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Posted on Mon, Apr. 28, 2008

INQUIRER SPECIAL REPORT: ENVISIONING A CURE

Phila. researchers bring sight to the blind

By Tom Avril
Inquirer Staff Writer

The young man on Albert Maguire's operating table had a big red mark stamped on the right side of his forehead.

The mark told the surgeon just where to insert his needle: straight into the patient's right eye.

Maguire didn't really need the reminder. He and his wife, molecular geneticist Jean Bennett, had been focusing on this moment for months - in truth, for decades.

The patient was blind. Maguire's hair-thin needle traveled through the "white" of his eye, all the way back to his badly scarred retina, where it would deliver billions of genetically modified viruses. Each virus carried a single gene: the recipe to produce a crucial enzyme that his eye was unable to make on its own.

Within weeks, beyond what anyone had predicted, the experiment worked. The young man and two other patients began to regain some vision.

The results, reported online yesterday by the New England Journal of Medicine, represent a dramatic advance in the field known as gene therapy, a field marked by sparkling - yet so far largely unfulfilled - promise.

The three patients, treated in a joint effort by the University of Pennsylvania and Children's Hospital of Philadelphia, remain legally blind. But there are indications that the procedure may work even better in children, and the lessons could one day apply to



MICHAEL PEREZ / Inquirer Staff Photographer

Months after surgery, patient Tommaso Ferraro, above, is tested. At left are geneticist Jean Bennett and surgeon Albert Maguire, who led the project.

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other forms of inherited blindness.

"This Philadelphia trial is exceptionally exciting," said Savio Woo, a gene-therapy specialist at the Mount Sinai School of Medicine who was not involved with the study. "It's absolutely remarkable."

The Inquirer followed the trial over eight months under the agreement that it would not print an account until the research was published in an academic journal.

The official goal of the surgery was to make sure such an injection was safe; no one promised the young man, who had flown from Italy for the experimental treatment, that he would see any better.

But luck was on his side.

Bennett and Maguire set the date of the surgery for Thursday, Dec. 13.

To them, it was just another day on the calendar. But to the Italian clinicians assisting in the operation, it was auspicious.

The 13th is the feast day of Santa Lucia, patron saint of the blind.

A 'simple problem'

Jean Bennett and Albert Maguire first talked about the eye idea as they were finishing up Harvard medical school in the mid-1980s - she exploring the fledgling field of genetics, he learning to be a surgeon.

The two had hit it off in neuroanatomy class. They were lab partners on the day they had to dissect a human brain.

After they cut the brain in half, Maguire took Bennett's hand and put it on top of the hypothalamus.

"I want to show you my favorite organ," he said, reminding her that it is sometimes called the "pleasure center."

Not missing a beat, she responded:

"That's my second-favorite organ."

They were married two years later.

It was 1985. Still in school, Maguire was working in a lab that specialized in retinal degeneration, and he knew that many such diseases were the result of a single defective gene. With the practical, fix-it approach common to those in the surgical profession, Maguire wondered if matters could be addressed in the operating room.

"I thought: 'Simple problem: Fix gene, fix disease,' " he said.

Of all the body's organs, the eye is one of the most accessible. So he asked his wife, who already had a Ph.D. in biology: Was it possible to inject a corrective gene?

Sure, she said - in theory. Researchers had been talking for years about the goal of inserting genes into living tissue.

Except that no one had identified any of the genes that cause retinal disease.

"Had I actually known how difficult and complex the problem really was, I probably would have dismissed the idea

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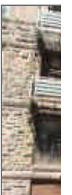
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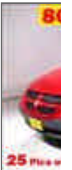
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immediately," he says now. "Jean has a more long-term view and didn't tell me."

The two did a stint at Yale, where Bennett had grown up, the daughter of a famous physicist who co-invented the gas laser.

Later, Maguire interviewed for a fellowship with Robert Machemer, a pioneer in retinal surgery, and eagerly told him what he and his wife were trying to do. The response was not good.

"It'll never work," Machemer said.

Maguire, a Philadelphia native and Episcopal Academy graduate, didn't get the fellowship, but the rejection inspired the couple. They came to Penn's prestigious Scheie Eye Institute in 1992.

The dogs

The notion that eye problems could be inherited dates back to Aristotle. But the first gene for retinal degeneration was not discovered until 1989. Today, more than 400 eye-disease genes have been identified, aided by the Human Genome Project.

At Penn, Bennett studied the genetics of retinitis pigmentosa - a group of inherited diseases that gradually destroy sight.

In 1997, scientists at the National Eye Institute found a mutation that caused a rare subtype that strikes children, called Leber's congenital amaurosis (LCA). They began to try to induce these mutations in mice in order to figure out how to fix them.

Then, in 1998, Cornell University's Gregory Acland and Gustavo Aguirre - now at Penn - reported that the same mutation occurred naturally in a certain breed of dog, the Briard.

In 2000, Bennett and Maguire joined them in a pivotal experiment. They injected three blind dogs with a virus - one that had been modified to deliver the recipe for a missing enzyme in their eyes.

Within weeks, the dogs' vision improved more than anyone had hoped. They could see so well they could navigate a maze.

By 2006, Maguire had performed the surgery on 55 blind dogs, restoring vision in more than 90 percent of them.

LCA is a rare disease, afflicting perhaps 3,000 people in the United States. But if Bennett and Maguire could get their gene therapy to work for that illness, the lessons might apply to other forms of retinitis pigmentosa - which strikes 100,000 people in the U.S.

It was time to try it on people.

In the family

Giuseppe Ferraro noticed, when his firstborn son was 5 months old, that the baby didn't seem bothered by bright lights. In fact, he looked straight at them.

Eventually, Ferraro learned that his son had LCA.

His vision had been impaired since birth, and it would become steadily worse.

There was no cure.

Four years later, the Ferraros had twins. Sadly, Tommaso and Josalinda were born with the same mutation.

Tommaso grew up and got a job as a dispatcher for the forest service, where a government-appointed guide helps him get around. Josalinda got married and began to raise two children. Both could see a little bit out of one eye, especially in bright sunlight. But under normal interior lighting, their vision was just about zero.



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Through doctors in Naples, they heard that scientists in Philadelphia were working on an experiment that might help them.

Tommaso and Josalinda were 26. The trial was limited to those 27 and under; any older, and the retina would likely be beyond rescue.

Tommaso was a little hesitant when he heard that a needle would be inserted into his right eye. And, the doctors warned him, his eye could become inflamed. The corrective genes, borne by the viruses, might not take hold. And his brain - starved of visual information for decades - might have trouble making sense of the new signals coming from his rejuvenated eye.

Yet the doctors seemed confident not only that the procedure was safe - but that he might even regain some vision.

He and his twin sister agreed to try it. They booked flights to Philadelphia.

Using viruses

Since scientists began trying gene therapy on humans in 1990, there have been hundreds of trials on thousands of patients, but scant success. There are some promising signs in treating hemophilia. In France, 10 children were cured of the immune disorder known as the "bubble boy disease." But three of them later developed leukemia.

And in 1999 at Penn, in the case that haunts the field, Arizona teenager Jesse Gelsinger had a fatal immune reaction after he was injected with genetic material to treat a metabolic disorder.

In that trial, as in most cases, scientists had delivered their corrective genes by piggybacking them on an agent that is extremely effective at invading human cells: the virus.

But the virus has another ability that is not so welcome: It hijacks the cell's machinery and makes copies of itself. Those copies, in turn, seek out and invade other cells. These modified cells can attract the attention of the patient's immune system, which attempts to snuff them out - thus defeating the whole purpose.

In Gelsinger's case, the problem was far more severe. Scientists used an agent called an adenovirus that had been stripped of its ability to replicate, yet his immune system became lethally overstimulated.

Bennett, on the other hand, decided to use a very primitive type of virus that never had the ability to reproduce. Called an adeno-associated virus, these bugs can copy themselves only by borrowing the machinery of the larger, more complex adenovirus.

Even if they were somehow to replicate, it is not a type of virus that causes disease. Of the roughly 300 human gene-therapy trials currently under way in the United States, more than 20 are using these adeno-associated viruses.

On their own, these simple viruses provoke at most a mild response. This is especially true in the eye, an "immuno-privileged" organ in which the immune system does not attack a foreign presence in a significant way.

For her trial, Jean Bennett enlisted the participation of Children's Hospital, a world leader in the treatment and study of pediatric genetic disease.

It is home to the Center for Cellular and Molecular Therapeutics, whose director, prominent gene-therapy specialist Kathy High, agreed it would sponsor the trial. A highly specialized lab would purify and tweak the virus so it could perform its job.

A flawed gene

In people with normal vision, a crucial protein is made by the retinal pigment epithelium, a layer of cells beneath the retina. The protein, an enzyme called RPE65, is used to metabolize vitamin A. The metabolized vitamin, in turn, allows the nearby "rod" cells to make a pigment that absorbs light, so it can be converted into an electrochemical message to the brain.

People with an RPE65 mutation develop LCA. Their eyes make flawed versions of the protein, if any at all.

Not only is their vision impaired to begin with, but over the years, their cells accumulate toxic levels of a vitamin A derivative that normally is broken down by RPE65. Their retinas become badly scarred.

To do gene therapy, Bennett's team took the virus and gutted it. They replaced its two genes with a single human gene - one with the blueprint for a healthy version of RPE65. All that remained of the original virus DNA was a pair of genetic bookends, one on each end of the DNA molecule.

Fraser Wright, director of the Children's Hospital lab that made the viral "vector" - the carrier - worked with Jeannette Bennicelli and others to fine-tune it. They added various bits of customized genetic material, including a "promoter" to enhance production of the needed enzyme, and another sequence to make the virus even better at penetrating the patients' eye cells.

The lab grew and purified billions of the viruses. It cultivated them inside cells derived from human kidneys, using a growth medium and other materials that had been subjected to rigorous tests to ensure purity. That process took a whole year.

Wright's lab performed dozens of FDA-mandated tests on the virus itself to ensure it would be safe for people - that there was no contamination by other viruses or bacteria, for instance.

The lab made hundreds of vials and stored them in a freezer.

Nine patients would receive the injection, each time in their worse eye - in case there were complications. The first three were the twins, Tommaso and Josalinda, and another Italian woman named Manuela Migliorati. (The disease is no more common in Italy than anywhere else, but researchers there have made an effort to identify those with mutations.)

If all went well, the viruses would latch onto and enter the sub-retinal cells, then travel all the way to the cells' nuclei. There, each virus would ordinarily release its own DNA. But in the patients, the lab-modified virus instead would release its cargo of the new RPE65 gene.

Because retinal cells do not divide, the impact of the corrective gene would not be watered down over time. It should be permanent.

The first three patients were to get 15 billion viruses each. If everything went OK, the next three would get three times that many. The third group would get 150 billion - 10 times the first dose.

Big numbers, but small invaders.

Compared to the retinal cells that they would be penetrating, each virus was about the size of a Frisbee on a football field.

The entire precious payload for each patient would be contained in 150 microliters of saline solution - less than one-thirtieth of a teaspoon.

The surgery

Al Maguire decided two days in advance just where he would insert the needle into Tommaso's right eye.

In October, with Tommaso's sister Josalinda, he'd injected the virus away from the center of the retina, in case it somehow impaired what little vision she had.

There were no complications with Josalinda, so Tommaso would get his injection closer to the center.

Maguire had been thinking intently about the surgery for days.

He had done hundreds of the operations on baby mice, whose eyes are the size of a pencil tip, and he'd done dozens of dogs.

The night before, to relax, he'd watched *The Pianist*, the tragic movie about a Jewish musician who lives in Poland during the Holocaust. Maguire found the context helpful; if others could endure such pain, surely his own challenges

were insignificant.

The day of the surgery, the hospital thawed out the vial containing the virus. Research coordinator Kathy Marshall carried it down the hall in a cooler.

Maguire's surgical team prepped Tommaso, stamping the red mark on his forehead. He was draped and put under anesthesia.

Because Tommaso was young, the clear substance inside his eye - called the vitreous - was still fairly firm and jelly-like. The needle, a flexible instrument called a cannula, could not be inserted all the way back to the retina.

So first, the surgical team removed the jelly and simultaneously replaced it with a saline solution - a procedure called a vitrectomy.

The surgeons cut three tiny holes in the surface of the eye: one for a vitrector, an instrument to snip and gently suck out the jelly; one for an infusion port to pump in the saline solution; and one for a "light pipe" to illuminate the back of the eye.

Maguire watched through a microscope as he and his team did the work. He operated in stocking feet because he had to control two of his tools, the vitrector and the microscope, with foot pedals. Each had a series of switches that he operated with his toes.

Outside, in the waiting room, Maguire's wife - the scientist - was nervous.

"It's scary, embarking on unknown territory," Bennett said. "At a certain point, it's time to say it's safe from every aspect we've looked at in animals. But humans is a different game."

It was time for the injection.

Maguire held the light pipe in his left hand. He carefully inserted the cannula with his right.

The flexible needle went through the sclera - the "white" of the eye - then through the saline fluid, until Maguire felt it come to rest at the back of the eye, gently, against the retina.

The needle was connected to a syringe in the hands of Penn ophthalmologist Eric Pierce, who stood ready to push the button that would release the precious genetic material.

"Push, push," Maguire told Pierce.

Looking through his microscope, Maguire saw a "bleb" - a small spot where the entering fluid was causing Tommaso's retina to rise. That meant he had gotten the needle in the right place.

"Go, go, go!" he urged Pierce, so he would release the rest of the virus-bearing fluid.

After years of preparation, the actual injection had taken just a few moments.

At 3:45 p.m., Maguire emerged in his hospital scrubs to give the news to the patient's father; an Italian doctor translated.

"He's doing very well," Maguire said. "He's waking up from the anesthesia. The injection went perfectly."

The surgeon walked out into the hallway. Bennett smothered him in a big hug.

"She's more relieved than I am," he cracked.

"Yeah, I am," his wife agreed.

It could be months before they'd learn if Tommaso's vision would get any better. It was time to wait.

An early sign

Maguire's focus is surgery, but he has the utmost respect for his wife's work as a scientist and her role outside the lab. She gamely attends black-tie fund-raisers, patiently explaining her work to potential donors. Ever cheerful, she acts like a big sister to her three patients.

She played tour guide while they recovered from surgery, taking each to FAO Schwarz and Times Square in New York, and to the Franklin Institute in Philadelphia, where they rode the flight simulator.

The third patient, Manuela, liked the simulator best. A 19-year-old university student, she was a bit of a daredevil and a downhill skier, with the best vision of the three.

Still, she was legally blind. When Bennett gave her some 8-by-10 photos of their sight-seeing trip to take back to Italy, Manuela couldn't make out the details.

Then, just two weeks after her surgery, she sent Jean Bennett an e-mail.

Manuela had looked at the photos again. To her delight, she wrote, she started to make out what was in them: herself, in the giant heart at the Franklin Institute, walking through Times Square, touching large stuffed animals at FAO Schwarz.

Bennett was elated. She grabbed the phone and started to call other members of the team. "Guess what? Manuela e-mailed me! She can see the photos!"

Tommaso and Josalinda had also reported some improvement in their vision, just weeks after their surgeries. They did not notice much difference in broad daylight. But they could see more indoors and at night. They were better at distinguishing lights and darks. At work, Tommaso relied less on his government-appointed guide and more on his cane. He felt confident pushing his baby son in a stroller.

Bennett knew there had been a chance that the patients' vision could improve, but these first three were older, their eyes severely damaged, and they'd received a weaker dose of the vision virus.

She wanted to jump up on a table and shout. Still, as a scientist, she was cautious.

It was one thing for the patients to think they could see better. But the team needed hard data.

In March, Bennett flew her three Italian patients back to Philadelphia for tests.

A new vision

With Bennett at her side, Josalinda peered into the twin eyepieces of the pupillometer, a device that repeatedly flashed light into her eyes.

Bennett needed to measure how much her pupils would constrict. Before the surgery, they barely responded.

For each round of testing, Josalinda kept her eyes closed until Bennett gave her the go-ahead, in a mixture of Italian and English.

"*Uno, due, tre . . .* Open!" Bennett called out each time.

Then finally: "*Bravo, bravo!* You did a wonderful job."

Bennett would need to scrutinize the data, but the machine seemed to confirm what Josalinda and the other two patients had told her: Their vision had improved. Their eyes were apparently making the enzyme they needed for sight.

Later analysis would show that the injected eyes of all three patients became roughly three times as sensitive to light.

Furthermore, all three were better able to read eye charts - though they did so slowly, haltingly, sitting less than two

feet away from letters a couple of inches tall.

Before the surgery, Tommaso's right eye could barely perceive someone waving a hand right in front of him. His eye was so bad it was hard to quantify, but compared to 20/20 vision, his right eye was at 20 over several thousand. After treatment, the eye improved to 20 over 710.

It had been 23 years since Bennett and her husband had first discussed the idea. Now, it had happened.

"To go from zero to anything, it's just . . ." She shrugged, unable to finish her sentence.

Within weeks, Bennett's team would send the results to the New England Journal of Medicine. She learned that a British team working on a similar experiment had submitted results, too. The journal would agree to publish both papers together.

Gene therapy remains in the experimental stage, and will be for years. The improved vision of three blind patients does not change that. It is just one study, involving an organ in which success may not translate elsewhere in the body.

Still, the results are promising for retinal disease.

After spending hours putting her patients through yet more tests, Bennett was done.

It was time to celebrate.

Eye to eye

With video screens pulsing a kaleidoscope of colors and waiters maneuvering platters piled with mega-burgers, Center City's Hard Rock Cafe was a chaotic environment even for someone with regular vision.

Walking to the table, Tommaso cradled his 6-month-old son in one arm, and held on to his wife with the other, her blonde curls splashing down his shoulder.

The group of 12 sat around a long table: patients, relatives, hospital staff. Manuela took a turn holding baby Giuseppe, leading everyone in an old Italian nursery rhyme: *batti, batti le manine, che arriva il tuo papa* - clap, clap little hands, your daddy's coming home. For a moment, they drowned out the restaurant's music.

Tommaso joined in the singing and - as Bennett looked down the table at him - he did something that just three months earlier would've been impossible.

He gazed across the table at his son.

Before and after video of a patient navigating a maze - and a story about the blind venture capitalist who helps fund this research: philly.com

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