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An American puzzle: funding embryonic stem cell research

BY KATHRYN GRIM

They call it "stem cell land."

The two-room laboratory on the 13th floor of Northwestern's Feinberg School of Medicine is about the size of a dorm room. It houses drawers full of slides and pipettes, a collection of microscopes and the progeny of four human embryonic stem cell lines.

According to the original design, the rooms were to be separated by a border not all researchers could cross. Federally approved stem cell lines – created before Aug. 9, 2001 – would live and grow on one side. Newer, privately funded stem cell lines would stay on the other, and never the twain would meet.

This compartmentalized design responds to a uniquely American conundrum.

In 2001 President George W. Bush prohibited the use of federal funding for research involving human embryonic stem cell lines created after Aug. 9, 2001. He said he opposed the creation of new lines because the process involves the destruction of a human blastocyst, a ball of about 100 to 140 cells that can eventually develop into an embryo.

Since then, the president has twice vetoed a bill passed by Congress to allow federal funding for embryonic stem cell research.

The creation and study of new embryonic stem cell lines is still legal, just complicated.

Dr. John Kessler, director of Northwestern University's Stem Cell Institute and the Feinberg Clinical Neuroscience Institute, has decided it's too difficult to study approved and unapproved cell lines at once. So the federally approved lines, paid for by the federal government's National Institutes of Health, now occupy both territories of "stem cell land."

Otherwise, not even a pen purchased with NIH funding could be used in connection with a privately funded line.

"That's exactly why I chose not to set it up," Kessler said, "because if I have a student who's on a training grant and they're federally funded, I can't have her work with non-federally approved lines. And if I have a technician who's paid for from NIH funding, I have to try and split the salary and do a strict accounting of how much time is spent in one room versus how much time is spent in another room."

As an NIH Center of Excellence in Human Embryonic Stem Cell Research, Kessler's lab receives much of its funding from the federal government. Maintaining the cell lines, paying staff and conducting experiments cost the lab about $200,000 a year, with maintaining the lines accounting for most of the expense.

Federally approved stem cell lines now cost $500, one-tenth of the price in 2001, when they sold for $5,000, Kessler said.

Some researchers give away newly derived, federally non-approved stem cell lines for free even though the process of deriving a new line can cost tens of thousands of dollars, Kessler said.

Federally approved lines vs. privately funded

Embryonic stem cells are non-specialized cells that can divide indefinitely into identical copies of themselves. Human embryonic stem cells have the ability to become any cell in the human body.

PhD student Chris Bissonnette works with two of the four stem cell lines in Kessler's lab.

He has been studying Alzheimer's disease since high school. Memory loss in Alzheimer's patients is associated with the death of a neuron that helps other neurons communicate with one another in the brain. Neurons are cells that transmit messages in the nervous sytem. When Bissonnette joined Kessler's lab, he began looking for a way to use stem cells to replace lost neurons.

"I was really excited," Bissonnette said, "because I think there's a very low chance for what I'm doing to work, but if it does work, then it'll have a large effect for millions of people."

Working with stem cells has not been easy, Bissonnette said, in part because no two embryonic stem cell lines are alike.

"There seems to be a huge difference in how each of these different cell lines work," Bissonnette said.

Of the two lines Bissonnette uses, one grows faster, but the other grows more robust neurons that tend to live longer. To divide them and grow new colonies, he has to use different concentrations of enzymes.

Bissonnette said one benefit of working with the federally approved lines is that so many of his peers have worked with the same lines.

The National Stem Cell Bank, associated with University of Wisconsin-Madison, lists only 18 federally approved stem cell lines for sale. Developmental biologist James Thompson derived the first human embryonic stem cell line there in 1998.

"Even though they're all embryonic stem cell lines, they generate different kinds of cells and they grow in different kinds of conditions," Bissonnette said. At least with the federally approved lines, "you can ask people in other labs how things have worked."

Bissonnette works with H7, a stem cell line originated in Madison, and HSF1, a line originated in San Francisco. Kessler's lab uses one other line from Wisconsin and a fourth from Israel.

The peculiarities of each cell line's personality also provide an argument in favor of creating new stem cell lines to study, Kessler said.

"Things that will affect cells from one person may not affect cells from another person the same way," Kessler said. "We really have to understand: What are some of the signaling mechanisms that cross backgrounds? So we need a diversity of cell lines."

Unless frozen, stem cell lines are continuously growing. They grow in round colonies of identical cells. Researchers duplicate a colony by moving it to another dish, breaking it into smaller clusters and allowing those clusters to continue to grow. This is called “passaging.”

Researchers are interested in newer cell lines because with each passage, a cell line risks developing abnormalities.

“The ones that we’re working with now are at, like, 56 passages,” Bissonnette said. “A whole lot could’ve happened in those 56 passages to change what they could become.”

To make sure the lines haven't been damaged, Kessler’s lab has them screened for defects about once a month, at a cost of about $400.

Growing stem cells

Once you get a stem cell line growing, it’s about as much work as raising a puppy.

“There are times that I’ve worked seven days a week for six months at a time,” Bissonnette said, “because once you’re doing experiments, you can’t stop them. You can’t go away for the weekend or take a break because these things need to be fed. Every single day.”

Kessler hired scientist Ljuba Lyass to cultivate the four stem cell lines in his lab. It’s a full-time job.

“Stem cells are very hard to grow,” Lyass said. “They’re not like other tissue culture cells. They’re more picky.”

Each line has its own preference for the kind of media in which it will grow, but the general recipe includes artificial protein, salt, sugar and growth factors that signal to the cells not to differentiate, that is, become other kinds of cells.

The first stem cell lines, including those created before Aug. 9, 2001, were grown on mouse feeder cells. These feeder cells are minced and treated embryonic mouse cells that secrete growth factors into the media, “which makes it tasty for human cells,” Lyass said.

Many lines still survive on this diet.

“You always have to have those mouse cells growing,” Lyass said. “That feeder’s only good for two weeks. And then you have to start all over again.”

Last year, Lyass started buying small quantities of a newly developed artificial medium that can replace the mouse feeder cells. The artificial medium costs $250 or more per bottle, whereas the medium that requires mouse feeder cells costs between $12 and $15, she said.

“I would’ve probably never even tried to buy it because it’s so expensive,” Lyass said. “But I saw how the cells look on that media, and I already knew it was a great thing… They don’t differentiate at all. They look very pretty, easy to maintain.”

Researchers do not know whether interaction with mouse cells has affected the validity of studies of human stem cell lines, Kessler said. But he would prefer to use lines that have not been in contact with animal cells.

“If we had a different federal policy, then I would’ve in an eye blink used some of the newer cell lines in the projects that are ongoing in the lab,” Kessler said. “I don’t think that in the long term it’s possible for this field to not study new lines.”

Whatever next inhabits “stem cell land” may depend on whoever next inhabits the White House.