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BIOTECHNOLOGY

Celebration and Concern Over U.S. Trial of Embryonic Stem Cells

Almost exactly 10 years after two groups isolated human embryonic stem cells, igniting tremendous hope for new cures, the cells are about to be injected into humans for the first time. Last week, the U.S. Food and Drug Administration (FDA) gave Geron in Menlo Park, California, permission to conduct a safety test in a handful of patients with a recent spinal cord injury.

For Geron and the scientists who work with it, FDA's decision was the culmination of a huge effort—including studies of nearly 2000 rodents with spinal-cord injuries and a 22,500-page application. "I actually have a glass of champagne in my hand right now," says a key player, Hans Keirstead, a neuroscientist at the University of California, Irvine. Several years ago, he approached Geron with the idea to commercialize his finding that stem cells could be used to mitigate spinal cord injury in rodents. He has been working with the company ever since. "I don't expect this treatment to allow patients to jump out of wheelchairs and play soccer," but "a meaningful and incremental advance" in mobility is a real possibility, he says.

But many stem cell researchers, particularly those in academia, who have struggled since 2001 with the Bush Administration's strict limits on the development and use of new stem cell lines, are concerned that this trial may not be the best first candidate. Safety is one worry: For example, a big fear is that the cells could form a type of tumor called a teratoma. Some also question the trial's scientific rationale.

Evan Snyder, a neuroscientist who directs the stem cell research center at the nonprofit Burnham Institute for Medical Research in San Diego, California, warns that a shaky start could set the field back enormously. "There's a lot of debate among spinal cord researchers that the preclinical data itself doesn't justify the clinical trial," says Snyder, who is working on using neural stem cells for drug delivery. Among the concerns he cited: The rodents Geron studied had more moderate injuries than patients expected in the trial, suggesting that the results might not translate, and the therapy has not been tried in larger animals. John Gearhart of the University of Pennsylvania, who led one of the teams that isolated the cells in 1998, adds that "we're still … a long way from really understanding a good deal about these cells and how to use them safely."

Geron will be testing oligodendrocyte progenitor cells, precursors to some nervous system cells the company developed from one of the original human embryonic stem cell lines—created with Geron funding in James Thomson's lab at the University of Wisconsin, Madison. Eight to 10 patients will receive the cells a week or two after a serious spinal cord injury. The goal is not to create new nerve fibers but to support those still intact by making the nerve insulator myelin. To prevent rejection, patients will take immune-suppressing drugs for about 60 days. Although the primary goal is to assess safety, Geron will be looking for hints that the cells had an effect—for example, improving bladder and bowel function, sensation, or mobility.

All smiles. Neuroscientist Hans Keirstead initiated the work that led to Geron's new therapy for spinal cord injury, using cells derived from an embryonic stem cell line (*inset*).

Geron CEO Thomas Okarma says he isn't concerned about one of the risks that people mention: ending up with the wrong type of cell. In rodents, he says the injected cells only formed glial cells, as expected—exactly the result he and FDA wanted. Geron has also performed extensive rodent studies that assured the company and FDA that the experimental cells did not cause tumors in the animals. Keirstead and Okarma assert that, despite the criticisms, they've done everything they can before taking the next step. "There's nothing we can do but go to humans now," says Keirstead. Animal testing has its limitations, he adds—including the fact that there are no large animal models of spinal cord injury. (FDA declined to comment in detail on its decision to let the trial begin.)

Okarma suggests that academic researchers may be concerned because they're not fully aware of what the company has accomplished. Geron has published or presented little of its oligodendrocyte work; so far only FDA officials have been privy to most of it. "There is so little expertise in the academic world about cell therapy that these people are rightly nervous," Okarma says. "We are so far ahead of them." Geron is also examining whether its oligodendrocytes might help Alzheimer's disease, stroke, or multiple sclerosis sufferers.

Other companies, meanwhile, are developing products derived from embryonic stem cells, and it's expected that upcoming trials will advance more easily. Keirstead, for example, is working with a second California company that is coaxing the cells to form motor neurons and plans to test them in infants with spinal muscular atrophy.

Gearhart says that for years "we were always told, 'Cure a patient and then all of this [controversy] will go away,' " and embryonic stem cells will quickly gain acceptance. Now, he says: "Here comes the first test out of the box." **–JENNIFER COUZIN**

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