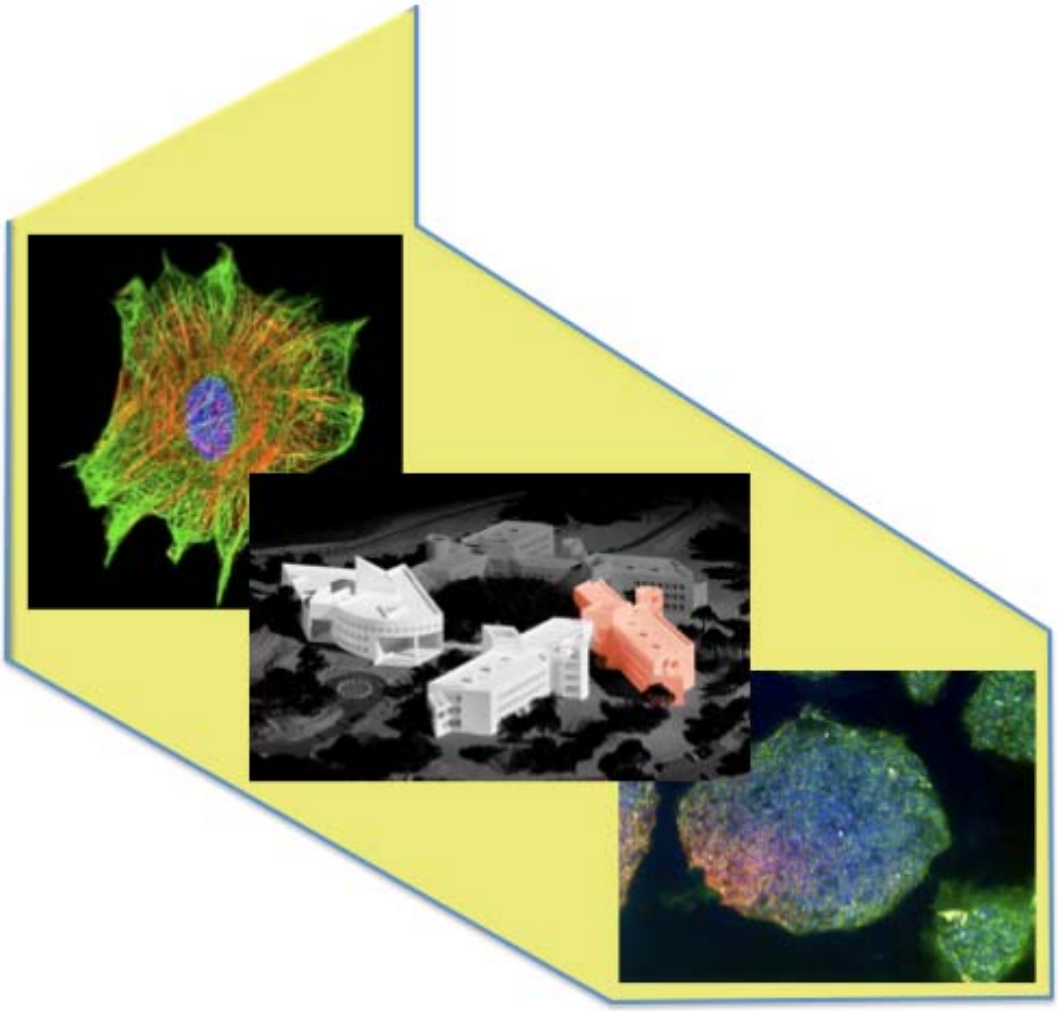
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Ethical and Policy Considerations for A Pluripotent Cell Resource Center (PCRC)



Summary of the 2010 Annual Meeting of the Medical Accountability Standards Working Group to The California Institute for Regenerative Medicine

May 26, 2010

San Francisco, California

Cover Photos:

Jiashan Wang Cytoskeleton in a Human Fibroblast Cell. Actin (Red), Microtubules (Green), Nucleus (Blue). http://www.flickr.com/photos/scientificrelevance/4248360334/

The Buck Institute: http://www.flickr.com/photos/cirm/3288003383/

William Collins in the lab of Deepak Srivastava and Christopher Schlieve at the Gladstone Institutes. http://www.flickr.com/photos/cirm/3314923906/

Top left is a human fibroblast cell. Bottom rignt image is a fibroblast cell transformed to an iPSC.

Acknowledgements:

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Introduction

CIRM's mission is to support and advance stem cell research and regenerative medicine under the highest ethical and medical standard for the discovery and development of therapies and cures for chronic disease and injury. A major operational goal for the Institute is to accelerate progress towards translational research, including pre-clinical and clinical research.

The Institute's Medical Accountability Standards Working Group's (SWG) charge includes recommending to the ICOC safe and ethical procedures for procurement and distribution of cells and tissue for research. Commensurate with this charge, the Working Group convened a public workshop for its 2010 annual meeting. The purpose of the workshop was to examine ethical and policy consideration related to derivation and distribution of induced pluripotent cells (iPSCs). This topic was chosen because CIRM is currently evaluating what role, if any, the Institute should play in supporting the derivation and distribution of iPSCs.

Workshop participants included individuals with experience deriving cell lines, operating bio-repositories, and distributing cells and tissue. The primary focus of the SWG is ethics / policy issues related to derivation, distribution and use of cells. Participants assisted the SWG in exploring these issues. Participants prepared remarks could be categorized into four general topic areas:

1. Scientific considerations for cell banking
2. Oversight, materials provenance and consent
3. IP and patents impact on banking and distribution
4. Costs and organizational capacity considerations

The workshop and this report are designed to provide a preliminary assessment of ethics and policy issues related to derivation and distribution of iPSCs. This assessment is presented in section III. The report also summarizes points raised in each of the four topic areas addressed in the workshop. Given the preliminary nature of discussions involving bio-repositories, this report includes a number of process recommendations to support further evaluation.

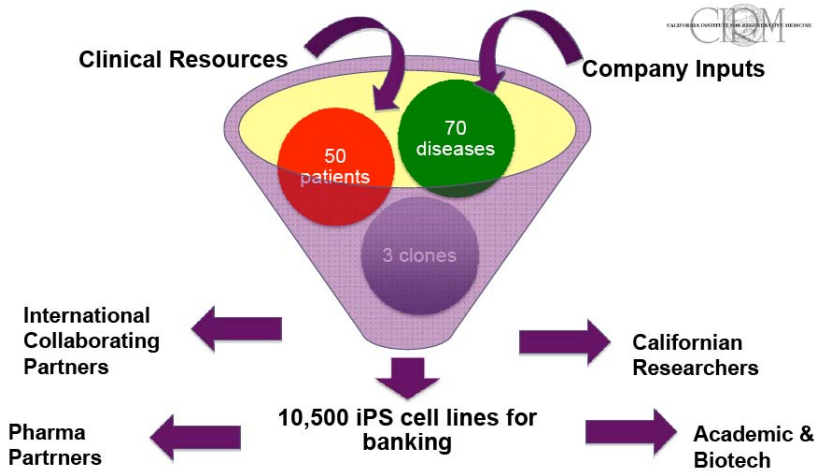
I. Scientific Considerations for Bio-Repositories for Basic Research

CIRM President Dr. Alan Trounson opened the workshop with a presentation discussing the value of induced pluripotent stem cells (iPSCs) for basic and clinical research. He described the importance of performing derivation under defined protocols to reduce technical variance between cell lines. Once created, it is important to maintain and monitor the cell lines. For example, ongoing genotyping should be performed to detect any abnormalities that might develop.

Dr. Trounson suggested that teams deriving iPSCs for clinical purposes under Good Manufacturing Practice (GMP) conditions have a strong economic incentive to maintain the lines. The upfront production costs for GMP-compliant materials are substantial, so cell lines will be very carefully managed. He cited experience with human embryonic stem cell lines where GMP-compliant lines under go rigorous quality control evaluation (a point reiterated by other speakers).

He indicated iPSCs intended for basic research purposes can be produced at a comparatively lower cost (Dr. Loring estimated current cost to be $10,000 per line). Given this cost structure the same quality control incentive may not exist for research grade iPSCs; therefore, a repository designed to maintain cell quality may be warranted. Also, Dr. Graff reported (see section III) that patent infringement appears to be less of a concern for basic research use compared with the development of GMP-compliant clinical products,.

Researchers are currently evaluating optimal procedures for iPSC line derivation. Consequently, technical variance exists in the derivation procedures utilized to develop existing iPS lines. Dr. Trounson suggested there might be value in a program designed to support iPSC derivation according to protocols that reduce technical variance. Dr. Trounson suggested creating iPS lines from multiple donors with a specific disease diagnosis. These lines could then be utilized to develop “disease-in-a-dish” models for studies ranging from disease etiology to responsiveness to drugs. Dr. Trounson suggested standardized derivation protocols might improve the sensitivity of drug screening assays. He also indicated a panel of iPSC reflecting population diversity may allow prediction of genotypic or immunologic related toxicities



A theoretical iPSC Pluripotent Cell Resource Center was used to focus ethics-policy considerations

Figure 1: Theoretical Pluripotent Cell Resource Center of 10,500 iPSC

To provide focus and specificity to the SWG deliberations, Dr. Trounson requested the SWG consider ethics-policy considerations in the context of a theoretical proposal for a Pluripotent Cell Resource Center (PCRC). The iPS Resource Center would consist of multiple cell lines for 70 disease phenotypes. For each disease an average of 50 donors would be required. In addition 3 clones of each cell line should be developed. The resulting Resource Center would consist of approximately 10,500 cell lines. These lines would be made available to international collaborators, pharma partners, California researchers and others in academia and biotechnology. Such a Center could support decades of research.

Process Recommendations Scientific Considerations

CIRM has proposed convening a future meeting to consider scientific considerations related to iPS bio-repositories. CIRM anticipates in-depth discussion of scientific considerations related to bio-repositories at that time. Participants at this workshop suggest the following issues deserve ongoing consideration.

- Consider the primary need for a Pluripotent Cell Resource Center (e.g. basic vs. clinical research):
  - Will GMP lines be adequately maintained and distributed?
  - Is there an immediate need for disease lines for basic research?
- Consider methods development:
  - Are derivation methods sufficiently developed to warrant creation of an iPS bio-repository?
  - What standards will be adopted for assessing pluripotency?
  - What type of ongoing maintenance and monitoring of cell lines will be required?
- Consider the pros and cons of derivation protocol diversity:
  - Can a single or limited numbers of teams reduce technical variance in derivation?
  - Is variance in derivation methods clinically relevant for toxicity screening?
  - Is there value to having multiple derivation methods used at this time?
  - What level of compatibility and comparability is needed between methods?

II. Oversight, Materials Provenance and Consent

The CIRM Standards Working Group has developed an extensive set of policies governing the procurement of human cells and tissue for Institute-sponsored

research.[1] The Institute has specific policies governing informed consent, donor payments, research oversight and allowable research activities. CIRM polices reference federal Office for Human Research Protections (OHRP) policies governing Human Subjects Research.

IRB / SCRO Review of Procurement Protocol

Critical Issue: Procurement and Cell Line "Diversity"

The value of population diversity for iPSC lines is frequently emphasized. Experience with bone marrow transplant demonstrates the importance of matching the donor and recipient according to their immune profile so transplanted cells are tolerated by the patient. There is general consensus among scientists that immunological compatibility is important for development of cell-based therapies.

During the workshop there was cogent discussion regarding the proxy role racial and ethnic distinctions may play in the recruitment process. Working group members recognized that using social constructed categories during recruitment could serve the goal of achieving population diversity. However, SWG members emphasized the imperfect, proxy, role of these categories and cautioned against any system of ongoing categorization that would relate genotypic characteristics to race.

This subject was raised recurrently with concentrated discussion recorded on pages 113-121 of the workshop transcript.

http://www.cirm.ca.gov/files/transcripts/pdf/2010/05-26-10.pdf

All CIRM-funded human subjects research must be performed in accordance with Title 45 Code of Federal Regulations, Part 46 (Protection of Human Subjects). Collection of cells and tissue for a repository is subject to oversight by local Institutional Review Boards (IRBs) convened by the collecting institutions under OPRR-approved Assurances. The IRB must review and approve the donation protocol including an evaluation of any risk to the patient or subject populations.

CIRM also requires a stem cell research oversight committee (SCRO) to review and approve certain activities. A designated SCRO committee may work with the IRB to support oversight activities.

Informed Consent

CIRM regulations are based the National Academies' (NAS) Guidelines for Human Embryonic Stem Cell Research. The NAS Guidelines and CIRM regulations include specific requirements for informed consent when funded research involves the donation of human somatic cells for the purpose of creating a pluripotent stem cell line. These detailed requirements may be found in section 100100(b).[2] At this time, the SWG believes the established CIRM framework requiring IRB oversight and active consent for all donated cells and

[1] see http://www.cirm.ca.gov/WorkingGroup_Standards.
[2] see http://www.cirm.ca.gov/reg/pdf/Reg100100_SM_Acct_Standards.pdf

tissue is adequate, and it should be incorporated into any bio-repository.

The SWG recognizes that it may be possible to derive scientifically important iPSC lines from existing somatic cells that may not have been procured in accordance with the CIRM regulations. For example, anonymous specimens, medical waste and older commercially available cells are examples of materials that comply with federal regulations for human subjects research, but may not have explicit consent for research use. Federally compliant materials may be used in CIRM-funded research if the donation process did not involve CIRM funds. Given the differences between federal and CIRM regulations, a process for evaluating and potentially providing a waiver for materials deemed to be scientifically important should be considered. However, the SWG would reiterate that any new collection for the express purpose of developing the PCRC should be performed in accordance with CIRM regulations.

Oversight of Repository Activities

Federal guidelines recommend IRB oversight of bio-repositories.[3] Guidelines state the IRB should review and approve a protocol specifying the conditions under which data and specimens may be accepted and shared, and ensure adequate provisions to protect the privacy of subjects and maintain the confidentiality of data.

To the extent research activities constitute human subjects research, IRB oversight is required by CIRM regulations and federal guidelines. However, it is likely that a substantial amount of research involving materials maintained by the theoretical Pluripotent Resource Center will not constitute human subjects research. Researchers using iPSCs would generally not need to know the identities of cell or tissue donors, a research with de-identified materials is not subjects to federal regulations for research with human subjects.

iPSCs may be utilized in a manner that would require a CIRM-funded researcher to obtain SCRO review and approval. For example, experiments designed to implant iPSCs into non-human animals require review. If a CIRM grantee were to propose such experiments, SCRO approval would be a condition of funding. However, this requirement would not necessarily extend to non-CIRM funded research. Consideration should be given to whether all research with iPSCs in a Pluripotent Resource Center should be governed by equivalent requirements for review and oversight.

Submittal Agreement

If CIRM were to fund the derivation of iPSC lines, then the oversight and consent requirements described above would apply. It is conceivable that a Pluripotent

[3] see http://www.dhhs.gov/ohrp/humansubjects/guidance/reposit.htm

Resource Center would receive lines derived without CIRM funding. CIRM requires all stem cell lines used in to be "acceptably derived." To be acceptably derived (with limited exceptions), donation must be overseen by an IRB or equivalent and donors must provide voluntary and informed consent. A documentation procedure should be considered to (1) verify that lines have been derived in accordance with CIRM requirements or (2) conform to the "acceptably derived standard." CIRM has developed a documentation procedure that may serve as a useful model for such verification.[4]

Usage Agreement

Federal requirements for the operation of cell repositories include a written usage agreement for recipient-investigators. Under the agreement the recipient should agree to comply fully with any conditions and to report promptly to the cell repository any proposed changes in the research project and any unanticipated problems involving risks to subjects or others. The agreement should also state material may only be utilized in accordance with the conditions stipulated by the repositories oversight body (e.g. IRB and/or SCRO committee).

Profile UK Stem Cell Bank

The UKSCB promotes global access to somatic and embryonic human stem cells. The UKSCB is housed and operated by the National Institute of Biological Standards (NIBS) and has two well defined levels of operation: (1) a research grade facility aiming at promoting basic research, and (2) a clinical grade one, whose purpose is to bank under GMP as a primary material for the development of therapies.

The UKSCB incorporates comprehensive policies for oversight, materials provenance and consent. In addition, the bank reviews proposed uses of deposited materials. These policies are detailed in Appendix B.

Withdrawal of Materials:

CIRM regulations require that donors be given the opportunity to impose restrictions on future uses of donated materials, but they also allow researchers to choose to use materials where donors have agreed to unrestricted future uses of their embryos, cells or tissue. In the context of CIRM-funded research with the goal of creating immortalized pluripotent cell lines, researchers report ample numbers of gametes, embryos and somatic cell donors willing to consent to future unrestricted research use. [5]

The CIRM regulations are silent with regard to subsequent withdrawal of materials. The NIH Guidelines for Human Stem Cell Research state:

[4] see http://www.cirm.ca.gov/files/PDFs/Standards/SCRO_Cell_Certification_02_11_10.pdf
[5] see http://www.cirm.ca.gov/sites/default/files/PDFs/Standards/CIRM_Summary_Report_5_1.pdf

> *Donor(s) should have been informed that they retained the right to withdraw consent for the donation of the embryo until the embryos were actually used to derive embryonic stem cells or until information which could link the identity of the donor(s) with the embryo was no longer retained, if applicable.*

Existing state and national policy, including the National Academies' Guidelines for Human Embryonic Stem Cell Research, does not include withdrawal provisions for donated cells and tissues.

The UK Biobank project, a longitudinal health surveillance system that includes biological specimens (blood, saliva, urine) and linkages to medical information, includes a number of withdrawal options (see appendix C). The Biobank project is akin to a research study given the ongoing interaction with participants and their medical information. Historically, cell repositories have not included this research component thus existing state and national policy has not included withdrawal provisions. The Common Rule does, however, require participants be informed of their right to withdraw from research.

In the context of an iPSC repository, consideration should be given to the level of interaction and follow-up contemplated with potential donors. For example, if a one-time donation with no follow-up is contemplated then existing state and national policy may be satisfactory. If some donors are tracked for medical history or health outcomes, then a policy analogous to the UK Biobank might be required.

Process Recommendations Oversight, Materials Provenance & Consent

While the current CIRM framework is deemed adequate, there are oversight, consent and usage-related issues that should be considered. These issues should be considered in light of national and international policies governing iPSC research and bio-repositories. The SWG believes the following considerations and questions should be addressed if CIRM were to sponsor a Pluripotent Cell Resource Center:

Informed Consent

- Consider special consent policies regarding donation of cells from special populations:
  - Will individual with a disease diagnosis derive potential benefit from donation?
  - Should researcher or others who may stand to benefit from research be donors?
  - What are appropriate consent protocols for infants or minors; are established Federal requirements sufficient?
- Consider explicit protections for gamete research:
  - Studies may propose to derive gametes from iPSCs (e.g. infertility research, early developmental research, gamete creation for SCNT

experiments); what is the appropriate consent requirement for research involving gamete creation or blastocyst formation?
    - Absent explicit consent should an iPSC not be utilized for gamete research?
- Consider policies for the re-consent of certain donors:
    - Should individuals who were not of adult age at time of donation be re-consented?
    - Should individual be offered the opportunity to consent to be re-contacted if a potentially clinically relevant finding emerges from research on donated cells?
- Consider the impact of whole genome sequencing on donor privacy and what demands this creates for the informed consent process.
- Consider a procedure for evaluating iPSC derived from "anonymized" somatic cells (cells where no donor links exist):
    - Should an exemption exist for scientifically significant lines not conforming to contemporary standards for consent?
    - Should the future use of anonymized or un-consented lines be limited to certain types of research?

Oversight, Use and Submittal

- Consider general oversight of repository activities:
    - Should oversight be provided by an IRB and/or SCRO specifically associated with the repository?
    - Should review and approval for use of pluripotent cells by **any** end-user conform to CIRM grantee requirements?
    - What is the best mechanism for assuring materials submitted to the repository are "acceptably derived?"

Withdrawal of Materials

- Consider degree of donor tracking and how donors may be given opportunity to withdrawal from research, limited by sharing of derived iPSC lines with other researchers and de-identification of materials:
    - Will donors be re-contacted or otherwise tracked?

Confidentiality

- Consider how repository can maintain links to donors (e.g., for re-contact regarding clinically relevant findings) while also maintaining confidentiality by sending only de-identified materials to researchers.

III. IP, Patents and Distribution

Participants indicated that there are already patents and licensing requirements associated with human cell lines. Dr. Couture suggested existing requirements appear manageable given there are a number of cell therapies going to the clinic. Numerous participants suggested the licensing requirements would likely be

addressed on a case-by-case basis, but perhaps CIRM should consider mechanisms for restricting or limiting exclusive licenses for basic research (a position already echoed in CIRM's intellectual property policy).

As a cautionary note, Dr. Gregory Graff cited research suggesting more intellectual property rights may lead paradoxically to fewer useful products for improving human health. This line of reasoning is based on the hypothesis that fragmented property claims (in this case numerous patents) result in under exploitation of a scarce resource. He also noted that in the stem cell field there are a comparatively high number of patent holdings in the public sector.

Dr. Graff also suggested the risk of IP infringement is comparatively small for basic / academic research and pre-clinical development. Given the Pluripotent Cell Resource Center is contemplated as a resource for supporting basic research, not the development of GMP-compliant clinical products, patent infringement appears to be less of a concern.

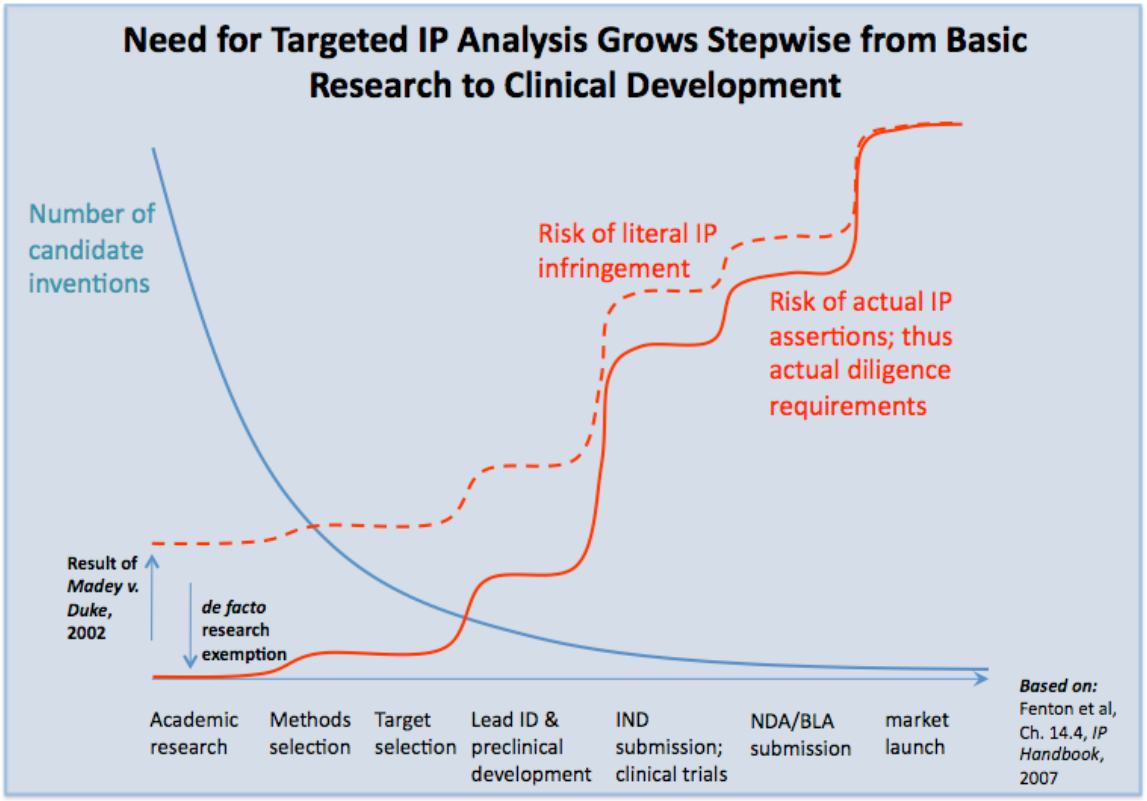


Figure 2: Risk of IP infringement in relation to therapy development

With regard to cell line distribution, Dr. Loring indicated researchers are encountering problem tracing the numerous iPSC lines that are being derived. Various laboratories are developing nomenclatures and data systems for internal materials accounting. However, Dr. Loring suggested there is an urgent need for standard nomenclature, "like a license plate," so lines can be uniquely identified

and tracked for inter-institutional exchange.

Process Recommendations Cell Distribution

- Consider opportunities to support the development of nomenclature and a system to register stem cell lines.

IV. Costs and Organizational Capacity Considerations

Dr. Loring provided cost estimates for iPSC lines from the donor recruitment to deposit in a bio-repository. These costs are summarized in figure 3. Dr. Loring emphasized the need for ongoing genotyping of the iPSC line to detect any genomic abnormalities that may develop. She suggested these cost are often omitted from estimates for iPSC derivation.

Estimated Costs from Materials Procurement to Ongoing Product Distribution for Research Grade IPSC Lines
Source: Loring, The Scripps Research Institute

Example:
Costs for iPSCs from one individual - recruitment to first phase banking

1.	Recruitment materials	$50
2.	Biopsy materials	$150
3.	Fibroblast banking	$350
4.	Genotyping	$500
5.	Reprogramming to iPSCs (3 clones per individual)	$1,180
6.	First phase quality control:	
	a. Sterility	$15
	b. Pluripotency marker assay	$155
	c. Differentiation assay	$160
7.	Expansion and initial banking of iPSCs (3 clones per individual).	$3,600
8.	Second phase quality control (one of 3 clones)	
	a. Sterility	$15
	b. Pluripotency marker assay	$155
c.	Genotyping iPSC line	$1,500
	Subtotal	**$7,830**
9.	Master Bank (one clone per individual)	**Total** ca.$10,000

Cost estimates were limited to figures for iPSC derivation. Participants suggested these costs could fall for larger scale operation.

Figure 3: Costs associated with iPSC derivation

Conclusion

This report is designed to provide a preliminary assessment of ethics and policy issues related to the derivation and distribution of iPSCs. The CIRM Medical and Ethical Standards Working Group considered ethics policy issues in the context of existing CIRM regulations governing Institute grantees. At this time, the SWG did not identify any insurmountable ethical issues that would preclude the development of a iPSC bio-repository. the SWG believes the established CIRM requiring IRB oversight and active consent for all donated cells and tissue is adequate and should be incorporated into any bio-repository. The SWG did indentify a number of considerations related to oversight, materials provenance

and consent that should be considered by the SWG if CIRM were to support a program designed to collect and distribute human iPSC lines. These considerations are identified in section II.

Appendix A: The United Kingdom's Stem Cell Bank (UKSCB)

I. Scientific Considerations

The UK Stem Cell Bank (UKSCB) is funded by a grant from the Medical Research Council (MRC) and the Biotechnology and Biological Sciences Research Council (BBSRC). It was established in 2003 by both organizations with the overall goal to promote global access to well characterized seed stocks of somatic and embryonic human stem cells. The UKSCB is housed and operated by the National Institute of Biological Standards (NIBSC) and has two well defined levels of operation: a research grade facility aiming at promoting basic research, and a clinical grade one, whose purpose is to bank under GMP as a primary material for the development of therapies.

The UKSCB is entrusted with providing ethically sourced and quality controlled adult, fetal and embryonic human stem cells. It has currently 15 research-grade human embryonic stem cell lines ready for distribution, 23 accessioned and 17 that are both due for release and accepted by the Steering Committee.

The processes and requirements for operating the UKSCB are detailed in the *Code of Practice for the use of Human Stem Cell Lines* [6] drafted by the UKSCB Steering Committee. The *Code of Practice* regulates the activities of the Bank in relation to the procuring, processing, testing, storing and distributing human stem cell lines. Furthermore, the *Code* provides best practice guidance for those working with stem cell lines and outlines oversight mechanisms for research involving hESC lines in the UK.

Quality Assurance:

In compliance with the Human Tissues (Quality and Safety for Human Applications) Regulations (2007) which sets up the requirements of the *European Union's Tissues and Cells Directive – HTA* (2004/23/EC, 2006/17/EC), the UKSCB has established a *Quality Management System*. The system covers all licensable activities, ensuring the safety and quality of the stem cell lines prepared by the bank. It is described in the *UK Stem Cell Bank's Quality Manual*.

Each cell line and the cell banks prepared from it are identified using unique identifiers traceable to the respective cell line's accession number. This is linked to the UKSCB Steering Committee's unique application number. The system of unique identifiers adopted by the UKSCB allows traceability from donor to recipient or vice-versa, while maintaining donor confidentiality. Traceability allows for donor identification in the event of a discovery, which might significantly affect the health of the donor. Furthermore, the Bank adopts a strict record keeping policy for each cell line, providing evidence that the cell line has been processed, tested, stored and released following the procedures detailed in the Quality Management System.

As detailed in the UKSCB's *Code of Practice* the Bank operates a system of internal quality audits to monitor compliance with the HTA regulations. Inspections are performed

[6] Code of Practice for the use of Human Stem Cell Lines, Steering Committee of the UK Stem Cell Bank (April, 2010) 6(http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC003132) ,

by the Health and Tissue Authority, which licenses the UKSCB for the purposes of processing, testing, storing and distributing (including import and export) of cell lines intended for clinical use.

Finally, the Bank's facilities, processes and equipment used in the processing, testing, storage and supply of cell lines have been qualified and validated to maintain the requirements of the HTA regulations. The cell culture procedures adopted by the UKSCB meet current best practice and include a process for recall, disposal and reporting of cell lines in the event of an adverse incident or event.

II. Oversight, Material Provenance and Consent

Ethics Review, Informed Consent and Material Provenance

As in the case of other national stem cell banking initiatives, the UKSCB receives cell lines from elsewhere but mandates deposit by its licensing authority. The UKSCB is the regulator-mandated repository for all embryonic stem cell lines derived in the UK. The Human Fertilisation and Embryology Authority (HFEA) requires as a condition for the licensing of newly derived hESC lines that a sample line be deposited in the UKSCB.

Before depositing a cell line, the UKSCB requires evidence from its Steering Committee that donor consent complies both with the HFE and the HTA requirements. Moreover, the line must meet the Bank's requirements for deposit in terms of viability, safety and characterization. Additional requirements are in place for clinical grade cell lines as mandated by the HTA.

The UKSCB can be accessed by researchers from both academia and industry in the UK and abroad. The same review procedures apply to local or foreign applicants, thereby compliance with both UK legislation and the legislation of the country where the research is to be performed is required. Applications for deposit and access to the cell lines are subject to approval on a case-by-case basis by the Steering Committee. The criteria adopted by the Steering Committee reflect the principles adopted in HFEA's policy. It states that the lines "have been ethically sourced, with fully informed donor consent, and that the cell lines present a valuable resource for the biomedical research community"[7].

Overall, the Steering Committee's expectation is to ensure that cell lines are used only by bona fide research groups for justifiable and valuable purposes that reflect the requirements of the HFEA regulations. The Steering Committee is thus responsible for ensuring that donor informed consent, ethical approvals, licenses and authorizations are in place for all stem cell lines that are deposited in the UKSCB, as well as for all those projects receiving cell lines from it. For hESC lines, audits of consent procedures are carry out by the HFEA.

Both the Human Tissue Act and the HFEA Act require, as a fundamental ethical principle, the donor's free and informed consent. Consent forms and all written information (e.g. leaflets) have to be approved by local ethics committees. For research

[7] Human Fertilisation and Embryology Authority (HFEA), Code of Practice (8th edition), October 2009. http://www.hfea.gov.uk/docs/complete_CoP8.pdf

involving human embryos, additional approval by the HFEA is required; while for somatic cells (e.g. adult or fetal tissue) informed consent processes should comply with the *HTA's Code of Practice on Consent*. The former requires specific informed consent for the creation and use of iPS cells.

Research Ethics Committee (REC) approval for laboratory-based research using established hESC lines is not required by the Steering Committee. While not being a legal requirement, REC approval is recommended for research involving human tissue. Moreover, REC approval must be obtained (a) as part of a HFEA research license, (b) for research involving human tissues, and (c) for clinical trials of all stem cell derived therapeutic products.

Oversight of Bank Activities

The UKSCB governance structure is perhaps the most comprehensive of all existing stem cell banks. The bank is governed by an independent, non-statutory national committee denominated the "Steering Committee". The Steering Committee has been created as an oversight body, whose role involves the supervision of both the ethical and scientific activities of the UKSCB. This is in addition to its role of overseeing all research involving established human embryonic stem cell lines, regardless of their provenance (i.e. the UKSCB or any other source). Among the Committees' terms of reference is to inform the work of two other governance bodies: the Management Committee and the User and Clinical Liaison Committees, by addressing issues identified and reported by them. The Committee has a multidisciplinary membership; it includes scientists, researchers, government representatives and medical experts among others.

The Steering Committee reports annually to the Medical Research Council (MRC) – one of the founders of the UKSCB, and it is also responsible for briefing and advising the health and sciences ministers. The Committee works closely with the HFEA, the Department of Health and the Medicines and Health Care Products Regulatory Agency.

A local Management Committee is responsible for the day-to-day operational issues relating to the Bank. The Committee is chaired by the Director of the NIBSC and its membership is also of a multidisciplinary nature, including in-house and external experts, professionals, lay members and representatives of local funding agencies. The mandate of the Management Committee relates to (a) overseeing the establishment, management, and development of the Bank; (b) developing a Curation Policy, (c) approving, monitoring and implementing financial strategies for the Bank and its projects; as well as (d) ensuring the implementation and compliance with the Steering Committee's Code of Practice and other relevant regulatory and legal requirements. The Management Committee is accountable to the Steering Committee.

The User and Clinical Liaison Committees complement the UKSCB internal governance structure. The former's role is to provide for a discussion and consultation on issues relating to both the UKSCB and to the oversight of stem cell research and therapy development in the UK. Reflecting the needs of its mandate, the Committee is formed by stem cell researchers and clinicians from both academia and industry. These Committees are not formally required to report to the Steering Committee, rather they are charged to bring relevant concerns to the latter.

Finally, the Medicines and Health Care Products Regulatory Agency (under the Department of Health), is the body with authority and mandate to inspect the UKSCB. The National Institute for Biological Standards and Control (NIBSC) is ultimately responsible for the bank's operations.

III. IP, Patents and Distribution

The UKSCB's main objective is to store and distribute quality controlled research and clinical grade stem cell lines, thereby facilitating their sharing. However, ownership of any intellectual property embodied in these cell lines remains with the originator.

The *Code of Practice* outlines the conditions for such distribution. For research grade cell lines deposited in the UKSCB before April 2010, a license covering intellectual property and ownership is required between the requestor and the originator. For those research grade lines deposited in the Bank after such date, a *Research Use License* (RUL) setting the terms of cell line usage is needed in order to both protect the depositor's rights to intellectual property and standardized the process of accessing lines from the Bank. This license is for laboratory use (excluding research in humans) of stem cell lines without an individually negotiated Material Use License (MUL)

A *Material Deposition Agreement (MDA)* is required before deposited stem cell lines are approved for release by the Steering Committee. This agreement is signed by the owner of the cell line and the Bank and it is negotiated on a case-by-case basis. The MDA sets out the terms under which the cell line is deposited, including conditions for usage and distribution. For hESC lines, the MDA should include a statement on existing intellectual property rights.

Specific licenses for commercial, manufacture and sale or for clinical use are required. The *Commercial Manufacture and Sale License* determines the terms for exploitation of the cell line. It is subject to standard commercial negotiation between the accessor and the depositor, without any restrictions imposed by the Steering Committee. Furthermore, intellectual property holders are not obliged to issue a *Clinical Use License* as a research grade component for each line is available for research use.

IV. Costs and Organizational Capacity

A schedule of charges for the provision of stem cell lines to users has been established between the UKSCB and its funders. Following recommendations by the Steering Committee, different charges are levied for academic researchers and for commercial users. The former are expected to pay full economic costs, while the latter contribute to the recovery of some of the Bank's operating costs. However, as of December 2009, no charges other than third party shipping fees have been levied for research grade cell lines.

In order to avoid conflicts of interest, the UKSC is prevented from conducting discovery research on the banked stem cell lines and from carrying research into stem cell biology. However, with previous approval from the Steering Committee, the Bank may pursue research aiming at improving banking, characterization, safety testing and preservation of the stem cell lines. Intellectual property arising from research and development activities carried out by the Bank –with funding from MRC/BBSRC – will be assigned to the MRC for the purpose of protection and exploitation. The operation of the bank will be

supported by the net revenues generated from exploitation of such intellectual property. The UKSCB Code of Practice further details the provisions for intellectual property generated by the Bank.

Web Links

- The UK Stem Cell Bank:
  http://www.ukstemcellbank.co.uk/

- Code of Practice for the use of Human Stem Cell Lines
  http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC003132

- UK Stem Cell Lines Registry
  http://www.mrc.ac.uk/Ourresearch/Ethicsresearchguidance/Stemcellbank/Usingthestemcellbank/MRC003079

- The Human Tissue Act (2004):
  http://www.legislation.hmso.gov.uk/acts/acts2004/20040030.htm

- European Tissue and Cells Directive:
  http://www.hta.gov.uk/legislationpoliciesandcodesofpractice/legislation/eutissueandcellsdirectives.cfm

- The Human Fertilisation and Embryology (HFE) Act (1990 and 2008)
  http://www.opsi.gov.uk/acts/acts1990/Ukpga_19900037_en_1.htm

- Medicines for Human Use (Clinical Trials) Regulations 2004
  http://www.uklegislation.
  hmso.gov.uk/si/si2004/20041031.htm

- EC Regulations on Advanced Therapy Medicinal Products 2007
  http://www.mhra.gov.uk/Howweregulate/Advancedtherapymedicinalproducts/index.htm

- The UK Stem Cell Tool Kit
  http://www.sctoolkit.ac.uk

Appendix B: Literature Review of Policy Issues Arising in the Context of Bio-Repositories

1. **Consent**
    a. Informed consent is difficult to obtain in some cases (during labor, from a graduate student involved in the study, from someone who stands to personally benefit from research because of an illness, iPS donations especially)
    b. For any sensitive applications, such as gamete research, explicit consent from the donor should be provided. Given not all future uses can be anticipated, repository my want to provide assurance samples will not be use for reproductive purposes.
    c. To the extent feasible, clarify that the research can be used for any and all future unforeseeable research. Clearly communicate extent to which identifiable information about the donor will be maintained or if the donor will be contacted in the future.
    d. If CIRM has a repository we should ensure that all biomaterials are properly procured with informed consent. Such a requirement may disqualify some lines derived under different standards.
    e. The possibility of withdrawal must be considered (especially for children once they turn 18)
2. **Giving Information Back to Original Donors**
    a. There needs to be an explicit protocol in place
    b. What sort of information should be given back to donors? Clinically significant results? Relevant information? All information? Specific criteria must be identified in the protocol.
    c. Donors should have to indicate on their consent form whether or not they would like information back (including on the behalf of minors)
    d. There may or may not be a need to require genetic counseling
3. **Ethnic Diversity**
    a. If CIRM sponsored a repository (in whole or part) a programmatic goal should be to ensure that the cell lines derived for potential cures are genetically and immunologically diverse to benefit the California population at large.
    b. Achieving genetic and immunologic diversity might require collaboration / harmonization with international banks and a comprehensive donor recruitment strategy.
    c. Very stringent protocol ought to be in place for CIRM grantees
    d. The effects the extent of illness can have on the appropriateness of participation in a study are ethically relevant. There is a trade off between the scientific usefulness and the potential human losses.
4. **IP Rights**
    a. Protocols for deposit and withdrawal from a bio-repository should be based on an open-source model that support unrestricted use for basic research.
    b. The repository should require acknowledgement of cell line derivers.
    c. A repository should be developed in conjunction with a cell registry(s) and include documentation of any IP rights associated with specific cell lines.

Appendix C: UK Biobank Level of Withdraw Options

UK Biobank will be most valuable if few people do withdraw from it, so potential participants are asked to discuss any concerns that they might have with a member of the project team before agreeing to participate.

After giving their signed consent, however, participants can withdraw at any time. This will allow particular concerns to be discussed and the desired level of withdrawal to be determined:

- *"No further contact":* This means that UK Biobank would no longercontact the participant directly, but would still have their permission to retain and use information and samples provided previously and to obtain and use further information from their records.

- *"No further access":* This means that UK Biobank would no longer contact the participant or obtain further information from their records in the future, but would still have their permission to use the information and samples provided previously.

- *"No further use":* This means that, in addition to no longer contacting the participant or obtaining further information about them, any information and samples collected previously would no longer be available to researchers. UK Biobank would destroy their samples (although it may not be possible to trace all distributed sample remnants) and would only hold their information for archival audit purposes. Participant's signed consent and withdrawal would be kept as a record of their wishes. Such a withdrawal would prevent information about them from contributing to further analyses, but it would not be possible to remove their data from analyses that had already been done.