TELL US MORE

TED W. LOVE '81:

Pioneering a New Therapy for Sickle Cell Disease

The science behind sickle cell disease (SCD) is cruel. For approximately 100,000 American children and adults (and 10-15 million people around the globe), a mutation in a single gene means a lifetime of unpredictable and excruciating pain—along with exhaustion, serious infections, and collateral damage to the brain, heart, lungs, and other organs. Anemia, strokes, pregnancy problems, kidney disease, and joint pain are common.

But the racial inequities that have hindered treatment advances for SCD—the most common inherited blood disorder in the United States—are far crueler. "I was at a conference recently where an older woman stood up and said she'd been in situations where she was effectively told, 'Sickle cell disease is an African-American problem. It's up to you guys to solve it,' " says physician Ted W. Love '81, M.D., CEO of Global Blood Therapeutics (GBT) in South San Francisco. "But there's no reason the greater society as a whole shouldn't be solving this. And thankfully we're starting to see it get the attention it deserves these days across the biotech industry and with drug regulators."

In the United States, more than 90 percent of people with SCD are African-American. The average life expectancy is 40-45 (up from age 14 in the 1970s). U.S. Food and Drug Administration-approved therapies are limited to a circa-1960s cancer drug with potentially serious side effects, or a bone marrow transplant—a cure that few opt for because it is risky, and donor matches are difficult to find. Children and adults with SCD who need relief for a crisis of acute pain wait 25-50 percent longer for emergency room care than others with severe pain, according to a recent study; too often, they're dismissed as "drug seekers."

Today, researchers and drug companies are investigating at least a dozen potential SCD therapies (from gene-editing to acacia-tree resin), aided with incentives from the FDA. Among the most promising is one that Love's company has developed, the experimental drug GBT440. Love spoke to *Haverford* magazine about the drug and its promise in treating people with SCD.

PHOTO: CHARLES HALL

How does GBT440 work?
GBT440 works by keeping hemoglobin molecules—the protein inside red blood cells that carry oxygen to cells throughout the body—from sticking together to form chains called polymers. This polymerization is the central problem in SCD; the polymers deform the shape of red blood cells. Normally red blood cells are round discs that glide through the bloodstream, but in SCD, they take on a crescent or sickle shape. These sickle-shaped red blood cells pile up in small blood vessels called capillaries, blocking blood flow and restricting oxygen to body tissues. That causes severe pain episodes that send people to the emergency room and body-wide tissue damage.

About one pound of an adult's body weight is hemoglobin; its job is to pick up oxygen from the lungs and make it available to cells throughout the body. It works like a dump truck. When it travels to tissues, it delivers as much oxygen as possible into a tissue. That's when polymerization happens in SCD. And that's where GBT440 comes in. It essentially keeps hemoglobin molecules in a flatbed position inside red blood cells, so it can't form polymers.

What have early clinical trials found?
We continue to study GBT440 in people with SCD, but the clinical trials we have conducted so far have shown that dramatically fewer red blood cells are sickling and healthier red blood cells are surviving, flowing through capillaries and delivering oxygen. Patients have less anemia, which should make them feel better. Almost anybody who understands the science behind GBT440 is excited about the potential of this investigational drug.

A pivotal Phase 3 GBT440 clinical trial is underway in adults and adolescents (12 to 17 years old), with plans to expand the program to younger children later this year. Why include kids at such a young age?
SCD is a lifelong, inherited condition; you have it from birth. In our earlier clinical trials, GBT440 has been shown to be safe. Now, in our phase 3 study, if GBT440 continues to have an excellent safety profile and can be shown to be effective, then arguably the greatest benefit effects will come from starting it very early, as soon as six to nine months after birth. Parents are very supportive and hopeful for a new option that can potentially help their child or children lead a normal life.

GBT440 got Orphan Drug Status from the FDA in 2016—the same year your company went public with a $1.2 billion IPO. That's a huge vote of confidence from investors and the government. When might GBT440 be ready for the public?
That's a few years away. We expect to report results of the current Phase 3 trial, which is designed to test whether the drug works in 400 people, in the first half of 2019.

You've called the need for better SCD treatments a social justice issue. Can you explain?
SCD was first described 100 years ago, and 60 years ago, the genetic basis was understood. Despite this, research into novel treatments has not kept pace with other diseases. When I was in medical school, patients with SCD were dying in their teens. Today, people still live only into their 40s. Right now, some people are treated with an older cancer drug called hydroxyurea, but it can cause concerning side effects. Complications of SCD are treated with hydration, pain relief, and pain medications. Bone marrow transplant is only an option for a few.

You were in retirement, living in California's wine country after three decades in biotech, when you decided to head GBT. Why?
I was already on the company's board but wanted to stay retired so I could devote my time to my wife and daughters. I'd had a good career working for biotech firms including Genentech, Nuvelo and Onyx, but the long hours and travel were brutal for family life. But I kept reviewing the GBT440 data from animal studies, and they strongly suggested it might work in humans. I was on a flight to Seattle and couldn't get it off my mind. I called my wife, Joyce, and she said, "Just come home, we'll talk about it." She and my daughters [Samantha, Haverford Class of 2017, and Alex, Class of 2015] were absolutely adamant that I had to do this—it was a critical opportunity to help the African-American community and people around the world with SCD. My family provided, and continues to provide, enormous and wonderful support. I now know this was the right decision as the team I joined, and help continue to grow, is similarly inspired to find a solution to the inequity of SCD. Our team's passion and drive, combined with the hope of the SCD community, keep me focused and motivated.

Other researchers are testing gene therapies for SCD. Would that make GBT440 obsolete?
Unlikely, as GBT440 would be taken as a once-a-day pill. We expect to announce top-line data from our Phase 3 study in 2019, meaning that GBT440 could potentially be available in the U.S. before gene therapies. In my opinion, patients will likely prefer to take a once-daily pill, and it may be more practical and affordable in areas of the world where people have less access to advanced medical care. If the SCD community gets to the point where people have several treatment options that directly target this disease, that will be a major win.

How do you feel when human volunteers take for the first time a drug that you're developing?
I feel hopeful. Before the first human trial, there's an enormous amount of work done to demonstrate that a drug is safe and has more benefits than risks. There are lots of precautions, including starting with very low doses in people. Both healthy volunteers and people with the targeted disease, in this case SCD, are critically important to the potential success of drug development. The people who volunteer usually will not get the benefits themselves—they do it to help others, potentially improving the lives of future generations. For that I am very grateful.

—Sari Harrar

Sari Harrar is a freelance health journalist published in national magazines, books, and online. She was a 2016 National Magazine Award finalist.