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Some Past Lessons from HIV/AIDS Research and Prospects for Eliminating the Virus

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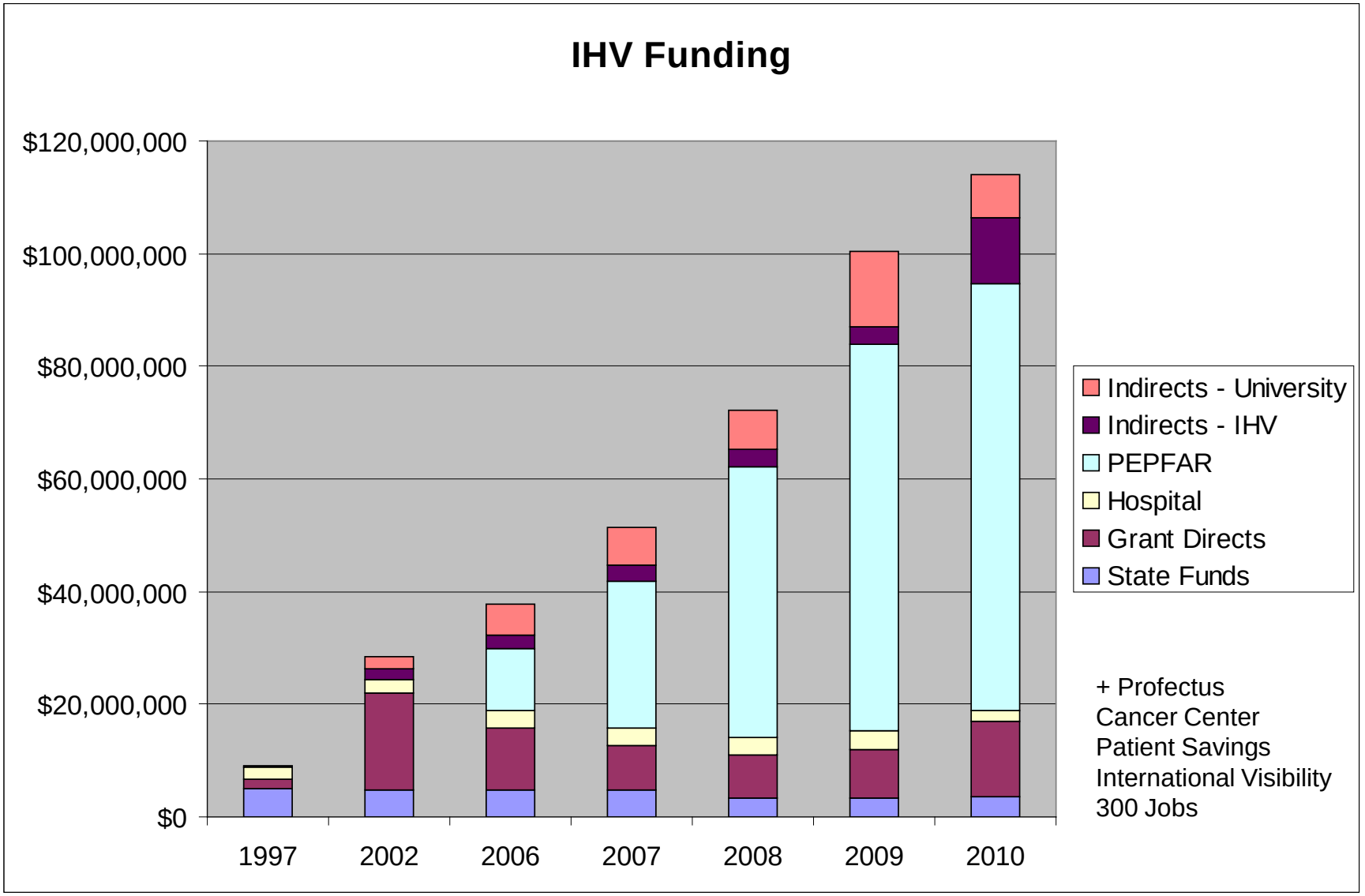
But first a bit of history about the Institute of Human Virology (IHV):

- **Formed 15 years ago (1996) with help from city, state, hospital, Abel foundation, and special individuals such as Stewart Greenebaum.**
- **IHV has an Advisory Board from its beginning—chaired by Stewart first and then and now by Kathleen Kennedy Townsend. We owe them much.**
- **A few years ago joined the new Dean, Al Reece, in the School of Medicine, moving from the "old" UMBI.**
- **Began with about 6 scientists from the Federal Government (National Cancer Institute and US Army Walter Reed program). None of us could come with any money in contrast to scientists who come from academic centers.**
- **From original group we have expanded to over 300 people, and from base support funding IHV is now an institute of about $115 million per year and 97 % is from external funding.**

Maryland's Return on its Investment

IHV's Budget has grown to $116 M



Major Interests at IHV: AIDS and Cancer

- **HIV basic research in search of better therapies**
- **Application of current anti-HIV therapies locally and in places abroad in need of help**
- **HIV Preventive Vaccine (coming later in this report)**
- **Some other viruses and diseases they cause**
- **Cancer Research: we became one of the 5 programs of the Greenebaum Cancer Center with our focus on viruses that play a role in human cancer.**

…and a bit of history on my interests:

- **Began and remains in the biology of human blood cells both normal and abnormal-- as in too many cells such as in leukemias/lymphomas or too few as in AIDS, but..**
- **My pathway was and is through a study of viruses.**
- **I focused on a special class of viruses known at first only in animals. They are called retroviruses.**
- **I focused on them because in animals they are a major cause of leukemia and other blood cell abnormalities.**
- **But the vast majority of scientists, including leaders in the field at the time, did not believe humans were infected or even could be infected by retroviruses. However…**
- **In 1979-80 we discovered the first one, known as HTLV-1 or Human T-Cell Leukemia Virus-1 and along with Japanese scientists showed it causes Adult T-Cell Leukemia. Others showed it also causes fatal neurological disease. In "82 we discovered the 2nd one (HTLV-2).**
- **In 1981-82 we developed blood tests for the HTLVs which later became required tests for preservation of the blood supply in the U.S., Japan and still later in some other countries.**

The Essential Role of the Studies with HTLV-1 and 2 for the Discovery of HIV

- **Convinced scientists that humans could be infected by aretroviruses.**
- **Gave us the IDEA that AIDS was likely caused by a virus of the same general class, i.e., a retrovirus.**
- **Provided the KEY TECHNOLOGY for finding HIV…..**
- **Namely how to grow human T-cells (the TARGET cells of HIV) in the laboratory. This is a necessary step for finding the virus, and was based on our discovery (1976) of a substance known as Interleukin-2 (IL-2) as well as sensitive techniques we developed for detecting this kind of virus and first applied to the finding of HTLV.**
- **This ultimately also gave us the ability to scale up HIV production—enabling the critical and life saving HIV blood test and providing a system to test drugs for therapy against HIV.**

WHAT WAS IT LIKE AT THE BEGINNING (1981-84)—

IF HIV/AIDS HAD TO COME

IT WAS THE BEST OF TIMES-
IT WAS THE WORST OF TIMES

It Seems that Humans Have Only a 25 to 30 Year Memory Span

- **Think of the great flu (influenza) epidemic of 1918-1919.**
- **Polio of the early 1950s.**
- **HIV of 1981----**

REMARKABLE BIASES OF THE RECENT PAST

1. **“Infectious diseases are over in the industrialized world, therefore . . .”**

2. **“Retroviruses do not infect humans and there are many reasons for this . . .”**

3. **“No viruses cause cancer in man.”**

IN THE EARLY 1980s THE BIASES WERE SHATTERED

1. **Viruses shown to be the cause of ~20% of human cancers.**
2. **Retroviruses discovered in humans, shown to cause some leukemia's and neurologic diseases HTLV-1 1980 and HTLV-2 1982.**
3. **One of the great pandemics of history (AIDS) appears and is caused by another retrovirus.**

AIDS IS RECOGNIZED IN I981

AND IN 1981-82 CDC EPIDEMIOLOGY SUGGESTS A NEW INFECTIOUS AGENT- THIS IS THE FIRST SCIENTIFIC CONTRIBUTION

WHAT IS THE ORIGIN OF THE VIRUS?

OF THE EPIDEMIC?

AND HOW WAS IT FOUND AND LINKED TO AIDS? (to follow)

IDEAS FOR THE CAUSE OF AIDS BEGIN IN 1982, SOME OF THE NOTABLE THEORIES:

Non-Infectious

1. **"Poppers": 1982→1988 (FDA)**
2. **Autoimmunity to autologous leukocytes: 1982-1983 (NIH)**

IDEAS FOR THE CAUSE OF AIDS BEGIN IN 1982, SOME OF THE NOTABLE THEORIES:

Infectious

1. **A specific Adenovirus: 1982-1983 (Albert Einstein Univ.)**
2. **A specific EBV :– 1982-1983 (several groups)**
3. **A specific CMV :-1982- 1983 (several groups)**
4. **Mycoplasma: 1983-1986 (Walter Reed)**
5. **A new Fungus: early 1984 (NIAID)**
6. **A new, HTLV related retrovirus: 1982-1984 (NCI, Harvard)***

Ridiculous

There is no cause and really no AIDS (Duesberg) 1984 to eternity

***What is HTLV?**

HIV WAS FOUND IN EARLY 1983 AND

- **LINKED TO AIDS AS THE CAUSATIVE AGENT IN LATE 83 EARLY 84**
- **GROWN IN CONTINUOUS CULTURE LATE 84 AND**
- **BLOOD TEST DEVELOPED IN EARLY 84**
- **KEY TECHNOLOGY THAT WAS NEEDED FOR ALL HIV FINDINGS WAS REVERSE TRANSCRIPTASE FOR DETECTION AND INTERLEUKIN-2 (IL-2) FOR CULTURING (GROWING) T CELLS FOR VIRUS ISOLATION AND PROPAGATION.**

FINDING THE VIRUS WAS ONE THING, BUT SHOWING CAUSATION WAS ANOTHER. AIDS PRESENTED UNIQUE CHALLENGES UNLIKE PAST VIRAL EPIDEMIC OR THE RECENT SARS OUTBREAK:

1. **Clinical latency of 5-15 years**
2. **Multiple other microbial infections (which one was causative?)**

FREQUENT DETECTION OR ISOLATION OF VIRUS (A TOTAL OF 48 ISOLATES FROM 48 DIFFERENT PATIENTS IN OUR FIRST REPORT FROM NCI IN 1984 AND 105 ISOLATES IN OUR EARLY 1985 REPORT) AND ADDITIONAL ISOLATES FROM PARIS WERE STILL NONETHELESS PROBABLY INSUFFICIENT TO CONCLUDE THAT …

…HIV WAS THE CAUSE OF AIDS BECAUSE VERIFICATION IS NECESSARY, AND VERIFICATION WOULD BE DIFFICULT SINCE:

1. **Tissue specimens were limited and not allowed in some institutions.**
2. **T cell culture technology was not widely available in virology labs at this time.**

The consequence was that very few groups could be soon involved.

FALL OF 1983- A KEY ADVANCE

Capacity for continuous cell line culture of 6 of our 48 isolates of HIV made many things possible:

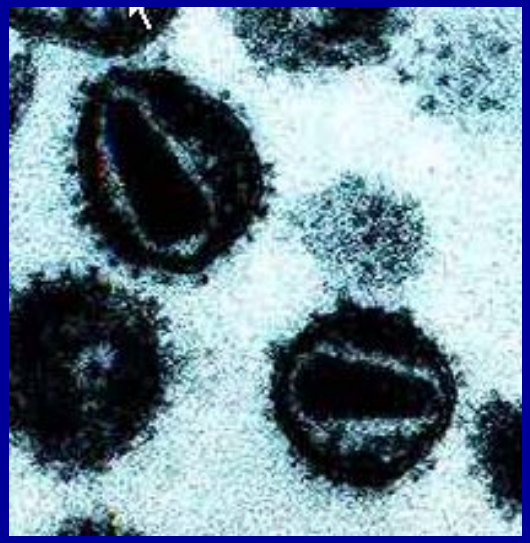
e.g., blood test, drug screening, detailed molecular analysis of HIV genes and proteins, etc.

THE BLOOD TEST WAS ESSENTIAL NOT ONLY FOR MAKING THE BLOOD SUPPLY SAFE, AND FOR ALLOWING THE EPIDEMIC TO BE APPROPRIATELY FOLLOWED FOR THE FIRST TIME, BUT ALSO FOR VERIFYING ETIOLOGY BECAUSE:

- The blood test was safe to work with
- " " " " simple " " "
- " " " " sensitive
- " " " " accurate
- " " " " inexpensive
- " " " " rapid

Thus, verification of HIV as the cause of AIDS was almost instant; it enabled surveys of thousands of sera samples globally. BUT THERE WERE UNNECESSARY DELAYS IN ITS APPLICATION TO BLOOD BANKS WHICH COST MANY LIVES.

Riddle: How is



like

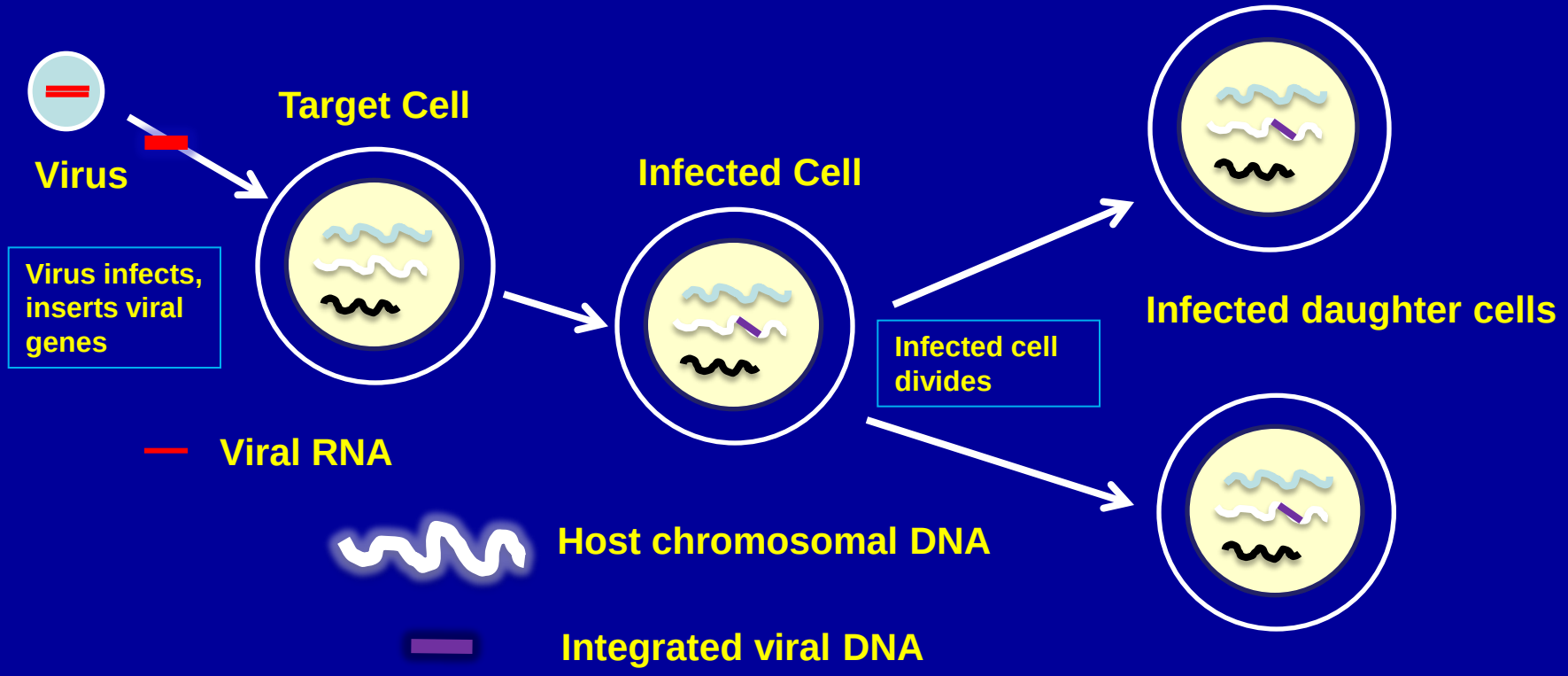
?

What is Special About a Retrovirus?

- **When It Infects Our Cells The Infection Is Always Permanent.**

- **It Does This BY Integration Of Its Genes Into Our Chromosomal DNA.**

Retroviral Infection: Permanent for the Life of the Infected Cell and all its Daughter Cells



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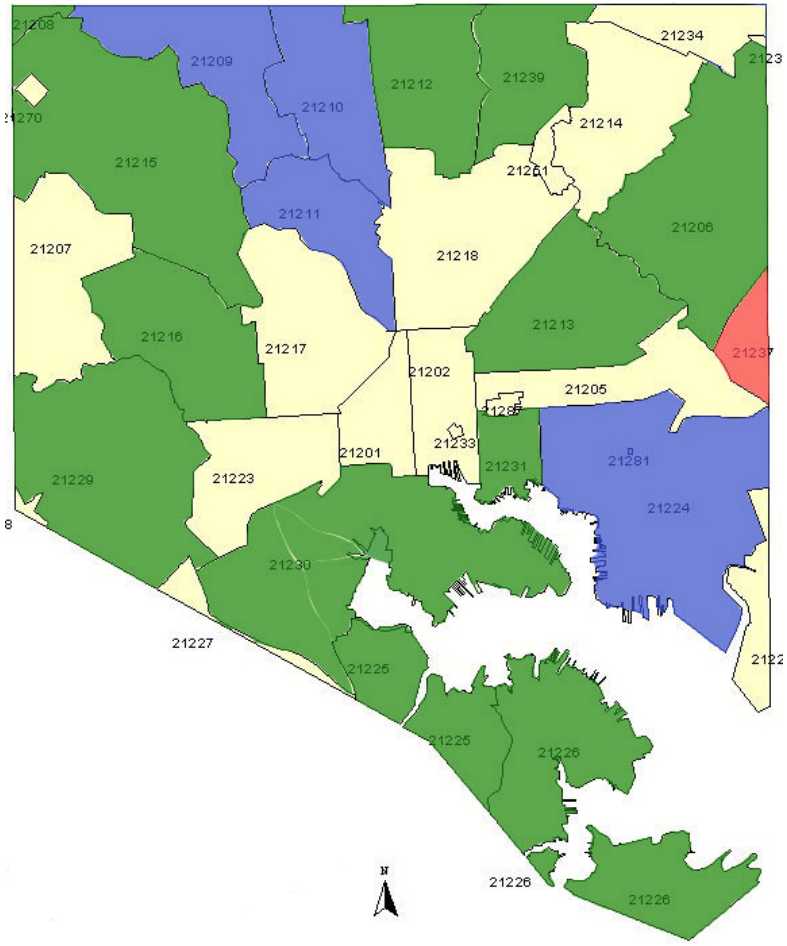
What is the Epidemic today?

- Globally---about 60 million infected and about 30 million died

- Locally—Baltimore and DC have been in the top 5 cities in the U.S. for the past 10 years

HIV in Baltimore City

- > 1%
- > 0.2% and < 1%
- > 0.1% and < 0.2%
- < 0.1%



Rates of HIV in Some Baltimore Zip Codes are as high as general population rates reported in Africa.

IHV's Baltimore Clinics

IHV treats 5500 HIV patients in 9 clinics throughout Baltimore

- Up from 500 patients upon inception
- Maryland's largest African American AIDS clinic
- The Jacques Initiative provides cutting edge treatment adherrance models
- Project Shalem involves the faith-based community towards testing thousands
- Significant healthcare $$ savings result from proper HIV care

Major Practical Advances from HIV Research to Date are:

1) Blood Test-1984

2) Anti-HIV Therapy-1986 first with AZT and then 1994-96 with the Combination of Drugs

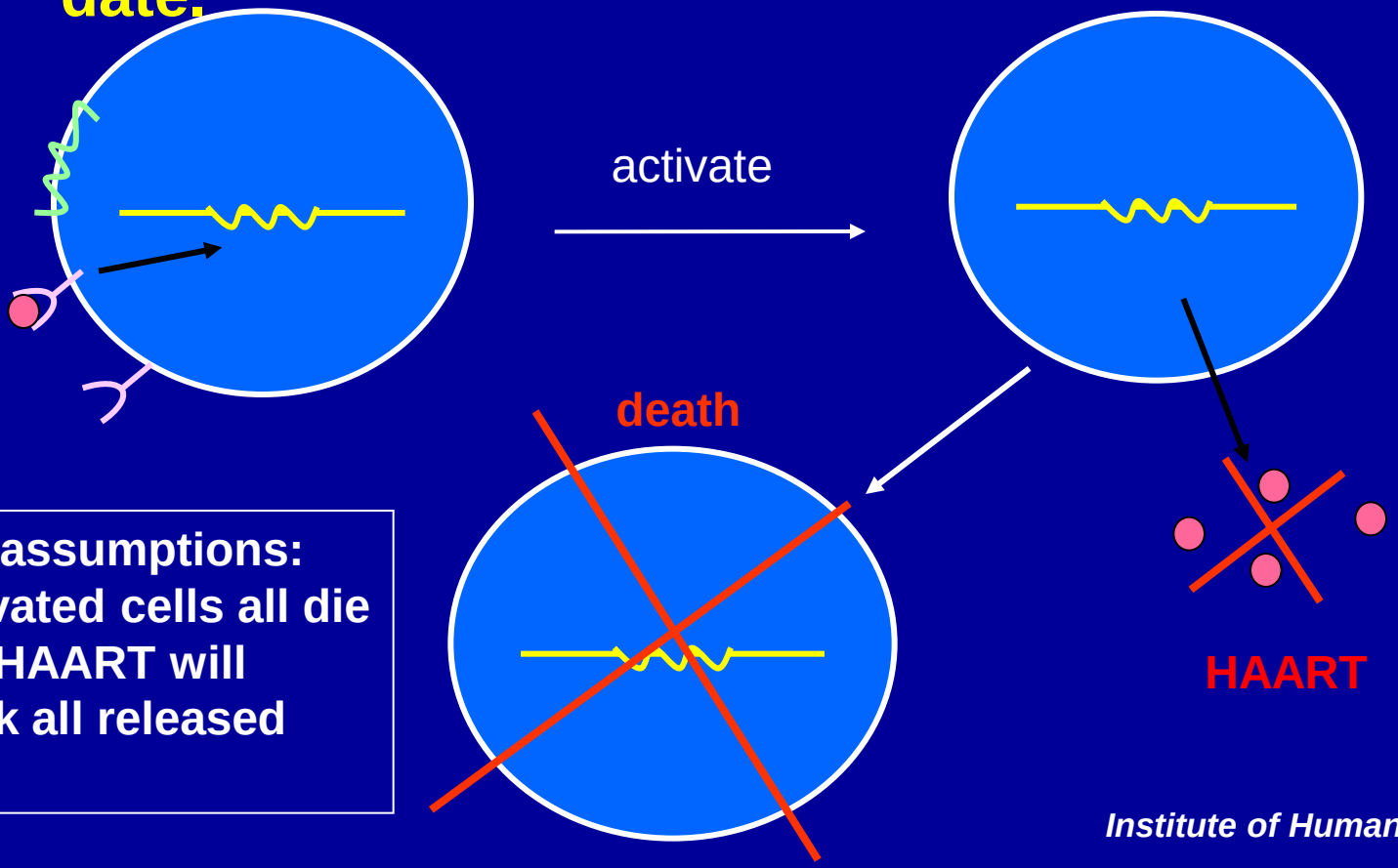
NEEDS FOR THE FUTURE

- **TRYING TO REACH A CURE.
- BRINGING THERAPY TO THOSE IN NEED.
- THE ULTIMATE---ELIMINATING HIV.

**Why is reaching a cure so difficult?

Because of latently infected cells--the“Reservoirs”

What to do? Activate cells and pray for cell death and suppression of any reinfection? No real advances to date.



Two assumptions: Activated cells all die and HAART will block all released HIV

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BRINGING PROPER ANTI-HIV THERAPY TO THOSE IN NEED

THE PEPFAR PROGRAM NOW REACHES OVER 5 MILLION PEOPLE IN AFRICA:

The Institute of Human Virology is involved in care and/or treatment of more than 500,000 patients in 9 African and 2 Caribbean nations. However, this has to be increased and sustained. There is little assurance that this will be the case.

So cures or elimination of HIV is mandatory.

ELIMINATING HIV/AIDS

- **EDUCATION—NECESSARY BUT FAR FROM SUFFICIENT.**
- **MICROBICIDES-RECENT POSITIVE RESULTS SUGGEST THIS WILL BE HELPFUL –BUT SEVERAL CAVEATS: STUDY WAS CONDUCTED IN AN ENVIRONMENT WITH MEDICAL EXPERTS. ALSO COULD LEAD TO DRUG RESISTANT VARIANTS.**
- **CHEMOPREVENTION—A CONCEPT NOW GETTING INCREASING ATTENTION WITH STUDIES ONGOING (TARGET AT RISK POPULATIONS). WILL LIKELY WORK, GET HEADLINES, BUT LOTS OF LIMITATIONS, GREAT COSTS IF WIDELY APPLIED, AND NOT WITHOUT HAZARD.**
- **PREVENTIVE VACCINE--THE ULTIMATE SOLUTION–**

PREVENTIVE VACCINE

- **I BELIEVE IT IS DOABLE (the modestly successful Thai Trial with US Army adds to this view).**

- **THE DIFFICULTIES**:
  (a) **VARIABILITY OF HIV AND**

  (b) INTEGRATION OF ITS GENES INTO THE TARGET CELL DNA UPON INFECTION (NOT ALWAYS APPRECIATED IN MOST PRIOR VACCINE TRIALS.)

  Progress has been made in regards to HIV variability. The real problem I believe is the integration. Contrast the problem with viruses, e.g., Polio, that we have successful vaccines.

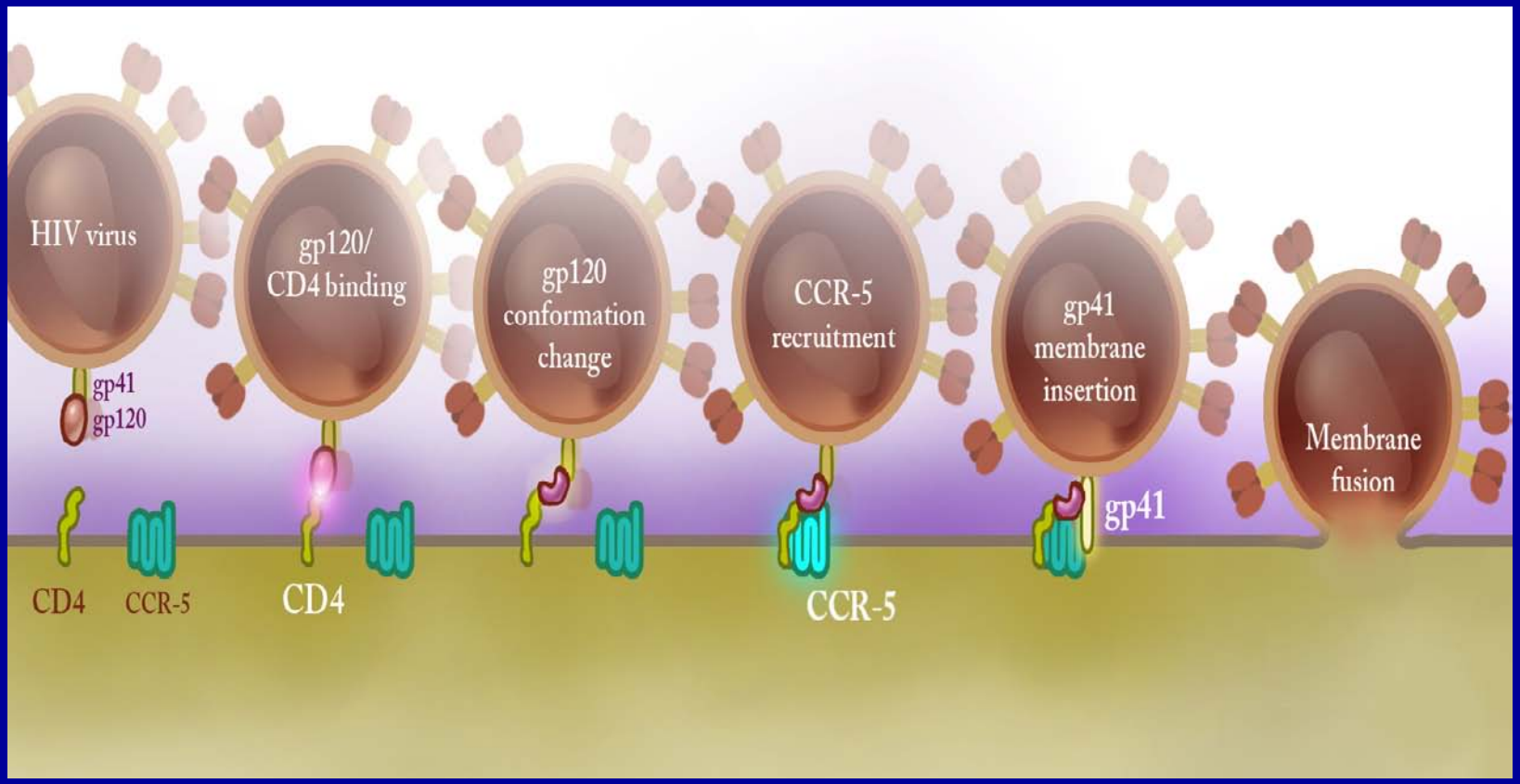
Since 1984 the General Principles Which Guide Our Thinking Remain Unchanged

- As a retrovirus HIV integrates its genes (as the DNA provirus) into the target cell DNA after cell entry, thereby establishing the permanency of infection, and then soon impairs immunity.

- This is the key difficulty to a successful HIV vaccine and a greater problem than the variability.

- Integration demands that we achieve or come close to **sterilizing immunity** AND that the immunity is **sustained**. THIS IS A NOVEL CHALLENGE FOR SCIENCE.

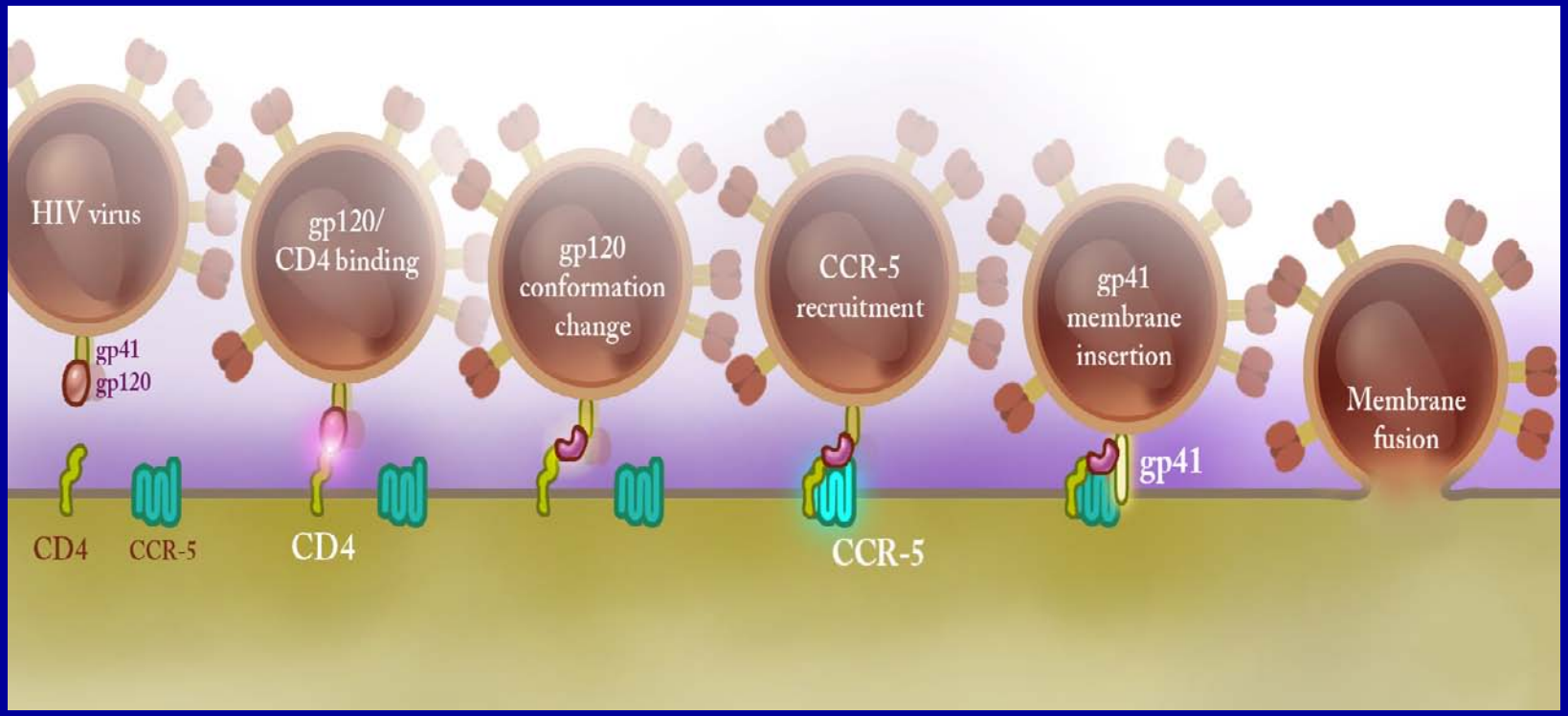
The Start of Infection: Steps in HIV Binding and Fusion: Note Various Transitional States of gp120



IHV Approach

- Select conserved, functionally required, immunogenic region of gp120. We chose CCR5 binding region.
- But Abs have difficulty in finding such sites due to gp120 flexibility, conformational masking by the protein, and carbohydrate coverage.
- We are testing a **transitional state gp120 envelope** which is “fixed” and with the conserved CCR5 binding region more exposed.
- This is done by making a single chain chimeric protein of gp120 joined to D1D2 of CD4 with a peptide linker. We call this the Full Length Single Chain (FLSC).

The Start of Infection: Steps in HIV Binding and Fusion: Note IHV Candidate HIV Vaccine is the Conformationally Changed gp120 Part of the Envelope Linked to Binding Region of CD4



GENETIC STRUCTURE OF SINGLE CHAIN GP120-CD4 COMPLEXES

Codon optimized BaLgp120

20 residue S-G-A Linker

hCD4 (D1D2)

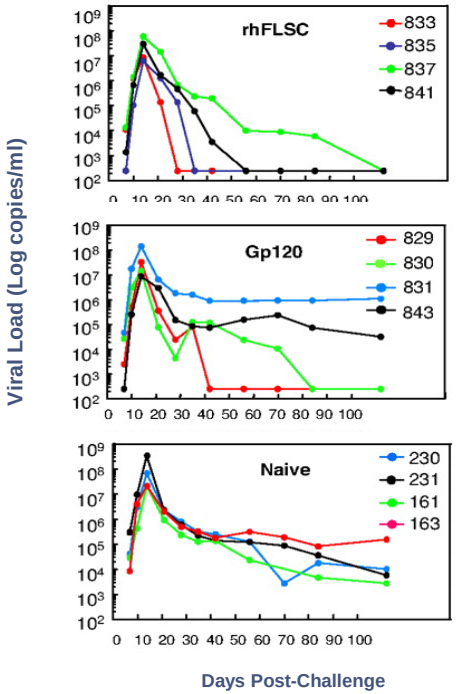
Full length single chain (FLSC)

Three Independent Macaque Challenge Studies Show that rhFLSC Affords Heterologous Sterilizing and Non-Sterilizing Protection Against SHIV162p3

Study 1

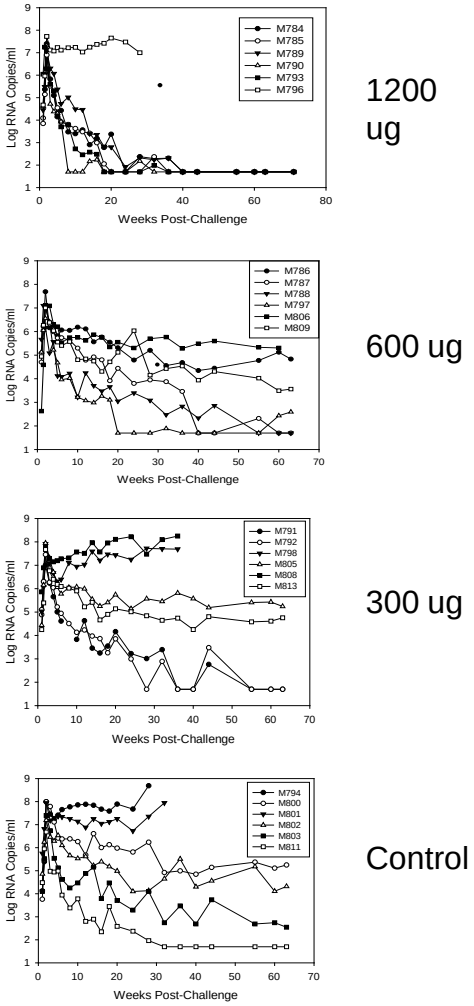
Non-sterilizing protection

DeVico A et al. PNAS 2007;104:17477-17482



Study 2

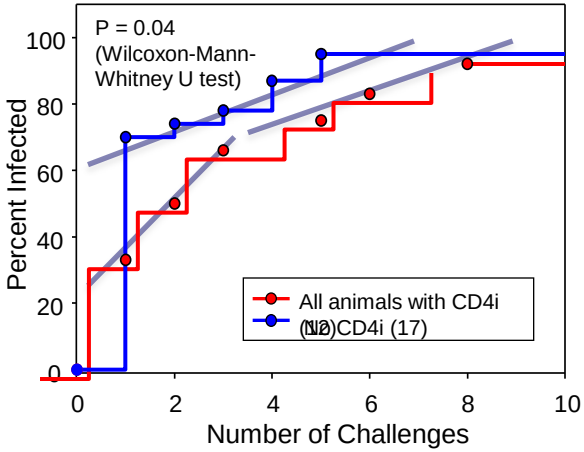
Non-sterilizing protection (dose-dependent)



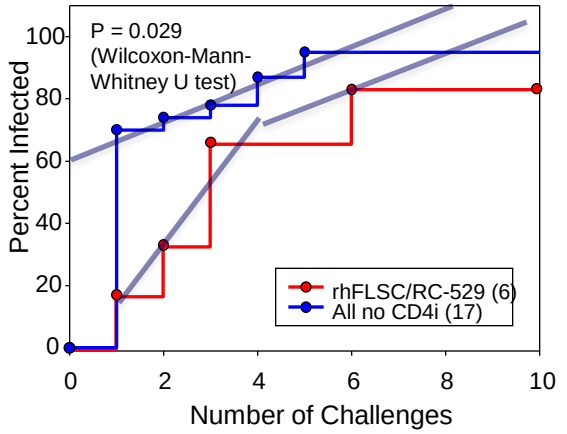
Study 3

Sterilizing protection

A role for CD4i…



Some formulations better (e.g. RC529 adjuvant)…



The Immediate Future for the IHV Vaccine Candidate:

The Bill and Melinda Gates Foundation Now Supports Us with a $15 Million Grant for Research on This Vaccine.

Within the Next 4 Weeks There Will be an Announcement of Very Major Additional Support Grant to Bring the Vaccine into Human Phase 1 Trials.

Co-Workers and Collaborators

IHV Division of Basic Science and Vaccine Research

George Lewis

Anthony DeVico

Yongjun Guan

Roberta Kamin-Lewis

Marzena Paziger

David Pauza

Joe Bryant

Profectus Bioscience, Inc.

Tim Fouts

John Eldridge

IHV—Division of Clinical Research and Patient Care

Mohammed Sajadi

Robert Redfield

CAVD Collaborations

Mike Seaman, Harvard

James Robinson, Tulane

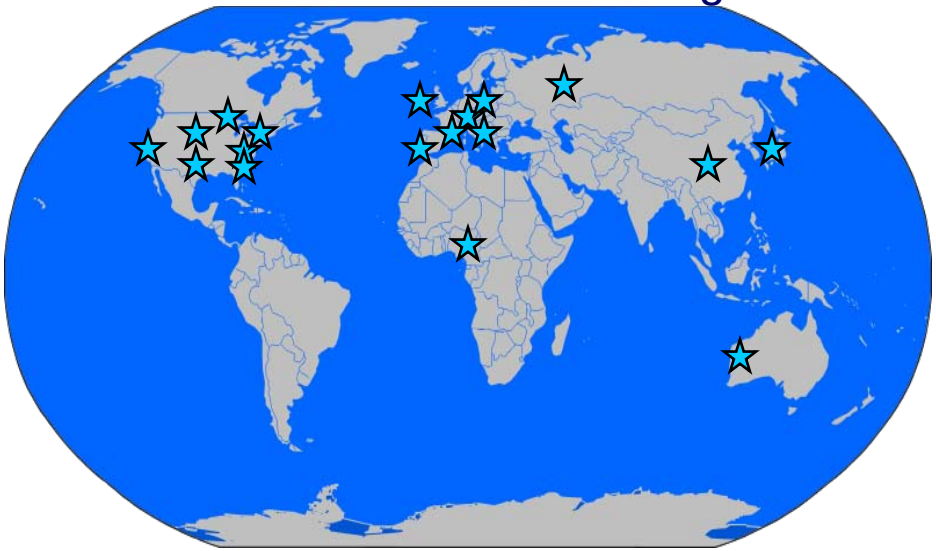
Ron Diskin, Pam Bjorkman, Cal Tech

David Montefiori, Duke and Members of the ADCC Comparison Group

Global Virology Network: a new initiative

IHV is in the process of developing a worldwide network of virus centers

- Using existing expertise, centers will work to identify new virus threats.
- Influenza (1918), Polio in the 50's & HIV taught us we need to prepare.
- 23 Centers will cover all important classes of viruses and geographic areas.
- As a new viral threat emerges, expertise will be triaged quickly.
- New virologists will be trained and developed
- Federal & Intl Health Organization Funding (WHO, UN, Gates, NIH)



Poxviruses	Retroviruses
Herpesviruses	Reoviruses
Adenoviruses	Arenaviruses
Papillomaviruses	Coronaviruses
Parvoviruses	Flaviviruses
Hepadnaviruses	Prions

Goals of the Global Virus Response Network

1. Create a network of expert medical virologists to respond to viral threats. In partnership with existing surveillance and public health organizations, the GVRN will formulate a rapid and rational first response and identify gaps in knowledge.

2. Build collaborative alliances within the network to undertake focused research on diseases with known and suspected viral causes.

3. Mitigate the current critical lack of trained future virologists through practical training programs.

4. Educate governments, public health organizations and the public-at-large about viral threats, and advocate for programs enabling effective disease prevention.

Eleven disasters that could have been averted, or at least diminished, if there had been a GVRN

1. Polio pandemic
2. HIV pandemic
3. Infection of thousands of people in 1984 due to delays in accepting the HIV blood test.
4. Case of the Libyan nurses
5. SARS debacle for China
6. The “Swine Flu” pandemic
7. The rise in global rabies incidence
8. Dengue hemorrhagic fever expansion
9. Outbreaks due to anti-vaccine sentiment (e.g. measles, YF)
10. Slaughter of healthy animals containing “potentially dangerous” viruses.
11. Global rise in pox outbreaks.