

NYSTEM: Capitalizing on opportunities and confronting challenges

A report by the NYSTEM External Review Panel

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Executive Summary

NYSTEM has successfully raised the profile of New York State as a leader in stem cell biology and regenerative medicine. It has accomplished this by funding programs to recruit young talent and retain established leaders. NYSTEM has created impressive new facilities that have significantly expanded stem cell research and accelerated the development of new therapies. In addition, NYSTEM has helped to create a sense of community and collaboration among investigators and institutions in New York.

NYSTEM has funded an outstanding portfolio of research on both pluripotent and somatic stem cells that has complemented federal support in very important ways. Continuing NYSTEM support is essential to maintain the vibrancy of stem cell research and regenerative medicine in New York State and to capitalize on the extraordinary opportunities created by the investments already made.

Multiple NYSTEM programs have had considerable impact, particularly the Investigator Initiated Research Projects that fund basic science, the Shared Facilities and Institutional Development grants, the training grants for graduate students and postdoctoral fellows, and the consortia for the development of stem cell-based therapies. Going forward, for NYSTEM to fully realize the value of its investments it must be able to issue RFAs and fund meritorious projects according to a predictable schedule and in a timely way. The New York State contracting system has significantly delayed NYSTEM's ability to issue RFAs and to fund projects, significantly undermining the impact of the program.

The impressive group of consortia designed to advance regenerative medicine treatments is particularly important for NYSTEM and for New York State. A commitment to more sustained funding of the successful consortia will be necessary for New York to reap the full benefits of the current investment in these programs, to allow commercialization, and to develop new therapies.

Specific recommendations:

1. NYSTEM has had a tremendously positive effect on biomedical research in the state of New York, allowing researchers to make discoveries that have influenced the field of stem cell biology internationally. If NYSTEM funding ceases or declines in the next several years it will have a very negative effect on stem cell research in New York and on the perception of the New York stem cell community internationally. NYSTEM funding should be renewed when the current appropriation expires.
2. To increase the impact of NYSTEM investments, NYSTEM should have a predictable budget that can be spent according to a predictable schedule.
3. Executive functions of NYSTEM are carried out by a small, highly dedicated, and effective administrative team. NYSTEM staffing should be increased to have the capacity and senior scientific expertise to provide appropriate oversight of the peer review process, clinical consortia, and to critically evaluate NYSTEM programs. The new staff should have the expertise and ability to identify and implement programmatic changes.
4. The New York State contracting process has seriously limited NYSTEM's ability to accomplish its mission. NYSTEM should be able to issue RFAs, to review, and to fund proposals according to a predictable schedule with reasonable turnaround times, comparable to major science-funding agencies in other states. The rigidity of the current administrative, review, and funding processes are compromising program effectiveness.
5. All members of the Empire State Stem Cell Board should have relevant expertise in biomedical research, health care, patient advocacy, or health-related corporate experience. In addition, the membership should be re-balanced to increase the numbers of accomplished physicians and scientists with expertise relevant to regenerative medicine, to reinvigorate the Board and enhance its ability to make strategic decisions about the direction of NYSTEM and its investments.
6. The peer review process is flawed and should be revised to enable NYSTEM to engage the highest quality reviewers. Scientific leadership within NYSTEM staff should be strengthened to enable effective oversight of the peer review process. Standing committees, chaired by leaders in the area of stem cell research who play an active role in recruiting committee members, should be established to provide expert peer review. The standing panels should meet and consider applications on a predictable schedule, determined at least a year in advance, providing continuity to NYSTEM's peer review and grants making processes.
7. NYSTEM should have mechanisms that allow it to keep the public informed of its activities and accomplishments. Formal acknowledgement of NYSTEM funding should be required on all published materials resulting from NYSTEM supported activities, not just papers in scientific journals.
8. NYSTEM support has started to stimulate the launch of new companies in New York State and is expected to contribute long-term to the development of the state's regenerative medicine and biotechnology sectors. However, NYSTEM and the field of regenerative medicine are both too young to measure impact in terms of commercial success at this time.

Advancing stem cell research in New York State

NYSTEM has had a substantial impact on life sciences research in New York and increased the prominence of New York as a leading state in the nation's research landscape. Prior to NYSTEM's launch a modest number of outstanding scientists worked in the area of stem cell biology and regenerative medicine in NY. Today New York is a recognized leader in these fields with transformative research attributable to NYSTEM funding and published in top scientific journals. Beyond the specific research projects that were made possible by NYSTEM funding, which are addressed in more detail below, NYSTEM has promoted stem cell research and regenerative medicine in New York in several ways:

DEVELOPMENT AND RETENTION OF TALENT:

NYSTEM support was cited as important for the retention of internationally recognized stem cell researchers in New York. NYSTEM financial support was critical for the development of programs to translate stem cell biology into clinical applications by Drs. Sally Temple, Lorenz Studer, Shahin Rafii, and others. These are prominent scientists who further distinguish New York science through their leadership roles in international organizations such as the International Society for Stem Cell Research. NYSTEM was also cited as playing an important role in recruitment. NYSTEM funding has drawn investigators from other disciplines into the field of stem cell research as well as enabling the recruitment of new scientists to New York institutions. Since the start of NYSTEM funding the number of New York based investigators focused on stem cells and regenerative medicine has grown from 256 to ~470. The number of individuals working in stem cell laboratories at institutions supported by NYSTEM has more than doubled, to over 2000. Thirty-seven institutions across the state are funded by NYSTEM, demonstrating its broad impact on science throughout the state.

INFRASTRUCTURE: Approximately \$87M has been dedicated to the development of state of the art facilities for stem cell research. These investments were essential for advancing the work of individual investigators as well as the field as a whole. Three calls for shared facilities in addition to the initial commitment

to institutional development have resulted in 23% of the overall budget building technical capacity within New York institutions. This led to the creation of facilities such as a small molecule screening facility at Columbia University that almost certainly would not have been possible otherwise. Dr. Chris Henderson, who supervised that project, stated that it "has taken off beyond our hopes" and has fostered work in both the stem cell and cancer arenas. Further, facilities such as the Upstate Stem Cell cGMP Facility enable clinical cell therapies and create domain expertise for a rapidly emerging area of medicine. Finally, cores like the Neural Stem Cell Bank provide reagents to many investigators and foster collaborative interactions among investigators, providing a nexus for the exchange of ideas and results.

CREATING COMMUNITY: An ecosystem that fosters innovation needs a sense of communal purpose and opportunity. NYSTEM has worked hard to create both. Dean Allen Spiegel of Albert Einstein College of Medicine indicated that NYSTEM had engendered a sense of community and fostered collaborations among New York investigators and institutions. The consortium model was cited by a number of those interviewed by the External Review Panel (ERP) as an important mechanism by which individual investigators now interact regularly and work collaboratively toward a common clinical goal. The ability to involve investigators outside the state who can provide unique expertise toward a shared goal was cited as particularly forward thinking and valuable. Overall, NYSTEM has been able to bring together stem cell investigators through both meetings and funding mechanisms. It is viewed as a valued partner within the community and not simply a funding agency.

SUMMARY AND RECOMMENDATIONS: NYSTEM has successfully raised the profile of New York as a leading state in stem cell biology and regenerative medicine. It has accomplished this by funding programs to recruit young talent and retain established leaders. NYSTEM has created new facilities that have accelerated and expanded stem cell research and regenerative medicine within the state. NYSTEM has helped to create a sense of community and collaboration among investigators and institutions.

Advancing science and education

The changing scientific landscape

In November 1998 James Thomson and his colleagues revolutionized our ability to study human development and disease through the derivation of pluripotent stem cells from human embryos. The adoption of this remarkable technology was slowed significantly by a prohibition against using federal research funds for human embryonic stem cell (hESC) research. On August 1, 2001, President Bush, convinced of the scientific potential of hESC by scientists and disease advocacy groups, announced a compromise policy: National Institutes of Health (NIH) funding could be used to support research but only with lines that had already been derived. In the end only 21 lines satisfied this criterion, severely limiting the ability of investigators to pursue hESC research.

Recognizing the need to explore fully the scientific opportunities provided by hESC, New York State created the Empire State Stem Cell Trust Fund with a commitment of \$600 million. The program, New York State Stem Cell Science (NYSTEM), had three goals: filling the gaps in federal funding, expanding biomedical research in New York State, and exploring the social, legal and ethical aspects of hESC research. Thus, NYSTEM played a critical role in promoting hESC science in New York State and nationally. Of particular note has been support from NYSTEM for generating new stem cell lines that enhanced the diversity of available lines.

The Bush policy remained in place for eight years. In March, 2009, President Obama issued an executive order “Removing barriers to responsible research involving human stem cells” that directed NIH to develop guidelines for hESC research. Released in August, 2009, the new guidelines detailed the requirements for embryo donation consent and the process of determining eligibility for NIH funding. The first lines approved for funding under the new guidelines were placed on the NIH registry in December, 2009. Seven months later, a lawsuit seeking to prevent federal funding of hESC research put NIH support in jeopardy, shutting down federal funding for several weeks. It wasn’t until January 2013 when the Supreme Court

declined to hear the case that the matter was finally settled and ongoing federal funding was assured. NYSTEM support for hESC research was particularly important during this difficult time when the future of federal funding was hanging in the balance.

The scientific landscape of pluripotent stem cells research has changed significantly. When NYSTEM was created, only 21 lines were available for NIH funding. The NIH registry currently lists 303 eligible lines, of which more than 80 have mutations that cause disease, including muscular dystrophy, Huntington’s Disease, spinal muscular atrophy, cystic fibrosis and others. By exploring the biology of hESC, investigators developed methods for creating pluripotent human cells without using human blastocysts. Adult cells from skin biopsies, blood and other sources can be induced by several different strategies to become pluripotent and exhibit properties essentially identical to those of hESC. The technologies for creating induced pluripotent stem cells (iPSCs) allow investigators to study pluripotent cells from individual patients to understand disease pathogenesis, screen therapeutic agents, and potentially use them for tissue replacement.

NYSTEM has also invested in somatic, or so-called “adult”, stem cell research. Support for research on neural, hematopoietic, skin and other somatic stem cells is no less important than support for pluripotent stem cell research. In these times of declining federal investment in research, state support plays a critical role in maintaining the vibrancy of the biomedical research enterprise. As detailed below, the specific funding mechanisms used by NYSTEM have allowed projects to go forward that would have been very unlikely to be supported with federal funds. By creating a balanced portfolio of support for both pluripotent and somatic stem cell research, NYSTEM has the opportunity to accelerate the development of new therapies, no matter what cells they come from.

Although one could argue that the challenges in supporting research using pluripotent human cells that motivated the creation of NYSTEM no longer exist, the ERP believes that continuing NYSTEM support is essential. First, NYSTEM funding supports activities that NIH cannot, including derivation of new hESC lines. For example, a NYSTEM contract awarded to the New York Stem Cell Foundation led to the first successful generation of pluripotent human stem cells

after somatic cell nuclear transfer. Second, NYSTEM provides support for very ambitious goal-directed projects that are focused on therapeutic applications and moving hESC-derived and somatic stem cell-derived cells from the bench into patients. A total of six consortia have been funded so far. While in principle NIH could fund such studies, in practice it rarely does. Continued funding of these consortia is required to deliver new therapies as a result of the research funded so far by NYSTEM.

Finally, the availability of NYSTEM funding gives New York State investigators a real competitive advantage over those in many other states. Significant budget constraints have made NIH funding extremely competitive: while one in four NIH grant applications received funding between 1998 and 2003, now only one in 8 or 10 is funded.

SUMMARY AND RECOMMENDATIONS: NYSTEM has funded an impressive portfolio of research on both pluripotent and somatic stem cells that has complemented federal support in very important ways. Continuing NYSTEM support is essential to maintain the vibrancy of stem cell research and regenerative medicine in New York State and to capitalize on the opportunities created by the investments that have already been made.

Grant Programs

There was uniform consensus that overall the NYSTEM program has been remarkably successful. There was some variability, however, in the enthusiasm for different components of the NYSTEM portfolio. The NYSTEM programs included:

1. Investigator initiated research projects including targeted hESC and iPSC projects
2. Shared facilities, equipment/instrumentation, and institutional development
3. Consortia to accelerate therapeutic applications of stem cells
4. Training and career development programs
5. Programs in ethical, legal, and social issues and education (ELSIE) in stem cell research

Peer review services and consortium Oversight Panels are discussed later in this report.

1. INVESTIGATOR INITIATED RESEARCH

PROJECTS: This is the largest program within the NYSTEM portfolio. Since 2008 approximately \$161M has been awarded to support investigator initiated projects involving both pluripotent and somatic stem cells. There was high praise for this program, which not only advanced stem cell biology but also helped to develop and support a large and impressive cohort of stem cell researchers in New York State. The group of projects funded from these RFAs is comprehensive and diverse. The only concerns that were raised focused on the quality of the review process that selected the projects and the time lag between approval of a grant and disbursement of funds – important issues that are discussed elsewhere in this report. The ERP considered this grant mechanism to be a high priority for future investment.

2. SHARED FACILITIES, EQUIPMENT / INSTRUMENTATION, AND INSTITUTIONAL DEVELOPMENT:

Approximately \$87M was awarded to build an infrastructure capable of supporting the enhanced research programs sponsored by NYSTEM. There was uniform praise for this program. The ERP considered this grant mechanism to be a moderate priority for future investment.

3. CONSORTIA TO ACCELERATE THERAPEUTIC APPLICATIONS OF STEM CELLS:

Approximately \$74M has been awarded to fund six consortia. As discussed elsewhere in this report, this program is absolutely critical for achieving the fundamental goal of NYSTEM to use stem cell biology to treat human disease. It provides funds that are not otherwise available to accelerate the development of promising potential new therapies. The major concern expressed by people interviewed by the ERP is that insufficient funds have been committed to this program with too short a window of funding to allow the consortia to make major clinical advances. The ERP shares this concern and believes that follow-on funding of the successful consortia will be required for the initial investments to yield successful therapies. Thus, a major limitation at present is the absence of a plan for the selection of successful consortia and for the provision of additional funding that would allow them to deliver on their promise. The ERP considered this grant mechanism to be a high priority for future investment.

4. TRAINING AND CAREER DEVELOPMENT

PROGRAMS: NYSTEM released two solicitations of applications for training grants to support predoctoral and postdoctoral fellows (\$15M) and two solicitations for the development of faculty in stem cell biology (\$3.2M) as well as solicitations for short term training of clinicians and undergraduates.

NYSTEM training grants for predoctoral students and postdoctoral fellows provide a critical source of support for trainees to learn about stem cell biology while supporting research projects and creating a well-trained work force for New York State. Four such contracts were funded at Rochester, Columbia, Sloan Kettering, and NYU in July 2011 for 5 years. The awards are more flexible than NIH training grants since they provide up to 5 years of support for graduate students and postdoctoral fellows. They also support foreign trainees who are not eligible for NIH training funds, thereby allowing New York State investigators to recruit the best trainees independent of citizenship. The ERP considered this grant mechanism to be a high priority for future investment.

The Empire State Scholars career development program was modeled on the NIH K99/R00 career transition award that allows the most promising postdoctoral fellows to transition to independent faculty positions. While this was an excellent experiment, in practice two of the three fellows funded through this program left New York State to pursue research careers elsewhere. Their departures may partly reflect problems with the general RFA process (discussed below) and the amount of time that elapses between an RFA and the actual disbursement of funds. Fellows and junior faculty are not able to wait for the protracted NYSTEM process to fund them. The ERP would endorse such a program if the process for disbursing funds matched the career trajectories of fellows and junior faculty. Otherwise it will never fully achieve its goals.

Two additional programs were funded to introduce undergraduates or clinicians to stem cell biology and research. In 2010 NYSTEM funded three institutions, Stony Brook, Cornell, and Columbia, for 4 years to support undergraduate students for summer research experiences. The clinician training programs were initiated in January 2013 for 3 years: one for veterinarians at Cornell and one for dentists at Stony Brook. The

ERP believes that the undergraduate summer research program is not a high priority for future funding but that it is too early to determine the value of the clinician program.

5. PROGRAMS IN ETHICAL, LEGAL, AND SOCIAL ISSUES AND EDUCATION (ELSIE) IN STEM CELL

RESEARCH: Approximately \$4.3M was awarded to a series of programs focused on educational programs at the undergraduate and graduate levels and most recently for pre-college teachers. This is the NYSTEM program with the least evidence of impact and marginal enthusiasm on the part of individuals who were interviewed by the ERP. Programs were aimed at educating the general public, including a museum education program, teacher education, and a pending RFA for journalists. In the first two cases all the applications received were funded. While each award has a relatively modest budget, averaging less than 300K for the curriculum development, significant effort was required to develop each RFA, conduct the competition and process the awards. Thus, while the ERP felt that support for such public education programs is laudable, the impact of these programs did not warrant the effort, given the staff and budget constraints.

Included in the ELSIE grants was \$1.4M for the development of an undergraduate curriculum focused on stem cell research and its ethical and social implications. Five three-year contracts were awarded to New School, Columbia, University of Rochester, Syracuse, and Binghamton. Each program was aimed at distinct audiences and outlined different goals. Again, it is also not clear whether the impact of this program is worth the considerable effort required to release the RFA and award the contracts. The ERP considered these grant mechanisms to be a low priority for future investment.

Evaluation of progress and disseminating information about funded projects

Progress reports detailing the activities of awardees are reviewed by the NYSTEM staff as well contract administrators. For infrastructure awards, these include appropriate measures of the number of users, additional sources of support, resulting intellectual property, and related clinical activity. For the training awards, the number of trainees, the curricula

developed and the sources of additional support are reported. These are appropriate and useful measures. Overall, NYSTEM mechanisms for evaluation are ones commonly used in academic settings.

An issue for all NYSTEM awards is whether there is adequate public dissemination of information related to NYSTEM's accomplishments. The ERP recommends that formal acknowledgement of NYSTEM funding be required on all professional and promotional published materials derived from NYSTEM supported activities to better track the productivity of the State's investment, not just papers in scientific journals. It is also recommended that any discoveries that lead to clinical testing be tracked in the Principle Investigator surveys.

Requests For Applications (RFAs), reviewing, and funding proposals:

The most consistent and pervasive concerns raised about NYSTEM activities involve the RFA process. This includes the length of time to develop and issue RFAs as well as the time to award funds to successful proposals. The problems with the RFA process reflect a number of serious issues that must be addressed for NYSTEM to have an impact commensurate with its investment and to meet the standards set by similar funding agencies in other states:

1. NYSTEM staff must be able to develop RFAs themselves. As discussed elsewhere, NYSTEM is significantly understaffed and the staff does not include enough scientific/clinical expertise to formulate and sharpen the RFAs or evaluate the success of programs. It is a testimony to the commitment of the current staff that they have been able to produce such a diversity of important RFAs despite these limitations.

2. There are many bureaucratic hurdles including reviews at multiple stages that slow the RFA process, even after the Empire State Stem Cell (NYSTEM) Board makes recommendations on individual awards. This can add many months to the process. Consequently, the times required to issue RFAs and then to fund projects after peer review are each unreasonably long and unpredictable. Other state science funding agencies, such as the California Institute for Regenerative Medicine and the Cancer Prevention and Research Institute of Texas, have been able to issue and fund RFAs on a predictable cycle of reasonable length.

NYSTEM must as well to fully deliver on its potential to benefit New York State.

3. Each year a budgetary assessment is made by state budgetary officials as to whether sufficient funds are available to spend the entire legislative appropriation. In some years this has cut available funds by more than ten million dollars, or 20%, of the overall budget. Unpredictable changes in the budget from year to year undermine continuity and impact in the grants programs.

This ERP feels very strongly that it is critical to correct these problems. The summary list of recommendations outlines the steps necessary to enable NYSTEM research programs to flourish within the structure of the state government.

SUMMARY AND RECOMMENDATIONS: Multiple NYSTEM programs have had considerable impact in promoting stem cell research and regenerative medicine in New York, particularly the Investigator Initiated Research Projects that fund basic science, Shared Facilities and Institutional Development grants, institutional training grants and clinical Consortia to accelerate the development of new therapies. Going forward, NYSTEM must be able to issue RFAs and fund meritorious projects according to a predictable cycle of reasonable length, just like science funding agencies in other states. To accomplish this NYSTEM will require more staff with additional scientific and clinical expertise and must be freed of the bureaucratic burdens imposed by the state contracting system. NYSTEM should also have mechanisms that allow it to keep the public informed of its activities and accomplishments.

Advancing the ethics of stem cell research

NYSTEM has allowed New York State to play a leadership role at the national level in navigating ethical issues. NYSTEM provided funding for hESC research when there were significant constraints on federal funding, providing a clear endorsement of hESC research at a critical time. The NYSTEM Board took on the thorny issue of monetary support for egg donation for research and established the policy that women who donated eggs for research should receive compensation equivalent to that of women who donated eggs for in vitro fertilization (http://stemcell.ny.gov/sites/default/files/documents/files/ESSCB_Statement_on_Compensation_of_Oocyte_Donors.pdf). See also *Regenerative Medicine* 7:397-408).

To aid investigators, the Empire State Stem Cell Board Ethics Committee developed a model consent form for egg donation (<http://stemcell.ny.gov/esscb-forms>) as well as for embryo donation which was approved by the Funding Committee and posted on the NYSTEM website. Finally, the Board established the expectation that hESC research should be overseen by Embryonic Stem Cell Research Oversight (ESCRO) committees. These committees enable scrutiny of research that may not be under the purview of Institutional Review Boards. Thus, while NYSTEM “Programs in ethical, legal, and social issues and education (ELSIE) in stem cell research” appeared to have limited impact, leadership from the NYSTEM Board in the area of ethics has been groundbreaking. The ERP believes NYSTEM is most likely to have future impacts in this area through Board leadership.

Advancing clinical translation

A major stated goal of the NYSTEM strategic plan is to “translate basic research discoveries into new therapies and diagnostic methods for testing in early phase clinical trials.” It was recognized that translation of stem cell biology into the clinic would require large multidisciplinary teams and substantial financial support. To accomplish this goal NYSTEM solicited two rounds of proposals for consortia, each of which included both the basic science and the clinical expertise necessary for clinical translation of stem cell biology.

Three consortia were funded during the first round of reviews:

C028502 Oligodendrocyte progenitor cell delivery for restoration of function in multiple sclerosis:

Principle Investigator: **Burk Jubelt—SUNY Upstate Medical University**—\$12,126,645, contract start date 3/1/13

C028503 Developing a human ES cell derived dopamine neuron source for cell therapy in Parkinson’s disease:

Principle Investigator: **Lorenz Studer—Memorial Sloan Kettering Cancer Center**—\$14,904,226, contract start date 3/1/13

C028504 Retinal stem cell consortium: Principle Investigator: **Sally Temple—Regenerative Research Foundation**—\$10,805,636, contract start date 3/1/13

Three additional consortia were funded during the second round of review:

Vascular niche platform to expand hematopoietic stem and progenitor cells engineered to cure sickle cell disease:

Principle Investigator: **Shahin Rafii—Weill Cornell Medical College**—\$15,717,575, contract start date 7/1/15

Programming hematopoietic stem cells for long-term targeted T cell therapy in patients with relapsed ovarian cancer: Principle Investigator: **Kunle Odunsi—Roswell Park Cancer Institute**—\$11,922,885, contract start date 7/1/15

Commercialization of valproic acid expanded cord blood stem cells as allogeneic grafts for adults with refractory hematological malignancies: Principle Investigator: **Ronald Hoffmann—Ichan School of Medicine at Mount Sinai**—\$8,782,529.

The ERP was impressed by the exceptional quality of the groups of investigators in the consortia and by the exciting and realistic goals of the proposals. The decision to allow collaboration with scientists outside of New York State was a wise one that significantly enhanced the excellence of the program. The panel views these consortia as a critically important part of the NYSTEM program for several reasons:

1. The basic rationale for New York State support of stem cell research rests on the exciting potential of stem cell biology to provide treatments for currently untreatable disorders and to repair damaged organs rather than simply treating symptoms. But this

potential can only be realized through support of large multidisciplinary consortia that have the skills necessary for clinical translation.

2. These programs have great potential for commercialization.

3. They have the potential to enhance the lives of citizens of New York State and elsewhere.

4. There is no comparable mechanism for funding of such programs by the NIH, so the impact of NYSTEM funding in this area is particularly large and important.

5. Because there are few alternative sources for funding of such large translational programs, the NYSTEM consortium program has helped to retain leading stem cell biologists in New York. For example, when the ERP interviewed Dr. Lorenz Studer, an internationally renowned figure, he stated explicitly that the NYSTEM program is what prompted him to reject recruitment offers and to remain in New York.

6. By funding large clinical consortia that could not be funded otherwise, NYSTEM is boldly accelerating the development of new therapies.

However the panel also has several specific concerns:

1. Although the budgets of the consortia are relatively large compared to those of individual investigator grants, they fall far short of what will be necessary to make the therapies a clinical reality. The stated goals are to develop protocols for potential clinical testing and, in a few cases, to undertake phase I (safety) testing. However, no plans are in place to provide the resources required for more expensive preliminary testing of efficacy (Phase II). This is necessary to attract commercial and/or venture capital funding for the critical Phase III testing required for validation and FDA approval. The lack of sustained funding creates the risk that New York State could invest substantially in the creation of potentially world-leading clinical programs only to see these efforts dissolve later for a lack of follow-on funding.

2. There is no mechanism for ongoing critical review of progress on these contracts and/or re-investing in the most promising projects. NYSTEM staff lacks the scientific expertise and bandwidth to provide the necessary oversight or to make the strategic decisions that will be required in coming years to determine which consortia merit further investment. So far,

NYSTEM has had to outsource the expertise required to monitor the progress of consortia by appointing Oversight Panels. These Oversight Panels received mixed reviews. The selection of panel members was driven by the requirement for relevant expertise, as should be expected. In some cases, however, there was not appropriate sensitivity to investigators' concerns about potentially competitive relationships with members of their Oversight Panels. The utility of a panel would clearly be compromised if investigators are guarded in what they present. It is understandable that the NYSTEM administrative team as currently composed would not be aware of overlaps in research among panel members and investigators. The scientific expertise of the NYSTEM administrative team should be increased to enable critical in-house evaluation of the consortium Oversight Panels. While it will always be advisable to have advice from leading scientists from outside the state, NYSTEM needs to have the internal bandwidth and expertise to critically evaluate the progress of its consortia.

3. The science and the investigators in the consortia that have been funded thus far are very strong but they are all focused either on the nervous system or on hematology/oncology. Additional clinical targets should be sought to balance the NYSTEM portfolio.

4. It is unclear whether there is broad public or legislative knowledge of NYSTEM programs. In view of the importance of these translational programs, more public visibility is appropriate and essential.

SUMMARY AND RECOMMENDATIONS: The impressive group of consortia designed to advance the clinical translation of stem cell biology is particularly important for NYSTEM and for New York State. A commitment to more sustained funding of successful consortia will be necessary for New York to reap the benefits of these programs, to allow commercialization, and to help stem cell biology realize its potential to treat currently incurable disorders. NYSTEM needs to have the internal expertise to critically evaluate the progress of its consortia and to make strategic decisions about which to continue funding in the future.

Advancing economic development

Collecting and analyzing the data required to assess the economic benefits of NYSTEM was outside the purview and expertise of the current ERP. Recognizing the importance of such information, NYSTEM will commission a separate study. Nonetheless, several qualitative indications of economic impact are clear, beyond the direct investments made by NYSTEM in New York institutions. First, NYSTEM funding has facilitated the ability of scientists in New York to compete effectively for subsequent federal funding. Because of the failure of the NIH budget to keep pace with inflation and the automatic spending cuts that were implemented in FY2013 (sequestration), competition for NIH funding is more intense than ever before. NYSTEM funding allowed investigators in New York State to collect essential preliminary data for grant applications and to bridge programs successfully until federal funding could be obtained. Using NIH Reporter (<http://projectreporter.nih.gov/reporter.cfm>), a preliminary assessment of the NIH funding of the 13 investigators who received more than \$500K in NYSTEM funding from solicitation N08T revealed that after receipt of the NYSTEM award all 13 had NIH funding. For 11 of the 13, the NIH funding was significantly more on an annual basis than NYSTEM had provided. It is important to point out that NIH funding not only provides support for research in individual laboratories and the institutions that house them, but also for city and state; NIH has estimated that every dollar of NIH funding generates \$2.21 dollars in the local economy. Further analyses need to be performed of all the major funded programs to determine whether or not this preliminary assessment reflects the behavior of the entire program.

NIH uses the number of publications as a metric for project success and takes into account the impact factor of the journal. According to this metric, there has been no shortage of publications in high impact journals from research conducted in New York State with support from NYSTEM. Another set of indicators that may be more closely aligned with economic impact is the number of invention reports, patent applications, patents issued, and start-up companies

launched. When NYSTEM queried investigators, they reported 38 invention reports, 49 patent applications and 6 patents issued as well as 10 startup companies launched.

Although evidence of NYSTEM's economic impact is starting to emerge with the launch of new start-up companies, partly as a consequence of NYSTEM funding, the fields of stem cell biology and regenerative medicine remain very young. While new jobs and treatments would seem natural parameters by which to measure success, they do not fully capture the value in very early fields. Stem cell biology and regenerative medicine will succeed only if a strong foundation of discovery science organically matures to engage the commercial and clinical sectors. New York State is to be praised for its visionary support for building this foundation. That foundation will promote the long-term generation of jobs and new therapies, but cannot yet be evaluated according to those metrics.

SUMMARY AND RECOMMENDATIONS: NYSTEM support has started to stimulate the launch of new companies in New York State and would be expected to contribute long-term to the development of the state's regenerative medicine sector. However, NYSTEM and the field of regenerative medicine are both too young to measure impact in terms of commercial success at this time.

Governance

NYSTEM reports to the New York Legislature and the Governor through the Department of Health (DOH). Its activities are overseen by the Empire State Stem Cell Board that is chaired by the Commissioner of Health and vice-chaired by his/her appointee. This Board is broadly broken down into two Committees focused on Funding and Ethics. The number of Board members (beyond the Chair and Vice Chair) and the expertise represented on the Board has evolved over time. There are now 18 members on the Board, down from 24 at the time of the first Strategic Plan. Meetings of the entire Board now occur with reduced frequency (once in each of the last two years), though the Funding Committee (which approves spending) meets more frequently, up to 3 times per year.

Board composition: The early involvement of scientific leaders on the Board has waned as prominent scientists have resigned from the Board and not been replaced with others of comparable stature and experience. A number of stakeholders noted that political appointees with backgrounds unrelated to the field now comprise a substantial fraction of board members. Given the role of the Board in providing strategic direction for new initiatives and approving awards, it is essential that its composition is aligned with the mission of the organization. This is particularly critical in light of the limited capacity and scientific expertise of current NYSTEM staff.

SUMMARY AND RECOMMENDATIONS:

1. Re-balance Board membership to reinvigorate and improve its ability to strategically direct NYSTEM investments. We recommend that most Board members should be accomplished physicians or scientists in areas relevant to NYSTEM activities.
2. Require that all Board members have relevant expertise in health care, medical research, patient advocacy, or science/health related corporate experience.

Administration

Executive functions of NYSTEM are carried out by a small, highly dedicated, and effective administrative team. The administrative director, Janet Cohn, was widely praised for her dedication and tireless work in support of NYSTEM programs, staff, and investigators. The ERP shares this assessment. NYSTEM is fortunate to retain an individual with genuine commitment to the goals of the organization, who is effective as an administrator and communicator and who has the necessary sensitivities to keep a diverse set of stakeholders engaged. The other two members of the full time staff, each of whom have PhDs and stem cell research experience, were also of high caliber with demonstrated competence and commitment.

As noted above, the size of the administrative team is currently much too small for the scope of responsibilities they carry. The three-member team is expected to conduct activities ranging from the design of funding initiatives, to budgeting, to reporting and fostering relationships with multiple constituencies. It was striking to the ERP that even the processing of reimbursements and organization of our travel was the direct responsibility of one of the three overstretched administrators. The limited engagement of the Board has exacerbated this problem. While the team possesses exceptional competence, scientific depth and experience are limited. Adding staff with sufficient expertise and senior research experience in stem cell biology and/or regenerative medicine is highly recommended to further develop NYSTEM's ability to develop RFAs and evaluate programs without depending entirely on external advisors.

The rigidity of the current review and funding processes imposed by the state are compromising the effectiveness of the administrative team and the program as a whole. The dependence of NYSTEM upon the Wadsworth Center for extramural grants administration introduces additional delays and uncertainties in the timing of issuing and funding RFAs. Other major state science programs (the California Institute for Regenerative Medicine and the Cancer Prevention and Research Institute of Texas) have more substantial staffs and senior internal scientific expertise that allow them to issue RFAs and fund projects according to a predictable schedule.

The peer review process

Peer review of grant proposals to NYSTEM has been contracted out to the American Institute of Biological Sciences (AIBS). AIBS is a nonprofit 501(c)(3) association with multiple responsibilities and missions related to biological research and education. AIBS invited stem cell biologists from around the country to participate in the peer review process. The scientific panels largely adhered to the format for reviews used by the NIH and other established funding organizations. Nevertheless the ERP had substantial concerns about the process based on its review of the membership of the peer review committees, discussion of the process with NYSTEM funded scientists, and the first-hand experiences of one member of the ERP.

1. AIBS recruited scientists for the review panels largely by sending emails to a large number of individuals, soliciting their CVs and interest in participating. Such an impersonal and broad approach is highly unlikely to get responses from many leaders in the field. It contrasts with the approach taken by in-house staff at the NIH, the California Institute for Regenerative Medicine, the Cancer Prevention and Research Institute of Texas, and other such organizations that first identify the strongest potential peer reviewers and then make personal contacts to recruit them.
2. The ERP looked carefully at the rosters of scientists participating in the peer review process (which twice included an ERP member). While there were a number of strong and leading scientists on some of the review panels, many of the participants did not have the appropriate standing in the field to identify the most impactful proposals.
3. There was no continuity in the review process among the more than 40 review panels, and each round of proposals was assessed by different groups of ad hoc reviewers. There was not even continuity within subspecialty areas (e.g. cancer stem cells or neural stem cells) from round to round. Coupled with the unevenness of the credentials of the reviewers, this undermines the consistency and quality of the review process.
4. The limited NYSTEM staff does not have the in-house expertise to independently evaluate the results of the peer review process and to make

recommendations about potential funding of projects that just miss the “payline” but that would be important additions to the NYSTEM portfolio. There is also no one within NYSTEM who could independently evaluate investigator concerns about the quality of peer review.

Despite these concerns, the ERP was impressed by the quality and breadth of the grants that were funded by NYSTEM. This reflects the overall quality of stem cell biology in New York State, more than the ability of the peer review process to consistently select the very best science.

SUMMARY AND RECOMMENDATIONS: The peer review process is flawed and needs to be revised to enable NYSTEM to have the highest quality reviewers. Scientific leadership within NYSTEM should be strengthened to enable effective oversight of the peer review process. Standing committees, chaired by leaders in stem cell research who play an active role in recruiting committee members, should be established to provide expert peer review. The standing panels should meet and consider applications on a predictable schedule, providing continuity to NYSTEM’s peer review and grants making processes.

The budget and contracting processes

Funding new research projects is currently an extremely cumbersome process. NYSTEM takes a long time to develop and issue RFAs, in part because the process involves not only NYSTEM’s limited staff, but also the NYSTEM Board, and the Wadsworth Center, each of whom must approve aspects of each RFA. Currently, there is not a set schedule by which this happens, and the process can be delayed for reasons that have nothing to do with NYSTEM. Even after proposals have been peer reviewed and approved for funding by NYSTEM, the funding contracts must be approved by the institutions and then reviewed and/or approved again at multiple administrative levels by the state to ensure adherence to state contracting rules and regulations. As a result, it can take years for RFA development through to project funding. This impedes innovation and undermines the NYSTEM mission.

To put the severity of these issues in perspective, investigators and their institutions often complain about how long it takes for NIH to review and fund grants. While the normal NIH grant cycle from application to funding may take 9 months, release of the funds can occur within 90 days once a grant has been reviewed. The typical NIH funding cycle is thus much more predictable and much faster than NYSTEM. The California Institute for Regenerative Medicine and the Cancer Prevention and Research Institute of Texas are also able to operate according to predictable time lines with turnaround times at least as fast as NIH. The intent of the recently-instituted CIRM 2.0 funding mechanism is to revise their administrative procedures to significantly accelerate funding decisions, with a goal of reducing it to 4 months.

A final concern relates to the fact that research funding to institutions is provided as reimbursement after spending. Consequently, even though \$468M has been committed through State Fiscal Year 2015-2016 and \$354M has been awarded for research, only \$205M has actually been disbursed. This introduces additional administrative difficulties for investigators and their institutions.

For NYSTEM to achieve its promise it must have a predictable budget and predictable schedules for RFA release, peer review, and project funding. Without achieving these goals, support for stem cell research in New York State will remain uncertain in magnitude, timing, and accessibility, undermining the impact of the investment.

SUMMARY AND RECOMMENDATIONS:

1. NYSTEM has had a tremendously positive effect on biomedical research in the state of New York, allowing researchers to make discoveries that have influenced the field of stem cell biology internationally. If NYSTEM funding ceases or declines in the next several years it will have a very negative effect on stem cell research in New York and on the perception of the New York stem cell community internationally. NYSTEM funding should be renewed when the current appropriation expires.
2. To increase the impact of NYSTEM investments, NYSTEM should have a predictable budget that can be spent according to a predictable schedule.
3. NYSTEM staff should be increased to have the bandwidth and scientific expertise to provide appropriate oversight of the peer review process, to manage and critically evaluate NYSTEM programs. Staff should have the expertise and capacity to identify and implement programmatic changes.
4. NYSTEM should be extracted from the state contracting system so that it can issue and fund RFAs on a timeline that is similar to other major state science funding agencies.

How the External Review Panel generated this report

The External Review Panel (ERP) that generated this report included:

JOHN A. KESSLER, MD

Ken and Ruth Davee Professor of Stem Cell Biology
Benjamin Boshes Professor and Chair, Department of Neurology
Professor, Department of Pharmacology
Northwestern University

STORY LANDIS, PHD

Former Director, National Institute of Neurological Disorders and Stroke
National Institutes of Health

SEAN J. MORRISON, PHD (ERP Chair)

Mary McDermott Cook Chair in Pediatric Genetics
Director, Children's Research Institute
Investigator, Howard Hughes Medical Institute
University of Texas Southwestern Medical Center

DAVID T. SCADDEN, MD

Gerald and Darlene Jordan Professor of Medicine
Co-Director, Harvard Stem Cell Institute
Chief, Center for Regenerative Medicine, Massachusetts General Hospital
Co-chair and Professor, Department of Stem Cell and Regenerative Biology
Harvard University

The ERP held a series of conference calls and two in-person meetings. The in-person meetings and some of the conference calls included conversations with NYSTEM staff as well as NYSTEM stakeholders. The stakeholders included scientists funded by NYSTEM, leadership from institutions funded by NYSTEM, leaders of foundations or disease advocacy groups with an interest in NYSTEM, and NYSTEM board members. ERP members also examined a large number of documents related to NYSTEM activities and had additional phone and email conversations with NYSTEM staff to understand those activities.