

The DISCUSS Project: Induced Pluripotent Stem Cell Lines From Previously Collected Research Biospecimens and Informed Consent: Points to Consider

GEOFFREY P. LOMAX,^a SARA CHANDROS HULL,^{b,c} JUSTIN LOWENTHAL,^c MAHENDRA RAO,^{d,e} ROSARIO ISASI^f

^aCalifornia Institute for Regenerative Medicine, San Francisco, California, USA; ^bOffice of the Clinical Director, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland, USA; ^cDepartment of Bioethics, Clinical Center, and ^dCenter for Regenerative Medicine, National Institutes of Health, Bethesda, Maryland, USA; ^eLaboratory of Stem Cell Biology, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland, USA; ^fCenter of Genomics and Policy, Faculty of Medicine, Department of Human Genetics, McGill University, Montreal, Quebec, Canada

SUMMARY

Human somatic cell reprogramming is a leading technology for accelerating disease modeling and drug discovery. Research organizations are sponsoring initiatives to create libraries of induced pluripotent stem cell (iPSC) lines for broad distribution and application. Donor informed consent plays a critical role in supporting the ethical conduct of iPSC research. To date, our organizations have focused on informed consent considerations for somatic cell collection intended specifically for iPSC derivation and distribution. This article considers how somatic cells obtained under general (biomedical) research protocols can be used for iPSC derivation. We present draft Points to Consider regarding the use of human somatic cells for iPSC research. Our goal is to initiate a process designed to develop consensus for the use of previously collected specimens for iPSC research. We anticipate publishing final considerations in early 2014. *STEM CELLS TRANSLATIONAL MEDICINE* 2013;2:727–730

INTRODUCTION

Human somatic cell reprogramming to derive induced pluripotent stem cells (iPSCs) has emerged as a leading technology for accelerating basic science and clinical research. Research organizations are sponsoring coordinated initiatives to create libraries of iPSC lines designed to be used in a broad spectrum of applications. To support these initiatives, we have developed recommendations to guide funded research involving the collection of human somatic cells. Our initial efforts focused on the prospective collection of biospecimens with informed consent procedures specifically designed for the derivation of iPSCs and their broad distribution and application [1].

Using existing and established (ongoing) biospecimen collections for research purposes represents another distinct and valuable pool of source material for cell reprogramming. Existing collections often have intrinsic scientific value because they may be well-characterized, be collected appropriately, and cover rare (“orphan”) diseases; they may encompass phenotypic progression within a defined cohort; or they may possess other special population characteristics that cannot be easily replicated. A number of existing collections also have robust “value-added” systems for tracking an individual’s health status, and some benefit from ongoing communication with donors.

Since our previous efforts focused on a specific context and purpose—prospective somatic cell collection for iPSC derivation and subsequent deposit to a repository for distribution [1]—we believe it is also important to consider how collections previously obtained under general (biomedical) research protocols can be responsibly

(i.e., ethically and scientifically) used for iPSC derivation and distribution. We are aware that ethics committees and institutional review boards (IRBs) have begun to grapple with questions about whether iPSC research on existing specimens is covered by the previous consent process. We are also aware of cases where administrators of repositories have expressed concerns over the deposit of iPSC lines that, in their view, do not conform precisely to our published protocols, as for instance with respect to provenance requirements [1]. We find that inconsistent interpretations are potentially problematic because they may conflict with established policy, potentially disadvantage valuable sources of somatic cells, and/or risk undermining respect for the interests of biospecimen donors.

Many ethics and policy issues have been previously addressed in the context of biomedical research, genetic and genomic data, and immortalized cell lines and may apply in iPSC research. Our aim in the DISCUSS (Deriving Induced Stem Cells Using Stored Specimens) project is to supplement this work by providing guidance for specific issues that emerge in the iPSC context. Our choice of issues is based on concerns that have been expressed about certain features of iPSC research (ubiquitous source material and pluripotency), the rapid growth in translational initiatives and commercial partnerships, the widespread banking and distribution of iPSC lines, and the ways in which several of the broad uses conceived for iPSCs—such as cell-based therapy and the creation of functional gametes—may raise issues that go beyond those typically addressed in the general context of stored specimens.

In this paper, we present Points to Consider (in draft form) regarding the use of human somatic cells to derive and distribute

Correspondence: Geoff Lomax, Dr.P.H., 210 King Street, San Francisco, California 94107, USA. Telephone: 415-396-9134; Fax: 415-396-9141; E-Mail: glomax@cirm.ca.gov Received May 13, 2013; accepted for publication July 1, 2013; first published online in *SCTM EXPRESS* August 29, 2013. ©AlphaMed Press 1066-5099/2013/\$20.00/0; <http://dx.doi.org/10.5966/sctm.2013-0099>

iPSCs where the original specimens were collected for other research purposes. The ultimate goal of the DISCUSS project is to develop consensus for the use of previously collected research specimens for iPSC derivation and distribution. The proposed approach is consistent with the 2010 National Academies' Guidelines for Human Embryonic Stem Cell Research [2], which state: "New derivations of stem cell lines from banked tissues obtained prior to the adoption of these guidelines are permissible provided that the original donations were made in accordance with the legal requirements in force at the place and time of donation. This includes gametes, morulae, blastocysts, adult stem cells, somatic cells, or other tissue. In the event that these banked tissues retain identifiers linked to living individuals, human subjects protections may apply."

Our approach is intended to support collaboration and exchange among national and international collaborators and funders of research. These Points to Consider are specifically intended to assist researchers, ethics review bodies, and funding agencies in designing policies to allow repurposing of previously collected research specimens for iPSC derivation under a coherent ethical and governance framework that encourages respect for donors.

PROPOSED GUIDING PRINCIPLES

Research funded by the U.S. National Institutes of Health (NIH) and the California Institute for Regenerative Medicine (CIRM) is governed by the U.S. Common Rule policy framework. This Points to Consider statement is consistent with the provisions of this U.S. policy framework, which is generally compatible with broader international consensus on ethical principles for research oversight and participant informed consent. This compatibility is present notwithstanding diverse sociocultural, religious, and historical national contexts shaping the interpretation and implementation of such core ethical principles [3]. Therefore, we anticipate that the principles articulated in this statement will be broadly applicable and can serve to facilitate cooperative research among national and international collaborators.

Scope of This Statement

For the purpose of this Points to Consider document, we limit our scope to existing and ongoing biospecimens collections obtained from human donors (human subjects) specifically for research purposes. We recognize that a much broader universe of human biospecimens exists (e.g., clinical specimens removed during surgery and commercially available lines), which may have differing ethical and policy considerations. The limited scope of this statement reflects our desire to address immediate policy considerations that have arisen in the context of publicly funded research—specifically, projects designed to derive and distribute human iPSC lines from existing research collections of biospecimens.

Furthermore, this statement is not designed to reiterate all aspects of a comprehensive informed consent process. Funded research projects are required to comply with established requirements for the protection of research subjects, including but not limited to the U.S. Common Rule 45 CFR 46 [4]. Here we focus narrowly on a subset of iPSC-specific issues that may be subject to conflicting interpretation in the context of human research participant protections.

Baseline Policy Requirements

Common Rule requirements, NIH guidelines, and CIRM regulations, as well as several international policies, establish *minimum* core ethical standards for the procurement of biological specimens from research participants (human subjects). These core standards generally include (a) voluntary and informed consent by donors or their representatives, and (b) oversight by an IRB (or an equivalent). (Funded research under the Common Rule may also involve the use of biological specimens obtained without research consent.) As a minimum prerequisite, we expect that existing/established biospecimens covered by this Points to Consider document would be obtained in accordance with these standards, that is, with appropriate informed consent and IRB oversight.

The following statements are intended to help determine whether the consent process under which existing/established biospecimens were originally procured is sufficient to permit the derivation and distribution of iPSCs using these biospecimens. (See <http://www.hhs.gov/ohrp/policy/cdebiol.html>. We also acknowledge that practices and requirements based on the identifiability and traceability of a specimen likely vary between jurisdictions, and that identifiability is a complicated concept that is currently being debated.) We note that, in some cases, the statements in this policy go beyond the requirements of the Common Rule. For example, the Office of Human Research Protections has interpreted that, in most cases, the use of previously collected, deidentified samples and data is not classified as human subjects research, obviating the need for IRB review and for the review of consent form language [5]. However, we have taken the position here that previous consent form language under which specimens were obtained should be reviewed before iPSC lines are derived, even if this review is not explicitly required under the current interpretation of the Common Rule.

Statement 1: A review should be performed to ensure that iPSC derivation and distribution are not specifically precluded by, or otherwise in conflict with, the original informed consent. (This review should include the consent form and any other materials used to support the process of informing participants.)

Common examples of where conflicts may arise include language indicating the following:

- The original principal researcher and/or the primary research team will manage the distribution of specimens or their products.
- The specimen will be used only to study a particular disease or condition.
- The specimen or resulting information will not be used for commercial purposes.
- The specimen will be used or distributed only within a certain jurisdiction.

iPSC lines containing limitations on use should be deposited in a repository only if transfer agreements address such restricted uses in conformity with the scope of the donor's consent. Moreover, subsequent transfer agreements for secondary or tertiary research should comply with any restrictions stipulated in the original donor's consent.

Statement 2: iPSC derivation and use should be considered a standard method for modeling disease and developing therapies. In cases where the original biospecimen collection is designed to study a particular disease condition, iPSC derivation and use (i.e., as a tool for research on that particular disease) should be considered consistent with this purpose.

If the consent protocol indicated that biospecimens would be used only to study a particular disease or condition, the use of biospecimens to derive iPSCs in order to study the specified disease condition should be considered consistent with the intended purpose (i.e., even if iPSCs were not mentioned explicitly in the previous consent protocol). Material transfer agreements accompanying distributed biospecimens and iPSC lines should reflect any limitations related to the disease or condition that may be studied.

Statement 3: A reference to the possibility of sharing biospecimens with other researchers in the original consent form is sufficient for distributing material via an iPSC repository.

Obtaining consent to share biospecimens with other researchers has become common practice and is consistent with broad data sharing goals that have been articulated in order to maximize the public benefits of funded research. Repositories are a primary means of distributing iPSC lines. Therefore, deposit in a repository can be deemed to be consistent with a broad reference to sharing biospecimens with other researchers. As the sharing of deidentified biospecimens to derive iPSC lines and the deposition of those lines become widespread, it is important to ensure that donors are broadly aware of such practices.

Statement 4: A reference to genetic research and the risks thereof should have been included in the original consent form if raw individual-level genotypic data are to be deposited in an open access database.

The reporting of raw, individual genotypic information in open access databases affects the privacy interests of the donor (see, for example, [6]), whether or not the data have been deidentified. Such reporting should not take place unless the donor is informed of, and has consented to, genetic studies or genomic analysis being an integral part of the proposed research. However, the absence of such a disclosure does not necessarily mean that genomic analysis is inappropriate in the context of a specific study, or that population-level genomic data cannot be shared. For example, genotypic analysis may be integral to research intended to elucidate a disease mechanism. This statement pertains only to the conditions under which “raw” individual genotypic data may be placed in the broadly accessible databases.

Statement 5: A reference to commercial use should have been included in the original consent form if resulting cell lines will be used to develop commercial products.

The donor should be informed that materials may be used for commercial purposes (e.g., as a drug assay by a pharmaceutical company) and that the donor will not have legal or financial interest in any resulting commercial development or patents. Absent this disclosure, materials or resulting cell lines should be used only for noncommercial (research use only) purposes.

Statement 6: If specimens are to be used to create a cell line or cell product intended for human transplantation, the donor

should have been informed that his or her specimen may be used to create human transplantation products.

Although we expect it to be rare that a biospecimen previously collected for research purposes will be redirected to create cell lines or products for human transplantation or clinical use, there might be a particularly valuable cell line amenable to this purpose. (As an example, the H9 embryonic stem cell line was originally derived under research-grade conditions but was subsequently adapted to clinical-grade conditions. See <http://www.news.wisc.edu/18020>, as well as the NIH Human Embryonic Stem Cell Registry. A similar approach is plausible with research-grade iPSC lines.) Donors should consent explicitly to the use of their specimens in human transplantation.

Statement 7: Reference to unspecified or unforeseen future studies or research in the consent document should be interpreted to refer to activities designed to develop or contribute to generalizable scientific knowledge. However, such a reference to unspecified or unforeseen studies or research should not be interpreted to include commercial product development or human transplantation.

See statements 5 and 6 above.

Statement 8: iPSCs should not be used for studies intended to generate gametes or embryos without a specific consent.

In addition to ensuring that applicable law, policy, and material transfer agreements are followed, the development of gametes from somatic cells should take place only with specific consent from the original donor. We are hesitant to suggest that exceptional conditions be placed on the use of iPSCs [7], but we also believe, especially in the context of previously collected specimens, that such use would be beyond what a donor could have reasonably contemplated during the consent process. We have previously recommended that gamete creation and embryogenesis be specifically highlighted and addressed in the prospective consent context [1]. Given the sensitivity of this line of research, researchers have a responsibility to be transparent with donors about the use of their specimens in this research.

Statement 9: Any limitations on a donor’s ability to withdraw from the proposed iPSC research should have been disclosed in the original consent form.

There are both practical and other justifiable reasons for limiting a donor’s ability to withdraw iPSC lines from research use [8, 9]. Many research proposals include a provision that derived iPSC lines may continue to be distributed, even when a donor withdraws from the research, though only if deidentified (i.e., anonymized). In such cases, we want to ensure that donors are aware of these limitations on their right to withdraw from iPSC research. Consistent with the 2010 NAS Guidelines for Human Stem Cell Research [2], we believe that derived iPSC lines may continue to be used and distributed if done so in a manner consistent with the original consent and with jurisdictional laws.

DISCUSSION

If the preceding criteria are not met, we believe existing biospecimens should *not* be used to derive iPSCs for research unless:

1. Donors can be recontacted and asked to provide consent that specifically covers the derivation and uses of iPSCs, according to the criteria listed above;
2. There is a particularly compelling scientific reason to use a particular collection of specimens, it is not feasible to recontact participants to get their specific consent, and the required IRB waiver is obtained; or
3. The current research proposal is modified to ensure that the creation and use of iPSCs is consistent with the previous consent process (no derivation of gametes, no commercial use, any restrictions on use can be honored, etc.).

The ability to recontact a donor will depend upon both the language of the previous consent process and the existence of a mechanism to trace the sample to the original donor. There may be reasons beyond the specific provisions discussed in this document for a repository to recontact donors if it is able to [10] (e.g., to share individual results [11] or aggregate study findings [12]; to get updated health information on the original donor before allowing an allogeneic cell product to be used in human subjects [1]; or to communicate with donors about the ongoing use of their specimens, obtain recontact, or enable enhanced donor control over the research conducted on their specimens [1]), and it might be advisable to do so in certain cases. We have refrained from being prescriptive about when researchers or repositories might have obligations to recontact a donor, but we leave open for discussion the idea that it might be appropriate for the research enterprise to recontact donors in certain cases. For prospective consent, reasons to recontact can of course be explicitly foreseen.

In the event that a compelling scientific reason exists to use a particular collection of specimens, the basis for decision should be documented and be available to the research community. Documentation should serve to enable the research community to strive for consistent application of these Points to Consider.

CONCLUSION

This Points to Consider statement provides criteria to determine when the use of existing/established biospecimens to create and distribute iPSCs is appropriate. The criteria are designed to suggest when the consent that was originally provided to procure those biospecimens is sufficient for iPSC research. Our proposal is also meant to be compatible with broader international consensus on ethical principles and research oversight governing human biomedical research in general, and genetic research and biobanking in particular.

ACKNOWLEDGMENTS

The opinions contained in this document are the authors' own and do not necessarily reflect the policies or positions of the NIH, U.S. Public Health Service, or U.S. Department of Health and Human Services. This Points to Consider document should not be construed as an official policy statement of any federal agency or of the International Stem Cell Forum. Rather, these Points to Consider are meant to guide policy deliberations and to provide a framework that can eventually be adopted by regulatory and funding agencies. This document is in draft form and the authors solicit feedback on its contents. Please send comments to discuss@cirm.ca.gov.

AUTHOR CONTRIBUTIONS

G.P.L., S.C.H., J.L., M.R., and R.I.: manuscript writing.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

R.I. has compensated research funding.

REFERENCES

- 1 Lowenthal J, Lipnick S, Rao MS et al. Specimen collection for induced pluripotent stem cell research: Harmonizing the approach to informed consent. *STEM CELLS TRANSLATIONAL MEDICINE* 2012;1:409–421.
- 2 National Research Council and Institute of Medicine. Final Report of the National Academies' Human Embryonic Stem Cell Research Advisory Committee and 2010 Amendments to the National Academies' Guidelines for Human Embryonic Stem Cell Research. National Academy Press. Available at <http://nas-sites.org/stemcells/>. Accessed May 7, 2013.
- 3 Isasi RM, Knoppers BM. Governing stem cell banks and registries: Emerging issues. *Stem Cell Res* 2009;3:96–105.
- 4 U.S. Department of Health and Human Services. Protection of Human Subjects. 45.CFR. 46. Available at <http://nas-sites.org/stemcells/>. Accessed May 7, 2013.
- 5 U.S. Department of Health and Human Services. OHRP: Guidance on research involving coded private information or biological specimens. October 16, 2008. Available at <http://www.hhs.gov/ohrp/policy/cdebiol.html>. Accessed May 7, 2013.
- 6 Knoppers BM, Isasi R, Benvenisty N et al. Publishing SNP genotypes of human embryonic stem cell lines: Policy statement of the International Stem Cell Forum Ethics Working Party. *Stem Cell Rev* 2011;7:482–484.
- 7 Lomax GP, Peckman SR. Stem cell policy exceptionalism: Proceed with caution. *Stem Cell Rev* 2012;8:299–304.
- 8 Lowenthal J, Hull SC. Framing the "right to withdraw" in the use of biospecimens for iPSC research. *Ethics Biol Eng Med* (in press).
- 9 Medical Accountability Standards Working Group. Ethical and policy considerations for a pluripotent cell resource center 2011 update. Los Angeles, CA: California Institute for Regenerative Medicine. June 28, 2011. Available at http://www.cirm.ca.gov/sites/default/files/files/about_cirm/SWG_April_2011_6_28_2011.pdf. Accessed April 22, 2013.
- 10 Isasi R, Knoppers BM, Lomax G. Sustained interaction: The new normal for stem cell repositories? *Regen Med* 2011;6:783–792.
- 11 Lomax GP, Shepark KA. Return of results in translational iPS cell research: Considerations for donor informed consent. *Stem Cell Res Ther* 2013;4:6.
- 12 Isasi R, Knoppers BM, Andrews PW et al. Disclosure and management of research findings in stem cell research and banking: Policy statement. *Regen Med* 2012;7:439–448.