To celebrate the 20th anniversary of the journal, we have invited several leaders in the field of Tissue Engineering to submit their personal views on past, present and future directions of our discipline. These will appear throughout the anniversary year to celebrate our mutual accomplishments and to point the way toward a bright future for the field.

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John P. Fisher, PhD

John A. Jansen, DDS, PhD

The Editors, *Tissue Engineering*
Parts A, B and C

Stem Cell Engineering

Robert M. Nerem, PhD

STEM CELL ENGINEERING, that is, the interface of engineering with the world of stem cells, has emerged over the past decade as an important field of research and application. Activities that are part of this field range from basic stem cell research to the development of models, tools, enabling technologies, and to advancing stem cell biomanufacturing and the development of stem cell-based products and applications. There thus are a variety of ways that engineers and engineering approaches can contribute to the development of stem cell research and to the translation of the basic biology of stem cells into therapies and commercial applications.

With the field of stem cell engineering growing, in 2008, the first International Conference on Stem Cell Engineering was held at Coronado, CA. This was followed in 2010 with the second conference on this topic held in Boston, and in 2012, the third conference was held in Seattle. This year, this conference, the fourth in the series, rotates back to Coronado. This conference has become the main one for researchers in this area, and it is jointly organized by the Society for Biological Engineering and the International Society for Stem Cell Research.

Also, as a result of the growing importance of this topic and stimulated by the 2010 International Conference on Stem Cell Engineering, the National Science Foundation (NSF) with additional support provided by the National Institute for Standards and Technology and the National Cancer Institute at the National Institutes of Health, funded a global assessment of stem cell engineering. This study was managed by the

World Technology Evaluation Center (WTEC), and the purpose of this WTEC study was to compare U.S. R&D and status with activities globally, and as part of this, to identify gaps and barriers, major innovations emerging globally, and possible opportunities for global cooperation and collaboration. The underlying intent of all this was to guide future research investments by the agencies that funded this study. The report on this global assessment was submitted by WTEC to the three funding agencies in 2012 and with a summary published in the journal *Tissue Engineering Part A*.¹

The WTEC study was followed in July 2013 with a workshop held in Sonoma, CA that also was funded by the NSF. The topic was “New Directions in Tissue Engineering and Regenerative Medicine”; however, the focus here also was on stem cell engineering. In addition to the report submitted to NSF, an editorial outlining the recommendations arising out of this workshop was published in the journal *Science Translational Medicine*.² In this editorial, the authors note that the involvement of engineers and engineering approaches will result in the following outcomes:

- A quantitative understanding of basic stem cell biology.
- Tools for both basic research and the translation of basic science into stem cell-based therapeutic applications.
- Acceleration in the development of new therapeutic products, while at the same time reducing the costs of development processes.
- The ability to address diseases and injuries for which there are currently no effective treatment options

through the development of stem cell-based therapies and the translation of stem cell technologies into commercial products.

These outcomes will contribute to the growth of the 21st century bioeconomy around the world.

As one looks to the future, there are many ways in which engineers and engineering approaches can contribute to the overall advance in our knowledge about stem cells and to the development of applications based on stem cells. In the context of basic research, and as already noted, engineering brings much needed quantitative analyses to the study of stem cells and to what regulates their decisions about fate and function. Engineering also brings a system perspective and the ability to do both analysis and synthesis. Also, it is now recognized that not only is the microenvironment of a stem cell highly complex, but in addition to cues that are biochemical in nature, there are equally important biophysical cues. An absolutely critical issue is to understand the emergent behavior of integrated cellular systems, that is, starting with a population of stem cells, how may an integrated cellular system emerge with the different cell types needed to form a tissue or an organ or even an integrated cellular system that does not even exist in nature. The application of such an understanding will help in the development of what are called organ-on-a-chip models, ones based on human cells. This will revolutionize the development of new drugs by providing a human cellular system for studies ranging from toxicity to even preliminary assessments of efficacy. An understanding of the emergent behavior of integrated cellular systems also could lead to biological machines, ones that do not even exist in nature and ones that will be based on stem cells and could exhibit a meaningful, useful function. It is this that is the goal of a Science and Technology Center funded by NSF with three primary partner institutions, Massachusetts Institute of Technology as the lead, Georgia Tech, and the University of Illinois at Urbana Champaign.

Beyond basic research, there is the need to continue to develop tools and a variety of enabling technologies. It is clear that new enabling technologies can and will take different forms. These include the development of high-throughput screening systems, the use and further development of microfluidic systems, and biosensors. Another enabling technology is that of computational modeling. Advances in this area will help us understand how the symphony of signals controls stem cell fate and function, and it will also be important in biomanufacturing, for example, in the development of feedback control systems for stem cell processing.

This leads into the other end of the spectrum in which engineers and engineering approaches can contribute, in fact are critically needed. This is the translation of our benchtop knowledge of stem cells into cell-based therapies and

products. Such a translation will require scaleup; as an example for a therapy involving the revascularization of the heart, a requirement in total of 10^{14} – 10^{15} cells annually. Currently, the processing systems being used are for the most part manual; however, in the near future, there will be, as a minimum, semiautomated systems and in the longer term, fully automated ones. Such an automation will lead to improved product quality, an increase in productivity, and to an ease in achieving regulatory compliance.

With the need for the involvement of engineers and engineering approaches in virtually all areas of the field of stem cells, there will be a continuing expansion in the number of individuals working in stem cell engineering. Furthermore, even though in this discussion some areas have been highlighted for future research and development activities in the field of stem cell engineering, there undoubtedly will be many other areas, ones to be pioneered by the next generation of investigators in tissue engineering and regenerative medicine

Acknowledgments

The author is deeply appreciative of all those who have mentored his move into stem cell engineering. Thanks also goes to the agencies and other organizations that have funded the activities referenced in this summary. Finally, for those interested in the full report on the global assessment of stem cell engineering, they should contact WTEC (448 Murry Hill Circle, Suite 120, Lancaster, PA 17601, Ph: 717-299-7130).

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Received: December 19, 2013

Accepted: January 2, 2014

Online Publication Date: February 13, 2014