

**Xenotransplantation:
Crossing Species To Bridge The Organ Gap**

INEDSYS Hepatology Club

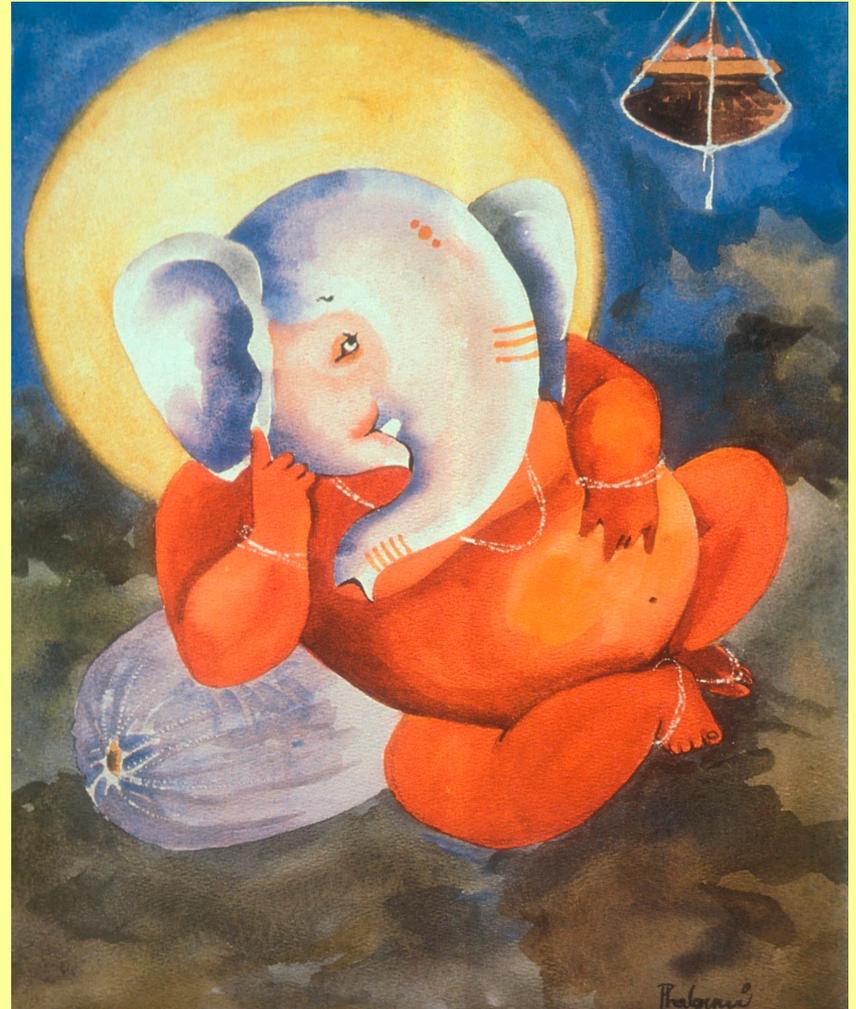
August 23, 2025

**John J. Fung, M.D., Ph.D.
University of Chicago**

Disclosures: Investigator – eGenesis, Eledon

Outline

- Background
- Immunology
- Current Advances
- Clinical Experience
- Future Concerns



First Successful Xenograft - Cockerel's Head With A Human Tooth Sticking Out Of The Top - 1778



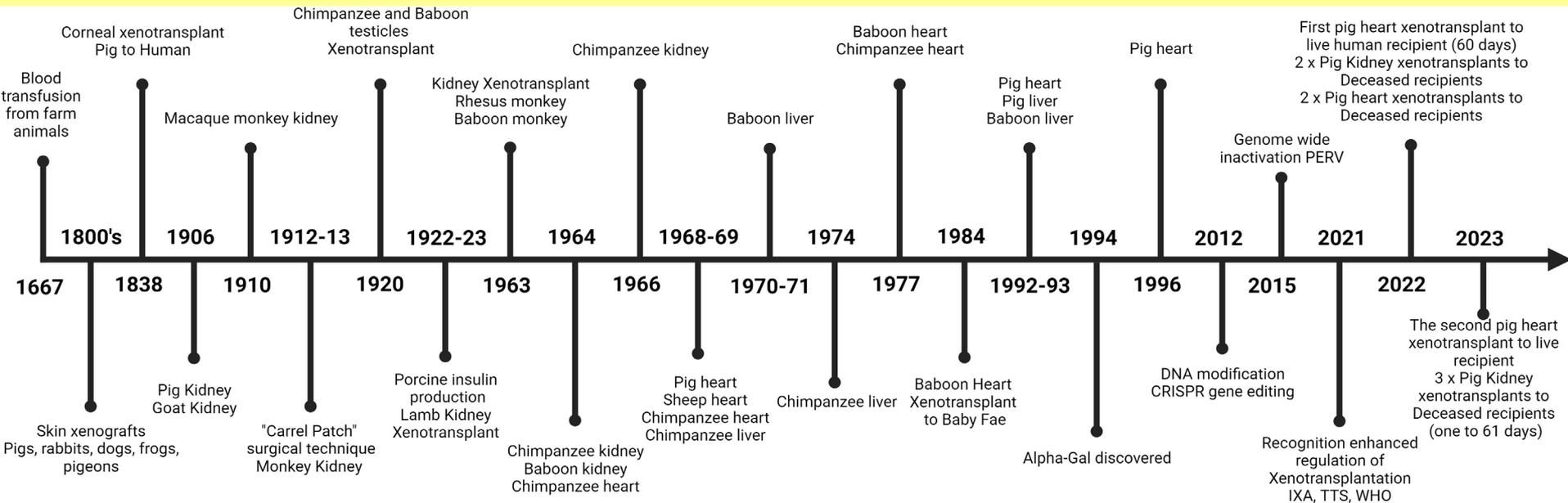
Surgeon John Hunter –from: *Treatise on the Natural History and Diseases of the Human Teeth*:

"I took a sound tooth from a person's head; then made a pretty deep wound with a lancet into the thick part of a cock's comb, pressed the fang of the tooth into this wound, and fastened it with threads. The cock was killed some months after ...I found the vessels of the tooth well injected.

I may here just remark, that this experiment is not generally attended with success. I succeeded but once out of a great number of trials."

Advances in Xenotransplantation

Timeline of Xenotransplantation



Definitions

Xenotransplantation is the transplantation of tissue or organs between disparate species

Discordant combinations are characterized by rejection mediated primarily through presence of preformed antibody

Concordant combinations are characterized by an accelerated rejection via up-regulation of cell mediated and antibody mediated immunity

Primates as Donor

Advantages:

- **Genetic similarity**
 - **Metabolic compatibility**
 - **Concordant rejection pattern**

Disadvantages:

- **Access restricted**
- **Potential for disease transmission**
- **“Humanization” - ethical considerations**

**1992-93: University Of Pittsburgh Team Performed
Baboon-To-Human Liver Transplants In 2 Patients**

THE LANCET

Vol 341

Saturday 9 January 1993

No 8837

Baboon-to-human liver transplantation

T. E. STARZL J. FUNG A. TZAKIS S. TODO A. J. DEMETRIS
I. R. MARINO H. DOYLE A. ZEEVI V. WARTY M. MICHAELS
S. KUSNE W. A. RUDERT M. TRUCCO

Clinical Features Of Baboon-To-Human Liver Xenotransplants

Patient 1

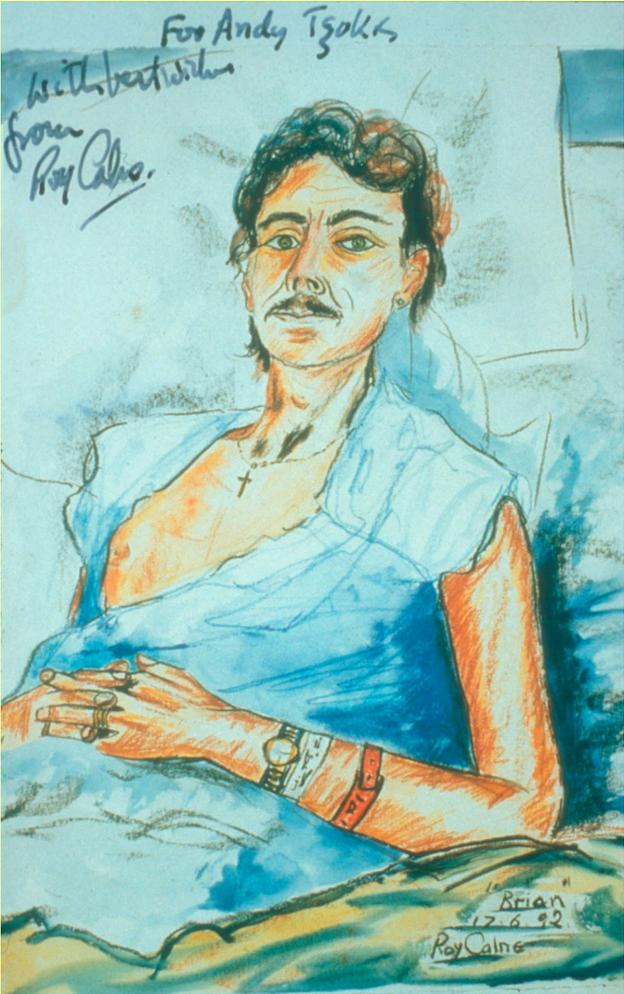
- 35 y/o male
- HBV positive 1984
- s/p splenectomy for MVA in 1989
- HIV positive
- Recipient ABO: A
- Donor ABO: A

Patient 2

- 62 y/o male
- HBV positive 1988
- Recipient ABO: B
- Donor ABO: B

Advances in Xenotransplantation

Baboon-to-Human Liver Xenotransplantation

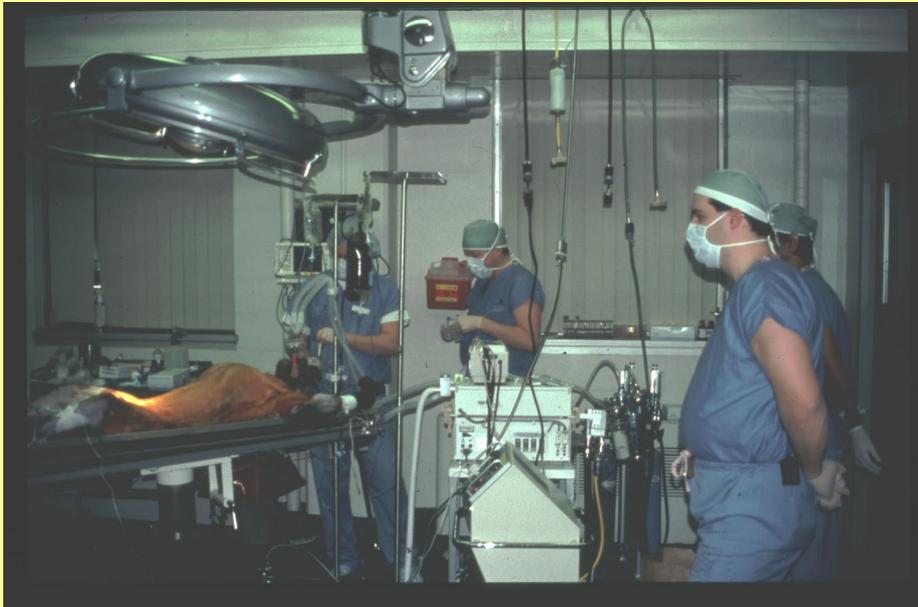


Immunosuppression Protocol

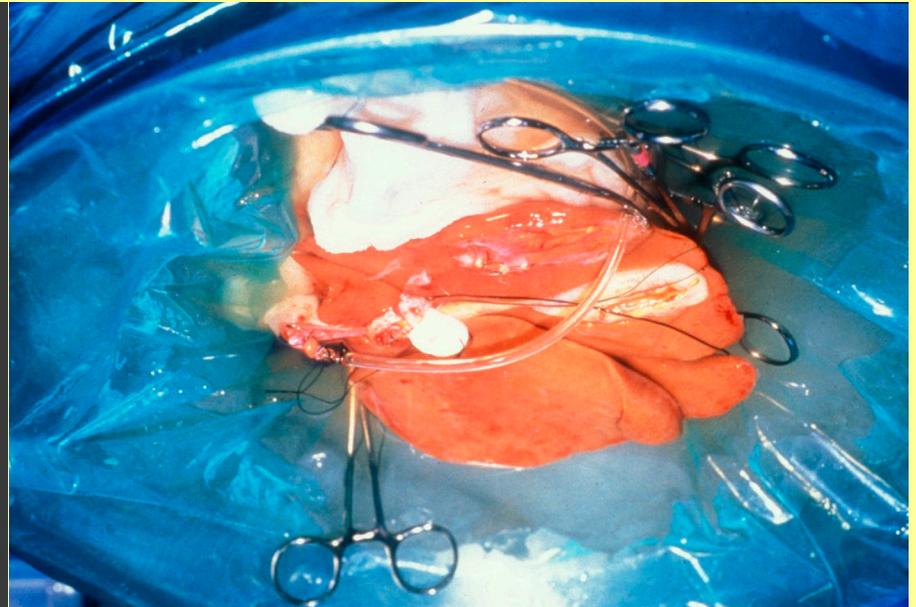


Advances in Xenotransplantation

Donor Aspects

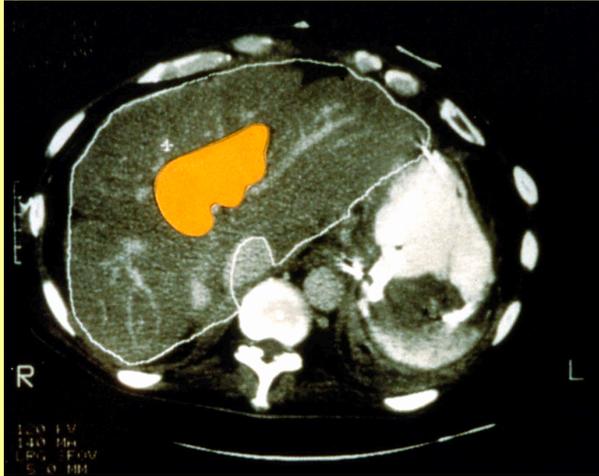


Donor weight: 40 kg



Donor liver weight: 610 gm

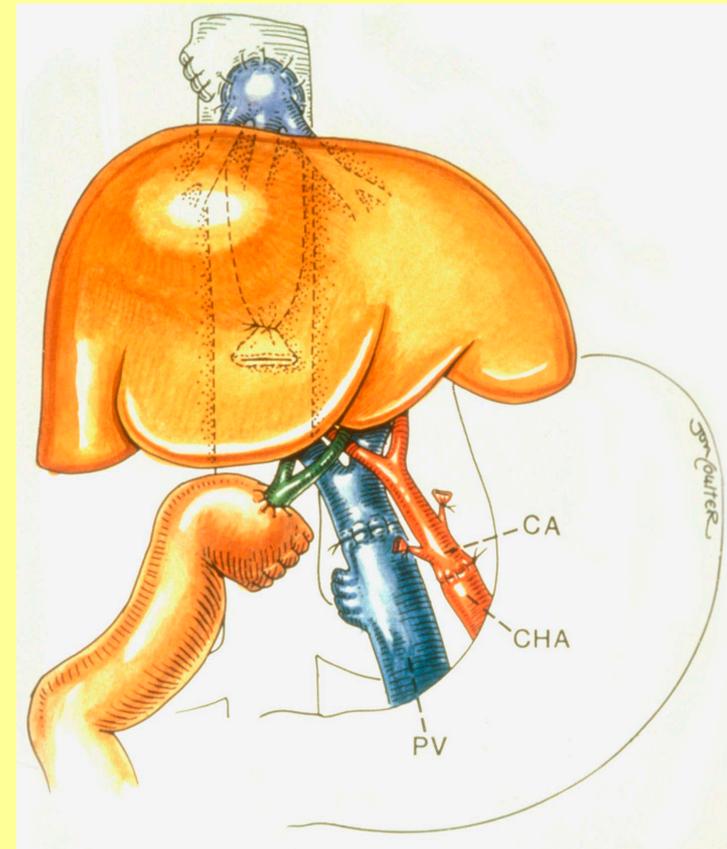
Baboon To Human Liver Xenotransplant



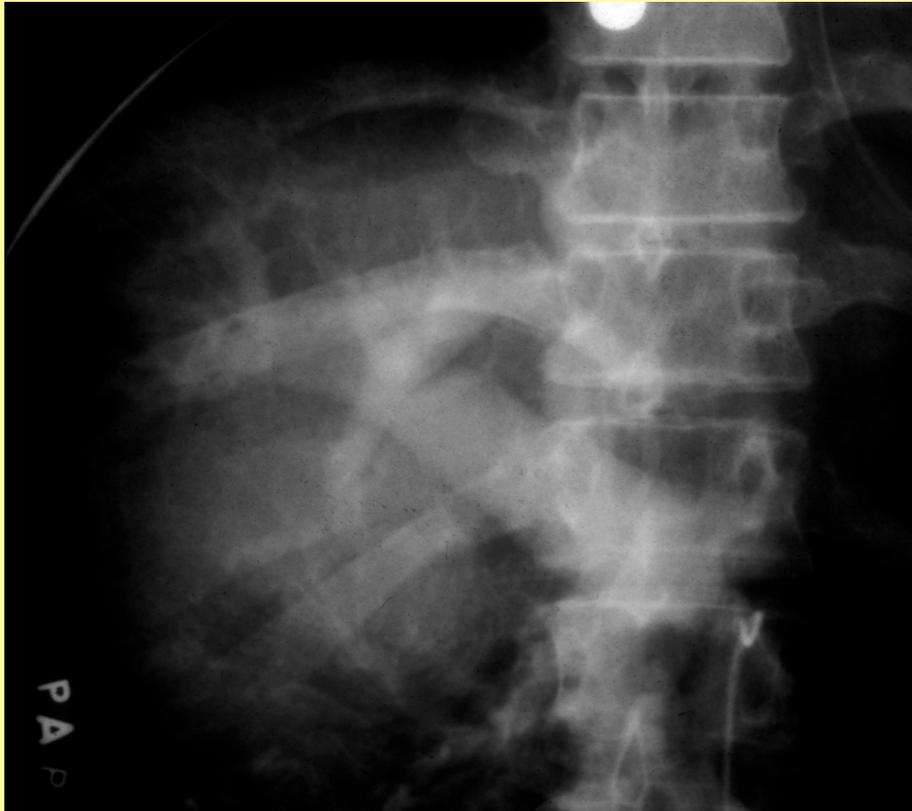
Postoperative course:

Immediate function:

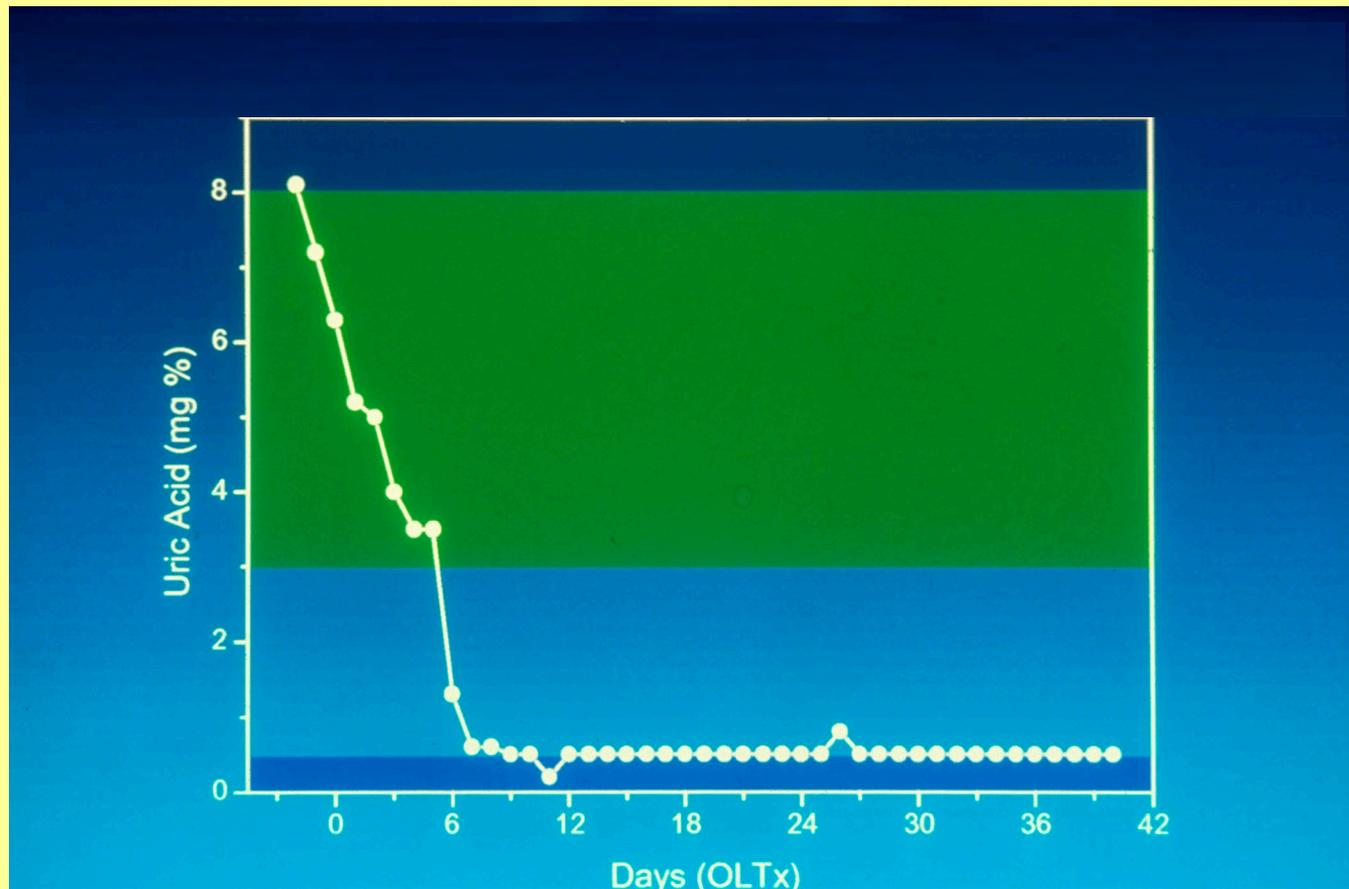
- Lactate clearance
- Correction of coagulopathy
- Clearance of ammonia
- Excretion of bile
- Synthesis of proteins - complement, albumin, transferrin
- Death from infection at 72 days



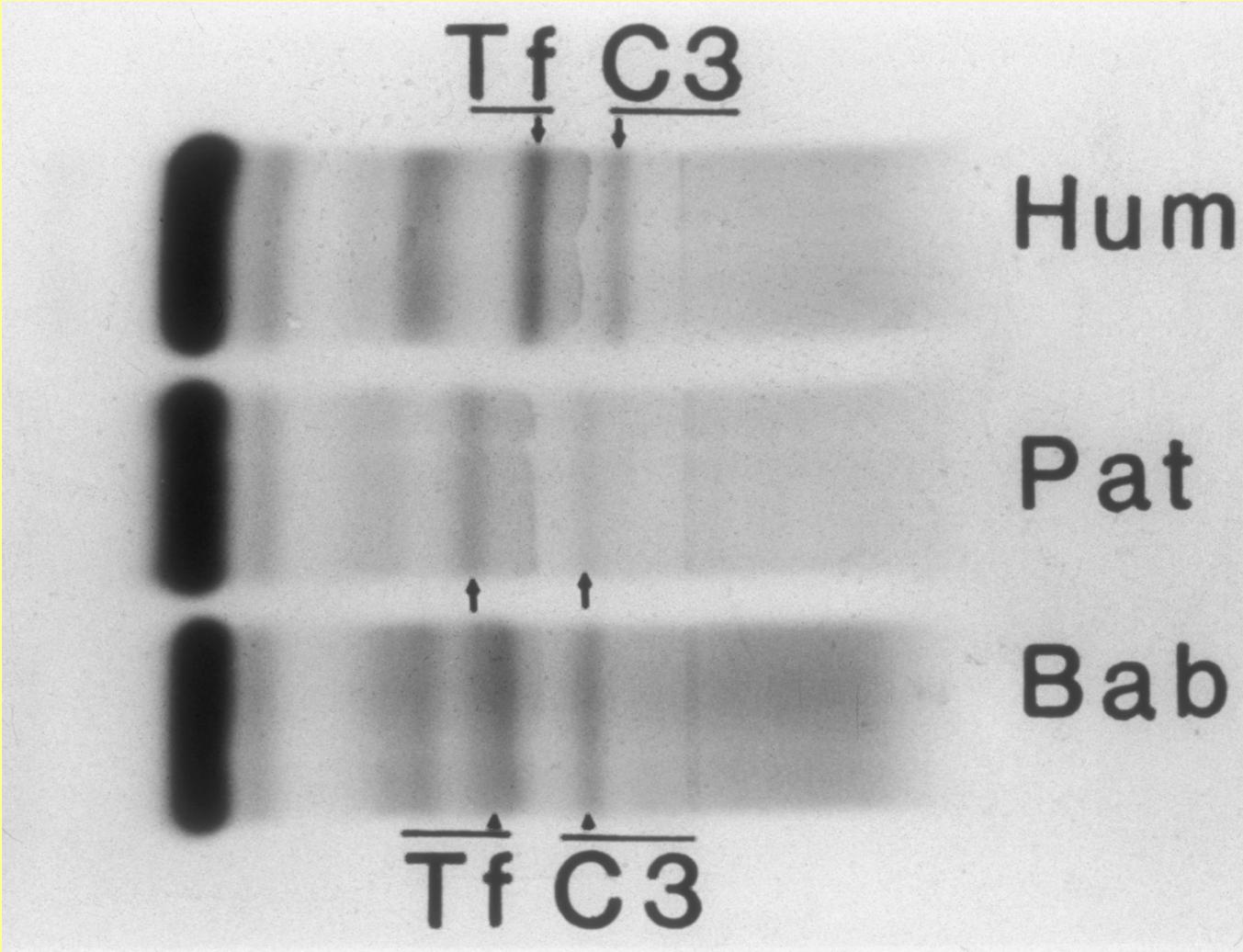
Imaging Xenograft Post-Transplant



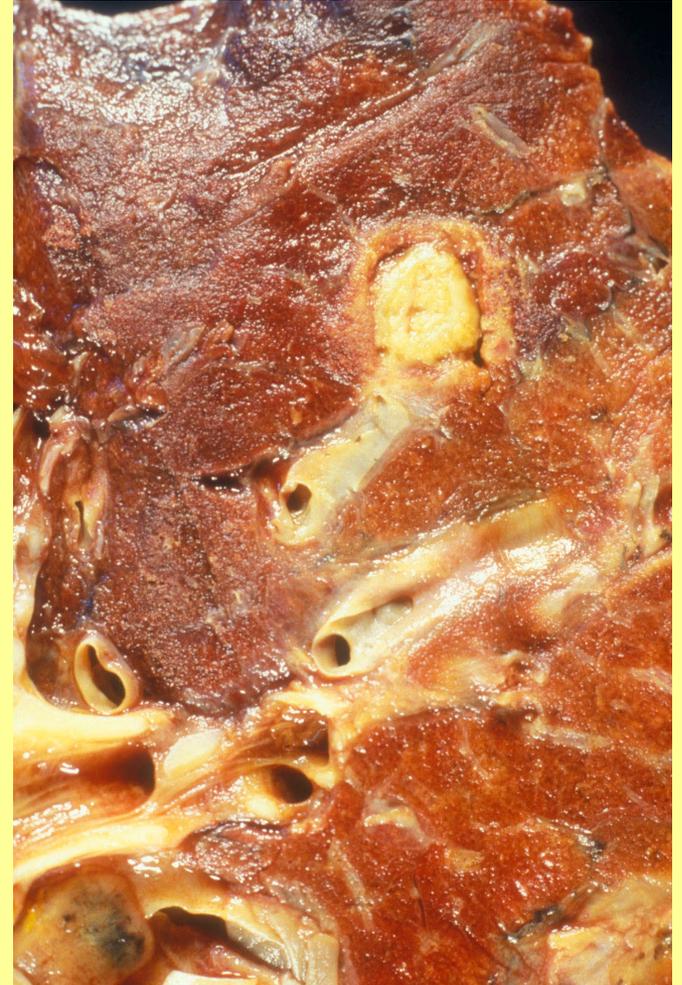
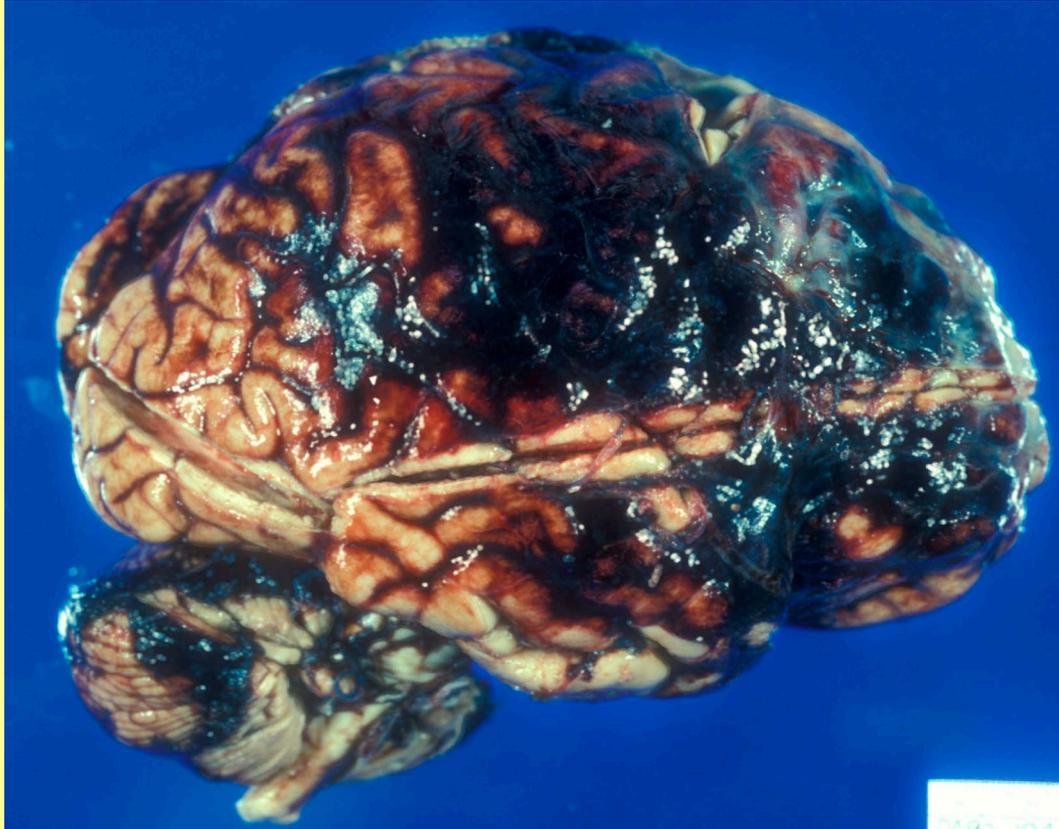
Change In Metabolism – Uric Acid



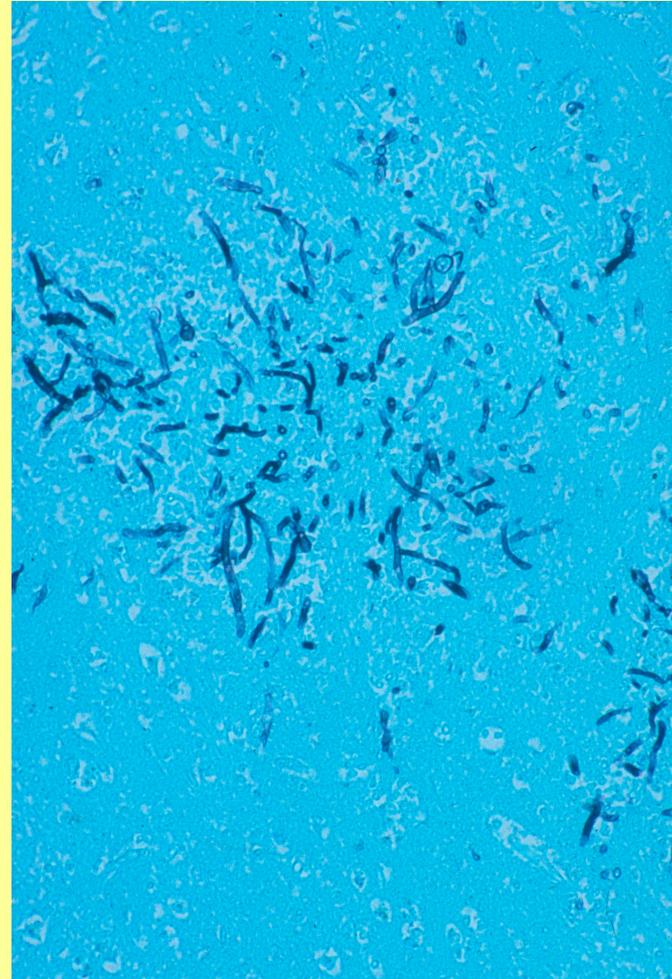
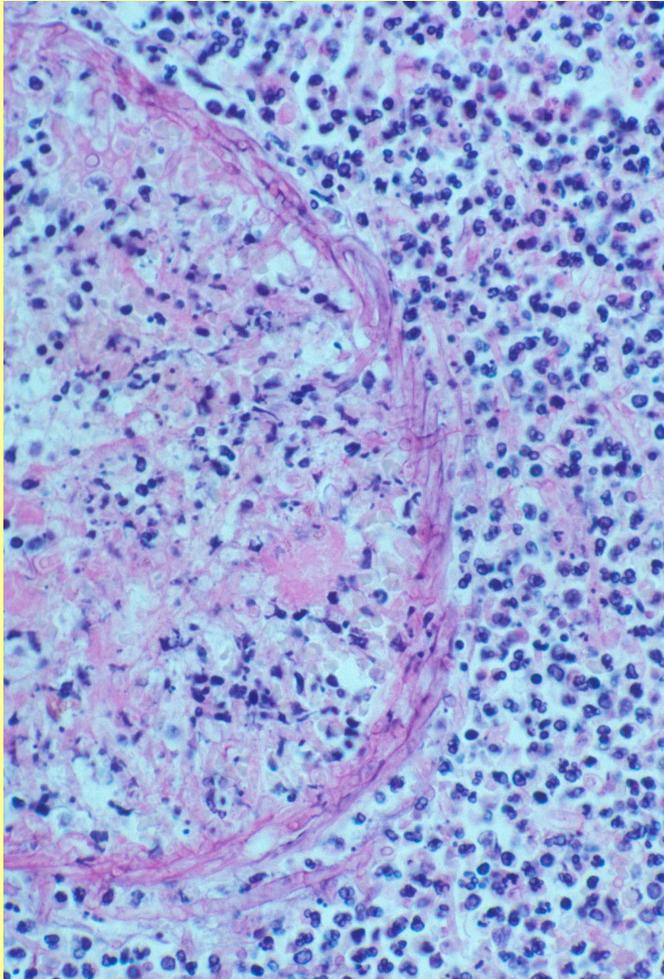
Change In Synthesis – Transferin/Complement



Consequences Of Over-Immunosuppression



Angio-invasive Aspergillus



Xenozoonosis

Spread of animal-derived pathogens into a transplant recipient potentiated by immunosuppression and avoidance of vector requirement

Potential novel pathogens

Potential new clinical syndromes

Unknown latency period

Infectious Agents Harbored By Nonhuman Primates

RETROVIRUSES

- Simian Immunodeficiency Virus [SIV]
- Simian Foamy Viruses [SFV]
- Simian T-Lymphotropic Viruses [STLV]
- Baboon Endogenous Retrovirus
- Simian Type D Retroviruses

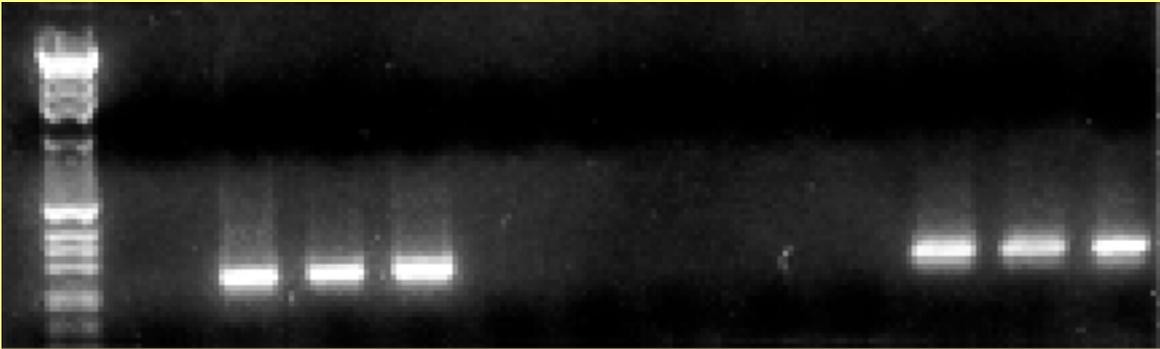
HERPES VIRUSES

- Herpesvirus papio
- Baboon cytomegalovirus [CMV]
- Simian Agent - 8 [SA-8]
- Cercopithecine herpesvirus 1 (or B virus)

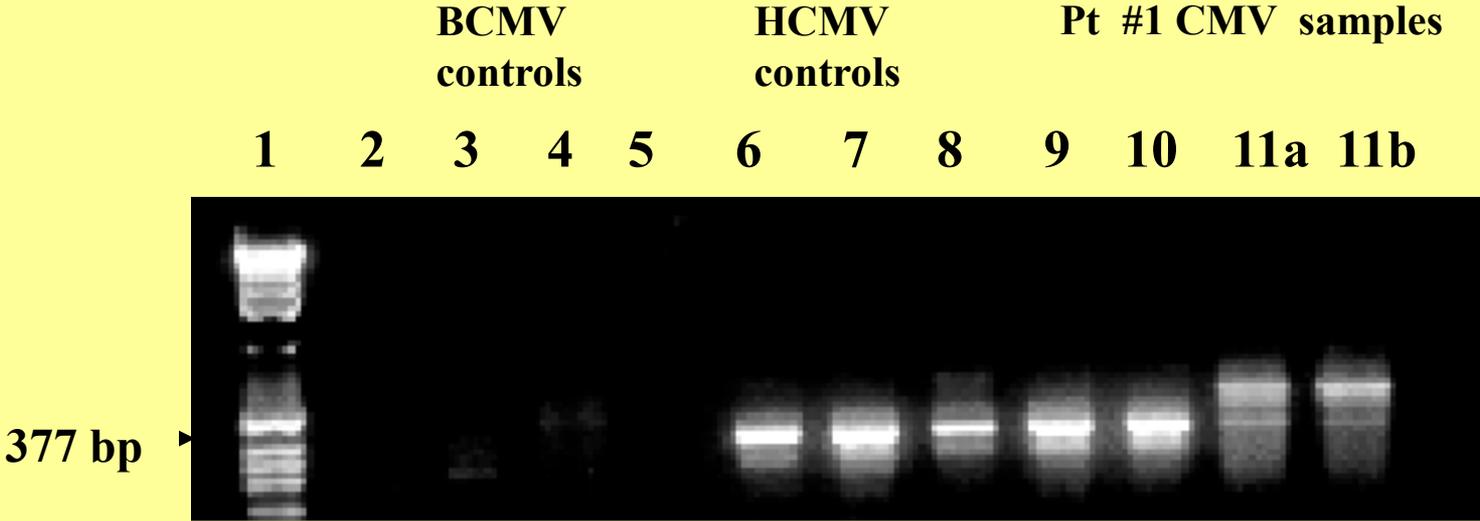
BCMV PCR After Xenotransplantation

	BCMV controls			HCMV controls			PT #1 CMV samples						
	1	2	3	4	5	6	7	8	9	10	11a	11b	12

246 bp →



HCMV PCR After Xenotransplantation



BCMV After Xenotransplantation

Preliminary data:

BCMV found from isolate from Buffy coat 1 month post transplant in 1 patient

Amplification using HCMV primers gives larger product than HCMV controls

Possibilities:

BCMV crossed species lines

BCMV - HCMV re-combined

Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
April 1999

“Xenotransplantation raises a major public health dilemma: how to balance the potential promise of this emerging technology ... with the risk of potential transmission of infectious agents to the patient, his/her close contacts, and the public at large.”

Pigs As Donors

Advantages:

- **Readily available**
- **Easily bred - potential for transgenic manipulation**
- **Domestic farm animals used for human needs**

Disadvantages:

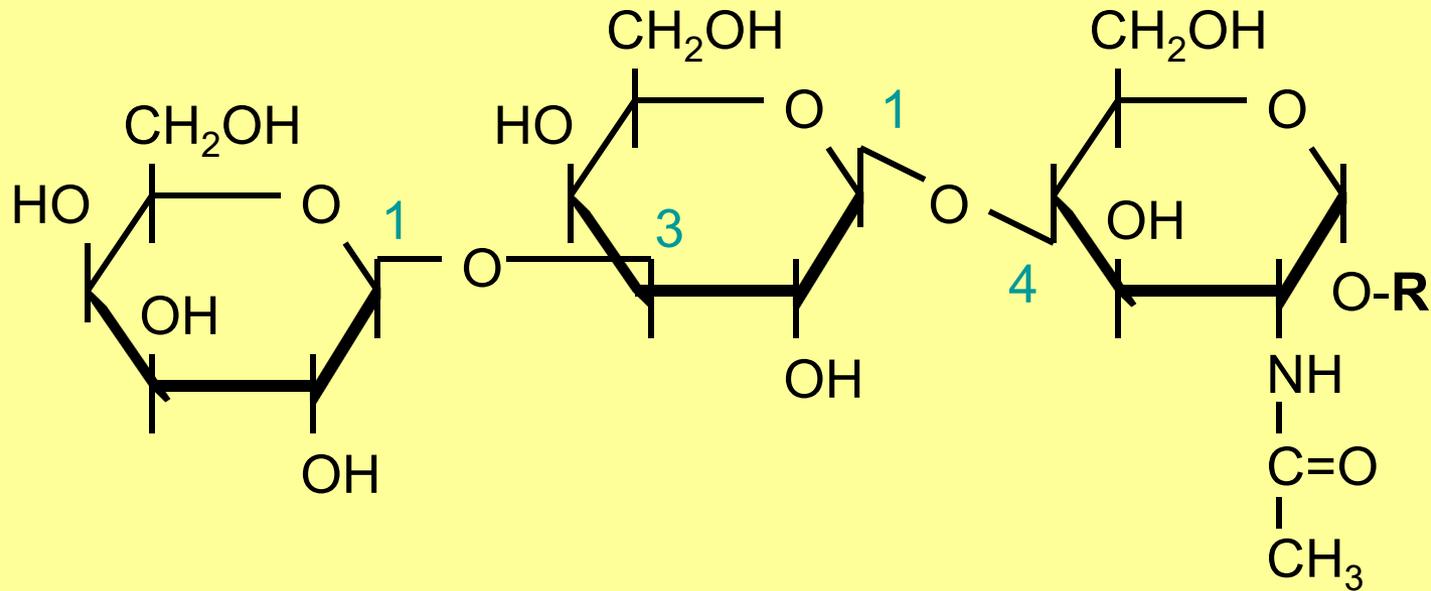
- **Protein incompatibility**
- **Discordant rejection pattern**

Xenoantibody Characterization

Xenoantibodies are preformed, naturally occurring antibodies, crossreactive to environmental antigens, usually directed towards glycoprotein moieties

Generally of IgM isotype, presumably synthesized by CD5+ B cells

Gal α 1,3Gal β 1,4GlcNAc-R



Galactose

α

Galactose

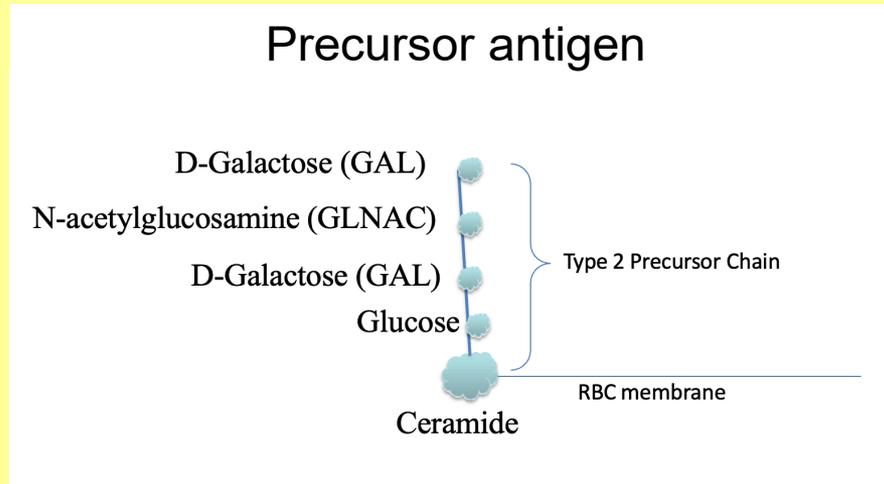
β

N-acetylglucosamine

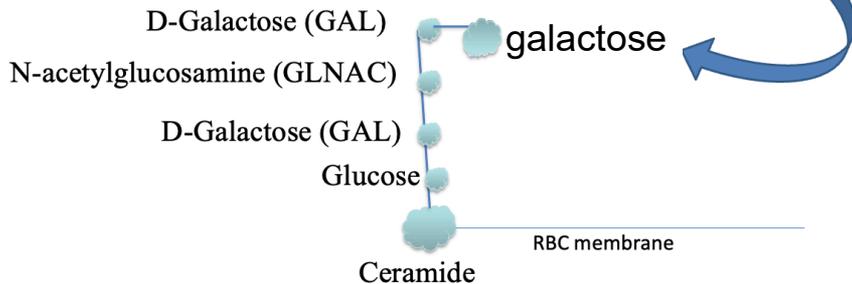
Common among mammals
except higher primates

Common among vertebrates

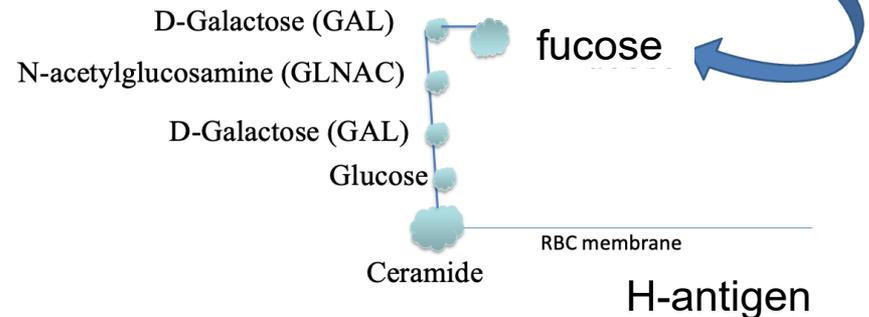
Generation of Blood Groups



galactosyl transferase



fucosyl transferase



Strategies To Overcome The Problem Of Human Xenoantibodies

Human Recipient

- Plasmapheresis
- Anti-Ig immunoabsorption
- Anti- μ chain antibody therapy
- Extracorporeal pig organ perfusion
- Gal(a1,3)gal immunoabsorption

Pig Donor

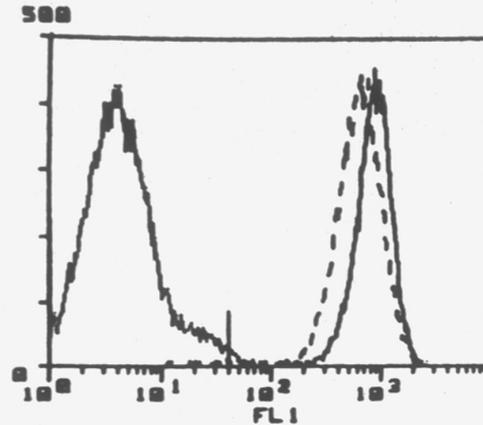
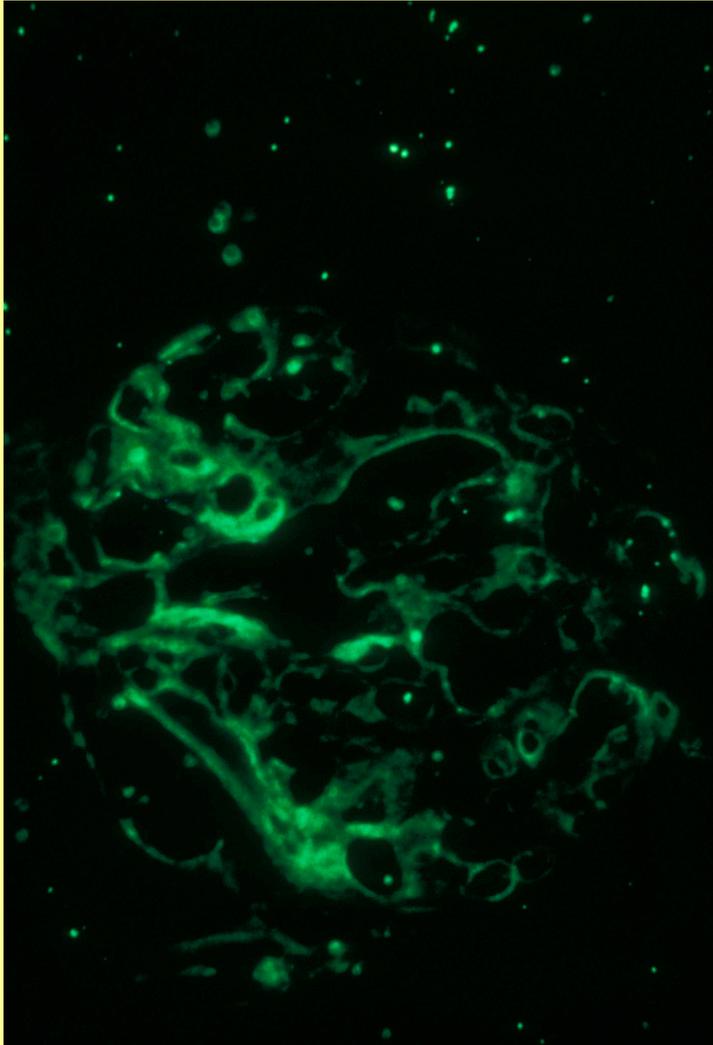
- Epitope elimination (gene knockout)
- Epitope suppression (antisense siRNA)
- Epitope masking/substrate competition (H transferase transgenic)
- Transgenes expressing human complement regulatory proteins

Pig-to-Human Liver Xenotransplantation – Mt. Sinai Medical Center - 1993

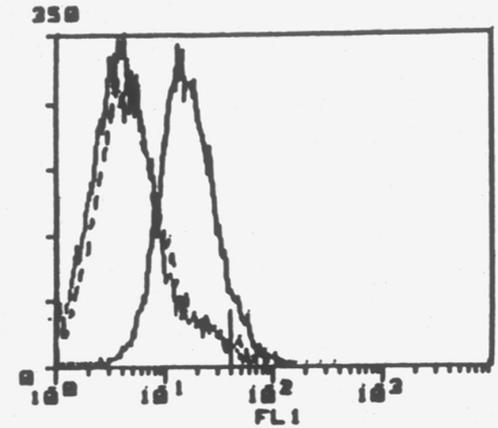
26 year old female with accelerated liver failure from autoimmune hepatitis progressing into Grade 3-4 coma
Listed for emergent liver transplant, no organs identified in 24 hours. Consent for pig-to-human liver xenotransplantation

Preformed anti-pig xenoantibodies depleted using plasmapheresis and specific antibody removal by passage of blood through pig kidneys

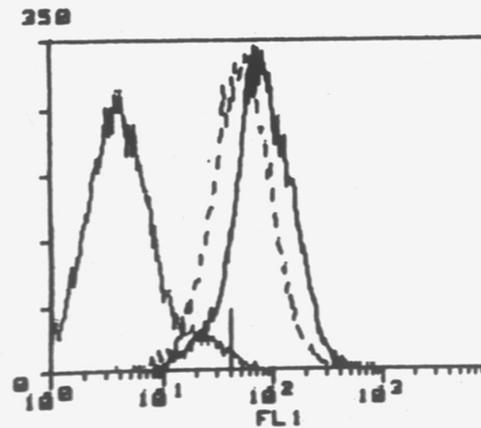
Xenoantibody Depletion In Pig-To-Human LTX



Pré-Transplant



Post Kidney Perfusion



32 hrs. Post-Transplant

— IgG Binding
--- IgM Binding
— Autologous Serum

Pig-to-Human Liver Xenotransplantation – Clinical Course

Heterotopic pig liver transplant as bridge-to-transplant

Immunosuppression

Azathioprine

Cyclophosphamide

Methylprednisolone

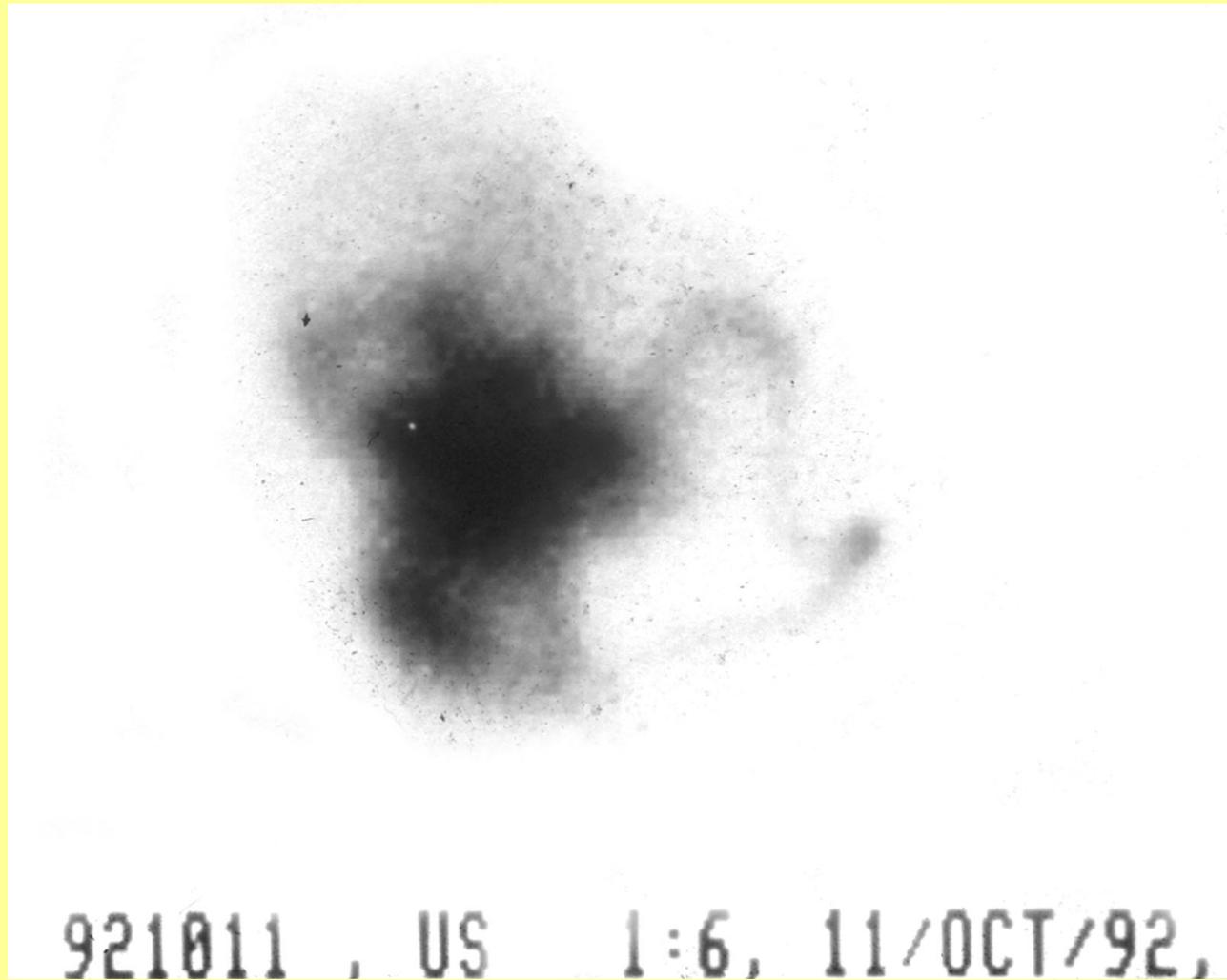
Cyclosporine

Initial lactate clearance and bile production

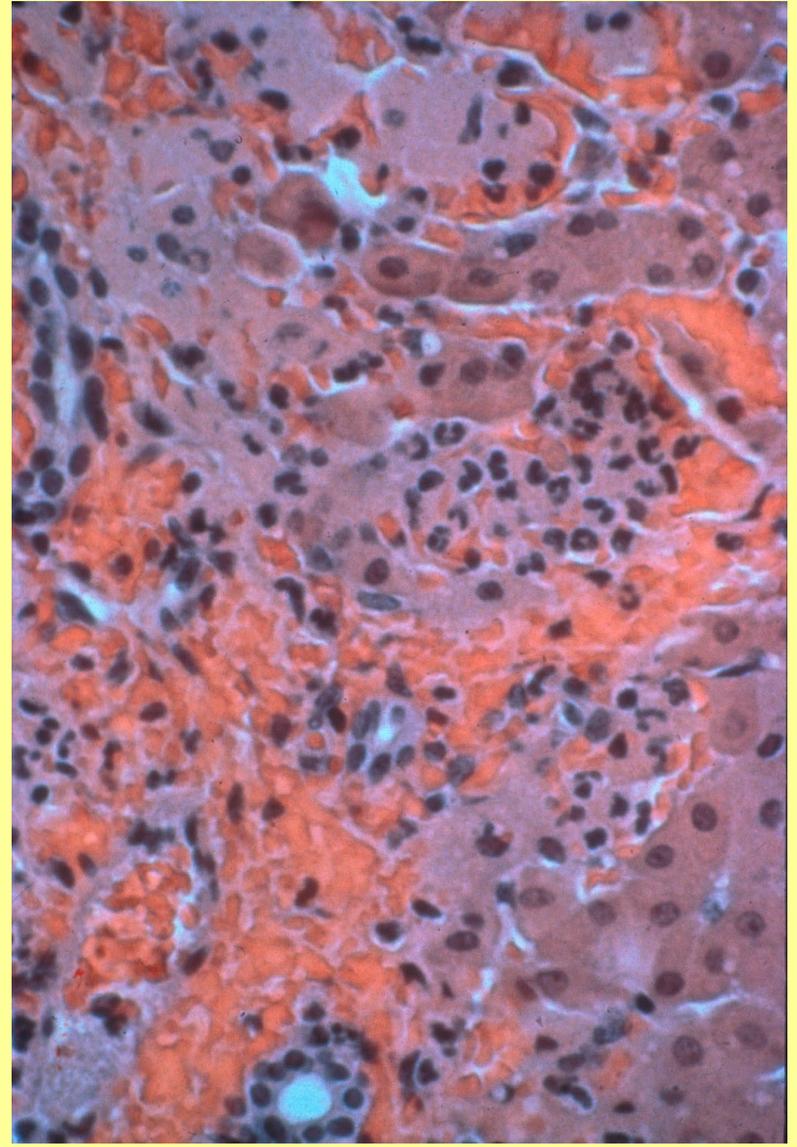
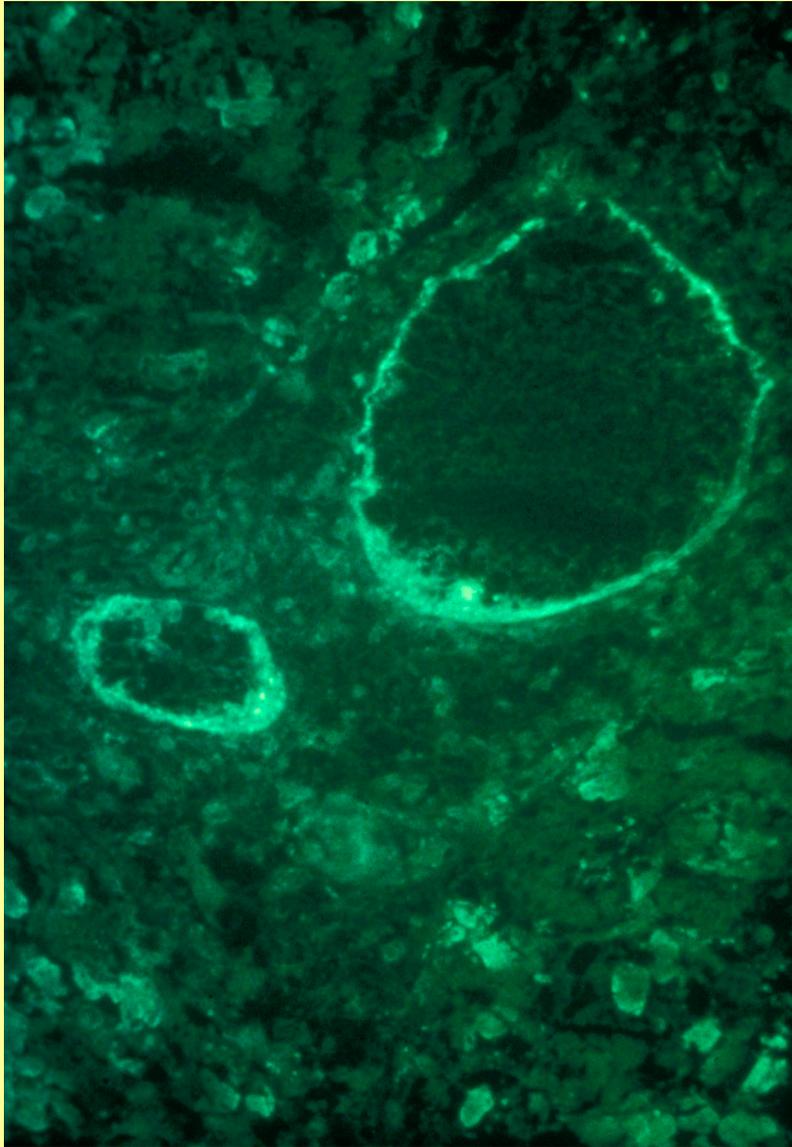
Worsening hyperammonemia, ICP

Death at 30 hours post-transplant

Advances in Xenotransplantation



Advances in Xenotransplantation



Strategies To Overcome The Problem Of Human Xenoantibodies

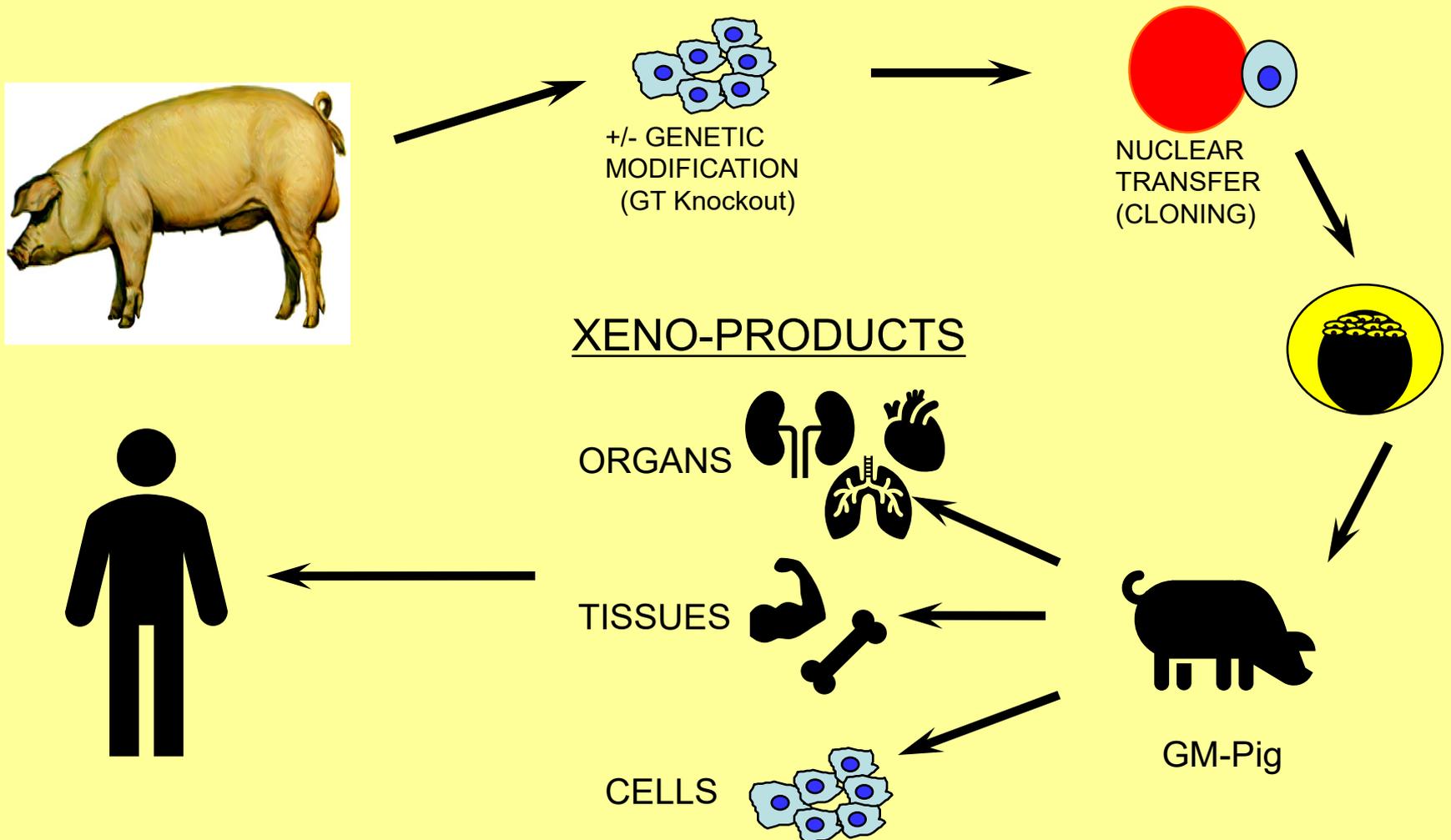
Human Recipient

- Plasmapheresis
- Anti-Ig immunoabsorption
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- Extracorporeal pig organ perfusion
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Pig Donor

- Epitope elimination (gene knockout)
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Elimination Of Hyperacute Rejection: α -1,3 GAL Knockout Pigs



α -1,3 GAL Gene Knockout Cloned Pigs



> [Science](#). 2003 Jan 17;299(5605):411-4. doi: 10.1126/science.1078942. Epub 2002 Dec 19.

Production of alpha 1,3-galactosyltransferase-deficient pigs

Carol J Phelps¹, Chihiro Koike, Todd D Vaught, Jeremy Boone, Kevin D Wells, Shu-Hung Chen, Suyapa Ball, Susan M Specht, Irina A Polejaeva, Jeff A Monahan, Pete M Jobst, Sugandha B Sharma, Ashley E Lamborn, Amy S Garst, Marilyn Moore, Anthony J Demetris, William A Rudert, Rita Bottino, Suzanne Bertera, Massimo Trucco, Thomas E Starzl, Yifan Dai, David L Ayares

Born: July. 25, 2002

- **Cloned Knockout Pigs with alpha 1,3 GT Gene Inactivated**
- **Platform pigs for additional gene modifications aimed at elimination of xenograft rejection**

Pre-Clinical and Human Trials

- **Begin Key pig-to-primate studies - April.03**
- **Dr. Thomas Starzl - University of Pittsburgh**
 - **Insulin producing islet cells**
 - **Long term survival**
 - **Correction of diabetes**
 - **Kidney transplant model**
 - **Survival without rejection (>90 days)**
 - **Function**
- **Human “pre-clinical” cadaver studies - seek IND approval in 2003**
- **Initiate human clinical trials (islets) - Q404**



Liver Allo- And Xenotransplantation

Allotransplantation

(controls)

Pig-to-pig (n=2)

Baboon-to-baboon (n=1)

Xenotransplantation

WT-Pig-to-baboon (n=1)

GTKO-Pig-to-baboon (n=10)

WT= Wild-type

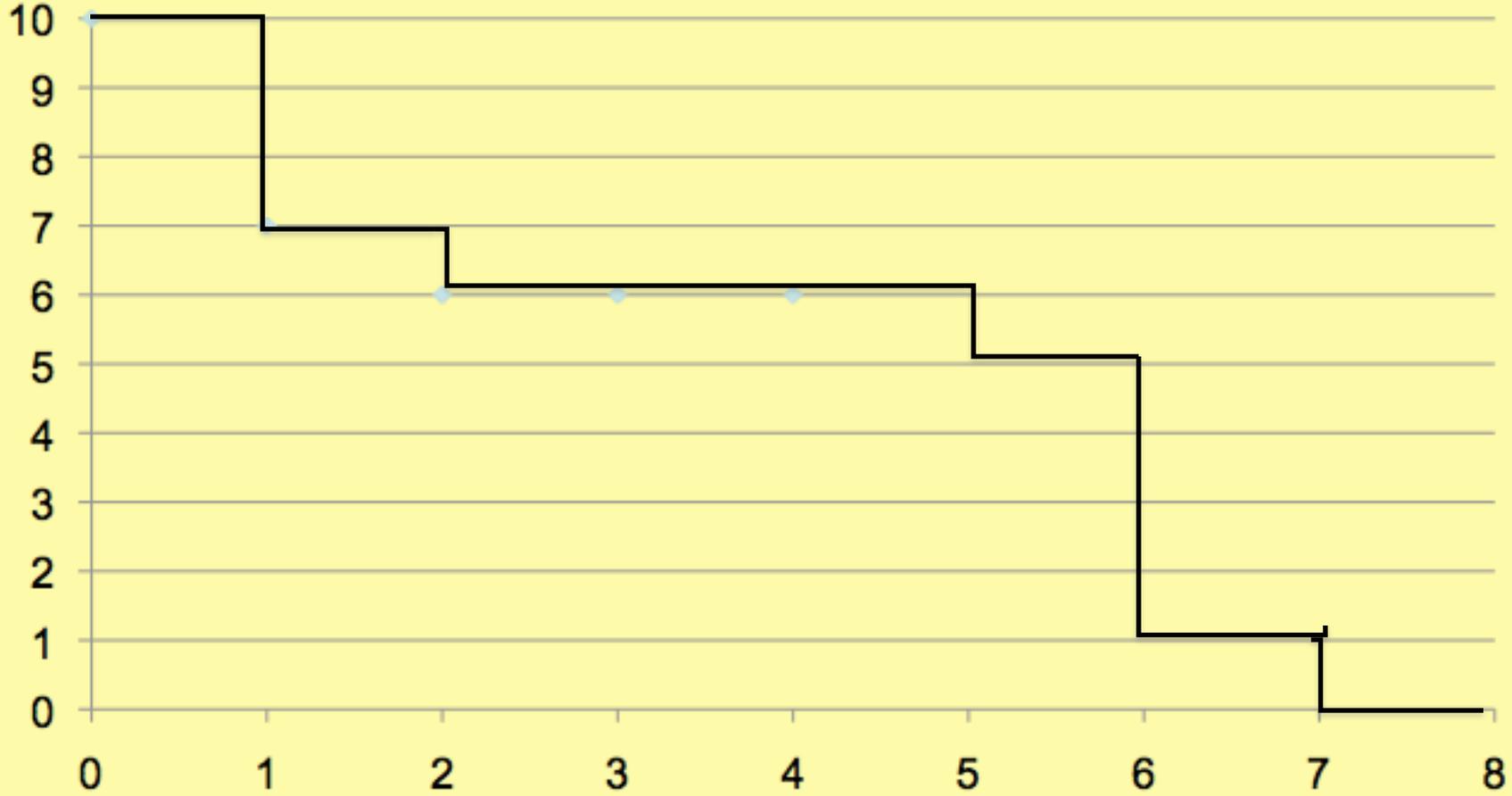
GTKO= α 1,3-galactosyltransferase knock-out

Immunosuppression

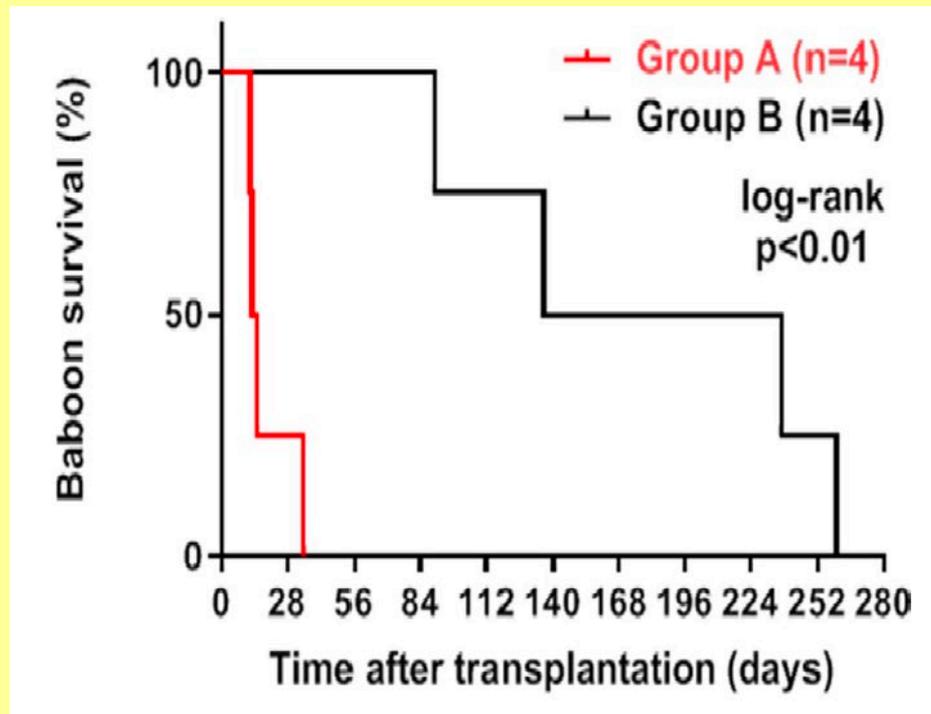
Induction	Day	Dose
Thymoglobulin	-3 and -1(if needed) T cell count	5-10 mg/kg IV
Cyclophosphamide	-2 and -1	40 mg/kg and 20mg/kg IV

Maintenance	Day	Dose
Tacrolimus	Starting from -4 or -3	0.05-0.2 mg/kg BID IM trough level 10-15 ng/mL
MMF	Starting from -6 or -5	110 mg/kg continuous IV trough level 3-5 µg/mL
Steroids	Starting from 0	10 mg/kg IV then tapering

Survival of GTKO Pig-To-Baboon Liver Xenotransplant

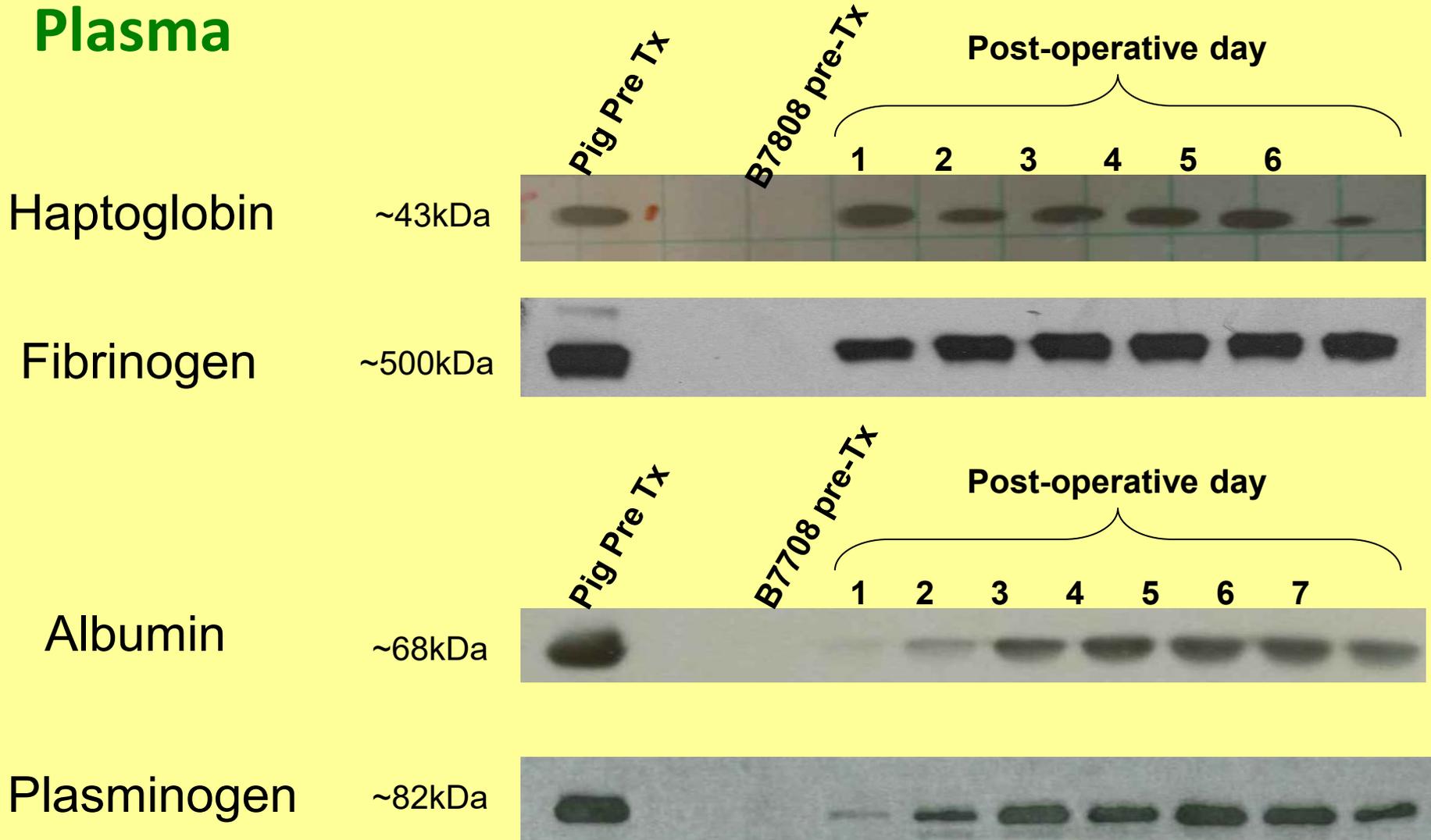


Modifications in Approaches to Immunosuppression

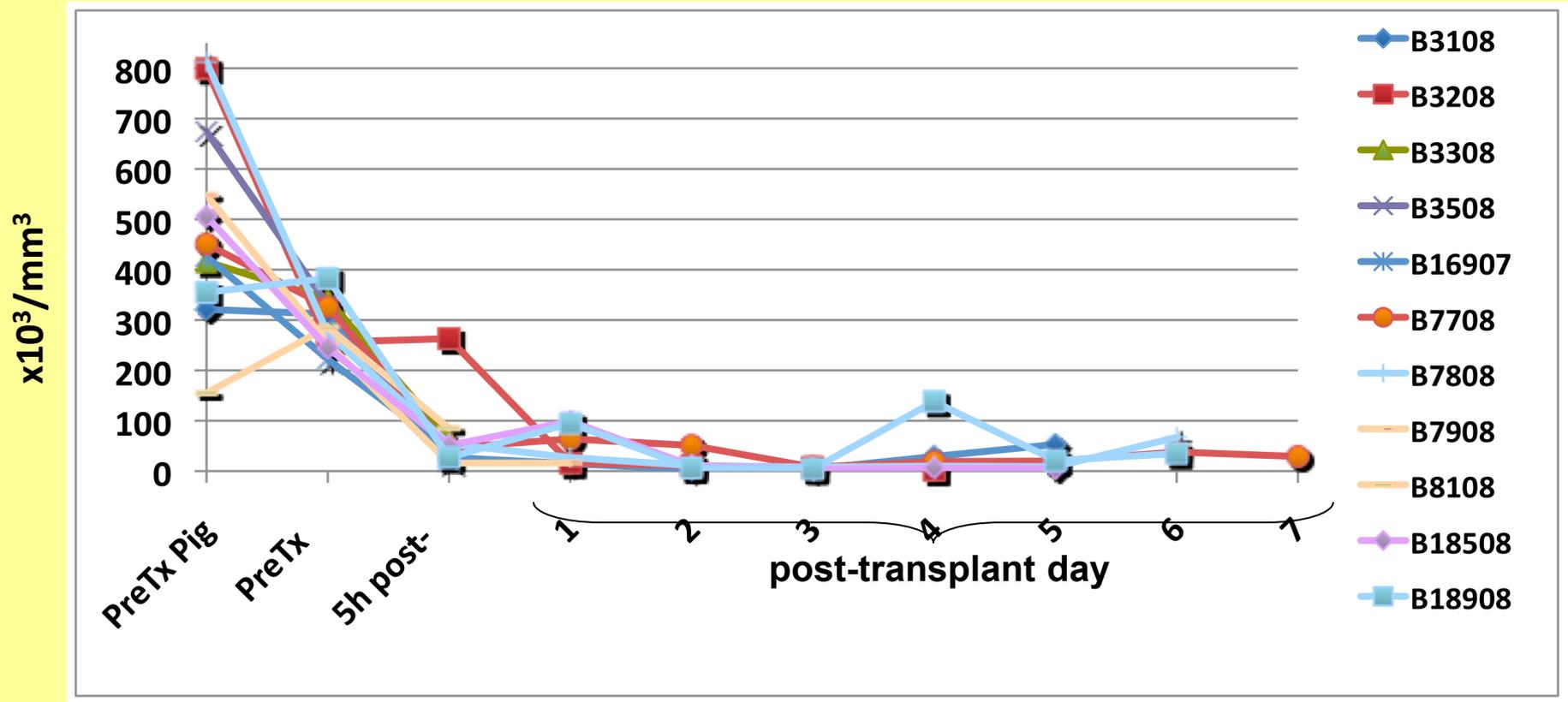


Pig kidney graft survival in baboons receiving either conventional (tacrolimus-based; Group A) or anti-CD40 mAb based (Group B) immunosuppressive therapy

Western Blotting For Pig Proteins In Baboon Plasma



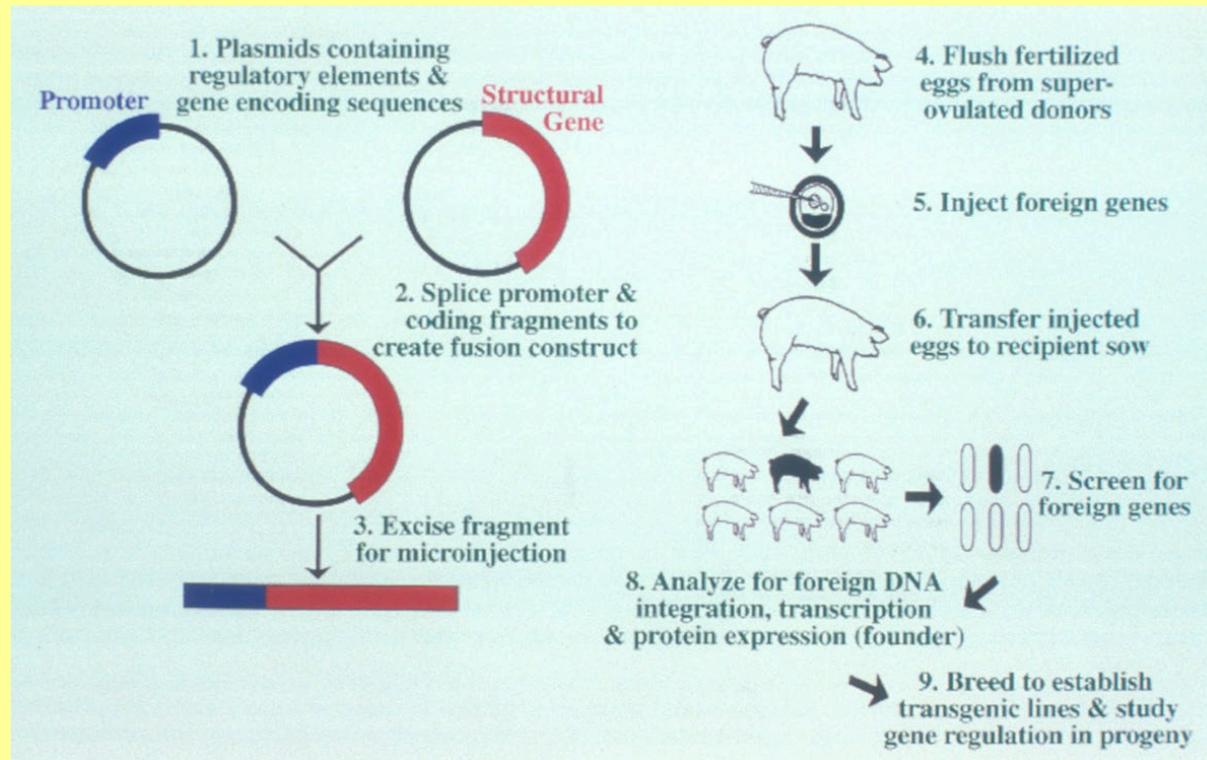
Platelets In GTKO Pig-To-Baboon Liver Xenotransplantation



Prolongation Of Genetically Modified Pig Xenografts In Primates

Combination	Antibody	Complement	Survival
Normal pig to primate	++++	++++	Few hours
Knockout pig to primate with immunosuppression	++	+	Few days - weeks
Transgenic pig to primate with immunosuppression	+++	-	Few days - weeks
Knockout/Transgenic pig to primate with immunosuppression	++	---	Few weeks - months

Creating Transgenic Pigs For Xenotransplantation

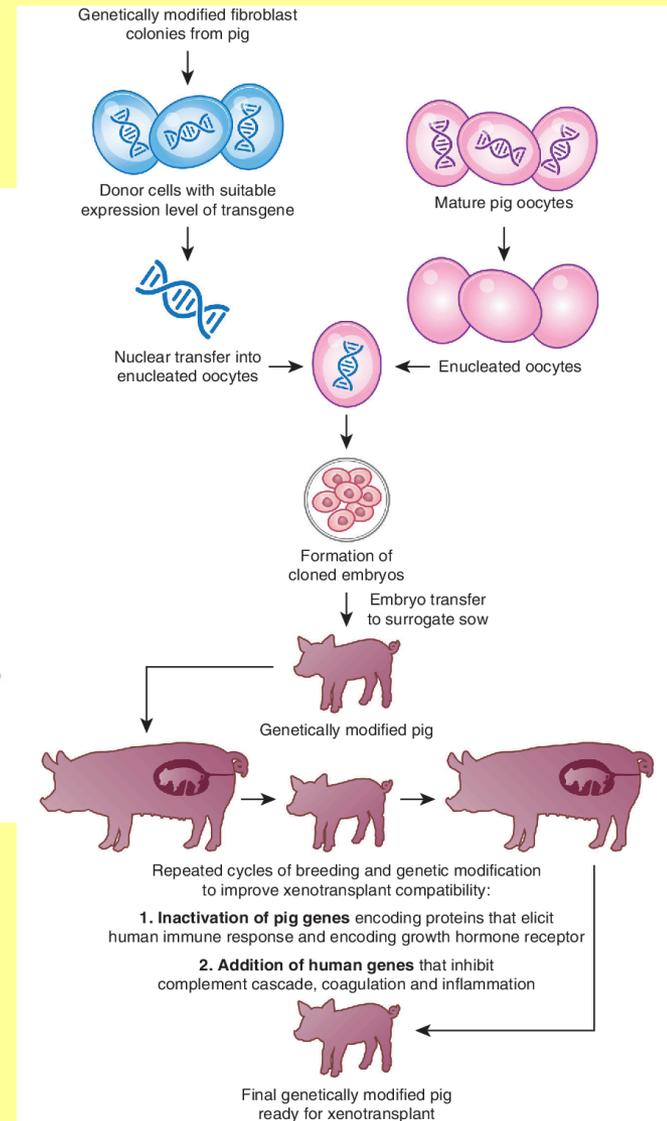
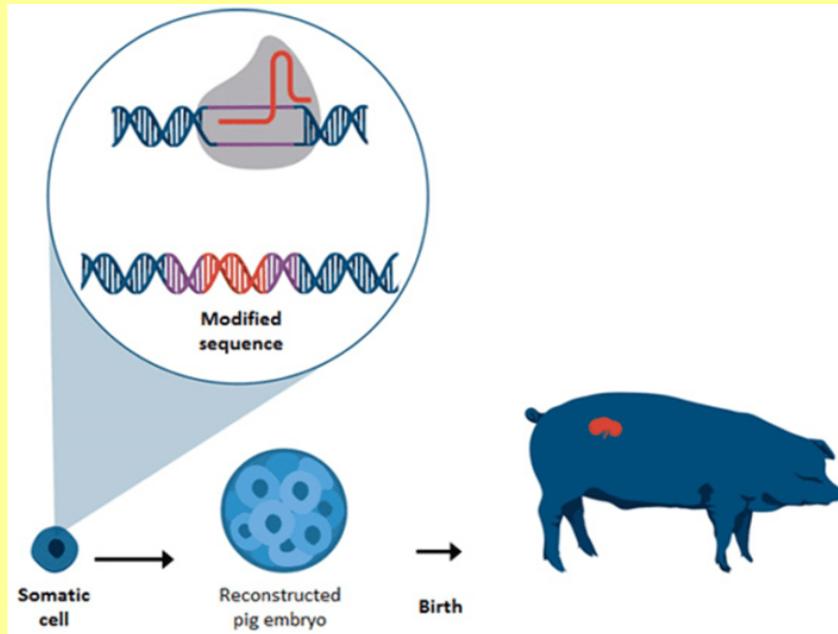


► Immunology. 2013 Aug 12;140(1):39–46. doi: [10.1111/imm.12107](https://doi.org/10.1111/imm.12107)

Human dominant-negative class II transactivator transgenic pigs – effect on the human anti-pig T-cell immune response and immune status

[Hidetaka Hara](#)¹, [William Witt](#)¹, [Tanner Crossley](#)¹, [Cassandra Long](#)¹, [Kumiko Isse](#)², [Liming Fan](#)³, [Carol J Phelps](#)⁴, [David Ayares](#)⁴, [David K C Cooper](#)¹, [Yifan Dai](#)^{3,1}, [Thomas E Starzl](#)¹

Creating Transgenic Pigs For Xenotransplantation



Categories of Genetic Modifications for Clinical Xenotransplantation



Carbohydrate Antigen Modifications

GGTA1-KO
cMAH-KO
B4GALNT2-KO
GLA-tg
a2FucT-tg



Complement Regulation

CD46-tg
CD55-tg
CD59-tg



Coagulation

hvWF-tg
hTBM-tg
hTFPI-tg
THBD-tg
hEPCR-tg



Anti-inflammatory

hHO-1-tg
hTNFAIP-3-tg



Miscellaneous

Infection Control -
PERV-KO
Growth Control -
GHR-KO

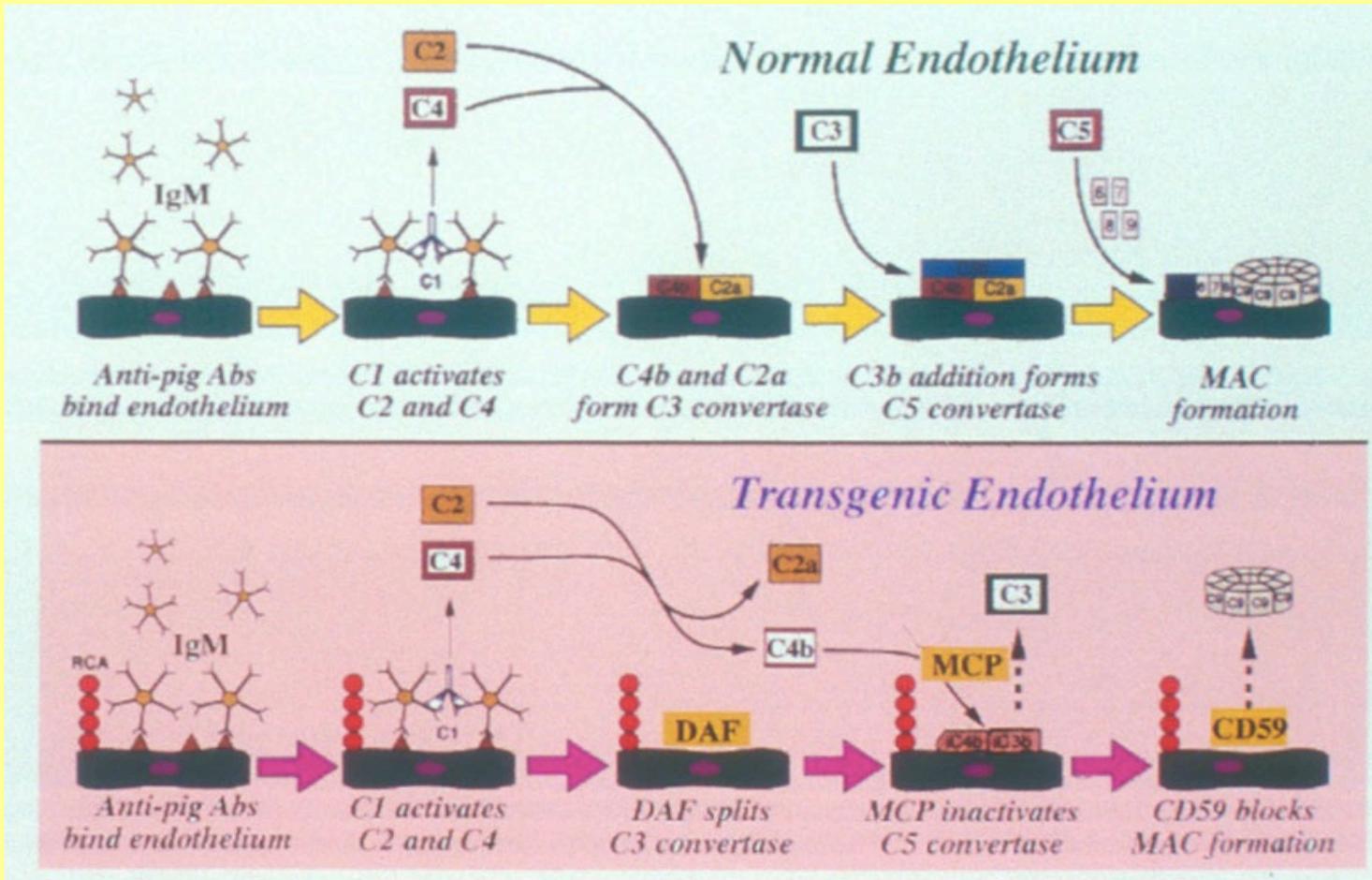


Modulate Cellular Immune Responses

CIITA-DN
SLA-KO
HLA-E/hb2M-tg
CTLA4-Ig-tg
CD47-tg
iGb3S-KO

Advances in Xenotransplantation

Transgenic Pig Endothelium With Human Complement Regulatory Proteins: DAF (CD55) – MCP (CD46) – CD59



Search for Cross-Species Transmission of Porcine Endogenous Retrovirus in Patients Treated with Living Pig Tissue

Paradis et al. *Science*, 285:1236, 1999

160 patients receiving living pig tissue up to 12 years

PCR on serum failed to demonstrate PERV viremia

No PERV identified in patient WBC by PCR

Pig microchimerism detected in 23 patients up to 8.5 yrs

Pig Endogenous Retrovirus

PERV is carried in the pig genome - approximately 8-15 full length PERV sequences per genome

PERV previously demonstrated to infect human cells in vitro and rescue a Moloney retroviral vector

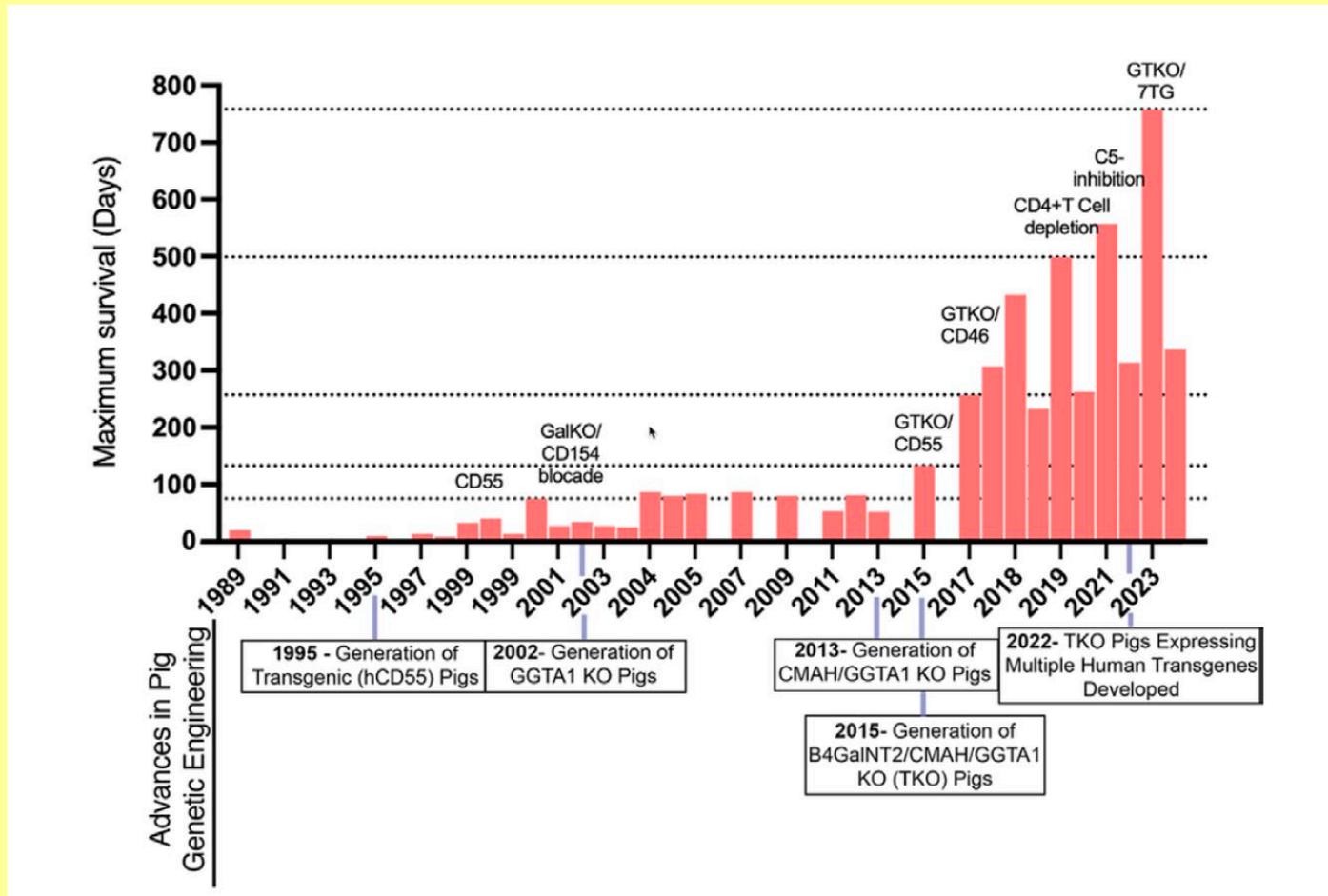
Neither zoonotic potential nor tissue tropism has been established

Characteristics of Gene Edited Pigs for Clinical Xenotransplantation

Genetic Modification	Revivicor	eGenesis	Makana
GGTA1KO	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
CMAHKO	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
B4GALNT2KO	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>
PERVPOLKO		<input checked="" type="checkbox"/>	
hCD46	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
hCD55	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
hEPCR	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
hTBM	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
hCD47	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
TNFAIP3		<input checked="" type="checkbox"/>	
hHO-1	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	
pGHKO	<input checked="" type="checkbox"/>		

α -galactosyltransferase 1 (GGTA1); cytidine monophospho-Nacetylneuraminic acid hydroxylase (CMAH); β -1,4-N-acetyl galactosaminyltransferase 2 (B4GALNT2); porcine endogenous retrovirus (PERV); endothelial protein C receptor (EPCR); thrombomodulin (TBM); tissue factor pathway inhibitor (TFPI); TNF Alpha Induced Protein 3 (TNFAIP3); membrane cofactor protein (CD46); decay accelerating factor (CD55); ligand for signal regulatory protein-a (CD47); membrane attack complex (CD59)

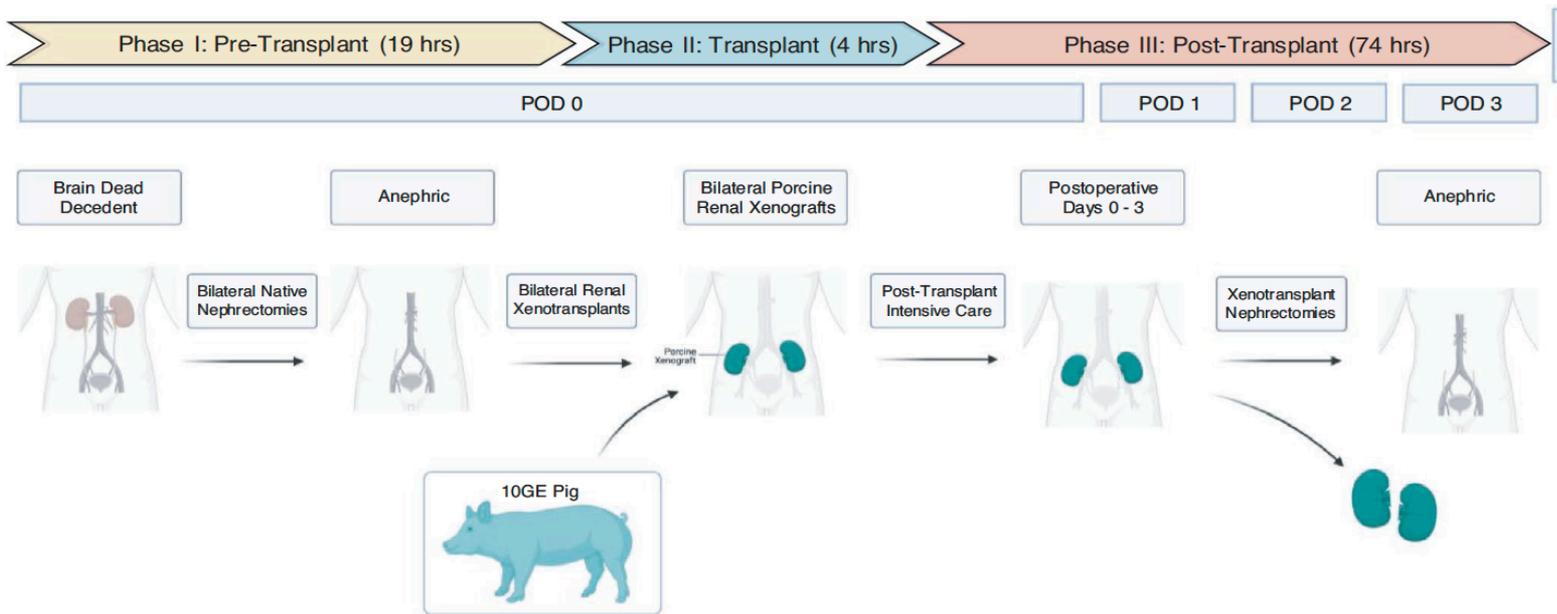
Maximum Life-supporting Pig Renal Graft Survival In Non-human Primates



Advances in Xenotransplantation

First clinical-grade porcine kidney xenotransplant using a human decedent model

Am J Transplant. 2022;22:1037-1053.



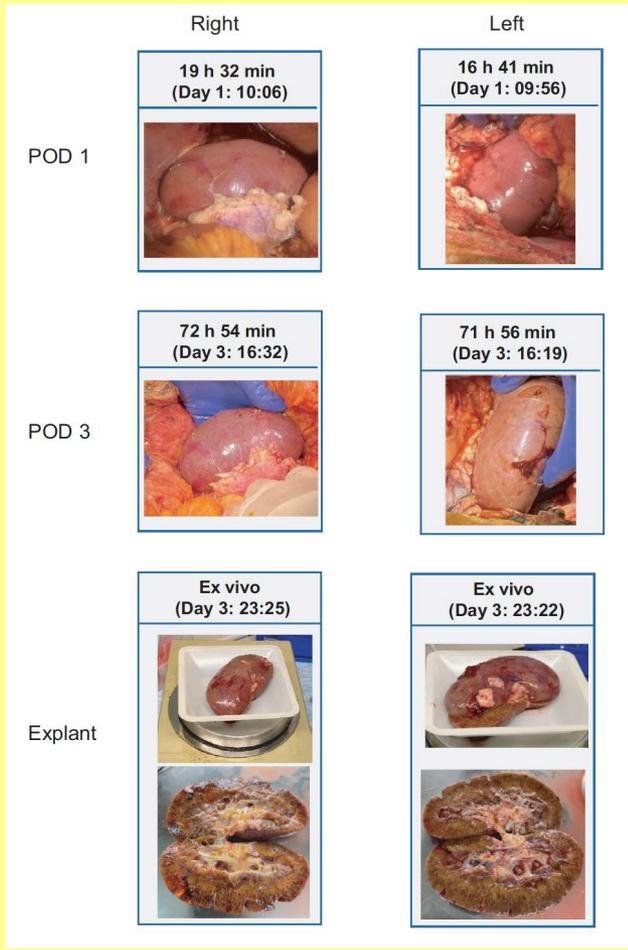
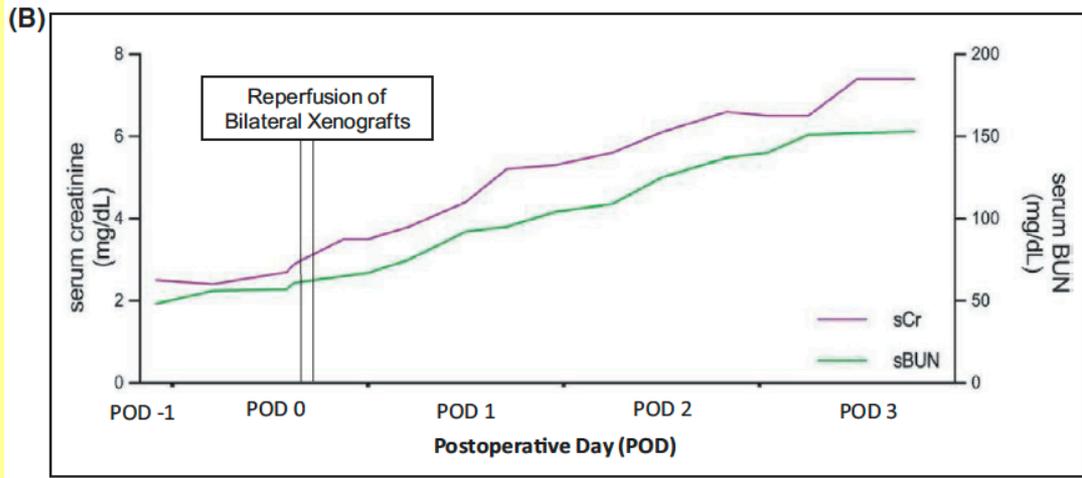
- Family authorization
- Prospective crossmatch
- Xenograft procurement
- Pre-transplant xenograft histology
- Removal of bilateral decedent native kidneys

- Induction immunosuppression
- Transplantation of right and left kidney xenografts
- Visual assessment for hyperacute rejection
- Visual assessment of xenograft perfusion
- Post-implantation xenograft biopsies

- Induction and maintenance immunosuppression
- Assessment of xenograft function
- Visual inspection of xenografts, including vascular and ureteral anastomoses
- Assessment of xenograft perfusion
- Assessment of sensitization (anti-HLA antibodies)
- Assessment for transmission of porcine endogenous retroviruses
- Serial xenograft biopsies
- Bilateral xenograft nephrectomies

Advances in Xenotransplantation

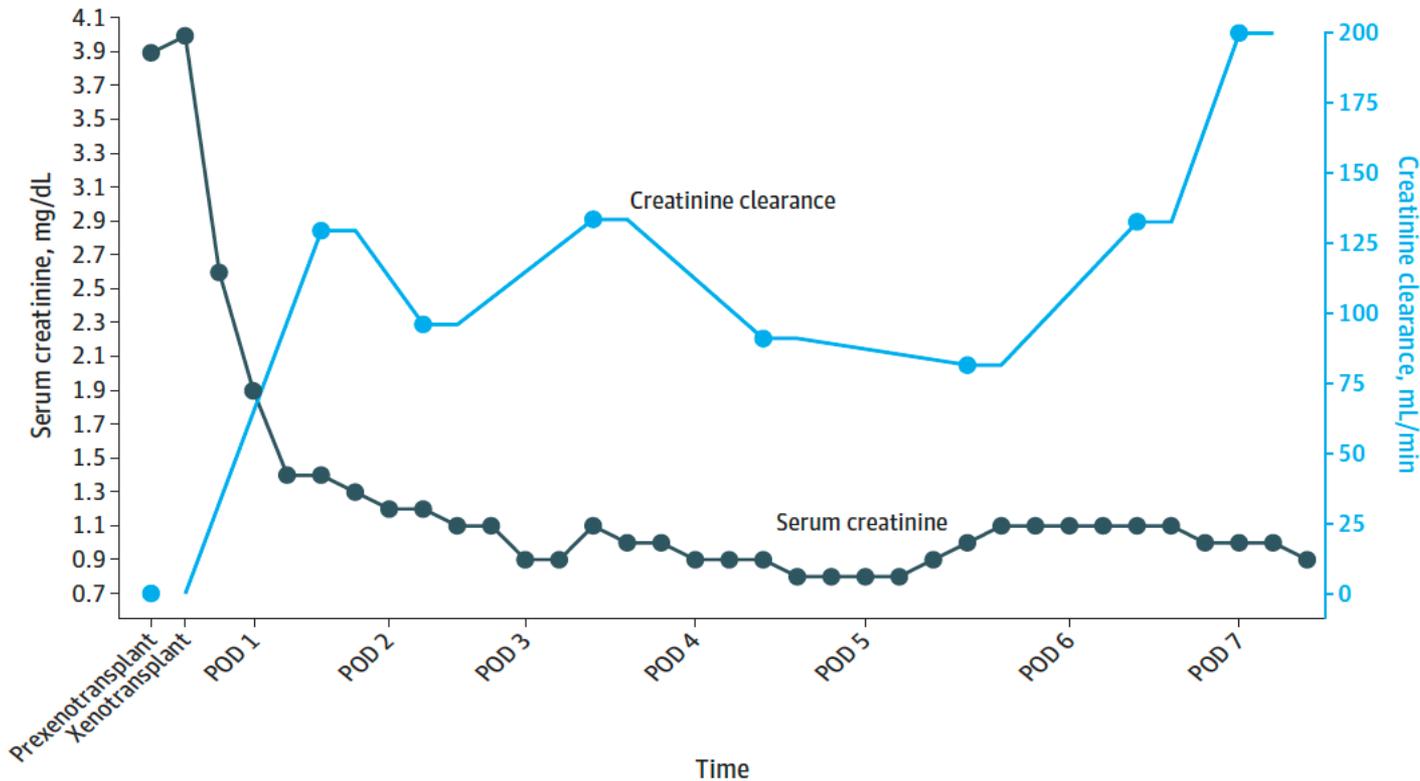
Immunosuppressive medication	POD 0	POD 1	POD 2	POD 3
Anti-Thymocyte Globulin (Rabbit)	175 mg	175 mg	175 mg	—
Rituximab	1800 mg	—	—	—
Tacrolimus	— 1 mg PM	1 mg AM 1 mg PM	1 mg AM 2 mg PM	2 mg AM —
Mycophenolate mofetil	— 2000 mg PM	1000 mg AM 1000 mg PM	1000 mg AM 1000 mg PM	1000 mg AM —
Methylprednisolone ^a	500 mg	250 mg	125 mg	90 mg



Normal Graft Function After Pig-to-Human Kidney Xenotransplant

JAMA Surgery October 2023 Volume 158,

Figure 1. Kidney Function Over Time After 10-Gene-Edited Pig-to-Human Xenotransplant

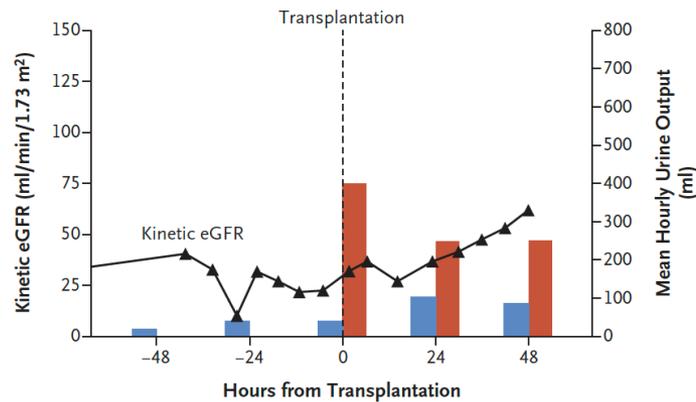


Results of Two Cases of Pig-to-Human Kidney Xenotransplantation

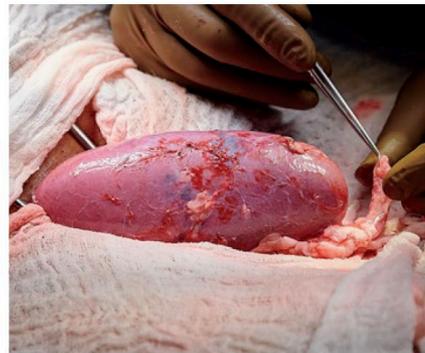
N ENGL J MED 386;20 NEJM.ORG MAY 19, 2022

■ Urine output from native kidneys ■ Urine output from xenotransplanted thymokidney

A Recipient 1



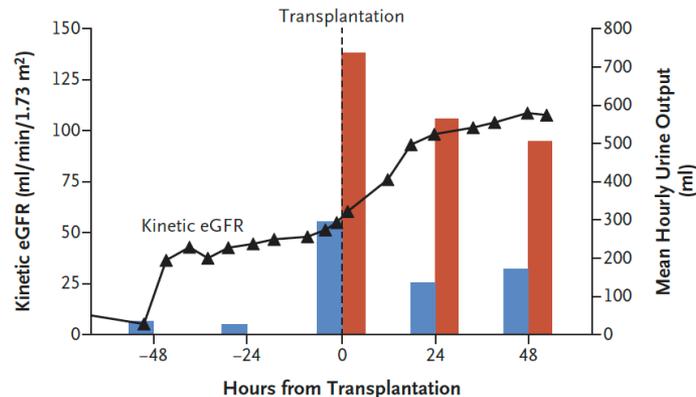
A Recipient 1, after Perfusion



B Recipient 1, at 54 Hr



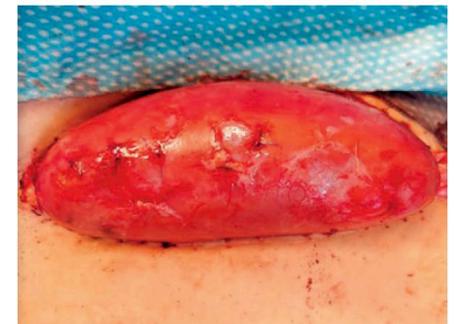
B Recipient 2



C Recipient 2, after Perfusion



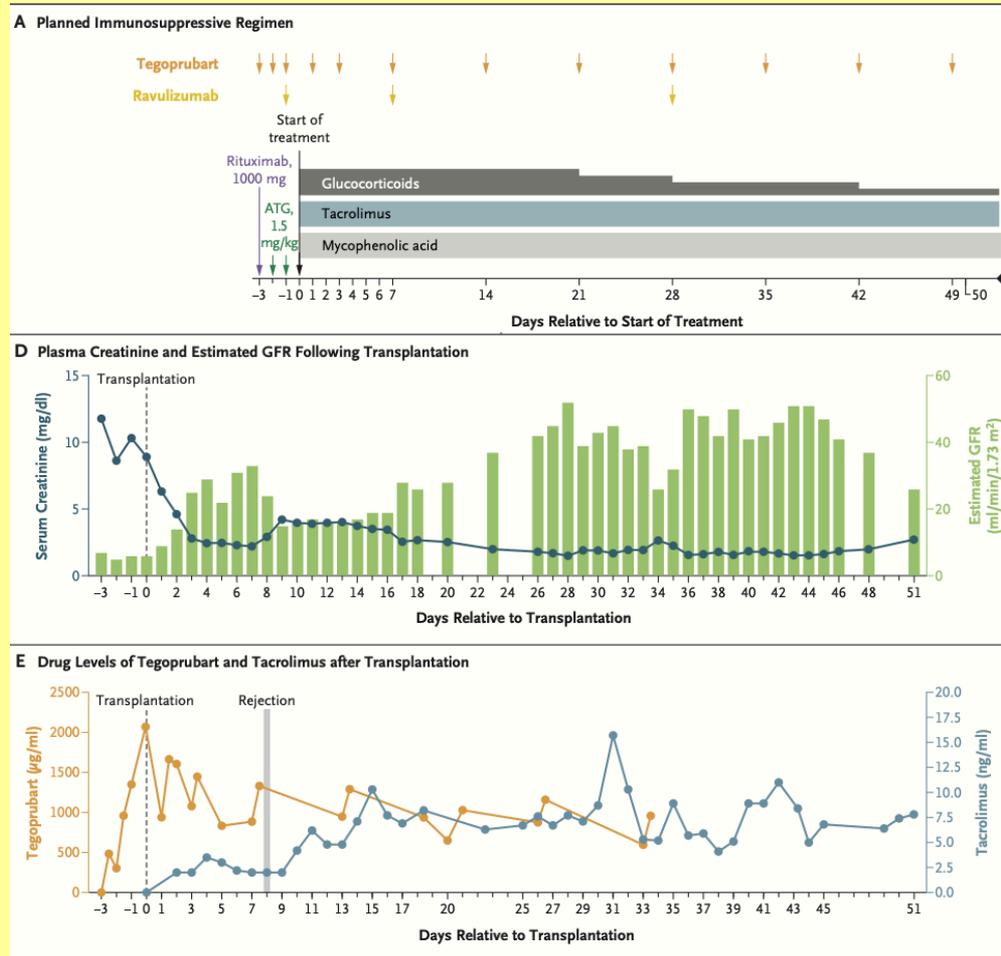
D Recipient 2, at 54 Hr



The NEW ENGLAND JOURNAL of MEDICINE

Xenotransplantation of a Porcine Kidney for End-Stage Kidney Disease

Tatsuo Kawai, M.D., Ph.D.,^{1,4} Winfred W. Williams, M.D.,^{1,4} Nahel Elias, M.D.,^{1,4}



Advances in Xenotransplantation

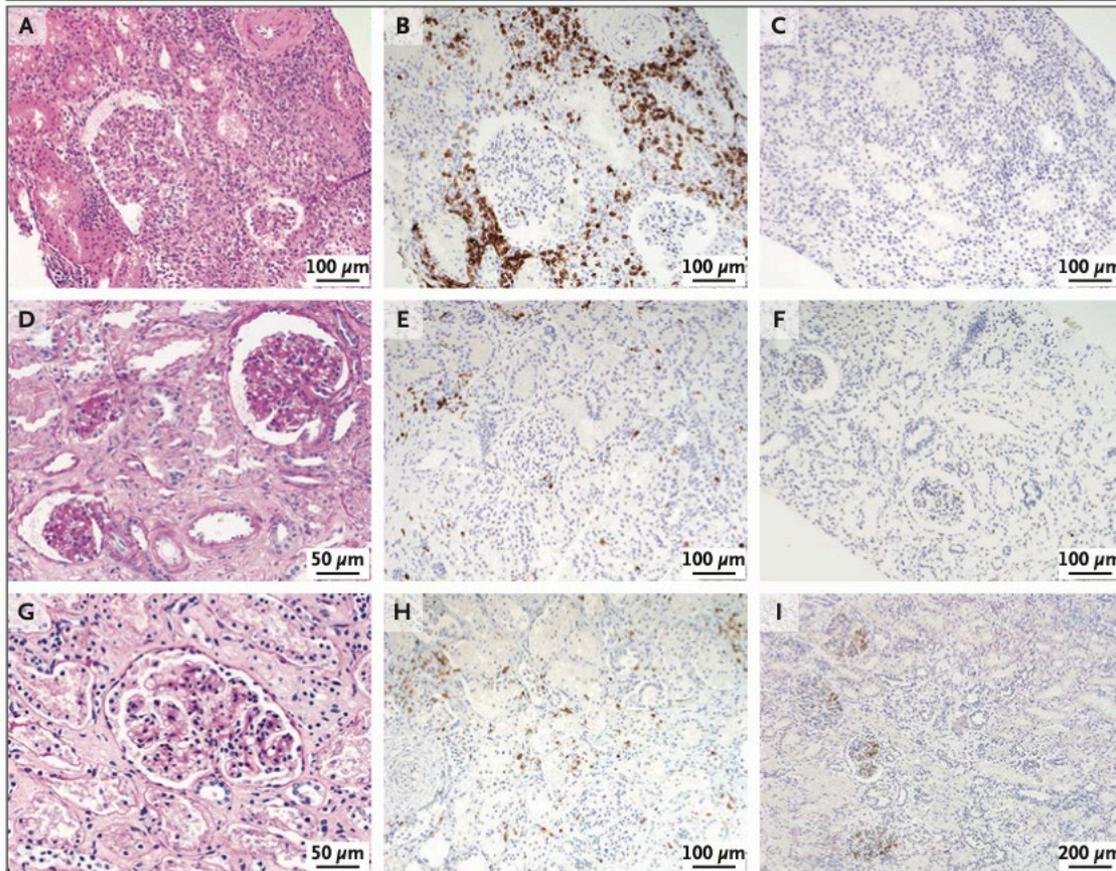


Table 1. Banff Scores on Xenograft Biopsy Samples.*

Variable	Interstitial Inflammation	Tubulitis	Endarteritis	Glomerulitis	Peritubular Capillaritis	C4d Deposition in Peritubular Capillaries	Thrombotic Microangiopathy
Contralateral donor kidney not transplanted	0	0	0	0	0	0	None
Timing after transplantation							
5 minutes after reperfusion	0	0	0	0	0	0	None
Day 8	3	1	1	1	2	0	None
Day 34	0	1	0	0	0	0	None
Day 52 on autopsy	0	0	0	1	0	0	None

* Banff scores range from 0 to 3, with higher scores indicating increasing extent or severity of the variable. An expanded version of these data with additional categories is provided in Table S5 in the Supplementary Appendix.

Advances in Xenotransplantation



Surgeons Perform Second Pig Kidney Transplant at Massachusetts General Hospital
January 25, 2025



>200 days

Advances in Xenotransplantation

TABLE 2 Summary of anatomic and physiologic comparisons and potential physiologic barriers between human and pig kidneys based on various aspects of renal function

Renal physiologic component	Comparison and potential barrier
Anatomy	Gross renal anatomy, including kidney size and vascular configuration, is comparable between humans and pigs. Pigs have fewer nephrons and a lower percentage of long-looped nephrons, and thus have a reduced ability to concentrate urine.
Global function	Markers of renal function, including glomerular filtration rate and renal plasma flow, are comparable between humans and pigs. It remains unknown how long these parameters would be stable following kidney xenotransplantation. Pigs also have similar levels of urine albumin, and recent experiments in in vivo models suggest that the development of proteinuria is associated with rejection.
Sodium handling	Human angiotensin is a poor substrate for pig renin and the clinical impact on the renin-angiotensin-aldosterone system following xenotransplantation is unknown. Major electrolyte levels, including sodium, potassium, and chloride, are maintained in nonhuman primates (NHPs) with pig kidneys, showing that a homeostatic system is functional. NHPs experience episodes of hypovolemia following xenotransplantation which may result from physiologic differences in renin across species.
Water handling	Human antidiuretic hormone (ADH) has a different structure to pig ADH and is less potent in pigs. This may lead to decreased water reabsorption and a reduced ability to concentrate urine after xenotransplantation.
Erythropoietin (EPO) production	Pig EPO has a high degree of homology to human EPO, although it is not known if it can activate human EPO receptors. The anemia seen in in vivo models following xenotransplantation could be due to this physiologic difference, although it may be multifactorial.
Renal response to hormones	Pig kidney grafts have been shown to grow rapidly after xenotransplantation independent of rejection. This phenomenon is reduced by using kidneys from growth hormone receptor knock-out pigs. Pig kidneys are able to process human growth hormones, catecholamines, and prostaglandins.
Acid-base balance	Humans and pigs have comparable blood pH levels, but the composition of metabolites is different as pigs have higher bicarbonate and phosphate levels. While a pig kidney can excrete acid and reabsorb bicarbonate at acceptable rates, it may not excrete as much phosphate, which could lead to an anion-gap acidosis.
Calcium/phosphorus handling	Following renal xenotransplantation in NHPs, serum calcium levels rise to high normal values while phosphate levels drop. It remains to be seen how the pig graft will respond to human FGF-23, parathyroid hormone, or Vitamin D.

Genetically Modified Porcine-to-Human Cardiac Xenotransplantation

Bartley P. Griffith, M.D., Corbin E. Goerlich, M.D., Ph.D.,
Avneesh K. Singh, Ph.D., Martine Rothblatt, Ph.D., Christine L. Lau, M.D.,
Aakash Shah, M.D., Marc Lorber, M.D., Alison Grazioli, M.D.,
Kapil K. Saharia, M.D., Susie N. Hong, M.D., Susan M. Joseph, M.D.,
David Ayares, Ph.D., and Muhammad M. Mohiuddin, M.D.



Induction

Rituximab and Thymoglobulin
Complement C1 esterase inhibitor
Humanized anti-CD40 monoclonal antibody
Corticosteroids

Maintenance immunosuppression
Mycophenolate mofetil
Anti-CD40 mAb
Corticosteroids

Jan 7, 2022

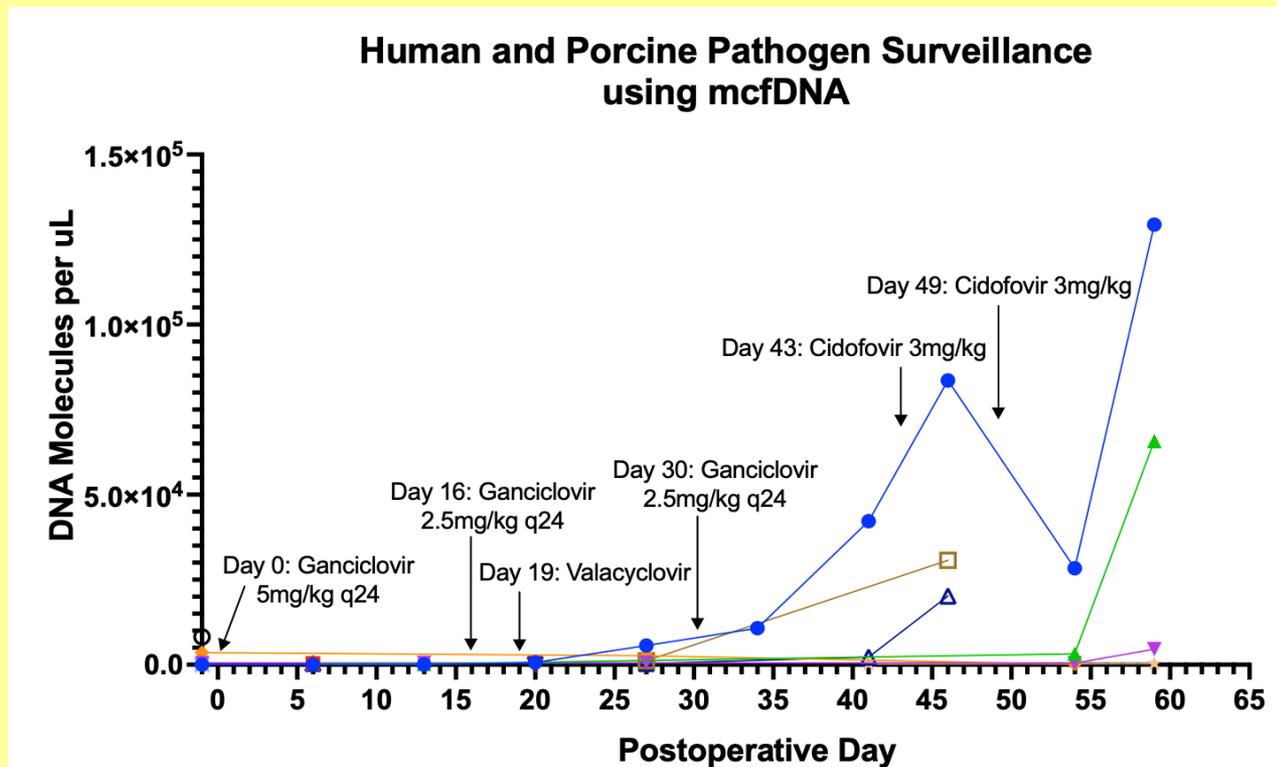
N Engl J Med 2022;387:35-44.

Advances in Xenotransplantation

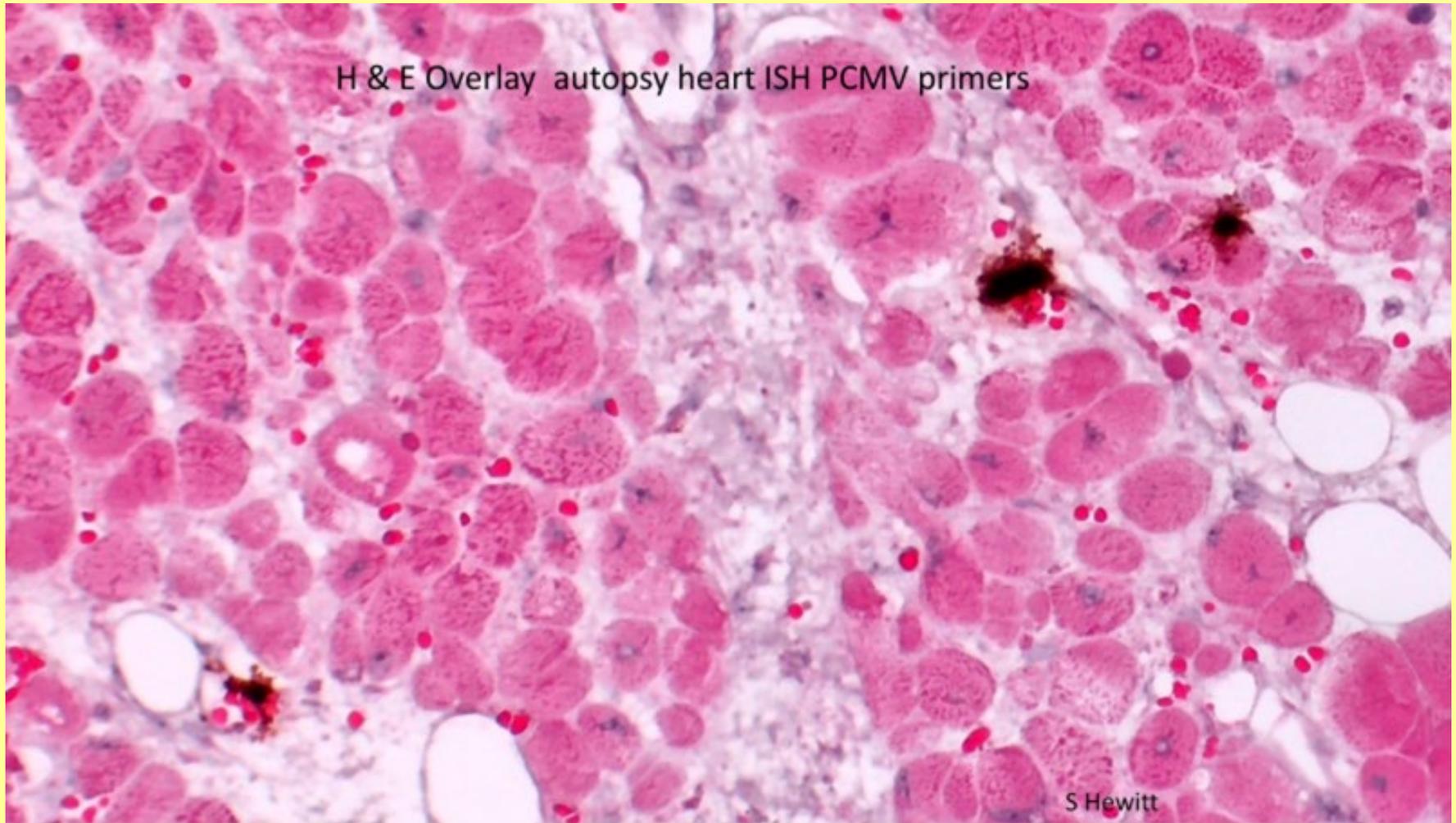
Graft dysfunction in compassionate use of genetically engineered pig-to-human cardiac xenotransplantation: a case report

www.thelancet.com Vol 402 July 29, 2023

After xenotransplantation, the graft functioned well on echocardiography until postoperative day 47 when diastolic heart failure occurred



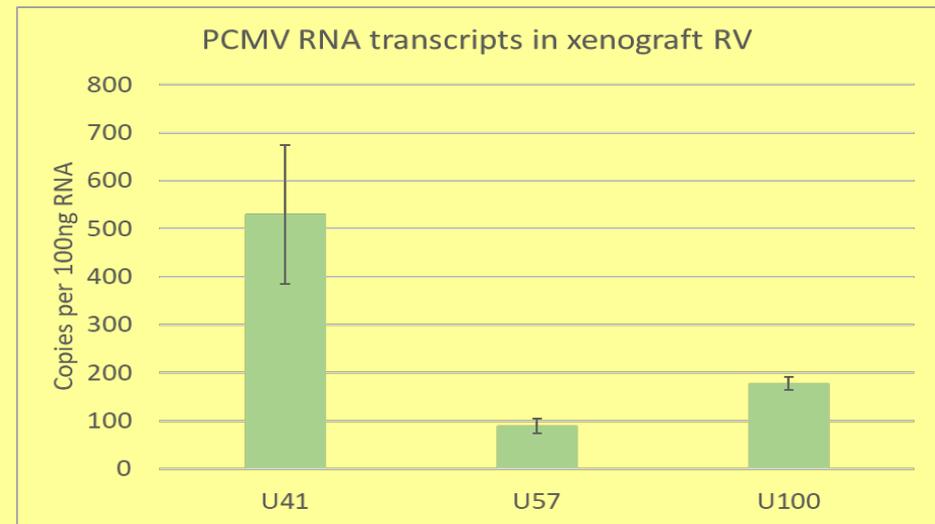
Advances in Xenotransplantation



Advances in Xenotransplantation

pCMV

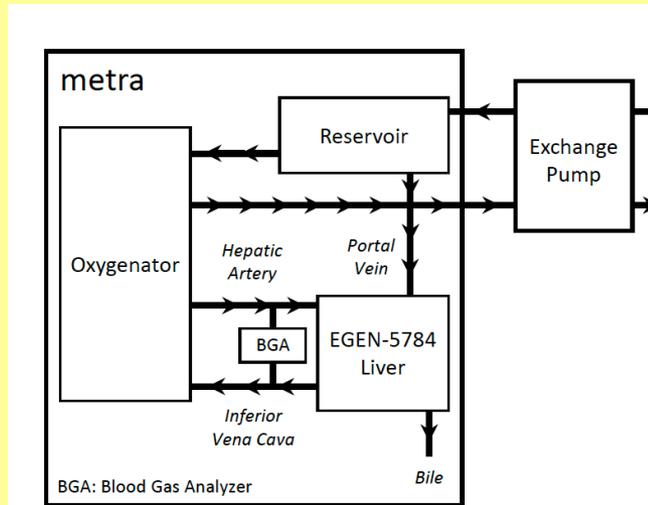
- Donor pig spleen demonstrated 150 copies of pCMV DNA on PCR
- pCMV DNA detected in explanted heart by PCR (low copies)
- **NO** Cytopathic changes
- **NO** Inclusions
- **NO** virus found on EM
- In-Situ Hybridization results shows evidence of viral DNA
- Evidence of Viremia in the heart
- **There is some association but no causation**



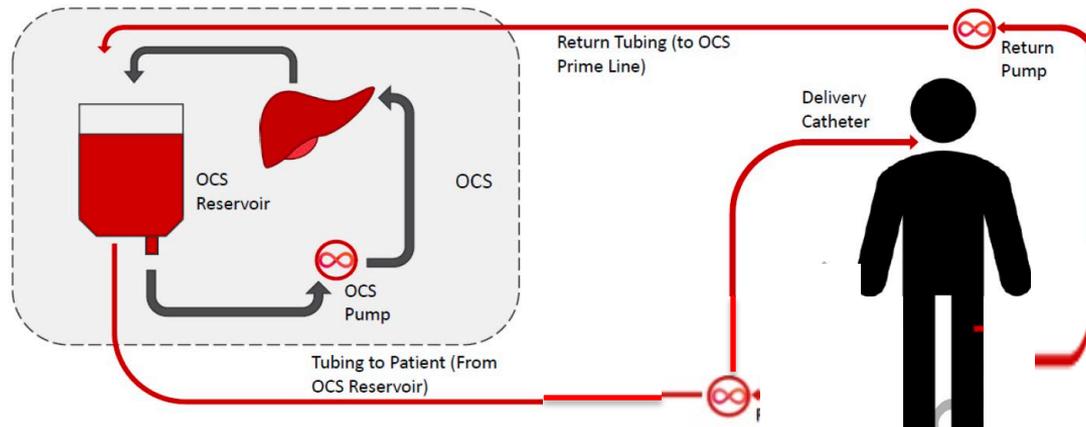
Target (HHV6 homologue)	Description
U41	DNA binding protein (early)
U57	Major capsid protein (late)
U100	Envelope glycoprotein (late)

Advances in Xenotransplantation

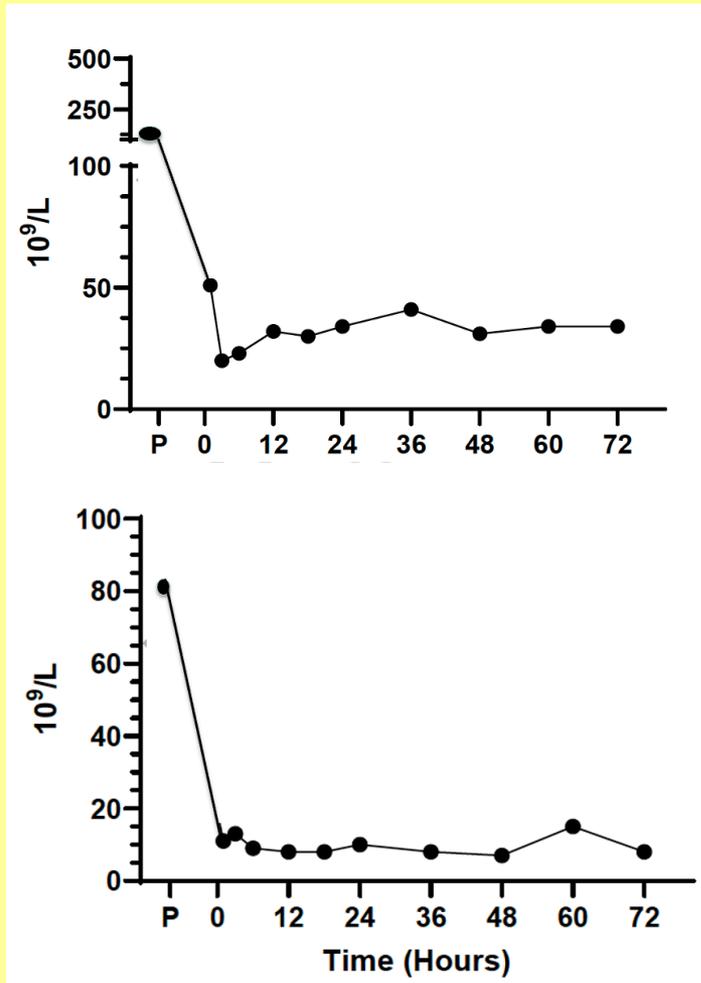
Ex Vivo Perfusion with Porcine Liver Xenografts



eGenesis 2-Pump Veno-Venous Cannulation Liver Circuit



Impact of Ex Vivo Perfusion of GE Porcine Livers in a Decedent Model



Advances in Xenotransplantation

Chinese scientists conduct world's first transplant of pig liver into human patient

By **Global Times**

Published: Mar 15, 2024 10:12 PM

First pig liver transplanted into a person lasts for 10 days

Pig organs could provide temporary detox for people whose livers need time to recover or who are awaiting human donors.



Photo: WeChat account of Air Force Medical University

Chinese scientists have successfully transplanted the liver of a gene-edited pig into a brain-dead human subject to mimic treatment for a patient with liver

At the Air Force Medical University, a research team of Drs. Dou Kefeng and Tao Kaishan successfully transplanted a liver of a multi-gene edited pig as an auxiliary liver into the body of a brain-dead patient

NEWS | 31 May 2024 | Correction [31 May 2024](#)

First pig-to-human liver transplant recipient ‘doing very well’

The transplant aims to prolong the the person’s life and provides important lessons for physicians.

By [Smriti Mallapaty](#)



A 71-year-old man in China has become the first living person to receive a liver transplant from a genetically modified pig – and the fifth person reported to have received a pig organ. More than two weeks after the surgery, the man is “doing very well”, says Sun Beicheng, a surgeon at the First Affiliated Hospital of Anhui Medical University in China, who led the transplantation.

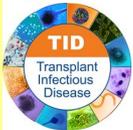
Advances in Xenotransplantation

TABLE 1 The major institutions for xenotransplantation research in China.

Donor/Organ Tissue/Cell	Teams	Research institutions
Gene-edited pigs	Liangxue Lai	Key Laboratory of Regenerative Biology, Guangdong Provincial Key Laboratory of Stem Cell and Regenerative Medicine, Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou
Gene-edited pigs	Yifan Dai	Jiangsu Key Laboratory of Xenotransplantation, Nanjing Medical University, Nanjing
Gene-edited pigs	Dengke Pan	Chengdu Clonorgan Biotechnology, Co., Ltd., Chengdu
Gene-edited pigs	Luhan Yang	Hangzhou Qihan Biotech co.,Ltd, Hangzhou
Gene-edited pigs	Hongjiang Wei	Key Laboratory of Animal Gene Editing and Animal Cloning in Yunnan Province, Yunnan Agricultural University, Kunming
Gene-edited pigs	Qi Zhou	National Stem Cell Resource Center, Chinese Academy of Sciences, Beijing
Gene-edited pigs	Yongguang Yang	Key Laboratory of Organ Regeneration & Transplantation of the Ministry of Education, The First Hospital, Jilin University, Changchun
Gene-edited pigs	Hongsheng Ouyang	Key Laboratory of Zoonosis Research, Ministry of Education, College of Animal Sciences, Jilin University, Changchun
Gene-edited pigs	Taiping Wang	Grand Life Science & Technology Ltd., Beijing

Advances in Xenotransplantation

TTS Xenotransplantation Collaborations



Transplant Infectious Disease

The First International Conference On Xenotransplantation In Chengdu, China



Changsha Communiqué Final.doc

First WHO Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials

Changsha, China, 19-21 November 2008

The Changsha Communiqué¹

Principles

1. Successful xenotransplantation has the potential to treat a wide range of serious diseases such as diabetes, heart and kidney disease. Successful xenotransplantation could provide transplants for people who currently would not get a transplant.
2. Potentially animals could provide a plentiful supply of readily available, high quality cells, tissues and organs for transplantation. Genetic modification of the animals may improve the effectiveness of such xenotransplant material. Animals used in xenotransplantation should be from a closed herd bred for the purpose and housed in a well-controlled, pathogen-free environment with high standards of animal welfare. Source animals should be extensively tested to ensure freedom from known pathogens with appropriate biosecurity and surveillance in place to ensure continued freedom from infectious disease.
3. Xenotransplantation is a complex process which carries risks, including graft rejection, inadequate graft function and transmission of recognized or unrecognized infectious diseases to the recipient. There is the risk of developing serious or novel infections which could infect not just the transplant recipient but also close contacts or the wider human or animal populations.
4. Because of these wider community risks, xenotransplantation clinical trials and procedures need to be effectively regulated. There should be no xenotransplantation in the absence of effective regulation by the government of the country. Regulation should have a legal basis with powers to ban unregulated procedures and enforce



Xenotransplantation Collaborations

- Along with TTS-focused work, IXA and TID held joint meetings with the FDA guidance on xenotransplantation. These have included the ISHLT, the American Society of Transplantation, Therapeutic Goods Agency (TGA), EMA, the Pontifical Academy for Life, and WHO.
- Further revising the Changsha Communique' guidelines on xenotransplantation, in conjunction with TTS & WHO to further refine and expand the Human xenotransplantation registry or find another mechanism to support it.
- Helping investigators and pig breeders to develop protocols to prevent any potential transmissions of zoonotic diseases through surveillance of xenograft recipients and herds for xenotransplantation.

Regulatory Issues Necessary Before Proceeding With Clinical Xenotransplantation

Framing benefit over risk through pre-clinical efficacy studies

Regulatory framework in place specifically dealing with clinical xenotransplantation

Careful consideration of issues regarding the use of animals

Safety profile of source animals

Detailed informed consent

Recipient, intimate partner and HCP sample collections for monitoring and archiving

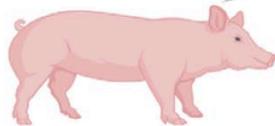
"Mandatory" life-long follow up of recipients

Assessing alloimmunization risk in cases of "bridge-to-allotransplant" cases

International Xenotransplantation Association (IXA) Position Paper on Kidney Xenotransplantation

Immunosuppression

- T cell depletion via thymoglobulin or alemtuzumab
- B cell depletion via rituximab
- Costimulatory blockade (CD154 mAb or CD40 mAb)
- Complement inhibition
- Mycophenolate mofetil
- Calcineurin inhibition and/or rapamycin



Source Pig

- GMP facility
- Miniature pig breed
- TKO pig (aGal, Neu5Gc, SDa knockout)
- Complement regulation:
 - hTG for CD55 and CD46
- Coagulation regulation:
 - hTG for CD141, CD39, CD201, TFPI
- Regulators of Inflammation
 - hTG for CD47, HLA-E/bTG, A-20, HO-1, CD177, CD178, CD253



Recipient

- Dialysis-dependent or referred for dialysis initiation
- Listed for a deceased donor kidney transplant or with a current exclusion from allotransplantation that is unlikely to compromise the xenotransplantation trial's study endpoints
- Life expectancy < Estimated waiting time
- Age: 60-69 years old, extendable to approximately 40-75 years old, provided other key eligibility criteria are met
- Acceptable functional status (e.g. Karnofsky \geq 60)
- Negative CDC crossmatch and/or minimally reactive IgM and IgG flow crossmatch, preferably without desensitization treatment
- Negative anti-SLA titers
- Able to participate in the informed consent process
- Multiple (\geq 2) episodes of primary disease recurrence
- Ineffective or unreliable dialysis access

Post-Xenotransplant Monitoring

- Length of stay, traditional hospital metrics
- Evidence of delayed graft function
- 30-Day postoperative complications/reoperation
- Rejection episodes/treatments
- Infections, zoonoses monitoring
- Drug toxicity
- PTLD, neoplasia
- Protocol biopsies at 3, 6, and 12 months, incorporating both histological and molecular analyses for precision diagnostics
- Quality of life assessment
- Patient and graft survival

Non-Emergency Intermediate-Size Patient Population – Expanded Access Kidney Xenotransplant Study

FDA Approves Transplant Trials for Gene-Edited Pig Kidneys

Two biotechnology companies will begin testing the procedures in patients suffering from kidney failure

The ideal candidate for a kidney xenotransplant is someone already approved for a human kidney transplant and on the waiting list but facing significant challenges with dialysis and a low probability of receiving a kidney offer in the near future.

- 1) Over age of 50
- 2) Diabetic
- 3) Blood groups O or B
- 4) Experiencing health deterioration related to dialysis

Advances in Xenotransplantation

United Therapeutics Corporation Announces FDA Clearance of its Investigational New Drug Application for the UKidney Xenotransplantation Clinical Trial

First-ever human clinical trial of a xeno-organ intended to allow for potential registration through the submission of a Biologics License Application to the U.S. FDA

First xenotransplant is expected to occur around mid-year 2025

The study is a multicenter, open-label, phase 1/2/3, safety and efficacy study and is intended to support FDA approval of a BLA.

Participants will receive a UKidney transplant followed by a 24-week post-transplant follow-up period, including the evaluation of all study endpoints and safety assessments. Efficacy endpoints include participant survival rate, UKidney survival rate, change in measured GFR, and change in QOL in participants at 24 weeks post-transplant.

After the 24-week post-transplant follow-up period, participants will continue to be followed for the rest of their lives, including for survival, function, and monitoring for zoonotic infections.

Conclusions

With discordant xenotransplantation, using genetically modified donor pigs, hyperacute (Ab-mediated) rejection appears to have mitigated

Early functional parameters of kidney and heart xenograft function appear normal or near-normal

In liver xenotransplantation, the mechanism for immediate development of thrombocytopenia is unknown (?von Willebrand factor disparity)

The impact of metabolic incompatibilities has yet to be fully studied

Further genetic modifications may be necessary

Future Of Xenotransplantation

Advances in the understanding of xenograft rejection

Advances in genetic manipulation

Unknown risk of zoonosis

Unknown impact of metabolic interactions

Public policy implications

