Editorial

Challenge and Change at the Forefront of Regenerative Medicine

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 of Health 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