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Scientists, using new method, coax bioengineered lungs to survive for prolonged period in pigs

By Justin Chen

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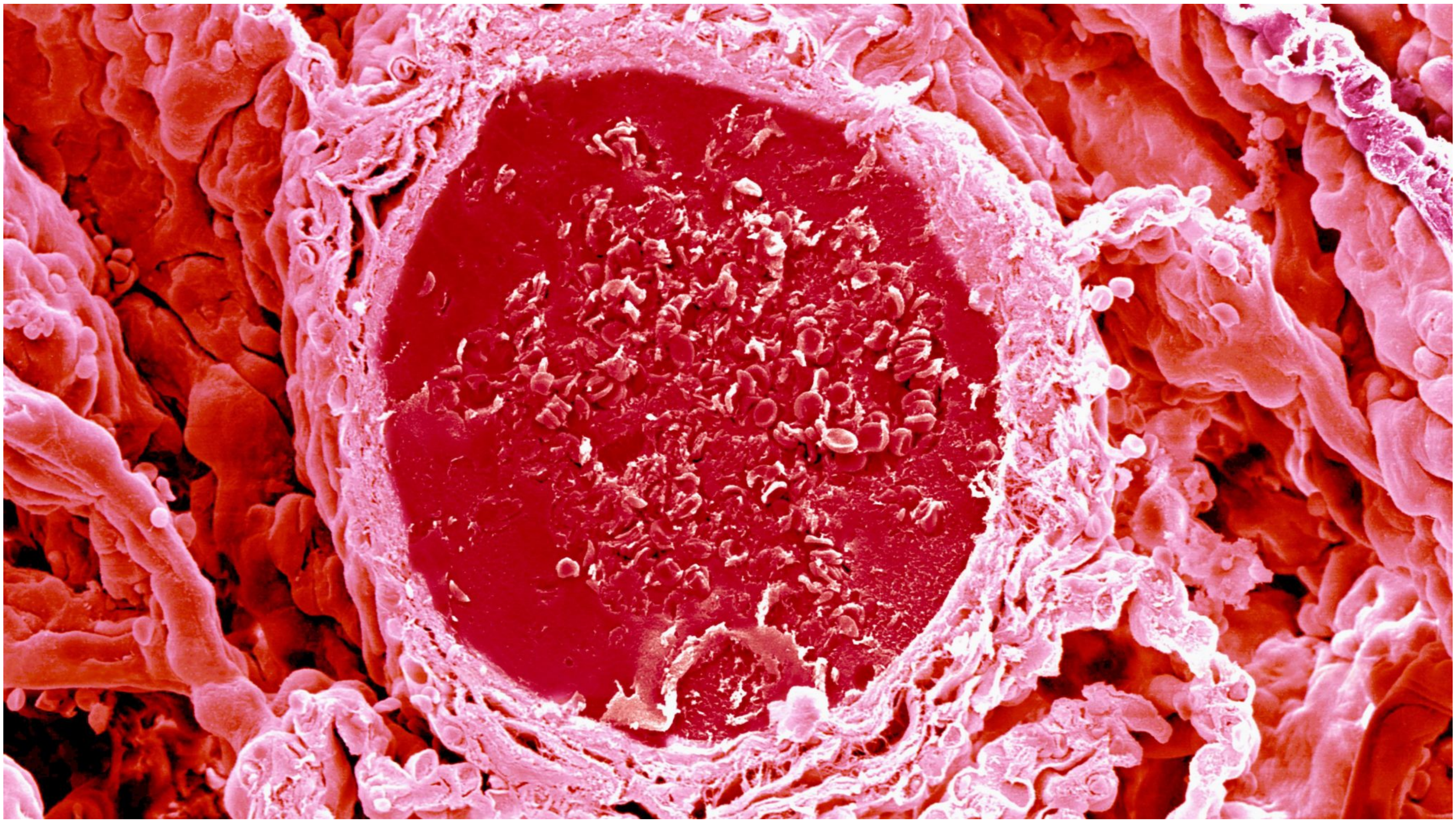

Scanning electron micrograph of a blood vessel in the lung, surrounded by alveoli. *David Gregory & Debbie Marshall via Wellcome Collection*

After 30 days of nourishment, the bioengineered lung — transformed from a white gauze-like material into a pale lobe of bloodless flesh — was ready for transplantation. It was carefully inserted into the patient, an 80-pound Yorkshire pig, and then the scientists waited. Together, the pig and the lung would survive for two months.

That a lab-made lung could be placed inside a pig is perhaps unremarkable given what's now possible in the fast-moving field of "designer pigs[1]." But that the lung survived as long as it did, and was grown using a new and possibly improved method, was significant, scientists say.

"You could argue that this is the first example of an engineered solid organ that's been implanted into a large animal and shown any evidence of any function," said Laura Niklason, a professor of anesthesia and biomedical engineering at Yale University who was not involved with the study. “It is definitely a step forward.”

The life of the pig and its lung was published Wednesday in Science Translational Medicine. The organ did not exchange oxygen like normal lungs. But in the study[2], researchers demonstrated they could grow lungs that better recreate the intricate system of blood vessels than their bioengineered predecessors — a technical hurdle that has vexed scientists for years. Previous attempts at implanting bioengineered lungs in small animals like rats ended after the organs clotted with blood or swelled with excess fluid.

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The research is a critical step in filling the demand for bioengineered lungs. Lung disease, which kills 400,000 Americans per year, is the third leading cause of death in the United States just behind heart disease and cancer.

“End-stage lung disease is a silent killer,” said Harald Ott, an associate professor of surgery at Harvard Medical School and a thoracic surgeon at Massachusetts General Hospital who was not involved with the study. “There are just not enough donor organs to go around … and patients are desperate.”

Engineering blood vessels is difficult, but growing them in lungs is especially challenging because of how the organ functions.

To facilitate breathing, lungs have a branching structure that ends in millions of microscopic, hollow cavities. These cavities, the site of gas exchange, are surrounded by blood vessels that, as Niklason said, are “tiny and delicate but also strong at the same time.” Their tiny and delicate nature ensures oxygen and carbon dioxide can pass in and out of the bloodstream; their strength ensures they can withstand pressure from the pumping heart without rupturing.

“There’s huge numbers of microvessels,” said Niklason. “Many, many millions and they are all operating at this very fine junction. Getting these to form is one of the big challenges.”

While engineering lungs, researchers in the study improved upon an existing technique that involves growing cells on top of a biological scaffold. As with previous efforts, scientists created the scaffold by chemically treating a pig lung to remove all cells, leaving behind a latticework of structural proteins like cartilage and collagen. They then populated the scaffold with a diverse mix of cells required to form a lung and grew the nascent organs in bioreactors — specialized tanks filled with nutrients that mimic the temperature, oxygen levels, and even the flow and pressure of fluids found in the human or pig body.

We tried “replicating the exact nature of the milieu of the cells themselves when they are in the lung,” said Joaquin Cortiella, the senior author of the study and professor of anesthesiology at the University of Texas Medical Branch. “We wanted to produce something very similar to the real thing.”

To make their system even more lifelike than previous studies, researchers added a key step. Before furnishing the scaffold with cells, they coated the structure with growth factors — chemical signals that guide the development of blood vessels.

“Developing the vascular system before developing the rest of the lung tissue was critical for this project,” said Joan Nichols, lead author of the study and professor of internal medicine, microbiology, and immunology at the University of Texas Medical Branch. “When we did it the opposite way, we failed.”

After growing their bioengineered lungs in a bioreactor for 30 days, researches implanted the organs into four pigs. To understand how the lungs developed, scientists euthanized the pigs for analysis after 10 hours, two weeks, one month, and two months.

All the pigs that received a bioenigeered lung remained healthy. Because researchers had tagged engineered cells with green fluorescent molecules, they could watch how the animal’s circulatory system merged with that of the transplanted organ. Within two weeks the engineered lung had grown the network of blood vessels required for long-term survival.

“It was very much like what you would have in wound healing,” said Nichols. “You develop new blood vessels and tissues in the injured area and now it connects back to you and becomes part of you.”

According to Niklason, one limitation of the study is that during the implantation process researchers connected the bioengineered lung to the trachea but not to the heart via the pulmonary artery and vein. This decision spared the implanted lung from the heart's high-pressured blood flow, which may have ruptured its blood vessels, but also made it impossible to test how well the organ was functioning.

"This was an interesting demonstration," Niklason said. But because the bioengineered lung was only attached to minor blood arteries, it "wasn't in position to add oxygen into the bloodstream." Much of the pig's breathing was likely accomplished by its one remaining normal lung.

Nichols and Cortiella believe that transplants connecting bioengineered lungs to the heart are on the horizon.

"This pilot study has taught us so much about what we need to do to mature these vessels," said Nichols.

"What other factors we need to add in and what equipment we need to develop."

According to Nichols, making custom equipment is a critical part of the research. Her team's first bioreactor comprised a fish tank purchased at Petco, plumbing from Home Depot, and a pump ordered on eBay. It is now working with a company that specializes in bioreactors and pumps to construct a chamber that slowly increases pressure over time to match the pressure levels found in an animal or human. In this system, engineered blood vessels would mature and strengthen in preparation for the rush of blood when connected to the heart.

Based on their past and current rate of progres, Nichols and Cortiella believe that within the next decade bioengineered lungs could be implanted into human patients through a compassionate use policy, which allows doctors to treat seriously ill patients with unapproved medical interventions.

The first recipients may be children with a diaphragmatic hernia — an often deadly condition in which defects in the diaphragm during fetal development allow abdominal organs to move into the chest and block lungs from fully developing.

For doctors, bioengineered lungs cannot come soon enough.

"If you ever sit across a table from a patient in end-stage lung disease … you realize that we need to push our research forward," said Ott. "As a physician, the worst thing you can say is that you don't have a solution for a patient sitting in front of you."

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