WHITE PAPER

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Organ Transplantation: 300 Years in the Making

Has the Time for Xenotransplantation Finally Arrived?

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On average, ten patients die every day waiting for an organ transplant, and with no prospect of a change in the availability of organ donors, this has been a problem with no obvious solution. The prospect of a new source of organs, not dependent on human donations, is, therefore, an intriguing possibility. Xenotransplantation, a process of using organs or tissues from another species, has recently come into focus as a potential solution to the problem. The idea of xenotransplantation dates back over 300 years, but it is only recently that advances in genetics and a better understanding of the immune system have at least cracked the door on the potential of animal-to-human transplants, with the focus on genetically engineered pigs. Currently, FDA can allow clinical use of pig organs handled on a case-by-case basis, but the agency is exploring whether to allow broader clinical trials. Despite the promise of this exciting new technology, Marwood's analysis suggests that xenotransplantation is still many years away from becoming a viable alternative for patients. In this paper, we explore the feasibility, potential problems, risks, and ethical concerns that come with this procedure.

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I. Introduction

More than 106,000 people are currently on the national organ waiting list, with thousands dying each year waiting to receive a necessary organ, either directly due to organ failure, or indirectly due to the profoundly negative health impacts associated with organ failure. For example, the life expectancy of an individual on dialysis is five to ten years. As a result of the chronic organ shortage, some scientists and doctors have shifted their focus to the feasibility of using organs and cells from animals instead of humans. If xenotransplantation becomes normalized in modern medicine, there could be an almost unlimited supply of non-human organs. As a result, the shortage of human organs could be greatly alleviated, and patient lives significantly extended.

While numerous species could potentially serve as potential organ donors, the general consensus is that pigs are the most viable potential source for organ transplants. Pigs are preferred because they mature quickly, produce large litters, and have organs that are comparable in size and function to those of humans in both infancy and adulthood. Additionally, pigs can be bred in controlled environments with high health standards.

Advances in genetic engineering have also allowed for the development of transgenic pigs that are immunologically much closer to humans. In comparison, monkeys and baboons, while evolutionarily closer to humans, are not domesticated, do not thrive in controlled environments, mature slowly, and have organs that are too small for human use.

II. Technology of Xenotransplants

"Xenotransplantation is the future, and always will be". This quote, attributed to Dr. Norman Shumway of Stanford University, the first surgeon to perform an adult human heart transplant, is often referenced by surgeons and researchers today. However, many are beginning to overcome their skepticism, as the feasibility of xenotransplantation comes closer to reality.

CRISPR-Cas9 has enabled researchers to manipulate the pig genome to enable a better match to human donors, and to help reduce the risk of zoonotic diseases (viruses that are transferred between humans and animals). There are a very large number of genetic manipulations that are being studied, but it is unclear which modifications are critical for success at this point. Other technologies may also have the potential to play a role.

Criteria	Pigs	Baboons
Availability	Almost unlimited	Limited
Breeding Potential	Good	Poor
Period to Reproductive Maturity	4-8 months	3-5 years
Number of Offspring	5-12	1-2
Growth	Rapid	Slow
Size of Adult Organs	Adequate	Inadequate
Immune System Relationship	Distant	Close
Experience with Genetic Engineering	Considerable	None
Risk of Transfer Infection	Low	High
Public Opinion	More in Favor	Mixed

Table adapted from NCBI

One significant cause of hyperacute rejection stems from the reaction to αGal, a carbohydrate found on proteins and lipids in most mammals, including pigs, but not humans. Inactivation of α1,3 galactosyltransferase (GGTA1) the enzyme that catalyzes the synthesis of αGal eliminates this hyperacute rejection response. Delayed graft rejection linked to minor pig antigens can also be eliminated by gene editing techniques. While gene editing techniques have proven to be a game changer in allowing multiple gene manipulations, there are some risks, including the potential for off-target effects. These off-target effects could lead to unintended genetic modifications to the donor animal, and potentially the donor organ.

The addition of human genetic sequences is a complementary approach to genetic deletions. The addition of human sequences for CD55, CD46, and CD59 to the pig genome are approaches that have been used to help "cloak" the pig organ from the human immune system. The addition of human thrombomodulin or human endothelial protein C receptor has also been employed to lower the potential for coagulation reactions that can occur in xenotransplantation.

Porcine endogenous retroviruses (PERV) are a significant concern. PERVs are retroviruses that can recombine with the pig genome and could potentially replicate in the human host. These viruses are similar to other mammalian viruses associated with leukemia, such as feline leukemia virus (FeLV), and Koala retrovirus (KoRV), CRISPR-Cas9 can potentially be used to inactivate these sequences in the donor pig.

Other viruses of concern include porcine circoviruses (PCV), porcine cytomegalovirus (PCMV) and porcine lymphotropic herpesviruses. Raising animals in pathogen free environments and thorough screening for infectious agents of interest can decrease the risk of zoonotic disease. However, one fear is that there may be porcine viruses that have yet to be identified, and therefore cannot be readily screened.

On the host side, immunosuppressive drug regimens will be required. It is unclear whether these may be simply standard drug regimens that are used today in human-to-human transplants or if modifications may be helpful for xenotransplants.

III. Early Clinical Tests

The University of Alabama School of Medicine was able to successfully transplant a genetically modified, clinical-grade pig kidney into a brain-dead individual. The individual had two genetically modified pig kidneys transplanted into his abdomen after the original kidneys were removed. The organs used in this xenotransplantation were from a genetically modified pig at a pathogen-free facility. The pig had been genetically modified with a 10 key gene edits, intended to make the pig kidneys more suitable for xenotransplantation. The transplanted kidneys produced urine, filtered blood, and were not immediately rejected by the individual. Seventy-seven hours after the transplant, the kidneys remained viable, although it is unclear if they were fully functional (the xenotransplants did not process creatine, which is a normal renal function).

The University of Alabama School of Medicine has been discussing the next steps for xenotransplants. However, two major approvals are required. Primarily, FDA's biologics division (CBER) must approve an Investigational New Drug Application (IND) to administer the biological product (genetically modified pig kidneys) to humans. Secondarily, the University of Alabama's School of Medicine

Institutional Review Board for Human Use must review and approve the proposed clinical trial before the start of Phase I to ensure that the transplant is safe in living humans. Progression of this procedure depends on approvals, success in future studies, and progression within clinical trials.

In January 2022, the first pig-to-human heart transplant was performed at the University of Maryland School of Medicine. A genetically modified pig heart was successfully transplanted into a 57-year-old man who was in the end stages of heart disease. The patient was able to move freely without cardiopulmonary bypass assistance. However, the patient died in March 2022, two months after receiving the genetically modified pig heart provided by Revivicor, a regenerative medicine company based in Blacksburg, VA. Ten genetic modifications were performed on the pig: four genes were inactivated, including one that encodes a molecule that causes an aggressive rejection response. Six human genes were inserted into the genome of the pig, allowing the pig's organs to be better tolerated by the human immune system. Although the patient died, this surgery represents a major advancement reinforcing encouraging pre-clinical results and suggests that pig hearts could at least provide an effective bridge to an allotransplant.

IV. Regulatory Outlook

FDA has expressed support for xenotransplantation clinical trials. However, it is unclear when these will begin. Dr. Robert Montgomery, who successfully performed two pig-to-human kidney transplants, believes the clinical trials could begin within three years. Doctors are still viewing the results of recent xenotransplants with cautious optimism. There are many questions left to be answered before a Phase I clinical trial can begin. For example, what specific genetic modifications are most effective in making pig organs viable in humans, and which accompanying interventions will help human immune systems accept such organs.

The FDA published guidelines for xenotransplants in 1999. These guidelines include long-term monitoring of recipients and establishment of a registry to archive patient records and donor samples. The Department of Health and Human Services (HHS), FDA, the Centers for Disease Control and Prevention, and the National Institutes of Health have all been involved as stakeholders in the process. HHS established the Secretary's Advisory Committee on Xenotransplantation to review clinical protocols, conduct discussions, and make recommendations about the appropriate conditions for the use of animal organs. The FDA updated its guidance in 2003, and again in 2016.

In June of 2022, the FDA held a meeting on cellular, tissue, and gene therapies to discuss the future of xenotransplantation. Pertinent topics included infectious disease risks associated with xenotransplantation, strategies for meeting regulatory requirements for measuring identity, purity, and potency of xenotransplantation products, current strategies to control xenotransplant rejection by modification of donor animals, and characterization studies to ensure the

functionality of the pig organ before and after transplantation. Preclinical studies are valuable in order to gain insight into safety issues that cannot be evaluated in human recipients for ethical or practical reasons. Additionally, studies should include a robust number of animals and demonstrate consistent, stable, long-term, functional graft survival post-transplant.

Interest in xenotransplants is not limited to the United States, although currently the United States appears to have the most advanced regulatory approach. Countries like the United Kingdom and Spain are working independently to establish or revise guidelines regarding the regulation of xenotransplants. In 1998, the United Kingdom and Spain released their guidelines for xenotransplants. Before human clinical studies, Spain announced that pre-clinical studies must demonstrate a minimum of a six-month survival and function period of transplantation and the absence of infectious pathogen transmission. The guidelines in the United Kingdom were created by the U.K. Xenotransplantation Interim Regulatory Authority (UKXIRA), which regulates cross-species transplants. The U.K. Secretaries of State of Health review each application for the human trial and decide based on guidance from the UKXIRA. However, the UKXIRA was disbanded in 2007, leaving the UK regulatory regimen for xenotransplants in an uncertain state. In the European Union xenogeneic cell therapies are regulated as advanced cell therapy medicinal products (ATMP). The ATMP regulatory framework uses a regulation adopted in 2007, and there have been calls to update this approach to reflect recent scientific advances. Researchers in China hope to begin xenotransplantation studies in 2022, although there is currently no clear regulatory framework for such studies.

V. Problems, Risks, and Ethical Concerns

There are several problems, risks, and ethical concerns with xenotransplants. The use of xenotransplants can pose a risk to public health including the potential transmission of infectious agents that are pathogenic for humans but may not be pathogenic or even detectable in the source animal host, the transmission of infectious agents that may not normally be pathogenic in healthy humans but can be so in the immunocompromised or immunosuppressed individual, and recombination or reassortment of viruses, with nonpathogenic or endogenous human viruses, to form new pathogenic entities. Viruses that have jumped the species barrier include HIV, Ebola virus, and the family of SARS viruses, including COVID-19. Efforts to prevent this include housing pigs under strict barrier conditions and extensive screening for potentially pathogenic microorganisms. However, it should be noted that organs from pigs should be safer than an allograft taken from a brain-dead human donor (where there is rarely sufficient time to screen for all infectious agents).

Ethical concerns come from several fronts. Certain religions view pig flesh as unclean, raising the question of whether this applies to organ transplants. Rabbis have generally opined that since the pork is not eaten, there is no conflict, although it remains to be seen if all individuals would take the same view. In the Islamic world, use of pig organs may be permissible because there is medical necessity, and it is not uncommon to use heart valves from pigs in human heart surgery. Animal rights advocates, such as People for the Ethical Treatment of Animals have condemned xenotransplantation as unethical.

VI. Conclusion

A radical solution is needed in order to address the issue of organ shortages. Xenotransplants present a potentially viable approach. Many doctors are excited about the possibility of xenotransplants and will continue to work towards clinical trials. However, more research and clinical trials are necessary before xenotransplants become normalized within modern medicine. Based on current data and commentary from doctors, Marwood expects clinical trials to begin within the next few years. Although xenotransplants represent a breakthrough in modern medicine, there are problems, risks, and ethical concerns that must be noted. If clinical trials proceed in the next few years (as expected), xenotransplants have the potential to revolutionize modern medicine and save thousands of lives, but it may take a decade or more to achieve this goal.

ABOUT THE AUTHORS

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