Letter to the Editor

Do Mesenchymal Stromal Cells Transdifferentiate Into Functional Cardiomyocytes?

To the Editor:
We would like to comment on the recent and interesting report by Pijnappels et al1 showing that mesenchymal stem (stromal) cells (MSCs) can transdifferentiate into cardiac lineage in culture. The ability of MSCs to transdifferentiate into cardiomyocytes is highly controversial, with numerous studies suggesting that the phenomenon occurs, whereas many others conclude that it does not. Pijnappels et al have provided data showing that under their cell culture conditions, some MSCs in coculture with neonatal cardiomyocytes undergo cardiac differentiation, as indicated by the expression of sarcomeric α-actinin, cardiac troponin I, and connexin-43. Furthermore, Pijnappels et al recorded action potentials in approximately 16% of the putative MSC-derived cardiomyocytes. We recently showed2 that MSCs do display plasticity toward the cardiac lineage when cocultured with embryonic cardiomyocytes, with the expression of sarcomeric α-actinin and cardiac troponin I, similar to Pijnappels et al. In contrast, we were unable to record action potentials (spontaneous or stimulated) in any putatively transdifferentiated MSCs, even after 15 days of coculture with embryonic cardiomyocytes. We, therefore, concluded that MSCs do not undergo true functional transdifferentiation.

What could cause this different pattern of results? Two key experimental differences exist between our studies. First, Pijnappels et al studied neonatal rat MSCs, whereas we used adult mouse MSCs. It is possible that the multipotent potential of neonatal MSCs is greater than those of the adult cell, although adult MSCs may be the more relevant cell type for cell therapy. Secondly, and we believe more importantly, greater than 1% of our cells were CD45−/H11001−/H11021− by flow cytometric analysis, whereas we were careful to ensure that <1% of our cells were CD45−. The guidelines for definition of MSCs clearly state that MSCs must be negative for CD45, a−/b− which is a pan-leukocyte marker. The presence of these CD45− cells may indicate significant hematopoietic stem cell (HSC) contamination in the study by Pijnappels et al. HSCs have been shown in some studies to undergo true electric and functional transdifferentiation into cardiomyocytes, suggesting that the cardiac differentiated cells in the Pijnappels et al study might have arisen from HSCs.

In conclusion, we acknowledge Pijnappels et al for their important work in this controversial field. As more high quality and rigorous studies are completed, we anticipate that the multipotent potential of MSCs, as well as HSCs, will become clearer and that the role each cell type could play in the treatment of heart disease will be better understood.

Robert A. Rose
Armand Keating
Peter H. Backx
Departments of Physiology and Medicine
Heart and Stroke/Richard Lewar Centre
Cell Therapy Program
Princess Margaret Hospital/Ontario Cancer Institute
University Health Network and University of Toronto
Toronto, Ontario, Canada
E-mail rob.rose@utoronto.ca

Sources of Funding
A. Keating holds the Gloria and Seymour Epstein Chair in Cell Therapy and Transplantation at the University of Toronto and University Health Network. This work was supported by funding from the Canadian Institutes for Health Research (MOP 79460) to P. Backx who is a Career Investigator with the Heart and Stroke Foundation of Ontario. R. Rose is the recipient of Fellowships from the Heart and Stroke Foundation of Canada, the Alberta Heritage Foundation for Medical Research, and the Canadian Institutes of Health Research—Tailored Advanced Collaborative Training in Cardiovascular Sciences (TACTICS) program.

Disclosures
None.

References