

APPROVED MEETING MINUTES
California Department of Health Services, Human Stem Cell Research Advisory Committee
September 20, 2006
Children's Hospital Oakland Research Institute
1:00 PM – 5:00 PM

Attendance:

**California Department of Health Services (CDHS), Human Stem Cell Research (HSCR)
Advisory Committee Members**

Otoniel Martinez-Maza, PhD
Gregory Stock, PhD, MBA (by phone)
Elliot Dorff, PhD (by phone)
Bertram Lubin, MD
David Magnus, PhD
Margaret McLean, PhD
Henry Greely, JD
Radhika Rao, JD

CDHS

Shabbir Ahmad, Manager, Human Stem Cell Research Unit, CDHS
Cindy Chambers, Human Stem Cell Research Unit, CDHS
Heidi Mergenthaler, Human Stem Cell Research Unit, CDHS
Amber Christiansen, Human Stem Cell Research Unit, CDHS

Members of the Public

Susan Fogel—Pro-Choice Alliance for Responsible Research (by phone)
Don Reed--California for Cures
Jesse Reynolds—Center for Genetics and Society
Kirk Kleinschmidt—California Institute of Regenerative Medicine (CIRM)
Elizabeth Langdon-Gray—University of California, Office of the President (UCOP)
Ellen Auriti—UCOP
Geoff Lomax-CIRM

Call to order: 1:06 PM

Agenda Item #2: Report on SB 1260

Professor Greely noted there are aspects of the proposed guidelines that were drafted on the presumption that SB 1260 will become law. Some of them may need to be slightly revised if SB 1260 does not become law. Professor Greely suggested the group note where the draft guidelines might need changes if SB 1260 does/does not pass.

Dr. Ahmad described SB 1260 as including all the provisions in SB 322 except for the continuance of the Advisory Committee. The sunset date of January 1, 2007, would be removed by SB 1260 and the provisions would be extended. In addition, SB 1260 adds the requirement of the use of Stem Cell Research Oversight Committees (SCROs), as well as a new section on the process of procurement of oocytes for research.

After the report on SB 1260, Dr. Stock asked whether the proposed guidelines had to conform to National Academy of Sciences (NAS) and CIRM guidelines with regard to prohibiting payment to oocyte donors (for research purposes). Professor Greely replied that SB 1260 bans any payment in excess of the amount of the reimbursement of direct expenses incurred as a result of the oocyte donation procedure; therefore any guideline that contradicts this will be in conflict with

state law. Professor Greely also noted that SB 1260 does not specify the amount of reimbursement for direct expenses, thereby allowing room to include lost wages in the guidelines, which is consistent with CIRM guidelines.

Dr. Stock followed up by asking if the ban on payment would then exclude using oocytes for research that were initially procured for reproductive purposes and the donor received financial remuneration greater than direct expenses from the procedure. Professors Magnus, Rao, and Greely and Geoff Lomax (CIRM) discussed the different options outlined in CIRM's discussion draft guidelines relating to oocytes procured for infertility treatment in which the donor was paid in excess of permissible reimbursement. Dr. Lomax clarified that the CIRM guidelines adopted the option to exclude from research any oocytes procured for infertility treatment in which the donor was paid in excess of permissible reimbursement (Option 3). However, this does not apply if the oocyte has been fertilized; these embryos can be used for research provided the original oocyte donor gives consent.

Approval of Minutes

The meeting minutes from the June 8, 2006 Advisory Committee meeting were unanimously approved. They can be viewed at: <http://cdph.ca.gov/services/boards/HSCR/Documents/MO-June8Minutes-08-2007.pdf>.

Agenda Item # 3: Recommendations for Guidelines on Issues other than Clinical Trials

The discussion draft guidelines can be viewed at:

<http://www.cdph.ca.gov/services/boards/HSCR/Documents/MO-PublicCommentsMatrix-08-2007.pdf>.

Professor Greely described the Preface as a means of providing background on the state of SB 322, SB 1260, and the role of Proposition 71. He then asked Dr. Lomax about the current status of the CIRM regulations. Dr. Lomax indicated the regulations had been submitted to the Office of Administrative Law and anticipated any modifications would be technical. As Professor Greely was comparing the statewide guidelines with CIRM's, he recommended that the statewide guidelines include research beyond just human embryonic stem cells, as this would be most consistent with CIRM and NAS. Professor Greely also noted that SB 253 (Ortiz, 2002) required IRB approval for all human stem cell research whether it is embryonic or not. It was his understanding that SB 253 had not been repealed and wondered how this might influence the reporting requirements delineated in SB 1260.

Professor Greely led the discussion of Guidelines on Issues other than Clinical Trials. In an effort to be consistent with CIRM and NAS, most of the guidelines were derived from the CIRM Medical and Ethics Standards regulations (www.cirm.ca.gov). The main deviations included:

- changing the Scope to include statutory language of SB 1260
- removing "funded research" definition (Professor Magnus) and consider revising the definition of "covered stem cell line" to include human pluripotent stem cell research, depending on the Committee's decision (Professor Greely)
- removing references to "CIRM-funded research"

Based on Section 100030(f) from the CIRM regulations involving activities not eligible for CIRM funding, there was discussion about whether to include CIRM's ineligible activity of "the transfer to a uterus of a genetically modified human embryo." Professor Magnus pointed out that currently this research is deemed universally unethical. The Committee agreed to discuss this issue later in the meeting.

The Institutional Assurance of Compliance Section (100040) of the CIRM regulations led to discussion about whether CDHS would be able to enforce restrictions on prohibited research activities. Professor Greely felt CDHS should determine the enforcement mechanisms.

Professor Rao suggested they be consistent with other methods of enforcement within CDHS. Professor Greely then introduced the broader issue of the enforceability of guidelines versus regulations. Dr. Stock stated that enforcement is not necessarily appropriate for guidelines. It was agreed to return to the issue later in the meeting.

Discussion continued with Guidelines on Issues other than Clinical Trials. Professor Greely recommended adopting the following CIRM regulations:

- §100060: While CIRM membership criteria was different than NAS with regard to having a patient advocate and non-scientist member of the public, the Committee chose to adopt CIRM criteria
- §100070
- §100080
- §100090
- §100095: Based on Dr. Lomax's previous clarification about this regulation, Professor Greely suggested adopting Option 3 as well.
- §100100
- §100110
- §100120

Professor Greely then reopened discussion of these remaining *Topics*:

1. Definition of covered cell lines
2. Compliance and enforcement
3. Implantation in a uterus of a genetically modified human embryo
4. Including lost wages in direct expenses of oocyte donors

Topic 4: Including lost wages in direct expenses of oocyte donors

Professor Greely read CIRM's definition of permissible expenses and compared it to SB 1260, which does not list examples of direct expenses of oocyte donation. Dr. Stock questioned why the Committee doesn't recommend inclusions other than lost wages. Professor Greely cited that this would be in conflict with NAS guidelines and SB 1260, which would become law if passed. Dr. Stock stated that they would not necessarily be illegal guidelines; rather a researcher could conform to the guidelines but not be in compliance with the legislation. Dr. Magnus responded that it should not be possible for a researcher to be simultaneously compliant with a guideline and in violation of the law; Dr. Stock agreed.

Professor Greely suggested that because SB 1260 does not list permissible expenses, using CIRM's definition could be considered consistent with the bill. Professor Rao agreed the issue was open to interpretation. Dr. Magnus suggested the Committee adopt CIRM's definition; no one disagreed. Professor Greely noted this definition would be used in the guidelines.

Professor Rao asked for clarification on whether the guidelines would also include CIRM's regulation on providing medical care for oocyte donors as a direct result of the procedure. Professor Greely replied medical care would also be included.

Topic 1: Definition of covered stem cell lines

Professor Greely asked the Committee members if they wanted to recommend to CDHS guidelines that address human pluripotent stem cell lines, or merely human embryonic stem cell lines. He expressed that most of the concerns about human embryonic stem cell lines are similar to human (pluripotent) stem cells lines as well. Dr. Dorff asked if there was any harm in including human pluripotent stem cell research and Professor Greely indicated he did not want the guidelines to inadvertently apply to special cases of research in which the guidelines are not meaningful.

Dr. Magnus asked if the placement of neural-progenitor cells into human brains should be included in the guidelines. Dr. Lomax explained that this issue was covered in the CIRM regulations under chimerical research and therefore would only need IRB review at this time. Dr. Magnus was concerned that not all neural-progenitor cells were defined as covered stem cells and therefore would not be subject to SCRO review. He suggested neural-progenitor cells be included in the covered stem cell definition. Professor Greely offered the alternative of addressing the issue in the Clinical Trials Section in order to avoid including neural-progenitor research projects that should not require SCRO review.

Professor Greely returned to the issue of the guidelines addressing human pluripotent stem cell research. Dr. Magnus asked Shabbir Ahmad (CDHS) if it was appropriate for the Committee to make a recommendation that exceeds its statutory authority. Dr. Ahmad stated the CDHS legal department would have to make that determination when it reviews the guidelines and that the Committee should be unhindered in making its recommendations. Dr. Magnus then recommended using the broader definition of covered stem cell line.

In addition to previous discussion of permissible expenses, Professor Greely asked for any other comments. Dr. Dorff wondered if lost wages were purposely not included in SB 1260, but felt the Committee should allow for lost wages and that this would not be inconsistent with the bill. Professor Rao asked the Committee to consider the issue of donors' salaries and whether it was fair for some women to be reimbursed more money because their hourly wages were higher. Dr. Magnus mentioned the donors were not being reimbursed for their oocytes but rather for the expenses incurred from donating oocytes, so there would be reimbursement differences in many areas, such as mode of transportation. Dr. Stock believed wage reimbursement would be rather negligible for salaried employees. Professor Greely noted, regardless of the Committee's decision, that wage reimbursement might be difficult to practically implement.

Topic 2: Compliance and enforcement

Professor Greely asked the Committee if it wanted to recommend the guidelines not be mandatory or to have enforcement mechanisms that CDHS will determine. Dr. Magnus believed SB 1260 intended for certain issues to be mandates (e.g. SCRO review) but felt CDHS should determine compliance mechanisms. Professors Greely and Rao indicated SB 1260 does not specifically mention enforcement but does require certain activities. Dr. Stock did not think the Committee should recommend whether CDHS should include enforcement mechanisms; it should only provide recommended guidelines. Dr. Magnus agreed. Professor Rao felt the Committee should recommend the guidelines be purely hortatory but that they have some enforcement mechanisms. Dr. Stock clarified that if the Committee wrote the guidelines with an overall suggestion for CDHS to determine enforcement, then he supported this. Dr. Magnus and Professor Rao concurred.

Topic 3: Implantation in a uterus of a genetically modified human embryo

Professor Greely mentioned the CIRM regulations prohibit implantation in a uterus of a genetically modified human embryo, even though it is not required by Proposition 71 or addressed in the NAS guidelines. Professors Greely, Rao, and Magnus wondered if this also included the product of germ line gene therapy. Dr. Lomax replied that CIRM did not define genetically modified embryo and that the prohibition was also used in the ISSCR guidelines. Professor Rao felt that research involving genetically modified embryos was beyond the scope of SB 1260 as it does not relate to stem cells. Dr. McLean agreed, adding that transferring the embryos was also beyond the scope. Professor Greely suggested the Committee state it does not condone this type of research but clarify the prohibition is not included as a guideline because it is outside the scope of SB 1260.

Public Comments

In reference to reimbursement of expenses for oocyte donors, Don Reed noted that homemakers should somehow be compensated for their time spent outside the home during the procedure. He also supported the Committee's decision to not include germ line gene therapy in the guidelines.

Jesse Reynolds then suggested the Committee reconsider including the genetically modified human embryo prohibition with a definition of terms, as well as consider a technological connection between germ line modification and stem cell research.

In reference to the Preface, Ellen Auriti was concerned that IRB review requirements seemed duplicative of SCRO review requirements. She thought the intent of SB 1260 was to eliminate the duplicative burden on institutions and suggested the Committee recommend SCROs are more appropriate than IRBs for stem cell research, as it was unclear whether SB 253 had been repealed. Ms. Auriti requested clarification on which level of review was required by IRBs versus SCROs. Drs. Martinez-Maza and Lubin explained their institutions had some review overlap, in part as an added precaution. Ms. Auriti also suggested the wording within the SCRO membership Section (CIRM, Section 100060) be changed so that the non-scientist members of the public are eligible for reimbursement of lost wages. Professor Rao was concerned that deviating from CIRM on SCRO membership eligibility could potentially require institutions to have two SCROs. Dr. Magnus stated there have been no issues at Stanford with recruiting members of the public and felt public confidence might actually be higher without wage reimbursement for these members. Dr. Lomax discussed the high level of public comment CIRM received on this issue and indicated in future deliberations CIRM would consider offering stipends to public members of SCROs.

Professor Greely then called for a vote on adopting CIRM regulations accept as technically required to deviate, using the broader definition of covered stem cell line, including lost wages as a direct reimbursement for oocyte donors (and possibly the SCRO public members as well), allowing CDHS to determine enforcement mechanisms, removing the statement on genetically modified embryos (as it is outside the scope of human stem cell research guidelines). The Committee unanimously passed the motion.

15 minute break at 2:55pm; 3:14pm reconvene.

Agenda Item #4: Recommendations for Guidelines on Clinical Trials

Dr. Magnus led discussion. He emphasized the importance of clinical trials having SCRO review and institutions having adequate field strength to perform trials (Section 1). Based on objections from the previous meeting to using the term "embryo," he explained the guidelines would use the term "embryo" and SCROs could decide whether to use a more scientifically accurate term. He suggested that SCROs should also review clinical trials involving neural-progenitor cells, as research involving their placement in the central nervous system requires a specific expertise. Dr. Lubin wondered if autologous stem cells should also require SCRO review. The Committee discussed possibly adding the term "adult non-autologous neural-progenitor stem cells" as requiring SCRO review.

Professors Greely, Rao, and Dr. Magnus discussed whether to keep the statement on prohibiting human stem cells from being placed in human embryos with the intent of creating an infant (Section 3). Professor Greely mentioned that the CIRM regulations Section 100030(d) may encompass this concept. It states "the introduction of any stem cells, whether human or nonhuman, into human embryos" is not available for CIRM funding. It was decided to return to this later in the meeting.

Section 1

Professor Greely asked the Committee for comments on Section 1.b. Dr. Dorff suggested that overall the guidelines should delineate the role of IRBs and SCROs in order to minimize

redundancy and overburdening institutions. Dr. Lubin described the IRBs and SCROs at CHORI often have one overlapping member to help reduce duplication. Professor Greely suggested adding this point in the Preface.

Dr. Martinez-Maza asked for clarification on the term “institutional field strength.” Dr. Magnus replied that it would be defined in the Definitions Section and further explained the term refers to ensuring an institution has adequate expertise and resources to perform a certain medical procedure/trial for the first time. Professor Greely noted that a SCRO would be more likely than an IRB to be able to assess the strengths necessary for performing stem cell trials.

In reference to Section 1.b.iii., Dr. Stock inquired how the “reasonableness” related to the anticipated benefits of a trial was determined and if this would restrict certain areas of research. Professor Greely and Dr. Magnus indicated this was language adopted from IRB requirements. Professor Greely also explained that Section 1.b.iv. (diversity of research subjects) is not currently something IRBs are required to consider but something that research institutions and researchers are highly encouraged to do.

Section 2

Dr. Magnus explained that the wording in Section 2.b. stems from discussions from previous meetings and he was attempting to decrease the chances of consent forms containing misleading information, which has occurred in gene therapy trials. Dr. Stock was concerned the wording in Section 2.b.i. was too narrow and suggested adding other terms to “therapeutic cloning.” Professor Rao suggested that any consent form which uses the term “direct benefit” is misleading. Dr. Dorff recommended discouraging the terms “stem cell therapy” and “gene therapy” as well. The Committee agreed to include the three terms (therapeutic cloning, stem cell therapy, and gene therapy) as not appropriate to use in consent forms.

With regard to Section 2.c., Drs. Magnus and Lubin noted the prevalence of Data Safety Monitoring Boards (DSMBs) for clinical trials and that institutions with appropriate field strength would likely have DSMBs.

Returning to Section 2.a., Dr. Martinez-Maza asked what information about the materials being used should be provided in consent forms. Dr. Magnus used “where the materials originated” to avoid limiting the terminology trials can use. After some discussion, Dr. Stock suggested replacing this phrase with “the biological source of materials and how they were produced”; the Committee agreed.

Section 3

Professor Greely thought the prohibition (on placing hESCs into a human embryo to be used to create an infant) might be redundant but may be worth reiterating. Dr. Stock questioned whether it was necessary because this type of clinical trial would likely not be possible for many years. Professors Greely and Magnus specified that this research would be akin to gene therapy in an embryo, which brought up whether the statement should say “fetus” and “embryo”. There was discussion on whether to delete the statement, keep it unchanged, or add “fetus and embryo.” Professor Greely asked each member about their recommendation. Based on Dr. Lubin’s concern of prohibiting research in which a malformed fetus might benefit from stem cell treatment, the Committee agreed with adding the word fetuses but changing “no human embryonic stem cells shall be placed...” to “no multi-generational germ cell lines shall be placed...”

Public Comments

For Section 2, Ms. Auriti asked the Committee to further explain using “hESCs and their derivatives” and how many generations of the derivative required IRB and DSMB review. Professor Greely sought to resolve this issue by using “hESCs or cells differentiated from human embryonic stem cells” instead, as these materials would more likely be used in research. He felt

there should still be both SCRO and IRB review. Dr. Magnus was concerned that “differentiated” would not capture research that involves immediate products of cells that are derived from hESCs and suggested specifying a boundary for the derivatives and ultimately allowing SCROs to determine if the material is still a derivative. Dr. McLean thought a single definition may not be adequate because Section 2.a. might require more information about the origin of the derivatives. Professor Greely recommended using “differentiated” in Section 1 and 2.c., “derived” in Section 2.a. for informed consent purposes, and not requiring SCRO review for non-cell factors derived from hESCs.

Mr. Reed expressed concern over prohibiting consent forms from using the phrase “therapeutic cloning” as it might appear there is something to hide; he suggested the negative phrase be allowed to be used with caution instead of being forbidden. Dr. Magnus believed using “therapeutic” was misleading to the research subject and the new phrasing which prohibits “therapeutic cloning,” “gene therapy,” and “stem cell therapy” clarified that the prohibition was based on preventing misinformation not on removing positive and/or negative word associations.

Susan Fogel appreciated Mr. Reed’s concerns but felt they were based on politics and that the core responsibility of the Committee was to promote quality of research and subject protection. She also supported prohibiting these phrases in the guidelines in an effort to reduce false claims about the field. After further discussion, Professor Greely suggested the guidelines indicate the impression of research being therapeutic would be inappropriate.

Dr. Lomax then voiced caution in coupling neural-progenitor cells with human stem cells. He did not want the Committee to inadvertently require review of certain research involving neural-progenitor cells, such as when progenitor cells are merely used as a delivery mechanism. Based on the Committee’s decision earlier in the meeting, Professor Greely stated the IRB and SCRO requirements for research involving neural-progenitor cells would be inserted in Sections 1 and 2. Dr. Lomax asked if the concern was the use of the cells or the location of their implantation. Professor Greely and Dr. Lubin agreed it was the location that was important and the guidelines should specify placement into the central nervous system.

For Section 2.b., Jesse Reynolds suggested removing “early phase” from clinical trials as he argued *all* phases should not convey an “unrealistic impression” about the direct benefits of trial participation, or including “early phase” in a clause with examples. Professor Greely agreed the Committee was not intending to endorse unrealistic expectations and suggested adding that early phase clinical trials should be watched particularly closely. He then called for a vote on the remaining issues from the Clinical Trials section.

Professor Greely felt the Committee seemed to be in agreement on the following issues:

- including research using neural-progenitor cells (for IRB and SCRO review) when they are being transplanted into the central nervous system
- replacing “hESCs and cells differentiated/derived from hESCs” with the term “covered cell lines” in Section 1 and 2.
- further explaining “institutional field strength” in the definitions section (Dr. Magnus offered to do the re-write).

Professor Rao mentioned adding a definition for “derivatives of hESCs.”

Professor Greely continued:

- Section 1, revise as “hESCs and cells differentiated from hESCs”
- Section 2, change to “covered cell lines” and add neural-progenitor cells phrasing
- Section 2.a., use broadest language for “derivatives” and change “where the materials originated” to “biological source”
- Section 2.b., include clause that there is particular concern of conveying unrealistic impression in early phase clinical trials
- Section 2.c., rather than “hESCs and their derivatives” use “hESCs and cells differentiated from hESCs”

- Section 3, add “fetuses” to human embryos and include “multi-generational germ lines”
- Preface, delete “In September 2006, SB 1260 became law”

The changes were unanimously approved.

Agenda Item #5: Committee Discussion of Areas that Need Modification

Professor Greely asked the Committee members if there were any other recommendations they would like to suggest. Ms. Auriti reminded the Committee of the concern about SB 253 and the potential issue of redundancy. Professor Greely agreed to write a letter to CDHS or the legislature mentioning the overlap in SB 253 and SB 1260; the Committee approved.

Professor Greely moved ahead to **Agenda Items #6 and #7** as he thought they might inform any other recommendations. He mentioned the uncertainty of the Committee’s future as the Committee would not be mandated or funded under SB 1260, although CDHS greatly values the Committee. He also noted that CDHS would like to post the guidelines for public comment, in which case it would be helpful to have another meeting in late November or early December. Before the meeting, the guidelines would be changed according to today’s discussion, sent to Dr. Ahmad, and then posted for public comment. If there are no comments, then another meeting would not be necessary. Dr. Magnus inquired if the guidelines would be reviewed by the legal department of CDHS before being posted for public comment. Dr. Ahmad mentioned they can be simultaneously posted for public comment and reviewed by the legal department.

Professor Greely then asked the Committee for any issues it felt would be important to discuss if the Committee exists beyond its mandated time. Dr. Magnus wanted IRBs and SCROs to distinguish between research subjects and research donors. He brought up the example of a researcher misunderstanding the distinction and therefore paying bone marrow donors for their bone marrow for research purposes without realizing that if the marrow is transferred into a living person, then that is a National Organ Transplant Act violation. He argued the distinction would be useful for capturing the relationship between the research (oocyte) donor and the physician responsible for doing the oocyte procurement because their relationship is neither subject/investigator nor patient/physician. Professor Greely agreed it was an important issue for stem cell research and suggested it be considered as an amendment to the guidelines if there is another meeting.

Dr. Stock and others expressed interest in quickly setting up a tentative meeting date and then cancelling later if necessary.

Public Comments

Ms. Auriti expressed appreciation for the Committee’s work and thought it would be useful for a committee of experts to have a continuing role in deliberating on the ethical and public concerns about stem cell research.

Mr. Reynolds talked about three upcoming events regarding stem cell research in the Bay Area. The Institute of Medicine is having a day-long scientific session on assessing the health risks to oocyte donors on September 28th; on September 28th and 29th, there is a brief conference at UC Berkeley and UCSF; and CHORI is having a conference entitled “Toward Cure: Integrating the Benefits of Diversity of California Stem Cell Research Program” on October 14th.

Dr. Lomax also found the Committee very useful and appreciated (from CIRM’s standpoint) having another deliberative body thinking about similar issues. Secondly, he suggested the development of the tracking system for egg donations be given thorough consideration so that the information gathered by CDHS is complete. Professor Rao mentioned an LA Times article about shortages of oocytes in states that have prohibited compensation for egg donation for stem cell research. She proposed CDHS gather statistics on this information, in addition to health risks.

Professor Greely concluded that if the Committee were to continue on, the expert advice of the Committee could be useful to CDHS in reviewing the health risks related to oocyte donation and assessing the effects of compensation limitations on stem cell research. He then thanked the Committee and the members of the public for their useful participation. Dr. Ahmad also thanked CHORI for hosting the meeting, as well as the Committee members for volunteering their services and providing their highly technical advice to CDHS.

Adjournment: 4:50 PM.

Post-Meeting Addendum

After this meeting, the committee chair, Professor Greely, learned that his tentative statements concerning the survival of the IRB review requirements of Health and Safety Code Section 125115, enacted as part of SB 253 in 2002, in the event SB 1260 became law were incorrect. Ellen Auriti from the University of California, one of the members of the public present at the meeting, discovered that SB 771, adopted in 2003, had previously renumbered Section 125115 as Section 125300, which would be amended by SB 1260 to replace the IRB review requirement with an SCRO review requirement. Therefore, the Chair will not prepare a letter concerning this issue.