Cell-based treatment represents a new generation in the evolution of biological therapeutics. A prototypic cell-based therapy, the mesenchymal stem cell, has successfully entered phase III pivotal trials for heart failure, signifying adequate enabling safety and efficacy data from phase I and II trials. Successful phase III trials can lead to approval of a new biological therapy for regenerative medicine.

The use of stem or progenitor cells therapeutically is under investigation for the treatment of chronic diseases, including cardiovascular pathologies.1 Not unusual for an early stage disruptive technology, early findings have led the field to an important and controversial cross-roads. Based in large part on disagreements surrounding mechanism of action of cell-based therapy, some authors have called for a reappraisal of the existing data, whereas others have concluded that the field has evolved too quickly into clinical practice and that we need to go back to the bench.2 However, there are many historical examples including the notable examples of aspirin and opioids that were used therapeutically before the mechanisms of actions were fully understood. In the midst of this debate about mechanism of action of cell therapy, an emerging field of investigation is the mechanism of action of mesenchymal stem cells, which has followed the characteristic trajectory of preclinical and clinical development, supported by data highly predictive of successful therapeutic outcome. Most importantly, because of its allogeneic potential, mesenchymal stem cells can be viewed as a true cellular biological therapy with the capacity for high volume quality-controlled production and off the shelf usage.3

What Are Mesenchymal Stem Cells?

Mesenchymal Stem Cells (MSCs) are mesoderm-derived multipotent stromal cells that reside in embryonic and adult tissues, prototypically bone marrow. Having the capacity for self-renewal, MSCs maintain stemness (e.g., multipotency) and exhibit immune-privileged, immunomodulatory, and proregenerative properties, in part, to their secretome.1 As such, culture-expanded MSCs represent a controlled and homogeneous stem cell population.

Why MSCs Became One of the Top Choices?

A large majority of early cell-based clinical trials for heart disease were designed for acute myocardial infarction (AMI) and conducted using autologous bone marrow mononuclear cells. The widespread use of bone marrow mononuclear cells can be attributed to immediate cell availability from the recipient. However, the efficacy was variable. Using global left ventricular ejection fraction as an end point, bone marrow mononuclear cell trials showed controversial results, and later trials tended to be negative.4 Perhaps, one of the factors contributing to this discordance was the innate diversity of cell populations found in isolated bone marrow mononuclear cells between patients. All this has led to the search of more specific stem cell subpopulations with more specific identifying characteristics. Particularly, the field needed an adult stem cell that is easy to isolate, culture, and manipulate in ex vivo conditions. In this regard, MSCs, in part, because of their long standing record in regenerative medicine, proven safety, and potency, have emerged as a lead candidate cell type with accumulating clinical investigations using this stem cell population for AMI and chronic heart failure.3

What Was Trajectory of Preclinical and Clinical Development of MSCs?

Following experiments in rodents, multiple preclinical studies in different animal models of acute and chronic heart failure have been conducted, which together demonstrate favorable impact on left ventricle remodeling, driven largely by a 30% to 50% reduction in infarct scar size.6 Accumulating data led to Food and Drug Administration (FDA) approval for testing MSC-therapy in early phase small clinical trials (pilot studies) that established the safety of both autologous and allogeneic MSCs.7 The pilot studies have, in turn, guided the design of phase II clinical trials suggesting the optimal use of stem cells, delivery methods, and cost-effective way to investigate clinical efficacy.
MSC as a Therapeutic Agent

It is valuable to consider MSC-based therapy in the context of general principles of therapeutic development. On the average, it takes 12 to 15 years and up to $5 billion to develop and launch a new drug. Given this paradigm, the decade of work on developing MSCs cannot and should not be dismissed. While only 1 of 10 investigational new drugs succeeds from phase I to FDA approval, the probability of success increases with the transition to later stages of clinical trial development. MSCs have decisively passed phase II, a rigorously controlled phase, and have recently entered phase III trials.1 New therapeutic development often must encounter The Valley of Death, which is a translational research gap during which time safety assessments for chemical and biological drugs are made. This period can often be intensified if animal models for the disease in question have deficiencies.9 As a consequence, it should be noted that substantial preclinical data supporting MSCs in the injured heart had emerged from highly representative large animal models, such as the porcine, which has similar cardiac anatomy and physiology as humans.11 The remodeling process in these models is highly reminiscent of left ventricular remodeling in humans and has accurately predicted phenotypic outcomes in clinical trials. Experiments in porcine models have been used to test both human cells in immunosuppressed animals,6 as well as autologous cells.12

Reasons for Failure of a New Therapeutic Strategy

The generic reasons that explain the failure of a new therapeutic include poor understanding of drug pharmacology,13 poor linkage between molecule-to-disease,14 and variability in the underlying genetics/epigenetics in animals and humans.15 MSC pharmacology has proven mechanisms of action which include MSC plasticity, secretion of numerous bioactive molecules, exosomes, and mitochondria transfer. These bioactive molecules, in turn, promote myocardial tissue growth through endogenous activation of angiogenesis, neurogenesis, immunomodulation, cardiac stem cell, and mature cardiomyocyte proliferation.1

With regard to genetics/epigenetics in animals and humans, the use of human cells in animal models has justified the safety and potency of human MSCs, demonstrating that these cells are capable of replacing tissue loss and restoring cardiac function.6 The use of allogeneic MSCs was initiated in animal models as well, contributing to a better understanding of the interdisciplinary nature of MSC biology particularly immune privilege proprieties that supported future studies in humans.

Where Are We Now With Regard to Clinical Trials of MSCs?

Since 2011, MSCs and related culture-expanded cell preparations have been tested in small trials for chronic heart failure. These trials have consistently shown that cell therapy in this clinical setting reduces MI scar size, reverses ventricular remodeling, improves 6-minute walk distance and quality of life, as measured with validated questionnaires (Table 1).16–20 Nevertheless, although multiple meta-analyses have debated whether or not the degree of cardiac functional improvements,

### Table 1. Results of Trials of Cell-Based Therapy in Chronic Heart Failure

<table>
<thead>
<tr>
<th>Table Name (No. of Patients)</th>
<th>Δ6MWT</th>
<th>ΔMLHFQ</th>
<th>ΔMI SIZE</th>
<th>ΔEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams et al6 (n=8)</td>
<td>…</td>
<td>…</td>
<td>−18.3±8.3%</td>
<td>…</td>
</tr>
<tr>
<td>SCIP029 (n=21)</td>
<td>…</td>
<td>−19.8</td>
<td>−9.8±3.5 g (−30%)</td>
<td>+8–12.3%</td>
</tr>
<tr>
<td>MESOBLAST32 (n=60)</td>
<td>+52.5 m*</td>
<td>…</td>
<td>…</td>
<td>+5.2±9.3%*§</td>
</tr>
<tr>
<td>CADUCEUS34 (n=25)</td>
<td>+33.0 m</td>
<td>−10.8†</td>
<td>−12.9 g (−42%)</td>
<td>†</td>
</tr>
<tr>
<td>POSEIDON35 (n=30)</td>
<td>+43.5 m</td>
<td>−7.6</td>
<td>−33.21%</td>
<td>+2.0%†</td>
</tr>
<tr>
<td>C-CURE36 (n=33)</td>
<td>+62.0 m</td>
<td>±10*†</td>
<td>…</td>
<td>+7.0%</td>
</tr>
<tr>
<td>TAC-HFT37 (n=59)</td>
<td>+32.6 m†</td>
<td>−6.3</td>
<td>−12.6 g (−32.9%)</td>
<td>†</td>
</tr>
<tr>
<td>MSC-HF† (n=59)</td>
<td>…</td>
<td>…</td>
<td>−4.4±5.1 g</td>
<td>+5.5±3.8%</td>
</tr>
</tbody>
</table>

Δ6MWT indicates 6-minute walk test; C-CURE, Cardiopoietic stem Cell Therapy in Heart failure; CADUCEUS, Cardiosphere-Derived autologous Stem Cells to Reverse ventricular dySfunction; EF, ejection fraction; MESOBLAST, A Phase II Dose-escalation Study to Assess the Feasibility and Safety of Transendocardial Delivery of Three Different Doses of Allogeneic Mesenchymal Precursor Cells (MPCs) in Subjects With Heart Failure; MI SIZE, myocardial infarction size/scar size; MLHFQ, Minnesota Living With Heart Failure Questionnaire MSC-HF, Mesenchymal Stromal Cells in chronic ischemic Heart Failure; POSEIDON, The Percutaneous Stem Cell Injection Delivery Effects on Neomyogenesis Pilot Study; SCIP0, Cardiac Stem Cell Infusion in Patients With Ischemic Cardiomyopathy; and TAC-HFT, The Transendocardial Autologous Cells (hMSC or hBMC) in Ischemic Heart Failure Trial.

*Not significant vs control.
†Not significant within-group.
‡Data not published.
§25 million mesenchymal precursor cell group.
including increases in left ventricular ejection fraction, are significant, there are not enough standardized clinical trials studying MSCs or related cells with appropriate sample sizes to confidently answer this question. A review of trials registered on clinicaltrials.gov revealed 34 MSC clinical trials for adult heart pathology (AMI, ischemic, and nonischemic chronic heart failure). Most studies remain in phases I and II (Figure A) but there are several phase III trials currently underway or completed (Table 2). A major issue of note is the diversity of MSC clinical trials. Seven of these trials are multicentered and I is double-centered. Most of them (27) are small-sized trials, enrolling <100 patients per trial (Figure B and C) and only some are placebo-controlled. The MSC route of administration (intravenous, intracoronary, intramyocardial, and transendocardial; Figure D), cell dose, and cell origin (fetal-umbilical versus adult, autologous versus allogeneic, and bone-marrow versus adipose derived) are dissimilar in these clinical trials as well. Indeed, it is crucial to mention that MSC origin and location may define MSC characteristics and therefore influence MSC behavior. These facts highlight the variability in MSC clinical trials, specifically with respect to study design, cell origin, and dose/delivery methods. In 2009, the first double-blinded allogeneic MSC clinical trial for AMI sponsored by Osiris demonstrated that intravenous infusion of allogeneic MSCs was well tolerated and lowered arrhythmic events and chest pain. This trial started the era of allogeneic MSCs for heart disease and today, allogeneic MSC products are used in large clinical trials with enrollment targets in the thousands of patients. Success with these efforts could lead to approval of these products by the FDA.

### MSC Therapy Perspectives

Given all of the above, MSC clinical trials have already crossed the Rubicon suggesting that cell-based therapy is safe, efficient, and efficacious. Biological drugs, such as stem cells, have a more arduous path to travel compared with

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**Table 2. Phase II/III and III Clinical Trials of Cell-Based Therapy in Heart Disease**

<table>
<thead>
<tr>
<th>Trial ID; Trial Location; No. of Patients</th>
<th>Trial Name (Trial Stage)</th>
<th>Cardiac Indication</th>
<th>Delivery Method</th>
<th>Cell Type</th>
<th>Sponsor</th>
<th>Primary End Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01753440; Greece; 30 (estimated)</td>
<td>Allogeneic Stem Cells Implantation Combined With Coronary Bypass Grafting in Patients With Ischemic Cardiomyopathy +CABG</td>
<td>Ischemic cardiomyopathy +CABG</td>
<td>Intramyocardial/Intraoperative</td>
<td>Allogeneic MSCs</td>
<td>AHEPA University Hospital</td>
<td>Change in LVEF by EchoCG and myocardial segmental perfusion</td>
</tr>
<tr>
<td>NCT01392105; Republic of Korea; 80 (final)</td>
<td>Safety and Efficacy of Intracoronary Adult Human Mesenchymal Stem Cells After Acute Myocardial Infarction (SEED-MSC) (completed)</td>
<td>Acute myocardial infarction</td>
<td>Infracoronary</td>
<td>Autologous human bone marrow–derived MSCs</td>
<td>Yonsei University, collaboration with FCB-Pharmicell Co, Ltd</td>
<td>Absolute change in global LVEF by SPECT</td>
</tr>
<tr>
<td>NCT01394432; Russia; 50 (estimated)</td>
<td>ESTIMATION (on-going)</td>
<td>Acute myocardial infarction +heart failure</td>
<td>Catheter-based transendocardial delivery</td>
<td>Autologous human bone marrow–derived MSCs</td>
<td>Meshalkin Research Institute of Pathology of Circulation</td>
<td>Change LVEF and LVESV by MRI</td>
</tr>
<tr>
<td>NCT01652209; Republic of Korea; 135 (estimated)</td>
<td>RELIEF (on-going)</td>
<td>Acute myocardial infarction</td>
<td>Infracoronary</td>
<td>Allogeneic human bone marrow–derived MSCs</td>
<td>Pharmicell Co, Ltd</td>
<td>Change LVEF by MRI</td>
</tr>
<tr>
<td>NCT02020304; United States and Canada; 1730 (estimated)</td>
<td>DREAM-HF (on-going)</td>
<td>Chronic heart failure (ischemic and non-ischemic)</td>
<td>Catheter-based transendocardial delivery</td>
<td>Allogeneic mesenchymal precursor cells (CEP-41750)</td>
<td>Teva Pharmaceutical Industries, Israel</td>
<td>HF-MACE</td>
</tr>
<tr>
<td>NCT00810238; Belgium, Serbia; 33 (final)</td>
<td>C-CURE (completed)</td>
<td>Chronic heart failure secondary to ischemic cardiomyopathy</td>
<td>Catheter-based transendocardial delivery</td>
<td>Autologous bone marrow–derived and cardiogenically oriented MSCs</td>
<td>Celyad, Belgium</td>
<td>Change in LVEF</td>
</tr>
<tr>
<td>NCT01768702; Belgium, Hungary, Israel, Italy, Poland, Serbia, Spain, Sweden, Switzerland, United Kingdom; 240 (estimated)</td>
<td>CHART-1 (on-going)</td>
<td>Chronic advanced ischemic heart failure</td>
<td>Catheter-based transendocardial delivery +C-Cath injection catheter</td>
<td>Autologous bone marrow–derived mesenchymal cardiopoietic cells (C3BS-CQR-1)</td>
<td>Celyad, Belgium</td>
<td>MLHFO 6-min walk test (absolute change ≥4%) in LVEF</td>
</tr>
<tr>
<td>NCT02317458; no location provided; 240 (estimated)</td>
<td>THE CHART-2 TRIAL (not recruiting)</td>
<td>Congestive heart failure secondary to ischemic cardiomyopathy</td>
<td>Catheter-based transendocardial delivery</td>
<td>Autologous bone marrow–derived mesenchymal cardiopoietic cells (C3BS-CQR-1)</td>
<td>Celyad, Belgium</td>
<td>6-min walk test</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; C-CURE, Cardiopoietic stem Cell therapy in heart failure; CHART-1, Safety and Efficacy of Autologous Cardiopoietic Cells for Treatment of Ischemic Heart Failure; CHART-2 TRAIL, Congestive Heart Failure Cardiopoietic Regenerative Therapy; DREAM-HF, Allogeneic Mesenchymal Precursor Cells (CEP-41750) for the Treatment of Chronic Heart Failure; EchoCG, echocardiogram; ESTIMATION, “ESTIMATION Study” for Endocardial Mesenchymal Stem Cells Implantation in Patients After Acute Myocardial Infarction; HF-MACE, heart failure–related major adverse cardiac events; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; MSC, mesenchymal stem cell; MLHFO, Minnesota Living with Heart Failure Questionnaire; RELIEF, A Randomized, Open labeled, multicenter Trial for Safety and Efficacy of Intracoronary Adult Human Mesenchymal stEm Cells Acute Myocardial infarction; and SPECT, single-photon emission computed tomography.
their chemical counterparts. The nature of a biological drug is more complicated, and in addition to safety and efficacy, raises ethical, political, and economic concerns that need to be addressed. MSCs are overcoming the majority of these challenges, and several efforts have resulted in phase III clinical trials that, if successful, could lead to approval. There are still unresolved issues regarding cell dose and number of treatments needed to reach the desired results. It is unclear whether MSC donors can influence cellular product efficacy. We certainly need to follow the established quality control standards for MSC products and define the patient population that is eligible and will benefit the most from cell therapy.

In conclusion, MSC-based therapy for heart disease can be viewed in the context of a novel class of biological therapeutics and one that is following a characteristic drug development pipeline. Appropriate preclinical models have been used that can predict findings in humans and ensure safety. Finally, allogeneic MSC products, a biological drug with standardized quality controlled manufacturing, are demonstrated to be safe and effective in phase I and II clinical trials for AMI and chronic heart failure.7,16 The current ongoing conduct of phase III trials are warranted and could lead to product approval. Enlarging efforts to conduct phase II and III trials should be encouraged and will contribute to advancing this field which has the potential to address large unmet medical needs and substantially influence human health.

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References


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