

Power Is Nothing Without Control The Enduring Search for the Best Cell in Cardiac Cell Therapy at a Crossroads

Beatrice Bassetti, Maurizio C. Capogrossi, Giulio Pompilio

*A few observations and much reasoning lead to error;
many observations and a little reasoning to truth.*

—Alexis Carrel, Medicine Nobel Prize 1912

Cardiac cell-based therapy, after a peak of untimely expectations of miraculous efficacy exceeding standard clinical practice, has faced the cardiological community and funding bodies with a predictable trough of disillusionment. In the light of more recent progresses, the field is by contrast moving toward a competitive differentiation phase, in which the resolution of the complex matching between potency of cell therapeutics and heart disease pathophysiology has the potential to make a difference for the most challenging unmet clinical needs in cardiovascular medicine.

The Paradigm Shift of Cardiac Cell Therapy

The exogenous administration of stem cells to repair the damaged heart has been clinically introduced on the basis of the revolutionary idea that by delivering cardiomyogenic potent cells, the substitution of dead or damaged myocardium with de novo cardiomyocytes able to directly contribute to contractile force generation would have been an achievable target. The confirmation that the heart possesses an intrinsic, although modest, self-renewal capacity¹ has further fueled the clinical exploitation of such an innovative therapeutic strategy.

However, from the progress in the field over the past 15 years, it has become evident that by means of available clinical-grade cell products, the salutary functional and clinical effects of cardiac cell therapy (CCT), when present, are more likely because of an indirect (paracrine) action exerted

by cells nested in the myocardium through the release of a miscellany of largely unidentified molecules, which promote endogenous reparative processes. Such a paradigm shift from a cardiopoietic to a cardioreparative concept may have profound implications for forthcoming CCT clinical research. Notably, different classes of compounds with a cardioprotective action have been recently unsuccessfully tested in clinical trials with the aim to prevent ischemia–reperfusion injury or heart failure (HF) progression.² We believe that CCT has the potential to fill this gap.

Searching for Potency Lacking the Power Source

Looking back over the past 15 years, the search for the best cell to repair the damaged heart has been heavily burdened by both the intricacy of biological mechanisms underpinning the mode of action and the lack of an indisputable demonstration of clinical benefit. This detrimental combination has produced a complex scenario in which subsequent cell generations have entered the clinical arena in the search for an increasing cardioreparative potency. Paradoxically, at present, no cell type, including skeletal myoblasts, has definitively left the stage because of a clear lack of efficacy, although none has proven so far to be the best one. The functional benefit observed has been cumulatively modest, regardless of the cell type used. In this context, the plethora of cell products under investigation has certainly represented one of the main obstacles for the advancement of the field, having contributed to the dispersion of the limited resources available.

Remarkably, the considerable number of cells under investigation, along with the relatively small sample sizes of exploratory and surrogate end point trials, have prevented clinically meaningful head-to-head cell comparisons. Little information is in fact available in this regard at a clinical level, likewise few articles have addressed this issue in preclinical large-animal models.

The REGENT trial (Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction)³ was the first study comparing the effects of 2 different populations of intracoronary injected bone marrow (BM) cells (unselected mononuclear cells [MNC] versus positively selected CD34⁺CXCR4⁺ cells) on the improvement of left ventricular (LV) contractility in patients with LV dysfunction after acute myocardial infarction (AMI). No significant differences in absolute changes of LV ejection fraction between the groups have been detected. The main shortcomings of this study were, however, the lack of the placebo arm, its open-label design, and, more importantly the

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low number of patients having magnetic resonance imaging both at baseline and at follow-up, a limitation that, the authors themselves acknowledged, may have negatively impacted primary end point analysis. The TAC-HFT trial (Transendocardial Autologous Mesenchymal Stem Cells and Mononuclear Bone Marrow Cells in Ischemic Heart Failure)⁴ compared fluoroscopy-guided intramyocardial injection of BM-derived mesenchymal stem cells (MSC) and placebo or MNC with placebo in patients with ischemic cardiomyopathy and left ventricular ejection fraction <50%. The authors' conclusions were limited to feasibility and safety of the procedure because the study was not powered to draw definitive efficacy comparisons between cell types. In addition, multiple comparisons were conducted, further limiting the conclusions. More recently, in the TECAM trial (Trial of Hematopoietic Stem Cells in Acute Myocardial Infarction),⁵ intracoronary injection of 3 different BM-derived stem cell approaches (MNC, granulocyte colony-stimulating factor alone, and MNC plus granulocyte colony-stimulating factor) have been compared with conventional treatment in AMI. No improvements of left ventricular ejection fraction or volumes were observed, but a mild although significant reduction of the infarct area regardless of the approach utilized was found. Once again, the open-label design and the small sample size, as acknowledged by the authors, put the result interpretation of the LV outcome parameters measured into question. Conversely, 2 adequately powered noteworthy studies are ongoing (TAC-HFT II NCT02503280 and HUC-HEART, NCT02323477), which respectively compare the efficacy of BM-MSC versus a combination of MSC/cardiac stem cells and BM-MNC versus umbilical cord-MSC to ameliorate ventricular function in an ischemic HF setting.

To further complicate this operational framework is the nature of cellular biological therapy itself, whose mode of action, unlike molecules, is dependent on a complex multi-variable equation, beyond the cell type, including cell source, isolation methods, manufacturing protocol standardization, environmental factors such as patient's profile (including age, genetics, comorbidities, and medications) and, importantly, the heart disease to be treated (including the delivery strategy and acute versus chronic setting). It is worth mentioning, as an example, the increasing relevant evidence that BM cell subpopulation characteristics are associated with a better clinical outcome in patients with AMI⁶ and the enduring lack of demonstration about which delivery approach (intracoronary versus intramyocardial versus coronary sinus) fits better with a given pathological condition.

The Long and Winding Road

The big picture of past and current CCT may be nevertheless of some help in understanding where the field is heading. If we overlook what has been done to date in clinical trials for ST-elevated AMI, refractory angina, and HF, some insights can be extrapolated in an attempt to shed light on cell therapeutics that are likely to finally take the highroad (Online Figure).

In AMI and refractory angina, the BM as a cell source has largely predominated in published studies with MNC, positively selected BM subpopulations (CD34⁺/CD133⁺ cells) and MSC, the preferred first-generation cell types tested.

The pathophysiological rationale behind this strategy is the attempt to therapeutically exploit the recognized role that BM-derived cells play in the healing and neovascularization processes of the injured myocardium. Although no indisputable positive clinical evidence has been generated to date after completion of more than 80 controlled clinical trials,⁷ BM cells are today in an advance line of clinical end point research in ST-elevated AMI with EU-funded Phase III BAMI (NCT01569178), actively enrolling patients with post-AMI LV dysfunction to BM-MNC intracoronary delivery versus standard care. Notably, recent positive findings from the prematurely stopped RENEW trial (The Efficacy and Safety of Intramyocardial Autologous CD34⁺ Cell Administration in Patients With Refractory Angina)⁸ have been obtained in patients with refractory angina by means of NOGA-guided intramyocardial injection of CD34⁺ cells. In light of these and previously published results, refractory angina seems to be a promising target for the introduction of CCT into standard clinical practice. CCT has shown a credible likelihood of efficacy on top of current therapies in terms of angina frequency reduction and improvement of quality of life. BM-derived cells, such as CD34⁺ subpopulation, clearly represent the frontline of biotherapeutics in this context, although other cell types such as MSC or cardiac stem cells may also possess exploitable angiogenic properties. Within the framework of BM-heart axis exploitation, the yet-to-be extinguished interest for BM cells mobilizing growth factors such as granulocyte colony-stimulating factor in ST-elevated AMI has to be positioned. In fact, this is the target of the currently active Phase III STEM-AMI OUTCOME trial (Stem Cells Mobilization in Acute Myocardial Infarction Outcome; NCT01969890).⁹

In HF, the scenario is even more complex, also depending on the higher number of new cell types that have been introduced in the clinical arena. This feature is likely because of an increased need for potency to revert the HF phenotype and a lack of clear evidence of which cardioreparative mechanisms can be best targeted. Figure A depicts the different cell types that are currently under active clinical investigation. MSC are clearly the preferred cell therapeutic, being tested in 49% of current controlled trials, the large majority of them (74%) addressing patients with HF. MSC-based therapy, originating from BM-, adipose tissue-, or umbilical cord-cells, is gaining consent and considered appealing because of the large body of preclinical evidence of higher paracrine cardioreparative potential exerted by the multitude of trophic factors endowed in the secretome of these cells. Autologous MSC are currently under investigation in different phase II/III studies and represent the frontline of first-generation cells for the treatment of postinfarction LV adverse remodeling. Similarly, BM-derived unfractionated MNC or selected subpopulations are in a late phase of clinical assessment, representing 50% of ongoing phase II/III studies for HF. Notably, in this context, the efficacy of repeated cell administration will be for the first time specifically addressed in controlled studies: the REPEAT study (Effects of Single Versus Repeated Intracoronary Application of Autologous Bone Marrow-Derived Mononuclear Cells on Mortality in Patients With Chronic Post-Infarction Heart Failure; NCT01693042) compares single versus double administration (4-month interval) of BM-MNC in ischemic congestive HF; the REMEDIUM

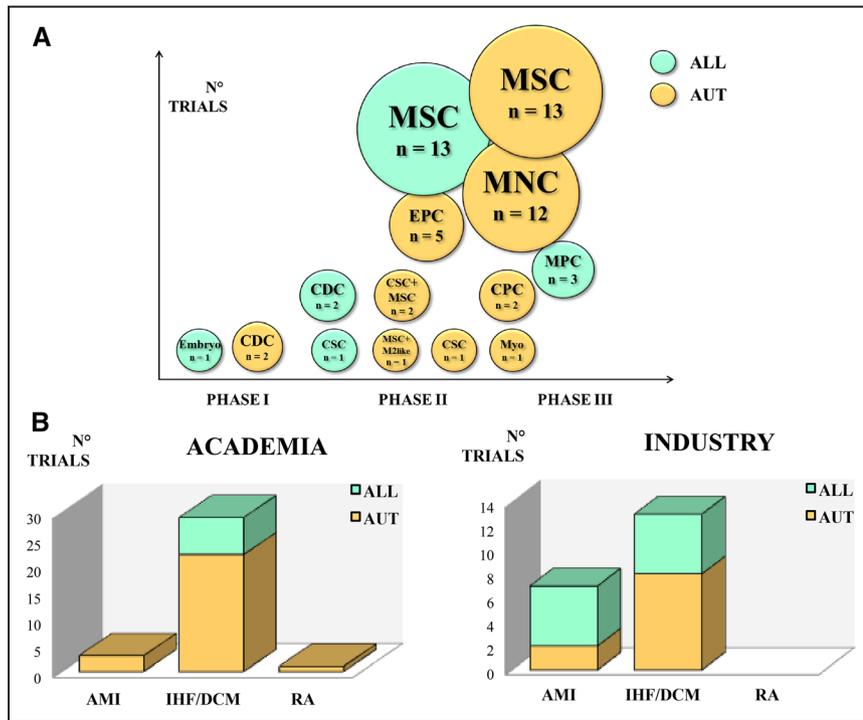


Figure. Cell types in actively enrolling trials. **A**, The figure depicts the number of registered on-going cardiac cell-based trials (clinicaltrials.gov) sorted for cell types and phase. Ongoing trials using autologous and allogeneic cell-based products are represented in yellow and pale blue, respectively. **B**, The bar graphs illustrate the proportion of registered ongoing studies using autologous and allogeneic cells for each cardiac scenario according to Academia vs Industry sponsorship. ALL indicates allogeneic cell-based products; AMI, acute myocardial infarction; AUT, autologous cell-based products; CDC, cardiosphere-derived cells; CPC, cardiopoietic stem cells; CSC, cardiac stem cells; DCM, dilated cardiomyopathy; Embryo, embryonic stem cells; EPC, endothelial progenitor cells; IHF, ischemic heart failure; MNC, mononuclear cells; MPC, mesenchymal precursor cells; MSC, mesenchymal stem cells; MSC/M2like, MSC and activated macrophages; Myo, myoblasts; and RA, refractory angina.

trial (Repetitive Intramyocardial CD34+ Cell Therapy in Dilated Cardiomyopathy; NCT02248532) tests single versus 6-month apart double intramyocardial injection of peripheral blood-CD34 cells in a context of dilated cardiomyopathy, and finally the RELIEF study (Randomized, Open Labeled, Multicentric Trial for Safety and Efficacy of Intracoronary Adult Human Mesenchymal Stem Cells Acute Myocardial Infarction; NCT01652209) evaluates single versus 2 doses of MSC intracoronary delivered at 30 and 60 days post AMI.

Among other cell types, it is worth mentioning that cardiac progenitors, such as c-kit⁺ cells or cardiosphere-derived cells, have shown in ischemic HF promising preliminary results in terms of recovery of viable myocardium and LV performance according to the published Phase I SCIPIO (Stem Cell Infusion in Patients With Ischemic Cardiomyopathy) and CADUCEUS (Cardiosphere-Derived Autologous Stem Cells to Reverse Ventricular Dysfunction) trials.^{10,11}

New Generations Come Out

As a result of the big effort in the search for potency, a new wave of enhanced cell therapeutics has more recently gained ground, having rapidly reached the clinical end point level in some cases. The common denominator of such innovative products is the search for an increased therapeutic potency in the HF context, while the dividing line is the allogeneic versus autologous formulation.

The allogeneic strategy is a novel concept in CCT that has emerged after evidence that MSC and other cell types possess immune privilege properties not requiring immunosuppression. Allogeneic cells can be then exploited as cell therapeutics and show some advantages versus autologous cell products because they are ideally derived from young healthy donors and being compatible with the readily available off-the-shelf format.¹²

Figure B depicts the proportion of active studies using allogeneic cell products by academia and industry. As predictable, allogeneic therapy seems to be highly appealing by the marketplace, possessing quality and manufacturing standards superior to the autologous formulation. It is of note that a series of industry-driven clinical end point trials with allogeneic cell products are currently in an advanced status of patient accrual. Among them, results are awaited from the DREAM-HF (A Double-Blind, Randomized, Sham-Procedure-Controlled, Parallel-Group Efficacy and Safety Study of Allogeneic Mesenchymal Precursor Cells in Patients With Chronic Heart Failure Due to Left Ventricular Systolic Dysfunction of Either Ischemic or Nonischemic Etiology; NCT02032004) and the AMICI (Allogeneic Mesenchymal Precursor Cell Infusion in Myocardial Infarction; NCT01781390) trials, which are testing BM-derived Stro-3 mesenchymal precursor cells in high-risk HF and AMI patients, respectively. Allogeneic cardiosphere-derived cells are also the object of clinical interest for ischemic and nonischemic HF treatment through the ALL-STAR (Allogeneic Heart Stem Cells to Achieve Myocardial Regeneration; NCT01458405) and DYNAMIC (Dilated Cardiomyopathy Intervention With Allogeneic Myocardially-Regenerative Cells; NCT02293603) trials. Furthermore, the investigator-driven EU-funded SCIENCE trial (Stem Cell Therapy in Ischemic Non-Treatable Cardiac Disease; NCT02673164) is actively enrolling patients with HF using adipose-derived allogeneic MSC in congestive ischemic HF. The tolerance and then practicability of repeated administrations of allogeneic cell products is, at present, unknown.

The autologous formulation has likewise produced promising innovative solutions specifically conceived to enhance the potency of cell biotherapeutics and to overcome issues related to interpatient variability and manufacturing bias. The use of in vitro treatments of stem cells with growth factors, hypoxic shock,

antiaging compounds, or genetic modifications aimed to potentiate survival, persistence, engraftment, or cell commitment may represent a further option.¹³ Toward this goal, it is worth highlighting the functional benefits reported by the C-CURE trial (Cardiopoietic Stem Cell Therapy in Heart Failure)¹⁴ in patients with ischemic HF after intramyocardial injection of lineage-specific BM-MSC-derived through cardiopoietic induction with cardioprotective factors. In addition, the final results of the phase III pivotal CHART-1 trial (Congestive Heart Failure Cardiopoietic Regenerative Therapy; NCT01768702) are expected soon. A second appealing innovative autologous approach is the combination strategy that use multicellular products. In this context, the ixCELL-DCM (Efficacy, Safety and Tolerability Study of Ixmyelocel-T Administered via Transendocardial Catheter-Based Injections to Subjects With Heart Failure Due to Ischemic Dilated Cardiomyopathy trial) clinical end point study in patients with advanced HF¹⁵ has recently published assessing the efficacy of intramyocardial injection of Ixmyelocel-T, an expanded cell product enriched for mesenchymal and macrophage lineages. Although probably not adequately powered for regulatory approval, the trial has shown for the first time in CCT an improvement of a composite primary end point of total deaths, cardiovascular admission to hospital, and outpatient visits for HF. Other studies testing different multicellular combinations are ongoing, for instance the CONCERT-HF trial (Combination of Mesenchymal and C-kit+ Cardiac Stem Cells as Regenerative Therapy for Heart Failure; NCT02501811) in which MSC/c-kit+ cardiac stem cells are currently being evaluated for functional efficacy in HF patients with ischemic pathogenesis.

Finally, it is noteworthy that CCT is breaking down the barriers of adult heart diseases. A limited number of studies are using cell therapeutics for congenital heart defects, as the academic PERSEUS trial (Cardiac Progenitor Cell Infusion to Treat Univentricular Heart Disease; NCT01829750), investigating the efficacy of intracoronary infusion of cardiosphere-derived cells in patients with univentricular heart disease.

Small Steps for a Huge Leap

The fundamental take-home message of the aforementioned scenario recalls the title of this viewpoint. A diversification of cell biotherapeutics in CCT is currently underway, mainly based on an increasing comprehension of the complex matching between mechanisms underpinning cell lineage potency and patient subpopulations at higher likelihood of benefit. This seems to be the high road to the foreseeable future that has already anticipated signals of clinical success.

The field seems, therefore, to be approaching in a stepwise fashion, a clinical maturity, even if it is hard to precisely predict its proximity to enter clinical practice. We believe that incoming findings from ongoing clinical end point trials that run to completion will be crucial not quite to provide the epochal answer to the question of which cell mends a broken heart better, rather more prosaically to advance the field toward the definition of which patients may benefit the most from a given regenerative approach.

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None.

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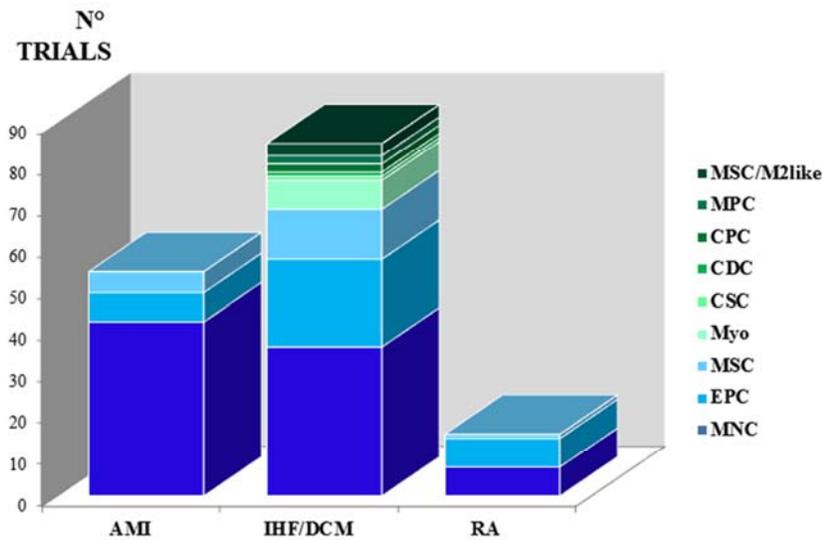
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ONLINE SUPPLEMENT



Online Figure I. Cell types in published trials of Cardiac Cell Therapy (CCT). The bar graphs indicate the number of published CCT studies (n=150) according to the clinical setting. Stacked bar graphs represent the proportion of tested cell types according to published studies. The vertical order of cell types reflects the development of cell-based therapy from the first to the third cell generation. AMI indicates acute myocardial infarction; IHF, ischemic heart failure; DCM, dilated cardiomyopathy; RA, refractory angina; MNC, mononuclear cells; EPC, endothelial progenitor cells; MSC, mesenchymal stem cells; Myo, myoblasts; CSC, cardiac stem cells; CDC, cardiosphere-derived cells; CPC, cardiopoietic stem cells; MPC, mesenchymal precursor cells; MSC/M2like, MSC and activated macrophages.