An Effective Therapeutic For Sickle Cell Disease

Virginia Commonwealth University

Donald Abraham's quest to find a new drug to treat sickle cell disease (SCD) has all the intrigue and plot twists of a suspense novel: It's a decades-long, against-all-odds pursuit filled with overwhelming obstacles, false starts, uncanny timing, dogged determination, international collaborations and not one, but two chance meetings.

Some 40 years after he began looking for a way to alter the underlying molecular mechanism of SCD, the compound Abraham discovered at Virginia Commonwealth University (VCU), is now a drug candidate being evaluated in clinical trials.

"I threw everything, my whole heart and science into sickle cell disease," says the retired Abraham, who served as professor of medicinal chemistry and director of VCU's Institute for Structural Biology and Drug Discovery at from 1988 to 2007. "For a long while it wasn't the wisest thing to do. But since my postdoctoral days in 1963, my great desire was to use structural biology to discover a drug."

Structure-Based Drug Design

Structural biology, or structure-based drug design, uses X-ray crystallography or nuclear magnetic resonance spectroscopy to obtain information on a three-dimensional structure — the drug target — to aid in the search for a small molecule to bind to the target in a way that achieves a therapeutic benefit.

"You can think of the structure as the puzzle with a piece missing," explains Abraham, who was one of the first scientists to attempt to use structural biology for drug design. "You know what the piece has to look like to fit in."

Abraham chose to work on SCD because it provided him with a ready-made puzzle.

The molecular structure of hemoglobin, a protein inside red blood cells that carries oxygen throughout the body, was the first protein to be decoded — along with a genetic mutation found in people with SCD. When mutant or "sickle" hemoglobin releases its oxygen, it sticks to other sickle hemoglobin (a process called polymerization), creating rigid rods that distort red blood cells from their typically round shape into narrow crescents. These sickle cells stick to each other and to blood vessel walls, causing anemia, organ damage and overwhelming pain.

Searching for a Missing Piece

In 1975, despite a lack of funding and support for SCD research, Abraham launched what would become a decades-long search for a molecule — the missing puzzle piece — to bind to sickle hemoglobin and prevent the polymerization process and the consequent sickling action.

"I was told that I had 0 percent chance of solving this," says Abraham, who remained undeterred. "I went into this field with the hope of one day discovering a new drug to relieve human suffering."

> *Sickle cell disease occurs in about 1 out of every 500 African American births. Millions of people are affected by the disease worldwide,*

According to the Centers for Disease Control and Prevention, SCD is a hereditary disease that mainly affects African Americans: Less than 100,000 people suffer from SCD in the United States — too few to warrant a billion-plus-dollar research program from major pharmaceutical companies.

Pursuing a rare or orphan disease meant Abraham would lose his funding from the National Institutes of Health (NIH) and his research team. But a chance meeting with a professional baseball player fundraising for SCD research led to new funding sources and, eventually, the opportunity to collaborate with Max Perutz at the Medical Research Council Laboratory of Molecular Biology in Cambridge, UK, who had won a Nobel Prize for his work unraveling hemoglobin. Their research, which spanned an eight-year period, in turn attracted a team of graduate students and postdoctoral fellows to Abraham's VCU lab.

Building Momentum

By the late 1980s, Abraham's research team had identified a number of compounds that inhibited polymerization in the test tube, but all proved to be too toxic for use in humans.

"Sickle cell patients have almost a pound of hemoglobin," explains Abraham. "So in the early 1990s we shifted gears and began searching for a food-like agent that could be tolerated at high doses throughout a patient's lifetime."

The common flavoring agent vanillin proved promising at first but metabolized too quickly in the body, leaving Abraham and his researchers at a dead end.

Food-Based Agents

Fate intervened once more when Abraham and his wife were on a train trip across Italy and shared a train cabin with a British food chemist.

"I asked him if he knew of any nontoxic food agents like vanillin that might be suitable candidates to test," says Abraham. "It was a last ditch effort because I had no idea what else could be out there."

The chemist sent Abraham a list of possible compounds that included a byproduct of browning sugar called 5-Hydroxymethylfurfural (5-HMF). Basic animal studies of the compound, conducted at Children's Hospital of Philadelphia, confirmed the efficacy of the compound.

In 2002, Abraham, Martin K. Safo, Ph.D., and Richmond Danso-Danquah, Ph.D., disclosed their discovery to VCU's Innovation Gateway. Safo, a former postdoctoral fellow in Abraham's group, is leading the ongoing sickle cell disease drug discovery effort at the Institute for Structural Biology and Drug Discovery.

"I don't think any of this would have happened if it weren't for [former VCU] President Eugene Trani," says Abraham. "He had a real can-do attitude and an interest in advancing science and our work through commercialization."

VCU's Innovation Gateway filed the first patent on 5-HMF in 2004 and licensed the compound to a startup company. When that company failed, a second startup based in Newton, Mass., AesRx, acquired the rights to the preclinical molecule in 2009 and renamed it Aes-103.

"The compound was the most attractive opportunity I had ever seen," says AesRx CEO Steve Seiler. "There is a crying need for a novel intervention for SCD that is disease modifying. SCD was first described in 1910, and more than 100 years later, there is still no drug to treat it except an anticancer drug that has side effects and compliance issues."

Ivelina Metcheva, executive director of VCU's Innovation Gateway, says Seilerprovided a great example of how to communicate with a technology transfer office.

"He continually kept us apprised of where he was in the development process and the obstacles he was facing," she says. "As a result, we modified the license agreement to give him some breathing room to grow the business."

Connecting With TRND

With the economy in a tailspin, financing was a major issue for AesRx until 2010, when Seiler connected with the National Heart, Lung and Blood Institute (NHLBI) and the Therapeutics for Rare and Neglected Diseases (TRND) program, part of the NIH's National Center for Advancing Translational Sciences.

"We created a multiphase, multi-institute, public-private research collaboration with researchers from the NHLBI and TRND," says Seiler.

Within a year, AesRx was able to apply to the Food and Drug Administration for an investigational new drug application and move into early stage clinical trials, which showed that patients who took one dose of Aes-103 experienced significantly less pain.

A phase II trial designed to test dosing and efficacy began in London in 2013. The NIH provided $5 million in funding to support the collaborative research effort, and AesRx also secured additional financing in the form of a Massachusetts Life Sciences Center Accelerator Loan.

Seiler credits the cooperation among highly skilled researchers, VCU's Innnovation Gateway and TRND's business model for the quick progress made on Aes-103.

Derisking Drug Development

"The NIH played a prominent role in getting the clinical data to derisk further development of this drug so it would be appealing to venture capitalists and pharmaceutical companies that could take it the rest of the way," says Seiler. "You need good science, but you also need good people to associate with. We had good partners."

In July 2014, the biopharmaceutical company Baxter International acquired Aes-103 and is continuing clinical development activities required for regulatory approval and commercialization, including completing Phase II and III trials.

"From a professional perspective, this was the most satisfying thing I've ever done," says Seiler. "It's really encouraging and I hope to see it work for patients."

If Aes-103 is able to improve the lives of SCD patients, it will not only provide a storybook ending for Abraham, it could a start a new chapter for other rare and underfunded diseases.

"The business model that TRND proposed works and can be used for other orphan diseases," says Seiler. "So there's an impact beyond the SCD, focus and that's something we should all be proud of."

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