STEM CELLS TOUTED FOR DRUG RESEARCH

SCIENCE

BY NEIL MUNRO

The controversy over stem-cell research is twisting in two new directions: Research advocates of stem cells drawn from human embryos are beginning to highlight the cells' potential use in accelerating the development of new drugs; rival advocates of less-controversial stem cells drawn from human adults and umbilical cords, meanwhile, are highlighting the accelerating use of these cells today in hospital treatments for a variety of ailments.

These new twists in the long-running debate over stem cells come as advocates for embryonic stem-cell research step up their promotion of new initiatives in several states that, like last year's successful initiative on the California ballot, would pump hundreds of millions of dollars into embryo-cell technologies. In Massachusetts, New Jersey, and New York, these measures have been promoted as steps toward the cure of deadly diseases, and also as providing benefits to local medical and drug companies and state economies.

In recent years, researchers and advocates have primarily held out the promise that embryonic stem cells could one day be transplanted to repair damaged spinal cords and organs in adults. But this promise is still years away. It will take 10 years of development to reveal whether the embryonic stem cells hold such potential, said Charles Jennings, executive director of the Harvard Stem Cell Institute.

So now, advocates are touting the use of embryonic stem cells as a way to speed the development of safe drugs. Advocates say the use of stem cells from human embryos—and especially from cloned embryos—can reduce the 15 years and roughly $650 million needed by the pharmaceutical industry to develop each new drug. "That may be the first low-hanging fruit from this [embryo-cell] platform," said James Battey, an advocate of embryo-cell research who chairs the stem-cell task force at the National Institutes of Health.

Researchers say that the use of embryonic stem cells in drug testing could be a breakthrough, because such cells can morph into all types of human cells and could be produced en masse for industrial-scale testing.

RICHARD A. BLOOM

JAMES BATTEY: Chairman of a stem-cell task force at the National Institutes of Health says that embryonic stem cells could be used to shorten the drug-development process.

CEOs say that the pharmaceutical industry spent $39 billion on research and development in 2003, often in partnership with smaller biotech companies, which alone spent about $10 billion on research that year. Even a minor percentage reduction in those drug-development costs could save the pharmaceutical industry hundreds of millions of dollars.

The drug-development process resembles the game of Chutes and Ladders. At any one point in the 15-year development process, a testing setback or misjudgment can send the researcher sliding back down a chute toward Square One. Every step up the ladder costs millions of dollars, especially once the drug reaches the testing phase on human volunteers in clinical trials. Setbacks often occur, for example, as a compound moves from testing on animals—such as mice—into testing on humans. That's mainly because the biochemistry of laboratory animals is similar, but not identical, to human biochemistry.

The costs of these setbacks and failures can be very high, especially for drugs almost ready for sale. And if unintended side effects or safety concerns crop up once a drug is in widespread use, its maker can face financial catastrophe. For example, the value of Merck's stock fell from $45 a share last September to $32 by March—wiping out about $30 billion in paper value—when its arthritis painkiller, Vioxx, was withdrawn from the market after a study showed that it increased the risk of heart attacks and strokes.

Errors in the testing phases can slow the drug-development process considerably or even cause a company to pull the drug from the market. Such costs add up to $8 billion each year, said Thomas Okarma, CEO of Geron, of Menlo Park, Calif., which holds several critical licenses to use embryonic stem-cell technology. "It is a huge issue, which is why [the pharmaceutical industry] is so interested in these kinds of technologies," he said.

If you're a researcher or a company, "you want to be sure of the effect of the chemical entity before you give it to a patient; you want to reduce the use of animals; and you want to reduce the time it takes to do all this stuff," said Michael Werner, chief of policy at the Biotechnology Industry Organization, whose members include small biotech companies but also large pharmaceutical companies like Merck and GlaxoSmithKline. Using embryonic stem cells in early drug research and testing is "a tremendous benefit that is often not discussed, maybe because it is not as sexy," he said.

During a March 17 hearing before the Health Subcommittee of the House Energy and Commerce Committee, NIH Director Elias Zerhouni said that NIH has been funding research on mouse embryonic stem cells for decades. The technology, he said, has led to the development of new mouse "models": mice that researchers have specially remodeled at the embryo stage for use in a wide variety of scientific and medical experiments. The same techniques, once applied to human embryos and their stem cells, could have a "very significant" impact on the drug-development process, Zerhouni told *National Journal*.

Here's another example. In New York state, a research team has developed an artificial womb that can nurture human embryos to the point when they can be used as models in experiments. "This model

would provide new avenues for testing new drugs, bypassing human subjects completely and substantially lowering costs involved with drug testing," Hung-Ching Liu, the team's lead scientist, told *National Journal* in 2004. Liu works at a private fertility clinic and at Cornell University's medical college.

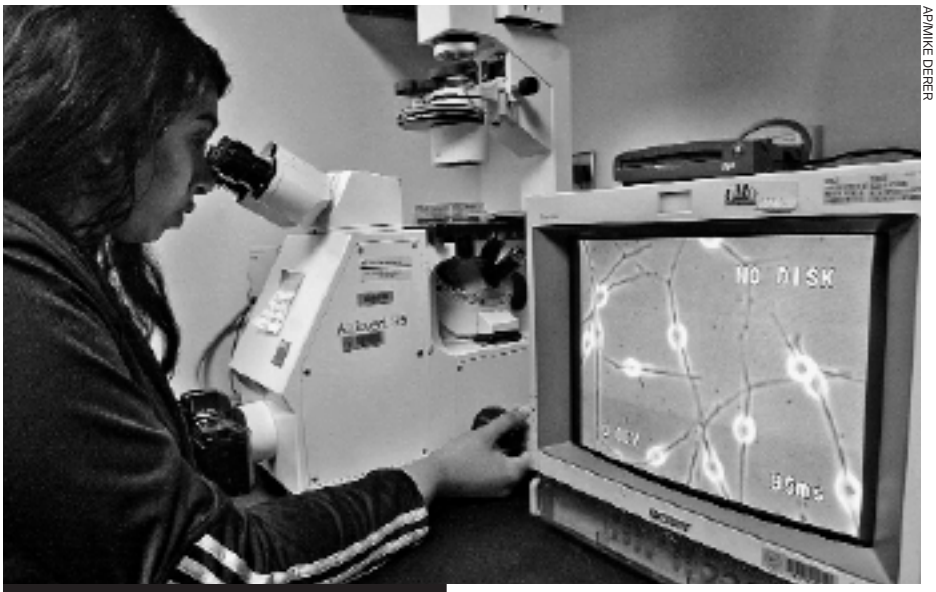
Embryonic cells, Okarma said, can also help scientists and researchers better understand the interplay of genes, and so allow them to better identify chemicals that will likely be useful as drugs. Embryonic stem-cell gene research, for example, might reveal classes of patients for which withdrawn drugs such as Vioxx are safe, allowing the companies to resume selling those drugs, he said. "The drug companies are dying to be able to do this thing."

And other sectors of the pharmaceutical industry could benefit as well from the use of embryonic stem cells in research, particularly companies that sell equipment, tools, and models to drug researchers. The annual market for laboratory animals, for example, is about $1 billion, and the market for laboratory embryo cells could also be large. The holders of patents on stem-cell technologies could get a boost, too. For instance, perhaps $1 billion of the $3 billion allocated by Californian voters to stem-cell research may end up in Wisconsin, suggested Carl Gulbrandsen, managing director of the Wisconsin Alumni Research Foundation, in Madison, Wis., which holds the legal rights to crucial stem-cell technologies. "What's going on in California will increase licensing opportunities for Wisconsin," he said at the AEI meeting.

In contrast to the long-term potential of embryonic stem cells, hospital-based doctors say they are making rapid strides—today—in developing therapies that use the uncontroversial stem cells found within adults and the umbilical cords from newborns. "We are seeing remarkable results in heart disease" from the use of adults' own stem cells, said John Gearhart, a professor of medicine at Johns Hopkins University in Baltimore. The results from clinical trials in South America show that adult stem cells are "remarkably effective, at least in the short term," he told a March 9 meeting at the American Enterprise Institute. Gearhart is a leading researcher in and advocate for the use of embryonic stem cells. But he also acknowledges the progress made in treatments with adult stem cells.

In the South American trials, hospitals in Brazil used stem cells drawn from an adult patient's bone marrow—then enhanced the cells in a laboratory and reinjected them into the body. The cells help rebuild heart veins and muscles, thereby strengthening the heart's pumping action by roughly 50 percent, said James Willerson, who recently launched a 30-patient trial at the Texas Heart Institute at St. Luke's Episcopal Hospital in Houston. Willerson heads the institute and the University of Texas Health Science Center, and he has asked the state Legislature to allocate $65 million to create a center for adult stem-cell research.

Stem cells drawn from adults have been used in a similar fashion since the early 1980s to treat cancers such as lymphoma, Hodgkin's disease, and leukemia. Back then, such a procedure killed 20 percent of the patients and cost $200,000 to perform; now it costs less than $100,000, and the mortality rate is down to 1 percent. Some 20,000 of the procedures are conducted in the United States each year.



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STEM-CELL BANDWAGON: New Jersey, like California, is looking to use state funds for stem-cell research, particularly at the fledgling Stem Cell Institute in Piscataway, N.J., pictured here.

Hospital doctors are also successfully using patients' own stem cells to treat a variety of other diseases, including sickle-cell anemia, Parkinson's, and spinal-cord injuries. And despite the small use of this treatment, confidence in the technology is growing.

At the Feinberg School of Medicine at Northwestern University, Richard Burt is already getting reimbursement from insurance companies that have agreed to cover his use of adult stem cells to treat patients with multiple sclerosis, lupus, Crohn's, and several other diseases. Burt draws stem cells from bone marrow; kills the patient's existing immune system with chemotherapy; and then rebuilds the immune system with the enhanced stem cells. Aetna, Blue Cross Blue Shield, UnitedHealthcare, Medicaid, and Medicare are paying for the treatments.

Kathryn Wright, a New York City resident, was treated recently at Burt's clinic for severe rheumatoid arthritis. For the 10 years before her surgery, she said, she suffered from "complete all-over body pain, except in my jaw, [and was] so achy you can't even think" or work. After the procedure, the pain almost disappeared; it "was incredible, phenomenal.... I could walk without pain [and] think much more clearly." Unfortunately, Wright later had a partial relapse, which, she said, might have been caused by a too-rapid reduction in the anti-swelling medication she had been taking.

NIH says it spends about $190 million of its $28 billion annual budget on adult stem-cell technology, and $24 million on embryo stem-cell research.

Many scientists say that more should be spent on adult stem-cell research. In light of its promise, "it is inconceivable that we would be spending only $190 million on that research," said Wise Young, director of the W.M. Keck Center and chair of the cell-biology department at Rutgers University in New Jersey. "I know many people who are not getting their umbilical-cord and adult-stem-cell research funded ... [because] NIH is not putting a high priority on this." ■

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