



A Setback for Stem Cell Therapy?

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Beta-cell replacement in diabetes is a red hot area of research, and no approach is getting more attention than stem cell therapy. Currently, islet transplantation from human donors is the only available option for curative therapy of type 1 diabetes, but limitations on transplant survival and the number of donor pancreata prevent this technique from being widely adopted. Gene therapy is very cool, and might ultimately be the way things are done, but the process is simply not technically feasible yet. Stem cells provide (in theory at least) a renewable pool of material that can be differentiated into insulin-secreting cells in culture and then implanted into diabetic recipients. While the technology is not yet ready-for-prime-time, there have been a series of exciting advances that have held out the promise that real people will benefit from stem cells in the not so distant future.

A new study, however, has given stem cell researchers something to chew on, and may indicate that we are not quite as far along as we had thought.

First, however, a little background. Several groups around the world have presented evidence that human and rodent stem cells can be tweaked and prodded using a variety of cell culture conditions to turn into beta-cells. These stem cells have been derived from both embryonic and adult tissues, and from liver cells in addition to pancreas. Bone marrow is another possible source of cells that is being investigated. There is extra excitement surrounding the use of adult tissues as a source of stem cells, because of the ongoing ethical and political debate concerning the use of embryonic tissue in this country.

Each of the half dozen or so published studies has used different criteria to support their claims, but all of them have shown that the cells can be made to stain positive for insulin, which is of course the hallmark of a beta-cell. Some authors have gone farther, and have shown that implantation of their cells into mice with type 1 diabetes rescues blood sugar levels to normal.

In the new study, a different group of researchers tried to copy the protocol used by another successful group, using embryonic stem cells from mice and humans. Like the first group, they were able to show that 10-30% of the cells in the dish stained positive with an antibody to insulin. However, the second group did some additional control experiments, such as expressing a marker gene from the

stretch of DNA that normally directs insulin expression in beta-cells. If the stem cells were truly turning into beta-cells, then the marker gene would turn on as well (in this case, turning the cells blue when a special stain is added). To their surprise, only one in every 100,000 cells turned blue.

So why did so many cells stain positive for insulin? Cells are grown in nutrients which include serum from cattle; this serum contains growth factors, including insulin, that help cells to survive in a dish. The stem cells, it appears, were merely collecting and storing the insulin from the serum, rather than producing it themselves. To add to the ruse, the cells are capable of releasing this stored insulin slowly over time. Theoretically at least, transplantation of these cells could thus "cure" diabetes in mice, as some groups have shown.

The new findings point to the need for strict and uniform criteria for deciding when beta-cell differentiation has been achieved. At a minimum, investigators will now need to show that cells are producing their own insulin, and releasing it in response to normal stimuli like glucose. Transplantation experiments will also have to be prolonged for more than a month to show that any reduction in blood sugar in diabetic mice can be sustained.

Ultimately, stem cells may still be our best bet for beta-cell replacement. Even the authors of the new study remain optimistic about the long-term chances for success; it's just going to take a little longer to get there than everyone hoped.

To review the original article [Potential Problem with Using Embryonic Stem Cells to Cure Diabetes](http://www.diabetesincontrol.com/features/i140.shtml). Go to <http://www.diabetesincontrol.com/features/i140.shtml>

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