
EXTRA

The true story of Barry Byrne's efforts to cure Pompe disease is even more compelling than the movie

ORDINARY MEASURES

By John Pastor

A decade ago, UF molecular geneticist Barry Byrne was just beginning to develop methods for transferring missing genes into people with Pompe disease, a rare form of muscular dystrophy.

Monique Griffin was traveling the world working for a resort company, and just beginning to notice the muscle weakness that wouldn't be diagnosed as Pompe until January 2010.

Ray Carson

And John Crowley had just quit his job with a pharmaceutical giant in New Jersey to join a small start-up company in Oklahoma that was researching new treatments for Pompe, which he knew was killing his two children.

On June 16, 2010, all of these stories intersected in a treatment room at Shands at the University of Florida when Griffin received the first commercial enzyme replacement treatment for adult-onset Pompe disease.

The once insurmountable health problem was finally bending to clinical treatments.

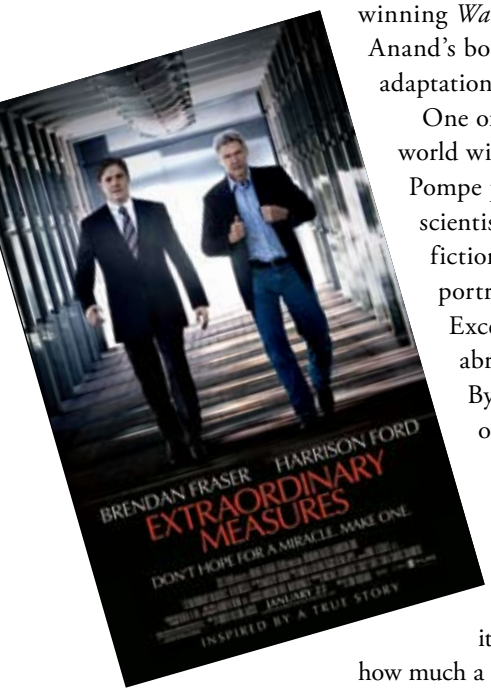
For Byrne, Griffin's treatment was the latest step in his efforts to reverse the effects of Pompe and many other genetic diseases.

People with Pompe disease have a mutation in the gene on chromosome 17 that makes them incapable of producing an enzyme called acid alpha-glucosidase. Without the enzyme, sugars and starches accumulate in muscle cells and destroy them, particularly those of the heart and respiratory muscles.

Children with Pompe disease often do not live beyond the age of 2. As the disease progresses, their breathing becomes so weak that they need to be assisted with invasive breathing devices called ventilators.

That's where Crowley's children, Megan and Patrick, were in 2000 when he left his job at Bristol-Myers Squibb to lead the start-up company Novazyme. Ultimately the company was purchased by Genzyme and an intravenous enzyme replacement drug was developed.

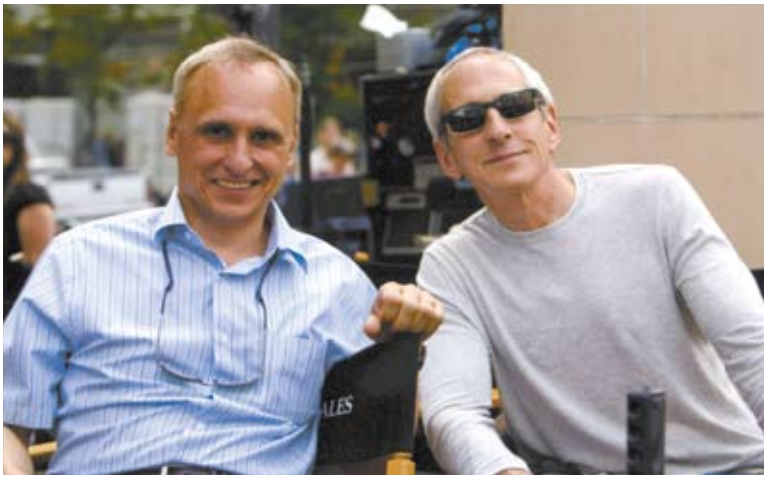
The Crowleys' story — including Byrne's collaboration with scientists at Novazyme and the ultimate treatment of Megan and Patrick — was documented in Pulitzer Prize-winning *Wall Street Journal* reporter Geeta Anand's book "The Cure" and the movie adaptation, "Extraordinary Measures."



One of a handful of doctors in the world with extensive experience with Pompe patients, Byrne among other scientists provided the basis for the fictional Dr. Robert Stonehill, portrayed by Harrison Ford.

Except the Stonehill character is abrasive and world weary, while Byrne is affable and tirelessly optimistic.

"The movie focuses on the struggle of John, his family and the scientists he worked with to develop a treatment," says Byrne. "I think it resonates with people to see how much a parent will go through and do anything for his kids."



Dr. Barry Byrne (left) and movie producer Michael Shamberg on the set of "Extraordinary Measures."

While the movie is a fictionalized account of the decades-long struggle to treat Pompe, the true story is no less extraordinary.

After earning his medical and doctoral degrees from the University of Illinois, Byrne completed his residency at the Johns Hopkins Hospital and then came to UF in 1997, where today he is a professor in the departments of pediatrics and molecular genetics and microbiology.

For years, Byrne and others have attacked Pompe and other glycogen storage diseases on two fronts — developing replacement enzymes that could be administered intravenously and developing gene therapies that would enable the body to produce the enzymes itself.

While the enzyme replacement therapy now available treats the symptoms of the disease, it does not address the underlying problem of the missing gene.

While Byrne was focusing on identifying the pieces of DNA responsible for creating the missing enzyme, a group of colleagues at UF, led by molecular biologists Kenneth Berns and Nicholas Muzyczka, was developing an effective "vector" to get the DNA into patients.

That vector is the adeno-associated virus, or AAV, that most humans already carry. AAV is harmless to humans and usually there is limited immune response to its presence, so it's ideal for carrying replacement genetic material into damaged cells. UF actually owns the patent on several AAV-related gene therapy protocols.

Byrne believed that by transferring corrective genes to Pompe patients, physicians might be able to free them from ventilators and improve their quality of life.

In a study of mice with the disease, Byrne and colleagues attached a functional copy of the gene that produces GAA — the missing enzyme in Pompe patients — to the AAV virus and injected it into the diaphragm muscle, where the virus infected cells and thus introduced the functional gene.

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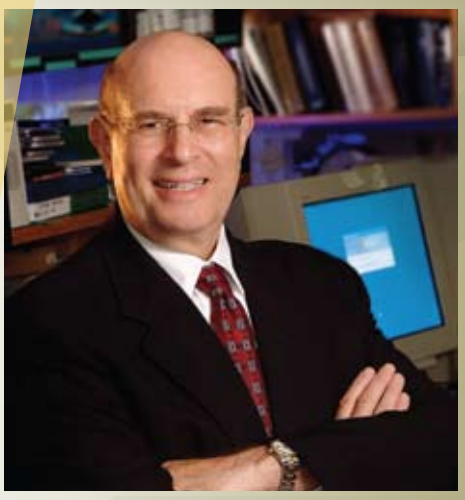
— Barry Byrne

The goal is to help patients in the late stages of the disease breathe on their own, says Byrne, and with the support of a $1.6 million grant through the Gene Therapy Resource Program of the National Heart, Lung, and Blood Institute, the moment has arrived when it will be tested in people.

"In disease treatment we always think prevention is better and easier than reversal, but we don't always have the opportunity to prevent some diseases," Byrne says. "When we find out that reversal of what could be considered permanent damage is possible, that is extremely encouraging. We think the gene therapy aspect will work alongside the traditional treatment. In many areas of medicine, a combination of treatments is used to benefit the patient, and we hope the gene therapy approach will work in the same way."



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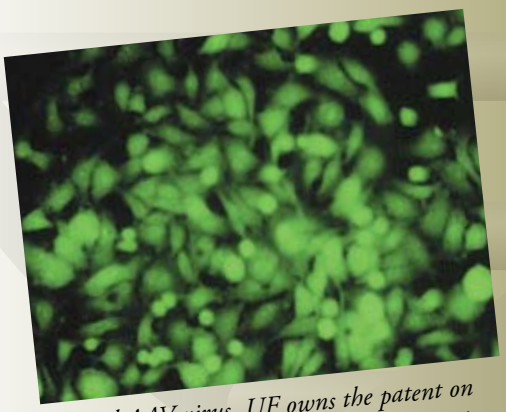


Actual AAV virus, UF owns the patent on several AAV-related gene therapy protocols.

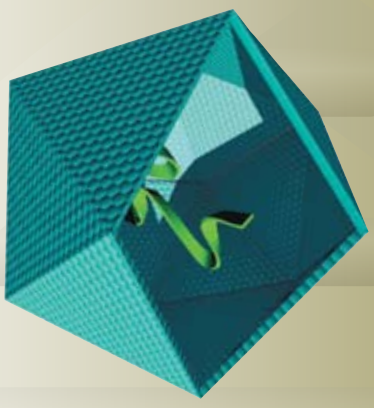


Illustration of the vector used to get the missing gene into the patient — adeno-associated virus, AAV.

In a "first-in-humans" gene therapy for neuromuscular disease, clinical scientists led by Byrne will infect cells of Pompe patients with the genetic machinery they have been missing since birth.

Enrollment for the trial began in November. Researchers will select six children between the ages of 3 and 16 who have been diagnosed with Pompe disease and depend on ventilators to breathe, even with enzyme replacement therapy.

The gene therapy "vectors" meet U.S. Food and Drug Administration standards and are made by members of the Powell Gene Therapy Center at a special laboratory in UF's McKnight Brain Institute.

Each child will receive a single treatment in which Dr. Salem Islam, a UF pediatric surgeon, will inject AAV carrying the healthy gene that Pompe patients lack into their diaphragm. Researchers will focus on the safety of the treatment and try to determine an optimum dosage. Additional studies by faculty researchers Shelley Collins, Cathryn Mah, David Fuller, Paul Reier and Danny Martin — coordinated by advanced practice nurse Lee Ann Lawson — will evaluate the patients' development and rehabilitation potentials.

Ultimately, the goal is to restore the function of the abnormal gene in the diaphragm muscle and possibly the phrenic nerve, which shuttles impulses from the brain to the diaphragm via the spinal cord.

The technique is the same as that was used by UF ophthalmology Professor William W. Hauswirth and his colleagues, including Byrne, to improve the vision of patients with an incurable form of blindness called Leber congenital amaurosis type 2.

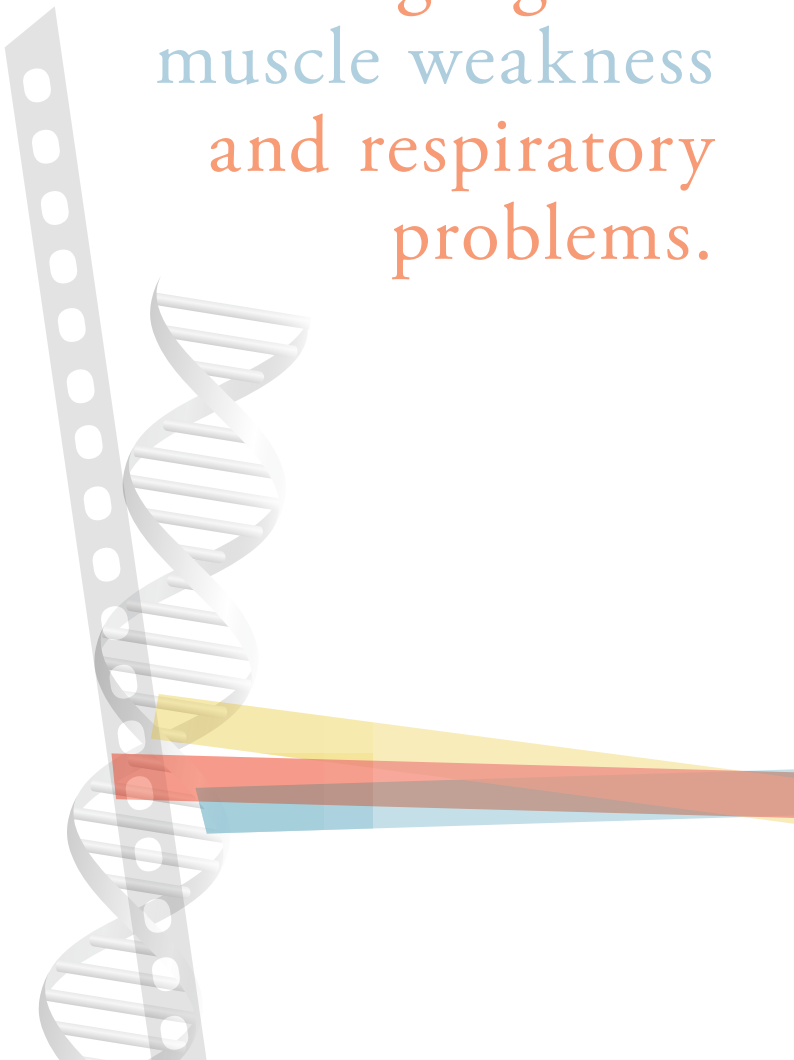
The most common cause of blindness in infants and children, LCA2 occurs when photoreceptor cells cannot respond to light because a gene called RPE65 does not properly produce a protein necessary for healthy vision.

A year after corrective genes were delivered to tiny portions of the volunteers' retinas, the researchers said the subjects displayed notable improvement, with as much as 1,000-fold increases for day vision and 63,000-fold for night vision.

Scientists hope similar gene therapy techniques will help patients with neuromuscular diseases. In addition to Pompe disease, the upcoming trial may provide valuable insight into motor neuron diseases, a group of incurable brain disorders that destroy cells that influence essential muscle activity, such as speaking, walking, breathing and swallowing. Notable among these is amyotrophic lateral sclerosis or ALS, commonly known as Lou Gehrig's disease.

"Studies have given us encouraging evidence that gene therapy for some very devastating diseases is a realistic possibility," Byrne says. "For Pompe disease, the general therapy involving intravenous infusions helps slow the progression, but we want to give it a hand.

Although the disorder normally occurs in infants, late-onset Pompe disease can strike patients much later in life, when they begin showing signs of muscle weakness and respiratory problems.



Sarah Kiewel

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Monique Griffin received several treatments as part of the final clinical trial then became the first patient to receive the treatment on a commercial basis.

"Imagine the improvement in the lives of some of these children if we can free them from ventilators," he says.

Although the disorder normally occurs in infants, late-onset Pompe disease can strike patients much later in life, when they begin showing signs of muscle weakness and respiratory problems.

That's what happened to Griffin, who found out she had the disorder in January 2010, a full decade after she began experiencing symptoms. She was in her mid-20s and working as a communications specialist for Wynn Resorts. Not long out of college, she worked in Las Vegas and even spent a year in China, helping open the Wynn Macau resort.

She had no idea that something out of the ordinary was happening to her until a routine visit to a doctor, who noticed she couldn't stand up from a seated position without using the armrests of her chair to support herself.

"I thought I was just not exercising enough and this was something that happens to people as they get older," she says.

She was initially misdiagnosed with inflammatory myopathy, but she grew weaker as years passed until finally a doctor at the Mayo Clinic in Minnesota identified Pompe disease.

"Finally knowing was a huge relief," she says. "Even though the disease is progressive, when you finally know what is making you sick, you can prepare yourself and start doing something about it."

Griffin moved to Orlando to be closer to family and to UF, one of only a handful of places in the country offering an experimental enzyme replacement therapy — Lumizyme — before it came on the market for late-onset patients.

She received several treatments as part of the final clinical trial and then became the first patient to receive the treatment on a commercial basis. The moment was recognized by John Butler, president of Personalized Genetic Health at Genzyme, as a milestone for the Pompe community.

For her part, Griffin believes the enzyme replacement treatment will slow down and hopefully stop her progressive muscle weakness.

"I noticed some improvement in mobility right after the first few treatments," says Griffin, who walks short distances, but largely relies on an electric scooter. "This has been a very long process. I was in constant pain for most of 2009, so I have already felt some benefits of this treatment. I still have flare-ups, but I am not as tired and have had some slight improvements in endurance and mobility."

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