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Editorial

Paracrine Heart Repair Comes of Age

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See article by Marvasti et al., pages 1311–1321 of this issue.

For almost 20 years, cell therapy has been touted as a natural solution to replace heart muscle lost at the time of myocardial infarction.[1-3] But recent scandals[4] and failed clinical trials[5] have done little to inspire confidence in a jaded medical community. Although a portion of the blame lies in the early hype and hyperbole raising unrealistic expectations, some of the initial mechanisms that assumed how transplanted cells would modify heart function have proved to be spectacularly wrong and prompted many to consider new directions to restore injured tissue.

Initially, cell therapy was considered as a tissue replacement strategy.[3] Skeletal muscle progenitors were one of the first cell products injected and had several early successes in small studies.[6,7] These hardy cells formed contractile islands of skeletal tissue between myocytes. But these gains came at a price. Electrically uncoupled skeletal muscle provided the ideal substrate for wavelet re-entry and resulted in many patients experiencing serious ventricular arrhythmias after cell treatment.[8] Despite efforts to overcome the electrical isolation of skeletal myoblasts, equivocal clinical benefits[9] and ongoing concerns related to serious proarrhythmia[10] arrested any progress toward clinical implementation. Embryonic stem cells have since become the unfortunate heirs of the skeletal myoblast legacy. Despite promising early studies in several small animal models,[11-15] proof of concept work in nonhuman primates has shown the electrical immaturity of transplanted embryonic or partially differentiated cells increases ventricular pro-arrhythmia as cells engraft within the larger hearts.[16] It is hoped that this problem can be corrected by re-engineering, but, at present, the prospect of post-transplant arrhythmias threatens to derail therapies directed toward replacement of lost heart tissue with primitive cardiomyocytes. Reflecting on the overall strategy, it occurs that the myoblast and embryonic cell solutions are not so very different from a surgical cut to cure mindset, as this strategy dogmatically states transplanted cells must engraft to replace lost tissue.

As outlined in this issue of the *Canadian Journal of Cardiology*,[17] more nuanced means of restoring cardiac function that are not reliant on the straightforward replacement of lost tissue by transplanted cells have since emerged. In their review, Marvasti et al. outline the evidence supporting the ability of CD34+ hematopoietic cells to promote new vessel growth within ischemic tissue. Although the function of the CD34 protein has yet to be "definitively ascertained,"[17] it appears to play an important role in the migration and proliferation of many cells while serving as a reliable indicator of proangiogenic potency. Preclinical studies have shown that intramyocardial injection of CD34+ cells improves heart function after injury and, although such studies are rare, CD34+ cells appear to be superior to other hematological progenitor cells. Of note, these salutary effects are not mechanistically linked to engraftment, differentiation, and creation of new blood vessels to ischemic territory by transplanted cells. Rather, transplanted cells are ephemeral, and few persist in treated tissue beyond a few days. During that short residency, CD34+ cells secrete cytokines and extracellular vesicles that stimulate endogenous cells to proliferate and increase blood vessel density within treated areas. Conceptually, this realization was one of the first to identify critical anomalies with the engraft and function cell treatment paradigm. Long-term engraftment and differentiation of any transplanted cell into working tissue is now recognized to be a rare event and has led to a growing consensus that all therapeutically potent cells work through paracrine secretion of cytokines and extracellular vesicles that stimulate endogenous growth of new tissue and the salvage of reversibly injured tissue.[18] A key tenet within this paradigm lies in the observation that transient retention of transplanted cells is enough to promote repair of injured tissue and long term engraftment of transplanted cells is not required.

Marvasti and colleagues also outline several of the important differences between murine and human CD34+ cells that include differences in transcriptional control and cell function. These differences may have important implications on the mechanisms underlying CD34+ cell-based repair. It follows that understanding these mechanisms may open avenues to improve the efficacy or potency of cell therapy.

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However, work remains to identify which differences in the paracrine signature of transplanted cells are important. Techniques such as humanized mouse models (ie, human CD34+ cells endogenously expressed within mice) will shed insights into how human cells interact with injured tissue and may help to identify which combination of the 20,000 molecules contained within secreted extracellular vesicles are needed to provide maximal benefit.[19]

Finally, the authors readily acknowledge that translational studies of preclinical work are a gamble, albeit an educated bet. What may work in young disease-free models with surgical injuries, using healthy young donor cells, may not necessarily work using cells from aged human donors with medical comorbidities injected back into aged recipients. Exploring the impact of real-life conditioned cells in models of disease or advanced aging may help identify caveats and opportunities before clinical translation. However, even if all the biological influences are considered, the design of clinical trials may adversely affect study findings. Market pressures often force clinical trials to deliver defined cell products into the widest patient group possible, using the widest available technique. As highlighted by the authors, these concessions may not individually affect the cell product efficacy but do have a cumulative influence. Cell preparation before injection provides a ready example. Many of the major cardiovascular cell therapy trials removed cells from cryogenic (−80°C [−112°F]) storage, briskly warmed the cells and then diluted with saline to limit the amount of cryopreservative injected.[20,21] Although this approach makes cell delivery easier, cell recovery and function are obviously not optimal after forced rewarming. Injection of cryopreservatives down disease coronaries may also have inadvertent effects that are not necessarily well understood. As suggested, modelling real-life cell delivery before clinical implementation may help to explain why the findings from a well-designed preclinical study fail after translation to the bedside.

The authors proffer the Efficacy and Safety of Targeted Intramyocardial Delivery of Auto CD34+ Stem Cells for Improving Exercise Capacity in Subjects With Refractory Angina (RENEW) trial as an example of the impact that translational challenges have on cell treatment effects, which may not be strictly accurate. The RENEW trial was a phase 3 trial of autologous (self to self) blood-derived CD34+ cells injected into the myocardium of patients with severe chronic angina.[22] These are patients without conventional revascularization options who continue to live with chronic (often severe) angina and repeated admissions for anginal episodes. In this instance, a therapy that stimulates the growth of new blood vessels to provide endogenous revascularization would be very well received. The trial was terminated after enrollment of 112 of the 444 planned patients but still showed CD34+ cell therapy had a very promising trend to improvement in the primary outcome (total exercise time) and angina frequency when compared with placebo. Although the RENEW trial represents the clinical translation of CD34+ cells, the decision to terminate the trial was based on the strategic business priorities of the sponsor and does not appear to reflect delivery of an attenuated or futile cell product.

As such, the future of blood-derived CD34+ cells in the treatment of ischemic disease appears promising and, based on the evidence to date, warrants investment. Fundamental work is still needed to optimize the potential of this readily available cell source. This therapeutic focus reflects trends in the field of cardiovascular cell therapy, which is increasingly adopting new paracrine-based paradigms rather than cell replacement strategies that have yet to show durable safe outcomes. Ultimately, there may soon be a time when Canadians can visit Canadian hospitals to receive biological products that promote the growth of new endogenous heart tissue rather than removing offending tissue or palliating with drugs and mechanical devices.

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