On November 16, 2017, the US FDA announced a comprehensive policy framework for the development and oversight of regenerative medicine products, including novel cellular therapies. This risk-based framework includes a suite of guidance documents focusing on safety and effectiveness of these therapies, and reiterates FDA’s commitment to bring new effective therapies to patients as quickly and safely as possible.

The origin of regenerative medicine can be traced back more than half a century ago to the first successful human organ transplantation. Unlike lower vertebrates such as zebrafish and amphibians, humans cannot regenerate organs (except the liver), and organ transplantation has been the cornerstone therapy to replace diseased or malfunctioning ones. Major stumbling blocks with organ transplantation include the lack of donors and that recipients often need to be HLA-matched and/or immunosuppressed to avoid transplant rejection. Despite the lack of regenerative capacity, most human organs can repair themselves upon injuries, and this tissue healing process serves as the principle of regenerative medicine.

Since their discovery more than three decades ago, stem cells have been at the heart of regenerative medicine development thanks to their ability to self-renew and differentiate into a variety of cell lineages. Stem cell transplantation has been used successfully in several human diseases, most notably in hematological cancers such as leukemia. However, stem cell therapy has not yet achieved the level of solid organ regeneration.

Let us take the heart as an example. We have learned a lot about the heart’s regenerative mechanism from animal models such as zebrafish and neonatal mice. But in humans and non-human primates, once the heart has fully developed, it cannot regenerate large areas of damage such as those that might arise after a heart attack, although it can heal minor injuries through scar formation.

There have been several stem cell-based Phase 1/2 clinical trials for heart diseases, primarily aimed at evaluating safety and improvement in cardiac functions, with the majority involving autologous mesenchymal stem cells for heart failure. The quality of autologous stem cells greatly depends on the patient’s age and health status. Allogeneic stem cells from young and healthy donors are an alternative, but this requires careful HLA matching and often immunosuppression to avoid serious side effects such as graft-versus-host disease. No stem cell therapy for heart diseases has reached regulatory approval stage. Progress has been hampered, in part, because we don’t yet fully understand the underlying mechanisms of how best to regenerate heart tissue from progenitor cells. Stem cells come in different flavors: cardiac progenitor cells, bone marrow-derived mesenchymal stem cells, hematopoietic stem cells, endothelial progenitor cells—and one question in the field is which “flavor” will achieve the best outcome for heart regeneration?

It is generally assumed that stem cells need to home to the injured site, engraft successfully, retain their self-renewal capability, and be able to proliferate and differentiate to relevant cell types. Preclinical studies have shown that systemic delivery by intravenous infusion (like in the treatment of hematological cancers) results in the majority of stem cells being caught up in the capillary network of the lungs with only a small proportion reaching the heart. Whether providing additional tissue injury signals can improve homing of those stem cells to the heart needs further investigation. Local delivery by intramyocardial injection directly to the damage site can be an alternative, but challenges remain for achieving successful stem cell engraftment and in situ differentiation, given that the microenvironment at the injured site is likely hostile and pro-inflammatory.

A major and unique obstacle, observed in non-human primate studies of cardiac repair using human stem cells, is arrhythmia–where the implanted cardiomyocytes beat spontaneously and out of synchronization with the host’s heart. To avoid arrhythmia, the cells in the implanted tissue would need to be matured to stop beating by themselves, and to contract synchronously in response to the host’s electrical signals. The best methods for maturation and synchronization of cardiac cells remain elusive. To that end, cell-free approaches using biomaterials (e.g., hydrogel patches) incorporating secretory factors that activate endogenous cardiac and vascular cells may be a promising alternative. In fact, local delivery of hydrogel patches containing cardio-, vasculogenic and cardioprotective factors to the site of heart tissue damage has been tested in preclinical models and is moving towards clinical trials.

Through several previous Editorials in EBioMedicine, we have voiced our support for regenerative medicine, such as in the December 2017 issue where we highlighted the de Luca et al. breakthrough effort in transgenic epidermis regeneration for junctional epidermolysis bullosa—a severe and often fatal genetic skin disease, or in the February 2016 issue where we appraised the development of organoids derived from patient iPSCs as disease models. EBioMedicine also frequently publishes original research papers in this area that we collate under “Regenerative Medicine and Stem Cells” collection on the journal’s website.

The announcement of FDA regenerative medicine policy framework has been welcomed by the industry and research community alike. As FDA Commissioner Scott Gottlieb perfectly put it: “We’re at the beginning of a paradigm change in medicine with the promise of being able to facilitate regeneration of parts of the human body, where cells and tissues can be engineered to grow healthy, functional organs to replace diseased ones; new genes can be introduced into the body to combat disease; and adult stem cells can generate replacements for cells that are lost to injury or disease. This is no longer the stuff of science fiction.
This is the practical promise of modern applications of regenerative medicine. But this field is dynamic and complex. As such, it has presented unique challenges to researchers, health care providers, and the FDA as we seek to provide a clear pathway for those developing new therapies in this promising field, while making sure that the FDA meets its obligation to ensure the safety and efficacy of the medical products that patients rely upon.” At EBioMedicine, we welcome such guidance and reiterate the importance of collaboration from all stakeholders, be it researchers, clinicians or regulatory bodies, in advancing the field of regenerative medicine for the patients’ benefit.

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