Pig-to-human lung xenotransplantation: A pioneering step toward clinical reality

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INTRODUCTION

Lung transplantation faces a persistent donor shortage, and xenotransplantation is considered a promising solution. While significant progress has been made in cardiac and renal xenotransplantation,[1,2] the lung remains the most formidable barrier due to its unique anatomy and physiology. Conventional nonhuman primate (NHP) models have limited predictive value, given fundamental interspecies differences in the immune and coagulation systems. Therefore, validation in humans is indispensable. A recent study in Nature Medicine by He et al. reported the first pig-to-human lung xenotransplantation, in which a lung from a six-gene-edited pig was transplanted into a 39-year-old brain-dead man. The lung xenograft maintained viability and function for the entire 216-hour monitoring period, without signs of hyperacute rejection or infection.[3] The authors also delineated the temporal dynamics of human immune responses to the lung xenograft. This work represents a landmark exploration in lung xenotransplantation, marking the field's transition from preclinical research to critical early-stage human validation.

OBSTACLES

The greatest obstacles in lung xenotransplantation stem from the organ's unique anatomy and physiology. The lung is an "open" organ: its alveoli are directly exposed to the external environment, increasing susceptibility to infection. Its extensive vascular endothelial surface area provides a broad interface for immune attack. The fragility of the alveolar-capillary barrier, together with abundant alveolar macrophages, triggers vigorous and complex rejection responses. Furthermore, the lung's sensitivity to ischemia-reperfusion injury predisposes to severe primary graft dysfunction (PGD). The study by He et al. is a pioneering attempt to address these challenges.

KEY ADVANCES

A central innovation of this study lies in the use of a highly targeted six-gene-editing strategy. Unlike in cardiac and renal xenotransplantation, where multigene editing is well-advanced, lung xenotransplantation remains

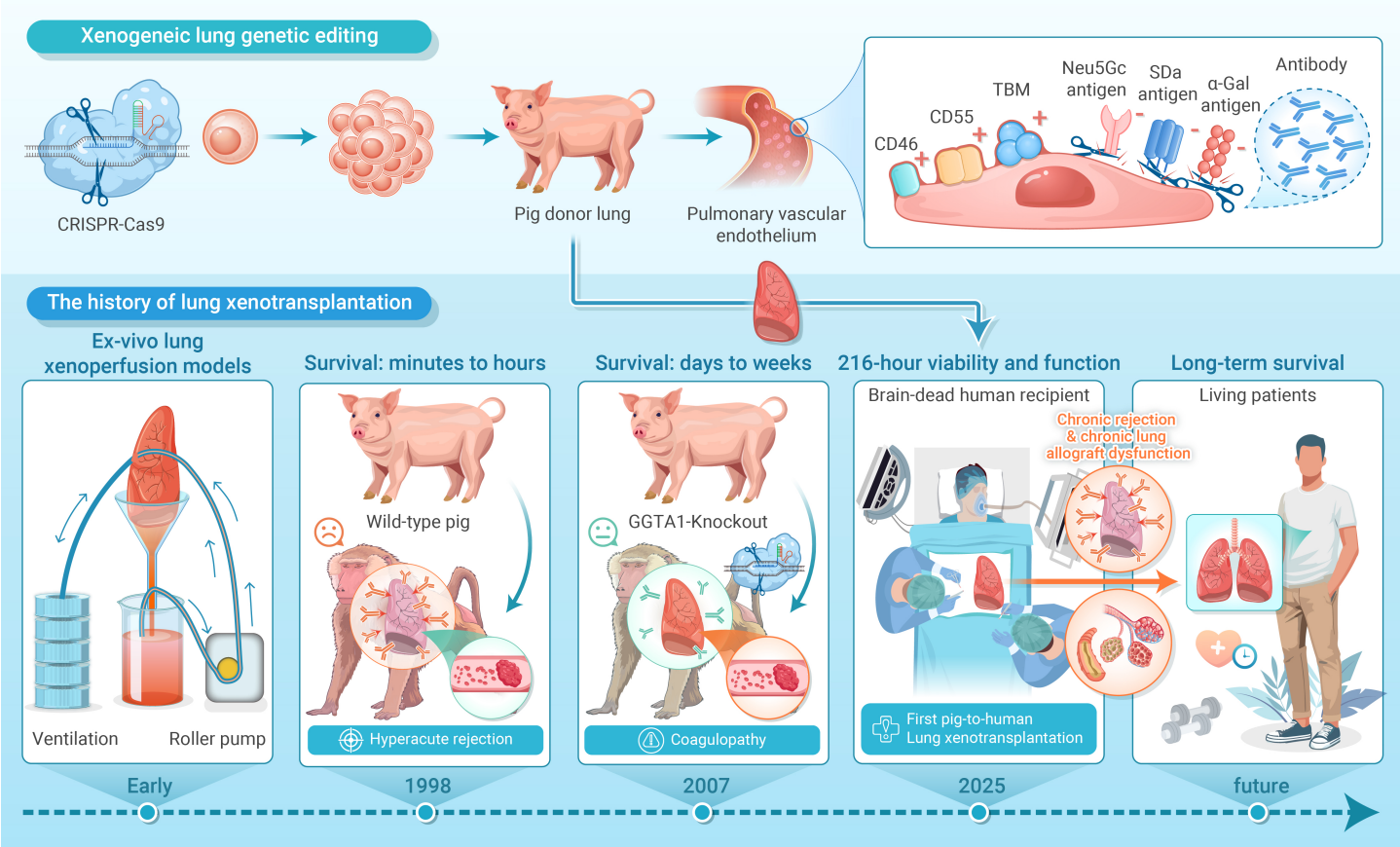

Figure 1. Historical milestones and key gene-editing strategies in lung xenotransplantation.

exploratory. Building on these models, He et al. strategically simplified the genetic design. This strategy focused on the knockout of key xenoantigens and modulation of the complement and coagulation pathways, thereby addressing the critical barriers of hyperacute rejection and complement-mediated injury. This reflects a conceptual shift from a "universal-donor" model toward an organ-tailored xenograft design. To mitigate the risk of hyperacute rejection, the knockout of *GGTA1*, *B4GALNT2*, and *CMAH* eliminated the principal glycan antigens (α-Gal, SDa, and Neu5Gc) from the porcine cell surface. To counter the lung's propensity for thrombosis and exuberant complement activation, transgenes encoding human complement regulators (CD46 and CD55) and thrombomodulin (TBM) were introduced. This "triple-knockout, triple-insertion" strategy represents the first gene-editing framework for lung xenotransplantation to demonstrate feasibility in a human recipient, and it provides a valuable logical blueprint for future donor

design. Despite these advances, xenogeneic lungs remain highly susceptible to post-transplant rejection and infection. Another key advance was a potent, multitarget immunosuppressive regimen, including T- and B-cell depletion, complement inhibition, and cytokine modulation. This regimen offers a critical reference for the development of clinically applicable immunosuppressive protocols in lung xenotransplantation. Informed by prior cardiac xenotransplantation failures potentially linked to porcine cytomegalovirus (PCMV), the team selected PERV-C-negative donor pigs to reduce endogenous viral risk. They also applied metagenomic sequencing and clinical biomarker screening to comprehensively exclude potential pathogens. No evidence of active infection was detected post-transplant, demonstrating a multi-tiered pathogen monitoring framework viable for clinical application. The study delineated for the first time the dynamic temporal landscape of the human immune response to a lung xenograft. This revealed challenges distinct from those in other forms of organ xenotransplantation and suggested that differentiated immunomodulatory strategies may be required during distinct post-transplantation phases. In summary, the central achievement of He et al. was the first successful validation of a lung-specific xenotransplantation strategy in a human model using a brain-dead recipient. This success reflected a finely tuned synergy among multigene editing, potent multitarget immunosuppression, and meticulous perioperative management. Remarkably, the six-gene-modified porcine lung maintained viability and function for 216 hours, thereby providing an essential proof-of-concept for the clinical translation of lung xenotransplantation. To contextualize this achievement within the broader trajectory of the field, Figure 1 provides an overview of the historical milestones and key gene-editing strategies that have shaped progress in lung xenotransplantation.

LIMITATIONS

The strategy reported by He and colleagues marks a milestone. However, it is essential to acknowledge its limitations, including the single-center, single-case study and the profound immunologic challenges it reveals. On one hand, the 216-hour observation period permitted monitoring of acute immune events but did not capture mid- to long-term graft function, chronic rejection, or risks associated with prolonged immunosuppression. Furthermore, although the brain-dead recipient model provides valuable data on human physiology and immune responses, its neuroendocrine disturbances and systemic inflammatory milieu differ from those in living recipients and may alter the magnitude and pattern of immune responses. Beyond technical hurdles, the clinical translation of lung xenotransplantation confronts significant practical and ethical challenges. A major practical impediment is scaling the production of genetically engineered pigs. These donor animals must meet stringent criteria for genetic stability and biosafety—a requirement that currently entails prohibitively high costs. Moreover, the use of brain-dead models and the eventual progression to clinical trials in living recipients remain subject to rigorous regulatory and ethical scrutiny. Both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require extensive nonclinical evidence of safety and efficacy before xenotransplantation can proceed. However, current guidelines do not explicitly define the role of brain-dead human models. Transitioning xenotransplantation into trials involving living recipients may also provoke public concern regarding human dignity and the ethical boundaries of research. Thus, establishing clear ethical guidelines and regulatory frameworks is essential to balance scientific progress with ethical responsibility, forming a necessary foundation for clinical translation.

FUTURE DIRECTION

Gene editing is the cornerstone of donor-lung engineering for xenotransplantation. He et al. demonstrated that current strategies remain insufficient to fully prevent immune-mediated rejection of pulmonary xenografts. Future breakthroughs will require more targeted, multigene-editing strategies. This could include introducing genes encoding proteins that further modulate complement activation (e.g., human CD59), enhance antioxidant and anti-inflammatory capacity (e.g., heme oxygenase-1), amplify anticoagulant signaling (e.g., human endothelial protein C receptor and tissue factor pathway inhibitor), and evade macrophage phagocytosis (e.g., human CD47). Equally important will be innovations in the gene-editing technologies themselves. CRISPR-Cas9 remains constrained by risks of off-target effects, incomplete edits, and challenges in engineering complex allelic combinations. Emerging tools, such as prime editing, promise more accurate, efficient, and safer genomic modifications. These tools provide a powerful technological engine to engineer more complex "humanized" donor organs. Despite an intensive, multitarget immunosuppressive regimen, significant antibody-mediated rejection (AMR) occurred. The authors noted that the protocol lacked CD40-CD40L costimulatory blockade. Substantial preclinical data indicate that anti-CD40L monoclonal antibodies suppress donor-specific antibody formation and markedly prolong graft survival in nonhuman primate xenotransplantation models.[4] Beyond optimizing donor engineering and immunosuppressive protocols, the development of noninvasive, high-sensitivity tools to monitor xenograft health will be critical. In xenotransplantation, preliminary progress has been made using assays that detect circulating porcine cell-free DNA to monitor graft injury and rejection. This approach shows promise as a real-time "sentinel" for early detection of xenograft rejection. Achieving long-term xenograft survival will ultimately require strategies that move beyond lifelong immunosuppression. Induction of immune tolerance may prove to be a decisive adjunct strategy. Mixed hematopoietic chimerism, which induces central tolerance, faces the major challenge of rapid clearance of porcine cells by the host immune system. By contrast, thymic co-transplantation has demonstrated encouraging results in kidney xenotransplantation. Transplantation of a thymic autograft under the capsule of the kidney (called a "thymokidney") mitigates the risk of host T-cell-mediated immune activation. Studies have shown that thymokidneys can prolong graft survival in pig-to-NHP models,[5] and have already been applied in pig-to-human xenotransplantation.[2] Extending this approach to the lung, however, poses unique challenges. Thymic tissue must be co-transplanted within the thoracic cavity, where ensuring vascularization and sustained viability is technically demanding. Moreover, the lung's uniquely complex immune environment raises additional uncertainty about the efficacy of this strategy.

CONCLUSIONS

The study by He et al. constitutes a milestone in lung xenotransplantation. It not only provides the first human evidence that gene-edited porcine lungs can achieve short-term functional viability, but also delineates the fundamental challenges imposed by the lung's unique anatomy and physiology. Future progress in this field will hinge on truly "lung-tailored" strategies. Breakthroughs will require multigene-edited donors, targeted immunomodulation, and development of novel tolerance-induction paradigms. This landmark work propels lung xenotransplantation into a new era of clinical investigation and provides important insights toward alleviating the persistent shortage of donor lungs. However, the path toward clinical lung xenotransplantation remains long and complex. In addition to further technological breakthroughs, practical challenges such as prohibitive costs and unresolved ethical issues must be addressed. Key prerequisites for clinical translation include expanding the production of gene-edited donor pigs, reducing manufacturing costs while ensuring biosafety, establishing clear ethical guidelines, and implementing a robust regulatory framework for xenotransplantation.

REFERENCES

1. Uzoigwe C. E. and Ali O. (2022). Genetically modified porcine-to-human cardiac xenotransplantation. *N. Engl. J. Med.* **387**:1337. DOI:10.1056/NEJMc2210401
2. Montgomery R. A., Stern J. M., Lonze B. E., et al. (2022). Results of two cases of pig-to-human kidney xenotransplantation. *N. Engl. J. Med.* **386**:1889–1898. DOI:10.1056/NEJMoa2120238
3. He J., Shi J., Yang C., et al. (2025). Pig-to-human lung xenotransplantation into a brain-dead recipient. *Nat. Med.* **31**:3388–3393. DOI:10.1038/s41591-025-03861-x
4. Mohiuddin M. M., Singh A. K., Corcoran P. C., et al. (2016). Chimeric 2C10R4 anti-CD40 antibody therapy is critical for long-term survival of GTKO.hCD46.hTBM pig-to-primate cardiac xenograft. *Nat. Commun.* **7**:11138. DOI:10.1038/ncomms11138
5. Yamada K., Yazawa K., Shimizu A., et al. (2005). Marked prolongation of porcine renal xenograft survival in baboons through the use of alpha1,3-galactosyltransferase gene-knockout donors and the cotransplantation of vascularized thymic tissue. *Nat. Med.* **11**:32–34. DOI:10.1038/nm1172

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AUTHOR CONTRIBUTIONS

Jiayang Xu, Fengjing Yang, Wenzhuo Luo, Yan Sun, Guoxu Tang: Visualization, Investigation, Writing-Original Draft. Sihua Wang, Song Tong: Conceptualization, Supervision, Writing-Review & Editing. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.