ACKNOWLEDGEMENTS

Many previous and current colleagues. Revivicor, Blacksburg, VA.

I have no Conflicts of Interest
“I am sometimes reminded of the differences between a rhinoceros and a cardiac surgeon. One has a thick skin, a small brain, and charges a lot. The other is a large animal that lives in Africa.”

David Wheatley
British cardiac surgeon
AN EXPERT

Definition:
“A guy from out-of-town with slides”
HISTORY OF XENOTRANSPLANTATION
La trasfusione di sangue
I hereby give full permission for left leg amputation and heart surgery on Boyd Rush. I understand that any clots present will be removed from the heart to stop them from going to still more arteries of his body. I further understand that his heart is in extremely poor condition. If for any unanticipated reason the heart should fail completely during either operation and it should be impossible to start it, I agree to the insertion of a suitable heart transplant if such should be available at the time.

I further understand that hundreds of heart transplants have been performed in laboratories throughout the world but that any heart transplant would represent the initial transplant in man.

Signed (for family): [Signature]
Witnessed: [Signature]
Witnessed: [Signature]

January 23, 1966
BABY FAE
it's not easy being perfect—but somebody has to do it.
XENOTRANSPLANTATION

Advantages 1:

1. Unlimited supply of donor organs.
2. Organs available electively.
3. Avoids effects of brain death.
4. Infection-free donors.
XENOTRANSPLANTATION

Advantages 2:

1. Borderline candidates

2. “Cultural” barriers to deceased donation (e.g. Japan)

3. Diabetes mellitus/cell transplants
ISLET TRANSPLANTATION

USA
Type 1 diabetes - 1-2 million
Type 2 diabetes - 30 million
<10,000 suitable deceased human donors/year

*Allotransplantation will never provide enough islets for clinical need.*
The sow, the result of a 10-year breeding programme, takes a nap after giving birth to her huge litter
HUMAN USE OF PIGS

USA: 100 million/year for food.
China: 500 million/year to produce heparin.
Worldwide: 250,000/year for heart valve replacement.
“There are three golden rules for achieving successful xenotransplantation”

Randall Morris
“Unfortunately, we don’t know any of them.”

Randall Morris
“The phylogenetic distance between man and pig comprises 80 million years.”

“We have to outwit evolution.”

Claus Hammer
GENETICALLY-ENGINEERED DONOR PIGS

This is the first time in transplantation that we are able to MODIFY THE DONOR rather than just treat the recipient.
CLINICAL PIG-TO-HUMAN XENOTRANSPLANTATION

Organs (heart, kidney, liver, lung)
Islets
Corneas
Neuronal cells
Hepatocytes
Skin
Red blood cells
BARRIERS TO XENOTRANSPLANTATION

IMMUNOLOGIC
Physiologic
Safety (risk of infection)
Ethical
Regulatory / Legal
BARRIERS TO XENOTRANSPLANTATION

Rejection of a pig xenograft is much more complex than that of a human organ (an allograft).
PROBLEM 1

The *innate* immune response:
- Antibody binding (IgM, IgG)
- Complement activation
- Coagulation dysfunction
- Activation of innate immune cells
- Systemic inflammatory response
PIG XENOANTIGENS

Humans (and NHPs) have ‘natural’ antibodies against 3 carbohydrate antigens:
1. Gal (galactose-\(\alpha 1,3\)-galactose)
2. Neu5Gc (N-glycolylneuraminic acid)
3. Sda
GENETICALLY-ENGINEERED PIGS

1. Knockout of the major pig (antigen) targets

2. Provide protection by transgenic expression of human ‘protective’ proteins (complement- and coagulation-regulatory)
GENETIC ENGINEERING

Knockout of expression of one or more of the known pig xenoantigens.
Human serum IgM and IgG binding to RBCs from TKO pigs

* p<0.05  ** p<0.01

n.s: not significant

Human sera: n=14
GENETIC ENGINEERING

Expression of one or more human complement-regulatory proteins, e.g. CD46, CD55.
GENETIC ENGINEERING

Expression of one or more human coagulation-regulatory proteins, e.g., thrombomodulin, EPCR.
PLATELET COUNTS AFTER PIG HEART XENOTRANSPANTATION

GTKO/CD46/hTBM (n=3)
GTKO/CD46/NoTBM (n=4)
PROBLEM 2

The *adaptive immune* response. Development of T cell-dependent rejection and elicited antibody formation. Directed to the 3 xenoantigens and to other xenoantigens, e.g., swine leukocyte antigens (SLA)
Time after transplantation (days)

Baboon survival (%)

Log-rank

P<0.01

Group A

Group B
CURRENT IMMUNOSUPPRESSIVE REGIMEN

Induction:
ATG 10mg/kg (1 dose) day -3
Rituximab 10mg/kg (1 dose) day -2

Maintenance:
Anti-CD40mAb 50mg/kg (weekly)
Rapamycin (trough level 6-10ng/ml)
Corticosteroids 0.125mg/kg
PIG-TO-NHP KIDNEY Tx

Maximum Survival (Days)

Year

1989 1991 1993 1995 1997 1999 2001 2003 2005 2007 2009 2011 2013 2015 2017
PIG-TO-NHP HETEROTOPIC HEART Tx

Maximum Survival (Days)

Year

PIG-TO-NHP ORTHOTOPIC HEART Tx

Maximum Survival (Days)

Year
ISLET XENOTRANSPLANTATION
RECENT DEVELOPMENTS

‘9-gene’ pigs as the sources of organs

TKO.CD46.CD55.TBM.EPCR.HO-1.CD47
Human serum IgM and IgG binding to RBCs from TKO pigs

* p<0.05   ** p<0.01

n.s: not significant

Human sera: n=14
SERUM CYTOTOXICITY ASSAY

- WT pRBCs
- GTKO pRBCs
- GTKO/β4GalIKO/CMAHKO pRBCs
- Human RBCs (auto)

Cytotoxicity (%)

Final human serum concentration (%)
POTENTIAL PHYSIOLOGICAL PROBLEMS
HYPOVOLEMIA/DEHYDRATION SYNDROME
RAPID PIG ORGAN GROWTH IN FIRST FEW WEEKS AFTER TX
Kidney graft growth

- Kidney graft length (cm)

- Days

Lines represent different grafts:
- B17315
- B17615
- B9313
- B10815
- B5916
1. Pig kidney xenotransplantation in patients whose life-expectancy is less than the time it will take to obtain a deceased human donor organ.
The survival of patients on chronic dialysis in the USA is 42% at 5 years.

Patients aged 65 years with blood group B may wait for >7 years for a deceased human donor kidney.
SELECTION OF PATIENTS FOR FIRST CLINICAL TRIALS

2. Pig heart xenotransplantation in neonates with life-threatening complex congenital heart disease.
The survival of heart \textit{allo}transplants in neonates with life-threatening complex congenital heart disease is almost 60% at 25 years.
As the mean waiting time for a deceased human donor heart in this age group is several months, most neonates undergo palliative surgery with poor results in some patients.

A pig heart would be available whenever needed.
The (limited) experimental evidence available today indicates that a prior failed organ xenograft would not preclude subsequent successful allotransplantation.
“There are many ways of losing money.

Women are the most fun.
Gambling is the fastest.
Research is the most certain.”

Lord Hives
Former Chairman of Rolls Royce
THE FINAL OBSTACLE?
NATIVE AMERICAN PROVERB

“Timing has a lot to do with the success of a rain dance”
“History tells us that procedures that were inconceivable yesterday, and are barely achievable today, often become routine tomorrow.”

Thomas E. Starzl, 1982
XENOTRANSPLANTATION

One day, allotransplantation will be of historic interest only.
THANK YOU