Europace (2010) **12**, 1520–1521
doi:10.1093/europace/euq374

EDITORIAL

Cell-based therapy of the failing heart: a need to connect for proper electrical and contractile function

Larissa Fabritz[1], Bernd K. Fleischmann[2], Boris Greber[3], and Paulus Kirchhof[1]*

[1]Department of Cardiology and Angiology, University Hospital Münster, Albert-Schweitzer-Straße 33, D-48149 Münster, Germany; [2]Institute of Physiology I, Life and Brain Center, University of Bonn, Bonn, Germany; and [3]Max Planck Institute for Molecular Biomedicine, Human Stem Cell Pluripotency Group, Münster, Germany

Received 8 September 2010; accepted after revision 19 September 2010

This editorial refers to 'Skeletal myoblast implants induce minor propagation delays, but do not promote arrhythmias in the normal swine heart' by J. Moreno *et al.*, on page 1637

Despite clear improvements in acute therapy and chronic management, myocardial infarction remains a severe threat to cardiac function.[1,2] In contrast to other organs, the heart has only limited regeneration capacity. Therefore, most of the cardiomyocytes that die in the process of acute myocardial ischaemia are replaced by dysfunctional scar tissue. In this context, regeneration of infarcted areas of the heart via application of progenitors/stem cells is a fascinating prospect. Clinical observations suggested a beneficial effect of injecting bone marrow-derived cells into coronary arteries[3–5] or skeletal myoblasts into hearts during open heart surgery[6,7] in survivors of myocardial infarction with heart failure, resulting in a high expectation that regeneration of the left ventricle could be instigated by such 'regenerative therapy'. Subsequent larger trials found modest or no effects after intracoronary injection of bone marrow-derived cells.[8–10] Furthermore, careful clinical follow-up of patients who received myocardial injection of skeletal myoblasts identified the proarrhythmic side effects of such therapy.[11,12] It is difficult to align these findings which have been disputed widely. Most likely, different properties of the injected material, including different techniques of preparing and administering cells, as well as different patient characteristics contributed to the heterogeneity of the clinical findings. Given the potential for benefit and harm of treatment of failing hearts with precursor cells, we clearly need a better understanding of the physiological effects of precursor cells that interact with healthy and diseased myocardium, and of their potential side effects in the heart.

Moreno *et al.*[13] report on the electrical effects of injecting skeletal myoblasts in healthy pig hearts. They identified marginal slowing of conduction distant to the implantation site *ex vivo* and did not identify any difference in arrhythmia induction between treated and SHAM-treated swine hearts, despite evidence of fibrous tissue close to the injection site. The authors are to be applauded for their systematic approach to the electrophysiological effects of implanting skeletal myoblasts in the beating large animal heart. This study provides important safety information by showing that the proarrhythmic effect that has been suggested by cell co-culture studies of healthy cardiomyocytes and mesenchymal precursor cells[14] does not translate into inducible arrhythmias in healthy large animal hearts.

Clearly, there is more to do, especially when considering potential differences in the degree of engraftment and that diseased myocardium such as the infarct zone is likely to be more vulnerable to slight conduction changes than healthy myocardium.[15] Furthermore, the molecular characterization of engrafted cells and potentially their genetic modification may help to improve the efficacy and safety of cell-based therapy of the heart in the future. In fact, genetically engineered enhanced electrical coupling between engrafted cells and the native myocardium via connexin expression may improve electrical stability and left ventricular function.[15–17] Furthermore, mobilization of bone marrow-derived cells by application of growth factors can improve cardiac contractile and electrical function in mice, especially in the infarct border zone, without affecting histological infarct size,[18] suggesting functional effects on the surviving 'normal' myocardium rather than true regeneration within the infarct.

Given that functional improvement after engraftment of adult progenitors and/or stem cells does not appear to be based on their transdifferentiation into cardiomyocytes[19,20] and that the overall effect is relatively modest, pluripotent stem cells appear to be an interesting alternative cell source.[17] However, their differentiation capacity into cardiomyocytes, their purification to avoid teratomas, and their long-term engraftment in the infarct to

The opinions expressed in this article are not necessarily those of the Editors of *Europace* or of the European Society of Cardiology.

* Corresponding author. Tel: +49 251 8345185; fax: +49 251 8347864, Email: kirchhp@uni-muenster.de

provide sustained functional improvement still require lots of effort from basic scientists.[21,22] A very attractive autologous approach is the recently reported direct transprogramming of fibroblasts into cardiomyocytes using a set of only three well-defined cardiac transcription factors.[23] This could either allow to re-inject or transplant *in vitro* generated cardiomyocytes or tissue patches or to directly re-convert the fibrotic scar into the cardiac muscle using gene therapy.

Understanding the beneficial effects and the potential harm of cell-based therapy of the failing heart will require an interdisciplinary, 'translational' research approach. This requires close interactions between clinical investigators, translational cardiologists, basic scientists with a broad cardiac physiological expertise, and cell biologists. Such an interdisciplinary understanding of the effects of cell-based therapy should probably guide therapy selection and hence precede further evaluation of cell-based therapy in controlled clinical trials. The study by Moreno *et al.* is a valuable addition to our knowledge as it confers relevant safety information on the interaction of skeletal myoblasts with healthy myocardium. It is most likely that effective cell-based therapy of the failing heart needs to use different cells than those implanted by Moreno *et al.* At present, we can only speculate which cell-based therapy will be most helpful, whom it will help, and how the effects of these cells are mediated in the failing heart. We hope that well-coordinated interdisciplinary and 'translational' research will characterize the right cell-based therapy and the most suitable patients.

Conflict of interest: A full list of financial disclosures for PK is available on the home page of the ESC. LF has received funding from DFG and IZKF Münster.

References

1. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T *et al.* Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2010;**31**:2501–55.
2. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA *et al.* ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J* 2008;**29**:2388–442.
3. Assmus B, Schachinger V, Teupe C, Britten M, Lehmann R, Dobert N *et al.* Transplantation of Progenitor Cells and Regeneration Enhancement in Acute Myocardial Infarction (TOPCARE-AMI). *Circulation* 2002;**106**:3009–17.
4. Britten MB, Abolmaali ND, Assmus B, Lehmann R, Honold J, Schmitt J *et al.* Infarct remodeling after intracoronary progenitor cell treatment in patients with acute myocardial infarction (TOPCARE-AMI): mechanistic insights from serial contrast-enhanced magnetic resonance imaging. *Circulation* 2003;**108**:2212–8.
5. Stamm C, Westphal B, Kleine HD, Petzsch M, Kittner C, Klinge H *et al.* Autologous bone-marrow stem-cell transplantation for myocardial regeneration. *Lancet* 2003;**361**:45–6.
6. Menasche P, Hagege AA, Vilquin JT, Desnos M, Abergel E, Pouzet B *et al.* Autologous skeletal myoblast transplantation for severe postinfarction left ventricular dysfunction. *J Am Coll Cardiol* 2003;**41**:1078–83.
7. Menasche P, Hagege AA, Scorsin M, Pouzet B, Desnos M, Duboc D *et al.* Myoblast transplantation for heart failure. *Lancet* 2001;**357**:279–80.
8. Wollert KC, Meyer GP, Lotz J, Ringes-Lichtenberg S, Lippolt P, Breidenbach C *et al.* Intracoronary autologous bone-marrow cell transfer after myocardial infarction: the BOOST randomised controlled clinical trial. *Lancet* 2004;**364**:141–8.
9. Zohlnhofer D, Ott I, Mehilli J, Schomig K, Michalk F, Ibrahim T *et al.* Stem cell mobilization by granulocyte colony-stimulating factor in patients with acute myocardial infarction: a randomized controlled trial. *JAMA* 2006;**295**:1003–10.
10. Strauer BE, Yousef M, Schannwell CM. The acute and long-term effects of intracoronary stem cell transplantation in 191 patients with chronic heARt failure: the STAR-heart study. *Eur J Heart Fail* 2010;**12**:721–9.
11. Menasche P, Alfieri O, Janssens S, McKenna W, Reichenspurner H, Trinquart L *et al.* The Myoblast Autologous Grafting in Ischemic Cardiomyopathy (MAGIC) trial: first randomized placebo-controlled study of myoblast transplantation. *Circulation* 2008;**117**:1189–200.
12. Hagege AA, Marolleau JP, Vilquin JT, Alheritiere A, Peyrard S, Duboc D *et al.* Skeletal myoblast transplantation in ischemic heart failure: long-term follow-up of the first phase I cohort of patients. *Circulation* 2006;**114**(Suppl. 1):I108–13.
13. Moreno J, Quintanilla JG, López-Farré A, Archondo T, Cervigón R, Aragoncillo P *et al.* Skeletal myoblast implants induce minor propagation delays, but do not promote arrhythmias in the normal swine heart. *Europace* 2010;**12**:1637–44.
14. Chang MG, Tung L, Sekar RB, Chang CY, Cysyk J, Dong P *et al.* Proarrhythmic potential of mesenchymal stem cell transplantation revealed in an *in vitro* coculture model. *Circulation* 2006;**113**:1832–41.
15. Roell W, Lewalter T, Sasse P, Tallini YN, Choi BR, Breitbach M *et al.* Engraftment of connexin 43-expressing cells prevents post-infarct arrhythmia. *Nature* 2007;**450**:819–24.
16. Roell W, Lu ZJ, Bloch W, Siedner S, Tiemann K, Xia Y *et al.* Cellular cardiomyoplasty improves survival after myocardial injury. *Circulation* 2002;**105**:2435–41.
17. Kolossov E, Bostani T, Roell W, Breitbach M, Pillekamp F, Nygren JM *et al.* Engraftment of engineered ES cell-derived cardiomyocytes but not BM cells restores contractile function to the infarcted myocardium. *J Exp Med* 2006;**203**:2315–27.
18. Kuhlmann MT, Kirchhof P, Klocke R, Hasib L, Stypmann J, Fabritz L *et al.* G-CSF/SCF reduces inducible arrhythmias in the infarcted heart potentially via increased connexin43 expression and arteriogenesis. *J Exp Med* 2006;**203**:87–97.
19. Murry CE, Soonpaa MH, Reinecke H, Nakajima H, Nakajima HO, Rubart M *et al.* Haematopoietic stem cells do not transdifferentiate into cardiac myocytes in myocardial infarcts. *Nature* 2004;**428**:664–8.
20. Nygren JM, Jovinge S, Breitbach M, Sawen P, Roll W, Hescheler J *et al.* Bone marrow-derived hematopoietic cells generate cardiomyocytes at a low frequency through cell fusion, but not transdifferentiation. *Nat Med* 2004;**10**:494–501.
21. Xu C, Police S, Rao N, Carpenter MK. Characterization and enrichment of cardiomyocytes derived from human embryonic stem cells. *Circ Res* 2002;**91**:501–8.
22. Passier R, Oostwaard DW, Snapper J, Kloots J, Hassink RJ, Kuijk E *et al.* Increased cardiomyocyte differentiation from human embryonic stem cells in serum-free cultures. *Stem Cells* 2005;**23**:772–80.
23. Ieda M, Fu JD, Delgado-Olguin P, Vedanthan V, Hayashi Y, Bruneau BG *et al.* Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors. *Cell* 2010;**142**:375–86.