

# **AIDS Vaccine Research: A Perspective from the U.S. National Institutes of Health**

**Anthony S. Fauci, M.D.**

**Director**

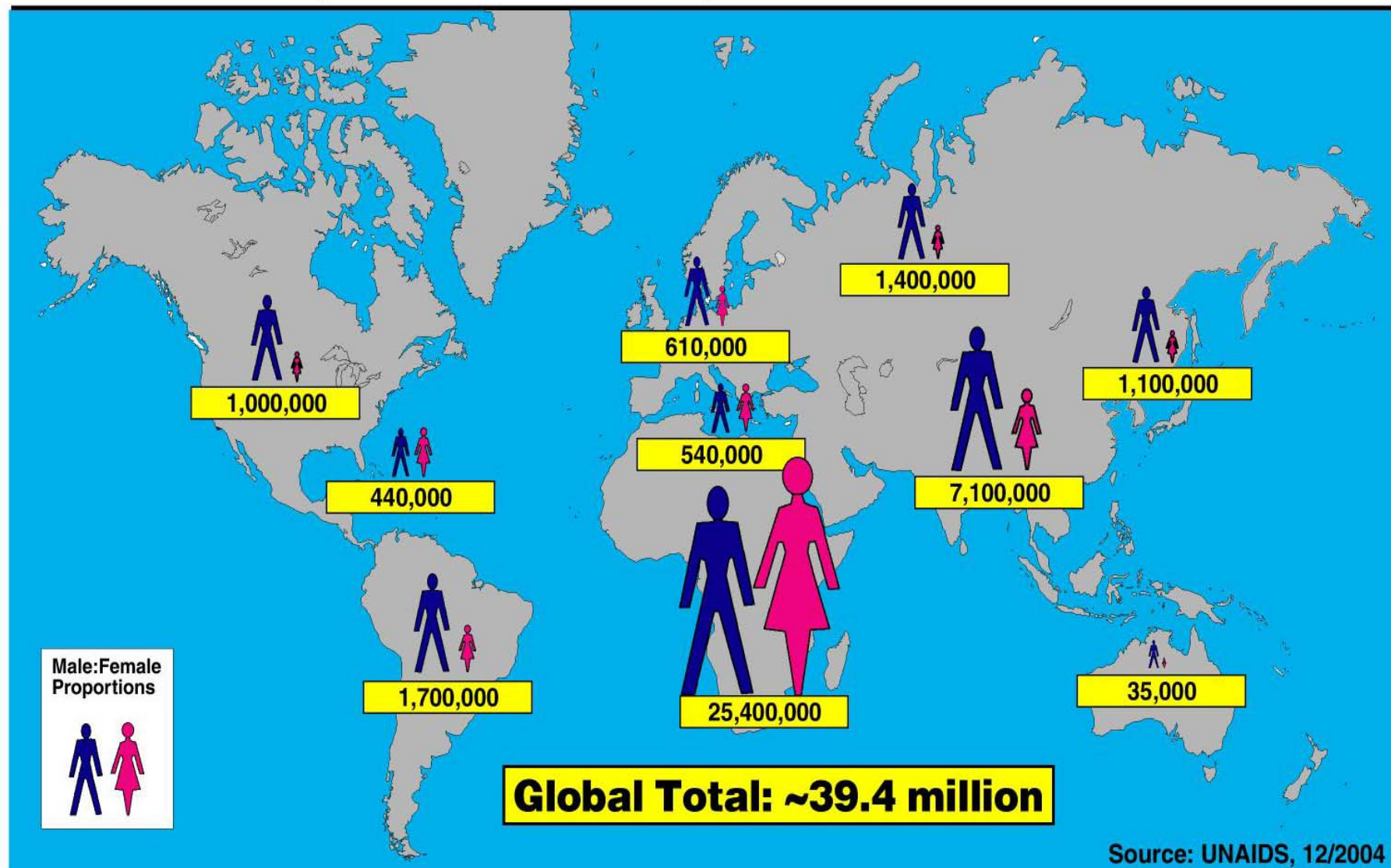
**National Institute of Allergy and Infectious  
Diseases**

**National Institutes of Health**

**September 6, 2005**



# Estimated Number of Persons Living with HIV/AIDS, December, 2004





# Estimated Number of Adults and Children Newly Infected with HIV During 2004



# **Approaches to HIV Prevention**

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- **Interruption of transmission from mother to child**
- **Education and behavior modification**
- **Drug abuse treatment (e.g. methadone)**
- **Condoms, clean syringes**
- **Topical microbicides**
- **Treatment of other sexually transmitted diseases**
- **Antiretroviral therapy**
- **Vaccination**



# **A Safe and Effective HIV Vaccine**

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- **Critical to the effective control of HIV globally.**
- **The most important and difficult scientific challenge in AIDS research.**

# **Duration Between Discovery of Microbiologic Cause of Selected Infectious Diseases and Development of a Vaccine**

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| <b>Disease</b>                | <b>Years to Develop Vaccine</b> |
|-------------------------------|---------------------------------|
| <b>Typhoid</b>                | <b>105</b>                      |
| <b>Haemophilus influenzae</b> | <b>92</b>                       |
| <b>Pertussis</b>              | <b>89</b>                       |
| <b>Polio</b>                  | <b>47</b>                       |
| <b>Measles</b>                | <b>42</b>                       |
| <b>Hepatitis B</b>            | <b>16</b>                       |
| <b>HIV</b>                    | <b>22.....</b>                  |

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# The Impact of Vaccines in the United States

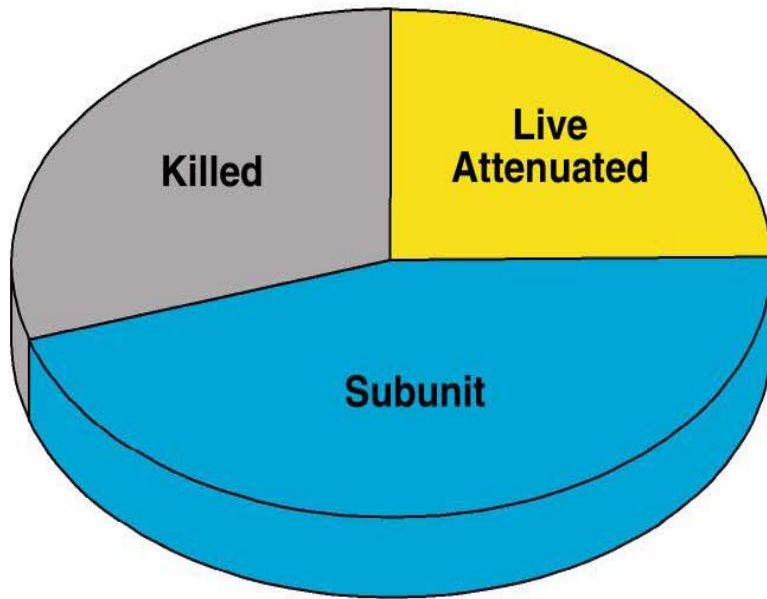
| Disease  | Baseline 20th Century Annual Cases | 2003 Cases | Percent Decrease |
|--|------------------------------------|------------|------------------|
| Measles  | 503,282                            | 56         | 99.9%            |
| Diphtheria                                     | 175,885                            | 1          | 99.9%            |
| Mumps  | 152,209                            | 231        | 99.9%            |
| Pertussis                                      | 147,271                            | 11,647     | 92.1%            |
| Smallpox                                       | 48,164                             | 0          | 100%             |
| Rubella  | 47,745                             | 8          | 99.9%            |
| <i>Haemophilus influenzae</i> type b, invasive | 20,000                             | 32         | 99.9%            |
| Polio, paralytic                               | 16,316                             | 0          | 100%             |
| Tetanus  | 1,314                              | 20         | 98.5%            |



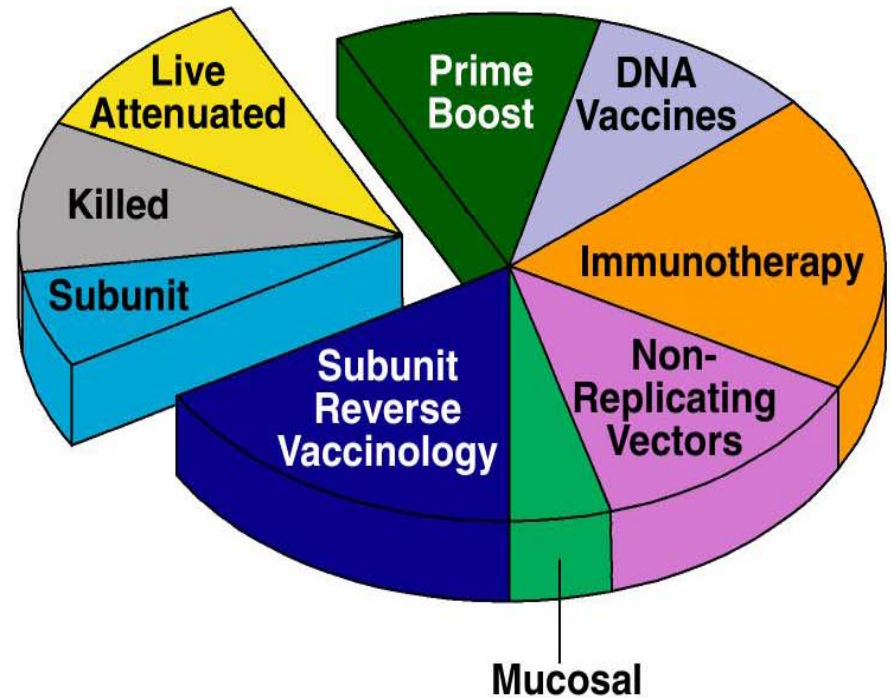
# Type of Vaccines Licensed in 2000 and Those Predicted to be Available in 2020

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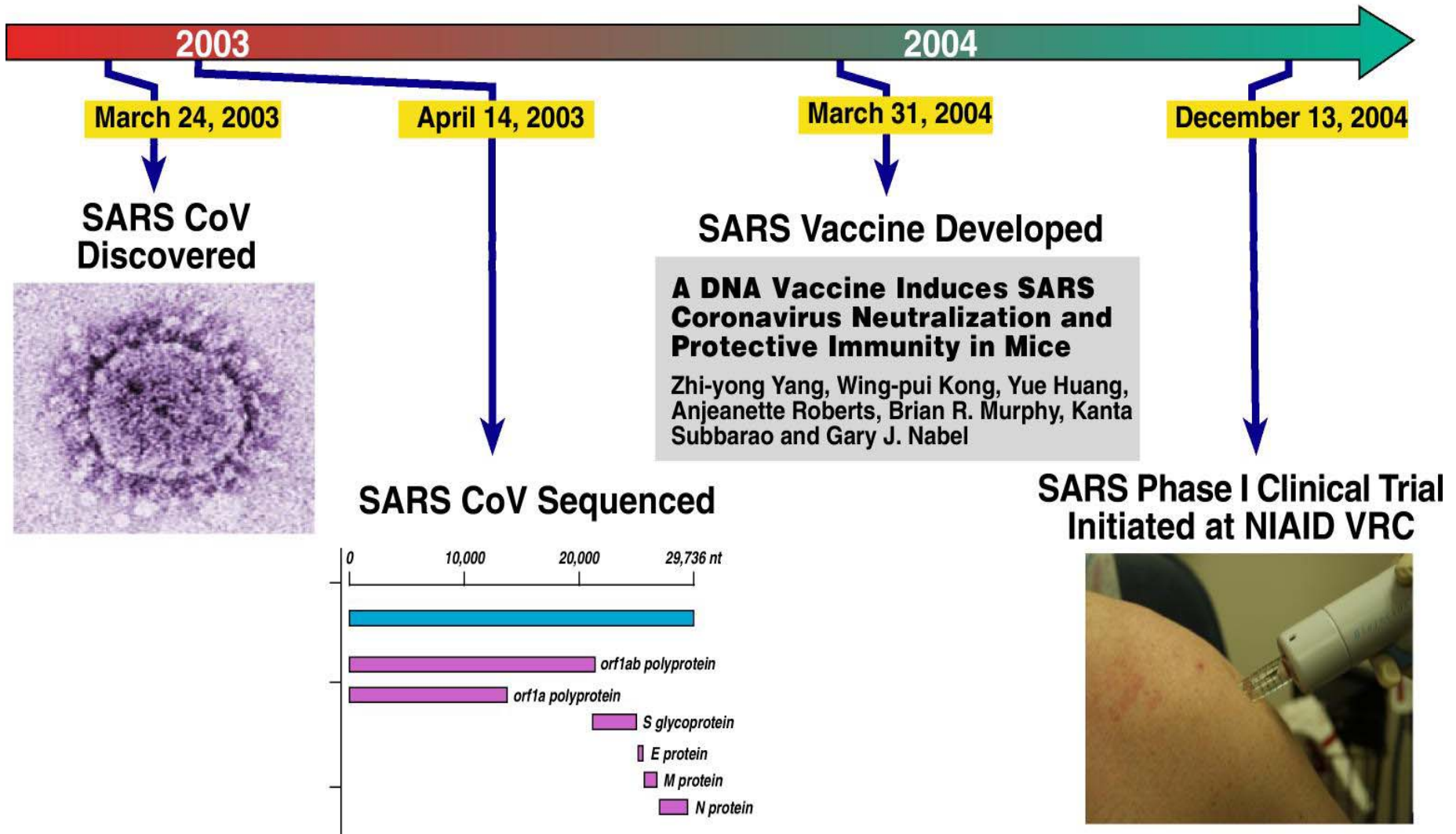
**2000**



**2020**



# SARS Characterization and Vaccine Development

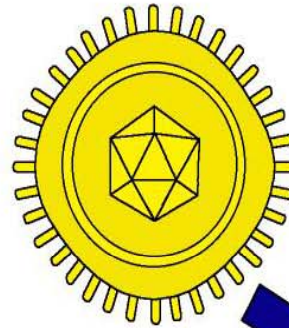


# Development of a “Chimeric” West Nile Virus Vaccine



Chimera of Arezzo, 6th century BC  
(lion/goat/serpent)

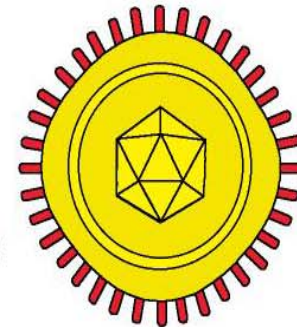
Attenuated Yellow  
Fever Virus  
Vaccine



Genes of Coat Protein  
of West Nile Virus

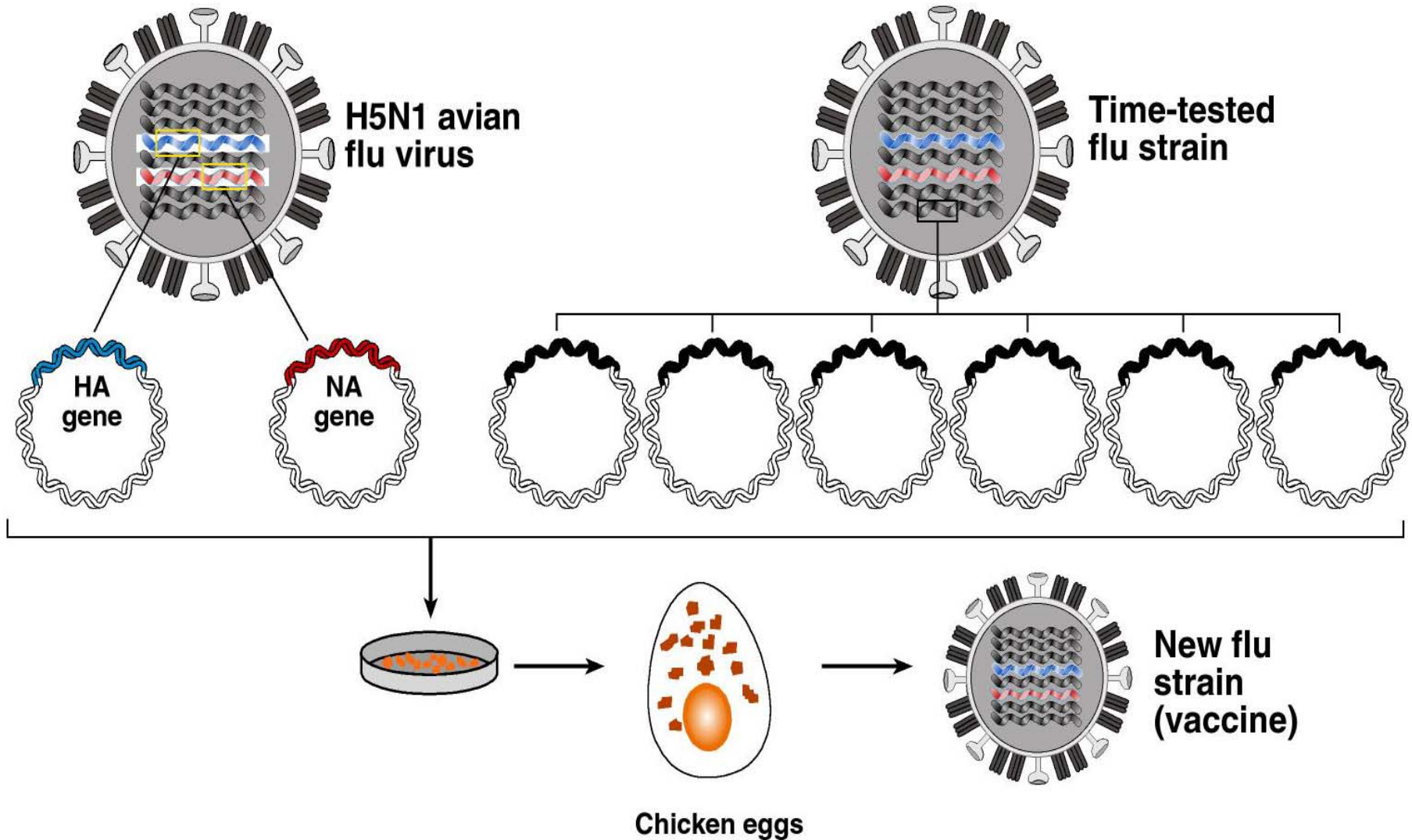


Attenuated  
Vaccine  
Presenting  
Antigens of West  
Nile Virus





# Production of a Human Vaccine Against H5N1 Avian Influenza Using Reverse Genetics



# Reuters

March 24, 2005

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## *U.S. Starts Human Tests of Bird Flu Vaccine*

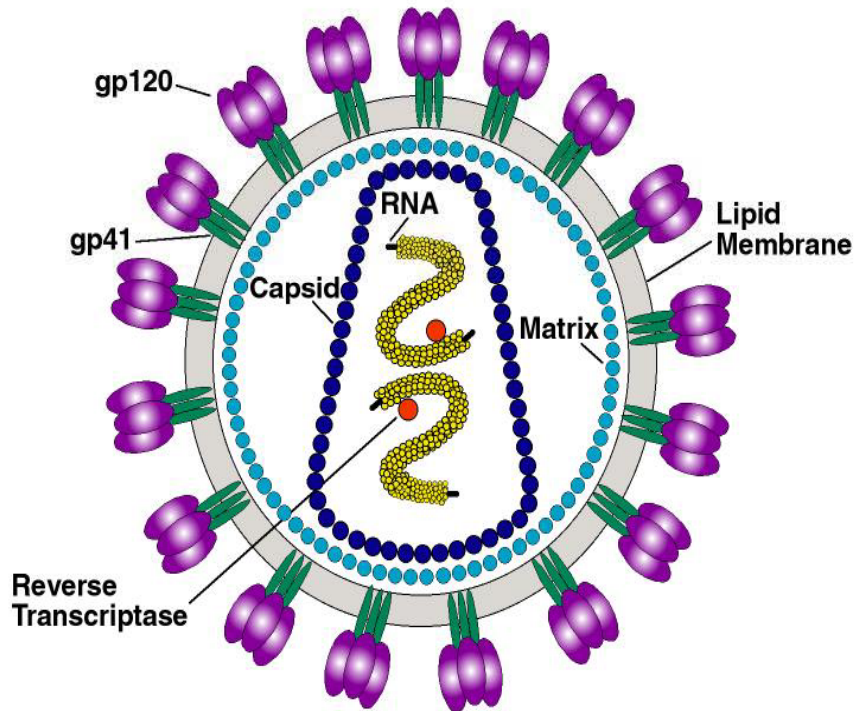
**Phase 1 trial on 450 adults will determine safety of shots**

U.S. health officials said on Wednesday they have started human tests of a vaccine against avian flu, which experts believe could kill tens of millions of people if it becomes easily passed from person to person.



# HIV is Different

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- The natural immune response to HIV is inadequate
- HIV hides from the immune system
- HIV targets and destroys the immune system
- HIV mutates rapidly



# **HIV Vaccines: A Timeline**

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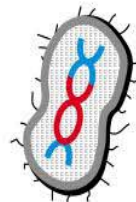
- **AIDS recognized in 1981**
- **HIV identified as the cause of AIDS in 1983/1984**
- **First Phase I HIV vaccine trial in 1987**
- **From 1987-2004:**
  - **>80 Phase I/II trials of >30 candidate vaccines**
  - **2 Phase III trials concluded, and one ongoing**

# The Spectrum of HIV Vaccine Strategies

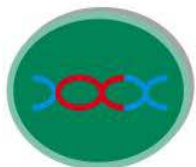
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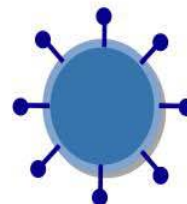
**Viral surface proteins**



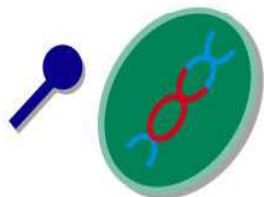
**Live bacterial vectors**



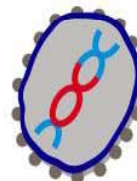
**Live vector viruses**



**Pseudovirions**



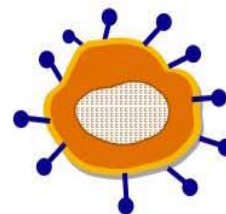
**Combination of elements**



**Replicons**



**Naked DNA**



**Whole, killed HIV**



**HIV peptides**



**Live, attenuated HIV**

# **Progress in HIV Vaccinology**

- **Production of multiple candidate vaccines that stimulate anti-HIV immune responses**
- **Protection (partial) in animal models**
- **Safety and immunogenicity in human trials**



**Although We Face Many  
Operational, Social and  
Financial Obstacles in the Quest  
for an HIV Vaccine,  
**SCIENTIFIC CHALLENGES**  
are the Most Significant  
Rate-Limiting Factors in HIV  
Vaccine Development Today.**

# **NIH Scientific Priorities in HIV Vaccinology**

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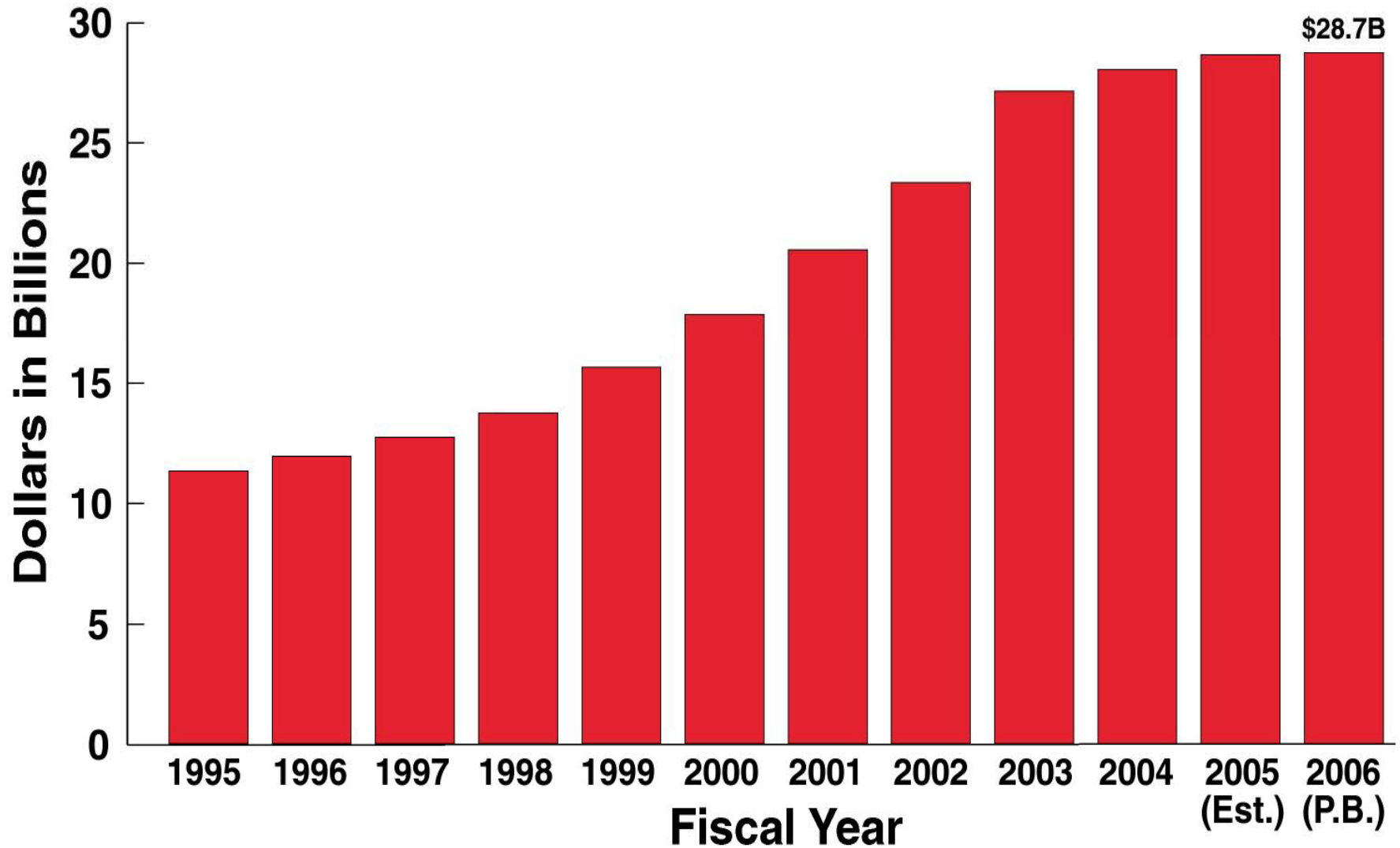
- **Continue fundamental research to inform vaccine design**
  - Characterizing transmitted virus
  - Relationship of envelope structure and immunogenicity
  - Correlates of immune protection
  - Role of host factors in immune response
- **Identify 'improved' vaccine designs**
  - Broadly neutralizing, high titer Ab
  - Broad, high level cellular responses
  - Mucosal responses ?
- **Identify and advance the most promising candidates**
  - Evaluate potential immune correlates in efficacy trials

# **A Commitment to HIV Vaccine Research in an Era of Fiscal Constraint**



# NIH Funding History

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# National Institutes of Health

## Budget Comparison by Institute/Center

(Dollars in Thousands)

| IC              | FY 2005<br>Enacted Conference | FY 2006<br>President's Budget | Percent<br>Change |
|-----------------|-------------------------------|-------------------------------|-------------------|
| <b>NIAID</b>    | <b>\$4,402,841</b>            | <b>\$4,459,395</b>            | <b>1.3%</b>       |
| NCI             | 4,825,258                     | 4,841,774                     | 0.3%              |
| NHLBI           | 2,941,201                     | 2,951,270                     | 0.3%              |
| NHGRI           | 488,608                       | 490,959                       | 0.5%              |
| NIDA            | 1,006,419                     | 1,010,130                     | 0.4%              |
| Other IC's      | 14,146,550                    | 14,201,359                    | 0.4%              |
| <b>Subtotal</b> | <b>\$27,810,877</b>           | <b>\$27,954,887</b>           | <b>0.5%</b>       |
| NLM             | 315,146                       | 318,091                       | 0.9%              |
| OD              | 358,046                       | 385,195                       | 7.6%              |
| B&F             | 110,288                       | 81,900                        | -25.7%            |
| <b>Total</b>    | <b>\$28,594,357</b>           | <b>\$28,740,073</b>           | <b>0.5%</b>       |

FY 2005 includes \$99.2M for the Global Fund and \$14.4M for the virtual VRC.  
FY 2006 includes \$100.0M for the Global Fund and \$34.0M for the virtual VRC.

# **Five High Priorities of NIH FY 2006 Budget**

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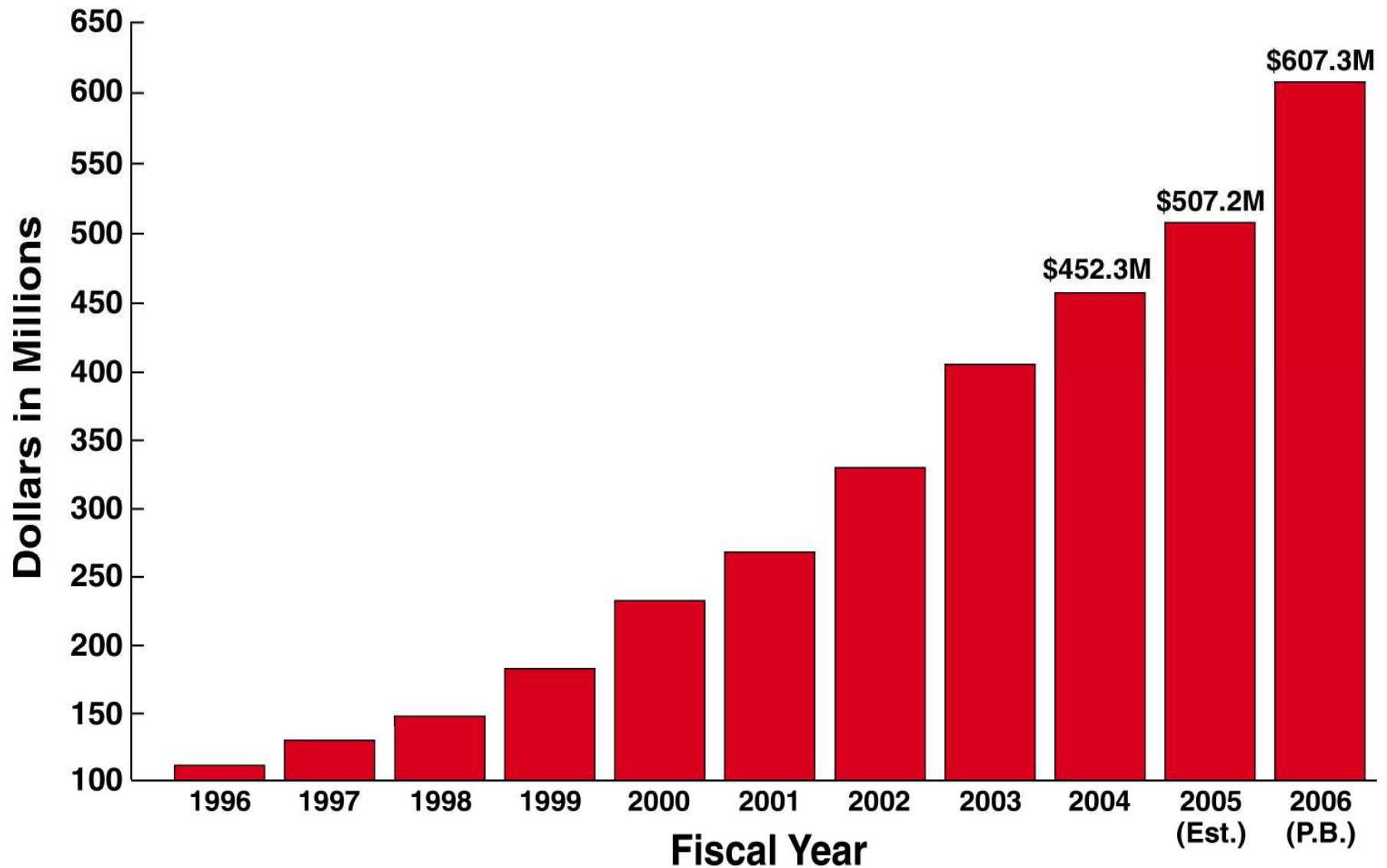
## **■ HIV Vaccine Development**

- Research Project Grants - preserve to the greatest extent possible the ability of scientists to obtain individual support**
- The Roadmap for Medical Research**
- Biodefense Research**
- Neuroscience Blueprint**

**Testimony of NIH Director Elias A. Zerhouni, M.D, to the Senate Subcommittee on Labor-HHS-Education Appropriations, April 6, 2005.**



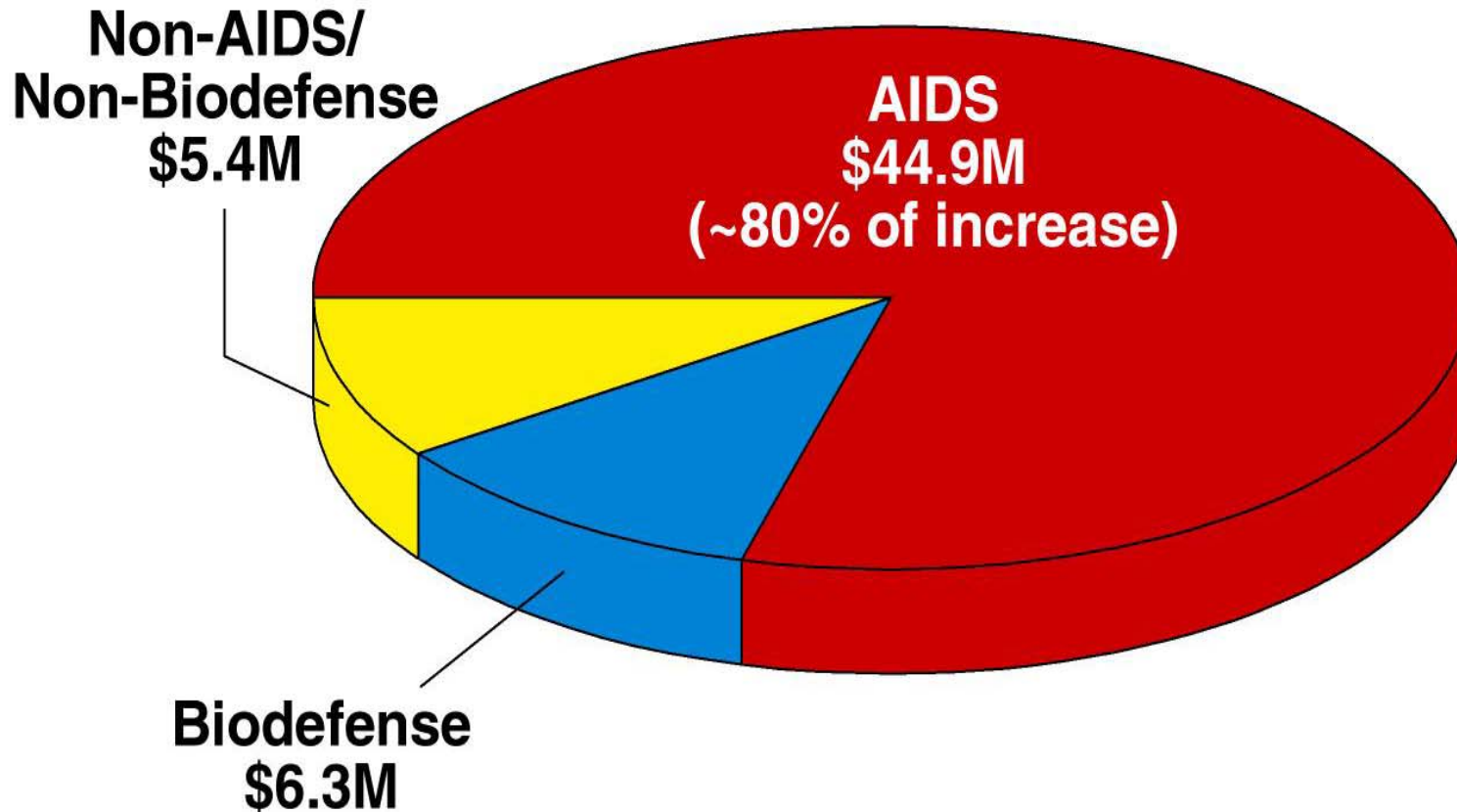
# NIH HIV Vaccine Research Funding



# **Increase in NIAID Budget, FY 2005 (est.) to FY 2006 (P.B.)**

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**Total Increase: \$56.6M**



# THE LANCET

Number 9214 • Founded 1823 • Published weekly

Volume 348

October 12, 1996

## **Biomedical Research in an Era of Unlimited Aspirations and Limited Resources**

**Anthony S. Fauci**

***"Resources for biomedical research in general are unlikely to increase substantially in the foreseeable future, and in some areas will be constrained. Yet the opportunities for advances in knowledge and the practical application of these advances will surely increase. Hence, the dichotomy between aspirations and resources will probably widen."***



# **Need for Portfolio Analysis and Re-Examination of Priorities**

# **The Necessity for Collaboration**

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- **No one sector can single-handedly address the complex challenges -  
- scientific, technical, social,  
economic and political -- involved  
in product development.**

# nature medicine

VOLUME 4 NUMBER 5  
MAY 1998

## **The Role of US Government Agencies in Vaccine Research and Development**

Gregory K. Folkers &  
Anthony S. Fauci

Vaccine supplement

***“The various partners  
in vaccine development  
bring perspectives,  
resources and skills  
that are sometimes  
unique, but more often  
overlapping and  
complementary.”***

# **Necessary Steps**

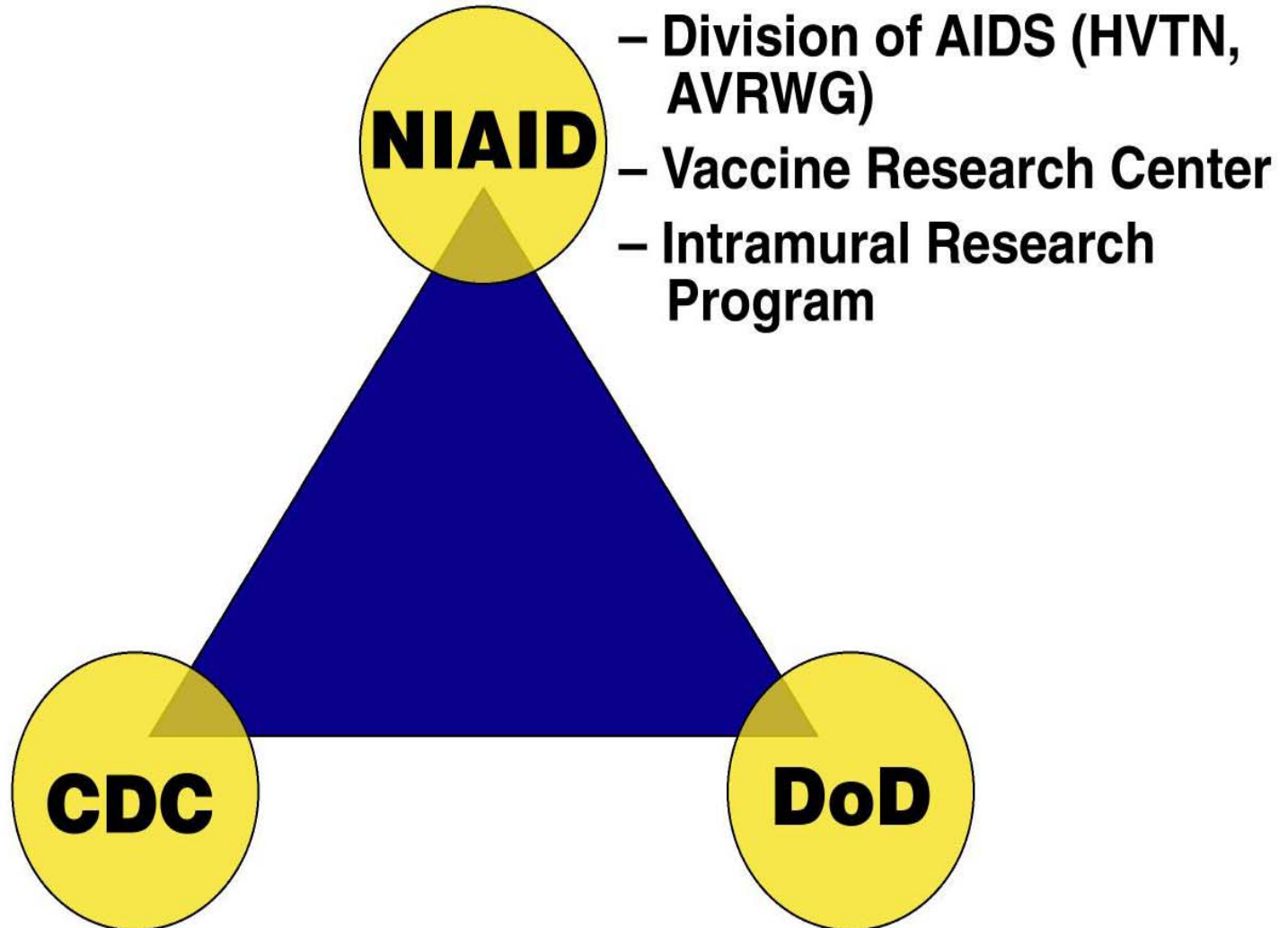
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- **Collaborate/Cooperate**
- **Harmonize**
- **Achieve Economies of Scale**
- **Eliminate Duplication**
- **Standardize**
- **Consolidate Clinical Trials Networks**
- **Push for Tangible Results, i.e. Products**



# Partnership for AIDS Vaccine Evaluation (PAVE)

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# Science

27 June 2003

Vol. 300 No. 5628  
Pages 1989–2124 \$10

## The Need for a Global HIV Vaccine Enterprise

R.D. Klausner, A.S. Fauci, L. Corey, G.J. Nabel,  
H. Gayle, S. Berkley, B.F. Haynes, D. Baltimore,  
C. Collins, R.G. Douglas, J. Esparza, D.P. Francis,  
N.K. Ganguly, J.L. Gerberding, M.I. Johnston,  
M.D. Kazatchkine, A.J. McMichael, M.W. Makgoba,  
G. Pantaleo, P. Piot, Y. Shao, E. Tramont, H.  
Varmus, J.N. Wasserheit



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Published online January 18, 2005

Policy Forum

## The Global HIV/AIDS Vaccine Enterprise: Scientific Strategic Plan

Coordinating Committee of the Global  
HIV/AIDS Vaccine Enterprise

[www.plosmedicine.org](http://www.plosmedicine.org)



AMERICAN ASSOCIATION FOR THE ADVANCEMENT OF SCIENCE

# What is the Global HIV Vaccine Enterprise?

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- A **virtual consortium** of independent organizations committed to accelerating the development of a preventive vaccine for HIV/AIDS.
- Enterprise partners will advance HIV vaccine research and development through:
  - the implementation of a shared strategic scientific plan
  - mobilization of additional resources
  - greater collaboration among HIV vaccine researchers worldwide.



# Science

18 June 2004

Vol. 304 No. 5678  
Pages 1701-1856 \$10

**“A plan to coordinate global HIV vaccine research got a moral boost last week when the leaders of the world’s richest countries endorsed the Global HIV Vaccine Enterprise at the G8 summit in Sea Island, Georgia.”**

AAAS

## AIDS VACCINES

# G8 Leaders Endorse Global Effort







**For Immediate Release  
Office of the Press Secretary  
June 10, 2004**

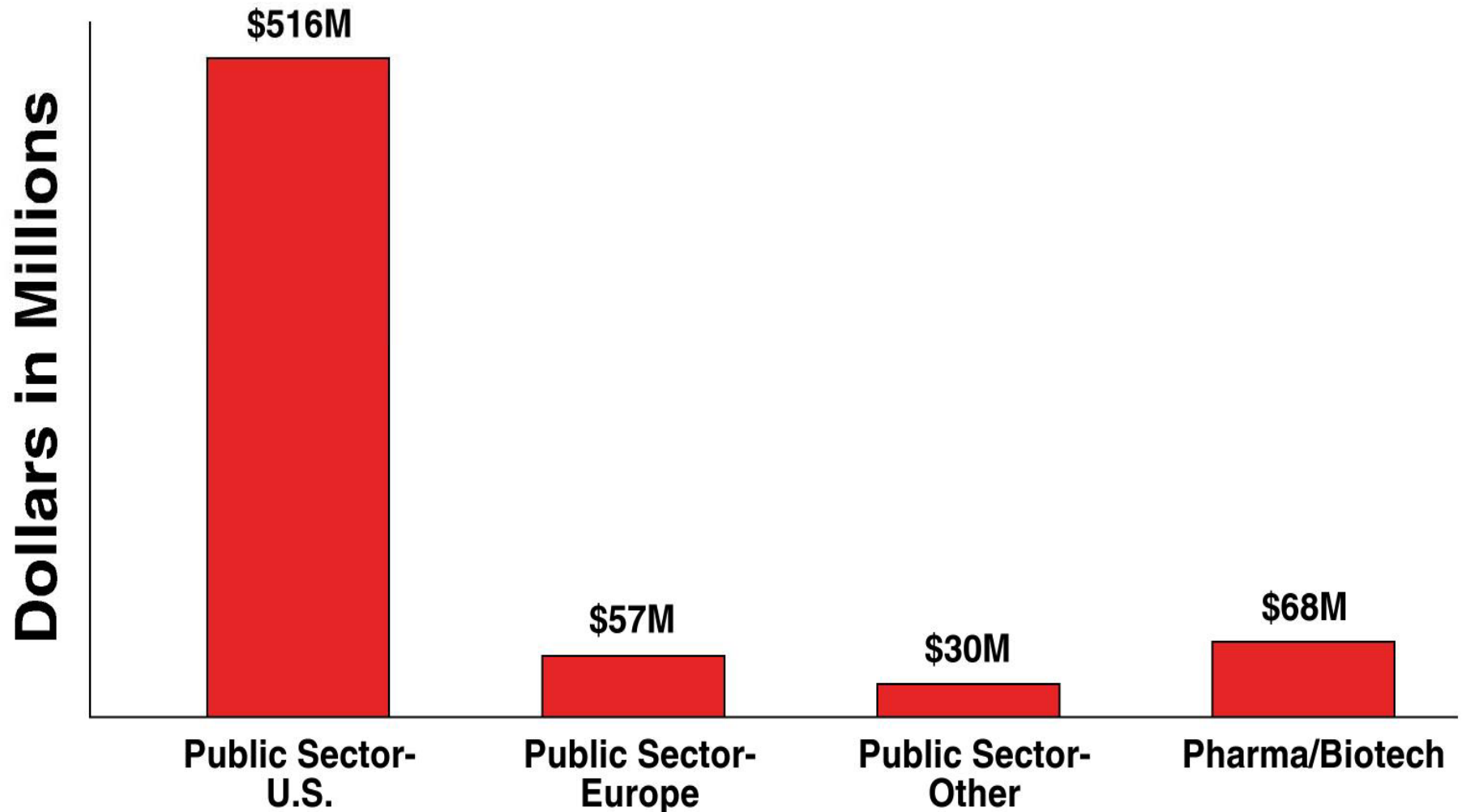
# **Global HIV Vaccine Enterprise**

## **Presidential Action**

**President Bush led the G-8 today in endorsing the establishment of a Global HIV Vaccine Enterprise, a virtual consortium to accelerate HIV vaccine development. The President also announced plans to establish a second HIV Vaccine Research and Development Center in the U.S., and urged his G-8 counterparts to increase their commitment to vaccine development.**

# Investment in Preventive HIV Vaccine R&D, 2004: Appx. \$682M

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Source: AVAC, 6/2005

# Science

27 June 2003

Vol. 300 No. 5628  
Pages 1989-2124 \$10

## **The Need for a Global HIV Vaccine Enterprise**

R.D. Klausner, A.S. Fauci, L. Corey, et al.

"Increasing the diversity of approaches and coordinating the types of vaccines entering clinical trials are fundamental to speeding global HIV vaccine development.

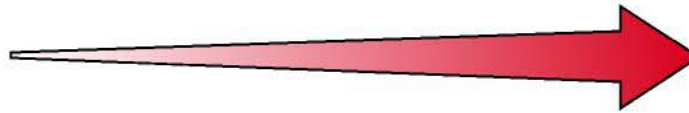
**We believe that this requires the creation of a series of coordinated global HIV vaccine centers...."**



# **NIAID Vaccine Research Center**

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**Basic Research**



**Clinical Trials**



- **5-story state-of-the-art facility, opened fall 2000**
- **170 employees**
- **HIV, smallpox, ebola and other HFVs, SARS, WNV**
- **Close collaborations with clinical trials groups - HVTN, WRAIR, CDC**

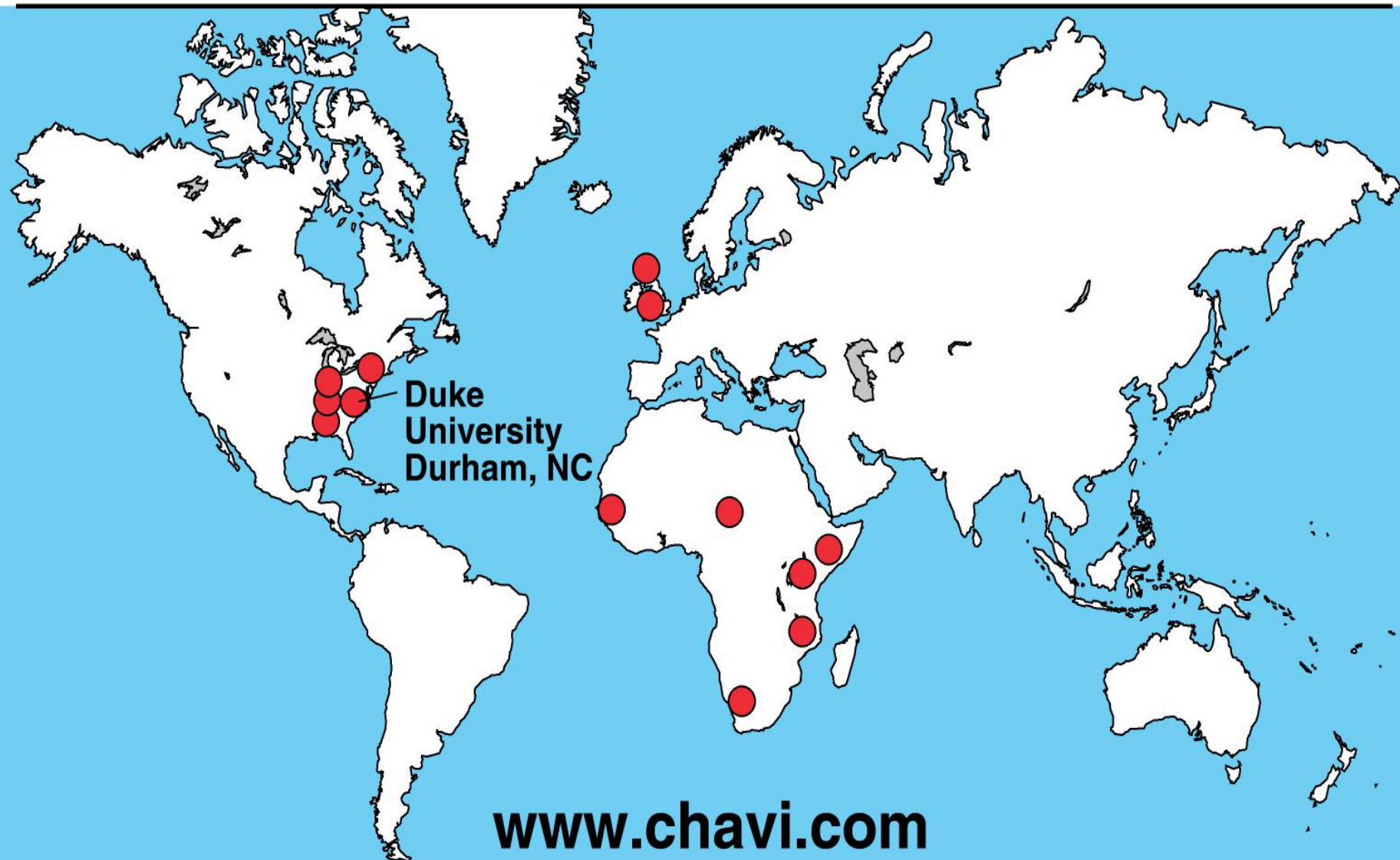


# **The Center for HIV/AIDS Vaccine Immunology (CHAVI)**

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- **Intensive, multi-resourced, coordinated, consortium approach to address key scientific roadblocks in HIV vaccine R&D.**
- **Goals are linked to Enterprise priorities.**
- **One 7-year award made in August, 2005**
- **Budget: 1<sup>st</sup> year: ~ \$14.9M  
2<sup>nd</sup> year: up to \$50.0M; expansion plan must be peer reviewed by external advisory board and approved by NIAID**

# CHAVI Members and Affiliates



# **CHAVI Goals**

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- **Elucidate early viral and immunological events and host genetic factors associated with HIV-1 transmission, establishment of productive infection, and (partial) containment of virus replication.**
- **Determine correlates of SIV immune protection in primates.**
- **Design, develop, and test novel immunogens and adjuvants that elicit persistent mucosal and/or systemic immune responses in humans and primates.**
- **Evaluate HIV-1 vaccine candidates in early phase clinical trials.**

Source: B Haynes



# **Two Examples of Promising HIV Vaccine Candidates**

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## **HVTN 502/Merck 023**

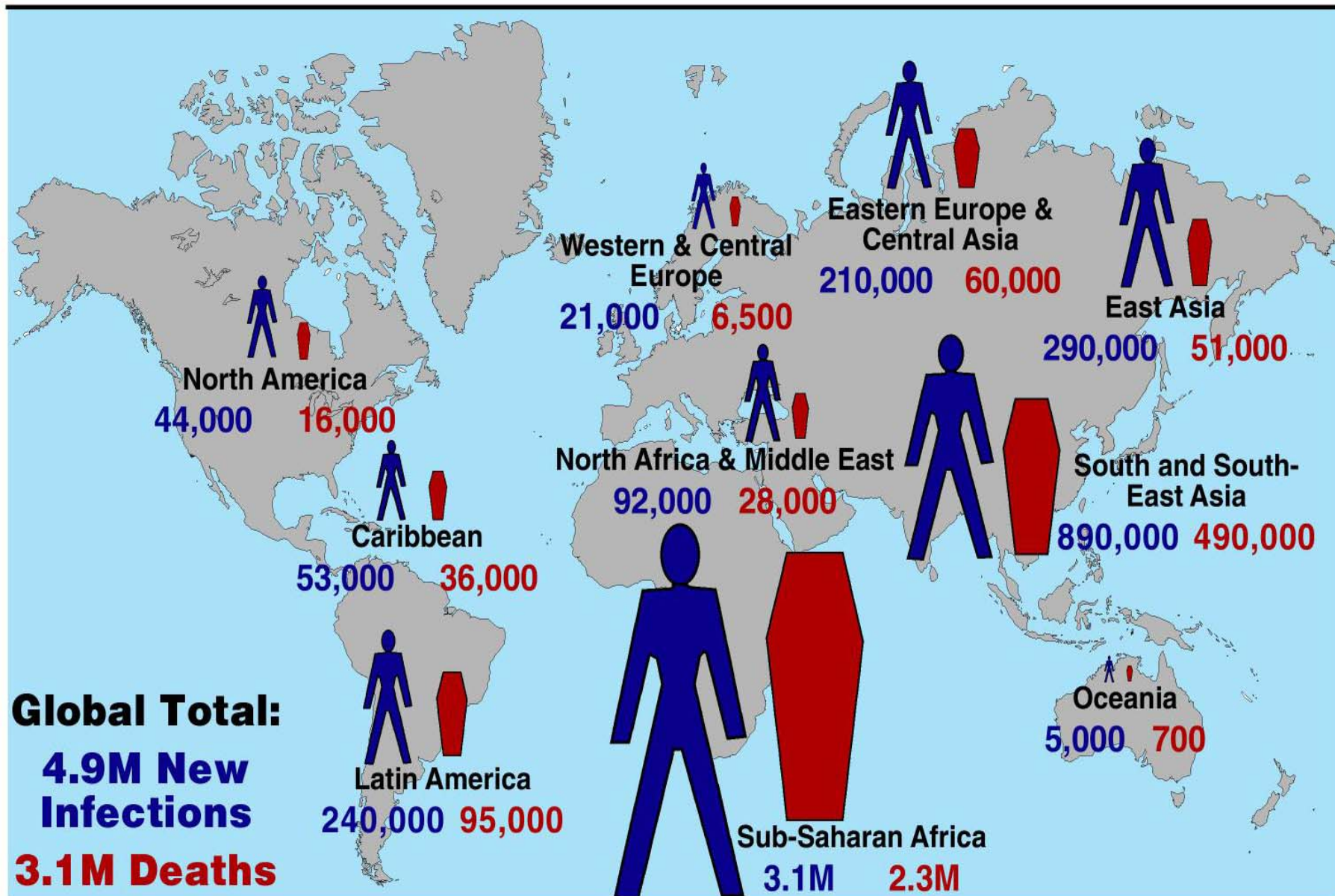
- Adenovirus vectors expressing gag, pol or nef
- Phase 2b trial underway in US, Puerto Rico and 5 other countries

## **NIAID/VRC DNA/rAd5 Candidate Vaccine**

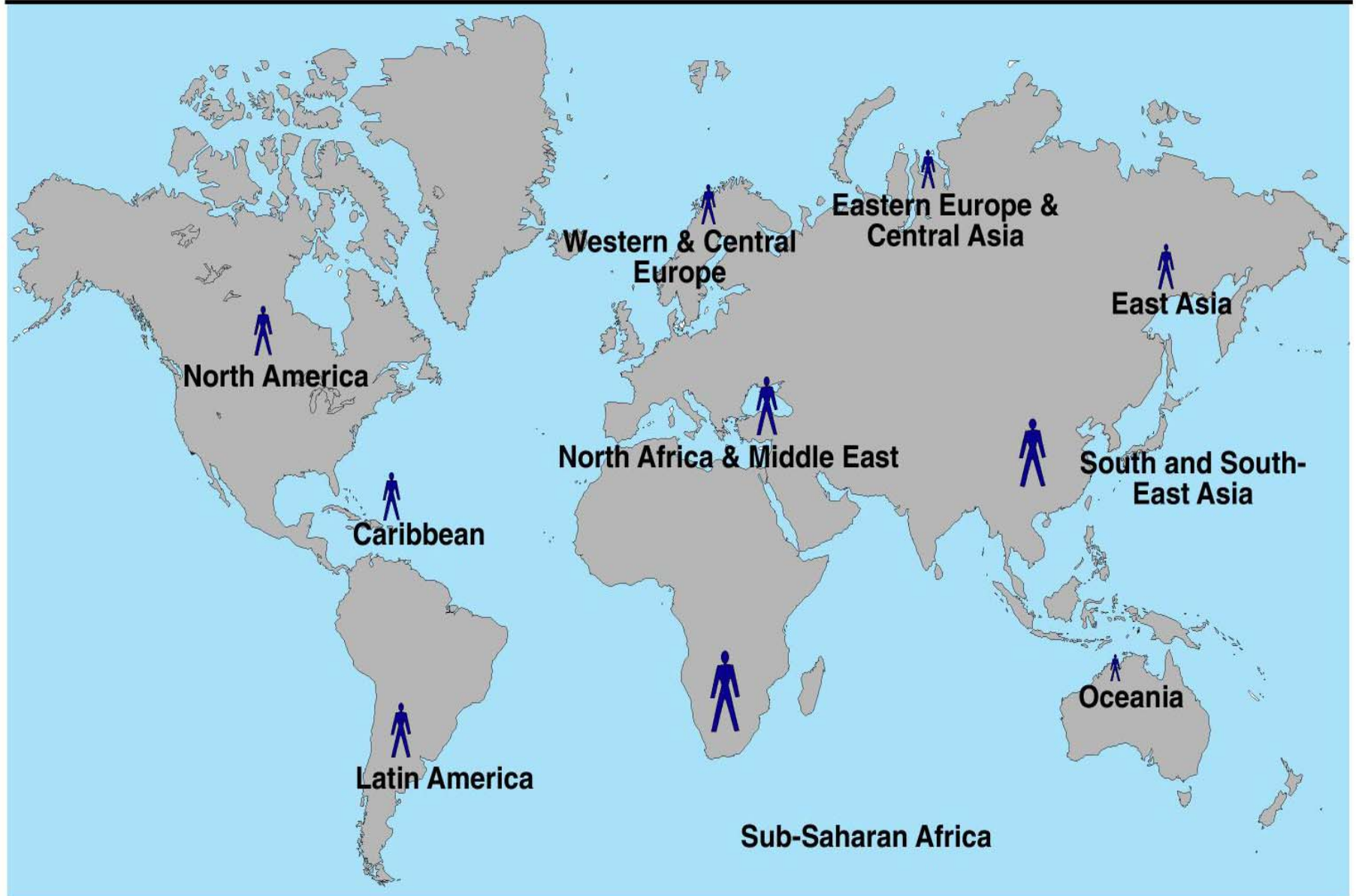
- Prime-boost strategy using multi-clade (A,B,C), multi-gene (including env) constructs -- DNA plasmid vector prime, followed by adenoviral vector
- Phase 2 human trials with NIAID clinical network partners (HVTN, DoD, IAVI) will commence in late 2005



# New HIV Infections and AIDS Deaths, 2004



# The End of AIDS, 20??



# **HIV Vaccine Research and Development: The Way Forward**

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