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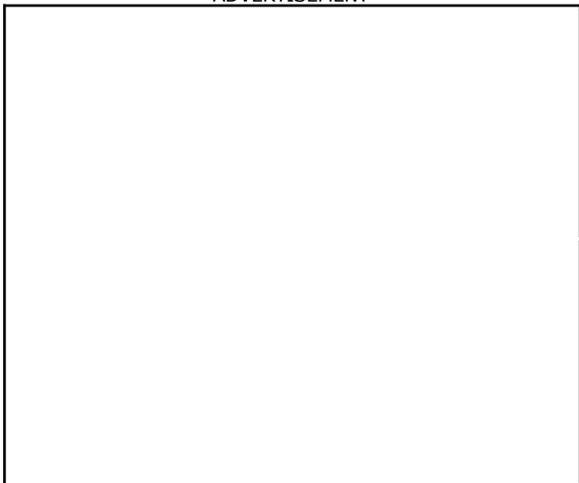
## US stem cell research lagging

The Boston Globe

May 23, 2004

**Page full of 4** -- BRNO, Czech Republic -- Last spring, biologist Petr Dvorak's cellphone rang with the news that his lab, a simple cement building not far from the rolling farmland of Moravia, had just entered the forefront of global science.

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He rushed to work, down a cracked blacktop walkway and past a sagging barbed-wire fence. Then Dvorak, 48, peered through a microscope and saw what had triggered the call: He and his team had isolated a new line of human embryonic stem cells.

"We were so happy," said Dvorak, who is a member of the Czech Academy of Sciences. "I couldn't sleep for a week."

Although the first human embryonic stem cell line was created in the United States, a Globe survey has found that the majority of new embryonic cell lines -- colonies of potent cells with the ability to create any type of tissue in the human body -- are now being created overseas, a concrete sign that American science is losing its preeminence in a key field of 21st-century research.

Nearly three years ago, the Bush administration prohibited the use of federal money to work with any embryonic cell lines created after Aug. 9, 2001, because of moral concerns over the destruction of human embryos. At the time, the president said there would be more than 60 lines of these cells available. But today there are only 19 usable lines created before that date, and that number is never likely to rise above 23, according to the National Institutes of Health.

However, the number of cell lines available to the world's researchers, but off-limits to US government-funded researchers, is now much higher: at least 51, according to the survey. It could rise to more than 100 over the coming year. There are three new lines in Dvorak's lab, with four more in progress. And there are also new lines in Sweden, Israel, Finland, and South Korea. Last week, the world's first public bank of embryonic stem cells opened in the

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United Kingdom, a country where there are at least five new lines and more on the way.

"Science is like a stream of water, because it finds its way," said Susan Fisher, a professor at the University of California at San Francisco. "And now it has found its way outside the United States."

At a time when reports show the United States is losing its dominance in other areas of science, Fisher and many other researchers say they are increasingly worried that America is not building a competitive foundation in one of the most active areas of biological discovery. Many scientists believe that embryonic stem-cell research has the potential to yield profound insights into a range of afflictions, including Parkinson's disease and diabetes, which affect millions of Americans. By restricting American use of these cells, they say, the government is effectively keeping them out of the hands of many top scientists -- both slowing the pace of research that could lead to cures, and potentially putting the country behind in technologies that could be major business opportunities in the new century.

Included on the list of off-limits cell lines created since 2001 are some cells that are easier to use and would be safer for patients than the Bush-approved lines. Others are tailored for the study of particular diseases.

Each cell line is a colony of cells derived from a single embryo, which share the same DNA. One of the new cell lines has the common genetic mutation underlying cystic fibrosis. This cell line, developed overseas and not yet described in a scientific journal, could reveal the biological underpinnings of a debilitating disease that affects some 30,000 Americans. The US government will not pay for scientists to grow or study these cells because they were created recently.

The ballooning list of forbidden cell lines could add energy to a rebellion over stem cell policy within the president's own Republican Party. Thirty-six Republicans were among the 206 members of the House of Representatives who signed a letter asking the president to reconsider the ban. And two weeks ago, Nancy Reagan delivered an impassioned plea for research that might one day prevent the horror of diseases like Alzheimer's, which she said has taken former president Ronald Reagan "to a distant place where I can no longer reach him."

For most diseases, embryonic stem cell research is likely many years from offering any help to patients. But it is becoming increasingly apparent that if researchers begin to make medical progress, the US government -- which funds the vast majority of basic science research in this country -- will be able to take little credit.

For many foreign scientists, the restrictions imposed on the world's leading biomedical power represent an opportunity. Dvorak once used old rum bottles as flasks in his underfunded lab. Now he is talking to a professor at Harvard Medical School, Dr. Ole Isacson, about collaborating on research.

"He is swimming," said Isacson, whose lab at McLean Hospital is famous for its research on Parkinson's disease. "But for us, it is like trying to swim on dry land."

\* \* \* When human embryonic stem cells were first isolated, the breakthrough happened in an American lab.

In November 1998, a team of researchers lead by biologist James Thomson of

the University of Wisconsin-Madison announced it had isolated human embryonic stem cells and could grow them in a dish. Embryonic stem cells, taken from a microscopic embryo in its first few days of development, are in a sense the most primordial and powerful human cells, and can develop into any part of the body.

The announcement created a sensation. It was clear these cells would be an important new tool for studying human biology, and they also raised the prospect that a wide range of diseases might be treated someday by replacing a patient's damaged cells. Yet the work is also ethically controversial, because growing stem cells requires destroying a human embryo. This led critics to charge the practice amounted to taking human lives and could not be justified no matter how great the potential benefits.

In 2001, President Bush attempted to broker a compromise: In a nationally televised speech, he said that federally funded research would be limited to cell lines already in existence. He said that the more than 60 lines already derived would be enough for researchers to continue their work without using government money to destroy more embryos.

Although much basic biological research remains to be done on the cell lines created before Aug. 9, 2001, it has become clear to American scientists that the Bush policy has put them at a disadvantage compared with many of their colleagues overseas. Human embryonic stem cells are notoriously difficult to handle, and deriving each new line gives the team in the laboratory a deeper understanding of stem-cell biology and essential practical skills. Abroad, this work is exploding, while in the United States only a handful of labs are able to do it.

"A lot of stem cell biology is like gardening," said Stephen Minger, who isolated the cystic fibrosis cell line and is an American scientist who now works at King's College London. "Some people can grow orchids, and some can't grow tomatoes."

Governments around the world are stepping into the gap, and a number are emerging as powerhouses in the field.

In the United Kingdom, as in the United States, there has been contentious public debate over embryonic cell research, but the government has designed a system of strict oversight. With the opening last week of the new UK Stem Cell Bank north of London, funded by the government at \$4.6 million over three years, that country is taking the kind of international leadership role which in other fields has fallen to the United States. The bank will accept cell lines that meet a set of ethical standards, carefully study and grow them to ensure they are scientifically useful, and then make them available to researchers.

"We see this as a truly international effort," said Glyn Stacey, the new bank's director.

In Australia, the government is funding research and helping to set up a national stem cell center. In the Czech Republic, Dvorak's lab at the Mendel University of Agriculture and Forestry is part of a Centre for Cell Therapy and Tissue Repair, supported by the government. South Korea has derived almost as many new lines of human embryonic stem cells as the United States, according to the Globe survey, and researchers there were the first to create stem cells from a cloned human embryo -- a scientific milestone that American researchers grumble should have happened in the United States.

\* \* \* This rush of work overseas is yielding other important advances, such as technology that could be key in turning the science of embryonic stem cells into usable therapies. All of the cell lines on the US government approved list are grown on a layer of mouse cells. These mouse cells, called a "feeder layer," sustain the human cells, but could also transmit mouse-borne viruses, making them potentially dangerous for use in humans.

Dvorak's laboratory has just begun working with human feeder cells instead, a technique that could yield cells safe to transplant back into humans. Already, laboratories in Singapore, Israel, Sweden, and Finland have isolated lines of stem cells that don't need mouse feeder cells. Only one American lab has done so: Susan Fisher's California lab, which is barred from receiving federal funding and is supported in part by the California-based biotech Geron Corp.

None of these lines, including Fisher's, can be used by government-funded scientists in America. The result is that American scientists with private funding are making advances that they can share freely with scientists overseas, but which they cannot share with colleagues in their own departments.

As much as the Bush rules have limited embryonic stem cell research, they have prompted a substantial private effort to keep the research moving forward. Harvard announced last month that it is building a privately funded effort to do the work, and it has a fund-raising goal of \$100 million. The University of California, San Francisco is already underway with a similar effort, started with a \$5 million gift from Intel's Andy Grove, as are a number of other academic institutions. Earlier this month, the governor of New Jersey signed an agreement opening the nation's first state-funded stem cell institute.

Thanks partly to this effort, none of the researchers contacted by the Globe said they had seen signs of a scientific "brain drain" that some critics predicted. But still they worry about the more subtle side effects of the Bush policy. Many of the world's top disease specialists work at universities in the United States, yet they are largely unable to work on embryonic stem cells, and the universities are likely to have more trouble recruiting talented foreign scientists interested in embryonic stem cells.

At the same time, top American researchers who might otherwise jump into the field are avoiding it because of the risks, scientists said. And some worry that younger stem cell scientists, who don't have an established lab to keep them in the United States, will move abroad, and perhaps stay there.

"That is really something to keep an eye on," said John Gearhart, one of the field's founders and a professor at Johns Hopkins Medicine. Gearhart said that many of the younger scientists in his lab are interested in pursuing further training abroad.

Yet there could be changes coming. Last weekend, the NIH issued a letter hinting the White House may be open to changing its policy at some point. The letter, written by NIH director Dr. Elias A. Zerhouni, was a response to a letter signed by 206 members of the House of Representatives. In it, he acknowledges that "from a purely scientific perspective more cell lines may well speed some areas of human embryonic stem cell research."

US Representative Michael N. Castle, a Delaware Republican who helped organize the House letter, said that it seems to represent a softening of the White House stance. In Congress, he said, support for stem cell research is increasing, and he added that he has been struck by the degree to which some people change their minds when they meet with patients who are

suffering. "There doesn't seem to be a lot of gray area," Castle said. "They become real advocates."

In the meantime, many scientists abroad are nearly giddy with the possibilities the field now presents them. Dvorak and a colleague, Ales Hampl, are preparing to come to Boston for a major conference next month, organized by the International Society for Stem Cell Researchers. While he is in Boston, Dvorak is going to make a presentation of his work at Isacson's lab.

Because of federal restrictions in the United States, Isacson said that he has been increasingly looking abroad for collaborators who are more free, and Dvorak is one possibility.

Sitting in his modest Czech office, next to a fax machine that doubles as his phone, Dvorak said that he is nervous about presenting at Harvard, and has already had nightmares. After many years of laboring in obscurity, a collaboration with Harvard would be a vindication for him, but he struggles to find the words in English.

"It would be like being in heaven," suggested Hampl.

"Yes," said Dvorak, "like being in heaven."

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