Sixth International Conference on the Future of Science: Viruses: The Invisible Enemy

"Science and HIV/AIDS: Perspectives from the Past and Prospects for the Future"

Robert Gallo
INSTITUTE OF HUMAN VIROLOGY (IHV)
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE, BALTIMORE

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OUTLINE OF PRESENTATION

- 1) COMMENTS ON THE 3 MAJOR EPIDEMICS OF THE LAST CENTURY
- 2) SOME SPECIFICS ON HIV/AIDS—PAST AND PRESENT
- 3) SOME SPECIFIC COMMENTS ON HIV/AIDS –THE FUTURE

THE 3 GREAT PANDEMICS OF THE 20TH AND 21ST CENTURIES:

Influenza of 1918-1919

Polio of the 1950ies

HIV/AIDS

WERE WE PREPARED?

YES and NO

YES, IN THE INSTANCES OF POLIO AND HIV IN TECHNOLOGY BUT

NO, IN ATTITUDE OF AWARENESS AND PREPARATION FOR NEW EMERGING VIRAL THREATS, AND NO IN HAVING DESIGNATED, RESPONSIBLE BASIC/MEDICAL VIROLOGISTS.

A GOOD EXAMPLE IS THE DIFFERENCE BETWEEN MID 1960S TO MID 1970S: 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.**

S0ME LESSONS FROM THE PAST

- **NEW VIRUS EPIDEMICS WILL ALWAYS BE A THREAT.**
- **GLOBILIZATION NARROWS THE WORLD NOT ONLY POLITICALLY, CULTURALLY, AND GENETICALLY BUT ALSO THE MICROBIAL WORLD.**
- **DO NOT ASSUME HUMANS ARE EXEMPT FROM ANY TYPE OF VIRUS.**
- **THOUGH WE HAVE SEEMINGLY ADEQUATE EPIDEMIOLOGISTS/ PUBLIC HEALTH PEOPLE WITH PLANS FOR FUTURE GLOBAL MONITORING, THERE ALSO IS A NEED TO ASSURE A CONTINUOUS POOL OF RESPONSIBLE, EXPERT "LABORATORY" VIROLOGISTS.**

DISCOVERING VIRUSES

OUR "OLD" APPROACH:

KNOW THE DISEASE,

HAVE AN IDEA THAT IT MAY BE CAUSED BY A VIRUS,

MAKE THE BEST GUESS AS TO THE VIRUS TYPE,

SELECT THE CELLS YOU BELIEVE TO BE THE LOGICAL TARGETS,

LEARN HOW TO CULTURE THOSE CELLS,

AND FIND SENSITIVE AND SPECIFIC TOOLS FOR DETECTION. HTLV-1, HTLV-2, HIV, AND HHV-6 ARE EXAMPLES

**NOTE THAT FINDING A VIRUS IS DIFFERENT FROM SHOWING IT IS A CAUSE OF A DISEASE..*

NEW APPROACH

We now have technology FROM MOLECULAR BIOLOGY-GENOMICS for much better potential for virus discoveries, and to detect new epidemics in early stages.

The limitations will be from:

1) the great variety of viruses;

2) the multiple false leads that will occur from this technology (the old approaches will still be necessary),

3) insufficient number of well trained virologists.

BASIC MEDICAL VIROLOGISTS ARE DECLINING IN NUMBER BECAUSE OF:

- **DECREASE IN MEDICAL SCHOOL GRADUATES GOING INTO SCIENCE.**
- **PERHAPS, ALSO BECAUSE OF THE GREAT EXPANSION (JUSTIFIABLY) IN GENOMICS.**
- **THOUGH THIS TECHNOLOGY IS VERY HELPFUL TO VIROLOGISTS, IT MAY DECREASE THE NUMBERS OF YOUNG PEOPLE GOING INTO VIROLOGY.**

WHAT TO DO ABOUT THIS AND ABOUT OVERALL PREPAREDNESS?

WE ARE CREATING THE GLOBAL VIRUS NETWORK: (GVN)

- **CREATING GLOGAL-LINKED CENTERS OF EXCELENCE IN VIROLOGY THAT PLAN TO INCLUDE ALL "CLASSES" OF VIRUSES, AND WILL GO BEYOND GENOMICS/INFORMATICS AND EPIDEMIOLOGY.**
- **THE FUNCTIONS WILL BE:-- REACTIVE (RESPONDING TO VIRUS THREATS OR THE NEEDS OF HEALTH OFFICIALS),**

  INTERACTIVE --(TO TRAIN NEW VIROLOGISTS),

  AND PROACTIVE-- (TO HELP ELUCIDATE POSSIBLE ROLES FOR VIRUSES IN SELECT DISEASES OF UNKNOWN ORIGIN).

A FOCUS NOW ON HIV: THE ORIGIN OF HIV

- OVERWHELMING EVIDENCE OF A ZOONOTIC INFECTION: FROM SOME AFRICAN PRIMATES TO MAN.

  (INFECTION OF HUNTERS ISOLATED AND OVER A LONG PERIOD- WITHOUT EPIDEMIC)

ORIGIN OF THE EPIDEMIC-1950-60s (FROM SOCIETAL CHANGES POST WORLD WAR II)

- WIDESREAD INTERNATIONAL TRAVEL
- INCREASED SEXUAL PROMISCUITY
- BLOOD PRODUCTS MOVING FROM NATION TO NATION
- GLOBAL INTRAVENOUS DRUG ADDICTIONS
- POSSIBLY A MUTATION IN THE CHIMP VIRUS FACILLITATING TRASFER TO HUMANS.

Recent Natural Disasters

HIV Deaths in 2007	2,100,000
HIV Deaths/Month	175,000
HIV Deaths/Week	**40,385**
HIV Deaths/Day	**5,753**
2004 Tsunami Deaths	170,000-250,000

There is still a Tsunami every month due to HIV deaths worldwide! Thiswas from 2005

Major Practical Advances from HIV Research

1) Blood Test-1984

2) Anti-HIV Therapy-1986 first with AZT and then the Combination of Drugs in 1994-1996

BLOOD TEST

- **BREAKTHROUGH WAS IN THE CONTINUOUS CULTURE OF HIV IN T-CELL LINES IN THE FALL OF 83—PROVIDING ADEQUATE AMOUNTS AND PURITY OF HIV. THE TEST:**
- **PROTECTED THE BLOOD SUPPLY AND GREATLY DECREASED THE EPIDEMIC AND….**
- **ALLOWED TESTING OF PEOPLE THEREBY DETERMINING: WHO WOULD DEVELOP AIDS IN ADVANCE, EDUCATION OF INFECTED PEOPLE, THE CAPACITY TO FOLLOW THE EPIDEMIC FOR THE FIRST TIME, AND WHEN THE ANTI-HIV DRUGS BECAME AVAILABLE, IT ENABLED THE PREVENTION OF MOTHER-TO- CHILD TRANSMISSION. FINALLY, THE BLOOD TEST IDENTIFIED THE PEOPLE WHO SHOULD BE TREATED.**

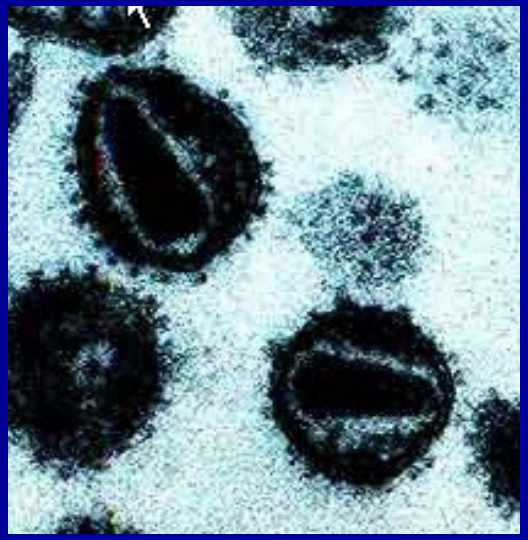
THERAPY

- **BEGAN IN 1985 WITH A COLLABORATION OF NCI SCIENTISTS AND BURROUGHS WELLCOME (AZT).**

- **FIRST POSITIVE CLINICAL RESULTS WITH ANTI-VIRAL THERAPY TARGETING ANY VIRUS—THOUGH WITH SIDE EFFECTS.**

- **BY 1995 A MAJOR SUCCESS DUE TO COMBINING VARIOUS DRUGS TARGETING DIFFERENT HIV ENZYMES NEEDED DURING THE VIRUS' REPLICATION CYCLE.**

Riddle: How is



like

?

SO, THERAPY MUST BE LIFE-LONG. THIS GIVES RISE TO THE PROBLEMS OF DRUG TOXICITY AND DRUG RESISTANSE. AS A RESULT WE ALWAYS NEED NEW APPROACHES TO THERAPY OR A CURE.

NEEDS FOR THE FUTURE

- CONTINUED RESEARCH ON NEW THERAPEUTIC APPROACHES.
- BRINGING THERAPY TO THOSE IN NEED.
- THE ULTIMATE---ELIMINATING HIV.

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 7 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.**
- **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.

PERSONAL VIEW ON A VACCINE: There are special requirements for a successful HIV vaccine because of HIV genes integrating upon infection.

- **VACCINE SHOULD PROVIDE OR COME CLOSE TO STERILIZING IMMUNITY (UNIQUE IN VACCINE HISTORY),.**
- **SHOULD BE ANTIBODY BASED RATHER THAN BASED SOLELY ON CELL IMMUNITY.**
- **THE ANTIBODIES SHOULD TARGET HIV ENTRY, AND THEREFORE , BE DIRECTED TOWARD THE ENVELOPE PROTEIN (GP120/GP41).**
- **THE ANTIBODIES MUST BE SUSTAINED (CONTRAST WITH OTHER VIRUSES, E.G., POLIO VACCINE).**
- **THESE ANTIBODIES MUST HIT A CONSERVED (NOT VARIABLE) REGION WHICH IS FUCTIONALLY REQUIRED BY HIV TO INFECT A CELL.**

Major Principles

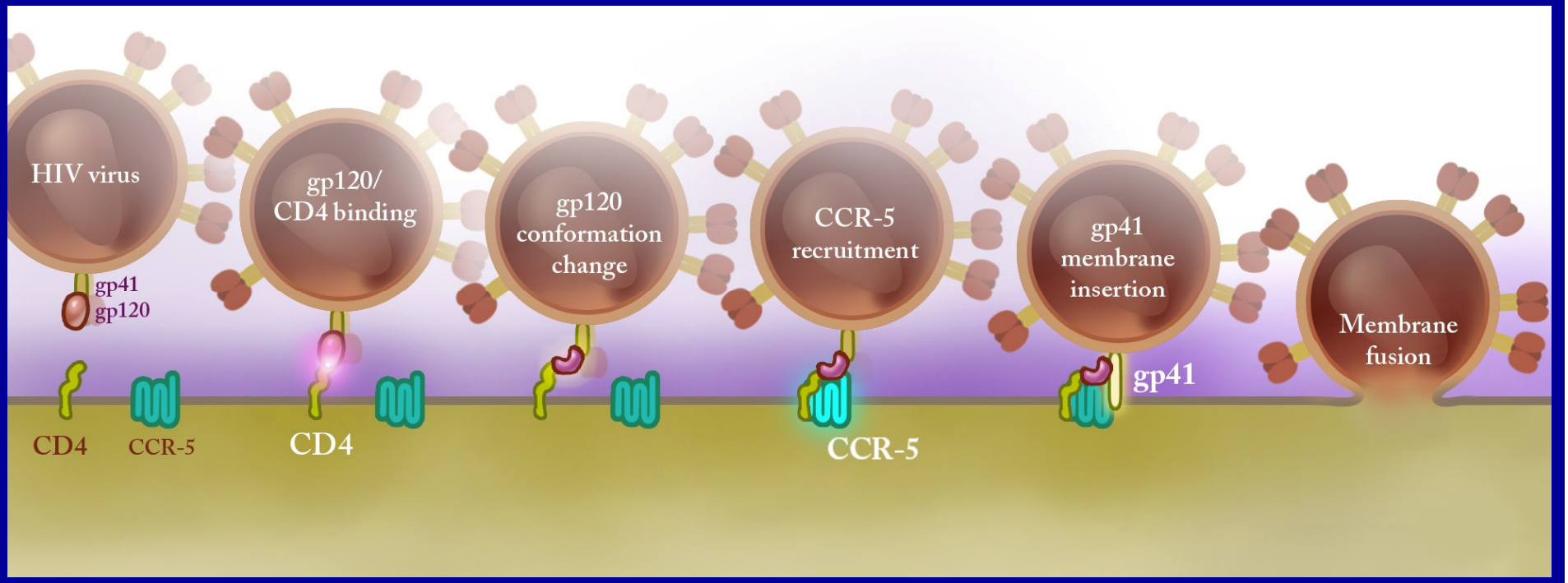
- Consequently an envelope or an envelope portion is part of the vaccine.
- BUT standard envelope-gp120- vaccines give type specific immunity.

  CAN WE GET AROUND THIS PROBLEM?
- We believe we can, but since the beginning of the field it has been apparent that approaches other than a standard gp120 would be required.

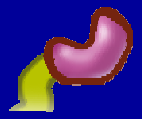
APPROACHES

- 1) Find and use conserved Env sequences that are functionally required for HIV infection.
- 2) These sequences are "hidden" to avoid Ab **attack—AND CHANGE THEIR POSITION** so find a way to expose them AND TO CONSTRAIN Env movement.
- 3) IHV selected the conserved CCR5 binding site of the HIV gp120, a site needed by HIV to begin infection.
- 4) This site is normally only marginally exposed due to gp120 flexibility, carbohydrate coverage and internal location—so a way to constrain ("fix") gp120 was needed) and to "open" critical sites..

HIV Binding and Fusion



IHV VACCINE CANDIDATE is gp120 BOUND to D1D2 of CD4



Co Workers on Vaccine Studies

- G. Lewis, IHV
- A. Devico, IHV
- Y. Guan, IHV
- D. Pauza, IHV

- T. Fouts, Profectus Biosciences INC