



The Politics and Promise of Stem-Cell Research

Robert S. Schwartz, M.D.

Related articles, pages 1199, 1210, and 1222

On July 19, 2006, President George W. Bush exercised his constitutional prerogative to veto a congressional act for the first time in the 6 years he has been in office. The bill, passed by a Republican-

controlled Congress, would have allowed a modest extension of embryonic stem-cell research. It called for federal funding to enable the derivation of embryonic stem-cell lines from fertilized eggs that are stored in freezers and already tagged for destruction. In his veto message, the President explained that, "stem cells . . . can be drawn from children, adults, and the blood in umbilical cords with no harm to the donor, and these stem cells are currently being used in medical treatments."

According to the *New York Times*, Karl Rove, head of the White House's Office of Political Affairs, has declared that embryonic stem cells aren't required because there

is "far more promise from adult stem cells." Yet the notion that adult stem cells have the same developmental potential as embryonic stem cells, let alone "more promise," is dubious. It seems that the White House received this idea from David Prentice, a senior fellow for life sciences at the Family Research Council and an advisor to Republican members of Congress. In a report of the President's Council on Bioethics, Prentice claimed that adult stem cells can effectively treat more than 65 diseases. Not only is this assertion patently false, but the information purveyed on the Family Research Council's Web site is pure hokum.

Prentice is not alone, however. A search of the Internet easily turns up dozens of companies offering cures involving adult or cord-blood stem cells. Prominently featured on the Web is the case of a woman, bound to a wheelchair by multiple sclerosis, who received cord-blood stem cells in a private clinic in Rotterdam, the Netherlands. Within minutes, she allegedly recovered her ability to walk. Such anecdotes are lures used to trap hapless patients into a treatment that has no merit whatsoever.

There is evidence in laboratory animals that an adult stem cell can differentiate into a cell that normally belongs to a different lineage — bone marrow stem cells into hepatocytes, for example. But such reports of a pluripotent stem cell that can transdifferentiate¹ have been challenged.^{2,3} The fact that a single, rigorously defined

hematopoietic stem cell from an adult mouse can reconstitute the entire hematopoietic system of a lethally irradiated mouse but has no capacity to differentiate into other tissues of the animal does not, however, rule out the existence of a pluripotent stem cell.⁴ Such a cell may not look like a hematopoietic stem cell, and it could lurk in the marrow, waiting to make an appearance only under special circumstances.

Experiments to establish the existence of a pluripotent stem cell in adults are crucial. Currently, there is no clinical evidence of such a cell in adults. The phenomenon of extramedullary hematopoiesis, which occurs in severe hemolytic anemia and other conditions, has never been associated with anything but a histologic picture of bone marrow nestled in a foreign tissue. There is no visible differentiation into host tissue. Even so, no prospective trial has formally tested the proposition that adult hematopoietic stem cells can improve the function of a tissue other than bone marrow. In this issue of the *Journal*, three important articles correct this deficiency (Lunde et al., pages 1199–1209; Schächinger et al., pages 1210–1221; and Assmus et al., pages 1222–1232). These three randomized, controlled trials investigated the influence of an intracoronary-artery injection of autologous bone marrow cells on ventricular function after a myocardial infarction. Two of the trials involved patients with acute myocardial infarction, and the other involved patients with chronic left ventricular dysfunction and a history of myocardial infarction.

The authors of these studies merit high praise for carrying out

very difficult studies in humans with myocardial infarction. The studies are, however, open to two important criticisms: the injected cells were not always rigorously purified hematopoietic stem cells, and they provide no evidence that the injected hematopoietic cells

Tens of thousands of fertilized eggs will be destroyed without a single one being permitted to contribute to our knowledge of cell differentiation.

actually settled in the heart and became cardiac myocytes. Nevertheless, the clinical results are valuable, especially because the type of bone marrow preparation these groups of investigators used is likely to be similar to, or even better than, the bone marrow preparations now being given *sub rosa* to thousands of patients for the treatment of a variety of cardiac, neurologic, and muscular diseases. VesCell, for example, offers to use stem cells from a patient's own blood to treat various types of heart disease. Zeiher and Dimmeler, senior authors of the articles by Schächinger et al. and Assmus et al., have themselves formed since the acceptance of their article a commercial venture (t2cure) with the mission of developing and offering re-

generative therapy for cardiovascular disease.

Overall, the results of the three studies of a combined total of 376 patients do not promote the use of intracoronary infusions of autologous bone marrow to improve ventricular function. Lunde et al. found no significant differences between the control and bone marrow-treated groups in left ventricular function or infarct size; Schächinger et al. and Assmus et al. found small, significant, but clinically uncertain improvements in ventricular function in the bone marrow-treated groups.

These results are not unexpected. In a mouse model of myocardial infarction, infused bone marrow stem cells differentiated only into blood cells, not cardiac myocytes, and they failed to contribute to myocardial regeneration.⁵ If there was no transdifferentiation in the studies of myocardial infarction, though, there is another possibility: the injected bone marrow cells may not settle in the heart for long, but while there, they could produce cytokines or other diffusible molecules that enhance myocardial regeneration. The heart does produce cytokines, and cytokines are involved in the pathogenesis of coronary artery disease, but whether cytokines can explain the small effects of bone marrow cells on ventricular function is a matter of conjecture.

These three clinical trials will probably not stop the exploitation of patients with promises that bone marrow (or cord blood) can cure almost any chronic disease. To put an end to false promises, President Bush should promote adequate support for studies of the clinical potential of bone mar-

row cells and research to determine whether a pluripotent stem cell with therapeutic benefit exists in adults.

On July 19, Bush missed an opportunity to show support for research on cells that do have the potential to differentiate into many different kinds of tissues. His veto thwarted new prospects for advancing embryonic stem-cell research and will result in a terrible waste: tens of thousands of fertilized eggs will be destroyed without a single one being permitted to contribute to our knowledge of cell differentiation. Fortunately, research on embryonic stem cells will proceed in a number of excellent scientific centers in this country, without federal funding and, one might argue, at a pace unfettered by the federal bureaucracy. But the lack of federal support and the political climate do hinder stem-cell re-

search in the United States. A new center in Singapore, for example, has recently attracted gifted American investigators who are fed up with political restrictions on their research. Other countries — such as China, Sweden, and the United Kingdom — are also entering the field.

We really don't know what will ultimately come out of research on embryonic stem cells. It is important to play down promises to the public that the work will produce anything of clinical value in the foreseeable future. We simply don't know how an embryonic stem cell will behave in a human, and we don't know whether human marrow contains a pluripotent stem cell that can transdifferentiate. Equally important, we don't yet know whether research on embryonic stem cells will teach us how to revise the differentiation program of a tissue-specific

stem cell, thereby circumventing the need for embryonic cells. Research on stem cells will encounter many twists and turns, but it is an endeavor that is eminently worth pursuing. The delay of medical advances by theological disputes is not in the best interests of the sick and disabled.

Dr. Schwartz is a deputy editor of the *Journal*.

1. Jiang S, Walker L, Afentoulis M, et al. Transplanted human bone marrow contributes to vascular endothelium. *Proc Natl Acad Sci U S A* 2004;101:16891-6.
2. Wang X, Willenbring H, Akkari Y, et al. Cell fusion is the principal source of bone-marrow-derived hepatocytes. *Nature* 2003;422:897-901.
3. Vassilopoulos G, Wang PR, Russell DW. Transplanted bone marrow regenerates liver by cell fusion. *Nature* 2003;422:901-4.
4. Wagers AJ, Sherwood RI, Christensen JL, Weissman IL. Little evidence for developmental plasticity of adult hematopoietic stem cells. *Science* 2002;297:2256-9.
5. Balsam LB, Wagers AJ, Christensen JL, Kofidis T, Weissman IL, Robbins RC. Haematopoietic stem cells adopt mature haematopoietic fates in ischaemic myocardium. *Nature* 2004;428:668-73.

Bit Player or Powerhouse? China and Stem-Cell Research

Fiona Murray, Ph.D., and Debora Spar, Ph.D.

For more than a decade, China has been shocking the West. Although it is still poor and officially Communist, the world's most populous country has turned old convictions on their heads, emerging from decades of isolation to become a hive of high-tech manufacturing, a major diplomatic and military power, and one of the world's largest holders of U.S. securities. The subtitle of a recent book described the China phenomenon most succinctly when it promised, breathlessly, to explain "how the rise of the next

superpower challenges America and the world."¹

In the area of scientific research, by contrast, both fact and prediction are more ambiguous. On the one hand, Chinese authorities clearly have bold ambitions. President Hu Jintao has repeatedly stressed the importance of "scientific development" to China's continuing growth, and in January he vowed that "China over the next 15 years will join the list of innovative countries."² The natural sciences figure prominently among the government's

areas of focus, and government spending on science and technology has more than doubled since 1999. On the other hand, China remains an exceedingly poor country, with a per capita annual income of only \$1,284 in 2005; hundreds of millions of Chinese peasants lack access to even the most basic medical services. China is still governed by a staunchly Communist regime, and both its industrial infrastructure and capital markets are dominated by state-owned enterprises. These are not the kinds of con-