

ORPHANS FIND A HOME

After years of neglect by pharma companies,
RARE DISEASE TREATMENT is coming into the limelight

LISA M. JARVIS, C&EN NORTHEAST NEWS BUREAU

ONE AFTERNOON A WEEK, usually on a Tuesday, a nurse arrives at the Elmwood Park, N.J., home of Jeff and Deena Leider to give their sons, Justin and Jason, their “muscle juice.” On each visit, she carefully inspects a handful of vials, empties them into an intravenous bag, and calibrates a pump that will slowly dole out the bag’s contents. Justin, who at four is the younger of the boys, is the first to be hoisted onto the kitchen counter. After taking off his shirt, he sits, swinging his legs and patiently waiting for his superpowers to be activated.

The nurse, whom the boys clearly adore, gently removes a bandage on Justin’s chest, revealing a small bump that allows her to home in on his implanted IV port. After she inserts an IV line, Justin pulls his shirt back on and shrugs on a Batman backpack holding the IV bag and the pump. Fully suited up, he reaches for a reward of a sour gummy worm and hops down. Minutes later, Jason takes his place on the counter, and the nurse repeats the process with him.

For the next four hours, while Justin and Jason go about their evening routine with their matching backpacks in tow, their muscle juice—known to technical-minded grown-ups as Shire’s drug Elaprase—slowly infuses into their bloodstream. The superpowers it imparts make it easier for them to run, jump, and climb like other kids their age.

The boys have Hunter syndrome, a rare and fatal genetic disease caused by a deficiency in an enzyme that breaks down sugar molecules. The missing enzyme is just one of more than 100 housed in the lysosome, the cell’s waste bin. Today, some

50 different inherited diseases—known broadly as lysosomal storage diseases—are caused by genetic mutations that disable one of those enzymes.

In Hunter syndrome, which affects only boys, the buildup of sugar molecules over time causes symptoms such as stiff joints, enlarged spleens, and difficulty breathing. For children like Justin and Jason, who have a form of the disease that affects the brain, the accumulation also causes a rapid decline in mental function. And it’s rare—just one in 155,000 boys are born with the disease.

Elaprase replaces the missing enzyme, iduronate-2-sulfatase, buying the boys valuable time by shrinking their spleens and helping their heart and lungs function. Yet it won’t save their lives. Elaprase can’t get past the blood-brain barrier, the cellular security gate that protects our most complex organ, so it can’t stop the mental deterioration that will cause the boys to lose their ability to walk and talk. Most boys with Hunter syndrome die by age 15.

Elaprase is also breathtakingly expensive. As his sons run in circles through



LISA JARVIS/C&EN

the kitchen and living room, Jeff Leider holds up a small glass vial filled with clear liquid. “That’s, like, \$10,000 right there,” he says, eying the bottle with a mix of awe and disbelief. Having two kids with Hunter syndrome who need several vials per treatment, the Leiders’ annual bill approaches \$1 million. Deena’s insurance covers the bulk of the cost, and Shire, the drug’s manufacturer, takes care of the rest through a patient assistance program.

Two-and-a-half years after Justin and Jason’s diagnosis of Hunter syndrome, the high price of treatment and its limited effectiveness have led the Leiders to start a nonprofit and to lobby Congress to make it easier for children to get diagnosed and for drugs to be developed.

That has put the Leiders in the middle of a movement that is creating new treatments for even the rarest of diseases. Because they afflict so few people, thousands of diseases have been ignored for decades. Now, a shift in big pharmaceutical companies’ business models away from multi-

billion-dollar blockbuster drugs is coinciding with a deeper understanding of the genetic underpinnings of rare diseases. And government policies introduced just last year have created new incentives to serve small patient populations.

The collision of factors has made rare disease drugs one of the fastest-growing areas of drug development. Orphan drugs will account for 15.9% of all branded-drug sales by 2018, up from just 5.1% in 1998, according to the health care consultancy EvaluatePharma. In five years’ time, orphan drugs will be a \$127 billion-per-year business, the firm says.

The surge in interest is made possible by the inverse relationship between patient population size and drug price. The high price for a treatment like Elaprase, which runs well into six figures, annually, per person, might raise eyebrows for those

ROUTINE A nurse gives Jason Leider his weekly dose of the treatment Elaprase, while his brother, Justin, watches. They are two of only a few hundred boys in the U.S. with Hunter syndrome. The boys carry backpacks containing an IV bag with the drug, which takes four hours to infuse into their bloodstream.

not immersed in the rare disease world. Because Hunter syndrome affects such a tiny group, Shire charges a high premium for Elaprase to offset the risk and cost of developing it.

The pricing paradigm has put rare diseases on drug companies’ radars. Even with few patients, there is money to be made. As big pharma tries to reinvent itself in an era of

few blockbuster drugs, that’s an attractive proposition.

When the Orphan Drug Act was introduced 30 years ago to create incentives to develop treatments for diseases with patient populations of less than 200,000, the drug pipeline for the estimated 7,000 rare diseases was barren. Even as recently as a decade ago, the number of major companies committed to developing drugs for rare diseases could be counted on one hand.

But as Christopher P. Austin, director of

the National Institutes of Health's National Center for Advancing Translational Sciences (NCATS), declared at an event in February marking World Rare Disease Day, such illnesses are no longer in the wilderness.

NIH and the Food & Drug Administration are trying hard to foster innovation and clear the drug development path for often-overlooked patient populations. Last year, FDA was granted a new set of tools that stakeholders describe as the most important advancement in promoting rare disease development since the Orphan Drug Act.

Patient advocates are the common denominator pulling together the rare disease movement. Their role in raising awareness and encouraging drug development has been critical to piquing the interest of both academia and industry.

Sometimes, patient advocates simply try to raise awareness so that others can be diagnosed and treated earlier. According to a recent study conducted by Shire, a specialty pharmaceutical firm with a large presence in rare diseases, it takes on average 7.6 years and eight physicians for people with a rare disease to be diagnosed. Often, they get two or three misdiagnoses before someone can tell them what's really going on.

The Leiders' foundation, Let Them Be Little x2, puts a spotlight on Hunter syndrome, with the hopes that awareness will prompt more research and, eventually, a cure. "I had a choice to make," Jeff Leider says. "I could go in a closet and hide from this evil world, or I could scream and yell as loud as I possibly can so that somebody will hear me."

Others are going further by directly funding research, setting up patient registries that can be useful for clinical trial recruitment, and even starting companies. They've pushed the government to adjust its policies to fit the current state of drug development for rare diseases, pointing to the estimated 10% of the population suffering from a rare disease as evidence for the common good the changes would bring.

They connect previously disparate research, invent new models for collaboration, and use social media to make their voices heard. They tick off acronyms for government programs like true Washington, D.C., bureaucrats, and they speak about research for their disease like Ph.D. scientists. Without their efforts and collaboration, company executives say, drug development would be difficult, if not impossible.

For these patient crusaders, the motiva-



tion is clear: They are in a race for their loved ones' lives. Jeff and Deena wince each time they see a Facebook photo of a friend's child with the caption, "Time Flies." That casual two-word refrain from fellow parents is another reminder that time is running out for their boys.

STICKER SHOCK
Elaprased, Shire's enzyme replacement treatment for Hunter syndrome, is one of the most expensive drugs in the world.

THE BUSINESS OF RARITY

The current groundswell of interest in rare diseases can be traced to Genzyme, the first firm to show that drugs for small patient populations could be profitable

ANYONE PUZZLING over the business case for developing drugs for tiny patient populations need look no further than Genzyme. Founded in Boston in 1981, the biotechnology firm pioneered the model for rare disease drug development that is followed today: make an impact on a previously untreated rare disease, charge high prices, and be rewarded with significant revenues and a long reign in the marketplace.

Genzyme made its mark by introducing the first treatment for Gaucher's disease, a lysosomal storage disease caused by a deficiency in the lipid-busting enzyme glucocerebrosidase. Similar to Hunter syndrome, Gaucher's occurs when the absence of that key enzyme causes a buildup

of molecules in the lysosome and results in a variety of problems. Complications from Gaucher's include enlarged organs, bone pain, and anemia.

When Genzyme embarked on developing an enzyme replacement therapy for type 1 Gaucher's, which does not affect the central nervous system, the disease was thought to affect just 1,500 people worldwide. Conventional wisdom at the time was that a company could not turn a profit on a drug for such a minuscule patient population.

But the naysayers were proven wrong. The Food & Drug Administration approved the drug in 1994, and Genzyme charged an unprecedented \$200,000 per year. Although insurance companies balked at the cost, they eventually agreed to cover it. Companies like Genzyme ensured patient access by introducing assistance programs that helped families with potentially high copays.

With a treatment on hand, the diagnosed patient population more than tripled, reaching roughly 5,000 people, industry watchers say. Moreover, Genzyme had a captive audience: The first competition for its drug, Cerezyme, didn't arrive until 2010, when Shire won approval to sell a rival, Vpriv. At their peak in 2008, annual sales of Cerezyme reached \$1.2 billion.

The success of that model—a small, genetically defined patient population and a high-priced drug—spawned two other companies that continue to be mainstays in the rare disease arena: Transkaryotic Therapies, founded in Cambridge, Mass., in 1988 and acquired by Shire for \$1.6 billion in 2005, and BioMarin Pharmaceutical, started in 1997 in Novato, Calif. Together, Genzyme, Shire, and BioMarin have gone on to develop some of the most expensive drugs—all enzyme replacements.

Those three firms laid the foundation for the current corporate interest in rare diseases. Alumni from Genzyme now populate the executive suites of many of the companies focused on rare diseases. Notably, the chief executive officers of Aegerion Pharmaceuticals, Amicus Therapeutics, Prosensa, and Synageva BioPharma all had stopovers at Genzyme.

But all this activity isn't just about high premiums, says Austin of NCATS. "I think people have really internalized the concept that rare diseases are a window into common diseases," Austin says. Rare genetic disorders occur when a gene is completely turned off; more common diseases often happen when that same gene's function is simply turned down.

He points out that the first scientific clue in the development of cholesterol-lowering drugs like Pfizer's Lipitor—for years the world's best-selling drug—was the discovery of a cluster of families with a rare, genetic mutation that causes very high levels of “bad” cholesterol.

Rare disease advocates have taken that concept to heart. Hunter syndrome belongs to a collection of more than a dozen diseases, each caused by a deficiency in a different sugar-busting enzyme. Many of these so-called mucopolysaccharidoses (MPS) diseases primarily affect the brain, and patient groups trying to win funding for MPS research often point to the connection between MPS diseases and common neurological disorders.

In 2009, for example, University of Cali-

& MORE ONLINE

has Sanfilippo type C, also known as MPS IIIC, tried to impress upon her local congressmen that although Sanfilippo research might directly affect only a few dozen children in the U.S., the greater good for society makes it a worthwhile investment.

Congressional staffers' eyes clouded when Wood uttered words like mucopolysaccharidoses. They sat up and listened when she said Alzheimer's.

Although rare diseases could open the door to treatments for common ailments, the flip side is that common diseases are starting to be segmented into smaller subpopulations on the basis of genetics. “The paradigm for orphan drug development

See images of the patients and hear scientists and parents talk about their challenges at <http://cenm.ag/rare>.

Pfizer's Xalkori, a drug designed to treat roughly 7% of lung cancer patients whose disease is caused by a mutation in the ALK gene, illustrates how segmenting can be profitable. Because the drug makes such a dramatic impact on patients' survival, Xalkori reached the market just four years after the discovery of the ALK mutation. Clear efficacy data and a small patient population enabled Pfizer to slap a \$9,600 monthly price tag on the treatment. Consultancy firm EvaluatePharma expects that Xalkori will bring in more than \$900 million in annual sales by 2018.

“Rare diseases in some ways set a template for the future,” says Kevin Lee, chief scientific officer of Pfizer's rare disease group. “We believe we're going to learn far more about some of these basic diseases, which will allow us to segregate them much more specifically by molecular mechanism. Ultimately, these large diseases will become constellations of many small diseases, all of which have the same symptoms.”

Meanwhile, scientific understanding of rare diseases has grown by leaps and bounds. Although the Human Genome Project failed to deliver on the promise of clear drug targets for common diseases, the rapid gene-sequencing and publicly available data it spawned have enabled scientists to swiftly figure out the underlying cause of many rare diseases, NCAT's Austin says. Two decades ago, scientists had teased out the molecular basis for fewer than 50 rare diseases, Austin says; today, they know the genetic underpinnings for roughly 4,500.

“That is a complete sea change,” Austin says. “Thirty years ago, when I was in training, I saw patients with these rare syndromes that were characterized in really arcane, clinical ways. We had no idea what the molecular basis was.”

That jackpot of genetic information has drawn new players to the rare disease space. Agios Pharmaceuticals, for example, saw exploring genetically defined rare metabolic diseases as a natural progression for its drug discovery platform, which was built to tackle cancer cell metabolism. At the same time, small patient populations mean Agios can develop its own pipeline of drugs without the infrastructure needed to commercialize treatments for more common diseases.

Investors like the strategy. In late 2011, Agios was able to raise \$78 million to support its foray into rare diseases.

RARE DISEASES BY THE NUMBERS

A disease is defined as orphan in the U.S. when it affects fewer than

200,000
people

There are approximately

7,000

types of rare diseases and disorders



95%

of rare diseases have no FDA-approved drug treatment

80%

of rare diseases are genetic in origin

Approximately

50%

of those affected by rare diseases are children

30%

of children with a rare disease will not live to see their fifth birthday

8:

Average number of physicians visits before diagnosis

3:

Average number of misdiagnoses

7+ years:

Average time until diagnosis

SOURCES: National Organization for Rare Diseases, Global Genes Project

fornia, Los Angeles, scientists discovered that children with a type of MPS disease called Sanfilippo syndrome produce high levels of tau, one of the two telltale proteins found in the brains of people with Alzheimer's disease.

The link means that better understanding the mechanism of Sanfilippo could lead to treatments for Alzheimer's. At a recent lobbying day for rare disease advocates, Jill Wood, a mom from Brooklyn whose son

today may become the paradigm of more common drug development tomorrow,” says Philip J. Vickers, global head of R&D for Shire's rare disease unit.

Industry experts like to hold up lung cancer as an example of this shift. As scientists pick apart the different biological drivers of lung cancer, they can provide more personalized treatments for the nearly 230,000 people diagnosed with the disease each year.

Big pharma's interest in rare diseases took longer to foment. When Summit Corp. was spun off from England's Oxford University in 2003 to develop drugs for Duchenne muscular dystrophy, a fast-moving muscle-wasting disease, it was clear that "big pharma just wouldn't look at a disease like DMD," says Andrew Mulvaney, a Summit cofounder and its director of business development. At the time, the biotech firms working on rare diseases were largely focused on lysosomal storage diseases, where the orphan drug model had been proven.

Today, a race for FDA approval between two firms—Prosensa and Sarepta Therapeutics—with drug candidates that treat a small slice of the DMD population is one of the closest-watched competitions in the biotech industry. And Summit, which has a drug with the potential to treat all children with DMD, suddenly finds itself being courted by big pharmaceutical companies, Mulvaney says.













The shifting interest comes as big pharma struggles to get new drugs across the finish line to offset revenue losses as, one after another, its blockbuster products lose patent protection. Suddenly, orphan products, including those for the rarest of the rare diseases, carry appeal.

In 2010, GlaxoSmithKline and Pfizer became the most visible new players when they formed dedicated rare disease units. Others, such as Roche, have made a series of deals that collectively amount to a sizable rare disease portfolio.

But it was Sanofi's purchase of Genzyme for \$20 billion in 2011 that really put the spotlight on rare disease assets, according to Ritu Baral, a stock analyst at the investment firm Canaccord Genuity.

Venture capital firms have become equally enchanted with the rare disease space. Not only is significantly more venture capital being devoted to rare disease drugs today than in the past, "but I think there's more venture capital money for orphan drugs than for any other type of drug, save oncology," Baral says.

Some firms have even started funds specifically targeting rare diseases. Among the biggest moves was a partnership between Atlas Venture and Shire to make early-stage investments in rare disease opportunities. And just last month, New Enterprise Associates and Pfizer Venture Investments committed \$16 million to Cydan, which will pluck rare disease projects from academia and start companies around the most promising ideas.

 <p>Disease: MPS I Common name: Hurler Deficient enzyme: α-L-Iduronidase Incidence: 1 in 144,000 Drug in development: Intrathecal ERT Approved treatments: BioMarin & Genzyme's Aldurazyme, hematopoietic stem cell transplant</p>	 <p>Disease: MPS II Common name: Hunter Deficient enzyme: Iduronate-2-sulfatase Incidence: 1 in 155,000 Drug in development: Shire's intrathecal ERT Phase of drug: I/II Approved treatment: Shire's Elaprase</p>
 <p>Disease: MPS IIIA Common name: Sanfilippo type A Deficient enzyme: Heparan N-sulfatase Incidence: 1 in 100,000 Drugs in development: Shire's intrathecal ERT, Lysogene's gene therapy Phase of drugs: I/II Approved treatment: None</p>	 <p>Disease: MPS IIIB Common name: Sanfilippo type B Deficient enzyme: α-N-Acetylglucosaminidase Incidence: 1 in 200,000 Drug in development: Shire's intrathecal ERT Phase of drug: Preclinical Approved treatment: None</p>
 <p>Disease: MPS IIIC Common name: Sanfilippo type C Deficient enzyme: Heparan-α-glucosaminide N-acetyltransferase Incidence: 1 in 1,500,000 Approved treatment: None</p>	 <p>Disease: MPS IIID Common name: Sanfilippo type D Deficient enzyme: N-Acetylglucosamine-6-sulfatase Incidence: 1 in 1,00,000 Approved treatment: None</p>
 <p>Disease: MPS IVA Common name: Morquio type A Deficient enzyme: Galactose 6-sulfatase Incidence: 1 in 200,000 (A+B) Drug in development: BioMarin's ERT Phase of drug: III Approved treatment: None</p>	 <p>Disease: MPS IVB Common name: Morquio type B Deficient enzyme: β-Galactosidase Incidence: 1 in 200,000 (A+B) Approved treatment: None</p>
 <p>Disease: MPS VI Common name: Maroteaux-Lamy Deficient enzyme: N-Acetylgalactosamine-4-sulfatase Incidence: 1 in 250,000–600,000 Approved treatment: BioMarin's Naglazyme</p>	 <p>Disease: MPS VII Common name: Sly Deficient enzyme: β-Glucuronidase Incidence: <1 in 250,000 Drug in development: Ultragenyx' ERT Phase of drug: Preclinical Approved treatment: None</p>
 <p>Disease: MPS IX Common name: None Deficient enzyme: Hyaluronidase Incidence: One known case Approved treatment: None</p>	 <p>Diseases: ML II, ML III Common names: Inclusion cell, Pseudo-Hurler Polydystrophy Deficient enzyme: N-Acetylglucosamine-1-phosphotransferase Incidence: 2–3 in 1,000,000 (II+III) Approved treatment: None</p>

TREATMENTS These 13 mucopolysaccharidosis diseases are caused by a deficiency in an enzyme that breaks down sugar molecules. Expensive enzyme replacement therapies are approved for three MPS diseases. But none of the marketed drugs address the neurological effects of MPS.

ERT = enzyme replacement therapy. **SOURCES:** Companies, J. Am. Med. Assoc., MPS Society, NIH

Figures for how much money has been poured into drugs for rare diseases are hard to come by. Many drug development pacts have been inked, but even venture capital firms working in the space can't quantify the overall investment, a kind of hand waving that contributes to worries that interest in rare diseases is a fad.

One statistic everyone touts is growth in R&D projects. According to a recent report by the Analysis Group and Pharmaceutical Research & Manufacturers of America, a drug industry trade association, 1,795 projects in the clinical pipeline as of October 2011 had orphan designation. And between 2001 and 2010, the number of products with orphan designation grew 10% annually, despite a decline in the total number of drug candidates during that period.

PATIENTS IN THE DRIVER'S SEAT

Although companies ultimately bring treatments to market, it's patient groups that are creating the awareness needed to start the drug discovery process

MOST PEOPLE think of a patient advocate as someone who is raising money for a charity. Many e-mail in-boxes and Facebook pages contain pleas for donations to the latest walk for breast cancer awareness or bike ride for AIDS research. But in the rare disease space, patient advocates aren't just walking in the 5K, they're organizing it and immediately sending the proceeds to a researcher. They tweet, they blog, and they create apps to update patients on research or keep tabs on clinical trials.

Jill Wood's son, Jonah, was diagnosed in May 2010 with Sanfilippo syndrome type C, one of four subtypes of mucopolysaccharidosis (MPS) III, each of which is caused by the lack of an enzyme needed to break down heparan sulfate. No treatments exist for Sanfilippo, and although the subtypes progress at different rates, each type leads to dementia and loss of motor function. Ultimately, patients succumb to the disease in adolescence or early adulthood.

"He's in the prime of his life at four-and-a-half years old," Wood explained to congressional staffers at a lobbying event in Washington, D.C., during a week of activities in February marking World Rare Disease Day. "This disease will progress

substantially over the next few years. He'll most likely be confined to a wheelchair, feeding tube, and won't really know who I am by the time he's 15 years old."

Whether it's to a congressman or a reporter, Wood speaks about Jonah's disease with urgency, rattling off scientific facts at a speed that can be disorienting for rare disease newbies. After she walks away from a group, there's often a moment of stunned silence while people digest what they've heard, followed by a quiet comment: "Wow. She is amazing."

She's also quick to laugh and has a warmth that inspires people to join her

Their motivation springs from necessity. Not all 7,000 rare diseases attract the same level of attention or offer the same commercial potential.

Under the Orphan Drug Act, a drug developed for any disease that affects fewer than 200,000 people is eligible for orphan designation. When created 30 years ago, the legislation was intended to draw orphan diseases out of the wilderness by creating incentives to develop drugs for small patient populations. A drugmaker that wins approval for an orphan drug enjoys seven years of marketing exclusivity regardless of its patent status, gets a waiver



DODI HOLM/RUSTIC PEAR PHOTOGRAPHY

fight for Jonah. Indeed, in the three years since Jonah's diagnosis, Wood has amassed a network of collaborators whom she groups into three categories: "my scientists," "my moms," "my mentors." With their help, she started a nonprofit that has raised substantial money for Sanfilippo type C research. More recently, she founded a virtual biotech company to develop any drug candidates that might arise from their work.

Wood is part of a legion of advocates taking on more active roles in the drug development process. Patient advocates "really are at the core" of the recent progress in rare disease R&D, according to Stephen C. Groft, director of the National Institutes of Health's Office of Rare Diseases. Because of their hard work and determination, he says, "all of a sudden, there are a lot of pieces of the puzzle coming together."

SUPPORT Jonah's mom, Jill Wood, is fighting for her son's life. Her foundation, Jonah's Just Begun, supports academic drug discovery efforts for Sanfilippo type C.

for the fee the Food & Drug Administration charges when a New Drug Application is filed, and is granted tax credits for half the cost of the drug's development.

The incentives have worked: Whereas just 10 treatments for orphan indications were approved in the decade before the act was introduced, more than 400 have come to market in the subsequent 30 years.

But there's the legal definition of an orphan disease, and then there's the reality that not all diseases have the same commercial potential. In the post-blockbuster-drug era, it's a no-brainer to take on a disease with a patient population nearing 200,000, no existing treatments, and reasonable science behind it. Convincing companies to invest in a disease affecting only 200 people is a much harder sell.

The 7,000 rare diseases include a long tail of disorders that affect anywhere from

a few dozen to a few thousand people. The tiniest patient populations struggle to get NIH funding for the kind of research that can spark interest from industry. Even if academic research efforts are under way, advocates think the regulatory incentives aren't enough to catch the eye of industry. "The Orphan Drug Act is great, but it doesn't meet our needs yet," Wood told her state's representatives at the lobbying day.

Some advocates for diseases with tiny patient populations have started to identify themselves as part of the "ultrarare" community. The term carries no legal significance, Groft warns, but patient advocates say it helps them unify the thousands of disparate patient groups. Alone, they are the orphans of the orphans. Collectively, their voice has heft.

The divide between the rare and the ultrarare became crystal clear for Wood in May 2010. When Jonah was diagnosed with Sanfilippo type C, which affects just a few dozen kids in the U.S., she was heartbroken to learn that not only were there no treatments, but scant research was under way to find them.

Her response was to take action. Just months after Jonah's diagnosis, Wood's mom and her best friend organized a wine-tasting fund-raiser in Oregon. With their help, by August 2010 Wood had pulled together \$20,000, started a nonprofit called Jonah's Just Begun, and wrote her first check to a scientist.

The money went to University of Montreal biochemist Alexey Pshezhetsky, one of two researchers who popped up on Wood's Internet search about the disease. In 2006, Pshezhetsky and his team discovered the genetic mutations that cause Sanfilippo type C, in which an enzyme called heparan- α -glucosaminide *N*-acetyltransferase (HGSNAT) is lacking.

Pshezhetsky was able to turn Wood's \$20,000 gamble into a five-year grant from the Canadian Institutes of Health Research. The \$130,000 in annual funding from the government agency helped the scientist better understand the pathology of the disease and create a mouse model for Sanfilippo type C, a critical tool if a drug is going to be developed.

Researchers have shown that sugar molecules don't aggregate in the cells of Sanfilippo type C mice that make as little as 10% of the normal amount of HGSNAT. With this in mind, Pshezhetsky is looking for drugs that can assist the faulty enzyme produced by Sanfilippo patients. This

"How long can you keep going to your tight-knit supporters of family and friends and ask for compassion for your story?"

"chaperone therapy" approach is being pursued for several lysosomal storage diseases and is the basis of Amicus Therapeutics' drugs in development for Fabry and Gaucher's diseases.

Meanwhile, Wood teamed up with three other families with Sanfilippo type C foundations—based in Massachusetts, France, and Spain—to jointly fund drug discovery and development efforts in labs across the globe. They brought researchers together for the first time with patients and physicians and in the past three years have supported many approaches to tackling the disease. In addition to Pshezhetsky's chaperone therapy, they have high hopes for a gene therapy project by stem cell specialist Brian Bigger at the University of Manchester, in England, and separate efforts by two scientists at the Telethon Foundation, in Italy.

Together, the four family-run organizations have sunk roughly \$500,000 into Sanfilippo type C research over the past two-and-a-half years. Wood has even started a company, prompted by a chance encounter at a conference with former pharma researcher Sean Ekins.

They launched Phoenix Nest last year. For now it's inactive while the families wait for their investments in academic science to pay off. If one of the projects is promising and an industry partner doesn't step in to support it, the idea is to develop it through Phoenix Nest.

The bootstrapping done by Wood and her partners reflects an increasingly common approach to early drug development. They are walking in the footsteps of venture philanthropy pioneers like the Cystic Fibrosis Foundation and nonprofits supporting Duchenne muscular dystrophy (DMD).

CF Foundation, which began investing in drug discovery efforts in 1998, reached the ultimate goal last year when FDA approved Vertex Pharmaceuticals' Kalydeco, the first drug to correct the underlying genetic defect in a subset of CF patients. Similarly, the DMD foundations are supporting several disease-modifying drugs, two of which are currently racing toward approval.

Small, family-run nonprofits look to larger organizations with both awe and envy. The hundreds of millions of dollars raised to

support CF research seems out of reach for nonprofits supporting diseases with names that are hard to pronounce and that personally touch so few. Although rare disease groups have gotten creative to pull in funds, they see the limits to that approach.

"How long can you keep going to your tight-knit supporters of family and friends and ask for compassion for your story?" asks Lori Sames, who has raised millions of dollars to support Hannah's Hope Fund, a nonprofit focused on an ultrarare disease called giant axonal neuropathy. "That well can only get drained so many times."

Even as Wood and her collaborators move as fast as they can to develop potential drugs, they are keenly aware of the unlikelihood that any firm—be it biotech, venture capitalist, or big pharma—will be willing to risk trying to commercialize their product.

Dozens of patients may seem like an impossibly small market, but drug executives say the bar for corporate investment is dropping. At the time the Orphan Drug Act was passed, no one was interested in investing in diseases affecting fewer than 100,000 people, says John F. Crowley, chief executive officer of Amicus. Crowley, whose two kids have Pompe disease, was instrumental in bringing the first treatment for that lysosomal storage disease to market.

"Now, if you find something that's 1,000, it's a home run," Crowley says. "Really, the break point in the last couple of years has been 500 to 1,000—and now we're measuring sub-500."

Many in the rare disease field hold up Ultragenyx Pharmaceutical's ability to raise \$75 million in venture funding in late 2012 as a sign that investors see opportunity in the ultrarare space. The company is pursuing a treatment for MPS VII, which affects just 200 patients in the developed world.

But Ultragenyx' CEO, Emil D. Kakkis, cautions against making sweeping assessments based on that product. "I'd say we're an outlier," he says. MPS VII affects tissues—the liver, spleen, and joints—that are accessible with an enzyme replacement therapy. "When you start talking about the bone and the brain, it becomes ever more difficult. Clinical trials are challeng-

ing, and the cost of doing them is high.”

Kakkis, who earlier in his career developed Aldurazyme, a BioMarin Pharmaceutical product that was the first drug for an MPS disease, thinks the bar is higher. “You probably will have trouble getting financial support to do development for a disease with less than 500 patients in the developed world,” he says.

And some observers are doubtful that big pharma firms will ever cross into the realm of the ultrarare. “It’s not hard for me to imagine a big biotech company looking at a disease that affects 1,000 people in the Western world,” says Philip R. Reilly, a partner at the investment firm Third Rock Ventures. “It’s still hard for me to believe that big pharma would fit that into its portfolio.”

Alvin Shih, chief operating officer of Pfizer’s rare disease unit, says the firm doesn’t have hard-and-fast rules to decide whether

a project is commercially viable but rather asks a few key questions: Are there clear endpoints for a clinical trial? Are there enough patients for a trial? And are there advocacy groups that can help the company navigate the space? “When you’re under 1,000 patients, it’s tough to have all that,” Shih says. A disease with several thousand patients is “more of our comfort zone.”

One way to get around the commercial limitations of the ultrarare world is to find treatments or technology that can benefit more than one disease. Back when Wood first heard a doctor utter the words Sanfilippo type C, just one company was working on a treatment that might help her son.

Zacharon Pharmaceuticals, with financial backing from the nonprofit Team Sanfilippo Foundation, was trying to prevent the cellular buildup by developing small molecules that block the synthesis of hepa-

ran sulfate. An effective drug could treat all four subtypes of Sanfilippo, bringing it into the realm of commercial viability.

Developing technologies that could yield multiple drugs or address multiple patient populations underpins Glaxo-SmithKline’s efforts in rare diseases. The big pharma firm’s establishment of a dedicated unit for rare disease research was a tacit acknowledgment that things must be done differently for this market.

With more traditional products, the commercialization plan is well defined, explains Mike Diem, head of business development for GSK’s rare disease unit. “Take diabetes,” he says. “GSK has been developing drugs here for many years, and we have a very simplified path we go down when we know a space well.” With small patient populations and no existing treatments, companies are walking into the unknown. “You’re defin-

GROWING INTEREST

Deals To Develop Rare Disease Therapies Have Proliferated In The Past Three Years

October 2009: In a pact worth up to \$680 million, Glaxo-SmithKline and Prosensa team to develop RNA-modulating therapies for Duchenne muscular dystrophy.

December 2009: Pfizer agrees to pay Protalix Biotherapeutics up to \$115 million for worldwide rights to taliglucerase alfa, to treat Gaucher’s disease.

February 2010: GSK launches a unit dedicated to developing treatments for rare diseases.

March 2010: GSK and Isis Pharmaceuticals establish a pact to develop antisense therapies for rare diseases.

June 2010: Pfizer establishes a dedicated rare disease unit.

September 2010: Pfizer acquires FoldRx Pharmaceuticals, which brings a portfolio of compounds to treat diseases caused by protein misfolding.

October 2010: GSK, the Telethon Foundation, and the San Raffaele del Monte Tabor Foundation join to develop gene therapies for rare genetic disorders.

October 2010: GSK partners with Amicus Therapeutics to develop Amigal, a small molecule to be used with enzyme replacement therapy for Fabry disease.

February 2011: Sanofi agrees to acquire Genzyme for \$20.1 billion.

April 2011: The International Rare Diseases Research Consortium is established to help coordinate global efforts in rare disease research.

November 2011: Agios Pharmaceuticals raises \$78 million to support a research effort around inborn errors of metabolism.

November 2011: Roche pays \$30 million for worldwide rights to PTC Therapeutics’ spinal muscular atrophy program.

December 2011: Shire and Atlas Venture team to identify and invest in early-stage rare disease therapeutics.

February 2012: GSK pays Angiochem \$31.5 million as part of a deal to develop compounds

that can cross the blood-brain barrier and treat lysosomal storage diseases.

June 2012: Roche and Seaside Therapeutics agree to jointly develop mGluR5 antagonists for the treatment of fragile X and autism spectrum disorders.

July 2012: Sanofi and Spain’s Centre for Genomic Regulation sign a three-year research collaboration that emphasizes genetic and rare diseases.

November 2012: Shire and Boston Children’s Hospital sign a three-year research pact to develop treatments for rare pediatric diseases.

November 2012: Pfizer and the Cystic Fibrosis Foundation establish a six-year preclinical research program to find drugs for people whose CF is caused by the F508 mutation.

January 2013: Shire buys Cambridge, Mass.-based Lotus Tissue Repair, gaining a protein replacement therapy for the treatment of dystrophic epidermolysis bullosa.

January 2013: BioMarin Pharmaceutical acquires Zacharon Pharmaceuticals, gaining small molecules to block heparan sulfate synthesis for mucopolysaccharidosis disorders and ganglioside synthesis inhibitors for Tay-Sachs disease.

February 2013: Roche pays Chiasma \$65 million up front for the rights to Octreolin, a peptide in a Phase III trial for acromegaly, a rare hormonal disorder.

February 2013: The European Commission sets aside \$187 million in funding for 26 rare disease projects.

March 2013: Shire acquires Premacure, gaining a protein replacement therapy for a rare eye disease that primarily affects premature infants.

April 2013: Roche pays Isis \$30 million as part of deal to develop antisense drugs to treat Huntington’s disease.

April 2013: New Enterprise Associates and Pfizer Venture Investments lead a \$16 million round of financing to launch Cydan, an orphan drug accelerator.

SOURCE: Companies

ing the path as you go along,” Diem adds.

To mitigate that risk and create a sustainable model for rare disease drug development, GSK has moved beyond the one-drug approach. Diem points to the company’s collaboration with the Dutch biotech firm Prosensa as an example of how a technology-based approach can generate a whole pipeline of products. The companies are developing antisense therapies for DMD, a disease that is primarily caused by deletions of one or more exons in the DMD gene.

Much attention is focused on GSK2402968, the partners’ lead candidate, which is in Phase III studies and addresses the roughly 13% of patients who have a deletion at exon 13 in the DMD gene. But behind that program are five or six additional therapies addressing other exon deletions. The regulatory path for the first drug will be rocky, but GSK is betting that it can “learn from the first one to develop the second, third, fourth, and others in a more efficient manner,” Diem says.

GSK is replicating the approach in other collaborations. A partnership with Angiochem around peptide-drug conjugates that can cross the blood-brain barrier is focused on treating the neurological impact of lysosomal storage diseases. “If you’re leveraging what you’re learning along the way, something ‘ultra orphan’ theoretically could be viable in the scheme of building a platform around five or six products instead of one,” Diem says.

Wood is well aware that attracting the attention of venture capitalists or biotech firms will require coming up with a drug or drug delivery method that could affect a larger patient group than the few dozen kids with Sanfilippo type C. She has one project up her sleeve that she thinks has a chance.

Montreal’s Pshezhetsky recently found something unexpected in the brains of mice with the Sanfilippo type C mutation. As the central nervous system of the mice is progressively debilitated by the buildup of sugar molecules, the mice become hyperactive, fearless, and lose their ability to learn. But Pshezhetsky made a curious observation: The symptoms aren’t caused by dying neurons.

That finding runs counter to common wisdom that the brain cells of Sanfilippo kids become clogged and die. The scientist hypothesizes that the buildup is instead causing defective synaptic transmission, or a disruption in the cross talk between brain cells, and he is searching for molecules that

could protect or restore that neurological function.

Synaptic markers in the brain appear to be reduced in all four types of Sanfilippo. Moreover, Pshezhetsky thinks the effect could exist in the broader MPS population; academic studies are ongoing to confirm the hypothesis. He is also testing existing neuroprotective drugs to see whether any show signs of efficacy.

Wood, meanwhile, is still waiting for more news of Zacharon’s heparan sulfate inhibitors. In 2011, Pfizer partnered with the biotech firm to develop rare disease drugs. The partnership gave Wood and other Sanfilippo families hope that big pharma was swooping in to speed the molecules through development. But that deal ran into trouble, and in the end, investors sold Zacharon to BioMarin.

Despite the new owner’s long-standing commitment to rare diseases, Wood is worried that research momentum has slowed. The relationship she had developed with Zacharon’s research chief, Brett Crawford, has changed. Now, when Wood runs into Crawford at conferences, she dissects his every sentence and parses his every gesture, trying to get a sense of what’s going on with the program. “You just try to analyze everything,” she says. “Nobody can tell us what’s happened, so there are lots of rumors going around.”

BioMarin says heparan sulfate inhibitors are an active project but that it is still in the process of optimizing the molecules. “It is too early to predict when, or even if, we will be successful at making a compound suitable to move into clinical development,” the firm says.

THE REGULATORY FRONT

Patient advocates and companies are encouraged by the recent introduction of new regulatory tools to speed the development of drugs for rare diseases but worry they may not go far enough for the smallest patient groups

EVEN AS JILL WOOD breathes a little easier knowing several drug discovery programs to treat her son’s rare disease, Sanfilippo syndrome type C, are under way, she’s also aware that the hardest part is yet to come. Testing a drug in kids for rare

diseases and gathering enough evidence to convince the Food & Drug Administration it is safe and effective is no cakewalk.

Trying to win approval by showing that disease progression has slowed or stopped is one of the bigger challenges in the rare disease space. Patient populations are often heterogeneous, meaning everyone declines at different rates and with different symptoms. With so few patients and so much variation, it’s difficult to choose endpoints for a clinical trial that can show a drug is, statistically speaking, making a difference.

Few clinicians know the challenges better than Joseph Muenzer, a pediatrics professor at the University of North Carolina, Chapel Hill. Muenzer has run clinical trials for several mucopolysaccharidosis (MPS) enzyme replacement therapies, including Aldurazyme, for MPS I, and Elaprase, for MPS II, or Hunter syndrome.

Muenzer’s experience with treating certain MPS diseases is so vast that his office is often the first stop for families with a recently diagnosed child. As Jeff Leider, whose two sons recently enrolled in a UNC study of the cognitive progression of boys with Hunter syndrome, puts it, “He’s the guru.”

Now Muenzer is contributing to the development of Shire’s HGT-2310, an enzyme replacement therapy for Hunter syndrome that is delivered directly into the spinal canal. Known among Hunter families as the IT trial because it is administered intrathecally, the study is intended to address the neurological effects of the disease.

Last month, on a sunny day in Chapel Hill, Muenzer was sequestered inside UNC’s North Carolina Children’s Hospital to give two boys in the study their monthly dose of HGT-2310. One of the boys was Case Hogan, a deliciously rambunctious six-year-old who, that morning, was darting around the hospital in red cowboy boots and a hat.

After about an hour of shuttling between rooms to check Case’s vitals and go over a long list of questions from Case’s mom, Melissa Hogan, Muenzer was ready to get the show on the road. A crew of nurses trailed the lanky physician into yet another room, where he hopped up on an examining table and lifted Case up next to him.

Hogan hovered over Case, who clutched his DVD player, not wanting to shift his focus from “The Princess Bride.” A mask delivering anesthesia was placed over Case’s mouth, and as he squirmed in protest, Hogan and the nurses broke into song to soothe him. After three short rounds of “You Are My Sunshine,” Case was out.



The nurses quickly slipped off his cowboy boots—purchased days earlier in Gatlinburg, Tenn., during the family’s trip from their home in Nashville to the hospital—and Hogan left the room to let Muenzer work his magic.

More than two years into Case’s participation in the IT study, the team has this routine down pat.

Between April 2010, when the family first suspected he might have Hunter syndrome, and early 2011, when he entered the clinical trial, Case’s mental decline was precipitous. He began to stutter and lose words, going from nine-word sentences to two- or three-word phrases. Hogan looks back at photos from a family vacation about a week before they realized Case might have an MPS disorder and sees a boy who looks vacant.

But by winning a spot in the clinical trial, the Hogans now have reason for hope. On each visit, Muenzer draws out a bit of spinal fluid—or, as he calls it, liquid gold—that he sends to Shire for analysis. Muenzer then injects a dose of the enzyme that Case’s body is unable to produce.

The entire process takes minutes, but for Hogan it’s nothing short of a miracle. As she broadcasts on her blog, *Saving Case*, the changes in her son’s behavior and cognitive ability were almost immediate after the first injection.

Two-and-a-half years into the study, Case can do simple puzzles, count to 20,

BRAVE COWBOY
Case Hogan, who loves his red cowboy boots, rests after his dose in a clinical trial to treat the neurological effects of Hunter syndrome.

and stay nimble on his feet. His behavior and ability to focus have improved as well. When he first arrived at UNC to be evaluated, Case was in a stroller with a six-point harness because he was too unfocused and hyperactive.

On their long drive to Chapel Hill last month, Hogan had a moment of panic when she thought she had forgotten something;

then she took a breath and realized they were simply traveling like a “normal” family—no wheelchair stroller, no special equipment or food. Indeed, the boy sitting in the recovery room after the procedure eating pudding, flirting with the nurses, and generally charming anyone in his vicinity was far from vacant.

In March, Muenzer and colleagues presented early data from the IT enzyme trial at the American College of Medical Genetics & Genomics’ annual meeting in Phoenix. They reported a drop in the level of the built-up sugars, glycosaminoglycans, in the cerebrospinal fluid of patients receiving two high doses of the enzyme, compared with high levels of glycosaminoglycans in four untreated patients.

Muenzer detailed signs of improvements in cognitive measures. Case is one of four boys in the small study who have shown stable or improved cognitive measurements. One child, who has been in the IT trial the longest, is now able to attend a regular kindergarten class, Muenzer notes.

Hogan is over the moon about Case’s progress, which also has raised hopes in the Leider household that Justin and Jason, their sons with Hunter syndrome, might benefit from the approach. But Muenzer is cautious about the next steps for the drug. The looming question is what kind of data FDA will want to approve the treatment. The challenge will be to come up with appropriate endpoints, or measurements to prove a drug’s efficacy, for an upcoming late-phase clinical trial, which Shire expects to begin by the end of this year.

As Shire considers the design of the trial, industry observers say the company’s experience mirrors what other firms face when trying to develop drugs for rare diseases. Those with a history in rare diseases argue that the challenge of pulling together the right patients and designing the right trials to get drugs approved goes underappreciated.

Newcomers look at the relatively small trials and see an easy path to approval. According to a recent study by Evaluate-Pharma, a Phase III study for an orphan drug enrolls on average 528 patients; the average Phase III trial for a nonorphan drug enrolls 2,234 patients. And several drugs have been approved on the basis of studies with just a few dozen patients. Moreover, FDA offers a slew of incentives designed to trim the timeline and cost for getting a rare disease drug to market.

Rare disease veterans suggest tempering those rosy assessments. “It’s a bit of a fal-

lacy that it's easier, or that the bar is lower," says Genzyme's Chief Executive Officer David Meeker.

The flip side of having so few patients is having only one chance to get things right. In April, Muenzer flew to Washington, D.C., to join Shire executives in a meeting with FDA to discuss the data needed to approve the drug. Earlier that day, Hogan quizzed him on what FDA wants. Muenzer, whose relationship with Hogan feels more like teacher and student than physician and parent, walked her through the complexities and realities of drug development for ultrarare diseases.

As he explained, all the kids in the study appear to have stabilized. They aren't all necessarily seeing the same cognitive improvements that Case is, but they also aren't declining. Yet that kind of soft measurement is unlikely to be enough to convince FDA that the IT delivery is working.

"I can't tell FDA at what rate they decline because we didn't ever have that quantitative data to say, 'Here's what we anticipate for this population,'" Muenzer says.

For more common diseases, information about patients is compared with a large pool of historical data culled from others with the disease. But another major challenge for rare disease drug development is the lack of understanding of the natural history of a rare disease—that is, how it progresses in the absence of medical intervention.

Companies usually have to conduct their own natural history study, an expensive and lengthy process in which a group of untreated patients is watched over time to determine what biomarkers could be useful in a clinical trial and to define endpoints that can show a potential drug is effective.

A natural history study is at the top of the mental checklist Wood keeps of things needed to get a treatment for Sanfilippo type C into the clinic. The consortium of families she works with is funding a natural history study of the disease, slated to start in the next month, that will collect the data they think will be essential if a drug candidate makes it into the testing clinic.

Wood is aware that a misstep in how resources are spent could cost both her son and other kids with Sanfilippo type C who haven't been diagnosed yet. "I'm the kind of person that jumps in headfirst, but I've found really fast that this is going to affect generations to come," she says. "I can't make rash decisions." She feels an

immense pressure to get the design of the natural history study right.

"We'll never be able to do it again," Wood says. "We don't have the patient population to do it again."

Patient advocates are hopeful that FDA is becoming more willing to accept surrogate endpoints, or measurements such as biomarkers that suggest a drug is working, rather than data that directly prove that a potential treatment helps people live longer or feel better. They are encouraged by a series of incentives and changes introduced



LISA JARVIS/C&EN

with the passage last year of the FDA Safety & Innovation Act, or FDASIA, which reauthorized FDA's ability to collect fees from industry.

Advocates are most excited about a measure that expands to rare diseases the accelerated approval path, which allows early approval of a drug on the basis of surrogate markers, and a measure creating "breakthrough status," an incentive to speed development of innovative drugs that show promise in early human studies. The legislation also calls for patients to

MARKED Case Hogan has a medical tattoo to distinguish his two ports; one is for intravenous delivery of Elaprase, and the other is for intrathecal delivery of an enzyme.

have more of a voice in the review process.

The National Organization for Rare Disorders (NORD) calls FDASIA the most important piece of legislation for the rare disease community since the Orphan Drug Act. John F. Crowley, CEO of Amicus Therapeutics, puts it succinctly, "We've just turbocharged regulatory science."

FDA appears to be taking the leeway offered by the new law seriously. Between July 2012, when FDASIA was signed into law, and April 25, FDA received 39 requests for breakthrough therapy designation. All of the requests were reviewed within 60 days of receipt, and 11 treatments received the designation.

Still, FDASIA alone isn't enough to bring more rare disease drugs to market, says Anne Pariser, associate director for rare diseases at FDA's Center for Drug Evaluation & Research (CDER). "If you look at drug development and disease research along a continuum, a lot of the work goes on pre-FDA," she notes. New ways to involve the National Institutes of Health, academia, and other stakeholders will be equally important to finding treatments.

And rare disease veterans point out that the new incentives and tools introduced with the passage of FDASIA are, for now, largely theoretical. The policy "creates a framework which has a high potential to have a positive impact," says Philip J. Vickers, global head of R&D for Shire's rare disease unit. "But it's really a framework at the moment, and the details need to be worked out."

The devil is indeed in the details. Although the agency has been quick to hand out the breakthrough designation, no one is sure what the status means in practice. FDA also has agreed to include patient voices, but it has yet to define a role for advocacy groups. The question of the role of surrogate endpoints, like the ones that the Hogans and other Hunter families hope will be useful in a trial of Shire's drug, also remains.

Still, some executives are confident common ground is forming between companies and regulators about clinical trial design. Genzyme's Meeker sees FDA moving toward an era where data suggesting a positive effect, combined with changes in biomarkers, could be enough for approval. "I think increasingly there will be a willingness to allow these products to be approved," Meeker says, provided that companies commit to monitoring patients over time.

While families and companies worry about what regulators want, FDA officials

“More access to accelerated approval could reduce the cost of development by almost two-thirds.”

point out that the agency has a long history of being flexible when reviewing New Drug Applications for rare disease treatments.

It’s “a pretty common misconception” that FDA has the same expectations for rare disease drug applications as it does for ones for more common diseases, says Gayatri R. Rao, director of the Office of Orphan Products Development at CDER. “I think folks believe that two randomized, well-controlled trials will always be required, even for small patient populations.”

That’s true in cases where there are enough patients, Rao says. But more often than not, FDA is willing to work with companies to support a clinical program that makes sense for the disease. At the same time, patients and drug developers need to remember the efficacy bar is not lower just because patients lack treatment options, Pariser says.

She stresses that FDA has “a long and established record of flexibility” when it comes to small patient populations. Pariser points to a 2011 study by NORD as proof of FDA’s willingness to adjust its standard mode of operation when it comes to rare diseases. NORD waded through the 135 noncancer orphan drugs approved between 1983 and June 2010 and found that the agency exercised a degree of flexibility in two-thirds of the cases.

Marc Beer, CEO of Aegerion Pharmaceuticals, is confident that the agency is evolving. Over the past two decades, he has participated in four review panels for orphan products, and in each case, “the FDA got it right,” Beer recounted earlier this year at a conference in New York City. The agency took the time to understand the intricacies of each disease and understand the drug at a deep level, he noted.

The difference between the FDA of the early 1990s and the FDA that reviewed Aegerion’s Juxtapid, approved last year for a rare form of high cholesterol, was the level of communication between the company and the agency. “It wasn’t a ‘pass it over the transom’ type relationship,” Beer said. “It wasn’t just ‘give us the data.’”

With more companies dipping their toes into the rare disease market, many question the ability for the inverse relationship

between patient group size and drug cost to hold up. Already, some governments are toughening their stance on big-ticket drugs. The U.K., for example, agreed to cover the cystic fibrosis drug Kalydeco, which costs nearly \$400,000 per year, only after a highly publicized campaign by patients. And although high prices are generally accepted in the U.S., more than 100 oncologists recently lodged a public protest over the cost of cancer drugs.

If scientists are to develop treatments for the 10% of the population that has a rare disease, the price of health care under the current model will skyrocket, warns Emil D. Kakkis, Ultragenyx Pharmaceutical’s CEO. “More access to accelerated approval could reduce the cost of development by almost two-thirds,” he says, citing a study he authored in *Orphanet Journal of Rare Diseases*. Instead of developing six or seven drugs with \$1 billion in investment, 36 drugs could be developed, he adds.

“We need to find that place where there’s comfort with the amount of data you really need and number of patients needed,” Kakkis says, “and accept the fact that we can’t spend hundreds of millions of dollars for every single rare disease and expect the system to work.”

THE KIDS ARE WAITING

Progress can’t happen fast enough for patient advocates, who worry that time is slipping away for their children

IF SHIRE DOES SUCCEED in getting the Hunter syndrome treatment HGT-2310 over the finish line, the door is opened for other lysosomal storage diseases where the brain is affected. The company is already testing an intrathecally (IT) delivered enzyme for Sanfilippo syndrome type A and has started a natural history study for Sanfilippo type B that could lay the groundwork for a clinical development program. “We’re very actively considering other programs,” says Philip J. Vickers, global head of R&D for Shire’s rare disease unit.

Even the mention of other lysosomal storage diseases that affect the brain brings hope to a legion of parents. But hope is a tricky word. It leads to a roller coaster of emotions with guaranteed highs and impossible lows.

For Melissa Hogan, Shire’s IT trial has fundamentally changed her outlook for her son Case. “When we started the trial, my whole goal was just to save his life. All I wanted was life,” she says. Now, with the dramatic improvement she sees in Case, she’s gone from no expectations to finding herself imagining her son as a grown man.

Around Christmas, someone sent the family a gift made by adults with special needs. Hogan was hit with the realization that Case could live and even have a job. And yet, she’s afraid to hope and has a hard time not analyzing the tiniest details about her son’s behavior and wondering whether the drug has stopped working.

Hogan’s progress reports about Case have kept hope alive for Jeff and Deena Leider. But they are in a torturous holding pattern while Shire settles the details of the next IT trial. They worry that by the time it is under way, their sons’ IQs won’t be in the right range or that they will miss other criteria to be included. They worry that each day they have to wait, Jason, who is older and whose disease is more advanced, will not benefit from treatment.

With no treatments available for her son Jonah, Jill Wood is careful about the word hope. She prefers to talk about action. As she says, “I busy myself controlling the controllable.”

Wood does believe that 2013 will be a big year for Sanfilippo research. Jonny Lee Miller, the star of “Elementary,” a television show that Wood’s husband, Jeremy, works on, agreed to fund-raise on behalf of Jonah’s Just Begun in conjunction with an ultramarathon he ran earlier this month. Thanks to corporate sponsorships, Miller’s tweets, and television appearances to promote the event, the nonprofit collected more than \$130,000. Wood already has plans for every last dime and is plotting where the next influx of cash might come from.

But amid that momentum came a reminder of the urgency of her efforts. While in Oregon in March, Wood got word that another child with Sanfilippo type C died in her sleep. Mia Pruett, who was 19, had been high functioning and hadn’t even been sick prior to her death. “I’m just heartbroken,” Wood says.

RESEARCH KICK-STARTER

Former Big Pharma Scientist Sean Ekins Hopes To Draw More ‘Champions’ Into The Rare Disease Arena

When Jill Wood learned in May 2010 that her son, Jonah, has Sanfilippo syndrome type C, a rare and fatal genetic disease, she did what any parent would do: Wood went online and looked up everything she could about research that might help him. Her next step was to raise as much money as she could to support scientists working on a treatment for Sanfilippo type C and bring them together to collaborate.

Wood is part of a legion of patient advocates navigating a scientific landscape that even seasoned researchers find challenging. The diseases affect so few people that the resources found for common ailments—large foundations and National Institutes of Health centers—simply don’t exist. While grappling with a painful diagnosis, these advocates find themselves in crash courses on basic science, drug development, and regulatory expectations.

About two years ago, Wood caught a break. Former drug company researcher Sean Ekins volunteered to join her ad hoc team of advisers, helping her plan to develop drugs for Sanfilippo type C.

The experience left Ekins, a computational chemist, wondering how to ease navigation of the rare disease world. His answer: create software tools to draw more scientists into the space. He’s also trying to foster a more collaborative environment that will accelerate the development of much-needed drugs.

Wood’s encounter with Ekins was “total luck,” she recalls. In November 2011, she decided to go to Partnering for Cures, an annual event in New York City that brings together patient advocates with other stakeholders in the drug development process. The meeting includes a session, akin to speed dating, during which advocates can request meetings with people who might be able to offer free advice.

Wood set up time with a lawyer, a hedge fund manager, and other patient advocates, and, on a whim, stuck Ekins on her schedule. His résumé included stints at Pfizer and Eli Lilly & Co., but he was a relative newcomer to the rare disease world. “He really had nothing to do with anything” related to Sanfilippo, Wood laughs.

Ekins had gone to the meeting to find rare disease groups that might be interested in using the data-sharing software his company, Collaborative Drug Discovery, was using to accelerate tuberculosis drug discovery. In his first one-on-one of the day, though, he found himself listening to Wood’s story.

On the verge of tears, Wood told Ekins about the academic projects she and other families were funding to find treatments for the disease. As she outlined everything she had done in the nearly two years since Jonah’s diagnosis, Ekins began asking himself how he could go beyond dispensing advice and really get

involved.

He came to the conclusion that he should help Wood start a biotech company.

Wood had already given the idea some thought. “I always kind of knew, in the back of my mind, that if I was going to take this all the way, it would probably be very smart to lay the foundation for a company,” she says. “I just wasn’t ready to delve in and see what it would take to form a virtual biotech.”

Ekins explained to Wood that, unlike the paperwork nightmare involved with starting a nonprofit, forming a for-profit company is as easy as filling out a short form.

That fateful meeting was Ekins’ first real glimpse of the rare disease world, and he was astounded at the challenges advocates face. “They have so much to learn,” he says. “These folks are not scientists.”

In the past year and a half, Ekins has become an invaluable adviser to Wood. He’s plugged himself into her network of scientists, and he’s helped Phoenix Nest, the biotech firm Wood started, apply for a Small Business Innovation Research (SBIR) grant, NIH’s outlet for funding for-profit research.

For her part, Wood introduced Ekins to Lori Sames, who had raised \$5 million over five years for Hannah’s Hope Fund, named for her daughter who has a rare disease called giant axonal neu-

ropathy. Sames has played a fundamental role in driving scientific research around giant axonal neuropathy and was also at the point of wanting to start a company.

Ekins agreed to help Sames, and before he knew it he met Allison Moore, who runs a nonprofit devoted to raising awareness and funding for a neurological disorder called Charcot-Marie-Tooth disease. Both Sames and Moore have since applied for SBIR grants.

Ekins’ experience with these three determined women has convinced him that more scientists need to step up to the plate. He’s also working on tools that make it easier for researchers to get involved.

One such tool is Open Drug Discovery Teams (ODDT), a free app for iPhones and iPads that’s intended to make connections among patients and researchers. He hopes it will accelerate the search for treatments for rare diseases through real-time data sharing.

Ekins is now working on a tool that could house project proposals, enable users to fund them through crowdsourcing, and allow researchers to share data. By making collaboration easier for patient groups and researchers, Ekins hopes more rare disease champions like himself will emerge.

