RAPID RESPONSE REPORT

Biomanufacturing Technologies for Regenerative Medicine

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EXECUTIVE SUMMARY

Regenerative Medicine has the potential to be a game-changer for patients who have damaged tissues or organs due to untreatable diseases, injuries, and congenital conditions. Lab-based innovations have shown great promise in restoring structure and function, but to deliver treatments to large numbers of patients in a clinical setting, new tools and technologies are needed. Regenerative Medicine is a new area of medical research that seeks to automate and scale-up the production and deployment of these groundbreaking solutions.

The technologies discussed in this report are intentionally pre-competitive, meaning that the Federal Government may choose to play a role in additional growth via well-informed initiatives. Governmental support can come in the form of additional research & development (R&D) dollars that are magnified by private co-investment, or can be in the form of non-pecuniary actions such as modifications to the regulatory environment to better support this rapidly changing field. Ideally, a cooperative relationship between government and private industry will result in cross-industry, pre-competitive tools that decrease development cost and time while still respecting individual intellectual property ownership within a competitive environment.

This report identifies promising biomanufacturing platforms that will provide a foundation for the automation and standardization of the processes associated with successful scale-up and scale-out. After evaluating a range of potential translational technology options according to their suitability for co-investment and cross-industry appeal, two platform technologies and two enabling tools were selected:

PLATFORM TECHNOLOGY #1: 3D CONSTRUCTS, INCLUDING ORGANOIDS, SCAFFOLDS, AND PRINTED TISSUES

Based on the potential for patient-specific applications, *3D Constructs, including Organoids, Scaffolds, and Printed Tissues* were selected as a key platform technology. 3D constructs are predicted to be a critical component of cell-based therapies for tissue- and organ-based regenerative approaches. The resulting three-dimensional structures can be used for the treatment of congenital conditions, and can treat tissue loss due to cancer or trauma.

PLATFORM TECHNOLOGY #2: BIOMANUFACTURING PROCESSES

Given the inherent process management challenges encountered when manipulating cells and biological tissues, the development of stable, consistent and safe *Biomanufacturing Processes* is a key platform in Regenerative Medicine.

Because of the range of topics under the heading “Biomanufacturing Processes,” the area was further divided into two key enabling tools:

(i) Scaled-up bioreactors for cell culture, and

(ii) Improvements in cell harvesting, cell processing, and preservation technologies; each directly affecting the supply of materials to the production process, and therefore requiring high-level management.

SUMMARY OF KEY OBSERVATIONS

- Pre-competitive and core technology development should be kept as open as possible to sustain the network effect gained from using standard biological platforms, data systems, and manufacturing and testing standards.
- Government should consider/nurture/recognize different models for technology commercialization. This would allow for the creation of ecosystems that bring academic, government, and industrial partners together in highly integrated environments that facilitate the engagement of commercialization teams in bio-product development at a very early stage.
- The ideal partnership for research institutions working with early-stage technologies is with an enterprise that has strong translational capabilities.
- The failure of large corporations to fully embrace many Regenerative Medicine products and technologies is a major barrier to investment for many small companies. Government can mitigate these barriers with reforms to the regulatory environment that improve clarity and timeliness to market, thereby de-risking and encouraging corporate investment.
- Many university tech transfer offices do not understand the complexities of maturing a technology into a market-ready state, causing an overvaluation of early-stage discoveries.
- NIST, federal regulators, industry and academic leaders should work together to establish relevant standards. One approach is to embed regulatory personnel within companies during the pre-competitive development process. The result will be regulations that are more suitably targeted to the technology under development.
- More flexible regulatory mechanisms could help accelerate Regenerative Medicine product development, particularly in the area of manufacturing process development.
- There is a need for enhanced development on process engineering, manufacturing, and more cost-effective clinical trials. The current status is seen as a major U.S. disadvantage and a serious obstacle to commercialization.
- Scientific researchers must collaborate with ethicists to be sure that all R&D work follows the highest ethical standards. Furthermore, experienced scientific researchers should take the lead in using science-based data to underscore the potential benefits of Regenerative Medicine to the public.
- New employees at biotechnology firms can require significant time (up to 2 years) to gain an understanding of core concepts. To meet the workforce challenges at various levels, universities should consider creating new certificate or degree programs in bioprocess engineering (directed toward cell therapy). Public/private consortia should be involved in developing curricula for these programs. Additionally, there is an acknowledged need for new associate-level training for operators working in clean room environments.
- Workforce development programs should include practical training through industry internships and apprenticeships, as well as undergraduate, graduate and post-doc research fellowships at national labs.

INTRODUCTION

Medicine has advanced in astounding ways over the course of the past century. With the development of drugs and technologies ranging from Penicillin and vaccines to modern X-rays and anesthesia, the average life expectancy at birth in the U.S. increased from under 50 years in 1900[1] to almost 80 years today.[2] A range of pernicious and previously untreatable diseases from polio to juvenile diabetes to various forms of cancer have finally become manageable or beatable due to the immense focused attention of medical researchers and practitioners.

The cumulative result of academic, governmental, and private medical research investments has been a massive flourishing of human life. Yet there is reason to believe that advances in medical technology in the decades to come could tower over the last century's innovations.

A case in point is the development of the new field of **Regenerative Medicine (RM)**. This emerging area of research could revolutionize the treatment of diseases, injuries, and congenital conditions by turning various basic tissues into fully functional human organs.

Regenerative Medicine combines diverse innovations to enable the use of bodily tissues like progenitor cells (from umbilical cord blood) or stem cells (from adults or embryos) to repair or replace failing systems in a human body. The operating principle behind Regenerative Medicine is simple and profound:

The human body can heal itself.

For people living with untreatable conditions or with loved ones coping with disease or injury, these innovations cannot come quickly enough. But there are serious hurdles that must be overcome before regenerative therapies can go mainstream.

To bring Regenerative Medicine to scale, smart investments in translational research are necessary to bring laboratory discoveries all the way to operating rooms. It is not enough to do the needed work in the lab or in product rollout—we need focused thinking and action to connect the "R" with the "D" of the R&D equation, translating initial discoveries and innovations into life-saving products and processes.

In spite of the ongoing work in the field of Regenerative Medicine,[3] research is only part of the challenge. It is also necessary to address underlying needs related to training the Regenerative Medicine workforce, designing prudent regulations, perfecting university technology transfer protocols, and forming new standards and guidelines for the ethical use of these transformative technologies.

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[1] Centers for Disease Control and Prevention. U.S. Decennial Life Tables for 1890 to 1961. http://www.cdc.gov/nchs/products/life_tables.htm#1890_1961.

[2] CIA. The World Factbook. Life Expectancy at Birth. https://www.cia.gov/library/publications/the-world-factbook/rankorder/2102rank.html.

[3] Between January 2012 and September 2013, Web of Knowledge database cites over 8000 original publications for tissue engineering or regenerative medicine.

ABOUT THIS REPORT

This report offers specific details on the partnerships, analyses, and investments that government, private sector, and university stakeholders can undertake to enable the prompt and safe development of Regenerative Medicine technologies.

From the development of 3D medical constructs to the creation of clear process standards for manufacturing and clinical environments, the recommendations follow a common thread: Regenerative Medicine can benefit from cross-sector collaboration to create pre-competitive tools to decrease development cost and time to market. These recommendations, based on inputs from subject matter experts, emphasize that carefully targeted research cooperation and coordination on workforce training can succeed without undercutting market forces.

The approach taken to develop this report includes:

1. The use of Technology Readiness Level (TRL)[4] indicators to identify today's promising translational platform technologies in Regenerative Medicine.
2. An identification of key barriers to translation at the interface of discovery, manufacturing, and clinical administration, including regulatory, technology transfer, and intellectual property barriers.
3. The selection of the critical advancements needed at biomanufacturing facilities to achieve commercial and technical viability.
4. An exploration of successful models of industry-government collaborations on the creation of non-competitive platform technologies to support future underlying therapeutic advancement to commercialization.
5. A discussion on the ideal R&D partnership model between academia, industry, and government, and an assessment of how Federal Government participation can minimize risks during the technology development process.
6. A look at U.S. competitiveness to ensure that manufacturing of RM technologies remains in the U.S., and to assess incurred challenges and opportunities in education and workforce training.

Of special note is the focus on technologies that are beyond the basic research stage, but not yet commercial. Referred to as *translational*, the selected technologies have Technology Readiness Levels ranging from TRL4 (*component-level validation in the laboratory*) to TRL7 (*system prototype in an operational environment*). This range of technological maturity is considered to have the greatest potential for transforming the manufacturing of RM therapies, but still face significant barriers to adoption.

The therapeutic platforms under consideration can be broadly characterized according to their ability to impact our understanding and proficiency in:

[4] Technology Readiness Levels (TRL) are used to assess the maturity level of a particular technology. TRL1 is the lowest level (initial scientific research) and TRL9 is the highest (successful operational use.) See http://www.ncbi.nlm.nih.gov/books/NBK201356.

- Regulating the immune system;
- Directing or controlling cellular differentiation;
- Engineering and growing functional 3D structures and organ systems; and
- Delivering agents directly to cells.

The manufacturing and enabling platforms of interest allow for the automation and standardization of several of the processes associated with scaling-up and scaling-out these technologies to effectively reach the potential of broader impact.

TARGET AUDIENCE

The goal of this report is to inform policy makers, funding agencies, and private investors about technology opportunities that can advance the field of Regenerative Medicine. The conclusions will be useful for professionals working across the field of Regenerative Medicine, including program managers at various federal agencies as well as researchers across various industry sectors, academia and federal laboratories – with a special focus on those readers who deal with medical innovations in the translational stage of development.

BACKGROUND ON REGENERATIVE MEDICINE

Regenerative Medicine focuses on the *replacement* of damaged or diseased organs and other bodily structures through the engineering of cells and tissues. It combines the technical expertise of biologists, geneticists, engineers and medical researchers. Research approaches in this field are diverse, including cellular and molecular pathways, growth factor biology, biomaterials, and pharmacology and drug delivery.

The basic idea of tissue replacement is not new. Humans have long sought to develop better surgical procedures and materials to replace or return damaged tissues to their normal function. In the distant past, only indigenous materials were available to repair injuries and defects. Evidence dating back to the Neolithic age reveals a Peruvian tribal chief whose frontal bone defect had been repaired by a gold plate applied with a hammer.[5] Skin grafts composed of free gluteal fat were first used to treat mutilations of the ear, nose, and lip as early as 2500 BCE.[6] Ancient Hindu texts written between 3500 and 1800 BCE chronicle Queen Vishpla, a warrior who lost her leg in battle and had it replaced with an iron limb before returning to battle.[7]

In modern times, the concept of tissue replacement has expanded to include tissue regeneration. Regeneration leverages the body's natural ability to heal, or uses of specific types of cells to restore tissue and organ function. The Regenerative Medicine toolkit is diverse, and

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[5] Donati, D., Zolezzi, C., Tomba, P. and Viganò, A. (2007). Bone grafting: historical and conceptual review, starting with an old manuscript by Vittorio Putti. *Acta Orthopaedica*, 78(1), pp.19-25.

[6] Kaul, H. and Ventikos, Y. (2015). On the Genealogy of Tissue Engineering and Regenerative Medicine. *Tissue Engineering Part B: Reviews*, 21(2), pp.203-217.

[7] Srivastava, K., & Chaudhury, S. (2014). Rehabilitation after amputation: Psychotherapeutic intervention module in indian scenario. *The Scientific World Journal*, http://dx.doi.org/10.1155/2014/469385.

includes: cells (particularly stem cells), natural and synthetic controlled release matrices, scaffolds, and soluble molecules to direct cell function (nucleic acids, proteins, hormones, and viruses).

This paradigm shift from *substitution* to *regeneration* is the defining impetus for further developments in tissue engineering and regenerative medicine. Tissue engineering involves the manipulation of artificial materials, not only to assist cells in reconstruction, regeneration, and repair of damaged tissue, but also to restore lost function.

The term *Regenerative Medicine* is often used interchangeably with *tissue engineering*, especially denoting the addition of stem cells and permanent/transient cell-replacement therapies. Regenerative Medicine can use a variety of cell types ranging from stem cells (adult and embryonic), progenitor cells (from umbilical cord blood) and induced pluripotent stem cells (iPSC), which are bioengineered cell structures. Cells are often combined with biologically compatible scaffolds to replicate damaged or diseased structures in the body. Working with the body's ability to heal itself, new tissue can be stimulated to grow into a fully functional replacement body structure. Both allogeneic and autologous cells can be used as foundational cells from which larger tissue structures can be built.

ADVANCING THE FIELD OF REGENERATIVE MEDICINE

To move promising research results from "bench to bed,"[8] crosscutting translational research is needed so that lab-based technology can be matured into practical and commercially viable products. Specifically, tools and technology are needed that automate and scale-up the production and deployment of Regenerative Medicine advances. In addition, a new generation of workers will require training in critical skills to operate bio-factories safely and cost-effectively. Targeted investment in translational research will result in new regenerative therapies reaching patients across the world.

While it is clear that the basic science of Regenerative Medicine has led to a wide assortment of published findings and documents,[9] the rate of significant translation from laboratory experiments to broad applications has been comparatively lower.[10] This leaves many to ask the question: ***What technological advances are needed to accelerate the transition of scientific discoveries from lab to patients?***

To gain insight into this question, a structured evaluation process was followed that weighs and filters specific translational technologies according to pre-defined criteria. The process starts by selecting promising platform technologies (both manufacturing and therapeutic) that are likely to

[8] The expression "bench to bed" refers to the multi-step transition from basic research and translational engineering (the "bench") to clinical use (the "bed").

[9] Harrison, R., St-Pierre, J. and Stevens, M. (2014). Tissue Engineering and Regenerative Medicine: A Year in Review. *Tissue Engineering Part B: Reviews*, 20(1), pp.1-16.

[10] van Osch, G., Burdick, J. and Liu, W. (2014). Emerging Issues in Translating Laboratory Experiments to Applications for Society. *Tissue Engineering Part A*, 20(19-20), pp.2547-2548.

have an impact on health outcomes and economic growth over the next 5-10 years.[11] The candidate technologies were sorted and filtered according to economic and technical maturity criteria to identify "Key Translational" technologies.

Note, however, that progress in ***technology readiness*** is not necessarily synonymous with progress in ***manufacturing readiness***,[12] which is defined to be "the ability for products to be manufactured in an affordable, operationally effective manner". [13] For any given innovation/technology, advancing its overall readiness requires improvements in both therapeutic platform technologies *and* manufacturing platform technologies.

The interplay between technology readiness and manufacturing readiness is characteristic to most rapidly advancing technologies, and is particularly important during the translational development process. This concept is shown in Figure 1, where therapeutic platform innovations (such as immunotherapies and cell-based R&D) will complement new innovations in the manufacturing platforms (such as bioreactors, material preservation and process control). The concept of dual technology-development tracks is a strong characteristic in an interdisciplinary field such as regenerative medicine, and presents unique challenges to successful commercialization.

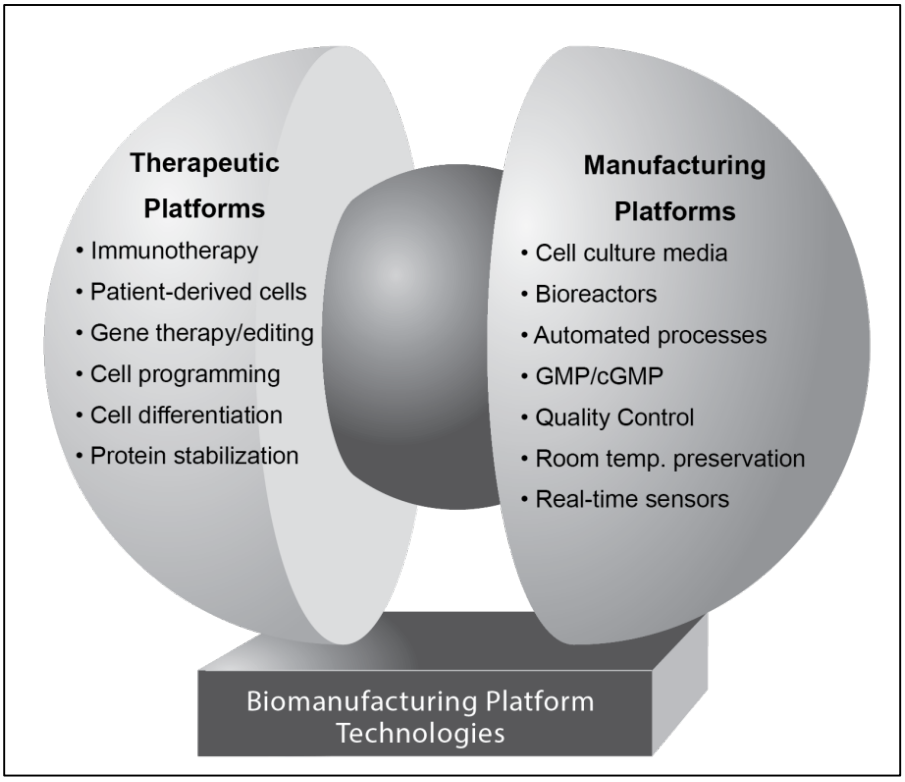

Figure 1: Simultaneous advances in therapeutic and manufacturing platforms are needed to enable biomanufacturing of RM

[11] Platform technologies are the foundation for multiple applications, allowing developers avoid the development of a tissue or organ from scratch.

[12] The Manufacturing Readiness Level (MRL) assessment was developed by the US Department of Defense to assess maturity and identify technology risks from a broader manufacturing perspective.

[13] Wu, C., Wang, B., Zhang, C., Wysk, R. and Chen, Y. (2016). Bioprinting: an assessment based on manufacturing readiness levels. *Critical Reviews in Biotechnology*, pp.1-22.

Figure 2 outlines some of the barriers encountered during the transition from “bench” (basic research and translational engineering) to “bed” (clinical use). Specific development barriers exist during each of the three key phases of development: 1) scientific discovery, 2) biomanufacturing (in an industrial setting) and 3) clinical administration. Once a technology has navigated the development path to the patient, many on-going barriers need to be addressed to ensure efficacy, safety and security. These barriers include the establishment of facilities that meet Good Manufacturing Practices (GMP/cGMP), application of appropriate FDA regulations, a supply chain of consistent biomaterials and a business model that allows for continued innovation and refinement of new Regenerative Medicine technologies. An example of the overlap between different barriers is with the current development in iPSCs.[14] An initial funding tranche for iPSCs will set the pace and enable discovery of molecular pathways controlling stem

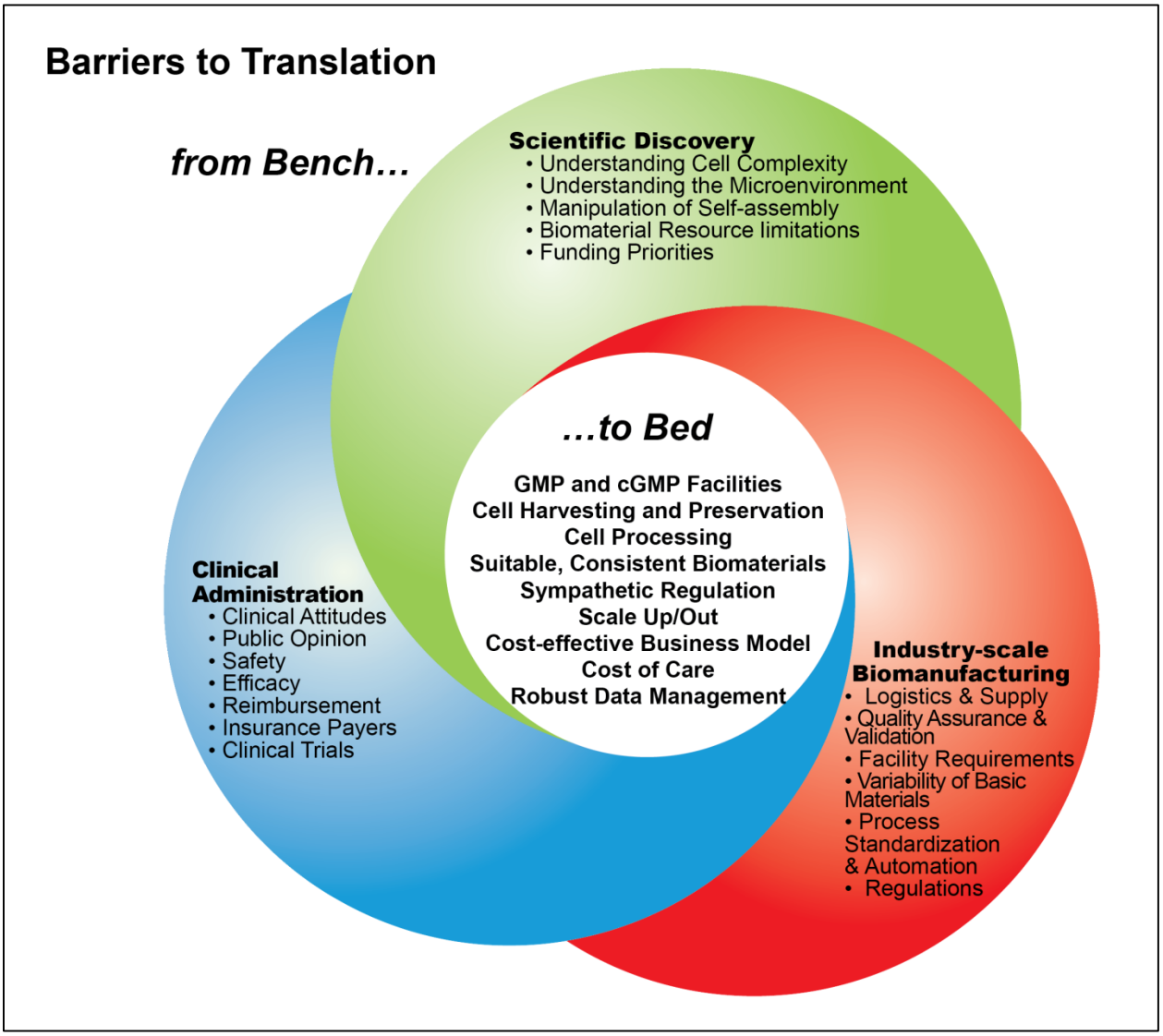

Figure 2: Barriers to translation are encountered at each stage of development

[14] A more in-depth discussion of the readiness of iPSC therapies for commercialization is addressed in *Other Technologies* section of the report.

cell differentiation, function, and fate. As these new pathways are used in therapies to advance through the stage of proof-of-concept (TRL levels 1-3), another funding barrier must be overcome to ensure the consistent and predictable large-scale production of stem cell products – for example, the creation of iPSCs for cell banking. Once development enters the translational stage, the goal is not simply to achieve mass production of cells (a numbers game), but also to understand and control the processing conditions that ultimately impact quality and consistency of the desired product outcome (TRL 4-7). At the point of readiness for clinical administration (TRL 8), barriers such as insufficient safety and limited efficacy clinical trial data can influence public opinion and attitudes of providers toward the adoption of these new therapies. For each stage leading to commercialization, the challenge of reliable and safe cell-harvesting, -processing, and -preservation, as well as the requirement for compliant facilities, regulatory issues, and cost-effectiveness concerns need be addressed and overcome.

IDENTIFYING TRANSLATIONAL TECHNOLOGIES

The process shown in Figure 3 was followed to identify key translational technologies in Regenerative Medicine:

1) A questionnaire was developed that covered a range of topics related to technical maturity, scale-up/scale out of translational platform technologies, private sector investment, regulations, technology transfer, workforce development and international benchmarking.

2) Based on recent academic, industry and government reports, a panel of nine national thought-leaders in the field of Regenerative Medicine was assembled. The Panel Experts supplied detailed answers to questions to the questionnaire in (1) to determine the candidate platform technologies. Additional experts were also consulted and are listed as Contributors at the end of the report.

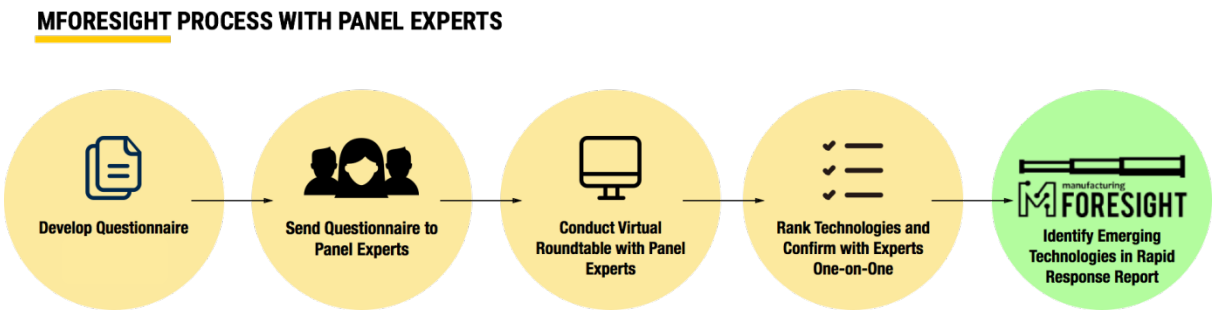

Figure 3: MForesight process

3) Two primary criteria were used to filter the full set of translational technologies:

- Crosscutting Appeal: The first criterion is to select those platform technologies in Regenerative Medicine that will be applied most broadly to the industry and also to the consumer. Crosscutting appeal leads to a larger market potential, thereby generating a future economic benefit that warrants government investment.

- Co-Investment Potential: The second criterion is whether private industry would be likely to co-invest with the Federal Government in the platform technology under consideration. The desire is to find platform technologies that are highly desirable across the industry, but are not sufficiently mature to warrant purely private investment.

The Panel Experts discussed various barriers that these technologies may face, including but not limited to: intellectual property (IP), technology transfer, regulations, and irregular funding patterns. Additional considerations include economic impact, job growth, and the likelihood of the U.S. gaining a first-mover advantage.

4) Data on candidate technologies was refined and ranked according to the crosscutting and co-investment criteria mentioned above. Virtual roundtables were conducted that allowed all participants to understand the trade-offs between different translational technologies, and to ultimately select those technologies that best meet the criteria listed above. See Figure 4.

5) Additional phone interviews with subject matter experts were conducted to clarify some of the points raised at the roundtable, and to seek more holistic responses on specific topics.

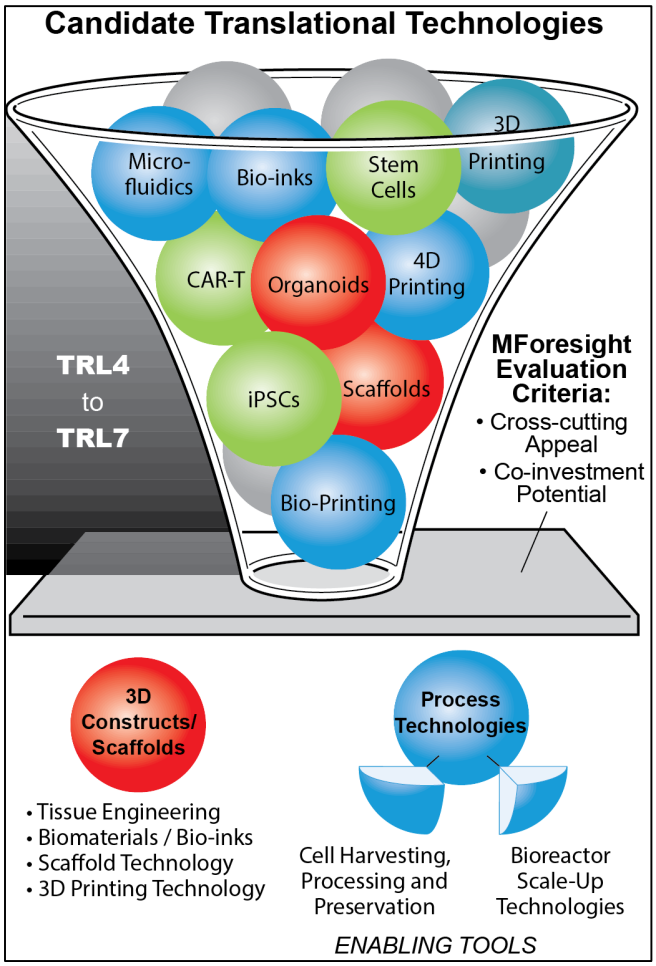

Figure 4: Key translational platform technologies were selected using specific criteria

Selection of Translational Platform Technologies

The primary objective for this report is to identify translational platform technologies in Regenerative Medicine that will enable biomanufacturing (scale-up and scale out) and offer improvements in health outcomes, and positive economic benefits over the next 5 to 10 years.

As part of the questionnaire, the Panel Experts were asked the following:

Q1: Please identify the promising platform technologies (both in manufacturing and in therapeutics) in your field that you feel will have the maximum impact in health outcomes and economic growth over the next 5-10 years.

Table 1 provides a listing of the nine (9) emerging technologies identified by the Panel Experts (A-G) in response to Question 1. The technologies shown in Table 1 represent a broad cross section of platform/enabling technologies in Regenerative Medicine that have matured beyond the basic research stage and are ready for translational R&D.

#	Technology	A	B	C	D	E	F	G
1	Bioreactor scale-up technologies: single-use bioreactors for cells (as opposed to secreted proteins); platforms tailored for cell culture, including microcarrier-based suspension cultures					X	X	
2	Immunotherapeutic technologies (allogenic and autologous), including universal T-cell, CAR-T, and dendritic cells		X		X			
3	Cell processing and cell harvesting technologies for safe and effective harvesting of functional tissues, as well as organ banking and cryo-preservation of cells and tissues post-harvest; off-the shelf CT products; bio- and cryo-preservation technologies enabling storage at room temperature		X					
4	Fill and finish technologies, including disposable manufacturing	X						
5	Technologies supporting Distribution, Logistics, and Clinical Administration, including hardware and software applications and processes to label, identify, and track products (from cells to product administration), and well as characterization of raw materials and enabling tracking back to raw materials			X	X	X	X	
6	Technologies supporting standardization and automation, including moving to fully closed systems to ensure GMP and cGMP, in both the manufacturing and clinical environments; utilizing more digitization and controls connecting production to manufacturing, lab management, and QA systems			X		X		
7	Technologies enabling quality control, including hardware, software, and data analytics to monitor (e.g. sensors for real-time monitoring) and collect critical process (CPP) data, as well as make real-time adjustments to processes parameters to ensure the production of materials expressing predetermined critical quality attributes (CQAs)			X				
8	Technologies enabling the development of 3D tissue constructs, including tissue engineering, biomaterials, and additive manufacturing technologies; improved resolution 3D printing/bioprinting, inks/printing materials for fabrication, automation, and integration in closed environments (for GMP and cGMP production) at manufacturing and clinical sites.	X	X				X	X
9	Stem cell therapies (allogenic and autologous), including MSCs and iPSCs, as well as therapies enabling control of stem cell differentiation and genetic mapping of stem cell behavior							

Table 1: Translational platform technologies and expert poll results

REFINING THE LIST OF TRANSLATIONAL PLATFORMS

To identify the manufacturing and therapeutic platforms with the ***most*** potential for revolutionizing regenerative therapies, Panel Experts ranked and prioritized the technologies in Table 1. Based on their poll, two platform technologies were identified as the front-runners: Technology #5 and Technology #8.

Several enabling tools were also identified that will be needed to fully support progress with Technology #5: Bioreactor scale-up (Tech. #1) and Cell processing and harvesting (Tech. #3) Bioreactor scale-up involves the use of single-use bioreactors for cell culture (as opposed to bioreactors for secreted proteins). Cell processing and harvesting technologies involve the safe harvesting and storage of functional tissues, and includes topics such as cryo-preservation and bio-preservation of materials, especially at room temperature. Figure 5 illustrates how the enabling tools support Technology #5, Biomanufacturing Processes.

Other technologies listed in Table 1 deemed worthy of discussion include: Immunotherapeutic Technologies, Fill and Finish Technologies and Stem Cell Therapies. These topics are discussed in the “Other Technologies” section below, along with a brief explanation as to why each topic was not a top selection.

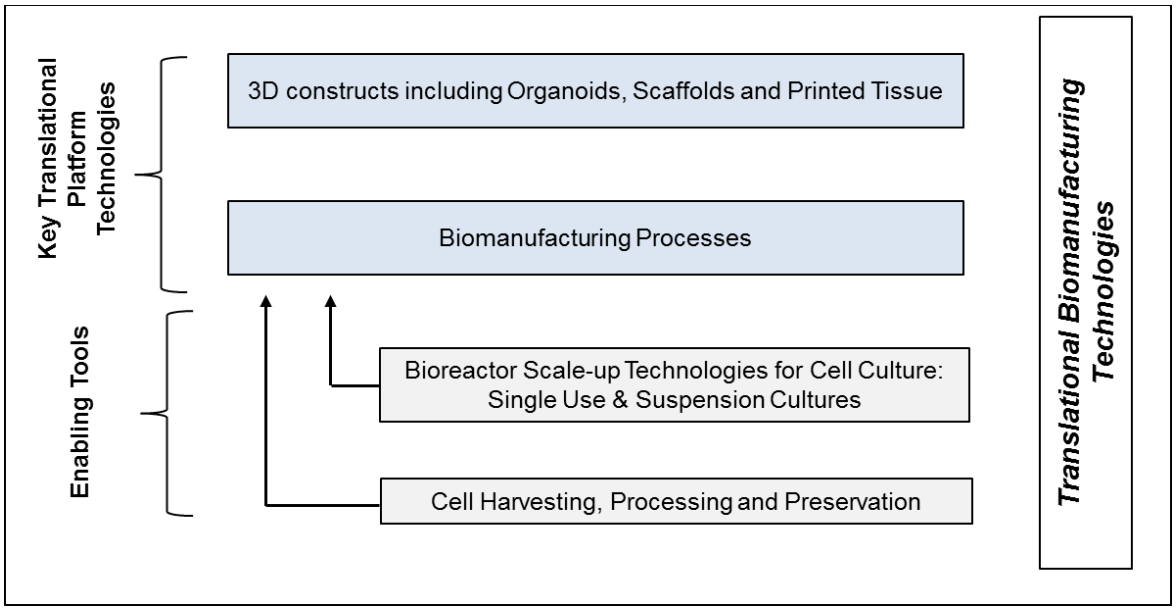

Figure 5: Translational platforms that meet cross-cutting and co-investment criteria

TRANSLATIONAL PLATFORMS FOR REGENERATIVE MEDICINE

PLATFORM TECHNOLOGY: 3D CONSTRUCTS, INCLUDING ORGANOIDS, SCAFFOLDS, AND PRINTED TISSUES

The key platform technology *3D Constructs, including Organoids, Scaffolds, and Printed Tissues* was selected based on the potential for patient-specific applications. The development of constructs requires the integration of subfields such as tissue engineering, biomaterials, nanomaterials, and potentially, drug or biofactor delivery and genetic programming. The resulting three-dimensional structures can be used for the treatment of congenital conditions, and can treat tissue loss due to cancer or trauma.

The pursuit of 3D constructs has clear value by enabling innovation in Regenerative Medicine to transition from bench to bed, from both the therapeutic and manufacturing perspectives. Ultimately, this will achieve the long-term goal of individualized medical care through the development of patient-specific, patient-tailored interventions including drug replacement with cell- or nanoparticle-based therapeutic and diagnostic agents and on-demand production of tissues, organs, and drugs. Within this context, scaffold technology, including smart scaffolds, de-cellularized scaffolds, designed scaffolds based on patient anatomical datasets, and *combination devices* comprised of scaffold-plus-biologics, is predicted to be a critical component of cell-based therapies for tissue- and organ-based regenerative approaches. Of special interest is the role these scaffolds play in matrix and stem cell niches for tissue and organ homeostasis and induced regeneration.

In order to effectively realize the potential of 3D construct development, the Regenerative Medicine community will need to overcome a number of manufacturing and processing challenges:

1. Limited understanding or control over cell complexity and self-assembly, both *in vivo* and *ex vivo*;

2. Inadequate understanding of the mechanisms for the recapitulation of signaling cues to induce regeneration;
3. The need for improved biomaterials, bioinks and 3D printing systems to ensure improved resolution, fabrication, and good manufacturing practice (GMP) compliance, specifically as it applies to closed environments;
4. The need for improved cell processing technologies, specifically for cell expansion, isolation, and separation;
5. Limited supply and inconsistency of current cell culture media; and
6. Current inability to control and standardize the process of blood vessel and nervous system innervation.

While the development of fully functional organs may not be realized for several years, advancements in the development of novel structures can be demonstrated with an incremental approach, i.e., a step-wise development and validation of functional tissue and cellular components. In order to overcome biomanufacturing challenges, the Regenerative Medicine community (industry and government) should collaborate on:

- Developing quality standards for materials, including drugs, biologicals, and cellular, nano-, and biomaterials,
- Demonstrating self-assembly or self-assisted assembly of tissues and/or tissue components, and
- Creating methodologies to address and advance media growth requirements, cell-matrix interactions, and ensure product sterility and stability, including preservation.

Value Proposition: Advances in 3D constructs will lead to a better understanding of self-assembly, as well as the ability to target cells or encourage vascularization in larger, thicker 3D constructs. Improvements in stability/sterility, and material processing in closed systems will ensure end products that not only demonstrate robustness over time, but also comply with current GMP standards. One area where 3D constructs may have an immediate impact is in providing advanced media for drug discovery and development research, enabling the use of partially developed, fully functional constructs or organoids for drug screening and toxicology studies. This approach offers reduced timelines and decreased costs of drug development.

Keeping in mind the goal of enhanced biomanufacturing, it is important to note that “making” is not “manufacturing.” Advances in “making” technologies such as 3D printing in terms of resolution could make important (or significant) progress in developing functional 3D constructs. However, process technologies need to be matured for products to be manufactured in large quantities in order to serve the patient population. From the manufacturing perspective, consistency in product performance under varying conditions is a critical goal.

PLATFORM TECHNOLOGY: BIOMANUFACTURING PROCESSES

Given the inherent process management challenges encountered when manipulating cells and biological tissues, the development of stable, consistent and safe biomanufacturing processes is a key technology platform in Regenerative Medicine.

Because of the range of topics under the heading “Biomanufacturing Processes”, the area is further divided into two key enabling tools:

(iii) Scaled-up bioreactors for cell culture, and

(iv) Improvements in cell harvesting, cell processing, and preservation technologies; each directly affecting the supply of materials to the production process, and therefore requiring high-level management.

Providing additional support for these enabling technologies will help to address the following technical challenges:

1. Limited availability of suitable cellular materials and lack of consistency in material quality;
2. Batch differences in raw biomaterials making process standardization difficult;
3. Instability of cellular products resulting in loss of effectiveness, or robustness, of final product or materials on the production line; and
4. Short product shelf life.

Of special note is the development of effective room-temperature material stabilization. While this is a technically challenging problem, the successful deployment of Regenerative Medicine materials without the need for cryogenic storage would be transformative for delivering solutions in a clinical setting.

Clear standards are paramount for both the manufacturing and the clinical environments. Ideally, standards should be set collaboratively between industry and regulators.

ON THE HORIZON: HUMANIZED ORGANS

Regenerative Medicine offers great hope for the future of health care – both by providing *ex-vivo* cells, tissues and even complete organs, and also by targeting the body’s own regenerative systems in developmental and immune molecular pathways. However, there is another approach that could also have a dramatic effect on the future manufacturing of human organs: organs could be grown in pigs for transplantation into humans. While a few, isolated attempts have been made, a major roadblock remains: porcine organs are not well tolerated by the human immune system since pigs contain more than 60 viruses imbedded in their own genomes which are a severe problem in immuno-compromised transplant patients. [a] CRISPR has now made it possible to remove all of the porcine viruses in a straightforward fashion. Immune genes could similarly be manipulated with CRISPR-like technology. Manufacturing of human organs in pigs could be a breakthrough analogous to auto manufacturing in the early 20th century, when Henry Ford created automated technology and the U.S. was able to supply a world-wide market. A consortium of government, industry, and academia could be a possible way to address the technical and IP challenges to large-scale humanized organ production.

[a] Reardon, S. (2015) Gene-editing record smashed in pigs. *Nature News*. https://doi.org/10.1038/nature.2015.18525.

OTHER TECHNOLOGIES

A number of other technologies were identified as potential platform solutions in Regenerative Medicine. However, these topics did not receive support from the majority of the Panel Experts during the poll.

IMMUNOTHERAPEUTIC TECHNOLOGIES (ALLOGENIC AND AUTOLOGOUS)

Immunotherapies are designed to control and regulate the immune system by targeting the inflammatory response, using the patient's own cells to fight cancer, infection or other diseases. Regulation of the inflammatory process—the first target—coupled with better knowledge of inflammation mechanisms, could yield therapeutic interventions that may ultimately lead to more functional medical devices and human interface interaction. Significant challenges lie in the immune rejection of cell- and tissue-based therapeutic agents, but the recent success in creating **universal blood** [15] suggests the possibility of developing scalable manufacturing processes for allogenic products that can be used for a wide variety of patients.

The other transformative platform technology, which targets a patient's own cancer cells with engineered autologous T-cells, has the potential for developing therapeutic cures for many cancers. This platform technology capitalizes on developments in personalized cell therapy, gene therapy, and immunotherapy to result in activated chimeric antigen receptor (CAR) T-cells that seek out cancer cells. Early-stage trials with these CAR T-cells have been very successful and this has allowed therapies from this platform technology to undergo expedited regulatory review with the FDA. To date, there have been four IPOs of CAR T-cell focused start-ups. The next generation of CAR T-cell products is being developed to address safety concerns and the field has begun to focus on solid cancer tumors.

Historically, the excitement and promise of this technology sector has been dominated by early successes of the cancer targeting CAR T-cell therapies. However, because CAR T-cell therapies have had a long history of development, this area is not suitable for further federal co-investment to take this technology further. That role has been embraced by private investors in this space which has seen tremendous growth. Furthermore, regulatory hurdles have been significantly reduced, which is likely a testament to previous government investment to de-risk the technology.

FILL AND FINISH TECHNOLOGIES, INCLUDING DISPOSABLE MANUFACTURING

Fill and finish technologies are used in the final step of the pharmaceutical or biological manufacturing process. It is a step that does not entice innovation because doing so potentially introduces regulatory risk and cost to the process. However, packaging of cells or active biologics requires fill and finish technology innovation because traditional filling processes use elements that require sterilization. Single use technology completely eliminates the risk of contamination and infection and is a potential solution to the packaging problem of cells and

[15] Kwan, D.H., Constantinescu, I., Chapanian, R., et al. (2015) Toward Efficient Enzymes for the Generation of Universal Blood through Structure-Guided Directed Evolution. *Journal of the American Chemical Society*. 137(17), 5695-5705. https://doi.org/10.1021/ja5116088.

biologics. Additionally, disposable technologies are very effective at minimizing the risk of cross contamination.

As with current medicine, application of disposable fill and finish technology for Regenerative Medicine applications has the same goal of zero contamination, but will require an innovative design of the manufacturing process when dealing with cell-based elements. Successful fill and finish solutions in Regenerative Medicine will impart stability (especially protein stability), ensure sterility and increase product lifespan.

Fill and finish technologies for biologics are a mature technology and therefore the technology is not considered to be suitable for investment by the government because many private companies are already active in this area.

STEM CELL THERAPIES (ALLOGENIC AND AUTOLOGOUS)

Stem cell therapies hold tremendous promise for eventual therapeutic interventions that can offer full recovery of lost tissue function and return patients to a satisfactory quality of life. From the perspective of the initial selection criteria, stem cell therapies are high in co-investment potential (as shown by government initiatives in California,[16] Canada,[17] and the UK[18]). Furthermore, the technology readiness of this group of therapies falls squarely within the targeted TRL 4-7 range.

One stem cell lineage with particular promise is based on induced pluripotent stem cells, or iPSCs. In the most basic terms, iPSCs impart the ability to transform committed differentiated somatic cells into pluripotent stem cells, capable of the functionality inherent to "natural" stem cells. When combined with other RM translational technologies such as 3D bioprinting, iPSCs could allow for the on-demand production of patient-specific tissues and organs. Looking to the future, the generation of whole organs populated by patient iPSCs could alleviate the donor organ shortage, and prove transformational for end-stage organ failure patients. Fundamental to the successful commercialization of iPSC therapies, then, will be the ability to generate in high volume, robust and consistent high-quality "living" products comparable across multiple lines. To do so, key manufacturing and engineering processing challenges need to be addressed.

Currently, there are several methodologies in use to reprogram somatic cells for the eventual creation of iPSCs. As such, there exists significant variability in source materials and processing, both potentially translating to significant variability in the iPSC end product. Since iPSCs are not the focus-product for RM therapies (differentiated target cell types are), the variability in processing required to generate comparably committed cell types may also be affected. The consistency of cell products across different sources is a substantial challenge, especially considering a patient's genetic heterogeneity, disease heterogeneity, as well as the need to create large repositories of iPSCs.

To circumvent many of these challenges, stricter standards will need to be enforced at the manufacturing stage than those applied at the laboratory-level for standardized methodologies

[16] California Institute for Regenerative Medicine, https://www.cirm.ca.gov/.
[17] Canadian Stem Cell Foundation, http://stemcellfoundation.ca/en/.
[18] UK Stem Cell Foundation, http://www.ukscf.org/.

and processes for iPSC production, differentiation, and maturation. Potential production vehicles include bioreactors, or the use of a platform cell such as patient-derived fibroblasts. [19] Additionally, there is a need to acquire knowledge of critical quality attributes and the processing parameters for pheno- and geno-typically stable products.

The decision to not add stem cell-based therapies to the current list of priorities was based, in part, on the recognition that successful commercial translation will also depend on harmony within the regulatory landscape and attitudes toward clinical adoption. Both areas underpin clinical administration and, ultimately rely on the availability of much needed safety and efficacy data obtained through clinical trials.

ON THE HORIZON: USE OF EX-VIVO ORGANS FOR SCREENING EXPERIMENTAL DRUGS

While the delivery of whole organ creation remains in the distant future, there are two offshoots of this technology that could, in the near term, dramatically affect the development/risk model for the production of pharmaceuticals.

1) Partially developed but functional, *ex-vivo* organs (or parts thereof) could be used to screen drug candidates for toxicological and other side effects much earlier than human clinical trials. This process has the potential to reduce the use of expensive human clinical trials in the drug development process.

2) Tissue systems or organoids built from human clinical trial progenitor cells with encoded various disease states could be used to more effectively screen drugs early in the pipeline and thus greatly increase the effectiveness of matching drug candidates with their targets. This could lead to significant upfront cost savings by reducing the amount of developmental working capital and by reducing the risks of the upfront pharmaceutical R&D model.

Both items could potentially improve the drug manufacturing process dramatically in the short/medium range. Ex-vivo drug screening offers the tantalizing option of identifying organ-specific toxicities much earlier than current screening methods.

BROADER CHALLENGES AND THE ROLE OF THE FEDERAL GOVERNMENT

REGULATORY PROCESSES FOR REGENERATIVE MEDICINE

Because of the unique regulatory challenges in Regenerative Medicine, a group of nationally recognized experts with direct experience in healthcare regulations was asked to comment on how regulations can be adapted to this field. (See Table 2.) Additional experts were consulted informally.

1: Regulatory mechanisms for Regenerative Medicine that ensure safety, efficacy and security

Regulatory mechanisms such as orphan drug designation and expedited review are designed to make drugs available to patients more quickly. While these current mechanisms are important

[19] To date, the ideal starting cell for iPSC products has not been determined.

pathways to accelerate drug development, there is support in industry for an accelerated regulatory pathway specifically designed for regenerative medicine.

For example, a significant challenge for the young field of cell therapy product development is to create and optimize manufacturing processes while the technologies themselves are quickly evolving. In particular, there is not a specific regulatory mechanism currently available to help streamline continuous process improvement. Nor is there a mechanism to guide the gradual optimization of that process as new technologies become available. Instead, what constitutes a minor versus major process improvement is not clear to the product developer. Industry finds it challenging to understand what triggers the need for a formal comparability exercise vs. continuous process improvement.

Ideally, a more flexible regulatory mechanism in the cell therapy space would exist for continuous process development. This concept follows the spirit of the adaptive licensing[20] approach, which is an iterative process of gathering evidence of potential therapeutic indications followed by progressive licensing adaptations.

A more flexible regulatory approach would improve upon the current status, where the accelerated clinical development (made possible by existing expedited regulatory pathways) places even more pressure on the need for process development to align with accelerated clinical development timelines, and potentially support earlier product marketing.

It would also be beneficial if Regulators were more liberal on how existing pathways could be used for new products. For example, conditional approval could be granted using a limited data set based on the assurance that more robust data would be provided at a later date.

2: Structure of the FDA's Centers

The FDA centers, offices, and divisions who currently have the oversight in this space are, in general, appropriate for the current technologies being developed. In particular, the Office of Combination Products (OCP) coordinates activities of several centers within the FDA. The OCP makes formal determinations on Center jurisdiction (e.g., biologic to be reviewed by CBER) and also coordinates cross-Center collaborative and consultative reviews. In the case of a sponsor of a biologic-device cell-based combination product, which is also an HCT/P, that sponsor will have to consider cGMP regulations for drugs (21 CFR 210 and 211), any applicable regulations not already addressed for the biologic component (21 CFR 600 to 680), the remaining applicable regulations not already addressed for device component in the QSRs (21 CFR 820), and the remaining applicable regulations not already addressed, given that the biologic component is an HCT/P, in the cGTP regulations (21 CFR 1271).

There are numerous regulations to follow and rules in place to avoid unnecessary duplication in regulatory oversights. It is not clear how/if a new Center or other mechanism would streamline this any further based on current regulations.

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[20] Adaptive Licensing can be defined as a prospectively planned, adaptive approach to bringing drugs to market. Adaptive licensing seeks to balance the desire to deliver new drugs to the public with the need to provide adequate information on potential benefits and possible harm. See http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2015/11/WC500196323.pdf.

As the development of complex biologics progresses, the need for a more flexible pathway to market also increases. The Panel Experts suggested that Regulators should consider processes that recognize this fact.

3: Engaging the public and establishing priority topics

As the regulatory stakeholders consider processes to correct possible regulatory misalignments, public workshops can be used to identify priority topics so that the public can be included in the process of developing solutions. Such workshops should address specific regulatory considerations for new products, potential pathways for approval of personalized medicine, etc.

An important question is how the regulatory process can be navigated when the product is not exactly like the product types described in the regulations. However, the issue is not simply a case of misaligned regulations, but rather a need for more specific regulatory considerations and requirements that can be further evaluated. The previous discussion on continuous process development under Item 1 is a good example. While this question may be addressed via new regulations, a more efficient method would be through regulatory policy and Guidance Document development, as well as the utilization of standards in the regulatory review process. Furthermore, there is room for additional guidance regarding comparability of manufacturing products either due to changes in process or donor variability. Of course, any changes to the regulatory requirements should also maintain the same levels of safety that are currently employed by the FDA and evidence of efficacy.

A related issue is the considerations necessary for the approval of technologies in personalized medicine. The current approval considerations for clinical efficacy are based on population effect with statistical power. However, for autologous products, a key question stands out: Is it still appropriate to measure clinical efficacy based on statistically meaningful population effects of an investigational drug/product when cell products, manufacturing process of each product, and treatment effects are so individualized? The answer lies in the identification of the appropriate methodology to evaluate clinical efficacy/treatment effect, irrespective of comparability.

4: Developing industry consensus on acceptable standards

A number of efforts by industry are underway to set standards.

The Alliance for Regenerative Medicine (ARM) has initiated the establishment of a Standards Coordinating Body, or SCB, for Cellular/Gene and Regenerative Therapies. The SCB is being established in order to: organize all stakeholders, and coordinate activities in identifying gaps and needs in standards, contribute to developing standards (including within existing consensus standards development organizations, where some standards are intended to help streamline regulatory review), and finally, to disseminate and implement standards once developed. The Cellular/Gene and Regenerative Therapies SCB can serve as the common voice.

In addition, organizations such as the IABS[21] have examined areas where there is a need to develop tools or approaches. As an example, see “Extent and Content of Data for Regulatory

[21] International Alliance for Biological Standardization (IABS), www.iabs.org.

Submissions: First-in-human and Marketing Authorization - Viewpoint from US Industry" by Harris.[22]

The ICH[23] may also play a role in regulatory convergence, and potentially standards, for testing donors, manufacturing intermediates and final product. Additional organizations that represent stakeholders include the ISCT[24] and the ASGCT[25] that have established standards in the past.

The question of "acceptable liability, or what creates customer satisfaction" will have to be established within each of the established therapeutic areas. Examples of such organizations include the American Heart Association or American College of Cardiology for Regenerative Medicine products used for cardiovascular disease.

Overall, the FDA is encouraged to recognize consensus standards developed via structured processes put in place by all the stakeholders, such as through ISO[26] and ASTM[27].

SUMMARY

The comments from the regulatory experts can be distilled to three main points:

- There are a range of comprehensive regulations in place with FDA Centers and Divisions to regulate the regenerative medicine space;
- More flexible regulatory mechanisms will help accelerate Cellular/Gene and Regenerative Therapy product development, particularly manufacturing process development;
- Developing standards is important, and several organizations have initiated such efforts, such Standards Coordinating Body, IABS, etc. The recognition of consensus standards (e.g. ISO and ASTM-developed) by FDA CBER to be utilized in the regulatory review process would be beneficial.

Regulatory Experts for Regenerative Medicine		
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[22] Harris, I. R. (2015). Extent and Content of Data for Regulatory Submissions: First-in-human and Marketing Authorization - Viewpoint from US Industry. *Biologicals,* 43(5), 402–405.
[23] International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), www.ich.org.
[24] International Society for Cellular Therapy, http://www.celltherapysociety.org/.
[25] American Society of Gene & Cell Therapy, http://www.asgct.org/.
[26] International Organization for Standardization, www.iso.org.
[27] ASTM International, www.astm.org.

Anthony Ting, Ph.D.	Vice-President, Regenerative Medicine & Athersys, Inc. Head of Cardiopulmonary Programs

Table 2: List of regulatory experts in Regenerative Medicine

INVESTMENT METRICS

As with most emerging industries, early-stage technology development in Regenerative Medicine has a high risk profile. Consequently, the potential for return on RM investment (ROI) is largely unclear. It was indicated that sympathetic changes in the regulatory environment would certainly improve the time to market. Beyond that, investment barriers could be lowered with 1) improved understanding clinical applications and outcomes; 2) investable milestones; 3) intellectual property protection; 4) presence of competing products (which show the potential for revenue); and 5) a clear understanding of reimbursement requirements and the ability to manufacture at reimbursable costs. These measures will achieve much in terms of de-risking technology and encouraging investment.

INVESTMENT BARRIERS

For larger companies (aka, “big pharma”), excess risk represents a substantial barrier to investment. Without the investment participation of larger companies in Regenerative Medicine, smaller companies face even larger hurdles to secure funding. Larger entities need to step in with financial support so that many of the revolutionary platforms under development can reach the required level of maturity for the market. At the current time, private funding is inadequate for further development of translational platforms on larger scales and the need for regulatory filings and clinical studies.

Investment is also hindered by long development times resulting from regulatory requirements. Regulators typically require large amounts of efficiency and comparability data (often difficult to produce) and this results in exceedingly long times to market approval and an added risk of being obsolete by the time the product is approved.

Additionally, the clinical utility of the technology must be clearly and tangibly identifiable. Investment should be directed towards developing technologies for commercialization and also into areas that require capital investment for proof of concept, largescale implementation, regulatory filings, and clinical studies. Moreover, private sector investment is likely to increase if regulatory clarity and pricing support from payers and government can be made more clear and transparent.

Other barriers-to-investment include:

i) Poor numbers of therapeutically active products—either coming to or currently on the market;

ii) Poor, or not well-understood “clinical fit”;

iii) Problems with bio-preservation; and

iv) An inadequate understanding of workflow and logistics.

There is also a need for new business models for profits—especially with regards to cell therapies—and an understanding of what can be mass-produced.

ROLE OF FEDERAL GOVERNMENT

The technology development process can be de-risked through government support in several ways, including reducing the regulatory burden and providing clear licensing paths. However, the caveat to government investment should be focused on pre-competitive biomanufacturing tools that are openly accessible across the industry.

Investment of taxpayer dollars in new therapies can be justified by demonstrating that a change in standard care will offset the largely wasteful spending on antiquated systems and treatments currently in place.

Justifications for investing taxpayers' dollars include:

i) The creation of a strong infrastructure for continuous growth of the industry;

ii) The elevation of spin-off companies into viable commercial companies;

iii) The development of ecosystems to facilitate interdisciplinary collaboration and commercialization;

iv) An improvement in the standard of care that will lead to reduced healthcare costs, as well as the delivery of scalable products to market that address unmet medical needs.

In addition to providing targeted funding, the Federal Government has a vital role in facilitating partnerships, including government-industry or industry-academia. Any collaborative partnership needs to have well-defined steps and options for managing attrition, and should focus on a recognized model for translation and commercialization.

Finally, the Federal Government has a uniquely important role in disseminating science-based data on cutting-edge Regenerative Medicine technology. Funding often slows or is cut for certain technologies where misinformation from opponents has engendered negative public sentiment. Consistent, reliable publication of objective, science-based data will contribute to a robust discussion on Regenerative Medicine topics. New technologies such as CAR-T therapy[28] are particularly prone to public debate that might slow down the pace of development.

TECHNOLOGY TRANSFER

There are a number of barriers to transferring technology from academia to the marketplace. First, many university technology transfer offices do not understand the complexities of maturing a technology into a market-ready state, often causing an overvaluation of early-stage discoveries. The academic community is typically unfamiliar with the amount of non-clinical testing and manufacturing that is necessary to transition a product from proof-of-concept in the lab to exploratory clinical research. Bringing a product to market is a multi-step process involving regulatory issues, marketing strategies and (ultimately) operation, especially within the GMP regime. University technology transfer offices often lack the seasoned staff and experience to correctly account for these development factors.

[28] Chimeric Antigen Receptor (CAR) T-Cell Therapy. Leukemia & Lymphoma Society, https://www.lls.org/treatment/types-of-treatment/immunotherapy/chimeric-antigen-receptor-car-t-cell-therapy

Second, federal funding for basic science will typically not fund work when it moves into the development stage. This often leaves a major gap in support at a critical time in the process. Some options such as SBIR/STTR exist to continue development work, but the relative funding level for this program is much smaller than is needed to make any real progress.

PARTNERSHIPS

In most cases, partnerships are critical for the transition of early-stage studies (done at the startup level) to more mature technologies. As an example, the development of new cell therapies has typically involved a partnership between larger companies (pharmaceutical conglomerates or international players) and small startups. This model results in a nimble development capability as well as the means and networks necessary to reach a global audience.

In general, successful strategic partnerships will combine entities with complementary capabilities across the spectrum of development to commercialization. In the realm of therapeutic development, partnerships should include three basic capabilities: research, application and translational development, and full development/commercialization.

For those research institutions working with early-stage technologies, the ideal partnership would include a relationship with an entity that has strong translational capabilities. Specific examples include:

- A biotechnology company with relevant domain expertise and capabilities that extend from research and application through proof-of-concept (POC) development and often into later clinical development and commercialization. It could involve federal funding (NIH, DOD, NSF, etc.).
- A translational group within a larger pharmaceutical company (e.g., NIBR in Novartis[29]). These entities provide the expertise to carry through to proof of concept, and often have defined channels for further collaboration, partnership, and advancement for late development and commercialization.
- Specialized entities and not-for-profit organizations, which can play the role of converting lab technologies with promise into verified development candidates. Examples include The Harrington Project / Biomotiv[30] and others.

An optimal partnership arrangement successfully aligns the level of co-investment with the risk absorbed by each party in the partnership at that level. For public/private partnerships, funding for the partnership could take a number of forms:

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[29] Novartis Institutes for Biomedical Research, https://www.nibr.com/.

[30] The Harrington Project is a novel tripartite collaboration between non-profit and for-profit organizations. The Harrington Discovery Institute provides financial and non-financial support to physicians-scientists working on targeted translational research. The Innovation Support Center provides additional financial support coupled with drug development infrastructure to further mature translational research. Late-stage commercialization partners are matched with academic project through BioMotiv, a mission aligned commercial development company. See: http://www.uhhospitals.org/services/harrington-discovery-institute/about/harrington-project-for-discovery-and-development

- The private entity could receive a direct grant by the public entity for participation;
- The public entity could supply a reimbursable contribution against the private partner's project costs; or
- The government entity could supply a simple tax offset to the private partner.

Another partnership possibility is an innovative clearinghouse concept, designed to bundle multi-component technologies. Financing would be enabled with an access fee to gain visibility, a pre-negotiated technology evaluation pathway, and preferred partner status allowing for rights of refusal elements.

The Federal Government can look to a number of existing structures that currently exist to transition basic research into more commercially viable technology. These include:

- Company-to-institution partnerships , e.g., GSK / Harvard and stem cells;[31]
- Consortia, such as CRC-CTM[32] in Australia, CSCRM[33] in Cleveland, CCRM[34] in Canada;
- Groups or foundations that fund or support translation or POC work, e.g., CIRM[35] (funding), Catapult (capabilities/expertise), the foundations (Cystic Fibrosis, Multiple Sclerosis, etc.);
- Government collaborations, such as,
    - SBIR/STTR program with specific RFA for Regenerative Medicine studies (U.S.)
    - Innovate UK[36] and Cell and Gene Therapy Catapult[37] (UK)
    - CCRM (Canada)
    - NHLBI-CCTRN[38]

Typically, public-private partnerships are most successful when publically-invested technology is "packaged for sale" to interested commercial parties. The technology package should clearly identify possible applications areas, technology readiness level (TRL) status, and estimated investment to complete development. The key issues of IP protection and freedom to operate (preliminary) should be sorted out *a priori.*

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[31] Colen, B. D. (2008). "GlaxoSmithKline and Harvard Stem Cell Institute announce major collaboration agreement." Harvard Stem Cell Institute. http://news.harvard.edu/gazette/story/2008/07/glaxosmithkline-and-harvard-stem-cell-institute-announce-major-collaboration-agreement/.

[32] CRC for Cell Therapy Manufacturing (CRC-CTM), http://www.ctmcrc.com/.

[33] Center for Stem Cell and Regenerative Medicine (CSCRM), https://www.bioohio.com/item/center-for-stem-cell-and-regenerative-medicine-cscrm/.

[34] Centre for Commercialization of Regenerative Medicine (CCRM), http://ccrm.ca/.

[35] California Institute for Regenerative Medicine (CIRM), https://www.cirm.ca.gov/.

[36] Innovate UK, https://www.gov.uk/government/organisations/innovate-uk.

[37] Cell and Gene Therapy Catapult, https://ct.catapult.org.uk/.

[38] National Heart, Lung, and Blood Institute (NHLBI), http://www.nhlbi.nih.gov/, and Cardiovascular Cell Therapy Research Network (CCTRN), https://ccct.sph.uth.tmc.edu/cctrn/.

INTERNATIONAL BENCHMARKING

The U.S. is a leader in scientific discovery due primarily to its large concentration of academic research and high numbers of spin-off startup companies in the Regenerative Medicine space. Furthermore, the U.S. business environment can attract the required highly-skilled researchers needed to work in startup companies, and also in larger more established firms. Several experts commented on the positive effect of government support of partnerships between industry and academia. One positive feature of government involvement is that that risk-tolerant venture capital firms are more likely to fund early stage development work when the government supplies both partial funding and an organizational structure for academic and private entities. A key advantage is the domestic development and infrastructure for key technologies such as artificial cellular systems (electrospinning and bioprinting), genetic-engineering-based technologies (liposome encapsulation and CRISPR), and organ-banking and next generation biopreservation.

The U.S. does, however, have substantial disadvantages compared to other countries. These include a lack of focus on process engineering, manufacturing, and clinical trials, leading to serious obstacles to commercialization. Disadvantages were identified associated with less-supportive regulatory, tax, and healthcare infrastructures and increased legal barriers. Public acceptance/reluctance on topics such as the use of human embryonic stem cells (hESCs) have led to uncertain (and erratic) funding, which is a huge disadvantage for technologies that may require as much as a decade to commercialize.

Also, because the U.S. healthcare system does not support universal healthcare, it is difficult to move innovation towards cost-effective solutions since reimbursement for such services remains unclear.

Several countries outside of the U.S. are very successful in the area of commercialization because they have established innovation centers that incorporate process engineering and manufacturing from idea inception through prototype development; from clinical trial, to nurturing and supporting spin-off companies.

SUMMARY

The objective of this report was to identify translational platform technologies with crosscutting appeal in Biomanufacturing for Regenerative Medicine that warrant investments in translational research through public-private partnerships. Several challenges and opportunities were identified across therapeutic platforms and manufacturing platforms. Topics that gained most support with crosscutting appeal and possess the correct maturity level to warrant co-investment by private industry were:

i) 3D constructs including organoids, scaffolds, and printed tissues. Advances in these technologies will have cross-cutting applications including development of partial or fully functional tissues/organs, as well as tools for predictive modeling and drug screening.

ii) Biomanufacturing process technologies that enable therapeutic platforms to transition from bench to bed, including bio-reactor scale-ups and tools for processing, harvesting, and preserving cells.

In addition to technology development, there is a need for science-based regulation, public acceptance, and the development of standards.

ADDITIONAL REPORTS

Many of the ideas and suggestions presented in this report are congruent with those of other recently published reports. A report by the Cell Manufacturing Consortium (CMC)[39] also recommended and prioritized, in a similar fashion, translational technologies and platforms, highlighting current and on-the-horizon applications of cell-based therapies. The CMC report concluded that the development of cell processing technologies, (as well as of several enabling technologies – supply chain, quality control, and preservation – for example) are on the critical path to successful scale-up or scale-out. This report independently arrived at similar conclusions.

This report's findings are also echoed in the World Technology Evaluation Center report[40] that evaluated RM technology transfer in Europe and Asia, and asserted that the seemingly insurmountable barriers to the widespread implementation of technological innovations in Regenerative Medicine may be overcome through cooperative collaboration and interdisciplinary work.

Both reports also emphasize the need for sustained focus on improvements in process engineering as especially key for the practical application of biomanufacturing for cell therapies, as well as the need to apply known principles early in the product conceptualization process.

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[39] "*Achieving Large-Scale, Cost-Effective Manufacturing of High Quality Cells: A Technology Roadmap to 2025.*" Georgia Research Alliance and Georgia Institute of Technology. December 2015.

[40] *"Global Assessment of Biological Engineering & Manufacturing."* World Technology Evaluation Center (WTEC). July 2015. http://www.wtec.org/bem/docs/BEM-FinalReport-Web.pdf.

PANEL EXPERTS

This report would not have been possible without the enthusiastic and dedicated participation by the national thought leaders on our Regenerative Medicine Panel Experts. During the course of the effort, the authors had the pleasure of personal communications with each Panel Expert, receiving valuable information on the topic. Whether by email or phone, each and every request was answered promptly and completely. The authors gratefully acknowledge their participation in the creation of this report.

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EYTAN ABRAHAM

Dr. Eytan Abraham heads up the Cell Therapy Research & Technology (R&T) group at Lonza, Inc. in Walkersville, MD. Dr. Abraham's R&T group develops and tests enabling technologies and methods to facilitate large scale cell therapy manufacturing for allogeneic and autologous clinical trials and commercial use. One major R&T initiative is the use of bioreactor platforms to produce large numbers of various cell types to meet cell therapy commercialization need; while maintaining high-cell quality and reducing costs. Previously Dr. Abraham was the Head of Product Innovation at Pluristem Therapeutics. This group developed a pipeline of MSC therapies tailored for different clinical indication, by altering various aspects of the 3-D bioreactor culture environment.

[41] Drs. Matosevic and Zylberberg (Akron Biotechnology) collaborated to submit a common response.
[42] Drs. Vanek and Zhang (GE Healthcare) collaborated to submit a common response.

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Ian Harris is the Product Development Team Leader for CNTO 2476, which is the lead allogeneic cell therapy product for geographic atrophy secondary to age related macular degeneration and is responsible for manufacturing development, mechanism of action aspects of the CNTO 2476 program. Ian joined the Johnson & Johnson (J&J) family of companies in 2000 and has held various positions of increasing responsibility within the area of cell-based therapeutics. Prior to joining J&J, Ian was a laboratory leader at Beiersdorf in Hamburg, Germany, developing skin care products.

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Dr. Ting is Vice President of Regenerative Medicine and Head of Cardiopulmonary Programs at Athersys, Inc. With more than 25 years of experience in cell and stem cell biology, he has been a key leader in the Regenerative Medicine division at Athersys for the past 14 years. He has both clinical and scientific expertise with the translation of adult stem cell therapies and has been responsible for all development stages of bringing MultiStem, an allogeneic adult stem cell, from the bench to the bed. Currently, he is the PI on an NHLBI-funded Phase II clinical trial for AMI with MultiStem and the project lead for a TSB-funded Phase I/II clinical trial for ARDS with MultiStem. Prior to joining Athersys, Dr. Ting was a Principal Investigator at the Institute of Molecular and Cell Biology at the National University of Singapore where he established a drug discovery program.

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Dr. Kaiming Ye is a Professor and Department Chair of Biomedical Engineering at the Binghamton University, State University of New York (SUNY). He was Program Director at NSF before joining Binghamton University. He is one of the most accomplished leaders in the field of Medical and Biological Engineering. He is Fellow of the American Institute of Medical and Biological Engineering (AIMBE) and Senior Member of IEEE.

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Dr. Jiwen Zhang is a Senior Regulatory Affairs Director at GE Healthcare (GEHC), leading regulatory strategy development for Cell Technology and Biotechnology. Before joining GEHC, she had worked in the pharmaceutical industry at companies including Centocor/Johnson & Johnson, Merck & Co., Wyeth Pharmaceuticals, and Sanofi-Aventis, where she led regulatory strategy development for both marketed products and development compounds in multiple therapeutic areas. She is currently leading various industry initiatives through Alliance for Regenerative Medicine, International Society for Stem Cell Research, ILSI Health and Environmental Sciences Institute, and International Standards Organization (ISO). She is on the steering committee for the FDA/CDER CiPA initiative (Comprehensive in vitro Proarrhythmia Assay), and co-chairing the human stem cell derived cardiomyocyte work stream.

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Dr. Zylberberg holds a Ph.D. in Biotechnology from the University of British Columbia and University of Buenos Aires and has over 30 years of experience in the international biopharmaceutical industry. Her expertise is focused on the areas of recombinant protein production, human-derived blood products, stem cell banking and new cryopreservation media.

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APPENDIX 1: INITIAL PROJECT GUIDANCE & RESOURCES

QUESTIONS

1. Advanced manufacturing technologies/processes
    a. For emerging industries, are there lessons they have learned in innovating new techniques when traditional manufacturing methods do not apply?
    b. What insights from traditional manufacturing might help this nascent industry (i.e., scaling up and/or scaling out for regenerative medicine) avoid potential problems?
    c. Are there unique features from the regulatory process for medical products?
    d. What are the implications for industry in the unique business environment of "price controls" for medical treatments, a world in which the payers and the consumers are usually different?
2. Industry investment
    a. What do investors (VCs, forward-leaning companies, etc.) want (i.e., what are they waiting for to make an investment)?
    b. How will emerging biotechnology platforms be de-risked sufficiently for industry to commercialize?
    c. There has already been significant activity addressing regulatory barriers and well as environmental risk/ impact – therefore it will be important to address this question in light of those public studies (out of JCVI and the Wilson Center in the area of synthetic biology) such that MForesight provides new insight to this question.
3. Technology transfer
    a. What are the barriers to technology transfer from academia to industry for these specific fields? Economic, technology, policy, legal, capital expenditure, governance, etc.?
4. Partnerships
    a. In what ways can these fields achieve strategic partnership?
    b. What types of industry/academic or public/ private partnerships might be successful to move basic research and largely public investments into these research areas into higher TRL endeavors that will more directly lead to commercialization?
5. International benchmarking
    a. What are the strengths of the US capabilities of commercializing biologics? And how does this impact the national and global economy?
    b. How will U.S. lead the way, rather than competing at the same ballgame?
    c. Are there growing competitive disadvantages from which we may never catch up?

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