Management of Xenoviral Risks

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Why Consider Xenoviral Risk?

- The need for organs far outweighs the human supply. We must expand our search to meet this need.

The Organ Gap: Supply Cannot Keep Up With Demand

- Last year in the U.S., there were more than 90,000 people on the organ transplant waiting list.
  - 14,488 organ donors were identified.
  - 28,108 transplants were performed.
- Every day in the U.S. approximately
  - 68 people receive an organ transplant.
  - 100 people are added to the waiting list.
  - 18 people die while waiting for a transplant.

Source: The Organ Procurement and Transplantation Network

The Need for Transplant Organs Is Great – and Growing

- Waiting list candidates in the U.S. (as of Oct. 2006)
  - All organs 93,233
    - Kidney 67,988
    - Liver 17,107
    - Lung 2,895

The list grows by 5 percent each year.

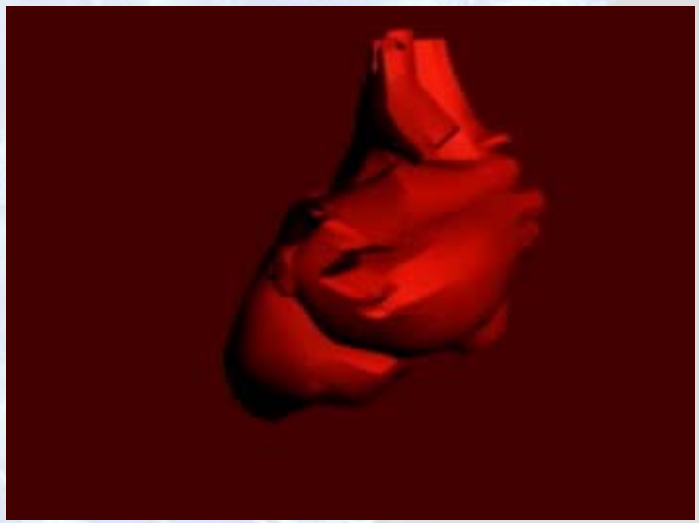
Latent (unreported) demand is estimated to be 10 times as great.

Source: The Organ Procurement and Transplantation Network

Human Resources Are Not Enough

- 47% of all cadaveric organs are deemed unsuitable for transplantation.
- The gap in the demand for vital organs is even greater

Organs	% of need met
Kidneys and livers	50%
Lungs	18%
Hearts	**2%**



Significant Gap in Heart Transplants

→Millions of heart transplants are needed each year.

- Heart disease is the leading cause of death worldwide, accounting for 1 out of every 3 deaths each day.
  - Heart disease is the number one killer in the United States, England and Wales, China, India, and the Russian Federation.
- Heart disease kills nearly 1 million Americans each year, and 2,500 each day.
  - There are 24.7 million adults in the United States living with diagnosed heart disease.

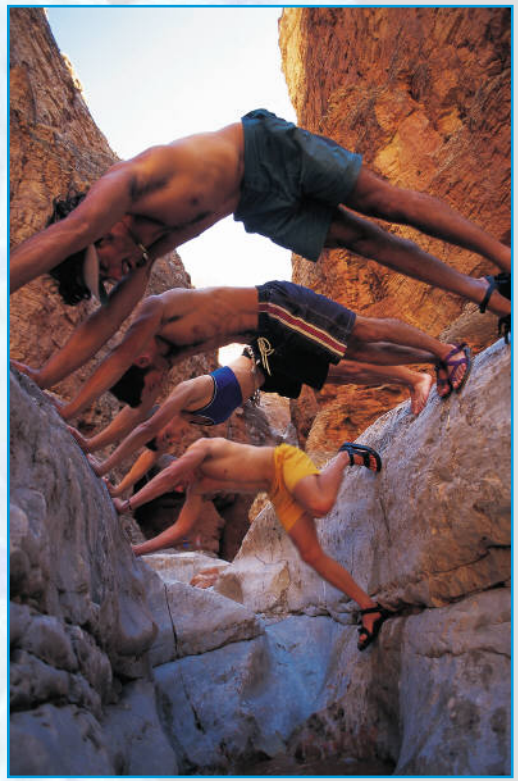
→ Despite the pervasive nature of heart disease, only 2,100 heart transplants were performed in the United States in 2005.

- It is estimated that 39 percent of people waitlisted do not receive a heart transplant.
- 16 percent of patients die while waiting for a heart transplant.

Sources: World Health Organization, Centers for Disease Control and Prevention, National Statistics (London), Scientific Registry of Transplant Recipients (SRTR), AHA Heart Disease and Stroke Statistics—2006 Update

Current Initiatives Aimed at Closing the Gap with Existing Human Resources

- Presumed consent
- Use of organs from persons in persistent vegetative state
- Use of organs from elective ventilated donors
- Use of organs from non-heart-beating donors
- Revisions to allocation criteria and improved infrastructure



Current Initiatives Aimed at Closing the Gap With Technological Innovation

- Initiative: Wholly artificial organs

  Drawback: Functional limitations

- Initiative: Bio-artificial organs (animal organs encapsulated in artificial membranes)

  Drawback: Currently not a realistic long-term replacement for any organ except the pancreas

- Initiative: Bio-engineered organs (organs grown from the recipient's own cells)

  Drawback: Stem-cell efforts still in their infancy

None of These Has Bridged the Gap

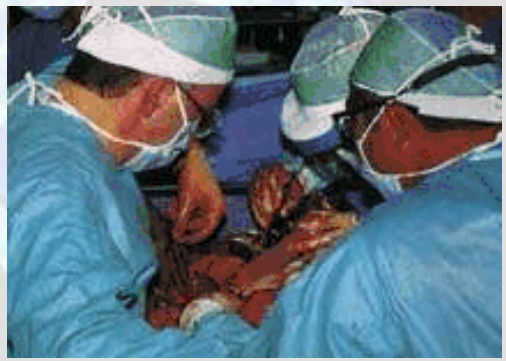
Another Option: Xenotransplantation

Xenotransplantation

- From the Greek xenos, meaning “stranger,” “guest,” or “host”
- Humanized organs are grown within animals and transplanted into humans.
  - Pigs are the only animals being seriously considered as sources.
- Supply of xenografts is unlimited.

“There's nothing mysterious about xenotransplantation. The creation of transgenic animals is a movement toward making pig organs look to the human immune system like an allograft or like the profile of a non-cytopathic organism. That means those mechanisms we described in 1998 will apply to xenotransplantation. I did not expect it to be the case even two years ago, but xenotransplantation will probably be on the clinical map in my lifetime — which isn't going to be long!”

- Thomas E. Starzl, MD, PhD

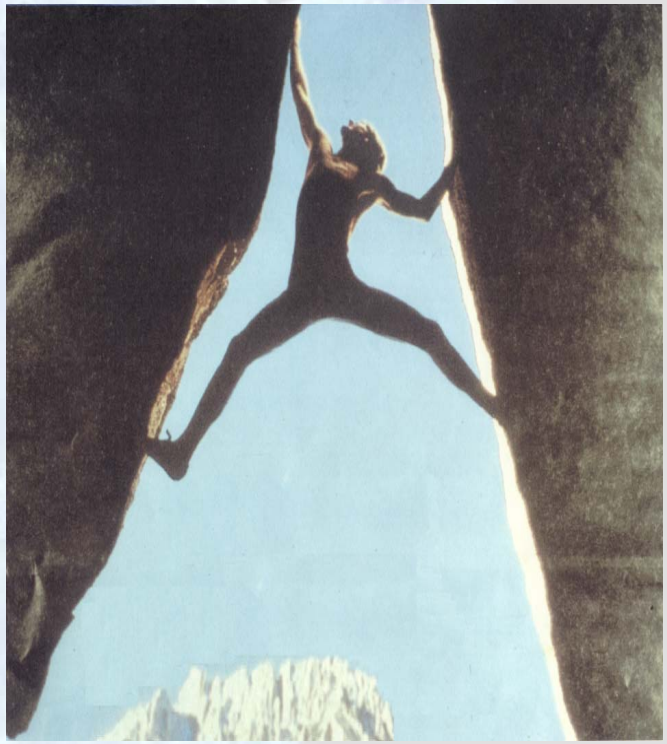


Advantages of Xenotransplantation Over Other Alternatives

- The science of xenotransplantation is comparatively advanced.
- Xenotransplantation has the potential to satisfy latent organ demand in the short term.
  - Possible to meet demand for heart, liver, kidney, and pancreas transplants within five years

A Steep Hill To Climb

- **The Catch-22:** Xenotransplantation may not deliver in the foreseeable future, but funding opportunities require emphasizing the bright side.
  - Advocates for gene therapy and stem cell biology have encountered a similar dilemma
- Before initiating fundraising, we need to demonstrate that xenotransplants are capable of prolonging meaningful life.



Xenotransplantation: Successes and Failures

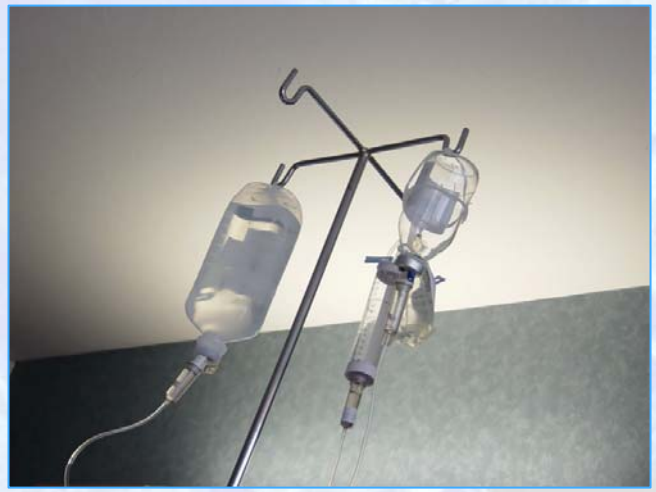
Stage 1

- Hyperacute Rejection
  - Pre-formed xenoreactive antibodies
  - Damage occurs in minutes
  - Can be addressed in two ways:
    - Genetic modification of animal donor organs
    - Transgenic animal genes (results in organ “de-animalization”)
- Perceived Threat of Xenogeneic Diseases
  - Zoonotic (animal-to-human) diseases arising from xenotransplantation
    - No zoonoses have yet occurred as a result of xenotransplantation.
    - Future risk must be measured and weighed.

Xenotransplantation: Successes and Failures

Stage 2

- Delayed Xenograft Rejection (DXR)
  - 1-5 days post-xenografting
  - Graft-induced xenoreactive antibodies
- Success in Combating DXR
  - Short-term therapy with immunosuppressive drugs



Xenotransplantation: Successes and Failures

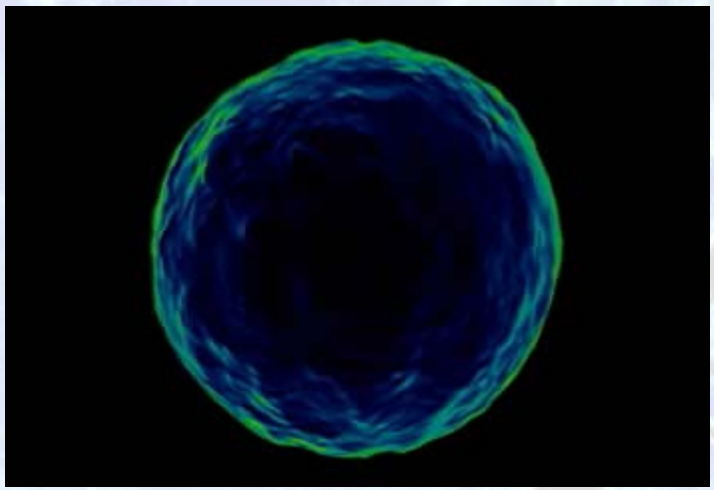
Stages 3 & 4

- Acute Cellular Rejection
  - Abrupt cytotoxic attacks by T-cells on organ lining
  - Addressed with cyclosporine or FK-506
- Chronic Rejection
  - Scarring and fibrosis lead to organ death.
  - Close vigilance and selective immunosuppressive drugs extend organ survival.

Xenotransplantation is a realpolitik and realtechnik solution to closing the organ gap.

With Brave New Organs Come Brave New Problems

Worst-case scenario:
Xenografts Causing New Epidemics

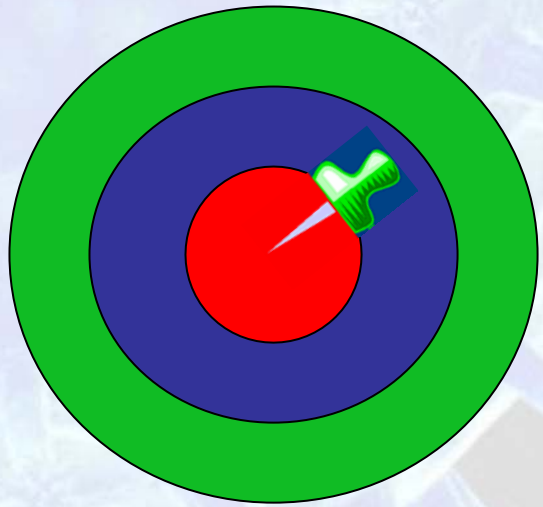


Exposure to Animal Viruses Poses Unknown Risk

- Xenogeneic disease would not occur without xenotransplantation.
  - Primate viruses
  - Porcine endogenous retroviruses
- Theory alone cannot tell us if this risk would be greater or lesser based on phylogenetic proximity to man or based on type of pathogen.

Pinpointing a Threat

- **Zoonotics:** Pathogens that afflict humans from non-human animal sources.
- **Xenogeneics:** Pathogens that afflict humans from non-human animal transplant sources.
- **Xenovirals:** Viruses, including pro-viruses and retroviruses, that afflict humans from non-human animal transplant sources.



Zoonosis Timeline

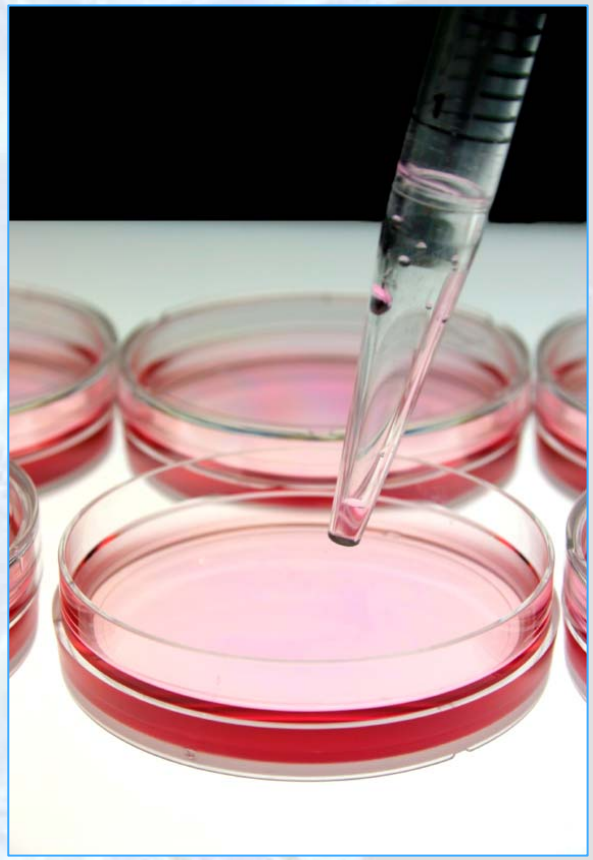
5 million B.C.	East African hominids descend from trees to the savannah; first exposure to mosquito-borne pathogens.
2.5 million B.C.	Meat becomes part of human diet, and animal skins are used for clothing; contact with more animal diseases.
80,000 B.C.	Humans migrate out of Africa, come in contact with new wildlife diseases.
8000 B.C.	First zoonotic infections appear in early agrarian societies: measles, TB, smallpox, influenza, pertussis.
430 B.C.	“Plague of Athens” (perhaps the measles) described by Greek historian Thucydides.
165 A.D.	“Antonine Plague” (smallpox) arrives in Rome; 5 million people die.
542-543	“Justinian’s Plague” (bubonic outbreak spread by rats) travels from Constantinople to Eastern Europe; one-third of eastern Mediterranean population dies.
1347-50	Black Death spreads when Mongols invade trading ports along Black Sea; one-third of all Europeans – 20 million people – perish.

Zoonosis Timeline

1520-1618	Stricken soldier in Cortés's conquering army triggers smallpox epidemic in Mexico's Aztec population. In less than 100 years, population decreases from 20 million to 1.6 million.
1650-1660s	European plague causes 300,000 deaths in Naples, 70,000 deaths in London and 50,000 deaths in Amsterdam.
1862	Steamship carrying passenger with smallpox arrives in British Columbia, triggering outbreak that kills 30,000 Northwest Indians.
1918-1919	Spanish influenza responsible for 60 million deaths worldwide.
1976	Ebola virus, one of the deadliest diseases known to man, is identified in Sudan and Zaire.
1984	U.S. researchers identify HIV, the virus that causes AIDS. To date, 25 million people have died from AIDS, and 40.3 million people worldwide are living with it.
1999	First known human case of West Nile virus in the Western Hemisphere. By 2006, 47 U.S. states have reported such cases.
2002	Severe acute respiratory syndrome (SARS) originates in southern China. In one year, the disease causes 774 deaths, mostly in Asia.
2003	First case of monkeypox reported in U.S. More than 70 people in six states fall ill from this rare disease of central and western Africa, most after having contact with pet prairie dogs.

Theoretical Risks, But…

There is no evidence of xenogeneic diseases caused by transplanted animal tissues or cells.



The Crucial Question

- Does the new medium of transmission involved in xenotransplantation meaningfully increase the zoonotic threat to public health above and beyond that which already exists?
- Are the potential benefits worth the increased risk?

Acceptable Regulatory Safeguards

- UK
  - UK Xenotransplantation Interim Regulatory Authority (UKXIRA), Kennedy Report
    - Primates should not be used as source animals
    - “Lifelong surveillance and agree never to have children”
      - Recommendation for xenograft patients

- USA
  - Food & Drug Administration (FDA)
    - Clinical hold placed on xenotransplantation until reasonably assured it could be carried out safely

Lessons Learned

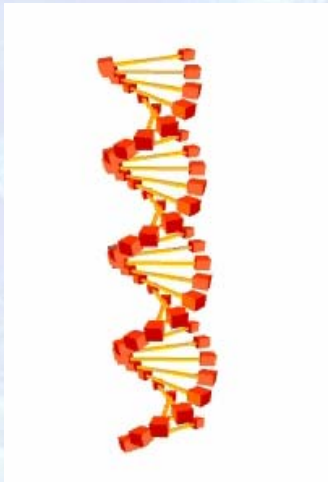
- The debates over antibiotics and recombinant DNA help shed light on the ethically appropriate course to follow in the realm of xenotransplantation technology.

"Don't forget to take a handful of our complimentary antibiotics on your way out."

The Recombinant DNA Precedent

- Today, there are many agricultural and medicinal products born of recombinant DNA.

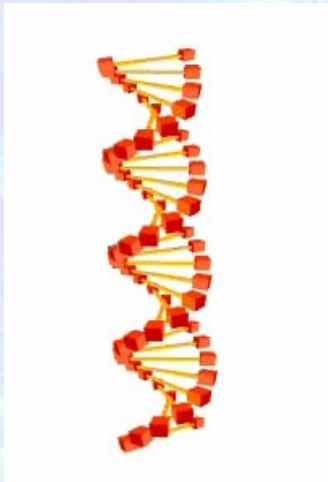
NO new diseases have been created.



The Bottom Line

- The risk of creating new infectious diseases in man cannot automatically pre-empt a new medical technology.

We tolerate risks for the sake of benefits.



Asilomar

- Conference, February 24, 1975
- Organized by National Academy of Sciences
- Aimed at answering one question:

How does society know whether or not endangerment of public health will occur?

Answer:

There was no way to know whether or not well-meaning genetic engineering experiments could produce unanticipated, malevolent results.

What Asilomar Gave Us

- Asilomar left a twin legacy:
  - Practical precedent for managing a new bio-threat (via levels of isolation and containment)
  - Practical precedent for managing a new bio-technology (via open discussion along with a willingness to sacrifice scientific freedom for social security)

What Asilomar Gave Us

- Isolation and containment rules will prove to be essential for managing the risk of xenoviruses.
- However, of commensurate importance, xenotransplantation freedom will have to be sacrificed to satisfy global demands for the safety of public health.
- Furthermore, that sacrifice will only be accepted by the public if it is debated with the same spirit of openness that was present at Asilomar.
- The new social contract baptized at Asilomar resonates well with the xenotransplantation ethics debate.

Moving Forward from Asilomar

- The antidote developed at Asilomar is that a double-defense of **isolation** and **containment** provides adequate protection against the hubris of biotechnology.
  - Isolate anything thought to be harmful from the environment where it can cause harm (e.g., outside a laboratory)
  - Contain anything that might be harmful in a way that gives it only a remote chance of surviving where it could cause harm

Addressing the Risks of Xenotransplantation

- It is helpful to apply Reschler's three cardinal rules of risk-taking in summarizing the risk assessment **"calculus."**
  - Maximize Expected Values
  - Avoid Catastrophes
  - Dismiss Extremely Remote Possibilities
- We apply these in reverse order to match everyday experience.

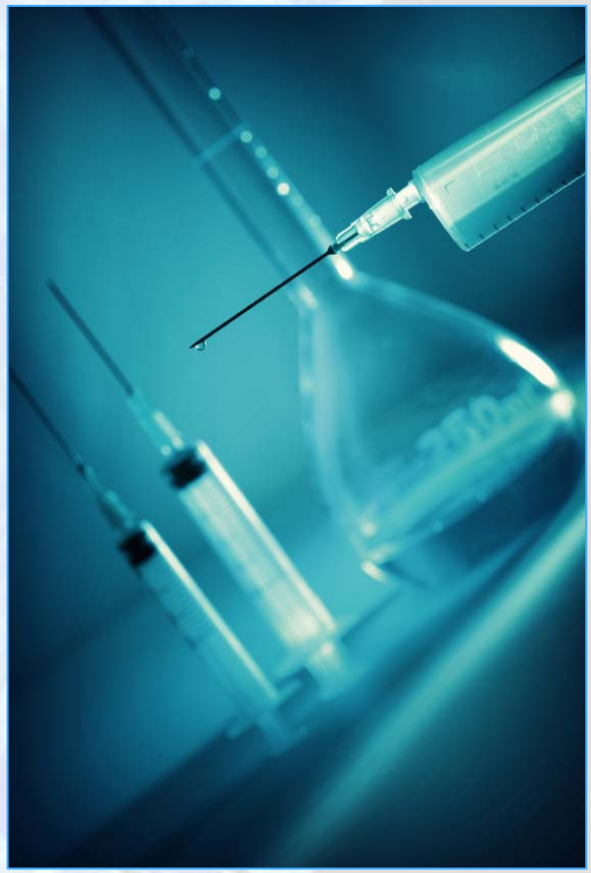
The Double-Defense for Xenotransplantation

Isolate xenograft animals from anything thought to be harmful to the human environment, such as known viruses, harmful bacteria and other pathogens (e.g., xenograft herds must be from specified pathogen-free sources)

Contain any xenograft that might be harmful so that it has only a remote chance of transmission into society (e.g., do not permit xenograft recipients to donate blood)

What Needs to Be Done?

- Xenotransplantation can be risk-managed with the understanding that it provides antibiotic-like health benefits but is susceptible to Asilomar-type regulation and control.



Getting It Done

- A global plan must be contemplated from the start to manage the risks of xenotransplantation and xenograft-borne viruses.

Is Xenotransplantation Worth the Risk?

- It can be expected that the benefits to public health from xenotransplantation will far exceed any harm it inflicts.
- For these reasons, it is worth the risk — especially given the all-important goal of delivering optimum human health to millions of people suffering from end-stage organ failure.

Recognizing a Global Risk

- Because viruses **“need no passports,”** the conflict between public and private interests in xenotransplantation cannot be resolved solely on a national level.
- Xenotransplantation, like antibiotics and recombinant DNA, poses global dilemmas.
- Consequently, any debate goes beyond bioethics — a geoethical solution is needed.

Proposing a Geoethical Solution

- Xenotransplantation in the U.S. and Europe creates a risk of unleashing an AIDS-type epidemic on the world.
- Applying the Asilomar learnings of isolation and containment to xenoviruses requires at least a basic, surveillance-competent, global health care system.

Pursuing an Open-ended Search

- A number of international surveillance systems were chartered with the rare mission of pursuing any and all zoonoses, but are limited to specific diseases and subsets of countries.
  - Centro de Epidemiologia Molecular/Network for Epidemiologic Tracking of Antibiotic-Resistant Pathogens (CEM/NET)
  - WHO Collaborating Center for International Monitoring of Bacterial Resistance to Antimicrobial Agents
  - WHO Gonococcal Antimicrobial Surveillance Programme
  - SENTRY Antimicrobial Surveillance Program
  - DoD Global Emerging Infections Surveillance and Response System
  - Antibiotic Resistance and Emerging Susceptibility Patterns in Europe (ARTEMIS)
  - Eurosurveillance
  - European Community Human Salmonella Surveillance Project (Salm-Net)
  - The Alexander Project
  - Infectious Disease Early Warning System

→A system is needed to transcend national ties and to break international boundaries.

Introducing GEOX

GEOX = Global Enforcement Organization for Xenobiology

Mandatory implementation of Asilomar-type isolation and containment procedures in the context of public health and xenotransplantation

Why GEOX?

- When medical technology has a global impact, the individual-focused norms of bioethics must be trumped by a new set of world-focused norms.

Thus, the creation of GEOETHICS

GEOX Can Be Implemented in 7 Years

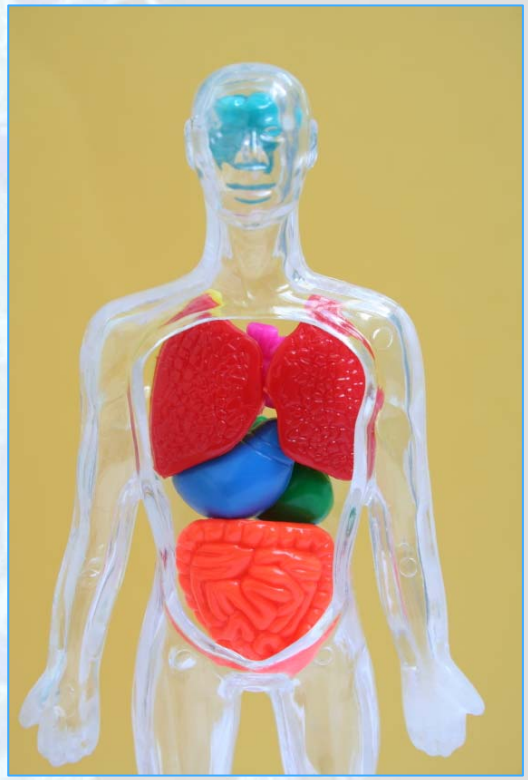
Year 1 Sentinel participants organize themselves:	• At their own annual meetings and/or via correspondence
Year 2 Sentinel participants converge on the basics:	• "Strawman" treaty to serve as a focus for discussions; • A meeting schedule for participation sectors; • Obtaining "seed funding" to cover start-up expenses.
Year 3 Sentinel participants announce a schedule of meetings:	• "Strawman" treaty provisions and information distributed • Announcement is made in many major publications.
Year 4 Intra-sector participant meetings held per registration procedures:	• Positions adopted on "strawman" treaty provisions • Sector representative elected by super-majority voting.
Year 5 All sector participant meetings held per registration procedures:	• Decisions taken by practical discourse among nine representatives; • Decisions informed by continuous input from all participants.
Year 6 National treaty ratifications occur and GEOX is formed.	
Year 7 Consolidation of GEOX	

What Is GEOX Charged With?

- Best-Possible Activities
  - Certify pathogen-free acceptability of donor animals
  - Certify compliance with xenograft recipient monitoring rules
  - Determine ethical acceptability standards for donor animals
  - Ensure equitable global participation in xenograft recipient pool
  - Conduct public health-based global surveillance for emerging bio-threats

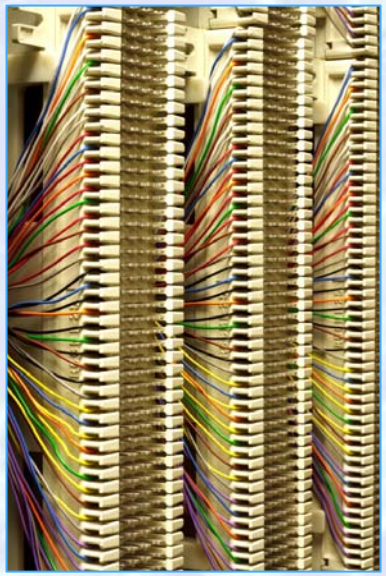
GEOX Tasks

- Certify that porcine organs used in xenografts are from specified pathogen-free herds that are raised and sacrificed in an ethical manner
- Require that acceptance criteria for xenograft programs are globally inclusive and based on informed consent adequate to cover post-operative monitoring and quarantine, if necessary



GEOX Tasks

- Conduct in-country surveillance for incipient signs of new zoonotic disease via national monitoring programs, or if adequate, new health care stations
- A global network of public health stations—where existing public health infrastructure is lacking—is not a utopian luxury in the context of xenotransplantation.



One Necessitates the Other

- Xenotransplantation needs to exist because people cannot donate enough hearts.
- GEOX needs to exist because, without it, xenotransplantation will be carried out selfishly and ultimately to the detriment of the entire human population.

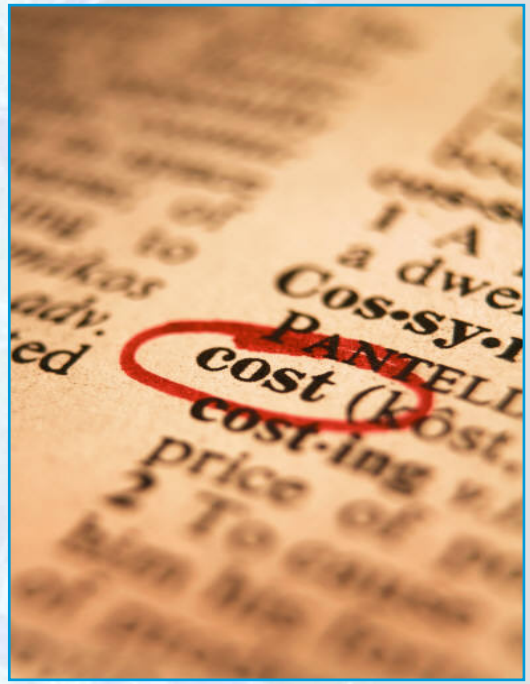
Global Public Health Surveillance Is Not Free…

GEOX Surveillance	$13,000,000,000
Xenograft Tax	$13,000 / organ @ 1M operations per year

- To bear the burden of this cost, there would be a necessary “xenograft tax” paid to GEOX of $13,000 per organ at the demand rate of one million operations per year.

The Xenograft Tax

- $13,000 per xenograft is a fair approximation of the price of managing the global risks imposed by xenotransplantation.
- The xenograft tax would be most logically levied on the pharmaceutical companies selling the xenografts — a kind of global sales tax.



An IPO Model

- GEOX would have the necessary prerequisites for a successful IPO under the following circumstances:
  - A GEOX Treaty to secure exclusive rights to authorize xenografts
  - Immunization from liability
  - The right to tax xenografts

Scenario for a Successful IPO

- If estimated future revenues are $13 billion/year and profits each year reflect a percentage of future revenues…

…then the net present value (NPV) of that profit stream would be in the billions several years prior to the actual revenues.

→With a successful IPO, GEOX could raise $1 billion by just selling 30% of itself to the public to fund start-up costs.

GEOX Funding

- GEOX uses the tax funds to pay the expenses of:
  - Xenograft certification teams
  - In-country basic health care stations (established in a rational sequence based on need and feasibility)
  - Managing a global registry of xenograft recipients
  - Global waiting list for developing country access to 5-10% of xenotransplantation procedures

GEOX Funding

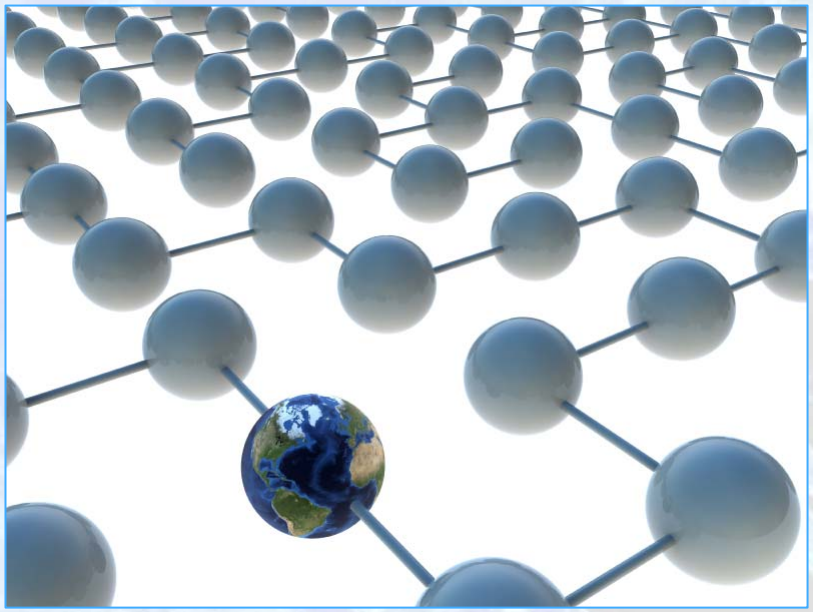
- Pharmaceutical companies charge health care payors (e.g., governments or health insurance companies) a fee for each xenograft, including tax.
- Health care payors indirectly pass costs on to the general public via general taxes or health insurance premiums.
- Effectively, individuals in xenotransplanting countries pay a slightly larger percentage of their disposable income for health care services in return for:
  - Availability of xenotransplantation
  - Meeting an obligation of funding basic health care worldwide through a xenograft tax

Legal Considerations for GEOX

- GEOX Treaty can achieve validity only by being authored by the same entities to which it will apply and affect.
- This could be accomplished through the identification and empowerment of “Sentinel Organizations.”
  - International Xenotransplantation Association
  - International Society of Heart and Lung Transplantation

It’s Not the First Time…

- GEOX would not be the first world organization empowered to control an important aspect of human affairs.
  - In 1866, the Telegraph Union (now the International Telecommunication Union) was empowered to control global use of electromagnetic frequencies.



GEOX Can Be a Reality

- The substantive financial and legal elements of a global enforcement organization for xenobiology are practically achievable.
- The costs of xenotransplantation are high, but the value of life is much higher still.

GEOX Is Imperative

- If society is unwilling to incur the cost of GEOX — then it cannot morally breach the barrier of xenobiology.

Organ Transplantation, 2021

- 100% of all xenogeneic organs are deemed suitable for transplantation.
- The surplus in organs available for transplantation continues to grow:

Region	Organs	Organ Needs Satisfied in 2007	Organ Needs Satisfied in 2021
US/EU	Livers/Kidneys	<50%	100%
	Lungs	<18%	100%
	Hearts	<2%	100%
ROW	Livers/Kidneys	<1%	>10%
	Lungs	<1%	>10%
	Hearts	**<1%**	**>10%**