ISSN Print: 2664-7184
ISSN Online: 2664-7192
IJPPR 2024; 6(1): 43-46
www.pharmacologyjournals.com
Received: 08-12-2023
Accepted: 10-01-2024

Tamanna Sharmin Tonny
Assistant Professor,
Department of Pharmacy
Primeasia University, Dhaka,
Bangladesh

Joya Rani Mitra
Department of Pharmacy,
Primeasia University,
Dhaka, Bangladesh

Moitry Baroi
Department of Pharmacy,
Primeasia University,
Dhaka, Bangladesh

Taslima Begum
Associate Professor,
Department of Pharmacy
Primeasia University, Dhaka,
Bangladesh

Corresponding Author:
Tamanna Sharmin Tonny
Assistant Professor,
Department of Pharmacy
Primeasia University, Dhaka,
Bangladesh

A review on xenotransplantation: Recent updates and the prospective dimension

Tamanna Sharmin Tonny, Joya Rani Mitra, Moitry Baroi and Taslima Begum

DOI: https://dx.doi.org/10.33545/26647184.2024.v6.i1a.30

Abstract
The rise in human life expectancy has resulted in an escalating population of individuals afflicted with chronic illnesses and end-stage organ dysfunction. Transplantation is a very efficient method for treating end-stage organ failure. However, the disparity between the availability of organs and the need for human organs poses a significant obstacle to the successful implementation of transplantation in clinical settings. Hence, xenotransplantation holds potential as a viable alternative method to address the disparity between the availability and need for organs, tissues, and cells. Nevertheless, the clinical application of xenotransplantation is hindered by immunological obstacles. The viability of clinical xenotransplantation has been enhanced due to advancements in gene-editing technologies, immunosuppressive medication, and the extended survival period of xenografts in pig-to-non-human primate models. This review centres its attention on the progression and present state of xenotransplantation analysis.

Keywords: Xenotransplantation, heart transplant, kidney transplant, lung transplant

1. Introduction
Xenotransplantation is a medical operation that entails the transfer, placement, or continuous administration of either:
a) Live cells, tissues, or organs derived from sources other than human animals, and b) Human bodily fluids, cells, tissues, or organs that have been indirectly exposed to live cells, tissues, or organs of nonhuman animals [1].
The ideal treatment for people with irreversible kidney failure, often known as end-stage renal disease (ESRD), is the transplantation of a kidney from either a deceased or living donor.
The transplant community has implemented a comprehensive range of strategies to address the disparity between the availability and the need for transplants. Efforts are undertaken to allocate organs to patients who are expected to have the longest lifespan, as well as to those who present challenges in achieving tissue matching. The allocation of donated kidneys is also determined by the quality of the organs, indicating an implicit recognition that an increase in the supply is expected to arise from unconventional sources, such as donors who have passed away due to cardiac events or older donors with higher levels of comorbidity. Donor/receiver relationship criteria have become more lenient, resulting in a significant number of living kidney donors who are genetically unrelated to their recipient. A growing proportion, specifically 15% in the United States, of transplant procedures are performed on individuals who have required desensitization to their donor due to incompatibility with their ABO blood group or major histocompatibility complex (MHC), or have successfully circumvented this incompatibility through kidney paired donation. The existing mechanism that facilitates the retrieval of human kidneys for transplantation should be regarded as significantly insufficient. In light of this context, contemporary endeavors employing genetically engineered porcine kidneys (as well as other organs) are progressing towards human clinical trials [2].

2. History of Xenotransplantation

Keith Reemtsma conducted the initial endeavor in organ xenotransplantation throughout the 1960s [3]. In an effort to transplant a chimpanzee heart into a patient, James Hardy encountered a failure of the transplanted heart within a few hours [4]. In 1983, Leanord Bailey made a noteworthy endeavor by performing a heart transplantation procedure on a female infant girl, involving the transplantation of a baboon's heart. Although the surgical procedure was effective, the transplanted organ experienced xenograft rejection after a period of 20 days [5].

3. Potential uses

Xenotransplants have the potential to rescue numerous people who are currently awaiting donated organs. The animal organ, likely derived from a pig or baboon, has the potential to undergo genetic modification using human DNA, so deceiving the patient's immune system into recognising it as an integral component of their own body [6]. They have resurfaced due to the scarcity of available organs and the ongoing struggle to prevent immune systems from rejecting allotransplants. The utilisation of Xenotransplants presents a potentially more efficacious alternative [7-9]. The transplantation of human organs into animals has emerged as a potent research methodology for investigating human biology, while ensuring the well-being of human patients [10]. As an illustration, a group of researchers affiliated with the Ganogen Research Institute successfully transplanted human foetal kidneys into rats, so showcasing their ability to sustain life and facilitate growth [11].

4. Different Types of Xenotransplantation

4.1 Heart transplantation

Most research conducted on pig heart transplantation in non-human primates (NHPs) has been heterotopic. The maximum survival time for heterotopic cardiac xenografts was increased to 236 days [12]. Since the introduction of GTKO pigs in 2003, the use of GTKO pigs or donor pigs expressing one or more hCRPs has been effective in extending the survival time of xenografts [13]. The study conducted by Mohiuddin *et al*. in 2012 involved the transplantation of GTKO/hCD46 transgenic pig hearts into baboons that were subjected to immunosuppression using anti-CD154 monoclonal antibodies [14]. After receiving a genetically engineered pig heart last week in Baltimore, Maryland, the first recipient is doing well. New York University Langone Health physicians transplanted kidneys from genetically engineered pigs into two legally dead patients with no brain function in 2021. The organs were not rejected and functioned regularly while the deceased recipients were on ventilators. Pig supply and regulatory difficulties limit transplantation. The only business with clinical-grade pigs and proper facilities is Revivicor in Blacksburg, Virginia, owned by United Therapeutics. The business took away three pig genes that trigger human immune system attacks and introduced six human genes to help the body accept the transplanted pig heart [15].

4.2 Kidney transplantation

In 2015, GTKO/hCD55 pigs donated and rhesus macaques with T-cell deletion received anti-CD154 mAb maintenance therapy. Lower antipig antibody titers extended kidney xenograft survival to about 125 days [16]. Analysis of xenografted kidneys showed that antibody-mediated rejection and coagulation dysregulation still induce transplant failure [17].

4.3 Liver transplantation

The performance of pig liver xenotransplantation appears to provide greater challenges in comparison to heart and kidney xenotransplantation procedures [18]. Genetically modified pigs were used to transplant livers into baboons, resulting in an increased survival time of the liver graft for up to 9 days. The primary cause of the short lifespan of liver xenograft was primarily the occurrence of a fatal coagulopathy [19]. The initial documentation of pig liver orthotopic xenotransplantation to non-human primates (NHPs) can be traced back to 1968. During that period, limitations on immunosuppression and the use of wild type donor pigs led to a maximum survival rate of 3.5 days. Liver xenotransplantation has been performed using GTKO and GTKO/hCD46 pigs since 2010 [20-22].

4.4 Lung transplantation

The majority of studies on lung transplantation have utilised ex vivo pig lung xenoperfusion with human donor blood models. [23] However, it is important to note that this particular model is constrained to examining only short-term effects, often those that manifest within a 4-hour timeframe. [24] Watanabe *et al*. recently found that the NHP recipients of lungs from GTKO/CD47/CD55 transgenic pigs experienced a 14-day increase in survival time. The aforementioned research have provided evidence that the incorporation of hCD47 has the potential to alleviate early vascular rejection of lung xenografts and extend the survival duration of pig lung transplants in non-human primate (NHP) models. Nevertheless, the restricted duration of survival indicates the need for supplementary approaches in lung xenotransplantation [25, 26].

4.5 Porcine Endogenous Retroviruses in Xenotransplantation

The spread of swine infections to human recipients is a significant concern within the field of xenotransplantation. The utilisation of negative donor animals, breeding under sterile and isolated settings, early weaning, and embryo transfer can effectively eradicate the majority of porcine viruses, bacteria, and fungus [27, 28]. To far, there have been no documented instances of PERV transfer in preclinical pig-to-NHP models or in clinical cell transplantations to humans [29]. In 2015, Yang *et al*. employed CRISPR/Cas9 to deactivate the PERV-A and PERV-B genes in pig cells that were devoid of PERV-C. The genetically modified cells decreased the transfer of PERV to human cells in a laboratory setting [30]. The utilisation of pigs in xenotransplantation presents a novel approach that effectively mitigates the potential hazards associated with PERVs.

5. Ethics and regulations regarding xenotransplantation

A recent and continuing clinical experiment has been begun in Mexico City to investigate the use of pig islet and Sertoli cell xenoTx in diabetic patients. Due to the absence of explicit legislation, individuals have the freedom to travel to other countries where clinical xenoTx experiments are being conducted or planned, allowing them to undertake such operations without any restrictions. These 'xenotourists' will

return home unsupervised after their travels and are susceptible to contracting or transmitting new infections. Resolution EB113.R5, titled "Human Organ and Tissue Transplantation", was concluded by the Executive Board of the World Health Organisation (WHO) in January 2004. This resolution encompasses guidelines pertaining to xenoTx. The present document comprises a preliminary resolution concerning xenoTx, which advocates for member states to adhere to explicit guidelines. These guidelines entail permitting xenoTx solely under the condition that national health authorities have established effective regulatory control and surveillance. Additionally, the report emphasises the need to develop protective measures to mitigate the potential secondary transmission of any xenogeneic pathogen that may have infected recipients of xenoTx [31].

6. The prospective dimension of xenotransplantation

The domain of xenotransplantation exhibits promising prospects for the future. Nevertheless, it is important to acknowledge that stakeholders beyond the confines of the laboratory play a significant role in the scientific process of xenotransplantation, as evidenced by its historical background and ethical considerations. Xenotransplantation is a multifaceted procedure that encompasses more than a mere surgical technique, a multifaceted medical concern, or a scientific innovation. Its intricacy is contingent upon several social, cultural, and historical factors [32].

7. Conclusion

Further investigation in the field of xenotransplantation is necessary, as the majority of clinical research findings presented in this article have primarily been conducted using animal models. It is important to take into account the ethical and religious concerns. Furthermore, it is imperative to incorporate the issue of animal rights. As stated in the text, it is crucial to acknowledge the possible risk posed by nonhuman organs in spreading pathogenic pathogens that are not yet detected through existing screening techniques.

8. References

1. United States Renal Data System. USRDS 2016 Annual Data Report. [Online]. [Accessed: 9 June 2017] Available: https://www.usrds.org/2016/view/Default.aspx
2. Ekser B, Cooper DKC, Tector AJ. The need for xenotransplantation as a source of organs and cells for clinical transplantation. Int J Surg. 2015;23:199-204.
3. Reemtsma K, McCracken BH, Schlegel JU, Pearl MA, Pearce CW, Dewitt CW, *et al*. Renal heterotransplantation in man. Ann Surg. 1964;160:384-410.
4. Hardy JD, Kurrus FD, Chavez CM, Neely WA, Eraslan S, Turner MD, *et al*. Heart transplantation in man. Developmental studies and report of a case. JAMA. 1964;188:1132-1140.
5. Bailey LL, Nehlsen-Cannarella SL, Concepcion W, Jolley WB. Baboon-to-human cardiac xenotransplantation in a neonate. JAMA. 1985;254:3321-3329.
6. Sachs DH. Transplantation tolerance through mixed Chimerism: From Allo to Xeno. Xenotransplantation. 2018;25(3):e12420.
7. Platt JL, Cascalho M. New and old technologies for organ replacement. Curr Opin Organ Transplant. 2013;18(2):179-185.
8. Windt VDDJ, Bottino R, Kumar G, Wijkstrom M, Hara H, Ezzelarab M, *et al*. Clinical islet xenotransplantation: How close are we? Diabetes. 2012;61(12):3046-3055.
9. Tisato V, Cozzi E. Xenotransplantation: An overview of the field. Xenotransplantation. Methods in Molecular Biology. 2012;885:1-16.
10. Lewis T. Growing human kidneys in rats sparks ethical debate. CBS News. [Accessed: 26 September 2015]. Online Available: https://www.cbsnews.com/news/growing-human-kidneys-in-rats-sparks-ethical-debate
11. Tentler JJ, Tan AC, Weekes CD, Jimeno A, Leong S, Pitts TM, *et al*. Patient-derived tumour xenografts as models for oncology drug development. Nat Rev Clin Oncol. 2012;9(6):338-350.
12. Simon PM, Neethling FA, Taniguchi S, Goode PL, Zopf D, Hancock WW, *et al*. Intravenous infusion of Galα1-3Gal oligosaccharides in baboons delays hyperacute rejection of porcine heart xenografts. Transplantation. 1998;65:346-353.
13. Mohiuddin MM, Singh AK, Corcoran PC, Thomas III ML, Clark T, Lewis BG, *et al*. Chimeric 2C10R4 anti-CD40 antibody therapy is critical for long-term survival of GTKO.hCD46.hTBM pig-to-primate cardiac xenograft. Nat Commun. 2016;7:11138.
14. Mohiuddin MM, Corcoran PC, Singh AK, Azimzadeh A, Hoyt RF Jr, Thomas ML, *et al*. B-cell depletion extends the survival of GTKO.hCD46Tg pig heart xenografts in baboons for up to 8 months. Am J Transplant. 2012;12:763-771.
15. Xenotransplantation: Are pigs the future of organ transplants? BBC News. [Accessed: 18 March 2022]. Online Available: https://www.bbc.com/news/health-55540243.
16. Higginbotham L, Mathews D, Breeden CA, Song M, Farris AB III, Larsen CP. Pre-transplant antibody screening and anti-CD154 costimulation blockade promote long-term xenograft survival in a pig-to-primate kidney transplant model. Xenotransplantation. 2015;22:221-230.
17. Kim SC, Mathews DV, Breeden CP, Higginbotham LB, Ladowski J, Martens G, *et al*. Long-term survival of pig-to-rhesus macaque renal xenografts is dependent on CD4 T cell depletion. Am J Transplant. 2019;19:2174-2185.
18. Ekser B, Lin CC, Long C, Echeverri GJ, Hara H, Ezzelarab M, *et al*. Potential factors influencing the development of thrombocytopenia and consumptive coagulopathy after genetically modified pig liver xenotransplantation. Transpl Int. 2012;25:882-896.
19. Calne RY, White HJ, Herbertson BM, Millard PR, Davis DR, Salaman JR, *et al*. Pig-to-baboon liver xenografts. Lancet. 1968;1:1176-1178.
20. Ekser B, Echeverri GJ, Hassett AC, Yazer MH, Long C, Meyer M, *et al*. Hepatic function after genetically engineered pig liver transplantation in baboons. Transplantation. 2010;90:483-493.
21. Ekser B, Long C, Echeverri GJ, Hara H, Ezzelarab M, Lin CC, *et al*. Impact of thrombocytopenia on survival of baboons with genetically modified pig liver

transplants: Clinical relevance. Am J Transplant. 2010;10:273-285.
22. Kim K, Schuetz C, Elias N, Veillette GR, Wamala I, Varma M, *et al*. Up to 9-day survival and control of thrombocytopenia following alpha1,3-galactosyl transferase knockout swine liver xenotransplantation in baboons. Xenotransplantation. 2012;19:256-264.
23. Laird CT, Burdorf L, French BM, Kubicki N, Cheng X, Braileanu G, *et al*. Transgenic expression of human leukocyte antigen-E attenuates GalKO.hCD46 porcine lung xenograft injury. Xenotransplantation. 2017;24:e12294.
24. Sahara H, Watanabe H, Pomposelli T, Yamada K. Lung xenotransplantation. Curr Opin Organ Transplant. 2017;22:541-548.
25. Watanabe H, Ariyoshi Y, Pomposelli T, Takeuchi K, Alper EDK, Boyd LK, *et al*. Intra-bone bone marrow transplantation from hCD47 transgenic pigs to baboons prolongs chimerism to > 60 days and promotes increased porcine lung transplant survival. Xenotransplantation. 2019. [EPUB ahead of print].
26. Watanabe H, Sahara H, Nomura S, Tanabe T, Ekanayake-Alper DK, Boyd LK, *et al*. GalT-KO pig lungs are highly susceptible to acute vascular rejection in baboons, which may be mitigated by transgenic expression of hCD47 on porcine blood vessels. Xenotransplantation. 2018;25:e12391.
27. Hryhorowicz M, Zeyland J, Slomski R, Lipinski D. Genetically modified pigs as organ donors for xenotransplantation. Mol Biotechnol. 2017;59:435-444.
28. Denner J. Why was PERV not transmitted during preclinical and clinical xenotransplantation trials and after inoculation of animals? Retrovirology. 2018;15:28.
29. Morozov VA, Wynyard S, Matsumoto S, Abalovich A, Denner J, Elliott R. No PERV transmission during a clinical trial of pig islet cell transplantation. Virus Res. 2017;227:34-40.
30. Yang L, Guell M, Niu D, George H, Lesha E, Grishin D, *et al*. Genome-wide inactivation of porcine endogenous retroviruses (PERVs). Science. 2015;350:1101-1104.
31. Persson M, Persson N, Ranstam J, Hermeren G. Xenotransplantation public perceptions: Rather cells than organs. Xenotransplantation. 2003;10:72.
32. Negri A, Wilson L. Future Systems of Xenotransplantation: Melding historical and bioethical methodology. Cell Transplantation. 2023;32:1-10. DOI: 10.1177/09636897231170510.