APPROVED MEETING MINUTES

California Department of Public Health
Human Stem Cell Advisory Committee Meeting
November 30, 2010

California Department of Public Health (CDPH) Human Stem Cell Research (HSCR) Advisory Committee Members
Elizabeth Blackburn, PhD (phone)
Samuel Cheshier, MD, PhD
Elliot Dorff, PhD (phone)
Fred Gage, PhD (phone)
Henry Greely, JD
Bernard Lo, MD (phone)
Bertram Lubin, MD
David Magnus, PhD
Otto Martinez-Maza, MD
Radhika Rao, JD (phone)
Gregory Stock, PhD

CDPH
Amber Christiansen, Human Stem Cell Research Program, CDPH
Heidi Mergenthaler, Human Stem Cell Research Program, CDPH
Lehoa Nguyen, CDPH Legal Counsel

Guest Speaker
Geoff Lomax, California Institute for Regenerative Medicine (CIRM)

Members of the Public
Sarah Cho, Stanford
Mario Garcia, Stanford
Molly Havard, Stanford
Shannon Smith-Crowley, Partners in Advocacy

Agenda Item 1: Welcome and Introductions
Professor Greely welcomed the Committee members, public attendees, and CDPH staff.

Agenda Item 2: Approval of Meeting Minutes from 05/19/09
Professor Greely suggested amending the meeting minutes to include the public location of the teleconference at Stanford Law School. CDPH staff agreed and the minutes were approved without further amendment.

CDPH staff then provided a summary of CDPH's legislative review of human embryonic stem cell research activity from January 1, 2007 – June 30, 2008. The legislative review was made available to the Advisory Committee and public on the HSCR Program website in July 2010.

Agenda Item 3: Current status of stem cell research in California (Dr. Lomax – CIRM)

Dr. Lomax presented on recent substantive changes to the CIRM regulations, as well as policy differences between CIRM regulations and the CDPH Guidelines for Human Stem Cell Research. He noted most of the recent changes have been minor and some of them based on feedback from grantees.

Dr. Lomax discussed the following recent changes to the CIRM regulations:

1. §100080(a)(2)(B): allows CIRM-funded research to use all embryos created using *in vitro* fertilization (IVF). This amendment served to align CIRM with CDPH and the National Institutes for Health (NIH) Guidelines.
2. §100070(c): requires notification of research involving identifiable somatic cells or *in vitro* research with de-identified somatic cells with the intent of deriving a pluripotent stem cell line. CPDH does not have this requirement as it does not address induced pluripotent stem cell (iPSC) research, except in special cases. The expanded notification requirements are appropriate given CIRM actively manages research awards.
3. 100090(a)(1)&(2): in the past, CIRM required the consent of both gamete donors in the case of embryo donation for research. CIRM has clarified that it will accept the use of embryos if there was an anonymous sperm donor contributing to the creation of embryos that were created prior to the date the CIRM regulations took effect.
4. The Independent Citizens' Oversight Committee (ICOC) is currently considering designating human embryonic stem cell (hESC) lines derived under the Australian Research Involving Human Embryos Act as acceptably derived for CIRM-funded research. This amendment is expected to pass.

It was pointed out that if the CDPH Guidelines were to incorporate the Australian lines as well, section 6 of the Guidelines would need to be amended.

Dr. Lubin asked Dr. Lomax if CIRM had compiled data regarding the various types of research its grantees are performing. Dr. Lomax indicated CIRM was doing work related to characterizing the grant portfolio based on types of diseases, the bodily systems being researched, etc. Dr. Lubin noted it might be helpful to compare the data results with CDPH as a way of assessing reporting compliance.

Professor Greely asked Dr. Lomax if CIRM has been involved in any of the clinical trials using hESC lines. Dr. Lomax did not know of any CIRM involvement in these trials. Professor Greely also inquired as to the longevity of CIRM and its anticipated end date. Dr. Lomax thought a five year time horizon was roughly accurate. He explained that the ten year timeframe started from when bonds were first sold, which was 2006. Dr. Magnus asked if at the current rate of pay out, if CIRM expected to use a majority of the bonds by 2016. Dr. Lomax indicated ICOC has had discussions about the strategy for expending the bonds--whether expenditures be used at a rate that eventually burns out

or whether to stretch out the funding as long as possible. Dr. Magnus wondered how CIRM's approach to expending funds might impact California researchers as research funding begins to rely more on private funding for clinical trials and NIH funding. Professor Greely thought it would also be interesting to see how the role of iPSC research plays out in terms of drawing research funding and regulatory oversight, as currently the CDPH Guidelines do not address iPSC research in general.

Dr. Lubin suggested another issue impacting California science was the creation of a state umbilical cord blood banking program with a steady funding mechanism. Dr. Gage noted that cord blood is being used more and more as a source of iPSCs for direct programming and re-programming, and wondered if this might complicate the discussion regarding the use of cord blood in stem cell research. Dr. Magnus interjected that the CDPH Guidelines now exclude derivation using somatic cells like cord blood stem cells because they do not raise the same level of ethical concerns and are already overseen by established review bodies. He contended it is the use of such iPSCs, for example in human clinical trials, not the derivation that requires special oversight.

With regard to iPSC research oversight, Dr. Lo indicated that some CIRM grantees were flummoxed by the differences between the CIRM regulations and CDPH Guidelines. Dr. Lo asked if others had experienced this at their institutions. Dr. Magnus did not think it was a problem for Stanford and noted the Guidelines were more permissive than CIRM. Dr. Martinez-Maza said the UCLA SCRO Committee typically defaults to the CIRM regulations with regard to requiring written notification to the SCRO Committee for purely in vitro research with de-identified somatic cells. Dr. Gage indicated the UCSD SCRO Committee also defaults to CIRM. Professor Greely noted that when CIRM funding ends, presumably SCRO Committees will adjust to the less intrusive standard of the CDPH Guidelines.

Agenda Item 4: Consideration of amendments to the CDPH Guidelines for Human Stem Cell Research due to revisions to CIRM regulations

CDPH began reviewing the list of differences between the CDPH Guidelines and CIRM regulations. The differences listed were:

1. In §2(e) of the Guidelines, CDPH revised the definition of "covered research" to exclude most research involving iPSC; CIRM still includes iPSC research.

   Discussion: Professor Greely and Dr. Lo indicated they would like to return to this issue once CDPH finished reviewing the list.

2. In §100070(a) of the CIRM regulations, CIRM added that the creation of human gametes requires SCRO Committee review.
3. In §100070(b) of the CIRM regulations, CIRM added that the procurement and creation of human blastocysts or embryos, not just the use, required SCRO Committee review.
4. In §5(d)(2) and §5(f)(2), CDPH noted "covered stem cell lines" should be revised to "human pluripotent stem cell lines".

5. In §100070(c) of the CIRM regulations, CIRM includes written notification for CIRM-funded iPSC research to help keep track of collected somatic cells and the informed consent process in case subsequent derived cell lines are used in non-human animals. The Guidelines do not address this issue as it falls under iPSC research.
6. §6(F) of the Guidelines currently matches §100080(a)(1). The Guidelines could be amended to automatically adopt future lines added to the list of authorized authorities; however, this could be problematic if the lines are derived in other states that conflict with the California statutes CDPH follows (e.g. New York).

   Note: Initially CDPH had compared §6(F) to §100081; however, it was clarified in the meeting that the intended comparison was to §100080(a)(1). After this was clarified, it was determined that there was not a need or concern at this time to revise the Guidelines to automatically adopt future lines added to §100080(a)(1).

7. §100090 of the CIRM regulations uses Proposition 71 as the cut-off date for requiring certain oocyte donor consent requirements for embryo creation. §7 of the Guidelines refers to deriving new covered stem cell lines and might be an avenue for encouraging researchers to incorporate informed consent into the research design so as to avoid “retrospective” consent.

Professor Greely summarized that the categories for discussion included addressing the differences with respect to iPSC research, the difference with respect to creation of human gametes, and the need to clean up some of the language. Dr. Lomax explained that CIRM added the “creation of human gametes” to §100070(a) because grantees were proposing to derive human oocytes from non-embryonic sources. Dr. Lo added that the current way consent is obtained for materials for human research is often general and that some somatic cell donors may not have given consent had they known their tissue was going to be used to derive gametes, which brings the research a step closer to the potential of creating embryos. Dr. Lo suggested that having a SCRO Committee be aware of this would offer the SCRO Committee the opportunity to recommend additional specific consent of the donor. Dr. Lo noted that current federal common rule regulations may not fully capture concerns donors may have in such scenarios.

Dr. Magnus noted that under the current CDPH Guidelines, if the derived gametes were going to be used to create embryos, then this would fall under the Guidelines. Dr. Lo pointed out that if the somatic cells were de-identified, there would be no oversight as IRB review would not be required. He suggested that there should be some type of oversight because using tissue to create gametes is more sensitive than using it to look at functional markers, for example. Dr. Martinez-Maza questioned why there was specific concern for deriving gametes if they are not going to be used to create embryos; they should be considered the same as any other tissue. Dr. Cheshier noted that it is technically less challenging to create an embryo if you have gametes. Dr. Martinez-Maza replied that if this were attempted, it would be covered under the Guidelines. Dr. Stock felt that state statute was clear that the concern for gametes was

primarily related to women's risks in donating oocytes and he did not see a case for revising the Guidelines on this issue.

Dr. Magnus suggested that having better consent language may help alleviate some of this concern. Professor Rao agreed but still felt donors would have greater concerns about their tissue potentially being turned into gametes. Dr. Magnus pointed out that sometimes gametes are unintentionally created when hESCs are introduced into non-human animals and teratomas form. Dr. Gage agreed with Dr. Magnus that gametes are unintentionally created and that should be the expectation since ES cells can give rise to every cell in the body.

Professor Greely asked Dr. Lo what SCRO Committee review would look like if the Guidelines included an amendment that required review of *in vitro* research involving derivation of human gametes and a researcher was using de-identified cells. Dr. Lo was sympathetic to the approach of encouraging researchers to use fresh tissue with explicit consent for gamete derivation. Dr. Lo suggested the intentional creation of gametes should be distinguished from the accidental creation and that the review of the derivation in the research project is potentially less important than recommending researchers think through the overall research plan. Professor Greely and Dr. Magnus suggested one option is to revise the Guidelines to include such a recommendation for intentional gamete creation. Professor Greely noted the Committee could also choose to amend §5(a) to include "creation of gametes" or decide not to mirror CIRM.

The Committee agreed to revise the Guidelines to include a statement encouraging consent forms to discuss specific uses of tissues as much as possible, particularly if sensitive uses are involved. The Committee voted to add §10(c), which would "encourage but not require that researchers incorporate informed consent in their research design for any tissue procurement that might potentially be used for any stem cell research, so as to avoid retrospective consent, paying particular attention to sensitive areas such as the creation of human gametes".

Professor Greely then asked if there was any further discussion regarding whether to add "creation of gametes" to §5(a). Dr. Lubin asked what percentage of CIRM funding actually went toward research involving the creation of gametes. Dr. Lomax indicated only a couple of grants were involved. Professor Greely called for a vote regarding adding "creation of gametes" to §5(a). The motion did not pass.

Professor Greely re-introduced the last remaining significant issue regarding review of iPSC research. Dr. Lomax clarified that in §100070(c) CIRM requires SCRO Committee notification if research involves identifiable somatic cells or *in vitro* research with de-identified somatic cells with the intent of deriving a pluripotent stem cell line (human subjects research). As some institutions do not have immediate access to a SCRO Committee, the grantee institution has the option of notifying CIRM directly indicating the research conforms to established requirements.

Dr. Magnus re-iterated that he felt the issue of iPSC research had already been thoroughly discussed by the Advisory Committee, that iPSC research is outside the scope of the intention of SB 1260, and that the Guidelines did not need to parallel CIRM on this issue given CIRM has funding authority that does not apply to the Guidelines. Professor Greely asked if Dr. Lo wanted to further elaborate on the topic; however, the discussion was postponed as Dr. Lo had temporarily left the meeting. Dr. Magnus suggested that some of Dr. Lo's concerns may have been alleviated by revising the informed consent section (§10(c)).

Professor Greely moved on to whether the Guidelines should be amended to include the "procurement, creation or use of human blastocysts or embryos" (§100070(b)). The addition of "creation" seemed benign. Various Committee members questioned if "procurement" was necessary. Dr. Blackburn asked if procurement for sale was covered; however, Professor Greely noted that it would need to involve research to fall under the Guidelines. Dr. Lomax suggested that if procurement were added, it could unintentionally require oversight of someone procuring embryos strictly for banking purposes, thereby expanding the scope of the Guidelines. Shannon Smith-Crowly (public) shared the Committee's concerns about adding procurement. The Committee voted to revise §5(b) to "covered research involving the creation or use of human embryos…"

The Committee voted to correct §5(d)(2) and §5(f)(2) by replacing "covered stem cell lines" with "human pluripotent stem cell lines". Dr. Magnus then brought up a potential correction to §10(b) by deleting "somatic cells or human tissue" so that the section would read "in addition to any other statutory requirements of sections of these guidelines, the following provisions shall apply when covered research involves donation of gametes, embryos, or donation of new covered stem cell lines if donation or derivation occurs after the effective date of these guidelines". Dr. Lomax felt retaining somatic cells or human tissue could be confusing since the definition of covered research only refers to embryos.

Mario Garcia (public) mentioned that somatic cell nuclear transfer (SCNT) would be excluded if somatic cells were removed from this section. Dr. Magnus agreed that would be a reason for the leaving the language as is. Professor Greely suggested leaving in somatic cells but adding "for the purposes of SCNT". Dr. Lomax suggested that making the definition of "covered research" more explicit by saying it "means research that derives a human embryonic stem cell line from embryos or SCNT". He noted that currently you have to refer to the definition of "covered stem cell line". Dr. Magnus agreed and felt that leaving somatic cells in §10(b) was correct but it could be misinterpreted as including iPSCs if one did not read the definitions carefully. Professor Greely offered that retaining "somatic cells or human tissue" would be appropriate if "for the purposes of somatic cell nuclear transfer" was added.

Dr. Lomax re-visited the issue of revising the definition of "covered research" to include that covered research "means research that derives a culture derived human pluripotent stem cell population from an embryo or product of SCNT". He noted that he has had

several conversations with researchers who express confusion about how the Guidelines define covered research and covered stem cell lines. Dr. Magnus agreed that making the definitions more duplicative may help clarify them. Dr. Stock noted that this change would be reinforced by adding the caveat "somatic cells or human tissue for the purposes of somatic cell nuclear transfer" to §10(b) and §10(b)(1). The Committee voted to revise §10(b) and §10(b)(1) accordingly. The Committee then voted to revise the definition of "covered research" (§2(d)) to say "covered research means research that derives a human pluripotent stem cell population derived from an embryo or product of somatic cell nuclear transfer."

It was determined that Dr. Lo had not returned to the call yet, so the issue of iPSC research was tabled for a future meeting.

As for new business or general questions, Dr. Dorff asked if the Committee was subject to reappointment given the change in Governor. Heidi Mergenthaler did not know of any impact the new Governor might have. She also indicated the Committee's advisement was still needed to recommend changes to the Guidelines based on new developments in the field and issues arising from the researcher reports.

Dr. Magnus suggested, for a future meeting, discussing whether the Guidelines should have standards for how SCRO Committees review provenance of and the justification for using hESC lines. Dr. Lubin also noted that if California is going to begin funding cord blood banks, there may be the need for an advisory committee to establish the necessary state regulations for the use of cord blood units in research. Professor Greely felt that might be a consideration for the Committee if they were asked for consultation by the State.

Shannon Smith-Crowley asked if the data collected by CDPH showed that the lack of financial compensation to oocyte donors for research purposes was creating a barrier to donation. Dr. Magnus noted that donation of oocytes strictly for research was virtually non-existent. He thought New York might be starting to get oocyte donors since it allows for compensation. Shannon Smith-Crowley indicated the American Society of Reproductive Medicine may consider introducing legislation repealing the prohibition on compensating oocyte donors for research. She suggested there were more than adequate protections in the law. Heidi Mergenthaler explained there were no reports thus far of oocyte donation for research purposes. Dr. Stock suggested that the evidence for willingness to donate oocytes lies in comparing rates of oocyte donation for reproductive purposes (which is paid) versus for research purposes. Professor Greely pointed out that at the time SB 1260 was written, there were expectations of needing vast amounts of oocytes for SCNT; however, iPSC research has largely mitigated this concern.

Professor Greely mentioned the possibility of having a teleconference for the next meeting.

The meeting adjourned at 11:45 a.m.