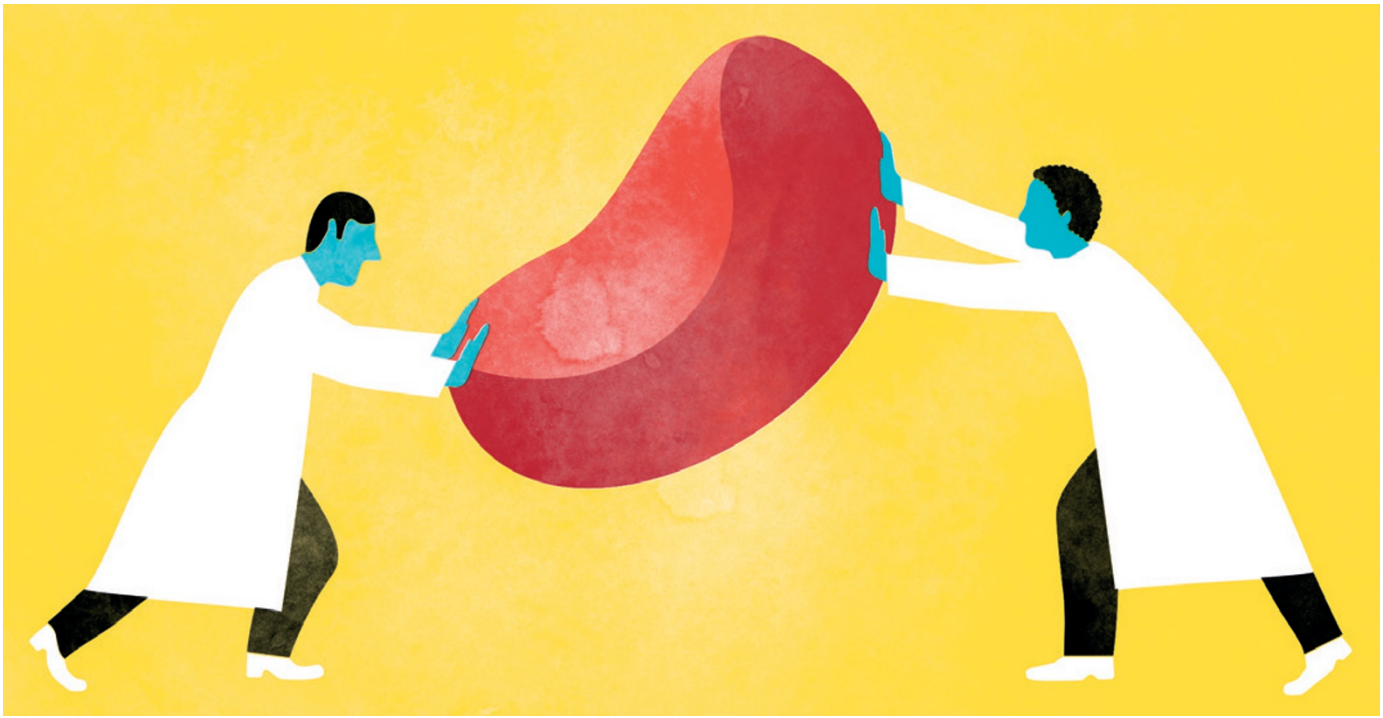

ANDRÉ DA LOBA

DRUG DEVELOPMENT

A complicated path

Only one drug is available to treat sickle-cell disease, but a wave of investment and industry attention is set to turn the tide.

BY COURTNEY HUMPHRIES

Sickle-cell disease makes a sweeping hit to the body. What begins as one small genetic alteration — a single faulty nucleotide in a haemoglobin gene — ends in a cascade of damage. People with sickle-cell disease have a mutant form of haemoglobin, the molecule inside our red blood cells that allows them to carry oxygen to tissues throughout the body. This form, called 'sickle' haemoglobin, is capable of carrying oxygen, but once the oxygen is released the haemoglobin joins with other sickle haemoglobin molecules to create rigid rods that bend the normally flexible, disc-shaped red blood cells into distorted, narrow crescents. The sickled cells are twisted, dense and dehydrated, and clog blood flow when they stick to the walls of blood vessels and to other blood cells. Over time, the consequences accumulate: anaemia, periods of overwhelming pain, greater risk of infection, damaged organs and tissues, and a shortened lifespan.

Treating the disorder has proved to be far more complicated than describing it. Drug development has been hampered by both limited investment from the pharmaceutical industry and limited trial enrolment, leaving patients with few options. In addition, the disease is rare in the US and Europe, which are responsible for the majority of clinical trials — there are millions of cases of the disease worldwide, yet only 100,000 people living in the United States have it. Researchers have a detailed scientific understanding of the condition, but there is only one drug available to treat sickle-cell disease: hydroxycarbamide (known as hydroxyurea in the United States), approved by the US Food and Drug Administration in 1998. And although it can reduce the number of painful episodes and hospitalizations by preventing blood vessels from clogging, only about two-thirds of adult patients have any response.

Bone-marrow transplants can provide a cure because they replace the faulty haematopoietic stem cells that produce sickled cells with ones that make healthy red blood cells (see page S14). But the procedure is expensive, has risks such as infections and life-threatening immune-system reactions, and is not yet widely available. Other treatments have been slow to emerge, but there are reasons to be optimistic. "A lot of new drugs are being pursued as specific agents for sickle cell," says Betty Pace, a paediatric haematologist and oncologist at Georgia Regents University in Augusta. Pharmaceutical companies are increasingly seeing potential for profit in treatments for diseases that are rare in the developed world. Therapies are being developed to prevent complications such as stroke or organ damage or to treat complications as soon as they arise. There are more clinical trials and research has uncovered potential disease targets that could lead to new therapies.

HAMMERING THE SICKLE

One sign of the growing corporate interest in sickle-cell disease occurred in July, when pharmaceutical and medical-device company Baxter International, headquartered in Deerfield, Illinois, acquired a potential drug called Aes-103, together with its parent company, AesRx. It took more than a decade to secure investment for Aes-103, which illustrates the challenges that scientists face when developing treatments for rare diseases.

Don Abraham, a chemist at Virginia Commonwealth University in Richmond, had been working since 1975 to develop a drug that binds to sickle haemoglobin and prevents it from distorting red blood cells into the characteristic crescent. His problem was one of scale. Patients with sickle cell have around 320 grams of haemoglobin in their bodies, and most of the

compounds he tried were too toxic at the doses needed to make a difference. Thinking that natural food components might be less toxic, Abraham began looking for safer solutions in the human diet. In 2000, his search for anti-sickling food agents led him to a naturally occurring chemical called 5-(hydroxymethyl)furfural, or 5-HMF, which is found in caramel, roasted coffee and dark beer. After decades of testing agents in his laboratory, says the now-retired Abraham, "it is by far the best thing we've seen". But in spite of promising results in animal studies[1], which showed that the molecule safely prevented red blood cells from sickling in mice engineered to have the gene for human sickle haemoglobin, it experienced a series of setbacks.

The drug was initially licensed to a now-defunct pharmaceutical company but "was sitting on a shelf", says Stephen Seiler, who formed biopharmaceutical company AesRx of Newton, Massachusetts, in 2008 so that he could buy the rights to develop the compound as Aes-103. When venture capitalists showed little interest in backing the work, Seiler went to the US government and received funding as part of an unusual public–private partnership.

As an anti-sickling agent, Aes-103 represents "a class of drugs that's been dreamed about for as long as we've thought about treatments for sickle-cell disease", says Gregory Kato, director of the Adult Sickle Cell Disease Center of Excellence at the University of Pittsburgh in Pennsylvania. But so far, it is the only such drug to enter clinical trials. AesRx worked with Kato, who was at the US National Heart, Lung, and Blood Institute in Bethesda, Maryland, at the time, and with researchers at the National Institutes of Health's Therapeutics for Rare and Neglected Diseases programme to take the drug through early-stage clinical trials. In a phase I/IIa safety study, 15 patients who took one dose of Aes-103 experienced significantly less pain than patients given placebo. The drug is now in a phase II trial — designed to test dosing and efficacy — in London, which is due for completion in 2015.

When Seiler first dreamed of bringing Aes-103 into clinical trials, he was one of a very few working on sickle-cell treatments. But interest has grown substantially. "Orphan drugs are a lot more attractive than people perceived them to be in 2008," he says. Because orphan diseases are uncommon, regulatory standards are more flexible to encourage companies to invest in them, so companies can run smaller, less expensive trials, which are often accompanied by government incentives, such as a US tax credit on the costs of clinical trials.

CRISIS INTERVENTION

Research is branching beyond anti-sickling agents to molecules that prevent sickle-cell interaction. Sickle cells do not act in isolation: not only do they stick to each other and obstruct blood vessels, but they also cause white blood cells, platelets and cells on blood-vessel walls to stick to each other. The result — blocked blood vessels and inflamed tissues[2] — worsens the effect of the disease, says Marilyn Telen, director of the Comprehensive Sickle Cell Center at Duke University in Durham, North Carolina. They cause a common complication, called vaso-occlusive crisis, that causes periodic episodes of pain so intense that they often require hospitalization (see page S8) and which, over time, can cause permanent organ damage.

"It's mind-boggling that there is still no specific therapy for vaso-occlusion," says Paul Frenette, director of the Gottesman Institute for Stem Cell and Regenerative Medicine Research at Albert Einstein College of Medicine in New York City. On the basis of the number of drugs in the pipeline, he is hopeful that this will soon change.

One such drug, called MST-188, is thought to work by binding to the damaged membranes of red blood cells to make them less likely to stick to other cells. "It's sort of like grease for your circulatory system," says Brian Culley, chief executive of Mast Therapeutics, the biotechnology company in San Diego, California, that owns the drug. Like Aes-103, MST-188 had been shelved by its creators. In 2010, Mast Therapeutics acquired the company that owned MST-188 to reboot the drug's development. Mast is now recruiting patients at medical centres around the world for a phase III trial, in which it aims to test MST-188 as a treatment for vaso-occlusion.

Other researchers are attempting to prevent blood-vessel blockages by targeting specific molecular interactions between cells. One of the most promising targets is a class of cell-adhesion proteins called selectins that, when activated on the surface of epithelial cells, cause white blood cells to stick to blood-vessel walls and have been implicated in the pathophysiology of sickle-cell disease in animals. The furthest along of these studies is being pursued by GlycoMimetics of Gaithersburg, Maryland, which has completed a phase II study of a drug called rivipansel that inhibits selectin molecules. In patients hospitalized for vaso-occlusion, rivipansel reduced the duration of the crises, shortened hospital stays, and decreased the amount of opioid pain medication by 83% compared with placebo. The company is now collaborating with Pfizer on a phase III trial.

Because vaso-occlusion involves a variety of processes, including pain and inflammation, combination therapy might be the best way to reduce its effects. But, Telen says, "we are hugely far away from that", and notes that developing such a cocktail is daunting for a rare disease with little funding.

FETAL INSPIRATION

The only therapy currently approved to treat sickle-cell disease, hydroxycarbamide, acts in a different way from the drugs being developed. Rather than treating the acute pain of vaso-occlusive crises, hydroxycarbamide prevents long-term consequences of the disease primarily by stimulating production of the fetal form of haemoglobin. This molecule is the dominant form at birth but is present only in very small amounts by the time a child is one year old. It functions like adult haemoglobin but, because it is produced by a different gene, is unaffected by the sickle-cell mutation.

"Our goal is to reactivate the fetal haemoglobin gene."

So researchers are investigating other drugs that stimulate fetal haemoglobin. Some are new agents and others have already been FDA-approved for treatment of unrelated conditions. These include pomalidomide, a drug used against multiple myeloma, and decitabine, a drug used for a type of bone-marrow cancer. In each case, says Pace, "our goal is to reactivate the fetal haemoglobin gene, or to keep it active, if you treat a very young child".

Beyond finding potential drug treatments, a major hurdle in getting promising therapies tested and approved is patient recruitment. Several clinical trials have stopped altogether because of low enrolment. "We're still trying to figure out different ways to overcome the problem," says Carlton Haywood, a bioethicist specializing in sickle-cell disease at Johns Hopkins University in Baltimore, Maryland. Studies suggest that the reasons why so few patients with sickle cell in the United States participate in clinical trials include a lack of trust in the medical establishment, either because of a history of discrimination or because of poor experiences in their own medical care, and parental unwillingness to expose children to an experimental drug.

But Haywood, who has sickle-cell disease, adds that it is also important for researchers to examine institutional factors that prevent enrolment, such as study designs that exclude too many people because of medical complications or if they have other diseases. Also, because the disease already causes people to take time off work or school, "factors like providing child care or transportation could make research participation less of a burden". And he has found that people with sickle cell in the United States, most of whom are African-American, also report racial or ethnic discrimination in the health-care system, and it is primarily US patients who are being recruited to sickle-cell drug trials.

Haywood believes that researchers should focus on helping patients feel more engaged in clinical research. "We should feel like we're an important part of the process", he says — something that is particularly important when the pool of potential subjects is already so small. Ultimately, even the most promising treatments will not advance without patients willing to test them. ■

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2. Manwani, D. & Frenette, P. S. *Blood* **122,** 3892–3898 (2013)