Response to Letter Regarding Article, “Embryonic Stem Cell–Derived Cardiac Myocytes Are Not Ready for Human Trials”

For good ideas and true innovation, you need human interaction, conflict, argument, debate.

Margaret Heffernan

Over the years, I have been asked several times whether there would ever be a sequel to the inaugural Point/Counterpoint JMCC editorial in which I squared off against my colleague Dr Murry, whom I feel privileged to call my friend as well as Chuck. In that treatise penned at the outset of growing controversy surrounding bone marrow stem cell therapy, we were asked to adopt opposing viewpoints for the sake of spirited debate, elevating scientific discourse, and demonstrating that difference of professional opinion can be held while preserving mutual respect and personal integrity. I agreed to join Chuck in that original meeting of the minds recognizing the importance of presenting multiple distinct interpretations of findings as long as the asserted positions remain consistent with the facts. Scientific research evolves and grows stronger through open and honest dialog, and I also believe that the field of regenerative medicine will gain strength from educated differences of opinion. With full awareness of the disturbingly acrimonious tone recently adopted by some researchers in the pursuit of a prevailing opinion to silence their critics, I sincerely hope and trust that Chuck et al will take the following rejoinder to our commentary entitled “Embryonic Stem Cell–Derived Cardiac Myocytes Are Not Ready for Human Trials” by agreeing with several significant points.

Indeed, the authors started their rebuttal to our commentary by agreeing with several significant problems: insufficient primates under treatment to provide valid interpretations, a lack of demonstrable functional benefit, and inconsistent induction of potentially lethal arrhythmias (which was the only truly meaningful conclusion). Thus, the authors essentially concur with the obvious concerns associated with pursuing embryonic stem cells for the treatment of human heart failure. With consensus on limitations of the study, our differences center primarily on how problematic these issues are. The following paragraph highlights these divergent perspectives.

Although the Nature article never made the assertion that hESC-CMs (human embryonic stem cell–cardiomyocytes) are ready for the clinic, the senior and corresponding author, Dr Murry, nevertheless has publicly declared that “[t]his is 10 times more heart muscle than anybody else in the world has been able to generate,” and predicted that his laboratory would be ready for clinical trials in humans within 4 years.2

The guinea pig heart model previously used by the authors may not be the most valid comparison for the primate heart promoted in the Nature study. For instance, the porcine heart is actually much closer in size to a human heart than the primate heart and is a universally accepted standard for Food and Drug Administration preclinical trials. Moreover, cardiac function cannot be profoundly altered in the primate model because they are much too sensitive to myocardial infarction and present a high risk of sudden death. Even the closest primate to humans, namely the chimpanzee, is separated from humans by ≈4 million years, and its genome differs from the human genome by ≈35 million single nucleotide polymorphisms, 5 million insertion/deletions (indels), and various chromosomal rearrangements.3

Injection of massive numbers of cells (such as the billion in the Nature article) into the heart with ongoing presence of cells by histology at 2 weeks cannot be interpreted as evidence of myocardial regeneration. Furthermore, 0.5 g of heart tissue (even if it is truly new myocardium) would be trivial for replacement therapy in the patients under consideration for this type of intervention.

Serious complications associated with immunosuppression should not be dismissed lightly simply because they have long persisted in the field; these complications remain a major issue that will pose a considerable challenge in this type of cell therapy. Patients’ subsequent quality of life should be a critical if not primary consideration when proposing clinical intervention. There is clear agreement that arrhythmias were present in all animals, which may be the only statistically valid conclusion from the study. Arrhythmia concerns are serious and basically a fundamental shortcoming of this approach. In the lone primate kept for more than a few weeks in the study, the diminished prevalence of arrhythmia should not be misconstrued as demonstration of safety, and we agree with the authors that this is a central issue. Many patients having atrial fibrillation also eat, drink, and groom themselves normally but find arrhythmias distressing.

Previous small animal model studies mentioned by the authors documenting images of the grafted cells obtained in studies separate from the Nature report should be kept distinct and not blurred together as one in the same. The authors have previously advocated circumspexion on claims of either GFP expression in immunolabeled sections or misinterpretation of engrafted tissue as autofluorescence.4,5 The prosurvival cocktail used in the Nature study was Matrigel (source: Engelbreath–Holm–Swarm mouse sarcoma cells), which is not feasible for human application. No current adult stem cell trial involves the injection of a mouse sarcoma protein mixed preparation, and the lack of clinical applicability challenges the relevance of this protocol as a therapeutic intervention. The idea of inconsistency by design as a strength in scientific investigation is peculiar. Lack of randomization, potential investigator bias, nonblinded data analysis, etc, are serious problems in biomedical sciences and a major source of nonreproducible data. With the Nature study conducted on a cohort of n=4, inconsistency would seem almost unavoidable and predictable.
Again, we find ourselves in agreement with the authors. We believe that the serious limitations as pointed out by the authors themselves validate our concerns as stated by the title of our commentary, “Embryonic Stem Cell–Derived Cardiac Myocytes Are Not Ready for Human Trials.”

**Sources of Funding**
Dr Sussman is supported by National Institutes of Health grants R01HL067245, R37HL091102, R01HL105759, R01HL113656, R01HL113647, R01HL122525, as well as an award from Fondation Leducq Transatlantic Network and is a founder and co-owner of CardioCreate Inc.

**Disclosures**
None.

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**References**
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*Circ Res.* 2014;115:e30-e31
doi: 10.1161/CIRCRESAHA.114.305341

*Circulation Research* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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