UNAPPROVED MEETING MINUTES

California Department of Public Health Human Stem Cell Advisory Committee Meeting
February 20, 2009

California Department of Public Health (CDPH) Human Stem Cell Research (HSCR) Advisory Committee Members
David Magnus, PhD
Henry Greely, JD
Bernard Lo, MD
David Martin, MD (in lieu of Bertram Lubin, MD)
Samuel Cheshier, MD, PhD (phone)
Margaret McLean, PhD
Radhika Rao, JD
Gregory Stock, PhD (phone)
Elizabeth Blackburn, PhD (phone)
Elliot Dorff, PhD (phone)

CDPH
Shabbir Ahmad, Manager, Human Stem Cell Research Program, CDPH
Elizabeth Carson-Cheng, Human Stem Cell Research Program, CDPH
Amber Christiansen, Human Stem Cell Research Program, CDPH
Heidi Mergenthaler, Human Stem Cell Research Program, CDPH
Pat Rodriguez, CDPH Legal Counsel

Members of the Public
Geoff Lomax, California Institute for Regenerative Medicine (CIRM)
Justine Durrell
Ellen Auriti, UC Office of the President
Shannon Smith-Crowley, Partners in Advocacy (phone)
Lily Mirels, UC Berkeley

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Agenda Item 1: Welcome and Introductions

Professor Greely welcomed the Committee members, public attendees, and CDPH staff. In addition to the agenda items, Professor Greely hoped the Committee would have time to address how the Committee should continue to provide long-term advisement to the Department given the continual advancements in stem cell research and changes to state and national standards on human stem cell research.

Dr. Ahmad made a few announcements. He noted that despite the state budget cuts funding for the Committee was intact so far. He thanked CHORI for hosting the meeting and the Committee members for continuing to volunteer their time. He also mentioned that the HSCR Program had developed a biennial legislative review of hESC research from the reports received by SCRO Committees and that it is currently going through the Department's approval process. Committee members will receive a copy of the review once it is finalized.

Professor Greely asked if the Department was planning to change the reporting forms for the second reporting year. The HSCR Program indicated it was planning to make minor changes to the forms.

Agenda Item 2: Approval of Meeting Minutes from 10/01/08

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

Before moving to Agenda Item 3, Professor Greely asked Dr. Lomax to update the Committee on CIRM regulation changes, how the state budget may affect CIRM, and if he projects any future challenges for CIRM.

Dr. Lomax mentioned that the CIRM Standards Working Group had considered a package of regulation changes at its previous meeting and had agreed to make two-thirds of the changes. The changes primarily involved looking at the area of use of somatic cells in research, particularly in iPSC research. CIRM surveyed various institutions, SCRO Committees, and researchers to determine possible sections of the regulations in need of change due to iPSC advancements. Some questions that arose dealt with whether a full SCRO Committee meeting was required for certain research involving iPSCs and whether research was allowed if a tissue/somatic cell donor had been paid. These questions arose in part because *in vitro* research involving somatic cells is generally considered minimally controversial compared to hESC research.

The changes to the regulations included issues related to SCRO Committee oversight, as well as to making consent requirements for somatic cells more flexible than for hESCs. The one proposed amendment that was not approved by the Working Group involved creating a carve out for IRB-approved protocols that use somatic cells whose procurement involved monetary compensation, which is usually a nominal payment. The Working Group is still consulting with CIRM's legal counsel on this issue. Overall, the regulation changes attempted to address the issue of basic *in vitro* research that involves somatic cells not requiring the same level of verification as hESCs do. The changes will likely not be approved via the Office of Administrative Law until the summer.

Dr. Lo then mentioned that the state's financial crisis will make it difficult for CIRM to raise money for grant funding. Professor Greely asked if passage of the state budget would help with bond sales. Dr. Lomax noted the queue for bond sales was lengthy and anticipated it would be about a year before bonds could be sold again for CIRM purposes. Given this delay, CIRM met with the state Controller's Office and determined it may have the authority to pursue different funding options, such as private sector funding. Professor Greely wondered whether the slow down in CIRM funding might impact non-CIRM funded research as well. Dr. Ahmad said this might be affected by NIH funding if the federal funding ban is lifted.

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Dr. Lo introduced a couple CIRM-related issues. He noted that at the latest Standards Working Group meeting, the Working Group had discussed approaching CDPH about strategies for instituting reporting requirements for CIRM grantees. If CIRM were to start funding oocyte donation for research, then it might be appropriate to use CDPH's mechanism so as to avoid duplicative reporting.

Dr. Lo also mentioned that for future grants CIRM may begin targeting translational research and early clinical trials. This will necessitate addressing the ethical issues involving stem cell clinical trials that go beyond the current FDA standards. Dr. Magnus noted that the CDPH Guidelines already address clinical trials and that they could be used as a reference for CIRM's deliberations. One issue to consider is whether CIRM should incorporate clinical trial amendments into its regulations or only provide advice/recommendations on the topic. Dr. Lo noted the ISSCR clinical trial guidelines are written at a high level of abstraction and, therefore, are difficult to apply to CIRM grantees.

The ISSCR guidelines are yet another body of standards with which the HSCR Advisory Committee must keep current. Professor Greely added an informal agenda item regarding the issue of the Committee maintaining awareness of the various stem cell research standards and their revisions.

Agenda Item 3: Discussion on developing a statement for SCRO Committees reviewing hESC research using the NIH-approved BresaGen stem cell lines

Professor Greely recalled that at the last Committee meeting the Committee discussed developing a guidance statement for SCRO Committees about how to address protocols that involve using hESC lines with ethical concerns, such as in the case of the BresaGen lines. Dr. Magnus thought the issue was more general and that the Committee discussed how to address hESC lines that are ethically questionable but have already been approved for use by a stem cell authority, such as NIH. This also raised the issue that standards will evolve over time such that more recent lines will meet higher ethical standards. Dr. Magnus asked how SCRO Committees should evaluate older lines that do not meet the current higher ethical standards. He also questioned how existing hESC lines should be evaluated if they have superior consent processes to some of the approved lines but are not on any existing approved lists and do not meet the current research standards.

Dr. Magnus drafted a proposal (revision to Section 6 of the Guidelines) that addresses this issue for the Committee to discuss. The idea behind the revision is to allow flexibility for SCRO Committees in evaluating cell lines. One way is for cell lines to meet the full standards of voluntary informed consent, including payment issues. The second way would be for a SCRO Committee to determine two things first: 1) that a cell line counts as a "permissible line", and 2) that the variation that exists between a "permissible line" and a line derived under less than ideal circumstances has a sufficient level of scientific rationale for use. "Permissible line" could include those lines already approved by recognized authorities, as is included in the Guidelines, and those

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approved through CIRM's petition process. A "permissible line" could also include lines that are determined by a SCRO Committee to have met the ethical standards and guidelines at the time the lines were created.

Professor Greely clarified that under the current Guidelines there are two ways cell lines are determined to be acceptably derived: 1) the lines meet the various ethical conditions, or 2) the lines are from the list of recognized authorities. The BresaGen lines, however, revealed that not all the lines listed by the recognized authorities meet a certain threshold of ethical acceptability. Professor Greely's understanding of Dr. Magnus' proposal was that a line is acceptable if: 1) it meets all of the various ethical conditions detailed in the Guidelines, or 2) it is listed on the approved list of lines and met the basic consent requirements that existed at the time of derivation, or 3) it met the basic consent requirements at the time of derivation but is not on the approved list. Dr. Magnus added that the proposal requires there to be sufficient scientific rationale for the latter two criteria. For example, while the BresaGen lines are already on the approved list, the proposal would require there to be scientific rationale for using these lines. The proposal would create a way for SCRO Committees to give priority to lines that have better consent processes. Professor Greely suggested that scientific rationale might include how long a researcher has been working with a particular line and if the researcher would have to start over if a line were disapproved by a SCRO Committee. Dr. Magnus thought this should qualify as good rationale but that this would still need to be weighed against the gap in the actual consent process versus ideal consent requirements.

Professor Greely offered two procedural options for the proposal. The proposal could be deemed advice from the Committee and posted on the CDPH website as guidance for SCRO Committees, and/or it could be used to revise Section 6 of the current Guidelines. Professor Dorff asked for clarification regarding the proposal because, as written, it seemed a SCRO Committee could approve a line in either one of two cases: either the line is on the approved list, or a SCRO Committee deems a line met the consent requirements at the time of derivation. Dr. Magnus clarified that a line not already on the approved list must be deemed by a SCRO Committee to have met the consent requirements at the time of derivation and to have sufficient scientific rationale. It was agreed that the proposal should be re-worded under section B to say that a line can be deemed acceptably derived if it 1) is on the approved list and has sufficient scientific rationale for use, or 2) met the consent standards at the time of derivation and has sufficient scientific rationale for use.

Dr. McLean asked if this means that one SCRO Committee might determine a line is acceptably derived while another does not. Dr. Magnus said this is a possibility and pointed out that currently SCRO Committees require researchers to provide scientific rationale for the use and destruction of embryos, which means there is likely already variation in SCRO Committees' determinations. Dr. Stock noted that the rationales used could go beyond scientific to include budgetary or logistical issues, for example. Professor Rao suggested the rationales should be significantly important or significant.

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Dr. McLean thought there should still be scientific rationale but that there could also be other considerations.

Dr. Lo agreed that providing a conceptual framework for SCRO Committees was helpful. A recent UCSF publication co-authored by Dr. Lo discussed the issue of considering different kinds of informed consent violations and balancing those against the scientific/pragmatic rationale of a line and the consent standards of the time. He stressed the importance of allowing variation while providing bounds that are logically or ethically defensible. He thought providing some case examples on the CDPH website might be helpful for SCRO Committees.

Professor Greely suggested that the proposal could be posted on the CDPH website and that relevant articles, such as the UCSF and Streiffer ones, could be posted as well. It might work to have a subgroup of the Committee develop or determine a couple applicable cases. Dr. Lo noted that posting various documents may require distinguishing between Committee-supported guidance versus materials for reference purposes only. Professor Greely agreed that materials would need to be identified appropriately. Dr. Magnus felt posting materials would be beneficial to SCRO Committees and suggested his proposal for Section 6 be considered for incorporation into the Guidelines since merely posting the document would not change the current language of the Guidelines.

Pat Rodriguez recommended providing more specificity on the categories SCRO Committees are to use in assessing the rationale for using particular cell lines as the APA process requires regulations to meet certain clarity standards. Dr. Magnus felt that some of the existing regulations have similar discretionary language and these were able to meet the standards for clarity.

Professor Greely suggested the Committee move forward on this topic. He proposed that the Committee consider whether the substance of Dr. Magnus's proposal be posted on the CDPH website as advice to SCRO Committees and whether the proposal should be re-worded and considered as a revision to the Guidelines at the next meeting. Dr. Martin was concerned there might be confusion about whether the document was an official recommendation or just advice. Professor Greely agreed the document would need to be prefaced appropriately indicating that this was the current thinking of the Committee but not included in the Guidelines yet. Some Committee members thought it would be more effective to wait to post the recommendation until it is incorporated as a revision to the Guidelines. Professor Greely agreed. He asked Drs. Lomax and Lo to comment on how this proposed revision compares with CIRM's regulations. Dr. Lomax noted that CIRM's new petition process places strong emphasis on scientific rationale; however, the petition process only applies to lines developed before the CIRM regulations first went into effect. Professor Rao wondered if the Committee should consider including a cutoff date as well. Dr. Magnus was concerned about using a cutoff date since it would be difficult to determine which one to use. Professor Greely suggested developing two versions of the proposed revision. One version would be more general and one would include the CIRM cutoff date.

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Public comments were then accepted.

Ellen Auriti expressed concern that the proposed revision was divergent from CIRM's regulations, which places a difficult burden on institutions attempting to comply with both standards. She also thought it might be problematic to have SCRO Committees making factual determinations about whether a cell line met the ethical requirements at the time of derivation. This might lead to SCRO Committees making different determinations. Professor Rao asked if, during the petition process, CIRM considers the issue of a line's scientific rationale simultaneously with the issue of meeting the ethical standards at the time of derivation. Dr. Lomax responded that the review process has to function and, therefore, once lines are deemed acceptable, they can be approved for use in different research contexts. Professor Greely offered alternatives, including setting up an administrative adjudicative process within the Committee or Department or requiring protocols to go through the CIRM petition process even if they are not CIRM funded. Neither option was desirable.

Lily Mirels questioned whether the proposed revision should require SCRO Committees to evaluate the rationale for using lines if they are already part of the approved list; there is more uniformity by following the approved list. Dr. Magnus commented that some of the approved lines did not have good informed consent and there should be an incentive for investigators to use lines with better consents. Ms. Mirels wondered then if ethically questionable lines should be petitioned for removal. She was concerned it would be complicated for SCRO Committees to assess and compare informed consents for various lines.

There was further discussion about what "scientific rationale" encompasses and if researchers will be driven to use lines with higher ethical standards in order to avoid the greater level of justification needed for substandard lines. Professor Greely felt the Committee was ready for a motion to use the substance of Dr. Magnus' proposal and develop a proposed revision to Section 6 of the Guidelines to be reviewed at the next meeting. The Committee agreed. Dr. Mangus was selected to lead the revision with the help of Professors Greely and Rao.

Agenda Item 4: Discussion on the impact that possible federal regulations for hESC research would have on current/future research projects and the Guidelines for Human Stem Cell Research

Professor Greely felt the Committee had already addressed this topic as much as possible given President Obama had yet to announce an official policy on hESC research.

Agenda Item 5: Discussion for revising the Guidelines for Human Stem Cell Research

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Professor Greely noted the agenda had several more items, but felt that they mainly dealt with one substantial issue: how should the Committee deal with induced pluripotent stem cells? Dr. Magnus and Professor Greely had developed two drafts of proposed amendments to the Guidelines with respect to the use of cell lines derived from somatic cells. Professor Greely's draft was an attempt to revise the Guidelines to be mostly consistent with CIRM. Dr. Magnus' draft took a different approach.

Dr. Magnus explained that his approach was based on the Department and CIRM having different scopes—CIRM's involves funding research while the Department's is focused primarily on providing guidance. He further felt that the focus of SB 1260 was on embryos and oocyte procurement, not on cells that are manipulated to be embryonic-like. For these reasons, he proposed changing the definition of "covered cell line" to include pluripotent cells that are derived only from embryos, instead of all pluripotent cells. One exception would be the transfer of neural-progenitor cells into the brain of a non-human animal. The carve out for this scenario already exists in Section 5(f) of the Guidelines, but the language would need to be changed from "covered cells" to "human pluripotent cells" in order to capture the use of iPSCs. Overall, he thought this approach was a bit broader than CIRM's but felt IRBs were equipped to review most iPSC research.

Professor Greely thought that Dr. Magnus' proposal took a significant step beyond just addressing the issue of iPSC research using somatic cells with substandard consent, except for the carve out for neural-progenitor cells. Legally the proposed revisions were in line with the Guidelines as statute does not require SCRO Committee review of iPSC research. Professor Rao asked if SCRO Committee review should be required for clinical trials using iPSCs. Dr. Blackburn mentioned that research is currently performed in which cancer cells are transplanted into non-human animal models and potentially those cancer cells could be made from iPSCs. However, it seems the primary ethical concern involves neural cell types used in clinical trials; therefore, the focus should be on neural cell types, not all iPSCs. Professor Greely and Dr. Martin also suggested there might be ethical concerns with implantation into early embryos of non-human primates, developing gametes with iPSCs for clinical use, and transplanting human cells into animals in a way that gives rise to human-appearing features.

Dr. Lo thought iPSC research was becoming more prevalent and expressed concern about downstream research projects since, often, the initial cell line derivation does not require oversight and consent to use the cells tends to be general. One example is the potential of somatic cells being used to derive iPSC lines that are used to create gametes for use in assisted reproduction. He recommended that a system should be developed that captures downstream uses in hESC research. Professor Greely summarized the specific ethical concerns already expressed about iPSCs and wondered if a checklist might be helpful for SCRO Committees that lists the iPSC activities that are of particular ethical concern, or whether SCRO Committees should review everything in case unanticipated sensitive issues exist that are not covered in the checklist. Professor Rao reiterated Dr. Lo's point that the initial research may not be sensitive, but that a researcher may want to use resultant cell lines downstream for

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sensitive research and would then lack adequate initial donor consent. So if there is not initially appropriate consent, then the situation of grandfathering cell lines comes into play again.

Dr. Lo explained that in the UCSF article they recommended researchers obtain permission to re-contact initial somatic cell donors. Dr. Magnus argued that iPSCs were not unique in the potential to be used downstream in ethically sensitive research. IRBs have had to address these issues for years. Professor Greely received clarification from Dr. Magnus that he agrees certain iPSC research downstream may require SCRO Committee review but that this type of review is unnecessary at the derivation stage. Dr. Lo returned to Dr. Magnus' point about whether ethical concerns should be different for iPSC research compared to other research involving biological materials that are being used for purposes other than their original intent. He thought that stem cell research tends to be more sensitive because it can involve cross-species use.

Dr. Magnus wanted to focus mainly on iPSC research, not necessarily concerns related to the use of pluripotent cells in animals. He was concerned that the current Guidelines were extremely prohibitive of iPSC research. Professor Greely wondered if researchers were inadvertently violating the Guidelines. Dr. Lo shared this concern and explained that if researchers do not have oversight upfront, then it is very difficult to obtain appropriate consent later.

Professor Greely pointed out that if it was useful to require oversight at the time of derivation of iPSC lines, then iPSC lines developed outside of California and used in California would have to abide by the Guidelines. If the focus is on the sensitive use of iPSC lines, then the location of derivation would likely not be an issue.

Pat Rodriguez noted that Section 3 of the Guidelines addresses the types of research that are prohibited. It was agreed that the wording in 3(c) and 3(e) would have to be revised to be consistent with Dr. Magnus' proposed revision to change the definition of "covered cell line".

Professor Greely summarized that the Committee, thus far, had discussed three approaches for resolving different potential problems.

- One is the possibility of requiring SCRO Committee regulation only of sensitive uses of iPSCs, which is Dr. Magnus' position, with the additions of what was discussed as constituting sensitive uses.

- The second issue is Dr. Blackburn's issue that transplanting iPSCs into animals is too broad a definition of a sensitive use because much research involving the transplantation of iPSCs into animals should not be considered sensitive use. Dr. Magnus pointed out that this also applies to embryonic stem cells and not just iPSCs. He supported the idea of carving out more narrowly what kinds of transplantation into animals require significant oversight for pluripotent stem cells, including embryonic and induced.

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- Third, Dr. Lo addressed the potential value and significance of creating a best practice for scientists to obtain more thorough consent at the derivation stage. The best practice would promote establishing informed consent at the derivation stage to avoid or limit downstream problems when researchers attempt to use cell lines for research not expressly included in the original consent.

To address the second issue, Professor Greely suggested revising the Guidelines to better define the types of transplantation into non-human animals that are considered ethically sensitive and should require SCRO Committee review. The first and third issues would require deciding how much and what types of oversight SCRO Committees should have.

Dr. Magnus reiterated that the current Guidelines are the same for both iPSCs and hESCs, which means some researchers are currently not following the Guidelines. He also thought the suggestion to address consent at the derivation stage would be a departure from the direction of CIRM's recent regulation changes. Dr. Lo clarified that the UCSF article does not call for more regulation, but rather poses the dilemma of reaching sensitive downstream research that does not fall neatly in a regulation framework. Dr. Magnus agreed this was an important issue but was not sure it could be resolved at this time.

Professor Rao asked if Professor Greely's proposed revision, more so than Dr. Magnus', addressed Dr. Lo's concerns since it still includes the regulation of iPSCs instead of completely carving them out. Then, if problems arise, it is possible to further revise the Guidelines. Dr. Magnus argued that the proposed revisions would have a similar effect. To be consistent with CIRM, Professor Greely's revision considers cell lines derived from de-identified somatic cells with certain confidentiality protections to be acceptably derived, which means the derivation process would not fall under SCRO Committee regulation. As most iPSC research involves lines derived from anonymized somatic cells, then most iPSC research does not involve issues of heightened consent. Therefore, by definition, the derivation stage for most iPSC research would not require SCRO Committee approval anyway (based on CIRM's recent regulation changes).

Professor Greely noted that the decision regarding the direction of the revisions will have workload implications for SCRO Committees. Dr. Lo suggested that researchers performing cell line derivations provide written notification to SCRO Committees and then the SCRO Committees could send researchers sample consent forms to help avoid downstream research consent problems. Dr. Magnus thought the Committee should distinguish between future research involving cell line derivation and research involving existing cell lines. Professor Greely agreed and noted that the Guidelines should be consistent, which they currently are not, with the CIRM regulations on allowing the use of existing cell lines. There seemed to be broad agreement from the Committee on allowing the use of these cell lines, but there seemed to be disagreement about whether to regulate the initial consent process.

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Dr. Magnus also pointed out that the Committee would still need to address the issue of payment for somatic cells, which CIRM is currently considering. He expressed concern, though, that attempting to parallel CIRM on iPSC research related issues would involve lagging behind CIRM's decisions. Instead, he suggested avoiding this problem by revising the definition of "covered research". Professor Rao thought this would apply for research using existing materials, but she felt Dr. Lo's concerns addressed research involving new materials and procurement such that researchers could incorporate additional consent requirements into their protocols. Dr. Magnus argued that IRBs should already be requiring researchers to use adequate consents, but Professor Rao was concerned that this was not happening and that IRBs would need to be required to implement additional consent standards. Dr. Magnus suggested requiring the highest informed consent standards for all tissue procurement, but noted this would be different from compliance with other requirements initially intended to apply to embryo procurement (e.g. limited reimbursement).

Professor Greely was unsure that this issue could not be resolved today, which meant the Guidelines would continue to be inconsistent with the CIRM regulations. Professor Greely called for a motion to adopt Dr. Magnus' proposed revisions to change the definition of "covered stem cell line" and change "covered" to "pluripotent" in Sections 3 and 9 of the Guidelines. During discussion of the motion, Ms. Mirels pointed out that Section 5(f) would also need to be revised to be consistent with the new definition by deleting "covered" from the first sentence. The Committee voted and the motion to adopt Dr. Magnus' changes was not sufficiently supported.

Professor Greely felt the Committee would be able to reach a consensus at the next meeting and determine how to limit jurisdiction over iPSCs to only those issues of particular ethical concern. Dr. Lo proposed another motion that the Committee move to be on record as supporting the use of human biological materials to derive new stem cell lines if there is specific consent from donors or the materials have been de-identified; this applies to both new derivation of iPSC lines and the definition of "acceptably derived". The motion passed unanimously.

Dr. Lo mentioned there was an inherent inconsistency between CIRM and CDPH standards with regard to donor payment because Proposition 71 restricts payment to donors in general, while statute applicable to CDPH only restricts payment for oocyte and embryo donors. Therefore, non-CIRM funded iPSC research involving payment for somatic cells is permissible. CIRM is currently working on this issue.

Dr. Lomax noted that, in addition to revising the definition of "acceptably derived", the Committee may also need to consider revising Section 6(e) of the Guidelines with regard to the conditions of derivation. Professor Greely agreed.

The meeting was adjourned at 1:45 PM.

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