THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
SCHOOL OF MEDICINE

What's New in Transplant

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2024 Inter-professional Transplant Symposium: Ensuring Excellence in Patient Outcomes
Birmingham, Alabama

Disclosures

- **Research support**
  - **United Therapeutics - Xenotransplantation Research**
    - **UAB receives grant support / funding from United Therapeutics and subsidiaries (Lung Biotechnology & Revivicor)**
    - **Will discuss investigational use of UKidney™, UThymoKidney™ and investigational immunosuppression used by the Univ. Of Maryland Xeno-Heart Transplant Decedent Case and Mass General First in Human kidney Xeno transplant**
  - **Sub-PI: CSL Behring, NIH CTOT, APOLLO, HANSA, MEMO**

- **Speaker honoraria**
  - **ASN/Medscape/AREP/AJKD/AKF/NKF/Elsevier/Nephronet**

- **Volunteer Service**
  - **American Society of Transplantation (AST) Board of Councilors 2001-Pres**
  - **Chair/Co-Chair/Past Chair:**
    - **American Society of Nephrology (ASN) Current and Emerging Threats, COVID 19 Taskforce**
    - **National Kidney Foundation (NKF) ELPFFD Xenotransplantation**
    - **AST Cutting Edge in Organ Transplantation (CEoT 2023)**
  - **Member:**
    - **ASN Transplant Workgroup**
    - **UNOS OPTN Living Donor Committee**
    - **American Board of Internal Medicine (ABIM) Exam Writing Committee**

Disclosures

- **UAB receives grant support / funding from United Therapeutics and subsidiaries (Lung Biotechnology & Revivicor)**
- **I will discuss the investigational use of UKidney™, UThymoKidney™ , egenesis kidney (modified pig kidneys)**
- **I will also refer to the investigational immunosuppression used by UAB, by the Univ. Of Maryland Xeno Heart Transplant Case and in the Non Human Primate Models and Mass General First inhuman Kidney Xenotransplantation case**

Objectives

- **At the end of this session, participants will be able to:**
  - **Outline the progress in Allotransplantation**
  - **List the major advances in Immunology**
  - **Understanding the historical and current status of Xenotransplantation**
    - **Discuss the need for Kidney Xenotransplantation**
    - **Outline the knowledge gained from the Kidney Xenotransplantation animal, decedent and recent in-human experiments**
    - **List the potential benefit, risks and unknowns of Kdiney Xenotransplantation**

Overview

- History of Allotransplantation
- Notable Advances
  - Immunology
  - Immunosuppression
  - Policy
  - Xenotransplantation
  - Patient engagement

History of Allotransplantation

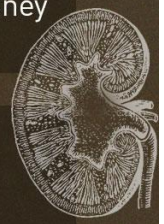
ORGAN TRANSPLANT

HISTORICAL MILESTONES

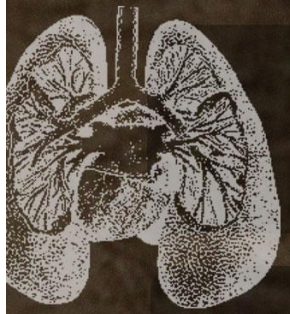
1869
First skin transplant performed.

1906
First transplant of a cornea performed.

1954
First successful kidney transplant performed.A living donor gave a kidney to his identical twin



1959
First successful kidney transplant performed between fraternal twins.



1960
First successful kidney transplant performed between siblings who were not twins.

1962/1963
First kidney, lung, and liver transplants recovered from deceased donors.

1963
First organ recovery from a brain dead donor.

1966
First successful pancreas transplant performed.

1967
First successful liver transplant performed.

1967
First simultaneous kidney/pancreas transplant performed

See the full timeline at **futurism.com/transplanthistory**

History of Allotransplantation

- **Many medical and surgical advancements were required to make transplant as successful as it is today**
- **First, needed the surgical technique**
- **Then, needed the medicine (immunosuppression)**
- **Many early advancements came from practicing surgical technique and immunosuppression in animals**
- **Simultaneously, needed ethical and medical consensus on brain death and consent**

Adopted from the AST APP COP slide deck

History of Allotransplantation (cont.)

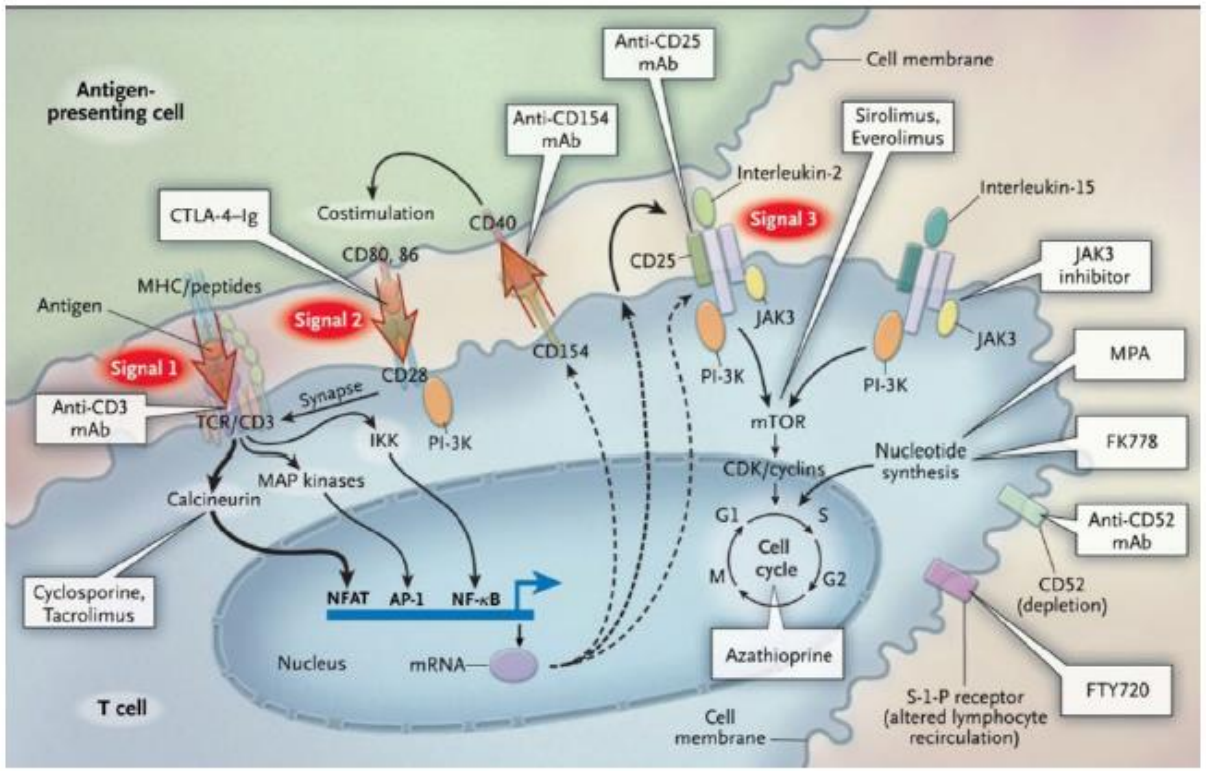
- 1902 - Carrel published on the vascular anastomosis
  1912 – Carrel wins the Nobel prize
- 1945 – Kolff successfully dialyzes a patient
- 1953 – Medawar publishes on acquired tolerance
  - Gibbon performs first successful cardiopulmonary bypass
- 1954 – Murray performs identical twin kidney transplant
- 1962 – Murray performs first successful deceased-donor transplant
- 1963 – Starzl performs first unsuccessful liver transplant
- 1967 – Starzl performs first successful liver transplant.
  - Barnard performs first heart transplant.
- 1968 – JAMA paper on brain death is published
- 1981 – Brain death becomes legal death in US
- 1983 – Cyclosporine gets FDA approval for transplantation

Adopted from the AST APP COP slide deck

History and Innovations in Immunology

Progress in Understanding Immunology

Figure. Individual Immunosuppressive Drugs and Sites of Action in the 3-Signal Model[1]



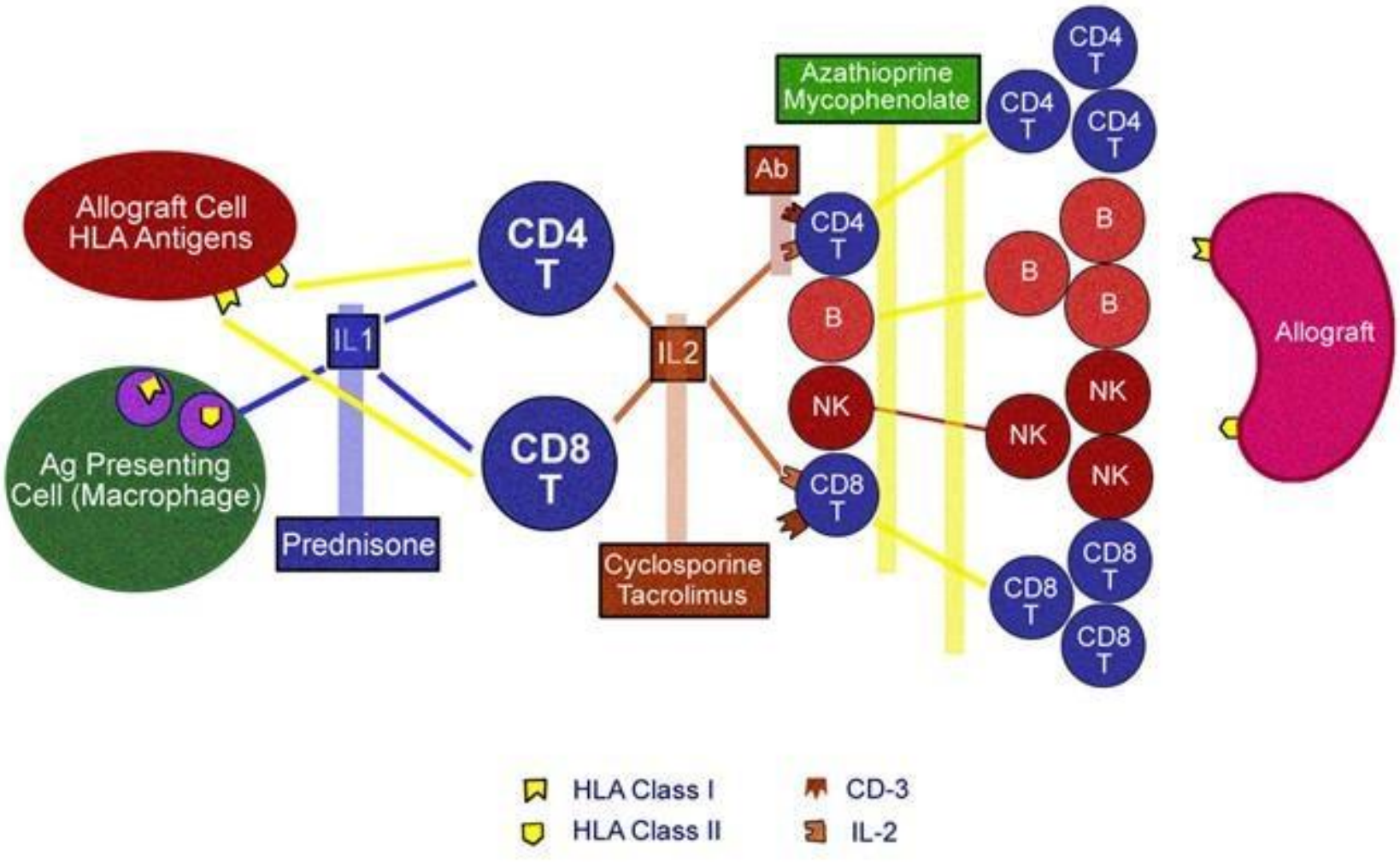
Anti-CD154 antibody has been withdrawn from clinical trials but remains of interest. FTY720 engagement of S-1-P receptors triggers and internalizes the receptors and alters lymphocyte recirculation, causing lymphopenia. Antagonists of chemokine receptors (not shown) are also being developed in preclinical models.

AP-1 indicates activating protein 1; CD, cluster of differentiation; CDK, cyclin-dependent kinase; CTLA-4–Ig, cytotoxic T-lymphocyte-associated protein 4 immunoglobulin; G1, gap 1; G2, gap 2; IKK, inhibitor of nuclear factor κB kinase; JAK3, Janus kinase 3; M, mitosis; mAb, monoclonal antibody; MAP, mitogen-activated protein; MPA, mycophenolic acid; mRNA, messenger ribonucleic acid; mTOR, molecular target of rapamycin; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor-κB; PI-3K, phosphoinositide-3-kinase; S, synthesis; S-1-P, sphingosine-1-phosphate; TCR, T-cell receptor.

An Overview of Immunosuppression in Solid Organ Transplantation

Am J Manag Care. 2015;21:S12-S23

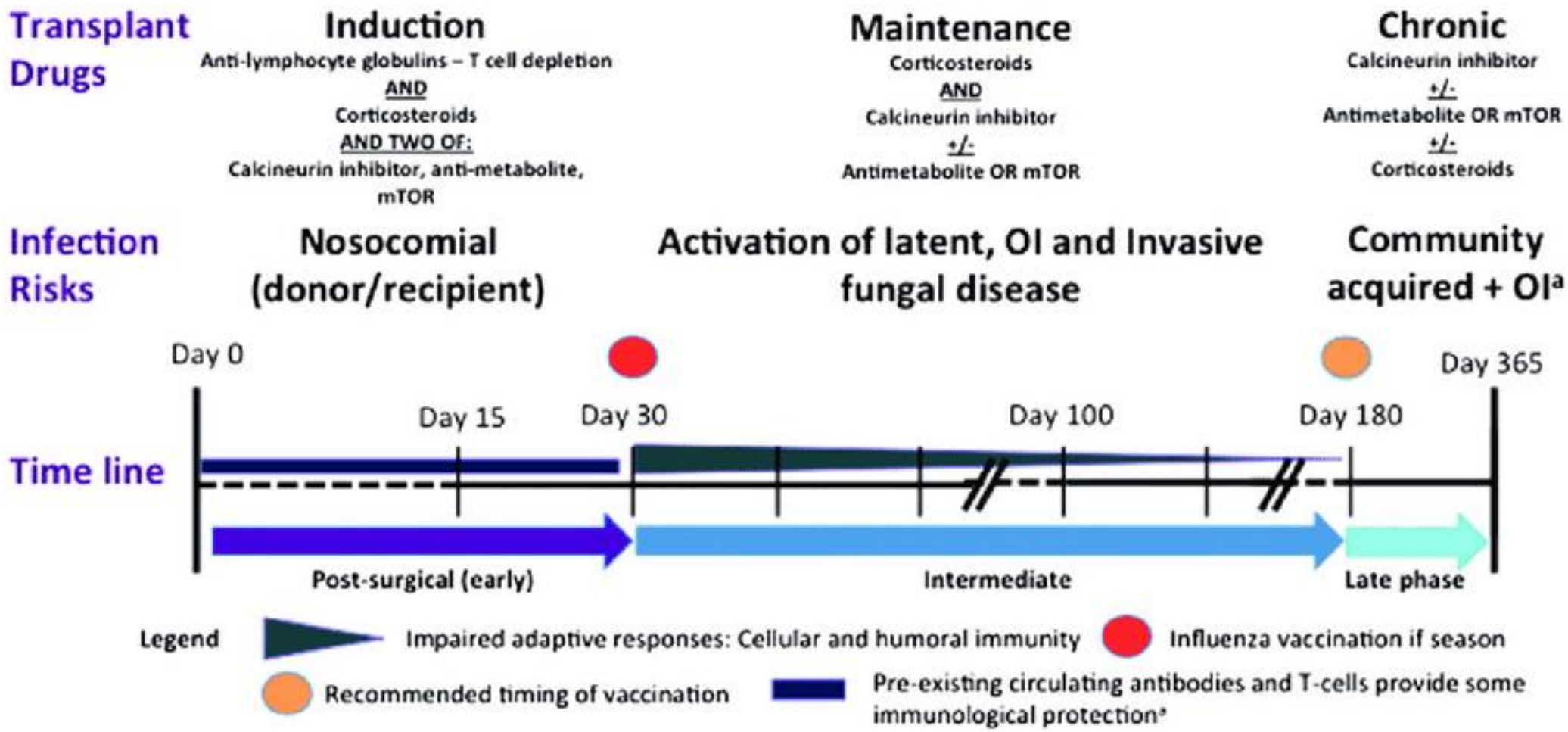
Simplified Diagram Illustrating the Points of Action of Immunosuppressive Drugs



Medscape 2021
Immunosuppression
https://emedicine.medscape.com/article/432316-overview

Immunosuppression and Progress in Transplantation

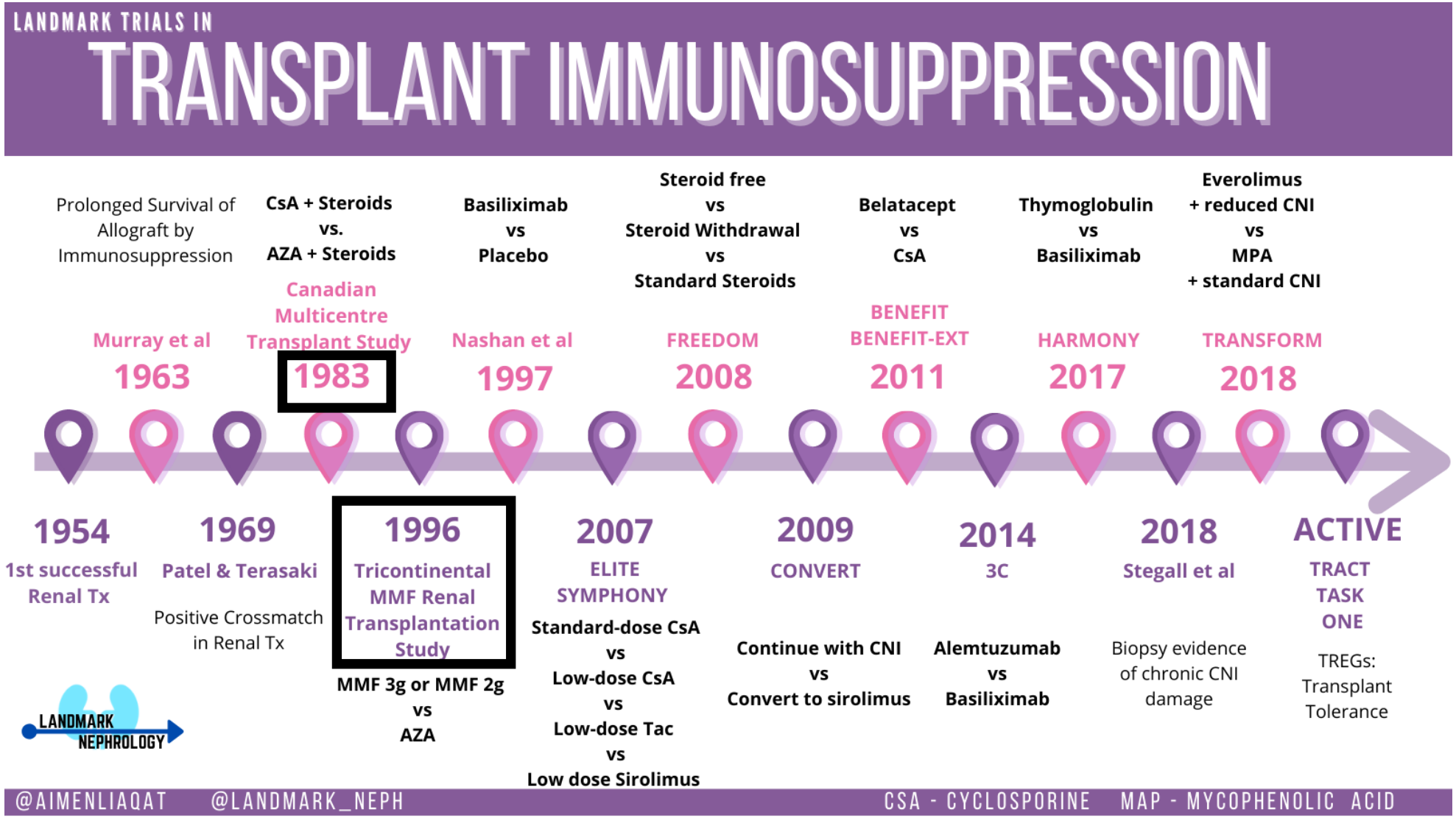
Immunosuppression Post Solid Organ Transplantation



Travel vaccination recommendations and endemic infection risks in solid organ transplantation recipients.

DOI: 10.1093/jtm/taw058

Landmark Events/Trials



Progress in Histocompatibility Testing

The evolution and clinical impact of Human Leukocyte Antigen technology

Howard M. Gebel and Robert A. Bray

Current Opinion in Nephrology and Hypertension 2010, 19:598–602

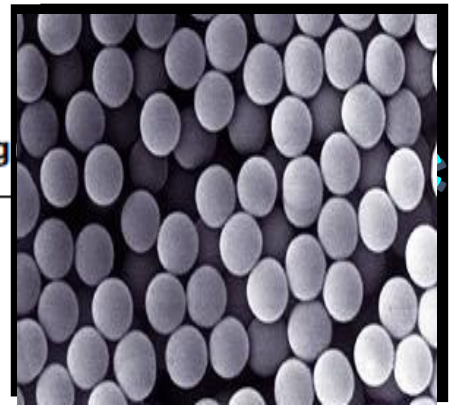


Figure 1 Evolution of human leukocyte antigen antibody testing

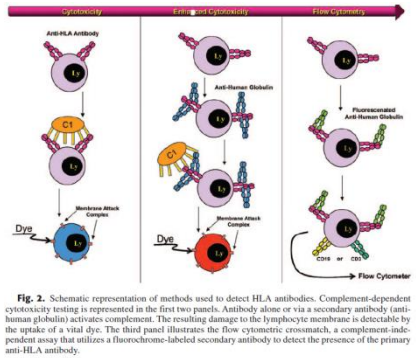
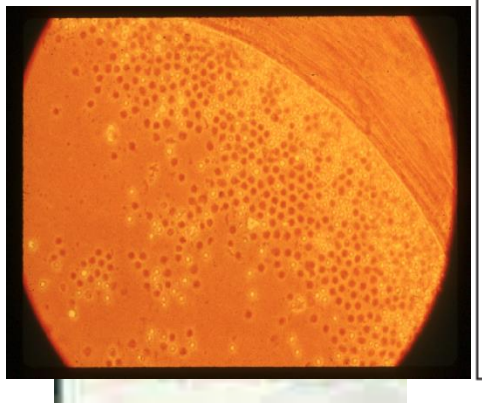
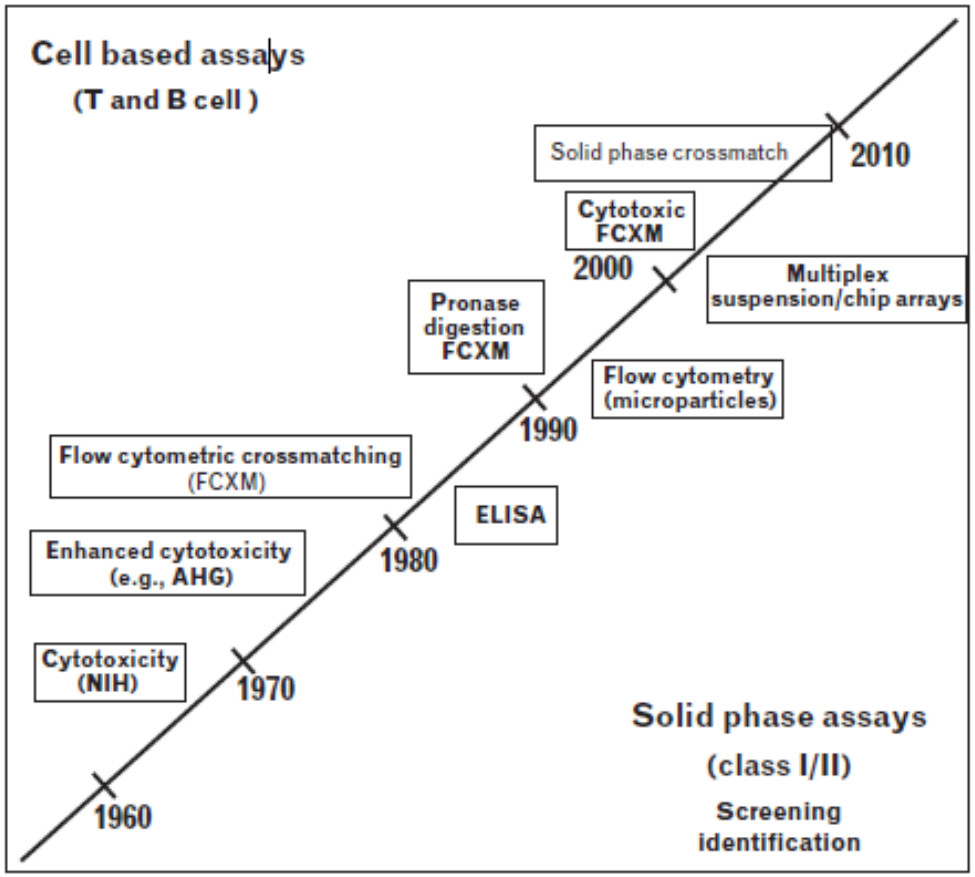
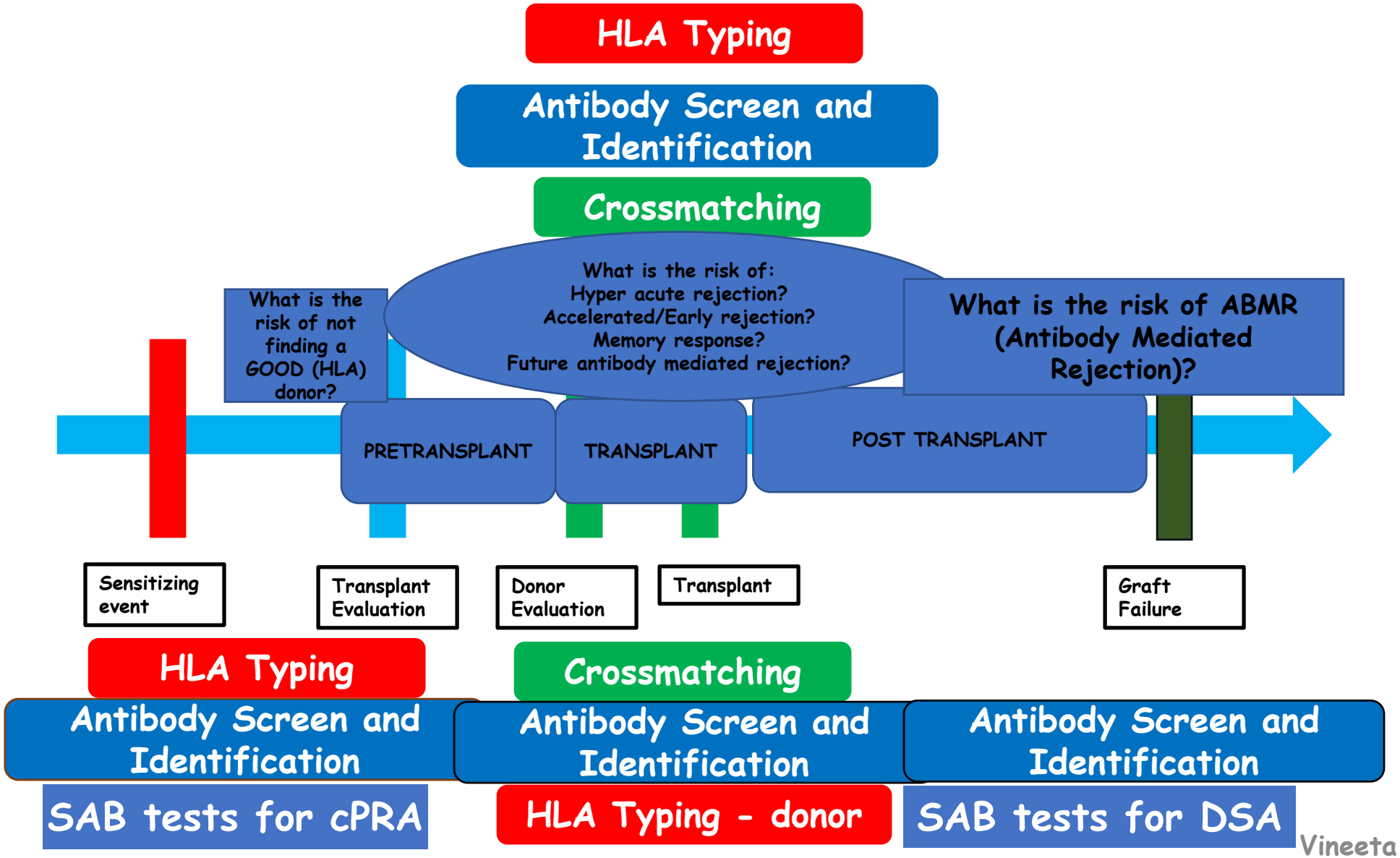


Fig. 2. Schematic representation of methods used to detect HLA antibodies. Complement-dependent cytotoxicity testing is represented in the first two panels. Antibody alone or via a secondary antibody (anti-human globulin) activates complement. The resulting damage to the lymphocyte membrane is detectable by the uptake of a vital dye. The third panel illustrates the flow cytometric crossmatch, a complement-independent assay that utilizes a fluorochrome-labeled secondary antibody to detect the presence of the primary anti-HLA antibody.



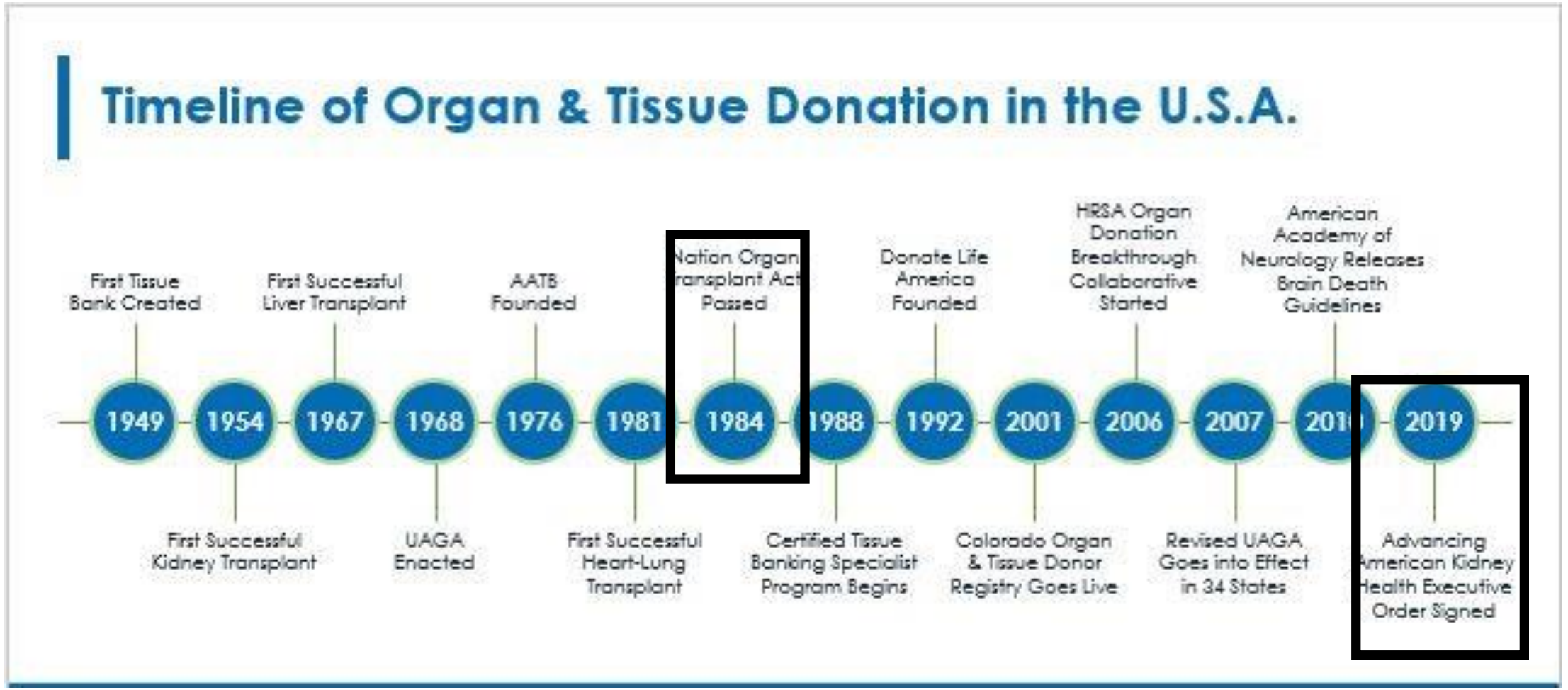


Immunologic Journey



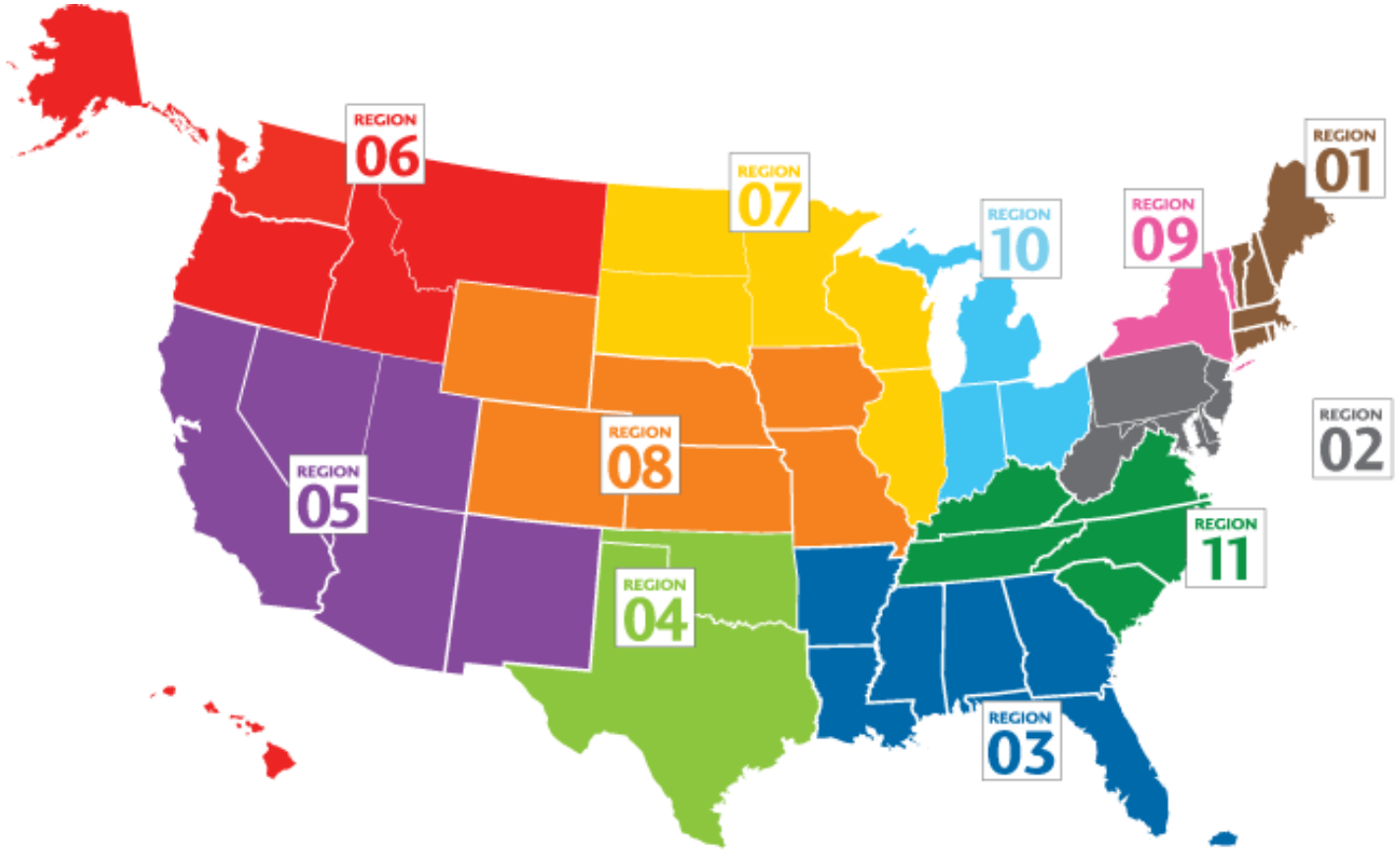
Vineeta Kumar, M.D.

Policy and Kidney Transplant



https://www.donoralliance.org/newsroom/donation-essentials/the-history-of-organ-and-tissue-transplants-in-the-usa/


THE
ORGAN AND TISSUE
DONATION
PROCESS
DIAGNOSIS
REFERRAL
FAMILY
DISCUSSION
MEDICAL
EVALUATION
MATCHING
SURGICAL
RECOVERY
PRESERVATION/
TRANSPORT
TRANSPLANTATION



Organ Allocation

- Organ Procurement and Transplantation Network (OPTN)
  - US Department of Health and Human Services
  - Comprised of medical professionals, transplant recipients and donor families to develop transplantation policy
- United Network of Organ Sharing – UNOS
  - A private, non-profit organization that serves as the nation's organ transplant system—the Organ Procurement and Transplantation Network (OPTN)—under contract with and oversight by the federal government.

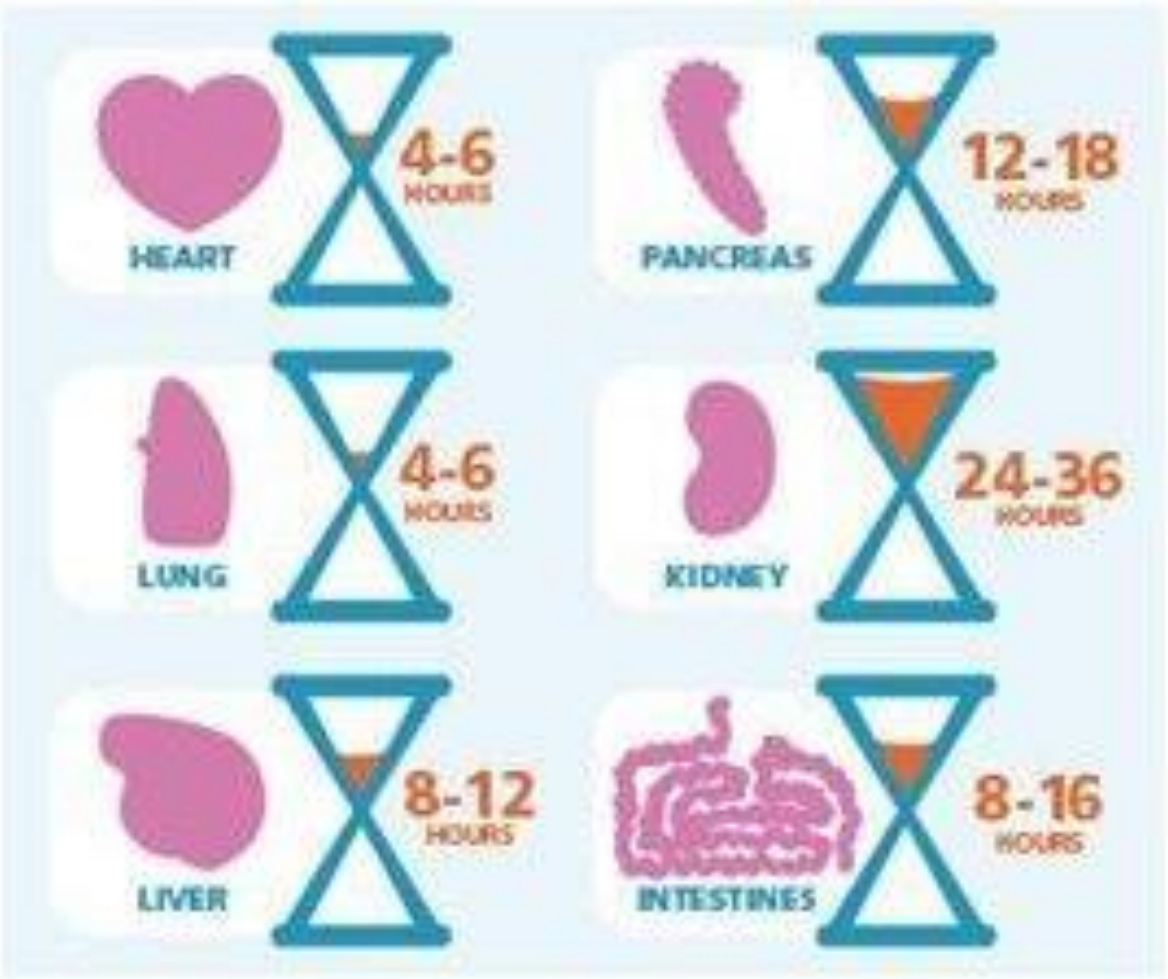
UNOS/OPTN Policy Changes – A Few Examples

- DQ/DR
- KAS 2014
  - Wait time back date to dialysis
  - cPRA allocation points (new change Jan 2023)
- A2/A2B deceased donor kidneys to B recipients
- HOPE Act
- KAS 2022
  - DSA to 250 nautical miles (enhancing equity)
  - Race neutral eGFR

Organ Preservation

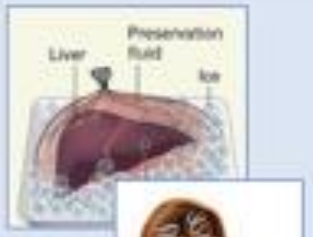
Organ Preservation

- **Minimize ischemic and hypothermic damage caused during the procurement process**
- **Two phases damage**
  - **Warm Ischemia**
  - **Cold Ischemia**

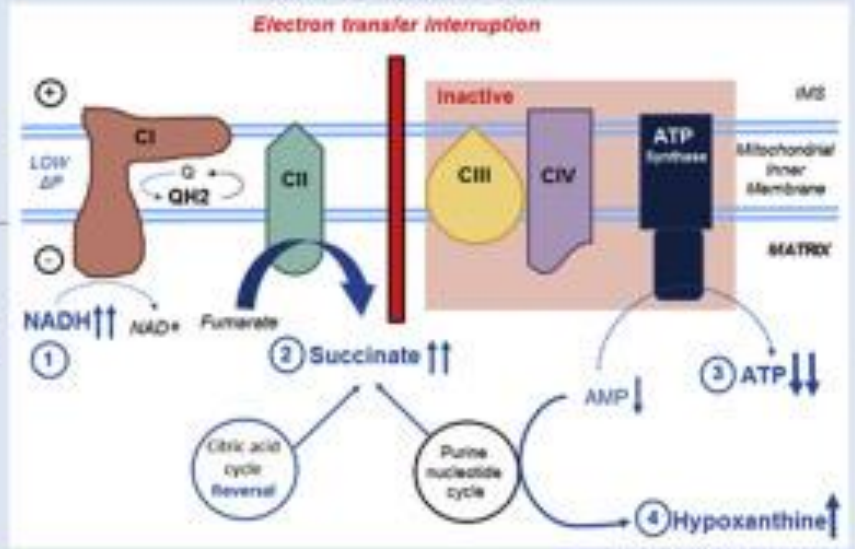


Health Resources and Services Administration
https://www.organdonor.gov/about/process/matching.html

Static cold storage

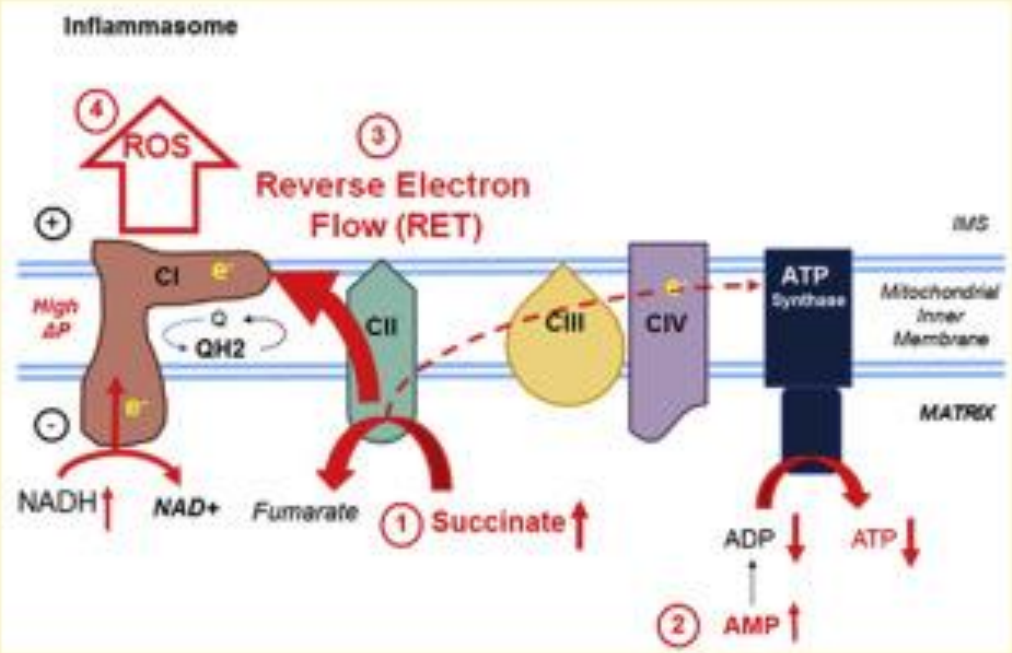


A Ischemia

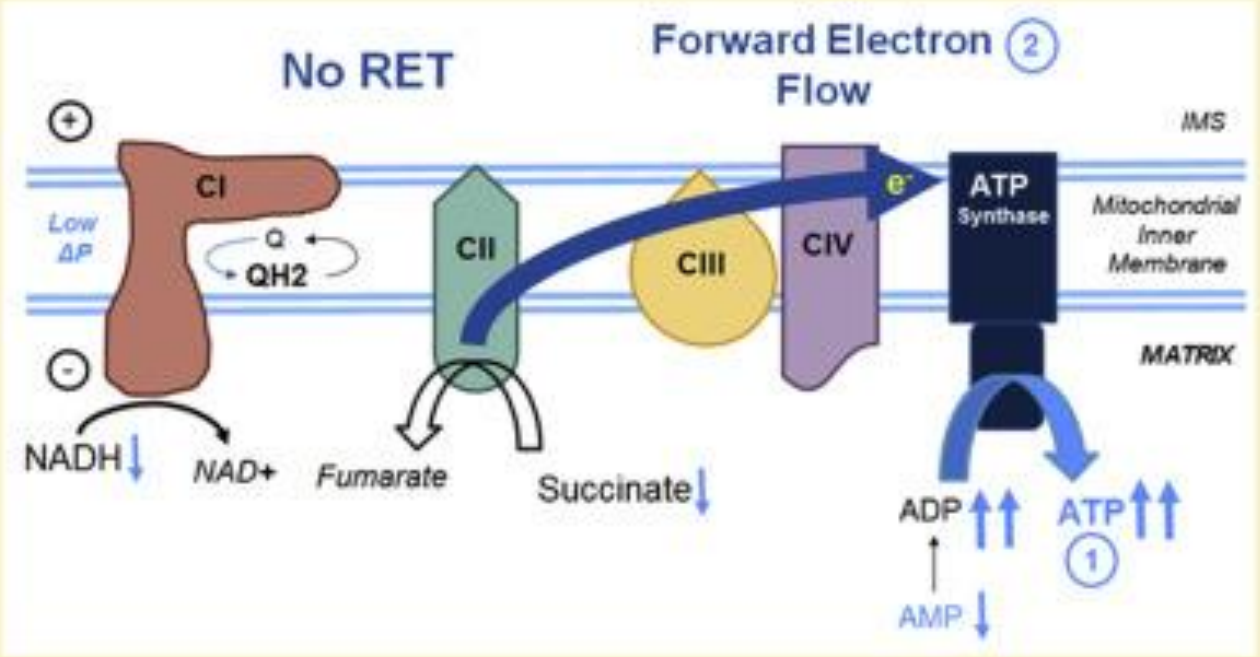


Machine Perfusion

B Normothermic perfusion

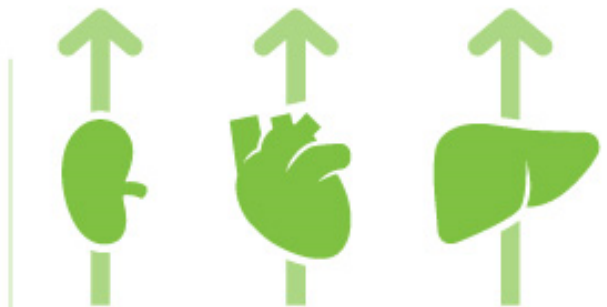


C Hypothermic/subnormothermic perfusion



2021 | Most lives ever saved in one year

More than 40,000 lifesaving transplants – *a first!**



Record numbers of **kidney, heart & liver** transplants*

11th record year in a row for deceased donation*

*Based on OPTN data as of Jan. 10, 2022. Data subject to change based on future data submission or correction.

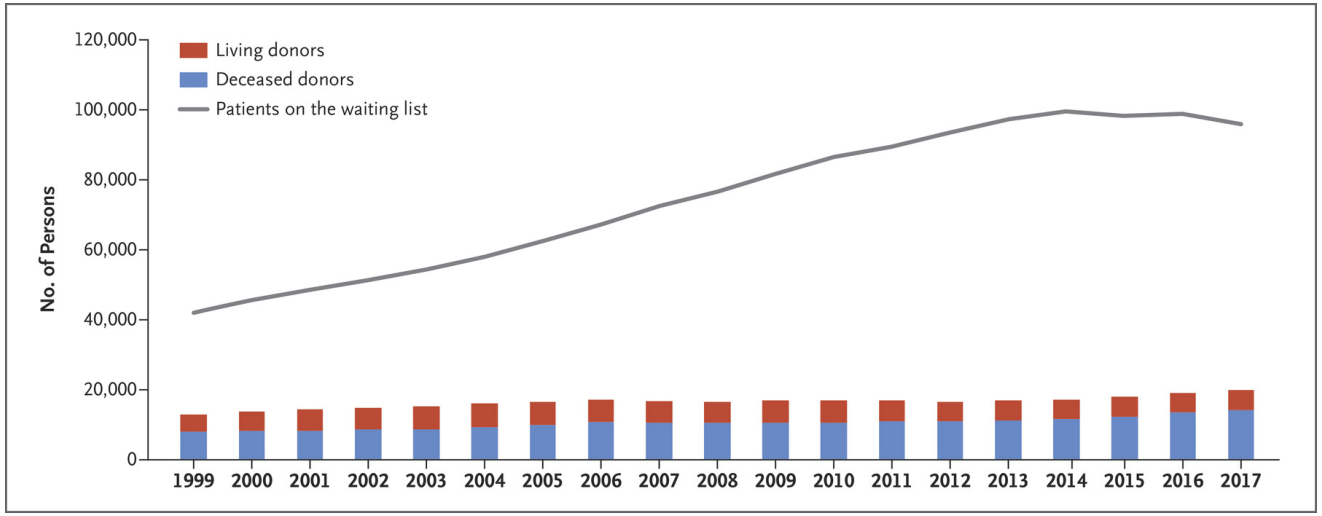
OPTN

https://optn.transplant.hrsa.gov/news/all-time-records-again-set-in-2021-for-organ-transplants-organ-donation-from-deceased-donors/

Wait list Mismatch and Xenotransplantation

The Facts in 2023

- **The gap between supply and demand is vast**
- **Annually, 25,000 individuals receive a kidney transplant (of the current 89,000 waiting)**
- **40% of those listed patients die within 5 years while waiting for a kidney transplant**
- **Fewer than 1 in 7 ESKD patients make it to the waiting list**



The ImPossible Solution - Xenotransplantation

Lamassu

- **Xenotransplantation is the transplantation of organs, tissues, or cells between two different species**

Minotaur

Gorgon

Ganesha

Mathieu Jaboulay

- 1906 - the first recorded solid organ kidney xenotransplantation procedure in humans
- 48-year-old woman with oliguria, hypertension, headache, hearing and vision loss
- A pig was chosen as the source of the organ

1906: Pig and goat kidneys transplanted onto arm vessels survive for 3 days

1910: A macaque kidney transplanted into a human survives for 32 hours

1963: A 23-year-old woman survives for 9 months with functioning chimpanzee kidneys

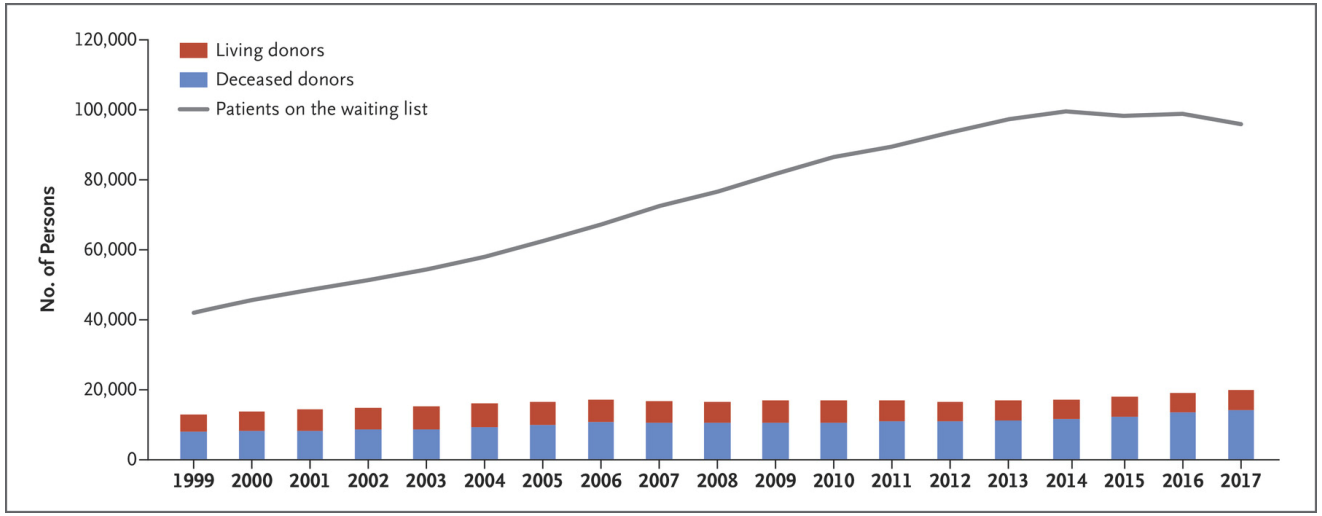
1984: A newborn, Baby Fae, survives for 20 days with a baboon heart

Overview

- **Brief History**
- **Why Xenotransplantation?**
  - **The Need**
- **Why Pigs?**
- **Progress in Barriers to Xenotransplantation**
- **Recent Events and Questions answered**
- **Limitation of the experiments to date, Known Barriers and Next Steps**

The Facts in 2024

- **The gap between supply and demand is vast**
- **Annually, 25,000 individuals receive a kidney transplant (of the 89,000 waiting)**
- **25 patients die or are removed from the wait list daily (9000 patients/year)**



The ImPossible Solution - Xenotransplantation

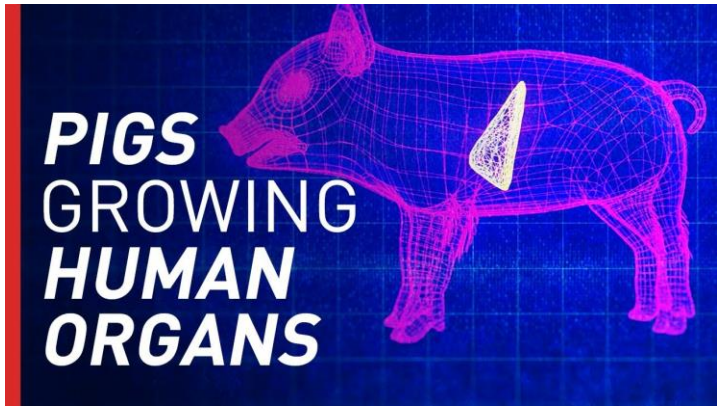
“. . .my approach to when people say something is impossible, is I just drive an axe right between the letter M and P. And I say, ‘No; “impossible” means to me “I’m Possible.” And I’m going to figure out a way to slice this problem up into little pieces.’”
Martine Rothblatt
Chairwoman, United Therapeutics

Overview

- Brief History
- Why Xenotransplantation?
  - The Need
- **Why Pigs?**
- **Progress in Barriers to Xenotransplantation**
- **Recent Events and Questions answered**
- **Limitation of the experiments to date, Known Barriers and Next Steps**

Why Pigs as an Organ Source?

- Nonhuman primates are scarce and may harbor deadly viruses
  - U.S. Food and Drug Administration banned their use for xenotransplantation in 1999
- Pigs are preferred because:
  - Available in unlimited numbers
  - Can be genetically engineered to lower rejection risk
  - Are appropriately sized for humans
  - Thought to have limited risk of transferring infectious agents
  - Pig source already in use for other reasons
    - Heart valves, cornea, skin



Overview

- Brief History
- 7
- Why Xenotransplantation?
  - The Need
- Why Pigs?
- **Progress in Barriers to Xenotransplantation**
- **Recent Events and Questions answered**
- **Remaining Barriers and Next Steps**

PIG ORGAN XENOTRANSPLANTATION MODEL
NHP (Non Human Primate) Model

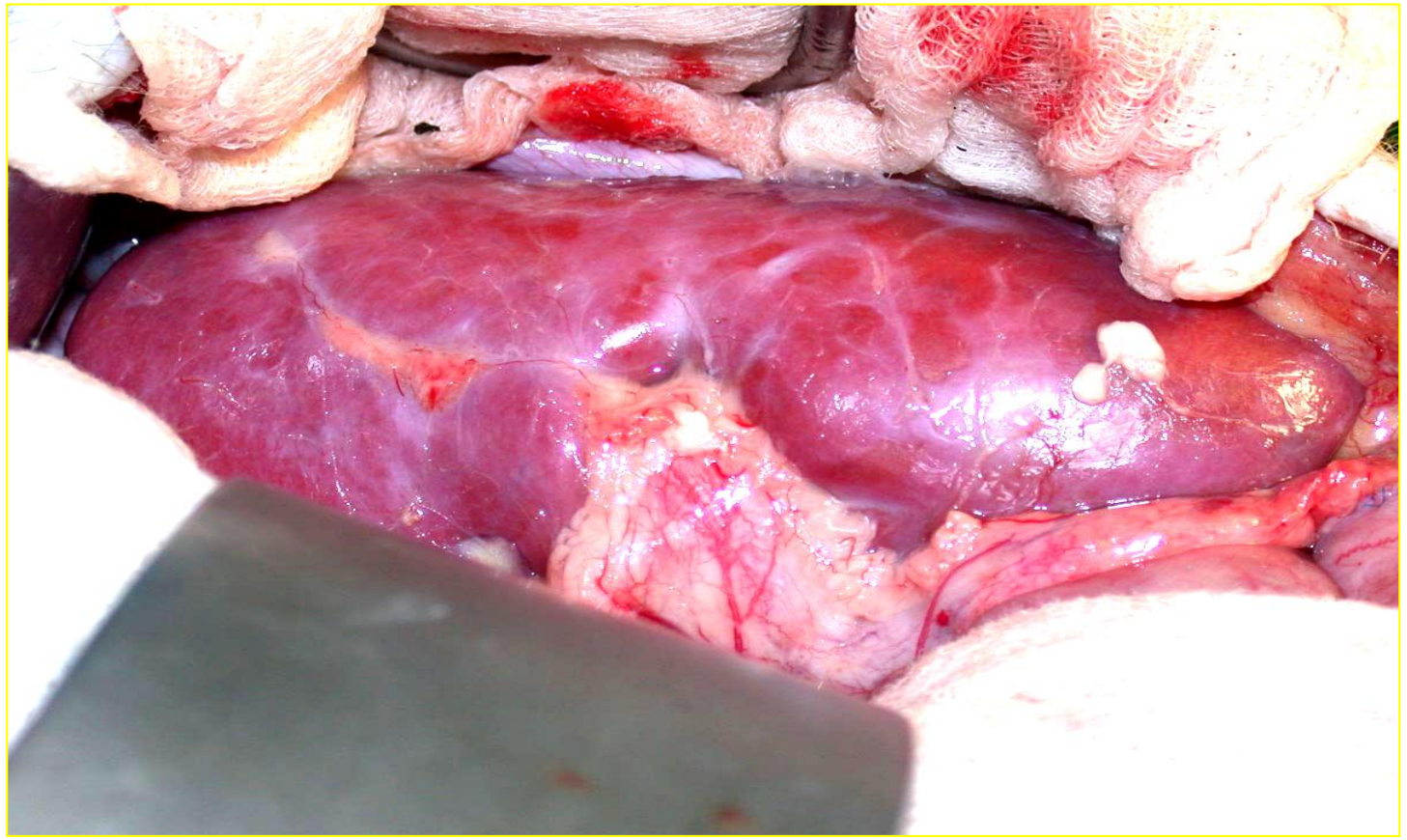
Nonmodified Donor Pig

Baboon (Recipient)

Cynomolgus Macaque

Pictures courtesy Dr. David Cooper

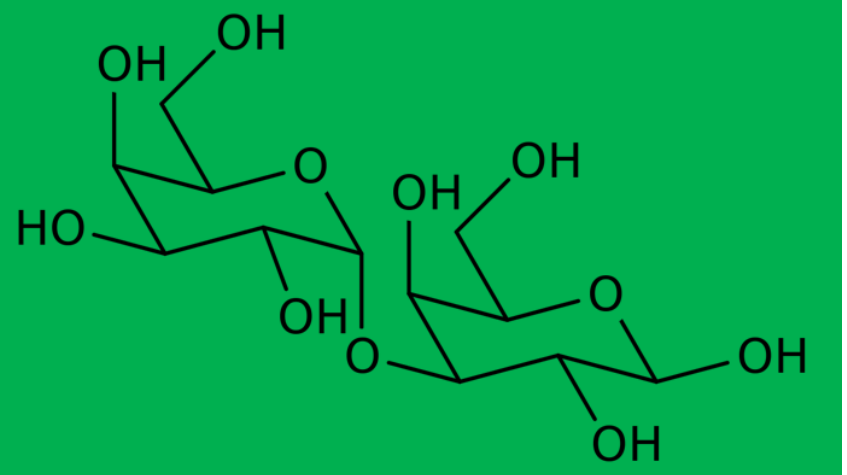
non-modified PIG-TO-BABOON KIDNEY TX (DAY 0)



Picture courtesy Dr. David Cooper

First Major Breakthrough: Recognition of the major Xenoantigen

Galactose-α1,3-galactose (Gal):
The major Xenoantigen



Hyperacute Rejection

Picture courtesy Dr. David Cooper – Pig Kidney with Immediate Rejection

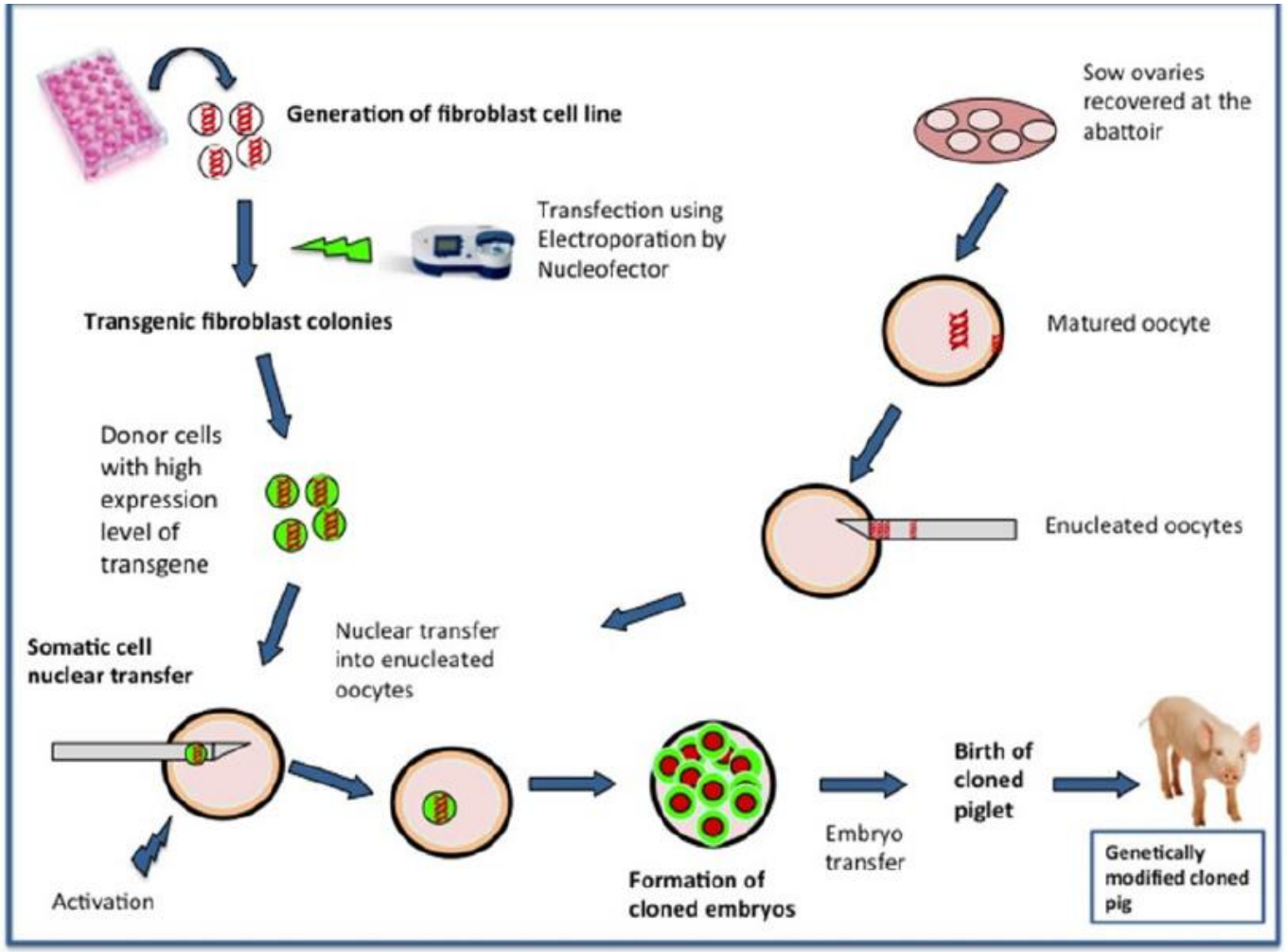
Baboons (and Humans) have naturally occurring antibodies to pigs that will attack the pig kidney

Solution:
Treat the recipient (Baboon) with Immunosuppression (over treated)

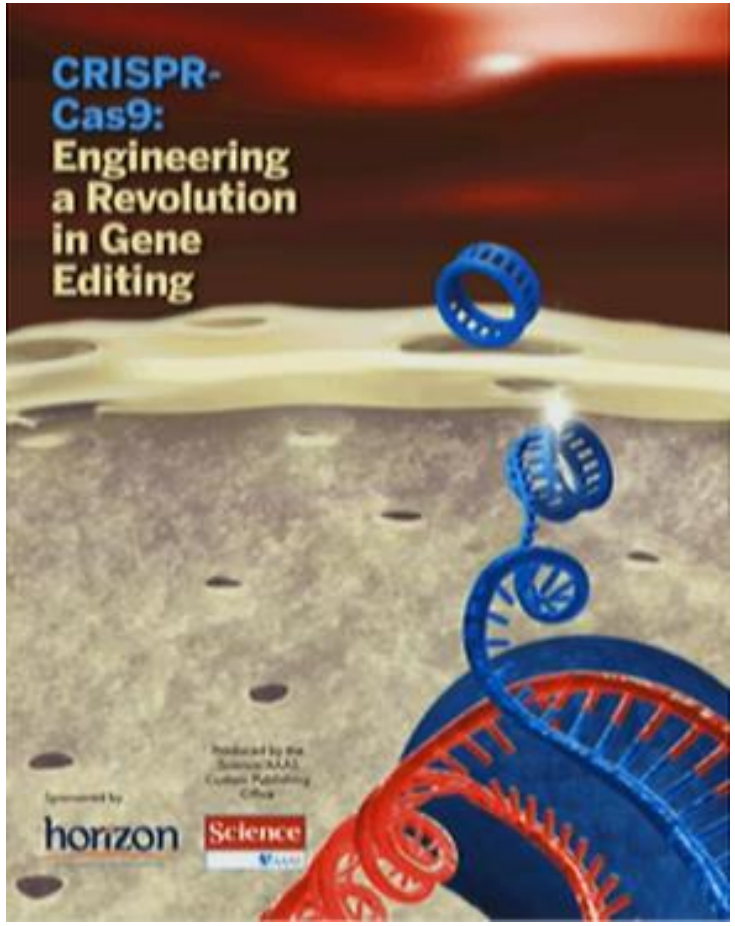
Modify the Donor:

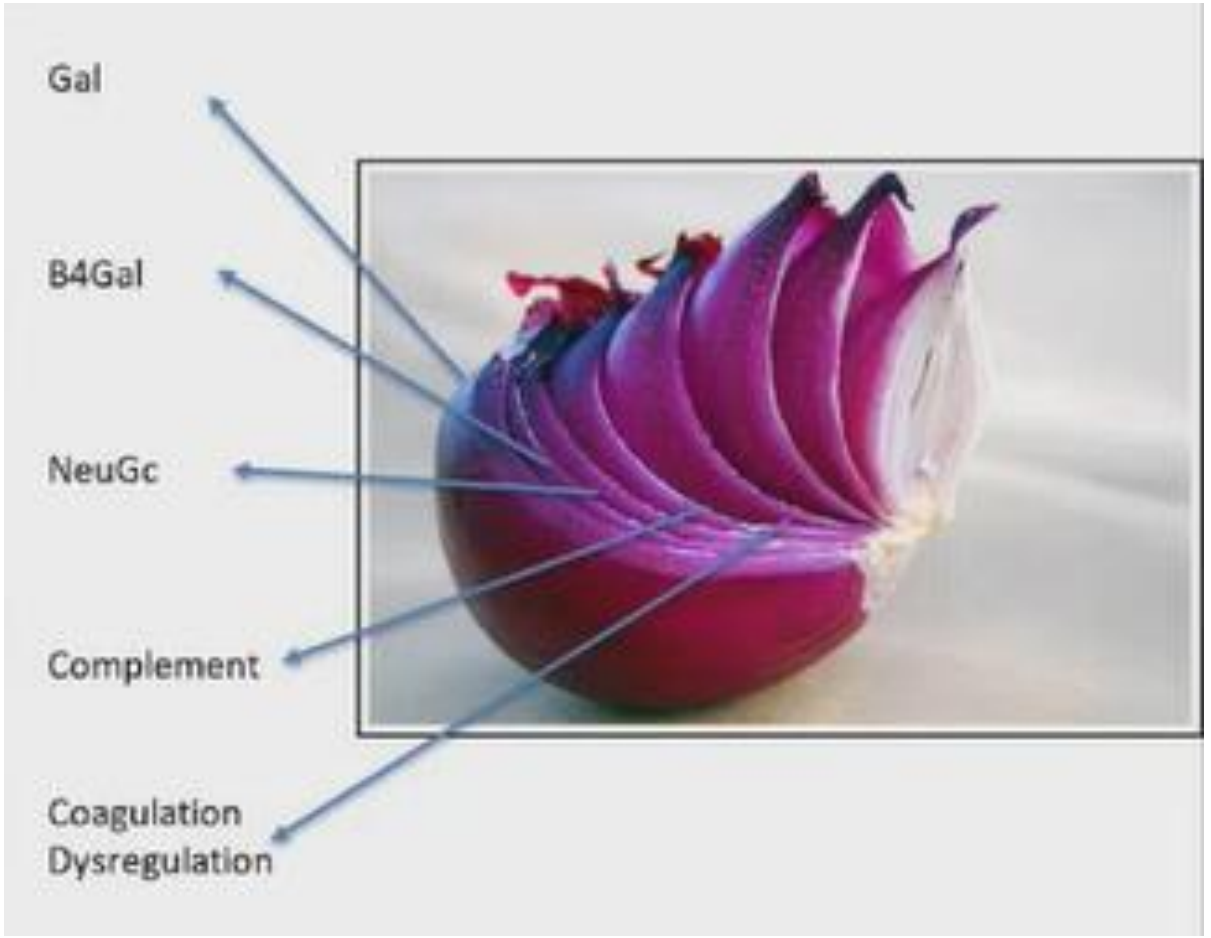
"Knock Out Pigs as Donors"

Steps Involved in Somatic Cell Transfer

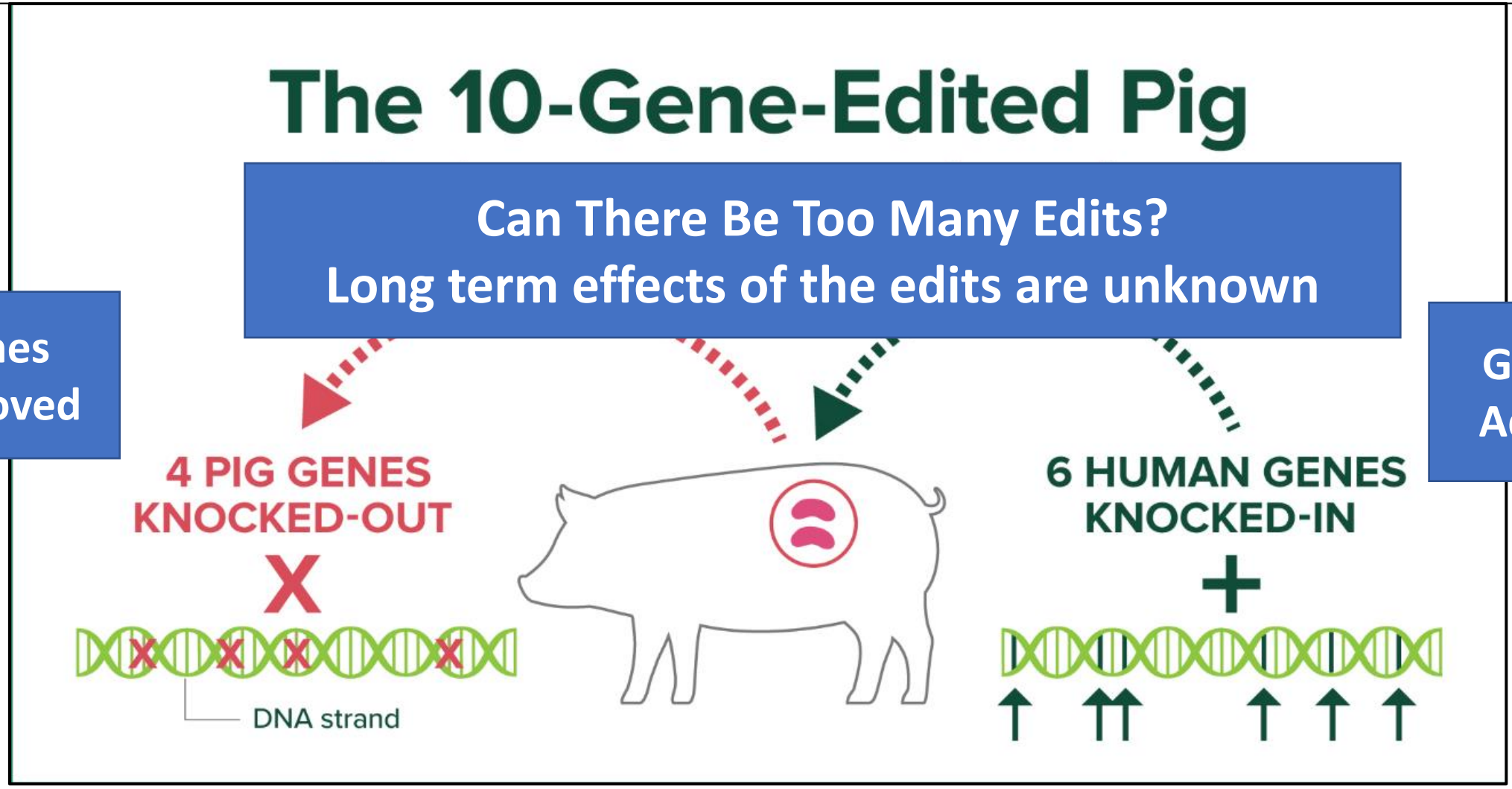


Additional Gene Discoveries and Knockouts





Make the Donor More Humanlike



Slide from UAB Xeno Deck

XENOTRANSPLANTATION NHP MODEL WITH KNOCK OUT PIGS ORGANS:

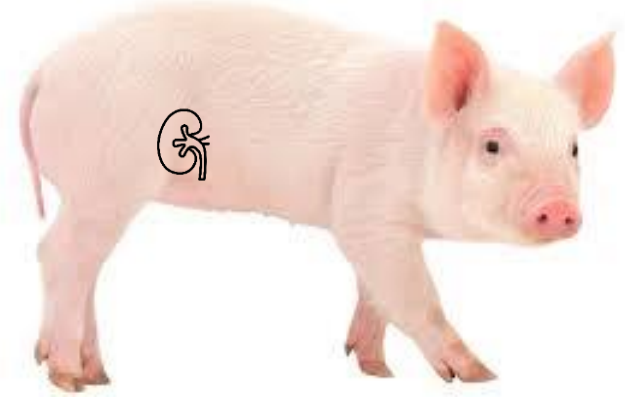
Modified (Edited/Knock Out) Donor Pig

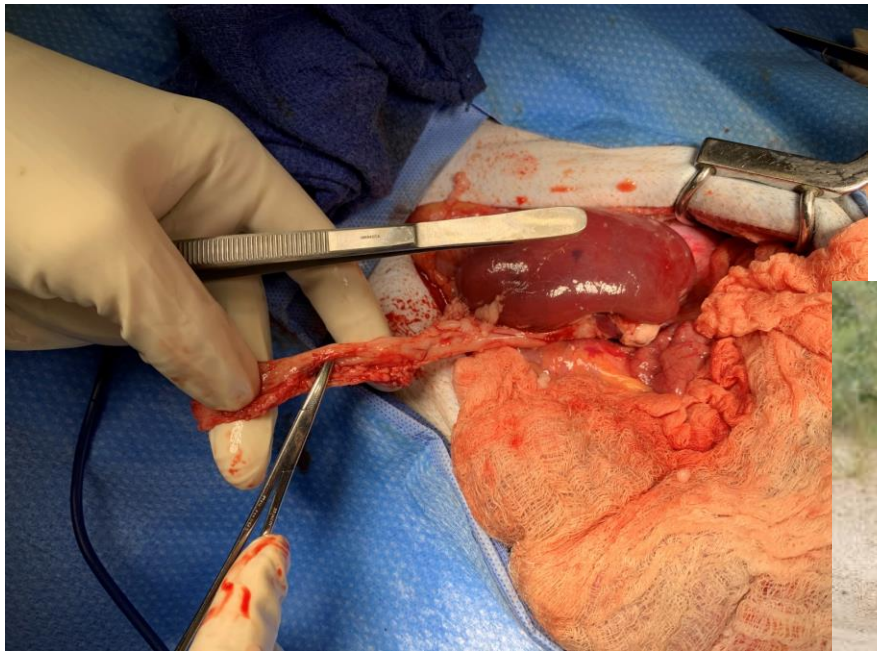
Baboon (Recipient)

Baboons are Requiring Experimental Immunosuppression to Prevent Long term Rejection. Will it be The Same in Humans?

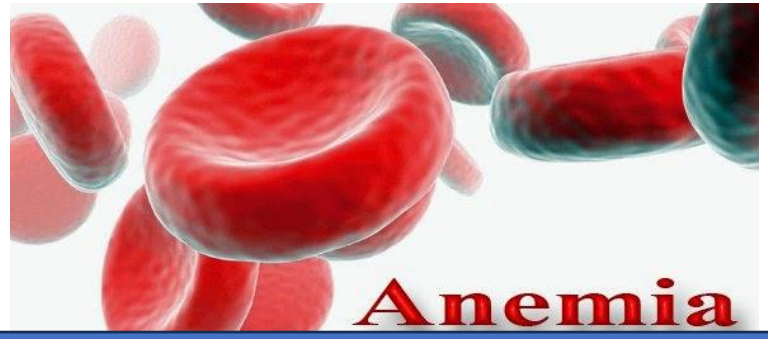
Pig Kidney Made to Be “Human Like” and Studied in Baboons (Not in Humans)

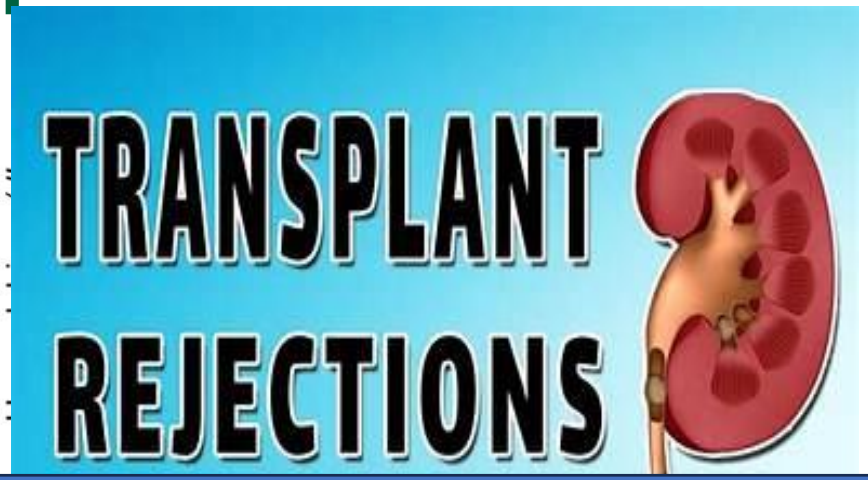
Modified Pig	→	Baboon
Modified Pig	X	Human





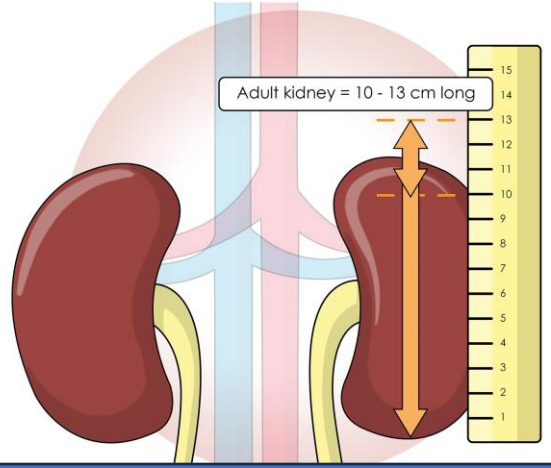
Modified Pig Kidney Function Similar to Human Kidneys BUT Some Important Differences (knowns and u





Pig and Human Hormonal Differences –
Nee Injections

Short term Rejections Minimized
Long-term Risk of Rejections an Issue



Increased Growth in Kidney Size
Few centimeters up to more

Large amount of urine output

A Human Model Is Needed-
The Brain Dead Decedent Model

Identify Decedent

LEGACY of HOPE
Alabama's Organ & Tissue Donation Alliance

Transplantation

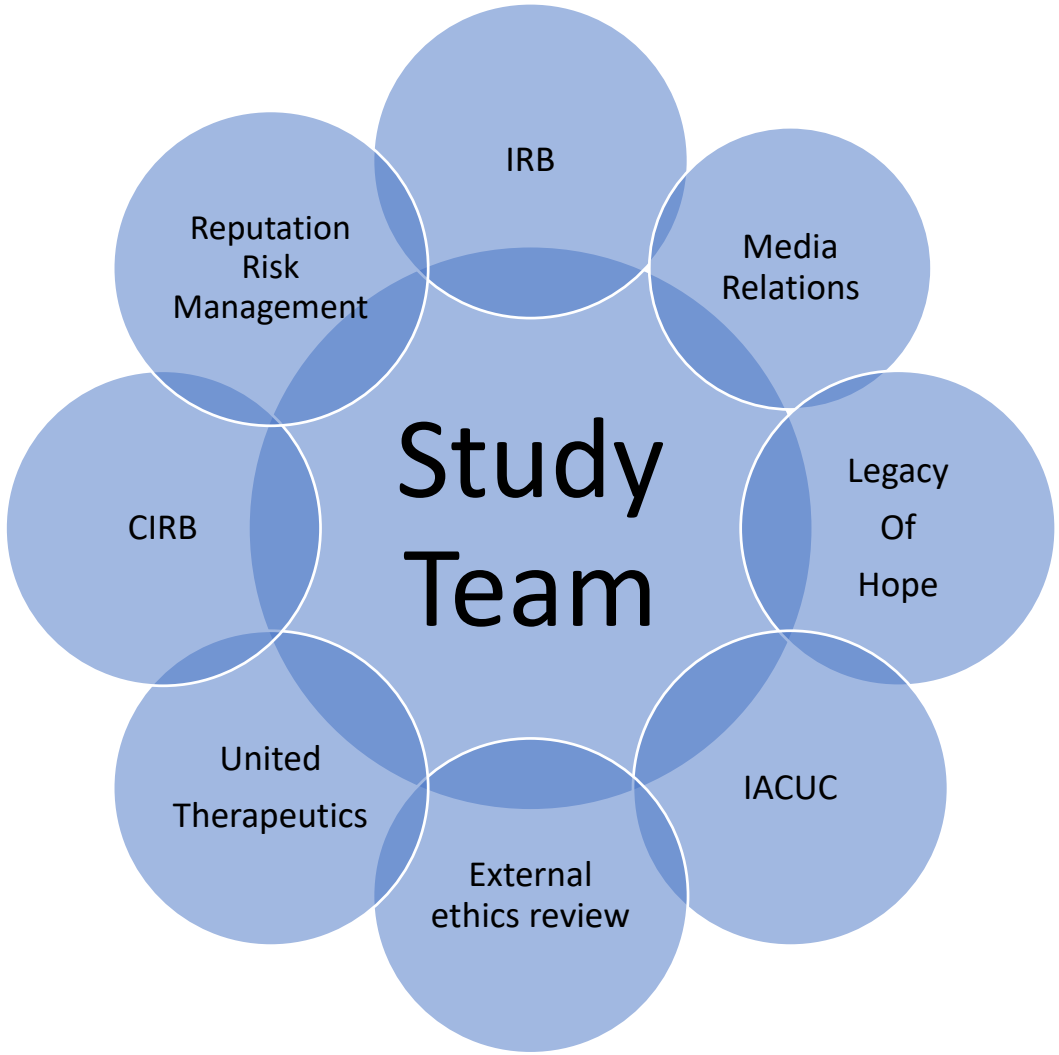
Post-transplant (7 days)

<u>Design advantages</u>:

1) **No harm to living person**
2) **Test our engineering & immunosuppression (in a brain dead human, before a living human)**

6. FIRST IN HUMAN – kidney xenotransplan

Decedent Model April 2021



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ORIGINAL ARTICLE

AJT

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

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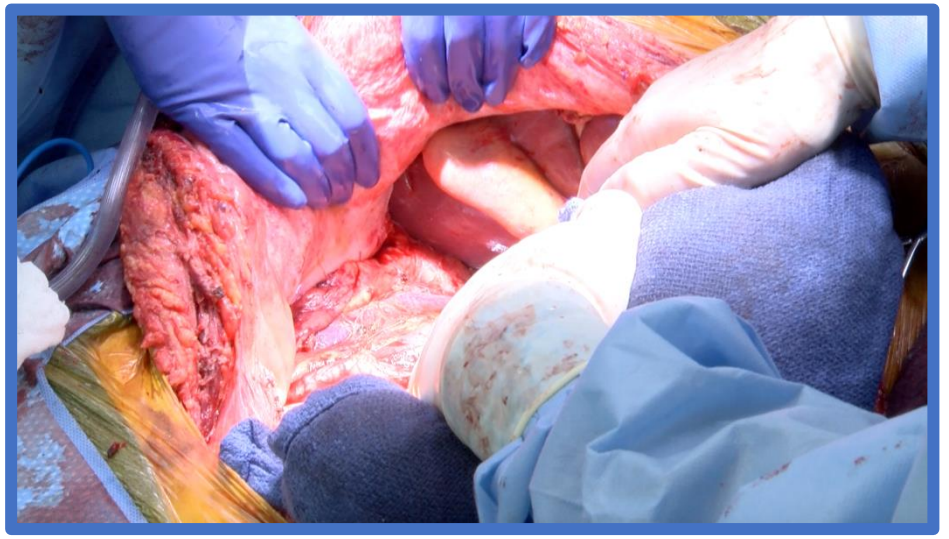
A radical solution is needed for the organ supply crisis, and the domestic pig is a promising organ source. In preparation for a clinical trial of xenotransplantation, we developed an in vivo pre-clinical human model to test safety and feasibility tenets established in animal models. After performance of a novel, prospective compatible crossmatch, we performed bilateral native nephrectomies in a human brain-dead decedent and subsequently transplanted two kidneys from a pig genetically engineered for human xenotransplantation. The decedent was hemodynamically stable through reperfusion, and vascular integrity was maintained despite the exposure of the xenografts to human blood pressure. No hyperacute rejection was observed, and the kidneys remained viable until termination 74 h later. No chimerism or transmission of porcine retroviruses was detected. Longitudinal biopsies revealed thrombotic microangiopathy that did not progress in severity, without evidence of cellular rejection or deposition of antibody or complement proteins. Although the xenografts produced variable amounts of urine, creatinine clearance did not recover. Whether renal recovery was impacted by the milieu of brain death and/or microvascular injury remains unknown. In summary, our study suggests that major barriers to human xenotransplantation have been surmounted and identifies where new knowledge is needed to optimize xenotransplantation outcomes in humans.

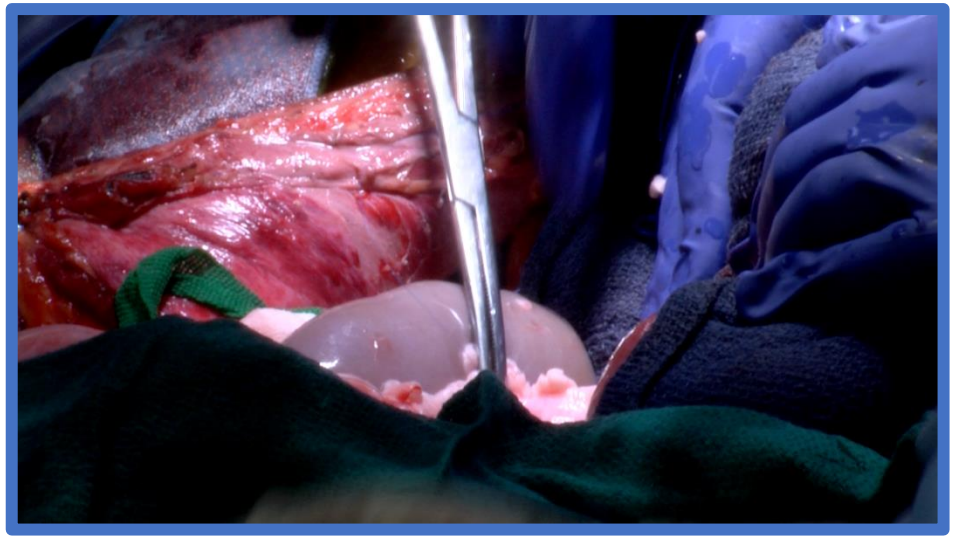
KEYWORDS
clinical research/practice, genetics, kidney transplantation/nephrology, translational research/science, xenoantigen, xenotransplantation

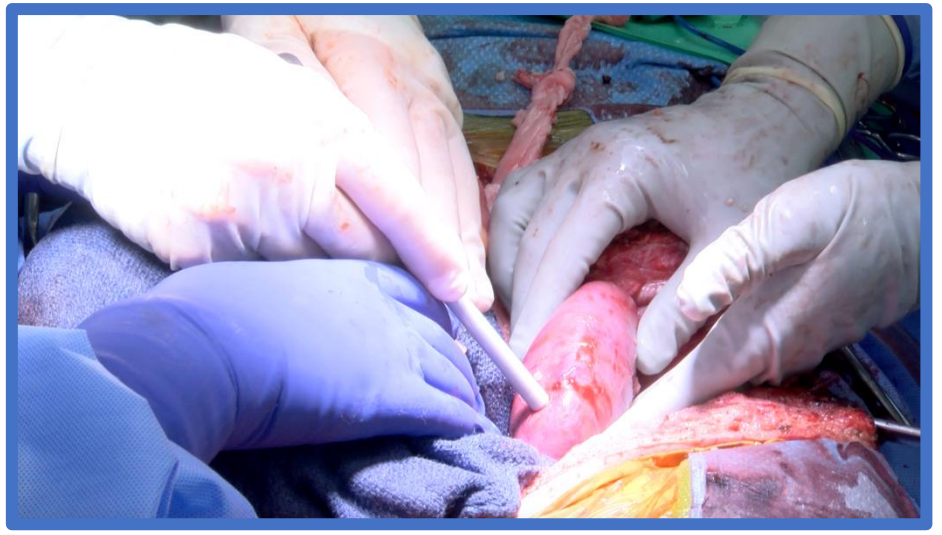
ukocyte antigen; NHP,
ent campus.

UAB HEERSINK SCHOOL OF MEDICINE
The University of Alabama at Birmingham

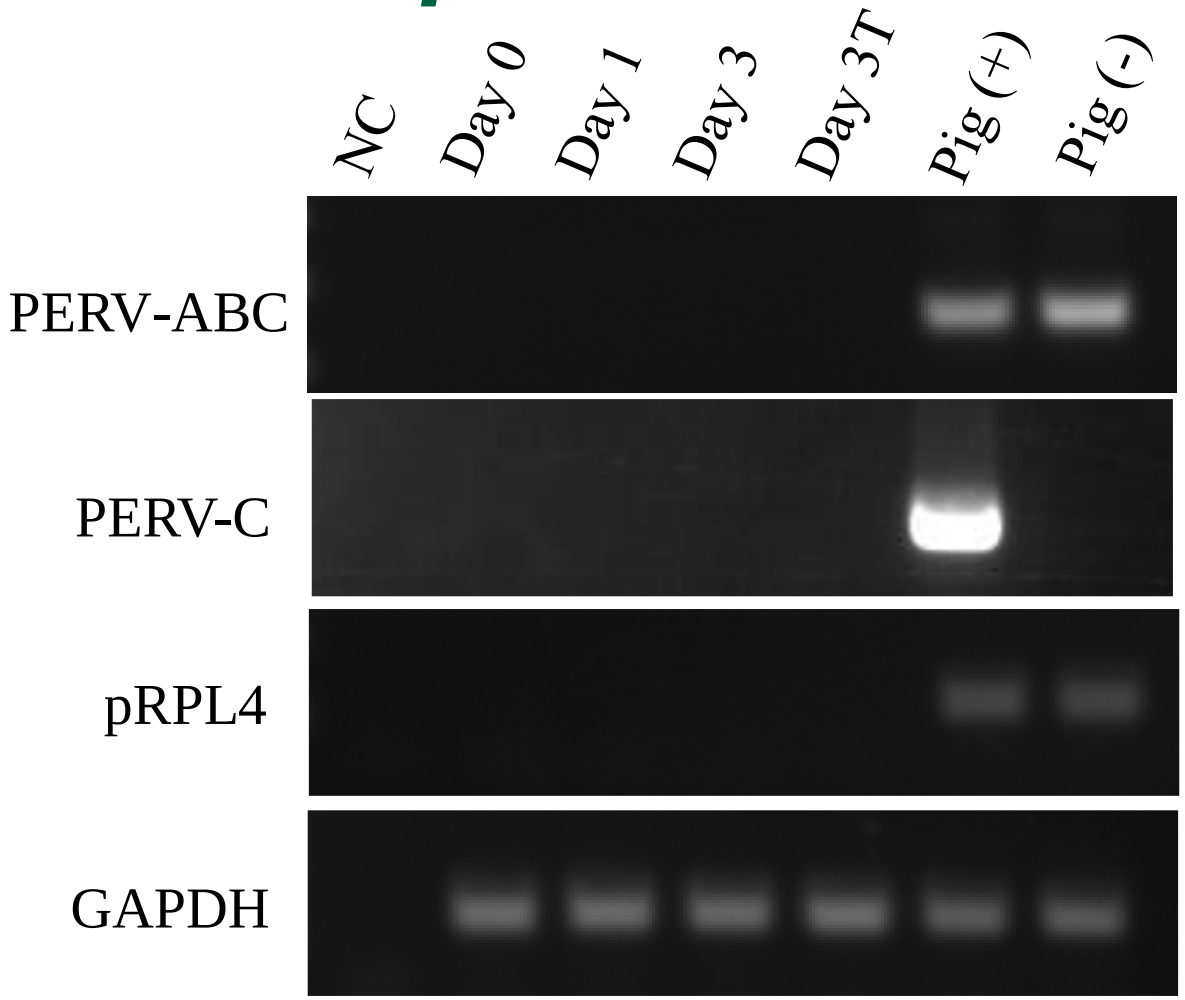
Clinical grade 10GE pig-to-human xenotransplant







NO pig-to-human disease transmission after solid organ transplant in that short time period (3 days)



NC = normal control
Pig(+) = wild type pig
Pig(-) = 10GE pig

Porrett PM / Locke JE. First clinical-grade porcine kidney xenotransplant using a human decedent model. *American Journal of Transplantation,* 2022 Jan 20. doi: 10.1111/ajt.16930. Online ahead of print

Porcine CMV Transmission: Lessons Learned from the first Pig-to-Human Heart Xenograft

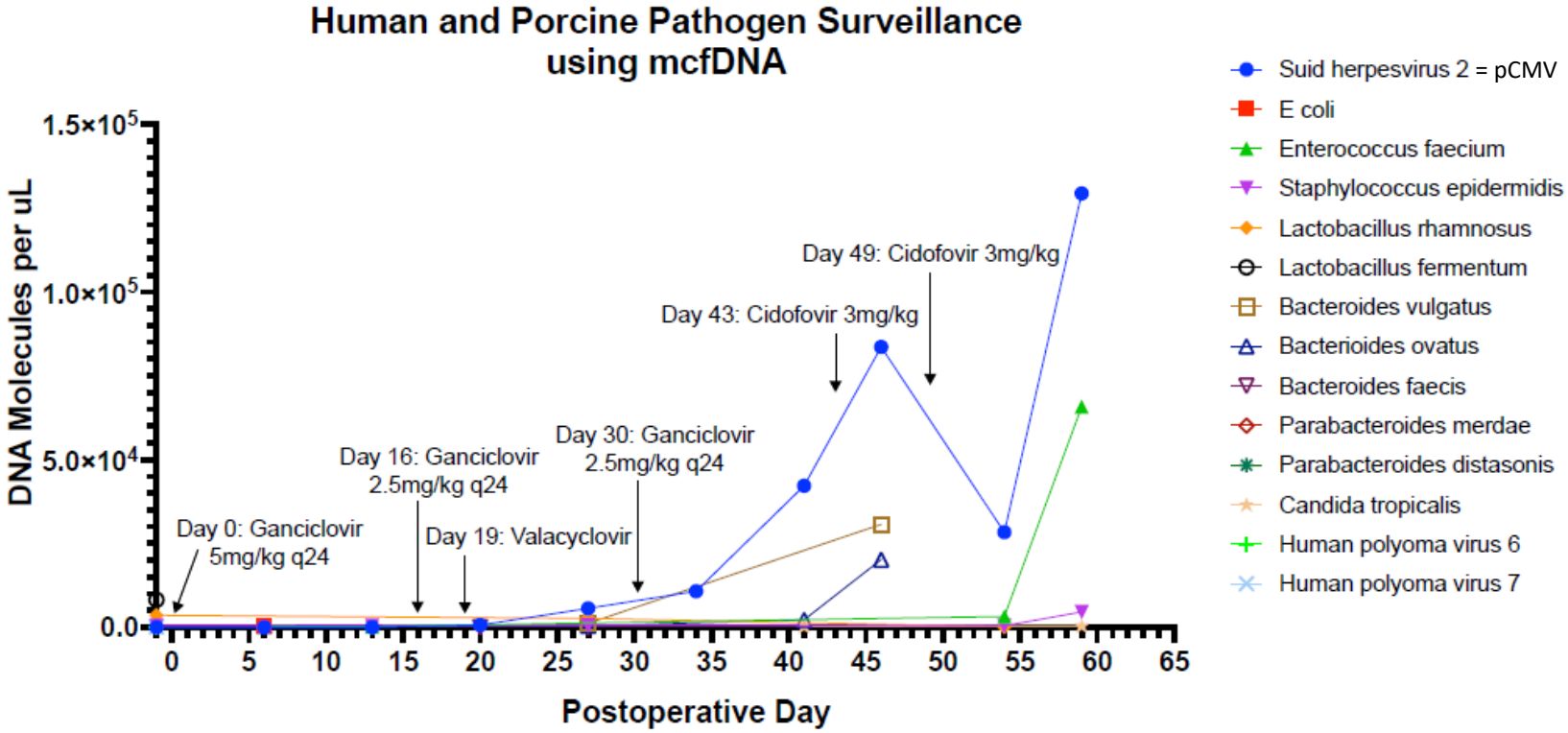
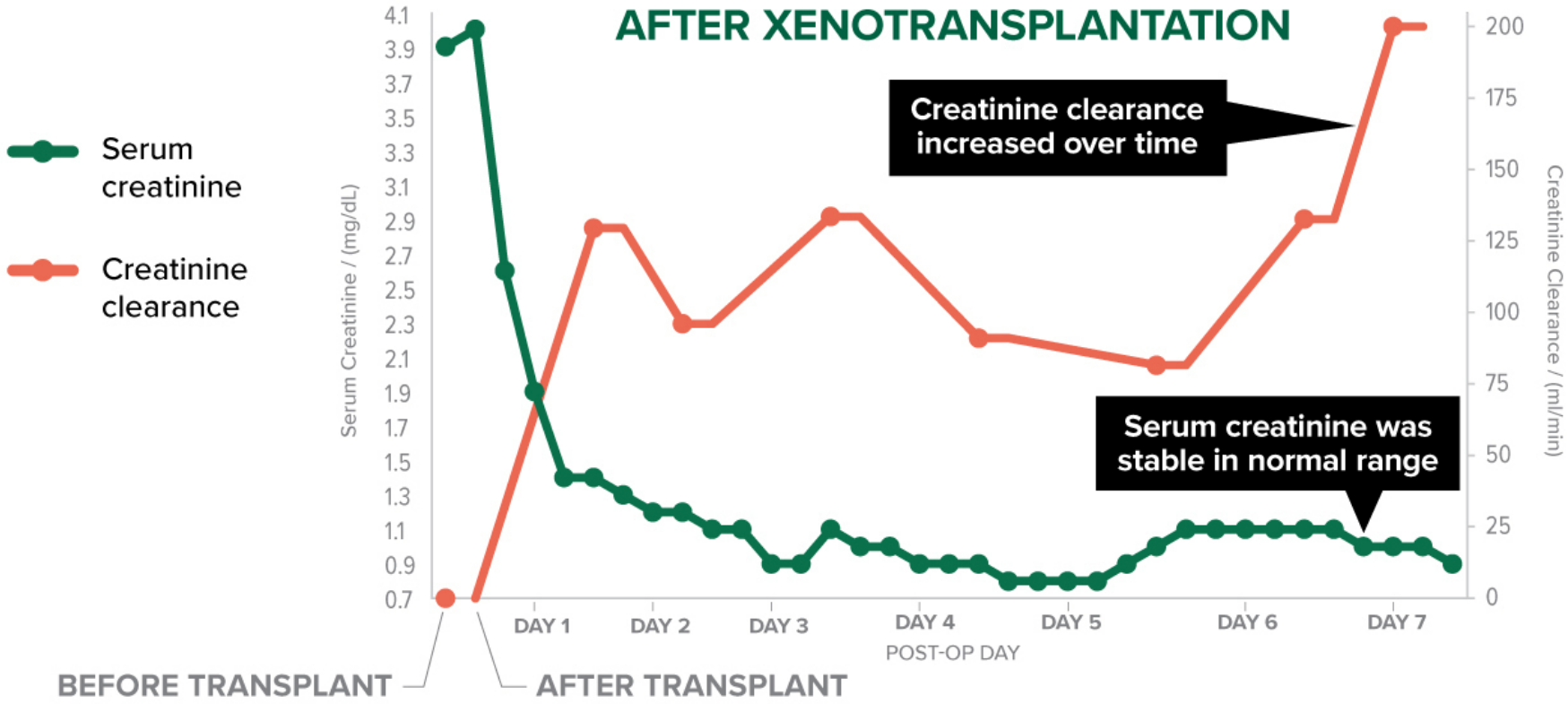


Figure S2: Unbiased longitudinal surveillance of recipient plasma by mcfDNA revealed presence of suid herpesvirus 2 (porcine cytomegalovirus, pCMV). Superimposed treatment for pCMV is indicated by arrows. There was no detection of latent human DNA viruses following xenotransplantation.

Griffith BP et al. NEJM, 2022; DOI: 10.1056/NEJMoa2201422

Kidney function over time after a 10-gene-edited pig-to-human xenotransplant

Transplanted pig kidneys showed life-sustaining kidney function after a recent pig-to-human kidney xenotransplant in a pre-clinical human research model.



THE UNIVERSITY OF ALABAMA AT BIRMINGHAM

JAMA Surgery Aug 2023 Locke JE, Kumar V et al

Two-Month Study of Pig Kidney Xenotransplantation Gives New Hope to the Future of the Organ Supply

NEWS PROVIDED BY
NYU Grossman School of Medicine and NYU Langone Health →
14 Sep, 2023, 10:00 ET

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PRESS RELEASE · 5 MINUTE READ · MAR | 21 | 2024

World's First Genetically-Edited Pig Kidney Transplant into Living Recipient Performed at Massachusetts General Hospital

Brandon Chase · bchase7@mgb.org

69 Genes edits

Pig Genes Removed

- Pig carbohydrates (αGal,Sd(a),Neu5Gc)
- Pig endogenous retrovirus inactivation

CRISPR gene-editing

Yucatan pig

Human Genes Added

- Complement inhibitors (hCD46, hCD55)
- Anti-coagulants (hTHBD, hPROCR)
- Immune regulators (hCD47, hHMOX1, hTNFAIP3)

Cynomolgus Macaque

Over 2-year survival in animal models

Recently Answered Questions

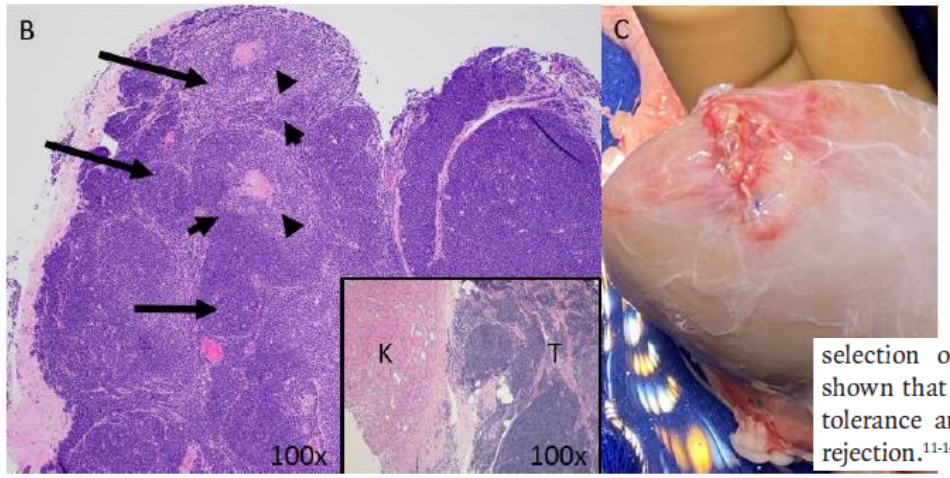
Knowledge Gap: *Optimal immunomodulation?*

UKidney™
Locke, Porrett, Kumar et al

TABLE 5 Pharmacologic immunosuppression regimen

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

UThymoKidney™
Montgomery et al

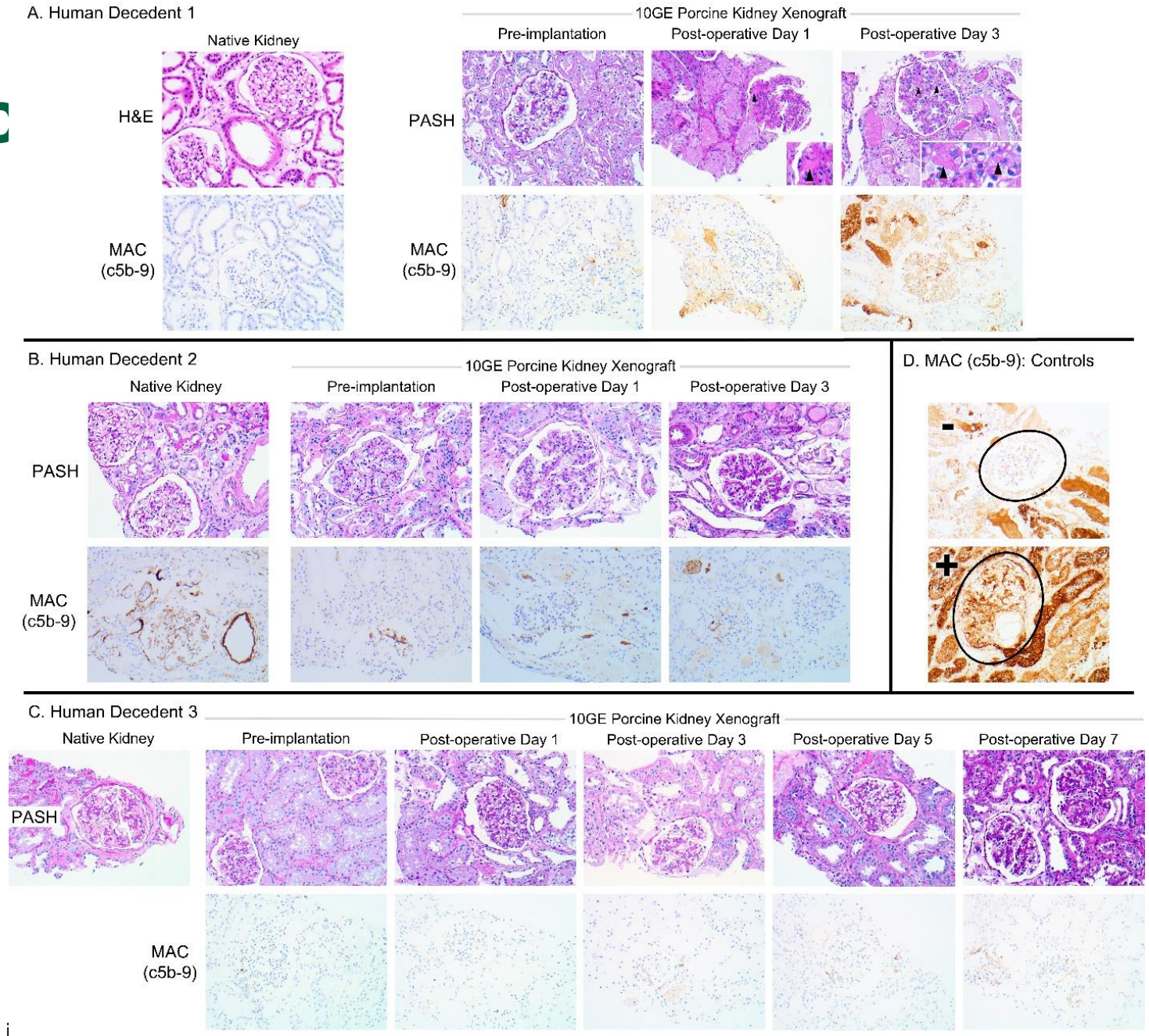


MMF
Steroids

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

Use of Anti-C5 Inhibitc

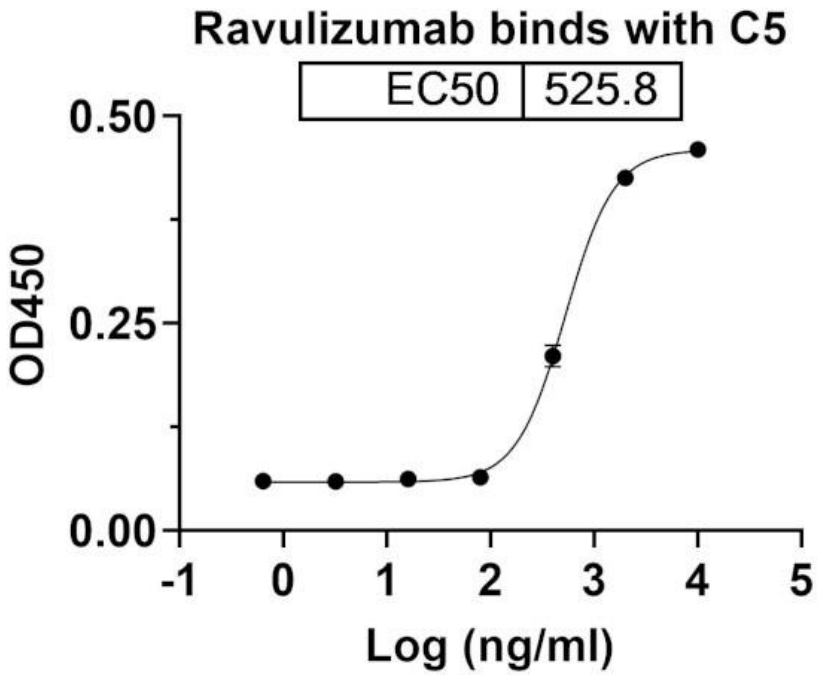
- Three male decedents, aged 57, 65, and 53 years
- 10GE pig kidneys
- Decedents 2 and 3
  - received anti-C5 monoclonal antibody therapy eculizumab
  - 24 hours prior to (1200 mg) and 24 hours after (900 mg) xenotransplantation
- No C5-B9 staining

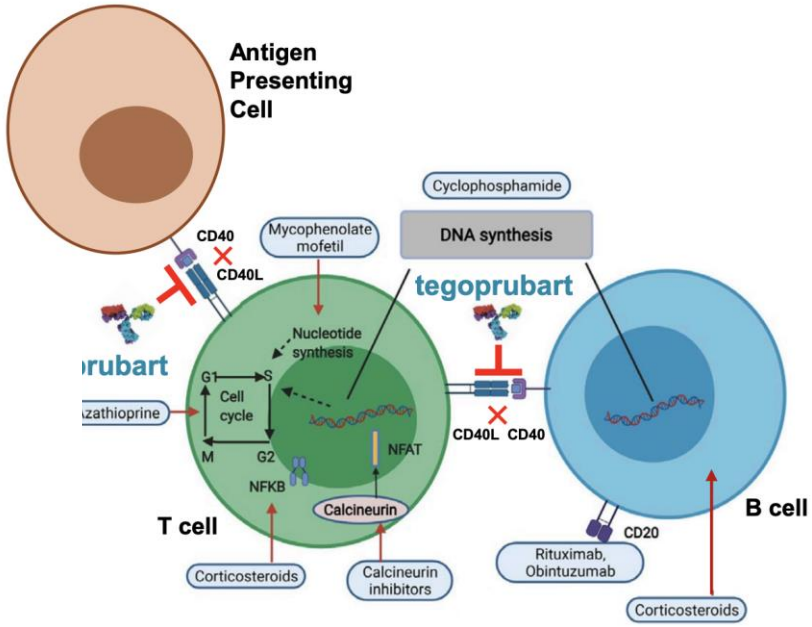


JCI – today Jan 25, 2024
C5 inhibition with eculizumab prevents thrombotic microangiopathy i… a case series of pig to human kidney xenotransplantation

Mass General Experiment Immunosuppresion

- **Standard – Thymo + 3 drugs**
- **Anti CD40 Ligand: Tegoprubart**
- **Anti C5 inhibitor: Ravulizumab**

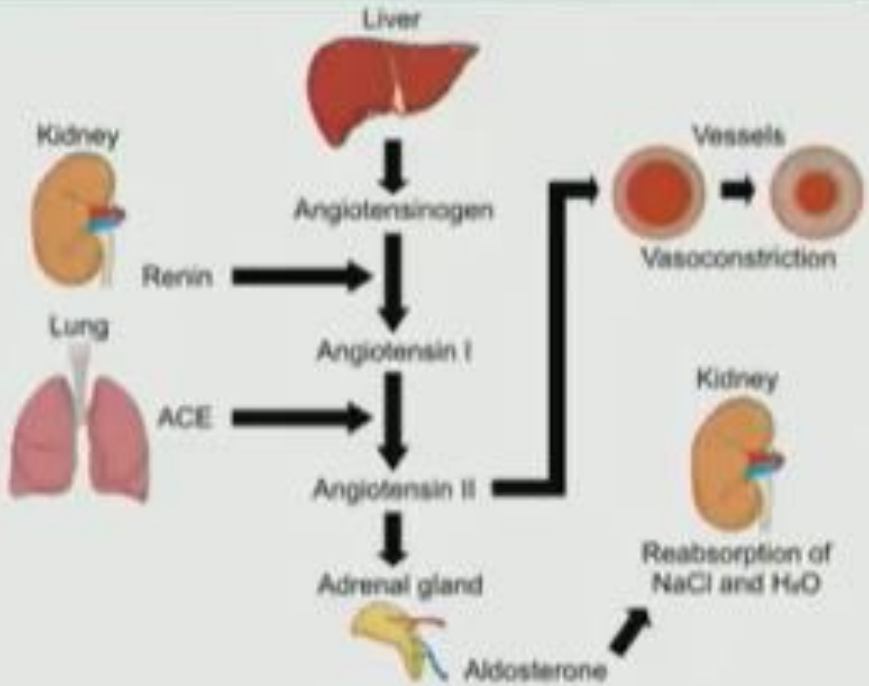




Physiologic Incompatibilities

Background – Hypovolemia in NHP Models

- Baboons with pig renal transplants experience episodes of hypovolemia (Iwase 2019)
- May be the result of a physiologic difference in the Renin-Angiotensin-Aldosterone system (RAAS)
- *In vitro* studies suggest that pig renin is not as effective in activating downstream mediators in primates (Evans 1990, Wang 1994)



(Vargas-Rodriguez 2022)

UAB MEDICINE
SURGERY

No Hypotension in Decedent

Detectable Angiotensin II and Aldosterone levels

- The undetectable PRA confirmed little ability of the pig renin to cleave human angiotensinogen
- The ability to maintain blood pressure without use of any inotropes in the absence of native human kidney renin production combined with measured levels of angiotensin II and aldosterone supports residual RAAS activity
- Renin and aldosterone levels are persevered in patients on hemodialysis for at least 27 months

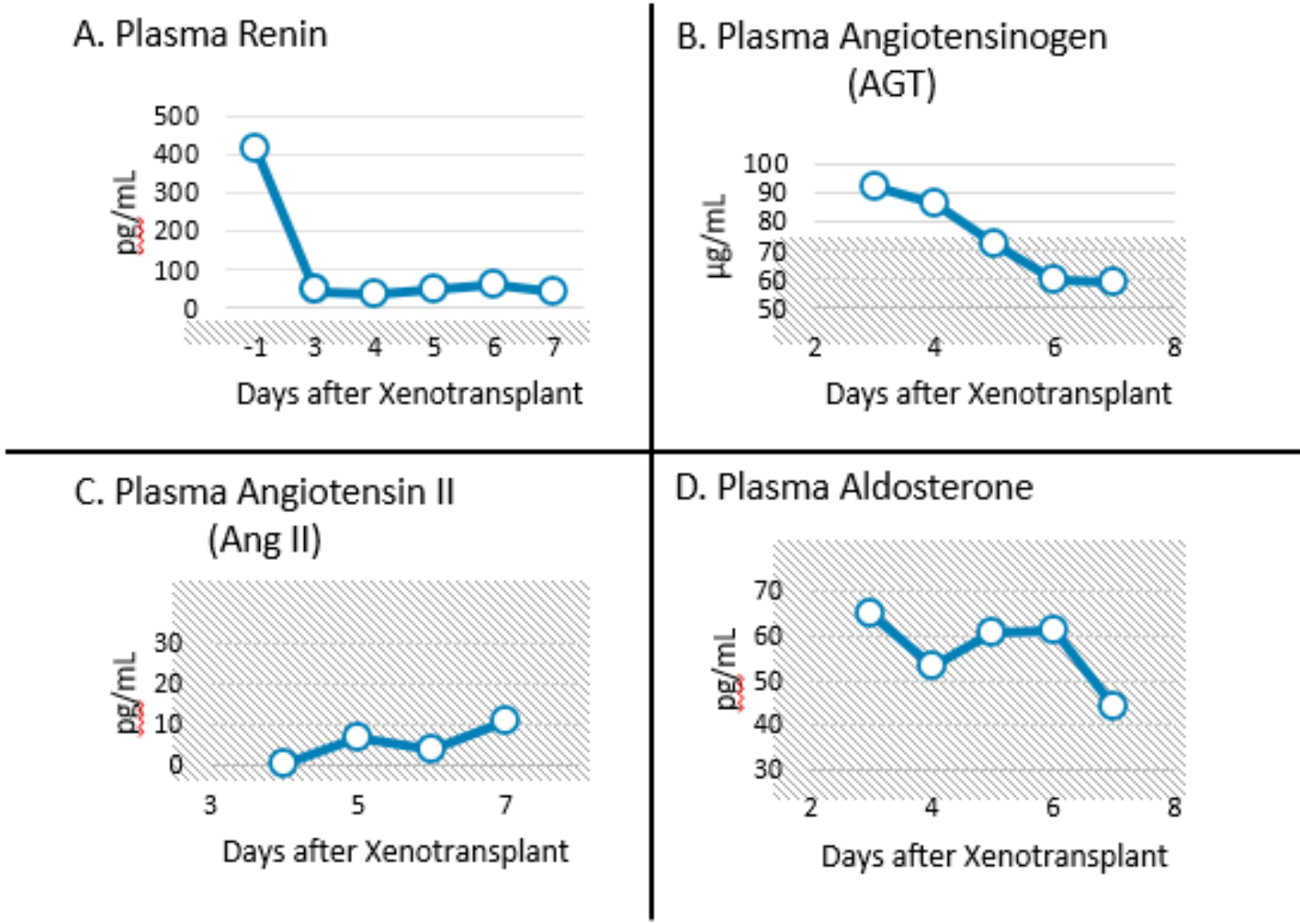
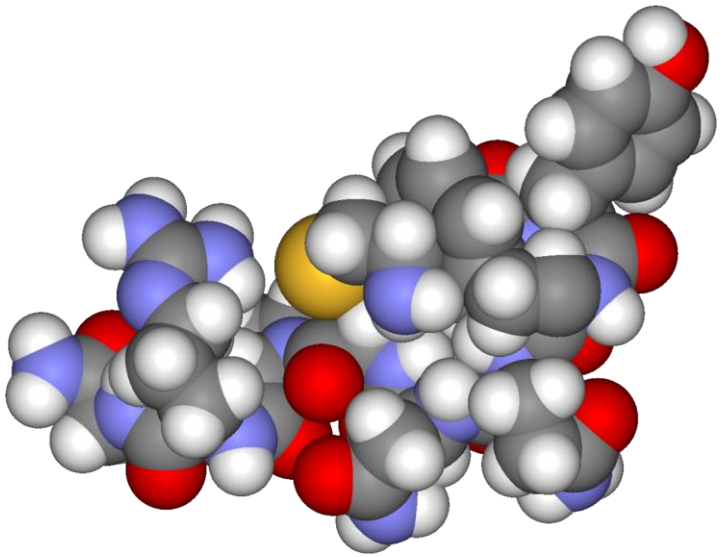
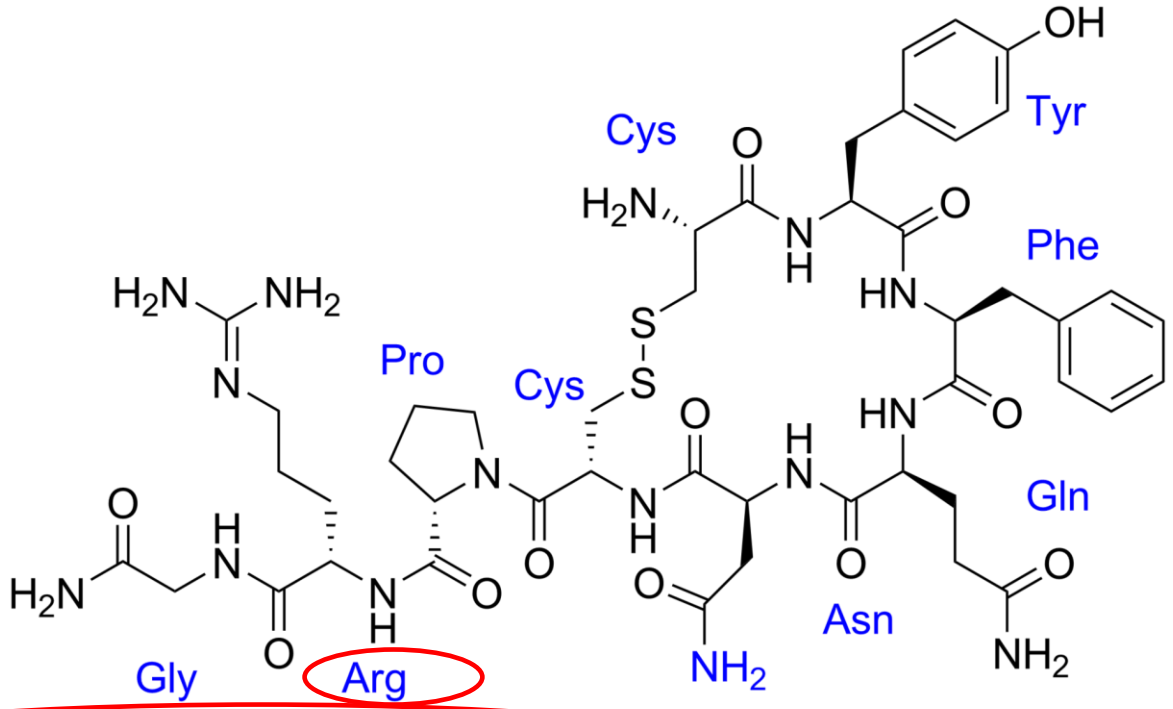


Figure 1. Renin-Angiotensin-Aldosterone System (RAAS). Xenotransplant recipient hormone plasma concentrations over time, shaded areas represent normal human ranges for each hormone: A. Renin (pg/mL), normal <45.7 pg/mL. Plasma renin activity was <0.6 ng/mL/hr at all time points. B. Angiotensinogen (µg/mL), 71 µg/mL is the upper limit of normal.[12] C. Angiotensin II (pg/mL), normal range 3-30 pg/mL.[19] D. Aldosterone (pg/mL), normal range 31-354 pg/mL.

Manuscript in Press: KI, Jan 2024 Physiologic Homeostasis after Pig-to-Human Kidney Xenotransplantation

Vasopressin: Human Arginine vs. Pig Lysine





Substitute Lysine for Arginine

Early Severe Hypernatremia

Corrected with DDAVP

Over the course of the 7-day study period, the urine output decreased, serum sodium normalized

Calculated urinary water losses between 3-4.5 L/day, and given the eGFR, this means 99% of the filtered water was reabsorbed

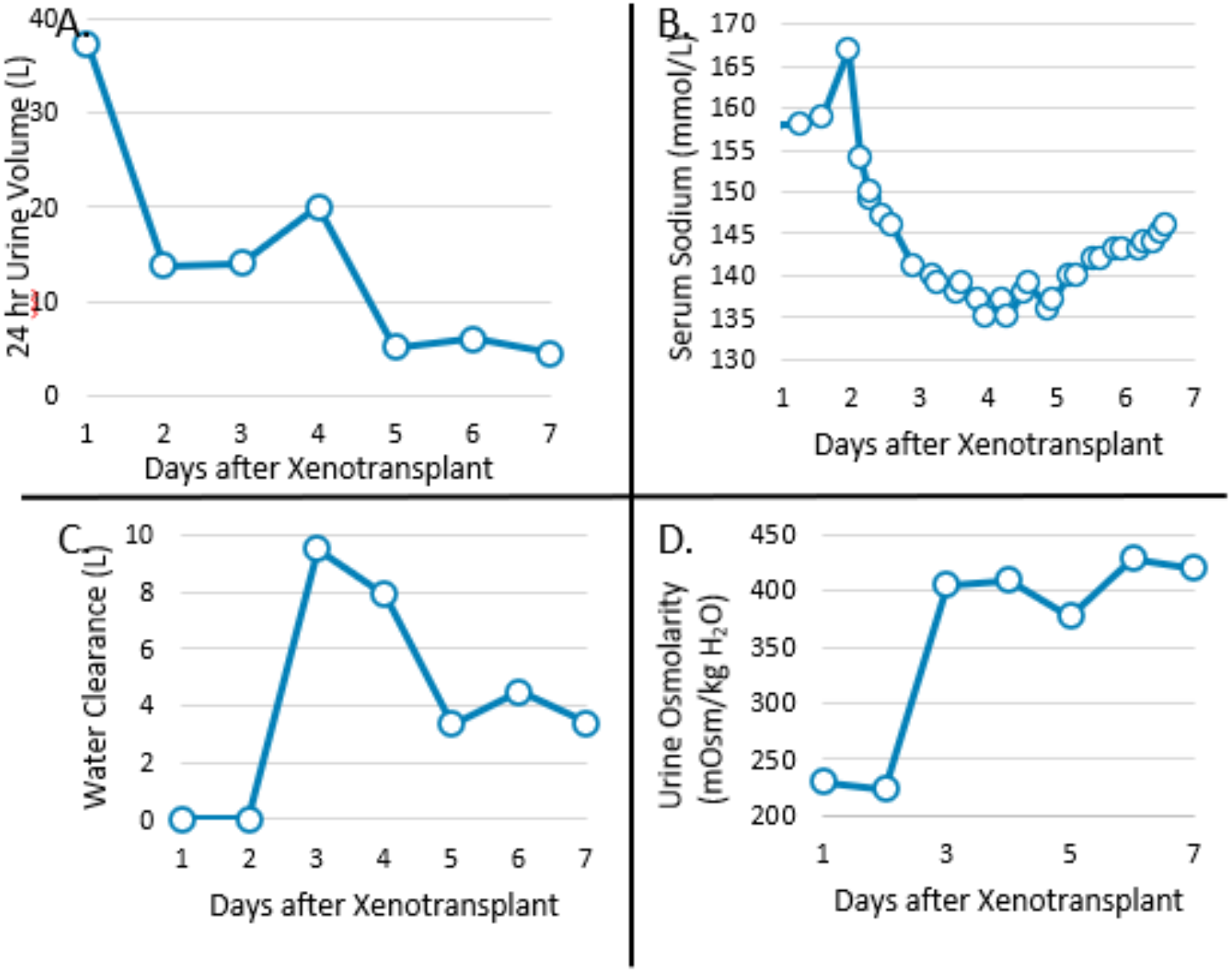


Figure 4. Water and sodium balance. A. Decedent's daily urine output after xenotransplantation (liters). Intraoperative Furosemide 100mg and Mannitol 25g were administered intravenously right before reperfusion. B. Serum sodium. C. Water clearance after xenotransplantation (liters). D. Urine osmolarity (mOsm/kg H_2O).

Manuscript in Press: KI, Jan 2024 Physiologic Homeostasis after Pig-to-Human Kidney Xenotransplantation

Aquaporins (AQP) were immunolocalized in the pig kidney

AQP2 is vasopressin-responsive and vasopressin results in increased trafficking of AQP2 to the apical membrane to drive water reabsorption. This is mediated through the phosphorylation of Serine 256 in the c-terminus of AQP2, and AQP2-S526 was detected in the apical membrane of the principal cells of the pig kidney

In the brain-dead model, a vasopressin infusion is required to replace reduced hypothalamic-pituitary function. Low levels of copeptin (< 1 pg/L) on post-operative day 5 confirmed little endogenous vasopressin release

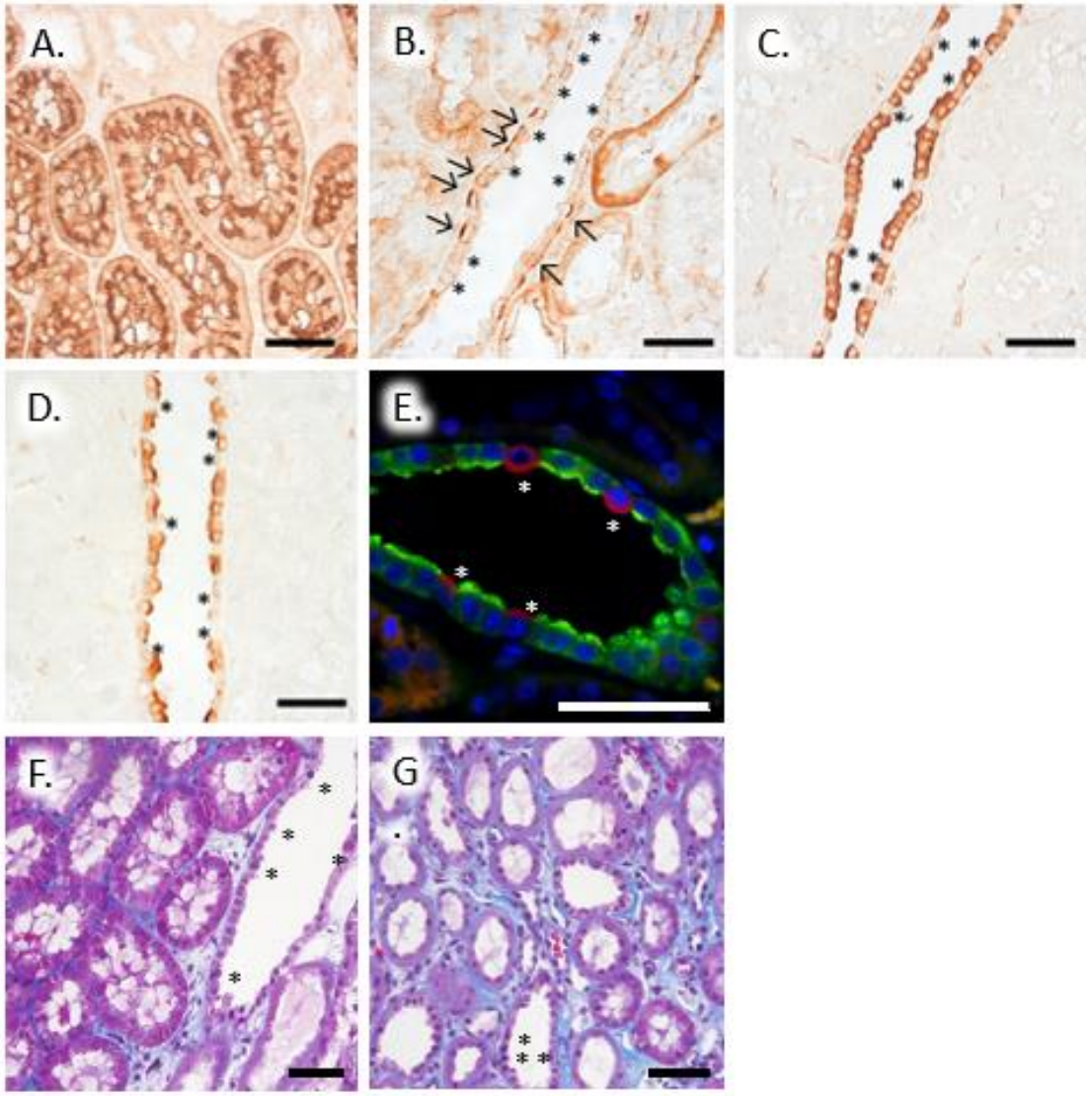


Figure 5. Aquaporin (AQP) expression in the 10 GE xenokidney. A. AQP1 in the apical side of the proximal tubule. B. AQP4 in the basolateral membrane of the principal cells of the collecting duct. Arrows indicate principal cells positive for AQP4. C. AQP2 in the apical membrane of the principal cells, and D. AQP2 phosphorylation S256, a known activated form of AQP2, is also expressed in the principal cells. F. Immunofluorescent labeling of principal cells with AQP2-488 (green) and V-ATPase positive staining of intercalated cells (red). F (cortex) and G (medulla): representative trichrome stained sections with proximal tubules (PT) and collecting ducts lined by pale staining principal cells and rare darkly stained intercalated cells. medulla. Asterisks (*) denote intercalated cells. Scale bar represents 50 micrometers.

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Proteinuria

- **Post-operative Day 1: 8.9 grams with 3.5 grams of albumin**
- **Post-operative Day 6: 3.2 grams**
  - **?Differences between pig and human glomerular permeability, reduced proximal tubular function, and/or injury to the glomerular filtration barrier, early antibody-mediated rejection**

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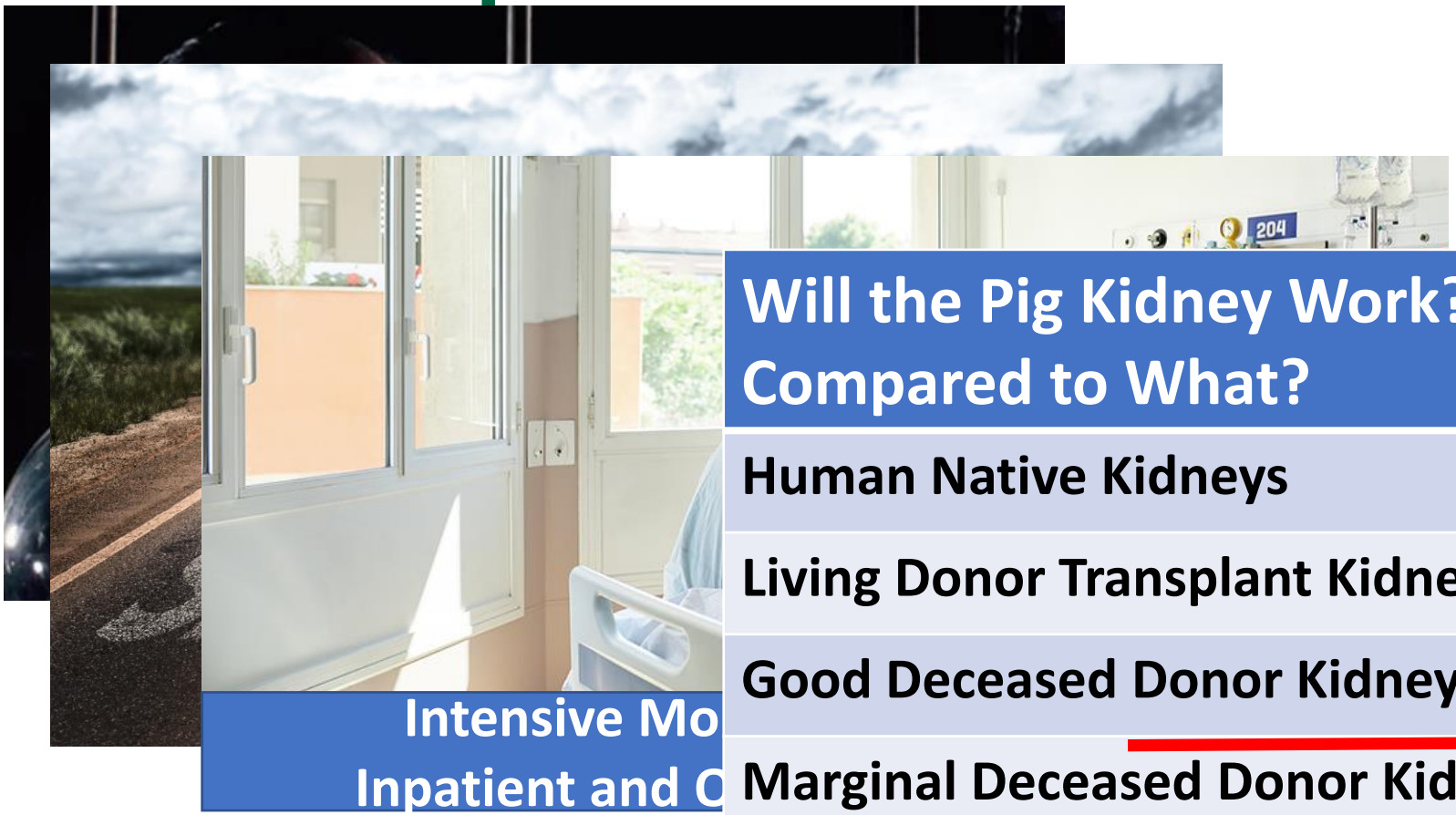
The Unknowns/Important Considerations

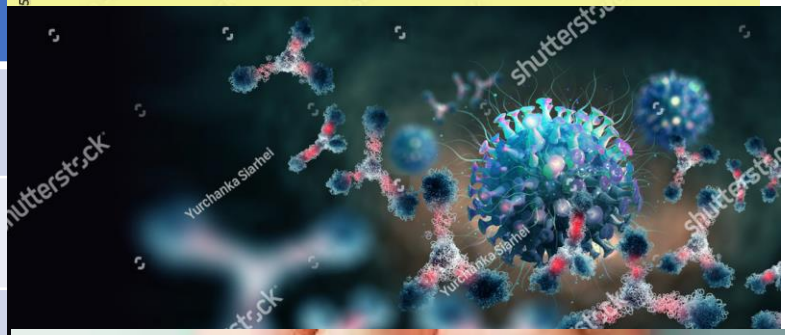
- **Optimal immunosuppression?**
- **What are the ideal genetic edits?**
- **Xenozoonosis, chimerism, malignancy risks?**
- **Physiology**
- **Long-term rejection and function?**
- **Social/Ethical Implications**
  - **Privacy concerns**
  - **Long term monitoring**
  - **Implications for Caregiver/close contacts**

Implications of First In-Human Trials



Intensive Mo
Inpatient and C

Will the Pig Kidney Work? Compared to What?
Human Native Kidneys
Living Donor Transplant Kidney
Good Deceased Donor Kidney
Marginal Deceased Donor Kidney
Primary Non Function kidney
Dialysis



Patient Are The True Pioneers


RIGHT KIDNEY
HANDLE WITH CARE

DOI: 10.1111/ajt.16963

EDITORIAL

When pigs fly

Watch out, it looks like the pigs are on the runway!!

KIDNEY TRANSPLANT RECIPIENT PERSPECTIVES ON KIDNEY XENOTRANSPLANTATION: INSIGHTS FROM THE PATIENT-FOCUSED MEETING WITH THE US FOOD AND DRUG ADMINISTRATION (FDA)