

Frontiers for Parkinson's

Stem Cell Research: *Beyond*

By **Gina Shaw**

Early last fall, the picture looked bright for embryonic stem cell research. The world's first stem cell bank opened in Seoul, South Korea, with plans to put Parkinson's disease and spinal cord injuries at the top of its research agenda. Its founder, Woo Suk Hwang, D.V.M., Ph.D., announced that the World Stem Cell Hub would create some 100 new embryonic stem cell lines annually.

Then Dr. Hwang's elaborate house of cards fell. One shocking revelation followed another in the span of just five weeks: The renowned scientist admitted ethical violations and resigned as the center's director. A groundbreaking research paper he'd authored in the journal *Science* was withdrawn amid allegations of fraud. And finally, by year's end, an investigative panel in Korea confirmed that he'd falsified the research on all 11 human embryonic stem cell lines he claimed to have developed.

What does all this mean for the future of stem cell research?

"Despite all of the hubbub, it really does not set the field back — it's more of a psychological setback than a biological setback," says Evan Snyder, M.D., Ph.D., who directs the Stem Cell and Regeneration Project at the Burnham Institute in La Jolla, Calif. "So we thought that we had a virtuoso to lead this symphony, and now we don't. Now all the members of the orchestra are going to have to get this going. The field is still very promising, and it's moving very quickly."

Especially for Parkinson's. The disease was at the top of the Korean scientists' agenda for a reason: because experts consider it one of the most promising avenues for applying embryonic stem cell research. That

hasn't changed, Dr. Snyder says.

At first glance, using stem cell therapies to treat Parkinson's seems almost simple. The disease debilitates by destroying brain cells known as midbrain dopamine-producing neurons. Taken from primitive human embryos only days old, embryonic stem cells are undifferentiated — they have not yet begun to become the specific cell types they will eventually be. Because of that blank slate, these cells are also "pluripotent"; that is, under the right conditions they can be coaxed into becoming virtually any type of cell in the human body. So in theory, scientists should be able to "teach" embryonic stem cells to grow into dopamine-producing neurons and then transplant them into the brains of people with Parkinson's. There, they will take root, grow, reproduce themselves, and ultimately halt or reverse the course of the disease.

The reality is infinitely more complicated — which is why progress toward therapies based on stem cells can seem agonizingly slow. One of the first challenges: finding exactly the right cell

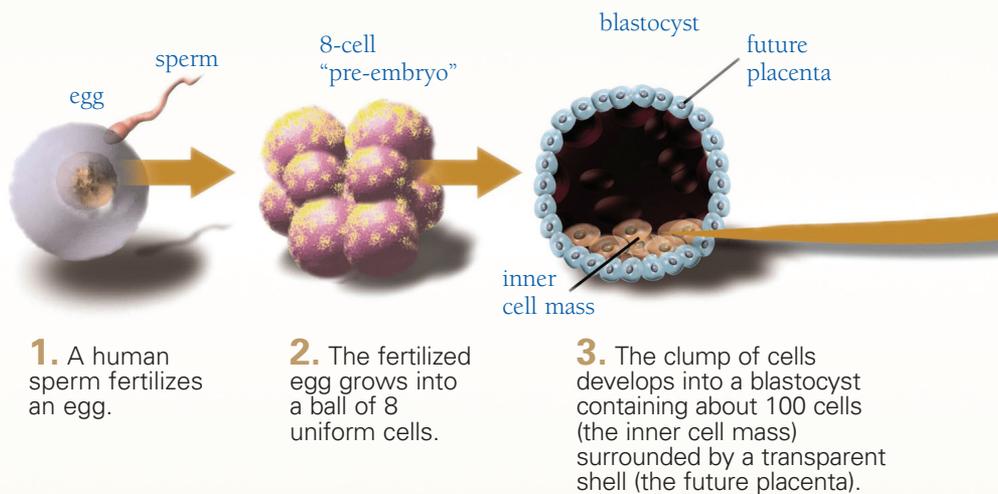
type for the stem cells to grow into. Many cells in the body produce dopamine, but not all of these cells can do the job that's needed in the brain.

"Our experiments have shown that only a particular type of dopamine cell, one we've labeled A9, will actually grow into the midbrain zone that dies in Parkinson's," says Ole Isacson, M.D., professor of neurology at Harvard Medical School and a leading Parkinson's researcher. "The others will avoid that target zone."

His team demonstrated these effects in a very dramatic way: by transplanting brain tissue from aborted fetuses into the brains of Parkinson's patients. In May 2005 the journal *Brain* published results from some of his work, a small exploratory study focused on two people with advanced Parkinson's who were treated with fetal tissue transplants. "They weren't cured," he says, "but the disease reversed back to a level slightly better than when they were on drug treatment five to ten years before."

Videos of one of the patients dramatically illustrate the remarkable

HARVESTING EMBRYONIC STEM CELLS



the Embryonic Stage?

change: On the first video, the woman shuffles down a hallway with the halting, struggling gait characteristic of Parkinson's. The next video, taken more than a year later to allow the transplanted cells time to do their work, shows the woman striding down the same hallway — still uncoordinated on one side, but vastly improved.

After both patients died of unrelated causes, Dr. Isacson studied their brain tissue and found further evidence of the treatment's effects: dopamine-producing neurons, growing along the sites where the fetal tissue had been grafted. And unlike previous experiments with fetal tissue transplantation in Parkinson's patients, there had been little inflammation and no negative side effects.

For ethical and practical reasons, fetal brain tissue transplants won't be a real-world treatment option for most people with Parkinson's disease. But Dr. Isacson is hopeful that scientists can stimulate embryonic stem cells to grow into those A9 dopamine-producing cells. He's just not sure how long it will take to produce cells of the quality

needed for use in patients. "It's a very daunting task; we're in a completely new, incredibly complex area."

A second hurdle: figuring out exactly what the stem cells should "fix."

"Treating Parkinson's is more than just replacing dopamine-producing cells," says Dr. Snyder. "For example, in amyotrophic lateral sclerosis, we've learned that even though the motor neurons die, the disease may live in the surrounding support cells. Very interestingly, we're starting to find out some of the same things in Parkinson's. So 'fixing' the disease requires stem cells to do many things."

And it looks as if they can. Dr. Snyder is studying the effect of stem cell transplantation into the brains of monkeys with Parkinson's. Preliminary studies show cell transplants have significantly improved the monkeys' symptoms — in unexpected ways.

"We think some of the stem cells do become the missing dopamine neurons, but that is a small part of their contribution," says Dr. Snyder. "Even

more importantly, the stem cells appear to be protecting the monkeys' own dopamine neurons from degenerating, and allowing them to restore their own functions."

Moving from monkeys to humans is a big step — one he's not yet ready to take. "We need to understand not only that this works, but also why it works, so we can troubleshoot it and make it better," he says. "We need to be sure we can get enough cells on demand, in the right form, to do what we want. And we need to make sure we can do it over and over and over again. We need other scientists to duplicate our results."

He and Dr. Isacson are both optimistic about the prospects for stem cell therapies in treating Parkinson's disease. "We have a long way to go, but there's a lot of potential here," says Dr. Isacson. "We're all eager to move to the stage where we can treat patients. I just wish we could work faster. But now, although we've been disappointed by some setbacks in the past, I think we're clearly on the right track."

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