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Developing pig-to-human organ transplants:

Recent advances raise hope for a promising solution to the transplant organ shortage

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Over 100,000 people in the US are currently waiting for organ transplants. Because the human organ donor pool cannot keep pace with this demand, many patients die without receiving the life-saving transplant they need. Pigs are similar to humans in organ size and physiology, so the transplantation of pig organs to humans offers a potential solution to this problem and raises the prospect of scheduled, elective transplantation of quality-controlled organs, even for patients who would not currently meet the criteria for allocation of a scarce human organ. Although other technologies, such as tissue engineering, may eventually offer alternative solutions to this shortage, there is currently no substitute for transplantation of a fully formed, functioning organ. Several developments in the past year, most notably the first pig-to-human transplants, bring this promising solution closer to fruition, but challenges remain.

Transplants from one species to another are called xenotransplants. Because nonhuman primates (NHPs) are closest to humans phylogenetically, early human xenotransplantation efforts used NHP organs. However, graft survivals were short, and the use of NHPs for xenotransplantation was later deemed to be unsafe owing to potential virus transmission, impractical because of limited animal availability, and more ethically challenging than the use of pigs, which consequently became the xenograft source animal of choice. However, transplantation of pig organs into NHPs resulted in rapid “hyperacute” rejection (HAR) owing to the binding of pre-existing “natural” antibodies (NAbs) in the NHP to targets on endothelial cells lining the transplant organ’s blood vessels. Activation of complement and coagulation cascades then resulted in ischemic organ death within minutes to hours.

NAbs exist in the absence of any known exposure to pig tissues owing to cross-reaction with antigens that are shared by common microbes. During the 1990s, pigs transgenically expressing human complement regulatory proteins were developed, and it was discovered that most human and NHP anti-pig NAbs recognize a single carbohydrate, α-galactose-1,3-galactose (Gal) (1), making it possible to remove these antibodies by adsorption. These advances extended the survival of pig organs to days or weeks in NHPs. Enthusiasm for xenotransplantation was nevertheless dampened by the identification of porcine endogenous retroviruses (PERVs) and concerns about the possibility that new viral illnesses might arise in humans as a result.

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With the advent of nuclear transfer–based methods for cloning large animals, in the 2000s pigs were produced that were deficient in the enzyme that produces Gal. Survival of pig-to-NHP xenografts was further prolonged, with some organs lasting months. Further advances have since improved immunosuppression of the recipient, and CRISPR-mediated editing has enabled additional genetic modification of pigs. Successful immunosuppression usually includes depletion of recipient T and B lymphocytes followed by post-transplant treatment with the anti-metabolite mycophenolate mofetil and anti-inflammatory agents. Moreover, blockade of the CD40-CD154 pathway involved in B cell and antigen-presenting cell activation by T cells is an important component. Recently, several other carbohydrate moieties have been identified as targets of anti-pig non-Gal NAbs (2, 3), and genes encoding the enzymes responsible for producing them have been deleted in pigs. Other genetic modifications to avoid rejection have included human transgenes to express complement regulatory proteins, modulators of coagulation, the macrophage-inhibitory protein CD47, and anti-inflammatory molecules. Although the need for each individual modification has not yet been demonstrated, survival of pig kidneys beyond 1 year has been achieved in NHPs. Ablating the gene encoding growth hormone receptor to prevent growth of pig hearts when in recipients has also been used to produce life-supporting pig heart grafts that survived for 9 months in NHPs (4).

Many of the organs transplanted to NHPs have shown evidence for rejection despite ongoing immunosuppressive medication. This suggests that inducing tolerance, which involves reeducating the immune system to regard the donor as “self,” could be advantageous. Approaches to achieve immune tolerance include induction of “mixed chimerism,” in which bone marrow–derived cells from the pig are transplanted into the recipient. This promoted tolerance among human T cells, B cells, and natural killer (NK) cells in humanized mouse models. Thymic transplantation, in which recipient T cells are educated in a pig thymus, also tolerizes T cells in NHPs and humanized mice (5–7).

Adding to this progress, guidelines have been developed to mitigate the risk of pathogen transmission from pigs to humans. Notably, PERV infection has not been detected in any pig-to-human or pig-to-NHP transplant recipient, although PERVs may have lower affinity for NHP forms of its receptor than of the human receptor. PERV loci have also been suppressed or deleted from some pigs, further improving safety. Consequently, there is broader acceptance of the likely safety of pig-to-human xenotransplantation with appropriate animal husbandry and microbial surveillance of the source animals, recipients, and their close contacts.

These encouraging developments have set the stage to proceed with clinical xenotransplantation. Although NHPs provide an outstanding transplantation model, they present some limitations. For example, one of the carbohydrate targets of human anti-pig NAbs, *N*-glycolylneuraminic acid (NeuGc), is also expressed by NHPs, which therefore do not produce NAbs against it. Indeed, deleting NeuGc in pigs increases NHP NAb binding to the xenograft (8) and rejection (4). The NHP model therefore cannot predict the impact of this modification for pig-to-human transplantation.

The first trials of pig-to-human organ xenotransplantation took place in 2021. Groups at New York University (NYU) and the University of Alabama at Birmingham (UAB) connected pig kidneys to the circulation of brain-dead human recipients. The NYU group circulated the blood of two decedents through a Gal-deleted pig kidney that was maintained outside of their bodies for 54 hours (9), whereas the UAB group transplanted pig kidneys with multiple genetic modifications to a nephrectomized decedent for 74 hours (10). Antibody-mediated rejection (AMR), coagulopathy, and clinical markers of a hyperactive immune response were not observed in any of the recipients, and there was no evidence of PERV transmission. In the two NYU cases, but not the UAB decedent, the pig kidneys were shown to function. Their short duration greatly limited the information obtained from these studies, and more could be learned from expanded studies with longer duration in more decedents. For example, the incidence of early AMR in recipients with different antibody levels against source pig organs with different genetic modifications might be identified, establishing standards for acceptable baseline anti-donor antibody levels in humans. However, these types of studies are extremely challenging, requiring careful attention to both the technical and ethical considerations involved in delaying the termination of life support.

In January 2022, surgeons at the University of Maryland transplanted a pig heart into a man with terminal heart failure who was dependent on life support and was not a candidate for a human heart transplant. The heart, which was from a pig with 10 genetic modifications (a “10-GE” pig), did not undergo rapid rejection and supported the patient’s life for 7 weeks. Considering that pig hearts have sustained the lives of NHPs for much longer periods, this duration of support of a human life is perhaps not surprising from a scientific viewpoint, but it nevertheless represents a milestone in clinical xenotransplantation. The patient was returned to life support after 49 days and the precise cause of the heart’s eventual failure remains to be determined. If porcine-specific cytomegalovirus (CMV) is found to have contributed to graft loss (11), this cause should be avoidable in the future with the development of more sensitive screening assays for effective elimination of CMV from the source pigs. It is encouraging that a pig heart has now been shown to be capable of sustaining human life.

Contemplation of clinical xenotransplantation trials highlights the many questions and hurdles that remain. The optimal or even necessary genetic modifications of source pigs have not been determined. Some of the gene modifications in the 10-GE pig may be superfluous or even deleterious. Although inhibition of coagulation by expressing transgenic human thrombomodulin and other molecules in the transplant organ may delay graft loss due to AMR, such modifications may not be needed when AMR is prevented by selection of source animals and recipients or by tolerance induction. One transgene, human *CD47*, has been shown to mitigate macrophage-mediated clearance of porcine hematopoietic cells when mixed chimerism is attempted for tolerance induction in NHPs (6), but its utility in solid organ xenografts has not been demonstrated. Indeed, widespread human CD47 expression in pig kidneys may initiate systemic inflammation in NHP recipients (12). Further investment in NHP studies will therefore be critical, even as clinical trials in humans begin, to optimize future xenotransplantation outcomes.

Other questions surround the optimal patient populations for initiation of xenotransplantation trials. Patients unlikely to receive allografts because of presensitization, very young age, or other factors, though having a short life expectancy, have been suggested for initial cardiac and renal xenotransplantation trials (13). Identifying and meeting regulatory requirements will be facilitated by collaboration of regulators with scientists, professional organizations, and industry. The development of appropriately biosecure facilities and the ability to maintain pigs free of known and potential pathogens are critical. Pig-to-NHP xenotransplantation studies have revealed that source animals must be free of latent infections such as porcine CMV, which can reactivate and trigger graft loss when placed in a NHP, which, unlike the pig, has not previously been exposed to or immunized against porcine CMV (14, 15).

Many questions remain before xenotransplantation can be optimized in humans, but this should not prevent preliminary clinical studies from proceeding. If the quality and safety of the source animals can be assured, existing NHP studies with orthotopic heart and life-sustaining kidney transplantation are sufficient to justify such transplants. The courage of the trial volunteers and altruism of the families of decedent study subjects will allow generation of knowledge that improves future efforts. Concurrent with the initiation of clinical studies, there must be continuous attention to safety concerns for these patients and infectious risks to the community, along with vigorous pursuit of the preclinical studies that will further improve this enormously promising therapy (see the table). These commitments to xenotransplantation now will ultimately pay off in incalculable dividends for human health in the future.

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Advancing organ xenotransplantation

Source pigs for organ xenotransplantation are genetically modified to remove the immunogenic carbohydrate a-galactose-1,3-galactose (Gal), to avoid rejection. They can be further modified to eliminate other carbohydrates, growth hormone receptor, and porcine endogenous retroviruses. Additionally, human transgenes can be expressed to suppress rejection, including genes encoding complement and coagulation regulatory proteins, regulators of inflammation, and immunosuppressive molecules. Xenotransplantation can then be studied in nonhuman primates and humans to understand the factors that allow successful engraftment.

SYSTEM	INFORMATION TO BE GAINED	LIMITATIONS AND BARRIERS
Nonhuman primates	• Effects of genetic modification • Effective immunosuppression • Tolerance induction	• Need sequential modifications • Differences between nonhuman primates and humans • Reagent availability is limited for nonhuman primate studies • Ethics • Cost
Decedents	• Effects of genetic modifications and acceptable natural antibody levels for short-term survival with each type of pig • Early immune responses • Effective immunosuppression in the short term	• Ethics • Burden on families • Biosafety must be assured: Effective animal husbandry, surveillance, and recipient monitoring are required • Cost
Clinical trials	• Patient populations who can benefit • Human immune response over the life of the xenograft • Effective immunosuppression in the short and longer term	• Risk to recipient • Cost • Ethics and consent issues • Regulatory hurdles • Biosafety must be assured: Effective animal husbandry, surveillance, and recipient monitoring are required