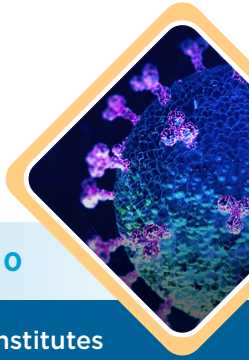


AN UNPRECEDENTED IMPACT

A SERIES OF FACT SHEETS ON COVID-19 AND BIOMEDICAL RESEARCH

JULY 2020



We must maintain and strengthen our nation's investment in medical research through the National Institutes of Health. This is an urgent priority for Congress, as our nation works to restart stalled research, keep up with pressing public health challenges, continue to fight COVID-19 and prepare for the next potential pandemic.

PART 3 | PROGRESS ON HOLD | Researcher Profiles

While research on the disease caused by the novel coronavirus has been on a fast track the past several months, most other medical research ground to a halt in March and has yet to resume at anything near its pre-COVID pace. It is impossible to know the full implications of suspended work, lost experiments and delayed clinical trials, but for those waiting for a cure, time matters.



After 17 years of work, **DR. MATTHEW GENTRY** is within reach of the holy grail — a potential treatment for Lafora disease, a devastating and extremely rare form of epilepsy that strikes healthy teens and takes their lives within 10 years. In March, his lab was preparing to conduct one final mouse test, a crucial step toward the goal of testing treatments in patients by next year. That's when COVID hit and the University of Kentucky was forced to shut down all non-essential activity — including his.

The episodes increase quickly, and regression is pretty fast. As we still don't know the window of opportunity to treat and find a response, every month matters to these patients.



A biochemist and professor at the University of Kentucky College of Medicine, Gentry's lab conducts research on neurodegenerative diseases and biofuels — there are many similarities between plant and human biology and specifically, in how they metabolize sugar. Lafora disease is caused by a mutation in one of two genes that control the way cells store glycogen, a form of sugar, resulting in a toxic buildup of Lafora bodies in the brain.

"We spent about ten years figuring out what's going wrong and the last five years on how to fix it," he said.

A recent major turning point has been an international collaboration made possible by a large program grant in 2016 from the National Institute of Neurological Disorders and Stroke (NINDS), part of the National Institutes of Health.

Matthew Gentry, PhD
Director, Lafora Epilepsy Cure Initiative | Antonio S. Turco Endowed Professor | Department of Molecular and Cellular Biochemistry | University of Kentucky College of Medicine

In the early 2000s, the genes that are mutated in Lafora disease had been recently discovered, but little else was known about the role the genes play in cells and what goes wrong to cause Lafora disease. That was until Gentry, doing his postdoctoral work at University of California, San Diego, discovered a plant protein that is similar to the human laforin protein, providing a model system to elucidate laforin's function. This sent him and others down their current path, beginning with the study of the plant system and then applying their discoveries to human disease and now, many years later, preparing to test drug therapies.

LAFORA DISEASE

- ✓ The rate of LD is about **4 in 1 million**
- ✓ Presently, **there is no treatment or cure**
- ✓ LD research **provides insights** into more common diseases

RARE DISEASE

- ✓ Rare disease affects **25-30 million** people in the United States
- ✓ The vast majority affected are **children**
- ✓ Of **7,000** rare diseases, only **5% have treatments**

UNPRECEDENTED IMPACT, *cont.*

While research on the disease caused by the novel coronavirus has been on a fast track the past several months, most other medical research ground to a halt in March and has yet to resume at anything near its pre-COVID pace. It is impossible to know the full implications of suspended work, lost experiments and delayed clinical trials, but for those waiting for a cure, time matters.



Now, through the Lafora Epilepsy Cure Initiative (LECI), Lafora researchers in the United States and Spain who previously had been working separately are working together toward their shared goal of treating and curing the disease. **“It’s been almost unreal how fast things have moved since the LECI formed,”** said Gentry, who serves as director of the LECI. He pitched the idea of the program grant to pursue treatments based on the researchers’ collective, pioneering work and serves as director of the LECI.

Today, there are four potential therapies in development. Three target the same pathway, reducing the buildup of sugar in the brain, and the other is a gene therapy. As Gentry explains it, **“the more shots on goal you have, the better the chance we have of curing the disease.”** A leading candidate is the therapy his group at University of Kentucky was prepping for clinical trials when the pandemic struck.

The critical mouse study was to begin May 1, when their mice would be six months old, the optimal age for testing. Kentucky did not reopen its research labs until June 1, however, and they missed that window. Now, in mid-July, having been able to borrow mice from another, less critical study they are hoping for an August 1 start date. But the mice are just one piece of the puzzle; the shutdown has caused a domino effect on a variety of other logistical hurdles that need to be worked out to meet that timeline.





For most people, a few months might not seem like much, but Gentry worries for the patients and families waiting for these treatments. **“The episodes increase quickly, and regression is pretty fast. As we still don’t know the window of opportunity to treat and find a response, every month matters to these patients.”**

While Lafora disease affects very few people, Gentry’s foundational research and discoveries are applicable to other more common diseases.

LECI PARTICIPANT LOCATIONS

USA



-  San Diego, CA
-  Dallas, TX
-  Indianapolis, IN
-  Lexington, KY

SPAIN



-  Madrid
-  Valencia
-  Barcelona

“The beauty of science is the connections ... you study a rare disease and it informs what you know about more common diseases,”

he explained. These connections have led to new research focused on Alzheimer’s disease, which shares some of the same clinical hallmarks as Lafora disease.

Gentry’s pioneering work on Lafora disease has been continuously funded by the NIH since 2006.

LAFORA DISEASE

The signs of Lafora disease generally appear during late childhood or adolescence. The most common feature of Lafora disease is recurrent seizures, which become worse and more difficult to treat over time.

With the onset of seizures, people with Lafora disease often begin showing signs of cognitive decline including behavioral changes, depression, confusion, ataxia (difficulty controlling muscles), dysarthria, and eventually, dementia. By the mid-twenties, most affected people lose the ability to perform the activities of daily living; have continuous involuntary twitching; and require feeding and comprehensive care.

There is currently no cure or way to slow the progression of Lafora disease. Those affected survive approximately 10 years after the onset of symptoms.