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MY APPROACH

# MY APPROACH to stem cell therapy for heart failure patients: Not all cells are created equally ☆

*Eugenio Cingolani, MD*

Heart failure (HF) is a clinical syndrome characterized by the inability of the heart to satisfy the metabolic demands of the body. HF can be divided into heart failure with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF). Most of the advances in the treatment of HF have been in HFrEF; little is known about the mechanism of HFpEF, and no therapeutic trial has shown reductions of mortality or morbidity in HFpEF patients.

Cardiac regenerative therapies using different cell types have been developed from the preclinical stages and advanced to clinical trials primarily in patients with ischemic cardiomyopathy. The goal here is simple: to reduce scar size (in those patients with previous myocardial infarction) and generate new myocardium, with the consequent improvement in cardiac function, functional capacity, and quality of life, and (hopefully) to prolong survival. Although initial studies focused on cell engraftment and differentiation into working myocytes, the current paradigm represents a shift toward factors secreted from the cells leading to anti-fibrotic and anti-inflammatory effects, and perhaps regenerative capacity.

Regarding the different cell types, it is important to remember the lessons learned from Skeletal Myoblasts (SkMs): Safety First! Although the preclinical data looked promising, clinical studies demonstrated a pro-arrhythmic effect, likely related to the inability to electrically couple to the surrounding myocardium due to the low levels of expression of the main ventricular gap junction (connexin 43). Of the other cell types, embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) have the potential of tumor formation (ESCs), and, in the case of iPSCs, generation of cells of different stages of differentiation with the potential for creating a heterogeneous substrate, which can be prone to arrhythmogenesis. Indeed, pluripotent cell-derived cardiomyocytes, when injected into primates, have shown troubling safety signals in terms of ventricular tachycardia post transplantation.

Among the different cell types that have been tested in clinical trials, the most data are available with cardiosphere-derived cells (CDCs) and mesenchymal stem cells (MSCs). Autologous CDCs have been tested in post-myocardial infarction patients (CADUCEUS trial) and in hypoplastic left heart syndrome (TICAP and PERSEUS trials), whereas allogeneic (unrelated donor) CDCs have been tested in patients with ischemic cardiomyopathy (ALLSTAR trial), patients with genetic cardiomyopathy (HOPE-Duchenne), and in patients with HFpEF (Regress-HFpEF trial [ongoing]). These cells have been characterized extensively at a preclinical level in more than 50 independent labs around the world. In general, CDCs have proven to be safe to date and have shown various signals of therapeutic efficacy clinically. Regarding MSCs, multiple studies (with different designs using both autologous and allogeneic cells) have addressed different populations, with mixed results, but again with consistent safety when administered to patients with HF.

The field of cell therapy has been soiled recently by revelations of extensive scientific fraud by Piero Anversa and coworkers dating back at least 15 years, prompting numerous retractions from prestigious journals (including The New England Journal of Medicine). Anversa had promulgated the concept, now discredited, that heart cells selected for the c-Kit antigen were true cardiac stem cells. The consequences of this scandal include the recent decision by NIH to pause the CONCERT-HF trial, which was studying c-Kit-positive heart cells (with or without concomitant MSCs) in patients with ischemic cardiomyopathy. The disgrace surrounding c-Kit-positive cells, however, should not be generalized to other cell types such as CDCs and MSCs, where evidence of efficacy is broad-based, and mechanistic insights are extensive…and point convincingly toward paracrine factors as being central.

Regardless, not a single cell type has been approved by the FDA for the treatment of any form of heart disease. Key to forward momentum will be solid, reproducible, hypothesis-driven proof-of concept and preclinical studies. Additionally, it would be important when designing clinical trials (with different cell types) to have strict requirements such as homogeneity of the population, proper controls, and hard endpoints, just to name a few. The future will only tell which cell type (if any) may win this race. For now, as always in science, solid basic science foundations are fundamental to continue to advance this exciting field.

Eugenio Cingolani, MD
*Assistant Professor of Medicine, Director, Cardiogenetics-Familial Arrhythmia Program, Division of Cardiology, Electrophysiology Section, Cedars Sinai Heart Institute, Los Angeles, California*

*E-mail address:* eugenio.cingolani@csmc.edu

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