17. Xenotransplantation

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17.1 Renal Xenotransplantation

Cooper, D. K. C., Kobayashi, T. (2024). Xenotransplantation experiments in brain-dead human subjects-A critical appraisal. *American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, *24*(4), 520–525. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38158188/

- Review article of the 3 initial experiments utilizing decedents for renal xenotransplantation and 2 cases of heart xenotransplantation in decedents.

Xu, H., He, X. (2024). Developments in kidney xenotransplantation. *Frontiers in immunology*, *14*, 1242478. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38274798/

- A minireview summarizing key issues from an immunological perspective: discovery of key xenoantigens, investigations into key costimulatory signal inhibition, gene editing technology, and immune tolerance induction.

Rosales, I. A., et al. (2024). De novo membranous nephropathy in a pig-to-baboon kidney xenograft: A new xenograft glomerulopathy. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, *24*(1), 30–36. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37633449/

- Case report of the first incidence of de novo membranous nephropathy in a pig-to-baboon kidney xenograft and discussion of associated antibody-mediated rejection, C4d deposition, and thrombotic microangiopathy that eventually led to graft failure.

Jones-Carr, M. E., et al. (2024). C5 inhibition with eculizumab prevents thrombotic microangiopathy in a case series of pig-to-human kidney xenotransplantation. The Journal of clinical investigation, e175996. Advance online publication. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38269581/

- Case series describing use of complement inhibition at C5 in pig-to-human xenotransplantation.

Loupy, A., et al. (2023). Immune response after pig-to-human kidney xenotransplantation: a multimodal phenotyping study. Lancet (London, England), 402(10408), 1158–1169. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37598688/

- Phenotyping of 2 pig kidney xenografts to humans completed and evaluated. Data suggest that AMR may occur with a relatively high degree of AMR. Both xenografts showed increased expression of genes biologically related to a humoral response, including macrophage activation, NK cell burden, complement activation, and T-cell development.

Locke, J. E., Kumar V, Anderson, D., Porrett, P. M. (2023). Normal Graft Function After Pig-to-Human Kidney Xenotransplant. JAMA surgery, 158(10), 1106–1108. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37585176/

- Case report that sought to measure kidney function post-xenotransplantation by assessing creatinine clearance.

Tector, A. J., Adams, A. B., Tector, M. (2023). Current Status of Renal Xenotransplantation and Next Steps. Kidney360, 4(2), 278–284. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36821619/

- Review articles summarizing the current immunologic barriers facing xenotransplantation.

Cheung, M. D., et al. (2023). Spatiotemporal immune atlas of the first clinical-grade, gene-edited pig-to-human kidney xenotransplant. Research square, rs.3.rs-2382345. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36711785/

- Pre-clinical analysis to distinguish human versus pig immunologic activity within a xenograft using spatial transcriptomic data to determine targets for the utilization of current and future pharmacologic therapies.

Porrett, P. M., et al. (2022). First clinical-grade porcine kidney xenotransplant using a human decedent model. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 22(4), 1037–1053. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35049121/

- Preclinical model using a human decedent for xenotransplantation with a porcine kidney. The study sought to mimic clinical trial conditions to evaluate the following: hyperacute rejection prevention by genetic engineering, negative prospective cross-matching role in hyperacute rejection prevention, intraoperative complications, porcine-derived products detected in human blood, and evaluate of the best practices for the future clinical trials.

Hansen-Estruch, C., et al. (2023). Assessment of glomerular filtration and tubular secretion in baboons with life-supporting pig kidney grafts. *Xenotransplantation*, 30(2), e12795. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36820525/

- First study to report the glomerular filtration rate and tubular secretory function of pig renal xenografts in non-human primate recipients.

Hansen-Estruch, et al. (2023). Renin-angiotensin-aldosterone system function in the pig-to-baboon kidney xenotransplantation model. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, 23(3), 353–365. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36695679/

- Pig to non-human primate study evaluating the renin-aldosterone system post-kidney xenotransplantation and its potential role in post-transplant hypovolemia and hypotension.

Montgomery, R. A., et al. (2022). Results of Two Cases of Pig-to-Human Kidney Xenotransplantation. *The New England journal of medicine*, 386(20), 1889–1898. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35584156/

- Case report of two decedents received alpha-1,3-galactosyltransferase-knockout pigs to evaluate for hyperacute rejection.

17.2 Cardiac Xenotransplantation

Cooper, D. K. C., Cozzi, E. (2024). Clinical Pig Heart Xenotransplantation-Where Do We Go From Here?. *Transplant international: official journal of the European Society for Organ Transplantation*, *37*, 12592. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10869462/

- A review of University of Maryland's two patients to undergo pig cardiac xenotransplantation

Dickfeld, T., et al. (2024). Baseline 12-Lead Electrocardiographic Characteristics in Genetically Modified Porcine Cardiac Xenotransplant. Circulation, 149(2), 164–166. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38190447/

- Comparison of 12-lead electrocardiographic parameters in the porcine xenotransplant to the porcine heart in their native pig body.

Mohiuddin, M. M., et al. (2023). Graft dysfunction in compassionate use of genetically engineered pig-to-human cardiac xenotransplantation: a case report. Lancet (London, England), 402(10399), 397–410. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37393920/

- Case report describing a porcine cardiac xenotransplantation progression into graft dysfunction, including signs of antibody-mediated rejection, immune activation by IVIG, and reactivation of PCMV/PRV.

Hong, S. N., et al. (2023). Longitudinal Echocardiogram Imaging in the First Genetically Modified Porcine to Human Cardiac Xenotransplant. JACC. Cardiovascular imaging, Retrieved from: https://pubmed.ncbi.nlm.nih.gov/136813614/

- Descriptive report of echocardiogram series in porcine-to-human cardiac xenotransplant.

Strauss, E. R., et al. (2023). Intraoperative Management of an Orthotopic Porcine-to-Human Cardiac Xenotransplant. The Annals of thoracic surgery, 115(3), 784–786. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36621667/

- Intraoperative management of a single porcine-to-human cardiac xenotransplantation.

Goerlich, C. E., et al. (2023). The growth of xenotransplanted hearts can be reduced with growth hormone receptor knockout pig donors. The Journal of thoracic and cardiovascular surgery, 165(2), e69–e81. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34579956/

- Pig-to-baboon xenotransplantation with pig donors genetically engineered to knockout growth hormone receptor in an attempt to prevent hypertrophy post-transplantation.

Mohiuddin MM, Singh AK, Goerlich CE. Preclinical rationale and current pathways to support the first human clinical trials in cardiac xenotransplantation. Hum Immunol. 2023 Jan;84(1):34-42. doi: 10.1016/j.humimm.2022.07.001. Epub 2022 Jul 15. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/3585182/

- Summary of 10-years of pre-clinical research in cardiac xenotransplantation.

Moazami, N., et al. (2023). Pig-to-human heart xenotransplantation in two recently deceased human recipients. *Nature medicine*, 29(8), 1989–1997. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37488288/

- Case report of 10-gene-edited pigs into two brain dead human recipients.

Singireddy, S., et al. (2023). Genetic Engineering of Donor Pig for the First Human Cardiac Xenotransplantation: Combatting Rejection, Coagulopathy, Inflammation, and Excessive Growth. *Current cardiology reports*, 25(11), 1649–1656. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37938425/

- Case report detailing post-transplant course of the first porcine heart to adult human recipient. The report includes infectious complications, immunosuppression challenges, and ultimate non-rejection mediated graft failure.

Griffith, B. P., et al. (2022). Genetically Modified Porcine-to-Human Cardiac Xenotransplantation. The New England journal of medicine, 387(1), 35–44. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35731912/

- Case report detailing post-transplant course of the first porcine heart to adult human recipient.

17.3 Xenograft-related Infections

Saharia, K. K., et al. (2023). Heart of the matter-infection and xenotransplantation. Transplant infectious disease : an official journal of the Transplantation Society, e14206. Advance online publication. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38055610/

- Case conference discussion of infectious course of a cardiac xenotransplantation patient.

Hansen, S., et al. (2023). Detection of porcine cytomegalovirus, a roseolovirus, in pig ovaries and follicular fluid: implications for somatic cells nuclear transfer, cloning and xenotransplantation. *Virology journal,* 20(1), 15. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36707837

- Analysis of the mechanism of PCMV/PRV transmission in cloned transgenic pigs

Mehta, S. A., Saharia, K. K., Nellore, A., Blumberg, E. A., Fishman, J. A. (2023). Infection and clinical xenotransplantation: Guidance from the Infectious Disease Community of Practice of the American Society of Transplantation. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons, 23(3), 309–315. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36695690/

- The Infectious Disease Community of the American Society of Transplantation guidance on managing swine-derived organisms in xenotransplant recipients.

Groenendaal, H., et al. (2023). Expert opinion on the identification, risk assessment, and mitigation of microorganisms and parasites relevant to xenotransplantation products from pigs. *Xenotransplantation*, 30(5), e12815. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37616183/

- Systematic assessment and evaluation of possible pig microorganisms and parasites into three risk mitigation group.

Otabi, H., et al. (2023). Development of a panel for detection of pathogens in xenotransplantation donor pigs. Xenotransplantation, 30(6), e12825. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37771249/

- Analysis and validation of an expanded PCR panel for pathogen testing of donor pigs for xenotransplantation.

Denner, J., Jhelum, H., Hansen, S., Kaufer, B. B. (2023). Comparison of methods for the detection of porcine cytomegalovirus/roseolovirus in relation to biosafety monitoring of xenotransplantation products. Xenotransplantation, e12835. Advance online publication. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38088083/

- Comparison study of proposed methods to screen donor pigs for PCMV/PRV. Highlights the challenges with viral latency and timing of testing.

Nellore, A., Fishman, J. A. (2018). Donor-derived infections and infectious risk in xenotransplantation and allotransplantation. Xenotransplantation, 25(4), e12423. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30264880/

- Article discussing the need for infectious risk assessment, identification of interspecies organisms, and methods of screening for infectious disease transmission.

Fishman J. A. (2014). Assessment of infectious risk in clinical xenotransplantation: the lessons for clinical allotransplantation. Xenotransplantation, 21(4), 307–308. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/25098837/

- Proposal of surveillance for unknown pathogens transmission as a result of xenotransplantation.

Fishman, J. A., Scobie, L., & Takeuchi, Y. (2012). Xenotransplantation-associated infectious risk: a WHO consultation. Xenotransplantation, 19(2), 72–81. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/22497509/

- Early assessment of the infectious risks that may be associated with future xenotransplantation.

17.4 Coagulopathy

Burlak, C., et al. (2023). Xenoreactive antibodies in α-granules of human platelets bind pig liver endothelial cells. *Xenotransplantation*, 30(6), e12834. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37971870/

- In vitro study suggesting platelet α-granules contain IgM and IgM that bind xenoantigens that may play a role in thrombocytopenic coagulopathy.

17.5 Antibody-mediated Rejection

Habibabady, Z., et al. (2023). Antibody-mediated rejection in xenotransplantation: Can it be prevented or reversed?. *Xenotransplantation*, 30(4), e12816. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37548030/

- Review of clinical, mechanistic, and histopathological features of acute antibody mediated rejection in pig xenotransplantation.

Adams, A. B., et al. (2021). Anti-C5 Antibody Tesidolumab Reduces Early Antibody-mediated Rejection and Prolongs Survival in Renal Xenotransplantation. *Annals of surgery*, 274(3), 473–480. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34238812/

- Porcine knock-out kidneys to non-human primates preclinical trial using early tesidolumab. Tesidolumab treated kidneys protected renal xenografts from early antibody-mediated rejection.

17.6 Immunosuppression

Zhou, Q., et al. (2022). Current status of xenotransplantation research and the strategies for preventing xenograft rejection. Frontiers in immunology, 13, 928173. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/35967435/

- Review of the mechanisms for rejection in xenotransplantation and the current strategies to prevent rejection including: glucocorticoids, calcineurin inhibitors, antiproliferative agents, costimulatory blockers, complement inhibitors, monoclonal and polyclonal antibodies, and genetic engineering.

Yoon, C. H., et al. (2020). Long-term survival of full-thickness corneal xenografts from α1,3-galactosyltransferase gene-knockout miniature pigs in non-human primates. Xenotransplantation, 27(1), e12559. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/31566261/

- Rhesus monkeys were transplanted with full-thickness corneal grafts from pigs. The subjects received steroids, basiliximab, intravenous immunoglobulin, and tacrolimus with or without an anti-CD20 antibody.

Längin, M., et al. (2018). Consistent success in life-supporting porcine cardiac xenotransplantation. Nature, 564(7736), 430–433. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/30518863/

- Nonhuman primates transplanted with porcine hearts received anti-CS antibody, anti-thymocyte-globulin and humanized anti-CD40L PASylated antigen-binding fragment. Methylprednisolone was gradually decreased during the maintenance period.

Shin, J. S., et al. (2018). Pre-clinical results in pig-to-non-human primate islet xenotransplantation using anti-CD40 antibody (2C10R4)-based immunosuppression. Xenotransplantation, 25(1), 10.1111/xen.12356. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29057561/

- Rhesus monkeys were transplanted with porcine islets. Immunosuppression regimens included: anti-CD40 only, anti-CD40 + belatacept, anti-CD40 + tacrolimus. All subjects received anti-thymocyte globulin, cobra venom factor, adalimumab, and sirolimus.

Iwase, H., et al. (2015). Pig kidney graft survival in a baboon for 136 days: longest life-supporting organ graft survival to date. Xenotransplantation, 22(4), 302–309. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/26130164/

- Porcine kidney graft transplanted into a baboon was given the following immunosuppressive therapy: ATG + anti-CD20mAb for induction and anti-CD40mAb + rapamycin + corticosteroids. The subject also received Anti-TNF-α and anti-IL-6R.

Muller, Y. D., et al. (2010). Anti-CD154 mAb and rapamycin induce T regulatory cell mediated tolerance in rat-to-mouse islet transplantation. PloS one, 5(4), e10352. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/20436684/

Singh, A. K., Horvath, K. A., & Mohiuddin, M. M. (2009). Rapamycin promotes the enrichment of CD4(+)CD25(hi)FoxP3(+) T regulatory cells from naïve CD4(+) T cells of baboon that suppress antiporcine xenogenic response in vitro. Transplantation proceedings, 41(1), 418–421. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/29057561/

- Study of inducing the production of Treg cells by using rapamycin to induce functional regulatory T-cells.

Zhong, R., et al. (2003). The long-term survival of baboon-to-monkey kidney and liver xenografts. *Xenotransplantation*, 10(5), 398–409. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/12950983/

- Baboon-to-monkey kidney xenotransplantation utilizing cyclosporine and steroids with the addition of the following: cyclophosphamide, mycophenolate mofetil, or cyclophosphamide + rapamycin.

Contreras, J. L., Eckhoff, D. E., Cartner, S., Bilbao, G., Ricordi, C., Neville, D. M., Jr, Thomas, F. T., & Thomas, J. M. (2000). Long-term functional islet mass and metabolic function after xenoislet transplantation in primates. Transplantation, 69(2), 195–201. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/10670626/

- Study with non-human-primates undergoing islet xenotransplantation. The subjects received anti-CD3-immunotoxin, cyclosporine, cyclosporine microemulsion, and methylprednisolone.

Rijkelijkhuizen, J. K., Bouwman, E., van der Burg, M. P., Ringers, J., Ossevoort, M. A., Kuhn, E. M., Frost, P., & Jonker, M. (2000). Successful suppression of the early rejection of pig islets in monkeys. *Cell transplantation*, 9(6), 909–912. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/11202577/

- Preclinical model of transplanted cultured porcine islets under the capsule of both kidneys in four cynomolgous monkeys. The monkeys received an immunosuppressive regimen of cyclophosphamide, cyclosporin A, and prednisolone. No signs of rejection were found between 3 and 7 days post-transplant.

Michler, R. E., McManus, R. P., Smith, C. R., Sadeghi, A. N., Marboe, C. C., Reemtsma, K., & Rose, E. A. (1987). Prolongation of primate cardiac xenograft survival with cyclosporine. Transplantation, 44(5), 632–636. https://doi-org.proxy.library.vanderbilt.edu/10.1097/00007890-198711000-00007

- Hearts of outbred cynomolgus monkeys were transplanted into the necks of outbred baboons. Hyperacute rejection was prevented by a dose of cyclosporine.

17.7 Miscellaneous

Kamberi, S., & Meier, R. P. H. (2024). Xenotransplantation literature update March 2023-November 2023. *Xenotransplantation*, *31*(1), e12837. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/38334060/

- Provides a literature update of xenotransplantation from 2023, focusing on studies in man, regulations, immunosuppression, infectious disease, and AMR

Arabi, T. Z., Sabbah, B. N., Lerman, A., Zhu, X. Y., Lerman, L. O. (2023). Xenotransplantation: Current Challenges and Emerging Solutions. *Cell transplantation*, *32*, 9636897221148771. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/36644844/

- Review to summarize recent xenotransplantation advancements, the role of immunity in xenograft rejection, and biomarkers.

Bobier, C., Rodger, D., & Hurst, D. J. (2023). Xenotransplantation and lifelong monitoring. American journal of transplantation: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons, S1600-6135(23)00871-7. Advance online publication. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/37995839/

- Summary of 2022 FDA meeting on key considerations facing xenotransplantation in human clinical trials.

Hu X, Geng Z, Gonelle C, Hawthrone WJ, Deng S, Buhler L. (2022). International Human Xenotransplantation Inventory: A 10-year Follow-up. *Transplantation*, 106(9), 1713–1716. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/34982756/

- 10-year review of human xenotransplantation cases with data collected from scientific journals, international congresses, internet searches, and declarations of International Xenotransplantation Association members
- Since last review (1995-2010) clinical activities were reduced but all were officially approved through local protocols /regulations

Siems C, Huddleston S, John R. (2022). A brief history of xenotransplantation. *The Annals of Thoracic Surgery*, 113(3), 706–710. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/3568782/

- Expert panel review of history of xenotransplantation

Ladowski, J. M., Hara, H., Cooper, D. (2021). The Role of SLAs in Xenotransplantation. *Transplantation*, *105*(2), 300–307. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32433239/

- Summarizes the challenges that swine leukocyte antigens (SLA) pose for xenotransplantation, and describes techniques for mutating target SLA amino acids.

Lu T, et al (2020). Xenotransplantation: Current Status in Preclinical Research. *Front Immunol.* 2019; 10: 3060. Retrieved from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6989439/

- Xenotransplantation has been proposed as an approach to solve the problem of human organ shortage. This is a summary of the history of xenograft research, immunological mechanisms of hyperacute and acute xenograft rejection, and longest survival time of solid organs in preclinical models.

Tector, AJ, Mosser M, Tectom M, Bach JM (2020). The Possible Role of Anti-Neu5Gc as an Obstacle in Xenotransplantation. *Front Immunol.* 2020, 11,622. Retrieved from: https://pubmed.ncbi.nlm.nih.gov/32351506/

- This article summarizes data on Neu5Gc immunogenicity and its potential impact on limiting xenotransplantation in humans.

Ekser, B, et al. (2012). Clinical xenotransplantation: the next medical revolution? *Lancet*, 379, 672-83. Retrieved from: https://www.ncbi.nlm.nih.gov/pubmed/22019026

- Xenotransplantation was initially limited by hyperacute rejection. However, as genetic manipulation has largely allowed many of those issues to be resolved, the focus has shifted to overcoming the other barriers to xenotransplantation.