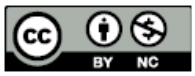
THE TEXAS HEART INSTITUTE® JOURNAL

*International Symposium on Cardiovascular Regenerative Medicine*

# Science Is a Self-Correcting Discipline: Revisiting the Biological Potential of Adult Cardiac Progenitors

Daniele Torella, MD, PhD[1]; Eleonora Cianflone, PhD[2]

[1]Department of Experimental and Clinical Medicine, Magna Graecia University, Catanzaro, Italy
[2]Department of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy



**Keywords:** Adult stem cells; cardiac remodeling, atrial; cardiac remodeling, ventricular; myocytes, cardiac; regeneration

## Introduction

Adult heart regeneration is currently an active and controversial area of biomedical research, representing a relatively new field within cardiac biology.[1] Given the widespread occurrence and poor outlook of heart failure,[1] the potential impact of successful strategies for regenerating the human heart cannot be underestimated. The biology underlying the regenerative process of the heart is highly complex, however, and the existence of compelling data demonstrating effective heart regeneration has generated fascination, contentious debate, and scientific scandal.[1] Although myocardial regeneration involves the replenishment of various cell types, such as cardiomyocytes, vasculature, lymphatics, conduction system cells, and the interstitium, its primary focus is on replenishing and renewing cardiomyocytes.[1] The mammalian heart was long believed to be a postmitotic organ incapable of self-renewal because of the terminal differentiation of its primary cell type, the cardiomyocyte, which permanently exits the cell cycle and lacks efficient reentry into it under normal physiologic and pathologic stimuli. This conventional belief supported the notion that the heart consists of a fixed number of cardiomyocytes established at birth and maintained until the organ's demise.[2] Recent discoveries, however, have revolutionized cardiac biology by demonstrating the ongoing formation of cardiomyocytes throughout life.[3] These findings include evidence of small, mononucleated cardiomyocytes undergoing division[3] and the existence of tissue-specific multipotent adult cardiac stem (ie, progenitor) cells (CSCs) with robust potential to differentiate into cardiac muscle and vascular cells within the adult heart.[4-7]

## The Controversy

Initially, these findings appeared to align logically, suggesting that, similar to other tissues in the body, the resident CSCs are activated in response to wear and tear or tissue damage, differentiating into immature, small, mononucleated cardiomyocytes capable of limited rounds of division, similar to neonatal cardiomyocytes, before undergoing terminal differentiation.[2] A few Cre-lox (and other, similar site-specific recombinase systems) cell fate mapping studies failed to show a significant contribution of CSCs to new cardiomyocyte formation during development, in adulthood, or after injury, suggesting that new cardiomyocytes are instead the product of preexisting terminally differentiated cardiomyocytes duplicating themselves.[8] This alternate view challenges the well-established evidence that adult mammalian cardiomyocytes, unlike contractile cardiac cells in lower vertebrates, cease dividing relatively early after birth. This finding has led researchers to propose the existence of a yet-undefined and scarce population

**Citation:** Torella D, Cianflone E. Science is a self-correcting discipline: revisiting the biological potential of adult cardiac progenitors. *Tex Heart Inst J*. 2023;50(5):e238241. doi:10.14503/THIJ-23-8241
**Corresponding author:** Daniele Torella, MD, PhD, Department of Experimental and Clinical Medicine, Magna Graecia University, Viale Europa. Loc. Germaneto, Campus "S. Venuta," 88100, Catanzaro, Italy (dtorella@unicz.it)

of hypoxic cardiomyocytes capable of slow, continuous turnover.[3] Resolving this biological puzzle is crucial to developing effective myocardial regeneration protocols in clinical settings.

## The Exogenous vs Endogenous Approach to Myocardial Regeneration

The ongoing controversy regarding the real cell identity to be targeted for effective cardiac regeneration has polarized the potential approaches into the exogenous and the endogenous, reflecting the 2 distinct perspectives on the regenerative biology of the adult myocardium. The exogenous approach is based on the belief that the adult myocardium is exceptional relative to other tissue types in that it lacks physiologically relevant, tissue-specific CSCs with the potential to generate new cardiomyocytes beyond the early postnatal period.[8] Therefore, the exogenous approach relies on transplanted external sources—either pluripotent stem cells or their derivatives (ie, cardiac progenitors or cardiomyocytes, reprogramming factors)—to achieve cardiomyocyte formation.[2] In contrast, the endogenous approach considers the heart a slowly regenerative organ that harbors dormant, tissue-specific CSCs that require proper activation to generate cardiomyocytes in sufficient number to repair or regenerate damaged myocardium.[2,9-10] Again, the endogenous approach has expanded to include the notion that adult terminally differentiated cardiomyocytes unexpectedly maintain a limited but targetable proliferative capacity. Despite having an endogenous cellular target for regeneration (the cardiomyocytes), however, this view aligns primarily with the exogenous perspective on the heart's biology, which is that it lacks a pool of tissue-specific CSCs. These 2 distinct approaches, though based on differing concepts of myocardial cell biology, are not mutually exclusive in practical terms and can in fact be complementary. Myocardial repair and regeneration protocols could be designed by stimulating endogenous CSCs and complementing them with the transplantation of exogenous CSCs or vice versa.[2]

### Abbreviations and Acronyms

CSC cardiac stem cell

## Conclusions

Unfortunately, these contrasting concepts of the adult myocardium and their corresponding approaches to myocardial repair have evolved along a competitive path, with their respective promises pitted against each other, thereby obscuring the scientific foundations of adult cardiac cell biology. Science is, however—luckily—a discipline that corrects itself over time. As controversies and misinformation are addressed, facts ultimately prevail. The undisputed data currently at hand clearly demonstrate the reality and the regenerative potential of CSCs in mitigating the growing epidemic of heart failure. Addressing the existing confusion and challenges in the field of myocardial regeneration—and of CSC biology in particular—will necessitate taking a step back to rebuild a stronger scientific foundation before the science can progress.

## Article Information

**Published:** 20 October 2023



**Author Contributions:** D.T. and E.C. were both involved in the conceptualization, original draft preparation, review, and editing of the manuscript. The authors have read and agreed to the published version of the manuscript.

**Conflict of Interest Disclosure:** None.

**Funding/Support:** This work was supported by grants from the Italian Ministry of University and Research (PRIN No. 2017NKB2N4_005; PRIN No. 20203YAYGB_005; PRIN No. 2020L45ZWA_005, PON-AIM No. 1829805-2; PNRR—National Center for Gene Therapy and Drugs based on RNA Technology No. CN00000041) and from the Italian Ministry of Health (POS4 "Cal-Hub-Ria" No. T4-AN-09).

**Section Editor:** Emerson Perin, MD, PhD.

**Meeting Presentation:** Presented at the 3rd Annual International Symposium on Cardiovascular Regenerative Medicine; May 12-13, 2023; Houston, TX.

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