Renaissance in new drugs for rare diseases

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Justin and Jason Leider's weekly treatments of Elaprase only address some symptoms of Hunter syndrome, and cannot stop the neurological damage it causes. Their parents hope to get the boys into an upcoming clinical trial, which will deliver the enzyme into their central nervous system. Credit: Lisa Jarvis/C&EN

Once famously described as "orphan diseases, too small to be noticed, too small to be funded" in the Hollywood drama Lorenzo's Oil, rare diseases are getting unprecedented attention today among drug manufacturers, who are ramping up research efforts and marketing new

medicines that promise fuller lives for children and other patients with these heartbreaking conditions.

That's the finding of a major examination, published today in the weekly newsmagazine of the world's largest scientific society, of the status of new drugs for the 7,000 conditions that affect 200,000 patients or fewer and fall into the "rare disease" category. Written by senior editor Lisa Jarvis after months of interviews with patients, parents, pharmaceutical industry officials and others, it is the cover story in this week's issue of Chemical & Engineering News (C&EN), which reaches more than 138,000 scientists, policy-makers, educators and others. The 4-part story, and a wealth of associated online-only content, is available at the contacts listed above.

"For most of the last century, people afflicted by rare diseases—especially the parents and families of young children—shared the heartbreak of knowing that medicines to treat their loved ones were little more than a dream," says A. Maureen Rouhi, Ph.D., editor-in-chief of C&EN. "As our story documents in such compelling fashion, that situation is dramatically changing. Pharmaceutical companies are making unprecedented investments in medicines for these enigmatic conditions, popularized in films, and treatments for some are on the way."

Jarvis describes how a combination of factors has coalesced to foster a renaissance in drug development for rare diseases.

Smaller drug companies, for instance, have shown that it is possible to make big profits from sales of medicines for rare diseases, and larger companies have taken notice, Jarvis explains in the article. Patient advocacy groups are another driving force. They are directly funding some research, and they're working smarter and getting creative about drawing attention and dollars for research. Deeper insights into the

genetics of these disorders and federal legislation extending patent protection for these medicines also have helped.

Jonah Weishaar has Sanfilippo syndrome, type C. It affects only a few dozen kids in the U.S, and no treatments exist. His mother, Jill Wood, has started a foundation to support academic drug discovery efforts and a biotech that could bring treatments if no one else will. Credit: Dodi Holm/ Rustic Pear Photography

Jarvis spent time with several families of children dealing with rare diseases, saw their passion first-hand and includes their stories in the article.

It describes how venture capital firms have become engaged in funding research on rare diseases—to the point where more venture capital money may be going toward drugs for rare diseases than for any other type of medication, except for cancer drugs.

Most of the 7,000 rare diseases result from genetic defects, and about half of those affect children. In some cases, children die before they reach adulthood without treatment. Many of the rarest of these diseases affect only a few dozen to a few thousand people. Hunter syndrome, for instance, affects fewer than 500 boys in the U.S., and Gaucher's disease affects about 5,000 people.

Misdiagnosis is a common theme, Jarvis writes. It takes the typical patient 7.6 years and consultations with eight physicians to finally discover what's really going on.

Jarvis reports that until recently, pharmaceutical companies often focused on "blockbuster" drugs, medicines for common conditions like high cholesterol, high blood pressure and diabetes that would have annual sales of at least $1 billion. However, companies like Genzyme, a subsidiary of Sanofi, showed that medications for rare diseases can make money by pricing them high enough to cover research and development costs, and having insurance companies reimburse most patient costs. That's an attractive scenario for larger companies, which are getting into the market, even creating special units focused on this segment, Jarvis adds.

Scientists know more about rare diseases than ever before, thanks to progress in genomics and other areas of biomedical science. About 20 years ago, scientists had teased out the molecular basis for fewer than 50 rare diseases. Today, they know the genetic underpinnings for roughly 4,500—it's a complete sea change, which could show scientists the path to develop many more treatments.

On the regulatory side, the Orphan Drug Act of 1983 fostered drug development for rare diseases by granting companies seven years of exclusivity, even when the patent runs out; a waiver for U.S. Food and Drug Administration (FDA) fees; and tax credits. The incentives have

worked—the number of treatments for these diseases has risen from 10 to over 400 since the Act was created. And just last year, the passage of the FDA Safety Innovation Act made it easier to get them through clinical trials—an expensive and challenging hurdle.

Patient advocacy groups, often led by patients themselves or relatives or friends of patients, also are driving the shift. They aren't just attending fundraisers—they're taking charge, organizing events and even establishing their own charitable foundations or companies, funding researchers directly. They're telling their stories on social media, lobbying Congress and talking to the media.

To learn more about rare diseases and their impact, Jarvis spent time with patients and their families. She reports about how Jason and Justin Leider, aged 6 and 4, get their "muscle juice," or Elaprase medication, in an IV line in their chests to treat Hunter syndrome. Both children have the rare disease, which affects only boys. Patients lack an important enzyme that breaks down sugars. It is one of the so-called mucopolysaccharidosis (MPS) diseases. Without that enzyme, sugars accumulate in cells across the body, causing a rapid physical and mental decline. Most boys with Hunter syndrome die by age 15.Their parents, Jeff and Deena Leider, founded "Let Them Be Little x2" to raise awareness and funds.

Case Hogan is a rambunctious six-year-old with Hunter syndrome, who is participating in a clinical trial of Shire's HGT2310, an enzyme replacement therapy delivered into his spinal cavity. After two and a half years in the study, his mother, Melissa Hogan, says his behavior and mental abilities have improved dramatically.

Jill Wood's son, Jonah, has Sanfilippo syndrome, another type of MPS disease that affects only a few dozen children in the U.S. She speaks with her local representatives, congressional staffers, the media and

scientists about research and funding. Wood has started a nonprofit organization called "Jonah's Just Begun," as well as a company called Phoenix Nest to develop promising drug candidates for Sanfilippo syndrome if companies don't step up to support them.

Among highlights from the story:

- Misdiagnosis is common. It can take an average of 7.6 years and eight physicians for people with a rare disease to discover what's really going on.
- Big drug companies, long focused on producing blockbuster drugs for common conditions like high blood pressure and high cholesterol, are adopting new business models that will make rare-disease drug production feasible.
- Medications for rare diseases can exceed $200,000 per year. Insurance companies typically cover most of the costs. The potential for big profits on expensive drugs is an incentive for companies to get into the game.
- Several big-name blockbuster drugs are going "off-patent," leading to increased competition from generic versions and lower profits. Fewer new blockbuster drugs are in the works. These factors also are making the rare-disease market attractive.
- Companies are realizing that some drugs for orphan diseases can help patients with more common ones, which makes such medicines even more attractive for further development. For example, patients with Sanfilippo syndrome and those with Alzheimer's disease both have high levels of a protein called tau.
- Genzyme, Shire and BioMarin are examples of companies that work on rare diseases. Larger companies involved in the market are Pfizer and GlaxoSmithKline.
- Some firms have even started funds specifically targeting rare diseases. Among the biggest moves was a partnership between Atlas Ventures 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.

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- Last year, FDA regulations changed with the FDA Safety Innovation Act, making it easier to get these drugs through clinical trials—an expensive and challenging hurdle.
- Some patient advocates are simply raising awareness, but others have become more creative, funding researchers directly and founding companies themselves. For example, Jill Wood founded a company called Phoenix Nest to develop promising drug candidates for Sanfilippo syndrome if companies don't step up to support them.

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