Megan Donnell set up the Sanfilippo Children's Foundation when her children Jude and Isla were diagnosed with Sanfilippo syndrome.

C. MAHONY

ADVOCACY

Strong foundations

Most rare diseases lack even one approved treatment. Regulators have tried to encourage drug development, but advocacy groups are having to fight to get the research done.

BY JAMES MITCHELL CROW

Isla Donnell was two and a half years old when her mother, Megan, first became concerned about her development. When other children her age began to speak in full sentences, Isla could string only a few words together. Paediatricians in the family's home city of Sydney, Australia, assured them that Isla's development was within the normal range, but by the age of four, her mental and physical development was clearly behind. Tests confirmed their suspicions: Isla had a rare genetic condition called Sanfilippo syndrome. Also known as mucopolysaccharidosis type III (MPS III), Sanfilippo is one of the 50 or so known lysosomal storage disorders (LSDs).

As the Donnell family struggled to take in this diagnosis, Isla's little brother Jude — by then a chatty two-year-old — was tested too. Four weeks after Isla's diagnosis, Megan and her husband discovered that Jude had the condition as well.

Sanfilippo syndrome affects 1 in around 70,000 children, and few make it to adulthood. There is currently no treatment, although ten research programmes have a therapy that is in or about to enter early stage clinical trials. "The message we were given was that research is happening, but a treatment is a long way away," says Megan, a former management consultant. "I began to look at what research was being done, and discovered there was quite a bit." But only two of the programmes were run by established pharmaceutical firms; the rest were within academia or small spin-out companies that struggle to finance human trials.

So Megan — like many parents before her — stepped in to help. In 2013, she set up the Sanfilippo Children's Foundation. Today, the charity is helping to fund one promising therapy through the first phase of clinical trials, and is considering which other programmes to support.

Foundations formed by parents and researchers are powerful advocates for the development of treatments for rare diseases. As well as helping to bridge the funding gap, many of these foundations are calling for an overhaul of the regulations that incentivize pharmaceutical companies to bring drugs to market, arguing that the current system is not working.

"For rare diseases, there is an enormous amount of bureaucracy to get a therapy trialled and approved. I'm sure all of that could be streamlined," says John Hopwood, an LSD researcher from the South Australian Health and Medical Research Institute in Adelaide.

"The reality is that not doing anything means these patients are going to die."

PARENT POWER

Emil Kakkis knows first-hand how important financial support from a family foundation can be. In the early 1990s, Kakkis was a medical-genetics researcher at Harbor-UCLA Medical Center in Torrance, California. He was working on an LSD called Hurler syndrome (MPS I). He had synthesized some of the enzyme that was missing in people with the condition and showed that it treated the disease in animal models. "My feeling was, my job was done," says Kakkis. "I'm going to hand it off to some company to develop the product."

But no company was interested. Kakkis went to Genzyme, which in 1992 had gained approval from the US Food and Drug Administration (FDA) for the first enzyme-replacement therapy for an LSD, Gaucher's disease. But whereas Gaucher's affects up to 1 in 50,000 people, Hurler affects only 1 in 100,000. "Genzyme said, 'This is kind of small'," Kakkis recalls. He then tried speciality pharmaceutical company Orphan Medical, whose mission was to develop 'orphan' drugs for rare diseases. "And they said no. My product was too small even for an orphan-drug company."

Fortunately, his research caught the attention of the Ryan Foundation, which was set up in Carrollton, Texas, by the parents of six-year-old Ryan Dant, three years after his diagnosis with Hurler syndrome. The foundation's support enabled Kakkis to produce pharmaceutical-grade enzyme for clinical trials. In 1997, newly formed Californian biotech company BioMarin stepped in to take it on.

Ryan was one of the first children enrolled in the trial the following year. Five years later, in April 2003, the FDA approved the therapy. "Ryan has been on the treatment for 18 years, and he's doing well, finishing college," Kakkis says. "The story opened the door to treatments for other rare diseases." But as Megan Donnell observed ten years later, that work is still going on, and foundations such as hers still need to provide support.

HOMES FOR ORPHANS

The US Orphan Drug Act was passed in 1983 to encourage companies to develop drugs to treat rare diseases by offering perks such as tax incentives and fee waivers. But so far only seven LSDs have an FDA-approved treatment. An analysis led by paediatrician Markus Ries at Heidelberg University Hospital in Germany showed that LSDs that mainly affect the body are now quite well treated — Gaucher's disease has five approved treatments, for example. But most LSDs have a neurological component, and there are no approved treatments for these conditions (see page S154). "LSD treatments are biased to enzyme-replacement therapies," says Ries. "The trouble is, the enzyme molecule is so big that if you infuse it into the blood, it doesn't cross the blood–brain barrier."

Gene therapy (see page S158) or other future treatments might be able to get over this physiological barrier. But the bigger problem, advocates say, is the regulatory barrier. Typical drug trials use clinical endpoints. "You compare your drug to the natural history of the disease, to show a difference," Ries says. For Hurler syndrome, for example, the endpoint was based on the distance a patient could walk in six minutes after therapy, compared with the distance they would be expected to reach without it.

But for many LSDs, their rarity means that the natural progression of the disease is not well known. Such complications are amplified when measuring the effect of a drug on cognitive development, Ries adds. Speech progression, for example, varies according to language. And there are few established, standardized protocols for testing neurological drugs. The lack of good endpoints is holding up drug development, he says.

These problems frustrated Kakkis so much that in 2009 he left BioMarin to found the EveryLife Foundation for Rare Diseases, and launched the Cure The Process campaign. One of the key issues on which the foundation is lobbying is the need for greater flexibility from the FDA in its approach to rare-disease clinical trials. The Cure the Process campaign urged the FDA to clarify its guidelines on the use of biological markers to make it easier to start such trials.

Rather than use clinical endpoints, a biomarker-based trial would measure changes in the body. Therapies for Gaucher's disease have previously used a physiological marker as an endpoint: a reduction in the volume of the swollen liver and spleen, says Kakkis. But the best example is HIV. "In HIV there is a really simple biomarker, the viral load," he says. By

COUNTING THE COST

Rare diseases, high prices

EVERYLIFE FOUNDATION

Today there are several medium-sized companies and dozens of smaller ones that specialize in developing 'orphan drugs' to treat rare diseases. "Rare diseases are worth investing in," says Emil Kakkis (pictured), chief executive of orphan-drug company Ultragenyx, which he founded in 2010.

Back in the 1990s, rare diseases were not considered a good investment. Drugs to treat common chronic conditions such as multiple sclerosis typically cost around US$25,000 per patient per year. For rare conditions that affect just a few hundred people, it is not viable to charge that amount, says Kakkis. "There's no way to earn back the $100 million or more you invested developing the drug."

This meant that rare-disease companies needed a new financial model. "In some ways, Genzyme's invention was of the very high price," Kakkis says. The company's enzyme-replacement therapy for Gaucher's disease costs around $200,000 per patient per year. "Without that high price, we end up sitting in the lab with our science and no one can benefit from it."

But as more therapies for rare diseases enter the market, "health systems are having more problems agreeing to pay", Kakkis says. This concern is acknowledged by paediatrician Markus Ries at Heidelberg University Hospital in Germany. "If companies don't make money with therapies, they don't develop any." But if companies keep pushing high prices onto health-care systems, he says, "what is the reaction of the system going to be?"

Orphan drugs represent a small proportion of overall health-care costs. Collectively, rare diseases affect around 10% of the population, and the cost of orphan drugs as a percentage of national health-care expenditure is below 5%. The cost will rise, but no faster than in the rest of the health-care sector, where costs are rising across the board. As health-care systems face increasingly tough budgetary decisions, rare-disease foundations may have to spend more time fighting to maintain a slice of the pie for their patients. J.M.C.

measuring the amount of virus in the blood, HIV researchers could conduct small, rapid drug trials to discover effective drugs and drug combinations. "The reason AIDS got solved is because the approval pathway allowed a biomarker endpoint," he says.

For neurological LSDs, Kakkis would like to use similar biomarkers that measure the amount of particular molecules in the patient's urine or blood. Many rare diseases have distinct biochemical markers, directly related to disease progression, that might be used in this way. But since 1992 the FDA has agreed only two new biomarker endpoints of any type, he says. "Nobody can break through with a new endpoint because the requirements are impossible," Kakkis says. The FDA needs to formulate clear scientific criteria for assessing new biomarkers, he adds.

But there has been some progress, says Kakkis. The FDA Safety and Innovation Act of 2012 stipulated that the FDA should consider novel endpoints, "especially in instances where the low prevalence of a disease renders the existence or collection of other types of data unlikely or impractical". And in August 2015, the FDA released draft guidelines for industry on the development of orphan drugs, including an initial discussion on biomarkers. "The ball is moving," says Kakkis, although he wishes it would move a bit faster.

FINDING FUNDING

Megan Donnell knows that her foundation's work will not end with the first approved therapy for Sanfilippo syndrome. "Advocacy will be critical when we have a treatment we need funding for from the government," she says (see 'Counting the cost'). But right now, getting a therapy through clinical trials remains her focus.

With advice from Hopwood, Megan has decided to fund a gene-therapy trial at the Nationwide Children's Hospital in Columbus, Ohio. Thanks in part to this seed funding, the research has led to the creation of a spin-off company, Abeona Therapeutics, which will commercialize the therapy. Abeona has just started its first clinical trial.

Isla and Jude Donnell are now seven and five years old. "The disease is progressing in them," says Megan, "but they are doing quite well, all things considered." She hopes that they will be eligible to join Abeona's trial later in the year.

The progress in finding treatments for rare diseases continues to rely on foundations such as Megan's. "There is a community of kids that needs treatment, and we are close to having something for them," Megan says. "A little bit of focus on research in this area is going to make a big difference to a generation of patients." ■

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DRUG DEVELOPMENT

Through the barrier

Treatments that can cross the blood–brain barrier are needed if doctors are to treat the devastating neurological symptoms of many lysosomal storage disorders.

BY SARAH DEWEERDT

The first time Tim Cox used enzyme-replacement therapy to treat a patient, the effects were "like magic", he recalls. The patient was a businessman who had been forced to retire in his forties and was now confined to a wheelchair. He had a massively enlarged liver and spleen, and needed frequent transfusions of blood and platelets to stay alive.

These are the effects of Gaucher's disease. The body cannot produce the enzyme that breaks down a fatty molecule called glucocerebroside, which then accumulates to toxic levels in various body tissues. The only established treatment at the time, a quarter of a century ago, was a risky bone-marrow transplant, but none of the man's three sisters was a viable match. So Cox, a metabolic physician at the University of Cambridge, UK, obtained a cutting-edge treatment from the United States — glucocerebrosidase enzyme purified from a human placenta — and administered it to his patient by intravenous infusion.

This was the first UK use of enzyme-replacement therapy to treat Gaucher's disease, and the result was dramatic. Within months, Cox's patient was no longer dependent on either blood transfusions or the wheelchair. "He never looked back, and he's still alive today," Cox says. Without it, "he would have been dead from bleeding or some complication a long time ago."

The advent of enzyme-replacement therapy in the early 1990s revolutionized the treatment of Gaucher's disease. It also led to a new era of drug therapies for other lysosomal storage disorders (LSDs), a group of around 50 genetic conditions that compromise the body's ability to break down specific molecules, which then build up to create severe health problems (see page S146).

Today, enzyme-replacement therapies are available for more than half a dozen LSDs. Treatment options have expanded to include drugs with other modes of action too, such as partly blocking the synthesis of the troublesome molecules, and rescuing the function of mutant enzymes. But despite this broadening range of therapies, it remains difficult to get drugs into the central nervous system to treat the neurological symptoms that are the most devastating aspect of many LSDs. Researchers hope that some of the molecules being developed may finally clear this barrier. "We're right on the verge of some incredible new opportunities," says John Marshall, senior principal scientist at biotech company Sanofi Genzyme in Cambridge, Massachusetts.

NEW FOR OLD

Enzyme-replacement therapy is exactly what it sounds like. "You're putting back the missing factor," says Paul Harmatz, a paediatric gastroenterologist at the Children's Hospital Oakland in California. He has been involved in developing enzyme-replacement therapies for a group of LSDs known as mucopolysaccharidoses.

But as so often happens, part of the development of enzyme-replacement therapy came about through a chance discovery. In the 1960s, researchers in the laboratory of Elizabeth Neufeld, a biochemist now at the University of California, Los Angeles, inadvertently mixed together cells from patients with two different mucopolysaccharidoses: Hurler and Hunter syndromes. Surprisingly, both sets of cells became physiologically normal. Neufeld and her colleagues showed that each type of cell secreted the enzyme that the other lacked, and absorbed the enzyme it needed from its neighbours — a concept known as cross-correction.

"We're right on the verge of some incredible new opportunities."

This finding was taken up by Roscoe Brady at the US National Institute of Neurological Disorders and Stroke in Bethesda, Maryland, who had already made important discoveries regarding the diagnosis and causal mechanisms of Gaucher's disease. His team altered the glucocerebrosidase so that a sugar called mannose appeared on its surface to help the enzyme enter macrophages, the