Xenotransplantation Unveiled: Breakthroughs, Challenges, and Public Perceptions

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ABSTRACT

Xenotransplantation has recently made headlines in media reports showcasing the advancement and potential of this process. However, with this recognition comes questions, doubts, and disbelief. This commentary reviews recent scientific breakthroughs, including CRISPR–enabled genetic modifications and human–pig chimeric organ development, while also addressing immunological barriers, ethical concerns, and public perception. Although major challenges remain–such as immune rejection and societal acceptance–xenotransplantation offers a promising strategy to address the critical organ shortage and transform future healthcare.

RÉSUMÉ

La xénotransplantation a récemment fait la une des médias, qui ont mis en avant les progrès et le potentiel de ce procédé. Cependant, cette reconnaissance s'accompagne de questions, de doutes et d'incrédulité. Ce commentaire passe en revue les récentes avancées scientifiques, notamment les modifications génétiques rendues possibles par la technologie CRISPR et le développement d'organes chimériques humains-porcins, tout en abordant les obstacles immunologiques, les préoccupations éthiques et la perception du public. Bien que des défis majeurs subsistent, tels que le rejet immunitaire et l'acceptation sociale, la xénotransplantation offre une stratégie prometteuse pour remédier à la pénurie critique d'organes et transformer les soins de santé à l'avenir.

INTRODUCTION

Organ donation can be a sensitive topic for many people. Furthermore, the question "would you like to be an organ donor?" is asked at a time of life when most people are just learning to drive, and the thought of death is incomprehensibly too far in the future. Unfortunately, there is still a lack of organ donors throughout Canada. Fewer than a quarter of Canadians are currently registered as organ donors.[1] Ultimately, this shortage is influenced by various factors, including social norms, reluctance to discuss death, a lack of awareness, and delayed decision-making.[2] Due to the ongoing shortage, two options are currently being explored. One, is legislative changes, specifically, most Canadian provinces still use an opt-in model for organ donation, though some are exploring or adopting opt-out systems, with Nova Scotia leading the way.[3]

Second, is a procedure called xenotransplantation. While commonly associated with the transplantation of animal organs or tissues into humans, xenotransplantation broadly refers to the transplant of living cells, tissues, or organs from one species to a different species.[4] This technique is also vital in biomedical research, where human cells or tissues are transplanted into animal models to study diseases or develop therapies. In this commentary, we will primarily focus on the transplantation of animal organs, tissues, or cells into humans.

Another rapidly advancing field aimed at tackling the organ shortage is the *in vitro* creation or "organ in a dish" phenomenon, where scientists aim to grow human organs or complex tissues from stem cells in the laboratory. While highly promising for personalized medicine and reducing immune rejection, this approach currently faces significant hurdles. These include the challenge of scaling up miniature organoids to full, transplantable organ sizes, achieving functional maturity, and developing a comprehensive, integrated vascular system crucial for organ survival.

Given these formidable challenges in growing whole, functional human organs *in vitro*, xenotransplantation emerges as a potentially more immediate solution for addressing the critical organ shortage. As such, the importance of xenotransplantation and its impact on potentially solving the organ shortage crisis has fueled a resurgence of research. Specifically, a pivotal study published in September 2023 by Wang et al., titled 'Generation of a humanized mesonephros in pigs from induced pluripotent stem cells via embryo complementation', showed promising results for functional, laboratory-grown human kidneys in animals, bringing xenotransplantation one step closer to reality. However, there is still a gap in knowledge concerning public awareness of xenotransplantation and its implications, which this paper will address. This commentary will discuss important background information, further details on the breakthrough study, the benefits, and challenges of xenotransplantation as well as the public perception and acceptance.

BACKGROUND

Interestingly, the idea of xenotransplantation is not new and has been around for centuries. Xenotransplantation has historical roots dating back to the 17th century, beginning with Jean Baptiste Denis' sheep-to-human blood transfusion in 1667.[5] Then, almost 200 years later, by 1838, physicians were already experimenting with xenotransplantation, including a pig-to-human corneal transplant.[6] Since then, several more historical clinical xenotransplantations took place using a variety of animals such as rabbits, pigs, goats, monkeys, sheep, and chimpanzees.[7] Unfortunately, the outcomes were not promising as most patients died within several weeks.[7] Nowadays scientists commonly rely on pigs as the main contributors. Pigs are especially suitable for xenotransplantation due to their early reproductive maturity, short pregnancy durations, large litters, and organ sizes that closely match human anatomy which offer considerable advantages over other animals.[8] Yet, despite finding the most suitable animal to implement xenotransplantation, one of the strongest obstacles remains, the immune system's tendency to reject the transplanted organ.[9] The most powerful and rapid rejection is called a hyperacute rejection (HAR), which occurs when the recipient's existing antibodies immediately recognize and attack the foreign antigens in the xenograft.[10] These antibodies quickly attack the new organ, causing damage to its cells and blood vessels within just a few minutes or hours. Therefore, to address the immunogenicity problem, scientists have turned to precision gene editing via the clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9 system (CRISPR/CAS9). CRISPR/CAS9 has permitted scientists to remove (*knock out*) or add (*knock-in*) genes to ensure immunological compatibility. For example, in 2022, David Bennett Sr was the first person in the world to receive a genetically modified pig's heart. The pig was genetically modified by having three genes deleted, *GGTA1, CMAH* and *B4GALNT2* in addition to the knockout of the growth hormone receptor (GHR).11 Additionally, to

improve compatibility, scientists inserted six human genes —*CD55, CD47, h-TBM, CD-46, H0-1*, and *h-EPCR*—into the donor pig.[11] Unfortunately, David died just two months after the surgery. However, his survival for that length of time marked a remarkable breakthrough, demonstrating that a genetically modified pig heart could sustain human life beyond the immediate post-operative period. This case underscored both the promise of xenotransplantation and the urgent need for continued research that could one day save the lives of thousands of individuals currently in need of organ transplants.

XENOTRANSPLANTATION: A BREAKTHROUGH

On September 7th, 2023, Wang et al., published a pivotal study demonstrating the feasibility of generating early-stage humanized kidneys within pig embryos. Their method involved several key steps. First, they engineered induced pluripotent stem cells (iPSCs) derived from a cultured human cell line with enhanced survival traits by expressing *MYCN + BCL2*, resulting in a competitive stem cell line known as 4CL/N/B iPSCs. These cells were cultured in a specialized medium (4CL) to further support their pluripotency.[12] Next, they created pig embryos which were genetically modified to lack kidney-forming potential by knocking out the *SIX1* and *SALL1* genes, which are essential for mesonephric tubule development.[12] By injecting the human iPSCs into these nephric-null embryos, they aimed to create a developmental "niche" that human cells could occupy. These embryos were transferred into surrogate sows (female pigs) and allowed to develop for 25 or 28 days before analysis.[12]

The results showed that the successful integration of human cells into developing kidney structures was possible. However, despite the promise, several critical challenges remained. Notably, the efficiency of human cell contribution was limited—typically less than 5%—raising questions about the functional viability of the resulting organs.[12] In addition, the study reported high gestational loss rates, with a large proportion of the chimeric embryos failing to develop properly or degenerating early in gestation.[12] These findings suggest that the host environment may not fully support cross-species organogenesis at this stage of research.

Moreover, several translational hurdles persist. One major concern is vascular chimerism, where blood vessels within the developing organ may remain of porcine origin.[12] This is problematic because recipient immune systems are more likely to reject non-human vasculature, potentially triggering acute or chronic rejection even if the parenchymal (functional) tissue is human-derived. Another challenge is ensuring long-term functional maturation of these organs.[12] At just 25-28 days gestation, the chimeric kidneys were at a rudimentary stage, and there is currently no evidence that these organs can grow, mature, and function long-term *in vivo*.

Perhaps most controversially, a small number of human cells were found to contribute to neural cell lineages within the developing pig embryo, raising ethical concerns about off-target integration.[12] This also ties into the critical issue of germline exclusion – ensuring that human cells do not integrate into reproductive tissues and pass on human genetic material to animal offspring. Without strict germline control, the clinical translation of this technology will likely face insurmountable regulatory and ethical barriers.

In summary, while the Wang et al. Study marks a significant step forward in xenotransplantation, the technical and translational challenges – low efficiency, gestational instability, vascular incompatibility, incomplete maturation, and ethical safeguards – are far from incidental. They remain core barriers that must be overcome before human-animal chimeras can become a reliable source of transplantable organs.

ADDITIONAL CLINICAL PROGRESS IN ORGAN XENOTRANSPLANTATION

In 2022, Griffith et al. Reported the first successful porcine to human heart xenotransplantation in a 57-year-old patient with terminal heart disease. The genetically modified donor heart functioned for 49 days post-transplant, demonstrating partial immune compatibility and no signs of hyperacute rejection at autopsy, though the patient ultimately passed away due to cardiac dysfunction unrelated to clear graft failure.[13]

Meanwhile, kidney xenotransplantation continues to advance in both preclinical and human decedent models. Allison (2022) outlines promising developments using gene-edited pig kidneys in brain-dead human recipients. These kidneys produced urine and showed no signs of hyperacute or acute rejection during the short observation period.[14] This model provides an ethically viable platform for testing functional outcomes and refining immunosuppressive protocols before transitioning to living patients.

Because brain-dead individuals are legally deceased but maintained on life support with prior consent from families or guardians, this approach avoids exposing living patients to undue risk while still allowing clinically relevant data to be collected.

BENEFITS AND CHALLENGES

As research advances in the field of xenotransplantation, we must continue to consider both the benefits and challenges. First and foremost, a notable benefit would be the alleviation of organ shortages. Xenotransplantation could greatly expand the organ supply that will be available promptly for use. Secondly, if the field reaches clinical maturity, xenogenetic donor organs could be produced under standardized, pathogen-free conditions and procured electively, potentially improving the consistency and predictability of organ quality compared with variable deceased-donor organs. Ordinarily, assessing the quality of donor organs remains a significant challenge, as it can vary widely and is often unpredictable, thus, patients may receive organs which differ in quality.[15] Thirdly, xenotransplantation could help reduce issues of coercion within families and lessen the financial burdens often faced by living donors. Unfortunately, in cases when a family member becomes ill and needs an organ transplant, family members may coerce other members to give their organs. Additionally, nearly one in four kidney donors reported experiencing financial difficulties as a result of their donation.[16] Finally, it could provide societal economic savings. The kidney is one of the most donated organs, and for those awaiting a kidney transplant, the typical long-term treatment often involves dialysis. In Canada, this treatment costs the healthcare system an estimated "$56,000–$107,000 per patient per year".[17,18] A successful xenotransplantation could reduce the need for such ongoing treatments, leading to potentially astronomical savings that could be redirected to other areas of the healthcare system that are underfunded or struggling to meet demand.

However, despite all these benefits, there remain pertinent challenges (**Table 1**). Firstly, as mentioned above, the main concern associated with xenotransplantation is immunological rejection. If this barrier cannot be addressed, xenotransplantation is unlikely to transition from experimental research to practical medical application. While hyperacute rejection (HAR) occurs within minutes due to pre-formed antibodies targeting a-Gal, other forms of rejection, such as delayed xenograft rejection, involve natural killer (NK)

Table 1. Key challenges in xenotransplantation and current mitigation strategies

Domain	Challenge	Mitigation Strategy	Status (2025)
Immunological	Hyperacute rejection (a-Gal antibodies)	*GGTA1* knockout; expression of human *CD46/C55*	Demonstrated in pig-to-human trials
	Delayed rejection (non-Gal antigens, NK/macrophages)	*CMAH, B4GALNT2* knockouts; anti-*CD40* therapy	Preclinical primate models
	Chronic rejection	Long-term immunosuppression; anti-inflammatory gene edits	Under investigation
Microbiological	Risk of porcine endogenous retroviruses (PERVs)	PERV-inactivated donor pigs via CRISPR; designated pathogen-free herds	Early-stage implementation
Ethical	Neural/germline chimerism in organoid models	Targeted organ niches; germline exclusion protocols	ISSCR oversight required
	Animal welfare concerns	Use of high-welfare donor herds; justification under saving-human-lives model	Ongoing debate
Regulatory	Long-term recipient surveillance	Lifetime monitoring; 50-year tissue archiving (FDA draft guidance 2024)	Regulatory drafts in progress

cells, macrophages, and antibodies against non-Gal antigens like *Neu5Gc* and *SDa*. Recent studies such as Bryne et al., 2018 have highlighted *B4GALNT2*, the enzyme responsible for *SDa* antigen synthesis, as a key barrier, with its deletion significantly reducing human antibody binding.[19] Although genetic modifications have improved early outcomes in preclinical models, chronic rejection and long-term graft acceptance remain major hurdles. Secondly, there is a concern regarding microbiological risks, such as transmitting infectious agents from animal to human. Pigs carry endogenous retroviruses in their DNA, and some of these viruses have the potential to infect human cells, raising concerns about cross-species disease transmission.[20] This poses a threat to the safety of not only the patient but their family, friends, and society as a whole if transmission becomes uncontrolled. Thirdly, there is concern about the potential rise of xenotourism, where patients travel abroad to undergo xenotransplantation procedures not available in their home countries.[21] When people become desperate, which often results from terminal diseases, travelling thousands of miles to different countries becomes the only solution. However, xenotourism can bring extreme challenges for the Centers for Disease Control and Prevention (CDC) about containing outbreaks of viruses. Finally, the ethical concern about raising animals solely for the use of harvesting their organs for human use. Realistically, the idea is not so different than what we do now, raising animals for the sole purpose of eating. But, in this context, we raise animals to save a life. Certainly, the health and well-being of the animals must be considered, therefore, we should evaluate the most ethical practices that minimize harm for both parties.

ETHICAL AND REGULATORY CONSIDERATIONS

While ethical concerns such as animal welfare and neural chimerism have been noted, formal guidance is now shaping the boundaries of both research and clinical xenotransplantation. The International Society for Stem Cell Research (ISSCR) 2021 guidelines classify full gestation human-animal chimeras as a Category 2 activity, meaning they are permissible only under specialized oversight and ethics review, and they prohibit the breeding of chimeric animals with potential human germline integration.[22] These distinctions are crucial when considering research using embryonic chimeras versus clinical applications involving organ transplantation. On the regulatory front, the FDA's 2024 draft guidance on xenotransplantation emphasizes lifetime patient monitoring, 50-year biological specimen storage, and rigorous genomic screening of donor animals.[23] These evolving frameworks reflect the growing translational momentum in the field, while ensuring that ethical and biosafety risks are managed proactively and transparently.

PUBLIC PERCEPTION AND ACCEPTANCE

As xenotransplantation becomes more popular, opinions surrounding it will become more pronounced. These views vary depending on who you ask—healthcare professionals, patients, or the general public—and are shaped by multiple factors. For example, in a hospital-based survey, 67% of healthcare professionals expressed support for xenotransplantation, 7% opposed it, and 26% remained undecided, whereas the public responded even more favorably at 74%.[24] Another study looked at the general public and patients (who were awaiting organ transplants) and found that both groups showed greater willingness to accept xenogeneic cells and tissues than entire organs.[25] This gradient in acceptance may reflect concerns about identity, infection risk, or the perceived invasiveness of the procedure. Religious beliefs and cultural values can also shape responses, particularly when mixing human and animal cells is involved. Media coverage, especially in high-profile cases like the 2022 pig-heart transplant, can further influence perceptions by framing xenotransplantation as either a miracle or a moral dilemma. Therefore, much like other controversial therapies, public attitudes will depend not only on who you ask, but also on how the therapy is presented, perceived, and ethically framed. As research progresses, clear communication and transparency will be key to building long-term public trust.

CONCLUSION

Xenotransplantation is a unique topic that is drawing attraction to the scientific community at a rapid speed. With this, questions and apprehension are surely to follow. Therefore, the aim of this paper was to unravel what xenotransplantation is and to enhance public understanding of its potential and challenges. Through the discussion of recent breakthroughs, benefits versus challenges, and public perception, the idea of xenotransplantation is beginning to evolve from a thought of science fiction to reality. The challenges of immunological and societal rejection could one day be overcome and showcase the true life-saving benefits. Xenotransplantation exemplifies the essence of scientific progress: investigation, innovation, and information.

REFERENCES

1. Government of Canada [Internet]. / Gouvernement du Canada; 2023 [cited 2023 Sept 14]. Available from: https://www.canada.ca/en/health-canada/services/healthy-living/blood-organ-tissue-donation/organ-tissue.html
2. Cotrau P, Hodosan V, Vladu A, Daina C, Daina LG, Pantis C. Ethical, Socio-Cultural and Religious Issues in Organ Donation. Maedica (Bucur). 2019 Mar;14(1):12-14. Greek, Modern. doi: 10.26574/maedica.2019.14.1.12. PMID: 31123506; PMCID: PMC6511665.
3. Tennankore KK, Klarenbach S, Goldberg A. Perspectives on Opt-Out Versus Opt-In Legislation for Deceased Organ Donation: An Opinion Piece. Can J Kidney Health Dis. 2021 Jun 16;8:20543581211022151. doi: 10.1177/20543581211022151. PMID: 34188947; PMCID: PMC8212358.
4. Center for Biologics Evaluation and Research. Xenotransplantation [Internet]. FDA; [cited 2023 Sept 14]. Available from: https://www.fda.gov/vaccines-blood-biologics/xenotransplantation
5. Yoon CH, Choi HJ, Kim MK. Corneal xenotransplantation: Where are we standing? Prog Retin Eye Res. 2021 Jan;80:100876. doi: 10.1016/j.preteyeres.2020.100876. Epub 2020 Aug 2. PMID: 32755676; PMCID: PMC7396149.
6. Cooper DK. A brief history of cross-species organ transplantation. Proc (Bayl Univ Med Cent). 2012 Jan;25(1):49-57. doi: 10.1080/08998280.2012.11928783. PMID: 22275786; PMCID: PMC3246856.
7. Rodger D, Cooper DK. Kidney Xenotransplantation: Future clinical reality or science fiction? Nursing & Health Sciences. 2022;25(1):161–70. doi:10.1111/nhs.12994
8. Villiers CB de. Xenotransplantation: Gene editing animals for organ transplants to humans [Internet]. 2022 [cited 2023 Sept 14]. Available from: https://www.phgfoundation.org/briefing/xenotransplantation#:~:text=Pigs have become the most, offer advantages over other animals.
9. Carvalho-Oliveira M, Valdivia E, Blasczyk R, Figueiredo C. Immunogenetics of xenotransplantation. Int J Immunogenet. 2021 Apr;48(2):120-134. doi: 10.1111/iji.12526. Epub 2021 Jan 7. PMID: 33410582.
10. Vadori M, Cozzi E. Immunological challenges and therapies in xenotransplantation. Cold Spring Harb Perspect Med. 2014 Apr 1;4(4):a015578. doi: 10.1101/cshperspect.a015578. PMID: 24616201; PMCID: PMC3968789.
11. Bender M, Längin M, Reichart B, Mokelke M, Radan J, Neumann E, et al. Clinical cardiac xenotransplantation first in the clinical arena. Xenotransplantation. 2022 Jan;29(1):e12734. doi: 10.1111/xen.12734. Epub 2022 Feb 15. PMID: 35165939.
12. Wang J, Xie W, Li N, Li W, Zhang Z, Fan N, et al. Generation of a humanized mesonephros in pigs from induced pluripotent stem cells via embryo complementation. Cell Stem Cell. 2023 Sep 7;30(9):1235-1245.e6. doi: 10.1016/j.stem.2023.08.003. PMID: 37683604.
13. Griffith, B. P., Goerlich, C. E., Singh, A. K., Rothblatt, M., Lau, C. L., Shah, A., Lorber, M., Grazioli, A., Saharia, K. K., Hong, S. N., Joseph, S. M., Ayares, D., & Mohiuddin, M. M. (2022). Genetically modified porcine-to-human cardiac xenotransplantation. New England Journal of Medicine, 387(1), 35–44. https://doi.org/10.1056/nejmoa2201422
14. Allison, S. J. (2022). A model of pig-to-human kidney transplantation. Nature Reviews Nephrology, 18(4), 199–199. https://doi.org/10.1038/s41581-022-00550-7
15. Von Moos S, Akalin E, Mas V, Mueller TF. Assessment of Organ Quality in Kidney Transplantation by Molecular Analysis and Why It May Not Have Been Achieved, Yet. Front Immunol. 2020 May 12; 11:833. doi: 10.3389/fimmu.2020.00833. PMID: 32477343; PMCID: PMC7236771.
16. Schover, L. R., Streem, S. B., Boparai, N., Duriak, K., & Novick, A. C. (1997). The psychosocial impact of donating a kidney. The Journal of Urology, 1596–1600. https://doi.org/10.1097/00005392-199705000-00014
17. Organ transplant [Internet]. [cited 2023 Sept 14]. Available from:https://www.healthlinkbc.ca/health-topics/organ-transplant#:~:text=Organs most often transplanted include, failure, and other heart problems.
18. [Internet]. [cited 2023 Sept 14]. Available from: https://secure.cihi.ca/free_products/report-corr-high-risk-high-cost-en-web.pdf
19. Byrne, G., Ahmad-Villiers, S., Du, Z., & McGregor, C. (2018). B4galnt2 and Xenotransplantation: A newly appreciated xenogeneic antigen. Xenotransplantation, 25(5). https://doi.org/10.1111/xen.12394
20. Denner J. Porcine Endogenous Retroviruses and Xenotransplantation, 2021. Viruses. 2021 Oct 26;13(11):2156. doi: 10.3390/v13112156. PMID: 34834962; PMCID: PMC8625113.
21. Kwon I (Bok-K, Mo H. Xenotransplantation. Encyclopedia of Global Bioethics. 2015;1–14. doi:10.1007/978-3-319-05544-2_449-1
22. ISSCR (2021). Guidelines for Stem Cell Research and Clinical Translation. https://www.isscr.org/guidelines
23. FDA (2024). Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products. Draft Guidance
24. Ríos A, Conesa C, Ramírez P, Galindo PJ, Rodríguez MM, Martínez L, et al. Hospital personnel faced with organ xenotransplantation: an attitudinal survey in a hospital with a pre-clinical liver xenotransplantation program. Xenotransplantation. 2006 Sep;13(5):447- 54. doi: 10.1111/j.1399-3089.2006.00334.x. PMID: 16925669.
25. Persson MO, Persson NH, Ranstam J, Hermerén G. Xenotransplantation public perceptions: rather cells than organs. Xenotransplantation. 2003 Jan;10(1):72-9. doi: 10.1034/j.1399- 3089.2003.01132. x. PMID: 12535228.

Conflicts of Interest Disclosure

There are no conflicts of interest to declare