

the making of a miracle

HOW ONE DUKE SCIENTIST'S PASSION INFUSED A MEDICAL CENTER, TRANSLATING—15 YEARS, MILLIONS OF DOLLARS, AND HUNDREDS OF HELPING HANDS LATER—INTO A LIFESAVING TREATMENT FOR A GENETIC DISORDER THAT ONCE KILLED EVERY BABY IT TOUCHED

Jean and Mitch Kelly lost their son Ryan to Pompe disease in 1995. Because the disease is an inherited genetic disorder, the couple—who also have a healthy son named Austen, now 14—decided not to have any more children. But then Jean became pregnant again. Amniocentesis showed that their third child indeed would be born with Pompe.

"It was horrible," says Jean Kelly. "I was five months pregnant. They called me at work with the results, and I went into the bathroom and I was just so angry. I was kicking the bathroom stall and crying, thinking this just cannot happen again.

I don't think I can go through this again. I just can't lose another child. And then I felt the baby move."

By the time Jean arrived home that day her husband was at their computer, e-mailing pediatric geneticist Y.T. Chen, MD, PhD, at Duke. The couple had visited Chen five years earlier, when Ryan was diagnosed, and they knew Chen's team hoped to eventually launch clinical trials for a potential treatment. If the Kellys were very, very lucky, the couple thought, perhaps their youngest son could—unlike all other babies born with Pompe disease to that point—have a fighting chance at life.

BY MARSHA GREEN
AND KATHLEEN YOUNT





need

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 and you just have to do something.”

—Y.T. CHEN, MD, PhD
 pictured with Deeksha Bali, PhD

THE TROUBLE WITH ENZYMES

The story of Myozyme—the first-ever treatment for Pompe disease, approved by the FDA just this spring—is one of awe-inspiring success. Like many such stories, though, it begins with a tragedy—and the consuming desire to never let it happen again. This is how Y.T. Chen describes his career spent fighting Pompe disease (pronounced “pom-PAY”), a glycogen storage disorder. The very rare disease results from what is essentially bad genetic luck—mutations on the gene that triggers the production of the enzyme alpha-glucosidase (GAA). Our bodies need GAA to break down the complex sugar glycogen for conversion into energy. If production of this enzyme is disrupted, glycogen builds up in the body’s cells, damaging tissues and causing progressive muscle weakness.

For those born with infantile-onset Pompe, the disease progresses quickly. Increasing muscle weakness that is first noticed as a sort of “floppiness” and head

lag leads to problems with swallowing and feeding; more critical, the heart muscle becomes thick and enlarged, and the baby develops respiratory problems. All babies with untreated Pompe disease die, most from cardiorespiratory failure, usually before their first birthday.

There is also an adult-onset form of the disease, and its progression can be slower and less severe. Ultimately this form of Pompe is also fatal, but since it can develop anywhere from childhood to late adulthood (patients have been diagnosed in their sixties), longevity is more varied.

Researchers like Chen have long sought a way to correct for these kinds of genetic mutations, set right the body’s metabolic balance, and give life back to babies whose parents were often told by doctors to simply take them home and enjoy the time they had left. “When you look at Pompe babies, they are so helpless and weak, but they are so bright,” says Chen, gesturing

to his eyes. “They understand. The baby is asking you to help, and you just have to do something.”

Chen has studied glycogen storage diseases since 1979, but he says in 1990 one infant in particular focused his sights on Pompe disease. The baby’s family was seeking treatment at Duke, and Chen and his team hoped a bone-marrow transplant could help. It was going to cost a hefty \$250,000; the family’s community rallied to help raise the overwhelming sum. Then, before the transplant could even take place, the baby died.

Chen and a colleague went to Greensboro, North Carolina, to attend the funeral. Chen says the minister’s eulogy changed his career. “He said, ‘God, you gave life to a little angel, yet you took it away in such a short time. You must have had a purpose.’ I looked at my colleague and we both knew, at that moment, that the purpose was for us to go back to the lab and find a cure.”

WHEN THE BIRD FLEW

The phrase “bench to bedside” is a friendly way to describe translational medicine, but seems almost too breezy to capture the relentless dedication required by so many researchers, clinicians, and families in an effort as monumental as the development of Myozyme. “In 1991 I thought it would only be a few years before we had a treatment,” says Chen. “It took us 15.” He points out that 15 years is the average time it takes for a drug to get from bench to bedside—but it feels much longer when parents are waiting for help for their fragile, weakening babies.

By 1995 Chen’s molecular genetics laboratory had engineered a line of cells that could overproduce the GAA enzyme Pompe patients were missing. They also established that the GAA produced by those cells worked in cultured cells from these patients. Chen says it took several tries to identify a model that could make GAA enzyme that would be taken up by humans. “We went from *E. coli* to yeast to insect cells to mammalian cells. We ended up using cells from the ovaries of Chinese hamsters.”

From there the researchers moved to animal studies. In 1996 they conducted an experiment using Japanese quail that, like humans with Pompe disease, were missing the gene for the GAA enzyme. These birds

were so weak that they couldn’t fly—when placed on their backs, they couldn’t even right themselves. But when Chen’s team injected the birds with their hamster-produced GAA enzyme, the results astounded everyone. After seven injections over 18 days, the birds could flip from their backs onto their feet. One of the birds even flew.

In Chen’s lab at that time was a young postdoc, Priya Kishnani, MD, who had joined the group because of her interest in glycogen storage diseases. But her true passion was translational medicine, and at the moment that quail’s wings stretched wide, her career, like Chen’s, took on a dogged and narrow focus: This success meant clinical trials would come next, and Kishnani would ultimately be the investigator to take the helm.

A TRIAL OF THREE

The flying quail experiment earned Duke FDA approval for a phase I/II clinical trial of recombinant-enzyme therapy for Pompe disease. A British-based Taiwanese company, Synpac, obtained licensing from Duke to manufacture enough clinical-grade enzyme to treat a human baby—but they could make enough for only three patients.

“We didn’t know how much we would

need, but we knew that if it worked, we had to keep giving the enzyme to these babies to keep them alive,” says study coordinator Joanne Mackey, a nurse practitioner. “That created a lot of tension, because we had to accept the babies on a first-come, first-served basis. And there were more than three babies whose families were pleading to be included.”

Among those families were the Kellys. “We had stayed in touch with Duke throughout my pregnancy,” says Jean Kelly. “We found the first spot filled. Then the second spot filled. And we were just lucky enough, the timing was just right for Jason to qualify for the third spot.” He, like the other babies, would get intravenous, in-hospital infusions of the enzyme replacement for three months, with a fourth month of outpatient treatment. He could start in September 1999.

Still, it wasn’t an easy choice for the family, who lived in Iowa. Jean would have to live with Jason in Durham, while Mitch stayed to work and care for Austen, who was seven at that time. Knowing firsthand how the disease would progress if the treatment failed, the family was reluctant to separate. “If it didn’t work, and he died before his first birthday, we would have spent so much of his time split apart,” says Jean. “It was really a hard decision.”

trial

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—JOANNE MACKEY, NP

The other two families in the trial traveled to Duke from Tennessee and Illinois. “At the beginning of the trial, the first baby was doing really well,” remembers Mackey. “He was getting stronger and almost sitting. But then he began to decline. The second baby followed almost the same pattern.” The mutations that lead to Pompe disease come in many types—researchers have identified more than 150 so far. Chen and Kishnani speculate that enzyme-replacement therapy is less effective in patients who have certain kinds of mutation (those resulting in no protein). Though the hearts of these first two babies responded well to the treatment, eventually both children died.

“We were nervous about enrolling the third baby,” says Mackey, referring to Jason. But, she says, it was clear early on that his response to the infusions was going to be different. “When he had been on the treatment for 10 to 12 weeks and was still getting better, that’s when we really

began to hope that we had something big.” That big thing was a big step—toward the development of a drug named Myozyme.

BREWING UP A TREATMENT

On the banks of the Charles River, just between the cities of Boston and Cambridge, sits a pretty brick building with rows of bright, green-tinted windows. Somewhere inside that building large metal cylinders are churning quietly and constantly, stirring a broth of vitamins and molecular growth factors around ever-multiplying batches of cells. These cylinders, called bioreactors, look something like giant moonshine vats—albeit with more tubes and a much smoother polish. But what they’re brewing is stronger than any spirit. What these machines are making is an enzymatic potion potent enough to save lives.

Since 1998 Genzyme, a Cambridge-based biotech company that specializes in treatments and cures for confounding dis-

eases, has been working on the problem of Pompe. Between 1998 and 2002 they purchased rights from three companies to cell lines that could potentially become viable therapies. One of those companies was Synpac, the previous licensor of the cell line developed in Chen’s lab, from whom Genzyme licensed rights in 2001. Then the company conducted what they called the “mother of all experiments” to evaluate their four candidate cell types. Ultimately, a Chinese hamster ovary cell line—similar to Chen’s but developed at Genzyme—showed the most promise in terms of manufacturing potential.

Manufacturing the drug would be no small task. “The program to develop Myozyme was the largest in our 25-year history,” says Bo Piela, spokesperson for Genzyme. “Through 2005 we spent approximately \$500 million and had several hundred employees working on it. We built two 2,000-liter bioreactors. And we’re now adding manufacturing capacity in Europe to ensure that we can produce enough enzyme to treat all the patients who need it.” This is because, though Myozyme may act like a cure in that it can give many patients nearly normal bodies, its effects are ephemeral. Patients must receive continuing intravenous infusions of the therapy—Jason Kelly, for example, now undergoes the four-hour infusion every other Saturday, at a medical center near his home. All Pompe patients will have similar needs, for their entire lives.

Deya Corzo, MD, medical director of the Myozyme program at Genzyme, explains that Myozyme was a unique challenge even for a company built on unique drug-making challenges. “Pompe is so different,” she says. “Everyone was so stressed because these babies would die, quickly, if we didn’t do something. But it

was a huge undertaking to produce so much enzyme.”

The cycle to grow Myozyme is three months; inside the huge bioreactors there are billions of cells producing the GAA enzyme, but every day scientists harvest only a bit of that fluid to carefully process it into what must be a frustratingly small amount of pure enzyme. And Corzo notes that Myozyme treatments require 20 times more drug than similar therapies developed at Genzyme. “The breakthrough came when our scientists were able to optimize the production of the enzyme,” she says. “Only then could we think of doing larger clinical trials.”

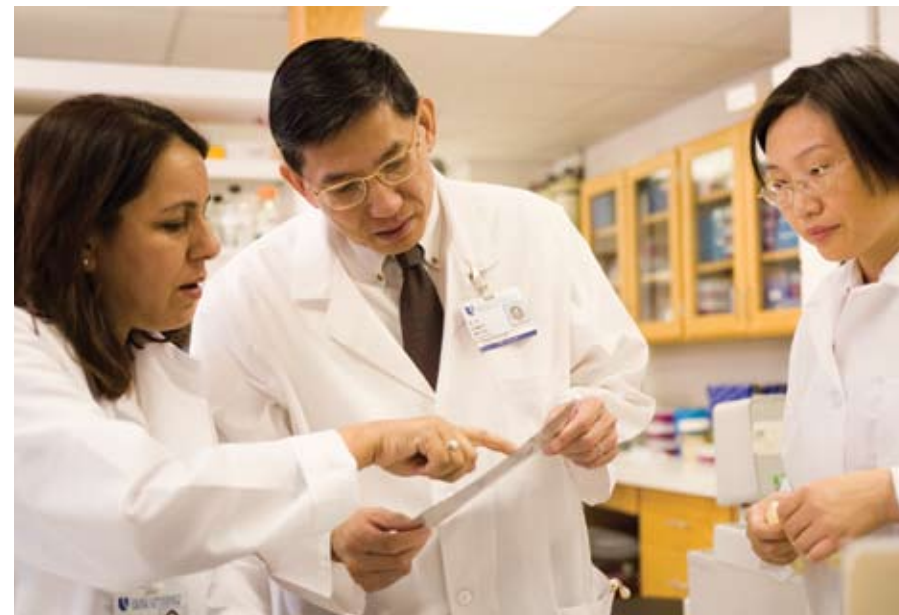
MAKING ROOM FOR MIRACLE BABIES

The trials were to continue at Duke, where a growing number of clinicians and study coordinators were fielding calls from families who, after the first trial was announced, simply started showing up. Genzyme and Duke launched a phase II trial in 2001 and a phase III trial in 2003, with Kishnani serving as Duke’s principal investigator.

“There was always a sense of urgency to get the children signed up for the clinical

trials,” says Kishnani. “That takes a lot of effort. The consent form itself was 25 pages long, and there were always changes that needed to be made based on what we had learned from the babies already enrolled. When we ran into a rough spot and changed the protocol, we had to change the consent form, inform the families, and take it back to the institutional review board. (IRB chair) Dr. John Falletta worked very hard to ensure this was done in a timely fashion so that everything would be in place for the next child.”

And the children kept coming, from all over the world. Genzyme reports that of the 40 families who participated in Myozyme clinical trials, all but one had to relocate, often from halfway around the world. One South African family, the Vaheds, took Duke by surprise when they arrived unannounced on the Fourth of July—they had been unable to obtain a medical visa and so traveled to Durham as tourists. “We’d take babies on Christmas Eve, Thanksgiving weekend,” says Kishnani. Everyone knew that these children couldn’t afford to wait on paperwork or national holidays—timely treatment with the enzyme was critical to give each baby the best chance of survival.



Bench to bedside: Jian Dai, laboratory research analyst for Y.T. Chen, MD, PhD; Chen confers with Deeksha Bali, PhD, and Dai in the lab; Priya Kishnani, MD, with patient Ryan Clark at a follow-up visit.



SUCCESS

“I like to call it Duke at its best.

But it’s also industry at its best and it’s also a marvelous statement about the courage of the patients and families.” —R. SANDERS WILLIAMS, MD

As each family arrived, Duke scrambled to help them settle in for what could be many, many months. “Genzyme representatives, Duke social workers, and others helped the families relocate to Durham by coordinating apartments and registering children for school,” says Stephanie DeArme, a Duke physician assistant and Pompe study coordinator. She says she and her colleagues became very attached to each uprooted family. “We were on page 24 hours a day for these families—not just for medical issues, but social issues as well. We spent a lot of time with the families and celebrated milestones such as birthday days for the kids.”

Genzyme administered trials of Myozyme at seven sites in the United States, Europe, and Asia; Duke was the first and largest site. But there were also many children who were likely to benefit from Myozyme but who didn’t meet the strict criteria for the trials or who came along after the clinical trials were full. So Genzyme got permission to launch an expanded access program, to provide Myozyme therapy to these patients before official FDA approval. Often these patients began their therapy at Duke, while Genzyme and Duke helped their local hospitals get set up to provide the infusions.

THE TESTING OF METTLE

Kishnani says that during the clinical trials, the team working on Pompe disease became more like a family. “Each and every person on the team has been so committed to this mission,” she says. “I never heard ‘no’ from anyone. It was always, ‘If I can’t do it, I’ll figure out who can.’”

It was an effort that ultimately required the whole Duke community to take a leap of faith. “It was not an easy road,” Kishnani explains. “These babies were so sick, and our effort was experimental and so time-consuming.” The trials needed anesthesiologists, cardiologists, pulmonologists, speech and language pathologists, social workers, physical and occupational therapists, nurses, physician assistants. “Everybody had to buy in,” Kishnani says, including the Duke administrators who allowed more and more institutional resources for the trials. “If it wasn’t for the goodwill of all these friends and colleagues at Duke, I don’t believe we would have had the same success.”

Mackey agrees that the clinical trials were not a clear-cut, easy path. “There were some very tough times,” she says. She and Kishnani both speak of the first child enrolled in the clinical trial for babies six months or older. “We had been following

her for a while,” says Mackey, “waiting for the trial to get her enrolled. When the protocol was approved and she was finally enrolled, the first thing that was called for was a muscle biopsy, which required anesthesia. The baby died while in the operating room. It was devastating.”

And, notes Kishnani, it rocked the whole trial on its heels. Part of the problem was the enlarged hearts of the Pompe babies, which grow weaker as the disease progresses. “These babies are so fragile when they come in—just turning them over in the crib can be a stress that changes their medical status,” says pediatric physical therapist Laura Case, DPT, who joined the team in 1999.

The team regrouped, working with Duke anesthesiologist Richard Ing, MD, to create a protocol for safe delivery of anesthesia, and Duke and Genzyme revamped the consent form. As always, the team worked at top speed. “There were babies ready to be enrolled,” says Kishnani, “but we couldn’t take them until we had fixed the anesthesia issues.”

“Over the years it has been amazing to watch how they fine-tune the treatment,” adds Lynda Everett, a nurse on the Duke Clinical Research Center’s Rankin Unit, where most of the Pompe patients received

their infusions. And as they learned and the trials wore on, one healthy baby became three, became eight, became two dozen and counting. Now, Everett says, “these kids are walking and talking. Sometimes patients come back to see us—that is amazing.”

NO MAGIC, BUT A MODEL

With four years of clinical success behind it, Myozyme earned FDA approval for use in infants and adults in April 2006. The drug is now being used by over 500 patients in more than 50 medical centers across 20 countries. Patients can still vary significantly in their individual response to therapy, so more refinements will continue—a new clinical trial of Myozyme for adult-onset Pompe disease began in 2005 and is still under way.

As Genzyme continues to expand production, Duke personnel are training staff at Genzyme and other medical centers to administer Myozyme. “This drug can seem scary-looking,” says Mackey. “It comes with a black-box warning about reactions and side effects. And it’s not magic, it doesn’t work overnight. It takes about eight infusions to see them get better, and there can occasionally be residual muscle weakness. We teach this to the families, to the nurses and others who are administering the drug. We’re all teaching and learning from each other.”

Genzyme’s Deya Corzo calls Myozyme a model for partnerships between industry

and academia. “There have been disagreements,” she says, “but people always saw the bigger goal, and were optimistic that this product could change the course of this horrible disease.”

This August Duke hosted a reunion, so that Pompe families and Duke and Genzyme investigators and administrators could gather to commemorate everything that led to Myozyme’s approval. Kishnani spoke to the many lessons that the Pompe trials represented—lessons in humility, in the benefits of working as a team, and of the many different aspects of this disease. “They are lessons that have really made us better human beings,” she said, “and lessons that I hope we can carry over to the treatment of other medically fragile children and infants.”

“I like to call this Duke at its best,” said R. Sanders Williams, MD, dean of the School of Medicine. “But it’s also industry at its best and it’s also a marvelous statement about the courage of the patients and families who participated in the clinical trials that proved Myozyme’s efficacy.”

At the reunion, Jason Kelly joined his mother at the podium to say hello to the guests and to thank Chen, Mackey, and the others who cared for him. Jean Kelly says that, though Jason has some slight muscle weakness—marathon running, for example, may not be his sport of choice—his disease is otherwise undetectable. The shy, towheaded, baseball-playing seven-year-old was all smiles—and maybe

a look of mild puzzlement. “He was sort of wondering, ‘What’s the big deal?’” says Jean Kelly. “‘Why does everybody want to take my picture?’ We told him ‘Well, you just aren’t seeing what you mean to a lot of people.’” After all, she notes happily, he’s just a normal kid, still too young to understand the enormity of what his life represents.

The story of Myozyme is indeed enormous, a story of millions—millions of tiny cells multiplying, millions of hours and dollars invested, millions of tears shed in joy, sorrow, and frustration. And, as the father of one baby lost to Pompe disease pointed out, millions of stars in Durham’s night sky, testaments to the babies whose short lives inspired the journey toward Myozyme. In memory of his brave young son, John—the first baby enrolled in the very first trial—Barry Koncel shared with those gathered at the reunion an excerpt from *The Little Prince*, which he and his wife used to read aloud to John: “Look at the stars and remember: In one of the stars I shall be living. In one of them I shall be laughing. And so it will be as if all the stars were laughing, when you look at the sky at night.” □

A joyful reunion: Pictured at the August 2006 Pompe reunion at Duke are (from left) Jason Kelly, who as a baby participated in the first Myozyme trial, with his parents Mitch and Jean; Y.T. Chen, MD, PhD, with Haydee and Jorge Romero of Peru and their daughter Yamila; Abdurrahman Vahed, whose family traveled from South Africa to attend.