officer, CIRM
10:40 am	Derek Hei, PhD – Director, Waisman Biomanufacturing, University of Wisconsin *Cell banking practices for pluripotent stem cells: Lessons from the National Stem Cell Bank*
10:55 am	Glyn Stacey, PhD – Director, The UK Stem Cell Bank *Banking pluripotent stem cell lines: The UKSCB experience*
11:10 am	Margaret A. Keller, PhD – Senior Director of Research and Development and Director of Stem Cell Biobank, Coriell Institute for Medical Research *iPSC biobanking, Coriell's experience*
11:25 am	**Discussion**

Questions to consider for presenters and for discussion • How should CIRM approach establishing an IPS cell bank? • What specifications should be included in a potential RFA/RFP regarding the banking aspects? • What considerations are important for distribution? • What considerations are important for data management • What should be considered in calculating the per sample cost? What aspects will most impact cost?	
11:45 pm	**Working Lunch**
PANEL DISCUSSION	
Chair	Alan Trounson, PhD – President, CIRM
12:00 pm	Final Panel – Michael Christman, Joe Ecker, Rusty Gage (via teleconference), Emile Nuwaysir, John O'Shea, Roger Pedersen, Clive Svendsen, Irv Weissman
Questions to consider for discussion • Would the proposed bank be a useful tool for the research community? • Are their improvements that could be made to the proposal to make it a more useful tool? • The proposal is for a research grade bank. Are there steps that should be taken to make this adaptable for clinical use? • What should be the primary requirements/considerations in a potential RFA or RFP? • What should be considered when deciding how many diseases to include, which disease, and how to select patient populations? • What cell source should be used? Should a single derivation method be employed? If so, how should CIRM or a potential applicant select a single method? • Should the both the original sample and the derived iPS cell be banked? What information should be attached to each sample? What should be included in the certificate of analysis?	
2:00 pm	**Wrap Up**