Analysis of causes affecting graft survival in xenograft kidney transplantation

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Xenograft transplantation: a realistic alternative to donor organs

Necessity of xenograft transplantation

- The only treatment for patients with end-stage renal failure is transplantation of a new replacement kidney
- Xenogeneic kidney transplantation can provide an unlimited supply of insufficient organs
- Donor organs can be prepared in advance and recipients can be identified in advance
- Possible production of patient-tailored transgenic organs using genetic engineering techniques
- Compared to other fields, it is realistically possible to solve the problem of organ shortage the fastest

Importance of preclinical primate xenotransplantation experiments

- According to international guidelines, non-clinical trials in primates must be performed when developing xenotransplantation products.
- Advancement of xenograft solid organ transplantation technology and establishment of safety/efficacy evaluation technology for clinical application
- Need to establish primate xenotransplantation platform and establish guidelines

Primate xenograft transplantation research results from 2021 to recently

(*n* = 27)

Date	Donor type	Recipient	Immunopression	2nd look	Graft survival
2021. 01. 21	DKO+CD46+TBM	Cynomolgus monkey, 3.5 kg	CVF+ATG+Rituximab +aCD154+Rapamycin	POD 14	POD 53
2021. 03. 11	TKO	Cynomolgus monkey, 4 kg	CVF+ATG+Rituximab +aCD154+ Rapamycin		POD 1
2021. 03. 25	GTKO+CD39+CD55	Cynomolgus monkey, 3.6 kg	CVF+ATG+Rituximab +aCD154+ Rapamycin	POD 14	POD 32
2021. 04. 22	GTKO+CD39+CD55	Cynomolgus monkey, 3.5 kg	ATG+Rituximab +aCD154+ Rapamycin		POD 0
2021. 05. 13	GTKO+CD39+CD55 +CD46+TBM	Cynomolgus monkey, 3.2 kg	CVF+ATG+Rituximab +aCD154+ Rapamycin	POD 14	POD 45
2021. 06. 17	TKO+CD46+TBM	Cynomolgus monkey, 2.7 kg	CVF+ATG+Rituximab +aCD154+ Rapamycin	POD 14	POD 49
2021. 07. 22	GTKO+CD39+CD55	Cynomolgus monkey, 3.8 kg	CVF+ATG+Rituximab +aCD154+ Rapamycin	POD 14	POD 43
2021. 08. 19	GTKO+CD39+CD55	Cynomolgus monkey, 4.4 kg	CVF+ATG+Rituximab +aCD154+ Rapamycin	POD 21	POD 43
2021. 10. 14	TKO+CD39+CD55	Cynomolgus monkey, 4.5 kg	CVF+ATG+Rituximab +aCD154+ Rapamycin	POD 21	POD 39
2022. 06. 24	GTKO+CD46+TBM	Cynomolgus monkey, 3.07 kg	CVF+ATG+Rituximab +aCD154+Rapamycin	POD 17	POD 51
2022. 08. 05	GTKO+CD46	Cynomolgus monkey, 4 kg	CVF+ATG+Rituximab +aCD154+ Rapamycin	POD 14	POD 115
2022. 08. 19	GTKO+CD39+CD55	Cynomolgus monkey, 4.4 kg	CVF+ATG+Rituximab +aCD154+ Rapamycin	POD 76	POD 80
2022. 09. 15	GTKO+CD39+CD55	Cynomolgus monkey, 2.9 kg	ATG+Rituximab +aCD154+ Advagraf 2 mg/kg	POD 50	POD 50
2022. 10. 20	TKO+CD39+CD55	Cynomolgus monkey, 2.8 kg	CVF+ATG+Rituximab +aCD154+ Advagraf 2 mg/kg	POD 50	POD 63
2022. 12. 01	TKO+CD39+CD55	Cynomolgus monkey, 3 kg	CVF+ATG+Rituximab +aCD154+ Advagraf 2 mg/kg	POD 75	POD 221
2022. 12. 09	GTKO+CD46	Cynomolgus monkey, 2.6 kg	CVF+ATG+Rituximab +aCD154+ Advagraf 2 mg/kg	POD 67	POD 75

Recognition number	Date of xenotransplantation experiment	Genetically engineered pig to monkey	Immunosuppression	Anti-inflammatory and other agent	Anti-coagulant	anti-C5 inhibitor	Contralateral Nephrectomy	Graft survival
K1-23	2023-07-26	TKO(GGTA1/CMAH/B4GalNT2)+CD39+CD55	C10+Rituximab+ATG+Advagraf+MMF+Solu-Medrol	Etanercept	CVF, Aspirin, Enoxaparin		POD 14	29
K2-23	2023-08-09	TKO(GGTA1/CMAH/B4GalNT2)+CD39+CD55	C10+Rituximab+ATG+Advagraf+MMF+Solu-Medrol	Etanercept, Erythropoietin	CVF, Aspirin, Enoxaparin		POD 14	46
K3-23	2023-08-23	QKO(GGTA1/CMAH/iGb3s/B4GalNT2)	C10+Rituximab+ATG+Advagraf+MMF+Solu-Medrol	Etanercept, Erythropoietin	CVF, Aspirin, Enoxaparin		POD 14	36
K4-23	2023-10-04	QKO(GGTA1/CMAH/iGb3s/B4GalNT2)+CD46+TBM	C10+Rituximab+ATG+Advagraf+MMF+Solu-Medrol	Etanercept, Erythropoietin	Aspirin, Enoxaparin		POD 14	29
K5-23	2023-12-27	TKO(GGTA1/CMAH/B4GalNT2)+CD46+TBM	C10+Rituximab+ATG+Advagraf+MMF+Solu-Medrol+Abatacept	Etanercept, Erythropoietin	CVF, Aspirin, Enoxaparin		POD 14	29
K6-24	2024-01-10	QKO(GGTA1/CMAH/iGb3s/B4GalNT2)+CD46+TBM	C10+Rituximab+ATG+Advagraf+MMF+Solu-Medrol+Abatacept	Etanercept, Erythropoietin	CVF, Aspirin, Enoxaparin		POD 14	28
K7-24	2024-01-24	QKO(GGTA1/CMAH/iGb3s/B4GalNT2)+CD46+TBM	C10+Rituximab+ATG+Advagraf+MMF+Solu-Medrol+Abatacept	Etanercept, Erythropoietin	CVF, Aspirin, Enoxaparin		None	72
K8-24	2024-05-22	QKO(GGTA1/CMAH/iGb3s/B4GalNT2)+CD46+TBM	PG-405+MD-3 +Rituximab+ATG+Advagraf(POD 53일부터 Prograf 투여)+MMF+Solu-Medrol	Etanercept, Erythropoietin	Aspirin, Enoxaparin	Crovalimab	None	61
K9-24	2024-05-22	QKO(GGTA1/CMAH/iGb3s/B4GalNT2)+CD46+TBM	PG-405+MD-3 +Rituximab+ATG+Advagraf+MMF+Solu-Medrol	Etanercept, Erythropoietin	Aspirin, Enoxaparin	Crovalimab	None	34
K10-24	2024-07-10	QKO(GGTA1/CMAH/iGb3s/B4GalNT2)+CD39+CD55+CD46+TBM	PG-405+MD-3 +Rituximab+ATG+Prograf+MMF+Solu-Medrol	Etanercept, Erythropoietin	Aspirin, Enoxaparin	Crovalimab	POD 28	34
K11-24	2024-07-10	QKO(GGTA1/CMAH/iGb3s/B4GalNT2)+CD39+CD55+CD46+TBM	PG-405+MD-3 +Rituximab+ATG+Prograf+MMF+Solu-Medrol	Etanercept, Erythropoietin	CVF, Aspirin, Enoxaparin		POD 28	34

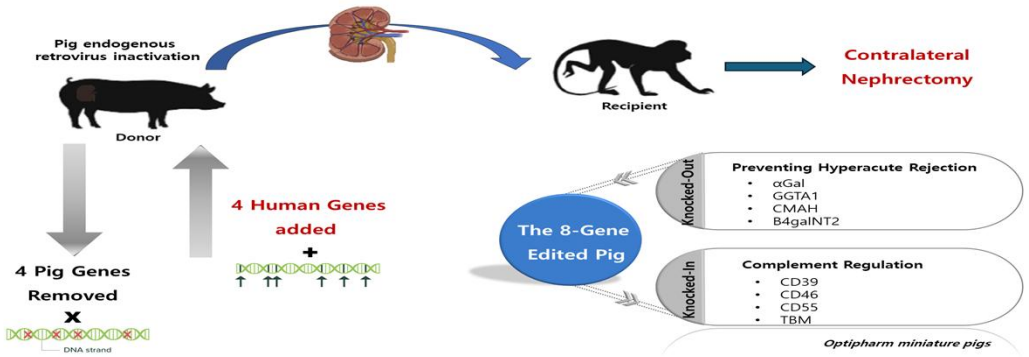
GTKO α1,3-galactosyltransferase gene knockout **; TKO**, GGTA1/CMAH/B4galNT2 gene knockout; **QKO**, GGTA1/CMAH/iGb3s/B4GalNT2, **CD46**, membrane cofactor protein; **TBM**, *thrombomodulin*; **CD 39**, ectonu-cleoside triphosphate diphosphohydrolase-1; **CD 55**, decay-accelerating factor; **POD**, post operative day

Immunosuppressant therapy

Recently Proposed Immunosuppressive Therapy

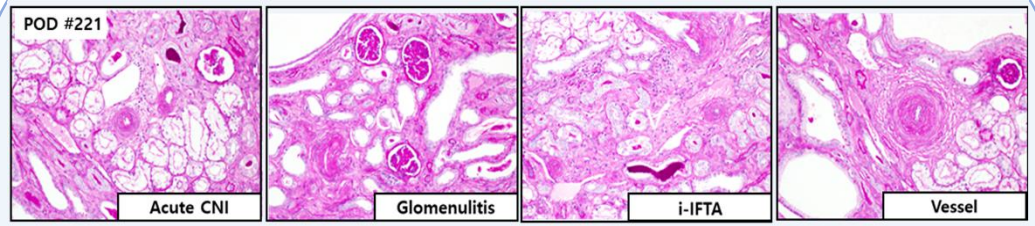
					Before surgery	After surgery
Immunosuppression	Rituximab	IV	10 mg/kg	qd	Day -7	Day 14
Immunosuppression (When MD-3 is not administered)	ATG	IV	6 mg/kg	qd	Day -1	Day 0
Immunosuppression (When administering MD-3)	ATG	IV	6 mg/kg	qd	Day -1	
Anti-coagulant	CVF	IV	0.1 mg/kg	qd	Day -1	Day 0~8
Anti-inflammatory	Etanercept	SC	0.8 mg/kg	qd		Day 0, 3, 7, 10
Immunosuppression	MD-3	IV	8 mg/kg	qd	Day -8, -6, -3	Day 0, 2, 4, 8, 14, 21, 28, 42, 56, 70, 84
Immunosuppression	Anti-CD154 (PG-406)	IV	20 mg/kg	qd	Day -1	Day 0, 3, 7, 10, 14 (Once a week thereafter)
Immunosuppression	Prograf	IM	0.026 mg/kg	BID		0~4 wks (10~12 ng/mL) 4~12 wks (8~10 ng/mL) 12 wks~ (6~8 ng/mL)
Immunosuppression	MMF	Oral	40 mg/kg	qd		Day 0~
Immunosuppression	Solu-Medrol	IM	10 mg/kg	qd		W1
	Solu-Medrol	IM	6 mg/kg	qd		W2
	Solu-Medrol	IM	2 mg/kg	qd		W3
	Solu-Medrol	IM	1.6 mg/kg	qd		W4
	Solu-Medrol	IM	1 mg/kg	qd		W5
	Solu-Medrol	IM	0.75 mg/kg	qd		W6
	Solu-Medrol	IM	0.5 mg/kg	qd		W7
	Solu-Medrol	IM	0.25 mg/kg	qd		W8~
Anti-coagulant	Aspirin	Oral	80 mg/day	qd		Day 0~
Anti-coagulant	enoxaparin	SC	1 mg/kg	qd		Day 0~
Other agent	omeprazole	Oral	10 mg/day	qd		Day 0~
Other agent	Erythropoietin	SC	500 IU/kg			Once a week
Anti-coagulant (Applies to 8th, 9th, and 10th kidney transplantation)	Crovalimab	IV	10 mg/kg	qd		Day 0, 1, 2
	Crovalimab	IV	10 mg/kg	qd		W2, 3, 4, 5, 6, 7, 8, 10, 12

Transgenic pig gene type



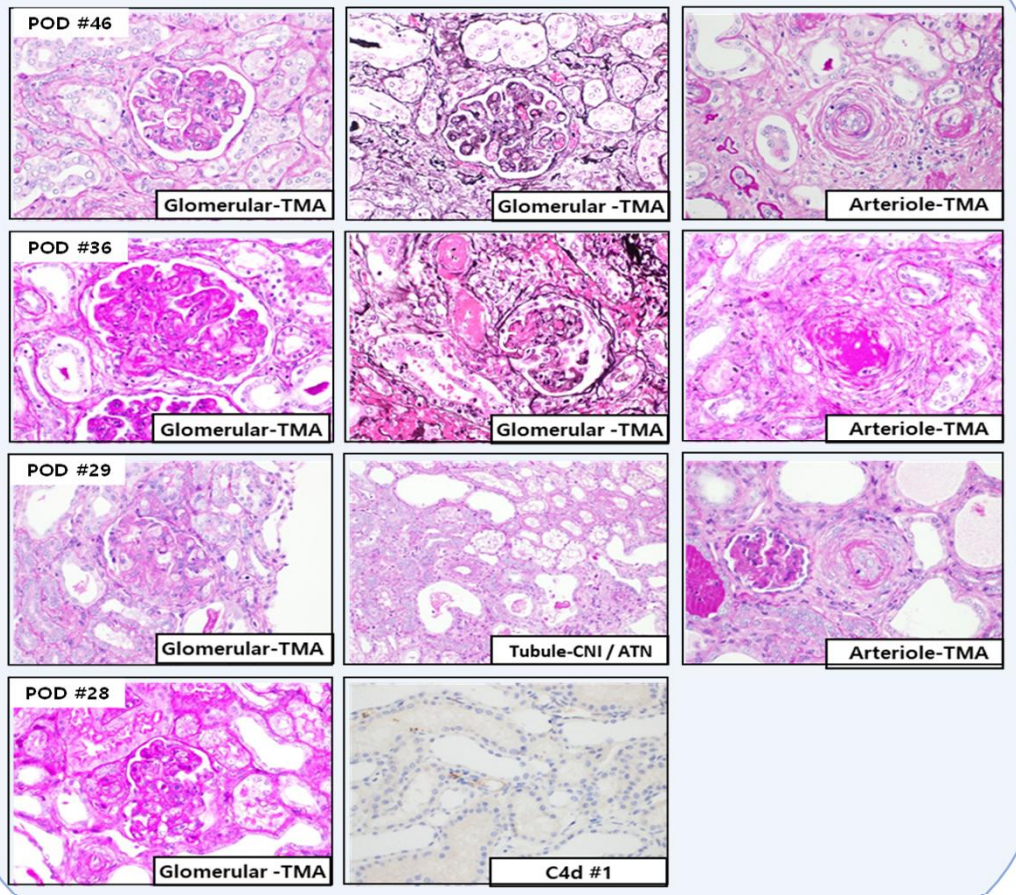
Observation of thrombotic microangiopathy occurring after kidney transplantation

Histopathological examination results observed in previous studies (Autopsy)



CNI, calcineurin inhibitor; **IFTA**, interstitial fibrosis and tubular atrophy

Thrombomicroangiopathy outcomes observed in recent studies (Autopsy)



TMA, thrombotic microangiopathy; **ATN**, acute tubular necrosis

Limitations and future challenges to overcome in this study

- Histopathological findings: glomerular microvascular damage with thrombosis in arterioles and capillaries
- Results are not yet sufficient to clearly determine the cause of thrombotic microangiopathy
- Need to identify mechanisms of microvascular thrombosis (inhibition of inflammatory cytokines, blood coagulation and complement activity)
- Further detailed investigation of which gene combination expression will be advantageous will be conducted in the future
- Need to improve immunological disorders and interspecies incompatibility technology
- Development of optimal immunosuppression protocol for immune monitoring and clinical application
- Control of rejection reactions using less harmful immunosuppressive treatments (antibody-mediated, cell-mediated rejection)
- Contributes to a positive impact on the survival and function of future transplanted organs
- Expected clinical applicability of xenotransplantation