Chimerism as a Mechanism of Self-Repair
To the Editor:

We read with interest the editorial by Taylor et al
d concerning the ongoing debate about cardiac chimerism. We were surprised that the authors cited the article of Glaser et al
d as proof that chimerism would not exist but failed to mention our study showing that cardiomyocytes can be regenerated by non-cardiac cells in human transplanted hearts. Importantly, in our article, which appeared in the same issue of Circulation,d we found chimerism to involve up to 1.6% of cardiomyocytes.

We agree with the authors of the editorial that there are differences among the studies published to date on cardiac chimerism.1,3-5 However, there are no qualitative differences, but simply variability in the extent of this phenomenon. There are also distinct methodological differences among the studies; the first used fluorescence microscopy,3 the second light microscopy,4 and the third confocal microscopy.5 The Y-chromosome probes and the time between transplantation and sampling varied largely among studies.

The claim of Taylor et al1 that potential acute rejection could be a cause for misinterpretation is not plausible. In our study,1 we also performed immunostaining for inflammatory cells and found them only in a small number. Furthermore, we were able to exclude cell fusion between donor and recipient cells using combined Y- and X-chromosome fluorescence in situ hybridization. The fluorescence picture by which Taylor et al1 try to prove that nuclei of overlapping lymphocytes mimic cardiomyocyte nuclei is more disappointing than convincing. The lymphocyte shown cannot be confused with a myocyte nucleus by any examiner with experience in cardiovascular pathology.

In summary, the existence of cardiac chimerism was proven sufficiently by 3 independent groups of investigators.1,3-5 The reasons for the different extent of cardiac chimerism need to be examined in future studies comparing different methodologies of detection, as well as different time points of material acquisition.

Patrick Müller, MD
Michael Böhm, MD
Department of Innere Medizin III
Universität des Saarlandes
Homburg/Saar, Germany
boehm@med.uni-saarland.de


Response

We welcome the comments by Dr. Müller and Böhm and their important contribution to the lively ongoing debate over the extent of cardiac chimerism in transplanted human hearts. Although we did not specifically address their study1 in our editorial2 because we were not aware of it (their study appeared in the same issue of Circulation), the study of Müller and Böhm nicely illustrates some of the issues we raised. Primarily, their study illustrates why data replication is so important. We agree that cardiac chimerism is an important phenomenon with significant biological and clinical implications. For that reason, we reiterate that any assertion of high degrees of chimerism must be definitively proved and replicated. We agree that the data presented by 3 groups indicate that chimerism is possible; in fact, Hruban et al1 demonstrated this many years ago. In their recent article, Müller and Böhm1 found that <2% of cardiomyocytes are chimeric. This is consistent with the previous data of Glaser et al2 who reported virtually no chimerism of cardiac myocytes, as well as that of Hruban et al1 but contrasts dramatically with the claim by Quaini et al3 that up to 30% of the myocardium is replaced within a month of transplantation.

In our editorial, we acknowledge that the degree of cardiac chimerism does matter clinically and biologically; in fact, we raise the point that because it has such important clinical potential that it must be rigorously proved and the findings replicated by numerous groups.

Are we to accept a 15-fold difference in the extent of chimerism or should we, as suggested in our editorial, demand a high burden of proof and reproducibility for a paradigm change with such exciting potential?

A second issue we raised in our editorial is the concern that inflammatory cells associated with acute rejection may be misinterpreted as chimeric cells. Indeed, in their study, where inflammatory cells were found in “only in small number,” Müller and Böhm1 were able to identify potential chimerism in only 1.6% of the cardiomyocytes. Again, this is in direct contrast to the data of Quaini et al5 who reported that approximately 30% of the transplanted myocardium appears to be regenerated within 4 to 28 days after transplantation, during a time associated with an intense alloimmune response. Certainly one potential explanation for the difference between the two studies could be accounted for by inflammatory cells.

Other explanations are equally possible, but they remain to be reproducibly shown.

Doris A. Taylor, PhD
Associate Professor of Medicine
Division of Cardiology
Duke University Medical Center
Durham, NC

Ralph Hruban, MD
Professor of Pathology
Johns Hopkins Medical Institution
Baltimore, Md

E. Rene Rodriguez, MD
Associate Professor of Pathology
Johns Hopkins University School of Medicine
Baltimore, Md

Pascal Goldschmidt-Clermont, MD
Edward S. Organ Professor of Cardiology
Chief, Division of Cardiology
Duke University Medical Center
Durham, NC

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Patrick Müller and Michael Böhm

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