Current Research Trend in Xenotransplantation

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Current Status of Xenotransplantation Research

From Genetically Engineered Pigs to Clinical Trials

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The Current Status of Organ Transplantation in South Korea

(Ministry of Health and Welfare, KONOS, 2024)

54,789

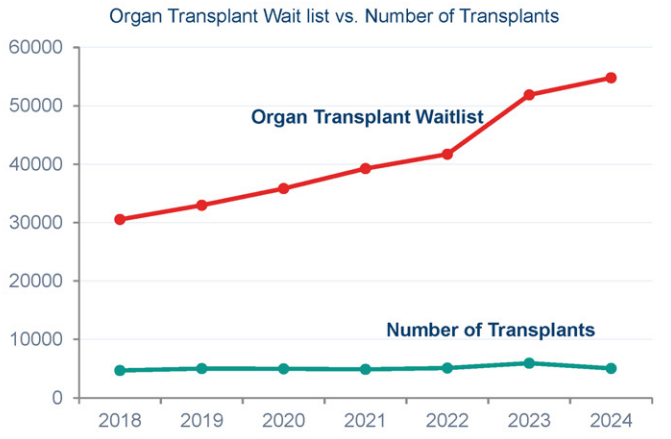
Organ transplant candidates
(As of 2024)

7.96 p/day

On the transplant waiting list
Average daily deaths

11%

Compared to the Number of People
on the Waiting List
Annual Transplant Rate



KONOS (국립장기조직혈액관리원), Ministry of Health & Welfare, 2024

Global Organ Shortage: An Unmet Medical Crisis

~106,000

Waitlisted in
the US alone

17/day

Americans die
waiting

>800,000

Deaths/yr attributable
to organ failure (global)

<10%

Demand met by
cadaveric donation

Organ transplantation is the only definitive treatment for end-stage organ failure — yet global demand vastly exceeds supply.

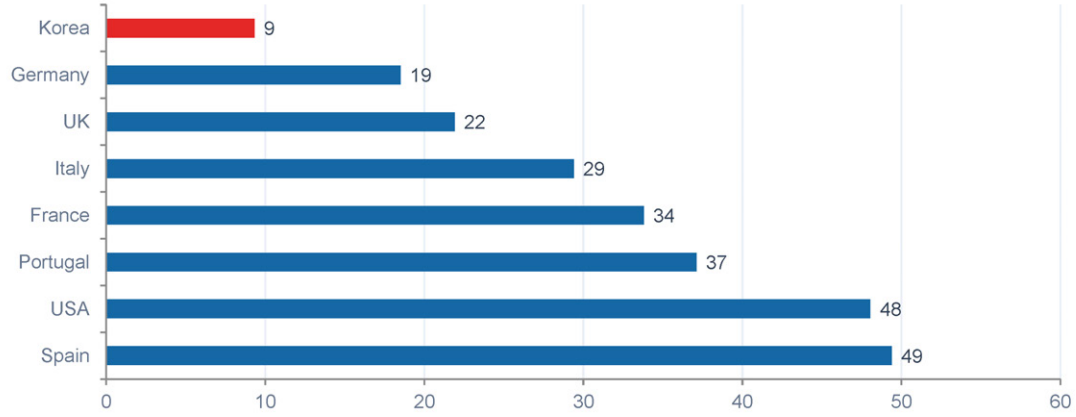
The xenotransplantation opportunity: unlimited supply of GE pigs → off-the-shelf organs on demand

Pig advantages:

- Similar organ size
- Rapid breeding cycle (5 months)
- Customizable genome
- SPF housing feasible
- 100+ million pigs available globally

UNOS, 2024; WHO Global Observatory on Donation & Transplantation, 2024

Brain-Death Donation Rate: Korea vs. World (per million population)



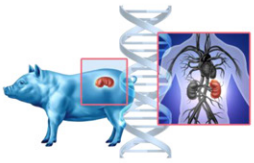
Korea 9.32 pmp = only 1/5 of Spain. Cadaveric organ donation alone cannot meet demand. Xenotransplantation is the only scalable solution.

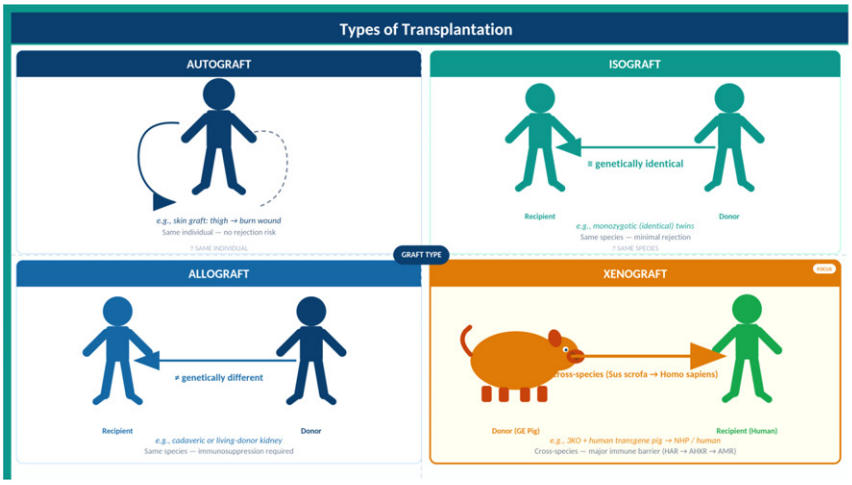
WHO Global Observatory on Donation & Transplantation; KONOS 2024

01

Introduction: Rationale

What is xenotransplantation?





Why the Pig? — Ideal Xenograft Donor

Anatomical Compatibility

Organ size matches humans; cardiovascular physiology is similar to humans

Genetic Editability

CRISPR/Cas9 enables precise multi-gene knock-out and knock-in modifications

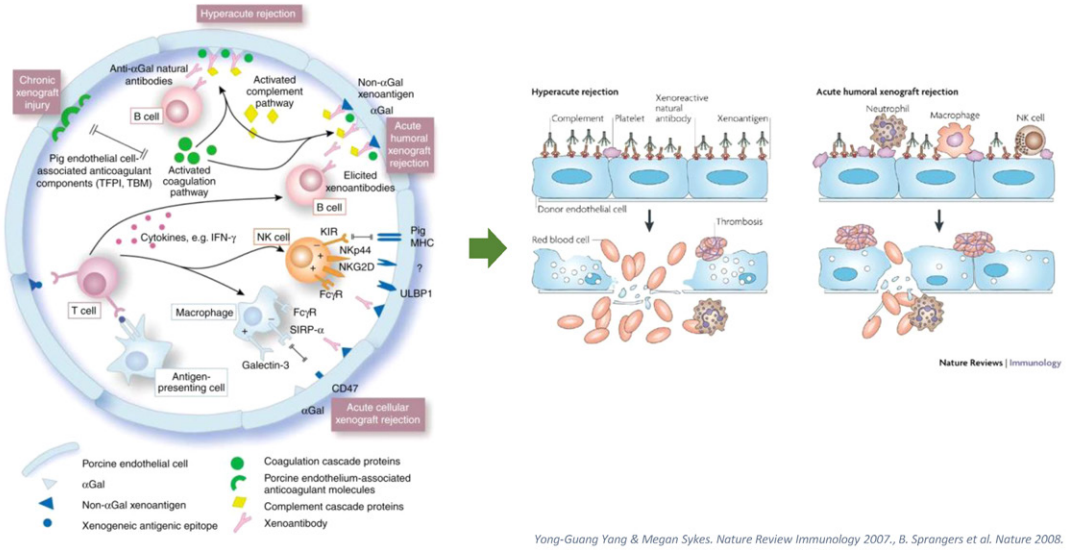
Short Gestation & Large Litter

Rapid production of transgenic animals for research scale-up and GMP production

Zoonosis

PERV-inactivated pigs (69-gene edit) show no PERV transmission to primates
Germfree available

Limitation of Xenotransplantation



Yong-Guang Yang & Megan Sykes. Nature Review Immunology 2007., B. Sprangers et al. Nature 2008.

Limitation of Xenotransplantation

Pigs are the best xenograft donor species: organ size, physiology, breeding speed, genetic tractability

Hyperacute Rejection (HAR)	Acute Humoral Rejection (AHXR)	TMA / Coagulation Dysregulation	Cell-mediated Rejection (CMR)	Chronic Rejection & AMR
αGal, Neu5Gc Pre-formed IgG/IgM Complement cascade	Non-Gal antibodies Complement activation Endothelial injury	Porcine vWF↔GPIbα Tissue factor activation Platelet aggregation	T cell infiltration CD4/CD8 activation Cytokine storm	Alloantibody production Fibrosis/remodeling Endothelial activation
→ 3KO strategy	→ hCD46/55/59	→ hTBM/CD39/EPCR	→ Costim. blockade	→ hCD47/HO-1/PD-L1

Genetic engineering of donor pigs is the central strategy to overcome each rejection barrier → enabling clinical xenotransplantation

02

Transgenic Pig Development - Current Status

From Bench to Bedside: Clinical Milestone Timeline (2022–2025)

Jan 2022 — **Univ. Maryland**

First 10-GE pig heart into a living human (Faucette). Survived 60 days.

2022–23 — **Brain-dead studies (NYU, Univ. Alabama)**

Multiple kidney & heart xenotransplants in brain-dead recipients confirm functional feasibility.

Mar 2024 — **MGH — eGenesis 69-GE pig kidney**

Richard Slayman: first living-recipient pig kidney. Functioned 47 days. Compassionate use.

Nov 2024 — **NYU Langone — Towana Looney**

Longest surviving pig kidney recipient. Discharged with functioning xenograft.

2025 — **Nature Medicine — Cardiac xenograft failure analysis**

Systematic study: AMR confirmed as dominant failure mode. 'Strategies to overcome AMR are needed.'

Nov 2025 — **United Therapeutics EXPAND Trial**

First patient transplanted with UKidney (10-GE) under FDA IND Phase I approval.

eGenesis: Genetic Engineering Strategy

Xenoantigen Knockouts	Human gene Knock-in	Anti-coagulation & Immuno-modulation
GGTA1 (αGal-KO) CMAH (Neu5Gc-KO) β4GalNT2-KO	CD46 (MCP) CD55 (DAF) CD59 hTBM, hEPCR hCD47, hHO-1	PERV-A, PERV-B, PERV-C (all 3 classes) CRISPR-Cas9 bulk edit
Outcome: Eliminates pre-formed Ab targets → Prevents HAR & AHXR	**Outcome:** Complement regulation Anticoagulation Immune evasion	**Outcome:** Biosafety: prevents retroviral transmission to human recipients

NHP results: Avg 176 days survival | Longest >2 years in cynomolgus monkeys | Total: 69 genetic modifications

First Living-Recipient Pig Kidney Transplant (MGH, March 2024)

Patient: Richard Slayman, 62 (End-stage renal disease)

Donor pig: eGenesis Yucatan miniature pig, 69-GE

Surgery: March 16, 2024, MGH (Kawai/Cosimi team)

Functional endpoint: Immediate urine production; normal GFR × 47 days

Creatinine: Fell from 3.5 → 1.4 mg/dL within 24h post-op

Outcome: Patient died May 11, 2024 (cardiac cause unrelated to xenograft)

NHP preclinical: Avg 176d, max >2 years cynomolgus monkey

Nat. Biotechnol. 2024

Key Outcomes & Lessons

- ✓ Short-term xenograft function is achievable -proof of concept
- ✓ 69-GE pig provides sufficient immunologic protection for >4 weeks
- ✓ PERV: not detected in any recipient blood samples
- ⚠ Antibody-mediated rejection: emerging at 4–6 weeks
- ⚠ Longer-term function limited: AMR, TMA still unsolved
- → More sophisticated GE needed for durable function

United Therapeutics: UKidney — EXPAND Clinical Trial (2025)

First FDA-approved Phase I IND for xenotransplantation — November 3, 2025, NYU Langone

UKidney Gene Edit Profile — 10 GE

KO: 4 knockouts

GGTA1, CMAH, β4GalNT2 (3 xenoantigens)
pGHR (porcine growth hormone receptor)

KI: 6 knock-ins

hCD46, hCD55 (complement)
hTBM, hCD39 (anticoagulation)
hCD47 (anti-phagocytosis)
hHO-1 (cytoprotection)

EXPAND Trial Design

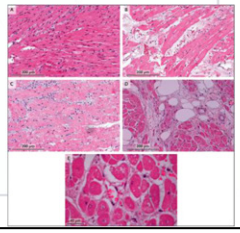
Trial type:	Phase I, safety & efficacy
Sponsor:	United Therapeutics
Site:	NYU Langone Medical Center
Eligibility:	ESRD on dialysis, no suitable living donor
Primary endpoint:	Safety at 12 months post-transplant
Immunosuppression:	Standard IS + anti-CD40 pathway
First transplant:	November 3, 2025

ClinicalTrials.gov EXPAND trial; Bhatt DL et al. Ann Thorac Surg 2024

First Clinical Pig Heart Transplant

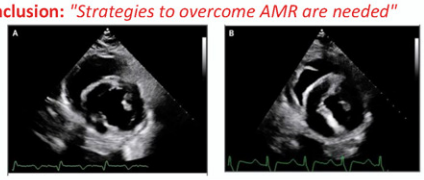
First case in the World

Patient: David Bennett Sr., 57
Donor pig: 10-GE (Revivicor/United Therapeutics)
Surgery: January 7, 2022 (Griffith team, UMMC)
Gene edits: 4 KOs + 6 KIs (no PERV inactivation)
IS protocol: Anti-CD40L (Tegoprubart) + MMF + steroids
Cardiac function: Good systolic function for ~30 days
Failure onset: Day 20: progressive diastolic dysfunction
ECMO: Day 50; patient died Day 60



Second Case - Key Findings

Patient: Lawrence Faucette, 58 (UMMC, 2023)
Donor Pig: 10-GE (United Therapeutics)
IS: Anti-CD40L (Tegoprubart) costimulation blockade
Survival: 40 days (diastolic failure onset ~Day 20)
Histology: Capillary endothelial injury; interstitial edema; early fibrosis
Diagnosis: AMR (antibody-mediated rejection)
Conclusion: *"Strategies to overcome AMR are needed"*



Griffith BP et al. (Bennett case), NEJM 2022. (Faucette case), Nat Med 2025.

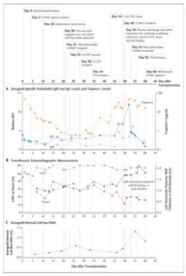
First Clinical Pig Heart Transplant

First Clinical Pig Heart Transplants: Lessons Learned

Case 1: David Bennett Sr.

Jan 7, 2022 - UMMC (Griffith team)

- **Day 0: Surgery**
  10-GE Revivicor pig; anti-CD40L + MMF
- **Day 1-30: Good systolic function**
  No immediate rejection
- **Day 20: Diastolic dysfunction**
  Progressive failure begins
- **Day 50: ECMO support**
  Hemodynamic deterioration
- **Day 60: Death**
  Cardiac failure



Griffith BP et al., NEJM 2022

Case 2: Lawrence Faucette

Sep 22, 2023 - UMMC

- **Day 0: Surgery**
  10-GE pig; anti-CD40L (Tegoprubart)
- **Day 1-20: Stable function**
  Good cardiac output
- **Day 20: Diastolic failure**
  AMR emerging
- **Day 40: Death**
  AMR-driven failure
- **Biopsy: Histology**
  Capillary injury; interstitial edema

Zhu Y et al., Nat. Med. 2025 - "Overcome AMR"

Griffith BP et al. (Bennett case), NEJM 2022; Zhu Y et al. (Faucette case), Nat Med 2025

03

Our Research: Pig-to-NHP Xenotransplantation

Transgenic Pig in Korea

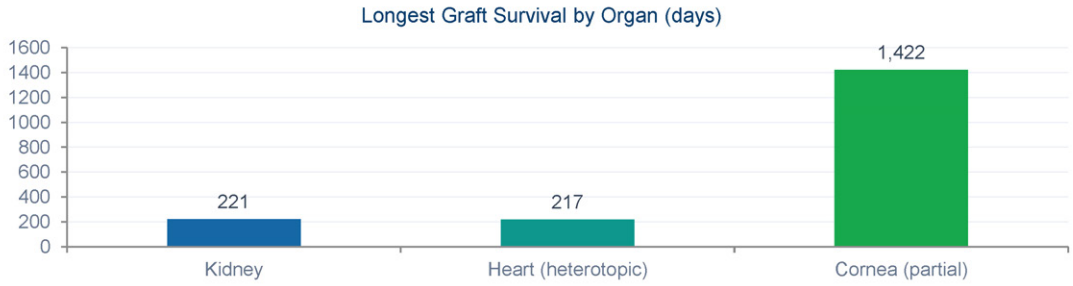
Institution	Pig Model	Genetic Modifications	Cases
Optipharm (Korea)	QKO Pig	GGTA1-KO + CMAH-KO + β4GalNT2-KO +B2M-KO CD39 + CD55 + CD46 + TBM (8 modifications)	8 models
NIAS (Korea)	Multiple-KI Pig	GGTA-KO + CMAH-KO + CD46+HO-1 + CD47 GGTA-KO + CMAH-KO + CD46+TBM + CD47 (5 modifications)	5 models

Korea's Transgenic Pig Models — Current Status (~4–8 GE)

Gene	eGenesis (US)	UKidney (US)	Optipharm QKO-KI	NIAS 5GE
Total GE	69	10	7–8	6
GGTA1 KO	✓	✓	✓	✓
CMAH KO	✓	✓	✓	✓
β4GalNT2 KO	✓	✓	✓	—
hCD46	✓	✓	✓	✓
hCD55	✓	✓	✓	—
hTBM	✓	✓	✓	✓
hCD39	—	✓	✓	—
hHO-1	✓	✓	—	✓
hCD47	✓	✓	—	✓
PERV KO	✓ (59)	—	—	—
Stage	**Clinical**	**Clinical**	**Preclinical**	**Preclinical**

100 Pig-to-NHP Xenotransplantation Cases (2011–2025)

100	43	34	3	21
Total cases (2011–2025)	Kidney transplants	Heart transplants	Liver transplants	Corneal transplants



Study Design & Methods

Donor Pigs	Recipients
αGal-KO-based transgenic pigs Optipharm: QKO+CD39+CD55+CD46+TBM; NIAS: GTKO+CMAH+HO1+CD47	Cynomolgus monkeys (Macaca fascicularis). Rhesus monkey (Macaca Mullata)

Immunosuppression	Monitoring & Endpoints
Anti-CD154 Rituximab (B-cell depletion) Anti-thymocyte globulin (ATG) Rapamycin / Tacrolimus Mycophenolate mofetil Steroids	Daily clinical assessment (scoring) Hematology (CBC) Serum chemistry Co-agulation Urinalysis Histopathology

04

Key Results
- Kidney xenotransplantation

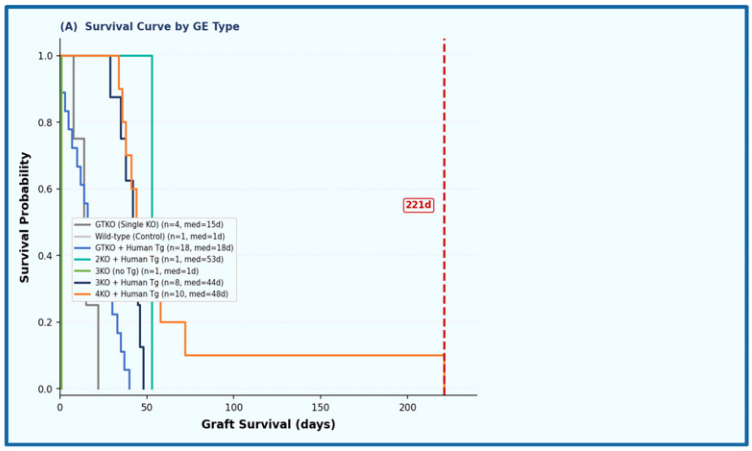
Kidney Xenotransplantation Results (n=42)

221

days
Longest graft survival
(2022)

43

cases
Total kidney
xenotransplantations



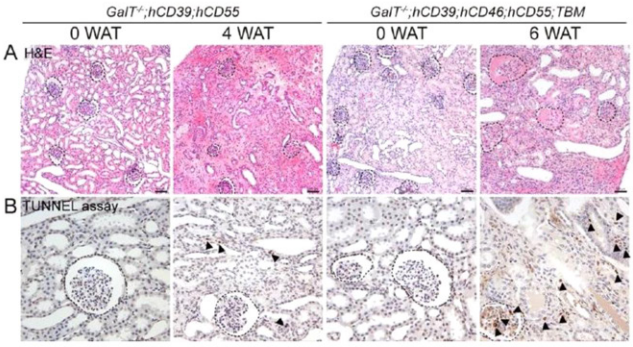
- Anti-CD154 costimulation blockade: key to survival extension
- Challenge: Thrombotic microangiopathy (coagulation dysregulation)

Date	Donor Type (GE Pig)	Recip. (kg)	Immunosuppression	Contra-replirect.	Graft Survival (days)
2011.11.09	GTKO	5.5 kg	ATG+Rit+CNI	—	2
2012.02.22	WT	5.5 kg	ATG+Rit+CNI	—	1
2012.05.31	GTKO	5 kg	CVF+ATG+Rit+aCD154+FK506	—	25
2012.06.25	GTKO	5 kg	CVF+ATG+Rit+aCD154+FK506	—	9
2014.04.14	GTKO	4 kg	CVF+ATG+Rit+FK506	POD 7	22
2017.01.16	GTKO+CD39	5.4 kg	CVF+ATG+Rit+aCD154+FK506	POD 8	32
2017.06.22	GTKO+CD46+CD73	4.2 kg	CVF+ATG+Rit+aCD154+FK506	—	14
2017.07.13	GTKO+CD39	5.1 kg	CVF+ATG+Rit+aCD154+FK506	POD 11	25
2018.05.28	GTKO+CD46	4.8 kg	CVF+ATG+Rit+aCD154+Rapa	—	12
2018.08.21	GTKO+CD39	5.31 kg	CVF+ATG+Rit+aCD154+Rapa	—	13
2018.12.03	GTKO+CD46	4.4 kg	CVF+ATG+Rit+aCD154+Rapa	—	7
2019.08.09	GTKO+CD39+CD55	6.13 kg	CVF+ATG+Rit+aCD154+Rapa	POD 5	84
2019.11.21	GTKO+CD39+CD55	5.2 kg	CVF+ATG+Rit+aCD154+Rapa	—	7
2020.12.17	GTKO+CD39+CD55	3 kg	CVF+ATG+Rit+aCD154+Rapa	POD 11	86
2021.01.21	2KO+CD46+TBM	3.5 kg	CVF+ATG+Rit+aCD154+Rapa	POD 14	53
2021.03.11	3KO	4 kg	CVF+ATG+Rit+aCD154+Rapa	—	1
2021.03.25	GTKO+CD39+CD55	3.6 kg	CVF+ATG+Rit+aCD154+Rapa	POD 14	32
2021.04.22	GTKO+CD39+CD55	3.5 kg	CVF+ATG+Rit+aCD154+Rapa	—	0
2021.05.13	GTKO+CD39+CD55+CD46+TBM	3.2 kg	CVF+ATG+Rit+aCD154+Rapa	POD 14	45
2021.06.17	3KO+CD46+TBM	2.7 kg	CVF+ATG+Rit+aCD154+Rapa	POD 14	49
2021.07.22	GTKO+CD39+CD55	3.8 kg	CVF+ATG+Rit+aCD154+Rapa	—	43
2021.08.19	GTKO+CD39+CD55	4.4 kg	CVF+ATG+Rit+aCD154+Rapa	POD 21	43
2021.10.14	3KO+CD55+CD39	4.5 kg	CVF+ATG+Rit+aCD154+Rapa	POD 21	39
2022.06.24	GTKO+CD46+TBM	3.07 kg	CVF+ATG+Rit+aCD154+Rapa	POD 17	51
2022.08.05	GTKO+CD46	4 kg	CVF+ATG+Rit+aCD154+Rapa	POD 14	115
2022.08.19	GTKO+CD39+CD55	2.5 kg	CVF+ATG+Rit+aCD154+Rapa	POD 76	80
2022.09.15	GTKO+CD46+TBM	2.9 kg	CVF+ATG+Rit+aCD154+Tac	POD 50	50
2022.10.20	**3KO+CD55+CD39**	**3 kg**	**CVF+ATG+Rit+aCD154+Tac**	**POD 75**	**3KiMax 221 days**
2022.12.01	3KO+CD55+CD39	2.6 kg	CVF+ATG+Rit+aCD154+Tac	POD 87	75
2023.07.26	3KO+CD55+CD39	6 kg	CVF+ATG+Rit+aCD154+Tac	POD 14	29
2023.08.09	3KO+CD55+CD39	5.3 kg	CVF+ATG+Rit+aCD154+Tac	POD 14	46
2023.08.23	4KO	5 kg	CVF+ATG+Rit+aCD154+Tac	POD 14	36
2023.10.04	3KO	7.5 kg	ATG+Rit+aCD154+Tac	POD 14	29
2023.12.27	3KO+CD46+TBM	5.5 kg	CVF+ATG+Rit+aCD154+Tac	POD 14	29
2024.01.10	4KO+CD46+TBM	6.4 kg	CVF+ATG+Rit+aCD154+Tac	POD 14	28
2024.01.24	4KO+CD46+TBM	4.7 kg	CVF+ATG+Rit+aCD154+Tac	—	72
2024.05.22	4KO+CD46+TBM	5.7 kg	Crova+ATG+Rit+PG-405+Tac	—	61
2024.05.22	4KO+CD46+TBM	4.6 kg	Crova+ATG+Rit+PG-405+Tac	—	34
2024.07.10	4KO	4.5 kg	CVF+ATG+Rit+aCD154+Tac	POD 28	34
2024.07.10	4KO+CD46+TBM+CD39+CD55	5 kg	CVF+ATG+Rit+aCD154+Tac	POD 28	34
2024.10.23	4KO+CD46+TBM+CD39+CD55	4 kg	Crova+ATG+Rit+PG-405+Tac	POD 40	44
2024.11.06	4KO+CD46+TBM+CD39+CD55	3.5 kg	Crova+ATG+Rit+PG-405+Tac	POD 50	55

GTKO only | GTKO + human Tg | 2KO + Tg | 3KO ± Tg | 4KO + Tg | ● Record survival

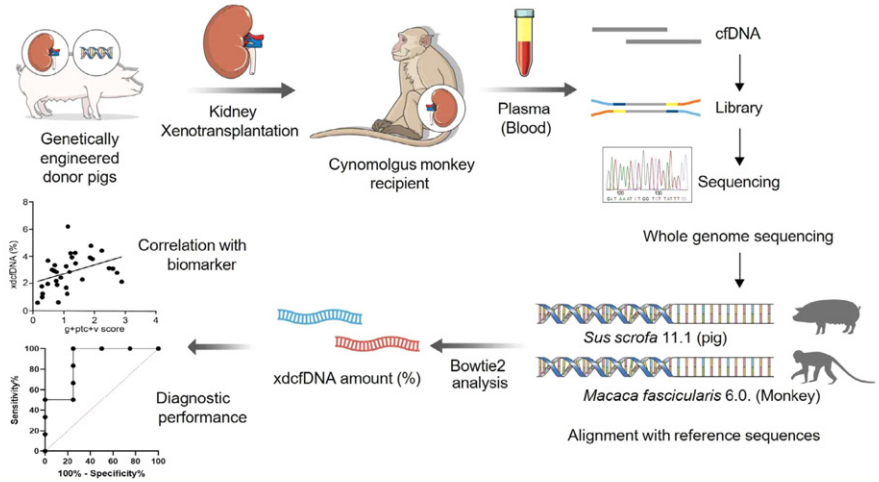
IS abbreviations: CVF = cobra venom factor; Rit = Rituximab; aCD154 = anti-CD154; Rapa = Rapamycin; Tac = Tacrolimus (FK); Crova = Crovalimab; PG-405 = anti-CD154 bispecific Ab

Kidney Xenograft Failure: Renal Histopathology



Suh et al., Cell Transplantation 2023.

xdcfDNA: Non-invasive Biomarker for Xenograft Rejection



Porcine donor DNA circulates in recipient plasma → detected by WGS → mapped to Sus scrofa 11.1. Rise in xgcfDNA = early graft injury signal before creatinine/BUN elevation.

Han et al., Xenotransplantation 2025

xdcfDNA: Kinetics & Diagnostic Performance for AMR Detection

Key findings:

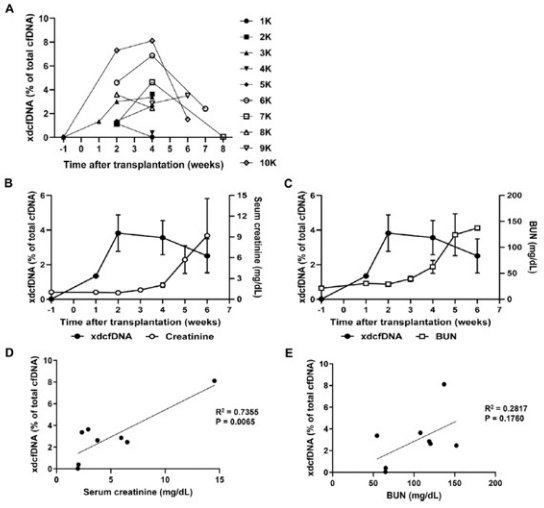
▶ xgcfDNA peaks at Wk 4–6 post-Tx

▶ Precedes creatinine/BUN rise

▶ AMR: AUC=1.000 at 2.545%

▶ 100% sensitivity & specificity

▶ Algorithm: ≥1.25%→alert; ≥2.545%→biopsy



Han et al., Xenotransplantation 2025

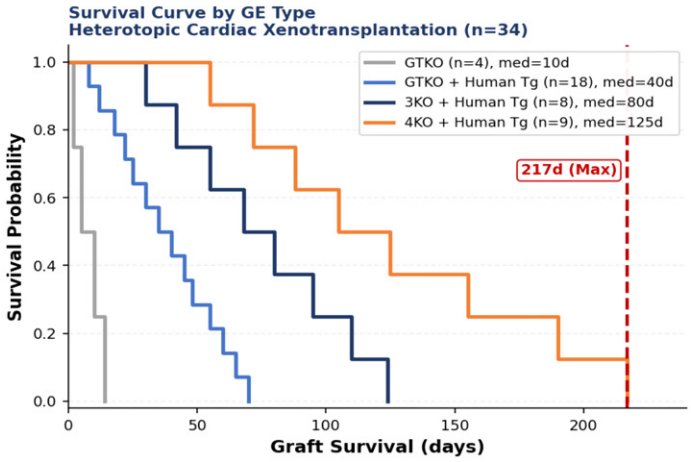
Cardiac Xenotransplantation Results (n=34)

217

days
Longest heterotopic heart graft survival

34

cases
Total cardiac xenotransplantations



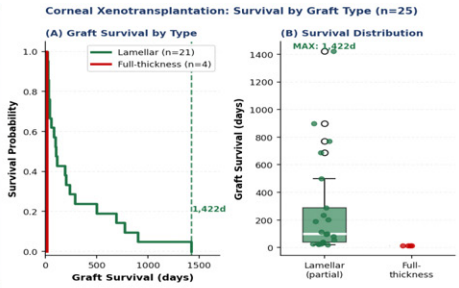
- PERV transmission: not detected in any recipient
- Transcriptome: heart failure mechanism differs between long/short-term survivors
- Refined immunosuppression (anti-CD154 + rapamycin) significantly extended survival

Corneal Xenotransplantation Results (n=21)

1,422

days
최장 각막 이식 생존
(lamellar transplant)

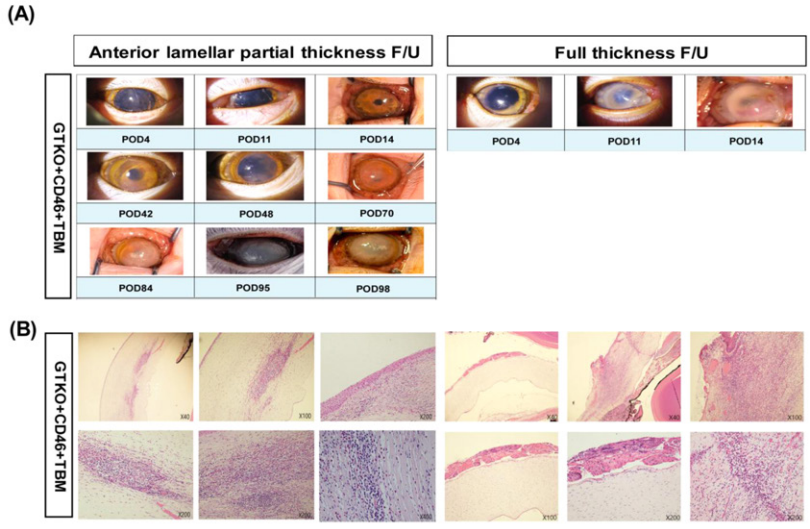
Donor Pigs	Recipient Monkey (Date of Surgery)	Graft Type	Initial Graft Opacity	Graft Survival	Size of Donor Cornea Punch	Size of Recipient Trephine
GTKO+CD46	2F2 (2021.07.23)	Partial thickness	14 d	28 d	7.0 mm	7.0 mm
	2F1 (2021.07.23)	Full thickness	14 d	28 d	7.5 mm	7.0 mm
GTKO+CD46+TBM	1F1 (2021.05.14)	Partial thickness	28 d	98 d	7.75 mm	7.25 mm
	1F2 (2021.05.14)	Full thickness	4 d	14 d	7.5 mm	7.5 mm
	3F2 (2021.11.26)	Partial thickness	105 d	463 d < (on-going)	7.0 mm	7.0 mm
	3F1 (2021.11.26)	Full thickness	16 d	21 d	7.5 mm	7.0 mm



Full-Thickness vs. Lamellar Corneal Xenograft

Parameter	Full-Thickness	Lamellar (Partial)
Immune response	Higher (MHC II exposure)	Lower
Graft survival	Shorter	Up to 1,422 days
Immunosuppression	Moderate–high	Minimal
Clinical recommendation	Higher risk	Preferred approach ✓

Corneal Xenograft: Serial Slit-lamp Photos & Histopathology



Partial Layer Corneal Xenotransplantation Results (2016–Present)

1,422d

Longest graft survival

>6mo

IXA clinical criterion MET

Table 5. Results of Partial Layer Corneal Transplantation from August 2016 to the Present

Date	Donor Type	Recipient	Graft Type	Immunosuppression	Graft Survival
2016. 08. 01	GTKO (5.8 kg)	5.9 kg	Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	100
2016. 09. 26	GTKO + CD46 (6.2 kg)		Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	234
2017. 05. 16	GTKO + CD46 (30 kg)		Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	202
2017. 05. 16	GTKO + CD46 (30 kg)		Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	1422
2017. 06. 22	GTKO + CD46 + CD73 (4.4 kg)		Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	39
2017. 06. 22	GTKO + CD46 + CD73 (4.4 kg)		Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	39
2018. 06. 01	GTKO + CD46 (14.2 kg)	1.9 kg	Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	56
2019. 02. 27	GTKO + CD46 (5.6 kg)	3.38 kg	Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	772
2019. 11. 27	GTKO + CD46 (14.5 kg)	4.38 kg	Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	499
2020. 04. 08	GTKO + CD46 (4.1 kg)	3.6 kg	Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	21
2020. 04. 08	GTKO + CD46 (4.1 kg)	3.05 kg	Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	112
2021. 03. 12	TKO (14 kg)	4 kg	Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	26
2021. 05. 14	GTKO + CD46 + TBM (10.6 kg)	2.96 kg	Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	98
2021. 07. 23	GTKO + CD46 (18.5 kg)		Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection 899	28
2021. 11. 26	GTKO + CD46 + TBM (4.3 kg)	2.5 kg	Partial thickness	Ster689oid + Antibio2tic eyedrop / Dexa + Genta injection	899
2022. 06. 24	GTKO + CD46 + TBM (6.1 kg)		Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	689
2022. 06. 24	GTKO + CD46 (18 kg)		Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	28
2023. 10. 04	QKO + CD46 + TBM (9 kg)	2.46 kg	Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	289
2023. 12. 27	TKO + CD46 + TBM (7 kg)	3.19 kg	Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	23
2024. 07. 19	QKO + CD46 + TBM (7.4 kg)	3.6 kg	Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	>191
2024. 11. 06	QKO + CD55 + CD39 + CD46 + TBM (11 kg)	3.68 kg	Partial thickness	Steroid + Antibiotic eyedrop / Dexa + Genta injection	>81

GTKO, aGal-knockout; TKO, GGTA1/CMAH/B4galNT2; QKO, GGTA1/CMAH/Bb3s/B4galNT2; CD39, ectonucleoside triphosphate diphosphohydrolase-1; CD55, complement-decay-accelerating factor; CD 46, membrane cofactor protein; TBM, thrombomodulin.

Table 5: Hwang SA et al., Transplant Proc. 57(8), 1674–1682, 2025

Liver Xenotransplantation — Persistent Challenge (n=3)

<2

day
Survival in all liver cases

Major Barriers for Liver Xenotransplantation

- Severe coagulation dysregulation — pig liver produces species-incompatible coagulation factors
- Thrombotic microangiopathy develops within hours of reperfusion
- Acute rejection amplified by high portal blood flow
- Alternative: Bioartificial liver (BAL) — genetically modified pig hepatocytes in extracorporeal device
- Liver remains the most challenging organ for xenotransplantation globally

05

Challenges & Future Strategy

Remaining Challenges: Immunology & Coagulation

Hyperacute Rejection (HAR) — SOLVED

αGal-KO eliminates natural antibody-mediated HAR. Largely overcome in current models.

Acute Humoral Xenograft Rejection — MAJOR BARRIER

Non-Gal antibodies (CMAH, β4GalNT2) and complement activation persist. Primary cause of failure in kidney xenotransplantation.

Coagulation Dysregulation — MAJOR BARRIER

Species-incompatible coagulation factors drive thrombotic microangiopathy. CD39, TBM, CD73, anticoagulants partially mitigate.

Chronic Rejection — UNDER INVESTIGATION

Long-term T cell-mediated rejection not yet fully characterized. Key hurdle for clinical durability.

Future Strategy: Toward Clinical Translation

1. **Next-Generation Transgenic Pigs**

   10+ gene-edited pigs: additional xenoantigen knockouts (SLA class I reduction), **human immune checkpoint ligands (PD-L1, CD47),** improved coagulation factors

2. **Refined Immunosuppression**

   Novel costimulation blockade (anti-CD40L, belatacept), complement inhibitors (C1-INH, eculizumab), **tolerance induction via mixed chimerism**

3. **Novel Biomarkers**

   Xenograft-derived cell-free DNA (xgcfDNA) for early non-invasive rejection monitoring — reduces biopsy need and enables timely intervention

4. **Clinical Trial Readiness (Korea)**

   Build on 100+ NHP cases, partner with MFDS for IND application, **establish GMP-grade pig production**, initiate compassionate use → Phase I by 2027

Korea Xenotransplantation Clinical Translation Roadmap

2011–2022	2023–2025	2025–2027	2028~
Preclinical Foundation	**Scale-Up & Optimization**	**Compassionate Use & IND**	**Phase I Clinical Trial**
100 NHP cases Max 221d kidney Max 1422d cornea	National funding XRC established New transgenic pigs Development	MFDS regulatory submission First human cases (bridge therapy)	IND approval Controlled trial 10–30 patients

Conclusions

- 100+ pig-to-NHP xenotransplantations performed in Korea since 2011; kidney (221d), heart (217d), cornea (1,422d) demonstrate robust preclinical efficacy.
- Lamellar corneal xenotransplantation with minimal immunosuppression is the most clinically mature application and nearest to clinical translation.
- Multi-gene transgenic pigs (QKO + complement regulators + anticoagulants) are essential for overcoming AHXR and coagulation dysregulation.
- Global clinical xenotransplantation has entered the Phase I trial era (FDA 2025). Korea is positioned to follow with national infrastructure.
- Next steps: Next-gen pigs, refined immunosuppression, xgcfDNA validation, MFDS IND submission by 2027.

Thank you for your attention