Stem Cell in the Rough

Repair Quotient Mined Out of a Bone Marrow Niche

Atta Behfar, Andre Terzic

Regenerative medicine aims to repair, replace, or restore diseased, damaged, or missing tissues. Cardiovascular indications account for over a quarter of all cell-based regenerative medicine products currently in development. Indeed, during the past decade, translation of stem cell technology has been increasingly realized, formulating an emergent body of clinical trial experience that defines the prospect of cardiovascular regenerative medicine.

In the setting of ischemic heart disease, regenerative approaches are deployed as protective and restorative strategies, designed to complement standard-of-care algorithms. Early postinfarction, the aim of cell-based interventions is to limit the extent of damage and prevent organ failure by altering the myocardial response to injury. In advanced heart failure, the goal of regenerative therapy becomes restorative in nature, aimed at re-establishing normative function and structure through direct cell-mediated or indirect paracrine-mediated repair mechanisms. Tested in phase I and phase II trials, within diverse patient populations and across healthcare systems, clinical-grade stem cell platforms demonstrate encouraging feasibility and safety profiles.

Experience to date has helped establish scalable standard operating procedures for isolation, expansion, and formulation of cell-based biotherapeutics intended to complement standard-of-care algorithms. Early phase III trials by the CCTRN, namely TIME, Late-TIME and FOCUS, were network-implemented across the United States as randomized, multicenter evaluations of bone marrow–derived mononuclear cell therapy. TIME and Late-TIME assessed regeneration of left ventricular function after acute myocardial infarction. In these trials, MRI follow-up revealed that intracoronary delivery of autologous bone marrow–derived mononuclear cells had no effect on left ventricular function compared with placebo-treated cohorts. Also, there was no significant difference between an earlier versus a later timing of intervention. The FOCUS trial evaluated the influence of autologous bone marrow–derived mononuclear cells on patients with symptomatic heart failure and reported no clinical benefit derived from intramyocardial delivery. In consideration of more favorable outcomes reported in European trials predating the CCTRN effort, the present analysis was undertaken to evaluate whether the material content of bone marrow mononuclear cells may underpin disparate results.

To this end, flow-cytometry and colony assays mined for regenerative propensity within heterogeneous mixtures of bone marrow cellular compartments. Bone marrows exhibiting increased CD34+ and decreased CD11b+ cell content were found to confer an ejection fraction benefit both in the setting of acute and chronic left ventricular dysfunction. The clinical use of this subpopulation is independently supported by separate trials with CD34+ cells delivered in purified form, as CD34+-based therapy has been shown to yield signals of improvement in refractory angina and in ischemic cardiomyopathy. Collectively these results point to the importance of particular stem cell niches within the bone marrow that are associated with the capability to direct cell repair behavior, serving thereby as putative predictors of myocardial restoration.

Of note, individual patients within CCTRN cohorts that harbored a proropeartative niche were exceptionally rare, at an incidence not exceeding 5% in studied populations experiencing myocardial infarction or heart failure (Figure). This finding is in line with previous studies establishing a low
incidence of patients with ischemic heart disease whose bone marrow progenitors exhibit a measurable cardioregenerative aptitude. Characterization of these rare reparative stem cell populations, within the bone marrow niche or in isolation, would inform the selection, or alternatively the induction, of progenitor population empowered to repair the failing heart (Figure). An opportunity to boost stem cell function is through targeting of the cellular microenvironment. In this context, lineage-specific stem cells derived through cardiopoietic induction embody the translation of such principle, achieving improved therapeutic effect beyond that attained with lineage-unspecific cell sources (Figure). Specifically, cardiopoietic stem cell technology uses purified stem cell populations from the patient’s bone marrow and imposes a guiding step to yield a reparative phenotype. This conditioning step, consisting of exposure to cardiotrophic factors mimicking natural cardiogenic cues, introduces a means to incorporate patients benefiting from cell therapy—beyond only rare subsets—to the general heart failure population, an optimizing strategy currently tested in advanced clinical trials (Figure). To this end, scalable standard operating procedures have been developed to generate a cell phenotype consistently that meets release criteria metrics set to ensure repair. Endowed with enhanced healing aptitude, next-generation stem cell products thus harness the growing understanding of critical determinants defining regenerative potency. Translating new knowledge into delivery of science-supported regenerative protocols is ultimately predicated on deployment of cost-effective algorithms to address the unmet needs of patients and populations.

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References

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