THE ORGAN FARM

Gene-edited pig kidneys are finally moving the long-stymied field of xenotransplantation forward

PHOTO: JOE CARROTTA/NYU LANGONE HEALTH

Surgeon Robert Montgomery holds the gene-edited pig kidney that Towana Looney received.

JON COHEN

On 8 January, a 66-year-old retiree in New Hampshire named Timothy Andrews sent a Facebook Messenger note to a 53-year-old stranger in New York City, Towana Looney, with an unusual question. He wanted to know how her new pig kidney was doing.

Six weeks earlier, surgeons at New York University (NYU) Langone Health had made international news when they gave Looney the organ from a pig genetically altered so its tissues would be less likely to be rejected by her body. Andrews himself was 2 weeks away from receiving a similar, engineered pig kidney. "There's one person on the planet that has one, and I'm going to talk to her," he told his doctors at Massachusetts General Hospital (MGH). "I was just curious if there was anything different, what she felt about it."

Andrews and Looney both had kidney failure and had relied on dialysis to cleanse their blood, a procedure that sustains life but stresses the heart.

Human kidney transplants routinely free people from spending hours a week on dialysis machines. But the waiting lists for the organs are long, and for biological reasons both Looney and Andrews were poor candidates for a human kidney. In his Facebook message, the former supermarket manager commended Looney, a former cashier

at a Dollar General discount store, for her bravery. Understanding her journey, he said, would help him with his own. They became fast friends and she eased his anxiety about the pig organ. "I learned it was working for her," Andrews says.

Attempts to provide humans with animal organs—known as xenotransplantation—date back more than a century, a history marked by hype and dashed hopes. As surgeon Norman Shumway, who helped pioneer human-to-human heart transplants, quipped 2 decades ago, "Xenotransplantation is the future—and always will be." But because of recent advances in gene editing, cloning, and immunosuppression, and major investor backing, many veteran researchers are increasingly confident that future is nearly here.

At the time Andrews reached out to her, Looney's kidney was pumping out copious amounts of urine—a sign it was working—and her medically suppressed immune system appeared to be adjusting to the porcine guest. The NYU Langone doctors had released her from the hospital, but instead of returning to her home in Alabama, Looney stayed in a New York City apartment so they could closely monitor her health.

Andrews received his own kidney on 25 January, the same day the Associated Press celebrated a milestone for Looney: "The only person in the world with a functioning pig organ is thriving after a record 2 months," the story read. Four other people had received kidneys or hearts from genetically modified pigs, and none had survived longer than 60 days.

On 13 February, Looney's kidney was functioning well when *Science* met her in an Upper East Side apartment building. "I haven't felt this good since high school," she said, beaming. "My dream is when you walk into a dialysis clinic, I want a sign to say, 'Have you ever thought about getting a xenotransplant?'"

That same month, the U.S. Food and Drug Administration (FDA) paved the way for Looney's vision when it gave a green light to a bona fide clinical trial of xenotransplantation—a first—by United Therapeutics, the parent company of Revivicor, a biotech that created Looney's kidney. After a series of one-off transplants like hers, the trial offers the company a regulatory path to prove the worth of its pig kidneys and then sell them. Later this year, eGenesis, which provided Andrews's kidney, plans to seek FDA approval for its own trial. A Chinese company, ClonOrgan Biotechnology, also has an aggressive gene-editing program in pigs, and an unidentified 69-year-old woman received one of its kidneys in March.

Many leaders in the small xeno field say this is the year pig organs will demonstrate, convincingly, that they can help alleviate the dire shortage of human organs available for transplant. "We are at a tipping point now," says MGH surgeon David Cooper, who began doing pig-to-baboon transplants in 1985 and has worked with both Revivicor and eGenesis. "What we need now is one or two patients, say, with a kidney transplant, who do well for several months or a year—or longer."

The need is pressing. In the United States alone some 90,000 hoped to get kidneys last year, nearly 10,000 wanted livers, and another 3500 needed a donor heart. But among xeno researchers there remain conflicting ideas about the ideal pigs to use, the most important edits to make to their genomes, and the best way to prevent the human immune system from attacking its porcine interloper. "At this point, there are a lot of open questions that haven't been answered," says David Sachs, an immunologist at MGH and Columbia University whose interest in xenotransplantation dates back to 1971.

The field is also prone to showmanship and bad blood. Although many of the field's researchers have collaborated, the intense media attention these bizarre-sounding experiments receive fuels enmities between star surgeons and can be unsettling for patients.

The latest twist illustrates how the field often takes two steps forward, one back. Not long after Looney spoke with *Science*, her pig kidney failed for reasons that are still unclear. Her surgeons removed it, and she's once again on dialysis—although she remains a candidate for a second pig kidney. Andrews, for now, is still doing well with his foreign helper.

"WIZARD SURGEON PLANS RENEWING ALL VITAL ORGANS," blared a *Chicago Tribune* headline on 20 June 1922. Serge Voronoff, the breathless report from Paris declared, had made "the startling discovery" that he could "rejuvenate" humans with transplanted "glands" from chimpanzees—these included testicles—and he was moving on to transferring every organ. "I can push back a man's age 20 or 30 years, making his faculties more vigorous," boasted Voronoff, a Russian who had relocated to France.

More than a decade earlier, two other surgeons in Europe had attempted to transplant monkey, goat, and pig kidneys to the arms and thighs of people who had chronic renal failure. Even earlier, physicians had experimented with tissue, bone, and cornea grafts from animals. But it was Voronoff who brought xeno-

Towana Looney's xenotransplant functioned for 130 days, a new record.

transplantation world renown—and, as increasing numbers of doctors scrutinized his results and dismissed them as chicanery, ridicule.

Human-to-human organ transplants had a slower start. A Soviet surgeon performed the first one in 1933—but the kidney failed, and the patient quickly died. At the time, surgeons understood only dimly that a person's immune system rejects organs from other people unless they're a close genetic match to the recipient. But in the 1950s, Boston surgeon Joseph Murray and colleagues succeeded in transplanting one of a man's kidneys to his identical twin, who was in renal failure. The brother went on to marry one of his nurses, have two children, and live for eight more years.

Few people needing a kidney have an identical twin. But because healthy donors can spare a kidney, surgeons gradually learned how to match many living donors to recipients, often seeking donations from siblings. They also found ways to dampen the immune responses that attack the organs.

In 1962, Murray showed that kidneys from a recently deceased person could also work, creating another, now

PHOTO: JACKIE MOLLOY/*THE NEW YORK TIMES* VIA REDUX

routine, source of organs. He won a Nobel Prize in 1990 for his pioneering work. And as human kidney transplants became more successful, demand soon outstripped supply.

Xenotransplantation re-emerged as a possible solution to the shortages in 1963 when Keith Reemtsma, a Tulane University surgeon who had been experimenting with transferring organs between lab animals, began transplanting chimpanzee kidneys into people. (Chimps, an endangered species, are no longer used for any invasive biomedical research.) "I feel fine, practically good as new," Reemtsma's first xeno patient said at a press conference after his surgery. "I will outlive you all." He died 3 weeks later. But one woman lived 9 months, even returning to work as a teacher. Joe Tector, a liver transplant surgeon at the University of Miami who has been doing xenotransplantation studies for 2 decades, says the transplant team got "lucky."

As with other xenotransplant patients, Towana Looney required many medicines after surgery to stave off immune rejection of her new organ and infection from the immunosuppression.

Then in 1984 came one of the field's highest profile, most scrutinized failures: the transfer of a baboon heart at Loma Linda University Medical Center to "Baby Fae." Born with a deformed heart condition that is nearly always fatal within 1 month, Baby Fae lived with the baboon organ for 20 days, under the media spotlight the entire time. The experiment was assailed by animal rights activists, bioethicists concerned about the consent process, and legal scholars appalled by a minor being subjected to such a high-risk experiment. The surgeon, Leonard Bailey, was once advised to wear a bulletproof vest before giving a public talk about the operation.

Eight years later, Thomas Starzl at the University of Pittsburgh transplanted a baboon liver into a gravely ill 35-year-old man who had both HIV and hepatitis B infections and had been refused a human liver elsewhere. Starzl, famed for having pioneered human liver transplants, had decades before tried baboon kidneys in humans and failed. The man went into a coma shortly before the June 1992 xenotransplant, but in a hopeful sign, he was eating and walking 5 days later. Animal rights activists gathered outside the hospital and protested against "Dr. Frankenstarzl."

The patient died 70 days after the surgery because of problems unrelated to organ rejection. Still, his death had long-lasting consequences. "The excitement around the future of xenotransplantation died with him," wrote Richard Horton, editor-in-chief of *The Lancet*.

PART OF THE OPTIMISM that led Bailey and Starzl to attempt these high-risk xenotransplants came from powerful new immunosuppressive drugs, first cyclosporine and then tacrolimus. Indeed, after the introduction of cyclosporine, which FDA approved in 1983, rejections of human organ transplants plummeted, and they became so popular that the first major registries formed to match people in need with living and deceased donors.

The success of the drugs also attracted deep-pocketed pharmaceutical companies to xenotransplantation, despite the discouraging outcome of Starzl's attempt. One Wall Street analyst predicted it would be a $6 billion market by 2010. At the same time, the field shifted away from using monkeys as the source of organs to pigs. Not only were swine far easier to breed and handle, but they also raised fewer ethical issues, and they cost less. Pig-to-monkey xenotransplants provided a helpful animal model to test ideas, too.

Firms started to genetically engineer pigs to prevent rejection and test their organs in monkeys in the 1990s. Still, progress was slow. "You have to be patient, patient, patient, patient, and you need guts," says Bruno Reichart, a retired surgeon in Germany who started in the field 35 years ago and recently co-founded the company XTransplant. And then came a flashing red light. A 1997 report in *Nature Medicine* showed that remnants of ancient retroviruses that had colonized the pig genome could infect lab-grown human cells. The threat that a xenotransplant could infect humans with these porcine endogenous retroviruses (PERVs) sent the field into a tailspin. Attacks by animal rights groups, the growing alarm around mad cow disease, and opposition to genetically modified organisms ("Frankenswine") also discouraged investors.

Immunologist Corinne Savill, who led a xeno program for Novartis, said the risks became too high for the company. "What if in doing this you basically started the world's next pandemic?" she asks. Savill, now an executive at Cullinan Oncology, says there was a more formidable impediment still. "The immunology, the science, is just really hard, and it wasn't as if at that time you had something that said, 'Hey, it works.'"

IN THE WINTER, the winding road that leads to Revivicor's main pig farm in rural Virginia has beautiful views of snow-covered hills. But imperceptible "black" ice can coat this scenic byway, making for a treacherous drive—not unlike the journey to practical xenotransplants.

This Blacksburg farm, which provided Looney's kidney, helped reignite the field more than 2 decades ago when it belonged to a company called PPL Therapeutics, which famously helped clone Dolly the sheep in the United Kingdom. PPL had overcome a major impediment to xenotransplantation: In pig embryos, it knocked out the gene for an enzyme that creates the sugar molecule, or carbohydrate, known in shorthand as alpha-gal, and then cloned the offspring. Alpha-gal studs the surface of pig cells, but those of humans, other great apes, and old-world monkeys don't make it because all the species have an inactivated gene for the enzyme. So when our immune system sees alpha-gal on a xenotransplant, it attacks. Within 24 hours, a massive antibody assault can lead to what's called hyperacute rejection, the bête noire of the transplant field.

Knocking out alpha-gal solves that problem. But when researchers put alpha-gal knockout organs from pigs into monkeys, other hurdles popped up. "Once we'd inactivated the alpha-gal gene, it's like peeling an onion—all of a sudden, you learn what else you need to do in order to modulate the animal to eliminate rejection," says molecular geneticist David Ayares, who spun off Revivicor—and got the

PHOTO: JACKIE MOLLOY/*THE NEW YORK TIMES* VIA REDUX

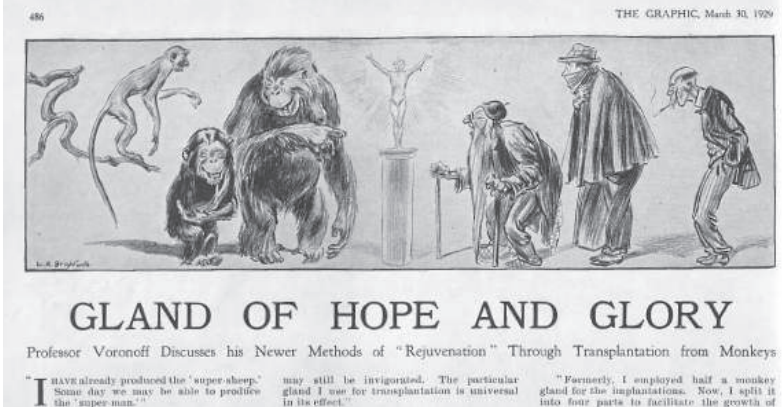
Blacksburg farm—in 2003 when PPL was heading for bankruptcy. "It was taking too long for them to get a return on investment," Ayares says.

Revivicor would conclude that its ideal pig would need far more edits than the alpha-gal knockout, but it began to run out of money itself. In 2011, when Revivicor only had 2 months of funding left in the bank, United Therapeutics came to the rescue. Martine Rothblatt, an entrepreneurial lawyer who started Sirius Satellite radio in 1990, had originally launched the company to develop drugs to help her young daughter, Jenesis, survive a deadly pulmonary disease that can require a risky lung transplant. By 2001 Rothblatt had developed a new interest, xenotransplantation, even earning a Ph.D. on ethical issues surrounding it. With its purchase of Revivicor, "United Therapeutics saved the field," Ayares says. Revivicor's competitor, eGenesis, "never would have even started if Martine had not demonstrated that this was a viable endeavor."

Revivicor not only had ample funding, it could soon take advantage of a new gene-editing tool, CRISPR. Two decades ago, knocking out a gene was an inefficient, multistep process, but CRISPR now allows scientists to edit animal genes with relative ease. At the farm, Ayares picks up a 2-month-old piglet that has the same edits as the animal that supplied Looney's kidney. "This has 10 genetic modifications: four pig genes inactivated and the addition of six human genes to modulate immune rejection," he explains.

After identifying the alpha-gal problem, researchers discovered two other carbohydrates on pig cells that kick human immune systems into overdrive: an Sd antigen—named after a man named Sid, who supplied the antibody sample that found it—and one known in shorthand as Neu5Gc. Nearly every xeno strategy being pursued by companies today knocks out all three genes needed to produce these carbohydrates.

The fourth knockout in Revivicor's pigs cripples their growth hormone receptor. Without that modification, they could grow to 300-plus kilograms, and their organs—which are "harvested" when they're about 6 to 8 months old—might continue to grow in humans. In contrast, eGenesis,


THE GRAPHIC, March 30, 1929

GLAND OF HOPE AND GLORY

Professor Voronoff Discusses his Newer Methods of "Rejuvenation" Through Transplantation from Monkeys

1929 Serge Voronoff popularizes transplanting monkey and chimp gonads.


Late Sports

Los Angeles Times

Morning Final

Friday, November 16, 1984

Heart Fails—Baby Fae Dies

U.S. There 31 Years

DMZ: Blend of Tension and Tedium

Lived for 20 Days With Implant From Baboon

1984 Baby Fae survives 20 days after getting a baboon heart.

Xeno's checkered history

Efforts to transplant animal organs into people—xenotransplantation—date back more than a century, but have been marked by failure after failure. Progress in human-to-human transplants, coupled with improved immunosuppressive drugs and gene-editing advances, have prompted new enthusiasm for xeno. Still, success remains far from certain.

Transplants
- Animal to human
- Human to human
- Research breakthroughs and U.S. Food and Drug Administration (FDA) approvals

1920 **1920–30** Serge Voronoff popularizes transplanting **monkey and chimp gonads** into people.

1940

1954 In first organ transplant success, Joseph Murray gives **kidney** from one **identical twin to another**.

1961 Murray succeeds with **first kidney transplant** between **unrelated people**, using immunosuppression.

1960

1964 Keith Reemtsma transplants **chimp kidney** into patient who **lives 9 months**; Thomas Starzl transplants **baboon kidneys** into six people.

1967 **First successful human kidney** transplant, by Starzl; **first human heart** transplant, by Christiaan Barnard

1980

1983 **Immunosuppressive drug** cyclosporine **approved** by FDA.

1984 "Baby Fae" survives 20 days after getting **baboon heart**.

1991 Pig **alpha-gal** molecule recognized as **major rejection trigger**.

1997 **Pig viruses (PERVs) found to infect** human cells.

2000

2002 Gene editing creates pigs **without alpha-gal**.

2017 CRISPR and cloning used to create pigs with **inactivated PERVs**.

2021 **Gene-edited** pig **hearts** and **kidneys tested** in brain-dead people.

2020

November 2024 to March 2025 events below

2022 David Bennett receives **gene-edited pig heart** (Revivicor).

November 2024 Towana Looney receives gene-edited **pig kidney**, which **lasts a record 130 days** (Revivicor).

January 2025 **Timothy Andrews** receives gene-edited **kidney** (eGenesis).

February 2025 FDA approves **first xenotransplant trials**, using Revivicor kidneys.

March 2025 Woman in **China** receives gene-edited **pig kidney** (ClonOrgan).

CREDITS: (PHOTOS, TOP TO BOTTOM) *THE GRAPHIC: AN ILLUSTRATED WEEKLY NEWSPAPER* 20 MARCH 1929; *THE LOS ANGELES TIMES*, 16 NOVEMBER 1984; (GRAPHIC) V. PENNEY/*SCIENCE*

Revivicor's David Ayares holds a piglet with 10 edited genes (top); a company researcher removes DNA from a pig egg (bottom) as part of the cloning process used to breed the edited animals.

ClonOrgan, and XTransplant leave the growth hormone receptor intact and get around the growth problem by using miniature pig breeds.

The human genes that companies add to the pigs aim to dampen other immune responses (see table, p. 911). Two attempt to shut down the "complement cascade," in which proteins in the blood activate each other to crank up inflammation and other immune responses. Two others tame inflammation-triggered blood coagulation and thrombosis, one reduces inflammation itself, and one prevents the pig organs from sparking an "eat me" signal that instructs a person's phagocytes, a type of immune cell, to gobble foreigners.

No two xeno companies target the same set of genes, because nobody knows what will keep a pig organ healthy in a person. "There are so many other antigens in the pigs that we are not worried about at the minute that we *should* be worried about," Cooper cautions.

Xenotransplant teams are also still experimenting with different cocktails of immunosuppressive drugs that may be crucial to long-term success. Unlike Looney, Andrews has been receiving a monoclonal antibody that inhibits a human cell surface molecule known as CD154, which plays a central role in activating immune cells and may drive the gradual formation of human antibodies against pig antigens. "Anti-CD154 is the key drug," Cooper insists.

Transplants of edited pig organs into monkeys suggest all this tinkering will pay off—xenotransplant survival in these animals is now measured in years, not months. Still, Tector, who is engineering pigs with his own company, Makana Therapeutics, contends that "no one has the right pig yet." The many gene edits done to pigs so far only dampen rejection, he says, and do not lead to the real goal: full tolerance of the foreign organ. That, he says, will require another round of edits to eliminate what are known as swine leukocyte antigens, or SLAs, which stud all pig cells. SLAs allow a pig immune systems to distinguish self from nonself but can ramp up human immune rejection of transplanted organs.

Others, however, suspect further gene edits and various drug cocktails may not solve the tolerance riddle. "I am skeptical that all these latest genetic modifications are really needed," says Columbia University immunologist Megan Sykes, a longtime collaborator of Sachs, one of the field's most experienced researchers. "The only important one so far that I know of is the alpha-gal knockout, and that was done years ago."

Sachs and Sykes have recently shown that an organ with that gene edit alone can survive remarkably long if they add one other ingredient to the transplant: a pig thymus. This gland helps educate an animal's immune system—specifically, its maturing T cells—to recognize self. A little bit of pig thymus might tell human immune cells to leave the new organ alone, the pair theorized. "If you control the T cell response, that's the important thing," Sykes says.

At a transplantation meeting in 2023, they described putting an alpha-gal knockout "thymokidney"—a piece of the pig's thymus grafted onto a kidney—into baboons. It functioned for more than a year with minimal immunosuppressive drugs. Sachs doesn't claim full tolerance has been achieved, however, and he is now testing further gene edits with support from a company he co-founded, Choironex. (The company is funded by Pablo Legorreta, a pharma billionaire who has a child with kidney disease.) Choironex expects to seek FDA approval to test its pig kidneys in humans later this year.

As for the PERVs that spooked the field in 1997, only eGenesis attempts to engineer them out of their donor pigs. Using CRISPR, Harvard University geneticist George Church, a co-founder of the company, and his team made 59 more edits to the DNA of their pigs to inactivate PERV sequences. Other companies, including Revivicor, say they can vastly reduce the likelihood of potentially dangerous PERVs in their pigs through screening and breeding.

"There's never been a transmission to a human," Ayares stresses, whether to xenotransplant patients or to workers in pig slaughterhouses. But Mike Curtis, CEO of eGenesis, sees it differently. "If I was a patient and had the choice between a fully retrovirally inactivated porcine donor and one that might carry retroviral risk, I know which one I would take," he says.

AFTER A LONG HIATUS, the new era of xenotransplant experiments began in September 2021 with transplants of gene-edited pig kidneys into people who were brain-dead but whose bod-

PHOTOS: JON CHO/*SCIENCE*

ies were volunteered by their families for tests of how the transplants would fare.

NYU Langone's Robert Montgomery, who has a transplanted human heart himself, was first, transplanting an alpha-gal knockout thymokidney, created by Revivicor based on the pig-to-monkey studies of Sykes and Sachs. Five days later, Jayme Locke at the University of Alabama at Birmingham (UAB) transplanted a 10-gene-edited kidney from another Revivicor pig. The two teams would do five more xenotransplants between them in brain-dead people, and other researchers in China and Pittsburgh have done similar decedent transplants of gene-edited pig kidneys and livers.

Some saw the experiments as macabre and pointless, but the researchers involved say they yielded valuable data on how the immune system rejects xenotransplants. MGH nephrologist Leonardo Riella, who cares for Andrews, says there was a sociological benefit as well. "We didn't know how the public would react about transplanting a pig kidney into humans," Riella says. "The way it was accepted, and how we saw patients actually very excited about the news, that was eye opening."

What's more, the UAB xenotransplantation program that did the decedent transplants helped pave the way for Looney's pig kidney. Launched in 2016 with $19.5 million from United Therapeutics, the program hired Tector as its director and other leaders in the field including Cooper. It built a new, "designated pathogen-free" pig facility nearby. And it was Locke who met Looney at the beginning of her search for a donor kidney.

After donating a kidney to her mother in 1991, Looney 25 years later suffered kidney failure herself and started dialysis. Her prospects for getting a donated human kidney turned out to be poor. She had high levels of antibodies against the tissue of most other people, a phenomenon sometimes seen in women who have had multiple pregnancies, resulting in prolonged exposure—via the fetuses—to antigens from the fathers. So that is how Looney moved to the front of the line for a pig kidney.

Administrative changes at UAB, ego clashes, and intellectual property concerns all combined to sink its xenotransplant program by 2021. "It was a terrible loss for Alabama," Cooper says, "because they could be dominant in the field now."

Instead, a team at the University of Maryland on 7 January 2022 was the first to transplant a gene-edited pig organ—a heart—into a living person. The man, David Bennett, was hospitalized for heart failure and required a machine to oxygenate his blood. He was told by several transplant centers that he wasn't a candidate for a human organ because he had a history of not complying with medical advice. "It was either die or do this transplant," Bennett said, the day before surgery, in which he received a heart from a Revivicor pig with its 10 edits. "I want to live. I know it's a shot in the dark, but it's my last choice." He lived 60 days before he died from heart failure, which his surgeons said may have in part been tied to inflammation from a pig cytomegalovirus inadvertently transmitted from the organ.

In September 2023, the team transplanted a second pig heart with the same edits to Laurence Faucette, who was ineligible for a human heart because of severe atherosclerosis and a recent gastrointestinal bleed. Faucette, who had been given little time to live if he did not get a new heart, died 6 weeks later. "You start with a great disadvantage with these patients," says Muhammad Mohiuddin, who co-led the surgical team for both xenotransplants and heads the International Xenotransplantation Association.

The first living patients to receive gene-edited pig kidneys similarly had complicated medical histories. In March 2024, MGH transplanted an eGenesis kidney into a man who had diabetes, hypertension, and previously received a human kidney that failed. A month later, NYU Langone gave a Revivicor thymokidney to a woman who also had a mechanical heart pump. Both died within 2 months, though doctors say the pig organs were still functioning.

Locke in May 2024 received FDA approval to do Looney's transplant at UAB. But with the demise of the xenotransplant program there, UAB would not let her proceed. Montgomery, who had been Locke's mentor, took over Looney's care at NYU Langone.

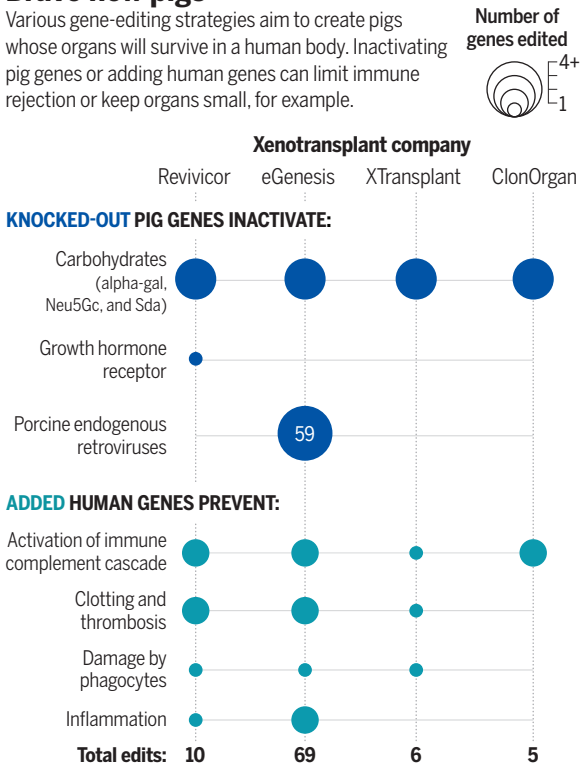
Her transplant, done with Locke's assistance, took place on 25 November 2024. On it rode not just her own hopes, but those of a burgeoning industry. By moving into healthier patients like Looney and Andrews, the xeno companies are hoping to finally have more success—and justify their expanding investment in a field that they contend will in the not-too-distant future produce enough organs for everyone in need.

IN A CHRISTIANSBURG, VIRGINIA, industrial park about 25 kilometers from the Revivicor farm, United Therapeutics last year built a $75 million facility dedicated to gene-edited pigs. From the outside the boxy building looks more like a drug manufacturing plant than a farm. If the company's vision becomes a reality and its pig organs receive FDA approval, they will, in effect, be drugs.

As with all drug manufacturing, sanitation is crucial: Pregnant sows from the Blacksburg farm are brought to an "introduction barn" at the Christiansburg site to give birth to their gene-edited piglets, which are carefully screened for viruses before they move into the pathogen-free facility. Humans who then work with the pigs wear personal protective equipment and must shower before and after entering. Elaborate systems eliminate waste, purify water, and constantly filter the air for the pigs. "They drink cleaner water and are in

Brave new pigs

Various gene-editing strategies aim to create pigs whose organs will survive in a human body. Inactivating pig genes or adding human genes can limit immune rejection or keep organs small, for example.



CREDITS: (GRAPHIC) M. HERSHER/*SCIENCE*; (DATA) REVIVICOR; EGENESIS; XTRANSPLANT; CLONORGAN

> **I did it knowing that no matter what happened, I did something for humanity.**
> **Timothy Andrews**

Timothy Andrews (right), leaving the hospital after his xenotransplant, thanks Tatsuo Kawai, who led the surgical team.

cleaner air than the employees," says Aaron Orkin, who runs the facility.

The company is investing $200 million more to build similar pathogen-free facilities in Texas and Minnesota. "We are envisioning multiple facilities with an organ output of 2000 a year across the United States, Europe, and Asia," Ayares says. eGenesis has two pig facilities of its own that it predicts can produce up to 1000 pigs a year.

Both companies still heavily rely on cloning to replicate animals with all the desired gene edits, because edits can be lost in conventional breeding. But cloning is slow and expensive. "It will be very difficult to produce several thousands of pigs" if you rely on cloning, says veterinarian and bioengineer Eckhard Wolf, the lead scientist at XTransplant, which is focusing on heart xenotransplants.

XTransplant and Choironex also clone their pigs to start but then rely on breeding the animals, which maintain gene edits better because they are so closely related. Similarly, ClonOrgan only breeds within its existing population of 500 gene-edited pigs, says its founder Dengke Pan. These pigs, he says, "can be used for mass production and supply of clinical xenotransplantation donor pigs, meeting the needs of hospitals in China."

A test of whether these investments will pay off is imminent, as United Therapeutics moves ahead with clinical trials of Revivicor's gene-edited pig kidneys at NYU Langone and Johns Hopkins University. If all goes well with the first six patients, the clinical trials can expand to 44 people at more sites. FDA has defined the "primary endpoint"—its criterion for success—as a kidney still working at 6 months, but it's unclear what percent of trial participants will have to hit that mark to win the agency's approval.

Beyond that hurdle lies the market. Curtis of eGenesis says the ultimate reception will depend on what the pig organs will cost—the companies haven't released any public estimate, but the bill will surely be steep at first—and how much insurers and government health systems will cover. What patients and families consider a successful outcome will also be crucial. "We're not convinced a 6-month end point is enough, but boy, it's a great target for [regulatory] registration," Curtis says. "Beyond that, I think you're going to have to show some patients can go beyond 6 months."

LOONEY, UNFORTUNATELY, didn't make it that far. Seventeen days after the transplant, protein levels in her blood rose, and a biopsy revealed an antibody onslaught against the kidney. To solve the problem, her physicians repeatedly did a procedure called plasmapheresis that pulls blood from the body, separates the plasma and removes the antibodies, then returns clean plasma to the body. After plasmapheresis, Montgomery says, "the antibody never comes back." But the immune system has myriad actors, and something else began to damage Looney's new organ in late March.

On 4 April, Looney had her pig kidney removed. She had lived with the xenotransplant for 130 days. "This is really a victory," Montgomery argues. "If you had asked me a couple of years ago whether we would be having this level of success, I probably wouldn't have thought we would," he said. Early indications suggest the kidney may have failed because an unrelated infection led doctors to reduce Looney's immunosuppressive drug, but the ongoing studies should better clarify what went wrong.

At the time, Anderson was hospitalized with an infection unrelated to the xenotransplant. He since has recovered and returned home. "I know there are no guarantees, but it is sobering to see it happened," he said about Looney's xenostransplant ultimately failing. "Two things I live by now: It is what it is, and this is what we signed up for," he said. "I was already committed to death with dialysis, so it wasn't that hard of a leap for me," Andrews added. "I did it knowing that no matter what happened, I did something for humanity."

Six days after having her kidney removed, Looney was back home and having her hair dyed orange. Her hairdresser posted a video of them on Facebook in which she asked her client what's the word for the day? "Blessed," a smiling Looney said.

"And highly favored," the hairdresser said.

"And highly favored," Looney agreed. □

PHOTO: KATE FLOCK/MASSACHUSETTS GENERAL HOSPITAL