

UNAPPROVED MEETING MINUTES
California Department of Public Health
Human Stem Cell Research Advisory Committee Teleconference
June 27, 2011

California Department of Public Health (CDPH) Human Stem Cell Research (HSCR)
Advisory Committee Members

Elliot Dorff, PhD
Fred Gage, PhD
Henry Greely, JD
Bernard Lo, MD
Bertram Lubin, MD
David Magnus, PhD
Otto Martinez-Maza, MD
Radhika Rao, JD
Gregory Stock, PhD

CDPH

Shabbir Ahmad, Manager, Human Stem Cell Research Program
Heidi Mergenthaler, Human Stem Cell Research Program

Guest Speaker

Geoff Lomax, California Institute for Regenerative Medicine (CIRM)

Agenda Item 1: Welcome and Introductions

After establishing that quorum was met, a couple Committee members mentioned they have new professional appointments. Dr. Lubin is now a member of the Independent Citizens Oversight Committee (ICOC), the governing board of the California Institute for Regenerative Medicine (CIRM). Dr. Gage is now the President of the International Society for Stem Cell Research.

Agenda Item 2: Meeting Minutes from November 30, 2010

The meeting minutes were approved without amendment.

Agenda Item 3: Discussion and Approval of Revisions to Sections 2, 5, and 10 of the CDPH Guidelines for Human Stem Cell Research

Professor Greely started with the revisions to Section 2. The new definition of “covered research” excludes induced pluripotent stem cells (iPSC). He suggested the language “Covered research means research that derives a human pluripotent stem cell population...” be changed to “Covered research means research that *involves* a human pluripotent stem cell population...” The Committee agreed to adopt the change from “derives” to “involves”.

Dr. Lomax asked if parthenote-derived cell lines should be addressed in the Guidelines and indicated these lines were being used in California. Professor Greely inquired whether the Committee thought they should be addressed. Dr. Gage questioned whether the same level of deep sequencing had been done with parthenotes to determine if they would fall into the same category scientifically as embryonic stem cells. Dr. Magnus thought that since parthenogenesis involves creating a potentially pluripotent stem cell from a human oocyte that this should fall under the Guidelines. He suggested revising the covered research definition to “population derived from an embryo, product of SCNT *or human parthenogenesis.*” Professor Greely suggested the concerns were similar to iPSCs as far as introduction into animals; parthenotes do not raise the same concerns regarding destroying an embryo or cloning. Dr. Lomax thought research involving parthenotes would be covered by the Guidelines when addressing research involving oocytes. Dr. Dorff asked whether parthenotes should be mentioned more explicitly in the Guidelines. After further discussion, various Committee members agreed parthenote-derived stem cells are covered under the oocyte provisions of the Guidelines, as well as under the provisions that require SCRO Committee review of clinical trials involving human pluripotent cells and research that introduces pluripotent cells into non-human animals. Professor Greely was open to continuing discussion of parthenote-derived stem cells and their level of inclusion in the Guidelines at the meeting.

Professor Greely reviewed the proposed changes to the Guidelines based on discussion from the previous Committee meeting. These changes were to Section 5(b), 5(d), 5(f), 10(b), and 10(b)(1). Professor Greely and Dr. Gage noted that in 10(b)(1) there should be an “or” after SCNT so as not to inadvertently exclude the derivation of stem cell lines through methods other than SCNT. There were no objections to the amendment.

Professor Greely noted the new Section 10(c) was added to encourage researchers to incorporate thorough informed consent regarding human stem cell research into their research design. Professor Greely asked if the Committee still wanted such language and whether this was the appropriate language to address the informed consent concerns. Dr. Lo suggested the Committee consider the other issues, in addition to human gamete creation, that researchers may want to include in their informed consent. Dr. Lo thought including allogeneic transplantation for therapeutic purposes in informed consent could be useful as some donors may be concerned about having their cells transplanted into another person. In considering the allogeneic transplantation issue, Dr. Lubin pointed out that CIRM may start to fund more clinical trials and studies that involve the infusion of cells into humans. Dr. Lo thought instead of using the term “sensitive areas” it might be more useful to give specific examples. He gave another example of including the potential of patenting and commercializing discoveries.

Professor Greely suggested language may need to be drafted after the meeting for consideration at the next meeting. Dr. Lo agreed and also proposed replacing the term “retrospective consent” as researchers could interpret the term differently. Dr. Dorff offered that the term “sensitive areas” could be replaced by saying “paying particular

attention to *applications of their donations to uses to which they would object*". Dr. Lo preferred this language. Professor Greely wondered if there should be a qualifier regarding the percentage of donors who might object to a certain use. Dr. Lo offered that the main concern was having donors object later in the research process to unanticipated uses of their donations. The potential for donors to withdraw their consent could be minimized by developing a more comprehensive or explicit informed consent regarding the possible uses of their donations.

Professor Greely proposed that the Committee pursue developing language along these lines for review at the next meeting. With respect to drafting language, Dr. Dorff wondered if the revision should include why the guideline is not considered a requirement. Professor Greely requested Dr. Lo take the lead in drafting the revised language. Dr. Lo agreed and followed up on Dr. Dorff's comment by asking the Committee about the rationale for having this revised section not be a requirement. Professor Greely thought it would allow for more flexibility as the standards evolve and help minimize the implication that the potentially objectionable uses listed in the section are the only ones to consider for informed consent. Dr. Dorff suggested the language read something like "because the uses of donated materials cannot be foreseen, informed consent is not required; but where the use of a particular donation is expected, then informed consent is encouraged..." Professor Greely noted that Section 10 already lists several other requirements for informed consent so Dr. Lo should keep this in mind when drafting the revised language. Dr. Lo asked CDPH staff to forward him the comments regarding the revisions.

Professor Greely proposed voting on the revisions to Sections 2, 5, and 10, including the minor amendments discussed earlier in the meeting but excluding 10(c). All members voted in favor of the amendments.

Agenda Item 5: Discussion of Section 6(a)(2)(B) of the Guidelines

Professor Greely skipped Agenda Item 4 to first determine whether the Committee needed to discuss Agenda Item 5. Professor Greely mentioned that CIRM had recently amended its regulations to allow the use of embryos, and any resulting cell lines, created for reproductive purposes in which gamete donors were paid. In developing the agenda for the Committee meeting, Dr. Magnus had suggested to Professor Greely that the Guidelines be consistent with CIRM's regulations in this regard. After further review, Professor Greely determined the Guidelines already address this issue and are consistent with CIRM's regulations; therefore, Agenda Item 5 can be stricken.

Agenda Item 4: Discussion of Section 5(f) of the Guidelines

Professor Greely asked Heidi Mergenthaler to explain the reference to Section 5(f). Ms. Mergenthaler explained that Dr. Lo's concern regarding consent and downstream uses that led to the addition of Section 10(c) from the last meeting also applied to Section 5(f). However, the Committee did not have a chance to discuss the issue at the previous meeting. Dr. Lo explained that Section 5(f) was another example of activities

that are generally regarded as a standard part of research but some potential donors may object to the use of their donations in animals. He reiterated the issue of making explicit in informed consent the expectation that donations could be injected into animals in downstream research. Professor Greely suggested the issue of research involving animals could be addressed in the revision to Section 10(c). Dr. Lomax pointed out that in Section 10(b)(1)(E) animal transplantation is already incorporated into the general consent requirements. Professor Greely asked Dr. Lo to consider this when drafting language for the revision.

Agenda Item 6: CIRM iPSC Research Repository and CIRM Clinical Trials Oversight

Dr. Lomax provided an update on CIRM activities. He started with the status of CIRM's progress in establishing a resolution for clinical trials to be funded by CIRM. In an effort to inform the CIRM Medical and Ethical Standards Working Group about the various applicable clinical trial requirements, Dr. Lomax explained that CIRM looked at the whole series of public policy and regulations that govern clinical trials. He described how the regulations would include testing requirements for product purity and safety, IRB review, and consent requirements. In light of this information, the Working Group encouraged CIRM staff to amplify the issues around research transparency and information reporting. Dr. Lomax noted this was a bit different than the Committee's approach of encouraging review up front as the Working Group's resolution promoted reporting results and any adverse events in a timely manner for clinical trials.

Dr. Lo noted CIRM is not yet proposing new regulations for clinical trials but, through the Working Group's resolution, is attempting to raise the awareness of potential recipients of CIRM grants involved in clinical trials, CIRM staff, and CIRM reviewers about both the ethical and scientific issues involved in clinical trials. Dr. Lomax noted that CIRM will require a clinical trial to be registered on clinicaltrials.gov and that the IRB must be registered with the Office for Human Research Protection. He also pointed out that CIRM itself would be providing active oversight, which would be another level oversight for clinical trials.

Professor Greely asked how many clinical trials were funded by CIRM. Dr. Lomax indicated only the Geron clinical trial is currently receiving CIRM funds, but there are roughly five CIRM-funded studies that are on a clinical trajectory.

Dr. Lubin mentioned CIRM recently released its annual report (<http://www.cirm.ca.gov/2010AnnualReport>), as well as a report by its President, which are both available on CIRM's website. Professor Greely asked CDPH staff to send the link to the Committee members.

Professor Greely asked Dr. Lomax if there were other issues the Working Group was considering. Dr. Lomax said the Working Group was looking into issues related to iPSC cell repositories (http://www.cirm.ca.gov/files/MeetingReports/SWG_April_2011_6_28_2011.pdf). CIRM

plans to collaborate with the National Institute of Neurological Disease and Stroke (part of the National Institutes of Health) who have an agreement with Coriell Institute, which has a large iPSC bank in New Jersey. CIRM is considering a collaboration with Coriell in which CIRM works with its grantees to store iPSC lines that relate to certain neurological diseases at Coriell such that these lines are widely available. In discussing this collaboration, a consent-related topic that arose was the issue of including as part of informed consent the potential of distributing stem cell lines to repositories for broad dissemination.

Dr. Lomax also mentioned that CIRM may develop its own repository of disease-specific iPSC lines through existing infrastructure in California. A CIRM report released earlier this year discusses how California's diverse population may allow for opportunities to develop cell lines that have unique value as a scientific resource (http://www.cirm.ca.gov/files/MeetingReports/Diversity_Workshop_Report_4_23_10b.pdf). Dr. Lomax noted that in developing these lines there may be a need for ongoing aggregation of health data such that donors would have extended human subject status. The CIRM report includes this scenario among others in exploring issues related to banking and distributing pluripotent stem cell lines. Dr. Lo explained the CIRM report was developed as guidance instead of regulations to allow the field to find the best ways of organizing this research area.

Dr. Lubin mentioned that at the last ICOC meeting members discussed CIRM requesting the Institute of Medicine to develop a report on CIRM's overall functions, progress, and funding mechanism. Along those lines, Professor Greely asked how much longer CIRM would be operational. Dr. Lomax did not have a definite timeframe but estimated that CIRM would continue to function for about six or seven years unless additional funding or a new initiative was secured.

Dr. Dorff wondered if CIRM's guidance on iPSC line banking should be incorporated into the CDPH Guidelines as the Guidelines address research but are not for application or banking. Professor Greely noted the Guidelines do address application to the extent the application is in a clinical research context. Professor Greely thought the Committee could discuss the issue further and would need input from CDPH on whether statute limits the Guidelines to research only or whether non-research applications could be addressed. Professor Greely suggested the Committee discuss this issue at the next meeting. Dr. Lomax mentioned that CIRM would be releasing its report shortly, which should help the Committee in considering these issues. Professor Greely asked CDPH staff to distribute the report upon its release to Committee members.

Agenda Item 7: General Stem Cell Research Update

Professor Greely inquired if there were any new topics, either new science or new ethical concerns, that should be addressed by the Committee. Dr. Gage suggested the Guidelines indicate that directed programming is outside the purview of the Committee and not included in the Guidelines. Directed programming involves taking somatic cells and directly programming them into other types of somatic cells. Although the cells do

not go through the pluripotent stage, the cells ultimately will be transplanted in similar ways to iPSCs. Professor Greely noted that not going through the pluripotent stage mitigates some of the concerns the Committee has about pluripotent and embryonic stem cells.

Dr. Lo asked if there are safety concerns about errors in directed programming that should be addressed. Dr. Gage indicated there are safety issues since in some cases viruses are still used in directed programming, which can lead to mutations. This may be abrogated in the future by chemical reprogramming, but there still could be DNA mutations. Professor Greely felt this would be a good topic for the next meeting to discuss how this issue may or may not fit within the context of the Guidelines and purview of the Committee. Professor Greely's initial thought was that direct programming does not fall within the scope of the Guidelines or Committee charge since it does not involve the destruction of embryos or introduction of pluripotent cells into non-human animals. For the next meeting, Professor Greely asked Dr. Gage to further explain the science and progress of the direct programming field in order to help the Committee determine if the topic should be addressed in the Guidelines.

Professor Greely reiterated it would be interesting to hear more about oocyte-derived cells (parthenotes) at the next meeting. Dr. Lubin suggested the next meeting be in-person instead of a teleconference. Other members agreed. Professor Rao mentioned that the National Institutes of Health (NIH) may be revising guidelines for human subject research. Professor Greely had heard this may be happening as well. Dr. Lo indicated the President's Commission for the Study of Bioethical Issues was charged with making a report on human subject research, so he guessed the NIH would wait until the Commission issued the report.

Dr. Ahmad noted that there was a change in CDPH leadership. Dr. Ron Chapman replaced Dr. Mark Horton as the Director of CDPH. The new Chief Deputies are Kathleen Billingsley for Programs and Policy and Daniel Kim for Administration. Dr. Ahmad reiterated the Administration's support of the continuation of the Committee and appreciation of the Committee's time. Dr. Dorff asked if the Committee members would have to be reappointed by the new Governor. Dr. Ahmad explained the Director of CDPH is the designated appointer. He also asked the Committee for suggestions on replacing Dr. Weissman's seat on the Committee. Professor Greely asked CDPH staff to send an email requesting recommendations for new Committee members.

Professor Greely adjourned the meeting.