

Gene-Edited Pig Organ Xenotransplantation: Translational Progress and Clinical Safety Challenges

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Abstract.

The persistent and widening disparity between the demand for transplantable human organs and their availability has precipitated a global health crisis driving the exploration of alternative therapeutic modalities. Xenotransplantation, specifically utilizing organs from genetically engineered porcine models, has recently transitioned from theoretical and preclinical paradigms to early-stage clinical reality. This transition has been fundamentally enabled by the advent of advanced genomic editing technologies, notably the clustered regularly interspaced short palindromic repeats associated protein 9 system, which allows for precise, multiplexed alterations of the porcine genome. These genetic modifications are designed to circumvent devastating hyperacute immunological rejection, mitigate coagulation dysregulation, and reduce the risk of zoonotic disease transmission, particularly concerning porcine endogenous retroviruses. This comprehensive paper examines the translational progress of gene-edited pig organ xenotransplantation, analyzing recent clinical milestones involving cardiac and renal grafts in human decedents and compassionate use patients. Furthermore, it deeply investigates the critical clinical safety challenges that persist, including the insidious threat of latent porcine pathogens such as porcine cytomegalovirus, the complex mechanisms of delayed graft rejection, and the intricate ethical and regulatory frameworks required to govern first-in-human clinical trials. By synthesizing current empirical data and theoretical models, this research highlights the transformative potential of xenotransplantation while underscoring the imperative for rigorous risk management and international regulatory consensus to ensure patient and public safety.

Keywords:

*Xenotransplantation,
Gene Editing,
Immunological
Rejection, Clinical
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1. INTRODUCTION

1.1 The Global Organ Shortage Crisis

The field of solid organ transplantation represents one of the most profound medical achievements of the twentieth century, offering a definitive, life-saving intervention for patients suffering from end-stage organ failure. However, the remarkable success and standardization of this medical procedure have paradoxically engendered an insurmountable supply and demand crisis. Across the globe, waitlists for viable donor organs continue to expand at a rate that vastly outpaces the acquisition of suitable allografts from deceased and living human donors. Epidemiological data indicates that tens of thousands of patients succumb annually while awaiting transplantation, a tragedy that underscores the severe limitations of the current human-to-human allocation system. The demographic shift toward aging populations, coupled with the increasing global incidence of chronic conditions such as diabetes mellitus, hypertension, and advanced cardiovascular diseases, further exacerbates the demand for renal, cardiac, and hepatic grafts. Despite rigorous public health

campaigns aimed at increasing voluntary organ donation registration, infrastructural improvements in organ procurement organizations, and legislative shifts toward presumed consent models in various jurisdictions, the allograft deficit remains functionally intractable [1]. This persistent shortfall has driven the scientific and medical communities to aggressively pursue alternative, scalable sources of transplantable organs. While mechanical circulatory support devices and extracorporeal therapies provide vital bridging solutions, they are frequently associated with significant morbidities, including device thrombosis, chronic infections, and substantial impairments to patient quality of life. Regenerative medicine and whole-organ bioengineering hold long-term promise, yet they remain decades away from routine clinical application. Consequently, xenotransplantation, defined as the transplantation of living cells, tissues, or organs from one species to another, has re-emerged as the most proximate and viable solution to resolve the global organ shortage crisis permanently.

1.2 Historical Context of Xenotransplantation

The conceptual genesis of xenotransplantation is not a contemporary phenomenon; rather, it possesses a complex, centuries-long history characterized by audacious experimentation and subsequent clinical failure. Early attempts in the twentieth century predominantly utilized non-human primates, such as baboons and chimpanzees, under the rationale of close phylogenetic proximity to human recipients. Notably, pioneering surgical efforts in the latter half of the twentieth century demonstrated the technical feasibility of primate-to-human organ transfer [2]. However, these historic endeavors were uniformly thwarted by insurmountable immunological barriers, culminating in rapid and catastrophic graft rejection. Furthermore, the use of non-human primates presented profound ethical dilemmas and formidable logistical constraints. Primates possess long gestation periods, yield single offspring, and require extensive, highly enriched environments for ethical rearing, rendering them entirely unsuitable for large-scale clinical application. More critically, the close genetic relationship between human and non-human primates significantly elevated the risk of cross-species pathogen transmission, raising profound public health concerns regarding the potential genesis of novel zoonotic pandemics. Recognizing these intractable limitations, the scientific consensus definitively shifted away from primates toward suids, specifically the domestic pig, as the optimal source species for xenotransplantation. The selection of the pig is underpinned by multiple compelling biological and logistical rationales [3]. Porcine anatomy and physiology exhibit remarkable similarities to those of humans, particularly regarding cardiovascular hemodynamics, renal filtration capacities, and general organ sizing. From an agricultural and logistical perspective, pigs are characterized by rapid maturation rates, short gestation periods, and large litter sizes, enabling the rapid and scalable generation of donor animals. Furthermore, centuries of agricultural domestication have established robust protocols for their breeding in highly controlled, specific-pathogen-free environments, substantially mitigating the baseline infectious disease burden. Despite these inherent advantages, the substantial evolutionary divergence between suids and hominids, spanning approximately eighty million years, instituted profound immunological discordance, manifesting primarily as hyperacute rejection when porcine tissue is perfused with human blood [4]. Overcoming this formidable species barrier required an unprecedented synthesis of transplantation immunology and molecular genetics.

2. Literature Review and Biological Background

2.1 Evolution of Gene Editing Technologies

The fundamental prerequisite for successful porcine xenotransplantation is the extensive genetic modification of the donor animal to humanize its physiological and immunological profile.

Historically, the process of generating transgenic pigs was an arduous, inefficient, and highly protracted endeavor. Early techniques, such as pronuclear microinjection and somatic cell nuclear transfer utilizing homologous recombination, suffered from exceedingly low targeting efficiencies, frequent off-target mutations, and significant limitations in the number of genetic loci that could be modified simultaneously [5]. The landscape of biological engineering was fundamentally revolutionized by the discovery and subsequent adaptation of programmable nucleases, most notably zinc finger nucleases and transcription activator-like effector nucleases. These first-generation targeted endonucleases facilitated precise double-strand breaks at specific genomic locations, allowing for directed gene knockouts and transgenesis [6]. However, the design and synthesis of sequence-specific DNA-binding domains for these platforms remained complex, costly, and time-consuming. The definitive inflection point in xenotransplantation research arrived with the elucidation and repurposing of the clustered regularly interspaced short palindromic repeats associated protein 9 system. This RNA-guided endonuclease technology democratized genetic engineering through its unprecedented precision, ease of design, and, crucially, its capacity for highly multiplexed genomic modifications. By deploying multiple customized single-guide RNAs concurrently within porcine somatic cells, researchers could simultaneously disrupt numerous endogenous porcine genes and precisely insert multiple human regulatory transgenes [7]. This multiplexing capability was transformative, as overcoming the multi-faceted xenogeneic barrier necessitated a combinatorial approach to genetic engineering. The resulting hyper-engineered somatic cells were subsequently utilized as donor nuclei for somatic cell nuclear transfer into enucleated porcine oocytes, culminating in the birth of founder animals possessing the exact required genetic repertoire. These extraordinary advancements in precise molecular scissors have thus accelerated the pace of xenograft development from a theoretical pursuit to an applied translational science.

2.2 Immunological Barriers in Cross-Species Transplantation

The immunological response mounted by the human immune system against unmodified porcine tissue is immediate, violent, and universally fatal to the graft. The most formidable immediate barrier is hyperacute rejection, a catastrophic event that occurs within minutes to hours of vascular anastomosis and reperfusion. This phenomenon is primarily driven by naturally occurring, preformed xenoreactive antibodies present in the human circulation. Evolutionarily, humans, apes, and Old World monkeys possess an inactivating mutation in the gene encoding alpha-1,3-galactosyltransferase, an enzyme responsible for synthesizing the terminal carbohydrate epitope galactose-alpha-1,3-galactose, commonly referred to as the alpha-gal antigen [8]. Because this epitope is abundantly expressed on the vascular endothelium of lower mammals, including pigs, humans continuously generate high titers of anti-Gal antibodies due to exposure to environmental bacteria expressing similar carbohydrate structures. Upon reperfusion of a porcine organ with human blood, these preformed circulating immunoglobulins rapidly bind to the alpha-gal epitopes lining the xenograft vasculature. This massive antibody-antigen complex formation initiates a profound cascade of immunological events, primarily through the activation of the classical complement pathway.

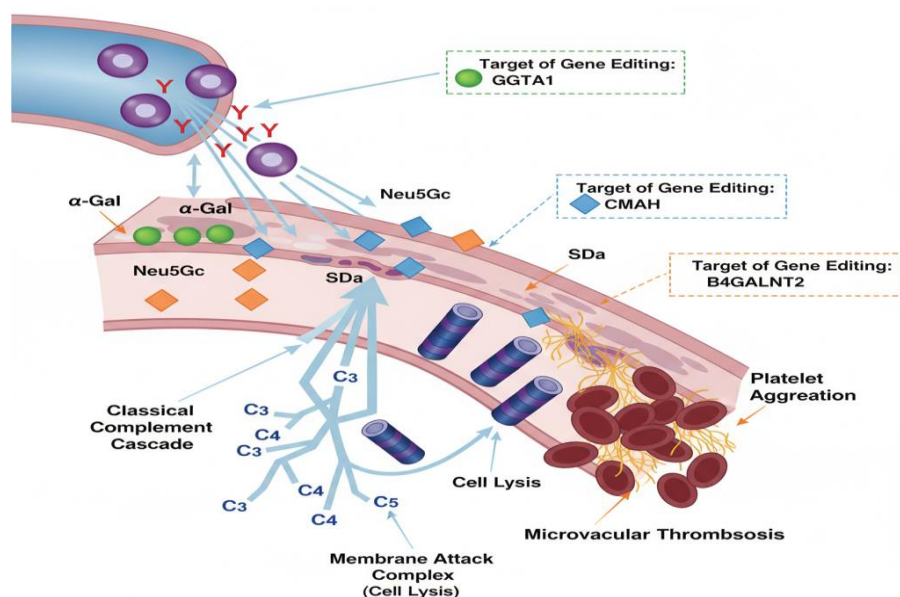


Figure 1: Immunological Rejection Pathways in Xenotransplantation

The activation of the complement system culminates in the assembly of the membrane attack complex, which physically ruptures the porcine endothelial cells, leading to rapid interstitial hemorrhage, edema, and the immediate cessation of organ function. To abrogate this mechanism, the primary genetic target in xenotransplantation became the GGTA1 gene [9]. The generation of alpha-1,3-galactosyltransferase knockout pigs essentially eliminated hyperacute rejection mediated by anti-Gal antibodies. However, subsequent research revealed additional, albeit less abundant, non-Gal carbohydrate xenoantigens that also precipitate rapid antibody-mediated rejection. Specifically, the N-glycolylneuraminic acid epitope, synthesized by the enzyme cytidine monophosphate-N-acetylneuraminic acid hydroxylase, and the SDa blood group-like antigen, synthesized by beta-1,4 N-acetylgalactosaminyltransferase 2, were identified as critical targets. Consequently, contemporary clinical-grade porcine models frequently feature the simultaneous disruption of the GGTA1, CMAH, and B4GALNT2 loci, colloquially termed the triple-knockout configuration, which dramatically reduces the binding of preformed human antibodies.

2.3 The Threat of Porcine Endogenous Retroviruses

Beyond the complex immunological hurdles, cross-species transplantation introduces unique microbiological risks that are fundamentally distinct from allotransplantation. While rigorous biosecurity measures and the use of specific-pathogen-free breeding facilities can eliminate the vast majority of exogenous bacteria, fungi, and transmissible viruses, these environmental controls are entirely ineffective against endogenous genetic elements. Porcine endogenous retroviruses represent a singular and profound challenge in the safety profile of xenotransplantation. These viral entities are remnants of ancient retroviral infections that occurred millions of years ago, permanently integrating into the germline DNA of all living suids [10]. Because they reside within the host genome, they are inherited in a Mendelian fashion and are present in every nucleated cell of the donor animal. While PERVs are generally innocuous to the host pig, extensive in vitro studies have demonstrated their capacity to cross the species barrier, productively infect human cellular lines, and subsequently adapt to replicate efficiently within human hosts. The fundamental concern lies in the potential for PERV virions, released by the xenograft post-transplantation, to infect the therapeutically immunosuppressed human recipient. Once established, these retroviruses possess the potential to cause novel infectious diseases or oncogenesis, mirroring the pathogenesis

of human immunodeficiency virus or human T-lymphotropic virus. Furthermore, a highly theoretical but catastrophic risk involves the potential transmission of the adapted virus from the initial recipient to the broader public, precipitating a novel iatrogenic pandemic. Given the existential threat posed by PERVs, substantial efforts were dedicated to mapping and neutralizing these proviruses. Utilizing highly multiplexed genomic editing strategies, researchers successfully targeted the highly conserved catalytic core of the PERV polymerase gene. In a landmark demonstration of synthetic biology, dozens of viral copies were simultaneously disrupted across the porcine genome, yielding the first viable PERV-inactivated porcine cell lines and subsequent living founder animals [11]. This profound achievement established a critical safety benchmark, ensuring that clinical-grade source animals possess negligible risks of endogenous retroviral transmission.

3. Translational Progress and Clinical Analysis

3.1 Recent Milestones in Cardiac Xenotransplantation

The culmination of decades of in vitro molecular biology and rigorous preclinical non-human primate experimentation recently facilitated a watershed moment in medical history: the transition to early-phase human clinical application. The preclinical evaluation phase heavily relied on the pig-to-baboon heterotopic and orthotopic heart transplantation models. Over successive iterations, researchers refined the required genetic background of the donor organ and the complex immunopharmacological regimens necessary for recipient survival [12]. These preclinical models demonstrated that while the triple-carbohydrate knockout significantly prevented hyperacute rejection, sustained graft survival required the transgenic expression of human complement regulatory proteins, such as CD46, CD55, and CD59, to control local complement activation [13]. Furthermore, the profound molecular incompatibilities between the porcine and primate coagulation cascades necessitated the insertion of human anticoagulant genes, including thrombomodulin and endothelial protein C receptor, to prevent devastating microvascular thrombosis and systemic consumptive coagulopathy. These comprehensive genetic profiles paved the way for the first authorized human xenotransplantation procedures. Under stringent compassionate use regulatory frameworks, critically ill patients suffering from terminal heart failure, who were categorically ineligible for standard allograft allocation or mechanical circulatory support, received complexly engineered porcine hearts. The donor animals utilized for these extraordinary interventions typically possessed up to ten distinct genetic modifications [14].

Table 1: Representative Multi-Gene Modifications in Clinical Porcine Xenograft Models

Gene Target	Modification Type	Functional Purpose in Human Recipient
GGTA1	Gene Knockout	Prevents hyperacute rejection by eliminating alpha-Gal antigen
CMAH	Gene Knockout	Reduces antibody binding by eliminating Neu5Gc antigen
B4GALNT2	Gene Knockout	Reduces antibody binding by eliminating SDa antigen
GHR	Gene Knockout	Prevents intrinsic organ overgrowth post-transplantation
Human CD46	Transgene Insertion	Downregulates local complement system activation

Human CD55	Transgene Insertion	Prevents assembly of C3/C5 convertases on endothelium
Human EPCR	Transgene Insertion	Attenuates pathological coagulation and thrombosis
Human THBD	Transgene Insertion	Modulates coagulation cascade via protein C activation
Human HO-1	Transgene Insertion	Confers anti-inflammatory and cytoprotective properties

The initial clinical courses of these pioneer cardiac xenotransplants were characterized by exceptional immediate organ function. Upon removal of the aortic cross-clamp, the genetically modified porcine hearts exhibited robust contractility, successfully weaning the human recipients from cardiopulmonary bypass without profound hemodynamic collapse or evidence of hyperacute rejection. These early physiological observations definitively validated the efficacy of the extensive genomic engineering in circumventing the immediate immunological barriers that had thwarted the field for decades. However, despite the initial optimism, the postoperative trajectories ultimately revealed complex, delayed mechanisms of graft failure [15]. Analysis of explanted tissue indicated a combination of insidious pathophysiological processes, including delayed antibody-mediated rejection, progressive diastolic dysfunction characterized by profound myocardial thickening, and unexpected infectious complications. These outcomes emphasize that while immediate survival is achievable, the long-term physiological integration of a discordant xenograft requires further refinement of both the donor genetics and the recipient medical management.

3.2 Advancements in Renal Cross-Species Grafting

Concurrently with the advancements in cardiac xenotransplantation, monumental progress has been achieved in the domain of renal cross-species grafting. The kidney shortage represents the most substantial component of the global organ deficit, rendering renal xenotransplantation an area of intense clinical focus. To systematically evaluate the physiological function and early immunological responses in a human environment without endangering living patients, researchers developed a highly innovative preclinical model utilizing brain-dead human decedents. With the ethical authorization of grieving families, whole-body donation facilitated the experimental transplantation of gene-edited porcine kidneys into human subjects maintained on somatic support systems [16]. This paradigm allowed for the rigorous, real-time assessment of xenograft viability, hemodynamics, and functional output over periods extending to several days or weeks. In these decedent models, the genetically modified porcine kidneys were anastomosed to the human vasculature, and immediate outcomes were meticulously monitored. Consistent with the cardiac observations, the grafts remained pink and well-perfused upon reperfusion, demonstrating no signs of the hemorrhagic necrosis characteristic of hyperacute rejection [17]. Crucially, the xenografts rapidly initiated physiological functions, producing substantial volumes of urine and effectively clearing creatinine from the human circulation. Detailed continuous monitoring revealed that the porcine nephrons were capable of filtering human plasma and concentrating urine, indicating a degree of physiological compatibility that exceeded previous expectations. High-resolution histological evaluation of the xenografts at the conclusion of the study periods revealed intact glomerular structures, absent of significant cellular infiltrates or complement deposition, further validating the protective efficacy of the multigenic modifications. These human decedent models have proven invaluable, serving as a critical transitional step that

bridges the gap between non-human primate research and formal phase one clinical trials in living, therapeutically responsive patients.

3.3 Strategies for Immunosuppression and Tolerance

The survival of an organ across a profound evolutionary divide necessitates an immunosuppressive strategy that is significantly more potent and complex than standard allotransplantation protocols. Conventional regimens, heavily reliant on calcineurin inhibitors, antimetabolites, and systemic corticosteroids, have proven largely inadequate for maintaining long-term xenograft viability in preclinical models [18]. The fundamental reason lies in the intense, multidimensional nature of the xenogeneic immune response, which involves highly aggressive elements of the innate immune system, including natural killer cells and macrophages, alongside an exceptionally robust adaptive T-cell and B-cell response. To control this intense reactivity, translational research has heavily focused on the blockade of critical costimulatory pathways that are required for full T-cell activation and antibody class switching. The most critical advancement in xenogeneic immunosuppression has been the integration of biological agents targeting the CD40-CD154 costimulatory axis. Preclinical trials utilizing monoclonal antibodies directed against CD40 have consistently demonstrated superior efficacy in prolonging xenograft survival compared to traditional pharmacotherapy [19]. By severing the communication pathway between T-helper cells and antigen-presenting cells, anti-CD40 therapy profoundly suppresses both cellular rejection and the de novo generation of detrimental donor-specific antibodies. However, the utilization of such profound systemic immunosuppression carries inherent, severe risks. Patients subjected to these intense induction and maintenance regimens are placed in a state of profound immunodeficiency, rendering them exceedingly vulnerable to opportunistic bacterial, fungal, and viral infections. Furthermore, chronic exposure to heavy immunosuppression significantly elevates the long-term risk of developing post-transplant lymphoproliferative disorders and other malignancies. Therefore, a critical challenge moving forward is the calibration of these regimens to achieve a state of immunological tolerance or accommodation, wherein the xenograft is accepted without necessitating drug levels that compromise host survival through infectious or oncological complications.

4. Clinical Safety Challenges and Risk Management

4.1 Zoonotic Disease Transmission Risks

While the integration of gene editing has successfully addressed the primary immunological barriers, the paramount safety concern in xenotransplantation remains the risk of zoonosis, the transmission of infectious agents from the porcine donor to the human recipient. As previously discussed, the peril of endogenous retroviruses was largely mitigated through advanced CRISPR multiplexing. However, the transmission of exogenous, latent viral agents constitutes an ongoing and formidable challenge. The most consequential example encountered in recent clinical trials is the porcine cytomegalovirus, a betaherpesvirus highly prevalent in commercial swine herds [20]. Unlike standard exogenous pathogens that can be easily screened and eradicated via strict biosecurity and specific-pathogen-free rearing, pCMV has the capacity to establish deep latency within the host cells, rendering it virtually undetectable in the donor animal's peripheral blood using conventional screening assays.

Multimodal Pathogen Screening and Clinical Safety Monitoring Framework

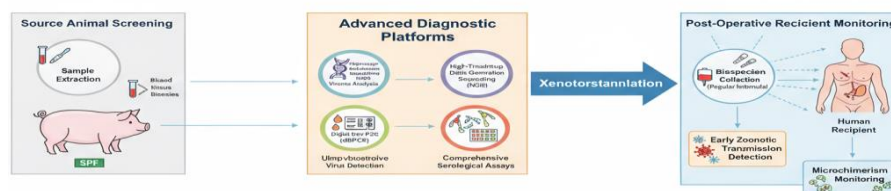


Figure 2: Multimodal Pathogen Screening and Clinical Safety Monitoring Framework

The pathophysiological consequences of latent pCMV transfer are devastating. When a latently infected organ is transplanted into an extensively immunosuppressed human host, the absence of species-specific T-cell regulation allows the virus to rapidly reactivate and disseminate. In the unique environment of a xenograft, pCMV does not merely cause systemic illness; it actively replicates within the porcine vascular endothelium. This targeted replication induces severe endothelial injury, upregulating pro-coagulant factors and precipitating extensive microvascular thrombosis and generalized consumptive coagulopathy within the organ [21]. This viral-induced pathology mimics severe acute rejection and rapidly leads to catastrophic organ failure. The recent clinical experiences heavily underscored the inadequacy of standard prescreening methodologies. Consequently, managing this profound safety risk demands the implementation of ultra-sensitive, multimodal diagnostic screening frameworks. Donor organs must be subjected to deep metagenomic sequencing and highly sensitive molecular assays derived from deeply seated tissues, rather than superficial fluid samples, to guarantee the absolute absence of latent viral genomes prior to surgical utilization.

4.2 Long-Term Graft Viability and Pathological Mechanisms

Assuming the successful navigation of immediate immunological barriers and early infectious complications, the ultimate benchmark of xenotransplantation efficacy is long-term graft viability. Currently, the precise mechanisms governing the chronic deterioration of gene-edited xenografts remain incompletely characterized. Preclinical extended survival models indicate that xenografts eventually succumb to a poorly defined process of delayed xenograft rejection or chronic xenograft vasculopathy [22]. This process is characterized histologically by progressive intimal hyperplasia, smooth muscle cell proliferation within the vascular media, and eventual luminal occlusion, leading to chronic ischemic injury and parenchymal fibrosis. Unlike the well-defined hyperacute rejection, this chronic deterioration is likely driven by a complex, synergistic interaction of low-level, continuous immune recognition, mechanical shear stress incompatibilities, and subtle physiological discordances between the species. Furthermore, the role of the innate immune system, particularly human macrophages and natural killer cells, remains highly problematic. These cells possess mechanisms to recognize non-self tissue independently of antibodies or T-cells. Specifically, signal regulatory protein alpha on human macrophages fails to interact properly

with CD47 expressed on porcine cells, resulting in an absence of the critical inhibitory signal required to prevent macrophage-mediated phagocytosis and tissue destruction. Addressing these intricate mechanisms of delayed rejection requires ongoing iterations of genetic engineering. Future generations of clinical source animals will likely require the precise integration of human immunoregulatory transgenes, such as human CD47 or human leukocyte antigen class I molecules, designed specifically to pacify the innate cellular response and promote long-term vascular health within the xenograft.

4.3 Ethical and Regulatory Frameworks

The clinical translation of xenotransplantation operates at the absolute frontier of medical ethics and regulatory oversight. The introduction of genetically modified animal tissues into human subjects presents unprecedented considerations that extend far beyond standard medical procedures. A central ethical dilemma involves the complex nature of informed consent for a highly experimental, first-in-human intervention where the risks, particularly concerning novel infectious diseases, are difficult to quantify fully. Patients participating in these early-stage trials are typically individuals facing imminent mortality, which necessitates stringent safeguards to ensure that their consent is truly voluntary and fully informed regarding the profound uncertainties involved. Regulatory bodies face the daunting task of establishing comprehensive frameworks to ensure safety without excessively stifling potentially life-saving innovation. Authorities must establish rigorous, standardized criteria concerning the exact genetic configurations of donor animals, the specific-pathogen-free standards of breeding facilities, and the precise analytical methodologies required for pathogen screening. Furthermore, due to the theoretical but non-zero risk of a xenogeneic infectious agent establishing a foothold in the human population, regulatory oversight must extend to comprehensive, potentially lifelong post-transplant monitoring of the recipients and their close biological contacts. Establishing global consensus on these complex ethical and regulatory parameters is absolutely critical before large-scale, multi-center clinical trials can be safely authorized and executed.

5. Conclusion

5.1 Summary of Translational Advancements

The trajectory of gene-edited pig organ xenotransplantation over the past decade represents a paradigm shift in translational medicine. Driven by the critical global shortage of allografts, interdisciplinary efforts encompassing molecular biology, immunology, and advanced surgical science have systematically dismantled the barriers that historically rendered cross-species transplantation impossible. The deployment of CRISPR-based multiplex genomic engineering has allowed for the creation of customized porcine models capable of circumventing devastating hyperacute rejection, mitigating profound coagulation derangements, and neutralizing inherent retroviral threats. The translation of these technologies from isolated in vitro experiments to robust non-human primate models, and most recently to compassionate use human patients and decedent models, provides unequivocal validation of the foundational scientific principles. These early clinical milestones have conclusively demonstrated that extensively modified porcine organs can sustain physiological function and support human life in the acute setting without immediately succumbing to the violent immunological reactions that plagued earlier attempts.

5.2 Future Directions in Xenotransplantation Research

Despite the profound optimism generated by recent clinical successes, xenotransplantation remains an experimental science fraught with critical safety challenges that must be comprehensively addressed. The path forward demands continuous, iterative refinement of both donor genetics and recipient immunopharmacology. Future genetic modifications will likely focus

heavily on dampening the innate cellular immune response, particularly macrophage and natural killer cell activation, which drive delayed mechanisms of graft failure [23]. Furthermore, the catastrophic consequences of latent zoonotic pathogens emphasize the imperative for the global standardization of ultra-sensitive, next-generation diagnostic screening modalities within specialized rearing facilities. Ultimately, the successful and ethical integration of xenotransplantation into routine clinical practice will require the establishment of cohesive, international regulatory frameworks, meticulously designed clinical trials, and an unwavering commitment to patient and public safety, ensuring that this extraordinary scientific endeavor ultimately fulfills its promise to eliminate the human organ shortage.

References

- Xie, C., Zhu, D., Wang, Z., Zhang, H., & Wei, Z. (2026). Compliance-Aware Discharge Agent for Auditable ICU Discharge Planning: A Pilot Feasibility Study Using Structured eICU Records. Available at SSRN 6429758.
- Wan, G., Huang, J. D., Xu, R. H., & Jin, M. (2025). Advances and Challenges in Pluripotent Stem Cell-Based Whole-Cell Vaccines for Cancer Treatment. *Medicine Bulletin*, 1(1), 60-76.
- Cai, Lie, et al. "Deep learning model for breast shear wave elastography to improve breast cancer diagnosis (INSPIRED 006): An international, multicenter analysis." *Journal of Clinical Oncology* 43.32 (2025): 3482-3493.
- Xiao, Y., Xiao-yue, Z., Yue, W., Ruo-tao, L., Xiang-jie, L., Xing-yuan, W., ... & Zhen-yi, J. (2022). Use of computed tomography for the diagnosis of surgical sarcopenia: Review of recent research advances. *Nutrition in Clinical Practice*, 37(3), 583-593.
- Kwaan, M. R., Wu, Y., Ren, Y., & Xirasagar, S. (2022). Prompt intervention in large bowel obstruction management: A Nationwide Inpatient Sample analysis. *The American Journal of Surgery*, 224(5), 1262-1266.
- Mi, L., Wang, W., Tu, W., He, Q., Kong, R., Fang, X., ... & Liu, Y. (2025, March). Empower vision applications with LoRA LMM. In *Proceedings of the Twentieth European Conference on Computer Systems* (pp. 261-277).
- Zhao, Haoyu, et al. "Dynamictrl: Rethinking the basic structure and the role of text for high-quality human image animation." *arXiv preprint arXiv:2503.21246* (2025).
- Xu, X., Bowtell, J., Fong, D. T., Young, W. R., & Williams, G. K. (2025). Kinematics of balance controls in people with chronic ankle instability during unilateral stance on a moving platform. *Scientific Reports*, 15(1), 1126.
- Yu, X., Zhang, Y., Yao, Y., Cho, W. C., & Shang, A. (2025). Biofilm-mediated immune dysregulation in chronic pulmonary diseases: mechanisms and clinical implications. *Frontiers in Microbiology*, 16, 1736384.
- Yang, Y., Lin, Y. T., Li, G., Zhong, Y., Xu, Q., & Cai, J. J. (2023). Interpretable modeling of time-resolved single-cell gene-protein expression with CrossmodalNet. *Briefings in Bioinformatics*, 24(6), bbad342.
- Dong, W., Su, H., Sun, X., Cai, Z., Wang, A., Jiang, K., ... & Cao, Y. (2025). Spontaneous Enlargement in Balloon Pulmonary Angioplasty With Undersized Balloon for Chronic Thromboembolic Pulmonary Hypertension. *Medicine Bulletin*, 1(1), 8-16.
- Wu, Y., Ren, Y., Wu, D., Xirasagar, S., & Johnson, J. (2022, June). Using D-dimer as a Biomarker to Predict COVID-19 Disease Severity from Clinical Data of Hospitalized Patients: A Machine Learning Approach. In *2022 IEEE 10th International Conference on Healthcare Informatics (ICHI)* (pp. 664-668). IEEE.

- Avsec, Ž., Agarwal, V., Visentin, D., Ledsam, J. R., Grabska-Barwińska, A., Taylor, K. R., et al. (2021). Effective gene expression prediction from sequence by integrating long-range interactions. *Nature Methods*, 18(10), 1196–1203.
- Li, Y., Liao, X., Tang, S., Wang, Q., Lin, H., Yu, X., ... & Zhong, T. (2025). Potential Therapeutic Targets for Androgenetic Alopecia (AGA) in Obese Individuals as Revealed by a Gut Microbiome Analysis: A Mendelian Randomization Study. *Nutrients*, 17(11), 1892.
- Xie, C., Zhu, D., Wang, Z., Zhang, H., & Wei, Z. (2026). Explainable AI for Mental Health Detection from Social Media: A Comparative Study of Traditional Machine Learning and a Large Language Model. Available at SSRN 6429778.
- Liu, Z. Q., Xiong, Y. J., Yu, X., Lv, T., & Xu, H. Y. (2026). Female reproductive factors, genetic susceptibility and incident osteoporosis risk. *Climacteric*, 1-8.
- Peng, Z., Lv, X., Sun, H., Zhao, L., & Huang, S. (2025). 3D tumor cultures for drug resistance and screening development in clinical applications. *Molecular cancer*, 24(1), 93.
- Poplin, R., Chang, P.-C., Alexander, D., Schwartz, S., Colthurst, T., Ku, A., et al. (2018). A universal SNP and small-indel variant caller using deep neural networks. *Nature Biotechnology*, 36(10), 983–987.
- Peng, Q., Zheng, C., & Chen, C. (2023). Source-free domain adaptive human pose estimation. In *Proceedings of the IEEE/CVF International Conference on Computer Vision* (pp. 4826-4836).
- Tao, X., Chen, D., Liang, R., Zhang, X., Yu, X., Chung, S., ... & Xiao, Y. (2021). A comparative study on knowledge towards COVID-19 prevention among undergraduate students in Macao and Zhuhai, China. *PeerJ*, 9, e11833.
- Wang, C., Li, C., & Yang, Z. (2025). Engineering Remyelination: Unlocking Oligodendrocyte Repair Through Medicine–Technology Convergence. *Medicine Bulletin*, 1(2), 97-99.
- Zhu, Di, et al. "RaX-Crash: A Resource Efficient and Explainable Small Model Pipeline with an Application to City Scale Injury Severity Prediction." *arXiv preprint arXiv:2512.07848* (2025).
- Chu, Y. B., Li, J., Jia, P., Cui, J., Zhang, R., Kang, X., ... & Zhang, S. (2021). Irf1-and Egr1-activated transcription plays a key role in macrophage polarization: A multiomics sequencing study with partial validation. *International Immunopharmacology*, 99, 108072.