Harvard Stem Cell Institute publishes first clinical trial results

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Corey Cutler, M.D., M.P.H., and Leonard Zon, M.D., of the Harvard Stem Cell Institute, headed the effort to take a discovery in zebra fish from the fish tank to the clinic, in the Boston Children's Hospital zebra fish facility. Credit: B. D. Colen/Harvard University

Starting with a discovery in zebrafish in 2007, Harvard Stem Cell Institute (HSCI) researchers have published initial results of a Phase Ib human clinical trial of a therapeutic that has the potential to improve the success of blood stem cell transplantation. This marks the first time, just

nine short years after Harvard's major commitment to stem cell biology, that investigators have carried a discovery from the lab bench to the clinic—fulfilling the promise on which HSCI was founded.

The Phase 1b safety study, published in the journal *Blood*, included 12 adult patients undergoing umbilical cord blood transplantation for leukemia or lymphoma at the Dana Farber Cancer Institute and Massachusetts General Hospital. Each of the patients received two umbilical cord blood units, one untreated and another treated with the small molecule, 16,16 dimethyl prostaglandin E2 (dmPGE2). All 12 patients had reconstitution of their immune systems and renewed blood formation, and 10 of the 12 patients had blood formation derived solely from the dmPGE2-treated umbilical cord blood unit.

The clinical testing is now entering Phase II, which will assess the treatment's efficacy at 8 medical centers with 60 patients. Results are expected within 18-24 months.

Like much of the work conducted under the HSCI umbrella, this "first" depended upon the collaboration of scientists at different Harvard-affiliated institutions, and, in this case, an industrial partner:

- The initial finding occurred in the laboratory of Leonard Zon, MD, chair of the HSCI Executive Committee and Professor of Stem Cell and Regenerative Biology at Harvard, who studies blood formation in zebrafish at Boston Children's Hospital;
- Clinical research was conducted at Dana-Farber Cancer Institute and Massachusetts General Hospital, led by hematologic oncologist and HSCI Affiliated Faculty member Corey Cutler, MD, MPH; and
- Fate Therapeutics, Inc., a San Diego-based biopharmaceutical company of which Zon is a founder, sponsored the Investigational New Drug application, under which the clinical

program was conducted, and translated the research findings from the laboratory into the clinical setting.

"The exciting part of this was the laboratory, industry, and clinical collaboration, because one would not expect that much close interplay in a very exploratory trial," Cutler said. "The fact that we were able to translate someone's scientific discovery from down the hall into a patient just a few hundred yards away is the beauty of working here."

Gastroenterologists have studied dmPGE2 for decades, because of its ability to protect the intestinal lining from stress. However, its ability to amplify stem cell populations—the first molecule discovered in any system to have such an effect—was identified in 2005 during a chemical screen exposing 5,000 known drugs to zebrafish embryos. That work, published in the journal Nature in 2007, was conducted by two former Zon postdoctoral fellows, and current HSCI Principal Faculty members, Wolfram Goessling, MD, PhD, and Trista North, PhD.

"We were interested in finding a chemical that could amplify blood stem cells and we realized looking at zebrafish embryos that you could actually see blood stem cells budding from the animal's aorta," Zon said. "So, we elected to add chemicals to the water of fish embryos, and when we took them out and stained the aortas for blood stem cells, there was one of the chemicals, which is this 16,16 dimethyl prostaglandin E2, that gave an incredible expansion of stem cells—about a 300 to 400 percent increase."

The dramatic effects of this molecule on blood stem cells made Zon, a pediatric hematologist, consider ways in which the prostaglandin could be applied to bone marrow transplantation, often used to treat blood cancers, including leukemia and lymphoma. Bone marrow contains the body's most plentiful reservoir of blood stem cells, and so patients with these conditions may be given bone marrow transplants to reconstitute

their immune systems after their cancer-ravaged systems are wiped out with chemotherapy and radiation.

Zon designed a preclinical experiment, similar to the one later done with cord blood patients, in which mice undergoing bone marrow transplants received two sets of competing bone marrow stem cells, one set treated with dmPGE2 and a second untreated set.

"What we found was the bone marrow stem cells that were treated with prostaglandin, even for just two hours, had a four times better chance of engrafting in the recipient's marrow after transplant," he said. "I was very excited to move this into the clinic because I knew it was an interesting molecule."

Zon and his team's next step was to visit Dana Farber Cancer Institute (DFCI), where they presented the mouse research at bone marrow transplant rounds and found physicians interested in giving the prostaglandin to patients.

"We basically sat down in a room and we brainstormed a clinical trial based on their scientific discovery, right then and there," said Farber oncologist Corey Cutler. "They knew that it was something they could bring to the clinic, but they just didn't know where it would fit. We said, if this molecule does what you say it does, significant utility would lie in umbilical cord blood transplants."

A cord blood transplant is similar to a bone marrow transplant, however the blood stem cells are derived from the umbilical cord blood of a newborn, rather than from an adult donor. One of the advantages of umbilical cord blood is that matching between donor and recipient does not need to be as exact because potentially fatal graft-versus-host disease is less common. Although about 10-20 percent of stem cell transplantation procedures now use umbilical cord blood, the downside

is that engraftment is more difficult, because the number of stem cells in an umbilical cord blood donation is far fewer than in an adult stem cell donation.

Umbilical cord blood transplants fail about 10 percent of the time; so increasing the procedure's success would significantly help patients who do not have adult bone marrow donors, including a disproportionate number of non-Caucasian patients in North America. Increasing the engraftment rate would also allow the use of smaller umbilical cord blood units that are potentially better matches to their recipients, increasing the number of donations that go on to help patients.

Once the go-ahead for the trial was received by Fate Therapeutics from the US Food and Drug Administration, and the DFCI Institutional Review Board, the umbilical cord blood processing was done by Dana-Farber's Cell Manipulation Core Facility, directed by HSCI Executive Committee member Jerome Ritz, MD. The study hit a stumbling block, however, once the human trial was underway with the first nine patients. The protocol that produced the dramatic blood stem cell expansion in mice did not translate to improved engraftment in humans.

"The initial results were very disappointing," Cutler said. "We went back to the drawing board and tried to figure out why, and it turned out some of the laboratory-based conditions were simply not optimized, and that was largely because when you do something in the lab, the conditions are a little bit different than when you do it in a human."

Fate Therapeutics discovered that the human cord blood was being handled at temperatures too cold (4-degrees Celsius) for the prostaglandin to biologically activate the stem cells and improve their engraftment properties. Fate further demonstrated that performing the incubation of the hematopoietic stem cells at 37-degrees Celsius and increasing the incubation time from 1 hour to 2 hours elicited a much

stronger gene and protein expression response that correlated with improved engraftment in animal models.

In running a second cohort of the Phase Ib trial, which included 12 patients, dmPGE2 appeared to enhance the engraftment properties of the blood stem cells in humans and was deemed safe to continue into Phase II. "It's probably the most exciting thing I've ever done," Zon said. "Basically, to watch something come from your laboratory and then go all the way to a clinical trial is quite remarkable and very satisfying."

Provided by Harvard University