

# News in focus

MASSACHUSETTS GENERAL HOSPITAL



A pig kidney is unpacked for transplant into 62-year-old Richard Slayman of Massachusetts.

## FIRST PIG KIDNEY TRANSPLANT IN A PERSON: WHAT IT MEANS FOR THE FUTURE

The operation's early success has made researchers hopeful that clinical trials for xenotransplanted organs will start soon.

By Smriti Mallapaty & Max Kozlov

**T**he early success of the first transplant of a pig kidney into a living person has raised researchers' hopes that larger trials involving pig organs will soon become a reality. Such trials could bring xenotransplantation – the use of animal organs in human recipients – into the clinic.

The recipient of the pig kidney is a 62-year-old man with end-stage renal failure named Richard Slayman. The kidney was taken from a miniature pig carrying a record 69 genomic edits, which were aimed at preventing rejection of the donated organ and reducing the risk

that a virus lurking in the organ could infect the recipient.

The case demonstrates that, at least in the short term, these organs are safe and function as expected, says Luhan Yang, chief executive of Qihan Biotech in Hangzhou, China, and one of the founders of the biotechnology firm that produced the pigs, eGenesis in Cambridge, Massachusetts. The company is in discussion with the US Food and Drug Administration (FDA) about planning clinical trials for pig kidney and paediatric heart transplants, and for the use of pig livers that would be connected to the recipient from outside the body, says Wenning Qin, a molecular

biologist at eGenesis.

So far, all US transplants of animal organs into living humans have received FDA approval on the grounds of 'compassionate use', granted in rare cases in which a person's life is at risk and there are no other treatments. But Yang hopes that the latest results will push the FDA towards approving full-scale clinical trials. Xenotransplants can "provide hope and life for patients and their families", Yang says.

### Hopes for trials

The surgery's success takes the xenotransplant community closer to a solution to the shortage of life-saving human organs. In the United

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States alone, there are nearly 90,000 people waiting for a kidney transplant. “Even though organ donation rates have increased massively, we still need millions of organs to transplant into patients,” says Wayne Hawthorne, a transplant surgeon at the University of Sydney in Westmead, Australia.

“This is great news for the field,” says Muhammad Mohiuddin, a surgeon and researcher at the University of Maryland School of Medicine in Baltimore, who in 2022 led the first pig-heart transplant into a living person. Mohiuddin, who is also president of the International Xenotransplantation Association, says clinical trials would produce much-needed rigorous data about the safety and efficacy of xenotransplantation.

Surgeons have previously transplanted gene-edited pig hearts into two living people. Modified kidneys have been transplanted into several people declared dead because they lacked brain function. Last month, surgeons in China transplanted a modified pig liver into a person considered clinically dead.

### Dozens of edits

The operation to give Slayman a pig kidney took four hours, says Tatsuo Kawai, one of the transplant surgeons. Kawai had previously performed surgery on Slayman to transplant a donated kidney in 2018. That had since begun to fail, requiring Slayman to resume regular dialysis. He developed complications that meant he required frequent hospital visits, which made him a candidate for xenotransplantation.

Slayman’s latest kidney came from a pig that had undergone CRISPR–Cas9 genome editing by eGenesis’s scientists to modify 69 of its genes. Monkeys that received the company’s pig organs with the same genomic edits survived for months to years<sup>1</sup>. Qin says she is hopeful that Slayman’s xenotransplanted kidney will survive for at least as long, particularly because her team devised the edits with humans, not monkeys, in mind.

The edits included the removal of three genes that contribute to the production of three sugars on the surface of pig cells. The human immune system attacks cells bearing these sugars, which it perceives as hallmarks of a foreign invader. Seven human genes were added because they produce proteins that help to prevent organ rejection.

Another 59 genetic changes were made to inactivate viruses embedded in the pig genome. These alterations address the risk that the viruses will become active once in the human body. So far, researchers have not seen this happen in transplants to living humans, people who are clinically dead or non-human primates, says Yang. But some laboratory experiments have shown that these viruses can be transmitted from pig tissue to human cells and to mice with weak immune systems<sup>2</sup>.

The first genetically modified pig heart to be successfully transplanted into a living person was later found to be tainted with a latent virus, which might have contributed to the organ’s eventual failure<sup>3</sup>. A major concern for the FDA before approving the kidney transplant was the risk that pig pathogens could infect the recipient, Kawai says. Qin says that eGenesis regularly tests its pigs for pathogens including porcine cytomegalovirus, which can linger quietly in its animal hosts.

### Healthy kidney

Before the procedure, the researchers collected and froze blood samples from Slayman, members of his family and his surgeons. If Slayman develops an infection, researchers can test these blood samples to determine whether any of these individuals were the source of the pathogen, says Kawai. Slayman will continue to be tested regularly for pathogens; if he develops symptoms, his family members and caregivers will also be tested.

Transplant recipients need to take immunosuppressive drugs to stop their bodies rejecting the new organ. No viruses, bacteria or fungi were detected in the pig that provided Slayman’s kidney. But such pathogens could be present even in apparently pathogen-free donor animals and could multiply in an immunocompromised person, Yang says. “We don’t know what we don’t know.”

Kidneys filter out toxic substances from the

body and produce urine. When the surgeons restored blood flow to the transplanted pig organ, it immediately turned pink and started to produce urine, says Kawai, a sign that the transplant had been successful.

Another metric of kidney health is the blood level of a compound known as creatinine – high levels indicate that the kidney is not performing its waste-filtering role well. Kawai says that before the transplant, Slayman’s creatinine level was 10 milligrams per decilitre, but it had gone down to 2.4 by the fourth day after the surgery. “It seems like so far this kidney is functioning the way that it is supposed to,” Mohiuddin says.

Slayman is receiving immunosuppressive medications, and has so far shown no signs of organ rejection. As of 25 March, he remained in hospital for observation. Qin says that eGenesis’s goal is to find a combination of genetic edits in pigs that make it unnecessary for organ recipients to take immunosuppressive drugs, which weaken the body’s ability to fight off pathogens.

“There was always a saying that xenotransplantation is around the corner, and will always be,” Qin says. “Well, now we have someone among us that carries a porcine kidney – it’s just amazing.”

1. Anand, R. P. *et al. Nature* **622**, 393–401 (2023).
2. van der Laan, L. J. W. *et al. Nature* **407**, 90–94 (2000).
3. Mohiuddin, M. M. *et al. Lancet* **402**, 397–410 (2023).

# NEW OBSERVATORY WILL MAKE DETAILED MAP OF BIG BANG’S AFTERGLOW

## The Simons Observatory will search for signs of gravitational waves that originated from the Big Bang.

By Davide Castelvecchi

**C**osmologists are preparing to cast their sharpest-ever eyes on the early Universe. From an altitude of 5,300 metres on Cerro Toco, in Chile’s Atacama Desert, the Simons Observatory will map the cosmic microwave background (CMB) – sometimes called the afterglow of the Big Bang – with a sensitivity up to ten times greater than that of the previous gold standard, Europe’s Planck space probe.

“It will be the best view of the CMB that we’ve ever had,” says Jo Dunkley, a cosmologist at Princeton University in New Jersey and one of the leading researchers in the observatory’s team. Construction of the US\$109.5-million

observatory is due to be completed in a matter of weeks.

One of the project’s goals is to find fingerprints left in the CMB by gravitational waves that originated from the Big Bang itself. These would provide the first incontrovertible evidence for cosmic inflation, a brief moment in which expansion is thought to have proceeded at an exponential rate. During that time, quantum fluctuations on a microscopic scale are thought to have seeded the Universe with what became its large-scale structure – including the current distribution of clusters of galaxies across space.

The scientific collaboration is led by five US universities and the Lawrence Berkeley National Laboratory in Berkeley, California.