

Doorway to a Cure



A nonprofit is taking
a financial gamble on
**eradicating
cystic fibrosis.**

So far, the
odds look good.

BY **BIJAL P. TRIVEDI**

THINKSTOCK

FOR THE FIRST TIME IN OVER A decade, a striking silence fills the Cheevers' barn-style home in North Andover, Mass. The deep, rumbling cough that plagued sisters Laura, 14, and Cate, 12, every night of their lives, leaving them exhausted and weak, has finally stopped. Their bodies are almost free of the life-threatening lung infections — requiring hospitalization and harsh organ-pummeling intravenous antibiotics — which end the lives of so many children with cystic fibrosis. Now calories once spent fighting disease add weight on their dainty frames and give them energy to play soccer and dance. “And,” says Rob Cheevers, Laura and Cate’s father, “they don’t taste salty anymore.”

“Yeah, I taste like an average person,” quips Cate, referring to the salty sweat that is a hallmark of the disease.

Laura and Cate are among thousands of Americans who have cystic fibrosis (CF), an inherited disease that clogs the lungs with thick mucus, encouraging chronic infections that eventually kill. Affecting one in every 3,900 births in the U.S., CF is one of the most common genetic disorders known. Yet it afflicts too few people — just 30,000 in America and an estimated 70,000 worldwide — for industry to recoup the enormous cost of developing drugs for the disease.

For Laura and Cate, the outlook has changed. They are beneficiaries of a gamble taken in 2000, when parents and volunteers running the Cystic Fibrosis Foundation (CFF) gave a start-up biotech company more than \$40 million to find a cure. Until that point, the advocacy group, established in 1955, had functioned much like other such groups. Battling a disease that, untreated, stole many of their children before age 5, CFF members compiled patient registries and established treatment centers nationwide. They ran regular fundraisers to develop new drugs, like those that broke up the mucus or delivered aerosolized antibiotics that penetrated deep in the lungs to fight infection. With slow and steady progress,



The Cheevers family stand near their home in Massachusetts. They are (from left) Rob, Cate, Laura and Kim. Thanks to CF drug development, clinical trial pioneers Cate and Laura have achieved robust good health.

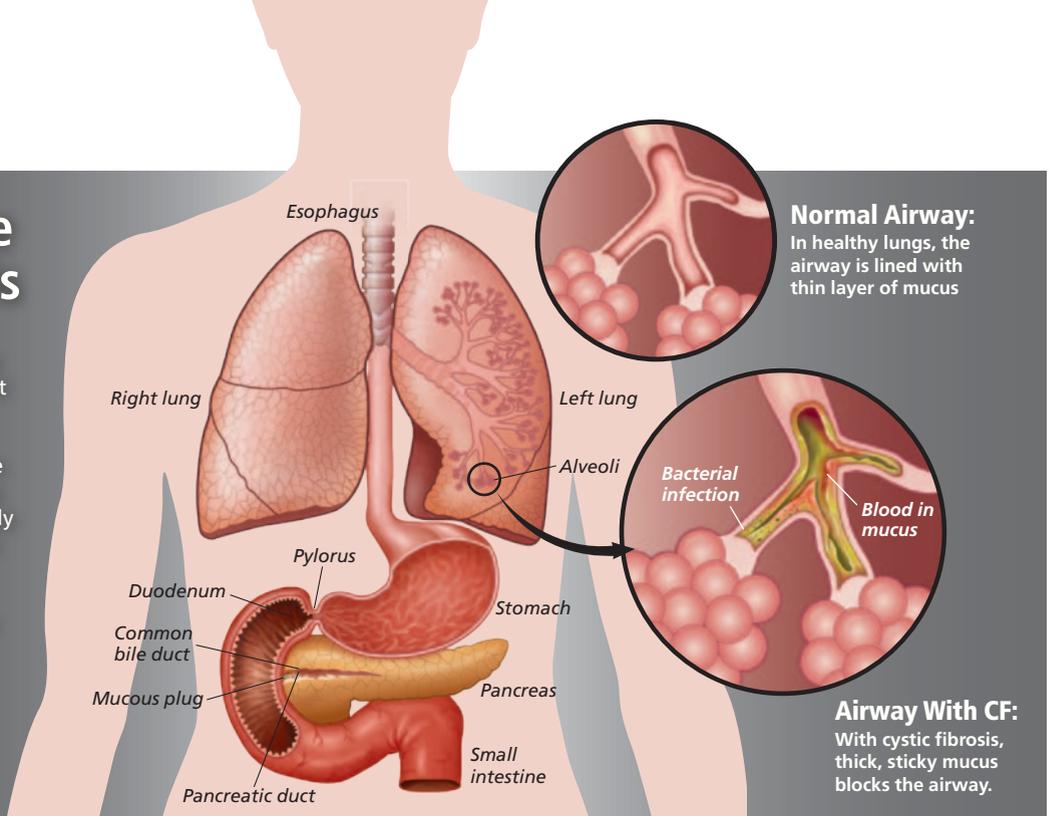
they extended their children’s life spans a decade or more.

Then 13 years ago, in a strategic roll of the dice, the group decided to fund the search for a cure that would target not the symptoms of CF, but the defective protein causing the disease. Urged by desperate parents, the board expanded the traditional nonprofit by launching Cystic Fibrosis Foundation Therapeutics Inc., an independent arm, to spearhead drug discovery. It used money the Foundation raised to hire companies to develop the drugs and then helped them test those drugs in clinical trials. In return, the Therapeutics arm earned royalties for drugs they co-developed, which were immediately folded into more drug discovery.

Along the way, the Foundation imposed an urgency and focus that a biotech or pharmaceutical company functioning alone could not muster. “We were like a racehorse with blinders on. The goal was getting a medicine to patients. Everything we did, we put it through that lens,” says microbiologist Eric Olson, who leads CF research at Massachusetts-based Vertex Pharmaceuticals, which discovered Cate and Laura’s drug. Collaboration with the Foundation, where everyone had a personal stake in the outcome, kept Vertex on target. “Nothing

A Look Inside Cystic Fibrosis

Cystic fibrosis is a chronic disease that affects the lungs and digestive system of about 30,000 children and adults in the United States (70,000 worldwide). A defective gene and its protein product cause the body to produce unusually thick, sticky mucus that clogs the lungs and leads to life-threatening lung infections. The mucus also obstructs the pancreas and stops natural enzymes from helping the body break down and absorb food.



Normal Airway:
In healthy lungs, the airway is lined with thin layer of mucus

Airway With CF:
With cystic fibrosis, thick, sticky mucus blocks the airway.

is more powerful than when it is your own kid, your brother, your sister, and it keeps focus on getting to something real, even if it takes 20 years.”

Vertex’s first CF drug, called Kalydeco, is a stunning testament to patient power. Participating in a clinical trial in 2010, Laura and Cate were given a drug that entered their cells and fixed the defective protein making them sick. With the protein functioning almost as it would in a healthy person, the girls took back their lives. Laura and Cate have an especially rare mutation — it causes only 4 percent of CF cases in the U.S. But the success of the transformative drug heralds similar treatments for the rest of the CF community. Vertex has already developed a drug cocktail for patients with the most common CF mutation — responsible for the overwhelming majority of cases — with phase III clinical trials underway.

ON THE TRAIL OF THE CF GENE

Little was known about the cause of cystic fibrosis in the 1970s, when Francis Collins, now head of the National Institutes of Health (NIH), took an interest in the disease. Collins was a resident in internal medicine in 1978 at North Carolina Memorial Hospital in Chapel Hill when he was assigned to care for a 19-year-old nurse just diagnosed with

CF. The case was unusual because the disease is typically diagnosed in childhood, yet she clearly met the criteria: Her lungs were being destroyed by thick, sticky mucus that served as a breeding ground for sickening bacterial infections, and she had salty sweat, a function of CF pathophysiology Collins didn’t yet understand.

“It was clear we didn’t know very much,” he says today. CF was variable. At one end of the spectrum, thick mucus derailed the function of the body: It blocked the pancreas from delivering enzymes needed for food digestion and absorption, resulting in malnutrition, and also caused severe lung infections, often killing children by age 5. At the other end was a milder disease with rare infections, few nutritional issues and a normal life span.

CF was known to be a genetic disorder, inherited as a recessive trait. That means you needed two bad copies of the gene — one from each parent — to get the disease. The mutated genes would then produce defective proteins that cannot perform their job inside the cell, causing it to malfunction and ultimately triggering the disease. Parents with just one mutant copy were healthy and often unaware they carried a defective gene. Although scientists like Collins knew the pattern of inheritance, no

one knew what the gene was or exactly which protein it produced. And as far as Collins was concerned, there was no obvious way to find out.

That changed in the early 1980s after scientists found the unique DNA pattern, or genetic marker, for Huntington’s disease, a crippling neurodegenerative disorder. The discovery “electrified everybody’s imagination,” Collins says.

Encouraged by this feat, Collins’ soon-to-be collaborator, Lap-Chee Tsui, a molecular biologist from Hong Kong, took up the search for the defective gene from a CF lab at The Hospital for Sick Children in Toronto. Tsui had read about a technique for locating a desired gene through DNA markers present in sick people but absent in healthy ones. Working closely with the doctors and nurses at his hospital, he was soon acquiring blood samples from some 20 CF families in Toronto and later from 30 more such families around Canada.

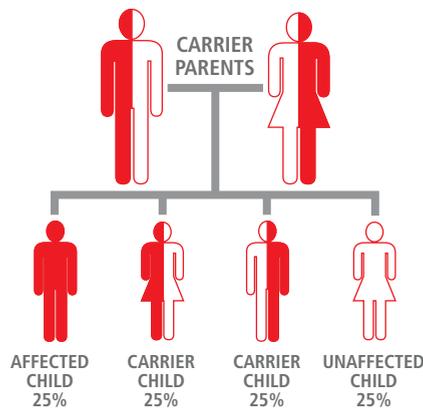
By 1985, running his own lab at the University of Michigan in Ann Arbor, Collins was doing the same thing. While no one had yet sequenced the full complement of human genes, researchers knew a thing or two about how genes could go awry. They knew the human genome was carved into 23 pairs of structures, called chromo-

somes, made from deoxyribonucleic acid, or DNA. DNA's alphabet consisted of just four letters, A, C, G and T, that stand for four chemical units, or bases: adenine, cytosine, guanine and thymine. The bases pair up, with adenine bonding to thymine and cytosine to guanine. The human genome has 3 billion of these base pairs on its 23 chromosomes pairs, but deleting or altering even a single A, C, G or T can cause disease or death.

“The genome is an enormously large place to root around when you are trying to find something subtle,” Collins notes. Still, the race was on to find the DNA pattern unique to CF families, and especially their sick children. In 1985 Tsui used DNA markers to track the CF gene to chromosome 7. A team, including members from the University of Utah in Salt Lake City and Saint Mary's Hospital Medical School in London, narrowed the region further by finding a couple of DNA signposts flanking the gene, whether defective or not. These markers are akin to road signs on a highway; the gene is like a hotel in between.

But the genetic distance between these markers was enormous — a stretch of about 1.5 million DNA letters. In 1985, the standard way to find a gene between two markers was to sift through the DNA letter by letter, a technique called chromosome walking. Then Collins developed a faster approach that he was itching to test: chromosome jumping, which allowed him to leapfrog over genetic terrain tens of thousands of letters at a time. “The idea was that if you know it's between these two markers, you could start jumping off both ends toward the middle, and you would get there faster than if you had to just walk, step by step,” he explains.

To speed things even more, Collins



Cystic fibrosis is passed genetically from parent to child. A child must inherit one defective gene from each parent to develop the disease.

and Tsui joined forces in 1987, unleashing a small army of some 20 scientists to find the suspect gene wreaking havoc in patients' sweat glands, pancreas and lungs — all organs affected by the disease. The moment of discovery happened on a rainy night in June 1989 at Yale University, as Collins and Tsui attended a strategic meeting on mapping the human genome. The two were lodging in the student dormitories during the meeting, uneasy about being so far from their labs while critical analysis of DNA from a large cohort of CF patients was in play. One evening at about 10 p.m. they holed up in Tsui's room, wearily combing through pages of genetic data spewing from a small fax machine (the high-tech data transmission of the '80s) connected to Tsui's lab.

As they sifted through the data, a troubling pattern on chromosome 7 became clear: Most of the CF patients were missing a sliver of DNA, a sequence of bases designated by just three letters, CTT. It was basic biology. In healthy subjects, the code was intact. The healthy gene produced a protein with 1,480 amino acid units. The damaged version produced a shorter, faulty protein with only 1,479 amino acids; it

was missing a vital amino acid called phenylalanine. That minute change was enough to cause this cruel, deadly disease. “That was the moment for me,” admits Collins. “I wanted to jump up and down and scream.”

BROKEN CELLS

Finding the mutation was the first step toward a cure, but Collins and Tsui still needed to figure out what the gene did and how the mutation on chromosome 7 derailed it. Whatever protein the gene coded for, they figured, it ended up skewing the body's balance of water and salt. Excess salt in the cells would cause them to suck in water from surrounding mucus, leaving it sticky and thick, allowing infection to set in. The excess salt also accounted for the salty sweat — all defining features of CF.

To explain the salt imbalance, one possibility stood out: blocking the flow of chloride ions — one half of the table salt molecule, sodium chloride — in and out of cells. A mutated gene that produced a broken protein involved in chloride flow could cause a salt imbalance and all the devastation observed.

To follow through, Collins and Tsui recruited biochemist Jack Riordan, who worked with Tsui. Riordan was an expert on proteins called ABC transporters, molecular elevators that shuttle things like fats, drugs and other molecules back and forth across cell membranes. Riordan analyzed cells from the salty sweat glands of CF patients, proving that the mutant gene was active and producing a defective protein. Then he used a computer to compare the string of amino acids making up the protein to the sequence of amino acids in all other known proteins. He was stunned when he noticed similarities to his ABC transporters: The CF protein had sections that gravitated to water and parts that repelled it. And

Search for the Cure

ALISON MACKEY/DISCOVER

1955

The Cystic Fibrosis Foundation (CFF) is established.

1978

Francis Collins, a resident in internal medicine, becomes interested in CF when he is assigned to care for a newly diagnosed 19-year-old CF patient.

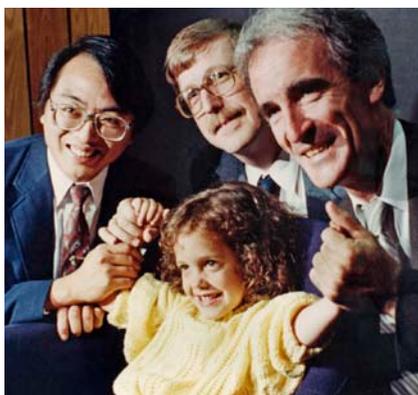
like those transporters, the protein was shaped like a tube and wedged in the outer surface of the cells, resembling the kind of biological valve that would move chloride in and out. That gelled perfectly with the Tsui-Collins hypothesis: A malfunctioning chloride channel apparently caused CF.

On Aug. 22, 1989, news that Tsui and Collins had discovered the gene causing CF leaked to the press. Two days later, the researchers, just 38 and 39 years old, were whisked to Washington, D.C., for a series of news conferences almost two weeks before the scheduled publication of three back-to-back papers in *Science*. The papers described the location of the newly named cystic fibrosis transmembrane regulator (CFTR) gene, its specific genetic code and the proposed structure and function of the protein it produced.

GENE THERAPY DEBACLE

With the CF gene in hand, a cure based on gene therapy seemed within reach. Although the disease affects many organs, it is lung infections that kill. So if healthy genes could be sent into the lungs, Collins and Tsui reasoned, they could cure the worst ravages of the disease.

Collins had been corresponding regularly with a leading human gene therapy proponent, James Wilson, who soon moved his lab to the University of Michigan, right next door to Collins' own. By 1990 Collins and Wilson were retrofitting a lab-built virus with healthy CFTR genes, then sending the package in, like a Trojan horse, to infect cells taken from a CF patient and kept alive in culture in the lab. The sick cells welcomed the healthy CFTR gene and used it to make functioning channels that allowed chloride to pass in and out of the cell. It was stunning proof that a healthy gene could trump a damaged



Celebrating a breakthrough in cystic fibrosis research in 1989 are (clockwise from left) collaborators Lap-Chee Tsui, Francis Collins and Jack Riordan. With them is CF patient Ashley Donnelle. Donnelle grew up and even had a daughter, but she had a lung transplant in 2009 and died from complications of that in 2011.

one and fix the cell, at least in a petri dish. By 1993, in trials with baboons, Wilson proved the virus could import the healthy CFTR gene into lung cells.

But translating the technique to humans was enormously challenging. That same year, efforts to install the healthy CFTR gene in CF patients hit a roadblock when the virus triggered alarming inflammation and fever, causing the researchers to reengineer the virus and rethink their strategy. Researchers kept trying until December 1999, when Wilson published phase I trial results in 11 volunteers with CF showing it was almost impossible to get the gene into lung cells permanently and efficiently, without immune rejection. "It took quite a few years of banging heads against the wall to realize just how hard this was," says Collins. Nobody anticipated how fiercely the immune system would respond to the viruses and "essentially doom our approach."

FORGING ANOTHER PATH

In the years after finding the CFTR gene at the root of the disease, Col-

lins, Tsui and others discovered the situation was far more complex than they had ever dreamed: Instead of just a single mutation in the gene, researchers found some 1,900 distinct mutations. Most of them caused disease, and the differences among them accounted for the sliding scale of severity that doctors saw.

The most common mutation had been identified by Collins and Tsui in 1989. They named it Delta F508, for the absent amino acid, phenylalanine, in position 508 of the CFTR protein. A CFTR protein with this mutation cannot fold properly and cannot navigate its way to the surface of the cell where it would normally reside, providing a channel for chloride to flow in and out. Instead, the defective protein remains stuck inside the cell, like a Cheerio trapped in a balloon.

Collins grasped that fixing this one mutation, carried by about 4 percent of Caucasians, could help almost 90 percent of patients with CF. But his lab halted efforts in 1994 after moving to the National Human Genome Research Institute in Bethesda, Md., to lead the massive government human genome sequencing effort that would eventually chart the entire human genetic code.

That same year, Robert Beall, a former biochemist who left NIH in 1980 to work at the nonprofit Cystic Fibrosis Foundation, became its CEO. Back in the '80s it was a grassroots operation. Parents brought the food, ran the projectors and catered to the few scientists who showed up. "They didn't have a lot of science," says Beall, "but I fell in love with the people and the parents, who were looking for some hope."

Beall rode the emotional roller coaster of the CF gene discovery, and, like others, he expected new therapies to emerge. When everybody got swept up in the gene therapy craze of the

Early 1980s

Scientists find the DNA marker for Huntington's disease. This leads researchers to believe they can use a similar approach to find the gene causing CF.

1985

Lap-Chee Tsui of the University of Toronto tracks the CF gene to chromosome 7.

1987

Tsui and Collins join forces.

early '90s, he explains, “we were the same.” But with CF gene therapy efforts failing, one after the next, Beall knew he had to find another way. “We had discovered the CF gene and knew the root cause of the disease,” he says, “but the pharmaceutical companies were still not getting involved.”

Beall told parents it was time to forge another path. He was scouring the scientific literature when he hit upon an article describing high-throughput screening, a new technique that used robots to test the therapeutic properties of thousands of chemical compounds a day in cells in laboratory dishes. Reflecting on the impasse, Beall thought this could provide an answer for CF: Instead of giving patients healthy CFTR genes, he would launch a massive search for chemicals to fix the mutant proteins in the patients' cells.

Without a large government grant, Beall knew that no academic team could take on this challenge. And no company would embark on such an expensive drug search because it would never recoup its investment with such a rare disease. Instead, the CFF would need to front the effort, protecting companies from risk. At the time it was unheard of for a nonprofit to take such a gamble. After all, Beall admits, he didn't know much about drug discovery. “This is a risky thing that we are about to do,” Beall told his board at the time. “We are going to invest big. But the biggest risk for us would be not to do it.”

With initial funding of \$3.2 million in hand, Beall called the five technology leaders specializing in the high-throughput screening mentioned in the article; two returned his calls. One was Aurora Biosciences, a San Diego-based start-up specializing in screening drug candidates. They agreed that it was possible to find a molecule to interact with



Robert Beall stands in front of portraits of CF children at the Chicago office of the Cystic Fibrosis Foundation. Beall is the nonprofit group's CEO.

the defective protein and correct it.

Aurora came with a perk no money could buy: Paul Negulescu, a cell physiologist who studied CF while a graduate student at Berkeley. As Negulescu well knew, the task was complex: Each of almost 1,900 mutations causing the CFTR protein to malfunction required its own unique fix. But it made sense to start with the most common mutation, Collins and Tsui's Delta F508, the one afflicting most of the CF population. (Of those with CF, some 50 percent carry two copies of the gene with the Delta F508 mutation, and another 40 percent carry one copy; those with just one copy of Delta F508 carry a second bad copy of the CF gene, with an alternate mutation that must be fixed as well.) Some 10 percent have rare mutations that don't involve Delta F508 at all.

Negulescu knew that patients with the Delta F508 mutation produced a CFTR protein that couldn't fold properly, like a crumpled origami sculpture, foiling its ability to even reach the sur-

face of the cell, where it was supposed to be. To relocate the protein required one drug — dubbed a “corrector” — to tweak its shape so that it could be trafficked to the cell's outer surface.

But once this defective protein was lodged in place, there was a second glitch: The protein still wouldn't allow chloride to pass in and out of the cell. It was as if a door had been jammed shut. To wedge it open would require a second, “doorman” drug.

Patients with the Delta F508 mutation would need two drugs. But those like Laura and Cate — who have an even rarer mutation, called G551D — might be easier to treat. Unlike the common Delta F508 mutation, the G551D mutation yielded a protein that could reach the cell surface and wedge itself into the membrane, but it suffered from the door-jamming problem: Chloride still could not flow in and out. The Cheevers needed only the doorman to remove the jam that stopped chloride from flowing back and forth.

TOM LYNN

1989

Tsui and Collins identify the cystic fibrosis transmembrane regulator gene (CFTR) that has been mutated in CF patients.

1990

Collins and James Wilson make a virus capable of carrying the CFTR gene. They hope it will transmit the gene to human patients.

1993

Gene therapy for CF is successful in baboons, but it fails utterly in humans.

HUNT FOR DRUGS

To accelerate drug discovery, Negulescu and the Aurora team searched for both corrector and doorman simultaneously. To execute their high-volume search starting in 1997, they grew cells carrying the malfunctioning CFTR protein in plastic trays, each containing 384 tiny wells in a 16-by-24 grid.

To identify correctors, a unique candidate drug was added to each well and allowed to steep overnight at body temperature, 98.6 degrees Fahrenheit. Next, a fluorescent dye was added to the mix. Then they added a chemical called genistein, a known door-opening drug that, unfortunately, was so weak it worked only in the test tube. Finally, a robotic eye scanned each mixture. If cells were unaffected, the dye caused them to glow orange. But if the mutant CF protein had been elevated to the cell surface by a corrector candidate drug, then genistein, as the doorman, would open the channel and allow chloride in and out, making the cells glow blue.

To search for a doorman drug, Negulescu's team followed almost the identical strategy, but they incubated cells with candidate drugs overnight at a much cooler 80.6 degrees. Conveniently, this cooler temperature acts as a corrector helping more proteins with the Delta F508 mutation to reach the surface, where they encounter the candidate doorman drug. If the chemical had no impact, the cells glowed orange. If the molecule could open the channel, the cells glowed blue.

The assay that Negulescu's team developed worked. Some of the candidate drugs were definitely boosting the mutant CFTR to the cell surface while others seemed like they could open the door. It was proof that this new automated screening system could find something transformative. Yet after



Fundraising activities, such as this Great Strides walk in Texas in 2012, are a key element to drug development for the CFF.

testing 122,000 chemicals in all, the researchers found that even those that showed early potential failed in later trials. Some were toxic, some too weak, and some, for whatever reason, couldn't activate the CF protein on a second try.

Aurora scientists were confident that it was just a matter of auditioning more molecules to find ones that worked. And in 2001, when Vertex Pharmaceuticals acquired Aurora, it decided to continue the quest as long as Beall could muster the money to keep projects moving and the dream alive.

PARENT POWER

That's when Beall recruited Joe O'Donnell, a CF parent and fundraiser extraordinaire. Joe and Kathy O'Donnell, Massachusetts natives, teamed up with the CFF the moment their son Joey was diagnosed with the disease in 1974. It was a brutal beginning. Tests were botched, the pediatrician hadn't seen CF babies before, and Joey couldn't eat, choking every time he tried sucking milk from a bottle. After three harrowing months, another pediatrician familiar with CF finally made the diagnosis. The news was devastating: at the time, CF children rarely lived

beyond 5. But after the correct diagnosis, Joey had a feeding tube inserted into his stomach to deliver predigested food and bypass the coughing and gagging, and he began to improve.

"Compared to the first eight months, the next five years were a party, almost," says his father. "He got better, and he was a magnificent kid."

By age 12, Joey was president of his seventh-grade class, a prankster, a grade-A student and a pinball wizard. "He loved girls," his mother adds with a smile, "and he loved baseball."

Yet the hospitalizations had become more frequent, and more serious. Many times they were told, "He wouldn't make the night," says his father, "but he always came through." Except when he didn't. He died in 1986. He was 12 and a half and barely 50 pounds.

Six months later, the O'Donnells, together with close friends, launched the Joey Fund to raise money for CF research. By 2001, it raised almost \$50 million. To continue the drug search, Beall needed a lot more — \$175 million, to be exact — and he asked Joe, a former board member, to bring it in.

O'Donnell admits it was an odd campaign. "That's how I billed it. We're not naming anything, endowing anything. We're taking every dollar you give us and putting it into research," he explains. "And guess what, we could end up with nothing. But for sure, we're going to end up with nothing unless we do this. So that was the whole speech."

O'Donnell insisted upon pure venture philanthropy, not venture capital. If there were royalties and other profits, he wanted that money rolled into more research, not someone's pocket. No other foundation had successfully bankrolled a cure in this fashion. But as everyone who knows him says, he has a gift, and he raised the money. That was crucial because Vertex was making progress.

between 1994 and 2001 122,000 compounds tested

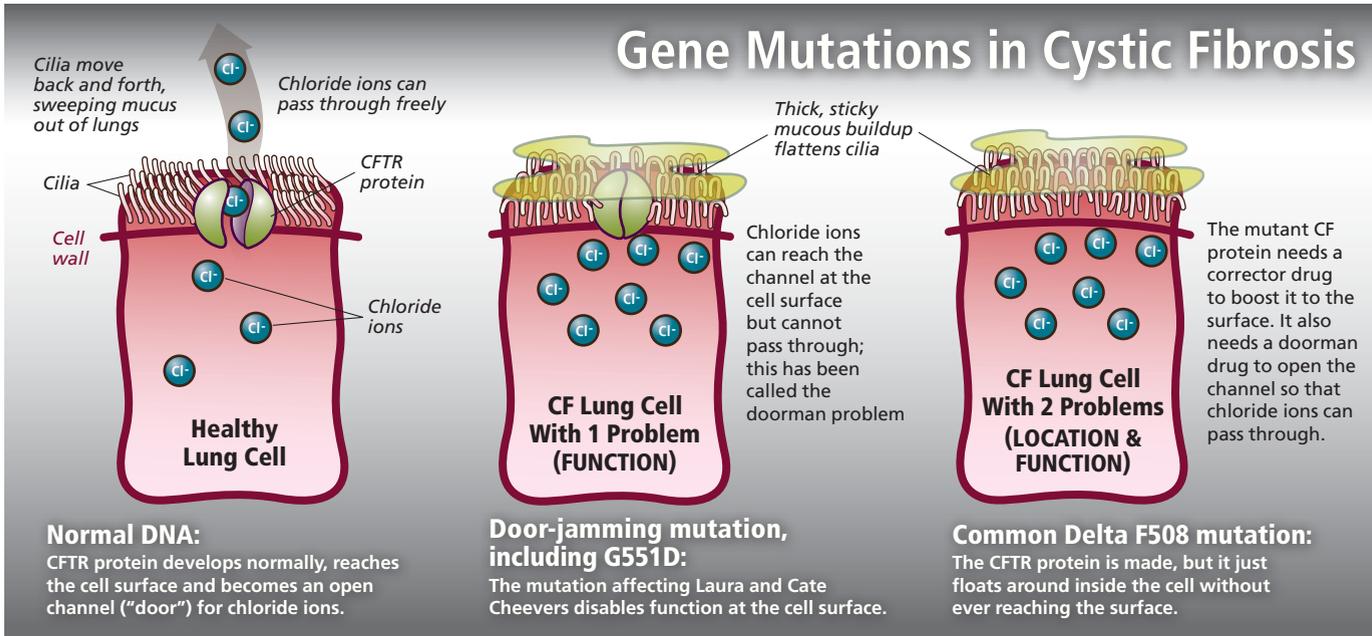
1994-1996

Collins' focus shifts to sequencing the entire human genetic code at NIH. He leaves CF research behind. Robert Beall becomes CEO of the CFF and, grasping the limitations of gene therapy, invests \$3.2 million in Aurora Biosciences Corp., where cell physiologist Paul Negulescu begins to look for a chemical cure using high-throughput methods to test large numbers of potential drugs.

1999

Wilson publishes phase I trial results showing it is almost impossible to get the CFTR gene into CF patients' lung cells without immune rejection.

Gene Mutations in Cystic Fibrosis



In 2002 and 2003 Vertex's San Diego facility, which does the drug screening, tested another 200,000 compounds, and a couple of them looked promising. The top candidates — dubbed VX-770 and VX-809 — doorman and corrector drugs, respectively, made the mutant CF cells in Negulescu's assay glow fluorescent blue, a sign that chloride was on the move. "That's when we got excited," says Negulescu, who was absorbed into Vertex to run the San Diego screens.

To test VX-770, the doorman drug, researchers used lung cells from a CF patient with the G551D mutation — the same one sickening the Cheevers girls, who required only a doorman drug to function in healthy mode. VX-770 made the cells glow blue, proving that the chloride channels were open. Scrutinizing the cells, Negulescu could see why: Lung cells are covered in fine hairlike structures called cilia. In healthy folks, these move back and forth and sweep mucus out of the lungs. On CF cells, however, the cilia are matted down with

mucus, like a shag carpet covered in glue. When Negulescu peered through a microscope at the sick G551D lung cells growing in dishes in the lab, they resembled a mat of small, still, gray spheres. But when his colleagues dosed these sick cells with VX-770, the tiny hairs sprang to life. Under the microscope, he could see cilia swaying back and forth, like a crowd at a stadium doing the wave. As the cilia swayed, the cells started to vibrate as if caffeinated. With an active chloride channel, the mucus would be watery, he thought, like in healthy people, and the revived cilia could sweep it away.

"That gave us so much optimism, some people were crying it was so beautiful," says Negulescu. Perhaps VX-770 could do the same thing in live patients.

By 2007, the drug had been tested on cells and in a phase I clinical safety trial in healthy volunteers. VX-770 was on its way to becoming the drug Kalydeco.

The phase II trials for those with the G551D mutation were small, just 39

patients, but they were cleverly done to squeeze out as much data as possible. In spring 2008, Vertex's chief physician showed Olson some data; a few numbers he saw were worth a thousand words. "It was remarkable," says Olson. After just two weeks, concentration of salt in the sweat had plummeted from around 100 millimolar — a typical value when the CFTR protein is dysfunctional — to about 50 to 60 millimolar, a bit higher than average but below the diagnostic bar for CF.

Then, in 2010, as part of phase III trials, VX-770 was given to patients with the G551D mutation, including the Cheevers sisters, Laura and Cate. "This is a once in a lifetime for a pharmaceutical scientist," says Olson, the project lead. "We are not just treating symptoms. We are fixing the protein that actually causes this disease."

Laura began the trial unaware whether she was taking the drug or a placebo. She continued to cough, couldn't gain weight and ultimately de-

between 2002 and 2003 200,000 more compounds tested

2000

CFF gives Aurora Biosciences \$44 million to find a cure and forms an arm called Cystic Fibrosis Foundation Therapeutics to spearhead research.

2001

Aurora Biosciences is acquired by Vertex Pharmaceuticals. Negulescu stays on, and Beall recruits Joe O'Donnell to help raise \$175 million to keep the project moving.

2002-2003

Vertex finds promising drug candidates among 200,000 compounds tested, including VX-770 (doorman drug) and VX-809 (corrector drug).

veloped a severe lung infection requiring heavy-duty antibiotics. For Cate, things were different. “I could just feel like I was getting better, like growing more, and I could see the difference between me and Laura,” says Cate, who coughed less, slept better, gained weight, ate like a horse and was bursting with energy. Later, Laura, who had been taking a placebo, was switched to the drug, and she, too, got well. The FDA approved the drug in 2012.

Experts agree the treatment is transformative for patients with the Cheevers’ form of CF. “We have just started using it in practice,” says Henry Dorkin, a pediatric pulmonary specialist and director of the Cystic Fibrosis Center at Children’s Hospital in Boston. “While it’s still early, the results are very encouraging.” Dorkin began treating patients more than 35 years ago, and the window ledge of his office is crammed with pictures of kids — patients he’s treated, many of whom died from the disease. Patients typically lose about 1 percent or 2 percent of lung function each year. If the decline slows, or stops, and they continue to gain weight, then, Dorkin says, “I would have to say that it’s a game changer.”

Laura and Cate’s daily regimen of two pills of Kalydeco costs \$841 per day; that’s \$307,000 each year, making it one of the world’s most expensive drugs. In most cases, private insurance picks up the bill. Medicare or Medicaid may pay as well. For patients themselves, the cost is about \$15 for one month’s supply of the drug. For those who lack insurance, Vertex offers financial assistance so they can access the drug.

The company can afford the largesse: Kalydeco saw windfall profits of \$172 million in 2012, boosting the company’s stock price and visibility. Although many have questioned the ethics of that profit and the burden of the drug price



on the health-care system, Beall says that without Vertex, there would be no drug. And, for the CFF to negotiate a drug price before there was even a drug would have been a deal breaker.

CFF has also profited from the discovery and sales of Kalydeco. It just sold a portion of the royalty rights for the drug, bringing in \$150 million. As per the business plan that O’Donnell vehemently supported, that entire amount will be reinvested to fund more CF research and drug development. That’s important because Beall is not complacent that Kalydeco is a cure. “We need to be careful about using the word ‘cure’ when talking about Kalydeco, although the drug is clearly a game changer and has fueled incredible optimism in the CF community — and for me personally,” says Beall, “but we have to be cautious. We only have two years of data on how patients are doing on the drug, and it’s premature to say whether it will be a cure for them.”

Indeed, even with Kalydeco, Cate

and Laura still must take 20 to 30 pills a day to digest their food. They also require 30 minutes of physical therapy — clapping and beating their sides and back — to help dislodge the mucus. But they are staying free of lung infections and gaining weight.

COMPLETING THE CURE

Those with two copies of the Delta F508 mutation — half the CF population — are watching the Cheevers to see if the treatment keeps working its magic. They are waiting as Vertex conducts phase III trials of the second drug, the corrector, VX-809, in combination with Kalydeco, the doorman, to see whether the defective proteins can reach the cell surface and open the door to get chloride flowing again. If it works, this drug combo could halt the disease in its tracks for the majority of patients — as Kalydeco seems to have done for Laura and Cate.

There’s reason for hope. Phase II of Vertex’s combo trial showed that the

2007

VX-770 passes Phase I safety trials.

2010

Laura and Cate start clinical trials of VX-770.

2012

VX-770 is approved by the FDA and renamed Kalydeco.

2013

Vertex is conducting Phase III trials of the corrector drug, VX-809 in combination with the doorman, Kalydeco.

Thanks to drug development, the Cheevers girls are enjoying active lives. Laura (left) takes dancing lessons. Cate plays for a local soccer team.



VX-809 plus Kalydeco improved lung function in patients with two copies of the Delta F508 mutation. The larger and longer phase III study of 1,000 patients will continue for 24 weeks and should yield an answer in 2014.

Beall isn't placing all his bets on Vertex. O'Donnell has embarked on another campaign for \$75 million to give to other pharmaceutical companies. The Foundation has already invested \$58 million with Pfizer to develop a second generation of similar but more potent drugs to treat those with two copies of the Delta F508 mutation. While Kalydeco and the corrector should work, Vertex or another company may ultimately be able to engineer more effective molecules. And Beall is still concerned about the 40 percent of patients who have only one copy of the Delta F508 mutation and one copy of another mutation: How effective will Kalydeco and corrector combo be in this group? So the search goes on. "We're not going to settle for less than 100 percent of patients," he says.

To this end, Vertex is expanding clinical trials to encompass other rare mutations. The R117H mutation, carried by about 3 percent the CF population, creates a protein that reaches its destination on the cell surface, but then malfunctions. While the impediment

is unclear, Olson guesses it may be the door-jamming problem. If so, as with the Cheevers' G551D mutation, Kalydeco might fix the defect. Olson adds that there are also two more corrector drugs in the pipeline, VX-661 and VX-983. "You want to fill your nest with lots of molecules, each of which has slightly different properties," he says. People carrying different mutations may require specific correctors, or more than one corrector, or a complex combination of these drugs, which is why Vertex continues it search.

"Robert Beall deserves a lot of credit for placing a huge and expensive bet on an enterprise that could well have failed," says Collins, the current NIH director. The CFF's strategy is a prom-



Laura Cheevers holds a handful of pills that she and her sister take each day to fight the symptoms of CF. The blue pills are Kalydeco, taken twice a day. The capsules are Creon 12, taken four at a time with every snack or meal.

ising model for attacking other genetic diseases, Collins adds, and other groups are trying to embrace the innovative drug development model as well.

CFF may soon succeed in creating a long-sought cure, but for Olson and Negulescu, the journey has been bittersweet. Over the past 15 years, the scientists have embraced the CF community. They've participated in fundraising walks and bake sales. They've become acquainted with CF families who have visited Vertex to share their stories and participate in research. Along the way, they've experienced many losses. Olson describes one family who lost three children within the past three years. "We just weren't fast enough for that family."

Every year the CFF holds its annual meeting in a different city, and over the past decade, Joe O'Donnell has gotten to know many members quite well — volunteers, mothers who have lost a child, others who are on the cusp. In October 2012 in Orlando, Fla., there were nearly 4,000 who refused to quit working toward a cure, all the time wondering whether it was really going to happen for them. **D**

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