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Could umbilical cords yield more stem cells for life-saving transplants?

Umbilical cords are a potentially life-saving source of blood stem cells for people with leukemia and other diseases. But there aren’t enough cells to meet demand. Now an experimental treatment offers hope for a solution.

By Tom Ulrich | May 22, 2015

Andrew Miller belongs to an exclusive club, but not one that everyone wants to join. At 19, he's had his blood and immune system replaced not once, but twice.

Eight years ago, Miller was diagnosed with an aggressive form of leukemia. His doctors decided his best bet was to start fresh—to replace his immune system with a new one by giving him a hematopoietic ("blood-forming") stem cell transplant.

The transplant knocked Miller's cancer into remission. But two years later it came roaring back, more dangerous than before. This time, his doctors opted for something different. They replaced his still-rebellious stem cells with ones collected from a newborn's umbilical cord—a procedure called a cord blood stem cell transplant.

Numbers game

First attempted in 1987, cord blood transplants have been a godsend for thousands of patients. What makes this approach attractive is that cord blood stem cells don't require as close a match between donor and patient as do cells from other sources, like bone marrow.

Andrew Miller received an umbilical cord blood stem cell transplant to treat an aggressive form of leukemia.

"For those patients who need a transplant but do not have a matched brother or sister, cord blood offers a rapid source of stem cells, without the risk of complications that would occur with bone marrow transplant with

the same level of mismatch," says Miller's transplant physician, John Wagner, MD, a pioneer in cord blood transplantation who is director of the Division Blood and Marrow Transplantation at the University of Minnesota in the United States.

Cord blood transplants have one major limitation: cell dose. A single umbilical cord holds relatively few stem cells, often enough to transplant a child, but rarely an adult or teenager.

Even in children, the small number of cells means it takes some time to rebuild a patient's immune system. On average, a cord blood patient takes between 22 and 25 days to reach engraftment—an important milestone where the transplanted cells start producing infection-fighting cells called neutrophils.

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>
> **Andrew Miller**, cord blood stem cell transplant recipient

Miller remembers that waiting period all too well. "For a month, I was in a ten-by-ten room with just my mom, because I couldn't be around anyone who might have a virus or anything like that," he recalls. "It was a long, lonely process."

Tools that accelerate engraftment could have practical benefits. "The more quickly a patient engrafts, the better their outcome," says Tony Boitano, an immunology researcher at the Genomics Institute of the Novartis Research Foundation (GNF). "They can also leave the hospital sooner, which reduces the cost of the transplant."

One approach for shortening the engraftment timeline is to transplant two cords' worth of cells, a strategy Wagner developed 15 years ago. However, the approach carries a higher risk of the patient’s new immune system rebelling – a phenomenon called graft versus host disease. That’s partly because the two grafts attack each other.

An ideal solution would be to find a way to grow blood stem cells in the lab before transplant. The result would be more cells from a single umbilical cord unit and accelerated engraftment. If such an approach can be found, it could help patients with a host of conditions.

"There are about 75 diseases for which stem cell transplant may be helpful," Wagner says. "Cord blood is an important source of those blood-forming stem cells."

A 10-year hunt

For 10 years, Boitano and his boss, GNF immunology director Mike Cooke, have been hunting for the ideal compound to stimulate the growth of stem cells. Over the last 8 years, they've focused on a specific compound from the Novartis archives.

Andrew Miller is working hard to get back to peak form in the sports he loves.

In Cooke and Boitano's experiments, cultures of blood stem cells treated with the compound yielded 50 times more cells than untreated ones. These cells kept their stem-like properties, including the ability to differentiate and produce all of the cells found in blood. Moreover, when transplanted into mice they readily rebuilt the animals' immune systems.

"I've seen lots of compounds that look like they're expanding stem cells, but when you transplant them, they do nothing," says Cooke. So the results in mice were exciting. "That's when I started to believe, 'Hey, this might work.'"

Cooke, Boitano and colleagues on the clinical team are currently working with Wagner to test the approach in patients. They hope that the cells grown from a single cord—which forms a cellular therapy dubbed HSC835—will help patients reach engraftment safely and more quickly than a standard cord blood transplant.

Meanwhile, researchers at the Novartis Cell & Gene Therapies Unit are working to scale up production of the experimental treatment. The project has taken them into unfamiliar territory.

"This treatment poses unique manufacturing challenges because it must be customized for each patient," explains global program head Bastiano Sanna. “But we’re determined to figure this out.”

A second, and third, chance at life

Miller’s cord blood stem cell transplant pre-dated the experimental new treatment. But his experience illustrates how important its development could be for other patients, if successful. Now a college sophomore, Miller is in good health. He aims to graduate in three years with dual degrees in finance and economics. He's also working hard to get back to peak form in the sports he loves, like baseball and basketball.

"Having had a second and third chance at life has made me want to be the best person I can be," he says. "That changes your outlook."

Read more about where HSC835 came from on the Novartis Institutes for BioMedical Research's NERD blog. Learn about early clinical results in an American Society of Hematology abstract.

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