

Empire State Stem Cell Board
Full Board Committee Meeting Minutes
November 14, 2011

The Empire State Stem Cell Board held a meeting on Monday, November 14, 2011, at the offices of the Department of Health, 90 Church Street, New York, New York. Commissioner Nirav R. Shah, M.D., M.P.H., presided as Chair.

Funding Committee Members Present:

Dr. Nirav R. Shah, Chairperson
Mr. Robin Elliott
Dr. Richard Gronostajski
Dr. David Hohn
Dr. Hilda Hutcherson

Dr. Mario Loomis
Dr. Michael Stocker
Dr. Allen Spiegel

Funding Committee Members Absent:

Dr. Bradford Berk
Dr. Gerald Fischbach
Ms. Madelyn Wils

Ethics Committee Members Present:

Fr. Thomas Berg
Ms. Brooke Ellison*
Dr. Robert Klitzman
*via videoconference

Rev. H. Hugh Maynard-Reid
Dr. Samuel Packer

Ethics Committee Members Absent:

Ms. Jann Armantrout
Ms. Nancy Dubler
Dr. Samuel Gorovitz

Department of Health Staff Present:

Dr. David Anders
Ms. Bonnie Brautigam
Dr. Kathy Chou
Ms. Janet Cohn
Ms. Susie Han

Dr. Matthew Kohn
Ms. Beth Roxland
Ms. Lakia Rucker
Dr. Lawrence Sturman

Observers Present:

Ms. Jennifer Becht
Dr. Dieter Egli
Mr. Joe Feldman
Ms. Elizabeth Misa
Ms. Caroline Marshall
Ms. Diane Mathis-Marr

Mr. David McKeon
Dr. Scott Noggle
Dr. Mahendra Rao
Mr. Edward Reinfurt
Ms. Susan Solomon

Welcome and Introductions

Dr. Shah called the meeting to order and welcomed Board members, staff, and the public. He introduced Dr. Richard Gronostajski, the newest member of the Funding Committee, and Mr. Edward Reinfurt, the new special liaison to the Board on economic development, from New York State Economic Development. He then asked members and staff to introduce themselves and provide their titles and affiliations.

Approval of the Document Honoring Dr. Richard F. Daines

Dr. Shah reminded members that it had been unanimously decided to present Mrs. Linda Daines with a framed statement in honor of Dr. Daines's contributions to the Board and directed members to the draft included in their meeting materials. He informed members that Mrs. Daines would attend the unveiling of Dr. Daines's portrait, scheduled for December 18, 2011, and that staff would present the Board's commemorative statement to her at that time.

Dr. Shah asked for a motion to approve the document for framing and presenting to Mrs. Daines. A motion was made and seconded. The motion passed unanimously.

Approval of Minutes for the May 23, 2011, Full Board Meeting

Dr. Shah directed members to the draft minutes of the May 23, 2011, meeting of the Empire State Stem Cell Board and asked for a motion to approve them. Dr. Stocker so moved and Dr. Klitzman seconded the motion. The motion passed.

Program Updates

Dr. Sturman directed members to the current fiscal report in their materials, noting that to date the Board had awarded \$196 million in contracts. He reported that the program had recently released four Requests for Applications (RFAs), which consisted of round three of the Investigator Initiated Research and IDEA awards, Consortia to Accelerate Therapeutic Applications of Stem Cells, Short Term Faculty Training Opportunities, and Research Training for Medical, Dental and Veterinarians worth up to \$25 million, \$80 million, \$1 million, and \$1.5 million, respectively. He noted that a Request for Proposals (RFP) for Scientific Oversight of the Consortia was also issued with the purpose of engaging teams of expert advisors to oversee progress on the consortia contracts.

Dr. Sturman stated that the Funding Committee has recently approved four RFAs: the Stem Cell Research Experience for Pre-College Teachers, another round of Institutional Training Programs, Public Education through Museums and Science Centers, and Stem Cell Science for Journalists, amounting to close to \$20 million earmarked for training and education. He said that there would be discussion later of a concept paper for an RFA to fund scholarly research on

subjects relative to Ethical, Legal and Social Issues and Education (ELSIE) at the Ethics Committee meeting.

Dr. Sturman advised members that Dr. Spiegel has been assisting staff in preparing the next strategic plan. He noted that two surveys were being drafted, which Dr. Berk had reviewed, to be sent to funded institutions and to principal investigators, to collect information demonstrating progress toward meeting program goals, including NYSTEM's impact on economic development.

Dr. Sturman noted that Stem Cell Awareness Day was October 5, 2011, and that the winning images of NYSTEM's annual stem cell image contest were selected for the 2012 calendar and posted to the website.

Dr. Sturman advised the committee members that beginning in 2012, the number of annual meetings would be reduced and would consist of two full board meetings each year, with the flexibility to add meetings as necessary. He stated that staff had scheduled a meeting of the full board and both committees for May 22, 2012, the day before the Annual NYSTEM meeting, with the second meeting to be held in November or early December. A special meeting of the Funding committee would likely be held in September if progress proceeds as hoped on the RFAs. Finally, he encouraged all board members to attend the Annual NYSTEM meeting to keep abreast of progress on NYSTEM-funded projects.

Federal and State Stem Cell Litigation

Ms. Roxland gave a brief history of the *Sherley v. Sebelius* litigation and reported that the trial court had granted defendants' motion for summary judgment. It rejected all of the plaintiffs' claims, including the claim that the new guidelines had violated the Dickey-Wicker Amendment. NIH has resumed funding the challenged research.

Ms. Roxland turned to the lawsuit brought against the Board by Feminists Choosing Life of New York, which alleged that the policy to compensate donors who provide eggs to be used in somatic cell nuclear transfer (SCNT) violated the provision of the NYSTEM authorizing statute which prohibits the funding of research involving human reproductive cloning. She reported that the state intermediate court had upheld the lower court's rejection of plaintiffs' claims. She stated that the court had deferred to the Board's interpretation of "human reproductive cloning" and found that it does not include "therapeutic cloning," in which SCNT is used to produce stem cells for research or therapeutic purposes. The court further found that the donor compensation program does not improperly make grant funds available to be "indirectly utilized" for human reproductive cloning. Ms. Roxland informed members that the plaintiffs had filed a notice of appeal to the state's highest court, but that the case would not necessarily be selected for review.

Conference Reports

Dr. Shah advised members that staff had attended several scientific conferences, which Dr. Anders, Ms. Roxland, and Dr. Chou would describe.

Dr. Anders reported that NYSTEM's 3rd Annual Conference was held on May 24-25, 2011, in New York City. He stated that the conference featured workshops, plenary and poster sessions, and a keynote address by Elaine Fuchs, the current president of the International Society for Stem Cell Research (ISSCR). Dr. Anders stated that the program also featured an education workshop convened by the Curriculum Development and Summer Undergraduate Internship awardees; a Shared Facilities session in which the new awardees described their projects; and a translation panel discussion by regulators, researchers and private industry. He noted that the program included 19 NYSTEM-funded speakers, including Viviane Tabar from Memorial Sloan Kettering Cancer Center, Gordana Vunjak-Novakovic from Columbia University, Shahin Rafii from Weill Cornell Medical College, and Ihor Lemischka from Mount Sinai School of Medicine. Dr. Anders concluded by stating that the next conference was scheduled to take place on May 23rd and 24th of 2012.

Ms. Roxland advised members that she had attended two conferences, held by the American Society for Bioethics and Humanities and the World Stem Cell Summit, and had made presentations at each on the subject of the Board's policies on oocyte donation and informed consent. Ms. Roxland noted that 1400 people attended the World Stem Cell Summit conference, which focused on translational research and featured a presentation by Rudolf Jaenisch.

Ms. Roxland reported that Massachusetts, in partnership with the United Kingdom, had established a stem cell registry and bank, leading Dr. Klitzman to inquire whether New York State should develop a similar facility. Ms. Roxland noted that the need did exist as the NIH would not list cell lines that had been derived in violation of its policies. Dr. Spiegel responded that Massachusetts's situation might be unique in that Dr. Doug Melton of the Harvard Stem Cell Initiative had derived numerous embryonic stem cell lines which were ineligible for the NIH's registry, and that nothing comparable had occurred in New York. Dr. Sturman noted that the topic of state involvement in cell banking and registries had been raised early on and the general view had been that it was not an appropriate function for state government.

Dr. Spiegel commented that the private sector had made strides in this area and noted that at the NYSCF annual meeting there had been a presentation about a small company in Madison, Wisconsin, which had developed a robust business of creating and banking a variety of stem cell lines and offering them to its customers. Dr. Klitzman responded that it would be interesting to learn more about the role and current activities of private industry in this capacity. Dr. Spiegel pointed out that Dr. Rao, who was present to make a presentation to the Board, was an expert on the subject. He also noted that as the field moves increasingly to developing therapies, the private sector will be particularly equipped to create cells under the stringent conditions the FDA will require for human testing, as opposed to a registry such as the NIH's, which exists to provide materials to investigators. Dr. Klitzman noted that it would help the Board's mission to learn more. Dr. Gronostajski added that there had been an excellent presentation on the subject at the NYSTEM Annual Meeting. Finally, Dr. Packer noted that while the role of industry is important, and while NYSTEM is not going to get into the business of making these products, it should be remembered that the pharmaceutical industry will focus on the products that bring in the biggest profits.

Dr. Chou reported that in October, NYSTEM staff and several board members attended the New York Stem Cell Foundation's sixth Annual Stem Cell Conference, which featured panel discussions on the future of regenerative medicine and the road to the clinic. Dr. Mahendra Rao, who was present today to speak to the full board, had been one of the panelists. There were also five scientific plenary sessions focusing on diabetes, cancer, blood disease, neuro-degeneration and spinal cord injury, and reprogramming technology; and that Dr. Dieter Egli, who was also present today to address the board, had given a featured presentation. Finally, the conference had concluded with a presentation by Dr. Peter Coffey, who was the first recipient of NYSCF's annual \$200,000 Robertson prize for his work using hES cells to treat age related macular degeneration.

Presentation: Reprogramming Adult Cells to the Pluripotent State

Dr. Shah introduced the first speakers, Drs. Dieter Egli and Scott Noggle of NYSCF. Dr. Egli is a senior research fellow at NYSCF and an adjunct associate research scientist in pediatrics and molecular genetics at Columbia University. He received his Ph.D degree from the University of Zurich and did his post-doctoral training with Dr. Kevin Eggan at Harvard University. Dr. Scott Noggle, NYSCF's Charles Evan Senior Research Fellow for Alzheimer's Disease and principal investigator, previously managed the Tri-Institutional Stem Cell Initiatives Derivation Core Facility at Rockefeller University after completing his post doctoral work. He obtained his Bachelors and Masters of Science degrees from the University of Arkansas at Fayetteville and his Ph.D from the Medical College of Georgia. He is also an adjunct associate research scientist in pediatrics and molecular genetics at Columbia University.

Dr. Egli described their recent work at the NYSCF laboratory. For the first time, researchers were able to show that human oocytes can reprogram a somatic skin cell nucleus into a pluripotent state and allow generation of pluripotent stem cell lines, using the nuclear transfer technique. Previous attempts had been stymied by an early blockade to development after nuclear transfer. Drs. Egli and Noggle discovered that by retaining the oocyte genome, rather than following the usual practice of removing it, they were able to prevent this developmental arrest, allowing for the production of stem cell lines.

The combination of the diploid genome from the somatic donor cell and the haploid genome from the oocyte resulted in stem cells which were triploid. These newly derived cells expressed all the markers typical of pluripotent stem cells and can give rise to different types of tissues representing all three germ layers. Further analysis showed that the triploid stem cell lines cluster closely with the control hES cell lines in gene expression profiles and that expression from the donor nucleus chromosomes is proportionally equivalent to that from the oocyte chromosomes, demonstrating their effective reprogramming.

Because they are triploid, these cells will not themselves be usable for therapies, but this breakthrough provides an avenue to identify the factors involved in the developmental blockade. Dr. Egli noted that understanding these factors should allow them to proceed toward their ultimate goal of generating pluripotent stem cells with therapeutic potential.

Dr. Loomis observed that the somatic nuclear transfer process was used to create Dolly the sheep and asked why the same process did not work with human cells. Dr. Egli surmised that the explanation was species-specific. He noted that hurdles remain, such as learning how to remove the egg genome without interfering with development. He described systematic approaches to overcoming this roadblock.

Dr. Klitzman asked why the presence of the oocyte genome allows developmental progression. Dr. Egli responded that it could be a question of efficiency, noting the need to look for other ways to increase efficiency. Alternatively, it could be that essential molecules associated with the genomes are removed with them. Ms. Ellison inquired about feedback to the breakthrough. Dr. Egli stated that it had been encouraging and mostly very positive.

Board members thanked Drs. Egli and Noggle for their groundbreaking work.

Presentation: Stem Cells and Translational Medicine

Dr. Shah introduced Dr. Mahendra Rao, Director of the NIH Center for Regenerative Medicine, and told members that Dr. Rao has worked in the stem cell field for more than twenty years, with stints in academia, government and regulatory affairs, and industry. Dr. Rao received his M.D. from Mumbai University in India and his Ph.D. in developmental neurobiology from the California Institute of Technology. Following postdoctoral training at Case Western Reserve University, he established his research laboratory in neural development at the University of Utah. He next joined the National Institute on Aging as chief of the neurosciences section, where he studied neural progenitor cells and continued to explore his longstanding interest in their clinical potential. Most recently, he spent 6 years as vice president of regenerative medicine at Life Technologies, Carlsbad, California. He also co-founded Q Therapeutics, a neural stem cell company based in Salt Lake City.

Dr. Rao expressed his gratitude to New York State for funding stem cell research, including important breakthroughs, which he will highlight in his talk. He stated that the theme of his talk will be the importance of coordinated activity in the field of regenerative medicine in surmounting the roadblocks that exist and added that these were his personal opinions, not the formal position of NIH. Noting that the field of regenerative medicine is quite active, Dr. Rao turned to his first slide, which listed publicly traded companies with stem cell products for sale in the market, with those relatively unregulated (like cosmetics) on the left and those subject to a great deal of regulation on the right. He noted that the chart distinguishes between autologous therapy and allogenic therapy because autologous therapy is more lightly regulated while allogenic therapy is more strictly regulated.

Dr. Rao stated that the field has changed quite a bit in the past few years and that he would focus his remarks on induced pluripotent cells (iPSC), which offer the possibility of personalized medicine as well as the option to obtain cells that could not be gotten easily from human sources otherwise. The process, he stated, begins with choosing a donor depending on the intended end product, selecting the kind of cells you want to use, following a set process with directed differentiation, and then taking your cells and deciding what to use them for, such as

basic science efforts like trying to discover disease mechanisms, screening for the pathways of existing drugs, or using the actual cells for clinical therapies which you will take to trial. The next slide showed a list of the different types of products with iPS cells in current clinical trials. Dr. Rao estimated that there are about 150 trials of these kinds ongoing, each supported by several pharmaceutical companies or universities.

Dr. Rao described the work his lab is performing and notes that parallel efforts were going on in New York under NYSTEM funding, such as Dr. Studer's initiative in which he has developed a radical new method for manufacturing Parkinson disease dopaminergic neurons; Dr. Sally Temple's group creating retinal pigment epithelium and retinal ganglion cells; and Dr. Steve Goldman's laboratory, among others, working on astrocytes and trophic support.

Dr. Rao then said that when you talk to all of these people you hear about several important roadblocks to creating successful therapies, which need to be addressed. These include limited federal government involvement due to legal, political and ethical issues; lack of a consistent regulatory policy; lack of uniformity of regulations, patenting and activities across countries; and the absence of standards and controls. There's been no business model for autologous therapies because established companies don't really know what to do with that, so it rests with the hospitals, which lack a business model. He also stressed the exceptionally high cost of goods needed for creating cells as compared to creating drugs. So our goal must be to think not just of the scientific breakthroughs which must occur but also the ancillary developments that need to take place so that these efforts can move forward.

Dr. Rao said he would talk about three categories of issues and the needed changes to get things moving: issues related to doing clinical trials; issues related to enabling technologies; and issues related to commercialization once you do have a therapy, such as whom do you partner with and how do you get this all done.

He said he would first discuss some problems which should be easy to solve, but require coordination, and then those which are more difficult. First, one that should be easy to solve but has become a big hindrance can be illustrated with a story. When Dr. Rao first came to the NIH he wanted to standardize some iPSC lines and make them available to the intramural program, which seemed easily accomplished as in the previous year alone the intramural program had created 81 lines. He was told there were only four lines which could be shared. This was because of a host of problems including the consent forms used, vectors used to make the lines, and issues related to patents and material ownership which came from the academic institutes, such as a prohibition against use for commercial products. But these can be solved by the institutions ensuring that the appropriate consent forms, distribution forms and material transfer forms are used so that cells can be distributed to a wider pool of investigators. Dr. Rao urged NYSTEM to insure this in the case of the work it funds.

The second piece, which is very important, is manufacturing support. The one big issue with iPSC work was in using integrating vectors. Regulations make it very difficult to get approval when animal products are used in humans. Several breakthroughs in the past few years have made that no longer necessary. We now know we can make them in feeder-free and xeno-

free conditions. Moreover, several places, including NYSCF, are making these lines by high through-put manufacture using banked tissues. Another important breakthrough has been the discovery that when you propagate the iPS cells long enough in culture, they will lose their memory over time. This is also true for the immune response problem, which is less when you differentiate the cells into more adult type cells.

Dr. Rao went on to describe two important scientific roadblocks that need to be solved before these cells can be produced for successful utility, which he suggested as topics for targeted funding.

The first roadblock is that there is no simple way of generating a pure population of differentiated cells using an efficient and clinically-compliant method. The second roadblock is the technical challenge of scaling the culture of pluripotent cells to the 96- and 384-well plates that allow for high throughput screening.

He then identified what NIH believes are important goals for agencies and institutes: the development of standards and controls which will be consistent among agencies; clear regulations for those in the field, like hospitals -- less familiar with regulation -- engaged in developing autologous treatments; outsourcing of cell manufacture after in house development of generalizable protocols; developing the right standards and controls; doing animal studies with Contract Research Organizations; running clinical trials at various hospitals; and thinking about who the commercialization partners will be. Dr. Rao pointed out that if you look at the FDA trials registry you will see that there are currently more than 150 mesenchymal trials. You will see that 90% are being done by academic investigators. “And how many therapies have been developed by academic investigators? The answer is: none.” Almost all are being done by companies. There is a great deal of effort but then the work is stalled because the academics do not know how to move it to the next stage. He went on to list current and potential breakthroughs for therapeutic approaches.

Dr. Rao concluded his talk by discussing what he believes that the funding and regulatory agencies should be considering. He suggested they continue to fund basic science, since that is what will lead to therapies. They must be careful of how they fund translational research so as to avoid the law of unintended consequences, and he told the story of having only one entity supplying embryonic stem cells with the goal of greater efficiency and how that led to a shortage. They must prioritize based on roadblocks and on where they see the greatest possibility for success. Otherwise, we could well end up with very broad, but very shallow knowledge. They must consider how to achieve synergy by forcing coordination and collaboration, as CIRM has done. He stressed the importance of public-private partnerships, and gave the genome sequencing experience as an example. There, by bringing companies in early on, commoditization drove down the price, making innovation possible. He noted that New York had many such promising companies. He also urged developing a model for personalized medicine.

Dr. Klitzman asked Dr. Rao to spell out with more specificity how the Board might assist in providing standards and regulation. Dr. Rao responded that regulations related to manufacture

are a big issue. Another need is developing assays which effectively measure safety and potency levels. He gave the example of hES cells causing teratomas and the lack of an assay for determining safe limits. Dr. Klitzman asked for Dr. Rao's suggestions on activities specifically for the Ethics Committee. Dr. Rao suggested that it focus on creating standard consent forms with explicit treatment of re-consent which contain unambiguous notice to donors that genetic anonymity can never be guaranteed; oocyte donation payments; and commercialization and the rights of donors.

Commissioner Shah asked Dr. Rao what he thought the Board should be considering for future endeavors in light of the state's particular strengths and NYSTEM's experience so far. Dr. Rao again urged that rather than try to cover the field, New York identify the areas where New York scientists have exhibited particular strength and build on that. Based on his knowledge of the publications, one area in which New York investigators have done is neural research and ALS.

Fr. Berg asked whether Dr. Rao believed that problems with tissue memory or barriers to epigenetic reprogramming would ultimately be show stoppers for iPS-derived therapies. Dr. Rao explained that he did not believe so. Fr. Berg asked when Dr. Rao expected to see trials involving human iPS derived products. Dr. Rao stated that for years his stock answer would have been ten to fifteen years, but things have moved so quickly of late that he expects we may see them in less time, perhaps as little as six years.

Dr. Spiegel raised some of his concerns about personalized medicine, including the length of time required to create a personalized, differentiated population of neural cells. He and Dr. Rao agreed that the window of time for therapy in the case of acute spinal cord injury, for example, was too short to wait.

In response to comments by Dr. Packer about the NYSTEM consent forms, Dr. Rao noted that if institutions and IRBs would collaborate to create and adopt uniform consent forms and policies, the life of the academic investigator would be far easier.

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

Adjourn

Dr. Shah then asked for a motion to adjourn the meeting of the Full Board. A motion was made and seconded. The motion passed unanimously.

*s/ Janet Cohn
Executive Secretary to the
Empire State Stem Cell Board
Approved: May 22, 2012*