UNAPPROVED MEETING MINUTES

California Department of Public Health
Human Stem Cell Advisory Committee Teleconference
May 21, 2009

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

CDPH
Shabbir Ahmad, Manager, Human Stem Cell Research Program, CDPH
Amber Christiansen, Human Stem Cell Research Program, CDPH
Pat Rodriguez, CDPH Legal Counsel

Members of the Public
Geoff Lomax, California Institute for Regenerative Medicine (CIRM)
Michael Kalichman, UC San Diego
Zana Parman, UC San Diego
Shannon Smith-Crowley, Partners in Advocacy
Rebecca Flores, Cedars-Sinai Medical Center
Adam Pucci, Cedars-Sinai Medical Center

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

Dr. Ahmad made a few announcements. He announced that the State government is facing a $21.3 billion deficit and that there will most likely be some major cuts in the area of education, corrections, social services and health. State workers are still being furloughed and layoff notices have been given in some instances.

Agenda Item 2: Approval of Meeting Minutes from 02/20/09

The minutes were approved and will be posted to the HSCR Program website.

Agenda Item 3: Discussion and approval of revisions to Sections 2, 5, 6, and 7 of the Guidelines for Human Stem Cell Research with respect to induced pluripotent stem cell research (iPSC)

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Professor Greely recalled from the previous Advisory Committee meetings that there were concerns regarding the consent status of some of the older stem cell lines being used for research and the role that Stem Cell Research Oversight (SCRO) Committees should have in regard to induced pluripotent stem cell (iPSC) research as contained within the CDPH Guidelines for Human Stem Cell Research. This is a follow-up meeting to create language and specify ideas that were adopted in principle at the previous Advisory Committee meetings through discussion of revisions made to the CDPH Guidelines.

Dr. Magnus spoke about the proposed amendments to the Guidelines that were based on recommendations made by the Committee at the February meeting. The proposed amendments to Sections 2, 5 and 7 of the Guidelines address the issue to restrict the scope of iPSC research that SCRO Committees would be obligated to review to the issues seen as arising fundamentally in application rather than in the derivation itself. However, SCRO Committee review would still be required for research involving the placement of cells that are derived from any pluripotent cell line into nonhuman animals, nonhuman primates and other humans. These proposed amendments would exclude issues surrounding the derivation of iPSCs due to the fact that IRBs already review research related to tissue procurement.

Additionally, it was proposed that in Sections 3(c) and 3(e) the word “covered” be changed to “pluripotent”, although these changes did not make it into the proposed amendments packet the Committee received for review prior to this meeting.

Professor Greely confirmed the proposed amendments that Dr. Magnus made to the Guidelines on behalf of the Committee as follows: 1) In Section 2, redefine “covered stem cell line” to make it clear that it is a culture derived human pluripotent stem cell population derived from an embryo or product of SCNT, thereby excluding iPSCs from the definition of covered cell lines; 2) In Section 5, require SCRO Committee review and approval for clinical trials involving the use of human pluripotent cells, cells derived from human pluripotent cells or research that would introduce human pluripotent cells or cells derived from human pluripotent cells into non-human animals; 3) In Section 3(c) and 3(e) change the wording from a “covered stem cell line” to a “human pluripotent stem cell line” for the introduction of stem cells into non-human primate embryos and the breeding of animals that have stem cells introduced; 4) In Section 7, replace the wording “human stem cell lines” with “human embryonic stem cell lines” so that the proposals reviewed by SCRO Committees would be narrowed.

The proposed amendments were then discussed among the Committee members. Professor Dorff expressed agreement with Dr. Magnus’ changes, however, he expressed concern that the distinctions being made between human embryonic stem cells and pluripotent stem cells would get lost in the Guidelines without an introductory paragraph explaining this to the reader.

Professor Greely agreed that a preface explaining the changes to the Guidelines and why they were made would be helpful.

DRAFT

Dr. Lubin also agreed with the changes Dr. Magnus proposed for the Guidelines citing the fact that Children's Hospital Oakland Research Institute has been working with pluripotent cells obtained from placenta and these cells would not have the same issues associated with the derivation of stem cell lines from human embryonic stem cells. Professor Magnus replied that under the existing Guidelines, stem cell research, such as that described by Dr. Lubin, would have to comply with all of the informed consent requirements even if they didn't seem appropriate.

Professor Rao questioned whether the changes to section seven of the Guidelines regarding voluntary informed consent for human embryonic stem cell lines would also include cloned embryos because the definition of "covered stem cell line" includes lines derived from an embryo or product of SCNT. Dr. Magnus suggested that the wording be changed in section 7 from "embryonic stem cell lines" to state derived from a "covered stem cell line".

Dr. Lomax questioned whether the term "covered cells" is still relevant to the Guidelines given the modifications that have been proposed. He suggested the Committee review the Guidelines and determine if the term is still relevant. Professor Greely replied that they would not be able to make that determination at the present time.

Without further comments from the public on the proposed amendments to the Guidelines regarding iPSCs, Professor Greely moved on to the proposed amendments to section six. Dr. Magnus explained that he wanted to address in the proposed amendments CIRM's recognition of any stem cell line approved by a recognized authority as acceptable for funded research. There are some stem cell lines that have not been approved by a recognized authority, despite having better consent processes than some of the lines that have been approved.

Dr. Magnus also expressed concern that some stem cell lines created prior to the National Academies of Science (NAS) Guidelines, which recommended IRB approval, and research done outside of California and Massachusetts would not have had IRB review and approval for research involving de-identified embryos. The 2002 OHRP guidance document states that the use of de-identified embryos is not considered human subjects research and IRB approval is not required. Dr. Magnus wondered if there would be any value in requiring IRB approval for those stem cell lines when the IRB would have deemed that it isn't human research, therefore, those stem cell lines would not have had any more oversight as compared to stem cell lines created at the same time by companies who did not go before an IRB. This creates a problem in terms of consistency for lines such as the Bresagen stem cell lines that don't meet the full informed consent standards.

Dr. Magnus wanted to create a radical new way of looking at things based on feedback from the previous Advisory Committee meeting and Dr. Lo's suggestion of putting existing literature on the CDPH website with recommendations on how SCRO Committee's should be reviewing particular cell lines that have been approved by a

recognized authority and so he made a few different changes. In order to parallel CIRM's regulations, the amendments to the Guidelines would deem stem cell lines that have been approved by a recognized authority as acceptable, and CIRM was added to the list of recognized authorities. References in section six that would have included iPSC derivation were also removed. Subsection three of section six was added to harmonize between stem cell lines that have been approved by a recognized authority and other stem cell lines that are equally or more ethically derived but have not been approved by a recognized authority. However, Dr. Magnus proposed that two minor amendments be made to section six: 1) In (2)(B) include "for participation in research" after "donors of human gametes or embryos did not receive valuable consideration" to distinguish between payment for research and for IVF, and 2) In (2)(B) remove "as defined in section 2(k)".

Professor Greely added that he would like to include in (3)(B) the exact date the NAS Guidelines were issued in parentheses and replace the current reference to the year of publication, 2005.

Professor Dorff asked if section 2(k) of the Guidelines defines acceptable payments. This reminded Dr. Magnus that section 2(k) of the definitions does define acceptable payments and, therefore, section 2(k) should remain in section 6(2)(B).

Professor Rao commented that although section 6(a)(1) used the same language as CIRM in stating "recognized by an authorized authority", the language seemed awkward and her preference would be to use Dr. Magnus' term of a "recognized authority". Dr. Lomax felt that the wording in the Guidelines could be changed to "recognized authority" and still parallel the CIRM regulations. Professor Greely suggested the wording be changed to "approved by a recognized authority."

Public comments were accepted on the proposed amendments.

Dr. Lomax pointed out that in 6(a)(1)(F) requiring a stem cell line be approved "in accordance" with CIRM regulations is technically incorrect as stem cell lines are found to be approved by the ICOC and not a condition of derivation. Dr. Lomax thought that Dr. Magnus' suggestion to change the wording to "approved by CIRM in accordance with California Code of Regulation, Title 17, Section 100081" was more accurate.

Dr. Lomax also mentioned that CIRM is in the process of establishing a procedure for verifying the provenance of a derived stem cell line funded by CIRM through the oversight committee at the institution where the line was derived and then creating a list of stem cell lines that have been derived in accordance with the CIRM regulations. Dr. Lomax questioned the need to include 6(a)(1)(F) in the Guidelines in light of CIRM's effort to establish a list of acceptable stem cell lines and distribute it.

Professor Rao questioned why the amendment to the Guidelines for section 6(a)(1)(F) states "derived in accordance with California Code of Regulation, Title 17, Section 100081" when the parallel section of the proposed amendments to the CIRM

regulations states "derived in accordance with California Code of Regulation, Title 17, Section 100090." Dr. Magnus replied that the language proposed for the Guidelines adds CIRM as a recognized authority for approving the derivation of stem cell lines while the parallel section in CIRM's regulations is a provision specific to CIRM funded projects. The proposed amendment to the Guidelines would include all stem cell lines that have been approved by CIRM through the petition process as "acceptably derived". The list of stem cell lines derived in accordance with CIRM regulations that Dr. Lomax stated was being developed may be referred to in the Guidelines once it is distributed, but Dr. Magnus thought that the stem cell lines on the CIRM list would already meet the criteria of 6(a)(2) and may not need a specific reference in the Guidelines.

Dr. Lomax asked if the change to section 5(f) for introducing stem cells into animals would require oversight by a SCRO Committee for all differentiated cells from a human pluripotent stem cell line. Dr. Magnus responded that if the stem cell line was derived from a pluripotent cell it was common SCRO Committee practice to provide oversight. Dr. Lomax thought the language included in the Guidelines would significantly expand the scope for SCRO Committee oversight by requiring downstream products of a pluripotent stem cell line introduced into animals be reviewed by a SCRO Committee. Professor Greely stated that the Stanford SCRO Committee already reviews projects where lines are derived from pluripotent cells because of concerns that these cell lines may still contain pluripotent cells that may revert. Dr. Magnus asked if other SCRO Committees have the same policy as the Stanford SCRO Committee in reviewing projects that use stem cell lines derived from pluripotent cells. Dr. Kalichman replied that UC San Diego's SCRO Committee does not require investigators to submit their project for review, but the Committee will review it if it is submitted to them. Dr. Martinez-Maza said the UCLA SCRO Committee would review the research and Dr. Lubin thought that Berkeley would also review it.

The Advisory Committee voted to approve the amendments as amended during the course of the discussion. A new version of the proposed amendments to the Guidelines will be drafted including a preface to explain the changes to the Guidelines and it will be circulated back to the Committee.

Agenda Item 4: Brief discussion of draft NIH Guidelines for Human Stem Cell Research

Professor Greely noted that the deadline for comments on the proposed NIH Guidelines for Human Stem Cell Research is next Tuesday, May 26th. CIRM has already circulated some comments on the NIH Guidelines as well as the Stanford SCRO Committee. The comments thus far focus on two major points: 1) the limitation under the federal guidelines of federal funding to research done on existing or to be created stem cell lines that were made from embryos created for reproductive purposes, and 2) concerns about the informed consent and other ethical requirements for stem cell lines that were created in the past.

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The first point on limitation of federal funding is straightforward and unlikely to change. The second point on consent and ethical requirements can get technical in terms of what specific amendments should be made. Professor Greely did not think that comments from the Committee could be drafted on the phone call. He suggested that the Committee may want to make a broader statement about the restriction being unfortunate or inappropriate and to recommend that the consent requirements or ethical requirements for already existing lines be given greater thought.

Dr. Magnus thought the Committee had two options in regard to submitting comments to the NIH: 1) make a statement of a very few broad principles, as Professor Greely suggested, such as cell lines that were created in accord with the generally accepted ethical standards for consent and oversight at the time should be allowable and a mechanism developed for grandfathering in older lines created before the NIH Guidelines, or 2) review the CIRM statements and join with CIRM in submitting comments.

Professor Greely offered another option for the Committee to consider suggesting to the NIH that they adopt the California position both through the CIRM regulations and the CDPH Guidelines that would expand funding beyond reproductive embryos and address the issues surrounding the ethics of the pre-existing lines.

Committee members Rao, McLean, Dorff, Lubin and Magnus agreed with recommending that the NIH consider the existing guidelines/regulations in California when developing a national set of guidelines for human embryonic stem cell research. However, Dr. Magnus has heard that the NIH is not inclined to grandfather stem cell lines as acceptable through a mechanism of recognized authority even though California has adopted this method.

The Committee voted to approve sending a letter by Tuesday with a recommendation to the NIH to consider amending their guidelines to follow the guidelines/regulations set forth for human embryonic stem cell research in California by CDPH and CIRM. Professor Greely thought that it might be possible to circulate a draft of the letter for the NIH to Committee members before Tuesday, although time may not permit that comments be fully discussed and incorporated.

Finishing the agenda items, Professor Greely made a final comment recognizing the work of state employees during the current state budget crisis and expressed uncertainty as to when the next Advisory Committee will be held. Dr. Ahmad replied that there have not been discussions at CDPH regarding the elimination of the Advisory Committee funds and that the Committee should proceed as normal.

Dr. Magnus suggested that in follow-up to Dr. Lo's suggestion from the last Advisory Committee meeting that the Committee begin collecting articles to serve as guidance for stem cell research investigators and SCRO Committees that can be posted on the HSCR Program website. He cited Dr. Lo's recent article on addressing provenance issues as well as articles by Dr. Sugarman and Dr. Streiffer as good examples of linked

articles that can be provided on the website. Professor Greely suggested that the Committee members send information on these articles to CDPH for posting to the HSCR Program website.

Dr. Lubin questioned whether it would be beyond the Committee's scope or too far down the line to look at therapies generated as a consequence of human stem cell activities in California and what the outcomes of these therapies have been to humans. Professor Greely agreed that it was an interesting issue that would be useful for the Committee to discuss and think about once the therapies are developed.

The meeting was adjourned at 2:05 PM.

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