TEXT - “We know what causes sickle cell disease. Where's the cure?”

AP Biology

*D*r. David Williams very much hopes the White House’s $755 million “cancer moonshot” finds cures, that Sean Parker’s $250 million “Dream Team” brings effective immune-system treatments to every kind of tumor, and that the $370 million raised by Hollywood-based Stand Up to Cancer fuels discoveries that make malignancies as treatable as headaches.

All Williams wants is $5 million — a rounding error to the billionaires making nine-figure donations to cancer research — to run a clinical trial that has a good chance of curing sickle cell disease. There is no moonshot for sickle cell. There are no “ice bucket challenges.” When fundraisers at Boston Children’s Hospital and Dana-Farber Cancer Institute, where Williams is president of the Cancer and Blood Disorders Center, ask donors to support sickle cell research, benefactors say they prefer to fund efforts that promise to help the adorable little kids stricken with cancer.

There are many theories about why that is, and why the lack of urgency and even interest extends to scientists. Fewer than a dozen US labs are working all-out on sickle cell disease, a number that has stayed constant for years, said Dr. Stuart Orkin of Boston Children’s. “I’m not sure why there are so few,” he said. “Maybe [the biology of sickle cell disease] seemed too simple, or maybe it isn’t sexy enough.” Or maybe the disease strikes the “wrong” people. “Sickle cell patients have never been at the front of the line,” said Dr. David Nathan, 87, a past president of Dana-Farber who helped discover the only drug that partly treats it. This work, especially clinical trials, is hugely expensive, and the National Institutes of Health and private foundations haven’t prioritized it.”

Virtually every scientist thinks the disease he or she studies is underfunded. What’s different about sickle cell is that scientists can point to specific turning points when a few more people at the lab bench would have made a significant difference to the pace of progress, and to specific studies now on the drawing board that could, with a concerted national effort, cure the disease. “This is the right time for a sickle cell moonshot, a concerted effort to focus resources — not just financial resources but intellectual resources — on a goal,” said Williams. “The technology has advanced to the point where we can talk about curing this disease.”

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Every year about 300,000 babies around the world are born with sickle cell disease, the result of a mutation in the gene for hemoglobin, the oxygen-carrying molecule in red blood cells. Only infants who inherit the defective gene from both parents — an estimated 100,000 people in the United States — have it. The mutation, discovered in 1956, causes red blood cells to cramp up into a crescent shape that makes them clump, impeding their flow through blood vessels. As a result, patients can suffer anemia, infections, fatal organ failure, tissue damage, strokes, and pain so intense it feels like a pickaxe-in-the-skull migraine everywhere in the body.

Camille Lonzer had her first such sickle cell crisis, as the severe pain is called, a year ago, when she was 13, the latest blow from a disease that for years had sent her to the hospital with fevers and infections seemingly as often as other little girls go to birthday parties. Her parents, who work for pharmaceutical companies near Chicago, have been tireless in managing Camille’s sickle cell disease, including massaging her in an effort to keep her blood flowing and the pain at bay. So far, the disease has not kept Camille “from doing everything I want,” she said. But the arrival of the pain crises, she and her parents worry, might change that. “I try not to think about it,” she said. “I try to imagine myself somewhere else.”

Camille began taking the only Food and Drug Administration-approved sickle cell drug, hydroxyurea, after the pain crisis. Hydroxyurea is an old cancer medication whose effect on sickle cell was discovered serendipitously by Nathan and his colleagues at Boston Children’s. It can reduce episodes of sickle cell crisis, but helps only about half of patients, can cause [serious side effects](https://www.nlm.nih.gov/medlineplus/druginfo/meds/a682004.html), and does nothing about the sickling itself. A bone marrow transplant can cure the disease, but most patients can’t find a match, the procedure has a fatality rate of up to 5 percent, and patients need to be on anti-rejection drugs forever. While other discoveries of disease-causing mutations led to treatments and even cures in, for example, 26 years for cystic fibrosis or 16 years for HER2-positive breast cancer, the discovery of the sickle cell mutation has led to exactly zero after 60 years.

Not that there haven’t been opportunities.

Physicians have long been struck by how some people with the sickle cell mutation are mostly fine, with few or none of the disabling symptoms. In 1948 scientists guessed why: These patients, hematologists wrote in a paper on “the paucity of sickle cells in newborn Negro infants,” were still making a form of hemoglobin that the body ordinarily stops producing in the first year of life. If just 15 percent or so of the body’s hemoglobin is “fetal hemoglobin,” scientists learned later, it keeps the disease at bay. Orkin, who had done pioneering research on thalassemia and other blood disorders as well as the genetics of normal blood cell development, began searching for the genetic magic that accomplished that.

He and his colleagues got clues by studying Saudi Arabian patients who had the sickle cell mutation but only mild symptoms thanks to the fetal hemoglobin they kept making into adulthood. But the genetic basis of that is “complex and requires interaction with additional factors,” Orkin and his colleagues wrote in 1989.

It wasn’t a surrender, or a warning that the genetics of sickle cell were too tough to decipher. It was what, in many other fields, would be taken as a challenge, drawing hordes of young scientists to an intriguing puzzle. That did not happen. By the late 1980s, scientists knew that genetic on-off switches — transcription factors — were important for the development of blood cells. “But no one had a clue which transcription factors regulated the switch from fetal to adult hemoglobin,” said Orkin, who is also chairman of pediatric oncology at Dana-Farber. With barely a dozen labs working on sickle cell, the field didn’t have the critical mass that might have led someone to figure out what kinds of cells to use in experiments seeking the fetal-to-adult switch.

They hit dead end after dead end, and with little incentive to keep hunting, “we went off and did other things,” said Orkin. “I like to do things that work, and sickle cell wasn’t working.” He turned away from sickle cell research for about a decade, spending the 1990s on the genetics of normal blood cell development. He still thought about sickle cell disease, trying to imagine how the genetics of the fetal-to-adult hemoglobin switch worked. But no one was banging on his door to fund sickle cell experiments, no Hollywood charity dangled millions of dollars in grants in front of him.

In the early 2000s, Harvard medical student Vijay Sankaran, working in Orkin’s lab, said he wanted to study the fetal-to-adult hemoglobin switch. For nearly three years, Sankaran’s experiments repeatedly failed. It turned out he was looking for the crucial transcription factor gene on the wrong chromosome. Sankaran finally bagged his quarry in 2008, when he identified the gene that turns on production of adult hemoglobin. Called BCL11A, it’s located on chromosome 2. When they suppressed BCL11A in human cells growing in lab dishes and in mice, they reported in Science in 2011, blood cells kept making fetal hemoglobin and the mice were cured of sickle cell. If many scientists had been competing with Sankaran to find the gene, who knows if he would have abandoned his search on the X chromosome in weeks, not years. And who knows how much faster key discoveries would have been made.

**sickle cell disease happens**

When David Williams was a newly minted physician 30 years ago, the Children’s Hospital hematology caseload was about evenly split between kids with hemophilia and kids in sickle cell crisis. Since then, treatments for hemophilia have become so successful that they’re practically cures, and children almost never show up with uncontrollable bleeding. “So we see almost all sickle cell,” Williams said, explaining why he jumped at the chance to build on Orkin’s discoveries. “It’s really sad that’s the case.”

He began developing an experimental therapy based on the genetics of sickle cell, in particular the idea that knocking out only enough BCL11A to reactivate some fetal hemoglobin production should avert the devastating symptoms of the disease. But Williams immediately hit the same speed bump that Orkin and Sankaran had: too few resources. He needed a way to slip genetic material into cells, using a harmless virus (viruses are great at infiltrating cells). It took his lab two long years to figure out how to do that safely, partly because “I had only one postdoc working on it,” he said. “With more people, it would have taken much less time.”

His plan is to pack molecules called antisense RNAs into lentiviruses, which would carry the RNA into blood stem cells isolated from a patient’s bone marrow. Antisense RNA basically hogties the messenger molecules that carry instructions from the BCL11A gene, triggering a sequence of events that cause some blood cells to make fetal hemoglobin. That should keep at least some fetal hemoglobin from being switched to the adult form. “Most people think you’d have to correct only 10 to 20 percent of cells to cure somebody,” Orkin said. About 30 percent was enough to cure the mice in his 2011 Science study.

Gene therapy would likely be too expensive for use in India and the African countries where sickle cell is common, so Orkin hopes a drug could tie up BCL11A. “That’s where I think a moonshot really is needed,” he said: drawing clever, imaginative researchers to find molecules able to disable enough BCL11A to keep enough cells making fetal hemoglobin to cure the disease. “A moonshot would bring in structural biologists and chemists [and others] who could find a drug targeting BCL11A,” Orkin said.

The what-ifs — if 50, not 10, labs pursued sickle cell; if Orkin had been able to enlist more scientists in the 1990s transcription-factor hunt; if Williams had had the resources to support four or five postdocs looking for a safe vector — are impossible to answer. But “as a scientist and a physician, it’s one of my major frustrations,” said Williams, referring to how little support and attention sickle cell gets from scientists, funders, and the government. “This is a disease that devastates the families and the lives of the children.” “Maybe it’s our fault,” said Nathan about the paucity of resources devoted to sickle cell over the decades. “Maybe we didn’t scream enough” for more funding, more bodies, more attention.

Pamela Lonzer seconds that. When Camille was born with sickle cell disease, “I thought my world was ending,” she said. Although Camille, whose favorite school subjects are science and writing, has participated in research on exercise and pain, the family is still waiting for a clinical trial of a drug or other therapy that might actually cure her. “This is a disease that doesn’t get the attention or the funding it should,” Lonzer said. “There’s a stigma that comes from thinking it affects only African-Americans. People dismiss it by saying, ‘Oh, sickle cell patients just have pain.’”

Williams is slowly getting governmental and other approvals for the small clinical trial he’s planning. He thinks a moonshot — with all the coordination, resources, and publicity that could bring — might organize multiple medical centers to participate in both this trial and, if it succeeds, larger ones. He hopes to start recruiting patients (two children, two teenagers, and two adults) in September. “This is absolutely going to work,” Williams said — if only someone would pony up $5 million.

Begley, Sharon. “We know what causes sickle cell disease. Where's the cure?” *STAT*, STAT, 9 Aug. 2016, www.statnews.com/2016/05/19/sickle-cell-disease-cure/. Accessed 27 Sept. 2017.