



Gene therapy raises hope for sickle-cell anemia cure

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Kameron Kinebrew, 12, spent a month hooked to a morphine pump to control the sickle-cell anemia pain, something he compared to "a couple of knives stabbing you in your back, over and over."

His twin brother, Kaleb, rattles off pain management techniques without thinking: slow breathing, plenty of fluids, distraction. "We know what to do," he said. "It's normal for us."

People with sickle-cell disease face a lifetime of pain and fatigue. They also risk stroke, blindness, organ failure and bone loss. The only effective treatments are bone marrow transplants and chemotherapy, and they don't work for everyone with the disease.

But researchers at [Cincinnati Children's Hospital Medical Center](#) offer hope for a cure for the tens of thousands of Americans afflicted by the life-shortening blood disease.

After a decade of research, scientists led by Punam Malik have developed a cutting-edge gene therapy that - in lab animals and human tissue samples - made the body stop producing the malformed red blood cells that characterize sickle-cell disease.

They want to start testing it next year if federal regulators sign off.

"If it works, it's a cure," said Malik, a hematology-oncology specialist who heads up all of the gene and molecular therapy research at Cincinnati Children's.

Sickle cell affects 600 to 800 people in Greater Cincinnati and Northern Kentucky, and some 70,000 to 100,000 people in the United States. One in 500 African-Americans has the disease. Worldwide, the disease affects millions.

In sickle cell, a genetic defect makes red blood cells carry an abnormal type of hemoglobin, called hemoglobin S, that changes their shape, making it harder for the blood cells to pass through blood vessels. The cells can't efficiently carry oxygen to tissue, and the tissues become damaged and eventually die. Over several years, people with sickle cell suffer organ damage and organ failure. One study found that organ failure, especially kidney failure, killed about 20 percent of adult sickle-cell patients.



The damage starts early. Kameron Kinebrew's doctors have already identified spots of dead bone tissue in his legs because of sickle cell.

The therapy developed at Cincinnati Children's would implant a gene that counteracts hemoglobin S, allowing the body to make the correct type of hemoglobin to form normal, doughnut-shaped red blood cells.

In the proposed clinical trial, researchers will collect bone marrow stem cells from the bone marrow of patient volunteers. In the lab, they'll implant engineered viruses containing a new gene in those stem cells, which make red blood cells.

Then, they'll return the stem cells containing the engineered viruses to the patient volunteers' bodies. Each patient volunteer will get his own stem cells back.

The viruses used in the experimental therapy have been altered so that they can't cause disease. Giving patients back their own stem cells means patients and doctors won't have to worry about organ rejection, Malik said.

Researchers hope the implanted gene would allow sickle cell patients to make hemoglobin F, which lets red blood cells form normally.

The engineered virus would continue to reproduce in volunteers' bone marrow and let volunteers permanently make normal red blood cells if the therapy works.

Federal health regulators are reviewing the therapy, which took a decade of groundwork to develop.

If the feds give the go-ahead, Malik and her team could begin the first phase of human trials in adults with sickle cell next year, possibly in the spring or summer. Malik expects to recruit 10 people for the first phase.

Testing the new therapy will be a slow process that could take another five years or longer. Regulators and researchers will monitor volunteers who undergo the therapy to make sure it's safe and to see if it works.

The experimental therapy might not work in people, Malik warned. Some therapies don't translate from mice to humans. Federal regulators could pull the plug at any time if there are signs the therapy could be dangerous. In a French gene therapy trial aimed at treating a rare immune disorder in children in 2003, some patients who received the therapy developed leukemia.

Malik and her colleagues, though, remain cautiously optimistic.



"If it works, the impact would be significant," said Clinton Joiner, director of the Comprehensive Sickle Cell Center and the Hematology Program at Cincinnati Children's. "This is a bad, bad disease to have."

About 500 people die of sickle cell and its complications each year in the U.S., Joiner said, and about half of sickle-cell patients die by age 45.

Sickle-cell patients don't have many treatment options now, he said.

Bone marrow transplants work well, but only about 10 percent of people with sickle cell get them because it's so hard to find a donor match if a sibling can't donate.

There's also a time limit for bone marrow transplants, Joiner said. By the time sickle cell patients are 16 or 17, the disease has caused enough damage that the risks from the transplant are too high to make it worthwhile, and the transplant itself can cause problems even in younger patients.

Some sickle-cell patients benefit from hydroxyurea, a drug that lets the body make hemoglobin F and reduces the number of sickle cells, but doesn't remove them completely.

Hydroxyurea doesn't work for everyone with sickle cell, though, and it's a form of chemotherapy, so it has its own side effects, including immune suppression.

The disease affects the entire family. The Kinebrews of Colerain Township never know when they're going to have to take Kaleb or Kameron to the emergency room for a pain crisis.

Both boys have suffered acute chest syndrome, a condition similar to pneumonia that occurs when lung tissue isn't getting enough oxygen. It's extremely painful and dangerous as lung function is lost.

Both have undergone blood transfusions, one temporary remedy for the disease.

"A lot of times, people look at the boys, and you can't see sickle cell. They live with it every day, and they don't look sick," said Kevin Kinebrew, the twins' father. "The reality is depending on the day, you never know if there's going to be a pain crisis or an emergency or a call from school that they're having problems."

Kinebrew and his wife, Robyn, both have the sickle cell gene, although Robyn was originally told she didn't have it.

When the boys were diagnosed at birth with sickle cell, doctors re-tested Robyn and found out she carried the trait.



The boys participate in ongoing research at Cincinnati Children's, including a study looking at what factors contribute to acute chest syndrome, she said.

"It's important to learn more, to find something that might help them and other families," she said.

Additional Facts

Sickle-cell anemia and its effects

Sickle-cell anemia is a hereditary disease affecting red blood cells, which carry oxygen to the body's tissues. Both parents have to carry the genetic trait for the disease for a child to develop it.

There is no cure, and few treatments. Average life expectancy for Americans with the disease is in the mid-40s, though sickle cell patients can live into their 60s.

Normal red blood cells are doughnut-shaped and can easily slip through arteries, veins and tiny capillaries to carry oxygen to tissue throughout the body. In sickle cell, the cells are shaped like crescent moons or sickles, making it harder for them to get through the blood vessels.

Sometimes, the misshapen cells get stuck or cause other damage that narrows the blood vessels. If the blood vessels are in the brain, stroke can result. If the blood vessels are in the eyes, blindness may result.

The cells become misshapen because the body makes the wrong kind of hemoglobin, the chemical that makes blood red.

Babies can be diagnosed with sickle cell at birth, but symptoms don't start until they're about 4 to 6 months old.

That's when the body stops making fetal hemoglobin, or hemoglobin F. At that point, a baby without sickle cell disease starts making hemoglobin A, which lets their bodies make normal red blood cells.

Babies with sickle cell make hemoglobin S, which deforms the red blood cells. The cells become fibrous and form sickles, especially when they're low in oxygen.

People with sickle cell suffer chronic pain, including severe episodes that may require narcotics. When blood flow to the organs is disrupted, permanent damage can result, including organ failure. Infections are common, as is damage to bones and joints. Sickle cell is the leading cause of stroke in children.