Drugs for rare disorder phenylketonuria hit the market

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Brady Connolly lives with the condition known as phenylketonuria, or PKU. Credit: Gus Ruelas

Brady Connolly is an 18-year-old rugby player who can barely eat any protein. No steak, no beans, no peanut butter shakes—none of the foods

you'd imagine a young athlete would crave. That's what it's like to live with phenylketonuria (PKU).

Thanks to a genetic anomaly, people with this rare condition lack a critical enzyme called phenylalanine hydroxylase. That enzyme normally helps break down an amino acid—phenylalanine—that's found in all proteins from food. If PKU is left untreated, this unconverted phenylalanine can damage the brain. There is no supplement PKU patients can take to break down phenylalanine. The condition is incurable.

For Connolly, that means a highly restrictive diet. He must take his own lunch to school and drink a special formula several times a day. When he travels for his rugby matches, he has to plan his activities so he can take his formulas and get the right food.

He also has to pack his PKU medication, a drug called Kuvan.

"Since I started taking Kuvan years ago, I've been able to eat a modified vegetarian diet, rather than a complete low protein diet," Connolly explains. "Before Kuvan, I couldn't eat things like breads, rice or pastas. Now, I can at least eat regular carbs with lots of fruits and vegetables. It makes a huge difference."

Connolly is just one of the thousands of Americans living with PKU. Nearly 7,000 of them have taken Kuvan since it was federally approved a decade ago. A second drug, Peg-Pal, for patients with a more severe form of PKU, was just approved this year.

In part, Kuvan and Peg-Pal trace their heritage back to a physician with the Keck School of Medicine of USC named Richard Koch. They are also the products of the persistence of Raymond Stevens '88, a USC alumnus and scientist who founded the Bridge Institute at the USC

Michelson Center for Convergent Bioscience in 2014. The stories of Kuvan and Peg-Pal are their stories.

Koch dedicated more than 50 years at the Keck School of Medicine and Children's Hospital Los Angeles to finding possible treatments for patients born with the rare metabolic disease. He was so passionate about caring for these patients and seeking a cure that he earned the nickname "Dr. PKU."

In 1997, Koch heard about Stevens' research and saw possibilities. Stevens at the time was a professor at the University of California, Berkeley. He had built a 3-D model of phenylalanine hydroxylase, the critical enzyme to PKU, together with colleagues in Norway. Koch knew it was a step toward developing a new drug, so he picked up the phone. Would Stevens come to Los Angeles to meet Koch's team of nurses and doctors? Would he want to meet families who were living with PKU?

Stevens had no idea then how much that phone call would change his life.

A Miracle Mission

Children inherit PKU when both parents are carriers of mutations in the PAH gene, which holds the body's instructions for making the phenylalanine hydroxylase enzyme. PKU was first identified as a genetic disease in 1934 by Norwegian doctor Asbjørn Følling, who invented a screening test for it. It did little to stop the developmental disruption for children diagnosed with PKU, who included the eldest daughter of the Nobel-winning author Pearl Buck.

Over the next 20 years, researchers determined that a highly restrictive diet could protect PKU patients from brain damage. Then, a researcher named Robert Guthrie, whose own niece was diagnosed with PKU,

developed a neonatal blood screen dubbed the "Guthrie test" to catch the disease only hours after birth. Doctors could then promptly intervene with a prescribed diet.

But studies show that many teens and adults with PKU struggle to stick to the diet, even though they must be on it for life. The costs of breaking the diet include a drop in I.Q., hyperactivity, lethargy and headaches. Koch developed a dietary formula, and companies developed a prescriptive set of medical foods, but even those didn't allow teens to feel part of the group when friends were eating sandwiches or pizza for lunch.

The challenge of following a restrictive diet can also depend on which form of PKU the patient has.

Tia Reynolds, a 15-year-old from the Washington, D.C., area, has the most severe type. Doctors determined she can ingest only about a quarter of an egg's worth of protein per day. Her mother, Alison Michaux Reynolds, has to weigh food and carefully read labels to look out for hidden sources of protein that could spike her daughter's phenylalanine hydroxylase enzyme levels.

"It is extremely taxing on the family," she says. She even had to stop working to care for Tia. Fortunately, the family has long had a support network of people who refuse to give in to PKU.

When Tia was just an infant, family friends and fellow alumni from the University of North Carolina-Chapel Hill stunned the Reynolds family with a gift for her first birthday: They had raised about $60,000 for a miracle mission to find a cure for PKU.

"They said, 'We want you to do something with this to help Tia,'" Alison Reynolds says. "So, I went searching for a researcher who was working

on PKU."

Alison Reynolds' parents, Richard and Ginny Michaux, helped with the hunt. Together, they found BioMarin Pharmaceutical, a Bay Area company whose mission was to develop drug treatments for rare diseases.

They also found Ray Stevens, who had moved to The Scripps Research Institute in La Jolla to conduct his research. He invited the whole family, including little Tia, to visit him at his lab. They were so impressed with their visit that they handed The Scripps Research Institute the $60,000 gift that had come from friends and Tia's grandparents—the Michauxs and the Pizialis. They knew Stevens was passionate about solving PKU. It was 2004, and Stevens was onto something.

A Team Effort

PKU was, in a way, a classic example of what can happen with research into rare diseases. "At the time, companies weren't really interested in it unless there was convincing data that a molecule could successfully complete the clinical trials process, and the NIH wasn't particularly interested in it," Stevens recalls. "What Dick and Ginny Michaux, Alison Reynolds, and Bob and Kathy Piziali did by contributing funds really opened up door for change and making a difference."

"It was a team effort at every level," Stevens adds, "from philanthropy to research to drug development, involving families, researchers and industry."

Determined to hasten efforts to find a treatment, Reynolds, the Michauxs and the Pizialis in 2004 organized a large gala, "Tuxes for Tia," in San Francisco. Stevens spoke at the event, connecting with even more families living with PKU. It raised about $400,000.

The gala's success signaled that the PKU network was growing. Families with PKU and organizations around the country began connecting to Stevens, BioMarin, the Michauxs and Reynolds, rallying in support. The Mid-Atlantic Connection for PKU and Allied Disorders group in New York learned about the gala and Stevens' work, and they also contributed.

Stevens found himself juggling invitations to picnics and fundraiser walks, phone calls with families and emails to update them on his progress in the field.

"The kids and families got me hooked on wanting to pursue PKU drug discovery and make a difference," he says.

Drug Discovery

In August 2004, BioMarin Pharmaceutical filed an investigational new drug application with the FDA, announcing that it would begin clinical trials for a new PKU drug.

But it wasn't the first drug target they had explored.

When BioMarin researchers first started working on a therapy for PKU, they ran across something interesting, says Emil Kakkis, a researcher at BioMarin who later became its chief medical officer. They noticed other research published on a different molecule, tetrahydrobiopterin, or BH4, that had been used to treat a few patients but wasn't moving forward toward drug approval.

Why was BH4 languishing? "You had to ship it frozen and store it frozen, or it would degrade," Kakkis explains.

Patients with PKU could take BH4 easily by mouth, and it improved the

liver's ability to break down phenylalanine, so it had potential, says Kakkis, now the CEO and president of the drug company Ultragenyx Pharmaceutical. So, the researchers took a chance. They focused on making a stable version of BH4.

The new drug, Kuvan, hurtled from phase I to phase III clinical trials at lightning speed, based on its effectiveness in lowering phenylalanine in some patients with mild and moderate forms of PKU. Within three and a half years of the investigational new drug filing, the FDA approved Kuvan, assisting patients like Connolly who had a less-severe form of the disease.

"We worked very hard to drive through the process, and it was the fastest that I have ever done it," Kakkis says.

For Connolly, Kuvan enables him to eat more protein and have more variety in his diet.

But for patients with severe PKU, like Tia, Kuvan didn't work. Researchers would have to keep working on a different drug. And they needed funding to do it.

So Dick Michaux hit the road in 2008 and biked across the country, raising $175,000 from sponsors. Soon after, he and Stevens used the funds and a match from BioMarin to establish a research-focused organization, the National PKU Alliance. It officially launched in 2009, with families and their supporters contributing millions.

"We've invested about $2.8 million into PKU research that led to another clinical trial and more scientific knowledge about how PKU affects the brain," says Christine Brown, president of the alliance. Today it has grown to 17 affiliates and about 3,000 to 4,000 donors.

Stevens, an ultramarathoner and mountain climber in his spare time, also launched a PKU awareness campaign and ran the infamous Marathon des Sables, covering 156 grueling miles across the sand dunes of the Sahara Desert in six days to help spread the word about the disease.

"Ray was a pretty unusual researcher," Michaux says. "We appreciated his determination and his ability to focus his energies on something he believed in so strongly. He trained for the ultramarathon in a sauna. He wore a backpack. Darn if he didn't finish. His feet were just raw. They taped him up like a mummy. He just endeared himself to the PKU community."

The ultramarathon seemed like a sprint compared to the time it took the scientists to discover and develop the second drug to fight PKU, a molecule called Peg-Pal. It is administered by injection. Kuvan took only a few years to hit the market, but the drug development timeline for Peg-Pal was 17 years, the first six of which occurred in the lab, before it was ripe for clinical trial, according to Kakkis and BioMarin.

Peg-Pal (ultimately renamed Palynziq) made it through clinical trials successfully, and the FDA approved it this year.

In February 2018, more than 200 students and faculty members listened to Stevens tell this story, his story, in a USC Dornsife lecture. In talking about his work with Koch and his involvement in the development of PKU treatments, he may have inspired future investigators to follow a similar path.

"So why do drug discovery?" he asked the crowd.

"Because you can make a difference in someone's life."