Chapter 18
Stem Cell Therapy for Ischemic Heart Disease

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Abstract Regenerative medicine aims to achieve functional and structural restoration of a failing organ. Applied to cardiovascular medicine and surgery, this emerging discipline offers a disruptive innovation poised to transform healthcare paradigms by providing the prospect of curative solutions beyond the reach of current standard-of-care. This chapter highlights recent advances fueling this promising multidisciplinary field in the context of heart failure management. Building on breakthroughs in stem cell science, the rapidly evolving regenerative armamentarium leverages natural mechanisms of heart development and lifelong innate rejuvenation. Stem cell therapies seek to boost an otherwise limited aptitude of the human adult myocardium for self-renewal by securing a tissue-specific reparative environment within the failing organ. Supported by favorable preclinical experience, translation of regenerative paradigms has been tested in the clinical setting in both acute and chronic conditions. Meta-analyses of stem cell-based clinical trials underscore the feasibility and safety of regenerative procedures in ischemic heart disease, yet commonly point to modest and variable outcome in parameters of recovery. These initial proof-of-concept trials rely on the use of purified human cells, typically delivered in their native state. Several areas of focus have developed to better establish the scope of clinical use and maximize regenerative benefit. Specifically, next generation trials aim to use the most appropriate cell sources and cell types, enhance cardiogenicity and therapeutic effectiveness, select patient populations most amenable to cell-based therapy, establish ideal timing of intervention, and optimize routes of administration. To inform early adoption in practice, the rigor of comparative effectiveness outcome analysis will ultimately be needed to empower the future

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J. Bartunek and M. Vanderheyden (eds.), *Translational Approach to Heart Failure*,
DOI 10.1007/978-1-4614-7345-9_18, © Springer Science+Business Media New York 2013

of heart failure care, enriched by regenerative strategies that address the unmet needs of a growing patient population.

1 Introduction

The World Health Organization recognizes the emergence of noncommunicable diseases, in particular heart failure, as the leading cause of morbidity and mortality [1]. The American Heart Association in the most recent Heart Disease and Stroke Report underscores that cardiovascular conditions account for 1 of every 2.9 deaths in the United States. More than 2,200 Americans die of cardiovascular disease each day, an average of 1 death every 39 s [2]. Indeed, heart failure is one of the most prominent challenges to public health. Modern management of acute myocardial infarction with rapid revascularization has reduced early mortality but has precipitated the incidence of chronic heart failure among survivors, an epidemic that is anticipated to expand worldwide accelerated by the pandemic trends of ischemic heart disease and the aging of the global population [3].

Recurrent hospitalizations and premature death, prevalent in this ever growing patient population, have imposed a major unmet need associated with the inability of current, largely palliative therapies to address massive tissue destruction post-infarction. The myocyte-deficit in infarction-induced heart failure is in the order of one billion cells with a 25 % loss of the left ventricular mass. A hallmark of this malignant pathology is the progressive maladaptive remodeling of the infarcted myocardium that perpetuates systolic and diastolic dysfunction, and ultimately leads to the overt syndrome of congestive organ failure. Repair of the failing infarcted heart is a formidable challenge, considering not only the magnitude of cardiomyocyte loss but also the requirements to reestablish optimal supply in support of functional and structural demands. Life-extending measures—such as left ventricular assist devices or heart transplantation—are often the only therapeutic option. However, a limited number of patients can benefit from such complex and costly interventions. A case in point is the United States, where an estimated 2,500 heart transplants are performed annually, yet over 100,000 additional patients wait without hope for this lifesaving procedure. Thus, a compelling clinical and societal need exists for the establishment of innovative cardiovascular therapies that will extend the reach of cardiovascular medicine and surgery of today.

Regenerative medicine aims to restore normal structure and function. Evolution of therapy towards reparative paradigms exploits the growing understanding of disease pathways and natural repair mechanisms to discover, validate, and apply therapeutics targeted to the cause of disease. The emergence of regenerative strategies, fueled by discoveries in developmental biology and stem cell science, has begun to transform the perspectives of clinical practice [4]. The U.S. Department of Health and Human Services report “2020: A new Vision” highlights that regenerative medicine is the most promising core component of modern medical practice at the vanguard of twenty-first century healthcare. Transformative practices have already

been documented in multiple medical and surgical disciplines. Prototypic examples range from the treatment of previously incurable blood disorders in hematology to advances in applying bionic regenerative principles for the purpose of achieving neo-organogenesis in thoracic surgery. Without the contribution of personalized products and services emerging from regenerative medicine technology, that offer the promise of definitive solutions in patient care, experts caution that healthcare will face an escalation in inefficient treatments and a rising global cost [5].

Strategies to promote, augment, and reestablish natural repair are at the core of translating the science of stem cell biology into the practice of regenerative medicine. Aimed at addressing the root cause of disease, stem cell-based regenerative medicine offers an expanded therapeutic armamentarium that drives the evolution of medical sciences from traditional symptom mitigation to previously unreachable curative algorithms. Stem cells demonstrate a unique aptitude to differentiate into specialized cell types, and to form new tissue providing thereby the active ingredient of regenerative regimens [6]. Applied to the management of heart failure, regenerative approaches target functional restoration of damaged heart tissues not mere alleviation of disease symptomatology. Leveraging rapid advances across complementary biological, medical, and engineering disciplines, successful application of regenerative medicine principles promises significant human health benefit with tangible outcomes for an improved patient care and an increased quality of life [7].

This chapter underscores progress made in stem cell therapy for ischemic heart disease. The present overview highlights the innate mechanisms of repair which provide the rationale for regenerative approaches; targets and mechanisms of therapy delineated respectively for acute vs. chronic disease, implicating both direct and indirect modes of action; cell delivery techniques which have catalyzed early translation of stem cell-based treatment; stem cell platforms which define the spectrum of available biotherapeutics; and ultimately the clinical experience to date, providing a synopsis of cardiovascular regenerative medicine from principles to practice.

2 Innate Cardiac Rejuvenation

Developmental biology has unraveled that most cells in the adult heart are derived from the mesodermal layer during early embryogenesis [8]. Knowledge of these cell populations has helped assess the molecular cues that establish cell fate decisions. Genetic fate mapping suggests that embryonic cardiogenesis proceeds according to a stem cell-based paradigm in which lineage-restricted progenitor cells give rise to the mosaic of cells present in the adult heart. A progenitor population that persists to adulthood might in fact be involved in stimulation of cardiomyocyte division in the adult heart.

Traditionally, the human heart has been viewed as a terminally differentiated postmitotic organ in which the number of cardiomyocytes is established at birth, and these cells persist throughout the lifespan of the organ and the organism. However, the discovery that cardiac stem cells live in the heart and differentiate into

the various cardiac cell lineages has changed profoundly our understanding of myocardial biology [9]. Cardiac stem cells regulate myocyte turnover and condition myocardial recovery after injury. This novel information imposes a reconsideration of the mechanisms involved in myocardial aging and regeneration.

Accordingly, stem cell-based regeneration applied to the treatment of heart failure is based on the realization that natural self-renewing processes, i.e., rejuvenation, are innate to the myocardium, yet are typically insufficient to salvage the infarcted heart muscle. The unexpected recognition that the heart is not a terminally differentiated organ as conventionally assumed, but rather harbors self-repair mechanisms to maintain tissue homeostasis has been recently documented and validated. Although the rejuvenation capacity is particularly prominent within a young heart, quantitative monitoring of innate cardiomyogenesis has established a significant renewal reserve even in the adult human heart capable of replacing both myocyte and nonmyocyte compartments (Fig. 18.1). Radio-isotope decay in the human body, a remnant of nuclear bomb testing half-a-century ago, has offered an unprecedented opportunity to quantify the birth date of single cardiomyocytes, indicating that more than half of the heart mass can be renewed over a lifespan [10]. Cardiomyocyte turnover rate has been estimated at least at about 1 % per year in young adults, and decreases to 0.5 % per year in elderly individuals. Notably, stem cell contribution to postnatal heart formation has been validated by the self/non-self chimerism characteristic of patients following allogeneic transplantation. Furthermore, within failing hearts, increase in stem cell load can contribute to the regenerative response, and involves derivation of cardiomyocytes from circulating as well as resident progenitors. Indeed, the possibility that stem cells migrate from the bone marrow to the heart and continuously repopulate the niche structures is favored by some investigators, while others consider asymmetric resident cardiac stem cell division the primary biological process controlling the number of stem cells in the myocardium [11]. In the context of large-scale destruction associated with massive ischemic injury, the native regenerative potential is typically insufficient to rescue a deteriorating myocardium. In fact, the overall efficiency for self-repair is further compromised by patient age, disease status, comorbidities or concomitant drug therapies, and defined by significant individual genetic and environmental variance. Extrapolating from the paradigms of natural heart rejuvenation and transplant-based organ replacement, activation of endogenous and/or introduction of exogenous progenitor cells into the injured infarcted heart offer legitimate strategies to ameliorate the burden of disease boosting innate reparative mechanisms [12]. Augmentation of endogenous regenerative activity is thus a compelling strategy for therapeutic cardiac repair [13].

3 Targets and Mechanisms of Regenerative Therapy

Stem cell therapy is targeted on halting or reversing progression of myocardial injury. Early after myocardial injury, the primary therapeutic goal is salvage of the jeopardized myocardium to prevent myocardial expansion and pathologic

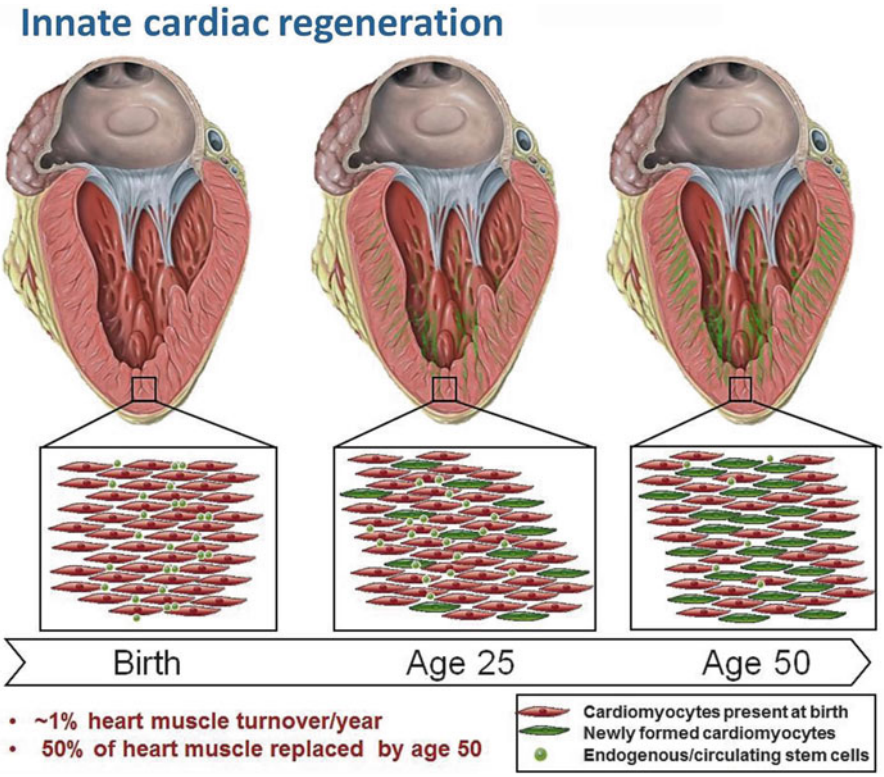

Fig. 18.1 Self-renewing processes are innate to the myocardium. The rejuvenation capacity is particularly prominent within a young heart, quantitative monitoring of innate cardiomyogenesis has established a significant renewal reserve even in the adult human heart capable of replacing both myocyte and nonmyocyte compartments. In fact, conservative estimates indicate that more than half of the heart mass can be renewed over a lifespan. The possibility that stem cells migrate from the bone marrow to the heart and continuously repopulate the niche structures is favored by some investigators, while others consider asymmetric resident cardiac stem cell division the primary biological process controlling the number of stem cells in the myocardium. In the context of large-scale destruction, the native regenerative potential is typically insufficient to rescue a deteriorating myocardium. Extrapolating from the paradigms of natural heart rejuvenation and transplant-based organ replacement, activation of endogenous, and/or introduction of exogenous progenitor cells into the injured infarcted heart offer legitimate strategies to ameliorate the burden of disease boosting innate reparative mechanisms

remodeling. At later stages of developed left ventricular dysfunction, the aim is to reverse maladaptive remodeling and ensure improved contractility [14]. In particular, excessive inflammatory response, oxidative stress, and apoptosis are the primary targets in initial stages, whereas fibrosis, loss of fiber organization, and impaired excitation–contraction coupling are key features of florid cardiomyopathy. Multidimensional interactions between cardiomyocytes, extracellular matrix, the immune system, and blood vessels determine the outcome of global remodeling and ventricular dynamics. Thus, differences in the molecular and cellular substrate

during the course of disease are likely to require distinct regenerative strategies to prevent progression or treat overt heart failure.

The recognition that stem cells can differentiate into specified cell phenotypes that produce beneficial outcome when transplanted into diseased heart, often beyond that achieved with current standards of care, has initially led to the hypothesis that direct replacement of nonviable myocardium through de novo cardiogenesis is the therapeutic mode of action. Recent iterations of the regenerative paradigm move beyond the notion that transplanted cells serve per se as the sole myocardial building blocks to a more interactive model that imposes, at the molecular level, a repair process encompassing an active role for the host myocardium [15]. In this model, the interaction of delivered stem cells with the injured/diseased myocardium and its microenvironment would ensure reparative signaling to modulate inflammation, ischemic tolerance, endogenous healing, and ultimately enhanced contractility to promote regenerative outcome. Several possible indirect activities have been proposed, including activation of endogenous cardiac progenitor cells, stimulation of cardiomyocyte division, and modification of the tissue niche with increase in neovascularization and reduction in scar burden [16]. To this end, modern repair models have been amended to include augmentation of endogenous capacity for neoangiogenesis, myocardial cytoprotection, and activation of reparative resident cardiac stem cells as contributing mechanisms of the overall stem cell benefit [17].

4 Modes of Cell Delivery

Safe and efficient delivery is a prerequisite for therapeutic benefit. Indeed, ensuring a practical and reliable delivery of a sufficient amount of a stem cell-based biotherapeutics is necessary to trigger processes of repair while ensuring minimal off-target delivery and diffuse cell dissemination [18]. Distinct delivery routes have been tested (Fig. 18.2). These include systemic, i.e., intravenous injection, vs. myocardially targeted approaches, such as percutaneous intracoronary delivery, endomyocardial transplantation, and in the context of cardiothoracic surgery epicardial injections [19]. Peripheral intravenous delivery is the least invasive, but provides the lowest degree of myocardial homing and would be applicable if the mode of action solely relied upon paracrine/endocrine secretion into the circulation. Though limited, if optimized this approach would be an attractive option due to the broad accessibility in clinical practice. Recent preclinical studies have provided proof-of-concept by demonstrating benefit without the need for homing due to the bioavailability of secreted anti-inflammatory proteins from the peripheral circulation. Alternatively, intracoronary delivery is limited to facilities with established catheter-based interventions [20]. This approach has been utilized to date by most of the clinical trials capitalizing on established interventional practices carried out in the setting of acute coronary syndrome. Myocardial delivery through endocardial transplantation has been utilized in the treatment of subacute infarction or chronic heart failure. Execution of this approach is limited to centers of excellence capable of coupling

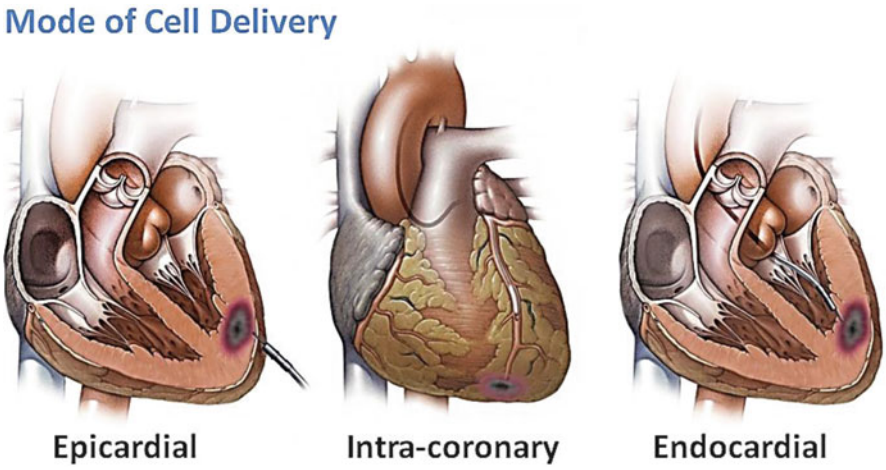

Fig. 18.2 Distinct routes for stem cell delivery have been established and applied. These include epicardial, intracoronary, and endomyocardial delivery. Epicardial cell transplantation is limited to patients with a primary indication for heart surgery. Intracoronary delivery is limited to facilities with established catheter-based interventions and is typically carried out in the setting of acute coronary syndrome. Myocardial delivery through endocardial transplantation has been utilized in the treatment of subacute infarction or chronic heart failure and is executed in centers of excellence capable of coupling cell delivery with advanced navigation and imaging to guide site-specific delivery

cell delivery with advanced navigation and imaging to guide site-specific delivery [21]. Although historically first introduced in the context of cell delivery, epicardial cell transplantation is limited to patients with a primary indication for heart surgery.

Using currently available techniques, delivery of stem cells demonstrates variable retention rates, typically not exceeding 5–10 % of the injected dose regardless of the method of administration. Progressive decrease in myocardial signals after delivery of labeled stem cells is consistent with rapid cell death or washout, within hours of administration. Although this limitation does not invalidate the efficacy of stem cells, it does suggest that reparative mechanisms involve paracrine or immunomodulatory processes that may not require local preservation of the regenerative biologics. In fact, the biodistribution of stem cells is variable, depending in part on the cell type, with cells potentially reaching remote organs such as the lungs, liver, or spleen. Although safety issues have not been raised, the consequence of extra-cardiac homing is unknown. Accordingly, long-term biovigilance has been incorporated in the development algorithm of stem cell products. Differences in the myocardial substrate and patient-specific molecular and cellular profiles governing cell retention and survival affect the choice and applicability of the technique of delivery. A concerted effort in clinical development is thus made to optimize delivery to dysfunctional but viable myocardium through increasingly optimized approaches.

5 Stem Cell Platforms and Clinical Trial Experience

Stem cells are the primary source for regenerative therapies in line with their documented capacity for self-renewal, proliferation, and differentiation [22, 23]. Multiple candidate cell types have been used in preclinical models and then further tested in clinical trials to repair the injured heart through formation of new transplanted tissue and/or indirectly through paracrine effects activating endogenous regeneration processes [24, 25].

Cell-based therapy includes autologous and allogeneic interventions [26]. Autologous stem cells are derived from noncardiac or cardiac self-sources, thereby avoiding immune intolerance. Applications for autologous stem cells are typically limited to chronic conditions given the time required to recycle stem cells from patients serving as donors through the stages of mobilization, collection, expansion, and preparation for delivery back to the same patient now serving as the recipient. In contrast, allogeneic stem cells are derived from a selected donor who is different from the recipient. In principle, allogeneic approaches can produce immune mismatch, including a host-versus-graft reaction where engrafted stem cells are recognized as non-self and attacked by the host. Yet, allogeneic tissue offers unique advantages, including the ability to generate master cell banks and store therapeutic doses to be available "off-the-shelf" for acute/subacute use or in cases where a patient has a genetically based disease that would in principle hinder the therapeutic potential of the autologous stem cell pool.

Cell-based products involve cell samples of limited amounts. This raises issues pertaining to quality-control testing. The manufacture of cell-based products must be carefully designed and validated to ensure consistency and traceability. Control and management of manufacturing and quality-control testing are carried out according to Good Manufacturing Practice requirements [27]. 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 allogeneic therapy. Accordingly, regulatory agencies impose guidelines for risk assessment, quality of manufacturing, preclinical and clinical development, and postmarketing surveillance [28].

Regenerative platforms include natural vs. engineered stem cells. Examples of naturally derived stem cells range across the embryonic to adult stem cell spectrum [29]. The newest technology of nuclear reprogramming enables moreover derivation of induced pluripotent stem (iPS) cells, an example of an engineered stem cell platform [30]. Distinct stem cell types display advantages and challenges associated with availability of the source tissue from which they are derived, differentiation capacity and pluri/multipotent potential, tumorigenic tendency and immunogenic profile, and ultimately socioethical considerations [31].

Embryonic stem cells, derived from the inner mass of a developing embryo in the blastocyst stage, are considered the stem cell archetype. They harbor the capacity of self-renewal, can be clonally expanded, and are capable of differentiating into any

cell type in the body, including functional cardiomyocytes [32]. Despite robust cardiomyogenic potential, significant obstacles limit their clinical translation, including risk for uncontrolled growth and immune rejection, in addition to fundamental ethical issues. In this regard, remarkable advances have been made in generating embryonic-like stem cells through dedifferentiation of somatic cells, providing an alternative and embryo-independent pluripotent source for derivation of cardiogenic lineages [33]. While applications for diagnostic and toxicology applications are already advanced [34], iPS cell-based therapeutic use faces a number of challenges, including risk of teratoma formation associated with pluripotency, time required to derive and characterize iPS cells obtained from any given patient, possible genetic instability, and ultimately low efficiency of cardiogenic differentiation [35]. Accordingly, methods to generate cardiomyocytes directly from somatic tissue, without transit through a pluripotent state, have been developed [36–39] but have not yet reached regulatory authorization for clinical translation. While in the future pluripotent stem cell platforms and their products are anticipated to be increasingly considered for human testing [40], current clinical experience has been limited to the use of multipotent adult stem cell types.

Adult skeletal myoblasts, bone marrow, or peripheral blood stem cells were in fact among first to be investigated in a clinical setting for cardiac regeneration [41]. Skeletal myoblasts, expanded from a thigh muscle biopsy, are conceptually attractive due to a potential contractile phenotype, opportunity for autologous transplantation, and resistance to ischemia [42]. Skeletal myoblasts however differentiate into multinucleated myotubes, not apparently cardiomyocytes, after injection into the heart. Myotubes lack gap junctions, resulting in possible electrical inhomogeneity that could predispose to ventricular arrhythmia. The first prospective, randomized, placebo-controlled skeletal myoblast trial (MAGIC trial) used an epicardial approach for delivery, but exhibited overall lack of functional efficacy [43]. Percutaneous intramyocardial delivery of skeletal myoblasts was alternatively applied in a subsequent trial (SEISMIC trial) which demonstrated symptomatic relief with however no significant effect on global left ventricular ejection fraction [44].

Clinical application of bone marrow and blood-derived stem cells has been catalyzed by the accessibility, and ease of cell isolation from a renewable source [45]. Case in point, the adult bone marrow contains different cell populations, including monocytes, hematopoietic, and mesenchymal stem cells. Human hematopoietic stem cells can be defined as $CD34^+$ cells capable of reconstituting blood lineages and, possibly, the ability to trans-differentiate into cardiomyocytes, endothelial cells, and smooth muscle cells in vivo. Mesenchymal stem cells can be defined as $CD105^+$ $CD90^+$ cells, isolated by preferential adherence to plastic in tissue culture, which are capable of osteogenic, chondrogenic, and adipogenic differentiation, and under guidance to cardiogenic specification [46, 47]. In the clinical setting, autologous bone marrow-derived mononuclear cells, unfractionated or enriched in progenitor subpopulations, have been most frequently used for the treatment of acute myocardial infarction typically delivered via the intracoronary mode. Experience to date highlights an excellent feasibility and safety profile, generally positive clinical outcomes, although primary endpoints have not always been met and a sustained

functional benefit remains uncertain. Indeed, meta-analyses of case-controlled trials in patients with recent myocardial infarction suggest significant, albeit limited, benefit with regard to recovery of left ventricular ejection fraction beyond standard reperfusion therapy [48, 49]. Among trials based on the use of blood or bone marrow-derived stem cell populations, the double blinded, placebo controlled REPAIR-AMI (Repair of Enriched Progenitor cells And Infarct Remodeling in Acute Myocardial Infarction) trial is considered a benchmark study [50]. Furthermore, the randomized, but not placebo controlled, BOOST (Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration) trial showed transient improvement in left ventricular function at 6 months compared to controls [51]. Conversely, the randomized controlled ASTAMI (Autologous Stem Cell Transplantation in Acute Myocardial Infarction) trial failed to demonstrate significant improvement in ejection fraction as assessed from cardiac MRI, single photon emission computed tomography or echocardiography [52]. These apparently controversial readouts may relate to different study design, heterogenous patient populations, cell number and processing, time of cell injection, or methods used to assess outcome [53, 54]. Collectively, these studies demonstrate both feasibility and safety of a stem cell approach in the setting of acute ischemic heart disease, furthermore suggesting that a stem cell source with a higher propensity to regenerate myocardium, directly and indirectly, might promote benefit [55, 56]. Bone marrow-derived cells have also been used for the treatment of refractory angina and chronic heart failure, albeit with inconsistent results in early trial experiences [57–59]. Larger trials are thus needed to dissect the true potential of stem cell therapy.

The most recent systematic review of 33 randomized controlled trials with a total of 1,765 participants indicates no statistically significant improvement in mortality with stem cell treatment or composite morbidity—which includes reinfarction, hospital readmission, restenosis, and target vessel revascularization—compared with placebo [60]. Short-term follow-up data showed that stem cell treatment can improve left ventricular ejection fraction significantly, and this improvement was sustained for 12–61 months. Also, some studies showed that the stem cell therapy improved left ventricular end systolic and end diastolic volumes as well as infarct size. The soon to be initiated large Bone Marrow Cells in Acute Myocardial Infarction (BAMI) trial will evaluate mortality benefits of bone-marrow stem cell therapy in over 3,000 reperfused myocardial infarction patients. The BAMI investigators will also develop standardized techniques for cell processing and delivery. Because the short-term mortality following successful revascularization of a culprit artery is already very low, studies looking for the benefit of stem cell therapy may have to combine mortality, reinfarction, and heart failure into a composite end point. Also, health-related quality of life should be measured to judge the full benefit.

As pointed out, trial results are not uniform owing to the current lack of standardization and optimization of cell isolation and delivery protocols. This lack of uniformity is prevalent despite newer techniques that allow point-of-care cell preparations, for example within cardiac catheterization or operating rooms, thereby providing short preparation time, facilitated logistics of cell transport, and reasonable cost-effectiveness. Beyond inter-trial variability, inter-patient variability has been

increasingly recognized triggering an ongoing quest for optimization and identification of the most appropriate cell source and cell type, stratification and selection of patient populations most amenable to cell-based therapy, targeting ideal timing of intervention, and most favorable routes of administration. In this regard, it should be noted that in contrast to traditional small molecule-based medications, regenerative cell products contain life cells as the active ingredient. Moreover, cell therapy is currently limited by low rates of cell engraftment and poor cell survival. Advanced patient age, cardiovascular risk factors, and underlying heart disease appear to also have a negative impact on the functionality of delivered cells. Mechanisms of improved benefit have implicated, among other variables, a defining role for the extent of cardiovascular lineage commitment [61]. Establishing the individual efficacy profiles is thus paramount to maximize benefit of cell-based therapy in the management of cardiovascular disease.

By processing myocardial tissue excised during cardiac surgery or by endovascular biopsy, it is now possible to derive resident stem cell populations. This advance provides the prospect of anatomically matching the regenerative cell source with the target organ. Clinical evaluation of resident cardiac stem cells has been initially tested in the SCIPIO (Cardiac Stem Cell Infusion in Patients With Ischemic CardiOmyopathy) and the CADUCEUS (CArdiosphere-Derived aUtologous stem CElls to reverse ventricULar dySfunction) trials [62, 63]. The CADUCEUS study utilizes the cell cluster or cardiosphere approach for derivation and propagation [63], while SCIPIO implements an antibody-based method to derive a homogenous C-kit^{+} population [62]. CADUCEUS focuses on individuals with subacute myocardial infarction, with harvest of the patient's own biopsy-obtained right ventricular tissue to yield an autologous therapeutics delivered via coronary arteries [63]. The SCIPIO study utilizes right atrial tissue obtained during coronary artery bypass for autologous, intracoronary (proximal coronary artery or graft supplying the infarcted left ventricular region) delivery of derived C-kit-expressing human cardiac stem cells [62]. Both studies are first-in-man trials powered to assess safety and feasibility. Both studies reported reduction in myocardial scar mass following cell treatment, but only the SCIPIO trial reported improved left ventricular ejection fraction. The number of patients in the treatment arm of each study was 16 in SCIPIO and 17 in CADUCEUS, and neither study included a placebo group because of the invasive nature of the treatment [62, 63]. Indeed, such approaches are hampered by the invasive nature of heart tissue sampling and the limited quantity of starting material. Orienting nonresident stem cells towards cardiogenesis would eliminate the need for the patient to undergo myocardial harvest [64, 65]. Recently, hallmark traits of cardiac development were successfully triggered within bone marrow-derived mesenchymal stem cells, establishing the first human scalable lineage-specified cardiopoietic phenotype derived without heart tissue harvest [66, 67]. Preclinical testing demonstrated that cardiac-specified progenitors reliably repair the failing myocardium, providing the foundation for clinical translation [68]. The ensuing C-CURE clinical trial is a first-in-man study to address the feasibility and safety of autologous bone marrow-derived cardiopoietic stem cell therapy, and assess efficacy signals in patients with ischemic cardiomyopathy.

6 Future Trends in Regenerative Therapy

At the core of upcoming practice, state-of-the-art regenerative principles are poised to increasingly leverage the emergent understanding of multiplex parameters defining therapeutic outcome in the setting of individualized heart failure management. Individualized medicine provides a powerful engine to tailor molecular profiles of patients in order to maximize therapeutic specificity, reduce treatment variability, and minimize adverse events [69]. 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, providing thereby previously unanticipated opportunities for patient-specific disease management [70]. The emerging field of regenerative medicine will thus grow in conjuncture 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. In this regard, systematic stratification of patients to match clinical traits and disease pathobiology with most adequate therapy will become integral in streamlining future evidence-based regenerative algorithms. To this end emphasis will be placed on delineating acute vs. chronic disease substrates to ensure proper target strategy, timing, and mode of intervention; separating ischemic vs. non-ischemic conditions to guide focal vs. diffuse therapy; preemptive management of comorbidities and co-therapies to limit modifiable confounding factors to regenerative regimens. Moreover, recognizing key pharmacodynamics and pharmacokinetics features of regenerative biotherapeutics will aid in the design of next generation therapies. In this context, methods to enhance the biological propensity for repair are central in processes aimed at regenerative optimization. Such ongoing efforts to translate optimized stem cell products, along with studies to clarify the duration and mechanisms of benefit as well as the implications of repeat therapy, mark the beginning of a new era in regenerative therapeutics [71–73]. While first-generation products consisted of purified, natural human cells typically used in their native state, second-generation cell products will refer to cells guided with growth factors or subpopulations selected based on tissue-specific biomarkers or genetically modified to direct cell differentiation, restrict tissue specification, and enhance the level of organ specificity. The goal with second-generation cell products is to produce derivatives with enhanced safety and efficacy profiles compared to the original stem cell source. Third-generation products would serve as delivery platforms, for example, as a gene delivery system for correction of genetic mutation or targeted therapy with recombinant protein, and/or engineered cell products with superior properties, such as enhanced stress tolerance and improved regenerative capacity. The goal with third-generation cell products is to maximize therapeutic potential beyond that inherent to the original stem cell source or the respective derivatives [74]. Furthermore, optimizing delivery procedures will entail engineering advanced methods to achieve increasingly uniform

distribution of cells and limit early loss at time of administration. Indeed, efforts are under way to design and produce optimized delivery systems. These may combine utilization of biomaterials designed to solidify at the time of injection to improve long-term cell retention and engraftment [75–77]. Moreover, organ engineering based on decellularized matrix scaffolds may provide a future in tissue replacement [78–80].

7 Conclusion

Stem cell-based therapies for ischemic heart disease have significantly advanced since the inaugural procedures a decade ago. The challenge of translating regenerative principles to practice has been increasingly answered with demonstrated clinical feasibility and safety for stem cell therapeutics. Whether it is direct incorporation and function within the damaged heart and/or indirect cellular secretome-mediated benefit, stem cell-based therapy has been independently tested across numerous clinical trial designs. With further development of tools to aid successful delivery, along with advances in the dissection of mechanisms driving stem cell-based repair, regenerative medicine is poised to transit from proof-of-principle studies towards clinical validation and ultimately standardization. However, lack of consensus on cellular production, storage and identity, site and method of delivery, efficacy of autologous "sick patient" derived stem cells vs. allogeneic "healthy donor" cells, the mechanism and duration of benefit, need for adjuvant growth factors and timing of delivery provide formidable challenges that need to be systematically addressed en route to adoption. In this regard, the international multidisciplinary community of regenerative science and practice has provided an unprecedented foundation for increasingly robust trials paving the way for next generation therapies capable to address the root cause of heart failure. Beyond safety and efficacy profiles, regenerative therapies will be tested for equivalence across distinct socioeconomic and healthcare settings, as an indicator that these new management strategies can potentially reach broader populations in need. Ultimately, the rigor of comparative effectiveness outcome analysis will be needed to inform on the value of introducing a personalized regenerative therapy in standardized heart failure management.

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