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REVIEW ARTICLE

Advances in Xenotransplantation and Bioengineered Kidneys for Overcoming Organ Shortage

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Abstract

The global burden of end-stage renal disease continues to increase and the availability of suitable donor kidneys remains critically insufficient. This extended gap between supply and demand has enhanced the significant research interest in alternative strategies for kidney replacement. Xenotransplantation techniques using genetically modified porcine donors has progressed remarkably due to advances in genome editing tools such as CRISPR-Cas9. It enables precise modification of donor animals to minimize hyperacute rejection and improve graft compatibility. Breakthroughs in immune tolerance induction, including targeted deletion of xenoantigens and introduction of human complement regulatory genes have transformed the feasibility of cross-species transplantation. Meanwhile, bioengineered kidneys derived through regenerative medicine approaches includes decellularized scaffolds, stem cell-derived renal organoids, 3D bioprinting, and biomimetic extracellular matrices. It offers a promising pathway toward personalized organ replacement. These technologies aim to recreate functional nephron structures capable of filtration, reabsorption, and endocrine regulation while ensuring biocompatibility and long-term stability. Furthermore, integration of microfluidic platforms and organ-on-chip systems has enhanced preclinical testing which accelerates the translation of engineered tissues into clinical evaluation. Despite these advances, significant challenges includes incomplete vascularization, immune complications, ethical considerations, and limited large-scale manufacturing capacity. Continued interdisciplinary collaboration is essential to overcome these obstacles. Collectively, innovations in xenotransplantation and bioengineered kidney development hold transformative potential to alleviate global organ shortages and pave the way for sustainable and patient-specific renal replacement therapies.

1. Introduction

The global burden of chronic kidney disease has reached extraordinary levels with millions of patients progressing to end-stage renal disease each year. This condition requires renal replacement therapy to sustain life. While dialysis provides a temporary means of maintaining metabolic function, kidney transplantation remains the most effective long-term therapeutic option. Transplantation improves survival and lowers morbidity associated with prolonged dialysis. It enhances quality of life and reduces economic burden over time (Wong et al., 2012). However, a persistent shortage of donor kidneys limits the number of patients who can benefit from this treatment. Waiting lists continue to grow and mortality among those waiting has become a critical public health concern. Innovations capable of expanding the pool of viable organs have therefore become essential to addressing this crisis. Among the most promising advancements are xenotransplantation, which seeks to use organs from genetically modified animals. The bioengineered kidneys created through advances in tissue engineering, regenerative medicine, and stem cell biology (Perin et al., 2008; Rogers et al., 2016). These approaches hold the potential to revolutionize transplantation science by creating an almost limitless supply of transplantable

organs. This review provides a detailed analysis of recent progress in xenotransplantation and kidney bioengineering. Also discuss about the scientific advancements with biological challenges and translational progress.

2. Overview of Xenotransplantation

Xenotransplantation refers to the transplantation of living cells, tissues, or organs from one species into another (Ekser et al., 2015). Historically, efforts to use organs from nonhuman primates were explored in the early 20th century but were ultimately unsuccessful due to acute rejection, infectious risks, and logistical barriers (Cooper, 2012). With the emergence of modern gene-editing technologies, renewed interest has focused on the use of pigs as donor species. Pigs offer several advantages that make them suitable for xenotransplantation. Since it includes physiological similarity to humans, manageable breeding cycles, scalability, and the potential for genetic modification to reduce immunological incompatibility (Lei et al., 2022; Niemann and Petersen, 2016). Advancements in genome engineering allow scientists to delete harmful xenoantigens that would otherwise trigger hyperacute rejection and to incorporate human genes that improve graft acceptance (Zhou et al., 2022). These innovations have dramatically transformed the feasibility of xenotransplantation which enables early clinical and preclinical results that demonstrate prolonged graft function.

Despite the renewed potential, xenotransplantation faces several enduring challenges. The human immune system reacts vigorously against foreign tissues, particularly through antibodies that target carbohydrate antigens expressed on pig endothelial cells (Breimer, 2011; Vadori and Cozzi, 2015). This leads to immediate complement activation and acute destruction of the graft. Long-term xenograft survival is further threatened by cellular immune responses, coagulation incompatibilities, and the potential transmission of pig endogenous retroviruses. The complexity of these immunological and physiological barriers has necessitated the simultaneous modification of multiple genes within donor pigs (Eisenson et al., 2022). Overcoming these obstacles requires the integration of immunosuppressive therapy, genetic engineering, and improved surgical strategies. As a result, xenotransplantation has moved from a theoretical possibility to a translational field nearing clinical adoption.

3. Genetic Engineering to Improve Xenograft Survival

The success of modern xenotransplantation depends heavily on the ability to genetically modify pigs so that their organs become more immunologically compatible with human recipients. Early attempts used conventional gene-targeting technologies to eliminate key xenoantigens such as the alpha-gal epitope, which is a dominant target of natural human antibodies. The elimination of the GGTA1 gene marked a pivotal moment in the field because it significantly reduced hyperacute rejection (Ko et al., 2022). Subsequent genetic modifications targeted additional carbohydrate antigens which includes Neu5Gc and SDa, by knocking out the CMAH and B4GALNT2 genes (Okerblom and Varki, 2017; Perota and Galli, 2019). These combined modifications produced triple-knockout pigs that are far less likely to provoke immediate antibody-mediated destruction of the graft.

Alongside antigen removal, researchers have introduced human genes that helps to regulate coagulation, complement activation, and inflammation. These include human complement regulatory proteins such as CD46, CD55, and CD59 which protect graft endothelial cells from complement-mediated damage (Keragala et al., 2018; Liszewski and Atkinson, 2015). Other transgenes such as CD47 inhibit phagocytosis by human macrophages. The combination of multiple knockouts and transgenes has transformed porcine kidneys into organs capable of surviving far longer when transplanted into primates. Several studies have reported that survival exceeded for months with stable function (Firl and Markmann, 2022; Iwase et al., 2015; Pathiraja et al., 2017).

CRISPR/Cas9 has accelerated progress dramatically on enabling rapid and precise modification of multiple genomic loci simultaneously. This technological leap has made it possible to generate pigs with ten or more combined genetic changes (Aboelhassan and Abozaid, 2024; Lu et al., 2024) (Figure 1 & Table 1). Recent work has even succeeded in inactivating porcine endogenous retroviruses which addresses the concerns about their potential transmission to human recipients (Łopata et al., 2018; Wilson, 2008). The continuous refinement of genetic engineering makes the porcine organs as more prominent to meet the safety and functional requirements necessary for widespread clinical use. While these advances are impressive, immunosuppression protocols and graft monitoring strategies still require optimization. But the groundwork for functional xenotransplantation has now been firmly established.

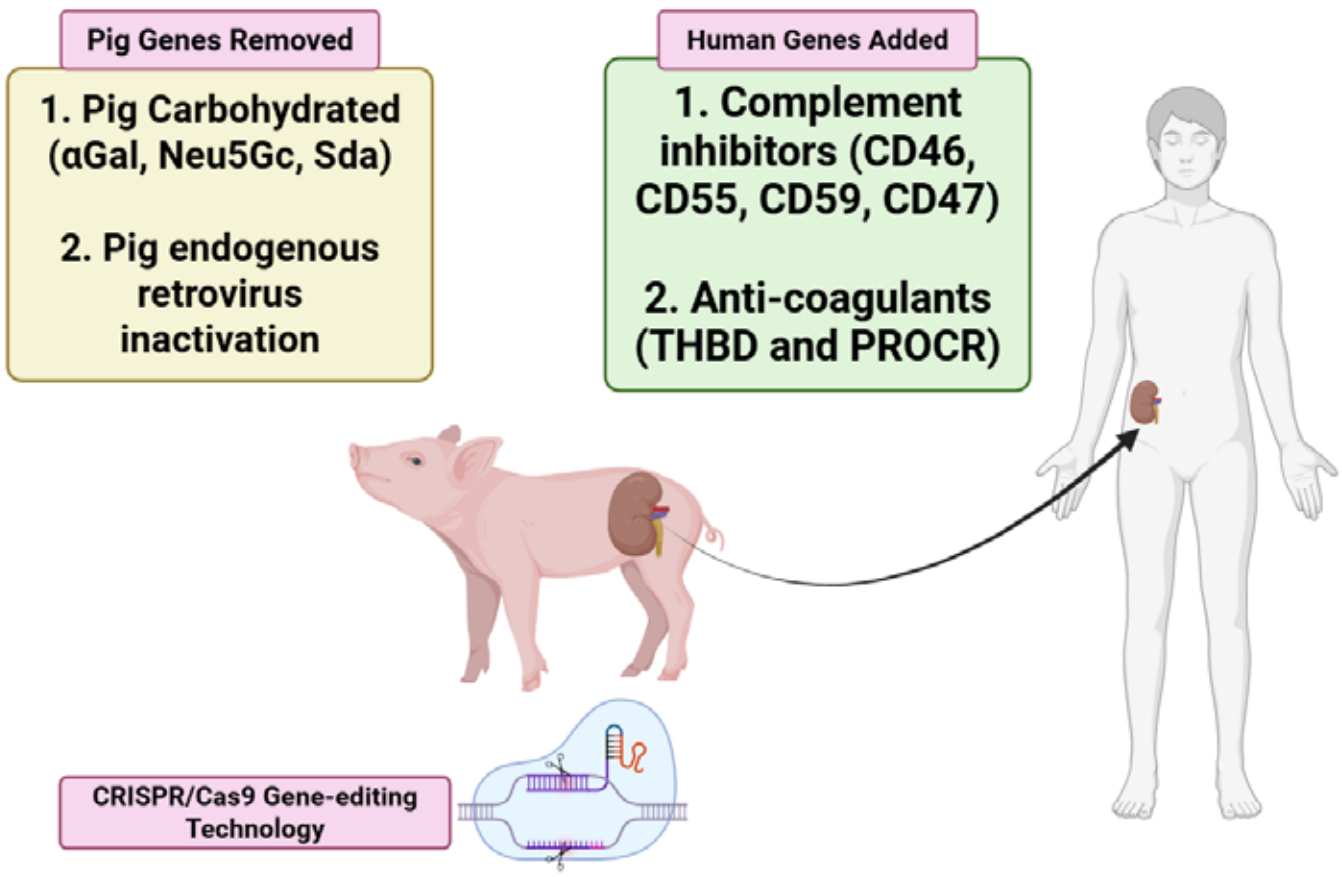

Figure 1: Genetic modifications required to create a bioengineered pig kidney. The immunogenic pig genes are removed and protective human genes are inserted to facilitate graft acceptance and function in a human recipient.

Table 1: Comparison of Xenotransplantation and Bioengineered Kidneys

Parameter	Xenotransplantation	Bioengineered Kidneys
Organ Source	Genetically modified pigs	Human-derived cells and scaffolds
Immunogenicity	Reduced with gene edits but still present	Minimal if autologous cells are used
Technical Complexity	Moderately high, mainly genetic engineering	Extremely high due to nephron complexity
Risk of Infection	Potential PERV concerns	Low, dependent on cell source
Time to Organ Availability	Immediate once donor pigs are bred	Lengthy due to cell expansion and maturation
Long-Term Potential	Near-term clinical application	Long-term future solution

4. Recent Advances in Porcine Kidney Xenotransplantation

Recent years have witnessed remarkable progress in porcine kidney xenotransplantation with several studies demonstrating extended graft survival in preclinical nonhuman primate models (Cooper et al., 2014; Kim et al., 2019; Lee et al., 2023). Many of these studies involve genetically engineered pig kidneys transplanted into baboons under carefully designed immunosuppressive regimens. In numerous cases, xenografts have exhibited prolonged function exceeding six months to one year, representing a substantial improvement over earlier outcomes (Adams et al., 2024; Montgomery et al., 2022). These advances reflect the effective integration of genetic modifications, optimized recipient conditioning, and better understanding of immune rejection pathways. One of the most important developments has been the use of humanized pigs expressing multiple human regulatory

genes. Kidney xenografts from such pigs demonstrate reduced endothelial activation and improved compatibility with human antibodies (Peterson et al., 2024). It lowers the incidence of graft thrombosis. Combined with costimulation blockade therapies targeting immune pathways such as CD40-CD154 or CD28-CD80/86, rejection rates have been significantly reduced compared to conventional immunosuppressive approaches (Malvezzi et al., 2016). These regimens help maintain long-term graft function without exposing recipients to excessive toxicity.

In addition to preclinical work, recent clinical events have drawn global attention. The surgeons successfully transplanted genetically engineered pig kidneys into brain-dead human recipients, demonstrating immediate urine production, stable function, and absence of hyperacute rejection for several days to weeks (Ganchiku and Riella, 2022). These groundbreaking procedures validated decades of research and provided crucial insights about organ compatibility, vascular anastomosis, and monitoring. In recent year, the first living human recipient of a pig kidney xenotransplant survived for several weeks with functioning graft physiology (Judd et al., 2024; Montgomery et al., 2026). It shows the potential of xenotransplantation as a clinical reality. Although long-term survival and immunological control remain challenges, the cumulative evidence suggests that xenotransplantation may soon become a viable therapeutic option for End-Stage Renal Disease patients.

5. Bioengineered Kidneys: An Emerging Alternative

While xenotransplantation offers a solution to organ shortages, kidney bioengineering represents a transformative long-term strategy for creating personalized and immunologically compatible organs. Bioengineered kidneys aim to replicate the structural and functional complexity of native kidneys using a combination of cells, scaffolds, and bioreactors (Torabinavid et al., 2025). Early efforts focused on decellularization of donor kidneys to create extracellular matrix scaffolds. These scaffolds retain the natural architecture of renal tissues, including the glomeruli, tubules, and vasculature. When recellularized with human renal progenitor cells or induced pluripotent stem cell–derived renal lineages, these constructs demonstrate partial restoration of filtration, resorption, and metabolic functions.

Stem cell technologies provide a powerful platform for generating renal cells. Induced pluripotent stem cells can be directed to differentiate into nephron progenitors, podocytes, proximal tubular cells, and other specialized renal cell types (Little and Wilson, 2026). Recent work has successfully produced kidney organoids capable of mimicking key developmental and physiological processes. Although organoids remain small and lack full vascular networks, they serve as essential building blocks for engineered kidneys (Nishimura, 2026). Advances in gene editing allow correction of disease-causing mutations before cells are introduced into scaffolds, offering personalized regenerative therapies for inherited kidney disorders.

Three-dimensional bioprinting has emerged as another major innovation in kidney bioengineering. Using bioinks composed of hydrogels, extracellular matrix components, and renal cells, scientists can print tubular and vascular structures that resemble components of real kidney tissue (Carreno-Galeano et al., 2025; Kim and Cho, 2024). While the complete recreation of a fully functional kidney is still out of reach, partial constructs capable of filtration and transport have been achieved. Bioreactors provide controlled environments for growing engineered kidneys ex vivo, ensuring proper oxygenation, nutrient supply, and mechanical stimuli. As these technologies converge, the prospect of creating fully functional and transplantable bioengineered kidneys becomes increasingly feasible.

6. Integrative Approaches in Regenerative Kidney Engineering

Integrative approaches in regenerative kidney engineering combine decellularization, stem cell biology, gene editing, organoid technology, and bioprinting to create complex kidney constructs capable of sustained function. One promising strategy involves using decellularized porcine kidneys as scaffolds for human cells. Because decellularized tissues remove antigenic components while preserving vascular architecture, they serve as ideal frameworks for recellularization with patient-specific induced pluripotent stem cells (Torabinavid et al., 2025). This hybrid approach blends the structural advantages of xenogeneic scaffolds with the immunological compatibility of autologous cells. However, achieving uniform recellularization remains a significant challenge, particularly for dense cortical regions and vascular compartments. Organoid-based strategies represent another integrative approach. Kidney organoids derived from pluripotent stem cells contain multiple nephron segments and demonstrate rudimentary filtration capabilities (van den Berg et al., 2025). When incorporated into biodegradable scaffolds or bioprinted frameworks, organoids can be assembled into larger constructs. Recent studies show that vascularized organoids can connect to host circulation when transplanted into animal models,

enabling oxygenation and improved maturation. The integration of microfluidic technologies further enhances organoid development by providing dynamic flow conditions that mimic physiological environments.

Bioprinting technologies are also increasingly incorporating multiple cell types and matrix components to more accurately replicate native kidney microenvironments (Hu et al., 2025). By printing vascular channels, tubular segments, and interstitial components layer by layer, researchers are building complex tissue analogs that support fluid transport and metabolic processes. The integration of computational modeling and artificial intelligence allows for improved prediction of scaffold design, mechanical stability, and cell viability. Combining these diverse advances creates a synergistic pathway toward functional kidney engineering and brings the field closer to developing organs suitable for clinical transplantation.

7. Limitation and Future Directions

Despite remarkable progress, both xenotransplantation and kidney bioengineering face substantial limitations that must be addressed before routine clinical adoption becomes possible. Xenotransplantation continues to struggle with immunological barriers that lead to rejection over time. Even with extensive genetic modifications, pig organs still exhibit differences in endothelial signaling, complement regulation, and coagulation can trigger chronic inflammation and vascular dysfunction. Long-term survival beyond one year remains challenging in most preclinical models, indicating that unidentified pathways still contribute to graft failure. Additionally, concerns about zoonotic diseases of porcine endogenous retroviruses require ongoing monitoring and rigorous screening. The human kidney contains millions of nephrons arranged in highly specialized structures which makes it one of the most complex organs to replicate artificially. Achieving full vascularization remains one of the most significant challenges, as engineered tissues often suffer from hypoxia and necrosis when scaled beyond small constructs. Ensuring mechanical integrity, long-term durability, coordinated filtration, and final urine production represents a massive engineering challenge. Furthermore, the process of generating patient-specific induced pluripotent stem cells is time-consuming and expensive, and large-scale manufacturing protocols have not yet been established.

Ethical and regulatory considerations also play a significant role in shaping the future of these technologies. The establishment of universal standards for organ manufacturing, storage, and transplantation will be critical to ensuring clinical success. Improvements in gene editing, stem cell differentiation, bioprinting resolution, and biomaterials will further accelerate progress. Artificial intelligence and computational modeling may streamline organ design and enhance cell–scaffold interactions. Ultimately, multidisciplinary collaboration among biologists, engineers, geneticists, immunologists, and clinicians will shape the next era of transplantation science and may soon provide sustainable solutions to global organ shortages.

8. Conclusion

The global shortage of donor kidneys has established an urgent need for alternative approaches that can expand the pool of transplantable organs and ensure timely access to lifesaving therapies for patients with end-stage renal disease. Xenotransplantation and kidney bioengineering represent two of the most promising solutions to this crisis. Together, these emerging technologies represent not only scientific triumphs but also profound opportunities to improve human health and longevity on a global scale.

Declarations

Ethics approval statement

Not applicable

Consent to participate

Not applicable

Consent to publish

Not applicable

Data Availability Statement

The data are available from the corresponding author upon reasonable request

Competing Interests

The authors declare that they have no conflict of interest

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Author contribution

P.D prepared and completed the whole manuscript.

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