Using A Pill, Rather Than An IV, To Treat Gaucher Disease

University of Michigan

During the 1980s, an important collaboration took shape at the University of Michigan between two researchers: Norm Radin, a neurochemist; and Jim Shayman, a nephrologist (a doctor who specializes in kidneys). They shared an interest in studying lipids, which are fatty substances found in cells. These fats play critical roles in our health, such as keeping cell membranes stable — but when they accumulate too much, they cause problems. That includes Gaucher disease, a rare genetic disorder affecting at least 10,000 people worldwide. Gaucher patients may now have a more flexible treatment option, thanks to Radin and Shayman's work.

Their research led to an FDA-approved drug called Cerdelga — a pill that offers convenience for certain Gaucher patients who would otherwise receive IV treatments.

> *The drug may ultimately have more widespread benefits too, as additional research at the*

University of Michigan explores its potential to treat common diseases.

Gaucher disease harms the body because it affects cell parts called lysosomes. When working properly, these tiny sacs contain enzymes that break down fatty substances. But in Gaucher disease, a gene abnormality causes enzyme deficiencies, leading to fat buildup in the liver, spleen, and other major organs. With symptoms including liver enlargement and anemia, it's a debilitating disease for adults. For children, it can be fatal.

Radin began studying this enzyme-deficiency problem in the 1950s. At that time, researchers sought ways to replace defective enzymes, allowing the body to effectively break down fats. Radin proposed a different solution: Find a drug that could block the synthesis of excess fats.

"Radin was one of the long-term leaders in the area of biochemistry that's most relevant to Gaucher disease," says Shayman.

In 1988, Shayman formed a research team with Radin to look for molecules that prevented the harmful creation of excess fats. Even after Radin formally retired in 1995, the two researchers continued their search for effective compounds to treat Gaucher disease. In addition to blocking fat synthesis related to Gaucher, the compounds needed low toxicity to make them suitable for long-term use.

"It's one thing to develop a drug that you might use for cancer, where the toxicity of the drug might be acceptable given that the end goal is to use it for a shorter period of time," says Shayman. "But for Gaucher disease, where we were looking for something that patients could take, in theory, for the rest of their lives, it's a real challenge. We had to find inhibitors that were quite specific and non-toxic."

By 1998, the research team identified compounds to fit that description. The compounds could be taken as a pill — unlike other Gaucher treatments, which require a couple hours of IV infusions every two weeks. In 2000, the University of Michigan's Office of Technology Transfer licensed the compounds to Genzyme Corp. The company was well-established in the field, which was critical for the success of clinical trials.

"With a rare disease like Gaucher, you have limited numbers of patients and you need a way of identifying them, as well as finding experts who can participate in the clinical trials on-site," says Shayman who noted that the clinical trials involved 60 medical centers in 29 countries.

In 2011, Sanofi-Aventis acquired Genzyme Corp. and by August 2014, the FDA approved the Gaucher treatment. Sold under the brand name Cerdelga (also known as eliglustat tartrate), the pill became the first FDA-approved small molecule drug based on research at University of Michigan. Cerdelga was studied in the largest Phase 3 clinical program ever conducted on Gaucher disease, says Shay Zukowski, Sanofi Genzyme's associate manager of corporate communications for rare diseases. She notes that the company's first FDA-approved therapy, Ceredase, was the world's first disease-modifying treatment for Gaucher disease — it was followed by a product called Cerezyme. Both are enzyme replacement therapies delivered via IV infusion.

"Because Cerdelga is a pill, it offers patients an alternative to enzyme replacement therapy requiring biweekly

infusions," says Zukowski.

Shayman has observed the benefits of that. "There are patients who've been on enzyme replacement, typically older, who feel more comfortable doing IV treatment," he says. "But when I talk to patients who are younger, they are quite happy to have the oral option available to them."

In addition to negotiating and executing licensing agreements, the university's Office of Technology Transfer also helped monetize a portion of Cerdelga's royalty stream. In November 2014, PDL BioPharma Inc. agreed to pay the university $65.6 million in exchange for 75 percent of all Cerdelga royalty payments due under the license agreement with Sanofi Genzyme. The university's Office of Technology Transfer already had experience with monetizing royalty streams, because it had done the same thing with the FluMist flu vaccine in 2007.

"The process was much smoother the second time around, because we had internal experience and knew what we were doing," says Robin Rasor, the university's Managing Director of Licensing at the time (now head of Duke University's office of licensing).

For Cerdelga's royalty stream, once the Office of Technology Transfer determined that there would be interest in a purchase of its royalty asset, it widely offered the royalty stream to find the most appealing investor package. "I think what people miss sometimes is all the work the tech transfer office has to do post-license, and this is one example," added Rasor.

Although estimates place the number of Gaucher patients at about 10,000, Shayman expects that to increase, considering many cases have gone undetected. That's due to Gaucher's wide-ranging effects: In some people, it causes severe neurological problems and premature death, while others may show few symptoms.

"How many people worldwide are affected? The short answer is, we don't really quite know," says Shayman. "The disease is well-studied in western populations such as the United States and Europe, but other regions — including China, India and Southeast Asia — are now receiving more attention," says Shayman.

In the coming years, Cerdelga may have uses beyond Gaucher disease. Shayman is researching other possible applications. "Eventually I'd like to see uses expanded to more common diseases," says Shayman. "That will take many years of development and work, but at some point perhaps we'll be there."

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