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Funding the Fight Against the Rarest of Diseases

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Could the push to find a cure for an extremely rare, devastating disease in teenagers serve as a roadmap for other diseases? A small band of researchers hope so—and so do funding agencies. Learn more...

Fewer conditions are more heartbreaking than Lafora Disease (LD). Identified in the early 1900s, symptoms of LD emerge during adolescence in apparently healthy teenagers, often presenting as epilepsy. Beginning with seizures and convulsions, LD patients soon progress to visual hallucinations where monsters and other horrific visions invade their thoughts. Anti-epileptic drugs keep some symptoms at bay initially, but they quickly fail. Seizures increase in frequency, hallucinations grow stronger, and dementia develops. Unfortunately, there is no treatment or cure for LD, and death generally occurs within 5 to 10 years of diagnosis.

If you haven't heard of LD before, that is not surprising—the disease is exceedingly rare, occurring in less than 1 in 1,000,000 people. This means that at any moment there will be only a few hundred people with LD in the United States. The rarity of the disease presents unique challenges for the small community of researchers dedicated to its study. Basic research funding is available, but when it comes to more significant funding aimed at developing treatments, money, like the disease, becomes rare.

The Chelsea's Hope foundation funded a conference on Lafora disease, which eventually led to a $9 million NIH grant with the goal of curing the disease.

Researchers on a Mission

LD is defined as a rare orphan disease. But even among its fellow rare diseases, LD is in a class by itself. The page for LD on Orphanet—an online site dedicated to providing information on a wide variety of rare diseases and orphan drugs—is a relatively short entry. While it includes information on what LD researchers have uncovered about the basic biology and genetics of the condition, clinical data such as small molecule studies are completely missing.

This is not uncommon for rare diseases; clinical studies and translational efforts require a large investment, something that is difficult to obtain for these diseases because pharmaceutical companies and funding agencies with limited resources tend to focus on diseases with larger patient populations.

But as luck would have it, LD has a few key features that might entice clinical funding agencies. At its core, LD is a form of

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epilepsy. Unlike the more commonly known and diagnosed epilepsies, however, LD is progressive and deadly. Also unlike other epilepsies, researchers know that LD results from mutations in only two genes, which alter energy metabolism in the body.

Glycogen, the body's primary energy reserve, is called upon by the liver, muscles and the brain when needed. Structurally, glycogen is simply a series of glucose molecules joined together in a very specific way. Enzymes break down glycogen to make the glucose available to the body. Over the years, LD researchers have come to realize that the glycogen found in LD patients is different—the basic structure is altered, resulting in an insoluble mass called a Lafora body (LB).

The generation of Lafora bodies and the problems with glycogen metabolism in general can be directly traced back to epilepsy progressive myoclonus 2 (EPM2A), a phosphatase that is commonly referred to as laforin, and epilepsy progressive myclonus 2B (EPM2B), a ubiquitin ligase more commonly called malin. Together, mutations in these genes account for more than 90% of LD cases, and the severity of LD is associated with particular mutation patterns.

It took decades for LD researchers to tease out these fundamental connections between glycogen formation and the genetic mutations in malin and laforin, not to mention working out links between LD and other epilepsy conditions. But LD research came to a tipping point a few years ago, when the greater research community and major funding agencies started to take notice of these advances.

Call to Action

In June 2014, University California, San Diego (UCSD) researchers Jack Dixon and Carolyn Worby along with LD patient advocate Kim Rice decided it was time to push the envelope. The three worked together to organize a special 2-day LD-focused workshop in San Diego. Their idea was to assemble leading researchers in the LD field from around the globe in a single location to discuss key questions associated with the disease and look toward the future of LD research.

Even though progress in the LD field had been swift, the research community was small, had limited funding, and—as is the case in many competitive research fields—the scientists tended to be quiet about their current and future research plans. The LD workshop included discussions on topics ranging from basic glycogen biology to the expected impact of personalized medicine on the future of LD research.

The workshop was funded through a special grant from a small charity called Chelsea's Hope. The research fund's homepage explains the foundation in the following way: "Chelsea's Hope began in the fall of 2007 as a means to share our story about our daughter Chelsea and her diagnosis of Lafora disease. Feeling helpless, hopeless, and alone in our sorrow, we began to realize we could no longer continue to live under the black cloud of despair that was Lafora." At the time, few at the meeting could possibly have understood that lifting this cloud would lead the LD community to its most ambitious effort to date.

Finding the Funds

Organizations such as Chelsea's Hope are essential in providing funding assistance for rare diseases. And while many workshop participants could see LD research was on the brink of impacting patient care, they were also keenly aware that it takes millions of dollars to translate basic research findings into usable treatments in the clinic, money only obtainable through large government grants. And with grant funding so tight at that moment, how could any of the attendees possibly convince the NIH or another major agency to support their clinical efforts toward an LD cure?

Biochemist Matthew Gentry was one of the LD researchers who took part in the 2014 workshop. After completing a postdoctoral fellowship at UCSD 8 years ago, Gentry moved to the University of Kentucky, where LD is his team's only focus. While he admits that he did not start with the intention of working on one of the rarest orphan diseases, his path toward LD research can be traced back to graduate school at Syracuse University, where he focused on the biology and chemistry of phosphatases.

As the LD workshop came to an end, Gentry and University of California, Los Angeles professor of neurology Antonio Delgado-Escueta, made a bold suggestion: Rather than individual researchers trying to obtain funding for clinical LD studies on their own, they should band together as a community and submit a U54 project grant to the National Institutes of Health. U54 grants establish specialized cooperative centers to encourage multidisciplinary attacks on specific diseases. The funding levels can be in the tens of millions of dollars—more than enough for a strong, international effort by the LD community. A U54 grant seemed the perfect path for bringing everyone together to work as a single team.

The suggestion, however, was met with apprehension by other researchers—the deadline for submitting a U54 application was 4 months away.

“The response was that with the timeline, it was not very realistic to pull together a grant of this size,” recalled Gentry. While he and Delgado-Escueta were insistent that it was possible, others at the meeting were uncertain at first.

One final plea would emerge from the most unlikely of sources at the meeting. “One of the parents basically said that he was going to pull the parent card and asked everyone to write this grant,” Gentry said. The words of someone dealing with the devastating impact of LD proved powerful enough to convince the other scientists. Everyone left San Diego knowing that the next 4 months would be hectic.

Taking the Good with the Bad

“We started writing at a crazy pace,” said Gentry, who organized the submission. The grant presented five major project areas, each led by a different investigator. Gentry served as the primary administrator, leading a project focused on defining the impact of glycogen metabolism and proteostasis on LD. Other projects included a genome editing mRNA suppression effort to inhibit glycogen storage as a therapy, a plan to use small molecules to inhibit glycogen storage, an effort to define the possible therapeutic window of LD, and finally, a clinical trial. With each investigator working on their particular section, everything came together and the researchers submitted the grant application to the NIH on time.

The wait was not long. The U54 LD grant application received strong scores from the study section, but ultimately it failed to get funded. (In fact no U54 grants submitted during that cycle were funded.) The window for submitting a potential U54 on LD was closed, and the LD community, which had pushed so hard to create a global network for driving research on LD into the clinic, came up short.

However, all was not lost. Good news came out of the U54 application process: The NIH saw value and potential in moving LD research toward the clinic and was interested in funding some form of a collaborative LD project. NIH representatives suggested that the researchers modify their proposal to remove the clinical trials portion of the grant and focus on building a stronger preclinical and translational knowledge base.

In August 2016, 2 years after the meeting in San Diego where a single parent’s plea spurred the LD community to come together and write a grant, the NIH funded an LD P01 project for 5 years at just over $9 million. LD scientists from around the globe who were once competitors will now work together in the hope of bringing LD treatment to patients. Perhaps as importantly, this small community working on one of the rarest of diseases now has a unique chance to demonstrate how strong basic research discoveries and effective community interaction can be translated into clinical outcomes—a model that can be applied to other diseases in the future.

After receiving the funds, the community is by no means ready to declare victory; quite the opposite. “Now the real work begins,” Gentry said.

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