Embyronic Stem Cell Research Moves Slowly Through Appeals Courts, Cancer Trials

By Susan Jenks

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certainty over federal funding for human embryonic stem cell research gained a temporary reprieve recently as a panel of federal appeals court judges ruled 2–1 to overturn a preliminary injunction.

But the legal issue of whether the National Institutes of Health violated the 15-year-old Dickey–Wicker law, which prohibits using taxpayer dollars for research that destroys or harms human embryos, moved back to the lower court and Chief Judge Royce C. LamBerth for a decision. LamBerth, a judge in the Federal District Court in Washington, imposed the ban last year, briefly disrupting intramural research on these earliest human cells on the NIH Bethesda campus, as well as grants to medical schools across the country.

“The action turns to the main event, the merits of the case,” said Anthony Mazzaschi, senior director of scientific affairs for the Association of American Medical Colleges, referring to Sherley v. Sebelius. LamBerth gave both sides in the legal action until June 24 to file supplemental briefs before he issues a final summary judgment. When that might come is uncertain, although Mazzaschi said he hopes it will happen within the next 6 weeks.

No matter which side prevails, the government or the two scientists—researchers using adult stem cells and who sued the government in August 2009—the case eventually could come before the U.S. Supreme Court. The scientists, James Sherley, M.D., Ph.D., of the Boston Biomedical Research Institute, and Theresa Deisher, Ph.D., of the Boston Biomedical Research Registry of embryonic stem cell lines has grown from 21 lines during the presidency of George W. Bush to 105 since President Obama’s March 2009 executive order revoking Bush’s more restrictive policies. All the new cell lines are derived from embryos initially created for reproductive purposes that otherwise might have been discarded, and they are used for research only after donor consent.

“The donors know the embryos are destined for creation of cell lines,” said Story Landis, Ph.D., director of the National Institute of Neurological Diseases and Stroke and head of the NIH Stem Cell Task Force. “The NIH will not support research if the embryo is generated for anything other than reproductive purposes.”

At least three clinical trials involving human embryonic stem cells, all privately funded, are now under way. Furthest along is a study by California-based Geron, involving injection of myelin-producing oligodendritic cells derived from human embryonic stem cells into patients with acute spinal cord injuries.

So far, just two patients have been treated, but no evidence of safety issues has emerged, according to Landis. “These are progenitor cells, not stem cells, that can only turn into the cells that make the myelin sheath.” That’s an important distinction, she said, ensuring the derived cells are fully differentiated or committed to a specific cell type, to avoid the germ cell tumors, or teratomas, that have developed in some animal models injected with stem cells.

Similarly, two other human trials, both of which Advanced Cell Technology in Worcester, Mass., is conducting, involve progenitor cells rather than pure stem cells to treat two eye diseases: age-related macular

Current Trials
As the legal battle plays out, NIH’s current registry of embryonic stem cell lines has
degeneration and a form of juvenile blindness called Stargardt’s disease (or fundus flavimaculatus). Derived from human embryos left over from in vitro fertilization, the newly created cells are committed to becoming retinal cells for treatment.

At present, the NIH would not approve funding for the stem cell lines in these particular trials, Landis said, because they were developed from preblastocysts, which appear in the first 5 days of embryonic development. “They’ve learned to take a single blastomere and make embryonic stem cell lines from it,” she said, adding that the NIH is proposing changing its guidelines to include cell lines from preblastocyst embryos in the future.

**Stem Cells in Cancer**

Compared with other diseases, such as Parkinson’s disease and heart disease, the potential of human embryonic stem cells to treat cancer attracts much less public attention. But in testimony before Congress last fall, Margaret Foti, M.D., Ph.D., chief executive officer of the American Association for Cancer Research, described research using these early cells as “potentially paradigm-shifting” for developing new ways to combat the 200 diseases collectively known as cancer.

And cancer researchers have begun moving promising therapies slowly out of the laboratory toward early clinical trials. Daniel Kaufman, M.D., Ph.D., associate director of the University of Minnesota’s Stem Cell Institute, and his colleagues, for example, reported in the journal *Blood* in June 2009 that natural killer cells, derived from human embryonic stem cells, cleared all leukemia cell lines in immune-deficient mice after several weeks of treatment. In vitro studies also have shown these cells capable of killing additional tumors, including those in prostate, breast, ovarian, and brain cancers, and in multiple myeloma.

“These results suggest the intriguing potential [of these cells] to provide a novel and highly potent resource for cell-mediated adoptive cancer immunotherapy,” the researchers wrote. Confirmatory in vitro studies have been completed, and the University of Minnesota team is now undertaking in vivo studies in mice to ensure that results are not limited to a single cell line.

The next step involves scaling up production of these stem cell–derived natural killer cells, finding funding, and “converting this process to conditions suitable for clinical trials,” Kaufman said in an e-mail.

Stem cells also lie at the heart of a new experimental treatment for blood cancers. Results of early phase I human trials for myeloproliferative disorders, involving 59 patients, appeared in *Cancer Cell* in 2008. Catriona Jamieson, M.D., Ph.D., director for stem cell research at the University of California, San Diego’s Moores Cancer Center and collaborators from Harvard, Stanford, and the Mayo Clinic stopped the characteristic overproduction of blood cells (which sometimes leads to leukemia) by inhibiting the JAK2 signaling pathway.

Before testing in people, Jamieson’s team put human stem cells engineered to carry a mutant JAK2 gene into mice to see whether too much of this gene would cause disease, which it did. Then, to confirm that finding, they injected stem cells from individuals with these disorders into the mice, with similar results.

“Human embryonic stem cells are giving us essential insight into self-renewal pathways,” such as JAK2 or the sonic hedgehog pathway, Jamieson said. “Without understanding this, there’s no way of knowing how to go after cancer.”

In the phase I study, “we saw anemia as the main downside of drug treatment,” she said. “But we also saw decreases in overt proliferation.” Phase II studies have not yet begun. However, “there’s big interest,” Jamieson said, as protocols work their way through the system.

Meanwhile, an important application of human embryonic stem cells, too often overlooked, holds promise for many diseases, including cancers, according to NIH’s Landis. “The first thing people think of when they think of human embryonic stem cells is [that] they make replacement cells,” she said. “But you can use these cells for drug testing by differentiating them” and then putting a drug of interest through screening tests “to see what will survive.”

Eventually, instead of using animals, she said, scientists may be able to test routinely for drug toxicity by “creating little liver cells in a dish.”

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