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ORIGINAL ARTICLE

Results of Two Cases of Pig-to-Human Kidney Xenotransplantation

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BACKGROUND

Xenografts from genetically modified pigs have become one of the most promising solutions to the dearth of human organs available for transplantation. The challenge in this model has been hyperacute rejection. To avoid this, pigs have been bred with a knockout of the alpha-1,3-galactosyltransferase gene and with subcapsular autologous thymic tissue.

METHODS

We transplanted kidneys from these genetically modified pigs into two brain-dead human recipients whose circulatory and respiratory activity was maintained on ventilators for the duration of the study. We performed serial biopsies and monitored the urine output and kinetic estimated glomerular filtration rate (eGFR) to assess renal function and xenograft rejection.

RESULTS

The xenograft in both recipients began to make urine within moments after reperfusion. Over the 54-hour study, the kinetic eGFR increased from 23 ml per minute per 1.73 m² of body-surface area before transplantation to 62 ml per minute per 1.73 m² after transplantation in Recipient 1 and from 55 to 109 ml per minute per 1.73 m² in Recipient 2. In both recipients, the creatinine level, which had been at a steady state, decreased after implantation of the xenograft, from 1.97 to 0.82 mg per deciliter in Recipient 1 and from 1.10 to 0.57 mg per deciliter in Recipient 2. The transplanted kidneys remained pink and well-perfused, continuing to make urine throughout the study. Biopsies that were performed at 6, 24, 48, and 54 hours revealed no signs of hyperacute or antibody-mediated rejection. Hourly urine output with the xenograft was more than double the output with the native kidneys.

CONCLUSIONS

Genetically modified kidney xenografts from pigs remained viable and functioning in brain-dead human recipients for 54 hours, without signs of hyperacute rejection. (Funded by Lung Biotechnology.)
E VERY YEAR, THE NUMBER OF PERSONS waiting for an organ transplant increases while the organ supply remains relatively stagnant. More than 100,000 persons are currently on the waiting list in the United States, and only one third of these patients will eventually receive a transplant.¹ Xenotransplantation (the transplanting of cells or organs across species) has the potential to address the greatest unmet need in transplantation by providing an unlimited, renewable source of lifesaving organs. The pig has been identified as the most acceptable donor species for xenotransplantation into humans.² Great progress has been made in modifying the porcine genome to reduce immunologic barriers and potential incompatibilities between pigs and humans.³ Kidneys from genetically modified pigs have been transplanted into nonhuman primates, with steady improvements in success rates, and survival now surpasses 1 year; however, questions remain as to whether these results can translate to humans.⁴⁻⁷

Old-world primates, apes, and humans do not express galactose-alpha-1,3-galactose (called “alpha-gal”), a terminal carbohydrate modification of many glycoproteins and glycolipids that is present in most species and is made by an enzyme called alpha-1,3-galactosyltransferase.⁸,⁹ Since many microbial species express the alpha-gal epitope, circulating antibodies that recognize alpha-gal develop in humans, and up to 1% of circulating antibodies are targeted against this epitope.¹⁰ These antibodies cause hyperacute rejection of transplanted alpha-gal–positive organs. A proprietary porcine model incorporating the deletion of alpha-1,3-galactosyltransferase (i.e., alpha-1,3-galactosyltransferase–knockout) from the pig genome could mitigate a major immune barrier to xenotransplantation.

Although the elimination of alpha-gal substantially reduces the preformed xenobody response, the adaptive immune response to xenografts remains a threat because the amino acid variations between pigs and humans represent the potential for the creation of a wide range of neoantigens that can be recognized by the human immune system. Transplantation of a thymic autograft from the pig under the capsule of the kidney (called a “thymokidney”) is a novel approach to mitigating the risk of host T-cell–mediated immune activation.¹⁰ The thymus supports T-cell development by positive and negative selection of immature T cells. Studies have shown that thymokidneys can promote immune tolerance and reduce the risk of late allograft rejection.¹¹⁻¹⁴ On the basis of such evidence, we transplanted kidneys from genetically modified pigs into two brain-dead human recipients (whose circulatory and respiratory activity was maintained on ventilators) to assess renal function and xenograft rejection.

M E T H O D S


The ethical foundations for the concept of whole-body donation and research in recently deceased persons have been previously published.¹⁵⁻²¹ Each of the recipients of the xenografts was declared brain-dead by the clinical care team according to standard criteria at the site where the decedent had been hospitalized. Once all the possibilities for organ placement had been exhausted, eligibility for the study was determined. If the family agreed to pursue the experimental xenograft transplantation, the primary investigator of the study (the first author) was contacted, and the study was described to the authorized family decision maker on a recorded telephone line. Written informed consent was obtained, and the decedent was transferred to the intensive care unit (ICU) at the New York University (NYU) Langone Hospital for initial assessment and stabilization before being transferred to a purpose-built isolation ICU and operating room.

In preparation for the transplantation, we contacted the Food and Drug Administration and were informed that an Investigational New Drug application was required only for living human participants involved in research. In addition, the New York State Department of Health reviewed our plan for zoonotic disease surveillance, handling of hazardous materials, and embalming of the body before transport and burial. The NYU Research on Decedents Oversight Committee reviewed the protocol and provided oversight. We performed the two studies with the xenografts that are reported here and have not performed any others using this model.
The study was supported by Lung Biotechnology, a wholly owned subsidiary of United Therapeutics. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

ORGAN SELECTION AND PROCUREMENT
The genetically modified alpha-1,3-galactosyltransferase–knockout pigs were supplied by Revivicor, a subsidiary of United Therapeutics. Preparation and procurement of the thymokidneys were performed at the Revivicor facility. The porcine thymus had been implanted under the renal capsule approximately 2 months before the organs were obtained.22,23 Organs were obtained by means of midline laparotomy performed by NYU surgeons. Once the kidneys had been obtained, they were flushed with Static Preservation Solution (SPS-1, Organ Recovery Systems) and transported by air in static cold storage before implantation.

INFECTIOUS DISEASE SURVEILLANCE
An infectious disease surveillance protocol was developed and implemented for the transplantation of a porcine kidney into a human in a non-survival study. We reviewed the medical literature, national regulatory policies on xenotransplantation into humans, and donor-pig, herd-specific infectious disease control protocols for stratification of zoonotic pathogen risks and for the development of a testing and sample storage protocol.24-26 Porcine endogenous retrovirus (PERV) was identified as the primary pathogen involving a risk of transmission from porcine xenografts, and a strategy for risk mitigation was implemented (Fig. S2). The proprietary pigs that were used in this study were positive for PERV-A and PERV-B but not for PERV-C, which reduced the risk of transmission.

TRANSPLANTATION, AFTERCARE, AND IMMunosUPPRESSION
The vessels of the xenograft were anastomosed to the femoral artery and vein, and the xenograft was left outside the body on the top of the thigh for ease of direct observation for signs of hyperacute rejection and for the performance of serial biopsies. A cannula was placed in the xenograft ureter, and urine output was monitored continuously and measured hourly. A Foley catheter was placed to measure urine output from the native kidneys separately from that of the xenograft.

Immunosuppression consisted of 1000 mg of methylprednisolone daily and 1000 mg of intravenous mycophenolate mofetil twice daily until the kidneys were explanted from the recipients at 54 hours after transplantation. The decedent recipients were given mannitol and furosemide to promote xenograft diuresis. Both recipients received heparin drips that were adjusted to therapeutic ranges for systemic anticoagulation.

HISTOLOGIC ANALYSIS AND ASSESSMENT OF RENAL FUNCTION
Hematoxylin and eosin staining, C4d staining by immunohistochemical testing or immunofluorescence, and electron microscopy were performed on all biopsy samples (see the Supplementary Methods section in the Supplementary Appendix). Biopsy samples were reviewed by a pathologist (the sixth author), and the findings were scored according to the standard Banff 2017 scoring system.27 We used the kinetic estimated GFR (eGFR) formula to analyze kidney function because it has been validated as being more accurate than standard eGFR calculation formulas in the context of acute kidney injury or renal recovery.28

FLOW CYTOMETRIC IGG AND IGM BINDING ASSAY
Peripheral-blood mononuclear cells were prepared for IgG and IgM binding assays (see the Supplementary Methods section). Forward-scatter and side-scatter gating was used to identify pig lymphocytes on the basis of size and granularity (cell-complexity gating). On the lymphocyte gate, the relative amount of bound non–alpha-gal anti-pig IgG or IgM was determined by calculation of the median channel shift from the negative control (secondary antibody only, no serum).

REAL-TIME COMPLEMENT-DEPENDENT CYTOTOXICITY ASSAY
Serum samples that were obtained from the recipient were tested by real-time complement-dependent cytotoxicity assay on porcine aortic endothelial cells obtained from the same pig as the transplanted thymokidneys (in Recipient 2) or a related surrogate (in Recipient 1). Details are provided in the Supplementary Methods section.
RESULTS

KIDNEY FUNCTION AND ELECTROLYTE HOMEOSTASIS

The first xenotransplantation was performed on September 25, 2021, and the second on November 22, 2021. The cold ischemic times were 7 hours in the first transplantation and 6 hours in the second. After implantation and reperfusion, the xenografts immediately appeared pink and began to make urine within minutes (Fig. 1).

In both recipients, the creatinine level, which had been at a steady state, decreased after implantation of the xenograft, from 1.97 to 0.82 mg per deciliter (from 170 to 70 μmol per liter) in Recipient 1 and from 1.10 to 0.57 mg per deciliter (from 100 to 50 μmol per liter) in Recipient 2. The calculated kinetic eGFR increased, from 23 ml per minute per 1.73 m² of body-surface area immediately before implantation to 62 ml per minute per 1.73 m² after transplantation in Recipient 1 and from 55 to 109 ml per minute per 1.73 m² in Recipient 2 (Fig. 2).

Hourly urine output with the xenograft was more than double that with the native kidneys (Fig. 2). The mean hourly xenograft urine output in Recipient 1 was 406 ml during the first 24-hour period and 255 ml during the second 24-hour period; in Recipient 2, the mean hourly output was 744 ml and 571 ml in the first and second 24-hour periods, respectively. At the end of the study, Recipient 1 had a spot urinary protein-to-creatinine ratio of 3.3; however, this information is difficult to interpret because there was microscopic hematuria. Recipient 2 had no proteinuria at the end of the study.

Selective measurements of the contribution of the xenograft and native kidneys to the total change in the kinetic eGFR were not performed, so conclusions about isolated xenograft function cannot be made from these data. No major alterations were seen in the recipients’ serum electrolyte levels except for those commonly seen in brain-dead donors (e.g., hypernatremia from diabetes insipidus) and in recipients of a renal transplantation (e.g., hypokalemia) (Fig. S3).

HISTOLOGIC AND ULTRASTRUCTURAL FINDINGS

Biopsies that were performed in the two xenografts 6 hours after reperfusion showed no evidence of hyperacute rejection. The results of subsequent core biopsies performed at 24 hours and 48 hours were similar to those of the biopsy performed at 6 hours and showed no interstitial inflammation, tubulitis, arteritis, glomerulitis, peritubular capillaritis, or any C4d deposition in the peritubular capillaries (data not shown). Banff scoring, which is a standard, systematic histologic assessment of kidney graft injury across multiple tissue elements, was negative for both xenografts, except for focal C4d staining in the second xenograft. (Details of the Banff scoring system and the scores in the two xenografts at 54 hours are provided in Table S1.) Neither xenograft satisfied the Banff 2017 criteria for antibody-mediated rejection. Wedge biopsies that were performed on the explanted kidneys 54 hours after reperfusion did not show any features suggestive of T-cell–mediated rejection in either xenograft (Fig. 3A and 3B).

Glomerular capillary loops did not show microcirculatory inflammatory infiltrates. Very mild peritubular capillaritis was noted in the xenograft for Recipient 1 but not in the xenograft for Recipient 2. Immunofluorescence microscopy did not reveal C4d deposition in the xenograft for Recipient 1, but focal C4d deposition was present at 54 hours in the xenograft for Recipient 2 (Fig. 3C and 3D). Arteritis and interstitial hemorrhage were not present in either case. Electron microscopy revealed normal thickness of the glomerular basement membrane and un-effaced podocyte foot processes in the two xenografts (Fig. 3E and 3F).

PRESENCE OF NON–ALPHA-GAL, ANTI-PORCINE IGM AND IGG ANTIBODIES

To determine the presence, titer, and possible physiologic significance of human IgM and IgG directed against non–alpha-gal epitopes, serum samples that had been obtained from the two recipients before transplantation were tested by flow cytometry on pig peripheral-blood mononuclear cells and by complement-dependent cytotoxicity assay on pig endothelial cells. Serum samples from the two recipients were compared with a known positive serum (control) sample with a known titer and reactivity against the target cells on the complement-dependent cytotoxicity assay (data not shown). The IgM antibody strength in Recipient 1 was similar to that in the control sample; however, samples from Recipient 2 showed a stronger IgM binding reaction and a higher titer than the control sample.
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recipient or the presence of microchimerism
to support the transmission of PERV in either
Porcine Endogenous Retrovirus Assays
Peripheral-blood mononuclear cells that had been
C-reactive protein, interferon-γ, interleukin-2 re-
tor acute rejection in pig-to-human transplanta-
and cytokine activation heralded irreversible hy-
recipient instability. Hyperacute rejection did not
CMAH) and beta-1,4-N-acetylglactosaminyl-
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Preclinical studies have shown that humans
have varying levels of preformed antibodies to
other pig carbohydrates, principally those that
are enzymatically modified by cytidine mono-
phospho–N-glycolyneuraminic acid hydroxylase
(CMAH) and beta-1,4-N-acetylglactosaminyl-
transferase 2 (β4GALNT2), which can be con-
tributors to xenograft loss. However, hu-
mans and nonhuman primates have different
expression and responses to epitopes that are
known to have been lost during evolution. With

**SYSTEMIC RESPONSES TO THE XENOGRAFT**

C-reactive protein, interferon-γ, interleukin-2 re-
ceptor, and interleukins 1β, 2, 4, 5, 6, 8, 10, 12, and 13 were measured in the two recipients at regular intervals. No specific biochemical evi-
dence of inflammation could be attributed to reperfusion of the xenograft. The platelet and white-cell counts remained stable. Reperfusion was not associated with any hemodynamic in-
ability, and no vasopressor support was neces-
sary to maintain the blood pressure. Details are
provided in Figure S5.

**PORCINE ENDOGENOUS RETROVIRUS ASSAYS**

Peripheral-blood mononuclear cells that had been
obtained at baseline and at 6 hours and 24 hours
in Recipient 1 and at baseline and at 24 hours,
48 hours, and 53 hours in Recipient 2 were all
negative for PERV-A, PERV-B, PERV-C, and PRPL4
(plastid ribosomal protein L4) according to
reverse-transcriptase–polymerase-chain-reaction
and quantitative real-time polymerase-chain-
reaction assays (Fig. S6). There was no evidence
to support the transmission of PERV in either
recipient or the presence of microchimerism
(i.e., the detection of circulating pig cells that,
theoretically, could increase the risk of PERV
transmission). Blood samples from all the study
personnel were successfully obtained and stored.
No breaches in isolation precautions were identi-
fied during the study.

**DISCUSSION**

Our study showed that in the two decedents in
whom we implanted alpha-1,3-galactosyltransfer-
erase–knockout pig kidneys, there was immedi-
ate urine output, doubling of the kinetic eGFR,
and no clinical evidence of dysregulated coagu-
lation, complement, systemic inflammation, or
recipient instability. Hyperacute rejection did not
occur, and with the exception of early, focal C4d
deposition (a possible sign of an early antibody-
mediated process), there was no histologic or im-
munohistologic indication of antibody-mediated
injury from preformed xenoantibodies, despite a
positive cytotoxic crossmatch in Recipient 2.

It has long been known that vascular rejection
occurs within a few minutes after reperfu-
sion in organs transplanted across phylogeneti-
cally distinct species. Key clinical experiments
that were performed in the 1990s serve as his-
torical reference points for the results presented
here. Breimer and colleagues performed ex-
vivo perfusion studies involving two patients
who received preconditioning with plasmapher-
esis, and their arteriovenous fistulas were used
to circulate blood through wild-type pig kidneys.
The studies were terminated after 15 minutes in
the first patient owing to hypotension and chest
pain (with electrocardiographic changes) and
after 65 minutes in the second patient owing to
increasing resistance to flow through the kid-
ney. Although both kidneys made some urine,
they showed substantial evidence of hyperacute
rejection. In the experiment by Breimer and
colleagues and in other studies in which human
blood has been used to perfuse unmodified pig
kidneys, features such as profound thrombocy-
topenia, neutropenia, complement deposition,
and cytokine activation heralded irreversible hy-
peracute rejection triggered by naturally occur-
ring human antibodies targeting alpha-gal car-
bohydrate epitopes.

The use of genetically modified pigs that lack
the alpha-gal epitope is a straightforward type of
genetic modification to test in clinical trials in-
volved humans, and our results suggest that the
elimination of alpha-gal alone can prevent hy-
peracute rejection in pig-to-human transplanta-
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transferase 2 (β4GALNT2), which can be con-
tributors to xenograft loss. However, hu-
mans and nonhuman primates have different
expression and responses to epitopes that are
known to have been lost during evolution. With
A  Recipient 1, after Perfusion

B  Recipient 1, at 54 Hr

C  Recipient 2, after Perfusion

D  Recipient 2, at 54 Hr

E  Urine Drainage System
Pig-to-Human Kidney Xenotransplantation

the use of similarly simple gene-editing strategies, extended graft survival of up to 435 days has been observed in rhesus monkeys that received kidneys from double xenoantigen (alpha-1,3-galactosyltransferase and β4GALNT2)–knockout pigs. Other research groups have increased the complexity of genetic modifications, including the addition of complement and coagulation regulatory proteins, yielding good results of renal xenograft survival in primates.6 The variable expression of transgenes, both within pig tissues and among individual pigs, will pose considerable challenges in producing a consistent xenograft for transplantation into humans. In our pig construct, the addition of the thymus autograft may have provided additional protection from adaptive human immune responses to pig neoantigens. In our study, however, the follow-up period was too short for the thymus transplant to exert an effect on the T-cell repertoire. Still, the demonstration of preserved thymic architecture and revascularization is encouraging, and the thymokidney may eventually facilitate reduction in immunosuppression (Fig. S7).

The two recipients were tested before xenotransplantation and found to be HLA antibody–negative. Crossmatching showed that Recipient 1 had low levels of xenoreactive antibodies and minimal serum cytotoxicity that was probably due to IgM. Recipient 2 had moderate levels of xenoreactive IgM and IgG. Despite a positive crossmatch on the complement-dependent cytotoxicity assay, we observed no glomerulitis or margination in the peritubular capillaries and only focal C4d staining (in Recipient 2). Immunofluorescence staining for IgG showed minimal deposition in the glomeruli in Recipient 1 and mild-to-moderate deposition in Recipient 2. Neither xenograft had IgG deposition. Because IgM is confined to the vascular space, it can, theoretically, be removed with plasmapheresis, which could be incorporated into future protocols involving humans. (For technical reasons, plasmapheresis is difficult in primates.) Antibody to non–alpha-gal epitopes can be present in humans at varying strengths, and pretransplantation xeno-crossmatches (mixing of the human recipient serum with donor pig endothelial cells to determine whether the cells are lysed in the presence of complement) will be neces-

**Figure 1 (facing page).** Photographs of the Thymokidney in Situ.

Panel A shows the thymokidney just after reperfusion in Recipient 1; the ureter is on the right side. Panel B shows the thymokidney in Recipient 1 at 54 hours just after reperfusion; the thymokidney was pink and viable without outward signs of ischemia or infarction. Panel C shows the thymokidney immediately after reperfusion in Recipient 2, and Panel D shows the kidney at 54 hours. Panel E shows the setup of the ureter connection to the gravity drainage system (to isolate the urine obtained from the thymokidney) and the plastic silo.

**Figure 2.** Mean Hourly Urine Output and Kinetic Estimated Glomerular Filtration Rate (eGFR).

Shown is the mean hourly urine output from the native bladder and the thymokidney in Recipient 1 (Panel A) and Recipient 2 (Panel B). The kinetic eGFR was calculated at each time point and showed progressive increases after implantation of the kidney.
Figure 3. Photomicrographs of Biopsy Samples from Pig Kidneys Explanted from the Recipients 54 Hours after Reperfusion.

Samples with hematoxylin and eosin staining (Panels A and B) revealed normal-appearing glomeruli with capillary loops, which showed no evidence of microvascular inflammation (arrowheads), and tubulointerstitium with no demonstrable lymphocytic infiltration (arrows). Immunofluorescence microscopy of a sample from Recipient 1 revealed no C4d staining in the peritubular capillaries (Panel C). Immunofluorescence microscopy of a sample from Recipient 2 revealed focal C4d staining in the peritubular capillaries (Panel D, arrowhead). Ultrastructural imaging at the same time points (Panels E and F) showed glomerular capillary loops with a normal-appearing glomerular basement membrane (arrows) and intact podocyte foot processes (arrowheads).
sary to determine compatibility in xenotransplantation into living humans.

The main limitation of this study is its short follow-up, which was related to the practical restrictions imposed by the development of this protocol in recently deceased persons. It is important to parse out which questions this study does and does not address on the basis of the short follow-up. We found preserved histologic architecture, both on light microscopy and electron microscopy, and the absence of substantial immune-mediated injury. In contrast to the development of proteinuria and nephrotic syndrome that have been reported in pig-to-baboon renal xenotransplantation studies, in our study, electron microscopy that was performed at 54 hours after reperfusion revealed completely intact architecture with preserved glomerular basement membrane and podocytes in the two xenografts.

Finally, the risk of infection from PERV that is present in the pig genome has caused concern historically, although the virus has never been transmitted to humans. The proprietary porcine herd that was used in this study undergoes routine surveillance for all known zoonotic pathogens. Future studies with increased time of exposure to xenografts may be able to evaluate the long-term safety of xenotransplantation; still, this risk is thought to be extremely low. Our study of two successful renal xenotransplantations is reassuring in that, with the use of organs from alpha-1,3-galactosyltransferase–knockout pigs with a negative or low positive cytotoxic xeno-crossmatch, the risk of hyperacute rejection was low and immediate catastrophic failure was unlikely. An assessment of the durability of positive outcomes in this model, as well as adaptive immune responses, will require longer-term studies involving recently deceased humans or clinical trials involving humans.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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