

**Empire State Stem Cell Board
Ethics Committee Meeting Minutes
December 11, 2009**

The Empire State Stem Cell Board Ethics Committee held a meeting on Friday, December 11, 2009, at the Department of Health offices, 90 Church Street, New York, New York. Commissioner Richard F. Daines, M.D., presided as Chairperson.

Ethics Committee Members Present:

Dr. Richard F. Daines, Chairperson

Fr. Thomas Berg

Ms. Brooke Ellison

Dr. Samuel Gorovitz*

Dr. David Hohn, Vice Chair*

*via video-conference

Dr. Robert Klitzman

Dr. Vivian Lee

Dr. Samuel Packer

Mr. Robert Swidler

Ethics Committee Members Absent:

Ms. Nancy Dubler

Rev. Maynard Hugh-Reid

Funding Committee Members Present:

Mr. Kenneth Adams

Dr. Bradford Berk*

Mr. Robin Elliott

Dr. Gerald Fischbach

*via video-conference

Dr. Bruce Holm*

Dr. Allen Spiegel

Ms. Madelyn Wils

Funding Committee Members Absent:

Dr. Richard Dutton

Department of Health Staff Present:

Mr. Marty Algaze

Ms. Bonnie Brautigam

Dr. Kathy Chou

Ms. Judy Doesschate

Dr. Matthew Kohn

Ms. Beth Roxland

Ms. Lakia Rucker

Dr. Lawrence Sturman

Dr. Ann Willey

Ms. Kathy Zdeb

Ms. Carrie Zolub

Special Guest Present:

Dr. William Lensch

Observers Present:

Ms. Lourdes Bahamonde

Mr. Matthew Bahamonde

Ms. Jean Ellison

Mr. Ed Ellison

Ms. Crystal Mainiero

Mr. David McKeon

Ms. Caroline Marshall

Ms. Katalin Polgar

Ms. Kristin Smith

Ms. Susan Solomon

Ms. Kelly Ryan

Approval of Minutes for the November 10, 2009, Ethics Committee Meeting

Dr. Daines directed members to the draft minutes for the November 10, 2009, meeting of the Ethics Committee included in their agenda books and asked for a motion to approve the minutes. Mr. Swidler so moved and Dr. Klitzman seconded the motion. The motion passed unanimously.

Update on Federal Policies

Dr. Daines turned the floor over to Ms. Roxland to provide members with an update on recent developments in national stem cell research policies.

Ms. Roxland advised members that the National Institutes of Health (NIH) approved the first stem cell lines for its registry for federally funded stem cell research. Eleven of the lines were from Boston Children’s Hospital and two were from Rockefeller University. Ms. Roxland advised members that there was a separate meeting held by an advisory workgroup that was reviewing documentation submitted by Harvard University to support the inclusion of another 28 lines on the registry. The workgroup recommended that one of the lines be rejected based upon an eight-month lapse between the Institutional Review Board (IRB) convening and the last review of the informed consent and research protocols used in the research project. She noted that the remaining 27 lines were accompanied by an informed consent document that stated that “the cells were to be used to study the embryonic development of endoderm with a focus on pancreatic formation, in which the long term goal is to rate human pancreatic isolates that contain beta cells for transplantation into diabetics.” Ms. Roxland explained that the advisory panel recommended that the lines be placed on the registry, but only for use in research authorized by the original donors. She noted that the NIH Director has yet to make a final determination on these lines. Ms. Roxland noted that some members of the panel objected to the limitation because the common rule allows other uses after the tissue has been de-identified.

Ms. Roxland informed members that documentation has only been submitted for one of the “presidential lines” authorized for use in NIH funded research during President Bush’s administration and that the documentation for two other presidential lines are in the process of being submitted. She noted that there has been speculation that the delay in the submission of documentation for these lines is due to confusion over whether the original researcher or the institution owning the patent is responsible for submitting the documentation.

The Committee then discussed the limitations contained in the Harvard informed consent forms and agreed that it would need to remain cognizant of these issues as it drafts model informed consent forms.

Presentation and Discussion: “Chimeras, Current State of the Science and Policy Considerations” by Dr. William Lensch

Dr. Daines reminded members that at the last meeting of the Ethics Committee members expressed an interest in understanding more about the types of chimeric or inter-species research that are being conducted currently. He advised members that staff contacted Dr. M. William

Lensch of the Harvard Stem Cell Institute at Brooke Ellison’s suggestion and that Dr. Lensch agreed to address the Committee and answer any questions that members might have.

Dr. Daines advised members that Dr. William Lensch is a distinguished instructor in pediatrics at the Harvard Medical School, faculty advisor for education at the Harvard Stem Cell Institute and a senior scientist in the laboratory of Dr. George Daley at the Children’s Hospital. Dr. Lensch is also a founding member of the Interstate Alliance on Stem Cell Research and has been quoted in publications ranging from the New York Times to the Salt Lake Tribune and Forbes Magazine. Dr. Daines then turned the floor over to Dr. Lensch.

Dr. Lensch provided the Committee with information regarding the proper terminology for organisms that are commonly referred to as chimeras and provided examples of the various uses of such organisms in scientific research. He advised members that a “hybrid” results from the fusing of two cells to make one cell, usually through fertilization. He stated that this creates a mixture of genomes at the DNA level so that any resulting organism has the genetic compliment of both of the original cells. He said that while some consider breeding the only way to make a hybrid, a hybrid can be made in other ways, including by inserting a single chromosome or gene into mouse embryonic stem cells. He explained that this technique can be used to understand the functionality of some of the genes on the chromosome and how they respond to various stresses and drugs. He noted that many experiments can be done on animals that would not be ethically acceptable if done on a human being and that the potential therapeutic and research benefit from this type of research is enormous.

Dr. Lensch advised members that the term “cybrid” refers to a “cytoplasmic hybrid.” He explained that a cybrid is created by removing the genetic material from the nucleus of an egg cell and replacing it with the genetic material from the nucleus of the cell of another species. Dr. Lensch said researchers in China have reported being able to create embryonic stem cells by inserting human genetic material into rabbit egg cells, but that no one has been able to repeat this experiment. In response to questions, Dr. Lensch advised members that although different labs have tried to do this using sheep and cows, they have not been successful. He suggested there may be some incompatibility between what is left behind in the egg cell when its genetic material is removed and the human nucleus being inserted. He also advised members that only a few labs are pursuing this because the process of nuclear transfer requires specific expertise and very expensive equipment. He said most researchers can use induced pluripotent stem (iPS) cells for experiments that could use cybrids.

Dr. Lensch explained that “mosaicism” is a term that is sometimes used synonymously with “chimera,” but it differs from chimeras in that it is the result of a single zygote in which some of the cells have made a different genetic contribution. He noted that Down’s syndrome is an example of mosaicism because some cells lose the extra chromosome 21 and end up chromosomally normal. He noted that individuals with Down’s syndrome can have different levels of chromosomally normal cells and that this can explain the reason for the great spectrum of developmental abnormalities and cognitive abilities in individuals with Down’s syndrome.

Dr. Lensch explained that a “chimera” is an organism that contains two or more genetically distinct populations of cells that are derived from two completely separate zygotes that come from two completely different fertilization events. Although the cells come together,

they each retain their own genetic identity. Dr. Lensch noted that chimeras can be intra-species or inter-species. He provided several examples of how chimeras have been used in research over the past hundred years and cited Dr. Peter Medawar's Nobel Prize winning work in tissue grafting and the discovery of acquired immunological tolerance that laid the foundation for being able to understand tissue matching for solid organ transplantation as evidence of the importance of chimeric research. Dr. Lensch also explained that when researchers insert human embryonic stem cells (hESCs) into a mouse to create a teratoma to verify pluripotency, scientists are creating a human-animal chimera.

Dr. Lensch then focused on the three most controversial types of chimeras: embryonic chimera, germ line chimeras and neural chimeras. He explained that embryonic chimeras raise concerns because when hESCs are injected into an early mouse embryo it is difficult to determine where those hESCs might wind up. He noted that the potential implantation of such an organism into an animal's uterus raises significant concerns.

Dr. Lensch advised members that chimeric experiments involving the germ line have been conducted for decades. He noted that there is interest in transplanting and fostering -- or understanding the biology of -- human germ cell tissue in part to address the potential for sterility in young boys who need to go through radiotherapy or chemotherapy. The concern raised by these experiments is that the animal could develop sperm that has human genetic material that you would not want used in breeding.

Dr. Lensch noted that experiments with neural cells are controversial because of the fear that cells might integrate into the brain of the animal and make them smarter or create a state that's ethically concerning. He said that when scientists have introduced cells at a later stage in development, they don't graft very well, but scientists have been able to increase the level of incorporation by damaging the tissue where the cells are inserted. In one experiment they injected human cells into a damaged portion of a chicken's spinal cord and were able to achieve incorporation into different areas of the central nervous system. The researchers were able to demonstrate that the cells were alive, metabolically active and integrated into the host. He said these types of experiments have helped scientists understand more about the capacity for human cells to develop into an integrated architecture in the central nervous system. He said this can be used as a platform to study development of the central nervous system and certain neural cell types, such as those that die in Parkinson's disease or are lost in other conditions.

Dr. Lensch noted that research involving humans and primates also create concerns for many. He observed that there seems to be an increasing level of concern as research involves species that look and behave more like us. Many feel that because primates are closer to humans behaviorally, there is a greater likelihood that scientists can push them into thinking and behaving like humans and that creates an ethically-concerning state for our species. He noted he does not hear about people expressing concern for the integrity of primates, so much as for the integrity of the human species.

Dr. Lensch noted that five factors impact the potential level of concern for chimeric research: 1. the species involved; 2. the stage of development when the cells are introduced; 3. the location of the injection; 4. the types of cells; and 5. the amount of cells injected. He noted that each of these variables, individually or collectively, can affect the level of concern.

Dr. Lensch provided the Committee with some information regarding the guidelines developed by the National Academies of Science (NAS) and International Society for Stem Cell Research (ISSCR). He noted that the NAS identified three different categories of research: research not requiring review by an Embryonic Stem Cell Research Oversight (ESCRO) committee, research requiring review and research that “should not be permitted at this time.” He noted that Dr. Richard Heinz, Co-Chair of the NAS committee that developed the guidelines, has gone to great lengths to make sure that people understand that the NAS guidelines are not a strict prohibition, but are guidelines that reflect the Committee’s thinking that such research is not a good idea at this time. He said the Committee anticipates having the ability to revisit these points in the future as more is learned.

Dr. Lensch provided some background on the 14 day rule articulated in many guidelines that allows human embryos to be maintained in a laboratory as long as it doesn’t develop beyond 14 days. He noted that there are no bright lines in development, but that there are different events that can impact an organism’s viability. For example, if fertilization doesn’t happen, there is no organism, or if implantation doesn’t happen or cardiac function doesn’t start, there is no organism, etc. He said the 14 day rule came out of discussions of the Human Fertilization and Embryology Authority (HFEA) in the United Kingdom. He said the primitive streak was identified as the first obvious visible distinction in a developing embryo where it starts to attain polarity. He noted that many other points in development could be picked, but that was where HFEA chose to draw the line and others have followed their lead. In response to a question as to whether there is a line when creating chimeras using primates, Dr. Lensch noted that the NAS guidelines are silent on research in fetal stages of primates.

Dr. Lensch advised members that he was an ad hoc member of an ISSCR committee that examined the issue of permissible versus non-permissible research for the ISSCR guidelines. He said that Dr. Ann McLaren encouraged participants to consider what could be some of the worst possible outcomes of stem cell research. She concluded that one of the worst things that could occur in human-animal chimeras would be for two animals, two mice, with human gametes to breed and allow the development of an early human embryo inside of a mouse. This was reflected in the ISSCR guidelines. Dr. Lensch also noted that since ISSCR was an internationally convened body and represented people from some countries that are not nearly as concerned with disposition of the embryo as people in other countries, a middle ground needed to be developed.

Dr. Lensch noted that there is not a lot of difference between the NAS and the ISSCR guidelines except the ISSCR is more liberal about being able to put cells into embryos as long as they’re maintained in vitro. He explained that the ISSCR committee questioned why it would be okay to maintain an embryo in vitro for 14 days, but that it would not be okay to have different forms of experimentation done on an embryo within the 14 day window as long as it is not allowed to incubate longer than that. He explained that is why the ISSCR guidelines ended up being different than the NAS guidelines.

Dr. Lensch ended his talk by addressing the issue of what people perceive as the problem if human cells contribute to an animal in a way that the animal attains an elevated state of consciousness or awareness. He said that many would argue that this is a good thing, as long as

you treat that animal with elevated respect and recognize that moral status. He suggested that this raised the question of whether an organism or entity should be shown an elevated level of respect based on the functionality of the organism or entity or because the organism is a member of a particular species. He noted that humans provide protections for homo sapiens regardless of whether they are brain dead, despots, criminals and the like and tend to conclude that being a homo sapien is enough to be warranted a certain level of respect. On the other hand, he questioned whether humans would stop an experiment on an animal if the animal asks for the experiment to stop. Dr. Lensch said most people would stop, but that it is difficult to determine when the animal has that capability. He cited Coco, a gorilla that could recognize over 2000 sign language gestures and had invented different signs to express what she wanted, as an example of an animal that might be able to express her wishes regarding experimentation. He noted that this was an animal that had not been experimented upon to elevate her level of consciousness. He concluded that some would argue that speciesism creates an arbitrary distinction; that you're just deciding based on a type of appearance. Dr. Lensch then offered to take any additional questions that Board members might have.

Mr. Swidler asked whether scientists have opposed any provisions in the ISSCR and NAS guidelines because they would bar or impede scientifically critical research. Dr. Lensch stated that some scientists take the position that if you have a scientifically compelling reason to do research, you should be allowed to do it; that science is amoral and that the morality needs to come from the individuals who practice it. He said that the committees developing the guidelines had the greatest difficulty when they were addressing the unknown. The committees did not want to be so prescriptive as to hamper the ability to move the science forward, but they also did not want to be too permissive in areas of significant concern. He noted that many of the guidelines were left vague intentionally to leave it open to interpretation and the expertise of members of the local ESCRO so that scientists would have the chance to make their case regarding the necessity and ethicality of the research.

Dr. Hohn asked whether the concerns about accidental breeding and mice carrying human embryos are carried over into Institutional Animal Care and Use Committee (IACUC) regulations. Dr. Lensch advised members that the IACUC is charged with taking care of the animals and that they are not specifically charged with monitoring aspects of the hESC research guidelines. However, he thought an IACUC would weigh in on the potential impact of accidental breeding on the animals themselves. He suggested that members of the IACUC may sit on the ESCRO committee to encourage a dialogue rather than being compartmentalized.

Ms. Ellison asked whether teratoma formation in mice is considered so routine that it should not be subject to ESCRO approval at this point. Dr. Lensch responded saying that he thought this was open to the interpretation of the local ESCRO. Some may want to review the experiment, some may just want to be notified of the research and others may decide that there is enough material in the canon of science that ESCRO review is not needed. He said he thought that most ESCROs would want to be informed of the research and may want to review experiments depending upon the novelty of the experiment, the type of cells involved, the location of the injection and the developmental stage of the recipient.

Fr. Berg asked whether there was any ethical boundary that would keep a researcher from attempting to perform tetraploid complementation in a human-derived host with iPS cells. Dr. Lensch noted that as tetraploid complementation is a functional test (i.e. do the “normal cells” combined with the tetraploid cells permit the generation of a viable organism), the primary concern is whether the result would be implanted and said that doing so would run counter to the spirit of the guidelines. He also said that he thought it would be very difficult to justify scientifically because you could potentially address the question using other means including animal cells. He said he didn’t think researchers should try to find a way to get around the prohibition in the guidelines by being clever with the experimentation.

Ms. Roxland inquired if there are any specific experiments that might be ruled out if the ESSCB adopted some of the more conservative positions expressed in the NAS or ISSCR guidelines. Dr. Lensch noted that the NAS guidelines would prohibit putting embryonic stem cells into human embryos and that some scientists have talked about conducting research in this area. He said those experiments would be allowed under ISSCR guidelines. He said that such an experiment could confirm that you have successfully reprogrammed an adult cell to be like a hESC and if you can insert that cell into an embryo and it divides in the embryo where hESCs come from and not in the outer layer. He said these types of experiments were discussed hypothetically and could provide better information on early development, malignancies and other relevant experiments. He stated that as long as you maintain the distinction that you can maintain an embryo in vitro for 14 days, he didn’t think it was egregious to do other cellular types of experiments on the embryo.

Dr. Klitzman inquired whether Dr. Lensch was referring to experiments that involved human or animal cells being inserted into the human embryo. Dr. Lensch responded saying that it was hard to make a distinction between putting human cells or animal cells into the human embryo as long as it’s not maintained more than 14 days in the lab. He noted that the distinction is focused on the disposition of that embryo and whether it is going to be implanted or just maintained in culture for up to 14 days.

Dr. Daines noted that while the dialogue could continue for hours, the meeting time had expired. He thanked Dr. Lensch for his informative and insightful presentation.

Adjourn

Dr. Daines then asked for a motion to adjourn the Ethics Committee meeting. Mr. Swidler so moved and Dr. Lee seconded the motion. The motion passed unanimously.

*s/ Judy L. Doesschate, Esq.
Executive Secretary to the
Empire State Stem Cell Board
Approved: May 3, 2010*