

Reparative cell therapy for the heart: critical internal appraisal of the field in response to recent controversies

Thomas J. Povsic¹, Ricardo Sanz-Ruiz², Andreu M. Climent², Roberto Bolli³, Doris A. Taylor⁴, Bernard J. Gersh⁵, Philippe Menasché⁶, Emerson C. Perin⁷, Giulio Pompilio⁸, Douwe E. Atsma⁹, Lina Badimon¹⁰, Anthony N. DeMaria¹¹, Joshua M. Hare¹², Timothy D. Henry¹³, Stefan Janssens¹⁴, Jens Kastrup¹⁵, Daniele Torella¹⁶, Jay H. Traverse¹⁷, James T. Willerson⁷ and Francisco Fernández-Avilés^{2*}

¹Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, USA; ²Department of Cardiology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Complutense, CIBERCV, Madrid, Spain; ³Department of Medicine, School of Medicine, University of Louisville, Louisville, KY, USA; ⁴Center for Cell and Organ Biotechnology, Texas Heart Institute, Houston, TX, USA; ⁵Department of Cardiovascular Medicine, Mayo Clinic College of Medicine, Rochester, MN, USA; ⁶Department of Cardiovascular Surgery, Georges Pompidou European Hospital, Paris, France; ⁷Center for Clinical Research, Texas Heart Institute, Houston, TX, USA; ⁸Vascular Biology and Regenerative Medicine Unit and Dept. of Cardiovascular Surgery, Centro Cardiologico Monzino IRCCS, Milan, Italy; ⁹Faculteit der Sociale Wetenschappen, Instituut Psychologie, Gezondheids, Medische-Neuropsychologie, Leiden, The Netherlands; ¹⁰Cardiovascular Program (ICCC), IR Hospital de la Santa Creu i Sant Pau, CIBERCV, Barcelona, Spain; ¹¹Sulpizio Cardiovascular Center, UC San Diego Health, San Diego, CA, USA; ¹²Interdisciplinary Stem Cell Institute and Division of Cardiology, Leonard M. Miller School of Medicine, University of Miami, Miami, FL, USA; ¹³The Carl and Edyth Lindner Center for Research and Education, The Christ Hospital, Cincinnati, OH, USA; ¹⁴Centre for Molecular and Vascular Biology, Department of Cardiovascular Sciences, KU Leuven, Leuven, Belgium; ¹⁵Department of Cardiology, Centre for Cardiac, Vascular, Pulmonary and Infectious Diseases, Rigshospitalet, Copenhagen, Denmark; ¹⁶Molecular and Cellular Cardiology LAB, Department of Experimental and Clinical Medicine, Magna Graecia University, Catanzaro, Italy; and ¹⁷Minneapolis Heart Institute Foundation, Abbott Northwestern Hospital, Minneapolis, MN, USA

Abstract

The concept that cell-based repair of myocardial injury might be possible was introduced almost two decades ago; however, the field of cardiovascular reparative medicine has been criticized as translation to clinically effective approaches has been slow. The recent retraction of a series of papers has further impacted perception of this area of research. As researchers, clinicians, and teachers in this field, we felt it incumbent to critically appraise the current state of cardiac cell repair, determine what can be learned from past mistakes, and formulate best practices for future work. This special communication summarizes an introspective assessment of what has fallen short, how to prevent similar issues, and how the field might best move forward in the service of science and patients.

Keywords Reparative cell therapy; Myocardial repair and regeneration; Stem cell therapy

Received: 29 December 2020; Accepted: 25 January 2021

*Correspondence to: Francisco Fernández-Avilés, Department of Cardiology, Hospital General Universitario Gregorio Marañón, Instituto de Investigación Sanitaria Gregorio Marañón, Universidad Complutense, CIBERCV, Madrid, Spain. Phone: +34 91 4265882; Fax: +34 91 586 8276. Email: faviles@secardiologia.es

Introduction

Research on myocardial repair and regeneration has substantially contributed to a better understanding of cardiomyocyte biology¹; however, cardiovascular reparative medicine has been criticized in part due to modest effects in clinical trials and the perception that translation to clinically effective approaches has been slow.² The field has been further affected by requests for or retractions of papers by former leaders.³ As researchers, clinicians, and teachers, we felt it

incumbent to critically appraise the field and formulate best practices for future work.

Light and shadows in the field

For almost half a century, stem cell therapy for haematopoietic diseases has been a reality. The concept that cell-based repair of damaged heart muscle might be possible was introduced almost two decades ago.⁴ Initially, the

assumption was that extracardiac cells could engraft, mediate repair, and potentially replace injured tissue. Two decades later, we now have a better understanding of the molecular and cellular mechanisms that govern cardiovascular response to injury; however, clinical studies have produced conflicting results.² While studies of bone marrow mononuclear cells in patients with acute infarction have not demonstrated consistent clinical benefit, studies with mesenchymal cells in chronic heart failure^{5,6} and CD34+ cells in refractory angina⁷ are more encouraging. Today, thanks to growing awareness that cells may act indirectly to promote endogenous repair, novel and exciting cell-based products are being developed. The discovery that adult cells can be reprogrammed to form induced pluripotent stem cells (iPSCs) has opened the possibility to 'build' human tissues. Engineered cardiac tissues, cell-derived products (e.g. extracellular vesicles and mitochondria), and (genetically) reprogrammed cells represent the forefront of current cardiac regenerative approaches.

Recently, we were shaken by the news that many papers from a leading laboratory in the field were retracted.³ Misbehaviour and fraud have occurred both inside and outside the cell therapy arena.⁸ While these acts of misconduct impact the perception of the entire field, these events should not unfairly taint the research conducted by the overwhelming majority of rigorous, principled investigators. Independent scientists, sceptical about claims of cardiac regeneration, performed and published experiments with contradictory results and were openly critical of now proven flawed, preclinical experiments.⁹ In parallel, multiple investigators questioned the concept of regeneration and published data demonstrating improvements in cardiac function despite limited or no direct regeneration.¹⁰

Recent criticisms, revisiting the field

Recently, the field has been beset by critical editorials and opinion pieces denouncing the National Institutes of Health for wasted funding and calling for a cessation of clinical work in favour of mechanistic and preclinical development of 'more promising' approaches.^{11,12} These opinion pieces, some of which were not openly authored,¹¹ decry the field for changing its understanding of the mechanisms of cellular reparative therapies (specifically, the shift from a cardiomyogenic to a 'paracrine' mechanism of action),² the lost opportunities for funding basic research at the expense of clinical funding, and the risk to patients in clinical trials of cell therapies. These claims require a response.

Cardiovascular cell therapies entered into clinical trials with positive preclinical data supporting safety and a potential for efficacy from *in vitro*, small animal, and large animal studies. Regulators would not allow otherwise. Clinical trials required evaluation and approval, based on preclinical data,

by the US Food and Drug Administration, the European Medicines Agency, and local regulatory bodies. We underscore the necessity for rigorous evaluation of potential therapeutics in appropriate preclinical, preferably large animal, models utilizing rigorous experimental and statistical methodologies. The need for better preclinical models is not new and has long been felt to contribute to the immense attrition of therapies that appear promising but fail to lead to clinical benefit.

It is easy to retrospectively criticize decisions to fund research that did not lead to immediately positive clinical results. This speaks not to poorly conducted preclinical or early clinical research, but to the difficulty in gleaning an understanding of efficacy in humans with variable genetic and epigenetic backgrounds, exposures, and broadly phenotyped disease states when utilizing preclinical models of syngeneic, young, healthy non-medicated animals. These limitations have plagued the development of therapies for various conditions, including heart failure with preserved ejection fraction and ischaemia–reperfusion injury, despite billions of dollars of research. Even with these past disappointments, clinical need continues to drive research in these fields. While conclusive evidence of clinical efficacy cannot be expected from phase I–II studies, the experience in thousands of patients shows no evidence of significant risk with the therapies studied to date, and some meta-analyses suggested a lowering of mortality or cardiovascular risk.^{2,7,13}

The idea of regeneration captures the imagination in ways that other therapies simply do not. This has led to hope but also to hype—by scientists who overestimated the potential and by purveyors of 'cures' who choose to sell unproven therapies in minimally regulated environments.¹⁴ This aspect of biological therapies can lead to untoward consequences. Patients lacking treatment options actively seek such therapies, often in unsafe and unregulated settings. The 'hype' raises unrealistic expectations among the public and investigators, enhancing the placebo effect in clinical trials and leading to greater disappointment when expectations are not met. The lofty goal of myocardial regeneration leads to criticism when this is not achieved, yet the goals of therapy for ST-elevation myocardial infarction, heart failure, refractory angina, or peripheral artery disease differ. While the ability to directly regenerate new myocardium remains elusive, the ability to improve myocardial perfusion and/or to modulate immune-inflammatory responses to injury is supported.

Steps forward

As scientists, clinicians, educators, and recipients of public funds beholden to the public trust, we recommit to ensuring that the field proceeds on pathways most likely to be beneficial. The intuitive concept of reparative therapies

results in far greater scrutiny, increasing our obligation to conduct well-conceived and executed preclinical and clinical studies.

We note that almost half a century passed between the identification of specific therapeutic targets (e.g. intracoronary thrombus) and the development of effective clinical therapies from these discoveries. History teaches that development of novel therapies takes time. While initial preclinical experiments fostered the hypothesis that adult stem cells might regenerate mature cardiac tissue, this now appears to be wishful thinking. Perhaps the most important advance has been the recognition that exogenous cells might improve cardiac function without significant engraftment or differentiation into adult cardiomyocytes. Our improved understanding of the mechanisms of cell therapies should not be decried but recognized as an advancement that may lead to new approaches. Revisiting working hypotheses in light of new evidence is the essence of scientific inquiry. Work with iPSCs and tissue engineering holds the promise of true 'tissue replacement', while new mechanisms of cardiac regeneration (e.g. release of cell cycle checkpoints) and modulation of the inflammasome in the heart are now being increasingly evaluated.² We see the following as key steps forward:

- 1 Open dialogue, debate, and questioning results are to be encouraged. Scientists should acknowledge that adult 'stem cell' formulations, to date, do not directly lead to cardiomyocyte regeneration in the human heart.
- 2 Enthusiasm was genuine, but at times excessive, leading to hasty translation of basic research. We should boost greater interaction between basic and clinical investigators, both to aid transition of promising approaches to the clinic in a timely manner and to encourage and facilitate 'bedside-to-bench' studies.
- 3 We should recognize the complexity of preclinical research. Standards of rigour analogous to those routinely used in clinical studies (blinding, randomization, trial registration, multicentre design) should be adopted. While generating more relevant (older, sicker, medicated) large animal models of human disease remains a laudable goal, for many disease states, this remains elusive; thus, cautious carefully designed human experimentation may represent the best path forward when clinical needs remain significant and unmet, and initial studies suggest no untoward risks.
- 4 This (as well as other fields) might benefit from greater crosstalk between preclinical and clinical investigators. Exposure of preclinical researchers and trainees to the rigour of clinical investigation would foster greater appreciation for the demands required by regulators, while clinicians might benefit from an understanding of preclinical methodologies, furthering both arenas.
- 5 The heterogeneity of cardiovascular disorders should be considered an opportunity to distinguish between different therapeutic targets (i.e. chronic ischaemia vs. myocardial loss vs. chronic dysfunction) and to generate specific products aimed at the repair of those different disorders.
- 6 Modestly sized clinical trials should be interpreted with caution. Early phase trials can inform feasibility and provide signals of biological effect and potency, but should not be interpreted simply as 'positive' or 'negative'. The caveats inherent to post hoc analyses of clinical trials should be appreciated. Significant time was lost by conducting small similarly designed trials using comparable products, instead of moving the field forward with adequately powered studies.
- 7 In the clinical arena, current cell formulations have demonstrated some efficacy in specific conditions like chronic heart failure^{5,6} and refractory angina.⁷ Properly designed clinical trials are warranted to conclusively address the effect of cell therapy in these conditions.
- 8 Fresh approaches challenging prevailing dogma should be fostered by funding and promotional mechanisms that reward innovative unconventional approaches and opinions. We urge changes to funding review processes that support and encourage research that runs counter to 'conventional' ideas.

The first two decades of research into the regenerative properties of the heart have brought both failures and successes. It would be an error to be dismissive of the progress made. We should remain dedicated to the field and confident that this line of investigation contains promise to substantively help patients with a variety of cardiovascular conditions, including orphan and undertreated populations for whom there are no other palliative or curative alternatives.

References

1. Eschenhagen T, Bolli R, Braun T, Field LJ, Fleischmann BK, Frisén J, Giacca M, Hare JM, Houser S, Lee RT, Marbán E, Martin JF, Molkentin JD, Murry CE, Riley PR, Ruiz-Lozano P, Sadek HA, Sussman MA, Hill JA. Cardiomyocyte regeneration. *Circulation* 2017; **136**: 680–686.
2. Braunwald E. Cell-based therapy in cardiac regeneration: an overview. *Circ Res* 2018; **123**: 132–137.
3. Oransky I. Harvard and the Brigham recommend 31 retractions for cardiac stem cell work. <https://retractionwatch.com/2018/10/14/harvard-and-the-brigham-recommend-31-retractions-for-cardiac-stem-cell-work/>. Accessed October 14, 2018.
4. Laflamme MA, Myerson D, Saffitz JE, Murry CE. Evidence for cardiomyocyte repopulation by extracardiac progenitors in transplanted human hearts. *Circ Res* 2002; **90**: 634–640.

5. Patel AN, Henry TD, Quyyumi AA, Schaer GL, Anderson RD, Toma C, East C, Remmers AE, Goodrich J, Desai AS, Recker D, DeMaria A. Ixmyelocel-T for patients with ischaemic heart failure: a prospective randomised double-blind trial. *Lancet* 2016; **387**: 2412–2421.
6. Mathiasen AB, Qayyum AA, Jørgensen E, Helqvist S, Kofoed KF, Haack-Sørensen M, Ekblond A, Kastrup J. Bone-marrow derived mesenchymal stromal cell treatment in patients with ischaemic heart failure: final 4-year follow-up of the MSC-HF trial. *Eur J Heart Fail* 2019; **36**: 1744–1753.
7. Henry TD, Losordo DW, Traverse JH, Schatz RA, Jolicœur EM, Schaer GL, Clare R, Chiswell K, White CJ, Fortuin FD, Kereiakes DJ, Zeiher AM, Sherman W, Hunt AS, Povsic TJ. Autologous CD34+ cell therapy improves exercise capacity, angina frequency and reduces mortality in no-option refractory angina: a patient-level pooled analysis of randomized double-blinded trials. *Eur Heart J* 2018; **39**: 2208–2216.
8. Bozzo A, Bali K, Evaniew N, Ghert M. Retractions in cancer research: a systematic survey. *Res Integr Peer Rev* 2017; **2**: 5.
9. Murry CE, Soonpaa MH, Reinecke H, Nakajima H, Nakajima HO, Rubart M, Pasumarthi KBS, Ismail Virag J, Bartelmez SH, Poppa V, Bradford G, Dowell JD, Williams DA, Field LJ. Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. *Nature* 2004; **428**: 664–668.
10. Hong K, Y G, Li Q-H, Cao P, Al-Maqtari T, Vajravelu B, Du J, Book M, Zhu X, Nong Y, Bhatnagar A, Bolli R. c-kit+ Cardiac stem cells alleviate post-myocardial infarction left ventricular dysfunction despite poor engraftment and negligible retention in the recipient heart. *PLoS One* 2014; **9**: e96725.
11. A futile cycle in cell therapy. *Nat Biotechnol* 2017; **35**: 291–291.
12. Epstein JA. A time to press reset and regenerate cardiac stem cell biology. *JAMA Cardiol* 2019; **4**: 95–96.
13. Jeevanantham V, Butler M, Saad A, Abdel-Latif A, Zuba-Surma EK, Dawn B. Adult bone marrow cell therapy improves survival and induces long-term improvement in cardiac parameters: a systematic review and meta-analysis. *Circulation* 2012; **126**: 551–568.
14. Goff ZD, Kichura AB, Chibnall JT, Hauptman PJ. A survey of unregulated direct-to-consumer treatment centers providing stem cells for patients with heart failure. *JAMA Intern Med* 2017; **177**: 1387–1388.