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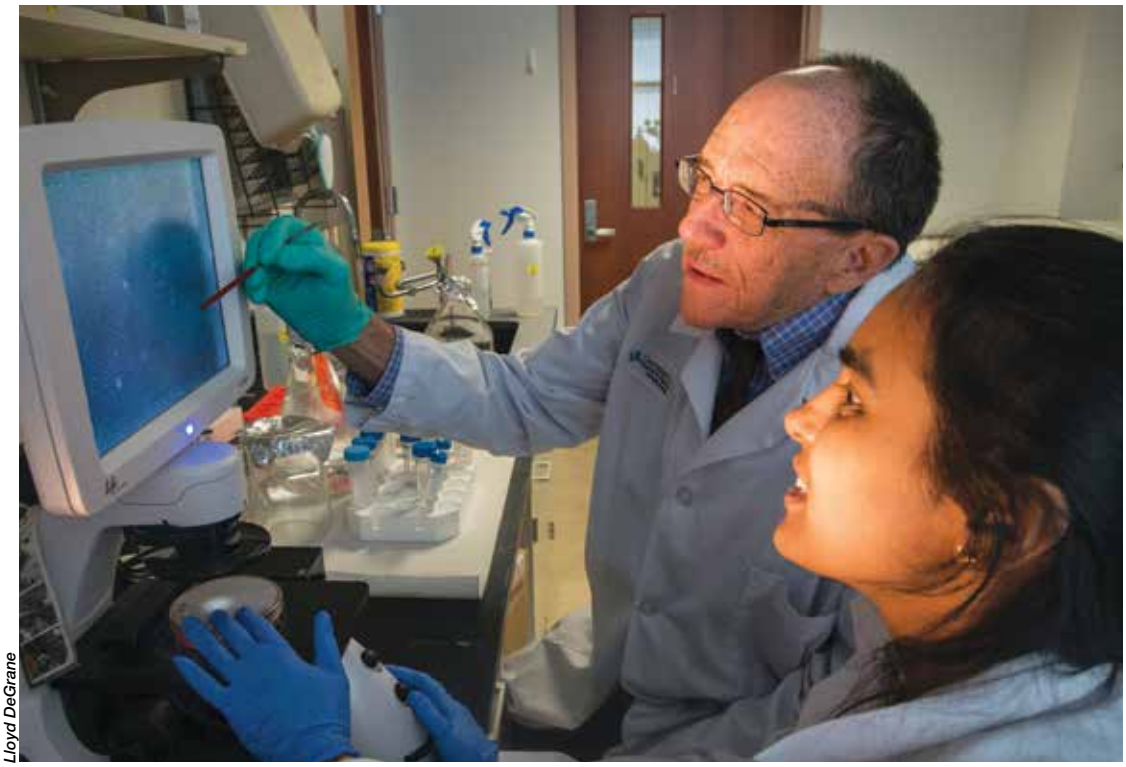
AK ROUGH

TRANSPLANTED STEM CELLS HOLD THE PROMISE OF CURING THOUSANDS AFFLICTED WITH SICKLE CELL DISEASE

BY PAUL ENGLEMAN

Imagine having debilitating pain throughout your body, with pressure in your chest so intense it feels like you are going to explode. Imagine living with the knowledge that this pain—which can come and go at any time and last for extended periods—is a symptom of an incurable disorder that ravages organs and reduces life expectancy by 30 years. That's what it's like to have a severe case of sickle cell disease, an inherited blood disorder in which red blood cells change shape and block the flow of oxygen to tissues.

Founded in 1972 with federal grant funds, the UIC Sickle Cell Center was one of the first of its kind in the nation. The program is headed by Dr. Victor Gordeuk (shown with Research Assistant Professor Binal Shah). He has co-authored more than 200 peer-review publications and is considered by many to be a "thought leader" in the field of sickle cell research. Dr. Santosh Saraf, UIC assistant professor of medicinal chemistry, is a corresponding author of a research paper published in *Biology of Blood and Marrow Transplantation* that validated an earlier National Institutes of Health study in which 26 out of 30 sickle cell patients appeared to be cured by stem cell transplants.



Lloyd DeGrane

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Chicagoan Kelvin Myrick, 42, did not have the luxury of imagining. He lived it for nearly three decades. "It's very, very painful," he says. "I can't think of a word to describe it." After a long pause, he settles on "excruciating."

Fortunately for Myrick, that pain now resides in his memory. In May 2013, he became a member of an exclusive club. Fewer than 50 people in the world have been cured of sickle cell disease as adults. Myrick is one of them. His cure took place at the University of Illinois Hospital.

In addition to being grateful to the doctors and nurses and members of a support group at the UIC Sickle Cell Center who are "like a family" to him, Myrick can thank his brother, Keith, who is two years older. It was Keith's transplanted stem cells that cured him. "We're as close as two brothers can be," he says. "This only made us closer. I lived most of my life believing I was going to die young. Now I can live a normal life and die of natural causes like any other person."

CURE FOR ADULTS

In what is unquestionably a remarkable medical accomplishment, physicians at UIC have succeeded in curing 12 of 13 patients who suffered from severe sickle cell disease by transplanting stem cells donated by their siblings. (The one patient who was not cured failed to take the medication required to prevent rejection of donated cells.)

The results of the UIC study were published last September in the journal *Biology of Blood and Marrow Transplantation*. Dr. Santosh Saraf, a corresponding author of the paper and an assistant professor of medicinal chemistry, says the UIC study validated research conducted at the National Institutes of Health in which 26 of 30 sickle cell patients appeared to be cured by stem cell transplants. By confirming the NIH results with their own independent study, researchers at UIC showed that the procedure constitutes an actual cure.

The wait for a cure has been difficult. According to Saraf, physicians have long known that it is possible to cure children with sickle cell disease by transplanting bone marrow, the soft tissue in bones that forms blood cells. The first such transplant took place more than three decades ago at St. Jude Children's Research Hospital in New York City. But in children, the procedure is preceded by intensive chemotherapy, which destroys bone marrow. Attempts to cure adults with sickle cell disease have been unsuccessful because adults cannot tolerate the required doses of chemotherapy.

The significance of the NIH

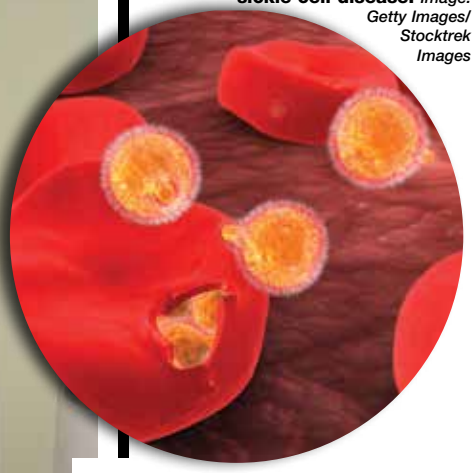
and UIC studies is that chemotherapy was not used, and the patients—all adults—still survived. Most saw significant relief within a month, as their deformed cells were replaced with healthy ones. In UIC protocol, Saraf explains, the patient was given a small dose of radiation prior to transplant and then prescribed a medication that suppresses the immune system to prevent the rejection of donated cells. Rejection is the biggest risk in stem cell transplants because it can lead to serious infection and graft-versus-host disease, a potentially fatal disorder. Ten of the 12 cured patients were able to discontinue their post-transplant medicine after a year.

GLOBAL TREATMENT CENTER

To anyone familiar with sickle cell research, it is no surprise that such a historic breakthrough would take place at UIC. In 1972, the University received a federal grant to become one of the nation's first comprehensive sickle cell centers. Saraf says Dr. Victor Gordeuk, current director of the UIC Sickle Cell Center—whose career includes six years of service in Africa—"is definitely a thought leader" in sickle cell research around the world. And his colleague, Dr. Joseph DeSimone, a research investigator at UIC for three decades, is an acclaimed pioneer in the field of hematology. DeSimone was the first person to show that it was possible to alter hemoglobin into a form that prevents cells from changing shape. (Hemoglobin is the protein molecule in red blood cells that carries oxygen through the bloodstream.) This research became the basis for treating sickle cell disease. In 1998, it led to FDA approval of the cancer drug hydroxyurea as the first and only accepted medicine for sickle cell disease.

Dr. Damiano Rondelli, who in 2002 came to UIC from Bologna, Italy, to serve as director of blood and marrow trans-

Gene mutations that help protect the body from malaria also cause sickle cell disease. *Image: Getty Images/ Stocktrek Images*



SICKLE CELL ROULETTE

AFRICANS AND HISPANICS DISPROPORTIONATELY AFFECTED

Nature is filled with ironies. One is that the gene mutation that causes sickle cell disease was developed to protect the body from malaria. Where malaria is present, there is likely to be sickle cell disease, which is why people of African and Hispanic descent are disproportionately affected.

People who inherit a single sickle cell gene from one parent do not get sickle cell disease. But they become carriers who can transmit the disease to their children. People who inherit two sickle cell genes get the disease and are more susceptible to malaria.

An estimated 100,000 people in the U.S. have sickle cell disease. Worldwide, the disease affects millions. About one in 500 African Americans is born with sickle cell disease; about one in 12 is a carrier. —P.E.

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Kamina Quinones underwent stem cell transplantation using cells donated by her brother, P.J. Hearns. "I gave her my stem cells, and I gave her my allergies," he says, laughing. "That was the trade-off."

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plant program, says, "UIC has a great mission—to reach the highest level of academic medicine through technology and research, and to offer these accomplishments to any patient, particularly those of limited social or economic resources. This is not common in many other places. It's what makes UIC special." To his point, in 2009, the UIC Sickle Cell Center opened the only acute care clinic in the Midwest.

Rondelli also has projects underway to develop stem cell transplant programs in India, Nepal and Nigeria, the country with the highest number of sickle cell patients. "We will be able to help our colleagues there save potentially millions of people," he says.

NEW BIRTHDAY

Some people would call it a new lease on life. Kamia Quinones says she and her husband call Oct. 24, 2013, her "new birthday." That's the day the 35-year-old nurse and mother of three underwent a stem cell transplant using cells donated by her older brother.

Quinones was diagnosed with sickle cell disease when she was two years old. Because an older sister had been diagnosed with a milder form of the disease, her mother recognized her symptoms. Although she had to be hospitalized three or four times a year as a child, Quinones did not consider her symptoms severe until she turned 16. By the time of her transplant, she says, she was going to the hospital every four weeks. Since the transplant, she has not required hospitalization.

"It's like being tortured from the inside out," says Quinones of her symptoms. "I don't mean to downplay childbirth in any way, but when you get the pain in your knees and back and it feels like your chest is going to explode, there's nothing you can do except pray and hope it goes away." Possibly worse than the physical pain is the mental anguish that goes with it. "You don't know how long it's going to last," she says, "and you don't know when it's going to come back." But what bothered her most was the impact the illness had on her children. "It was hard for them—going back and forth to grandma's house, their mom not being there when they had a play or a concert or a game."

One low point came shortly before the transplant. "I had been ill the whole night, and it had gone to full-blown crisis," she recalls. "My son came to hug me goodbye before school. His elbow hit my knee, and I screamed in pain, and he started to cry. I had to get control of myself even though it hurt so bad."

Quinones prefers to talk about her "awesome support system" of family and friends, and the improved quality of her life after the transplant. "I was in the hospital on my

FOR MEMBERS OF THE RESEARCH AND MEDICAL STAFF, THERE IS GREAT SATISFACTION IN KNOWING THEY CAN CURE A DISEASE THAT ONLY 40 YEARS AGO MEANT A LIFE EXPECTANCY OF 14 YEARS.

The Center has "a great history of caring for people with sickle cell disease," says Dr. Damiano Rondelli, director of the UIC Blood and Marrow Transplant.

daughter's 10th birthday," she reflects. "My best friends took it upon themselves to throw her a surprise party, and that meant the world to me.

"I'm blessed that I was chosen to have the transplant. It's a relief for the whole family. Sickle cell doesn't just affect you, it affects everyone around you."

Quinones now delights in activities that many people might take for granted. "Taking my kids to the beach, swimming with them, going out in the cold and building a snowman—those are things I can do now," she says. "It's been over two years, but I still have to pinch myself and say, 'This is real.'"

Quinones is considering going to graduate school to become a nurse practitioner. "I eventually want to work with sickle cell patients," she says. "I'd love to help people who are going through what I went through. I want to do what Mary Ann does."

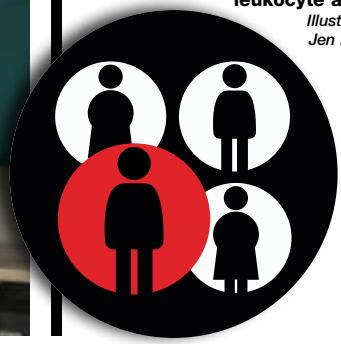
Mary Ann Enriquez is an acute care nurse practitioner at the UIC transplant center. She works closely with patients who opt to undergo the procedure. "I've been a nurse for 30 years, and I've seen a lot, including open heart surgery," she says. "But I never thought I'd see this. It's definitely amazing. I meet the patients when we do our initial consultation. The before and after—it's unbelievable. They become more independent, more self-confident. It's really beautiful to see."

An engineer in a family of nurses, P.J. Hearns says it was "no big deal" to inject himself with medicine five days in a row if there was a chance to cure his younger sister, Kamia Quinones, of sickle cell disease. "My mother raised us to look out for each other," he says, "and we do that to this day. I'm her big brother. We were always close. Now, we're even closer." So close, his sister points out, that they now share the same immune system—a fact that gives them something to laugh about. "Yes," he says. "I gave her my stem cells, and I gave her my allergies. That was the trade-off."

IMPROVING THE ODDS

At about $250,000, the cost of a stem cell transplant is not

The donor and recipient must have a match of human leukocyte antigen.
Illustration by Jen Dahlgren

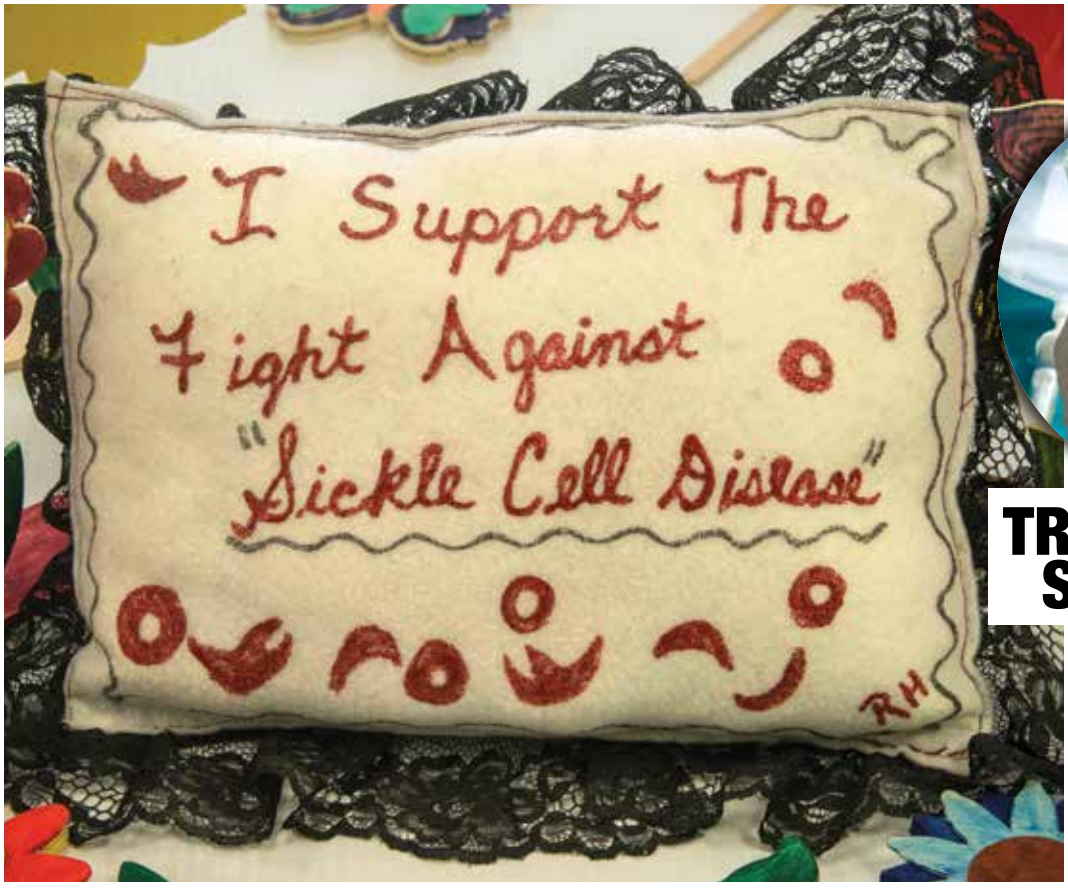


MATCHING DONATIONS

ONLY ONE OUT OF FOUR SIBLINGS SHARE ALL 10 REQUIRED MARKERS

The biggest obstacle to transplanting stem cells to cure sickle cell disease is that a recipient's body can reject the stem cells. For a successful stem cell transplant, donor and recipient must have a match of human leukocyte antigen, a protein found in cells that Dr. Santosh Saraf describes as a "fingerprint." At birth, a person receives two sets of fingerprints—one from each parent. Saraf says there are 10 different markers on the HLA fingerprint. In the UIC study, all patients and donors were siblings with all 10 markers—100 percent matches.

The chance of a sibling with the same parents being matched is one in four. Saraf says that, in the bone marrow donor registry pool, the chance of finding a full human leukocyte antigen match among unrelated donors and recipients is between 30 and 40 percent. But though stem cells from unrelated donors have been compatible in transplants for other blood disorders, that hasn't been the case for sickle cell patients. —P.E.



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A pillow from Quinones' home. "Sickle cell doesn't just affect you," she says, "it affects everyone around you."

cheap, and there are issues related to insurance coverage that must get resolved on a case-by-case basis. Saraf says much of the cost is related to the required hospital stay of at least a month after the transplant to monitor the body's acceptance of donor cells. A fact sheet issued by UIC says that when the costs of emergency room visits and hospital stays are considered, a transplant results in a savings of nearly $140,000 per patient per year.

For members of the research and medical staff, there is great satisfaction in knowing they can cure a disease that only 40 years ago meant a life expectancy of 14 years. But their sense of fulfillment is somewhat diminished by the limits of what they have accomplished so far—the stem cells can be transplanted only from siblings with a full match of human leukocyte antigens.

"I get very attached to my patients and their families, so it's very fulfilling," Enriquez says. But ever since the results of the UIC study were announced, she says, "I get calls from all over the world. When I ask callers if they have a sibling and they say no, my heart just stops for them."

"To see sickle cell patients get better so quickly and then return to their normal lives without pain feels almost like a miracle," Rondelli says. "This is only possible because of so many people—doctors, nurses, social workers, hospital staff—all working together. But the satisfaction is limited by not being able to offer cures to patients who do not have a matched donor."

Among the 650 adult sickle cell patients at UIC, between five and 10 die each year. According to Saraf, about one in four patients have had strokes and require blood transfusions. Although he and his colleagues try not to see their work as a race against time, "for the patients who are experiencing acute chest syndrome, I do worry a lot," he says.

Saraf and Rondelli are hopeful that, in the near future, transplants will be successful with family members who are only half-matched in human leukocyte antigen. As of this past spring, at least six stem cell transplants for sickle cell patients with only a half-matched family member had taken place. Rondelli says the early results look "promising," but not enough time has elapsed for a full evaluation.

"This is a place with a great history of caring for people with sickle cell disease," Saraf says. "More advances are on the horizon, and UIC is going to play a very important role in that."

Stem cells are typically frozen in nitrogen.
Image: Getty Images/ Lebazele

TRANSPLANTING STEM CELLS

TECHNICAL CHANGES HAVE STREAMLINED THE PROCEDURE

Dr. Santosh Saraf says that in 2012, when the first patient in the UIC study was having a stem cell transplant, "We were all very nervous, and the whole transplant team watched every second." But the procedure is not very complicated. "In the past, the donor would go to the operating room, and we would actually inject needles to aspirate the bone marrow fluid with stem cells," he says. "Now we have a medication that helps the donor increase production of stem cells and mobilize them into the blood. We collect the stem cells similar to a blood donation." The difference is there are two lines—one for collecting stem cells and the other for returning red blood cells to the donor. The donor is connected to a machine for about three hours.

"Implantation is even simpler," Saraf says. "It's like a transfusion. We can do a fresh infusion, but more often we freeze the stem cells in liquid nitrogen." The patient is given a small dose of radiation beforehand; the entire procedure takes less than 90 minutes. —P.E.