Charleston 2009

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Current Status of Xenotransplantation

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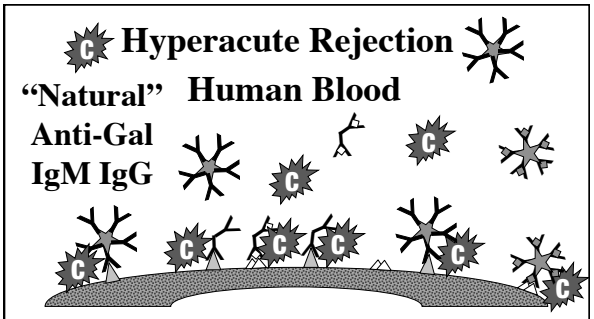
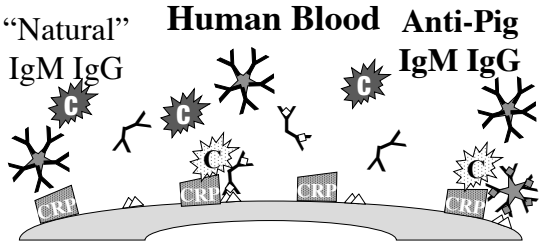
- **Current science: What is holding us back?**
  - **Organ xenografts**
  - **Islets**
- **Regulatory progress: Where are we?**
  - **Changsha, Islets, and beyond**
- **A view forward**

Hyperacute Rejection



Two Key Pig Modifications Together



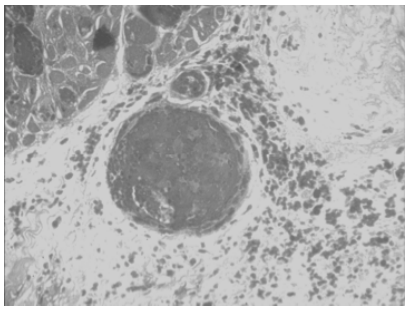
GalTKO+CPRP Tg
Gal 1,3 aGal sugars

Pig Cell
Other Pig Proteins

GalTKO and/or hCRP organs in non-human primates

- **Early graft failure (EGF) unusual**
  - **with one modification: ~0-40%**
  - **with two modifications: <10%**
- **Where are we today in preclinical models?**
  - **Heart: up to 6 month survival, but TM limiting**
  - **Kidney: up to 3 month survival, Rx complic. limiting**
  - **Liver: up to 7 days, thrombocytopenia limiting**
  - **Islets: over one year, clinically acceptable Rx needed**

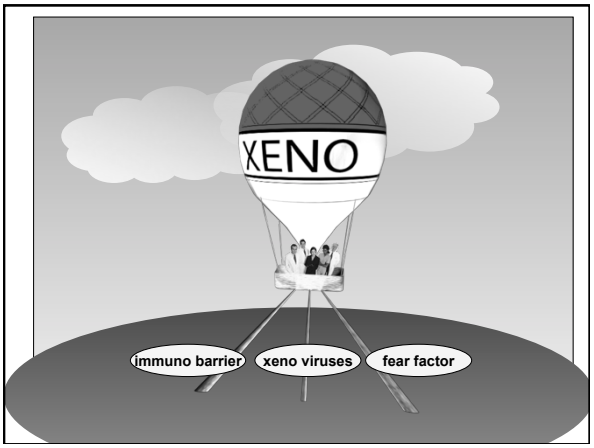
Thrombotic Microangiopathy



Caused by anti-pig antibody? Complement? Coagulation pathway activation?

GalTKO and/or hCRP organs in non-human primates

- Multiply modified pigs
  - GalTKO, hCPRP, coag regulator, immunomodulator
- Where are we today in preclinical models?
  - Heart: elicited Ab vs thrombodysregulation
  - Kidney: (elicited Ab vs thrombodysregulation)
  - Liver: prevent thrombocytopenia
    - CD47-SIRPa (Wang/Yang, Venice 2009: IXA-O-12.6)
    - αGP1B/ vWF (Deckmyn, Venice 2009: IXA-O-6.2)
  - Islets: islet modification, anti-CD40 Rx



Transmission of xenogeneic pathogens

J. Fishman, Xenotransplantation 2009

- Extensive studies of xenogeneic pathogens have furthered understanding of risks
- Transplantation of pig tissues to humans and primates has not yet resulted in viral infection, even with immunosuppression
- It seems reasonable to initiate carefully monitored clinical trials *when efficacy likely*

"Xenonauts": When to Launch?

- International regulatory guidelines (Changsha)
  - Monitoring of recipient and close contacts
  - Archive cells and serum
- Ethical consent
  - Correct patient
  - No better options
- Scientific basis secure
  - Likely to succeed
  - Likely to be safe
- Public education, consultation

When to proceed: Regulatory

National regulatory body approval

Hospital IRB approval
- Published IXA guidelines
- Address local concerns

Monitoring, oversight
- Each jurisdiction (country) must decide who will do this
- Registry (WHO)
- Archiving (FDA-equivalent)

Crucial step: international consensus

Changsha Communique (2008)

WHA action ~2011

IXA Islet Consensus Statement (2009)

Ongoing comment process in Xenotransplantation

Expert advice ad hoc to review proposed exceptions

"Xenotransplantation is

the future of transplantation…..

and always will be"

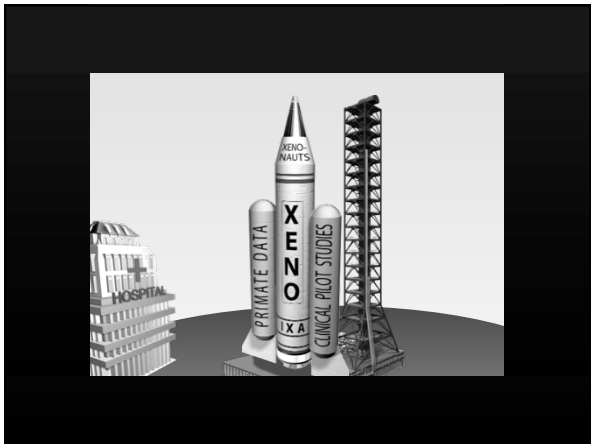
Sir Roy Calne/ Norman Shumway

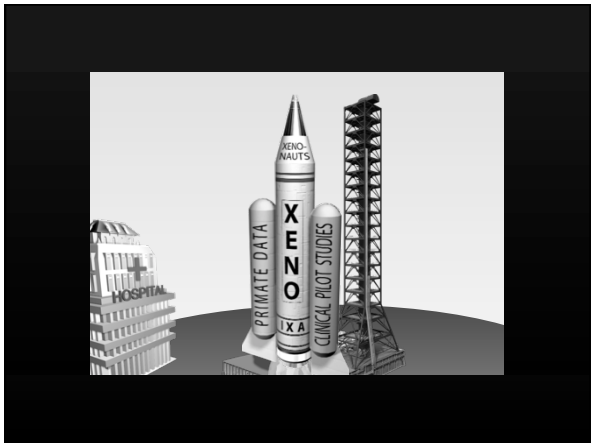
The future

The history tells us that procedures

- **that were inconceivable yesterday,**
- **and are barely achievable today,**
- **often become routine of tomorrow.**

– Thomas E. Starzl, 1982





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What do you think?