

University of Louisville Researcher May Hold Key to a Cure for Sickle Cell Disease

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It strikes thousands of African Americans every year, clogging blood vessels with sickle-shaped cells – causing strokes, blindness and excruciating pain as it damages the heart, liver, lungs and kidneys. Half of its victims die by age 40. But University of Louisville researchers are testing a revolutionary cure for sickle cell disease, giving hope to a new generation of families that carry the potentially fatal gene. Amos Igwe, 13, believes the procedure has given him a future. Before getting a bone-marrow transplant from his sister in 2006 as part of the experiment, Amos was often so sick that he had trouble breathing and could barely leave the living room couch. Today he plays quarterback on a football team at St. Albert the Great, where he's an eighth-grader, is preparing to go to Trinity High School next year and hopes to one day become a dentist or heart surgeon.



“We are grateful to God,” said his father, Tony Igwe of Eastern Louisville. “It’s really a miracle.” Amos was one of six patients treated as part of a study that aims to make bone-marrow transplants safe enough to be used widely and possible beyond the small portion of patients with perfectly matched donors. Such transplants can potentially cure sickle cell disease, but are considered too dangerous in most cases because they can lead to deadly complications such as graft-versus-host disease, in which a donor’s cells attack the recipient as foreign.

Dr. Suzanne Ildstad, research leader and director of UofL’s Institute for Cellular Therapeutics, is attempting to overcome such complications by inducing a patient’s tolerance to the donor cells. She said study results are promising – with two of six patients basically cured and a third recent one doing well – and it shouldn’t be long now before new, safe transplants are available to many of the nation’s 70,000 sickle cell patients.

“Amos was one of our first two successes,” said Ildstad, whose team is collaborating with Duke University.

“He’s making normal red cells. He grew more than a foot in the past year ... he’s living a normal life.”

Central to Ildstad’s work is her discovery in 1994 of a “facilitating cell” in bone marrow, which helps stem cells in a donor’s marrow to “take” in a recipient, lessening the chance that the patient’s immune system will reject the donor cells.



Safe bone-marrow transplants may also offer new treatments for conditions such as Type I diabetes and multiple sclerosis, she said, and a better approach to organ transplants that doesn’t require a lifetime of anti-rejection drugs.

Ildstad's research has sparked excitement among scientists across the nation and has attracted ongoing funding of up to \$7 million a year to UofL from such organizations as The National Institutes of Health, the U.S. Department of Defense and the National Foundation to Support Cell Transplant Research.

But not everyone is certain that Ildstad has found a widespread cure for sickle cell disease. Dr. John DiPersio, chief of oncology at Washington University in St. Louis, said it's unusual that her results haven't been replicated by many other teams, and that there hasn't been more follow-up on facilitating cells. "I think she's a little on the fringes here," DiPersio said.

Ildstad countered that other researchers have studied these cells, which have also been the subject of numerous medical journal articles and international talks. And Dr. Joanne Kurtzberg, a Duke collaborator on the project, said skepticism accompanies "every new innovation in the field."

To Amos, Ildstad is a champion. "I used to have trouble breathing. Now I'm gaining some muscle. I can play basketball with my friends. I can jump high," said the teen, who stands 5 feet 4. "She made all this happen. I feel like I'm cured."

'MIXED CHIMERISM' Blending Two Systems of Bone Marrow Into One

In Ildstad's office are images of the chimera, a mythical creature with a lion's head, a goat's body and a serpent's tail. It symbolizes the premise of her work – "mixed chimerism," in which two bone marrow systems exist and function in one person.

Ildstad, a 57-year-old married mother of two grown children, graduated from Mayo Medical School in Minnesota, trained in Harvard University's general surgery program and was a staff fellow at NIH. It was there that she helped establish a model for a blood stem-cell chimerism, in which two genetically different stem cell populations co-exist.

One of her most well-known and controversial efforts took chimerism to the extreme. In 1995, while at the University of Pittsburgh, she won federal approval to give a 38-year-old AIDS patient a transfusion of baboon bone marrow with added facilitating cells. While the marrow didn't take, the patient's health improved. But the procedure was heavily criticized, with some scientists worrying it could introduce baboon viruses into humans.

Ildstad also applied the idea of chimerism to sickle cell disease. In the United States, the inherited condition is most common among those of African descent, and is marked by defective hemoglobin, the oxygen-carrying protein in red blood cells. Patient's red cells carry less oxygen than normal, and many are shaped like crescents, or sickles, instead of doughnuts. The misshapen cells don't move easily through tiny blood vessels, causing clogs and resulting in terrible pain and damage to such organs as the kidney's, brain and heart.

Ildstad reasoned that a safe bone-marrow transplant could halt this destructive cycle by helping patients make normal red blood cells. And chimerism, achieved with the help of facilitating cells, could make a transplant safer, even for donor-recipient pairs who aren't perfect matches.

She came to UofL in 1998 under Bucks for Brains, a state program designed to bring top researchers to Kentucky universities, and she tested her procedure on her first sickle cell patient in November 2005. The first two, including Amos, were treated at Kosair Children's Hospital.

Treatment of patients moved to Duke in North Carolina about three years ago, Ildstad said, after the NIH encouraged her team to branch out beyond Kentucky. But while Duke is a larger research institution with more clinicians available to do the work, Ildstad said she hopes to resume enrolling patients for treatment in Louisville as well in about a month.

Kurtzberg, director of Duke's Pediatric Blood and Marrow Transplant Program, said her team "very much wanted to participate" and believes the procedure holds great promise. "We wouldn't be doing it if we didn't," she said.

Researchers at Northwestern University in Chicago also plan to begin treating sickle cell patients through the study in about six months.

Russ Prough, Vice Dean for Research at UofL's medical school, said he's excited about the collaborations, and counts Ildstad among the most high-powered medical researchers at UofL.

"Before Bucks for Brains, we had one or two people who were really doing impressive research," he said. "Bucks for Brains brought a whole critical mass of people."

'WORK A MIRACLE' Transplant Gave Boy Entirely Different Life

When Tony Igwe heard about Ildstad's study, he consulted with his wife, Eucharia. Both decided it was worth a try for their son. The Nigerian-born couple had watched Amos suffer for years. At 3, he developed a pneumonia-like complication called acute chest syndrome that almost killed him.

As Amos grew older, he was pale, tired, hardly ate and suffered joint pain that made it difficult to get around. He needed transfusions almost monthly. He was often absent from school. The Igwes ran their lives around his illness, skipping vacations and curtailing activities for their other three children, who do not have the disease. "You didn't know what was going to happen day to day," Eucharia said.

To get sickle cell disease, a child must inherit one gene from each parent, and parents can either have the disease or be carriers, as are the Igwes. Doctors eventually tested everyone in the family to see if they could donate marrow to Amos. Youngest daughter Chi-Chi proved a perfect match. "God gave me this child," Tony said of Chi-Chi, now 8. "Maybe He's trying to work a miracle."

Amos was among the 17 percent of sickle cell patients who have perfect bone-marrow matches. Some other study subjects do not, but Ildstad's technique also allows a partially matched mother, father or sibling to donate.

In the procedure, marrow cells are harvested from the donor, sent to Louisville, and processed in a clean room to remove active immune system cells and bring out the facilitating cells. Meanwhile, recipients are “conditioned” with chemotherapy and radiation, but in much lower doses than someone getting a traditional bone-marrow transplant. Such low doses are one reason the technique is safer than a traditional bone-marrow transplant.

Another is that the facilitating cells, and marrow processing, are thought to greatly reduce the possibility of graft-versus-host disease. Ildstad said a traditional bone marrow transplant carries a 25% chance of graft-versus-host and a 10% chance of death – a price doctors deem too high for treatment of a non cancerous condition. But Ildstad’s procedure, though safe enough to be done on an outpatient basis, is not without risks. Even low doses of radiation carry a long-term risk of cancer, she said, and anti-rejection drugs can increase the chance of infection even if tapered after six months, and ended after a year.

Amos no longer takes anti-rejection drugs and hasn’t had any problems since the transplant. Jeanne Flowers, Principal at St. Albert, said his health is so much better that “he’s a different child.” During a recent gym class, his sneakers squeaked as he scrambled for a basketball, grabbed it from a classmate and shot toward the basket.

“For the past four years, he’s never been at the hospital, overnight,” his father said. “Before, he never eats. Now he eats more than anyone.” In Amos, Ildstad said, chimerism worked. About 30 percent of his marrow can now be traced to 8-year old Chi-Chi – who said she’s happy to have helped. “He’s my brother,” she said. “I love him.”

‘HEALTHY SKEPTICISM’ Not All Persuaded, But Optimism Exists

Amos and the other patient treated in Louisville, who has since moved out of state, were successes, but not all cases have been. While one of the others appears successful in the early stages, and another recent case is still pending, two of the transplants didn’t take.

DiPersio, of Washington University, is skeptical about chimerism and predicts that researchers will have trouble recruiting enough test subjects in the long run because African Americans are often reluctant to join clinical trials. It’s a legacy of the infamous Tuskegee experiment, in which black men with syphilis were left untreated.

“The question is whether we can do this on a large scale,” he said. “You must have health skepticism when you look at these things.” Other researchers are much more optimistic. Dr. Catherine Wu, an assistant professor of medicine at Harvard who does similar work, said Ildstad’s trial fits into a growing field of modified bone-marrow transplants that other scientists are testing. This line of research, along with gene-therapy studies, represent the leading edge of the search for a lasting and widespread sickle cell cure, she said.

But Wu and others caution that it’s still early in the research process. Even if all goes well, Duke’s Kurtzberg said the procedure would need to go through the lengthy process of federal approval before being offered as standard treatment.

Yet Dr. Ashok Raj, a UofL physician who treats sickle cell patients at Kosair, said research success would be a godsend for the suffering children he sees everyday.

While sickle cell treatments have improved over the years, the disease remains disabling and deadly. “It would be fantastic if this technology makes a big impact on our kids,” he said. “That would be a very remarkable achievement.”

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