Navigating the Manufacturing Process and Ensuring the Quality of Regenerative Medicine Therapies

PROCEEDINGS OF A WORKSHOP

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Forum on Regenerative Medicine

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BOXES

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Acronyms and Abbreviations

aHSCT	autologous hematopoietic stem cell transplantation
ALL	acute lymphocytic leukemia
ARMI	Advanced Regenerative Manufacturing Institute
BLA	biologics license application
CAR	chimeric antigen receptor
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and control
CQA	critical quality attribute
FDA	U.S. Food and Drug Administration
FIRST	For Inspiration and Recognition of Science and Technology
GMP	good manufacturing practice
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
IND	investigational new drug
IP	intellectual property
iPSC	induced pluripotent stem cell
ISBT	Information Standard for Blood and Transplant

MS	multiple sclerosis
MSC	mesenchymal stem/stromal cell
NEDA	no evidence of disease activity
NIIMBL	National Institute for Innovation in Manufacturing Biopharmaceuticals
NIST	National Institute of Standards and Technology
RCR	replication competent retroviral
STEM	science, technology, engineering, and mathematics
URS	user requirement specification
USP	U.S. Pharmacopeia
WHO	World Health Organization

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Introduction[1]

Regenerative medicine, as defined by the National Institutes of Health, is the "process of creating living, functional tissues to repair or replace tissue or organ function lost due to age, disease, damage, or congenital defects" (NIH, 2013). The multidisciplinary field of regenerative medicine encompasses many areas of study, such as tissue engineering, gene and cell therapies, the development of cell-free materials designed to aid in tissue regeneration in vivo, and three-dimensional scaffolding. In addition to relying on scientific experts in the drug and biotech industry, those involved in the research and development of regenerative medicine therapies are increasingly drawing on the unique expertise of regulatory scientists, engineers, physicians, and patients to inform an integrated and efficient development process.

Although regenerative medicine has great potential for producing both health and economic benefits, this relatively new field faces unique regulatory and manufacturing challenges. The reliance of regenerative medicine products on living cells and tissues, which are inherently dynamic, adds a fundamental complexity to the manufacturing and scale-up process that is not present in the manufacture of most non-biologic therapies. Since the variety of cells and tissues used in regenerative medicine is vast and

[1]The planning committee's role was limited to planning the workshop, and this Proceedings of a Workshop was prepared by the workshop rapporteurs as a factual summary of what occurred at the workshop. Statements, recommendations, and opinions expressed are those of individual presenters and participants and are not necessarily endorsed or verified by the National Academies of Sciences, Engineering, and Medicine, and they should not be construed as reflecting any group consensus.

the characteristics of cells can differ between in vitro and in vivo environments, defining and assessing the quality of products is challenging. In addition, it can be difficult to accurately measure or test for critical quality attributes (CQAs) (i.e., physical, chemical, biological, or microbiological characteristics that should be within an appropriate limit, range, or distribution in order to ensure the desired product quality[2]) of cells because these attributes can change over time as they are affected by the cell maturation process and exposure to environmental stimuli.

In October 2016 the Forum on Regenerative Medicine hosted a public workshop,[3] State of the Science in the Field of Regenerative Medicine: Challenges of and Opportunities for Cellular Therapies. Discussions at the workshop focused on challenges along the path to bringing promising new therapeutics to market (NASEM, 2017). Several critical challenges to commercialization were described, including the need for reliable methods to scale up the production of cell-based therapies in a safe and cost-effective manner that fits within regulatory parameters (Haddock et al., 2017). Identifying and measuring markers of quality in regenerative medicine products is one possible way to support the consistent development of higher-quality products that are both safe and potent. Forum members were interested in examining issues related to CQAs for cell-based therapies and also how deep characterization of cells could potentially lead to a more streamlined manufacturing process.

Therefore, on June 26, 2017, the Forum on Regenerative Medicine hosted a public workshop in Washington, DC, titled Navigating the Manufacturing Process and Ensuring the Quality of Regenerative Medicine Therapies in order to examine and discuss the challenges, opportunities, and best practices associated with defining and measuring the quality of cell and tissue products and raw materials in the research and manufacturing of regenerative medicine therapies.[4] The goal of the workshop was to learn from existing examples of the manufacturing of early-generation regenerative medicine products and to address how progress could be made in identifying and measuring CQAs. While there are increasingly more regenerative medicine products in the clinical pipeline and on the market,

[2]FDA defines the term "critical quality attributes" in the Guidance for Industry, Q8(R2) Pharmaceutical Development document, which is available at https://www.fda.gov/downloads/drugs/guidances/ucm073507.pdf (accessed August 28, 2017).

[3]The Forum on Regenerative Medicine held a previous workshop titled State of the Science in the Field of Regenerative Medicine: Challenges of and Opportunities for Cellular Therapies in October 2016. Workshop materials including presentations, videos, and the Proceedings of the Workshop can be found at http://www.nationalacademies.org/hmd/Activities/Research/RegenerativeMedicine/2016-OCT-13.aspx (accessed August 22, 2017).

[4]The workshop agenda, speaker biographical sketches, statement of task, and list of registered attendees can be found in Appendixes A, B, C, and D, respectively.

BOX 1-1
Objectives of the Workshop

- Explore how unique cell populations are defined and evaluated for quality and purity.
- Highlight the importance of establishing a strong scientific understanding of source cells, as well as of the characteristics of regenerative cellular and tissue products.
- Learn about the logistical challenges and successes associated with identifying and measuring critical quality attributes and developing effective regulatory and manufacturing standards.
- Examine possible mechanisms and technologies to improve the ability of researchers, manufacturers, and regulators to ensure that new therapies are safe and effective and can be produced efficiently.

there is not yet consistency in the approaches to cell sourcing, product characterization, manufacturing processes, or logistics and delivery models. This may be due in part to the rapid evolution of the field and the wide variation in regenerative medicine products. Thus, it was hoped that by bringing the regenerative medicine community together to discuss the development of common approaches and standards for crosscutting tools, measurements, functional assays, and manufacturing platforms, the community could identify common challenges and share innovative new practices that might help advance the field and support valuable collaboration. The workshop also addressed the challenges of designing and adhering to standards as a way of helping those who are working to scale up processes and techniques from a research laboratory to the manufacturing environment. Stakeholders, including research scientists, clinicians, regulators, and representatives from patient groups and pharmaceutical and biotech companies, presented their perspectives and participated in discussions throughout the day. The specific workshop objectives are listed in Box 1-1.[5]

OVERVIEW OF THE WORKSHOP

Producing regenerative medicine therapies relies on using advanced manufacturing technologies. The workshop explored the different steps along the research and clinical development pathway from the point when

[5]While the workshop objectives focused on exploring the importance of cell populations for defining quality and purity, the concepts discussed during the workshop include other raw materials that are important to manufacturing and developing standards for regenerative medicine therapies.

a promising discovery is made in the laboratory to when it has become a therapeutic product available on the market. Speakers highlighted lessons from their current experiences and addressed issues regarding scaling and commercialization, identifying and measuring the CQAs of regenerative medicine products and their source cells and raw materials, developing new production technologies for regenerative medicine, and understanding regulatory challenges and opportunities. In each of the five sessions, experts discussed the main challenges to and opportunities for progress as well as the research and regulatory efforts aimed at addressing those challenges.

Inherent Challenges to Preparing and Regulating Biologics

Many of the approaches and practices that the day's presentations and discussions would highlight are rooted deeply in the history of biologics development, said Jay Siegel, a forum co-chair and the chief biotechnology officer and head of scientific strategy and policy at Johnson & Johnson. Vaccine production is centuries old, he noted, with the use of antisera products to treat infections going back to the 1890s. Monoclonal antibodies and cell and gene therapies are examples of more recent biologic products used to treat disease. Although each of these biologics has its unique manufacturing obstacles, he said, they share common challenges, such as difficulty in characterizing the final product and the variations that inherently occur when living cells and tissues from several different sources are used. Unlike the case with non-biologic drugs, there is no method to sterilize a cell-based biologic in its final packaging, Siegel said, and the cell-based biologics can be reactive, immunogenic, and relatively unstable.

Today's regulatory requirements for any human or animal therapeutic are based on regulations created in the early 1900s, Siegel said. After a batch of horse antisera used to treat diphtheria resulted in the death of 13 children in 1901, it was discovered that one of the horses used to produce that antisera had contracted tetanus, but without a means of tracing the source of the contaminated serum, regulators were unable to identify the underlying problem efficiently. The incident gave rise to the Biologics Control Act of 1902, which mandated that vaccine producers be licensed annually, undergo regular inspections, and implement new labeling protocols for their products.[6] This regulation was followed by the Federal Food and Drugs Act of 1906, which outlawed the production of any foods or drugs that were produced using inferior or impure ingredients or that

[6]More information about the Biologics Control Act of 1902 can be found here: https://history.nih.gov/exhibits/history/docs/page_03.html (accessed August 22, 2017).

made misleading claims about their health effects or benefits.[7] Years later, Congress passed the Food, Drug, and Cosmetic Act of 1938 that authorized the U.S. Food and Drug Administration (FDA) to oversee drug safety and to address issues of quality and consistency. This law formally classified biologics as drugs, relying on the stipulations of 1902 Biologics Control Act to regulate them. Today, biologics are regulated under the Food, Drug, and Cosmetic Act of 1938 and the Public Health Service Act of 1944, which gave the U.S. Public Health Service control over biologic products (FDA, 2012).

The challenge with producing biologics, Siegel said, is how to assess quality and consistency when, unlike a defined drug molecule, it is impossible to characterize every detail of the final product. This can only be addressed by controlling the manufacturing process, controlling raw materials, testing donors, and developing standardization processes and reliable assays to characterize the unique markers of consistency, efficiency, and potency for a product, said Siegel.

Additional unique factors are spurring the rapid evolution of the regenerative medicine industry, said Claudia Zylberberg, workshop co-chair and the president and chief executive officer of Akron Biotech. Regenerative medicine is entering an era of automation, she said, which will require shifting from a model of product development based on vertical integration to one based on horizontal integration that relies on manufacturers, customers, suppliers, and researchers working together to create manufacturing solutions for new therapies. Open and frequent communication, in addition to the implementation of effective methods for data sharing, will be vital in implementing this approach, she added. Zylberberg called on the workshop participants to embrace collaboration in order to address the shared challenges of developing and implementing manufacturing standards, identifying CQAs, creating new technologies to enable product consistency and analytics, and improving comparability between regenerative medicine products. "Serving patients worldwide and helping them not only live longer, but better, is our community's responsibility," she said.

Workshop speakers were asked by Stephen Oh, workshop co-chair and the acting deputy director of the Division of Cellular and Gene Therapies in the Office of Tissues and Advanced Therapies at FDA, to emphasize how important it is to develop a clear scientific understanding of what is involved in characterizing the cell populations of a regenerative medicine product and in testing them for quality and purity. Oh also asked the speakers to discuss the challenges and successes associated with identifying

[7]More information about the Federal Food and Drugs Act of 1906 can be found here: https://www.fda.gov/regulatoryinformation/lawsenforcedbyfda/ucm148690.htm (accessed August 22, 2017).

and measuring CQAs as well as possible approaches for developing effective regulatory and manufacturing standards. Finally, he asked that the speakers explore specific mechanisms and technologies that might improve the field's ability to ensure that regenerative medicine products are safe and effective and that they can be manufactured efficiently.

ORGANIZATION OF THE PROCEEDINGS OF A WORKSHOP

Following this introductory chapter, Chapters 2 through 6 explore issues in the manufacturing of regenerative medicine therapies, discuss the obstacles that hinder progress, and identify opportunities to address these obstacles. Chapter 2 provides background and context about the manufacture of regenerative medicine therapies by discussing the challenges and opportunities associated with translating discoveries from the laboratory to production and navigating the process of scaling manufacturing of new therapies. This chapter also presents examples of the methods and capabilities for manufacturing and collecting quality control data to inform the transition from research and development to the implementation of good manufacturing practices (GMPs).

Chapter 3 addresses issues related to identifying and measuring CQAs of regenerative medicine products and source cells. This chapter discusses methods and processes used to identify and measure CQAs for raw materials and regenerative medicine products.

Chapter 4 describes various technologies that facilitate the efficient and cost-effective development of products that meet manufacturing and regulatory standards, and it explores opportunities for new technologies and manufacturing models to increase efficiency and quality. The chapter also discusses novel and more precise in-process and final-release testing technologies and reviews the existing manufacturing infrastructure available in academic centers and the commercial sector.

Chapter 5 considers the regulatory landscape for regenerative medicine, including developing standards, enforcing regulations, and meeting the needs of patients. Chapter 6 summarizes the lessons learned throughout the day and discusses ways to support the development, manufacture, and regulation of safe and effective regenerative medicines.

2

Transitioning from Discovery and Development to Manufacturing

Highlights Presented by Individual Speakers

- Cells from healthy humans are not the same as cells from patients with advanced disease, and, as a result, researchers need to work with clinical-grade reagents, other materials, and equipment early in order to understand and account for those differences in the development process. (Levine)
- While automation can reduce the risk of deviations and error in the manufacturing process, the variability of human cell materials from patients still requires human judgment and intervention, which creates the opportunity for deviations and the need for more training of research personnel. (Levine)
- Investigators should focus on demonstrating the efficacy of their products before engaging in further product development because understanding potency and the important biological effects of a given cell or tissue therapy is the most critical aspect of being able to generate reproducible results and reach production scale. (Niklason)
- A strategic manufacturing process that relies on a series of discrete steps and uses quality by design to improve the process one step at a time reduces the risk of changing the product's properties and performance and allows for flexibility within the manufacturing process. (Preti)

In his opening keynote, Adrian Gee, a professor of cell and gene therapy at Baylor College of Medicine, described the issues facing the field of regenerative medicine and set the stage for the ensuing panel presentation and discussions. There is increasing interest in the field from both researchers and the public, Gee said, and, accordingly, the global market for regenerative medicine therapies is growing rapidly. By some estimates, the market is projected to reach $53.7 billion by 2021 (Kelly Scientific, 2017). As patient demand for new forms of treatment continues to grow, Gee cautioned, the regenerative medicine industry must work closely with regulators to ensure that new therapies are safe and effective.

During the first session following Gee's keynote presentation, a panel discussed the challenges and opportunities associated with bringing new discoveries from the laboratory to manufacturing and with navigating the process of scaling the production of new regenerative therapies. The three speakers—Bruce Levine, the Barbara and Edward Netter professor in cancer gene therapy at the University of Pennsylvania Perelman School of Medicine; Laura Niklason, a professor of anesthesiology and biomedical engineering at Yale University; and Robert Preti, the president and chief executive officer at PCT Cell Therapy Services and chairman of the Alliance for Regenerative Medicine—also described potential opportunities and models to enable the scaling of regenerative medicine therapies for production using the currently available infrastructure and addressed probable future needs as the regenerative medicine field evolves and grows. An open discussion moderated by Krishanu Saha, an assistant professor at the University of Wisconsin–Madison, followed the three presentations.

KEY CHALLENGES FACING THE REGENERATIVE MEDICINE INDUSTRY AS SAFE AND EFFECTIVE THERAPIES ARE DEVELOPED FOR PATIENTS

In the United States, FDA is responsible for regulating this field, and the agency is working closely with researchers and manufacturers to foster the responsible development of regenerative and cellular therapies, said Gee. FDA's approach, he added, has been to hold meetings with stakeholders, publish guidance documents about how it will develop and implement regulations, and designate regenerative medicine as an advanced therapy.[1]

In setting the stage for the day's panel discussions, Gee raised some of the issues that stakeholders face as they work to develop and gain approval for cellular and regenerative therapies. These issues and needs for the field

[1]More information about FDA's approach to regulating the regenerative medicine field can be found here: https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm (accessed July 27, 2017).

are listed in Box 2-1. The ideal regenerative medicine product, Gee said, would have a starting material that is easy to collect or generate from induced pluripotent stem cells (iPSCs) or embryonic stem cells. The manufacturing method for this ideal product would be automated and would use simple closed systems, and there would be rapid and predictive testing methods to determine whether the product has met appropriate release standards. If possible, the ideal product would be made available any time a patient needed it, so that the product would either have a long shelf life under simple storage conditions or just-in-time shipping methods could be employed. Finally, the ideal regenerative medicine product would be easy to

BOX 2-1
Suggested Ways for the Field of Regenerative Medicine to Move Forward (as presented by Gee, June 26, 2017)

An ideal regenerative medicine product would have a starting material that was easy to collect or generate from iPSCs or embryonic stem cells, its manufacturing would be automated and use simple closed systems, and there would be rapid and predictive testing methods to determine whether the product has met appropriate release standards. The product would have a long shelf life under simple storage conditions, it would be easy to distribute and administer, and its production would make possible a high-quality, low cost therapy. However, there are challenges that must be overcome to achieve each of these features:

- There is a need for approved manufacturing devices that can conduct the monitoring required during the production of cells for regenerative medicine products and aid in the process of scaling up or scaling out.
- Rapid assays are needed to test for sterility and potency in regenerative medicine products. These assays must meet regulatory requirements and be standardized to allow for comparison between manufacturing centers.
- High-quality ancillary materials and processing agents (e.g., scaffolds) are needed to enable robust manufacturing platforms and ensure product safety.
- There is a need for additional staff and training and certification programs to train employees who are capable of overseeing the unique manufacturing processes associated with regenerative medicine products.
- There is a need to re-evaluate long-term storage and shipping methods for regenerative medicine products. Current methods, such as cryopreservation or dry-ice shipping, can affect the potency and complicate the process for the clinical application of a therapy.
- There is a need to standardize the labeling of regenerative medicine products to reduce confusion when shipping products between centers, both nationally and internationally.

distribute and administer, and each step in its production would be designed to ensure high quality at low cost.

The challenges involved in creating such a product are significant, Gee acknowledged. The collection process is often complex and involves using various ancillary agents such as anticoagulants and suspended media, some of which have not received regulatory approval for use in manufacturing. The source cells themselves may also vary, depending on the technical ability of the person collecting the starting material and the nature of the donor. If the starting material comes from the intended patient, those autologous cells are likely to be affected by the disease state of the patient and any prior therapies the patient has received, and they may be more difficult to collect. Cell therapy products that use allogeneic cells obtained from healthy donors are more likely to be uniform, Gee said, because fewer screened donors will provide the starting material for most of the product and their target cell populations are less likely to contain variations because of disease, but not all therapies will be amenable to using allogeneic cells (Malik, 2012).

While the ideal manufacturing process would use closed systems at every stage, some products require source cells that are not available in large quantities, and there do not yet exist closed systems for culturing and increasing the number of these cells, Gee said. A closed system is defined as "a process system with equipment designed and operated such that the product is not exposed to the room environment. Materials may be introduced to a closed system via mechanisms that avoid exposure of the product to the room environment (e.g., delivery through sterile ports and filtration), but the addition must be done in such a way to avoid exposure of the product to the room environment (e.g., by 0.2-μm filtration)" (Palberg et al., 2017). There is a need for approved manufacturing equipment that can conduct the in-process monitoring required during the production of cells for these products, Gee said. Such devices should be easy to use for scale-up (increasing the capacity of a single manufacturing process) or scale-out (increasing the number of processes performed in parallel), he added, noting that scale-up and scale-out are a significant challenge for many centers because they can be costly and time-intensive. Many centers also encounter difficulties when implementing manufacturing analytics to meet GMP operations and assess complex variables relating to quality control. It would be ideal for manufacturing devices to have integrated software capable of monitoring quality control variables as a product is being manufactured instead of having to rely on the relatively few available software packages that focus on quality systems variables, Gee said. Another issue, he said, is that there are not enough available people who have been trained to oversee these kinds of manufacturing processes, and there is an associated lack of training and certification programs for regenerative medicine product manufacturing.

To illustrate one approach to addressing the above challenges, Gee

discussed Baylor School of Medicine's experience producing virus-specific T cells. In the early 1990s, researchers at Baylor developed procedures for producing Epstein-Barr virus-specific T cells that eventually went into clinical trials and produced promising results (Heslop et al., 2010; Louis et al., 2010). By 2013 the specificity of the cells had been expanded to include cytomegalovirus and adenovirus, and since then the Baylor team has expanded the specificity again to include activity toward BK virus and human herpesvirus 6. Since the early 1990s manufacturing time has been reduced from 3 months to 10 days, which makes the cells more easily available for any suitable patient in a therapeutically relevant time-frame, Gee said, and the manufacturing process has moved from an open system to a closed system. Most importantly, he said, the safety and efficacy of these cells has remained the same as those first put through clinical trials. Studies have shown that these cells can be used across human leukocyte antigen (HLA) compatibility barriers without the risk of triggering graft-versus-host disease, suggesting that they will be able to gain an "off-the-shelf" designation. "I think it shows that even in one particular field, advances can be made moving toward the goal of the ideal product," Gee said.

With regard to testing and release protocols for regenerative medicine products, Gee said, there are a few rapid testing assays, such as that for endotoxin, but there is still a need for a rapid assay to test for sterility. There is also a need for potency assays that correlate with clinical efficacies, which are required to conduct registration-enabling clinical trials. The cost of testing is also a barrier, Gee said, noting that some testing procedures such as those used to evaluate cell products produced using viral vectors, can have significant costs. "We need to develop and get regulatory approval for new release assays," he said, "and we desperately need standardization of these assays so that we can compare them between centers." To do that, he said, will require standardization of the appropriate controls.

The storage of regenerative medicine products is another issue facing the field. For example, the cryopreservation of cellular therapy products can affect their potency. "We need to consider whether storing products at ultra-low temperatures is suitable or whether other forms of storage may be preferable," Gee said. It may be possible, for instance, to develop techniques to keep cells viable and potent without cryopreserving them. Another opportunity for further development is improving formulation and packaging methods to eliminate the need to manipulate the product upon receipt at the treatment center, Gee said. This would allow hospitals to use the product with minimal on-site manipulation and would reduce reliance on laboratories and technicians to prepare the product for clinical application.

Concerning the distribution and transport of these products, both from the source collection site to the manufacturing center and then from the

manufacturing center to the therapeutic centers, standardized labels are needed to make the production and delivery of a cellular therapy more consistent, accurate, and safe for donors and patients, Gee said. The Information Standard for Blood and Transplant (ISBT) 128, a global standard for identifying and labeling medical products of human origin, is the most generally agreed upon system, Gee noted.[2] He also said that improved dry shipping methods (i.e., those methods that do not involve using free liquid nitrogen), perhaps using warmer temperatures, may be needed and that the field should consider developing just-in-time shipping approaches that deliver fresh cells for administration to the patient immediately upon arrival.

Current regulations are based on pharmaceutical standards, but a question exists as to whether those standards are appropriate for cell- and tissue-based products, particularly as they continue to evolve, Gee said. A number of bodies have developed professional standards for collecting source cells, manufacturing cellular products, and administering these cell therapies, raising the issue of what the proper interface should be between these standards and the regulatory environment prescribed by FDA.

The final challenge, Gee said, is how patients and insurers will pay for these therapies, given that they are likely to be expensive. "Will the average patient have the ability to pay for these?" he asked. "Or will the insurance companies be willing to cover the costs?" He also raised the issue of developing new methods for compensation, beyond standard licenses and intellectual property (IP) agreements. Specifically, Gee wondered if it would be feasible to return a portion of the profits from the sale of cellular therapy products back to the original centers where they were developed since many products arise from publicly funded research. Additionally, many products are developed at academic manufacturing centers or hospitals to treat a small number of patients, making them unattractive for large-scale commercialization and the challenge, Gee said, is that "most hospitals do not want to be in the business of manufacturing cell products."

"Cellular regenerative medicine therapies are likely to revolutionize the practice of medicine in the future," Gee said, but ultimately, researchers and manufacturers of regenerative medicine therapies must adapt their production processes and environments to best suit the needs of patients.

[2]More information about the ISBT 128 can be found here: https://www.iccbba.org (accessed August 23, 2017).

TRANSITIONING ENGINEERED T CELLS FROM DISCOVERY TO MANUFACTURING AND REGULATORY APPROVAL

Interaction between the fields of human immunodeficiency virus (HIV) and oncology research led to the submission of the first biologics license application (BLA) for a cellular gene therapy to FDA, Levine said. In an effort to better understand T cell growth and senescence, Levine created artificial dendritic cells that allowed for the delivery of growth signals to T cells through bead-linked antibodies. This accelerated the development of a chimeric antigen receptor (CAR) which was delivered to T cells using a lentivirus. The lentivirus genome could be edited to encode a genetic sequence for the expression of a specific CAR when transcribed and translated in a T cell. The lentivirus was used as a "Trojan horse"—that is, the virus would enter a T cell and deliver its double stranded RNA, which would then be reverse transcribed and integrated into the T cell DNA, permanently incorporating the sequence into the cell's genome (a process called transduction) and allowing the cell to produce both its original antigen receptor and the CAR. In his presentation, Levine reviewed the technology and methodology behind the first CAR clinical trials that used a murine retrovirus to edit the T cell genome. The resulting CAR T cells were used to treat patients with HIV (Mitsuyasu et al., 2000; Walker et al., 2000). Levine described how the technology used in those trials led to the University of Pennsylvania group's work to develop CAR T cells with potent and long-lasting antitumor effects in patients with advanced chronic lymphoid leukemia (Kalos et al., 2011; Porter et al., 2011) and the more aggressive acute lymphocytic leukemia (ALL) in children who had failed previous therapies (Grupp et al., 2013; Maude et al., 2014). In initial trials studying both conditions, Levine said he and his team found that their CAR T cell treatments demonstrated significant anti-cancer effects in patients, and in their trial on ALL he and his colleagues found that 93 percent of patients had a complete response rate at 1 month post treatment.

The technology for producing CAR T cells has since been transferred to Novartis, which will take this technology through pivotal clinical trials and develop it commercially, something that Levine and his colleagues at the University of Pennsylvania are not equipped to do, he said. The research team at Novartis refined the production technology to further enhance the control and consistency of the process by closing some process steps and automating some manual processes. The Novartis team also developed new analytical methods to demonstrate that the resulting product was the desired one; that it met purity, identity, and potency requirements; and that it was free of adventitious agents.

Following comparability studies, FDA accepted that the Novartis product was comparable to the one that Levine and his colleagues used in

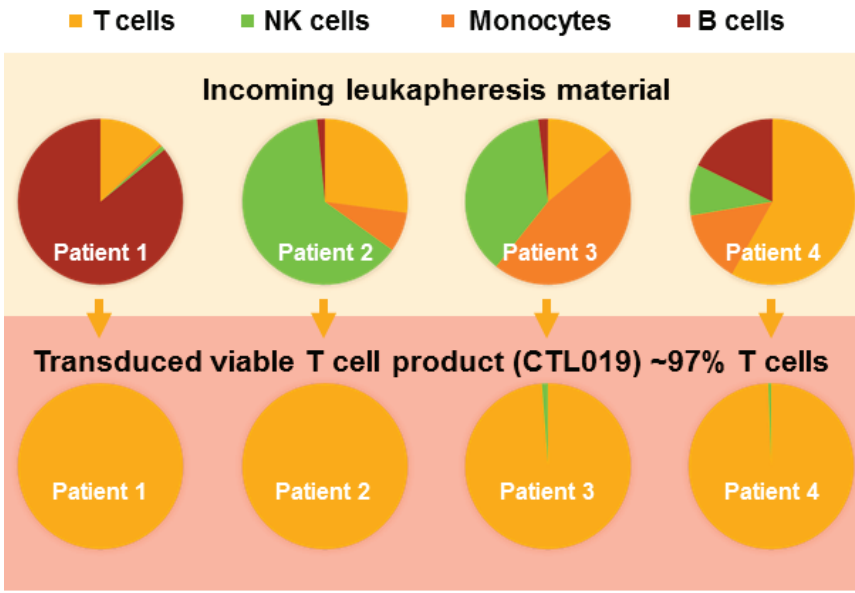

FIGURE 2-1 Using a protocol for consistent transduced T cell product from individual patient material.
NOTE: CTL = cytotoxic T lymphocyte; NK = natural killer.
SOURCES: Bruce Levine, National Academies of Sciences, Engineering, and Medicine workshop presentation, June 26, 2017. Originally from Novartis Cell and Gene Therapy Analytical Development, 2016.

conducting its initial clinical trial and permitted the company to open its own investigational new drug application and conduct global clinical trials. Still, Levine said, there is the issue of individual patient variability. "We have some patients that come in with very low T cell counts," he explained. The solution, he said, was to integrate a conditional manufacturing pathway based on a patient's phenotype and incoming material (see Figure 2-1). The result has been a consistent transduced T cell product regardless of the makeup of the incoming patient material. A clinical trial using this approach in pediatric patients with relapsed and refractory B cell ALL, which was conducted at 25 sites in 11 countries on 4 continents, found a 6-month overall survival rate of 89 percent (Buechner et al., 2017). FDA accepted the resulting BLA on March 29, 2017, and granted priority review.[3] Novartis is also conducting a Phase II clinical trial with

[3]On August 30, 2017, FDA approved the first gene therapy available in the United States—Kymriah (tisagenlecleucel)—for certain applications in pediatric and young adult patients

this product in adults with diffuse large B cell lymphoma, and preliminary results show that 79 percent of patients were relapse-free at 6 months after treatment (Schuster et al., 2017).

Addressing the lessons learned from efforts to develop materials for the first human clinical trials, Levine said that patient-derived materials such as cells from healthy humans, are not the same as cells from patients with advanced disease. To accommodate for those differences, researchers need to work early with reagents, other materials, and equipment that are clinical grade. The variability of human cell materials from patients currently requires human judgment and intervention, he said, which creates the opportunity for deviations and the need for more training of research personnel. "There are things we can automate," Levine said, "but many things that we cannot yet automate." Another lesson he mentioned was that studying a few patients thoroughly can "radically accelerate" clinical development. His final lesson was that an academic scientist can and should understand the industry terms, methodologies, and nuances associated with the commercialization of a new therapy.

Levine concluded his comments with a list of critical issues to consider when developing products for commercialization and increasing patient access to new cell therapies:

- Ensuring that there is a consistent supply chain for complex reagents and materials, such as serum-free media, and that there are alternatives available with comparable growth and potency properties.
- Near-term out-scaling and the mid- to long-term automation of manufacturing processes.
- Developing rapid and modified-release tests to assess product quality.
- Increasing the consistency and comparability of regenerative medicine products and managing complex manufacturing processes.
- Reducing the cost of goods, labor, and services.
- Recruiting, training, and retaining skilled technologists and engineers.
- Addressing ethical questions of patient access and moving from an investigational clinical trial for a potential new therapy with strong positive results to a larger clinical trial, given the complexities of scaling the production of these therapies and allocating enrollment in larger clinical trials.

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with acute lymphoblastic leukemia. See https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm574058.htm (accessed September 14, 2017).

LEARNING FROM PAST EXPERIENCES IN VASCULAR ENGINEERING

When Laura Niklason surveyed ClinicalTrials.gov, a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world, last year, she found roughly 30 ongoing trials involving implanted engineered tissues. These trials, she said, mainly involved connective tissues—skin, cartilage, blood vessels, and others—rather than solid organs such as heart, kidney, or liver. The function of each of these connective tissues relies, in part, on cellular components, but the extracellular matrix confers many of their functional attributes, she explained.

In the late 1990s Niklason and her collaborators developed methods to collect autologous vascular smooth muscle cells, culture them in a bioreactor for approximately 8 weeks, and generate autologous blood vessels that functioned like normal blood vessels when transplanted into the host that provided the original cells. However, transitioning the application of this technology from healthy young adults to older individuals with vascular disease proved to be difficult. As a result, her group modified its approach to vascular regeneration, opting instead for an allogeneic approach that uses vascular smooth muscle cells harvested from the aortas of organ donors to generate a cultured blood vessel. Niklason's team expands and banks these donor cells and, after testing them for function, seeds them onto a degradable scaffold in a single-use, tubular bioreactor where they are cultured for approximately 8 weeks (Dahl et al., 2011; Niklason et al., 1999). Once the cells grow into an artery-like structure in the bioreactor, the resulting construct is decellularized, producing a bioengineered graft with the mechanical characteristics of the remaining extracellular matrix. "The final product is an engineered, human vascular matrix that seems to remodel after implantation into patients," Niklason said.

Except for the initial step when they first open a vial of cells, the process that Niklason and her colleagues have developed is functionally closed, she said. The engineered matrices are 6 millimeters in diameter and 42 centimeters long, and they are transplanted subcutaneously into kidney dialysis patients who need a conduit between an artery and a vein so they can undergo hemodialysis therapy. The grafts are allowed to heal for 1 month, and the transplanted vessels then undergo puncture with needles three times per week during the patient's routine dialysis treatments.

Niklason and her team have conducted initial Phase I and Phase II trials involving 60 patients across 6 centers in the United States and Poland. The patients were followed for an average of 36 months, at which point Niklason and her colleagues found that the implanted vessels retained their structural and functional integrity, which Niklason said was better than

comparable synthetic materials had performed in clinical use (Lawson et al., 2016). She added that some of the first patients in the trial are still using their grafts for dialysis 4.5 years after implantation. FDA has since approved a Phase III trial that will compare the performance of Niklason's grafts against expanded polytetrafluorethylene and Propaten vascular grafts in 350 patients, which she said is the largest clinical trial ever conducted in vascular access for hemodialysis. The first patient was enrolled in May 2016, and preliminary results should be available in late 2018.

Moving from the Lab to Commercialization

Humacyte, the company Niklason founded to commercialize this technology, has approximately 100 employees who have developed equipment and processes capable of producing 10 vessels at a time. While sufficient for a Phase III trial, commercial production will require tens of thousands of vessels, so the company is now working to develop the capacity to produce between 100 and 200 vessels in a batch using many small containers. While this approach has engineering challenges, it is preferable to growing 100 vessels in one large container, Niklason said, because it allows for greater control over the cell biology of the vessels.

Speaking of the lessons she has learned in moving this technology from her academic laboratory to a commercial enterprise and working with regulators and manufacturing experts, she said she would encourage academics who want to follow a similar path to first demonstrate the efficacy of their products. "I have seen many academic investigators become enthused about a mediocre outcome in a small number of animals, which leads them to get distracted and focus on trying to develop their product based on . . . fairly weak pre-clinical data," she said, noting that she strives to obtain the most robust pre-clinical data possible before moving forward with product development. In her case, that meant conducting experiments in non-human primates matched to each other as closely as possible in terms of their immunological characteristics—an approach that cost $100,000 for each animal that she and her collaborators studied. That investment paid off, however, because the results from this non-human primate model were predictive of the subsequent outcomes in humans.

After demonstrating reproducible and quantifiable results, the next important step, Niklason said, is to attend to the biology and science in the early phases of development. "Cost reduction and the regulatory pathway will follow," she said, emphasizing the importance of getting the science correct so that any following efforts will have a strong evidence base. Understanding potency and the important biological effects of a given cell or tissue therapy is the most critical aspect of being able to generate reproducible results and reach production scale, she said. Knowing what

characteristics make a product potent, she added, can ensure that potency is retained as the production scales up.

At the same time, Niklason said, although many academic scientists tend to characterize a product with a complex set of biological markers, in many cases such a complex set of markers will not be tied closely to the product's important biological effect and desired potency. "You can actually muddy the waters by telling FDA that your cells need to express 55 different markers to be your cell target of choice," she said. "Focusing on the biological effect and potency are probably more important than a large battery of markers."

One stumbling block Niklason has seen when transitioning a technology from academia to Phase I trials is a failure to focus on reproducibility. After confirming that an effect is reproducible, she said, it is important to switch both mindset and personnel from "academic" to "industry," which can necessitate hiring additional people with training that is relevant to the unique regulatory, engineering, and process needs of scaling up and testing a new product. "Identifying a robust process that is not dependent on a single technician is absolutely critical," Niklason said. Concerning potency, Humacyte and FDA have had thoughtful discussions about what should constitute the potency of an implanted connective tissue. Her initial response to FDA's question about potency was to describe how strong the implant is and how well it holds a needle and thread, but FDA wanted something different. Potency, she said, is turning out to be a combination of mechanical properties, biochemical composition, cell remnants, proteomic characterization, dimensions, and cell interactions.

Concluding her presentation, Niklason emphasized to the academic investigators attending the workshop that the key to developing a reproducible production process is to understand the vital aspects of a cell system, rather than cataloguing all potential identifying cellular markers, and to maintain control over the process parameters that affect those aspects. Her final piece of advice was to collaborate early and often with FDA. "On these types of projects, [FDA] can be incredibly helpful with regard to thinking about your cell source, your safety endpoints, and potency," she said. "Conversations with FDA are helpful, but they are not binding. They are guidance and guidelines." She also commented that the usefulness of FDA's guidance depends on the quality of the questions they receive.

GETTING TO THE FACTORY OF THE FUTURE

PCT Cell Therapy Services, Robert Preti said, was started 18 years ago to help companies and academics develop cellular therapies. In May 2017 the company was acquired by Hitachi Chemical Company. Initially, the company's focus was on delivering clinical manufacturing expertise,

which included helping with technology transfer, delivering GMP-grade manufacturing, and establishing global logistics and storage services around the world. Preti and his team soon realized they needed to integrate manufacturing and technology development, particularly engineering, analytical, and process development.

The field of regenerative medicine is challenged by the complexity of developing, analyzing, and producing new therapies, Preti said, and companies that are developing regenerative therapies are looking for methods to improve consistency. The search for faster, better, and cheaper production is likely to be frustrating, but this is a problem that needs to be solved if the industry is to move forward. The field is at an inflection point where mass production and treating patients with these transformative therapies is a reality, Preti said.

The goal for product developers and manufacturers such as Preti's company is to achieve commercially viable manufacturing strategies, but the complexity of manufacturing regenerative therapies has proven to be a significant barrier to this goal. This complexity can create inefficiencies, Preti said, because every product and service solution must be a custom one. These inefficiencies need to be reduced, he said, which raises the question, "How can we, as a community, begin to establish consistency in these products and services to drive toward the creation of platform solutions and enable a reduced cost of goods?" Establishing platform solutions, he said, is what helped the biologics industry make substantial progress in manufacturing. The field of regenerative medicine would, he suggested, benefit from the expertise of engineers as researchers and manufacturers are working to adopt new strategies and infrastructure to facilitate the production of consistent products while recognizing that it is not yet possible to fully standardize manufacturing platforms. Toward that end, Preti's company has taken a unit operations approach, which involves breaking down the manufacturing process into small pieces or clearly defined activities. Each activity that is examined is intended to accomplish a specific outcome based on the personnel, procedures, equipment, analytical methods, and materials in a given environment. Preti also reiterated Niklason's statement that when developing a new regenerative medicine product, it is important to have a deep understanding of the key characteristics that influence potency, but it is not important to have the same understanding of every biomarker or aspect of a product.

Current challenges in the cell therapy industry can be categorized into four different areas, Preti said: quality, scalability, the sustainability and robustness of the supply chain, and the costs of goods. Within these areas, he highlighted three main challenges: the current state of manufacturing, idle capacity (and the effect it has on manufacturing business models), and scalability. Regarding the current state of manufacturing, Preti said

that the challenge is that manufacturing processes today are inadequate to sustainably produce large-scale and high-quality goods at a cost consistent with market expectations. He acknowledged the inadequate manufacturing processes that can lead to delays in getting viable therapies to patients. As a potential solution, Preti said, the field would benefit from sponsors developing strategic commercial manufacturing plans based on objective process capability analyses. These analyses break the manufacturing process into steps and use quality-by-design methodologies to improve the process one step at a time, reducing the risk of changing the product's properties and performance. Developing the right business model, he said in closing, depends on the product and the company, and it may change over time. Some products may be amenable to in-house manufacturing, while others might require contract manufacturing or a combination of the two or, at some future date, production at the point-of-care. "Each product is different, and that model will fall out of a carefully devised strategic manufacturing plan," Preti said. The ultimate goal, he added, is a scalability paradigm that results in the "factory of the future" for this industry.

DISCUSSION

Addressing Technical and Scientific Hurdles

The panel of speakers discussed the scientific and technical challenges of finding donors of cells and tissues that could be used for research and product development. There is variability in both the quality of donor cells and the ability to increase the number of donor cells in vitro prior to the inoculation step, said Laura Niklason, describing the challenges she and her team encountered in finding donors for the development of Humacyte's vascular grafts. In the long term, she said, her goal is to use a finite number of "super donors" whose HLA phenotypes can yield grafts that may be tolerated by many recipients. She believes the company can reach that goal in a couple of years and that doing so will improve reproducibility even further.

Academic researchers sometimes encounter difficulties in obtaining cells or tissues from patients with disease or who may have the phenotype of the "super donors" that Niklason plans to use. In his experience, Levine said, it is easier in academia than in industry to obtain raw materials from patients with disease. For example, his group has protocols in place to collect leukapheresis products from healthy donors as well as from those with cancer and HIV. His group also receives tissue samples from resected tumors and lymph nodes.

The workshop participants discussed how researchers and manufacturers can be sure they have selected the correct type of cell to fill the right niche in vivo, given that cells can express different markers in different

environments. What matters more, Niklason said, is how the cell functions, not, say, what specific molecule is in the lipid bilayer, so one approach to product development is to "devise assays around [in vivo] function and capture that rather than relying on specific [cell] markers." Levine added that while it is important to learn everything possible about a product, in the commercial world it is essential to set aside the desire for complete cell characterization and instead define what characteristics must be present and quantifiable in order to release a product for a clinical trial or for a particular development stage in the manufacturing process.

Specificity of cell identity and function is an extremely important part in analyzing a product to ensure that it is performing as it is supposed to and not causing any toxicities or off-target effects, Preti said. He pointed to GlaxoSmithKline's achievement in determining the pharmacokinetics and pharmacodynamics of Strimvelis, a stem cell gene therapy product for a rare inherited immunodeficiency syndrome called severe combined immunodeficiency due to adenosine deaminase deficiency. "For a long time," he said, "we said we could not [characterize the mechanism of action] in cellular therapy, but I have seen evidence that it is possible."

Those in the regenerative medicine manufacturing industry, Preti said, need to begin to focus more heavily on critical process parameters when considering the types of assays that are needed for inline testing to monitor how cells and tissues are growing during the manufacturing process. There is not enough known about critical process parameters, he said. One approach to inline testing, he said, is to break the manufacturing process into discrete unit operations, create a technology roadmap that addresses those different unit operations, and then determine if better monitoring methods are needed for each of those operations. Levine added that simple inline testing, such as measuring glucose or lactate levels, provides information on the health of the cells and their potential for expansion, but it does not take the place of all of the testing required before the release of the final product.

Each of the panelists described the single biggest hurdle they faced in developing their therapies, specifying whether the challenge was technical, scientific, regulatory, intellectual property, legal, or ethical in nature. The biggest difficulties encountered were technical and remain technical, Preti said, adding that FDA has been extremely helpful in overcoming those challenges. Niklason agreed with Preti that aside from raising money, technical challenges were the biggest obstacles, and she added that identifying key inputs and process parameters for the 8-week protocol to grow vascular structures was particularly challenging. Intellectual property was not an issue, she said, because there is so much know-how available to help in that regard. Levine agreed that technical issues, particularly those relating to scaling up or scaling out production, have presented the biggest challenges.

Training a Workforce for Regenerative Medicine Manufacturing

According to a workshop participant, the bottleneck in training occurs with equipping students with manufacturing skills prior to the doctoral level. It is important for the people who will work in production facilities to be able to identify innovative solutions to problems they encounter during the manufacturing process. The issue is not just about training manufacturing operators and quality control technicians, Preti replied, but about retention and promotion. In his experience, he said, he found that hiring bright young people with advanced degrees can be challenging because they are excited to work in the clean room for about 1 year, and then they want a promotion or to move into development. At some level, he said, the manufacturing environment is not a thinking environment. "You need capable people who can do things over and over and over again, very consistently, and be good at it," he said. Given how difficult it is to find such people, moving toward scalable manufacturing processes cannot include increasing the need for people that require training, he added.

Organizations such as NIIMBL (the National Institute for Innovation in Manufacturing Biopharmaceuticals)[4] and BioFabUSA[5] are interested in and play a role in training and education, as do professional societies, Levine commented. An additional challenge, he said, will be developing standards for training technicians or engineers who want to work in this field. The bulk of manufacturing personnel for other industries come from 2-year and technical colleges, said Krishnendu Roy of the Georgia Institute of Technology, adding that the National Cell Manufacturing Consortium,[6] NIIMBL, and BioFabUSA are all interested in partnering with technical and 2-year colleges nationwide to train the manufacturing workforce this industry needs. That would be a good start in addressing these training issues, Preti agreed, one that in the long term would meet a growing industry's needs.

There are training courses for those who work in blood processing and banking operations, and a workshop participant suggested that those programs could serve as a foundation for training programs for the regenerative medicine industry. There are a few potential candidates from blood banks and from medical technology schools, both of which train people in procedures and documentation, which are the underpinnings of GMP, Levine said. He added, however, that he is really looking for people with

[4]More information on NIIMBL can be found here: http://www.niimbl.us (accessed August 28, 2017).

[5]More information on BioFabUSA can be found here: https://www.armiusa.org (accessed August 28, 2017).

[6]Resources from the National Cell Manufacturing Consortium can be found here: http://www.cellmanufacturingusa.org (accessed August 28, 2017).

cell culture experience, and those individuals are not coming from blood banking or medical technology schools. Relying on technicians from the blood banking industry could be a good short- to mid-term solution, especially since blood bank staff and medical technology school graduates would have the right mentality for the manufacturing environment, Preti said. He said, though, that he is concerned that the physical environment of a regenerative medicine manufacturing facility is restrictive and uncomfortable and that, as a result, the degree of burnout will be high, regardless of the workers' training. He added that this is why he believes the industry cannot develop a model that will require finding thousands of individuals to fill manufacturing positions.

Convening Stakeholders for Collaboration and Standards Setting

The workshop participants discussed the challenge of balancing competition and the development of shared standards across the regenerative medicine industry. One workshop participant asked the panelists how they handle the transition from open academic science to proprietary commercial development and how they view the ethical considerations in making that transition. There is no defining line where one goes from the public sphere and publishing results to the commercial, proprietary space, Niklason said. She noted that disclosure and publication are important for policing science. "Once you stop disclosing what you are doing, except to FDA, then that policing function goes to the leadership of the company," she said.

In addition to disclosure, reproducibility is another important consideration, Levine said. In his area of research on CAR T cells, he said, there are now many companies with products in advanced clinical trials, and the clinical results from these different trials appear to be validating the superior performance of this category of product versus conventional therapies.

Manufacturing standards are available, including clear standards for GMP and good tissue practices from FDA,[7] Preti said, and the Alliance for Regenerative Medicine[8] has standards covering different types of therapies. The Foundation for the Accreditation of Cellular Therapy has standards that draw on FDA regulations and guidelines and guidelines for quality in blood banking operations, Levine added. The University of Pennsylvania, for example, has an accredited facility. Standards are important, and a public–private partnership has established a standards coordinating body

[7]Information on drug applications and Current Good Manufacturing Practice (CGMP) regulations can be found on FDA's website here: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/Manufacturing/ucm090016.htm (accessed August 29, 2017).

[8]The Alliance for Regenerative Medicine launched the Standards Coordinating Body for regenerative medicines in 2017. The Standards Coordinating Body website can be found here: https://www.standardscoordinatingbody.org (accessed August 29, 2017).

for the industry. However, he said, past attempts to develop common analytics and assays have failed, and he said that he did not see industry sharing assays and analytics.

Collaborations will be important in addressing technical challenges as the regenerative medicine industry moves forward, Levine said, and academic institutions and companies can only do so much in isolation. The National Institute of Standards and Technology (NIST) and FDA can play a critical role, he said, particularly where the regulatory realm and analytical standards are involved. The National Academies' Forum on Regenerative Medicine has a unique and important role to play in bringing all of the necessary parties together to talk about how to address the challenges this industry faces as it moves forward, Levine said.

3

Identifying and Measuring Critical Quality Attributes

Highlights Presented by Individual Speakers

- Developing and validating assays for CQAs as early as possible in the pre-clinical product development process leads to better decision making at each step along the translation process and more confidence that an observed effect is reproducible in the clinical phase. (Deans, Plant)
- Understanding an assay's parameters and the points at which variability can occur makes it possible to create an assay protocol that generates comparable inter-laboratory results. (Plant)
- Developing assays that generate comparable data and that allow for a better understanding of the important characteristics of a given product or system will facilitate learning from one another's experiences, sharing those data, and perhaps developing a better understanding of the biological mechanisms of action, thereby enhancing product development. (Plant)
- The time to design and undertake CQA testing is during original product development, when transferring technology, and whenever the manufacturing process changes. (Kelley)
- Establishing acceptance criteria using known reference and patient samples before clinical trials and identifying critical reagents will help streamline the manufacturing process. (Kelley)

- Product development can be effective when there is a breakthrough clinical effect associated with a well-understood mechanism of action such as in the products resulting from the development of CAR T cell technology. (Deans)
- Quality attributes for safety, such as the formation of ectopic tissue and teratogenicity, have not been adequately developed and are rate-limiting factors in the clinical development pipeline. One potential solution may involve implanting cells into pre-existing tumors, which would provide a tumor microenvironment in which to test for the development of teratomas. (Deans)
- The field needs better models to predict what will happen to a cellular therapy inside the human body. (Plant)

Methods and processes used to identify and measure CQAs for raw materials and regenerative medicine products were examined during this session. The three panelists—Anne Plant, the chief of the biosystems and biomaterials division at NIST; Linda Kelley, the director of the cell therapies processing facility at the Moffitt Cancer Center; and Robert Deans, the chief technology officer at BlueRock Therapeutics—discussed measurement methodology and approaches to ensure that measurements are accurate and reproducible. They also described future needs and new technologies for measuring CQAs.

ACHIEVING CONFIDENCE IN MEASUREMENTS FOR REGENERATIVE MEDICINE PRODUCTS

The process of defining and measuring the critical characteristics of regenerative medicine products is often listed as one of the fundamental challenges in the field, Anne Plant told the workshop participants. "Figuring out what the quality attributes are that define a product is not a straightforward thing to do," she said. The quality attributes of regenerative medicine products can include identity, quantity, purity, sterility, viability, and markers of biological activity, Plant said. While FDA defines a number of quality attributes that must be provided with any regulatory submission, there are many different types of products in development, each with its own set of unique characteristics, making it challenging to develop common assays for product characterization. Furthermore, Plant said, for many regenerative medicine products that are in development there is not yet a complete understanding of their mechanisms of action. As a result, it can be unclear what needs to be measured in order to assess biological activity or identity.

Furthermore, it is often unclear which in vitro metrics will predict in vivo activity, Plant said, which can be challenging when the goal is to

develop products that are both safe and effective at treating disease. Gaps in fundamental knowledge about biology are partly to blame for this situation, she said, but so too is the fact that there are many variables in the analytical assays and in the differences between the samples harvested from the patients who will receive these therapies. Because there are so many assay and sample variables, it is difficult to design experiments and measurement methods that can get a handle on all of these things simultaneously, Plant said. To complicate the situation even more, the cells and tissues under study are dynamic, living entities that are growing and possibly even changing.

Defining CQAs for a particular product is challenging without accurately measuring endpoints. It is important to ensure correct measurements, Plant said, but it is also important to take measurements that are meaningful to the clinical outcome. Ensuring the comparability of measurements is another major challenge for researchers and product manufacturers in this area, she said. Given the complexity of the measurements needed to characterize these products, she continued, it is important to have confidence that measurements can be compared. Comparability is especially important because there may be many changes to how a material is handled as a process moves from the research laboratory to the manufacturing setting, Plant said. Changes during the scale-up process can include new raw materials, new suppliers, new storage conditions, and even new technicians. Therefore, she added, product characterization is needed as the manufacturing process changes to make sure that the product generated in the manufacturing pipeline has the desired characteristics. If manufacturers are unable to demonstrate that a product has the same characteristics as it did in the past, they may be asked to perform additional experiments or even perform another clinical trial, Plant said. She noted that there is FDA guidance about how to qualify and validate measurements.[1]

Characterizing an assay's precision, reproducibility, accuracy, robustness, sensitivity, specificity, dynamic range, response function, and limit of detection can lead to confidence that measurements are yielding data that can support good decision making, Plant said. Knowing these variables can help manufacturers draw comparisons during the process of scaling up and allows them to have confidence that when they get an answer that is unexpected, it is due to changes in the product and not the assay.

FDA requires validated assays for registration-enabling clinical trials. However, Plant said, validating assays as early as possible leads to better decision making at each step along the translation process and to more

[1]The FDA guidance document *Potency Tests for Cellular and Gene Therapy Products* is available here: https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/cellularandgenetherapy/ucm243392.pdf (accessed August 11, 2017).

confidence that an observed effect is real. Developing confidence in an assay and collecting accurate measurements may be easier in the pre-clinical stage, she said, because there will be less variability in the samples being tested.

In Plant's experience, academic researchers will often not have a problem getting reproducible results from an assay in their laboratories, but when results of that assay are compared across laboratories, the results can vary considerably. One approach to addressing this issue is to go back and re-examine the parameter space and where variability in an assay can occur; by doing so, it is possible to create an assay protocol that generates comparable inter-laboratory results. "That gives you confidence that you know what you are measuring and that your measurement process is under control," Plant said.

In some cases, the availability of reference materials can lead to measurement assurance. For example, NIST is using a standard reference material to calibrate flow cytometry beads made by different manufacturers.[2] Calibrating each manufacturer's beads to the NIST reference material will mean that each manufacturer's beads will be normalized to one another, Plant said. In other cases, when the measurement is too complex for a reference material composed of cells, it may be possible to build rigorous statistical models based on fundamental principles that researchers can use to evaluate relative precision and accuracy, as NIST has done for cell counting, she added.

Plant noted that a NIST-led consortium, in partnership with the Standards Coordinating Body, is working to improve measurement assurance in gene editing.[3] This project will compare existing assays, define minimum metadata to report, design benchmark materials, and compare informatics platforms. A number of elements can contribute to more robust assay development, Plant said, including

- inter-laboratory studies
- experimental design
- testing assumptions
- traceability to a reference material
- statistical methods
- assay qualification
- consistent reporting

[2]Background information on the Flow Cytometry Quantitation Consortium can be found here: https://www.federalregister.gov/documents/2016/07/15/2016-16761/flow-cytometry-quantitation-consortium (accessed August 16, 2017).

[3]More information about the NIST-led consortium on measurements in gene editing can be found here: https://www.nist.gov/programs-projects/measurements-targeted-genome-editing (accessed August 15, 2017).

While working through this list can be time consuming and requires a great deal of effort, doing so may reduce the risk of making decisions based on wrong answers and potentially slowing down a development project, Plant said. Community efforts can mitigate the challenge of working through this list, she added, and standards development organizations can be good partners in such an effort. These organizations can codify best practices and define reliable protocols. Workshops, white papers, and data sharing can then spread these best practices and reliable protocols.

In summary, Plant said, developing assays that generate comparable data and allow for a better understanding of the important characteristics of a given product or system will allow the researchers and manufacturers in the field to learn from one another's experiences, share those data, and perhaps develop a better understanding of mechanisms of action and complex biology. NIST is trying to help the regenerative medicine field through hosting a number of workshops, many held in collaboration with FDA,[4] she added.

POSSIBLE OPPORTUNITIES AND CHALLENGES FOR DETERMINING CRITICAL QUALITY ATTRIBUTES IN EARLY-PHASE CLINICAL TRIALS

The comparability testing of CQAs could be carried out more efficiently by tapping into global collaborations as a way of accessing a larger number of patients and managing costs, Linda Kelley said. As of April 2017, there were 55 approved cell-based therapeutic products (Bersenev, 2017), and only one-third of those had received regulatory approval in the United States. This difference is due in part to the geographic location of the patients who participated in clinical trials, Kelley said, but it is also a result of new infrastructures that are being implemented in other countries. The number of industry-sponsored and academia-sponsored clinical trials continues to increase, she said, making partnerships between industry and academia more common as a means of leveraging the science, know-how, and cost-sharing (see Figure 3-1).

When such collaborations first started, there was a very steep learning curve on how to make them work, Kelley said, but that learning curve is starting to plateau. Valuable experience has been gained on how to make these collaborations effective, she said. Nonetheless, global collaborations still have constraints, particularly in navigating the different regulatory frameworks that exist worldwide. In the United States and Europe, for

[4]Additional information from NIST on regenerative medicine biomanufacturing can be found here: https://www.nist.gov/programs-projects/regenerative-medicine-biomanufacturing (accessed August 11, 2017).

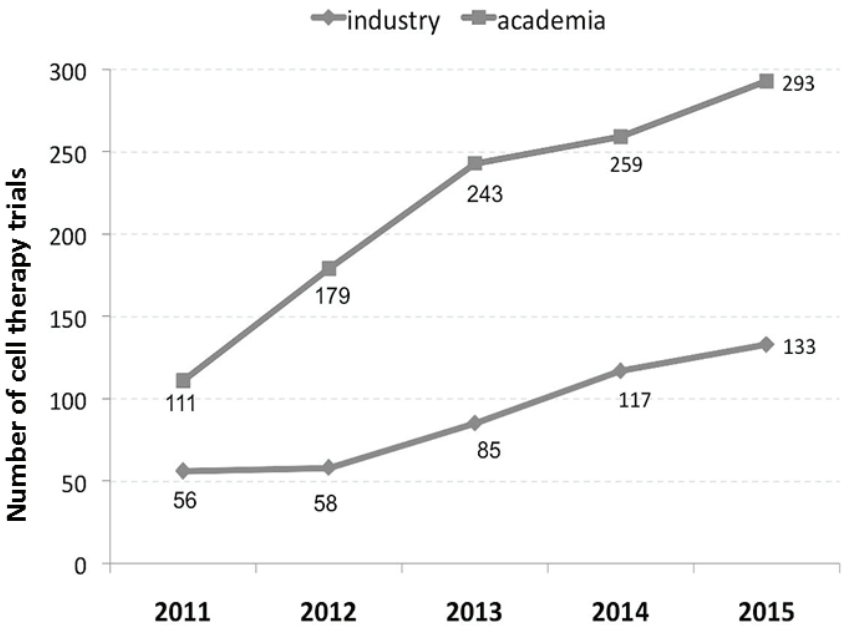

FIGURE 3-1 Total number of academic versus industry-sponsored cell therapy trials, listed in databases.
SOURCES: Linda Kelley, National Academies of Sciences, Engineering, and Medicine workshop presentation, June 26, 2017. Originally from A. Bersenev. 2016. Number of academic versus industry-sponsored cell therapy trials, listed in databases. https://doi.org/10.6084/m9.figshare.1504124.v4 (accessed August 11, 2017).

example, select cell and tissue products require pre-market approval, while in Japan many of the products are considered on a decision-to-treat basis. With regard to CQAs, the U.S. Pharmacopeia (USP) and the European Pharmacopeia play similar roles.

As an example of an international, multi-centered trial, Kelley discussed her experience carrying out Phase I and Phase II clinical trials with autologous CAR T cells. The trial originated in Brussels and included her institution in Tampa, Florida. Part of the purpose of the collaboration was to treat patients in both countries and to manufacture the cell products in two places. The idea, she explained, was not for her facility to manufacture cells for U.S. patients and for her collaborators in Brussels to be manufacturing cells for European patients, but rather for the products created at the two

sites to be interchangeable. By creating redundancy in their manufacturing capacity, the hope was that this would allow the team to mitigate issues that arose at one site by potentially allowing manufacturing to continue at the other site, she said. Another reason for the dual site manufacturing was to create flexibility in the production process to accommodate the European regulatory agency's regulations regarding audits that can require facilities to shut down completely.

The challenge for Kelley and her collaborators was to demonstrate that the two manufacturing sites could produce comparable products so that the data from both sites could contribute to the results of the clinical trial. The process of creating autologous CAR T cells is lengthy and can take approximately 3 to 4 weeks, Kelley explained. The first step involves collecting T cells from a patient, and this is followed by transduction, expansion, and cryopreservation of the cells. Next the cells are subjected to a variety of quality control assays and release tests before the final product is shipped for treatment of the patient.[5] Kelley and her colleagues hypothesized that by making sure that these steps were executed in the same way in both locations, they could create the same product in both facilities.

Ideally, Kelley said, the time to address CQA testing is during the original product development and also during technology transfer and whenever the manufacturing process changes. In the case of this particular collaboration, both she and her collaborators started with well-validated analytical methods with well-developed standard operating procedures, although at first there was no consensus between the two groups as to whose methods were the best. Where possible, the collaborators used known reference samples, and they used actual patient samples when doing their comparability testing. The collaborators also identified critical reagents, and in their initial studies the two groups shared exactly the same reagents, not just reagents from the same vendor or with the same lot number. The two groups established acceptance criteria, a process that required having technical experts in the same place at the same time. Ultimately, the team from Brussels traveled to Kelley's laboratory and spent 1 month working on this approach.

Kelley and her collaborators went through the process of establishing acceptance criteria before they started tackling the manufacturing process. Given the desire of the stakeholders in the collaboration to begin the clinical trial quickly, Kelley said, it was challenging to convince some of them that this time-consuming approach was necessary, but with all the planning for logistics and resources it would have been difficult to do it all at the same time. By agreeing on CQAs, analytical methods, and acceptance criteria,

[5]Additional information on how CAR T cells are made and used can be found here: https://www.cancer.gov/about-cancer/treatment/research/car-t-cells (accessed August 15, 2017).

Kelley and her team gained confidence in the products they plan to manufacture in this collaboration moving forward (see Table 3-1).

Implementing timely and cost-effective CQA rapid release assays has been particularly challenging, Kelley said. One example concerned sterility testing, which has been a subject of conversation with regulators and stakeholders in the field for a long time. Currently, FDA requires that all parenteral biological products undergo sterility testing to ensure that the products are sterile when they reach the patient. Previously, the gold standard assay for sterility testing was the compendial sterility method, which takes 2 weeks, but FDA has now sanctioned validated and automated systems for sterility testing such as BacT/ALERT and BACTEC. Historically, the automated systems utilized culture media that is only FDA approved for testing blood products, and therefore they are being used off-label for cell therapy products. New media for sterility testing has recently been introduced to the market with enhanced characteristics that make them more appropriate for cell therapy products (e.g., "industry bottles"), Kelley said. There is good reason to move forward with using this type of technology, she said, but it will require lengthy revalidation. Revalidation can be a time- and cost-intensive process, but Kelley said she is planning on moving forward with a new study with the help of consultants to demonstrate the value of using industry bottles in her laboratory. In thinking about testing for every

TABLE 3-1 Critical Quality Attributes, Analytical Methods, and Acceptance Criteria

Criteria	Methods	Limits
Viability	Flow cytometry	≥ 70%
Purity (CD3+ cells)	Flow cytometry	≥ 80%
Cell count	Flow cytometry	Specified dose ± 25%
Identity (NKG2D+ cells)	Flow cytometry	≥ 50%
Microbiological tests		
• Sterility	Ph. Eur. 2.6.27	No growth
• Endotoxin	Ph. Eur. 2.6.14	≤ 8.67 EU/mL
• Mycoplasma	Ph. Eur. 2.6.7	No mycoplasma
Safety tests		
• Vector copy number	Ph. Eur. 2.6.21	< 5.0 copies/cell
• Replication Competent Virus	Ph. Eur. 2.6.21	No detection

NOTE: CD3 = cluster of differentiation 3; EU/mL = Endotoxin units per milliliter; NKG2D = natural killer group 2, member D; Ph.Eur = European Pharmacopoeia.
SOURCE: Linda Kelley, National Academies of Sciences, Engineering, and Medicine workshop presentation, June 26, 2017.

organism on the U.S. and European Pharmacopeia lists, Kelley held discussions with both organizations about reasonable expectations, and she was able to narrow the list based on the likely contaminants.

Another challenge Kelley mentioned was related to testing for replication competent retroviruses (RCRs), which, if present, can result in multiple integrations within host cell genomes and potentially lead to oncogenesis. RCR testing is currently required by FDA if a cell product is in culture for more than 4 days after transduction. However, a 2012 study found no RCR-positive samples across 29 ongoing gene therapy trials, Kelley said (Bear et al., 2012). Based on their findings, the study authors proposed that master cell banks used for production of infectious virus should continue to undergo rigorous RCR testing but argued that final T cell products that incorporate retroviral vectors and patient peripheral blood samples do not need to undergo active screening at defined time intervals. The reason, Kelley said, is that the original RCR testing method is costly and lengthy. Despite the findings from the 2012 study, FDA requirements have not changed, she said. Therefore, most groups are migrating to using quantitative polymerase chain reaction assays, a faster and more cost-effective option, she said. Doing so requires each laboratory to validate their assays, which can be time-consuming and costly. In closing Kelley asked, "Are we requiring too much for validation and not embracing the recommendations of scientists in the field?"

A COMMERCIAL PERSPECTIVE ON BUILDING PRODUCT ATTRIBUTES

In the early phase of translating products into the clinic, investigators often worry about the core biological hypothesis and demonstrating that the therapeutic approach is safe, said Robert Deans, the third presenter in the session. Regulatory agencies encourage that focus by asking questions of investigators about proof points and whether their methods and assays are providing statistical confidence regarding pre-clinical and early clinical results. On the commercial side, however, there are other attributes that become important, such as whether the product will meet effectiveness endpoints, if it can be produced at a reasonable cost that payers will reimburse, and whether physicians will adopt the new product.

To address these concerns as early as possible in the commercial phase of development, Deans said, companies build what is called a target product profile to guide decisions over the course of the development process (see Box 3-1). The target product profile is an extensive document that covers both the biological properties of the product and its safety and quality

BOX 3-1
Example of Questions Addressed in a Target Product Profile (as presented by Deans, June 26, 2017)

- Is the mechanism of action for the product well-defined and measureable for bioprocess development?
- Are the clinical endpoints quantitative and strongly linked to the mechanism of action?
- What improvement or innovation in patient response against standard of care merits development resources?
- Are the manufacturing attributes or product composition measureable and sufficient to ensure competitive edge (i.e., trade protection)?
- Will patients use the product? Is it easy to deliver?
- Can patients afford the product?

attributes.[6] It also addresses many of the product's financial and commercial considerations, such as whether the ease and frequency of delivery is linked to compliance problems and whether patients can afford the product.

The wave of new products resulting from CAR T cell technology shows how effective product development can be when there is a major clinical effect tied to a well-understood mechanism of action, Deans said. Also important from a commercial perspective is the ability to forecast how technological advances, such as the development of gene editing and gene therapy, might affect how competitive a product will be in the future against the current standard of care approach.

To demonstrate how a company assesses important product attributes, Deans discussed two examples. The first concerned an assay his company developed to demonstrate potency for a mesenchymal stem/stromal cell (MSC)[7] product in the cardiovascular area. Once industry scientists had identified what Deans called the black box benefit they observed when their cells were injected into an in vivo animal model, they developed an in vitro surrogate assay that had comparable benefits to those seen in the animal model. The company next worked on identifying a negative control by using a cell line that did not stimulate angiogenesis, Deans said, and it used

[6]The FDA Guidance for Industry and Review Staff on the target product profile can be found here: https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm080593.pdf (accessed September 19, 2017).

[7]The term "mesenchymal stem cell" is often used interchangeably with "mesenchymal stromal cell" or "multipotent stromal cell." MSCs are a diverse population of multipotent cells that include osteoblasts, chondrocytes, myocytes, and adipocytes.

that cell line to compare proteomic and transcriptional profiles and identify key parameters that differed between the successful product and the unsuccessful product. The company also used genetic knockdown and antibody inhibition to find the core angiogenic factors involved in the product's beneficial effects. The knockdown models enabled the company to add those factors back in order to get an understanding of the minimal threshold for biological activity. This approach gave Deans and his colleagues a statistical basis for defining pass/fail criteria. Using the information gained from these studies, company researchers were able to quantify how its production lots varied in terms of their functional performance and the measurement of these parameters (Lehman et al., 2012). This effort resulted in these assays being implemented in a lot release assay panel and also in the development of intellectual property around cell composition.

Overarching Challenges to Product Identity Testing

On the subject of product identity testing, Deans said that he sees many potential challenges with using individual markers or cell surface markers as a distinguishing mark if they do not correlate to a specific cellular function. Instead, his company has used a unique approach to identify a functional distinction between its product and another product and then defines a molecular surrogate that correlates with that distinction that could be used reproducibly as an assay for in-process development or lot release. Deans and his colleagues took a reductionist approach to characterizing the cell type using a number of different epigenetics-based methods, including transcriptional profiling, gene methylation, miRNA profiling, and proteomic surveys. Next, they analyzed many donors, bioprocess variants, and a competitor's product to understand the principal components that defined their product. This analysis identified a block of microRNAs that can regulate a cascade of genes that reflect functions within their cell population, and further studies across the manufacturing process resulted in a fingerprint profile for miRNA patterning that serves as a rapid process and lot release assay (Crabbe et al., 2016). miRNA-mRNA interactions and cell phenotypes were studied and Deans and his colleagues concluded that miRNA markers could be linked to cell differentiation and cycle cell regulation in human MSCs and multipotent adult progenitor cells.

With regard to the attributes of living medicines such as CAR T cells or MSC products, Deans said, it is important to understand how cells distribute, amplify, and persist in vivo, and currently there are only poor surrogates for these biological attributes. For example, the patient response to CAR T cell therapies is poorly linked to cell production numbers. Circulatory distribution and tissue penetration are critical therapeutic attributes, he said, yet those do not have sufficient in vitro surrogates.

Another area that needs further study, Deans said, is the development of standardized attributes for safety, such as the formation of ectopic tissue and teratogenicity. These measurements have not been adequately developed and are major rate-limiting factors in the clinical development pipeline. The current teratogenicity assay, in Deans's experience, takes about 9 to 12 months in immuno-compromised mice and can cost upward of $1 million. The time and expense of this assay is precluding the field from doing comparability studies between embryonic stem cells and iPSCs, he said, and is hindering the development of personalized iPSC therapeutics. A challenge for the field, he said, will be to develop efficient and effective assays linked to key safety attributes so that the development cycle can accelerate. One potential solution may involve implanting cells into pre-existing tumors, which would provide a tumor microenvironment that might speed up the development of teratomas, if they were going to develop at all.

It may be challenging for the community to come together to define quality attributes or standards, Deans said. One reason is that therapeutic sponsors do not want to reveal upfront their cell sourcing or gene manufacturing trade secrets. As a result, most co-development opportunities focus on downstream processing. Analytical testing and assay development are two areas that are ripe for co-development, Deans said, and the field could benefit from pursuing those opportunities. However, he added, tool providers and contract manufacturers are not enthusiastic about leveling the playing field and making all processes common.

Therapeutic societies have focused on assay harmonization and have constructed assays for key product class attributes. However, these organizations do not have much leverage for encouraging widespread adoption of those assays across the field. Societies are often unaware of standards-setting organizations and the processes involved in having assays accepted as standards by those organizations, Deans said. He commended NIST for working with the Alliance for Regenerative Medicine to build a standards coordinating body.

Regulatory Pathways and Commercial Development

In closing, Deans said that regulatory science is changing industry's development strategies. Regulatory approval pathways have become critically important levers in commercial development, he said, particularly with regard to securing capital to continue development. Those pathways are also having a significant effect on regional economic development in the life sciences. The regulatory pathway in Japan has an accelerated approval option that is aimed at measuring safety and efficacy, Deans said. Allowing more rapid market approval and cost recovery for clinical trials has

resulted in products reaching the market faster, and post-market studies have allowed for the collection of additional data and statistical depth, which helps to stratify patients and further refine product indications. Australia's regulatory process features two distinct pathways. One of them, the Clinical Trial Notification path,[8] allows for the accelerated entry of emerging therapeutics, Deans said. Companies are required only to have an institutional review board approval regarding the safety of a manufactured product before beginning studies looking at early patient experience. This has led an increasing number of companies to perform first-in-human trials in Australia followed by Phase I or Phase II trials back in the United States or Western Europe, he said. It is very important to figure out how to gain early human clinical experience in a safe and responsible way, Deans concluded.

DISCUSSION

Novel Technologies for Improving Cell-Based Manufacturing

Synthetic biology may offer new avenues for programming cells to grow and differentiate as part of the manufacturing process, but safety testing standards associated with gene editing and gene modification have yet to be defined. One of the exciting things about this field is the merging of synthetic biology and genome engineering to create products, Plant said. There are still many details to work out, she said, which is why she is currently speaking with experts about the state of the science and the issues associated with using gene editing for therapeutic purposes.

With regard to whole-genome sequencing, Plant said that NIST formed a public–private academic consortium called Genome in a Bottle that is establishing important benchmarking data on a limited number of human genomes from de-identified individuals.[9] A number of groups using different platforms are sequencing these genomes and analyzing the results using unique bioinformatics tools. The goals are to compare methods, learn how they differ from one another, and perhaps identify those areas of the genome that are either easier or more difficult to sequence with confidence. "I think that those kinds of benchmarking data will help us understand how to interpret whole-genome sequencing and some of the slight modifications that might show up, whether they are real or not, and whether they are meaningful or not," Plant said.

[8]For more information on the Clinical Trial Notification pathway and the Australian scheme for clinical trials, see https://www.tga.gov.au/clinical-trials-glance (accessed August 14, 2017).

[9]More information about the Genome in a Bottle consortium is available here: http://jimb.stanford.edu/giab (accessed August 14, 2017).

The pace of technology may be outstripping the ability to establish and implement an assay, Deans said. "We are going to get way in front of ourselves with potentially very effective new therapeutics and an inability to understand the development path."

One workshop participant described an effort in his laboratory to use artificial intelligence to define the quality of cell therapy products as part of ongoing work to develop an autologous iPSC-derived retinal pigment epithelium patch for retinal regeneration. His team is developing an imaging-based convolutional neural network, which is a computing system inspired by physiological neural networks that is used to analyze visual imagery. The research goal is to use the convolutional neural network to effectively predict measurable cell functions. According to the workshop participant, the neural network was powerful enough that with one training session it could differentiate among the quality of cells and could potentially be implemented during the manufacturing process across different centers with no raw materials required for the assay. He said that his concern was how to validate this type of system for regulatory purposes.

NIST is very interested in this type of approach, Plant said, adding that she and her colleagues are learning what would be required to validate it for regulatory purposes. The challenge, she said, is deciding who the experts are that develop a training set, given that one expert is likely to produce a different training set than another one would. The key will be to validate the algorithm and training sets against a thoroughly validated functional assay.

Sharing Data in the Pre-Competitive Space

Both the issue of assay variability and the challenges associated with getting people to share assays were raised by speakers in this session. Martha Somerman, the director of the National Institute of Dental and Craniofacial Research of the National Institutes of Health, asked panelists if they had any suggestions on how to improve data sharing efforts in the field. One suggestion was to start in the pre-competitive space. It may be challenging to share information about characteristics or CQAs of a particular product, Plant said. An easier approach might be to encourage sharing of information about analytical methods or tools that everybody uses, such as approaches for counting cells reliably. Regardless of where the process starts, she said, it has to be a grassroots effort. The Standards Coordinating Body is putting together several projects in the pre-competitive space, said workshop co-chair Claudia Zylberberg.

Deans said that the problem he sees in co-development is the high expense of generating raw materials for testing. "One of the barriers to getting standardized testing or getting group assessment of common mate-

rials is deciding who is going to pay for the process," he said. There may be opportunities for the clinical academic community to develop and use CQA assays related to function much earlier in the development process (i.e., before researchers turn a product over to the commercial sector). CQA assays should be used as early as possible, Deans said, and he predicted that as the field gets feedback from some of the epigenetic analyses from patient follow-up assays, academic laboratories will start using those data in their work. "We are really just beginning the cycle of going from bedside back to bench," he said. "I think we are now positioned to apply those early, apply them to mode of action, and then have improved processes going forward."

Regarding early phase clinical data, there is an opportunity for the collection and dissemination of more epigenetic analyses and clinical trial data including that of patients treated with placebos, Deans said. Sponsors are logically and justifiably conservative about revealing patient response data, he said, but there is information on placebo or control groups that, if deposited into a public database, would be extremely helpful. Making that happen, however, will require an edict from a reputable organization, he said.

Potential Opportunities for Developing Reference Materials

The MSC research community has debated the value of a gold standard reference MSC line and the idea of agreeing on standards that adequately define an MSC product, Deans said. It can be frustrating that the community has not been able to agree on a consensus identity definition or to work collectively together to harmonize cell characterization, he said, noting that there currently a few hundred different names being used to describe very similar cell products. The field should define the cell type by the bioprocess used to make it, not by phenotypic comparisons or epigenetic traits, he said, in addition to creating functional profiles and assays that correspond to phenotypic or epigenetic traits.

Together with the World Health Organization (WHO), international reference laboratories such as the National Institute for Biological Standards and Control in the United Kingdom have played a critical role in providing standards and assays as well as in funding that work, one workshop participant said. WHO has shown interest in the cell therapy area and NIST often collaborates with it, Plant said, though its way of generating standards differs slightly from NIST's approach.

Ongoing Financial, Logistical, and Technical Challenges

The inter-laboratory comparison that Kelley and her colleagues undertook was expensive and required having people from the laboratory in

Brussels come to Tampa and live there for 1 month, something that will happen again when the researchers start the transfer of manufacturing technology. In the end, though, the results were valuable, and, perhaps more importantly, a consensus developed within the team and team members gained the confidence to move forward as true collaborators who are on the same page.

A unique challenge to certain cell-based regenerative medicine products is that part of the manufacturing process occurs in the patient, where the cells expand, proliferate, and change phenotype after injection. A workshop participant asked the panelists for their thoughts on the responsibilities that developers have to understand that part of the process and what type of assays might be needed to understand what is happening to the product. It depends on the cell type and the purpose of using that cell type, Kelley answered. One approach that she is taking is to address the specificity of the cell types her team is manufacturing using real-time assays that look at appropriate function over time. Currently, she said, her group is in the process of collecting enough data to determine if there are CQAs that are more meaningful and that can be incorporated into the manufacturing process cost-efficiently. There are many new technologies becoming available for quickly screening for cytotoxicity, phenotype, and other important attributes that the field could explore, she said.

Biomedical imaging with novel tracers—an approach that needs to be further developed—might provide information on cell persistence, Deans said. The field needs model systems to predict what will happen inside a patient, Plant said. "Everything we are going to be measuring is in vitro, and we are assuming the environment we are creating in our in vitro assays has something to do with the in vivo environment," she said.

When conducting an evaluation of comparability based entirely on in vitro assays, it is important to know what the CQAs are, but in many cases, a workshop participant said, they are not known. It may be helpful to identify an experimental in vivo situation that can distinguish in a meaningful way between a product that works and one that does not as well as determining what magnitude change in an attribute results in a product that does not work. The true population variance of many of these parameters may make it difficult to conduct a study with sufficient statistical power to know if the difference between two products is real. Getting all the critical process parameters worked out early in development can save many headaches down the line, the participant noted.

4

Designing Technologies to Meet the Manufacturing Needs of New Regenerative Medicine Therapies

Highlights Presented by Individual Speakers

- Early in the treatment development process consider what data should be collected by academic institutions so as to ensure a smooth transition to industry partners during the manufacturing stage. (Rivière)
- Reverse transfer of manufacturing technology from industry to academia could accelerate the development of new cell therapies and make processes more efficient. (Rivière)
- Automating the manufacturing process will be critical for producing safe, robust, reproducible, and cost-effective regenerative therapies. (Rietze)
- By focusing on analytic automation, manufacturers can better define the starting patient material and have a more in-depth understanding of the final product. This in turn improves the consistency of data collection across patients. (Rietze)
- Defining a user requirement specification (URS) is an important part of the process of developing a novel manufacturing device for automation that requires significant vendor input. Ultimately, those specifications will help ensure that a device best meets stakeholder needs for improving a manufacturing process. (Rietze)

- To improve the scaling and manufacturing of cellular therapies, product developers should focus on managing risk, understanding basic biology, and data management and transfer instead of concentrating on cost per dose. (Vanek)
- The optimal time to alter a variable in the manufacturing process is before or during Phase I clinical trials. (Rivière, Vanek)
- For autologous therapies it is important to identify patients' active cells and develop methods for isolating those cells in order to reduce dose size, manufacturing scale, and the ultimate cost of a therapy. (Rietze, Rivière, Vanek)
- Determining whether new and high-risk technologies for manufacturing cellular therapies (such as microfluidics) are more cost-effective than existing technologies will require device companies to share the financial risk for new product development. (Rietze)

Speakers in the workshop's third session explored existing technologies and new enabling technologies that could facilitate the efficient and cost-effective development of regenerative medicine therapy products that meet manufacturing and regulatory standards. Three panelists—Isabelle Rivière, the director of the cell therapy and cell engineering facility at Memorial Sloan Kettering Cancer Center; Rodney Rietze, the lead of current GMP (cGMP) process automation for cell and gene therapies at Novartis; and Philip Vanek, the general manager of cell therapy technologies at GE Healthcare—discussed opportunities for new technologies and manufacturing models that could increase efficiency and product quality, and they also considered novel and more precise technologies for in-process and final release testing. The panelists described the open and closed system models (i.e., systems in which cell cultures, respectively, are or are not exposed to the external environment during the manufacturing process) applicable to the manufacturing setting, and they discussed the feasibility of manufacturing therapies at the point of care. The discussion that followed focused on tools and models that could be developed and implemented to make the manufacturing process more efficient.

MODELS FOR MANUFACTURING CELL THERAPY PRODUCTS

Researchers at Sloan Kettering have helped develop a number of cell therapy platforms over the past 15 to 20 years, including CAR T cells for treating solid and hematologic cancers and platforms to genetically modify hematopoietic progenitor and stem cells for treating genetic deficiencies and cancer, Rivière said. More recently, she and her colleagues have worked on

producing cells derived from embryonic stem cells and iPSCs by differentiating them in various tissues for treating Parkinson's disease and cancer. They also have experience with various genetic platforms for modifying embryonic stem cells and iPSCs that they are developing in collaborations and in consortia with academic and industry partners.

Focusing on her team's experience manufacturing CAR T cells, Rivière described how they have taken advantage of the unit operations that are available for manufacturing these cells, breaking down the process into discrete steps, which has allowed them to develop a robust platform for manufacturing CAR T cells for a number of oncology indications (Hollyman et al., 2009; Przybylowski et al., 2006; Themeli et al., 2015), including acute lymphoblastic leukemia (see Figure 4-1 for the manufacturing process flow).

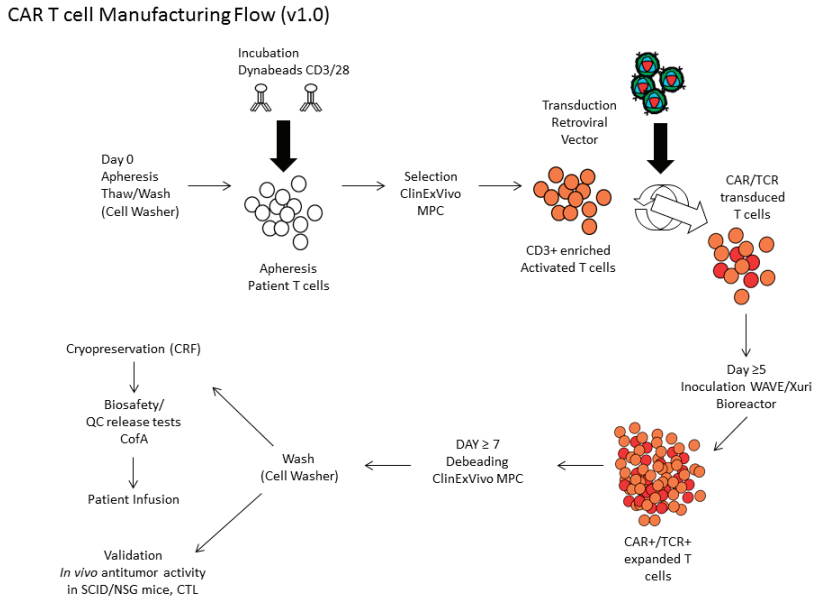

FIGURE 4-1 CAR T cell manufacturing flow at Memorial Sloan Kettering.
NOTE: CAR = chimeric antigen receptor; CofA = Certificate of Analysis; CRF = controlled rate freezer; CTL = cytotoxic T lymphocyte; MPC = magnetic particle concentrator; NSG = NOD scid gamma; QC = quality control; SCID = severe combined immunodeficiency; TCR = T cell receptor.
SOURCES: Isabelle Rivière, National Academies of Sciences, Engineering, and Medicine workshop presentation, June 26, 2017. Adapted from Figure 1: Scheme of the manufacturing process, in Themeli et al. (2015), and Figure 3: General schema of autologous T cell manufacturing in Hollyman et al. (2009).

One clinical trial using these CAR T cells been able to observe 77 to 90 percent of complete remission in patients with this disease (Park et al., 2016). Sloan Kettering researchers are conducting additional clinical trials in other leukemias, lymphomas, and solid tumors, and her team has used this process to produce more than 200 products, most of which have been infused into patients, she said. The team also uses this manufacturing scheme to make products for collaborators at other sites, and they have been able to transfer the manufactured products to their trial partners.

Potential Ways to Optimize the Manufacturing Process

Despite these successes, Rivière and her collaborators have encountered several challenges to maintaining the robustness of the manufacturing platform. Some of these challenges, she explained, are inherent to the apheresis products, given that hospitals perform this step on many different devices. Patient apheresis products also vary according to the specific disease, the stage of the disease, and any previous chemotherapy a patient has received. One approach the Sloan Kettering team uses to decrease the variability of the incoming apheresis product is to start by selecting cell types that will create a more homogeneous starting material; however, Rivière said, a current limitation is that the product developers have yet to define the active cells within the CD3, CD4, and CD8 populations. While selecting subsets of cells and removing undesirable cell types is important for streamlining the manufacturing process, she said, the limited number and high cost of GMP antibodies used to select the starting material limits the applicability of this approach.

Another issue that Rivière's team has encountered is the limited availability of reagents that are not encumbered by intellectual property concerns. At one point her group had to change the magnetic beads used to activate T cells because another user had exclusive rights to use the beads in a commercial application. Eventually, Rivière's team modified the process to eliminate the use of magnetic beads altogether, which had the added benefit of simplifying the manufacturing process. They are now validating the new process, which is proving to be a challenge because they do not know the precise identity of the active ingredients in their cell products. For validation, Rivière and her colleagues are using a well-calibrated in vivo antitumor activity model, but it is a slow and tedious approach to assess comparability. Her hope is to develop an in vitro model that can be used to assess comparability and accelerate their current process, given that her team is also refining and improving other steps in the manufacturing process.

Working with equipment providers to develop better tools for the manufacturing process is something that her team would be interested in

doing, Rivière said. For example, the cell washers her team uses perform well, but the current process requires different cell washers to achieve the various desired parameters. Available cell separation techniques that do not require GMP antibodies are expensive today and are limited in the scope of the phenotypes they can select, something that Rivière said she hopes equipment manufacturers will address soon. Other pieces of equipment have only one manufacturer, raising concerns as to whether they will remain in business or if issues arise in their production chain.

Rivière offered several other lessons she has learned from her experiences transferring the manufacturing process to industry. For example, providing patient data to industry partners that would allow them to improve processes and develop new assays would be helpful, but her team has learned that it can be difficult to provide patient samples to industry partners, Rivière said, particularly if the consent forms signed by the patients at the time of treatment do not include permission to transfer their materials to other institutions. At her center, the transfer to industry of manufacturing data for analysis is relatively limited because of this reason. Thinking about transfer protocols and the type of data that need to be collected early in the manufacturing process could help ensure a more smooth transition from academia to industry, she said. The reverse transfer of manufacturing technology back to academia is also challenging because of intellectual property issues as well as the cost and time in implementing these changes at an academic center, she said. If the transfer of data and processes between industry and academia could be facilitated during Phase I clinical trials, Rivière said, we could accelerate the development of cell therapies in a much more efficient manner.

THE ROLE OF AUTOMATION IN MANUFACTURING

Automation is one key to producing a safe, robust, reproducible, and cost-effective therapy, Rietze said. What automation provides is the ability to control the process by removing the variability between operators and lowering the risk associated with variability, which should lead to fewer manufacturing failures and, ultimately, an increased rate of success and lower costs, he said. Focusing on analytics in the manufacturing process provides manufacturers with a deep understanding of the process and the opportunity for continual improvement of that process, Rietze said, describing how his group at Novartis went about automating and commercializing the CAR T cell production process that Bruce Levine and his collaborators developed at the University of Pennsylvania.

Designing a scalable and robust manufacturing process starts with the science and with understanding the product, how it is produced, and what mechanisms are available to control variability. Next, Rietze said, manufac-

turers must identify the key technologies needed to make the product and determine if there are off-the-shelf devices available to automate or remove variability in certain steps in the process. For example, an automated cell-washing device could replace centrifugation and get rid of the variability that comes from human involvement. In thinking about developing a process, he said, one should keep in mind that emerging technologies can play a role in automation. Even though it may require an investment in time and resources to integrate and validate a new technology, that investment can pay off if the technology can be used in other processes and in multiple unit operations. When his group was working on the CAR T cell process, Rietze said, they targeted specific unit operations for optimization to generate value and lower risk, and they started rethinking some of the analytics with an eye toward what assays would work best in an automated system.

With the device selected, the next step is to think about the manufacturing facility. For example, automated closed systems allow for processing to occur in rooms with less stringent classifications thereby reducing the burden on the facility's clean room and the need for biosafety cabinets, Rietze said. At the same time, automating one step in a process might eliminate the need for several individuals to perform a unit operation, but given how long it takes to leave and enter a clean room, workers might need something else to do while waiting to perform the next manual operation without entering and exiting the clean room, creating new challenges in workforce management. In the end, "the development and integration of automation changes your manufacturing, changes your process flow and your footprint, and it reduces your overhead and changes how you train your staff," Rietze said. The ultimate goal of automation is to enable a global supply of a product by moving from a manufacturing facility that may require more space for equipment down to a small space, thereby improving the efficiency of the manufacturing process, and then ultimately moving toward a device capable of manufacturing these products in a point-of-care device, he added.

Rietze described the roadmap (see Figure 4-2) of how he and his team developed the commercial version of the academic CAR T cell process. The first step was to define the highest need for each unit operation, and he did that by surveying each of the key stakeholders in his company, including its process operators, its analytical group, and management. These survey questions fell in the areas of safety, process, product, and cost. From the answers, his team generated a heat map showing that the highest needs were at the beginning and end of the process.

At that point the Novartis team identified and engaged providers to develop a novel device that reflected stakeholder needs. They built a project team and defined a formal user requirement specification (URS), an important step that involves defining what the new automated devices need to do, the environment in which they will do it, and the criteria to judge

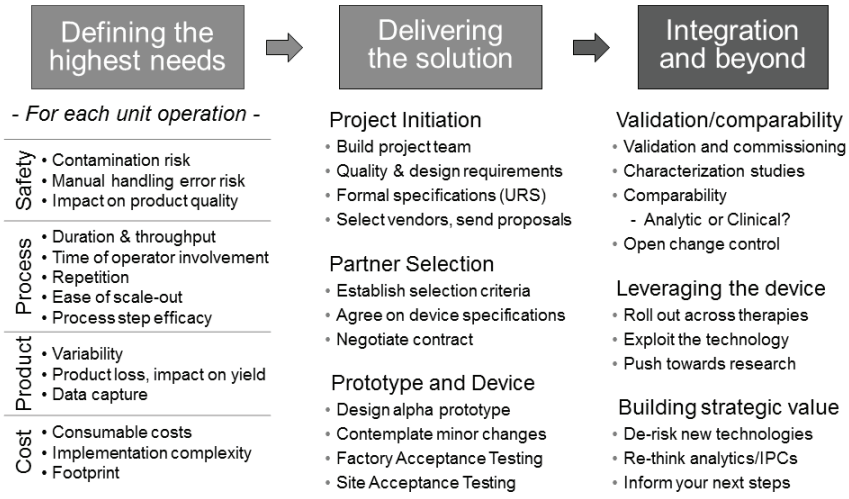

FIGURE 4-2 Roadmap for developing a novel manufacturing device.
NOTE: IPC = in-process control; URS = user requirement specification.
SOURCE: Rodney Rietze, National Academies of Sciences, Engineering, and Medicine workshop presentation, June 26, 2017.

whether the devices are successful. The team sent the URS to a number of vendors, selected one, and then moved through the device-manufacturing process, which involved building alpha and beta prototypes and testing them in-house. The final step before the integration of the devices into the manufacturing process was to conduct product characterization studies to determine if the devices changed the product.

It is important to begin to use the device in early research (as new products are being developed for the product pipeline) to enable the use of the same system that will ultimately manufacture those products as a means of lowering the barrier for process transfer, Rietze said. They also rethought the analytics and in-process controls since the device was able to do the same operation reproducibly.

The eventual device that the Novartis team settled on was named FlowSPA (Flow Sample Prep Automation, Acquisition, and Analysis), and it has the ability to automate flow cytometry-based analytics. This device, made by combining pre-existing technologies, starts with a liquid-handling platform to which the team added a flow analyzer to automate data acquisition from the liquid handler. A liquid handler reduces the high variability of manual pipetting, which allowed the team to use smaller volumes of

antibodies and yielded more accurate analytics, Rietze said. The team used publicly available data to develop a computer-controlled gating process for the cytometer, which made it possible to automate the analysis of the cytometer data. The idea is that the automation is not only about the cost of goods or a reduction in throughput, but also about a reduction in hands-on time, increased quality, and an increased consistency and integrity of the data that are generated, Rietze said.

Automating the analytics also allowed the Novartis team to develop a more in-depth understanding of the product and of the patient material it receives. This, in turn, improved consistency across hundreds of patients, Rietze said. Analytic automation also creates the possibility of more closely integrating the manufacturing process and the clinical process by breaking down data silos, he said.

The field of cell-based therapies is evolving, as are the analytics and devices, Rietze said. This evolution is leading to shorter manufacturing timelines and non-destructive and in-process analytics that remove the need for humans to "touch" the product. People involved in the field should understand that the patients affect the cells they provide, which in turn affects the manufacturing process and the drugs that the patients ultimately receive.

SCALING PERSONALIZED CELL THERAPY MANUFACTURING

Tool providers, or companies who develop enabling technologies such as bioprocessing equipment for manufacturing cellular therapies, have a different perspective than therapy manufacturers, Vanek said, because they have to be agnostic as to cell type or therapy and instead build platforms with broad applicability. When building a tool, it is important to identify the needs of the end user, he added. For cell-based therapies, those needs include operational excellence, compliance, reproducibility, and the ability to make a safe and effective product. One challenge, he said, is that companies come to GE Healthcare and ask for very broad solutions for their problems that also leave open the possibility of optimizing each unit operation. Everyone wants a future technology today, Vanek said, and that is a challenge for tool providers.

Tool providers must also take into account how the market will likely evolve, Vanek said, so to help forecast where technology needs to be in order to keep up with that evolution, he and his colleagues conduct market analyses to understand where CAR T cell therapy and gene therapies are going. For example, he said, projections indicate that the number of patients treatable with these therapies will increase and that the cost per dose will have to come down from its current cost of goods of greater than $100,000 per dose. The key, he said, is to not focus on the cost per dose,

but rather focus on managing risk, biology, and data. "The rest will come with scale and better integration and automation," he said. New and better therapies will be coming, and the number of patients treated with these technologies will increase, and both of these factors create challenges for tool providers. The demand for integration of analytics, automation, and embedded sensors as well as tools for data management and handoff also creates challenges for tool providers, he added.

Market research is key when defining the company's investment priorities, Vanek said, explaining that "it takes years and a huge investment to bring new platforms to the market." While U.S. programs will account for most of the new products, Asian and Pacific counties are expected to grow their cell therapy programs significantly, he said.

Refining investment priorities is important because it can take 3 to 7 years and $1 million to $25 million (or more) to take a new platform from idea to product (see Figure 4-3). Platform development occurs in three broad phases: research, early development, and late development and launch. The research phase, characterized by what he called an "innovation loop," is a period when companies are hesitant to invest because it is costly and high risk. Late development and launch, and its product care loop, is when companies are more likely to spend money because development at that stage largely iterates on a given theme. Closing the gap requires that companies look at all of the derivatives of technology, such as company spinouts, new intellectual property, and out-licensing, that can fund the innovation loop.

An important piece of the development process is determining what drives the cost of each unit operation. The costs for reagents and consumables are predicted to fall as they move into large-scale production to meet growing demand, Vanek said, and that is an area in which GE Healthcare is investing. While capital expenditures for hardware do represent a cost to a business, consumables are the real drivers of the cost of a therapy because they are not produced at scale today, he said. Labor is also a big part of the cost today, but as the industry automates, simplifies, and combines unit operations, those costs are expected to fall. The lack of optimization of manufacturing capacity adds to the overall cost, too. Costs should fall as researchers improve the effectiveness of these therapies, which should reduce the number of cells needed per dose. A move from autologous to allogeneic cells, with the potential for manufacturing at scale, would also have a significant beneficial effect on cost, Vanek said.

Concerning the transition of manufacturing from the clinical scale to a commercial scale, there are times when it is easier to implement change, Vanek said, including early on when the cost of change is not that high. As a trial moves into Phase II or Phase III, the costs can be more substantial. His company's philosophy is to develop technologies that are scalable so

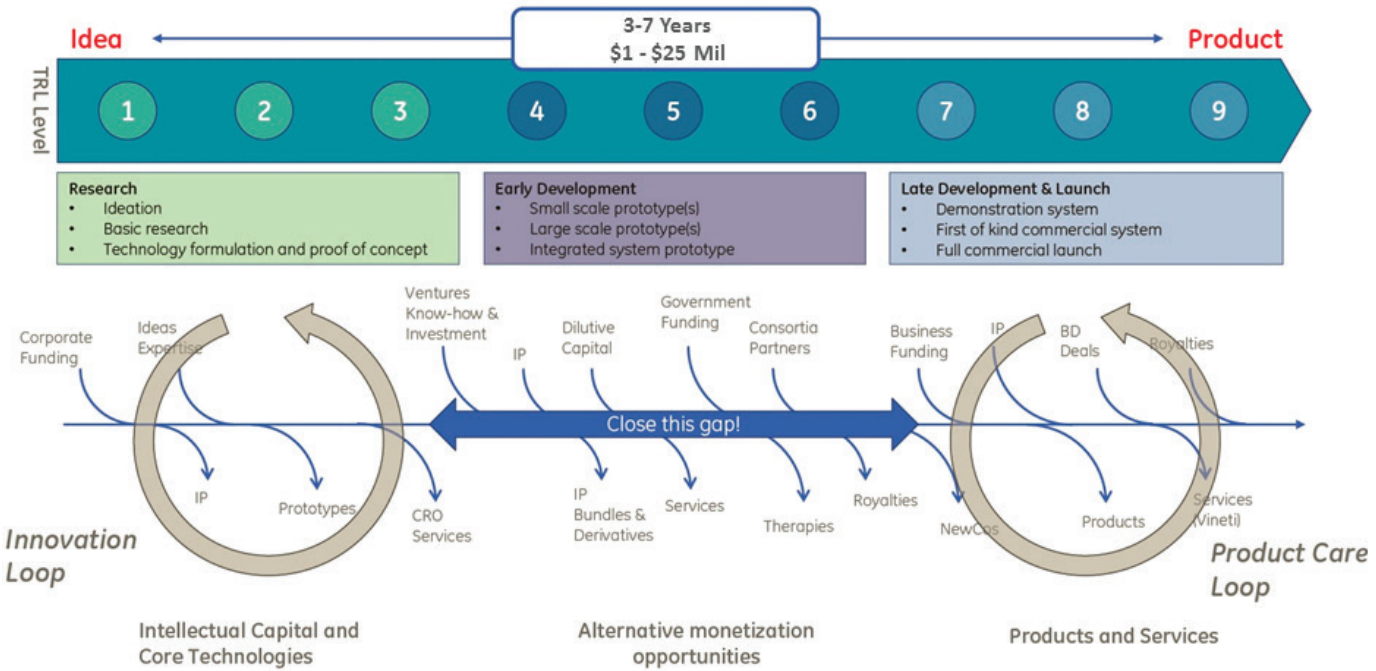

FIGURE 4-3 GE Healthcare's product development vision highlighting the investment and time needed to bring new platforms to the market.
NOTE: BD = business development; CRO = contract research organization; IP = intellectual property; TRL = technology readiness level.
SOURCE: Philip Vanek, National Academies of Sciences, Engineering, and Medicine workshop presentation, June 26, 2017.

that they can be introduced early in the development process and grow in scale as demand increases, he said. By looking across the different therapies currently undergoing research and development, the company has tried to identify common subroutines of activity for which tools can be developed that would be translatable across the production of multiple types of therapies and at different scales. However, he acknowledged, that approach does not solve the problems of data portability and data integration.

While he is not a proponent of taking a complex, multistep process and oversimplifying it, Vanek said, he does see the need for some automation and simplification. At the end of the day, GE Healthcare either invents new technologies or acquires them from other inventors, he said, and in either case, data integration is still an issue. All of the components must communicate to make the complete process work. Toward that end, he said, the company has built and made a significant investment in technologies to power digital connectivity.

DISCUSSION

During the session panel discussion, speakers and workshop participants highlighted some of the challenges and opportunities for using new technologies and automating processes to enable a robust manufacturing platform for cellular therapies. Individual participants identified some of the financial considerations for device and tool companies as well as the technical challenges in the manufacturing process for academic and industry partnerships. The logistics and feasibility of point-of-care manufacturing, which takes a scaled-down and decentralized approach to manufacturing and providing therapies to patients, were also discussed.

Utilizing Technologies to Optimize the Manufacturing Process

Building on the comments heard throughout the day on automation, Rietze highlighted some of the logistical considerations regarding automated manufacturing. When identifying whether a manufacturing process being used in the development of a new device is ready for automation, it is crucial to know the process thoroughly and to think about automation at the beginning, Rietze said. From a practical perspective, most commercial firms are going to receive a process from an academic institute, in which case the "sweet spot" would be around the time Phase II trials start. By that time, there should be a deeper understanding of the manufacturing process without automation.

Before automation can be built into the manufacturing process, there are other challenges that researchers can address. Workshop participants discussed the importance of identifying what makes a product therapeuti-

cally active early in the development process in order to be able to optimize production and reduce spending. For example, one participant said, it is likely that, at least with CAR T cells, that only a few clones, not billions of cells, are therapeutically active, and if those cells can be identified, the manufacturing process and automation models will change drastically. Researchers need to identify those cells at a much earlier stage before industry devotes a tremendous amount of energy and money building tools and technologies, another participant said. Rietze agreed, and acknowledged that the current process for CAR T manufacturing will likely evolve as the technology advances. To reflect the reality that manufacturing is likely to change as additional products are developed, Novartis moved its process development group back into the company's basic research institutes so that process and product are being developed together. Data will drive the development of new processes that rely on early product characterization during the discovery phase, Rietze said. GE Healthcare's approach to development is to design scalable manufacturing platforms that will solve a problem regardless of scale, Vanek said.

From a financial perspective, Vanek said, capital expenditures are not the most important cost driver in the long run when developing a new tool. According to the modeling his group has conducted, when production reaches a scale of tens of thousands or hundreds of thousands of patients at a time, the overall capital expenditure shrinks in comparison to the consumable demand on a per-patient basis. That is not to say that the operational expenditures related to repairs and maintenance and idle capacity are inconsequential, but if manufacturing facilities can be designed with efficiency in mind to support more than one indication, those costs get absorbed across multiple products.

Engineers have the ability to unitize a process, gather the available data, and create integrative solutions, a workshop participant noted, and an important part of the tool development process is identifying those areas in the development pathway where current tools are not sufficient and need updating. One of those areas, Vanek said, is the characterization and qualification of starting cells. Addressing that bottleneck may require the development of more efficient processes of cell selection and of in-process smart devices and sensors that enable machines to become smarter on their own. Investments made in developing novel platforms such as microfluidics that are very high risk compared to existing technologies that have been around for decades (and in many cases are off patent) is challenging, Rietze said, but sharing the risk for product development could help move the field forward. There are very few systems that can be used in the laboratory to expand cells that will then be scalable for commercial application, Rivière said. Researchers and manufacturers need to better understand how to identify the active cells in order to reduce dose size, she added, and eventu-

ally the manufacturers need to think about how to make pseudo-universal products derived from iPSCs, which would eliminate the need to use patient materials.

Manufacturing at the Point-of-Care

Manufacturing at the point-of-care versus in a centralized location is a viable and important option for orphan diseases, Rivière said. Unless the analytics are automated too, there will need to be a huge amount of training and standard operating procedures that will need to be transferred from one center to another. For diseases with a large number of patients, she said, hospitals should focus their efforts on the clinical trials and leave manufacturing to biotechnology or pharmaceutical companies.

One problem with point-of-care manufacturing is that it makes multicenter trials difficult because of the need to validate and demonstrate comparability across sites. The requirement to have centralized analytical laboratories is another obstacle for point-of-care manufacturing in multicenter clinical trials, unless the analytics are integrated and fully automated. Automation is expensive, however, and, as Rivière pointed out, there are limited funds available to develop manufacturing automation and analytics for point-of-care applications. Furthermore, there are issues to address before point-of-care manufacturing becomes feasible, including building the necessary infrastructure and identifying resources. Automation could eventually provide an answer to this issue, she said, and researchers are working on accomplishing that feat (Roh et al., 2016). There is some confusion about what CQAs need to be monitored in an automated process, Rivière said (see Chapter 5 for further discussion on CQAs). Some in the field hope that the large datasets now being collected from patients who have received some of the first commercialized products will provide insights about what attributes are critical to measure in order to monitor the manufacturing process.

Several things have to happen for point-of-care manufacturing to become realistic, Vanek said. First, the dose would have to be of the right size in order to be able to be manufactured at that scale, and the time to produce that dose would have to be relatively short, he said. Second, the understanding of data analysis and cell characterization would have to reach a level sufficient to enable automation of the manufacturing process.

5

Considerations for Improving and Regulating Regenerative Medicine Products

Highlights Presented by Individual Speakers

- The key to clinical trials and effective treatment are the same in the case of small molecules or cell therapy: deliver a material with the right properties into the right patient at the right time in the right concentration. (McBurney)
- In order to bridge the gap between the expectations and the reality of available treatments there need to be better educational initiatives for patients and caregiver communities about the importance of high-quality clinical trials. (McBurney)
- Through biorepositories, patient advocacy groups can play an enabling and neutral role in processing, storing, and distributing research materials and mandating data return and sharing. (McBurney)
- Virtual collaborations, which often do not require complex legal agreements, can enable and accelerate data sharing and research collaborations among organizations. (McBurney)
- MSC surface markers that the researchers in that field have agreed upon and proposed to use as potential CQAs, do not reveal significant differences between cell lines and their function. (Bauer)

- Morphological responses of MSCs to relevant stimuli, which can be detected and quantified using automated methods, can predict relevant biological responses and may be useful for screening donor samples for desired biological activity and assessing manufacturing processes. (Bauer)
- Understanding a product's CQAs provides the foundation to answer questions from regulators, deal with challenges, and think of innovative approaches to address those challenges. (Tsokas)
- Regulatory guidance should allow for flexibility in the development process and recognize and emphasize the iterative nature of the development process, the need for a risk-based approach to development, and differences in product type. (Tsokas)
- To facilitate the global development of advanced therapeutics, regulatory agencies should harmonize regulations, guidance, and regulatory processes across regions to create some consistency in the regulatory approval process. (Tsokas)

The regulatory landscape for regenerative therapies is evolving, and this chapter explores relevant issues including approaches to developing standards and establishing and enforcing regulations that meet the needs of patients. The speakers in this session were Robert McBurney, the president and chief executive officer of Accelerated Cure Project for Multiple Sclerosis and co–principal investigator of the iConquerMS Patient-Powered Research Network; Steven Bauer, the chief of the cellular and tissue therapy branch in the Center for Biologics Evaluation and Research at FDA; and Katherine Tsokas, the senior director for global regulatory affairs at Johnson & Johnson.

IMPROVING STEM CELL–BASED PRODUCTS: PERSPECTIVES FROM A PATIENT-CENTRIC RESEARCH ORGANIZATION

Multiple sclerosis (MS) is an autoimmune disorder of the central nervous system that causes damage to the myelin sheath that insulates the nerve fibers. This damage can lead to conduction failures and, ultimately, the death of nerve cells, McBurney said. People living with MS experience such symptoms as loss of mobility, loss of vision, cognitive problems, fatigue, sleep disorders, and mental health problems, he said. Over the past 25 years, there has been remarkable progress made in treating the symptoms of the disease, he said, with 15 FDA-approved therapies available today and 2 or 3 more that should be ready for regulatory review over the next couple of years. However, there is still no cure for MS. All of the

approved therapies, he said, address aspects of the immune system's role in MS, but none address the fundamental cause of the disease.

The Accelerated Cure Project[1]—founded in 2001 by an engineer who was diagnosed with MS—has two main programs: a biorepository containing DNA, RNA, plasma, serum, and white blood cells from 3,200 consenting individuals collected at 10 MS clinics around the United States, and a people-powered research network called iConquerMS™ which was started in 2014 with funding from the Patient-Centered Outcomes Research Institute.

The biorepository, McBurney said, has supported more than 100 studies with a mandated return of data from any researcher who receives samples from the biorepository. This mandated data return, he said, has allowed for the creation of virtual collaborations among participating organizations. One advantage to these virtual collaborations, he said, is that they often do not require participating organizations to complete legal agreements, a feature which has accelerated collaborations. The iConquerMS network includes approximately 4,000 MS patients who are involved in the conception and conduct of research studies, the dissemination of information, and advocacy as a means of improving care for MS patients. iConquerMS currently has 36 individuals on its governing board, research committee, and engagement committee, 22 of whom are lawyers, scientists, neurologists, and biorepository experts who have MS.

Speaking about the regenerative medicine opportunities in MS, McBurney highlighted three areas in particular: rebooting the "confused" immune system with hematopoietic stem cells or MSCs; repairing the damaged myelin sheath with oligodendrocytes regenerated from MSCs or iPSCs; and regenerating lost nerve cells and reforming appropriate connections using MSCs or iPSCs. Currently, he said, there are approximately 50 clinical studies under way worldwide in these 3 areas. Of the 16 studies based in the United States, 12 academic studies are completed or are no longer recruiting, and 4 industry-sponsored trials, primarily using MSCs, are in the recruitment phase. However, McBurney said, he considers the four U.S. industry-sponsored trials that are patient-funded to not be traditional clinical trials. In fact, he said, while there are excellent academic and industry-sponsored studies going on outside of the United States, there is also a great deal of medical tourism aimed at MS patients.

One therapeutic approach uses autologous hematopoietic stem cell transplantation (aHSCT) to attempt to reach an endpoint known as "no evidence of disease activity," or NEDA. NEDA is indicated by three measures of MS activity: no relapses, no progression to disability, and no new

[1]Additional information about the Accelerated Cure Project for MS can be found here: https://www.acceleratedcure.org (accessed August 17, 2017).

or enlarging lesions upon magnetic resonance imaging. The multi-step process of aHSCT involves ablating the patient's immune system and attempting to reconstitute it using hematopoietic stem cells. Preliminary results indicate that certain groups of patients have a higher likelihood of achieving NEDA with aHSCT than with other available disease-modifying therapies, although additional work is needed to verify these findings (Muraro et al., 2017a,b; Sormani et al., 2017). The regulatory environment needs to be in good shape, McBurney said, so that if future trials for aHSCT go well, then the therapies can reach the MS community as quickly as possible.

Early results from using autologous hematopoietic stem cells to treat MS have spurred the development of another upcoming trial, called the BEAT-MS trial. McBurney said he hopes that the BEAT-MS trial will carefully develop analytical aspects so that the researchers can ensure that the cells are in the best possible state prior to transfusion. Ultimately, he said, the goal of clinical trials and successful treatment are the same for small molecules and cell therapy—to deliver a material with the right properties into the right patient at the right time in the right concentration.

Patients are an extremely valuable resource, McBurney said, because they can facilitate the conduct of clinical trials and product approvals through their involvement from the beginning of the process. Patients can be involved at many stages, from the development of a clinical trial protocol through to the end of the process when developers are seeking approvals and reimbursement. It is extremely important to educate the patients and caregivers, McBurney said, specifically regarding the characteristics of high-quality clinical trials and as a way to bridge the gap between expectation and reality which often develops because of the normal human tendency to hope.

Biorepositories play an important role in therapeutic development, McBurney said, because they allow for research on the properties of cells at various stages. Biorepositories can process, store, and distribute research materials and mandate data returns in an agnostic manner, he said. "We need neutral management and oversight of the activities of a biorepository," he said, "including study approval, material distribution, and return of data."

STRATEGIES TO IMPROVE CHARACTERIZATION OF STEM CELL–BASED PRODUCTS

FDA sees product characterization as encompassing chemistry, manufacturing, and controls (CMC), Bauer said. The goals of characterization are to ensure product safety, ensure the consistency of the process and product, and, ideally, predict in vivo activity; the last of these three is a particular challenge for this field, he said. In his view, Bauer said, product

characterization also includes the identification of CQAs. The field will move forward rapidly if there is progress on developing better strategies for identifying and measuring CQAs, he said. The assessment of each of these aspects of CMC should be guided by a detailed understanding of the manufacturing process and the product.

Several years ago, when FDA conducted a survey of the investigational new drug (IND) applications submitted for MSC-based products, it found that, generally, MSCs are quite diverse in terms of their characterization, manufacturing, and sources (Mendicino et al., 2014). The issue of CQAs for MSCs is still an open question, Bauer said, and the understanding of their relationship to performance in clinical trials needs more work. The review from Mendicino et al. (2014) demonstrated that investigators working with MSCs define these cells by their characteristics of having immunomodulatory and anti-inflammatory activity; being capable of generating adipocytes, chondrocytes, and osteoblasts; and having the property that when manufactured in large number the cells will maintain the relatively few CQAs measured when the cells were harvested from the patient. Most research teams, he added, follow the MSC research community's guidelines concerning how to define an MSC, though researchers often give themselves more latitude than what is in those guidelines.

To address the issue of identifying CQAs for MSCs and correlating them with in vivo and in vitro assays of safety and efficacy, FDA started a regulatory science program known as the MSC Consortium.[2] While it is important to relate CQAs to performance in an in vivo model, Bauer said, there were some advantages of correlating measurements with in vitro bioassay outcomes in terms of improving the characterization in an iterative, stepwise approach. The raw materials for the consortium came from Bauer's laboratory, which manufactured MSCs from eight different human bone marrow donors obtained from commercial sources. The consortium has subjected this material to a variety of analytical methodologies, including gene expression and epigenetic analyses and in vivo and in vitro models of immunosuppression and wound repair. For example, his group looked at in vitro quantitative differentiation assays that may be useful as in-process controls or surrogate potency assays. The consortium has not yet progressed to the stage of finding an animal model that is sensitive to differences among the cell lines from the eight different human donors, he noted.

One finding from these studies was that the current MSC surface markers being measured by researchers in the field do not reveal significant differences between donors, nor do they show significant differences with

[2]More information about FDA's research on MSCs can be found here: https://www.fda.gov/biologicsbloodvaccines/scienceresearch/biologicsresearchareas/ucm127182.htm (accessed August 16, 2017).

an increase in passage number (Lo Surdo et al., 2013). This finding was important, Bauer said, because the consensus MSC surface markers at the time of that study did not predict the observed functional biological heterogeneity of MSCs. His team also found that the adipogenic potential varied between cell lines obtained from different donors and that it decreased with passaging. "This theme of stem cell–like activity dropping with duration and tissue culture is something that we saw in this and other MSC biological assays," Bauer said. The finding suggests that it should be possible to develop a molecular characterization scheme that would help identify the subpopulations of cells that define the activity of the entire mixture of cells, he said.

Bauer and his team also discovered that the size of the cells increased routinely with passaging, which led them to carry out a morphological characterization study. The study, which assessed 96 different morphological measures of cell and nuclear shape, found that morphological characterization 3 days after stimulating the cells with osteogenic media, predicted mineralization activity of the cells at day 35 (Marklein et al., 2016). "The morphological response of the MSCs to the stimuli seems to predict what is going to happen biologically," Bauer said. In another study, the consortium demonstrated that changes in MSC morphology after stimulation with interferon-γ predicted the extent of the immunosuppressive activity of the cells (Klinker et al., 2017).

Assessing morphological changes can be automated and quantified, Bauer said, which implies that it may be possible to use this kind of assay to screen samples from different donors for the desired quantitative biological activity. This type of assay might also be useful for evaluating the impact of a manufacturing process, particularly tissue culture conditions, on desired biological activity. In fact, consortium researchers examined the effects of different manufacturing conditions on osteogenic activity, as predicted by morphological changes, finding differences according to the manufacturing conditions (Marklein et al., 2016).

FDA is hoping that the thorough examination of MSCs will improve researchers' ability to use quantitative bioassays to identify CQAs that are indicative of potency and activity, Bauer said. The agency is also hoping to use multifaceted cell characterizations to gain a better understanding of the active subpopulations of cells and to identify markers that are correlated with bioassay outcomes as a means of guiding enrichment techniques. It is also possible, Bauer said, that such assays could be used to measure osteogenic, adipogenic, immunosuppressive, angiogenic, and wound repair potential, among other biological activities.

REGULATORY IMPLICATIONS FOR DEVELOPMENT AND GLOBAL MANUFACTURING OF REGENERATIVE MEDICINE PRODUCTS

The Code of Federal Regulations (CFR), specifically Title 21, parts 1270[3] and 1271,[4] are the regulations that sponsors must follow when developing a new therapeutic product, Tsokas said. There are also guidance documents from FDA and other regulatory authorities, such as the International Conference on Harmonization, and standards such as those issued by USP that industry can use when developing its manufacturing processes. The variability with which industry applies these standards and guidelines and with which it handles the different requirements creates challenges, she said.

As a detailed example of both the flexibility and specificity of the regulatory framework, Tsokas discussed how 21 CFR 1271 specifies the ways in which investigators must handle human cells, tissues, and cellular- and tissue-based products as well as the types of tests that should be conducted in in order to prevent the introduction, transmission, or spread of communicable diseases. One of the challenges is that the regulation applies to a broad range of products and must therefore be flexible, she said. FDA's CMC guidance recommends that sponsors refer to USP sterility tests, which provide the details needed to conduct those assays. The challenge, she said, is to make sure the sponsor can apply that test to its particular product and follow the procedure exactly. Another issue, she added, is that the USP procedure is not designed to ensure that each product batch is sterile. "To do that, we as sponsors need to make sure that we validate the procedure for our particular process," Tsokas said.

While it is easy to focus only on U.S. requirements and guidance, other countries may have different requirements and guidance to follow, Tsokas noted. "One of the challenges we face as sponsors is that there is information from multiple sources, and the information is all slightly different," she said, referring to the various international regulatory bodies. "The earlier you try to make sure you are meeting all of those global requirements, the easier it will be for you."

From a regulatory perspective, understanding a product's CQAs provides the foundation with which to answer questions, deal with challenges, and think of innovative approaches to address those challenges, Tsokas

[3]More information about the CFR Title 21 Part 1270 can be found here: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1270 (accessed August 28, 2017).

[4]More information about the CFR Title 12 Part 1271 can be found here: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=1271 (accessed August 17, 2017).

said. Understanding the basic science early on is important because it leads to informed decisions about how to handle various regulatory requirements. Having a deep understanding of the product, its mechanism of action, and its structure–function relationships is important for determining CQAs and developing potency assays as well as for understanding the effect of the manufacturing process on product attributes, she said. CQAs are also critical for ensuring comparability of a product throughout development, including when the manufacturing process inevitably undergoes changes, so that early results remain relevant to the final product's performance.

One of the biggest challenges faced by sponsors, Tsokas said, is the need to interpret information from multiple sources and to develop a comprehensive strategy to comply with the regulations and implement them in a quality system. Regulations in the United States, Europe, and Asia all contain the same concepts but apply them differently. The earlier a group can focus on international guidelines and try to meet those requirements, the easier it will be, she said. Regulations do give sponsors flexibility as to how they build their manufacturing control strategy, but once a sponsor implements its strategy, the regulations require strict adherence to GMP, good tissue practice, and good documentation practices.

The use of non-standardized tests can increase costs and inefficiency because of the need to validate the tests, Tsokas said; it is much easier to use an accepted, standardized test whenever possible. Additionally, the information required for an IND application may not include all regulatory requirements from a quality system perspective. For example, an IND application might specify the specific sterility test the sponsor plans to use, but an FDA inspection prior to the start of a Phase III trial may require sampling plans with additional details such as when the test will be conducted and the sample volume that will be tested. It is important to pay attention to all of the details that go into the manufacturing process and be prepared to document and answer questions about those details, Tsokas said.

One way to stay ahead of regulatory requirements is for sponsors to define their quality systems, or plans for managing the quality of manufactured products, in a way that ensures compliance with all applicable regulations. Quality systems, Tsokas explained, provide a framework for sponsors to feel comfortable that they are heading down the right development path for their products. One way that regulators could help sponsors during the development of a product is by providing additional feedback or assessment tools, Tsokas said, noting that such information would help sponsors understand whether they are implementing regulations and guidance appropriately. Another helpful approach, she said, would be to increase the number of USP monographs and specific checklists for standardized platform activities in order to help sponsors have confidence they are meeting regulatory requirements. Examples of potential standardized platform activities

include rapid mycoplasma and microbial testing for non-cryopreserved cell therapies; potency assays for CD19 CAR T cell products; testing for residual process-related impurities, such as bovine serum albumin, proteases, and foreign DNA; adenovirus, lentivirus, and adeno-associated virus vector quality; and monitoring for replication-competent viruses.

Regulatory guidance should allow for flexibility in the development process and should recognize and emphasize the iterative nature of the development process, the need for a risk-based approach to development, and differences in product type, Tsokas said. To facilitate the global development of advanced therapeutics, regulatory agencies should encourage the convergence of regulations, guidance, and regulatory processes across regions in order to create consistency in the regulatory approval process, she said. Getting to a state of harmonization and convergence requires an understanding of where the gaps are in the global regulatory institutions and identifying the most promising and valuable areas for harmonization, convergence, and making use of standards, Tsokas said. It also requires regulators, industry, and academia communicating with one another and working together to determine where to make improvements that will help industry develop advanced therapies for the benefit of patients worldwide.

DISCUSSION

Increasing Collaboration Among Stakeholders

FDA, NIST, and various standards determining organizations such as ASTM International, the American Type Culture Collection, the Standards Coordinating Body, and the National Institute for Innovation in Manufacturing Biopharmaceuticals are working together to determine where standards for regenerative medicine product manufacturing can be developed. FDA has active research collaborations with NIST in areas such as the standardization of cell counting and flow cytometry and also has internal regulatory research aimed at helping people better understand and characterize their products in cell therapy and regenerative medicine. FDA is also part of the International Pharmaceutical Regulators Forum,[5] which has cell therapy and gene therapy working groups that are collaborating with regulators in 13 countries, some of which do not have regulatory frameworks for cell and gene therapy. The International Pharmaceutical Regulators Forum is also working on the convergence of regulatory approaches, which are surprisingly more alike than many people would realize, a workshop participant said.

[5]More information about the International Pharmaceutical Regulators Forum is available here: https://www.i-p-r-f.org/index.php/en (accessed August 16, 2017).

Defining the Role of Patient Advocates in Shaping Regulatory Policy

The National Patient-Centered Clinical Research Network and Genetic Alliance are examples of umbrella organizations that facilitate patient contributions to the regulatory process. Genetic Alliance currently includes approximately 2,000 advocacy organizations; two other umbrella patient groups involved in this effort are the National Organization for Rare Disorders and the National Health Council.

When communicating with patient advocates regarding regulatory policies, FDA tries to engage actively by including the advocates in some of the agency's advisory panels. FDA is at the intersection of many different interests, Bauer said, but its interaction with patient advocacy groups is very highly valued. Johnson & Johnson also connects with patients in the specific therapeutic areas in which it works and shares data with advocacy organizations, Tsokas said. Regarding "right to try" legislation, which is a concern for some patients, Tsokas said that Johnson & Johnson supports the idea that products should be made available if possible, but the company firmly believes it is important to make sure such products are safe before they can be used for additional indications.

Biorepositories and Data Sharing

The Accelerated Cure Project for MS and other patient-focused groups, such as Genetic Alliance, have written resources on establishing a biorepository, but in general, McBurney said, he prefers to speak directly with groups who are interested in starting a biorepository about their needs because one approach does not necessarily work for another. His organization found it was beneficial to pay for sample collection and on-site study coordinators as a means of avoiding the involvement of the provider systems with regard to sample access. While it cost $15 million to do that, he said, "it is an important part of a model like this because it does provide flexibility to support research in different contexts." The management of this process is fairly straightforward, McBurney said. "It is not without work, but the ability to create these virtual collaborations and return data to a central source is something that does accelerate progress," he said. These data, he explained, have not been used for regulatory purposes, and the system was not set up to do so.

In the field of regenerative medicine, biorepositories and data sharing may be easier in the pre-competitive space, Tsokas said, noting that careful consideration should go into determining the best approaches for sharing resources. It has sometimes been easier to get companies than academics to return data generated from biorepository samples, McBurney said. Industry has conducted one-third of the studies from his organization's bioreposi-

tory, and in each case those companies have returned their data once they completed those studies. McBurney said that his organization does not have the resources or time to retrieve all of the data from academics who do not return them.

Unregulated Therapies and Medical Tourism

Clinics offering unproven stem cell–based therapies are becoming more prominent in the United States (Turner and Knoepfler, 2016). There may be opportunities for patient advocacy groups and regulators to provide education to the public on what elements they should look for concerning a clinic offering cellular therapies. The issue of unproven stem cell therapies came up at a recent public workshop held by FDA in September 2016, Bauer said. The workshop focused on the scientific considerations and challenges to informing the development of human cells, tissues, and cellular- and tissue-based products subject to premarket approval and included speakers who discussed approaches to educating consumers about clinics offering unproven therapies.

Medical tourism is most likely driven by many factors. According to one workshop participant, patients with serious unmet needs can see promising and reputable data from an early MS trial, and if they do not have access to that therapy through conventional approaches in the United States, they may seek alternatives. While there are reputable clinics abroad offering therapies for MS, those clinics are not publishing any definitive data, McBurney said. The upcoming BEAT-MS trial will examine the autologous hematopoietic stem cell therapy, he said, and those running the trial plan to compare the results of that treatment to the best available therapy, he said. Early evidence has demonstrated a large amount of variance in the response of MS patients to the autologous hematopoietic stem cell therapy, McBurney said, but that may be due to the small number of patients in the early trials. Furthermore, the benefits of these hematopoietic stem cells seem to wane after 4 years for reasons not yet known.

Japan's revised Pharmaceutical Affairs Law is a regulated accelerated or conditional approval pathway, as opposed to medical tourism, which is not regulated, Tsokas said. Sponsors still need to meet with Japanese regulators and review their manufacturing processes, she said. "You can, with safety data and minimal efficacy data, get conditional approval," and then a confirmatory trial is needed in 7 to 10 years. It is still too early to tell if this approach has helped reduce medical tourism or increased the speed with which products can obtain full approval, she said.

6

Potential Next Steps for Supporting the Development, Manufacture, and Regulation of Regenerative Medicine Therapies

The workshop's final session included a keynote address by Dean Kamen, founder and president of DEKA Research and Development Corporation and founder of the Advanced Regenerative Manufacturing Institute (ARMI) and For Inspiration and Recognition of Science and Technology (FIRST). The keynote address was followed by reflections from Robert Preti, Anne Plant, Phil Vanek, and Robert McBurney. There were several areas of discussion that arose as the panel reflected on the workshop and the important ideas that had emerged throughout the day (see Box 6-1). These areas included emerging technologies and scientific challenges, developing standards and a regulatory framework, interdisciplinary collaboration, workforce training and management, the role of the patient in the discovery and development process, and planning for the future in the regenerative medicine industry.

FOSTERING INNOVATION AND COLLABORATION: AN INTERDISCIPLINARY APPROACH TO REGENERATIVE MEDICINE

In preparing to respond to a funding opportunity announcement from the U.S. Department of Defense that sought to establish a facility to develop advanced manufacturing technologies for regenerative medicine, Kamen said, he led a team that visited cutting-edge academic laboratories, where they were impressed by "22nd-century science fiction" being accomplished using equipment and techniques that would have been familiar to Louis Pasteur. "It was astonishing what [researchers and graduate students] could do with virtually no modern process control, no tools of robotics, sensors,

BOX 6-1
Ways to Facilitate Progress in Regenerative Medicine Therapy Manufacturing as Suggested by Individual Speakers

- The biggest opportunities for innovation in regenerative medicine are to be found in robotics and automation. Automating the manufacturing process will reduce variability and help to clarify what characteristics are vital to a product's potency, how best to measure them, and what manufacturing parameters influence those characteristics. (Plant)
- The regenerative medicine industry is encountering difficulties recruiting and retaining a trained workforce. Developing effective training programs and identifying ways to motivate the workforce will be key to overcoming these challenges. (McBurney, Vanek, Zylberberg)
- A successful manufacturing process to develop an effective product relies on researchers and manufacturers hiring and retaining a workforce with diverse skill sets, skill levels, and areas of expertise. (Preti)
- Applying an interdisciplinary approach using mathematics, engineering, and scientific principles to the discovery and development processes will generate transformative technologies and regenerative medicine therapies. (Kamen)
- The first step in transforming the manufacturing industry and accelerating analytical and production processes is to understand the underlying biology. After that, it will be important to address scalability and comparability by developing tools that can facilitate both effectively. (Vanek)
- When collaborations are prioritized and a design framework is applied to the development and manufacturing processes, regenerative medicine will start to become a more substantial part of therapeutics available. (McBurney)
- Understanding how various international regulatory agencies approach manufacturing processes and quality assurance will be important for addressing current manufacturing gaps and moving toward point-of-care manufacturing. (Oh)
- Fostering an environment that can maintain a good balance among technology innovation, safety and quality, and patient benefit is crucial to the success of navigating the manufacturing process and ensuring the quality of the regenerative medicine products. (Oh)

high-precision feedback systems, or documentation systems," he said. From these visits, he said that he realized that the research and discovery being carried out in these labs could be accelerated and supported through the application of engineering, mathematics, and robotics. The idea for such a collaboration between scientists and engineers resulted in the formation of the nonprofit BioFabUSA in conjunction with ARMI.[1] ARMI's mission

[1]More information about ARMI and BioFabUSA can be found here: https://www.armiusa.org/about-us (accessed August 28, 2017).

is to make practical the large-scale manufacturing of engineered tissues and tissue-related technologies, Kamen said. In support of that mission, BioFabUSA was created as a ManufacturingUSA Innovation Institute to drive technological innovation in five areas: cell selection, culture, and scale-up; biomaterial selection and scale-up; tissue process automation and monitoring; tissue maturing technologies; and tissue preservation and transport. "As part of the BioFabUSA coalition, we have some of the most creative and brilliant engineers and we think out of the box, but we don't think inside the cell," Kamen said. Though his group has little experience in regenerative medicine, he believes that the engineers at BioFabUSA can help in achieving progress in these five areas of innovation, he said.

The collaborative model used for BioFabUSA is based on the model used to establish the nonprofit FIRST, Kamen said. The mission of FIRST is to inspire the next generation of young people to become interested in science and technology by engaging them in programs that focus on innovation and building self-confidence (see Chapter 2 for further discussion on manufacturing workforce issues). Founded 25 years ago with the goal of increasing the number of children with backgrounds in science, technology, engineering, and mathematics (STEM), FIRST was created to bring industry, universities, parents, teachers, and governments together to create a fun environment in which children, particularly women and groups underrepresented in the STEM fields, would see science and engineering as attractive fields to pursue, said Kamen. The intent is that BioFabUSA will follow a similar growth trajectory as FIRST, resulting in a thriving collaborative effort that will advance innovation in the field of regenerative medicine, he said.

FIRST started with a competition in which 23 teams participated, about the same number of teams that have now joined BioFabUSA, Kamen said. Initially, he said, he encountered skepticism from people who claimed the program would not grow in scale and that he would not be able to convince engineers and scientists to take time to be mentors for these children. Twenty-five years later, he said, FIRST now has 55,000 teams from 83 countries participating in 140 events. The program collaborates with approximately 200 universities, which provided $50 million in scholarships, and 3,700 corporate sponsors who are active members. Most of the major aerospace and technology companies sponsor FIRST teams, Kamen said, and the top two sponsors are the U.S. Department of Defense, with 651 teams, and the National Aeronautics and Space Administration, with 230 teams.

Though BioFabUSA was only a few months old at the time of the workshop, Kamen said that the parallels with the origins of FIRST offer hope that it will experience similar growth in participation and enthusiasm across its stakeholder groups. The constituents of the two groups are very similar, Kamen said, with government, industry, universities, and citizens

collaborating through BioFabUSA much as they do through the FIRST program. As much as the world needs more scientists and engineers like those that FIRST is creating, Kamen said, there also needs to be a massive coalition of technical experts who will contribute their expertise and help move today's exciting therapeutic breakthroughs to a practical industrial scale. ARMI and its partners are now evaluating 21 quick-start proposals with the intent to foster technical and scientific innovation through collaboration. The more radical an idea is, he said, the harder it is to set a regulatory precedent. To that end, the organization has emphasized including FDA throughout the discovery and development process as it begins to integrate science and engineering to create new technologies. There is a lot that the engineering community has sitting on the shelf that could be modified to help bring scientific discovery out of the "roller bottle" (where cell cultures are grown and stored) and into scale, Kamen said.

The goal of BioFabUSA, Kamen said, is to help the field navigate the existing gap between basic research and commercialization. In this gap, the advancement of new therapies and discoveries can become overwhelmed by the technical and financial challenges of scaling up and thus fail to reach commercial production. By applying engineering principles to the scaling-up process and modifying existing technologies, those at BioFabUSA plan to develop a new vision for regenerative medicine therapies. For example, a proposal currently under consideration uses the model for a home dialysis machine as a basis for the development of a self-contained biosystem capable of processing cells and other biomaterials in a small, sterile system that does not require clean room facilities. "We are going to change the world," Kamen said. "Along the way, we are going to build a coalition that will be the next big advance in health care."

REFLECTIONS AND TAKE-AWAY MESSAGES FROM THE WORKSHOP

Scientific Challenges and Emerging Technologies

The biggest opportunity to move the field of regenerative medicine manufacturing forward lies in robotics and automation, Anne Plant said. Successful automation would not only help control the manufacturing process and improve the quality of measurements, but would also provide clarity about what parameters affect the clinical potency of a product, she said. The number of potential parameters is very large, and today the field relies on individuals and the execution of manufacturing processes by hand to determine which parameters are relevant to a product's potency. Automation can reduce variability and make it easier to minimize the "parameter space" because while it is dependent on knowing what to measure and how

to control a manufacturing process, the desire to automate will help to clarify what to measure, what characteristics are critical to a product, and how to control the various parts of the manufacturing process that affect those characteristics. "Right now, there is so much variability in a process, a product, or how a patient responds that [it is difficult to know] where to start with respect to understanding how to minimize that variability," Plant said. Automation is the way to reduce that variability, she concluded, but it must be designed with both statistical and engineering principles.

There is a need to constrain the "parameter space" appropriately and to develop a greater understanding of fundamental scientific principles as a more practical approach to derive realistic solutions, a workshop participant said. "This is a critical idea, and even though those of us who are physical scientists and engineers understand this, it does not get explicitly expressed enough," he said. "Understanding the laws of nature, the 'rules of life,' so to speak, is a practical approach to problem solving."

One technical challenge facing the field is that the current understanding of CMC issues is lagging behind clinical development, Preti said. There remain many unknowns and variables when producing regenerative medicine therapies, and research and process analysis must be ongoing in order to better understand what chemical, biological, and process parameters affect the effectiveness of a new therapy. To move the field forward, researchers and manufacturers must understand that product identity is not potency and that the process is not the product, he said, emphasizing that a list of a product's characteristics does not necessarily indicate its potency and that following a manufacturing protocol does not necessarily yield an effective product. Vanek agreed, adding that it will be vital to improve techniques for characterization, process development, and assay development for measuring comparability. As a tool-providing company, GE is greatly concerned with comparability and scalability, he said, and it will be a challenge to introduce new tools that can provide both in an effective and innovative way.

Developing Standards and a Regulatory Framework

A common theme throughout the day was the importance of communication and collaboration among academia, industry, government, patients, and advocacy groups. A workshop participant said that the field is on a good track with regard to developing guidance documents and standards, which take a tremendous amount of effort to develop, and he asked how the panelists would suggest that FDA communicate and engage with stakeholders in the field to support these efforts. There are a number of venues where these conversations do occur, Vanek said, such as through the Alliance for Regenerative Medicine, the International Society for Cellular

Therapy, and the National Academies' Forum on Regenerative Medicine. Regulators do understand the challenges facing the development of these therapies, Preti added, noting that he has had many interactions with FDA over the years and found them to be very useful. "I do not know what else FDA could do," he said. "The fact that FDA listens and responds the way it does has been really helpful." Increasing transparency about the ongoing activity at FDA that might affect some of the challenges that industry faces when it runs into roadblocks could be beneficial, he suggested. It would also be helpful, he said, if FDA would continue to educate industry stakeholders about how they can improve the materials they submit for FDA review and about where they could improve on their implementation of FDA advice and guidance.

FDA and industry should both be working to get better clinical solutions to people that will improve health and reduce costs as quickly as possible, Kamen said, adding that he would like to see FDA become more of a partner without giving up its role as a regulator. If something causes delays or prevents patient access to new therapies, he said, it violates both of those objectives. Kamen suggested that FDA should act more like a government building department, which approves plans before a building is built and provides advice and review throughout the building process, so that the final approval is almost a formality. Partnering with FDA throughout the development process may depend on how a company approaches them, Preti said. FDA has been a good partner through programs such as special protocol assessments, he said, and in his experience the problem has been that industry has not developed transformative therapies.

FDA has provided tremendous assistance to the biotechnology industry as biological therapies such as monoclonal antibodies were developed, even before the science of these therapies was well understood, Siegel said, citing FDA's mission statement that includes the responsibility to "advance public health by helping to speed innovations that make medical products more effective, safer, and more affordable by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health."[2] Cell therapy is following a similar pathway to that of monoclonal antibodies, Siegel said, adding that his hope is that it will lead to improved manufacturing processes, more automation and standardization, and a detailed understanding of the CQAs that will accelerate the process of bringing products to market. In addition, he said, the ongoing efforts to create standards and invest in the science and automation will get the field to where it can generate therapies much faster.

[2]More information about FDA's mission and regulatory responsibilities can be found here: https://www.fda.gov/aboutfda/whatwedo (accessed August 29, 2017).

Interdisciplinary Collaboration

All stakeholders, including scientists, patient advocates, standards organizations, companies, clinicians, and regulators, should participate in the effort to automate the production of regenerative medicine products, Kamen said. That is the intent of the U.S. Department of Defense's investment in ARMI, he added. While acknowledging the importance of competition and intellectual property, Kamen said that there is a pre-competitive space in which all stakeholders can work together. Biologists and clinicians should start working with mathematicians and engineers to identify fundamental ideas that can dramatically increase the rate at which the field progresses, he said.

Transformative solutions to the challenges facing the field of regenerative medicine will likely come from mathematicians, a workshop participant said. In his view, he continued, the "design space" of the living cell—i.e., the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that provide assurance of quality—is too large for the human brain to fully visualize. Improving the development process will require software that can accommodate the complexity of the living cell's design space and generate the particular conditions that an engineer needs to scale a manufacturing process, he said. In the future, he predicted, researchers will use this type of approach to design cells with the characteristics desired for a specific application.

Training the Workforce of the Future

Addressing the lack of trained workers will be a major challenge, McBurney said. Vanek agreed, saying that training and motivating the workforce that the regenerative medicine industry needs to be successful will be a significant hurdle. It will be important to engage the STEM community and instill a sense of ownership and passion for this work, Vanek continued, and it will require companies to think creatively about the range of skill sets and expertise levels needed to support the manufacturing process. The manufacturing environment is challenging, Preti added, and advancing the potential for companies to develop innovative products will be dependent on bringing together individuals with the right expertise rather than on relying on generalists to carry out the full development process. Zylberberg added that the workforce should be trained to meet the industry's future needs. Although automation may replace some jobs, she said, there will be many others that require humans, and she suggested that the existing consortia can play an important role in training that workforce.

The Role of the Patient in the Discovery and Development Process

Patient advocates have a rational approach to therapy development, Preti said. They want more than simply getting treatments as soon as possible; they would prefer to participate in the development process themselves and to support the advancement of efficient, evidence-based therapies. Levine said that there should be continued and enhanced participation of patients through the National Academies' Forum on Regenerative Medicine, through BioFabUSA, and through the National Institute for Innovation in Manufacturing Biopharmaceuticals because that is how the field will communicate with the rest of the world. "The rest of the world will not see the data," Levine said. "They are going to see patient stories."

Transforming the Industry

Five years ago, manufacturers in the regenerative medicine industry were not aware of what they did not understand about the development of regenerative medicine therapies, Vanek said, but that has started to change. Big data, artificial intelligence, and machine learning have the potential to improve this understanding and transform the industry, he predicted. "How can the industry prioritize moving forward more rapidly in a way that incorporates all that has been learned about quality and regulatory oversight?" he asked. The first step, he said, will be to truly understand the science in order to improve analytical and production processes, followed by addressing the issues of scalability and comparability. "Attend to the biology and the science first," he said, "and the cost reduction will follow."

From a big picture point of view, Preti said, there are three important points regarding the future of regenerative medicine manufacturing that emerged from the workshop presentations and discussion: There is organic growth happening in the industry. There is funding coming into the field to support the development of these products. And this is a community of people who continue to collaborate with each other in order that patients worldwide will have these therapies accessible to them in the very near future.

The regenerative medicine community must move forward with an inclusive approach to the discovery and development of new therapies, McBurney said. Training should not be regarded in terms of science versus engineering, product development should not be approached in terms of complexity versus consistency, and the regulatory environment should not pit patient demand against regulation. Once the field starts prioritizing collaboration and applying a design framework to the development and manufacturing processes, he predicted, progress will accelerate to a degree that it will take a mere 20 years for regenerative medicine to become a dominant part of therapeutics.

FINAL THOUGHTS

In offering some final thoughts on the day, workshop co-chair Steven Oh said that it was clear from the day's presentations that there are numerous challenges facing the field, many of them related to science and technology, others related to successfully navigating the manufacturing process and ensuring the quality of regenerative medicine products. Other challenges, he said, are related to information technology issues, such as how to manage and share data, while still others have to do with workforce training.

The day's discussions highlighted the fact that fostering an environment that can maintain a good balance among technology innovation, safety and quality, and patient benefit will be crucial to the success of navigating the manufacturing process and assuring the quality of the regenerative medicine products, Oh said. Another important lesson, he said, was that when issues such as demonstrating product comparability or validating new manufacturing methods arise, taking a science-based approach will offer the best chance of addressing those issues. "From the regulatory perspective," he said, "we whole-heartedly agree that [science-based approaches] should guide us as we move forward with any of the manufacturing problems we want to deal with in this regenerative medicine therapy product space."

There are differences in the ways that regulatory agencies around the world think about manufacturing processes and quality assurance, and in turn, how manufacturers approach their processes as a result of these differences, Oh said, agreeing that the field needs to consider how to narrow those existing gaps between regulators and manufacturers. The industry's desire to develop point-of-care manufacturing will be a complex challenge to address from the regulatory, manufacturing, and quality assurance perspectives, he said, and he challenged workshop participants to start thinking about how to address the issues that will arise in moving to point-of-care manufacturing of regenerative medicine therapies.

Continued dialog among all of the stakeholders in the regenerative medicine field will important moving forward, Oh said. "I think it is essential that we have a good dialog early on," he said, adding that stakeholders are still figuring out the best way to initiate or continue that dialog.

Workshop co-chair Claudia Zylberberg said that organizations such as the Standards Coordinating Body can help move the field forward and that they should do so in coordination with FDA. In the quest to understand what cells are doing and to move the field forward, she said, progress is sometimes limited by the available technologies. There is an opportunity, she said, for biologists, engineers, and physical scientists to innovate together to come up with ways that existing technologies or ones yet to be developed can measure the important attributes of cells and provide the insights that will drive progress.

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Appendix A

Workshop Agenda

Navigating the Manufacturing Process and Ensuring the Quality of Regenerative Medicine Therapies:
A Workshop

June 26, 2017
National Academy of Sciences Building
Lecture Room
2101 Constitution Avenue NW
Washington, DC 20418

8:30 a.m. **Opening Remarks**

R. Alta Charo, *Forum Co-Chair*
Warren P. Knowles Professor of Law
University of Wisconsin–Madison

Jay P. Siegel, *Forum Co-Chair*
Chief Biotechnology Officer
Head, Scientific Strategy and Policy
Johnson & Johnson

8:35 a.m. **Charge to Workshop Speakers and Participants**

Claudia Zylberberg, *Workshop Co-Chair*
Founder and Chief Executive Officer
Akron Biotech

Steven Oh, *Workshop Co-Chair*
Acting Deputy Director, Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

8:45 a.m. **Opening Keynote**

Adrian Gee
Professor of Cell and Gene Therapy
Baylor College of Medicine

SESSION I: TRANSITIONING FROM DISCOVERY AND DEVELOPMENT TO MANUFACTURING FOR REGENERATIVE THERAPIES

Session Objectives:

- To discuss challenges and opportunities associated with bringing new discoveries from the lab to manufacturing and navigating the process of scaling up the manufacturing of new therapies.
- To learn about methods and capabilities for manufacturing and quality control data collection for the purpose of informing the transition from research and development (R&D) to the implementation of good manufacturing practices (GMPs).
- To illuminate potential opportunities and models to reach scale and commercialization with current infrastructure and to assess probable future needs.

Moderator: **Krishanu Saha,** Assistant Professor, University of Wisconsin–Madison

9:10–9:55 a.m. **Speakers:**

Bruce Levine
Barbara and Edward Netter Professor in Cancer Gene Therapy
University of Pennsylvania Perelman School of Medicine

Laura Niklason
Professor of Anesthesiology and Biomedical Engineering
Yale University

Bob Preti
President and Chief Executive Officer
PCT Cell Therapy Services, LLC

9:55–10:30 a.m. Discussion with Workshop Participants

10:30–10:45 a.m. BREAK

SESSION II: IDENTIFYING AND MEASURING CRITICAL QUALITY ATTRIBUTES OF REGENERATIVE MEDICINE PRODUCTS AND SOURCE CELLS

Session Objectives:

- To examine methods and processes used to identify and measure critical quality attributes for raw materials and regenerative medicine products.
- To discuss measurement methodology and how to ensure that measurements are accurate and reproducible.
- To survey technologies and future needs in the measurement of critical quality attributes.

Moderator: **Martha Somerman,** Director, National Institute of Dental and Craniofacial Research, National Institutes of Health

10:45–11:30 a.m. Speakers:

Anne Plant
Chief of the Biosystems and Biomaterials Division
National Institute of Standards and Technology

Linda Kelley
Director, Cell Therapies Processing Facility
Moffitt Cancer Center

Robert Deans
Chief Technology Officer
BlueRock Therapeutics

11:30 a.m.–noon Discussion with Workshop Participants

Noon–1:00 p.m. WORKING LUNCH

SESSION III: DESIGNING TECHNOLOGIES TO MEET THE MANUFACTURING NEEDS OF NEW REGENERATIVE THERAPIES

Session Objectives:

- To explore existing technologies that facilitate the efficient and cost-effective development of products that meet manufacturing and regulatory standards.
- To illuminate opportunities for new technologies and manufacturing models to increase efficiency and quality.
- To discuss novel and more precise in-process and final release testing technologies.
- To review existing infrastructure such as GMP facilities in academic centers and the commercial sector.
- To understand the open and closed systems models applicable to the manufacturing setting and information technology support.

Moderator: **Thomas Petersen,** Vice President, Regenerative Medicine, United Therapeutics Corporation

1:00–1:45 p.m. **Speakers:**

Isabelle Rivière
Director, Cell Therapy and Cell Engineering Facility
Memorial Sloan Kettering Cancer Center

Rodney Rietze
Lead, cGMP Process Automation for Cell and Gene Therapies
Novartis

Philip Vanek
General Manager, Cell Therapy Technologies
GE Healthcare

1:45–2:15 p.m. **Discussion with Workshop Participants**

SESSION IV: REGULATORY CHALLENGES AND OPPORTUNITIES FOR REGENERATIVE MEDICINE THERAPIES

Session Objective:

- To consider the regulatory landscape for regenerative medicine, including
  - developing standards
  - enforcing regulation
  - meeting the needs of patients

Moderator: **Jiwen Zhang,** Senior Director, Regulatory Affairs, Cell Therapy and Regenerative Medicine, GE Healthcare

2:15–3:00 p.m. **Speakers:**

Robert Mcburney
President and Chief Executive Officer
Accelerated Cures Project for Multiple Sclerosis
Co-Principal Investigator
iConquerMS Patient-Powered Research Network

Steven Bauer
Chief, Cellular and Tissue Therapy Branch
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration

Katherine Tsokas
Senior Director, Global Regulatory Affairs
Johnson & Johnson

3:00–3:35 p.m. **Discussion with Workshop Participants**

3:35–3:50 p.m. **BREAK**

SESSION V: CLOSING KEYNOTE AND PANEL

Session Objectives:

- To summarize the lessons learned and topics discussed throughout the workshop day.
- To discuss ways forward to support the development, manufacture, and regulation of safe and effective regenerative medicine therapies.

Moderator: **Krishnendu Roy,** Robert A. Milton Chair and Professor and Technical Lead, National Cell Manufacturing Consortium, Georgia Institute of Technology

3:50–4:10 p.m. **Closing Keynote:**

Dean Kamen
Advanced Regenerative Manufacturing Institute
DEKA Research & Development Corporation

4:10–4:30 p.m. **Panelist Reflections**

Bob Preti
President and Chief Executive Officer
PCT Cell Therapy Services, LLC

Anne Plant
Chief of the Biosystems and Biomaterials Division
National Institute of Standards and Technology

Philip Vanek
General Manager, Cell Therapy Technologies
GE Healthcare

Robert Mcburney
President and Chief Executive Officer
Accelerated Cures Project for Multiple Sclerosis
Co-Principal Investigator
iConquerMS Patient-Powered Research Network

4:30–5:00 p.m. **Discussion with Workshop Participants**

5:00 p.m.	**Final Remarks from Workshop Co-Chairs** Claudia Zylberberg, *Workshop Co-Chair* Founder and Chief Executive Officer Akron Biotech Steven Oh, *Workshop Co-Chair* Acting Deputy Director, Division of Cellular and Gene Therapies Office of Tissues and Advanced Therapies Center for Biologics Evaluation and Research U.S. Food and Drug Administration
5:15 p.m.	**Adjourn**

Appendix B

Speaker Biographical Sketches

Steven R. Bauer, Ph.D., is the chief of the Cellular and Tissue Therapy Branch (CTTB), Division of Cellular and Gene Therapies in the Office of Tissues and Advanced Therapies at the Center for Biologics Evaluation and Research (CBER) in the U.S. Food and Drug Administration. As the chief of CTTB, Dr. Bauer supervises CBER scientific staff engaged in review of cell-based biological therapies, policy development in emerging areas of cellular therapies, and research relevant to their use in clinical trials. His current research focuses on mesenchymal stem cell biology and stromal cell–hematopoietic cell interactions that influence the development of lymphocytes. Dr. Bauer received his Ph.D. in biochemistry from the University of Maryland in 1986. From 1986 through 1991, Dr. Bauer was a scientific member of the Basel Institute for Immunology in Basel, Switzerland. In 1991, Dr. Bauer joined CBER's Division of Cellular and Gene Therapies.

Robert Deans, Ph.D., is the chief technology officer at BlueRock Therapeutics, a biotechnology company creating innovative cell therapeutics by harnessing gene editing tools and pluripotent stem cell biology. Prior to joining BlueRock, he was the chief scientific officer at Rubius Therapeutics, a red cell therapeutics platform company. Dr. Deans was previously the executive vice president at Athersys, Inc., an adult stem cell therapeutics company now in late-stage clinical development, and prior to that the vice president of research at Osiris, Inc., developing the Prochymal MSC-based product line. Dr. Deans was also experienced in hematopoietic stem cell isolation and gene therapy while director of the Immunotherapy Division of Baxter

Healthcare. Dr. Deans has also contributed to numerous regulatory and industry commercialization workshops and societies.

Adrian Gee, Ph.D., received his bachelor's degree from the University of Birmingham, England, and his Ph.D. from the University of Edinburgh, Scotland. He did his postdoctoral training at the National Institutes of Health and the University of Toronto before taking a faculty position at the University of Florida. There he performed some of the first applications of immunomagnetic tumor purging in the United States, and his laboratory became a central cell processing facility for this procedure. He joined Baxter Healthcare in 1987, where he worked on the development of the MaxSep and Isolex magnetic cell separators. He co-founded the International Society for Hematotherapy and Graft Engineering (now ISCT) and the *Journal of Hematotherapy* (now *Cytotherapy*) in 1992. From 1992 to 1997 he helped establish the stem cell transplantation program at the University of South Carolina. He then directed the Cell Processing Laboratory at The University of Texas MD Anderson Cancer Center until 1999, when he joined the Center for Cell and Gene Therapy at Baylor College of Medicine in Houston. He was involved in the development of standards for the collection processing and transplantation of hematopoietic stem cells for the Foundation for the Accreditation of Cell Therapy (FACT), the AABB, and the National Marrow Donor Program. He has written more than 180 scientific articles and has authored and edited a number of books on graft engineering and stem cell processing. He currently is a member of the Health Resources and Services Administration committee on Blood Stem Cell Transplants, the FACT committee on Regenerative Medicine, and the Program Review Group for the California Institute of Regenerative Medicine. He received the FACT Career Achievement Prize in 2017.

Dean Kamen is an inventor, an entrepreneur, and a tireless advocate for science and technology. His roles as inventor and advocate are intertwined—his own passion for technology and its practical uses has driven his personal determination to spread the word about technology's virtues and by so doing to change the culture of the United States.

As an inventor, he holds more than 440 U.S. and foreign patents, many of them for innovative medical devices that have expanded the frontiers of health care worldwide. While still a college undergraduate, he invented the first wearable infusion pump, which rapidly gained acceptance from such diverse medical specialties as oncology, neonatology, and endocrinology. In 1976 he founded his first medical device company, AutoSyringe, Inc., to manufacture and market the pumps. Then, working with leading diabetes researchers, Mr. Kamen pioneered the design and adoption of the first portable insulin pump. It was quickly demonstrated that using a pump could

much more effectively control patients' blood glucose levels. At age 30 he sold AutoSyringe to Baxter Healthcare Corporation.

Following the sale of AutoSyringe, Inc., he founded DEKA Research & Development Corporation to develop internally generated inventions as well as to provide research and development for major corporate clients. Mr. Kamen led DEKA's development of the HomeChoice™ peritoneal dialysis system for Baxter International Inc. The HomeChoice™ system allows patients to be dialyzed in the privacy and comfort of their home and quickly became the worldwide market leader. Mr. Kamen also led the development of technology to improve slide preparation for the CYTYC (now Hologic Inc.) ThinPrep® Pap Test. Kamen-led DEKA teams have also developed critical components of the UVARTM XTSTM System, an extracorporeal photophereisis device marketed by Therakos, a unit of Johnson & Johnson, for treatment of T cell lymphoma. An advanced prosthetic arm in development for DARPA should advance the quality of life for returning injured soldiers. Other notable developments include the Hydroflex™ surgical irrigation pump for C.R. Bard; the Crown™ stent, an improvement to the original Palmaz-Schatz stent, for Johnson & Johnson; the iBOT™ mobility device; and the Segway® Human Transporter.

Mr. Kamen has received many awards for his efforts. Notably, he was awarded the National Medal of Technology in 2000. Presented by President Clinton, this award was in recognition for inventions that have advanced medical care worldwide and for innovative and imaginative leadership in awakening America to the excitement of science and technology. Kamen was also awarded the Lemelson–Massachusetts Institute of Technology Prize in 2002, and was inducted into the National Inventors Hall of Fame in May 2005. He is a fellow of the American Institute for Medical & Biological Engineering and has been a member of the National Academy of Engineering since 1997. In 2010 Mr. Kamen hosted the Planet Green television series Dean of Invention. In addition to DEKA, one of Mr. Kamen's proudest accomplishments is founding FIRST® (For Inspiration and Recognition of Science and Technology), an organization dedicated to motivating the next generation to understand, use and enjoy science and technology. Founded in 1989, this year FIRST® will serve more than 1 million young people ages 6 to 18 in more than 86 countries around the globe. Last year, high-school-aged participants were eligible to apply for more than $50 million in scholarships from more than 200 leading colleges, universities, and corporations.

Linda Kelley, Ph.D., is the Cell Therapy Facility director and a senior member at Moffitt Cancer Center as well as a professor at the University of South Florida. Dr. Kelley has provided leadership for cellular therapy facilities for more than 20 years at three institutions: University of Utah,

Dana Farber Cancer Institute, and Moffitt Cancer Center. She received graduate and postdoctoral training in immunology and hematology from Vanderbilt University in Nashville, Tennessee. Her scientific career evolved from a fundamental interest in immunological mechanisms of T lymphocyte function, the growth mechanisms of hematopoietic stem and progenitor cells, and the molecular changes associated with malignant transformation. Knowledge of the hematopoietic system led to an interest in stem cell biology and therapies. As the director of the Cell Therapy Facility at the University of Utah from 1994 to 2011, she was responsible for developing and expanding a Cell Therapy and Regenerative Medicine Laboratory. During her tenure she was responsible for pre-clinical and clinical cell therapy product development to support investigational new drug (IND) applications for the production of allogeneic mesenchymal stromal cells (MSCs), autologous bone marrow-derived mononuclear cells, and allogeneic fetal-derived oligodendrocytes. As director of the Cell Manipulation Core Facility at the Dana Farber Cancer Institute at Harvard from 2011 to 2012, she oversaw management of 20 FDA-approved INDs for the manufacture of gene-modified CD34+ cells, tumor cell vaccines, dendritic cells, MSCs, and others. As director of the Cell Therapy Facility at Moffitt Cancer Center, she oversees 22 active INDs for a variety of products largely to support immunotherapy for adult and pediatric patients. She currently serves as the principal investigator for production assistance for cellular therapies–cell processing facilities to perform pre-clinical cell therapy product development in collaboration with the National Heart, Lung, and Blood Institute and other Production Assistance for Cellular Therapies Centers and as core laboratory technical director for the Moffitt Cancer Center Support Grant. Dr. Kelley excels at bridging the gap between laboratory-based discoveries and new therapies for patients.

Bruce Levine, Ph.D., the Barbara and Edward Netter Professor in Cancer Gene Therapy, is the founding director of the Clinical Cell and Vaccine Production Facility (CVPF) in the Department of Pathology and Laboratory Medicine and the Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania. He received a B.A. in biology from the University of Pennsylvania and a Ph.D. in immunology and infectious diseases from the Johns Hopkins University. The CVPF develops and tests novel cell and gene therapies in clinical trials in patients with hematologic malignancies, solid tumors, HIV infection, and genetic disease. First-in-human trials include the first use of a lentiviral vector, the first infusions of gene edited cells, and the first use of lentivirally modified cells to treat cancer. Dr. Levine has overseen the production, testing, and release of 2,700 cellular products administered to more than 1,000 patients in clinical trials since 1996. Through these technologies, personalized and enhanced immunity

has been engineered. T lymphocytes from HIV+ subjects have been rendered resistant to HIV infection and reinfused. T lymphocytes from cancer patients have been redirected with chimeric antigen receptors to hunt and destroy their malignancies, an investigational therapy that received the first Breakthrough Designation from the U.S. Food and Drug Administration for an academic institution and is currently in commercial development. Dr. Levine is co-inventor on 23 issued U.S. patents and co-author of 130 publications with a Google Scholar citation h-index of 66. He has been interviewed by *The New York Times*, *The Wall Street Journal*, *National Geographic*, *Forbes*, BBC, and other international media outlets.

Robert McBurney, Ph.D., is the chief executive officer of the Accelerated Cure Project for Multiple Sclerosis and a co-principal investigator for the iConquerMS™ Patient-Powered Research Network. In a career spanning more than 35 years, Dr. McBurney has conducted basic and clinical research and managed research groups for drug discovery, personalized medicine, and clinical decision support systems at medical schools, research institutes, biopharmaceutical companies, and nonprofit organizations in Australia, the United Kingdom, and the United States.

Dr. McBurney is currently a member of the American Academy of Neurology, the Society for Neuroscience, the PhRMA Foundation Informatics Advisory Committee, and the International Society for Pharmacoeconomics and Outcomes Research. He is also a trustee emeritus of the F.W. Olin College of Engineering. Dr. McBurney received B.Sc. and Ph.D. degrees from the University of New South Wales, Australia.

Laura Niklason, M.D., Ph.D., is the Nicholas M. Greene Professor at Yale University in anesthesia and biomedical engineering, where she has been on faculty since 2006. Dr. Niklason's research focuses primarily on regenerative strategies for cardiovascular and lung tissues. Her engineered blood vessels are currently in clinical trials and are the first life-sustaining engineered tissue to be studied in any Phase III trial. Dr. Niklason's lab was also one of the first to describe the engineering of whole lung tissue that could exchange gas in vivo, and this work was cited in 2010 as one of the top 50 most important inventions of the year by *Time* magazine. She was inducted into the National Academy of Inventors in 2014 and was elected to the National Academy of Medicine in 2015.

Dr. Niklason received her Ph.D. in biophysics from the University of Chicago and her M.D. from the University of Michigan. She completed her residency training in anesthesia and intensive care unit medicine at the Massachusetts General Hospital in Boston and completed postdoctoral scientific training at the Massachusetts Institute of Technology.

Anne Plant, Ph.D., received her Ph.D. from Baylor College of Medicine in Houston, Texas, in Biochemistry. She is the chief of the Biosystems and Biomaterials Division at the National Institute of Standards and Technology (NIST). She served for 1 year in the White House Office of Science and Technology Policy and is currently the NIST representative to the National Science and Technology Council (NSTC) Life Science Sub-Committee. She serves on the National Institute of Biomedical Imaging and Bioengineering's National Advisory Council for Biomedical Imaging and Bioengineering, co-chairs ASTM International Committee F04.46 on Standards for Cell Signaling, and is on the editorial advisory board of the journal *Biointerphases*. She is a fellow of the American Institute for Medical and Biological Engineering. Her research has recently been focused on the robust quantification of cell response through quantitative cell imaging and theoretical approaches for the prediction of complex biological response.

Robert Preti, Ph.D., is the co-founder of PCT and the visionary behind its successful growth and development strategy over much of the last two decades. Upon PCT's acquisition by Hitachi Chemical Co. America, Ltd. (Hitachi Chemical's consolidated subsidiary) in May 2017, Dr. Preti's role expanded to chief executive officer and president of PCT, responsible for development, management, and oversight of the global business operations of Hitachi Chemical's regenerative medicine business unit. Dr. Preti is currently the chairman of the Alliance for Regenerative Medicine (ARM). He holds a B.S. in biology from Fordham University and an M.S. and doctorate, both in biology, from New York University.

Dr. Preti built PCT to meet a recognized need for high-quality manufacturing and development services in an emerging industry. As the cell therapy field has grown, so too has PCT. The company has now served more than 100 clients and performed more than 20,000 cell therapy procedures. His leadership has been instrumental in creating PCT's client-focused model which helps bridge the gap between discovery and patient care through the efficient transfer of cell-based therapies from laboratory into clinical practice. His vision for PCT includes expansion of its manufacturing capacity in the United States, Asia, and Europe as well as the development of new technological and engineering innovations that will help streamline and automate many cell processing techniques, leading to faster scale-up, appropriate cost of goods, and robust quality for the industry.

Rodney Rietze, Ph.D., began his graduate training in regenerative medicine in the laboratory of Samuel Weiss (director, Hotchkiss Brain Institute), who is credited with the discovery of adult neural stem cells (NSCs). After completing a master's degree on the role these cells played in adult hippocampal neurogenesis, he moved to the laboratory of Perry Bartlett (Walter and Eliza

Hall Institute of Medical Research, Melbourne) and focused his studies on the successful purification of an adult mammalian NSCs. His doctoral work enabled the direct interrogation of this elusive population and opened the door to uncovering the biology that underpins this highly regenerative population of cells. As a founding faculty member of the Queensland Brain Institute (Brisbane, Australia) and principal investigator of the Neural Stem Cell and Aging Laboratory, Dr. Rietze continued to investigate the biology of adult NSCs, cumulating with the discovery of the essential role that growth hormone receptor signaling plays in stimulating endogenous precursors and reversing age-related cognitive decline.

In 2008 Dr. Rietze abandoned academic pursuits to join the newly created Pfizer regenerative medicine unit (Cambridge, UK), where he led research teams in the development of both small molecule and cell-based therapeutics for a variety of neural, autoimmune, and cardiovascular indications. Following the closure of Pfizer's Sandwich facility, Dr. Rietze was recruited by the technical research and development team at Novartis's Cell and Gene Therapy Unit (CGTU) in Cambridge, Massachusetts, to lead process automation and deliver innovative and enabling technologies for the manufacture of cell-based therapeutics across the unit's portfolio. In 2016 Dr. Rietze transitioned from CGTU to the exploratory immuno-oncology group at Novartis Institutes for Biomedical Research, where he continues to develop novel CAR T-based technologies and therapeutics under the direction of Glenn Dranoff.

Isabelle Rivière, Ph.D., received her Ph.D. in cellular and molecular biology from the University of Paris. She initiated her graduate studies at the Institut Curie in Paris and completed her thesis in the laboratory of Richard Mulligan at the Whitehead Institute in Cambridge, Massachusetts. During this time, she developed novel retroviral vectors to investigate the in vivo long-term expression of transgenes in hematopoietic cells using MFG/SFG-based retroviral vectors. These vectors are widely used in clinical studies for the treatment of genetic and acquired disorders. She subsequently worked as a postdoctoral fellow in the laboratory of Dan Littman at New York University. Her studies focused on the regulation of cytokines produce by T helper lymphocytes in vivo.

Dr. Rivière joined the faculty of Memorial Sloan Kettering Cancer Center in 1999. She is currently the director of the Michael G. Harris Cell Therapy and Cell Engineering laboratory where she investigates the genetic modification of hematopoietic cells to increase or retarget the immune response against tumors and to treat genetic disorders. Her laboratory has developed cell manufacturing processes under GMP conditions for several Phase I/II clinical trials in the academic setting. She actively participates in the National Cell Manufacturing Consortium workshop that led to the

establishment of the Technology Roadmap to 2025 for Achieving Large Scale, Cost effective, Reproducible Manufacturing of High-Quality Cells. She is a member of the board of directors of the American Society of Gene and Cell Therapy, the Alliance for Regenerative Medicine, and the Center for Commercialization of Cancer Immunotherapy (Canada). She is also an active member of the International Society of Cell Therapy and the International Society of Stem Cell Research.

Katherine A. Tsokas, J.D., is the senior director of Global Regulatory Affairs at Johnson and Johnson. She has 26 years of progressive global regulatory experience in small- and large-sized pharmaceutical companies. She has worked on products at various stages of development, from early through to filing, approval, and commercialization. Currently, her responsibilities include providing strategic regulatory oversight to advanced therapy projects in several therapeutic areas by ensuring that regulatory strategies contribute to and support the development plans for the products and that all opportunities for collaboration internally and externally are used. Furthermore, through the RMAT Network, Ms. Tsokas leads Johnson & Johnson cross-sector efforts to enhance awareness and connectivity for the development of processes that enable assessing, partnering, and developing safe and effective advanced therapies globally. In addition, she represents global regulatory affairs on the Johnson & Johnson First in Human Committee. Ms. Tsokas received her bachelor of science degree in biology from Temple University and a juris doctorate from Widener University Law School and is admitted to the practice of law in Pennsylvania and New Jersey.

Philip Vanek, Ph.D., is the general manager of GE Healthcare's Cell Therapy Technologies business strategy, a business initiative funded in part by GE Healthymagination, a $6 billion strategy to revolutionize the world's health by improving the quality, access to, and affordability of care. Prior to joining GE, Dr. Vanek was the head of innovation for Lonza's pharmaceutical division, leading a group of research scientists, process development engineers, and commercial strategists to drive new technology initiatives focused on cell, protein, and viral therapeutic manufacturing.

Dr. Vanek's career has included a number of senior innovation, business, and market development roles at Becton Dickinson, Invitrogen, and Life Technologies as well as two start-up biotechnology companies in the Washington, DC, area.

Appendix C

Statement of Task

An ad hoc planning committee will plan and conduct a 1-day public workshop to examine and discuss challenges, opportunities, and best practices associated with defining and measuring the quality of cell and tissue products and raw materials in the research and manufacturing of regenerative medicine therapies. The goal of the workshop will be to learn from existing examples of manufacturing of early-generation regenerative medicine products and to address how progress could be made in identifying and measuring critical quality attributes as well as designing and adhering to standards to help in the navigation of the scale-up process from a research laboratory to the manufacturing environment. Gathering this information will help inform and facilitate future forum discussions around the issues of implementing regenerative medicine therapies and technologies, such as designing and implementing effective manufacturing processes, examining regulatory pathways, and considering bioethical matters. Discussions during this workshop will be held with a broad array of stakeholders which may include research scientists, clinicians, patients, regulators, and representatives from pharmaceutical and biotech companies. The planning committee will develop the workshop agenda, select and invite speakers, and moderate the discussions. Proceedings from the workshop will be prepared by a designated rapporteur in accordance with institutional policies and procedures.

Appendix D

Registered Attendees

Joe Alper
Consultant

Salomon Amar
New York Medical College

Rachael Anatol
U.S. Food and Drug Administration

Judith Arcidiacono
U.S. Food and Drug Administration

Gillian Armstrong
PACT

Chris Ballas
WuXi AppTec

Steven Bauer
U.S. Food and Drug Administration

Steven Becker
National Eye Institute

Kimberly Beer
Christopher & Dana Reeve Foundation

Kapil Bharti
National Eye Institute

Sarindr Bhumiratana
EpiBone Inc.

Catherine Bollard
International Society for Cellular Therapy

Tom Bollenbach
Advanced Regenerative Manufacturing Institute

Lizbet Boroughs
Association of American Universities

Melissa Carl
American Society of Mechanical Engineers

Preethi Chander
National Institute of Dental and Craniofacial Research

R. Alta Charo
University of Wisconsin Law School

Gray Chynoweth
Advanced Regenerative Manufacturing Institute

Michelle Cortes
National Institute of Dental and Craniofacial Research

Robert Deans
BlueRock Therapeutics

Cynthia Dunbar
American Society of Gene and Cell Therapy

Donald Fink
U.S. Food and Drug Administration

Ellen Gadbois
National Institutes of Health

John Gardenier
Independent

Turkan Gardenier
Pragmatica Corporation

Lindsay Garvin
National Heart, Lung, and Blood Institute

Adrian Gee
Center for Cell and Gene Therapy, Baylor College of Medicine

Larry Goldstein
University of California, San Diego

Daniel Gossett
National Institutes of Health

Joseph Griffin
MassMEP

Rachel Haddock
GlaxoSmithKline

Patrick Hanley
International Society for Cellular Therapy

Joshua Hare
University of Miami

Brian Harvey
Global Liver Institute

Daniel Hayes
The Pennsylvania State University

Susan Howley
Christopher & Dana Reeve Foundation

Deborah Hursh
U.S. Food and Drug Administration

Laarni Ibenana
The Emmes Corporation

Shekhar Jha
National Institutes of Health

Ping Jin
National Institutes of Health

Naynesh Kamani
American Association of Blood Banks

Dean Kamen
DEKA Research & Development

Linda Kelley
Moffitt Cancer Center

Walter Koroshetz
National Institutes of Health

Paul Kotturi
Pacific Biosciences

Audrey Kusiak
Department of Veterans Affairs

Larissa Lapteva
U.S. Food and Drug Administration

Cato Laurencin
University of Connecticut

Timothy LaVaute
National Institute of Neurological Disorders and Stroke

Anh Le
University of Pennsylvania

Bruce Levine
University of Pennsylvania

Rachel Levinson
Arizona State University

Jinhua Lu
U.S. Food and Drug Administration

Erin Luetkemeier
National Institutes of Health

Martha Lundberg
National Heart, Lung, and Blood Institute

Terry Magnuson
University of North Carolina at Chapel Hill

Keith March
Indiana University School of Medicine

Kurt Marek
National Heart, Lung, and Blood Institute

Ross Marklein
U.S. Food and Drug Administration

Nancy Markovitz
Diamond Pharma Services, Inc.

Jessica Mazerik
National Eye Institute

Robert McBurney
Accelerated Cure Project for Multiple Sclerosis

Richard McFarland
Advanced Regenerative Manufacturing Institute

Mark McMenemy
MassMEP

Kaye Meier
International Society for Stem Cell Research

Phyllis Mitchell
National Heart, Lung, and Blood Institute

Jason Moore
Smithfield Foods

Kirsten Moore
The Pew Charitable Trusts

Malcolm Moos
U.S. Food and Drug Administration

Jack Mosher
International Society for Stem Cell Research

Melissa Moss
Biomedical Engineering, University of South Carolina

Eleanor Nicoll
American Society for Reproductive Medicine

Laura Niklason
Department of Anesthesia, Yale University

Kim O'Connor
Tulane University

Steven Oh
U.S. Food and Drug Administration

David Owens
National Institute of Neurological Disorders and Stroke

Diana Pankevich
Pfizer Inc.

Duanqing Pei
Guangzhou Institutes of Biomedicine and Health, CAS

Thomas Petersen
United Therapeutics

Russell Pirlo
BioFabUSA

Anne Plant
National Institute of Standards and Technology

Nicole Polinski
The Michael J. Fox Foundation for Parkinson's Research

Kristy Pottol
U.S. Army Medical Materiel Development Activity

Libbie Prescott
National Defense University

Robert Preti
PCT Cell Therapy Services, LLC

Jiaqiang Ren
National Institutes of Health

James Richardson
Foundation Fighting Blindness

Rod Rietze
Novartis Institutes for Biomedical Research

Joseph Rimsa
TauTona Group Research and Development Company, L.L.C.

Isabelle Rivière
Memorial Sloan Kettering Cancer Center

Kelley Rogers
Office of Advanced Manufacturing, National Institutes of Health

Heather Rooke
International Society for Stem Cell Research

Krishnendu Roy
Georgia Institute of Technology

Beth Russell
Alder Data-Driven Solutions

Stephanie Saddic
GlaxoSmithKline

Krishanu Saha
University of Wisconsin–Madison

Sumona Sarkar
National Institute of Standards and Technology

Stephanie Scarmo
The Pew Charitable Trusts

Basant Sharma
Janssen Research & Development

Jay Siegel
Johnson & Johnson

Ilyas Singec
National Center for Advancing Translational Sciences

Aparna Singh
National Institutes of Health

Martha Somerman
National Institute of Dental and Craniofacial Research

Courtney Stanton
Smithfield Foods

Binil Starly
North Carolina State University

Sohel Talib
California Institute for Regenerative Medicine

William Tente
Humacyte

Sharon Terry
Genetic Alliance

John Thomas
National Heart, Lung, and Blood Institute

Zehra Tosun
U.S. Food and Drug Administration

Katherine Tsokas
Janssen Research & Development

Philip Vanek
GE Healthcare

Jason Wan
National Institute of Dental and Craniofacial Research

Fei Wang
National Institute of Arthritis and Musculoskeletal and Skin Diseases

Rachel Weissman
Research!America

Anthony Welch
National Cancer Institute

Lisbeth Welniak
National Institutes of Health

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Northwestern University

Angela Whatley
U.S. Food and Drug Administration

Celia Witten
U.S. Food and Drug Administration

Michael Yaffe
The New York Stem Cell Foundation

Shaomian Yao
Louisiana State University

Carolyn Yong
U.S. Food and Drug Administration

Michael Yost
Medical University of South Carolina

Jiwen Zhang
GE Healthcare

Yuji Zhang
University of Maryland Baltimore

Claudia Zylberberg
Akron Biotech