Regenerative Medicine
Advancing Health Care 2020*

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Regenerative medicine has begun to define a new perspective of future clinical practice. The U.S. Department of Health and Human Services report “2020: A New Vision—A Future for Regenerative Medicine” highlights that regenerative medicine is the vanguard of 21st-century health care (1). Patients and society increasingly expect that regenerative medicine will lead to repair of diseased organs, injured tissues, or congenital anomalies. From pioneering success with bone marrow transplants for select hematological disorders that are now standard of care (2) to the most recent advances in bioengineered stem cell platforms that provide unlimited sources of autologous pluripotent progenitors and broaden the scope of individualized diagnosis and therapy (3), National Institutes of Health and National Academies recognize regenerative medicine as a most promising core component of modern medical practice (4,5).

Without the contribution of personalized products and services emerging from regenerative medicine technology, experts caution that health care will face an escalation in inefficient treatments and a rising global cost (6). Aimed toward functional restoration of damaged tissues, not a mere abatement or moderation of symptoms, regenerative medicine offers a “disruptive innovation” strategy uniquely poised to add value and transform health care by providing tailored, curative solutions for the unmet needs of our patients (7,8).

Tissue repair might provide a sustained therapeutic advantage in a spectrum of conditions ranging from congenital diseases to acquired, age-related pathologies. Applied in the management of cardiovascular diseases, the rapidly developing regenerative medicine armamentarium promises significant human health benefit with tangible outcomes for increased quality of life and improved patient care, building on breakthroughs in stem cell biology paired with successes in transplant medicine. Maximizing potential return, however, mandates an integrated roadmap across the translational continuum of discovery-development-regulation-use (9) to ensure optimal application of regenerative medicine algorithms in practice.

The “R3” paradigm of repair. The framework for heart repair relies on the general principles of “rejuvenation→replacement→regeneration” (Fig. 1). The “R3” paradigm of therapeutic repair underscores the complementary strategies that conceptualize the scope of regenerative medicine (8). From heart muscle self-renewal (“rejuvenation”) to transplantation-based organ recycling (“replacement”) and, ultimately, biogenesis of new tissue parts for de novo tissue restoration (“regeneration”), the core components of the repair triad offer natural or engineered means to ensure tissue homeostasis and achieve sustainable cure (Fig. 1).

Fundamental to the innate processes of cardiac tissue rejuvenation is cardiomyocyte renewal, characterized by the ongoing recruitment of resident progenitor pools within or outside the heart (10,11). Self-repair mechanisms continuously contribute to tissue homeostasis (12), although their efficacy is variable among individuals and is compromised by patient age, disease status, comorbidities, concomitant pharmacotherapy, as well as genetic, epigenetic, or ecogenetic influences. Radioisotope decay in the human body, a remnant of nuclear bomb testing half-a-century ago, has recently offered an unprecedented opportunity to quantify the birth date of single cardiomyocytes, indicating that one-half of the heart mass can be potentially renewed over a lifespan (13). Notably, stem cell contribution to postnatal...
heart formation has been validated by the self/non-self chimerism characteristic of patients after allogeneic transplantation (14). Furthermore, stem cell loads increase in failing hearts, involving derivation of cardiomyocytes from circulating as well as resident progenitor pools (15,16). Rejuvenation revitalizes the innate cardioprotective potential, yet in the context of large-scale destruction—as is the case after massive infarction—inherent repair mechanisms are typically inadequate to salvage a deteriorating myocardium (17).

Likewise, transplant medicine exploits a replacement strategy as a valuable option to recycle used parts and restore failing organ function by means of exogenous substitutes—it is limited, however, by donor shortage. There are an estimated 2,500 heart transplants performed annually in the U.S.; yet over 100,000 additional patients would benefit from this lifesaving procedure in this country alone (18). Due to the magnitude of such growing clinical need, alternative strategies, including mechanical assist devices, are increasingly explored. From the initial intent of “bridging” to transplant or recovery, success of this technology has led to newer indications, including permanent or “destination” therapy in selected patients. However, these significant advancements do not prevent the increasing pandemic of refractory heart failure, currently managed by treatments to limit symptomatic progression of incurable disease.

A boost in healing processes would stimulate the adaptive response and promote adequate biogenesis of functional tissue to abrogate the progression of heart disease. Extrapolating from the paradigms of natural heart rejuvenation and transplant–based organ replacement, reactivation of endogenous and/or introduction of exogenous progenitor cells into the injured heart would thereby offer a legitimate target to ameliorate the burden of disease. In this regard, stem cell–based regeneration has revealed the next frontier of medical therapy aimed at achieving structural and/or functional repair (19–21). The regenerative strategy refers to engraftment of progenitor cells that requires in vivo growth and differentiation to establish a repair outcome within the host environment. Collectively, approaches for stem cell–based regenerative medicine are poised to drive the evolution of medical sciences from traditional palliation toward curative therapy by supplementing resident progenitor pools and facilitating chimeric healing of damaged tissues.

**Stem cell–based regeneration.** Classified as “biologics,” stem cells are a distinct class of medications produced by means of biological processes (22,23). In contrast to traditional pharmaceuticals, regenerative cytotherapy products contain viable cells as the active ingredient (24). Worldwide, over 3,000 patients with ischemic heart disease have received stem cell therapy in a clinical trial setting. Meta-analyses underscore feasibility and safety of stem cell–based therapy and point to modest albeit variable improvement in functional parameters of recovery (25). These initial trials rely on the use of first-generation products consisting of purified, natural human cells, typically in their native state, such as naïve mesenchymal stem cells isolated from the patient’s bone marrow (20,26). Ongoing optimization and identification of the most appropriate cell source and cell type, means to enhance safety and effectiveness, selection of patient populations most amenable to cell–based therapy, ideal timing of intervention, and most favorable route of administration are among the areas of focus to determine the clinical scope and maximize benefit of cell–based therapy in the management of cardiovascular disease (26–28).

Indeed, beyond initial concerns of feasibility and safety, establishing the functional and structural efficacy profiles of specific stem cell–based treatments is paramount to foster a conscious application in future practice (28). It should be noted that most clinical studies to date have tested heterogeneous cell populations associated with mixed results (25–28).

Head-to-head comparisons between stem cell platforms, as exemplified in this issue of the *Journal* with the careful characterization of distinct adult progenitor populations (29,30), are critical in directing the selection of the most valuable stem cell cytotypes and guiding the rational design of next–generation clinical trials. These prototypic, well–designed studies rely on blinded, randomized, clinically relevant approaches, and use high stringency parameters of differentiation potential and repair outcome (29,30). Specifically, Armuñán et al. (29) report that intramyocardial transplantation of human mesenchymal stem cells and CD34+ hematopoietic cell progenitors—isolated from bone marrow and umbilical cord blood, respectively—improve left ventricular function and increase cell proliferation and neangiogenesis in healing infarcted myocardium. At equipotent dose with regard to benefit on fractional shortening, mesenchymal stem cells were found superior in reducing infarct size and preventing ventricular remodeling in this nude rodent disease model (29). The propensity of mesenchymal stem cells to migrate from the site of injection to the infarcted zone and their additional aptitude to reduce collagen deposition were suggested contributors to favorable outcome (29). Dubois et al. (30), with selected porcine progenitor populations delivered by intracoronary infusion in a large animal model of acute myocardial infarction, report that autologous late–outgrowth endothelial progenitor cells are particularly effective in improving myocardial remodeling favoring greater vascular density than naïve allogeneic mesenchymal stem cell counterparts. Pro–angiogenic and paracrine matrix–modulating effects were inferred on the basis of the gene expression and protein release profiles of cultured progenitor cell populations, consistent with a greater neo–vascularization potential of autologous late–outgrowth endothelial progenitor cells capable of secreting placental growth factor, a member of the vascular endothelial growth factor family, and a key molecule in angiogenesis and vasculogenesis (30). The authors indicate that modes of delivery, immunological status, and cardiomyogenic pre-
specification are all critical in influencing long-term outcome (30).

Together these studies underscore the necessity for continuous advancements in discovery science to increase the understanding of stem cell biology in the context of the recipient diseased environment and the mechanisms of myocardial repair. The nature of autologous versus allogeneic stem cell sources, the degree of cardiomyogenic versus vasculogenic potential, and the severity of disease-affected segments are all critical variables raised by these studies that need consideration for a more efficient translation from proof-of-concept studies to targeted application (29,30). In fact, it is anticipated that an increasing number of comparative studies will be the focus topic of imminent basic and clinical studies in cardiovascular regenerative medicine. Ultimately, the rigor of comparative effectiveness outcome analysis with the potential to inform practice, improve care, and influence costs (31) applied across regenerative platforms as well as between stem cell-based therapies and current medical/surgical state-of-the-art management options will provide the cornerstone of future evidence-based standard of care and define reimbursement policy.

**Clinical development.** At this stage of product development, proper pharmacodynamic and pharmacokinetic certifications are mandatory steps (21,22). Suitable markers of biological activity are needed to adequately identify primary pharmacodynamic properties, even if the mechanism(s) of action remain only partially understood. In addition, establishing the optimal amounts and formulation of safe cell-based medicinal products needed to achieve the desired effects is a critical component of proving overall efficacy and applicability. Pharmacokinetic considerations include parameters of cell biodistribution, cell viability, and cell proliferation following single- or multiple-dose regimens. Ongoing clinical studies are increasingly designed to provide an adequate demonstration of efficacy in the target patient population, demonstrate an appropriate dose schedule for optimal therapeutic effect, and/or evaluate the duration of therapeutic effect for risk-benefit assessment (26). Accordingly, clinical safety databases are developed to annotate adverse events, including procedural risk, immune response, infection, malignant transformation, and long-term safety. Continuous rigor in product development will be particularly needed as novel cell types, autologous or allogeneic, naive or lineage-prespecified, natural or bioengineered, are considered for human testing in the upcoming decade (21,32–34).

Cell-based medicinal products involve cell samples of limited amounts, mostly to be used in a patient-specific manner. This raises issues pertaining to quality-control testing designed for each product under examination. Therefore the manufacture of cell-based medicinal products must be carefully designed and validated to ensure product consistency and traceability. Control and management of manufacturing and quality-control testing are carried out according to Good Manufacturing Practice requirements (24). Screening for purity, potency, infectious contamination, and karyotype stability have become necessary elements (i.e., release criteria), in compliance with standard operating practices for production and banking of cells used as autologous or “off-the-shelf” allogeneic therapy. Accordingly, the U.S. Food and Drug Administration and the European Medicines Agency impose regulatory guidelines for risk assessment, quality of manufacturing, preclinical and clinical development, and post-marketing surveillance of stem cell biologics for translation from bench to bedside to populations (22,23).

**Individualized applications.** Individualized medicine provides a powerful engine to tailor molecular profiles of patients to maximize therapeutic specificity, reduce treatment variability, and minimize adverse events (35). Insights in the regenerative basis of cell, tissue, and organ function and their interface with the environment will increasingly define disease risk, identify processes mediating disease susceptibility, or target mechanism-based therapies, thereby providing previously unanticipated opportunities for patient-specific disease management. The emerging field of regenerative medicine will thus grow in conjunction with the realization of the individualized medicine paradigm to create predictive, personalized, and preemptive solutions for tailored patient-specific strategies. Individualized treatment algorithms for regenerative medicine will require quantification of the inherent reparative potential to identify patients who would benefit from stem cell therapy (24). In this context, the “stem cell load” specific to each patient will serve as an “index for regenerative potential” that will prove useful for prediction, diagnosis, prognosis, and targeting of safe and effective therapies at the earliest stage of disease in the new era of individualized regenerative medicine.

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**REFERENCES**


