COMMENTARY

The rapid development of gene-editing technology is making xenotransplantation increasingly common in clinical practice

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Xenotransplantation refers to the transplantation or infusion of living cells, tissues, organs, and body fluids of animal origin into human recipients. Xenotransplantation is driven by the extreme shortage of human organs for clinical transplantation. Currently, organ donation is not sufficient to meet the requirements of the number of patients who need organ transplantation, which is why xenotransplantation is an important means to redress the dearth of organs. According to WHO statistics, every year there are approximately 3.0 million patients with organ failure all over the world, and 600,000 of these patients need to be treated by organ transplantation; however, only 20,000 or more patients can be transplanted every year.[1] Even though organ transplantation is the only effective radical treatment for organ failure, nearly 80% of patients in need of a transplant die while waiting for an organ donor. Xenotransplantation does not depend on the number of donor livers, and this can benefit a large number of patients with end-stage organ failures and may completely replace organ transplantation in the future. Animal studies reveal that the survival time of liver xenotransplantation recipients is not as long as that of kidney and heart xenotransplantation, signifying an urgent clinical need for research. Compared with the kidney and the heart, the liver is

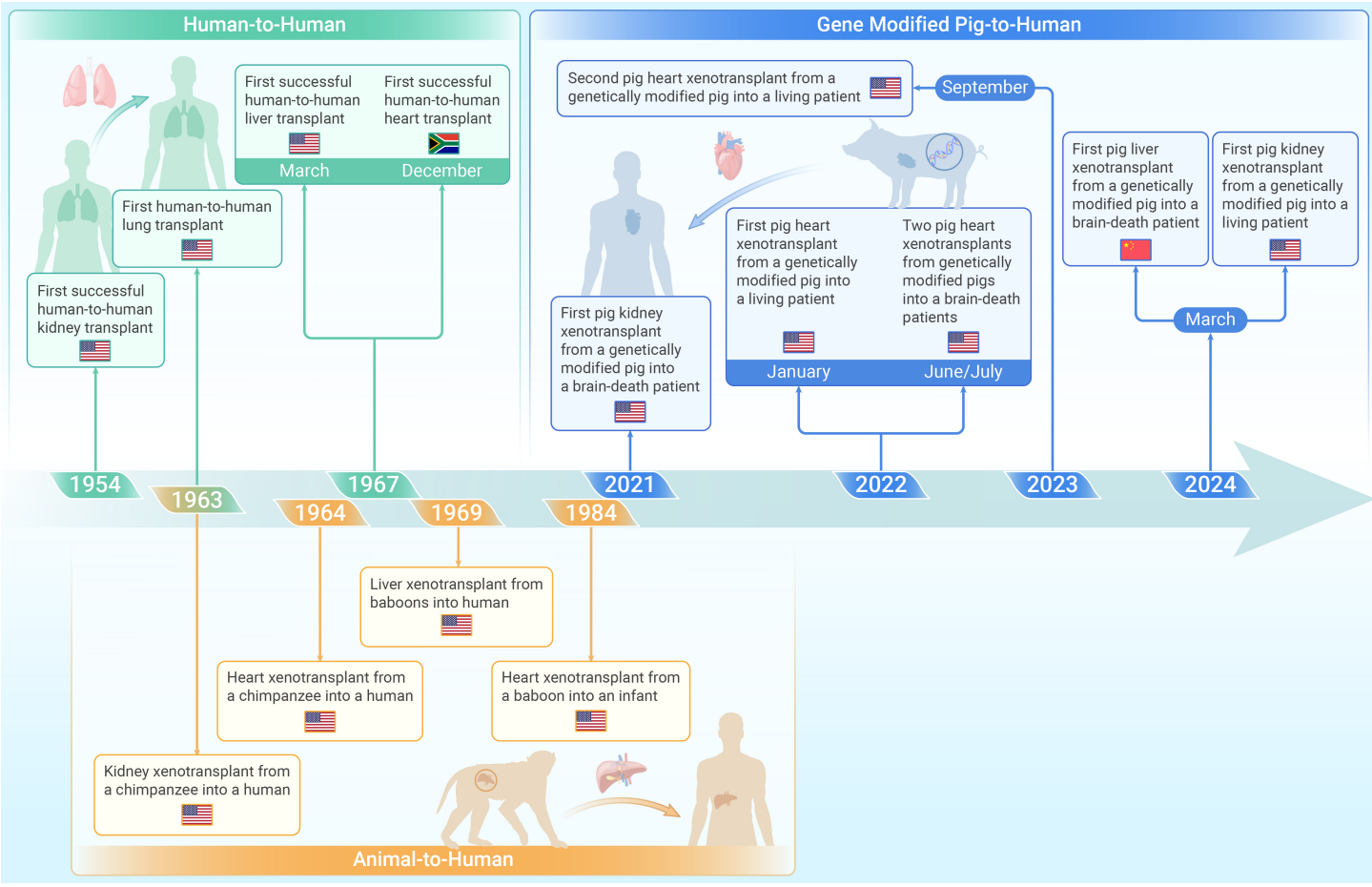

Figure 1. Brief history of the development of organ transplantation and xenotransplantation.

involved in the synthesis, decomposition, coagulation, detoxification, immunity, and other functions, while its anatomical structure and physiological function are more complex than those of the kidney and the heart. Therefore, the gene-edited pig liver cannot completely functionally replace the human liver, and the technical difficulty and scientific significance of xenotransplantation are greater than those of transplantation of human-donated organs. The popularization of liver xenotransplantation in clinical practice is a difficult scientific problem to which researchers in the field pay great attention. Liver transplantation is the only way to save life, especially when a patient has acute fulminant liver failure. Hence, at present, liver xenotransplantation is a temporary alternative treatment for liver transplantation, and it is also used to allow the function of the patient's liver to be restored with the help of the transplanted liver. As a result, liver xenotransplantation has great clinical application significance.

On March 10, 2024, Xijing Hospital successfully transplanted the whole liver of a multi-gene-edited pig into the body of a brain-dead patient in an auxiliary way. During the surgery, the graft produced bile immediately after blood flow was restored. There was no hyperacute rejection, and the graft had been working continuously for more than 96 hours. Twenty-four hours after the procedure, the recipient's hemodynamics were found to be stable, the bile secretion of the transplanted liver was good, ultrasound of the transplanted pig liver indicated good blood supply of the transplanted liver, and the biopsy of the graft showed no rejection reaction. Within 96 hours of the current observation, the transplanted gene-edited pig liver was able to perform physiological functions in the human body and secrete bile normally, indicating the practicability of replacing the human liver. The present study is the first to explore the feasibility of gene-edited pig-to-human liver xenotransplantation. In this connection, it was reported that on March 21, 2024, Massachusetts General Hospital in the United States had successfully transplanted a genetically modified pig kidney into a living human. To date, the patient's immune system has not appeared to reject the pig kidney, and the patient's blood pressure and vital signs have been stable. According to the medical director of the Kidney Transplant Program at Massachusetts General Hospital, the ultimate goal is to phase out dialysis and use it only as a temporary measure. Between 2021 and 2023, the basic and clinical research on xenotransplantation has made great progress (see Figure 1). Surgeons in the United States have successively performed four cases of kidney transplantation,[2] one case of heart transplantation,[3] and two cases of heart transplantation of gene-edited pigs and brain-dead recipients.[4]

Xenotransplantation with gene-edited pigs as donors has given researchers and medical practitioners a new hope to alleviate the shortage of transplanted organs. At present, the international research on liver xenotransplantation is limited to using animals such as baboons and macaques as transplant recipients, and the results of this have not been satisfactory. There are several reasons for this. First, monkeys and humans are very different, and there is still a serious rejection reaction. Second, similar to humans, monkeys are mainly singlets and have a long reproductive cycle, making it very difficult and expensive to use these animals for xenotransplantation. Third, the body of a monkey is smaller than that of a human, whereas the organ size of pigs is closer to that of humans. Finally, many people may have deeper feelings for primates, as a result of which experiments involving primates are an emotionally unacceptable thing. Hence, pigs are the preferred xenotransplantation donors.

Although gene-edited pig kidneys and hearts have been transplanted into humans, xenotransplantation still results in complex immune rejection and biosafety issues. Various types of genetically modified pigs are currently available, and most of these are being tested in preclinical pig-to-non-human-primate (NHP) xenograft models. There may be discoveries of new xenoreactive antigens, and gene editing technology may allow us to produce new types of genetically engineered pigs in a short period of time. Combining different transgenic pigs with different immunosuppressive therapies is indispensable for the effective transplantation of different organs. Consequently, determining the optimal genetically engineered pig and immunosuppressive regimen in the pig-NHP model is crucial for clinical studies. On January 7, 2022, attracting worldwide attention, the University of Maryland Medical Center announced that the world's first gene-edited pig heart was successfully transplanted into a 57-year-old male patient with end-stage heart disease. Xenotransplantation caught considerable public attention after the University of Maryland Cardiac Surgery had made history by performing the first pig-to-human heart transplant without early signs of rejection. Biosafety concerns refer to the risk of cross-species infection, such as bacterial infection, exogenous viral infection, and endogenous retroviral infection. Unpurified pigs may harbor pathogens that can infect humans, including Brucella and Mycobacterium tuberculosis. Furthermore, other pig-borne pathogens such as influenza virus, porcine lymph herpesvirus, and porcine endogenous retrovirus may be transmitted from pigs to humans. To avoid the risk of bacterial infection and exogenous viral infection in transplanted organs, specific pathogen-free (SPF) pigs can be bred through a barrier environment, in combination with a cesarean section. It is generally believed that porcine endogenous retrovirus (PERV) is integrated into the porcine genome and has multiple copies. The copy number, which varies greatly among different breeds and individuals, can be divided into three subtypes—PERV-A, B, and C. Most of these subtypes are defective, and only a few are complete. The consensus of clinical research is that the donor pig should have no PERV-C subtype. In 2017, Yang et al.[5] used CRISPR/cas9 technology to knock out PERV-related genes and eliminate the risk of endogenous virus infection in pigs. Nevertheless, it is important to further investigate the necessity of PERV knockout and its infectivity in humans. In several reported clinical studies of pig-to-human kidney and heart transplantation, none of the donor pigs underwent PERV knockout, nor was there evidence of PERV infection in postoperative monitoring results. Another issue of importance is the cost of gene editing, which should be factored in if xenografts are used by patients in the future.

Given the progress of clinical xenotransplantation studies, safety and ethical considerations have become the focus of research, and strict ethical regulations are needed. Regulatory challenges and ethical issues regarding clinical xenotransplantation are being discussed worldwide. As early as 2003, the US Food and Drug Administration (FDA) issued guidelines for xenotransplantation, and to better regulate and safely conduct clinical trials for xenotransplantation, the FDA updated the guidelines and regulations for xenotransplantation in 2016. Nevertheless, the approval process for xenotransplantation, the preparation of gene-edited pigs, and some basic work have not reached a high level of clinical research. The main difficulty of xenotransplantation lies in overcoming rejection and biosafety issues. Organ transplantation has stronger immune rejection than cell transplantation, and the mechanism of rejection is also complex, a fact that necessitates further research.

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DECLARATION OF INTERESTS

The authors declare no competing interests.