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Commentary: Neonatal applications of cardiac cell therapy: It's good to be young!

Christopher T. Ryan, MD, and Todd K. Rosengart, MD

The decades-long march to harness the regenerative properties of stem cells for the purposes of myocardial regeneration has been frustrating, with recent meta-analyses and expert consensus reports questioning the efficacy of these efforts and the validity of purported underlying mechanisms of action.^{1,2} Sano and colleagues³ summarize these and other recent reports and propose that the answer to this challenge may be found by turning to youth. Specifically, cardiac progenitor cells and cardiosphere-derived cells harvested from neonatal hearts may offer greater regenerative therapeutic benefit compared with use of adult cells. This potency is ascribed to a higher prevalence of these cells in juvenile heart tissue, their improved proliferative and differentiation potential, and their increased secretion of paracrine mediators with regenerative properties.

One intriguing implication of this observation is that neonatal patients with congenital heart disease may derive greater benefit from cell therapy compared with adult patients. Patients with complex congenital heart disease typically undergo multiple operations in a relatively short period, providing an ideal opportunity for harvesting and administering autogenous pluripotent cells. More importantly, cell therapy can be administered to these individuals before myocardial damage occurs and thereby delay or prevent the development of heart failure, a near-universal

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Neonatal hearts possess progenitor cell populations that may have regenerative properties greater than that demonstrated by corresponding adult cell populations.

outcome after the performance of palliative procedures for congenital heart disease.⁴ Although heart failure in this population is multifactorial, a key underlying mechanism is insufficient adaption of myocardium to combined pressure and volume overload, leading to progressive cardiac dilation, fibrosis, and contractile failure.⁵ Cell therapy at the time of palliation may reduce this damage by promoting physiological adaption. This preventive therapeutic role contrasts starkly with cell therapy applications in adult ischemic heart disease, where cellular implantation has typically been applied as a rescue rather than preventative therapy.

Although findings for cardiac cell therapy in the pediatric population are encouraging, it would be imprudent to ignore hard-won lessons from the past 2 decades of preclinical and clinical investigations in adult patients. Short-term improvements in surrogate outcome measures in early, underpowered trials were embraced with unrealistic exuberance in these adult studies. The resulting enthusiasm prompted a flood of subsequent trials despite a limited understanding of critical potential success factors, including definition of an optimal target patient population, cell type, dosing, route of administration, or even a strong base of knowledge of underlying mechanisms of action. This lack of understanding allowed for inappropriate application of cell implantation, including, in retrospect, its illogical administration to large areas of ischemic chronic infarction with the goal of generating functional muscle.^{6,7}

Whereas extensive basic and translational research is ongoing to fill persistent knowledge gaps in the utility of cell therapy, only a small portion of this work is directed toward examination of its use in congenital heart disease. This is particularly true for analysis of the effects of progenitor

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Dr Ryan is supported by the National Institutes of Health/National Heart, Lung, and Blood Institute Research Training Program in Cardiovascular Surgery (grant No. T32 HL139430). Dr Rosengart is supported by a grant from the National Institutes of Health/National Heart, Lung, and Blood Institute (grant No. 1R01HL152280-01).

Disclosures: Dr Rosengart reported Xylocor Therapeutics: board member, consultant; significant equity interest; and Cornell University: intellectual property royalty payments. The other author reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication Sept 24, 2020; revisions received Sept 24, 2020; accepted for publication Sept 25, 2020; available ahead of print Oct 7, 2020.

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J Thorac Cardiovasc Surg 2022;163:248-9

0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2020.09.107>

cell administration to young patients with systemic right ventricle pathology or pronounced abnormalities in structure, cellular composition, and functional responses to hemodynamic perturbations.^{5,8}

To avoid the mistakes of premature cell therapy trials in adult patients, proponents of pediatric cell therapy should ideally perform rigorous optimization of cell therapy in preclinical models of congenital heart disease. The resulting base of knowledge will provide the best opportunity for success in future clinical trials, preferably with adequately sized study populations and appropriate randomized, blinded trial design.

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Commentary: Defining the role of stem cell therapy in neonatal cardiac regeneration

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Over the past several years, preclinical and clinical studies about the potential cardiac application of stem cell therapy have been conducted extensively, primarily in adult ischemic heart disease.^{1,2} More recently, this potential therapeutic option has gained attention in the world of congenital heart disease. This has been due, in part, to the discovery that neonatal myocardium retains greater regenerative potential than adult heart tissue.^{3,4} Moreover, despite excellent surgical results in complex single-ventricle patients, we

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Neonates have a higher cardiac regenerative potential when compared with adults, but much is yet to be learned regarding stem cell therapy in congenital heart disease.

have come to realize that it will take additional therapies to improve the long-term cardiac outlook for these children. Several cell types from many sources utilizing various delivery techniques are currently being investigated in multiple cardiac pathologies across the spectrum of patient age groups. Patients with single-ventricle physiology are deemed more suitable to study this potential treatment due to limited conventional options for treatment of their heart failure. It is important for cardiac care providers to

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Disclosures: The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Received for publication Sept 2, 2020; revisions received Sept 2, 2020; accepted for publication Sept 3, 2020; available ahead of print Sept 10, 2020.

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J Thorac Cardiovasc Surg 2022;163:249-50
0022-5223/\$36.00

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<https://doi.org/10.1016/j.jtcvs.2020.09.013>