Editorial

Challenge and Change at the Forefront of Regenerative Medicine

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Despite formidable scientific advances in therapeutic and preventive medicine over the last several decades, there remain relatively few efficacious and cost-effective treatments for certain injuries, as well as many inherited diseases and chronic conditions, especially those related to old age. An estimated 22 patients die each day in the United States alone waiting for an organ transplant; this situation is particularly dire in countries such as Japan, where cultural factors make organs for transplants even scarcer. Of the 7000 known rare diseases that occur in the United States, <10% have specific treatments, even after 30 years of government incentives to find such treatments under the Orphan Drug Act. The International Labour Organization estimates that 785 million working-age persons worldwide are unable to work due to chronic disease or injury.[1] Moreover, musculoskeletal disease, even in many economically developed countries, often occurs as a comorbid condition for persons living with chronic disease or injury in almost one third of patients aged >45 years and almost one half of those aged >65 years.[2] Musculoskeletal disease is a therapeutic area that historically has been overlooked by mainstream biopharmaceutical developers. However, it represents 1 of the top 5 therapeutic areas for products in the pipeline for regenerative medicine (RM).

RM offers the potential for the repair, replacement, and regeneration of damaged tissues and organs at the cellular level, utilizing the body's own power to "heal from within." Although many development challenges remain, there has been significant progress in both basic and applied research in RM. Currently, there are ~50 RM products in the marketplace worldwide that in large part distinguish themselves from conventional therapy by offering cures for, instead of merely management of, chronic diseases. Broadly speaking, some examples of RM are gene therapy for enzyme deficiency disorders and stem cell–mediated therapies for musculoskeletal and cardiac damage and dysfunction.

Behind the current upsurge in activity in new products, processes, and platforms are recent policy changes that have served to jump-start the nearly 50 years' worth of research developments across many fields, to establish RM as a new medical discipline. One of the most fundamental changes has been the increasing interest by government research institutions, such as the U.S. National Institutes of Health (NIH), with a consequent up-swell in RM research funding at 22 of 27 institutes within the NIH during 2012 to 2014; six of these institutes provided RM awards that comprised as much as 7% or more of their research grants.[3] Europe and Japan have followed suit. Europe has offered attractive funding opportunities for innovative technologies, such as RM, through its Innovative Medicines Initiative and its Horizon 2020 €10 billion funding call. In addition, Japan, in 2015, established a Division of Regenerative Medicine Research within its own government research funding organization, the Agency for Medical Research and Development.

Similar to biotechnology and precision medicine in previous decades, many challenges remain in the research and development continuum for RM, from negotiating passage through the "valley of death," to clearing the basic hurdles of regulatory approval, and, of equal importance, establishing value for truly novel but often expensive treatments in a cost-constrained and complex global marketplace. Although regulatory agencies in the mature market countries of Japan, Europe, and the United States have moved rapidly to expedite the development and approval process for RM

products, specifically through the application of facilitated regulatory pathways, pricing and reimbursement authorities in those same markets have been slower and less focused in targeting RM for special consideration.

Another obstacle in RM development is manufacturing. With the currently available technology, early-stage clinical material is typically manufactured with manual, small-scale methods, but parallel development for up-scaling, such as automation technologies and 3-dimensional bioreactors, will have to be vetted by regulators to be built into the late clinical development plan or integrated postapproval to reach commercial scale for launch.[4] This situation is not without regulatory work-arounds, however. For example, Japan has built these into its regulatory regime a priori by allowing companies to outsource their RM manufacturing needs as they scale up. In addition, the US Food and Drug Administration (FDA) has already addressed similar challenges postapproval while implementing the breakthrough therapy designation for products of other innovative technologies when approval jumped ahead of the launch schedule by 2 to 3 years.

Even though the prospect of the "valley of death" (where many therapeutic candidates end up being terminated, often because they lack efficacy or sufficient financing to continue development) looms large for many small- and medium-sized enterprises, a recent report by McKinsey & Company, a major business consultancy, is optimistic.[1] The report notes that stakeholders, including federal and state governments around the world, are coming together to nurture a global research ecosystem, even while recognizing that it will require new distribution models, more convincing methods for assessing long-term economic benefits, and optimized pricing to amortize the cost of goods and manufacturing to achieve sustainable business models on a global scale.

Another major challenge for RM is one that it shares with all innovative fields: the protection of intellectual property (IP) rights. IP protection is crucial for attracting investment, whether from venture capital or potential "big business" partners, and ensuring fair market opportunities without the risk of competing duplicate products. In terms of proving the basic criteria for patent eligibility (ie, non-obviousness, utility, novelty), RM shares a conundrum initially faced by biotechnology product developers: distinguishing the treatment from products of nature. Of paramount consideration is the difference between a particular sponsor's RM product and the products of nature. How well a sponsor establishes that difference will determine whether its product passes the utility threshold of patent eligibility. If the sponsor cannot, all is not lost, as often peripheral products or processes related to the product, including apparatus, devices, culture media, stem cell reagents, biological markers, clinical test systems, and the like, may be patentable.[5]

However, unlike biopharmaceutical products in general, RM faces a somewhat unique challenge in asserting its IP rights; the best-quality RM is the one that is closest to being 100% identical to the properties of the tissues or cells it is replacing or repairing, the body parts of a healthy human being (ie, a natural product). The US Supreme Court has held that the limitations of patent eligibility in this regard should be strictly scrutinized, and the US Patent Office has issued an interim guidance proposing a 2-step test to do just that. Unfortunately, it amounts to a Catch-22; that is, the more an RM product approaches the ideal of being identical to the body part it seeks to replace, the more likely it is to be unpatentable, at least with a strong patent such as "composition of matter."[6]

Drug development is a risky business. Timelines are long, costs are high, and the likelihood of success is exceedingly small, with nearly 90% of drug candidates failing to make it through the clinical development phase to reach the market[7]. Nonetheless, RM is attracting its own cadre of ardent supporters, from US FDA Commissioner Scott Gottlieb, to the Asia-Pacific Economic Cooperation Pact. Considering the challenges, how can one explain the significant interest in RM? There are a number of possible reasons, some speculative (ie, to increase medical tourism), some cultural (ie, lack of organ donors, as in Japan), and some practical (ie, numerous unmet medical needs are not being addressed by conventional biopharmaceuticals). Most importantly, however, the reality is that many of the new and often expensive medicines introduced to the market today achieve only marginal therapeutic benefits. For example, one study reported that the median gain in progression-free survival for new cancer drugs approved between 2002 and 2014 was only 2.1 months.[8] In contrast, the promise of RM is to break out of this marginal value mold and provide true curative therapies.

RM therapies that make it through the development phase and reach the market are likely to be expensive, driven by the following: higher research and development, manufacturing, and delivery costs; the personalized nature of some products (eg, autologous stem cell treatments); and the high therapeutic value these products are expected to provide. To keep development and other costs down, developers are working closely with regulators in different

countries to utilize new and efficient adaptive clinical trial designs, conditional marketing, and facilitated regulatory pathways. These pathways include the regenerative medicine advanced therapy designation promulgated by the FDA; the Advanced Therapy Medicinal Products regulation implemented by the European Union's European Medicines Agency; and, the most proactive of all, the Regenerative Medicine Law, within Japan's Ministry of Health, Labour and Welfare.

At the same time, health economic and outcomes research and health technology assessment authorities are experimenting with new approaches for assessing therapeutic value of treatments that hold great promise but offer little evidence of comparative/cost-effectiveness. One such approach is the so-called headroom analysis, which is actually the first step in an evaluation process with multiple components, one of which is the Value-Engineered Translation framework. This framework draws upon insights from clinical landscaping of how the condition is currently managed in targeted health care systems and from technology landscaping that surveys relevant patent, clinical trials, and trade publication databases to identify potential competitor technologies. Ultimately, pricing and reimbursement authorities may use innovative reimbursement strategies involving risk-sharing (ie, payments to sponsors based on acceptable treatment outcomes, number of treatments, or innovative models such as annuity-based pricing).[8]

The following special section of *Clinical Therapeutics* provides an insightful and informative bird's-eye view from a multiregional perspective on the challenges faced in RM and the changes necessary to nurture a promising and fertile field creating a productive source of innovative treatments and cures. In the first article in the section, Glicksman[9] details the history, types, uses, and sources of the research tool that has been most responsible for bringing RM to the forefront of medical advances: stem cells. In particular, the author discusses the most promising of stem cells development; that is, induced pluripotent stem cells that can be differentiated into any number of specific cell types as starting material for creating replacement cells in cases of injury or disease. Going forward, the challenge is to create enough banks of human leukocyte antigen–matched cells to serve as a readily scalable, economic, and well-characterized source of these biomaterials.

In the second article, Okada et al[10] describe the new legislative landscape laid by Japan, beginning in 2014, to provide the regulatory and logistical infrastructure for rapid development of the RM field. The authors also discuss Japan's national consortium, composed of academia, industry, and government, to construct and promote a clinical data registry in Japan and, at least in concept, throughout the Asia-Pacific region.

The third article originates from the United Kingdom. Banda et al[11] used 18 interviews within 10 case studies to discuss the actors, linkages, and influences that will determine the future trajectory of RM in the United Kingdom. The authors present a cautionary tale for government authorities, highlighting the need to better identify and understand potentially disruptive innovations, such as RM, to plan and provide regulatory and infrastructure support.

The final article in the section focuses on the United States. In it, Hossain and Milne[12] reveal the irony and public health paradox of the fact that the number one causes of mortality and morbidity in the United States (ie, cardiovascular disease and musculoskeletal disorders, respectively) are currently under-addressed in terms of investment and resources dedicated to understanding and finding treatments for these conditions. The authors argue that RM holds particular promise in these areas and is deserving of greater attention by drug developers, regulators, and policy makers.

This special section underscores the indisputable therapeutic opportunities presented by RM, an area of research and investigation that should be prioritized on international public health agendas. The World Health Organization predicts that the second wave of the double burden of disease (ie, noncommunicable diseases) is rapidly approaching. We should be devoting more resources to exploring a field of research that has the potential for delivering cures for noncommunicable diseases on the near-term horizon.

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REFERENCES

1. Agarwal A. et al. Aging with tech support—the promise of new technologies for longer and healthier lives. Report by McKinsey & Company (September 2016 at 23).
2. Duffield SJ, et al. The contribution of musculoskeletal disorders to multimorbidity: Implications for practice and policy. *Best Practice Res Clin Rheumatol*. 2017;31:129–144.
3. U.S. Government Accountability Office. *Regenerative Medicine Federal Investment, Information Sharing, and Challenges in an Evolving Field (GAO Publication No. 15-533)*. Washington, DC: U.S. Government Printing Office; June 2015.
4. Challener CA. FDA framework spurs advanced therapies. *BioPharm International*. 2018;1:36–38.
5. Komatani TS. Intellectual property strategy for regenerative medicine: is it time to 'regenerate'? *Pharm Pat Anal*. 2014;3:475–479.
6. Komatani TS. Upcoming challenges in intellectual property presented by emerging pharmaceutical technologies. *Pharm Pat Anal*. 2017;6:1–4.
7. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: new estimates of R&D costs. *J Health Econ*. 2016;47:20–23.
8. Bubela T, et al. Bringing regenerative medicines to the clinic: the future for regulation and reimbursement. *Regen Med*. 2015;10:897–911.
9. Glicksman M. Induced pluripotent stem cells: the most versatile source for stem cell therapy. *Clin Ther*. 2018;40:1060–1065.
10. Okada K, Sato Y, Sugiyama D, Sawa Y. Establishment of the National Consortium for Regenerative Medicine and National Regenerative Medicine Database in Japan. *Clin Ther*. 2018;40:1076–1083.
11. Banda G, Tait J, Mittra J. Evolution of business models in regenerative medicine: effects of a disruptive innovation on the innovation ecosystem. *Clin Ther*. 2018;40:1084–1094.
12. Hossain I, Milne CP. Can regenerative medicine help close the gap between the medicine pipeline and public health burden for cardiovascular and musculoskeletal disease? *Clin Ther*. 2018;40:1066–1075.

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