Introduction

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This report provides an assessment of the state of stem cell engineering (SCE) globally. This is based on a yearlong study that was conducted by six panel members and managed by the World Technology Evaluation Center (WTEC). This opening chapter provides background for this study, outlines the scope of the study, identifies the six panel members, describes the study process, provides an overview of the principal findings, and finally states conclusions that hopefully provide the basis for stem cell engineering moving forward and for the acceleration of the progress being made in the broad field of stem cells.

Background

In the last 15 years, our knowledge of stem cells has increased, seemingly at an exponential rate. The result is that there is an ever-increasing arsenal of stem cells. This arsenal includes embryonic stem cells, various types of adult stem cells, and what are called induced pluripotent stem cells, i.e., iPS cells, that are reprogrammed from fully differentiated cells such as a skin fibroblast. A few years ago iPS cells were heralded as “a significant breakthrough” and this year the key scientists whose work resulted in this technology shared the award for the Nobel Prize in physiology and medicine. There still are many questions to answer in regard to these cells; however, it is clear that they provide a unique tool for the stem cell field. In addition, engineers have become increasingly involved in the area of stem cells, all the way from basic research to the variety of applications that are evolving.

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Concurrently there have been two other "streams of thinking" that have emerged. One of these is that of interdisciplinary research. The 2009 National Academies report entitled "A New Biology for the 21st Century" makes the point that to achieve the deeper understanding of biology necessary to address the major problems that society is facing will require not just breaking down the "silos" within biology itself, but incorporating chemists, computational researchers, engineers, mathematicians, and physicists into basic biological research. Furthermore, only through such an integration of disciplines will it be possible to address major society problems. There is no area of biology where this might be more true than that of stem cells.

A second "stream of thinking" that has emerged is that of translational research. Not only are Federal agencies in the United States interested in fostering the translation of bench-top science into a variety of commercial/clinical applications, but this also has become a priority for many states. Furthermore, what is happening in this area in the United States simply "mirrors" what is taking place in the rest of the world. It is thus timely that a global assessment of stem cell engineering be conducted, and it is such an assessment that is reported here.

What is stem cell engineering? As defined for the purposes of this study, it is not just tissue engineering and regenerative medicine, but the entire interface of engineering with the "world" of stem cells. It thus ranges from basic stem cell research to models and tools, to enabling and scalable technologies, to stem cell biomanufacturing and the development of stem cell-based applications and products. It is in this context that this global assessment was conducted and that is reported here.

A preliminary workshop on Stem Cell Research for Regenerative Medicine (RM) and Tissue Engineering (TE) was held at National Science Foundation (NSF) on February 1–2, 2007. It was sponsored by NSF and also by the National Institutes of Health (NIH) and it was facilitated by WTEC (Shoichet and Caplan 2007). The workshop speakers presented an overview of the research activities in North America. The workshop confirmed the increasing convergence of these research areas in the drive toward clinical solutions that will address the deterioration of various human tissues and organs impacted by injury or disease. The workshop revealed that, although substantial research has been accomplished, there was much to be done to meet any expectations for improvement in human health and for commercial success. It was also clear that there was much to be learned abroad—other nations have been making rapid progress while the U.S. research community has been handicapped by Federal restrictions.

Bibliometric studies show the skyrocketing interest in the field—from 360 papers worldwide in 2005 to almost 1,000 just 4 years later. Using this simple filter, the United States leads the world in stem cell engineering, but not by much as the European Union countries as a whole are essentially equal to the United States, as also is a group of five top Asian countries. There thus are clearly valuable opportunities to be learned from research taking place overseas.

In May 2010, the NSF and others funded the Second International Conference on Stem Cell Engineering in Boston, MA. The conference emphasized how research in stem cell biology and engineering can combine to aid in the development of stem cell therapeutics and bioprocesses. The goal of the conference was to accelerate progress towards innovative solutions to basic and translation problems in regenerative medicine. Topics emphasized how quantitative approaches could yield an increased understanding of the biological mechanisms that underlie stem cell fate choices, cancer stem cells, iPS cells, technologies to study stem cell function, and the development of bioprocesses to culture stem cells for commercial applications. This conference not only provided background for this study, but was followed by the Third International Conference on Stem Cell Engineering held April 29–May 2, 2012 in Seattle, WA.

Scope of the Study

The purpose of this study, funded by NSF and also the National Cancer Institute at NIH and the National Institute for Standards and Technology (NIST), was to gather information on the worldwide status and trends in stem cell engineering, i.e., the interface of engineering with the world of stem cells. The study panelists gathered hands-on information on stem cell engineering activities abroad that will be used by the U.S. Government to modify its own programs. This report intends to critically analyze and compare the research in the United States with that being pursued in Asia and in Europe, to identify opportunities for collaboration, and to suggest ways to refine the thrust of U.S. research programs. To obtain the intended benefits, this study focused on a range of issues in which the R&D occurring abroad will best inform our own Government programs and the research community of the challenges, barriers, and opportunities in SCE. The study panel developed and refined the scope of the study, with the guidance of the sponsors. The scientific areas of focus for this study include:

- Understanding and controlling the signals for cellular response
- Formulating biomaterial scaffolds and the tissue matrix environment
- Scalable expansion and differentiation
- High-throughput screening and microfluidics
- Real-time, non-destructive phenotyping
- Systems-based quantitative analysis
- Computational modeling approaches
- Biomanufacturing and bioprocessing
- Targeted delivery of stem cells

Beyond the technical issues, this report also intends to address to the extent possible the following broader issues:

- Mechanisms for enhancing international and interdisciplinary cooperation in the field
- Opportunities for shortening the lead time for deployment of new SCE technologies emerging from the laboratory

- Long range research, educational, and infrastructure issues that need addressed to promote better progress in the field
- Current government R&D funding levels overseas compared to the United States, to the extent data are available

Prior Work at WTEC

With core funding and management from the NSF Directorate for Engineering, WTEC has conducted over 60 international R&D assessments. Other U.S. Federal agencies have also provided funding for various WTEC studies: Department of Defense, the Department of Energy, several institutes at NIH, NIST, and most other NSF directorates. Recently, panels of experts assembled by WTEC have assessed Asian and European R&D in nanotechnology, human-robot interaction, brain-computer interfaces, catalysis by nanostructured materials, and simulation-based engineering and science. Full text versions of the final reports are available free at http://wtec.org. WTEC also compiles cross-cutting findings to help evaluate national positions in science and technology; a recent example is Shelton and Leydesdorff (2012).

Panel Members

A panel of experts (Table 1) proposed by the chair and nominated by the sponsoring agencies, conducted this study, using the WTEC methodology of peer reviews of research abroad, visiting the sites of the research institutions and researchers who are noted for the most advanced work in Asia and Europe.

Some biographical information on each panel member is provided in Appendix A. It should be noted, however, that Dr. Jeanne Loring who was selected to be the resident stem cell biologist also has considerable experience in the biotech industry. Furthermore, the four other panelists have each co-chaired the International Conference on Stem Cell Engineering. This started with Dr. Schaffer co-chairing the inaugural meeting in 2008, Dr. Zandstra co-chairing the 2010 meeting, Dr. Palecek the 2012 meeting, and Dr. McDevitt who has been selected to co-chair the 2014 meeting. This is clear evidence that these four engineering members of the panel are recognized leaders in the field of stem cell engineering.

Table 1 Panelists and their affiliations

Panelist	Affiliation
Robert M. Nerem (Chair)	Georgia Institute of Technology
Jeanne Loring	The Scripps Research Institute
Todd McDevitt	Georgia Tech/Emory University
Sean Palecek	University of Wisconsin
David Schaffer	University of California at Berkeley
Peter Zandstra	University of Toronto

Study Process

There were many components to the process used in this global assessment of stem cell engineering. This starts with the knowledge provided by each of the panelists, knowledge not only about activities in the United States, but knowledge each of them had about activities in other parts of the world. To this foundation was added the following four components:

- Site visits in Asia and Europe
- Workshops in Atlanta and in Seoul, Korea
- Participation in the 3rd International Conference on Stem Cell Engineering
- Virtual site visits

The process actually began with a "kick-off" meeting at the National Science Foundation in Arlington, Virginia on June 22, 2011. This was followed by a series of conference calls that led to the Asia site visits, which occurred in November of 2011. The Asia site visits were carried out with the panel dividing into two teams, one that conducted site visits in China and the other site visits in Japan. At the end of the week the two teams came together for a meeting at Narita Airport outside Tokyo before traveling back to the United States. The countries visited are shown on the map in Fig. 1 and the institutions visited are listed in Table 2.

The next event or component in the study was the workshop held at Georgia Institute of Technology, December 15–16, 2011 on the topic of "Stem Cell Biomanufacturing." This workshop was financially supported by both Georgia Tech and Emory University Woodruff Health Sciences Center as well as WTEC and the British Consulate in Atlanta. The participants numbered approximately 40 with a mixture of academics and industry individuals. It included participants from the United States, Ireland, Japan, Korea, and the United Kingdom.

On January 17th, 2012 a workshop was held in Seoul, Korea on stem cell engineering. This workshop did not involve the panel, with the exception of the chair of the panel who was co-organizer of this meeting. The workshop was help at the Korean Institute of Science and Technology (KIST) with the host being Professor Soo Hyun Kim. More than 100 participants attended, and this meeting provided the opportunity to assess activities in stem cell engineering in Korea.

Next came the European site visits, which took place from February 26 through March 3, 2012. Here again the panel divided itself into two teams, and the countries visited are shown in Fig. 2 and the specific institutions visited are listed in Table 3.

The next component to this study was the participation of the panel in the 3rd International Conference on Stem Cell Engineering held in Seattle, Washington, April 29–May 2, 2012. At this conference the organizers provided the opportunity for what in effect was a town hall meeting with discussion taking place not only among the panelists seated up front who each were asked to make brief opening comments, but also with members of the audience.

Just three weeks later, a workshop was help at the National Science Foundation in Arlington, Virginia. At this one-day workshop on May 24, 2012, the WTEC panel

Fig. 1 Countries visited (*black star*) and virtual site visits (*white star*) in Asia

Table 2 Sites visited in Asia

China	Academy of Military Medical Sciences, Tissue Engineering Research Center
China	Chinese University of Hong Kong (CUHK)
China	Fudan University, Zhongsan Hospital
China	Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences
China	Institute of Biophysics, Chinese Academy of Sciences
China	Institute of Zoology, Chinese Academy of Sciences
China	National Natural Science Foundation of China (NSFC)
China	National Tissue Engineering Center, Shanghai Jiao Tong University School of Medicine
China	Peking University, The College of Life Sciences
China	Shanghai Jiao Tong University, School of Medicine
China	State Key Laboratory of Bioreactor Engineering
China	Tongji University School of Medicine
China	Tsinghua University, School of Medicine
Japan	Keio University, Yagami Campus
Japan	Kyoto University – CiRA (Center for iPS Cell Research and Application)
Japan	Okayama University, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences
Japan	Osaka Univ. at TWMU (Kiro)
Japan	RIKEN Institute, Kobe
Japan	Tokyo Women's Medical University (Kano)
Japan	University of Tokyo, Hongo Campus, Department of Biomedical Engineering
Japan	University of Tokyo, Hongo Campus, Laboratory of Cell Growth and Differentiation
Japan	University of Tokyo, Komaba Campus, Research Center for Advanced Science and Technology
Japan	University of Tokyo, Komaba II Campus, Institute of Industrial Science
Japan	University of Tokyo, Shirokanedai Campus

Fig. 2 Countries visited (*black star*) and virtual site visits (*white star*) in Europe and Mideast

Table 3 Sites visited in Europe

France	Institute for Stem Cell Therapy and Exploration of Monogenic Diseases (I-STEM)
Germany	Berlin-Brandenburg Center for Regenerative Therapies
Germany	Fraunhofer Institute for Immunology and Cell Therapy
Germany	Institute for Medical Informatics and Biometry (IMB), Dresden University of Technology (TUD)
Germany	Life&Brain Center, Bonn
Germany	Lonza Cologne GmbH
Germany	Max Planck Institute for Molecular Biomedicine
Netherlands	Netherlands Initiative for Regenerative Medicine
Netherlands	Leiden University Medical Center
Sweden	Karolinska Institute and Karolinska University Hospitals
Sweden	Lund University Biomedical Centre (BMC)
Sweden	University of Uppsala
Switzerland	Basel Stem Cell Network (BSCN), University Hospital Basel and University of Basel
Switzerland	Laboratory of Stem Cell Bioengineering (LSCB), École Polytechnique Fédérale de Lausanne (EPFL)
Switzerland	Swiss Center for Regenerative Medicine (SCRM), University Hospital Zurich, and University of Zurich

Table 4 "Virtual" site visit reports

Australia	Stem Cells Australia
Iran	Royan Institute for Stem Cell Biology and Technology (RI-SCBT)
Korea	Workshop on Stem Cell Engineering
Korea	MEDIPOST, Co., Ltd.
Korea	Pharmicell Co., Ltd.
Portugal	Stem Cell Bioengineering Laboratory, Instituto Superior Técnico (IST)
Portugal	Instituto de Engenharia Biomédica (INEB)
Singapore	Bioprocessing Technology Institute
Singapore	National University of Singapore (NUS)

had the opportunity to provide through a series of oral presentations their assessment of activities globally. There were approximately 60 people in attendance; however, the audience was in fact much larger as the workshop was webcast, with 69 sites, an estimated 200 people around the world, looking at the presentations.

In addition to the above components, there were other mechanisms that are referred to by the panel as virtual site visits. This included site visits where information was gathered solely though the internet and/or by e-mail exchange. The term virtual site visit was also used for a site visit where only one panel member visited. The institutions/organizations that were assessed through virtual site visits are listed in Table 4.

There were some countries with active stem cell engineering activities that were not visited because the WTEC panelists believed that, through a variety of interactions, they had a reasonable idea of what was going on in that particular country.

One example is Ireland where, because of the close relationship between Georgia Tech and several universities in Ireland, considerable knowledge of stem cell activities already existed. Furthermore, Dr. Frank Barry from the National University of Ireland, Galway participated in the Atlanta workshop in December 2011. Another example is the United Kingdom. Here again there is a close relationship between Georgia Tech and Imperial College London. Furthermore, Dr. McDevitt has visited both Cambridge University and Loughborough University, and both Loughborough University and University College London were represented at the Atlanta workshop. A third and final example is Israel. The WTEC panel chair intended to visit this country at the end of March 2012; however, for personal reasons it was necessary for him to cancel the trip. Still because of the active participation of Israeli scientists and engineers in North American stem cell meetings, the WTEC panel believed that they had a reasonable idea of activities in Israel.

Finally, it must be noted that Canada has a particular concentration of stem cell engineering activity. Examples of groups include James Piret (University of British Columbia), Michael Kallos (Calgary), Eric Jeris (Waterloo), Peter Zandstra, Molly Shoichet, Julie Audet, Craig Simmons (Toronto) and Alain Grainer (Laval). A critical component in the establishment and growth of the Canadian stem cell engineering effort has been the availability of funding targeted specificity at bringing stem cell biologists and bioengineers together on both basic and translational research teams. Perhaps the best example of this funding strategy is the Canadian Stem Cell Network (www.stemcellnetowrk.ca), a federally funded National Center of Excellence (NCE) that has, over the last 13 years, invested over $42 million (not including partner cash and in-kind contributions) in interdisciplinary projects. These projects have in a number of cases been led by bioengineers and the work has benefited from this intimate interdisciplinary collaboration. The outcomes of the Stem Cell Network (SCN) are significantly greater than one would expect given the financial investment (962 peer-reviewed articles, of which 21 % appeared in high impact journals (impact factor >10), 399 patent applications, 60 issued patents, and 43 licenses granted). SCN-supported intellectual property has catalyzed the growth or launch of 11 start-up biotechnology companies and, critically, the SCN has also brought together teams around these basic discoveries and translational technologies to initiate nine phase I or II stem cell-based clinical trials. Globally across the SCN approximately 20 % of these activities have involved at least one engineer and one biologist/clinician. The Canadian government has continued to foster this interdisciplinary (and now multisectoral) activity with the recent funding of the Centre for the Commercialization of Regenerative Medicine (www.ccrm.ca), which is discussed later in this chapter.

Although the WTEC panel was able to see much of the stem cell activities going on around the world, they certainly did not see everything. They easily could have spent 2–3 weeks in both Asia and Europe, could have visited Australia, perhaps even India, and could have site visited activities in the Middle East. Even so, one can make the argument that the process outlined above in terms of the various components, as well as the knowledge base that each panelist had coming into this study, provided for a global assessment of this field of stem cell engineering. It is from this that the principal findings to be discussed next were derived.

Overview of the Report

In this section, the principal findings will be summarized. This section has been organized into four parts, representing the four chapters that follow, and then with some additional comments on translational models, education, opportunities for collaboration, and a brief summary of the status in the countries where an assessment of stem cell engineering was conducted, government policy, and conclusions. Appendix B has the detailed site visit reports from the 38 sites studied and Appendix C has "virtual" site visits from some additional organizations and laboratories. Also, a glossary of abbreviations and acronyms is given in Appendix D.

Engineering and Physical Sciences Principles in Stem Cell Research

The lead person for assessing this activity was Dr. David Schaffer, who has indicated that engineers be educated to do both analysis and synthesis. Through analysis one can identify key components of highly complex systems and then understand how these function collectively. From this one can also understand how the inputs from a cell's microenvironment can result in functional outputs.

Currently, it is well recognized by stem cell biologists that soluble components of the cellular microenvironment play important roles in regulating stem cell function including fate. Furthermore, many methods have been developed for controlling stem cells that involve serial or combinational application of a small number of factors, in many cases inspired by knowledge from developmental biology. What is not so widely recognized is the importance of biophysical cues in addition to those that are biochemical in nature. This is an area where engineers and the engineering approach can make a real contribution.

The engineering approach can also be used to develop novel systems that allow an investigator to pursue analysis by synthesis, i.e., the creation of new technologies and experimental systems that better enable basic investigations. An example is the development of innovative systems to control cell function, ones that can be used to monitor cells or that can be used in the separation of cells.

The microenvironments of stem cells are extremely complex in nature. The signals provided by a stem cell's microenvironment include complex networks of biochemical reactions as well as mechanical cues and electrostatic signals. Within this environment there are transport phenomena that must be taken into account. The engineering approach can contribute to the understanding of this complex microenvironment, ultimately to the engineering of synthetic niches for stem cells that provide the necessary input to result in the desired output. As an example, biomaterials can be engineered to be ideal platforms that can be used to elucidate principles by which biology controls stem cell function and fate. Furthermore, engineered biomaterials can be used to create culture systems for use in clinical translation.

High-Throughput Screening, Microfluidics, Biosensors, and Real-Time Phenotyping

The lead person for this part of our report is Dr. Sean Palecek from the University of Wisconsin, Madison. As he has pointed out, there are a number of challenges in engineering the stem cell microenvironment. These include identifying the factors that regulate stem cell fate and understanding the combined effects of different cues, constructing culture systems that apply the desired cues, and ultimately developing systems that allows one to direct the fate of stem cells.

High-throughput screening is an area where engineers and the engineering approach can make significant contributions. Challenges in this area include the designing of high-throughput cell analytic assays, systems that minimize false positives and negatives, and systems that allow for targeted screening. Such systems must be rapid, inexpensive, sensitive, specific and reproducible.

A technology that is taking on increasing importance in stem cell R&D is that of microfluidics. A variety of microfluidic systems have been developed, and such systems can facilitate the analysis of the dynamic response of stem cells to their microenvironmental cues, can be used to enable the isolation and analysis of clonal populations, and can provide proof-of-concept demonstration of the isolation of low abundance stem cells from a mixture of cells. Some of the challenges in the area of microfluidics include developing robust microfluidic culture platforms, incorporating integrated, real-time analysis, and the translation of microfluidic systems to commercial and/or clinical applications.

Another area is that of biosensors. Here stem cells can be a source for cells to be used in the creation of *in vitro* models of tissues. Using iPS cell technology, the cells could be either normal or represent a disease state. Such *in vitro* biosensors could be used in drug discovery for either drug screening or drug toxicity testing. Such systems are now called organ-on-a-chip, and these need to be designed to model tissue and organ level function in an *in vitro* microdevice. Important will be real-time analysis of the behavior of the system. If such systems can be engineered to provide in general a physiological environment, one that in many cases will need to be multicellular and have a three dimensional architecture, that may as a minimum supplement animal testing in the development of a drug and perhaps even replace it.

Computational Stem Cell Engineering

The lead person for this part of the report is Dr. Peter Zandstra from the University of Toronto. He has suggested that stem cell properties make these cells especially suitable for computational modeling approaches, with both fundamental and translational applications. An example is the rarity of stem cells in a population of cells. Because of this, signals may be diluted across many potential targets, the behavior of other cells may overwhelm that of the stem cells, and stochastic responses within a small population may be important determinants of behavior. Stem cells are rarely in equilibrium, and they are responsive to both local and global control. These characteristics are a challenge to experimental investigators, and the use of computational models together with experiments may help in unraveling the behavior of stem cells.

A variety of computational/mathematical approaches are being employed. These range from the use of differential equations, to Markov chains, to Boolean models, to Bayesian networks, to statistical mining. Questions that need to be answered include: does the model need to be deterministic or stochastic in nature? Is it a model of a single cell or of a population?

Computational modeling has the potential to emerge as a foundation to understanding complex systems such as stem cells. Computational models can provide tools for the design of experiments and novel technologies, can be used to predict system behavior and to devise methods for improving control, can provide novel insight into mechanisms, and can be utilized to both explore hypotheses regarding stem cell biology and to suggest the design of novel experiments. Computational models have already made a significant impact on the development of better ways to grow and control stem cells and have provided new fundamental insights into how stem cell fate decisions are made. The power of computational modeling in stem cell R&D will only increase with new and larger data sets and more sophisticated cell growth control strategies.

Stem Cell Bioprocessing and Biomanufacturing

The lead person from our WTEC panel in this fourth area is Dr. Todd McDevitt from Georgia Tech and Emory University. As defined by Dr. McDevitt, there is a slight difference between the term "bioprocessing" and the term "biomanufacturing." The former is the development of systems for the scalable growth and differentiation of stem cells while the latter is the implementation of bioprocessing for stem cell commercialization.

Current approaches have used formats and platforms optimized for biological engineering, i.e., where the cells are the vehicle for producing a product. They may involve systems engineered for optimal cell growth, but in general have a "hands on," manual processing of the various culture steps. The challenges to be addressed include the development of scalable culture systems, ones that scale "up," not "out," the incorporation of real-time monitoring, feedback control systems, and the development of robust, reproducible automated processes. All this is needed for the transformation of biomanufacturing from cells being the vehicle for the product to cells being themselves the product.

The issue of scale "out" versus scale "up" is an important one. If one has adherent cells and one wishes to increase the number of cells by a factor of 10, maybe even a 100, then one needs to increase the surface area by a factor of 10 or a 100. This at some point becomes impractical, and thus there is considerable need for suspension culture formats. Such formats include microcarrier beads with adherent cells on the outside of the bead, the use of cell aggregates either with or without materials, and the microencapsulation of stem cells. The use of suspension formats makes the significant increase in the number of cells much more doable.

Another issue is the multitude of parameters that are capable of affecting cell growth and phenotype. For process optimization there is a large experimental space that must be explored, and current high-throughput formats and screening platforms are inherently incapable of simulating bioprocess parameters.

Finally, stem cell manufacturing facilities need to be developed as closed culture systems with a miniaturized "foot print" and composed of modular elements. They need to incorporate real-time monitoring, feedback-based control, and learning-based algorithms. There thus are plenty of opportunities for engineers and the engineering approach to make a contribution to the further development of bioprocessing systems and to biomanufacturing.

Translational Models

One of the important aspects of this global assessment was identifying some of the interesting models that have been developed to translate bench-top stem cell science into clinical therapies and into commercialization. Four such models are listed below.

- Berlin-Brandenburg Center for Regenerative Therapies
- Cell Therapy Catapult in the United Kingdom
- Centre for Commercialization of Regenerative Medicine in Canada
- Tokyo Women's Medical University

The uniqueness of the Berlin-Brandenburg Center for Regenerative Therapies is that they do an opportunity analysis early in the development of a research project. There are three multidisciplinary platforms. These are basic science, biomaterials, and translation technology. Several of the groups within the Center are organized in a matrix structure, supporting the work of a particular host platform as well as those of other platforms by delivering basic technologies and principles. In addition, there is a Department of Clinical Development and Regulatory Affairs and a Department of Business Development. These support all projects within the center.

In the United Kingdom the Cell Therapy Catapult is one of seven such catapult initiatives established by the Technology Strategy Board of the U.K. government in order to create new industries. The Cell Therapy Catapult will support the development and commercialization of cell therapies and advanced therapeutics as well as the enabling technologies for manufacturing, quality control, and safety. It will be based in London, and it will be a center, independent of higher education institutions, but where academics, business, and clinicians can work together, focusing on the commercial development of innovative technologies.

In Canada, Dr. Peter Zandstra, a member of this WTEC panel, is the Chief Scientific Officer of the Centre for Commercialization of Regenerative Medicine. This is a federally incorporated, nonprofit organization supporting the development of technologies that accelerate the commercialization of stem cell- and biomaterials—based products and therapies. The business strategy is to enable unique translational platforms that address key barriers in regenerative medicine commercialization, integrate Canada's strength in stem cells and engage industry partners so as to make the Centre a global nexus for regenerative medicine commercialization.

Finally, at Tokyo Women's Medical University Dr. Teruo Okano heads the Institute of Advanced Biomedical Engineering and Science, and he has provided the leadership to create a unique activity. The focus has been on cell sheet tissue engineering, and the institute has partnered with the Waseda University's Graduate School of Bioscience and Medical Engineering. In 2008, the Tokyo Women's Medical University-Waseda University Joint Institution for Advanced Biomedical Sciences (TWIns) opened. There also is a partnership with Professor Masahiro Kino-Oka from Osaka University to develop a tissue factory for cell sheet manufacturing.

It is these four that are discussed in this report; however there are of course other models for translation. One of these is the Global Stem Cell and Regenerative Medicine Initiative recently established by the Korean Ministry of Health and Welfare as part of a national Korean strategy to exercise global leadership in the stem cell and regenerative medicine field. The operation and management of this initiative is being assisted by the Global Stem Cell and Regenerative Medicine Acceleration Center whose activities include strategic planning, project design, performance assessment, global networking, and many other supporting activities. This center has an international advisory board on which the author of this chapter has been asked to serve. The major focus of this initiative is on translational research to accelerate therapeutic development, clinical research aimed at the delivery of treatments, and infrastructure development to speed up commercialization. As this initiative is brand new, the exact details are still somewhat unclear; however, it will be interesting to see how this activity in Korea develops.

Education

It is clear to this WTEC panel that, for engineers to be accepted by biologists, they need to be viewed as understanding biological mechanisms and making a contribution to biology. Thus, for training programs to be successful, they need to include what might be called a "high level" of biology, and this is certainly what is done in the leading bioengineering programs in North America.

Outside of North America an excellent example of a unique training program is that at Loughborough University. The Doctoral Training Centre there was established with funding from the U.K.'s Engineering and Physical Sciences Research Council and in partnership with Keele University and with the University of Nottingham. There are more than 50 Ph.D. students in this program. The program introduces the students to the principles of bioprocessing and manufacturing and provides "hands on" research experiences with stem cells in existing and new, novel platforms. The intent is to train the future leaders of industry in the biomanufacturing area.

One of the outcomes of the Atlanta Workshop on Stem Cell Biomanufacturing was the agreement to establish an international school in the area of cell manufacturing. The initial offering of this school will be April 28–May 4, 2013 in Portugal. The school is being organized by faculty at Loughborough University in the U.K., Georgia Tech, and the Instituto Superior Técnico in Portugal; however, the participation of faculty, staff, and students from other universities also is anticipated.

Opportunities for Collaboration

Research today in general is very interdisciplinary in nature and this is true of biology and the stem cell field. This is certainly a theme for the National Academies report already referred to previously. As part of this, collaborations almost become a necessity. These might be with an investigator at one's own institution, somewhere else in the city, or even at a longer distance.

In today's world where research and the development of technology is done within the global community, collaborations can also exist between investigators in different countries. In fact, U.S. investigators need to leverage the excellence of activities in other countries, and it thus was encouraging for the WTEC panel members to see the hosts of the different sites visited being so open and very interested in the possibility of collaborating.

What is needed, however, if we are to encourage international collaborations are government programs that foster this. Included should be realistic levels of funding. Also, the review process needs to be one that uses a single review committee with membership from both of the countries sponsoring the program.

State of Stem Cell Engineering Outside of North America

Appendices B and C of this report contain the site visit reports for each institution. These site visit reports provide more detail than can be stated here; however, in the listing below for each country visited or in some other way assessed the state of stem cell engineering is briefly characterized.

Europe Sites

France: Observed some engineering involvement
Germany: Strong engineering involvement at the Berlin-Brandenberg Center for Regenerative Therapies and at the Fraunhofer Institutes

Ireland: A major stem cell center at NUI Galway with engineering involvement
Netherlands: A good integration of engineering with biology and medicine in NIRM
Portugal: Strong engineering involvement in bioprocessing
Sweden: Significant activity including translation into the clinic, some government funding, some engineering involvement of engineering and the physical sciences
Switzerland: Strong engineering and physical sciences involvement at EPFL and in Zurich and Basel (ETH)
United Kingdom: Major engineering activities, largely in bioprocessing and manufacturing

Asia Pacific Sites

Australia: A new stem cell initiative with the involvement of some engineers
China: Excellent young investigators, massive investments by the government, high impact biology, engineers involved in more traditional roles
Japan: A leader in iPS cells, engineering integrated with biology and medicine at Tokyo Women's Medical University, other engineering activities more independent
Korea: Significant activities with major government funding, a number of start-up companies, some engineering involvement
Singapore: Excellent Bioprocessing Technology Institute with engineering involvement

Other Countries

Iran: A major stem cell research institute but limited if any engineering involvement
Israel: Considerable activities involving both biologists and engineers, also some commercial activities

Government Policy

From the assessment conducted, it is clear to this panel that there are countries that recognize the importance of investing in science and technology and are actually doing it. A list of such countries includes China where the R&D budget continues to be increased on an annual basis, Japan where it appears that the country has identified as a priority making regenerative medicine a key component of their twenty-first century economy, Korea where there is a new global regenerative medicine initiative, and Singapore. This list also includes such European countries as Germany, The Netherlands, Sweden, and the United Kingdom. Taking the United Kingdom as a specific example, at the end of 2011 the British government launched a new strategy for U.K. Life Sciences. This comprehensive strategy includes significant new investments in life sciences research and in the development and commercialization of research. The Cell Therapy Catapult initiative is a part of this strategy. The British government, in spite of the global economic recession and a very significant U.K. budget deficit, is doing this because its goal is for the U.K. to be the global "hub" for the life sciences in the future.

In contrast, in the United States the budgets of the Federal agencies that support R&D are "flat" with little indication that this situation will change soon. This is highlighted in a recent report entitled "Leadership in Decline" (Atkinson et al. 2012). This potential decline in leadership is true in the life sciences in general and certainly could happen in the stem cell area. This could threaten the U.S. leadership in the development of enabling technologies, new clinical therapies, and other innovative stem cell-based applications, areas where engineers and the engineering approach has a critical role to play. Having said that there is a potential for a decline in the historical leadership of the United States in the life sciences, the White House Office of Science and Technology Policy back on April 26, 2012 released a National Bioeconomy Blueprint. This document outlines what are called five strategic imperatives that potentially will result in the generation of new markets and economic growth. These are as follows:

1. Support R&D that will provide the foundation for the future bioeconomy;
2. Facilitate the translation of research to the market;
3. Develop and reform regulations so as to reduce barriers and increase the speed and predictability of regulatory processes and thus reduce costs;
4. Update training programs and provide institutional incentives for student training for national workforce needs; and
5. Identify and support opportunities for the development of public-private partnerships and precompetitive collaborations.

With the exception of the third recommendation above that deals with regulatory issues, the conclusions offered in the next section align with the above recommendations.

Conclusions

From this global assessment of stem cell engineering as conducted by the WTEC panel, it is clear that engineers and the engineering approach with its quantitative, systems-based thinking can contribute much more to basic stem cell research than it has to date. As stated in the National Academies report on "A New Biology for the 21st Century," to achieve the deeper understanding of biology required in this century there will need to be an integration of many disciplines into biological research and this certainly includes engineering. Engineering analysis can be used to identify the components of highly complex stem cell systems and provide an understanding of how these components work together. Furthermore, computational models will be increasingly important in our efforts to achieve a better understanding of complex biological systems. In all of the above engineers are in a position to take a leadership role.

Engineers also can take the lead in developing new, innovative enabling technologies. This includes high-throughput screening techniques, improved culture and differentiation systems, and *in vitro* models engineered to be more physiologic. The last of these include organ-on-a-chip models and also engineered *in vitro* tumor models that can lead to a better understanding of cancer.

Finally, for stem cell biomanufacturing there is a need for further advances in culture systems, techniques for real-time monitoring, and for process automation. Underpinning these specific application areas, computational modeling has an important role to play throughout the spectrum from discovery to translation.

In summary, from the assessment conducted there is a need for an increasing involvement of engineers in the field of stem cells and related technologies. Although one might argue that the United States today has a leadership role, to capitalize on this and to build on the current existing momentum, and most importantly to accelerate the translation of bench-top research into various applications including clinical therapies and into commercialization, will require the United States taking bold steps. The panel thus offers the following conclusions.

- The United States has a unique opportunity to maintain a leadership position in the stem cell field through the continued support of R&D that will provide a foundation for the generation of new markets and that will lead to economic growth.
- Because of the contributions that engineers can make in all areas of the stem cell field, as elaborated in the global assessment reported here, this needs to include increased investment in engineering, applied research, and commercialization as it relates to stem cell research and related stem cell-based technologies.
- A major component in this could be that the Federal agencies that support R&D should establish a broad interagency program for stem cell engineering, one that provides grants to interdisciplinary teams that include engineers, computational researchers, and biologists as well as individuals from other disciplines.
- Another component that would be beneficial is the establishment of new, innovative mechanisms that support academic-industry partnerships and unique translational models that facilitate the translation of research into the private sector.
- To address national workforce needs, the development of training programs at universities and advanced short courses should be encouraged and supported by Federal agencies.
- Finally, in today's global economy and with the excellent activities taking place in other countries, the United States would benefit from forming strategic partnerships with other countries so as to leverage the existing and emerging strengths in institutions outside of the United States; to implement such partnerships will require binational grant programs with appropriate review mechanisms.

As noted in the previous section, these conclusions align with the National Bioeconomy Blueprint released by the White House Office of Science and

Technology Policy. It is up to the Federal agencies to implement a plan based on the conclusions from this assessment study. Without the implementation of the above, however, this unique opportunity could be lost. In this case, it might be possible that the United States in the future is relegated to the second tier of countries in this critical area of stem cell engineering. On the other hand, if implementation takes place in some form, and there is an urgency to do this, then the United States can expect to continue to be in a leadership position and at the forefront in advancing the sciences, developing new, innovative enabling technologies and platforms that lead to clinical therapies, to commercializing the results of stem cell research, and to the generation of new markets and economic growth based on advances in the stem cell field. Some of the results from this will be:

- The acceleration of the development of new drugs while at the same time reducing the costs of this development process
- The development of cell therapies that address diseases and conditions of injury for which today there are no real treatment options available for patients in need
- The growth of the twenty-first century bioeconomy in the United States based on advances in our knowledge of stem cells and the translation of this into applications and products

This has been the dream for at least 20 years; however, with the right strategy by the United States it can be realized and be the reality of tomorrow.

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