

## Asia, Europe moving to stake claims in promising stem cell research industry

by Terri Somers

While President Bush remains steadfastly against human embryonic stem cell research, limiting federal funding on moral grounds, nations around the globe are pouring millions of dollars into the field.

In the United Kingdom, the government has committed to spending \$1.3 billion on stem cell research in the next 10 years. Some of the money will support the construction of five manufacturing facilities to produce millions of pure stem cells for research.

**STEM CELL FUTURE** - Larry Goldstein, a professor at University of California San Diego, says the U.S. still has one thing ahead of other countries in stem cell research: a concentration of senior researchers to ask the right scientific questions. CNS Photo by Scott Linnett. Chinese scientists educated at top universities in the United States are being drawn home by their government with the promise of funding and leadership of labs staffed with eager young researchers. Some scientist-physicians there already are treating patients with stem cell discoveries they have made.

The Singapore government is funding Biopolis, a high-tech hamlet for biotech with an emphasis on human embryonic stem cell research. The \$400 million complex can accommodate 2,000 scientists working at government-funded laboratories or private biotech and global pharmaceutical companies.

As these countries and others surge ahead in their research, they see the prospect of creating new treatments and cures for chronic illnesses while saving billions of dollars on health care.

They also see the chance to stake a claim in a potentially lucrative new industry while the United States is sidetracked by a political and moral debate.

"For the first time, we have a lot of competition ... I don't think we've had as much concern for another country besting us in science since the race to the moon," said Dr. Evan Snyder, who runs the embryonic stem cell research program at the Burnham Institute in San Diego.

It is a competition with crucial consequences for San Diego County and California, home to leading stem cell researchers and 50 percent of the world's biotechnology research.

The field is seen as especially promising for creating treatments for incurable diseases and money-saving tools for drug discovery.

California voters have tried to help. In 2004, they approved spending \$3 billion on stem cell research, but the money has been held up by legal challenges.

NO CLEAR LEADER

To be sure, it is a race that is hard to predict.

Until November 2005, South Korean scientist Woo Suk Hwang was considered a leader in the field after he claimed to be the first to efficiently create embryonic stem cell lines through a complicated cloning process that no one had been able to master.

Hwang turned out to have falsified some of his studies, and his work was discredited. Researchers around the globe have had to backtrack and try to master that feat.

China reportedly is doubling its investment in stem cell research. But an air of mystery and skepticism surrounds China's work, because the country's regulatory guidelines differ from those in the West and because research from Chinese scientists has not been widely published.

The United Kingdom already has invested about \$198 million in stem cell research at 90 laboratories, of which 11 are licensed to conduct human embryonic stem cell research.

Singapore, with just 4 million citizens, is investing \$25 million to \$29 million annually in research, excluding overhead costs and infrastructure.

That investment may seem wimpy compared with the \$609 million the United States government spent on stem cell research last year. But because of federal funding restrictions on human embryonic stem cell research, only \$20 million to \$40 million a year - about 6 percent at best - has been directed to that field.

Money is not the sole catalyst of success. Scientists say supportive government policies that free them to concentrate on their work, national commitment and contagious scientific enthusiasm are just as important.

"Here we are again, sitting on the beginning of another revolution, a possible way to provide cures rather than treatments," said Chris Mason, a stem cell researcher at University College London. "The U.K., Singapore and other countries realize what might be within their grasp if they spend the money on the front end, and they don't want to miss it."

The United States, long the world leader in biomedical research and commercialization, is getting a taste of being the underdog.

## PRICELESS SUPPORT

Scientists working in the United States, such as Larry Goldstein at the University of California San Diego,

must troll for nonfederal funding sources so they can work on all types of embryonic stem cells.

To stay on the right side of the law, Goldstein and the 25 people in his lab must be vigilant not to use government-funded microscopes or cell sorters to look at embryonic stem cells created after Aug. 9, 2001.

That was the day President Bush issued an executive order that federal dollars would not fund the destruction of human embryos for the creation of new stem cell lines. Many Americans, Bush included, see these embryos as a life that should be protected, rather than sacrificed to science.

Scientists say the original embryonic stem cell lines are mutating with age and don't provide enough genetic diversity. The cell lines could never be used to develop therapies for use in humans because they are contaminated, having been grown in nutrients polluted with mouse cells.

Outside the United States, governments are funding scientists' efforts to create new, diverse and uncontaminated cell lines.

In Singapore, a private company called ES Cells International, or ESI, is coaxing human embryonic stem cells into becoming insulin-producing pancreatic cells. Run by British scientist Alan Colman, a member of the team that cloned Dolly the Sheep, ESI is also collaborating with a government lab to develop a plant to manufacture millions of the pure cells that eventually will be needed to test new therapies.

In a synergy, government-funded researchers in Singapore have come up with an animal-cell-free substance, the culture medium in which stem cells are grown, so that ESI can begin to cultivate the large number of cells it will need.

The only manufacturing facility in the United States as advanced as Singapore's belongs to Geron, a Menlo Park, Calif., company that is readying an embryonic stem cell therapy for spinal injury for the next step of clinical trials in human patients.

Scientists in Sweden and India are developing tests that use embryonic stem cells to determine the toxicity of potential therapies.

In Israel, scientists are changing the genetic makeup of embryonic stem cell lines by deactivating specific genes. Such lines enable scientists to determine how the gene functions, and the cells can serve as a model for a human disease on which treatments one day may be tested.

Scientists at Kyoto University in Japan reversed the cell-development clock when they turned skin cells from a mouse back into embryonic stem cells by introducing four genes. They now are trying to replicate that work on human cells.

President Hu Jintao of China has stressed the importance of embryonic stem cell research to his country, where staggering poverty makes health care inaccessible to millions of people.

"China is the sleeping giant," said Fred Gage, an embryonic stem cell researcher at the Salk Institute for Biological Studies in San Diego.

Chinese physician-scientists with access to hundreds of patients are testing experimental therapies directly on humans. In the United States, only Geron has reported approaching readiness for clinical trials of a human embryonic stem cell treatment.

Although the Chinese government has often hyped its investment in the field, it is hard to say how much support the government is really providing.

An article in *The New England Journal of Medicine* in September said China's national and local governments, specifically Shanghai and Beijing, have invested roughly \$38 million in stem cell research since 2000.

A report by the United Kingdom Stem Cell Initiative said the Chinese government is expected to funnel as much as \$132 million annually into the research over the next five years.

Stephen Minger, an American stem cell scientist who moved to London more than 11 years ago, said every lab he saw during a recent visit to China had hugely expensive, state-of-the-art equipment and was buzzing with young scientists. Many of those scientists had been educated in the United States and Europe.

One area in which the United States' biotech prowess has enabled it to stay ahead of the global pack is in figuring out the role that genes in different embryonic stem cell lines play in biological functions, including a disease.

But much of the interesting work in that field is now happening in Finland and Singapore, said Mahendra Rao, who was formerly one of the top researchers at the U.S. National Institutes of Health.

Foreign scientists also repeatedly cite the efforts of Harvard scientists to attract private funding and push human embryonic stem cell research forward despite the lack of federal government support.

Some American scientists have moved overseas to pursue stem cell research, or now divide their time between the United States and one of the nations considered to be more open to stem cell research.

And there is criticism that many scientists in the United States are spending too much time trying to develop techniques that would allow them to create embryonic stem cells without destroying an embryo. Such a discovery might circumvent the moral and political debate.



The United States, however, isn't the only nation engaged in vigorous debate about the morality of using human embryonic stem cells.

Germany does not allow the importation of human embryonic stem cells from other countries. A license for human embryonic stem cell work in Germany can be obtained only if a scientist proves his research cannot be conducted in any other way.

But most of the scientific world has moved on.

On Dec. 6, Australia's government eased restrictions by permitting therapeutic cloning to create new stem cell lines. That debate played out in the United Kingdom during the 1970s and 1980s, when scientists there were pioneering in-vitro fertilization. In China, it is considered immoral not to try to help ease someone's suffering if the possibility of a remedy exists.

LOSING GROUND

There are already signs that the United States may be losing its commercial edge.

As the head of stem cell research for Invitrogen, a Carlsbad, Calif.-based biotechnology company, Rao sees many potential licensing opportunities.

"In the past, the large majority were from the U.S.," Rao said. "(In the case of human embryonic stem cell research), it is more like 60 percent from outside the U.S. and 40 percent from inside the U.S."

Invitrogen's sales figures on tools and materials for human embryonic stem cell research suggest the same trend, he said. Usually the United States is the biggest market in the world.

Now other countries, including India and some European nations, are pushing to move possible therapies into the clinic faster than the United States, Rao said.

One thing that might help the United States stay competitive is that embryonic stem cell scientists worldwide share the same hurdle: the science itself.

"The biology is tough, and sometimes it just doesn't matter how many people you have working on something, or how much money you throw at something, because understanding the science is the greatest obstacle," said Snyder, who runs the Burnham Institute's embryonic stem cell program.

The United States also possesses something other countries cannot buy or steal: the breadth and depth of its scientific prowess.

"We might not have all the money or all the toys, but we still have what you really need: the experienced people to ask the right scientific questions," said Goldstein, a Howard Hughes investigator at University of California San Diego.

But some scientists feel that even if U.S. policy were to be reversed, it would be difficult for the United States to regain lost ground.

Still, many American scientists remain optimistic because the U.S. market and venture capital pool remain globally dominant.

"There is something indomitable about the American spirit that allows American scientists who are really driven and really smart to figure out a lot of ways to circumvent any difficulty," Snyder said. "We have a lot of confidence despite the competition internationally that we will probably, somehow, win the game in terms of bringing therapies to patients."

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