Pig-to-human transplants take a leap toward reality

The use of transgenic pigs as a source of organs and tissues for patients in need could revolutionize medicine — but to achieve that goal, data from clinical trials and forthright assessment of the ethics of animal-to-human transplants will be critical.

The shortage of donated organs for transplantation is dire. In the United States alone, more than 100,000 people are on waiting lists for organ and tissue transplants, and 17 people die each day while waiting. Xenotransplantation — the process of transplanting organs or tissues between different species — with its promise of providing a virtually unlimited supply of organs, has been pursued for decades with little success. But over the past 6 months, a series of stunning reports has provided the first results showing the feasibility of transplanting organs from transgenic pigs into humans.

On 25 September of last year and then again on 22 November, Robert Montgomery of NYU Langone's Transplant Institute transplanted a pig kidney into a recently deceased recipient maintained on a ventilator. Over the course of the following few days, the transplanted kidneys survived immunological rejection and maintained their function, producing urine and clearing creatinine from the blood. A second team, led by Jayme Locke at the University of Alabama at Birmingham, reported similar results in another recently deceased recipient. Then, on 7 January of this year, Bartley Griffith and Muhammad M. Mohiuddin, of the University of Maryland Medical Center, transplanted a heart from a transgenic pig into a living person who had terminal heart failure and was too sick to qualify for a human heart transplant or a mechanical assist device. The heart was not initially rejected, and the patient was reported to be doing well after surgery but died 2 months later for unclear reasons.

These clinical studies, marking a watershed moment for the field of xenotransplantation, have been enabled by a series of technological breakthroughs. Researchers have zeroed in on a set of three pig genes, encoding enzymes that make sugars recognized as foreign antigens, that need to be deleted to avoid acute immunological rejection of the transplanted organ. Transgenic pigs have been engineered to express a set of approximately ten human genes with the goal of preventing long-term organ rejection and preserving organ function, including genes encoding molecules that block the complement arm of the immune response, dampen systemic inflammation and reduce the risk of coagulation. Strides have also been made in improving the immunosuppressive regimens given to transplant recipients. These advances have culminated in preclinical studies, using pig–to–nonhuman primate models, in which pig kidneys have been able to support life for more than 1 year, and pig hearts have been able to do so for more than 6 months.

A potential concern about the safety of xenotransplantation is the presence of a large number of porcine endogenous retroviruses in the pig genome. These retroviruses, known as 'PERVs', could theoretically jump into other tissues in the recipient and lead to tumorigenesis or immunodeficiency. Although transmission of PERVs has not been seen in people with diabetes given transplantation of pig pancreas cells, the safety risk of PERVs is still far from clear, and PERV-free pigs suitable for use in xenotransplantation have recently been generated by CRISPR technology.

The time is now ripe to put the safety and efficacy of xenotransplantation to the test in clinical trials, studying immune responses to the transplanted organ, the ability of the organ to function, and the survival and quality of life of recipients. Initially, transplantation of pig kidneys may be the most feasible, as in the case of organ failure or adverse events, the transplanted kidney can be removed and the patient can be given rescue therapy with dialysis.

Given the large number of people who are waiting for a donor organ, the question of equitable access to trial participation may be a thorny one. Should patients most likely to die before receiving a human organ have priority to enroll in a trial? What other types of eligibility criteria should be considered, such as the overall health of the patient or evidence of immunological reactivity against pig antigens?

Such trials will also need to take into account the risk of transmission of PERVs or other viruses, with long-term follow up to monitor the potential for transmission of infectious diseases. Indeed, the US Public Health Service has called for lifelong surveillance to assess the public health risk from zoonotic infectious disease following xenotransplantation.

Concerns about animal welfare also need to be taken into consideration. Although the use of transgenic pigs does not present the same types of ethical concerns that would arise from the creation of pig–human chimeras, which have also been proposed as a source of organs for xenotransplantation, large-scale farming of pigs under the strictly hygienic conditions required does raise novel ethical concerns. Ultimately, patients, healthcare workers and the overall public will need to support the concept of using pig organs as a life-saving intervention.

The recent groundbreaking clinical results showing the feasibility of transplanting transgenic pig organs into humans raise hopes that xenotransplantation can help solve the critical shortage of human donor organs. The challenge now is in taking the next steps for demonstrating efficacy and safety in clinical trials and making xenotransplantation an everyday reality for patients in need of transplants. ❐

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