Empire State Stem Cell Board
Full Board Committee Meeting Minutes
December 17, 2010

The Empire State Stem Cell Board held a meeting on Friday, December 17, 2010, at the offices of the Department of Health, 90 Church Street, New York, New York. Dr. David C. Hohn, M.D., presided as Vice Chair.

Funding Committee Members Present:
Dr. David Hohn, Chairperson
Mr. Kenneth Adams
Dr. Bradford Berk*
* via videoconference
Mr. Robin Elliott
Dr. Mario Loomis
Ms. Madelyn Wils

Funding Committee Members Absent:
Dr. Richard Daines
Dr. Gerald Fischbach
Dr. Hilda Hutcherson
Dr. Allen Spiegel
Dr. Michael Stocker

Ethics Committee Members Present:
Ms. Jann Armantrout
Fr. Thomas Berg
Ms. Brooke Ellison*
Dr. Samuel Gorovitz
Dr. Robert Klitzman
*via videoconference
Dr. Vivian Lee
Rev. H. Hugh Maynard-Reid
Dr. Samuel Packer
Mr. Robert Swidler

Ethics Committee Members Absent:
Ms. Nancy Dubler

Department of Health Staff Present:
Dr. David Anders
Mr. Andrew Bentley
Ms. Bonnie Brautigam
Dr. Kathy Chou
Ms. Janet Cohn
Ms. Susie Han
Dr. Matthew Kohn
Ms. Beth Roxland
Ms. Lakia Rucker
Dr. Lawrence Sturman

Presenter:
Dr. Derrick Rossi

Observers Present:
Ms. Jennifer Becht
Mr. Joe Feldman
Mr. Mike Jolin
Ms. Elizabeth Misa
Ms. Caroline Marshall
Mr. David McKeon
Ms. Valeria Vavassori-Chen

Welcome and Introductions

Dr. Hohn called the meeting to order and welcomed Board members, staff, and the public. He introduced Ms. Jann Armantrout, the newest member of the Ethics Committee. Dr. Hohn then asked members and staff to introduce themselves and provide their title and affiliation.

Dr. Hohn stated that during the lunch break, several members had approached him to request special recognition of Dr. Daines and his extraordinary service and leadership, as well as his commitment to the stem cell cause. He indicated that Mr. Adams would propose a resolution, which Dr. Hohn would then ask the Board to ratify, in order that it be entered formally into the minutes.

Mr. Adams recommended a formal resolution to express gratitude to Dr. Richard Daines for his excellent service as leader of both the Department of Health and the New York State Stem Cell initiative. He noted that Dr. Daines had launched the stem cell program and gotten it to where it is today. Mr. Swidler moved that the resolution be ratified and Dr. Gorovitz seconded, adding the suggestion that a formal document be prepared, framed and presented. The motion passed unanimously.

Fr. Berg asked that special note be made of Ms. Roxland's important contributions to the Board and expressed the concern that she remain in her position. Rev. Maynard-Reid also asked that Mr. Swidler's invaluable service be recognized as well. All members concurred.

Approval of Minutes for the May 21, 2010, Full Board Meeting

Dr. Hohn directed members to the draft minutes of the May 21, 2010, meeting of the Empire State Stem Cell Board and asked for a motion to approve them. Dr. Packer so moved and Ms. Wils seconded the motion. The motion passed.

Program Updates

Dr. Hohn then asked Dr. Sturman to provide program updates. Dr. Sturman directed members to the current fiscal report. He noted that to date the program had initiated contracts representing 57 percent of the $342 million the Board had designated through 2010 to support stem cell research. Dr. Sturman stated that the Board has recommended 227 awards, totaling over $196 million. He noted that contracts would be executed shortly for general research and IDEA grants, Shared Facilities and Fellow-to-Faculty, representing a combined total of $64.5 million in additional funding.

Dr. Sturman advised the Board that the goal for early 2011 was to release Request for Applications in the following six categories it had already approved: consortia, general research, generic research and IDEA, short term faculty training for medical doctors, dentists and

veterinarians, teacher education and education for journalists. These would create a total opportunity of $116 million.

Dr. Sturman noted that the Board had been established by statute in the spring of 2007; successfully issued its first RFA in November of 2007; recommended funding awards by vote at its January 7, 2008 meeting; and developed the Strategic Plan by May.

The Board effectively used the Strategic Plan to guide distribution of research funds within defined categories during the first five years. He informed members that it would be appropriate to begin considering the next phase of strategic planning. Dr. Sturman noted that Dr. Stocker had chaired the first strategic plan workgroup, which included Dr. Spiegel and Dr. Varmus, and that Dr. Spiegel had agreed to chair the workgroup for the second strategic plan. Dr. Sturman said that Dr. Spiegel and NYSTEM staff will be recruiting additional people to serve on the workgroup.

Dr. Sturman informed members that NYSTEM's Annual Conference is scheduled for May 24-25, 2011, at the CUNY Graduate Center and will focus on accelerating therapeutic applications of stem cell science. He noted that the conference will include a panel discussion on the translational path from stem cell research to therapies and that other workshops will be held on Shared Facilities and on the education initiatives. The keynote address will be presented by Elaine Fuchs of Rockefeller University, who is the current President of the International Society for Stem Cell Research (ISSCR). Other confirmed speakers include Ihor Lemischka from Mount Sinai School of Medicine, Vivian Tabar from Memorial Sloan Kettering, Shahin Rafii from Weil Cornell University College and Gordana Vunjak-Novakovic from Columbia University. Dr. Sturman stated that the translation workshop panel discussion will be moderated by Steven Goldman from the University of Rochester and will include representatives from the Food and Drug Administration (FDA), industry and an expert in clinical trial design. Board members are invited and encouraged to attend the entire conference or particular sessions.

Dr. Sturman concluded by reminding the Board that the 2011 meetings are all scheduled for Mondays. He noted that the Ethics Committee will meet on March 7, May 23, September 12, and November 14, 2011; the Funding Committee will meet on March 28, May 23, September 26, and November 14, 2011; and the Full Board will meet on May 23 and November 14, 2011.

Report on Federal Litigation and Interstate Alliance in Stem Cell Research (IASCR) Meeting

Dr. Hohn advised members that Dr. Kohn and Ms. Roxland had attended the Interstate Alliance on Stem Cell Research (IASCR) meeting on October 19-20, 2010, which examined the legal and policy ramifications of *Shirley v. Sebelius*, as well as other related issues. He turned the floor over to Dr. Kohn to provide updates on activities in other states

Dr. Kohn advised members that Geoff Lomax, from the California Institution for Regenerative Medicine (CIRM), had informed attendees that CIRM now maintains a registry of

cell lines deemed "acceptably derived," of which 14 lines have now been reviewed and approved for use by CIRM researchers. These lines are independent of those approved by the National Institutes of Health (NIH) and all came from either the University of California, Los Angeles (UCLA) or the University of California, San Francisco (UCSF).

Dr. Kohn mentioned that CIRM developed guidelines for oocyte donation for research that appear in *Fertility and Sterility*. He noted that Robert Klein plans to ask Californians to approve another $3 billion to support the program. Dr. Kohn also stated that in August, CIRM received applications for their second Tools and Technologies for Translational Bottlenecks to support the inception, early stage development and evaluation of innovative tools and technologies to overcome current roadblocks in translational stem cell research. He stated that the awards would give grantees $1.2 million over three years, a $40 million total.

Dr. Kohn stated that CIRM had released a Targeted Clinical Development RFA that will fund the development of novel cell therapies derived from pluripotent stem cells with the goal of early stage clinical trials, Phase 1 and/or Phase 2 trials. He noted that CIRM intends to fund $25 million or 50 percent of the total cost, whichever is less, and requires 1:1 matching from applicants. Dr. Kohn reported that CIRM had just announced an RFA for their equivalent of our Generic Investigator Initiated Research Project (IIRP) awards as well as a second round of their Disease Team awards, with applications due in January.

Dr. Kohn stated that Dan Gincel, from Maryland, reported that his state's program had awarded $10.4 million in the past year for 40 projects, including 12 collaborations between industry and academia. Dr. Kohn noted that Maryland has supported two stem cell centers to date, with intentions to support a third in the near future at the University of Maryland's dental school. He stated that Maryland was beginning to prioritize regenerative medicine and established an agreement with CIRM to fund collaborations between Maryland and CIRM researchers that receive Early Translation awards.

Dr. Kohn advised members that Marianne Horn, who represented the Connecticut program, stated that Connecticut had awarded $9.8 million this past June and plans to make awards of $9.8 million each year through 2015. He noted that Connecticut will also be adding a Disease Team award similar to CIRM's, but with significantly less money, at $2 million per award. Dr. Kohn stated that CIRM has committed $20 million per award to its Disease Team awardees and that it will be interesting to see how Maryland and Connecticut leverage their smaller budgets toward regenerative medicine.

Dr. Kohn informed members that Heather Rooke from the International Society for Stem Cell Research (ISSCR) described its new website entitled, "A Closer Look at Stem Cell Treatments," which provides information to patients considering stem cell treatments. He stated that ISSCR is also establishing a process whereby people can request that a clinic be reviewed by ISSCR for patient safety, ethical practices and sufficiency of oversight. Dr. Kohn concluded by stating that funding for IASCR has been depleted and that Fran Sharples, from the National Academies of Science (NAS), hopes to be able to scrape together funds to support future meetings. He opened the floor for questions.

Dr. Klitzman questioned whether NYSTEM should offer more specific RFAs to foster treatments and clinical trials like California's. Dr. Kohn responded that NYSTEM's consortia RFA was designed to target specific diseases and encourage the development of therapies.

Mr. Elliott noted that while the Strategic Plan included clinical trials, they were often prohibitively expensive. He questioned whether involving industry could increase opportunities. Mr. Adams responded that there are many collaborations going on between technology and life science companies to foster economic development within New York State and that he has reviewed proposals with different scientific approaches. He offered to serve as an intermediary between the Board and the industry to foster future opportunities.

Dr. Hohn then turned the floor over to Ms. Roxland to report on the federal litigation discussion at the IASCR meeting. First she gave a history of the litigation to date, reminding board members that the Court of Appeals had reinstated the case as to a limited class of plaintiffs after the District Court had dismissed for lack of standing. Specifically, it found that the adult stem cell researcher plaintiffs had alleged a sufficient injury to sue by claiming that they faced increased competition for funding as a result of the change in NIH policy. The District Court then issued a preliminary injunction suspending funding of the challenged research. The Court of Appeals stayed the injunction and heard argument on the merits of the preliminary injunction. In the meantime, the parties briefed a motion for summary judgment in the District Court. Ms. Roxland commented on the unusual posture of the case, with litigation ongoing in both the lower court and the appellate court simultaneously.

Mr. Swidler asked whether the standing issue was in front of the appeals court at this stage. Ms. Roxland responded that it was not, but that the amicus briefs had nonetheless addressed it.

Fr. Berg questioned whether the preliminary injunction had halted NIH funding. Ms. Roxland responded that funding had stopped completely after the preliminary injunction was first issued, but that activity had resumed.

Ms. Roxland summed up by stating that the rulings from both the District Court and the Court of Appeals would be forthcoming. A brief discussion was held on the wisdom of the Board's submitting an amicus brief. Ms. Roxland's opinion was that the issues had been adequately addressed in the existing briefs and the Board could consider joining one of those.

Interim Report on Educational Initiatives Workgroup

Dr. Hohn then turned the floor over to Mr. Robin Elliott, Chair of the Educational Initiative Workgroup, to update the Board on the group's activities.

Mr. Elliott reminded members that the workgroup was initiated by Dr. Sturman to explore informal avenues of education to present stem cell research to the public. He noted that museums are a viable option that can target the largest audience and that a meeting was being

arranged to discuss a possible collaboration between NYSTEM and the American Museum of Natural History.

Mr. Elliott informed members that the second option is utilizing the internet and social media, and requested help with the online education portion. He noted that the group will be looking into ways to utilize NYSTEM's own resources to create an interactive, user-friendly website. Mr. Elliott then presented a brief slide show of a stem cell museum exhibit he had visited while in Newcastle, England.

He concluded by noting that the workgroup was expected to meet in January and would present to the Board at the March meetings.

In response to a question from Dr. Klitzman, Mr. Elliott advised members that a couple of million dollars were expected to be allocated for this initiative, which could fund some larger opportunities.

Presentation: Directing Cell Fate with Modified RNA

Dr. Hohn introduced Dr. Derrick Rossi and advised members that Dr. Rossi is an assistant professor in the Stem Cell and Regenerative Biology Department at Harvard University, where his lab examines the effects of aging on the function of hematopoietic stem cells. Dr. Rossi received a Bachelor of Science and Masters of Science from the University of Toronto and in 2003 received his PhD degree from the University of Helsinki. He did his post-doctoral training with Dr. Irving Weissman at Stanford University, and from there moved to the Immune Disease Institute and Cellular and Molecular Medicine program at Children's Hospital in Boston. He is the recipient of many awards for his work, including from the NIH, the National Institute of Aging, and the New York Stem Cell Foundation. After this introduction, Dr. Hohn turned the floor over to Dr. Rossi to address members on the latest advancements in stem cell reprogramming.

Dr. Rossi stated that his project was inspired by the induced pluripotent stem (iPS) cell technology developed by Dr. Shinya Yamanaka at Kyoto University in 2006. Dr. Yamanaka's groundbreaking work demonstrated that ectopic expression of four transcription factors could reprogram a somatic cell into a pluripotent stem cell. Dr. Rossi advised members that the long-term goal of this research is to generate patient-specific tissues and organs for transplantation. One key attribute of iPS cells in this arena is that because they come from the patient, if any product derived from them is transplanted back into the patient, there would be no risk of immune rejection.

However, Dr. Rossi advised members that there are a number of hurdles to overcome before iPS cell technology can be translated to the clinic. The first hurdle is the inefficiency of converting these cells into a pluripotent state, although that problem is manageable provided sufficient patient samples. The more serious concern is the use of viruses to deliver the reprogramming factors, which carry risks, both known and unknown. One method to avoid the use of viruses is by delivery of ribonucleic acid (RNA), although the delivery of unmodified

RNA triggers an interferon, or immune, response, as the target cells think they are being invaded by pathogens. Dr. Rossi then went on to explain his major contribution to the field of iPS technology, the use of RNA that has been modified to abrogate the interferon response. This modified RNA technology is advantageous in that it works with a wide variety of human cell types and, unlike viral infection; it is transient and does not result in changes in the genome. He stated that his team derived a number of iPS cell lines with this new technology, including from a cystic fibrosis patient. When these iPS cells were compared to human embryonic stem (hES) cells, the iPS cells had many of the same molecular properties as the hES cells. Dr. Rossi also briefly described trans-differentiation experiments, in which he demonstrated proof of principle by using a modified RNA to convert a fibroblast directly into a muscle cell.

Dr. Rossi concluded by stating that his modified RNA technology not only eliminates the hurdle of low efficiency, but also the risk of genetic mutations inherent in the viral approaches to generating iPS cells. Further, this technology can generate high quality iPS cells. Ultimately, this brings us one step closer to translating new discoveries in stem cell research into treatments for patients. Dr. Rossi then offered to take questions from board members.

Fr. Berg asked what dangers would be present if scientists were to use cells derived from this technology in a clinical trial. Dr. Rossi advised members that although they had overcome the hurdle of genetic mutations induced by viruses, the cells his lab produced were not generated in compliance with good manufacturing practice (GMP) and requirements of the Federal Drug Administration (FDA), which would render these particular cells unsuitable for patient use. He noted that when such research does not comply with GMP, there is a risk of viral transmission from animal to human cells, which could potentially create new diseases. Other researchers would have to do the work under GMP conditions before clinical trials could be contemplated.

Dr. Gorovitz asked how Dr. Rossi selects the RNA modifications to test. Dr. Rossi responded that his staff based their hypotheses on reports in the literature. He stated that they hoped to make the RNAs more stable yet, and eventually use sets of modified RNAs to treat patients directly.

Dr. Klitzman asked whether there is still a need for hES cells with the discovery of iPS cells and how essential hES cells are as a control. Dr. Rossi responded that most scientists would argue that hES cells continue to be needed as the gold standard benchmark against which all other pluripotent cells are measured. He also stressed that limiting the tools of researchers would not benefit patients.

Dr. Loomis asked if there was any evidence for genetic defects or effects on aging as a result of the cell fate changes induced by the reprogramming. Dr. Rossi responded that telomerase extends the length of chromosomes during cell division and DNA synthesis, and that the gradual loss of telomeres and telomere caps are believed to be an underlying cause of aging in many cell types. He noted that reverting cells to an hES cell-like state by making iPS cells reactivates telomerase, and further, that reprogramming cells from older people is much more challenging than from younger people and may yield cells of lesser quality.

Fr. Berg asked if mitochondrial DNA is an issue during reprogramming as it is thought to undergo modifications during aging. Dr. Rossi responded that mitochondrial DNA has not been well looked at, but a colleague of his at Lund University is actually addressing that very issue, although the research is at an early stage.

Dr. Hohn asked if the functional iPS cells have been introduced into diseased tissue. Dr. Rossi responded that accurately directing the differentiation of stem cells is still a work in progress; for example, scientists can derive cells that look like hepatocytes (liver cells), but these cells do not function properly.

Ms. Ellison asked if his RNA technique eliminated the epigenetic memory problem previously associated with iPS cells. Dr. Rossi responded by citing reports in the literature that iPS cells generated from a skin cell retained some epigenetic memory. Thus it might be easier to direct the fate of iPS cells toward their source of origin than ES cells because the iPS cells are primed to differentiate into that fate. He concluded that epigenetic memory in iPS cells is an outstanding issue and that there will be more studies on this subject in the near future.

Board members thanked Dr. Rossi for his informative and insightful presentation.

Adjourn

Dr. Hohn moved a resolution thanking Robert Swidler for his service to the Board and to the Ethics Committee, noting that it was always above and beyond the call of duty.
Rev. Maynard-Reid seconded and the motion passed unanimously.

Dr. Hohn then asked for a motion to adjourn the meeting of the Full Board.
Dr. Packer so moved and Dr. Klitzman seconded the motion. The motion passed.

s/ Janet Cohn
Executive Secretary to the
Empire State Stem Cell Board
Approved: May 23, 2011