

## **APPROVED MEETING MINUTES**

### **California Department of Public Health Human Stem Cell Research Advisory Committee October 1, 2008**

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

David Magnus, PhD  
Henry Greely, JD  
Bernard Lo, MD (phone)  
Bertram Lubin, MD  
Samuel Cheshier, MD, PhD (phone)  
Margaret McLean, PhD  
Radhika Rao, JD  
Otto Martinez-Maza, PhD  
Gregory Stock, PhD (phone)  
Elizabeth Blackburn, PhD (phone)

#### **CDPH**

Shabbir Ahmad, Manager, 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)  
Lori Cavanaugh, UCSF  
Jesse Reynolds, Center for Genetics and Society  
Leslie Spalding, American Society for Reproductive Medicine  
Shannon Smith-Crowley, American Society for Reproductive Medicine  
Justine Durrell

#### **Speakers**

Allan Robins, Novocell

#### **Agenda Item 1: Welcome and Introductions**

Dr. Ahmad briefly updated the Committee regarding the state budget's impact on the Maternal, Child and Adolescent Health Division at CDPH. He also summarized information about the human embryonic stem cell research (hESC) reporting forms (form HSCR1260-1) received from Stem Cell Research Oversight Committees (SCRO) by the HSCR Program. The HSCR Program received nearly 250 reports on hESC research projects. There were also two projects that intended to retrieve human oocytes for use in research, which will require future reporting in form HSCR1260-2. Dr. Ahmad noted that the HSCR Program had ordered copies of the newly revised National Academies of Science Guidelines for hESC Research and would distribute copies to the Committee members.

#### **Agenda Item 2: Approval of Meeting Minutes**

The meeting minutes from the Committee meeting on July 28, 2008 were approved.

Professor Greely then brought up a legislative issue relevant to the Committee. Senate Bill 1565 (Kuehl, 2008) was passed by the Senate and Assembly and would have impacted stem cell research activity in a variety of ways, particularly with regard to CIRM and its grantees. Professor Greely and Dr. Lubin, independent of the Committee, sent a letter to the Governor recommending he veto the bill. The reasons for this recommendation were similar to CIRM's; the bill was ultimately vetoed by the Governor. Copies of this letter were distributed at the meeting.

Professor Greely noted there were three remaining agenda items possibly requiring Committee approval and one (agenda item 6) requiring discussion of the ethical and scientific problems with the informed consent forms used in developing some of the NIH-approved hESC lines, as detailed in the Robert Streiffer article (published in the May/June issue of the Hastings Report). Professor Greely suggested the Committee discuss agenda item 6 first as Allan Robins of Novocell was present to address the consent form concerns with the lines developed by BresaGen, prior to its merger with Novocell. Additionally, Professor Greely was not sure that the Committee would necessarily vote on any actions this meeting, but would likely focus more on open discussion of the ethical issues related to the agenda topics.

**Agenda Item 6: Discussion on ethical and scientific problems with the consent forms for the NIH-approved embryonic stem cell lines**

Professor Greely noted that the informed consent concerns were primarily directed at the BresaGen lines and Cellartis lines. Professor Greely asked Dr. Lomax of CIRM to elaborate on the position CIRM was taking towards these lines. Dr. Lomax explained that CIRM sensed researchers were expecting CIRM to change its regulations so it released a statement clarifying that CIRM did not plan to revise its regulations and would remain consistent with the NAS guidelines. However, SCRO Committees can use their discretion in determining whether to approve or disapprove use of these lines. Dr. Lomax also noted that in the latest round of revisions to the CIRM regulations, the language has decoupled stem cell lines considered acceptably derived from authorized authority stem cell lines, such as from the NIH or HFEA. Dr. Magnus asked how CIRM would handle the situation in which an authorized authority began offering lines that were in conflict with the definition of acceptably derived. Dr. Lomax indicated that the demarcation in stem cell lines was to help address the issue that lines already accepted for use could continue to be used but that changes to the regulations would apply to lines used in future research projects. In an effort to address any future conflicts regarding stem cell line use, CIRM would have to use the usual process of regulation development.

Professor Greely briefly explained the concern expressed in the Streiffer article regarding the Cellartis and BresaGen lines. The Cellartis consent form was consent for culturing embryos for a few additional days and then destroying them; stem cell line development was not included. Similarly, the BresaGen consent form was a clinical consent for IVF treatment and did not address the potential for use in stem cell line development or research. Professor Greely indicated Dr. Magnus would update the Committee on the Cellartis lines, but first wanted Dr. Robins to further explain the consent process used by BresaGen.

Dr. Robins provided company background on BresaGen and described that BresaGen decided to begin isolating its own hESC lines as it was having difficulty growing the lines received from WARF. BresaGen drew up an agreement with an IVF clinic in Atlanta in which it agreed to use fresh embryos deemed unfit for reproductive use; BresaGen also developed a specific informed consent form for the clinic. Dr. Robins felt the consent form followed the existing research

guidelines except they were using fresh embryos instead of frozen ones. It was agreed that the form would be approved by an IRB before use.

BresaGen was able to isolate hESC lines within a few months and begin characterization. Concurrently, the Bush Administration was determining its stem cell policies. The NIH contacted BresaGen for information about the availability of its stem cell lines and mentioned the Administration may grandfather in existing hESC lines to the list of federally approved hESC lines. In anticipation of this decision, the NIH asked BresaGen for its informed consent forms/processes. The IVF clinic provided the form that was used, which differed from the agreed upon form. The IVF clinic explained to BresaGen that it did not want to put its patients under additional stress by having them sign more paperwork, but that it had globally consented the patients. Additionally, the IVF clinic explained in a letter to BresaGen that it did appropriately verbally consent the patients. However, Dr. Robins noted that there were inaccuracies in the letter so he could not assure the veracity of all the information in the letter.

BresaGen explained this situation to the NIH and the NIH decided to include the lines on the federally approved list. Professor Greely asked if BresaGen considered attempting to locate the IVF patients to obtain written consent. Dr. Robins explained that the IVF clinic anonymized the embryos and that it was not possible to locate and consent all of the IVF patients whose embryos may or may not have led to an hESC line. He also noted that BresaGen did not anticipate at the time of procurement that its lines would ultimately be distributed nationally and internationally. He postulated that BresaGen distributed about 120 lines themselves and then began empowering other centers to distribute its lines.

Professor Greely further inquired whether BresaGen had used an IRB for its intended informed consent form. Dr. Robins said they considered going through an IRB but decided against it for expediency and funding purposes. Dr. Lo asked if there are characteristics of the BresaGen lines that were particularly useful and if BresaGen had considered asking the IVF clinic to provide signed copies of the consent forms along with the embryos. Dr. Robins indicated that two of the lines make neuroectoderm very efficiently and that the lines are able to grow robustly. With regard to asking for copies of signed consent forms, Dr. Robins explained that the process of determining if embryos were unfit for reproductive purposes, transferring those embryos to the BresaGen staff stationed at the clinic, and beginning the derivation process occurred within a few days. Ideally, BresaGen would have required the signed copies, but the overall process of obtaining embryos and developing hESC lines happened very quickly (within a few months).

Professor Greely then turned to Dr. Magnus for an update on the Cellartis consent forms cited in the Streiffer article. Dr. Magnus indicated that Cellartis determined its initial consent forms were not adequate and re-consented everyone with forms that met the ethical standards of the time before beginning derivation of the embryos. While the initial concerns with Cellartis' forms were alleviated, Professor Greely acknowledged that BresaGen made reasonable efforts to obtain adequate consent and questioned whether this should impact the ethical status of the lines eight years later. He also questioned to what extent the Committee should be interested in this issue.

Dr. Magnus found it helpful to hear that the IVF patients from whom BresaGen received embryos had been verbally consented and appreciated Dr. Robins' honesty in pointing out that there were inaccuracies in the letter provided by the IVF clinic. Dr. Magnus suggested that it might be helpful for SCRO Committees, when confronted with ethically substandard hESC lines, to provide them with guidance on assessing the scientific necessity of using such lines versus other lines of higher ethical standards. He also suggested that researchers would have to provide scientific justification for using ethically suboptimal lines. Dr. Stock wondered whether

there were ways of going back to try to improve the consent used in developing the BresaGen lines and, if not, what were the dangers of keeping those lines active. He also questioned how SCRO Committees should evaluate the justifications provided for using ethically substandard lines. Professor Greely pointed out that, in the case of BresaGen, it would be very difficult at this point to locate and determine the potential IVF patients for re-consent. In addition to locating the possible IVF patients, it would require genotyping of the donors, which would be expensive and time consuming. Dr. Robins said that at this point those BresaGen lines did not have much commercial value. Invitrogen is currently using the BresaGen lines for genetic modification, but it is a small percentage of the company's income.

Dr. McLean revisited Dr. Magnus' point regarding researchers providing justification for using ethically substandard lines. She agreed that researchers should have to provide a good argument for using lines with a less robust informed consent process compared to lines with appropriate consent. Professor Greely commented that it is difficult to recommend action that might disadvantage parties, BresaGen for example, if they attempted to obtain appropriate consent. Dr. Magnus noted that it sounded as if the BresaGen lines were not necessarily of high commercial value to the company; however, if researchers are interested in using the genetically modified Invitrogen lines developed from the BresaGen lines, then they should have strong justification for using these lines versus others. He further pointed out that the judgment needed by SCRO Committees in evaluating if lines reach a certain ethical threshold was already the judgment they use in evaluating any research protocol.

Dr. Robins asked how neural progenitors derived from hESC lines should be addressed. Dr. Magnus thought that they too would need to be acceptably derived and should be evaluated based on their research value.

Professor Greely felt the discussion thus far did not necessarily lead him to think the guidelines should be amended, but he wondered if the Committee should consider developing a resolution or statement for SCRO Committees to consider that even if lines are grandfathered in by the NIH or UK, for example, they still have an obligation to evaluate any ethical issues associated with the lines. Professor Greely posed to the Committee to consider the process for it to develop a statement that would be available to SCRO Committees as advice and also to consider the content that would be in this statement.

Professor Rao thought it was a good idea to develop a statement for SCRO Committees. Although she could not imagine this scenario arising, she expressed concern about the situation in which a line would be selected purely for financial reasons. For example, lines with substandard consent might be less expensive and therefore more appealing to some researchers. Or the opposite situation may occur in which the developer of an hESC line knows the line has high research value and, therefore, charges a high price for the line. Overall then researchers should be required to give a good reason for using their selected lines and SCRO Committees will determine what constitutes a good reason.

Dr. Lo returned to the issue of balancing the scientific value of lines with their provenance. He suggested that the default should be to not use a line whose provenance is questionable and the more questions raised, the stronger the presumption not to use it. He also wondered if the strength of the reason to use a particular line could be framed differently, such as if the reason is plausible, convincing, etc., and how researcher convenience should factor into assessing the validity of the reason. Dr. Robins explained that for his company it is standard upon receipt of a frozen line to expand that into a master cell bank and to then use this cell bank for characterization. These steps are expensive and take about 8-12 months. From a convenience

standpoint, researchers would be loathe to repeat these steps with a new line if it was determined that the line being used was of questionable provenance.

Dr. Magnus added to the more nuanced approach of evaluating the lines by suggesting that the less concern there is with a line, the less justification will be needed for using that line. He also recommended that the value of or objections to a line be based on more than just the level of consent. He shared a colleague's argument that people's ethical concerns about hESC research can be broken down into two main issues, 1) people have concerns about using/destroying an embryo for research and 2) people have concerns about creating chimeras as they may pose a threat to human dignity. Professor Greely returned to Dr. Lo's earlier point and agreed with using a burden of proof concept in evaluating a line. He wondered if this should be advice that the Committee develops for SCRO Committees or whether this was at the discretion of the individual SCRO Committees to determine how to weigh the ethical issues of a line.

In response to this, Professor Rao asked Dr. Lomax if CIRM considered the issue of having researchers provide justification for using their lines. He explained CIRM has developed a petition process for lines that are not listed on approved registries. The petition seeks to gather information that is similar to the type of information the Committee is discussing. The application is then evaluated and brought before the ICOC for a vote.

The Committee discussed whether it should develop a statement or guideline for SCRO Committees and how that information should be distributed. The Committee agreed to develop a statement and have it posted on the HSCR Program website for public comment and also for more immediate advice to SCRO Committees. The Committee would then discuss at the next meeting the feedback received and finalize the document for distribution.

### **Agenda Item 3: Approval of revisions to Guidelines with respect to informed consent requirements for iPSC research**

Professor Greely moved on to agenda item 3 and passed out hard copies of draft language he had recently developed to address the informed consent requirements for somatic cells used in iPSC research that were not initially collected for stem cell derivation. Since the Committee and public had not had time to review the document, he suggested it be considered for the next meeting.

### **Agenda Item 4: CDPH technical amendments**

To be addressed at the end of the meeting.

### **Agenda Item 5:**

Professor Greely then moved on to agenda item 5 to more thoroughly discuss the implications of iPSC research for the CDPH Guidelines and whether it was appropriate to develop guidance on iPSC research since it does not involve embryos. He felt that, based on Dr. Magnus's earlier point, iPSC research did not raise people's concern regarding embryo destruction; however, people may be concerned about the potential for transplanting iPSCs into animals. He noted the 2008 NAS Guideline amendments recommend that iPSC research primarily be reviewed by IRBs/IACUCs, not necessarily SCRO Committees. He further pointed out that the CIRM regulations, by the definition of "covered stem cell line", incorporate iPSCs. Dr. Lomax

explained that the operational aspect of the regulation is whether there is intent to derive a covered stem cell line, which means iPSCs would fall under this definition.

Dr. Magnus felt the Committee's charge should focus primarily on embryonic stem cell research. He had concerns about using intent to define the types of research under the purview of the guidelines, in part because the burden of determining intent would be on the part of the researchers. He proposed revising the definition of "covered stem cell line" in the Guidelines from saying "a culture-derived human pluripotent stem cell population that is capable of sustained propagation..." to "a culture-derived human pluripotent stem cell population derived from a totipotent cell that is capable of sustained propagation..." He argued that since one of the main concerns people have is with regard to using embryos, this will limit the guidelines to only covering pluripotent stem cells derived from gametes instead of any pluripotent stem cells regardless of their source. He also suggested mirroring CIRM's informed consent language and providing this as a model to IRBs for good informed consent. For iPSC research then, SCRO Committees would act as more of a resource for IRBs.

Professor Greely had a concern with this scenario because iPSC research would not be required to be reviewed by SCRO Committees, who would be useful for addressing the pluripotent stem cell issues with which IRBs and IACUCs would likely not be familiar. Dr. Lubin noted that research involving human cells being placed in animals has occurred for decades and the review process for this type of research is very thorough. Professor Greely argued that IACUCs are primarily concerned with the welfare of animals and do not address issues of human dignity that some people are concerned with in the context of chimeras. Dr. Magnus felt that the main concern with chimeras stems from placing neural progenitor cells in animals; however, this concern is addressed with a carve out in the Guidelines such that SCRO Committee review and approval is required when neural progenitor cells are involved. Professor Greely had concerns that this carve out does not capture placing undifferentiated iPSCs into the brain of an early fetal mouse, which might raise similar chimera concerns.

For clarification, Professor Rao asked if Dr. Magnus was proposing that iPSC research be reviewed by IRBs/IACUCs and not fall under the Guidelines. Professor Greely said that the Committee could only suggest IRB/IACUC review but did not have the power to force this type of review. Professor Rao raised an additional concern to the two main ethical concerns discussed previously (destruction of embryos and creation of chimeras). She felt that the Guidelines also expressed concern over the commodification of the human body and that the embryo and chimera concerns did not necessarily incorporate this. Dr. Magnus argued that there was nothing ethically special about pluripotent research and did not feel there was a need for developing guidance on the issue of commodification and pluripotent research. Professor Rao suggested that neither totipotency nor pluripotency were necessarily the concern, but that because there is heightened public awareness surrounding this issue, commodification is likely more of a concern. Dr. Magnus felt that people were only concerned about hESC research, not iPSC research, and that the Guidelines should therefore focus on totipotency, not pluripotency, and bypass the informed consent issue.

Professor Greely did not necessarily agree that the trigger for informed consent should not be attached to the intention to develop a covered stem cell line. He felt that the issue might be resolved by making the distinction clearer for review committees instead of trying to remove the informed consent issue. Dr. Lomax explained that CIRM needed to revise its informed consent regulations because the old language posed a potential roadblock for iPSC researchers trying to replicate research if their original research involved anonymized somatic cells that then could not be used under the CIRM regulations. Dr. Lomax also noted that CIRM was in a different

position with respect to deciding whether to revise its regulations in light of the BresaGen informed consent concerns because its scope is narrower than the Committee's. Professor Greely mentioned that many of the proposals reviewed by Stanford's SCRO Committees have multiple funding sources and if CIRM is one of the funders, then the project has to follow CIRM's regulations. Additionally, some of the projects involving iPSC research also use CIRM funding, so a SCRO Committee would still be required to review these projects.

Dr. Magnus expressed concern about the informed consent issue with regard to the CIRM revisions because he thought it might be restrictive long-term to require too much information in the informed consent forms to help allay people's fears. Dr. Lomax clarified that the CIRM revisions include the informed consent language as applicable; therefore, not all of the listed consent elements in the regulations need to be in informed consent forms. Professor Greely commented that it is difficult to know who may eventually use a particular cell line and for what purposes.

Professor Greely encouraged further discussion of the Committee's thoughts on the iPSC issue. Dr. Lo emphasized the role of SCRO Committees in being able to handle issues in depth and felt that IRBs/IACUCs do not have the capacity to consider some of the human ethical issues that SCRO Committees are designed to evaluate. Dr. McLean felt it was important for the Committee to continue analyzing the ethical issues surrounding iPSC research, particularly since some people initially labeled iPSC as resolving the ethical concerns surrounding stem cell research. For example, she noted the safety concerns involved with using oncogenic viral vectors to derive iPSCs. Dr. Magnus agreed there were still ethical issues but wondered if these concerns were new or similar to what IRBs have historically considered. He also felt that those claiming iPSC resolves ethical issues were referring to removing the ethical concern of using and destroying embryos. Professor Greely noted that applicable Health and Safety Code *{insert here}* includes research involving embryos, and adult and fetal stem cells, implying the ethical concerns extend beyond destroying embryos. Dr. Lubin reiterated how quickly the field is changing and that, in general, the Committee will need to be ready to respond to those changes.

Professor Greely felt the discussion was very productive and asked if there were other iPSC issues to consider. Dr. Martinez-Maza wondered if IRBs would, in fact, be able to address concerns related to oncogenicity with iPSCs and whether Animal Review Committees (ARC) would be able to address chimeric concerns. Professor Greely did not disagree but felt it could not be assumed that IACUCs/ARCs would be involved in the review. Dr. Lo commented that it seemed like an integrated review might be necessary and one solution would be for the Committee to define what issues need to be covered overall and then give institutions the flexibility in determining the institutional framework for handling the review efficiently and effectively. Professor Greely thought this was an interesting approach and suggested Committee members write their views on the iPSC research issue and send them to the Department for posting on the HSCR Program website. He also felt it might be productive to organize a workshop on the issue, funded by outside sources not the Department. Dr. Lomax mentioned that CIRM was considering developing grants for conferences.

Professor Rao brought up one more issue regarding which review committee should review iPSC research. In the context of an institution with an IRB and no SCRO Committee that is interested in starting iPSC research, she wondered if Dr. Magnus' approach would be helpful to an institution in this situation because it would not have to create a SCRO Committee just to oversee the iPSC research. Dr. Magnus also mentioned that many smaller institutions do not have the expertise in-house to staff SCRO Committees.

Pat Rodriguez, CDPH legal counsel, offered a cautionary comment that the Committee may receive some pushback if it recommends guidelines beyond the scope of the statutes and developing a balancing test for informed consent issues may be difficult because the APA requires specific language to be used.

Professor Greely proposed continuing the iPSC research discussion at the next meeting. He then returned to Agenda Item 3 and asked the Department to present its technical changes to the Guidelines. Department staff indicated the change was in Section 11(c) of the Guidelines. Staff proposed making a correction to the section by replacing “covered research” with “human embryonic stem cell research”, as SCRO Committees are required to report only on hESC research, not all covered research. The Committee voted to approve the change.

The meeting was adjourned.