

APPROVED MEETING MINUTES
California Department of Public Health, Human Stem Cell Research Advisory Committee
September 24, 2007
Children's Hospital Oakland Research Institute
2:00 PM – 5:00 PM PST

Attendance:

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

Samuel Cheshier, MD, PhD
Elliot Dorff, PhD
Fred Gage, PhD (by phone)
Henry Greely, JD
Bernard Lo, MD
Alex Lucas (representing Bertram Lubin, MD)
David Magnus, PhD
Otoniel Martinez-Maza, PhD
Margaret McLean, PhD
Radhika Rao, JD

CDPH

Shabbir Ahmad, Manager, Human Stem Cell Research Program, CDPH
Cindy Chambers, Human Stem Cell Research Program, CDPH
Amber Christiansen, Human Stem Cell Research Program, CDPH
Kate Cordell, Human Stem Cell Research Program, CDPH
Heidi Mergenthaler, Human Stem Cell Research Program, CDPH
Patricia Rodriguez, CDPH Legal Counsel

Members of the Public

Ellen Auriti, University of California Office to the President
Susan Fogel, Pro-Choice Alliance for Responsible Research (by phone)
Geoffrey Lomax, PhD, CIRM
Jesse Reynolds, Center for Genetics and Society
Shannon Smith Crowley, the American College of Obstetrics and Gynecologist (by phone)
Charis Thompson, UC Berkeley

Definitions

- The California Department of Public Health – CDPH, “The Department”
- The California Institute for Regenerative Medicine – CIRM, “The Institute”
- Stem Cell Research Oversight Committee – SCRO Committee
- Human Stem Cell Research Advisory Committee – HSCR Advisory Committee, “The Committee”
- Guidelines for Human Stem Cell Research Pursuant to Health and Safety Code 125118 – HSCR Guidelines, “The Guidelines”
- The CIRM Medical and Ethical Standards Regulations – “CIRM Regulations”, “The Regulations”
- Independent Citizens Oversight Committee – ICOC
- Human Embryonic Stem Cell – hESC
- University of California Office to the President – UCOP
- Reproductive Technology – SART

Opening Remarks

Professor Henry Greely invited Dr. Shabbir Ahmad to speak about the purpose of the meeting. Dr. Ahmad explained that the intent of the meeting was to discuss the forms drafted pursuant to the two requirements in SB 1260 (Ortiz, 2006) for reporting to the Department 1) by the SCRO Committees regarding the projects they reviewed over the year and 2) of oocyte donor demographics and the health effects of oocyte retrieval for research. Dr. Ahmad noted that the meeting was for discussion purposes and that no decisions would be made at this meeting as the public had not yet had a chance to comment on the documents being reviewed.

Approval of Minutes

The December 05, 2006 CDHS HSCR Advisory Committee meeting minutes were approved. They can be viewed at:

<http://www.cdph.ca.gov/services/boards/HSCR/Documents/MO-Dec5Minutes-09-2007.pdf>

Agenda Item #3: Report on Guidelines and Committee Status

Topic 1: California Department of Public Health Changes ("The Department")

Dr. Shabbir Ahmad briefly explained the July 1, 2007 reorganization of the California Department of Health Services into the California Department of Public Health and the California Department of Health Care Services. Dr. Ahmad also noted that Dr. Susann Steinberg, Chief of Maternal, Child and Adolescent Health Division has gone on extended leave and the department has asked Dr. Ahmad to step in to be the Acting Chief for at least six months.

Topic 2: Guidelines for Human Stem Cell Research Pursuant to Health and Safety Code 125118
In review of the Guidelines, Dr. Ahmad summarized that Professor Greely had provided final recommendations to the Department, which were submitted to and signed by the Director of the Department. An informational packet about the Guidelines was sent to the Health and Human Services Agency and the Governor's Office. The Guidelines have been posted on the web page of the Department:

http://www.mch.dhs.ca.gov/documents/Stem_Cell/Stem%20Cell%20Research%20Guidelines.pdf

Topic 3: Umbilical Cord Blood Banking Bills

Dr. Ahmad informed the committee on the current bills relating to umbilical cord blood banking, bills AB 34 (Portantino, 2007) and SB 962 (Migden, 2007), explaining that the bills have gone through the Senate and Assembly and are now enrolled and awaiting the Governor's decision. Dr. Ahmad notified the committee that the Department may request assistance and technical recommendations from the Committee regarding cord blood banking in the case that these bills are signed by the Governor. The bills can be found at the following web sites.

- SB 962 (Migden, 2007): http://www.leginfo.ca.gov/cgi-bin/postquery?bill_number=sb_962&sess=CUR&house=B&author=migden
- AB 34 (Portantino, 2007): http://www.leginfo.ca.gov/cgi-bin/postquery?bill_number=ab_34&sess=CUR&house=B&author=portantino

Comments:

Radhika Rao inquired as to how long the committee would be in effect. Dr. Ahmad remarked that on December 31, 2006 the Stem Cell Research Program, and the California Department of Health Services, at that time, now the California Department of Public Health, decided to extend the committee for another two years. Professor Greely commented that at the time of extension, all participants had been asked to continue their membership, and that there would be points in the future which would allow members of the committee to gracefully resign from their participation.

Agenda Item #4: Report on Status of California Institute of Regenerative Medicine (CIRM)

Geoffrey Lomax provided a written and oral summary in response to specific questions regarding CIRM's activities. The funding program to date has authorized approximately \$208 million dollars in funding through the training grants program, Scientific Excellence through Exploration and Development (SEED) Grants, the comprehensive grants, and the shared laboratory grants. There are two additional major programs underway, the major facilities and the faculty awards. There were not specific applications pursuant to the CIRM strategic plan of Community's of Science and Responsibility to the Public initiatives at this time, but CIRM welcomed any input from the Committee.

Geoffrey Lomax also noted that CIRM is awaiting a \$250 million bond sale in October which will allow The Institute to move forward on the grants program. Also of note, Alan Trounson from Australia was announced as CIRM's new president.

CIRM is in the phase of proposing amendments to their Regulations, and the proposed revisions were slated to go into the Office of Administrative Law by the next week. The Standards Working Group recommended and the ICOC subsequently approved a series of amendments for the Regulations that would accomplish three major objectives. The first is to expand lists of authorized cell lines that could be used by CIRM-funded researchers, specifically stem cell lines derived under the Japanese guidelines. A second amendment removed language that described allowable costs for cell lines. It was determined that that language was redundant with language in Proposition 71. The third objective authorized the use of human somatic cells in stem cell line derivation experiments in response to a number of papers published this summer regarding the possibility of generating a pluripotent stem cell line from the genetic reprogramming of a somatic cell. CIRM decided that prohibiting funded researchers from utilizing these well characterized cell lines that have been the basis for early research in this area, would severely undermine the opportunities to advance the science. In addition, edits were made for the purpose of clarity in response to early public comments.

Comments:

Professor Greely noted that everyone had a copy of CIRM's proposed amendments to their Regulations in the packet document marked at the bottom "CIRM - Rev 08/29/07".

Dr. Elliot Dorff commented that the change in wording of the CIRM Regulations in section 100100.b.2 (Page 9 of CIRM - Rev 08/29/07 at the bottom) to the wording "a donor must have the opportunity to oppose restrictions on future use of donated material" was substantively different from the wording of the HSCR Guidelines. The Guidelines for Human Stem Cell Research Section 8(a)(14), require that donors be offered an opportunity to document their preferences regarding the future uses of their donated materials. The consent process is tailored toward determining whether donors have objections to any specific forms of research to ensure that their wishes are honored, but it does not say that their wishes have to be honored. Dr. Dorff proposed the question as to whether the Committee should consider adopting a similar change in wording for this section.

Professor Greely summarized Dr. Dorff's comment into two concerns:

1. It is useful to be as similar as possible to the CIRM Regulations given that the statute that governs both entities aren't exactly the same but are broadly similar.
2. Is there a desire to use stronger language than the current language of the section?

Radhika Rao noted that current language in the Guidelines tracked the former language of CIRM Regulations for the sections in question.

Dr. Lomax commented that CIRM's modification to this section was to clarify that researchers could enter into conversations with potential donors with declarations that only unrestricted donors would be considered. The former wording was perceived as requiring a donor to go

through the entire process of donation before the researcher disclosed whether they were going to accept the donation. However, Dr. Lomax made note that additional changes may have been made to the wording since the CIRM - Rev 08/29/07 document was printed.

Dr. Dorff raised the concern that if there are not a lot of donors, remembering that donors are not being paid, it seems important to offer them the opportunity to make restrictions on their donation if they're willing to donate under those restrictions. Dr. Lomax reminded the Committee that the Regulations applied to both embryo and oocyte donation. Based on feedback, researchers feel that in many cases it is logistically impossible to ensure that restrictions are met, and due to the nature of material exchange in research, researchers do not want to be held liable for potential violations of those restrictions. Professor Greely suggested that there was a possibility for members of the Committee to comment individually on CIRM's proposed Regulation changes, and in addition, the Committee could collectively comment on the new proposed Regulations. Additional comments were made by the Committee regarding the benefits and burdens of allowing restrictions on donations. Further discussion was tabled until the most up to date wording of CIRM's proposed Regulation changes becomes available.

Professor Greely posed concerns to Dr. Lomax regarding the safe harbor for the British cell lines from United Kingdom Human Fertilization and Embryonic Authority (HFEA), which is now authorizing cell lines that would appear to violate California law due to compensated donations. In the UK, women who are undergoing IVF for clinical purposes can share some of their harvested eggs with researchers and in return get discounts on the IVF procedure. Both CIRM Regulations and the HSCR Guidelines safe harbor the United Kingdom Stem Cell Bank and the United Kingdom HFEA.

Committee and public discussion included suggestions to drop listing of individual countries and to establish some kind of authority that would be reliable to ensure that cell lines are ethically derived. Dr. Lomax commented that the regulation process is continual, and the working group at CIRM is in place to address changes in the scientific field.

Agenda Item #5: Discussion and Feedback on Proposed Reporting Forms

Dr. Ahmad reviewed the two main requirements regarding reporting from SB 1260 (Ortiz, 2006):

- 1) The SCRO Committee that has reviewed hESC research pursuant to Section 125119 shall report to the Department annually on the number of human embryonic stem cell research projects that the SCRO Committee has reviewed and the status and disposition of each of these projects, including the information collected pursuant to Section 125342. The Department shall provide a biennial review to the legislature on hESC research activity. These biennial reviews shall be compiled from the reports of the stem cell researchers' activities.
- 2) Section 125342 states a research project or the research program that involves assisted oocyte production or any alternative method of oocyte retrieval shall ensure that a written record is established and maintained to include but not be limited to demographics of donors, and provenance and disposition of oocytes. Records should also reflect adverse health outcomes. The Department will develop aggregate information on its web site for public use.

Professor Greely reminded the Committee that all comments were welcomed but no decisions would be taken at this meeting.

Feedback on the Stem Cell Research Oversight Committee Reporting Form:

1. Limiting the Scope of Collection to hESC: A suggestion was made for this reporting form to amend where it says "human stem cells" to instead state "human embryonic stem cells". SB 1260 (Ortiz, 2006) only requires reporting of

- human embryonic stem cell research so the suggestion was to restrict reporting to the language of SB 1260 (Ortiz, 2006). (Dr. David Magnus)
- a. *Comment:* Including derivatives of pluripotent cells or HESC's? (Professor Greely)
 - b. *Comment:* No one knows what derivatives of stem cells means, and there's no definition from NIH. Reporting requirements should not include things other than embryonic stem cells. SB 1260 (Ortiz, 1260) and Senator Ortiz's letter dated November 2006 intended to make sure the concerns about the health, well-being, and safety of those who might be involved in either stem cell research or oocyte donation were protected. Adult stem cell research does not raise those kinds of issues and it is not clear that research with derivatives of stem cells once the lines have been derived from embryos or oocytes implicates those kinds of concerns. The Department should not extend beyond SB 1260 (Ortiz, 2006) without clear rationale as to why and a clear understanding about the burdens for that extra reporting. (Dr. Bernard Lo)
2. Including Parthenotes in Reporting: Parthenotes do not count as embryos, but it seems clear from the concerns manifested in SB 1260 (Ortiz, 2006) that they should be covered by the reporting because they involve oocytes. (Dr. Rao)
 - a. *Comment:* The Department will have to be very clear about what sorts of things are included, but it seems reasonable to include SCNT. (Dr. David Magnus)
 - b. *Comment:* If the driving force behind this is the concern about embryos and oocytes, then the Department could think of defining it in terms of something derived either from an embryo or from an oocyte, and then the oocyte would take into consideration parthenogenesis and SCNT. (Professor Greely)
 3. Including Sperm Donation in Reporting: Would there also be concern for donation and research from sperm based on recent advancements in the science? (Dr. Dorff)
 4. Defining Pluripotent: The reporting form currently includes pluripotent cells, and if it becomes possible to reprogram somatic cells into pluripotent cells, then the issues surrounding the donation of somatic cells include questions of consent with a lesser level of concern regarding safety. (Dr. Lo)
 - a. *Comment:* Although the guidelines do cover pluripotent cells that are put into the central nervous system. (Professor Greely)
 5. Summary of Discussion Thus Far (Professor Greely):
 1. The breadth should be narrowly tailored to the reasons for the reporting requirements.
 2. Adult stem cell research, at the very least, shouldn't require the same sort of reporting.
 3. The Department should think carefully about how to define what specific kinds of research one's to report on.
 4. SCRO Committees will have to continue to review adult stem cell research, but will not have to report on this type of research to the Department.
 6. Defining 'Derivatives': The discussion about derivatives should be addressed and probably dropped if possible, because it's not clear what "derivatives" means. As it is now, it's quite inclusive and some people are interpreting it as much as to mean photographs taken of stem cells and subsequent data collection. (Dr. Fred Gage)
 7. Limiting Information Collected: The reporting form requires more information than is specified in the statute, creates an unnecessary reporting load on SCRO Committees, and it is unclear why this particular information is required. (Dr. Otoniel Martinez-Maza)

8. Drafting Reporting Form: The Department might want to create two versions of the reporting form, 1) one that includes the minimum requirements and 2) one that includes other information that the Department would find useful. (Professor Greely)
 9. Multiple Versions of Reporting Form: A suggestion was made that there might be a more extensive form for research involving oocytes and a simpler form for research involving non-oocyte hESC. (Dr. Martinez-Maza)
 10. Soliciting Feedback: A suggestion was made to distribute the forms to SCRO Committees for additional feedback. (Dr. Magnus)
- Public Comments:**
11. Including Sperm Donation in Reporting: Procurement issues regarding testicular sperm cells have already come up as an issue. (Charis Thompson)

Feedback on State of California Human Oocyte Retrieval Reporting Form

1. Target of Form: Define who would fill out this form. (Dr. Margaret McLean)
 - a. *Comment*: The language in SB 1260 (Ortiz, 2006) is "research program or projects". Now this could be programs in a department or the clinic. (Dr. Ahmad)
 - b. *Comment*: One concern is that this is a very expansive data set, and the person to whom this form is directed may dictate how this form is constructed. (Dr. McLean)
 - c. *Comment*: There's no specific language in the statutes that describes what is a program or a project. (Pat Rodriguez)
 - d. *Comment*: The target might be whoever is the responsible person on the protocol that has to go through the IRB for oocyte procurements. (Professor Greely)
 - e. *Comment*: Make it somewhat flexible. A model is being formed for a centralized system for oocyte and embryo procurement, and then the PI will be able to work through the centralized program to obtain samples. Therefore, the centralized program might be filling out the form as opposed to the individual PI on the particular protocol. (Dr. Magnus)
 - f. *Comment*: The reporting requirement in the statute (125342.b.1) does not indicate the target for the reporting form. (Professor Greely)
2. Reporting of Adverse Events: Reporting of complications is an excellent idea, but should be limited to more serious complications, and terms (e.g., ovarian hyperstimulation, severity of adverse event) should be well defined to ensure consistency of reporting. (Dr. Lo)
 - a. *Comment*: A copy of "Assessing the Medical Risk of Human Oocyte Donation for Stem Cell Research" will be provided to all members at the next meeting. (Dr. Ahmad)
 - b. *Comment*: Give examples in each one of these cases about what constitutes severe, moderate, and mild. (Dr. Dorff)
 - c. *Comment*: Dr. Magnus does not agree with the approach of giving examples because it may be an invitation for misinterpretation. Instead he recommends defining discreet concrete measurable endpoints classified into categories which preclude individual interpretation. For example, define a serious adverse event as something that requires hospitalization. (Dr. Magnus)
3. Confidentiality and Demographic Information: There are probably going to be very few oocyte donors, and it may be likely that people can be reidentified on the basis of the demographic information collected on the form (1-10). (Dr. Lo)
 - a. *Comment*: The Department is told in the statute to aggregate the data and release it in a way that doesn't provide personally identifiable identification. (Professor Greely)
 - b. *Comment*: The Department should consider reporting or not reporting to the public if it is less than five donors in a year. (Dr. Ahmad)

4. Page Numbers: Page numbers should be added. (Dr. Dorff)
5. Formatting: Questions 16 & 17 need more room for filling out. (Dr. Dorff)
6. Reimbursement: In number 11, the form asks how much was the donor reimbursed for direct expenses related to donating her oocytes. That's what's legal. Should the form inquire about what's also illegal? Did the donor receive any other reimbursement? (Dr. Dorff)
 - a. *Comment*: There is worry that this would be an invitation to a misunderstanding, because it might assume that if such a question is asked, then those actions are condoned by the Department. (Dr. Magnus)
7. Limiting Reporting to Donors that Provide Oocytes Solely for Research: A suggestion was made to clearly state on the collection form that reporting is only necessary for donors that provide oocytes solely for research purposes, and that by definition, the failed-to-fertilize eggs that are used for research should not be included in these reporting forms. (Dr. Magnus)
 - a. *Comment*: The third paragraph on the first line states that if the "facility or project has collected oocytes that were or will be used or sent for use in stem cell or other medical research..." This wording would lead one to believe that any AOP for clinical reasons would require reporting. This should be changed to reflect more closely the research definition. (Dr. Martinez-Maza)
8. Summary of Structures to Consider: (Professor Greely):
 1. Statutory requirements of reporting for the purpose of creating a database of the extended adverse effects for assessing the risks and the dangers that are associated with procurement
 2. Privacy of the subjects themselves
 3. The regulatory burden and the implementation at the institutional level

Public Comment

9. Target of Form: One person you might consider for the reporting is whoever the (SART) reporter is for the clinical setting for extracting the eggs (Charis Thompson)
10. Protecting the Health of the Donors: Additional potential predictors of adverse events that are of concern are:
 1. Parity
 2. Age (especially young – is there something that can be done to discourage those 19 and under from being allowed to donate?)
 3. Dose (e.g., mg/kg)
 4. Number of times donated
 - a. *Comment*: Dropping the 19 and under age category from the reporting form could have undesirable consequences in that clinicians/researchers may then ignore age altogether rather than discourage that age group from donating. (Professor Greely)

Feedback on the CDPH Informed Consent Checklist for Research Involving Human Oocyte Retrieval

1. Page 1, for 6, 7, and 8, should read "whom to contact with questions." (Dr. Dorff)
2. Page 1, for 12: should be more clearly stated with regard to legal rights.
 - a. *Comment*: This statement tracks the language of the federal regulation which is also unclear about what legal rights should be. (Professor Greely).
3. The checklist that is being put together at Stanford may be helpful to the Department. (Dr. Magnus)
4. Use the format "e.g.," (Dr. Dorff)
5. Page 2, number 1 –state in layman's terms (Dr. Dorff)

6. Page 3, number 11 states that “donors should be offered an opportunity to document their preferences regarding future uses of their donated material”. This regulation may be changing. Otherwise, the Department should define how to spell out the preferences and determine how the guarantees are to be formulated. (Dr. Dorff)

Agenda Item #6: Remaining Issues from the December 5th HSCR Advisory Committee Meeting and Public Comments on the Guidelines

Research Registry: Professor Greely commented that the summary of positive and negative results of any non-CIRM funded research or clinical trial was handled by requiring in the Guidelines in Section 9(a)(5) to register the clinical trial with clinicaltrials.gov.

Privacy/Confidentiality Wording: There was the matter that the UCOP had some concern about a change of language and the committee was going to look into it. Ellen Auriti recalled that the recommendation was a semantic wording change such that donors don't have confidentiality rights but they have privacy rights. Although the wording in the current version appeared correct to her.

Limiting Reporting to hESC: Radhika Rao noted that the letters from the Center for Genetics and Society, the Pro-Choice Alliance for Responsible Research, and Senator Ortiz all suggest that the data and the reporting should include an overview of all human stem cell research being done at institutions – as opposed to simply human embryonic stem cell research. Recent suggestions by the Committee to include just hESC may receive adverse comments. Professor Greely felt that the field that included non-hESC stem cells was too large/broad for reporting, and the field was already well accepted such that fewer ethical issues were in need of SCRO Committee monitoring.

Agenda Item #7: Update on Clinical Trials

There was no speaker scheduled to give a clinical trials update.

Agenda Item #8: Public Comment (general)

Ellen Auriti asked for clarification on the timing and availability of the reporting forms. Dr. Ahmad expected the forms would be finalized through the Committee and approved by the Department for distribution to SCRO Committees in early 2008 for reporting in the summer of 2008. The Department is due to create a legislative review by the end of 2008.

Note: An invitation for public comment was made after each agenda item, and additional public comments can be found in those sections.

Agenda Item #9: Next Meeting

The next meeting was tentatively planned for November in a southern California location.

The meeting was adjourned.