

# Up Front

## New Discoveries Propel Stem Cell Research

*Findings suggest new avenues to possible treatments.*

**B**y all accounts, the first half of 2004 proceeded at a record clip for HHMI investigator Douglas A. Melton. In March, Melton's research team at Harvard University unveiled 17 new human embryonic stem (ES) cell lines—just days after the announcement that Melton would codirect the university's new stem cell institute. In May, Melton's group discovered that insulin-producing beta cells in the pancreas are replenished through duplication of existing cells rather than through differentiation of adult stem cells. And in June, Harvard President Lawrence H. Summers announced that Melton would chair the university's Faculty of Arts and Sciences Life Sciences Council.

While Melton has become a public figure, his true passion is being in the laboratory, where he devotes as much time as his schedule permits to understanding human ES cells. Melton is among those who believe that these cells have the potential to yield treatments for devastating human diseases, as well as to enhance understanding of human development.

Melton made international headlines when he announced that he and colleagues had derived the 17 new human ES cell lines. Developed with funding provided by HHMI, Harvard, and the Juvenile Diabetes Research Foundation, the new cell lines have been made available to researchers around the world. The work was published in the March 25, 2004, issue of the *New England Journal of Medicine*.

### Therapeutic Promise

In 2001, Harvard, HHMI, and Boston IVF began a collaborative research effort that sought to realize the great therapeutic promise offered by human ES cells. Melton, Andrew P. McMahon, Chad A. Cowan, and colleagues at Harvard worked with Douglas Powers and scientists

from Boston IVF to produce the supply of human ES cells.

Melton hopes that the availability of the new cell lines will speed research developments in the area of stem cell biology. "Consistent with the general practice among academic scientists, these cells are a reagent that will be shared," says Melton. "We hope that sharing these cells will quicken the pace of discovery."

The availability of the cell lines should provide a boost to stem cell researchers worldwide. According to the National Institutes of Health, about 15 human embryonic stem cell lines are available for researchers in the United States who are doing federally funded research. The International Society for Stem Cell Research (ISSCR), an independent, nonprofit organization formed to foster the exchange of information about stem cell research, says the number of available human ES cell lines is a matter of some debate. The ISSCR Web site states that only about 8 to 10 cell lines in total are currently widely accepted as true human embryonic stem cells. Melton says that the cells that he and his colleagues developed "are robust, grow well, and are easy to handle."

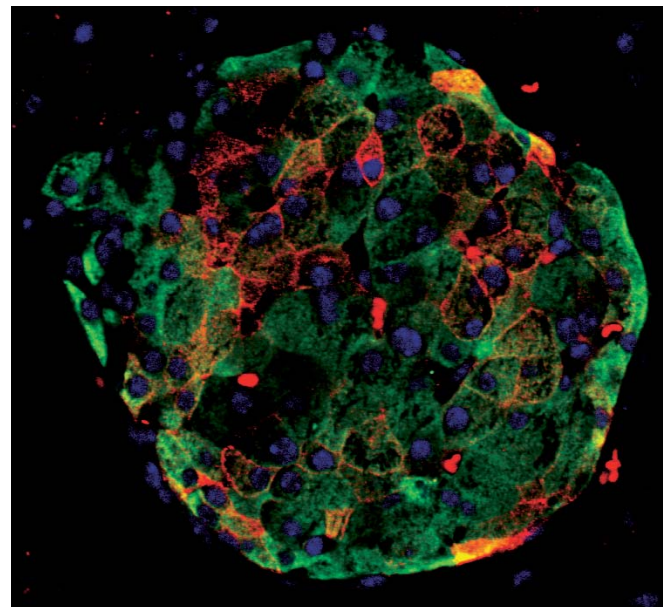
The techniques Melton and his team used to derive the human embryonic stem cell lines were based, in part, on technology developed decades ago for mouse ES cells and on more recent work by Ariff Bongso at National University Hospital in Singapore and James A. Thomson and his colleagues at the University of Wisconsin–Madison. Melton notes, however, that in the course of his group's

experiments, they discovered an easier way to tease stem cells free from surrounding tissues by using enzymes. "One of the things our paper shows is that it's possible to select for cells that can be easily grown by using enzymes rather than by the tedious process of hand-dissecting them," Melton says. "I would anticipate that in the future, researchers would use this method."

Distribution of the cell lines is being handled through Melton's HHMI laboratory at Harvard. Melton is impressed by the number of inquiries for the cell lines, and he is confident that his group is ready to meet the growing demand. "We are planning to distribute [the cells], to the extent possible, more or less the same way that we distribute any reagents we publish, be it a DNA clone or any other cell line," he says.

The availability of the new cell lines should also propel Melton's own research program, which uses a multipronged approach to understanding type 1 diabetes. His research team has been studying the insulin-producing pancreatic beta cells that are destroyed in patients with type 1 diabetes, a disease that commonly afflicts children. Melton's long-term goal is to learn how to direct the differentiation of human

**Melton made international headlines when he announced that he and colleagues had derived 17 new human ES cell lines.**





*Douglas Melton's research includes study of the genetic lineage of beta cells in the pancreatic islet (left).*

embryonic stem cells, so that they can generate pancreatic beta cells that can be used as a therapy for type 1 diabetes.

In May, Melton and his colleagues reported that the insulin-producing beta cells in the pancreas that are attacked in type 1 diabetes are replenished through duplication of existing cells rather than through differentiation of adult stem cells.

Although the experiments, which were done using mice, do not rule out the possibility that there are adult stem cells in the pancreas, the researchers say that they do suggest strongly that ES cells or mature beta cells may be the only way to generate beta cells for use in cell replacement therapies to treat diabetes. The findings were reported in the May 6, 2004, issue of the journal *Nature*. Melton's coauthors include Yuval Dor, Juliana Brown, and Olga I.

Martinez, all from Harvard.

In cell culture, ES cells retain the properties of undifferentiated embryonic cells. ES cells have the capacity to make all cell types found in an adult organism. One of the most hotly debated questions in biology is whether adult stem cells, which have been isolated from blood, skin, brain, and other organs, have the same developmental capacity as ES cells.

Researchers have known for some time that ES cells can give rise to pancreatic beta cells during development. "But the more interesting question for us has been what happens in mature pancreatic tissue to both maintain the pancreas and regenerate it," says Melton. "Previous studies have suggested that there are sources of adult stem cells that might give rise to beta cells. However, those studies had largely depended on histological 'snapshots' of tissues." Those

snapshots can only suggest the "geographic" origin of new beta cells and not the identity of the cells from which they arise, Melton notes.

Melton and his colleagues knew that they could finally put such questions to rest if they could tag beta cells in such a way that they could determine unequivocally whether the new cells were made from existing beta cells or from a different reservoir of stem cells. For these studies, they devised a "genetic lineage tracing" technique that involved engineering a mouse whose beta cells contained a telltale genetic marker that could be switched on by administering the drug tamoxifen to mice.

#### REPLICATIVE CAPACITY?

When the researchers applied their technique to the mice, they discovered that all the new beta cells they examined—whether arising in the usual process of renewal or during regeneration following partial removal of the pancreas—were generated from preexisting beta cells. According to Melton, the finding highlights a largely unappreciated capability of beta cells.

"No one has really paid much attention to the replicative capacity of the beta cell," he says. "And this work shows the cells to have a significant proliferative capacity that could be clinically useful."

According to Melton, the findings might have implications for developing treatments for type 1 diabetes, a disease that destroys beta cells. "If such people have residual beta cells, these findings suggest that a useful clinical direction would be to find a way to boost the proliferative capacity of those beta cells, to restore insulin production in such patients.

"On the other hand," he says, "if type 1 diabetics don't have any beta cells left, then these findings suggest that the only source of new beta cells is probably going to be embryonic stem cells, because there don't appear to be adult stem cells involved in regeneration."

The genetic lineage tracing technique can now be used to trace the origin of cells involved in the maintenance and repair of other types of tissue. Melton and his colleagues are already using the technique to determine the origin of new cells in lung tissue. And it should be possible to apply the technique to understand the origin of cancer cells in tumors and to understand the role of stem cells in such malignancies, Melton says.

—DENNIS MEREDITH and  
JIM KEELEY