International Journal of Current Science Research and Review
ISSN: 2581-8341
Volume 05 Issue 06 June 2022
DOI: 10.47191/ijcsrr/V5-i6-15, Impact Factor: 5.995
IJCSRR @ 2022
www.ijcsrr.org

Current Aspects of Xenotransplantation in Human

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ABSTRACT: Xenotransplantation is an approach which will be able to support the increasing demand of organ donation since the organ does not need to come from humans. Up till now, xenotransplantation is still barely performed since its risk and chance of success are still not proven to be safe. One of the biggest obstacles is rejection which may lead to xenograft failure and can occur in certain types and from certain causes. However, the risk of rejection can be minimized by the process of genetic engineering and applying anti-rejection drugs in which scientists and researchers are developing so that the procedure becomes safer in the future. Although the patient who was considered as the first successful xenotransplantation in human case had died a few months after the surgery and the cause of death still remains unsolved, the field of xenotransplantation still keeps developing by researchers, medical universities, and biotechnology companies since they all agree that xenotransplantation will produce lots of advantages and will be a big step of the medical treatment field. Despite the fact that xenotransplantation is a procedure that is risky and raises public concerns and ethical issues, the procedure is still believed to give more benefits towards the patient and medical development since serious problems like organ shortage and high number of deaths on the waiting list will be solved.

KEYWORDS: Cardiac xenotransplantation; PERV; Xenotransplantation.

INTRODUCTION

Over the past decade, the demand for donated organs, which are used in transplantation, is increasing significantly all over the world [1, 2]. This is due to the improvement in the medical field, the higher chance of success, and the better outcome after the transplantation [3]. However, the number of organs donated are not able to support the increasing demand [4]. As a consequence, the organ shortage crisis became one of the biggest obstacles of a successful transplantation field [5, 6]. Although the crisis still remains in the modern day, xenotransplantation might be a promising solution to match the supply with the increasing demand [1, 2]. Although the limitations of heart transplantation are the restricted availability of donated organs and have been a major obstacle, Cardiac xenotransplantation (CXTx) might be a promising way to match the supply with the increasing demand Xenotransplantation is any procedure that involves the transplantation, implantation or infusion of live organs, cells, or tissues from a nonhuman animal source into a human recipient [1, 7, 8]. The field of xenotransplantation has experienced a great development in the past decade, as a result of a combination of several breakthroughs such as the improvement of immunosuppression, genetic engineering, and understanding of cross-species incompatibilities [4, 9]. The objective of this article is to summarize the process, development, and advantages and disadvantages and to publish the information for further development of heart xenotransplantation.

A. The problem of xenotransplantation

Despite the fact that xenotransplantation is an approach that produces a considerable amount of benefits, it also raises concerns on the possibility of harmful consequences such as the risk of infectious disease and immunological barriers which is the main cause of rejections that may lead to xenograft failure [10, 11]. Rejection after the xenotransplantation can occur in certain types including hyperacute rejection, acute vascular rejection, cellular rejection, and chronic rejection [12-14]. The 2 stages that are mediated by antibodies against oligosaccharide determinants, which can be found on vascular endothelium of pig, are hyperacute rejection and acute vascular rejection [15].

Hyperacute reaction is a type of humoral rejection and occurs when there is a binding of preformed antibodies to the xeno antigenic epitopes which are located on porcine endothelial cells and will cause the activation of complement proteins [5, 10]. The activation of the proteins causes lysis of endothelial cells which leads to the destruction of the graft vascular, a surgical procedure that redirects blood flow, and vascular integrity failure [11]. However, hyperacute reaction can be avoided by removing the anti pig antibodies or inhibiting complement activation in the recipient by plasmapheresis. The major xenoantigen is galactose-α1,3-galactose (α-Gal), which is expressed by α1,3-galactosyltransferase that is functional in most mammals, including pigs, but not in humans [5, 16].

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Acute vascular rejection, also can be referred as acute humoral infection, is a type of rejection that occurs when there is a combination between cellular immune response and endothelial [13]. After the combination, the possible effects are massive interstitial hemorrhage, infarction, necrosis, thrombosis, and deposition of immunoglobulin IgG, IgM, C3, C4d, and platelets [17, 18]. Although this type of rejection could not be controlled currently, the development of new immunosuppressive drugs and genetically engineering pigs are still in progress [3, 19].

Cellular xenograft rejection is different to the hyperacute reaction and acute vascular rejection as this type of rejection is associated with both whole organ grafts and cellular grafts [10]. Cellular rejection can be mediated by innate and adaptive immune response which consist of varieties of immune cells including NK cells, macrophages, neutrophils, dendritic cells, T cells, and B cells [10, 11]. In this type of rejection, the rejection may occur days to weeks after the transplantation. In order to overcome this type of rejection, a great deal of immunosuppressive drugs and scientific breakthroughs in human immunology will be required in the future [13, 19]. The risk of xenotransplantation does not only include the rejection in each patient, but it also puts the public health at risk too since xenotransplantation might produce a new infectious disease that may lead to a pandemic [20, 21].

B. Solution to solve the problem

In the modern day, pigs are considered as the best donor for xenotransplantation since its anatomy and physiology are similar to humans [10, 11]. Moreover, pig breeding is highly developed, cost-effective, and the variety of breeding allows the size of the organs harvested to be able to match with the recipient [22]. However, the molecular incompatibility between the donor and the recipient is the main obstacle as it would result in a rejection and finally lead to xenograft failure [23]. Although the immunological barrier which leads to the rejection still remains as the main obstacle, advances in genetic engineering create the possibility to modify the genome of donor animals in a way that will prevent the human recipient's immune system from recognizing its organs and inhibiting the processes which lead to xenograft rejection [24]. Many useful methods for genetically modifying animals can be made [25]. This includes pronuclear and cytoplasmic microinjection, somatic cell nuclear transfer (SCNT) and viral transduction of DNA [26]. In order to tackle the molecular incompatible problem, the Galα(1,3)Gal antigen in the donor organ must be removed from xenograft cell surfaces. This antigen is also the main cause of the hyperacute rejection as the rejection will occur when the preformed antibodies recognize it [24]. The best technique to prevent the formation of Galα(1,3)Gal epitopes is to inactivate the gene encoding GGTA1, which catalyzes the Galα(1,3)Gal epitope forming reaction [27]. *GGTA1 or* alpha 1,3 galactosyltransferase1 gene can be found in all mammals except humans, apes, and old world monkeys [25]. Knocking out the GGTA 1 gene will not only significantly increase the survival length of the patients after the transplantation up to 6 months, but will also highly reduce the hyperacute rejections, as studies of xenotransplantation in baboons suggested [28, 29]. Moreover, hyperacute rejection can be further reduced by expression of human complement regulatory proteins such as CD46, CD55, or CD59 together with the *GGTA1* deletion [30-32]. A more advanced method which is to remove two xeno antigens which are α-Gal and N-glycolylneuraminic acid also can be combined, as it will further reduce the humoral activity compared to a *GGTA1* knockout alone [16]. The fast development of genetic engineering techniques in recent years has made it possible to perform virtually any kind of genetic manipulation *in vitro* [24]. Therefore, the prospect of producing multi transgenic pigs whose organs would resist rejection after transplantation is becoming increasingly realistic [30, 33].

C. First Successful Case

On 7th January 2022, the first successful heart xenotransplantation was made to help a 57-year-old patient with terminal heart disease named David Bennett [34]. The surgery was performed by University of Maryland School of Medicine (UMSOM) faculty at the University of Maryland Medical Center (UMMC) [23]. Before the surgery was performed, the surgical team had spent more than five years developing the surgical technique for transplantation of pig hearts into non-human primates [34]. In this surgery, the patient received a successful transplant of a genetically-modified pig heart [34]. After the transplantation, the surgery marked the first time that the genetically-modified heart from an animal donor showed that it can function like a human heart [35]. In addition, the sign or response of rejection also does not present immediately after the transplantation [34]. Before the surgery, Mr. Bennett had been admitted to the hospital for more than six weeks with life-threatening arrhythmia and a heart-lung bypass machine, called extracorporeal membrane oxygenation (ECMO) [34]. Moreover, he had been fully informed of the risk of the procedure, and that the surgery was experimental with unknown risks and benefits [34]. In detail to the process, the genetically-modified pig heart for the xenotransplantation was provided by Revivicor, a regenerative medicine company based in Blacksburg. In the process of

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modifying the pig's heart, three genes in the donor organ were knocked out to prevent the hyperacute rejection and six human genes which are responsible for immune acceptance of the pig heart were also inserted into the genome [23, 34]. Additionally, one additional gene in the pig was knocked out to prevent excessive growth of the pig heart tissue [23, 34]. On the morning of the surgery, the surgical team, led by Dr. Griffith and Dr. Mohiuddin prepared the process by first removing the pig's heart and placing it in the XVIVO Heart Box which is a machine that keeps the heart preserved until surgery comes [36]. The physician-scientists also used a new drug, which was made by Kiniksa Pharmaceuticals, together with conventional anti-rejection drugs, which are designed to suppress the immune system and prevent the body from rejecting the foreign organ [34]. Despite the fact that the surgery was successful as the pig's heart was completely transplanted into the patient, functions normally, and shows no sign of rejection, Mr. Bennett was reported dead on 8 March 2022 [23, 34]. The doctor admitted that the cause for the death was not clear [23, 34]. However, further investigations will be made to determine the ways to solve the xenotransplantation failure and the global shortage of transplant organs [23, 34].

D. Development of Xenotransplantation

As xenotransplantation provides a way out for the shortage of organs, which has become one the biggest problems in medical treatment, many medical universities and biotechnology companies are increasingly interested in developing the procedure [35, 37]. For instance, in January 2022, the University of Alabama at Birmingham Marnix E [37]. Heersink School of Medicine or UAB has announced that they have made the first peer-reviewed research outlining the successful transplant of genetically modified pig kidneys into a brain-dead human by replacing the recipient's kidneys after significant investments in the xenotransplantation field for almost a decade [37, 38]. In this study, the UAB researchers transplanted the genetically modified pig's kidneys in order to test the first human preclinical model [37]. The pig's kidneys were modified with 10 major genes edited, 4 pig's genes were knocked out and 6 human genes inserted [37]. The modification was provided by Revivicor,a subsidiary of United Therapeutics. The study also proposed the 4 steps that could be taken in a Phase 1 xenotransplantation [37]. The first step was storing and processing the genetically modified pig's kidney for the implantation. Afterwards, the brain-dead recipient and donated organ undergent a crossmatch, which was developed and first used at the UAB compatibility test, to prevent the occurrence of rejections [37]. When the implantation performed, the pig kidneys were placed in the exact anatomic locations used for human donor kidneys and connected to the renal artery, renal vein, and the ureter. In the last step, the brain-dead recipient received an immune-suppression therapy which was also used in human to human kidney transplantation [37]. After the transplantation, the kidneys' function and sign of rejection were observed, the results were that the transplanted pig's kidneys were able to filter blood, produce urine, and do not show any signs of rejection during the 77 hours period of observation [37].

The preclinical model research of xenotransplantation made by the UAB is such a significant study as it identifies points that new knowledge is still needed to develop the outcomes of the xenotransplantation humans [37]. Moreover, the research also provides information about the preclinical human model which can be used for further study in the xenotransplantation field as it is the best solution to the organ shortage crisis and give patients a better life [37].

E. Advantages and disadvantages

Despite the fact that the first successful case of xenotransplantation from animal to human has just been made in the beginning of the year 2022 and the patient of the case also has only survived for only 2 months after the transplantation, xenotransplantation still remains as a significant goal for researchers and surgical fields since the approach can produce huge advantages [39]. Once xenotransplantation becomes available and reliable, organ shortages which is one of the major problems in the transplantation field will be either mitigated or even solved as the source of organ donated does not need to rely on only humans [39]. This means that the death on the waiting list for transplantation will dramatically decrease as the source of organ donated does not only rely on humans only [3, 40]. Furthermore, with access to xenotransplantation, a commonly developing animal donor which is pig, allows the elderly patients to be able to receive the organ that is compatible to them since the donated organ from pig will solve the age limits the transplantation [34]. A further advantage of xenotransplantation is that the procedure can be pre-scheduled which will allow patients to have pre-treatment of receiving immunosuppressive agents to prevent the rejection after the surgery [4, 41, 42]. Apart from medical terms, xenotransplantation will also produce two significant benefits to patients and donors [43]. One is that it will allow people to avoid ethical issues, which are related to the donor, such as selling organs which is an unlawful act [43-45]. Another benefit is that xenotransplantation will allow patients to have significant cost savings because of the need for costly

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and intensive treatment such as chronic dialysis treatment and end-stage liver, heart, and lung disease [46]. However, although xenotransplantation can bring significant benefits, disadvantages which are microbiological risks and ethical issues still remain [44]. In xenotransplantation, there is a risk of transmitting infectious agents from animal to the human recipient [47]. The porcine endogenous retrovirus or PERV is a permanent part of the genome in all mammals which means that not only all recipients will be exposed to the virus, but the risk of transferring the virus to the recipient also cannot be minimized by just selecting the animal from strictly controlled herds [24, 37, 48]. Although the virus cannot replicate itself or cause disease under physiological conditions, the transmission can occur after the cells of the transplanted organ were co-cultured with human cells [3, 13].

Ethical issues are also one of the biggest disadvantages and obstacles [44]. One such controversial issue is whether xenotransplantation does more good than harm or not [44]. The issue was raised from the fact that the procedure is complicated and the patients will need to be monitored for possible infectious diseases for a long period of time or possibly for their whole life [20]. Moreover, there is a considerable public health concern on the possible transmission and activation of PERV over the recent years [2, 24]. Nowadays, a number of countries such as the USA and the UK already have guidelines for clinical trials with xenotransplantation, while some countries are still far behind [3, 48, 49]. This also raises concern that countries might take advantage of attracting desperate patients who need transplantation by creating xenotransplantation programs [7, 30, 47].

F. Conclusion

In conclusion, xenotransplantation is a significant approach in medical treatment since it will address the scarcity of organs and save patients' lives as they will no longer be required to wait for the donated organ from humans. In the modern-day, immunological rejection, risk of the procedure, and other problems remain the main challenge for the xenotransplantation to be performed safely and widely. However, with the improvement of medical technologies and advance in medical research will be considerable keys for success in xenotransplantation.

REFERENCES

1. D. A. Qualls, G. D. Lewis, V. Sanchorawala, and A. Staron, "Orthotopic heart transplant rejection in association with immunomodulatory therapy for AL amyloidosis: a case series and review of the literature," *American Journal of Transplantation*, vol. 19, no. 11, pp. 3185-3190, 2019.
2. R. N. Pierson Iii *et al.*, "Progress toward cardiac xenotransplantation," *Circulation*, vol. 142, no. 14, pp. 1389-1398, 2020.
3. S. S. Raza, H. Hara, D. C. Cleveland, and D. K. C. Cooper, "The potential of genetically engineered pig heart transplantation in infants with complex congenital heart disease," *Pediatric Transplantation*, p. e14260, 2022.
4. D. K. C. Cooper and R. N. Pierson, "The future of cardiac xenotransplantation," *Nature Reviews Cardiology*, pp. 1-2, 2022.
5. M. Längin *et al.*, "Consistent success in life-supporting porcine cardiac xenotransplantation," *Nature*, vol. 564, no. 7736, pp. 430-433, 2018.
6. S. B. Egerer, "Provision of safe donor pigs for xenotransplantation," 2020.
7. C. P. Thompson *et al.*, "A perspective on the potential detrimental role of inflammation in pig orthotopic heart xenotransplantation," *Xenotransplantation*, vol. 28, no. 4, p. e12687, 2021.
8. D. K. C. Cooper, "A Brief History of Clinical Cross-Species Organ Xenotransplantation," in *Clinical Xenotransplantation*: Springer, 2020, pp. 3-26.
9. N. Perico, F. Casiraghi, and G. Remuzzi, "Clinical Kidney Xenotransplantation: Major Progress but More Work Needs to Be Done," *Nephron*, pp. 1-6, 2022.
10. S. Shu, J. Ren, and J. Song, "Cardiac xenotransplantation: a promising way to treat advanced heart failure," *Heart Failure Reviews*, vol. 27, no. 1, pp. 71-91, 2022.
11. L. Burdorf, A. M. Azimzadeh, and R. N. Pierson Iii, "Progress and challenges in lung xenotransplantation: an update," *Current Opinion in Organ Transplantation*, vol. 23, no. 6, pp. 621-627, 2018.
12. B. Q. Yang, A. C. Park, and J. D. Schilling, "Cardiac Xenotransplantation: Five things every cardiologist should know," ed: American College of Cardiology Foundation Washington DC, 2022.
13. R. P. H. Meier *et al.*, "Xenotransplantation: back to the future?," *Transplant international*, vol. 31, no. 5, pp. 465-477, 2018.

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IJCSRR @ 2022
www.ijcsrr.org

14. S. Narayan, R. Verma, and I. Ali, "XENOTRANSPLANTATION–A REVIEW," 2018.
15. A. Barone *et al.*, "Glycosphingolipids of porcine, bovine, and equine pericardia as potential immune targets in bioprosthetic heart valve grafts," *Xenotransplantation*, vol. 25, no. 5, p. e12406, 2018.
16. A. J. Tector, M. Mosser, M. Tector, and J.-M. Bach, "The possible role of anti-Neu5Gc as an obstacle in xenotransplantation," *Frontiers in immunology*, vol. 11, p. 622, 2020.
17. M. Naeimi Kararoudi *et al.*, "Clustered regularly interspaced short palindromic repeats/Cas9 gene editing technique in xenotransplantation," *Frontiers in immunology*, p. 1711, 2018.
18. J. M. Thurman, S. E. Panzer, and M. Le Quintrec, "The role of complement in antibody mediated transplant rejection," *Molecular immunology*, vol. 112, pp. 240-246, 2019.
19. D. K. C. Cooper, M. Ezzelarab, H. Iwase, and H. Hara, "Perspectives on the optimal genetically-engineered pig in 2018 for initial clinical trials of kidney or heart xenotransplantation," *Transplantation*, vol. 102, no. 12, p. 1974, 2018.
20. C. E. Goerlich, J. L. Chan, and M. M. Mohiuddin, "Regulatory barriers to xenotransplantation," *Current Opinion in Organ Transplantation*, vol. 24, no. 5, pp. 522-526, 2019.
21. M. Jorqui-Azofra, "Regulation of Clinical Xenotransplantation: A Reappraisal of the Legal, Ethical, and Social Aspects Involved," *Xenotransplantation*, pp. 315-358, 2020.
22. G. Haddow, "'Dirty pigs' and the xenotransplantation paradox," *Medical Humanities*, vol. 47, no. 4, pp. 417-424, 2021.
23. R. P. H. Meier *et al.*, "Recent progress and remaining hurdles toward clinical xenotransplantation," *Xenotransplantation*, vol. 28, no. 3, p. e12681, 2021.
24. D. Niu *et al.*, "Porcine genome engineering for xenotransplantation," *Advanced Drug Delivery Reviews*, vol. 168, pp. 229-245, 2021.
25. M. Hryhorowicz, D. Lipiński, S. Hryhorowicz, A. Nowak-Terpiłowska, N. Ryczek, and J. Zeyland, "Application of genetically engineered pigs in biomedical research," *Genes*, vol. 11, no. 6, p. 670, 2020.
26. Y. Zhai *et al.*, "Epigenetic states of donor cells significantly affect the development of somatic cell nuclear transfer (SCNT) embryos in pigs," *Molecular Reproduction and Development*, vol. 85, no. 1, pp. 26-37, 2018.
27. J. Wiater *et al.*, "The effect of recombinant human alpha-1, 2-fucosyltransferase and alpha-galactosidase A on the reduction of alpha-gal expression in the liver of transgenic pigs," *Folia Biologica (Kraków)*, vol. 68, no. 4, pp. 121-133, 2020.
28. A. W. Matson, N. Hosny, Z. A. Swanson, B. J. Hering, and C. Burlak, "Optimizing sgRNA length to improve target specificity and efficiency for the GGTA1 gene using the CRISPR/Cas9 gene editing system," *PloS one*, vol. 14, no. 12, p. e0226107, 2019.
29. G. Byrne, S. Ahmad-Villiers, Z. Du, and C. McGregor, "B4GALNT2 and xenotransplantation: a newly appreciated xenogeneic antigen," *Xenotransplantation*, vol. 25, no. 5, p. e12394, 2018.
30. H. Tritschler *et al.*, "New Insights into Xenotransplantation for Cartilage Repair: Porcine Multi-Genetically Modified Chondrocytes as a Promising Cell Source," *Cells*, vol. 10, no. 8, p. 2152, 2021.
31. G. A. Kim *et al.*, "Generation by somatic cell nuclear transfer of GGTA1 knockout pigs expressing soluble human TNFRI-Fc and human HO-1," *Transgenic Research*, vol. 28, no. 1, pp. 91-102, 2019.
32. J. E. Buchwald and P. N. Martins, "Designer organs: The future of personalized transplantation," *Artificial Organs*, vol. 46, no. 2, pp. 180-190, 2022.
33. P. Brenner *et al.*, "Study for Comparison of CD40-mAb and CD40L-Ab Costimulation Blockade after Life-Supporting Orthotopic Cardiac Xenotransplantation of Multi-Transgenic Pig Hearts into Baboons with a Worldwide First Successful Long-Term Survival," *Transplantation*, vol. 102, p. S312, 2018.
34. W. Wang, W. He, Y. Ruan, and Q. Geng, "First pig-to-human heart transplantation," *The Innovation*, vol. 3, no. 2, p. 100223, 2022.
35. W. J. Hawthorne *et al.*, "Third WHO global consultation on regulatory requirements for xenotransplantation clinical trials, Changsha, hunan, China december 12-14, 2018:" the 2018 Changsha communique" the 10-year anniversary of the international consultation on xenotransplantation," *Xenotransplantation*, vol. 26, no. 2, p. e12513, 2019.
36. H. Watanabe *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*, vol. 27, no. 1, p. e12552, 2020.

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IJCSRR @ 2022
www.ijcsrr.org

37. P. M. Porrett *et al.*, "First clinical-grade porcine kidney xenotransplant using a human decedent model," *American Journal of Transplantation*, 2022.
38. J. M. Ladowski *et al.*, "Swine leukocyte antigen (SLA) class II is a xenoantigen," *Transplantation*, vol. 102, no. 2, p. 249, 2018.
39. P. Brenner *et al.*, "Worldwide first successful long-term survival after orthotopic cardiac xenotransplantation of multitransgenic pig hearts into baboons using a CD40mAb or CD40L Costimulation blockade," *The Thoracic and Cardiovascular Surgeon*, vol. 66, no. S 01, pp. DGTHG-V271, 2018.
40. R. N. Pierson Iii, L. Burdorf, J. C. Madsen, G. D. Lewis, and D. A. D'Alessandro, "Pig-to-human heart transplantation: who goes first?," *American Journal of Transplantation*, vol. 20, no. 10, pp. 2669-2674, 2020.
41. S. Stevens, "Genome engineering for xenotransplantation," *Genet. Eng. Glimpse Tech. Appl*, 2019.
42. H. Iwase *et al.*, "Indicators of impending pig kidney and heart xenograft failure: Relevance to clinical organ xenotransplantation-Review article," *International Journal of Surgery*, vol. 70, pp. 84-91, 2019.
43. L. R. Garcia *et al.*, "Clinical trials in cardiac xenotransplantation: Are we ready to overcome barriers?," *Journal of Cardiac Surgery*, vol. 36, no. 10, pp. 3796-3801, 2021.
44. J. D. Loike and A. Kadish, "Ethical rejections of xenotransplantation? The potential and challenges of using human-pig chimeras to create organs for transplantation," *EMBO reports*, vol. 19, no. 8, p. e46337, 2018.
45. W. J. Hawthorne and P. J. Cowan, "Xenotransplantation in Australia: development of the regulatory process," *Xenotransplantation*, vol. 27, no. 3, p. e12603, 2020.
46. E. M. DeFilippis, K. K. Khush, M. A. Farr, A. Fiedler, A. Kilic, and M. M. Givertz, "Evolving characteristics of heart transplantation donors and recipients: JACC focus seminar," *Journal of the American College of Cardiology*, vol. 79, no. 11, pp. 1108-1123, 2022.
47. E. Cozzi *et al.*, "Organ transplants of the future: planning for innovations including xenotransplantation," *Transplant International*, vol. 34, no. 11, pp. 2006-2018, 2021.
48. J. A. Fishman, D. H. Sachs, K. Yamada, and R. A. Wilkinson, "Absence of interaction between porcine endogenous retrovirus and porcine cytomegalovirus in pig-to-baboon renal xenotransplantation in vivo," *Xenotransplantation*, vol. 25, no. 5, p. e12395, 2018.
49. M. Bikhet *et al.*, "The immune system in infants: Relevance to xenotransplantation," *Pediatric transplantation*, vol. 24, no. 7, p. e13795, 2020.