

**Secretary's Council on Public Health Preparedness**

# **NIH Biodefense Research and Development**

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

**Director**

**National Institute of Allergy and Infectious  
Diseases**

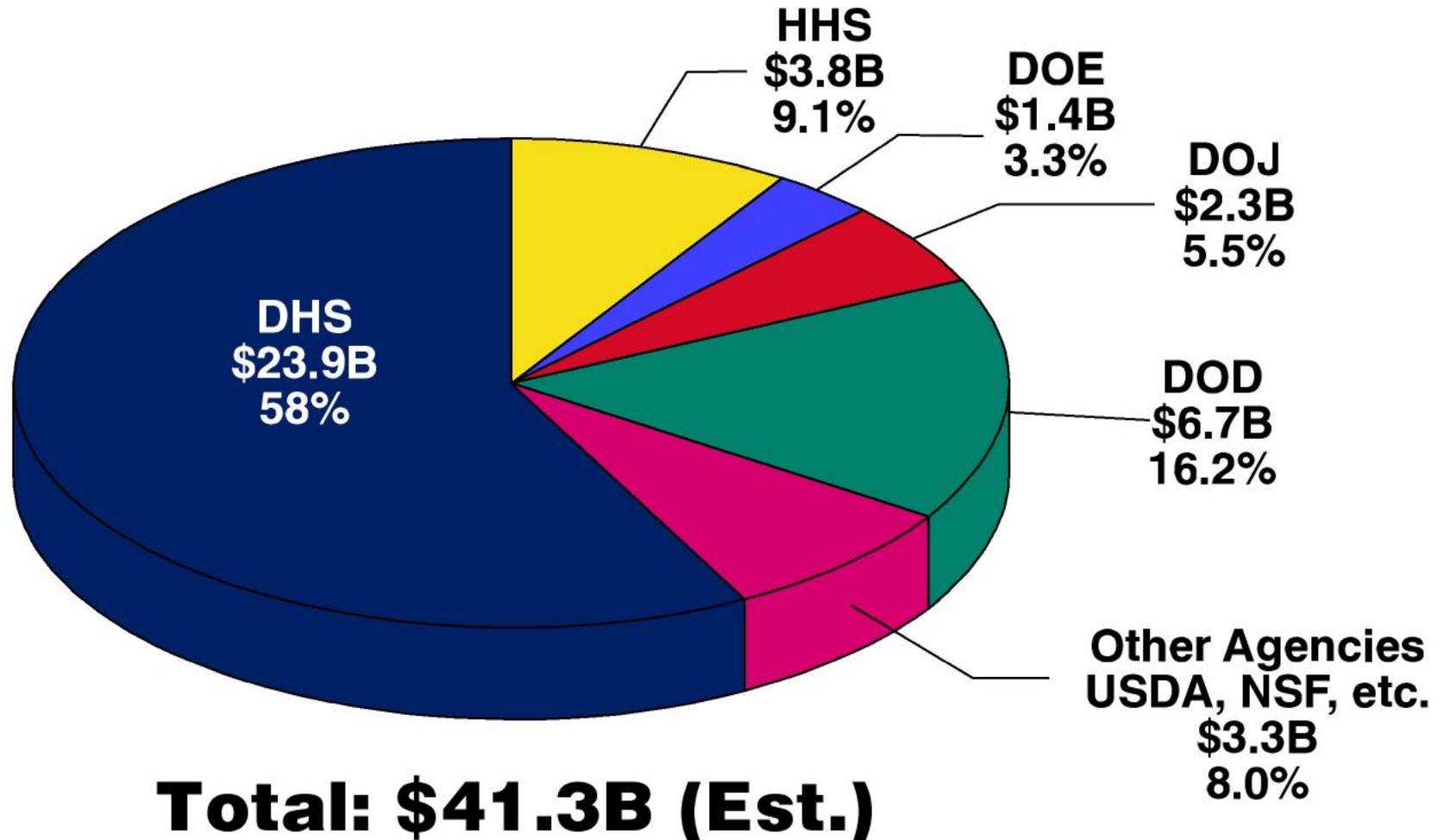
**National Institutes of Health**

**January 22, 2004**



# U.S. Homeland Security Funding by Agency, FY 2004 (Est.)

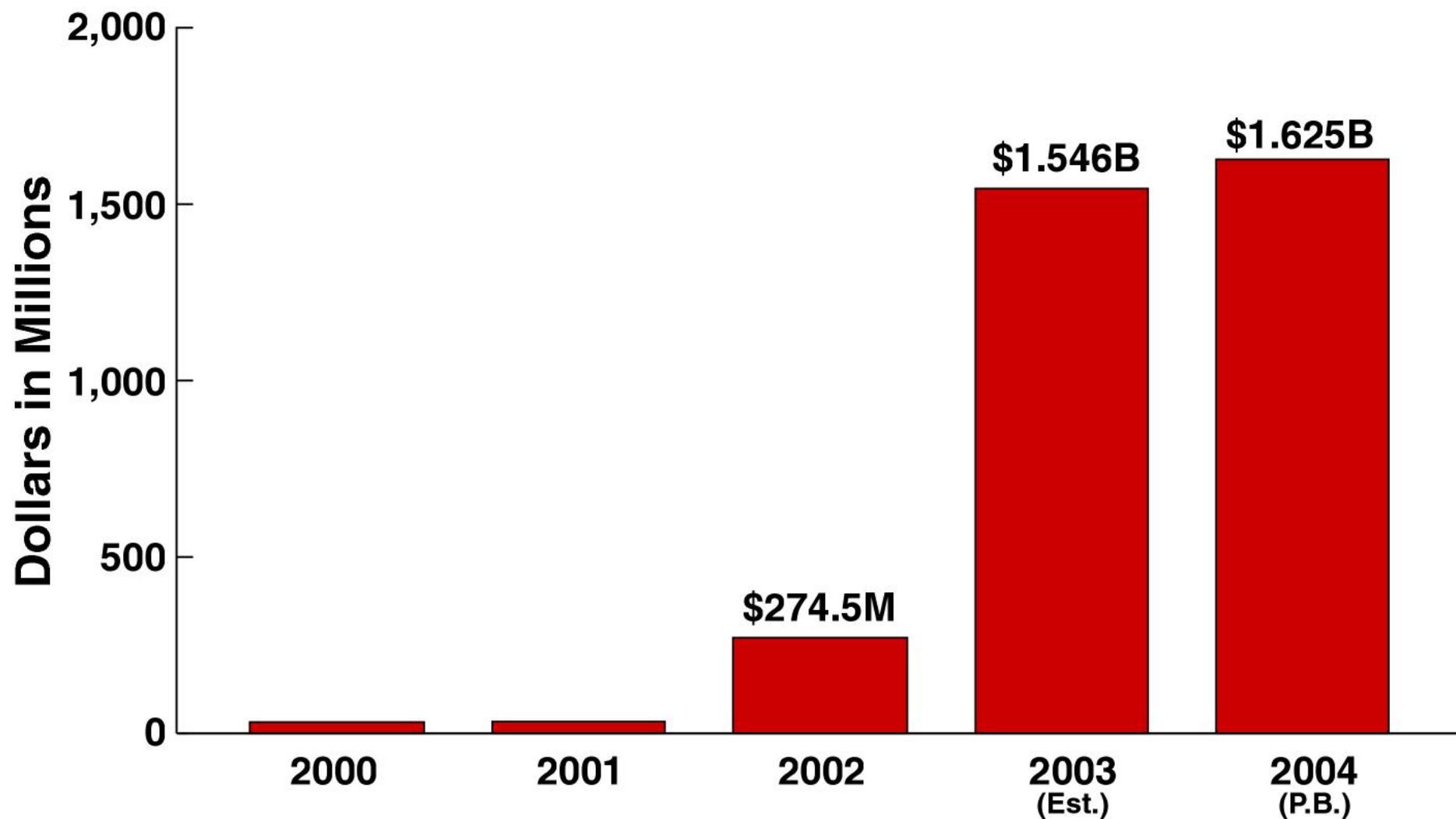
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Source: OMB

# NIH Biodefense Research Funding, FY 2000-2004

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## NIAID Strategic Plan for Biodefense Research



February 2003



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
National Institutes of Health  
National Institute of Allergy and Infectious Diseases



## NIAID Biodefense Research Agenda for CDC Category A Agents



February 2003



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
National Institutes of Health  
National Institute of Allergy and Infectious Diseases



## NIAID Biodefense Research Agenda for Category B and C Priority Pathogens

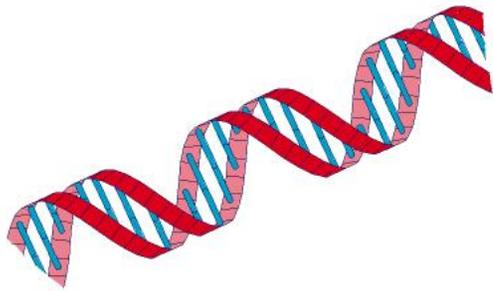


January 2003

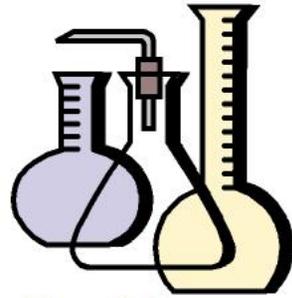


U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
National Institutes of Health  
National Institute of Allergy and Infectious Diseases

<http://www.niaid.nih.gov/biodefense/>



**Genomics**



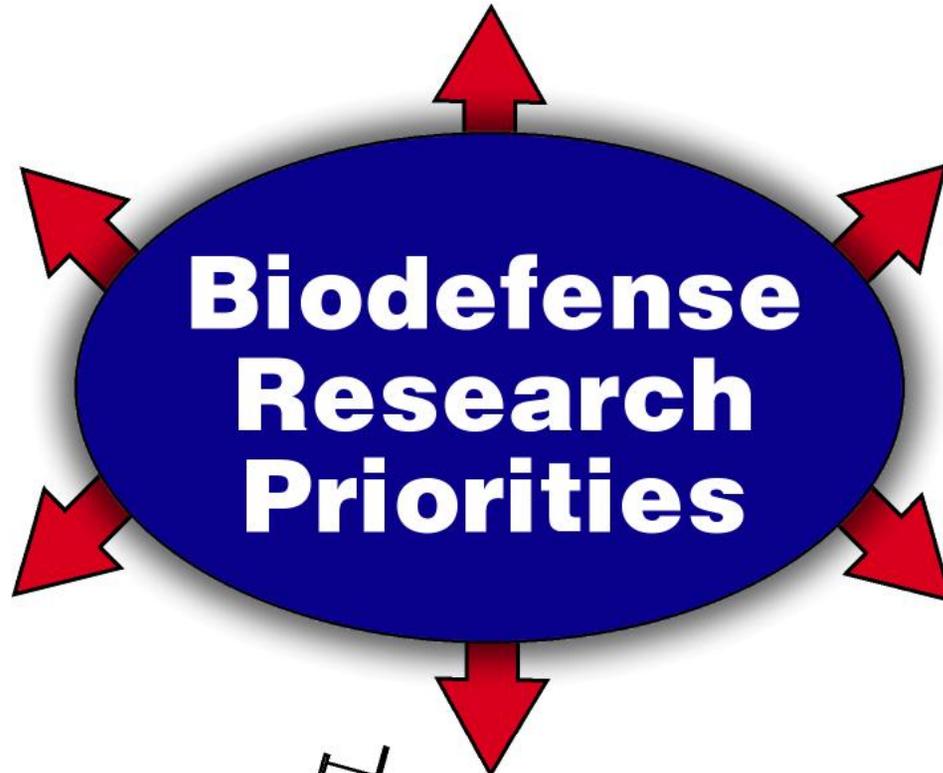
**Basic Research**



**Therapeutics**



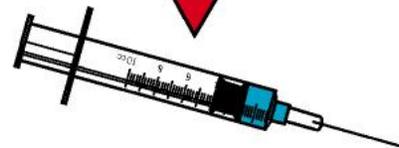
**Diagnostics**



**Biodefense  
Research  
Priorities**



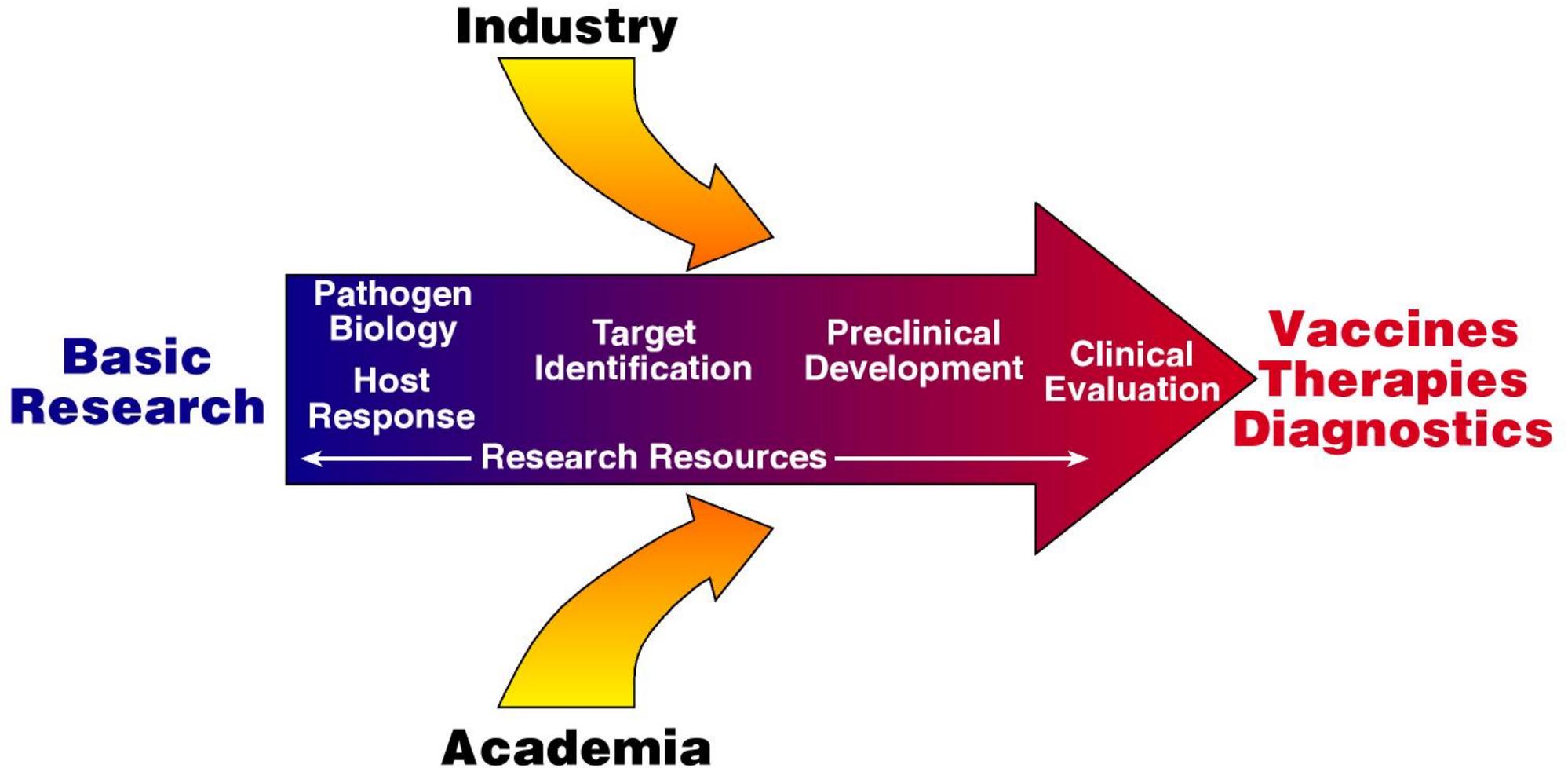
**Expansion of  
Research  
Capacity**



**Vaccines**

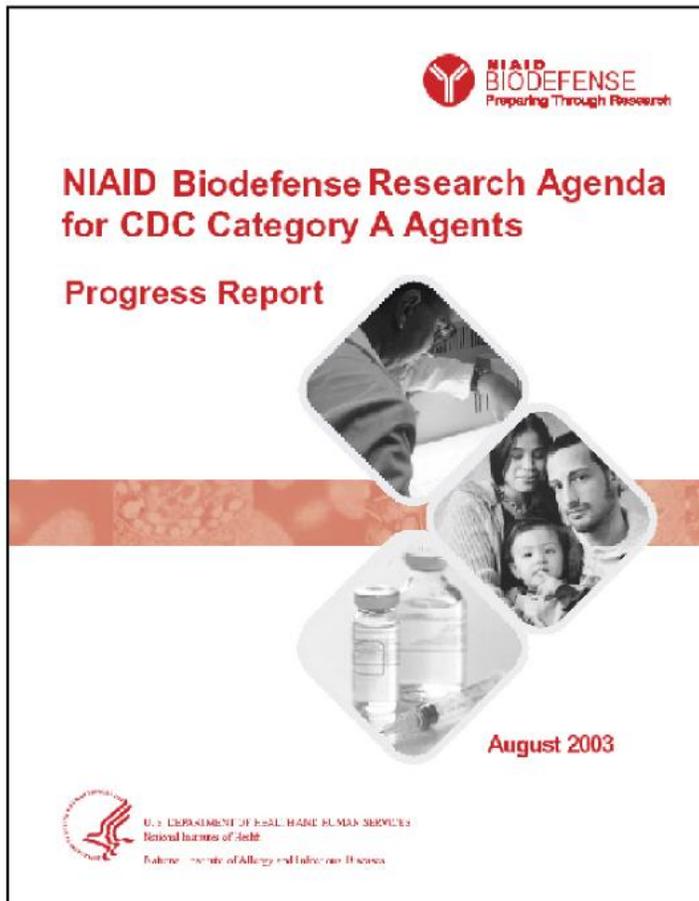
# NIH Biodefense Research Pathway

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# Significant Progress in NIH Biodefense Research

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- **>50 major initiatives involving intramural, academic and industrial partners**
- **Expansion of research capacity**
- **Important discoveries related to priority pathogens and host responses**
- **Development of countermeasures**

# Countermeasure Development

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## ■ Immediate

- Smallpox vaccine dilution studies
- rPA anthrax vaccine
- MVA smallpox vaccine
- Ebola vaccine
- Botulinum toxin-human monoclonal antibodies

## ■ Intermediate

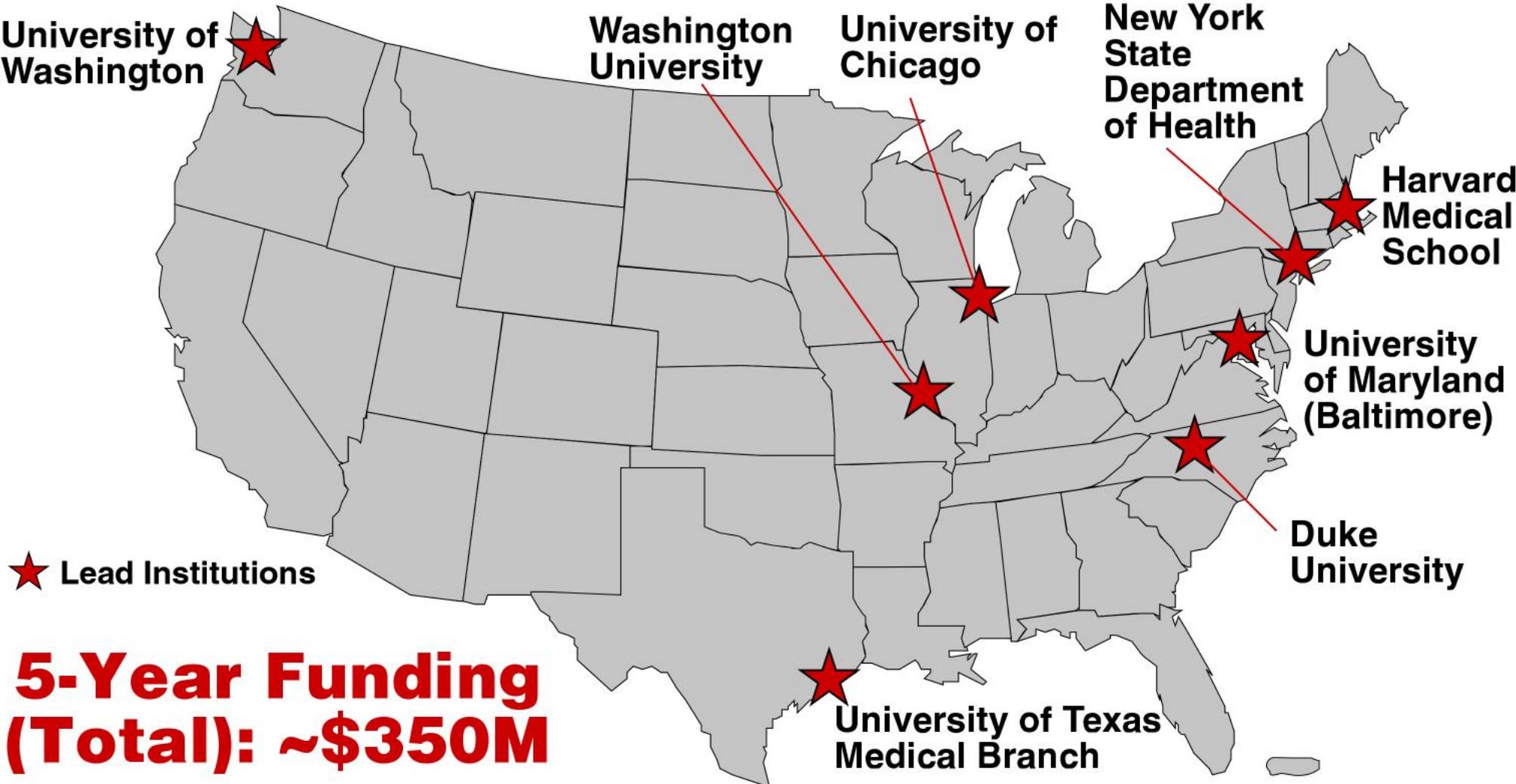
- Smallpox therapeutics
- Plague vaccine
- Tularemia vaccine
- Botulinum toxin vaccine

## ■ Long-term

- Universal antibiotics and vaccines

# **Expanding Research Capacity**

# NIAID Regional Centers of Excellence for Biodefense and Emerging Infectious Diseases Research (RCEs)



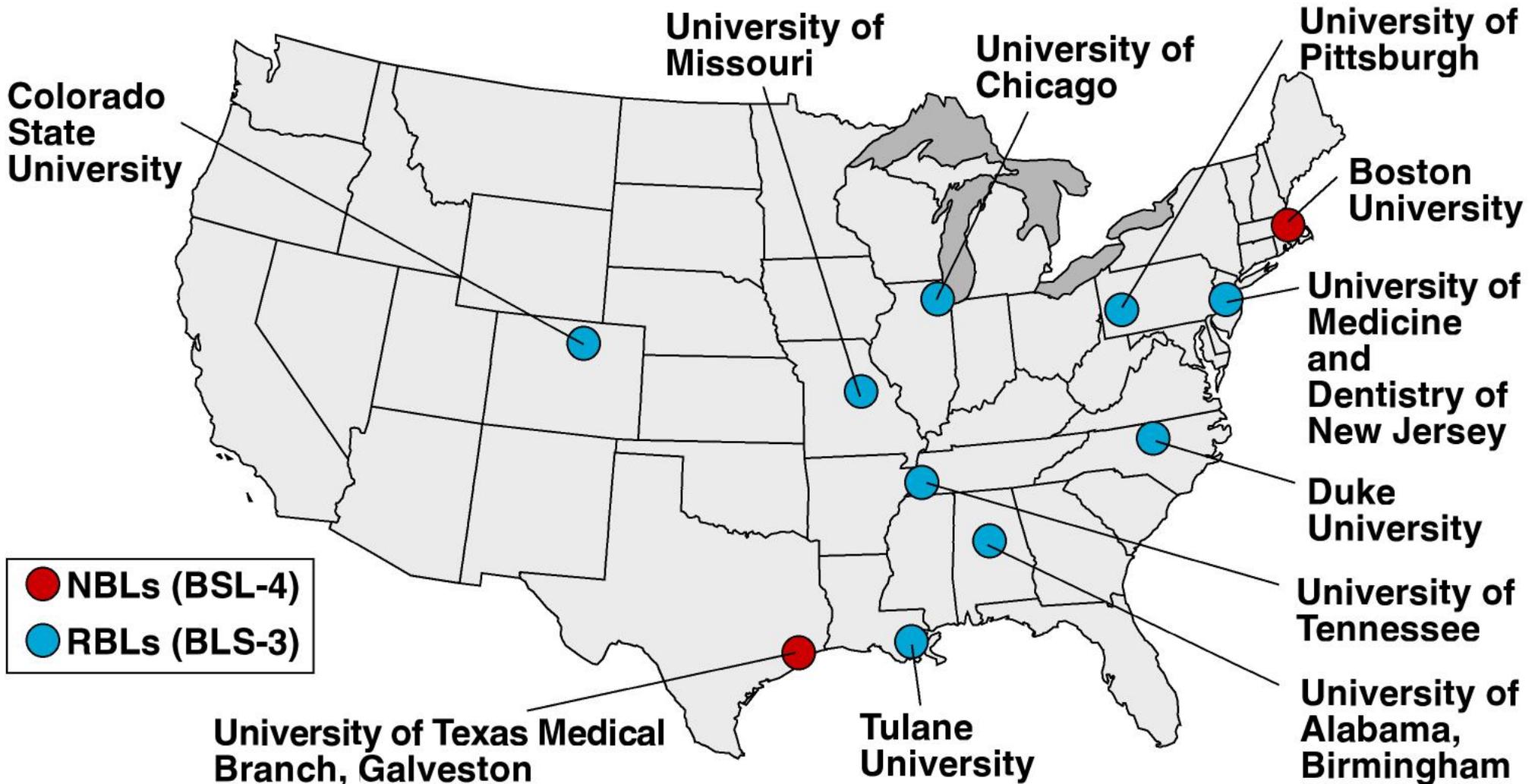
**5-Year Funding (Total): ~\$350M**

# **NIAID Regional Centers of Excellence (RCEs)**

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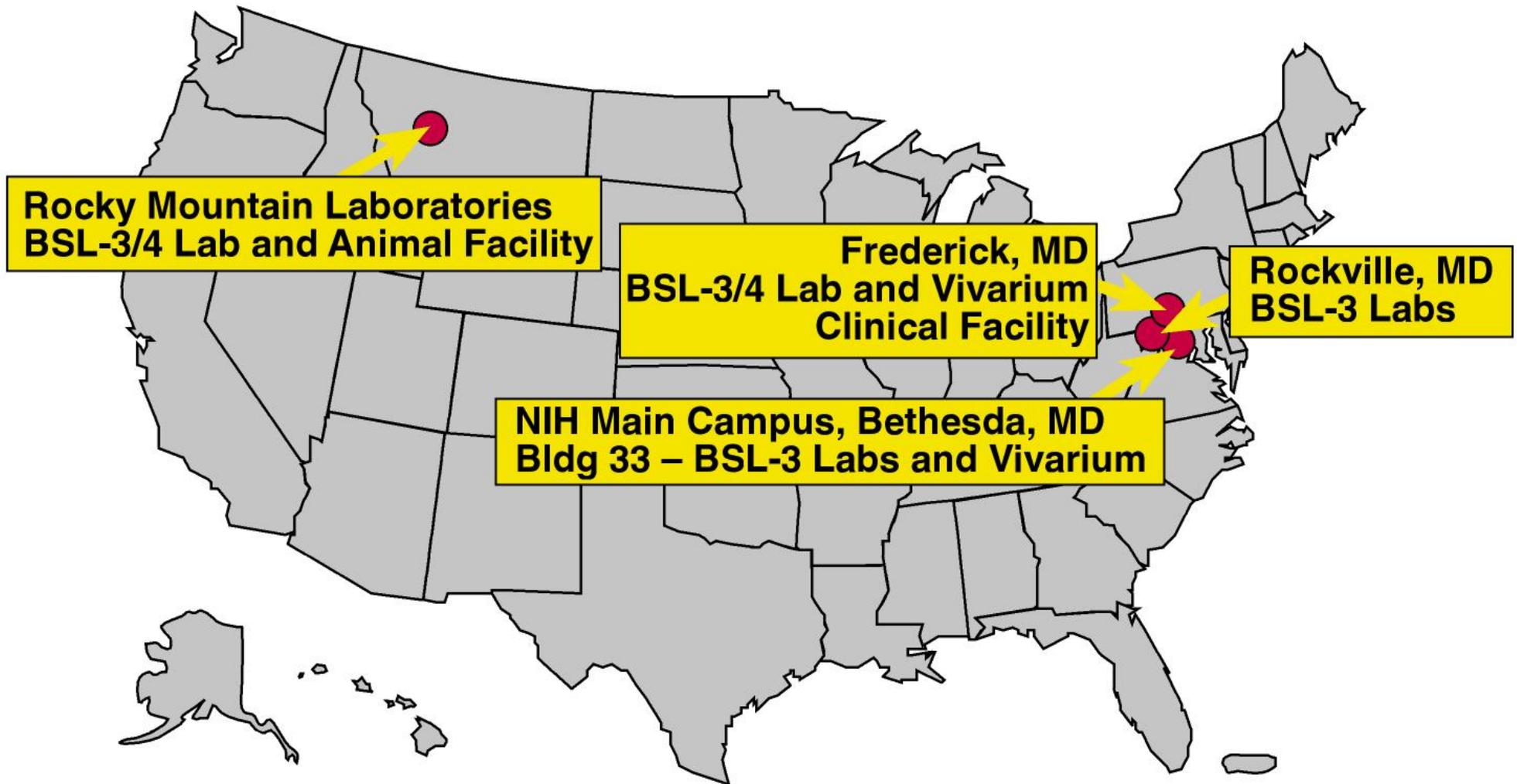
- **Basic research to understand category A, B, and C agents**
- **Interdisciplinary research**
- **Translational research leading to the identification of new drugs, vaccines and diagnostics**
- **Training of new researchers**
- **Developmental research projects**
- **Research for National emergency responders**

# NIAID-Supported National Biocontainment Laboratories (NBLs) and Regional Biocontainment Laboratories (RBLs)



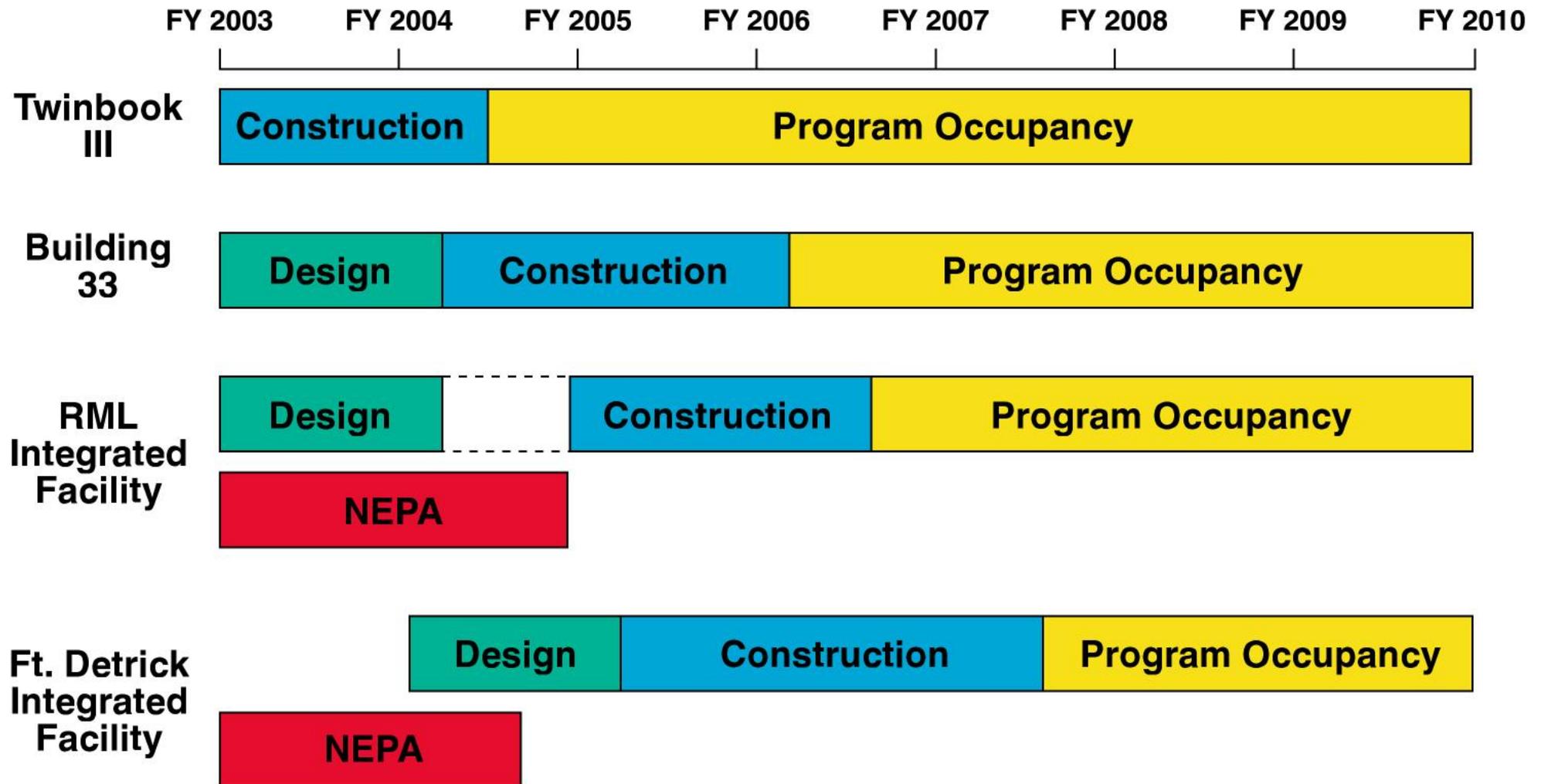
# New NIH Facilities to Study Agents of Bioterrorism and Emerging Diseases

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# Facility Overview

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# Twinbrook III

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**Occupancy: FY 2004**

# Building 33 – Main NIH Campus

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## **Occupancy:**

FY 2006

## **Size:**

65,000 nsf of lab space

## **Cost Design/Construction:**

\$186.1 M

## **Research Areas:**

Anthrax, poxviruses, TB, TBEV/dengue, tularemia, hantavirus, influenza, botulism, host-parasite interactions

## **Features:**

High security; capability for BSL-3 on every floor; vivarium; multi-level parking garage



# Building 33 Construction, Jan. 21, 2004

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# Proposed Rocky Mountain Labs BSL-3/4

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**Occupancy** FY 2006

**Size** 15,000 nsf of assignable lab

**Cost Design/Construction** \$70M

## **Research Areas**

MDRTB, tularemia, plague, host-parasite interactions, Q fever

## **Features**

Capacity to do animal BSL-4 research, including primates

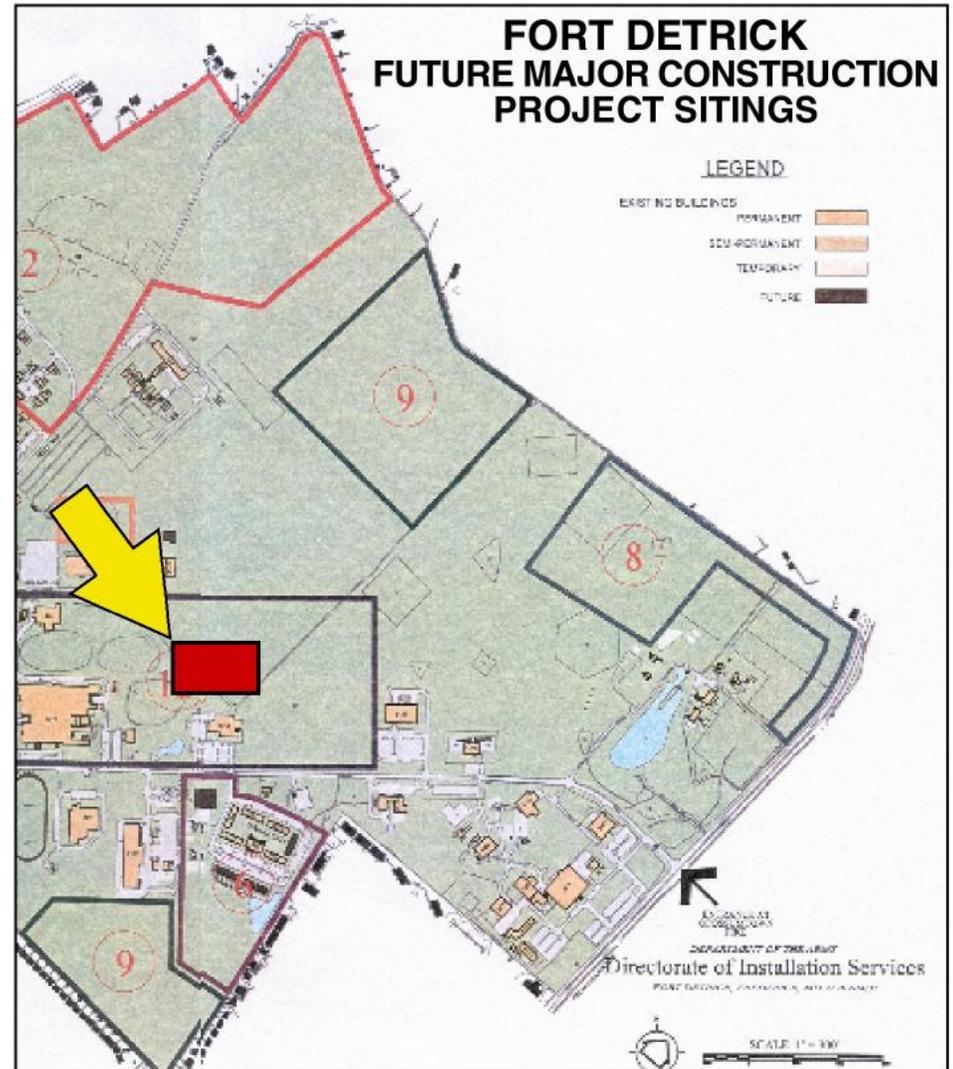


# NIH BSL-3/4 Pre-Clinical and Clinical Research Facilities, Fort Detrick, MD

**Occupancy** FY 2007  
**Size** 120,000 gsf  
**Cost Design/Construction** \$105 M

**Research Areas**  
Anthrax, poxviruses, viral hemorrhagic fevers, drug-resistant bacterial infections

**Features**  
BSL-4 lab and animal facility with clinical capability



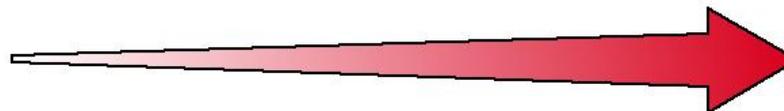
# NIAID Vaccine Research Center

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- 5-story state-of-the-art facility, opened fall 2000
- 170 employees
- Pilot lot plant
- HIV, smallpox, ebola and other HFVs, SARS, WNV
- >150 publications
- Close collaborations with clinical trials groups - HVTN, WRAIR, CDC

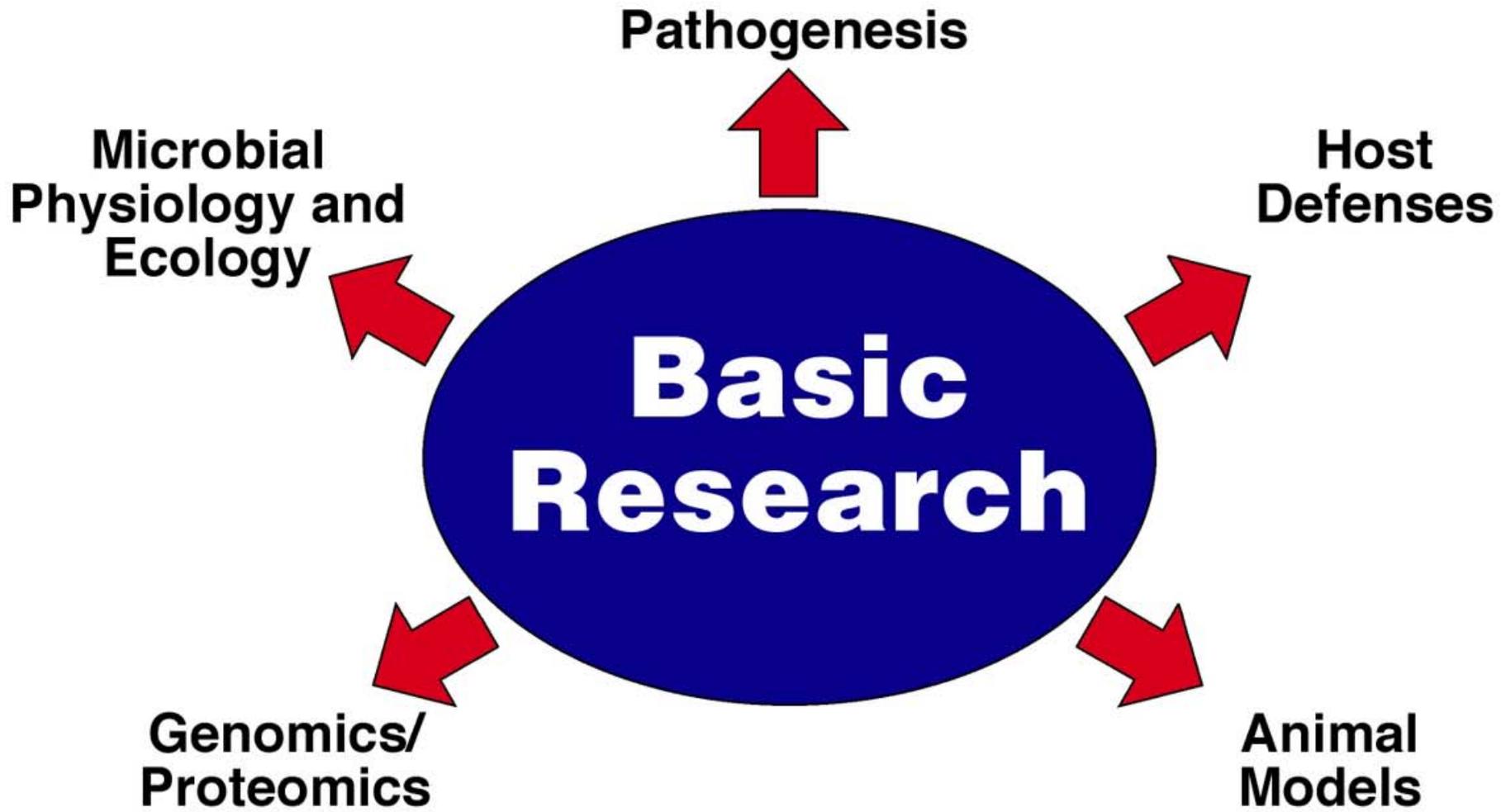
**Basic Research**



**Clinical Trials**

# Basic Research in Biodefense: Progress and Priorities

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# THE WALL STREET JOURNAL

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September 24, 2002

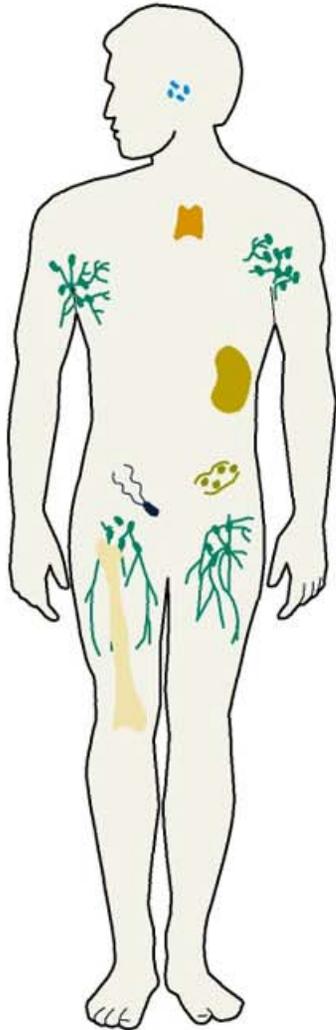
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## **To Fight Bioterror, Doctors Look For Ways to Spur Immune System**

By MARILYN CHASE  
Staff Reporter

# Biodefense Progress and Priorities: Immunology/ Host Response

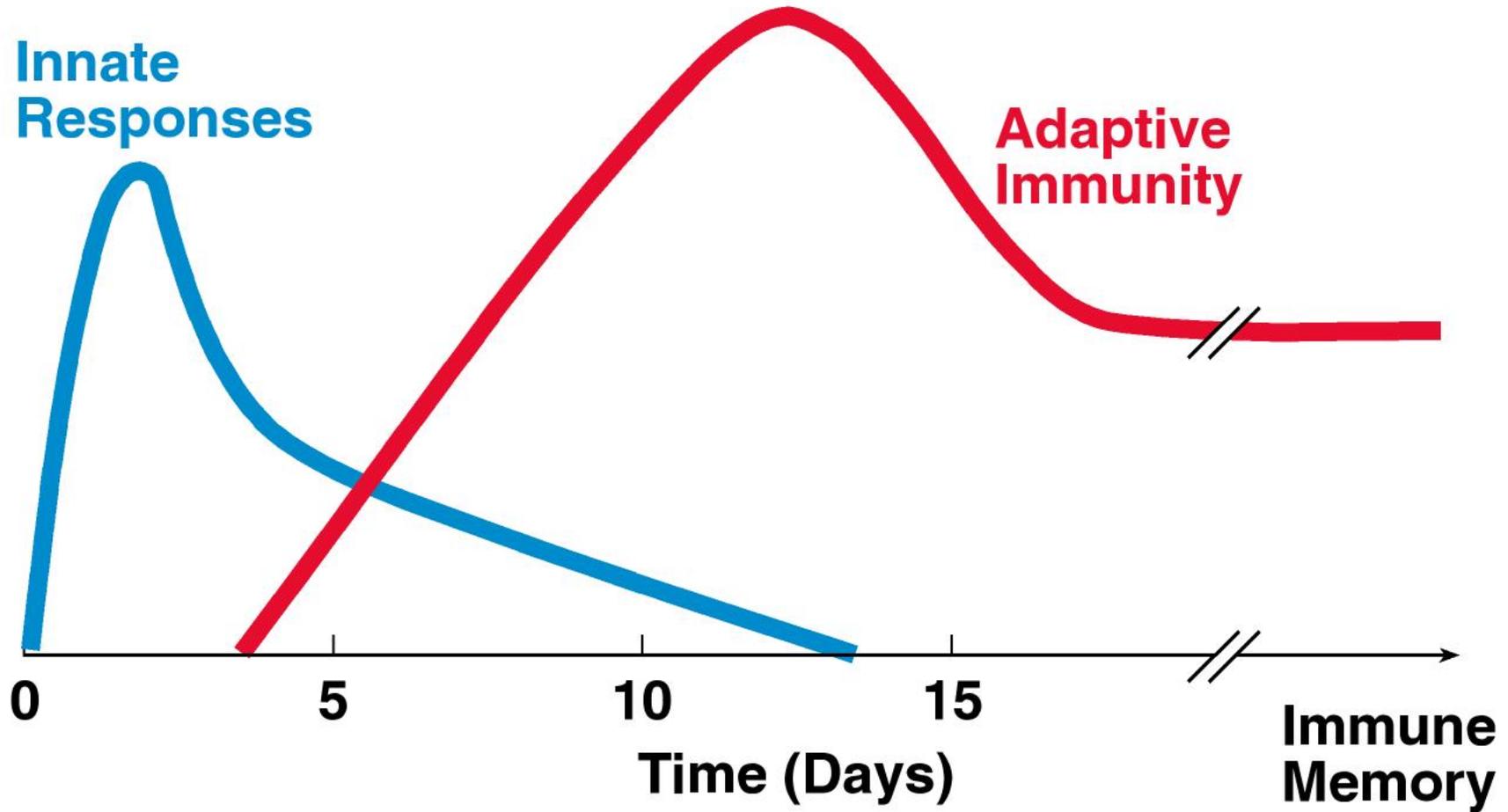
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- Innate immunity
- Adaptive immunity
- Immunotherapy
- Vaccinology
- Mapping of protective epitopes

# Innate vs. Adaptive Immune Responses

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# **Innate vs. Adaptive Immunity**

## **Cells Involved**

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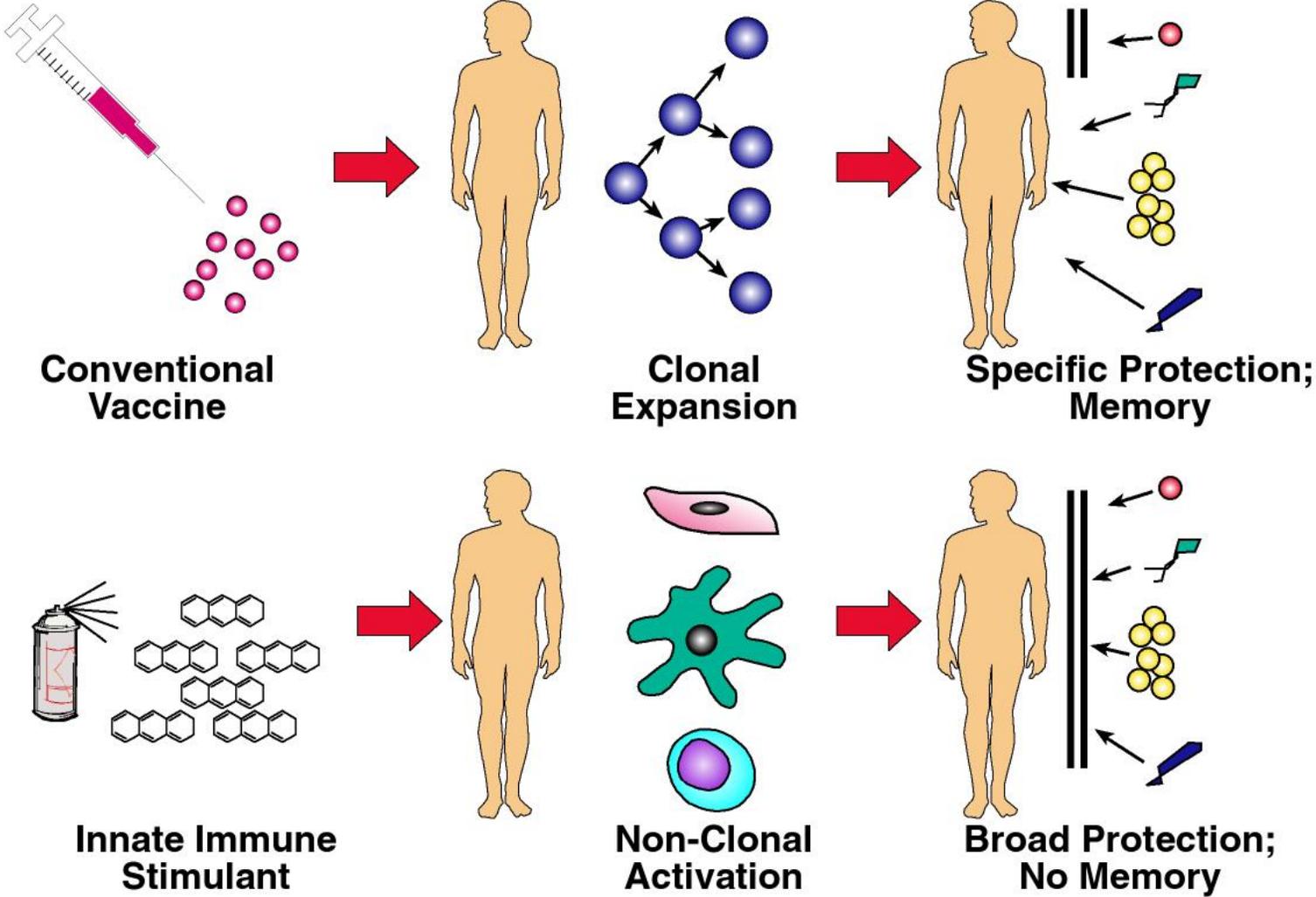
### **Innate**

- **Macrophages**
- **Dendritic Cells**
- **NK Cells**
- **Neutrophils,  
Others**

### **Adaptive**

- **T Cells**
- **B Cells**

# Innate Immune Stimulation vs. Conventional Vaccination



**nature**  
**REVIEWS**

January 2004

Vol 5 No 2

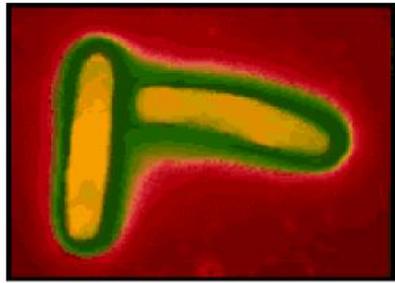
**GENETICS**

**A GENOMICS-BASED  
APPROACH TO  
BIODEFENCE  
PREPAREDNESS**

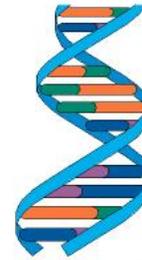
Claire M. Fraser

**"...genomics-based approaches will provide one of the cornerstones of efforts to develop more accurate diagnostics, new therapeutics and vaccines, and further capabilities for microbial forensics."**

# Mining Microbial Genomes to Develop Countermeasures



**Pathogen**



**Cloned  
Genomic  
Sequence**



**Mechanisms of  
Pathogenesis**

**Virulence Factors**

**Structural Proteins**

**Metabolic Pathways**

**Immune Evasion Factors**

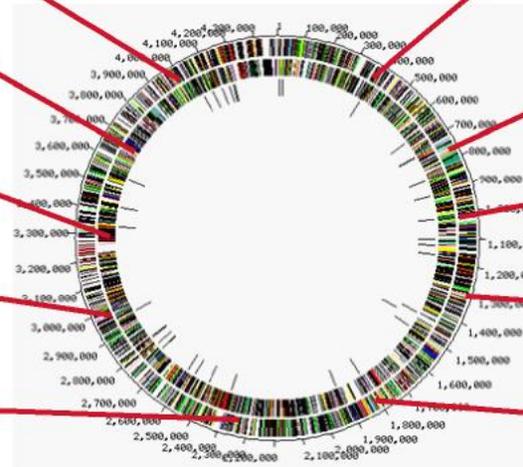
**Biosynthetic Pathways**

**Drug-resistance Mechanisms**

**Receptors**

**Unique Sequences  
(Rapid Diagnosis)**

**Immunostimulatory  
Proteins**



**Whole Genomic Sequence**

28 July 1995

# Science

## Whole-Genome Random Sequencing and Assembly of *Haemophilus influenzae* Rd

R. D. Fleischmann, M. D. Adams, O. White, R. A. Clayton, E. F. Kirkness, A. R. Kerlavage, C. J. Bult, J.-F. Tomb, B. A. Dougherty, J. M. Merrick, K. McKenney, G. Sutton, W. FitzHugh, C. Fields, J. D. Gocayne, J. Scott, R. Shirley, L.-I. Liu, A. Glodek, J. M. Kelley, J. F. Weidman, C. A. Phillips, T. Spriggs, E. Hedblom, M. D. Cotton, T. R. Utterback, M. C. Hanna, D. T. Nguyen, D. M. Saudek, R. C. Brandon, L. D. Fine, J. L. Fritchman, J. L. Fuhrmann, N. S. M. Geoghagen, C. L. Gnehm, L. A. McDonald, K. V. Small, C. M. Fraser, H. O. Smith, J. C. Venter

# Genomic Sequencing of Potential Bioterror Agents: Selected NIH Projects Completed or Nearing Completion

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Agent	Disease	NIAID Category
<i>Bacillus anthracis</i> (multiple strains)	Anthrax	A
<i>Brucella suis</i>	Brucellosis	B
<i>Burkholderia mallei</i>	Glanders	B
<i>Clostridium perfringens</i>	Gas gangrene	B
<i>Coxiella burnetii</i>	Q fever	B
<i>E. coli</i> 0157:H7	Hemolytic uremic syndrome	B
<i>Mycobacterium tuberculosis</i>	Tuberculosis	C
<i>Rickettsia typhi</i>	Typhus	C
<i>Staphylococcus aureus</i>	Bacteremia, endocarditis	B
<i>Yersinia pestis</i>	Plague	A
<i>Variola major</i>	Smallpox	A

# NIAID Microbial Genome Sequencing Centers

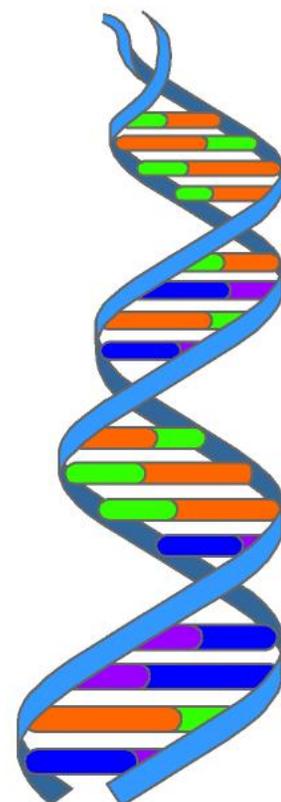
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## Goal:

Rapid and cost-efficient production of high-quality genome sequences of human pathogens and invertebrate vectors of disease.

## Features:

- **Two Genome Sequencing Centers**
  - The Institute for Genomic Research (TIGR)
  - MIT
- **Capacity to sequence genomes for:**
  - Other government agencies
  - Scientific community
  - Response to national emergencies



# **NIAID Pathogen Functional Genomics Resource Center**

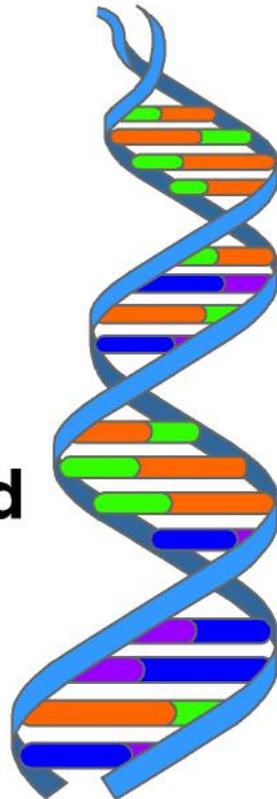
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## **Goal:**

**Develop and distribute genomic reagents, resources and technologies for the functional analysis of pathogens and invertebrate vectors of disease.**

## **Genomic Resources:**

- **Organism-specific microarrays and protocols**
- **Protein expression clones**
- **Genotyping/genome analysis**
- **Development of computational tools for array and comparative genomic data analysis**
- **Technology development**



# Countermeasure Development

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- **New and Improved Vaccines**
- **Therapies**
- **Diagnostics**



7 August 2003

International weekly journal of science

# nature

• Nature 2002 impact factor 30.42 •  
30.4  
No Nature  
no impact  
Source: Thomson ISI, Philadelphia, PA, USA, 2003

\$10.00

[www.nature.com/nature](http://www.nature.com/nature)

## **Accelerated vaccination for Ebola virus haemorrhagic fever in non-human primates**

*The physics of*  
**Nancy J. Sullivan, Thomas W. Geisbert, Joan B. Geisbert,  
Ling Xu, Zhi-yong Yang, Mario Roederer, Richard A.  
Koup, Peter B. Jahrling and Gary J. Nabel**



# NIH NEWS RELEASE

Tuesday, November 18, 2003

National Institutes of Health

National Institute of Allergy  
and Infectious Diseases

## **NIAID Ebola Vaccine Enters Human Trial**



**The first human trial of a vaccine designed to prevent Ebola infection opened today. Scientists from the Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases (NIAID), one of the National Institutes of Health (NIH), designed the vaccine, which was administered to a volunteer at the NIH Clinical Center in Bethesda. The vaccine does not contain any infectious material from the Ebola virus.**

# **HHS News**

*U.S. Department of Health and Human Services*



[www.hhs.gov/news](http://www.hhs.gov/news)

FOR IMMEDIATE RELEASE  
Thursday, October 3, 2002

## **HHS Announces Contracts for Developing a New Anthrax Vaccine**

HHS Secretary Tommy G. Thompson today announced that the National Institute of Allergy and Infectious Diseases (NIAID) has awarded two companies contracts designed to spur development of a new anthrax vaccine.

“There is an urgent need to devise more effective measures to protect U.S. citizens from the harmful effects of anthrax spores used as instruments of terror,” said Secretary Thompson. “These awards represent the first step toward our goal of securing an initial 25 million doses of an improved anthrax vaccine for our emergency stockpile.”

# **Anthrax rPA Vaccine Development Highlights**

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## **Development and Testing of Vaccines Against Anthrax (RFP 02-26)**

- **Three-year contracts awarded to Avecia and VaxGen in 9/2002**
- **\$20M funding**
- **Production of 4,000 doses completed**
- **FDA Animal Rule efficacy studies initiated in monkeys and rabbit**
- **Phase 1 human trials underway**
- **Drug substance and drug product stability testing on-going**

# **Anthrax rPA Vaccine Development Highlights**

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## **Production & Testing of Anthrax rPA Vaccine (RFP 03-29) Awarded September, 2003**

### **VaxGen:**

- Submitted Phase 2 protocol to FDA for review
- Phase 2 investigator meeting January 2004
- 1,000L engineering runs are complete
- Clinical, non-clinical and regulatory development plans to be included in the January 2004 monthly technical report

### **Avecia:**

- Clinical, non-clinical and regulatory development plans to be included in the January 2004 monthly technical report
- Three 100L fermentation batches complete
- One 3000L large scale engineering run complete



The  
**New England  
Journal of Medicine**

Established in 1812 as THE NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

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VOLUME 346

April 25, 2002

NUMBER 17

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**Clinical Responses to Undiluted  
and Diluted Smallpox Vaccine**

Sharon E. Frey, M.D. et al.

# **HHS News**

*U.S. Department of Health and Human Services*



[www.hhs.gov/news](http://www.hhs.gov/news)

FOR IMMEDIATE RELEASE

February 25, 2003

## **HHS Announces Contracts To Develop Safer Smallpox Vaccines**

HHS Secretary Tommy G. Thompson today announced the award of two contracts totaling up to \$20 million in first-year funding to develop safer smallpox vaccines. The three-year contracts were awarded to Bavarian Nordic A/S of Copenhagen, Denmark, and Acambis Inc. of Cambridge, Mass. The National Institute of Allergy and Infectious Diseases (NIAID) will administer the contracts.

# MVA Development Highlights

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- **Three year contracts awarded to Acambis Inc. and Bavarian Nordic A/S, Feb. 2003**
  - Up to \$20M first year funding
  - Production of >10,000 doses completed
  - FDA Animal Rule efficacy studies initiated in monkeys and mice
  - Phase 1 human trials underway
  - Trials in HIV<sup>+</sup> patients planned for late 2004
- **RFP 04-49 (released to public on Dec. 4, 2003)**
  - Follow-on awards to be made in summer of 2004
  - Designed to continue fast-paced product development
  - Production of 3M doses of licensure-grade vaccine
  - Continued testing in animal models in fulfillment of FDA Animal Rule
  - Completion of extended Phase 2 safety trials
  - Production plan for 50M doses of MVA



# **Developing Safer Smallpox Vaccines**

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## **■ MVA**

- Human trials underway**
- Shown to protect monkeys against challenge with monkeypox**
- Immunity develops more rapidly than with standard smallpox vaccine (Dyvax)**

## **■ Recombinant subunit protein vaccine shown to protect mice better than Dryvax**

## **■ DNA vaccine (expressing 3 viral membrane proteins) shown to protect monkeys against challenge with monkeypox**

## **■ High throughput assay for neutralizing antibodies in vaccine recipients developed that will speed testing of new vaccines.**

# Plague and Tularemia Vaccine Development

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## Plague:

RFP issued for Development, Testing and Evaluation of Candidate Vaccines Against Plague. Proposal receipt date was 12/2003.

## Tularemia:

Collaborative research project between DoD and NIAID for live vaccine strain development against Tularemia

- DoD to provide product
- NIAID to provide testing
  - Animal toxicity
  - IND filing
  - Phase I clinical trial



# **Biodefense Therapeutics Research**

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**Screening**

**New Targets**



**Drug  
Resistance**

**Broad-Spectrum  
Therapies**

# **Botulinum Antibodies/Antitoxins: Development and Acquisition Plan**

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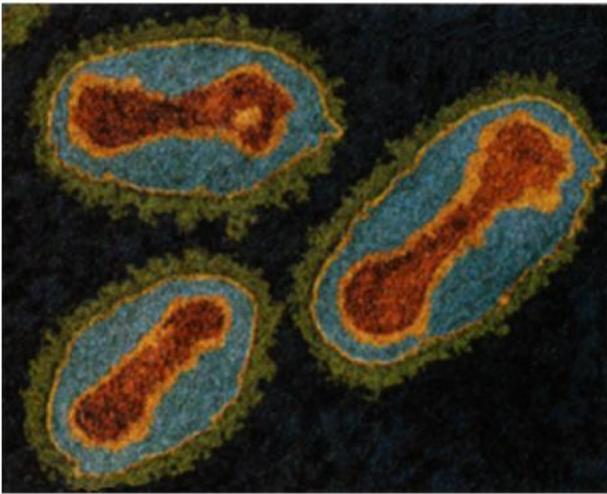
- **Currently available immune globulin**
- **Plasma available for processing**
- **New horse immunization program**
- **Monoclonal/polyclonal antibodies**

# Smallpox Therapeutics Development

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## Goal:

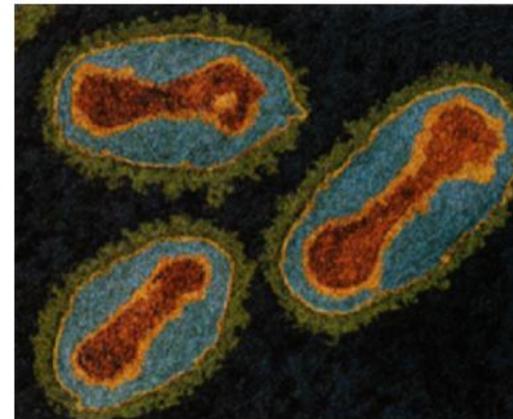
- Increase the number of available antivirals to include at least 2 orally administered agents with different mechanisms of action.



# Cidofovir

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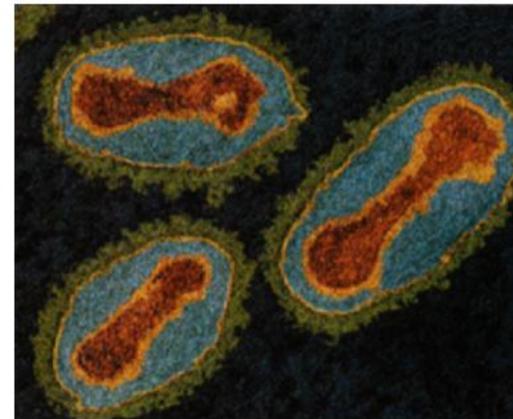
- **Effective vs many poxviruses in multiple animal models**
- **Licensed product**
- **INDs prepared for treatment of smallpox and complications of vaccination**
- **IV delivery**
- **Renal toxicity**



# Lipid-CDV Analogs Show Promising Activity Profile

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- Extremely potent *in vitro* against *Variola* and other orthopoxviruses
- Oral bioavailability ranges from 88 to 97% in mice
- Improved distribution vs. intravenous CDV
  - Elevated exposure in liver and lungs
  - Reduced exposure in kidneys
- Certain Lipid-CDV analogs are completely protective in lethal mouse orthopoxvirus models



# Other Recent Accomplishments

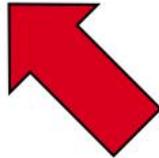
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- **Poxvirus Bioinformatics site up and running:**  
<http://www.poxvirus.org/>
- **30 complete genomes**
- **Useful new analysis software**
- **New collections of monoclonal antibodies against the 5 major vaccinia neutralization antigens. Several of these antibodies cross-react with variola proteins.**
- **Characterization of two NHP models for smallpox (Peter Jahrling and John Huggins, USAMRIID)**
  - **IV infection of cynomolgus monkeys with Monkeypox**
  - **IV infection of cynomolgus monkeys with Variola**

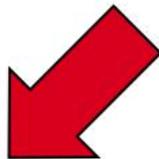
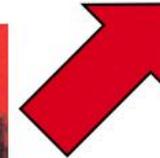
# Medical Diagnostics for Biodefense

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*In vivo*  
molecular  
imaging



Inhaled  
biological  
radiotracers



Integrated systems/platforms  
for screening and detecting  
multiple agents



Nanotechnology

# A Comprehensive Biodefense Research Agenda

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**NIH**

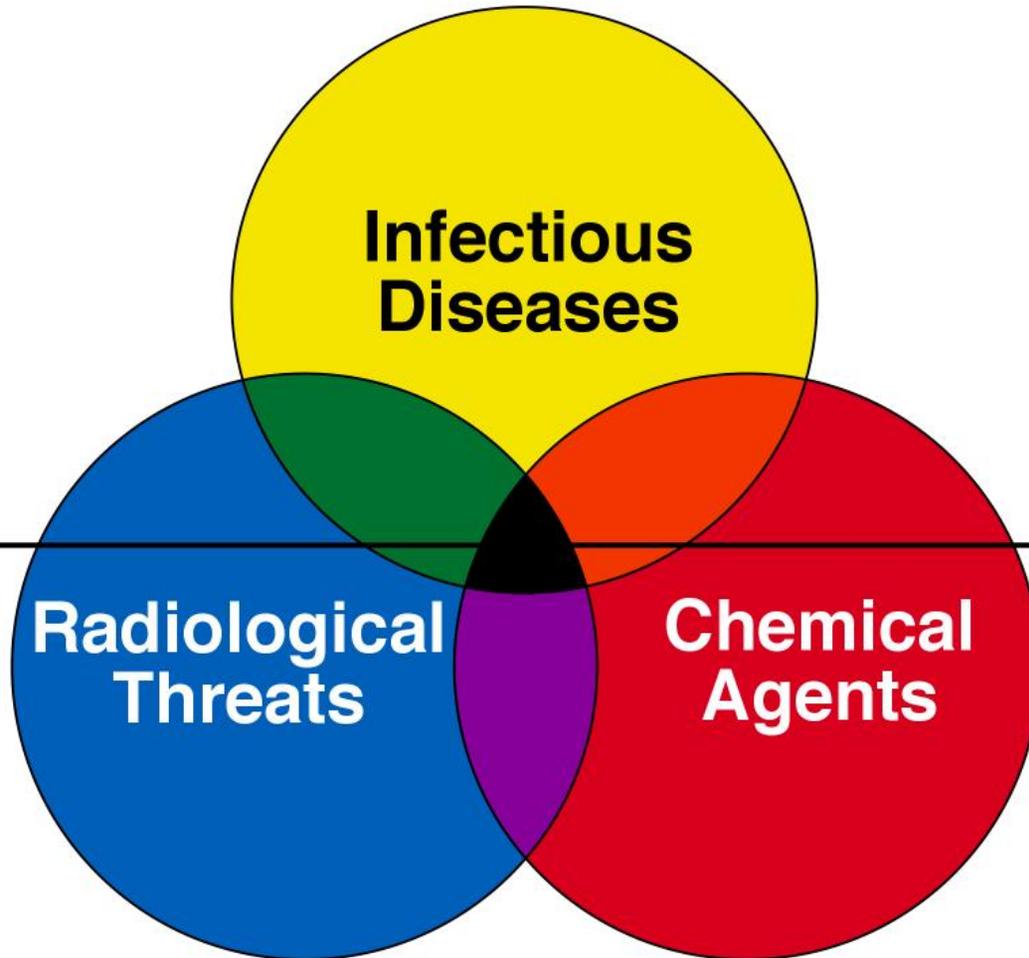
**Infectious  
Diseases**

**Radiological  
Threats**

**Chemical  
Agents**

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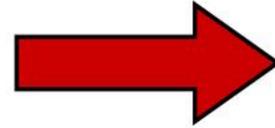
**DHS  
EPA  
DOE  
DoD  
FDA  
USDA  
etc.**



# Opportunities for New Medical Countermeasures for Radiological & Nuclear Incidents

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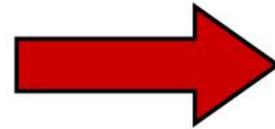
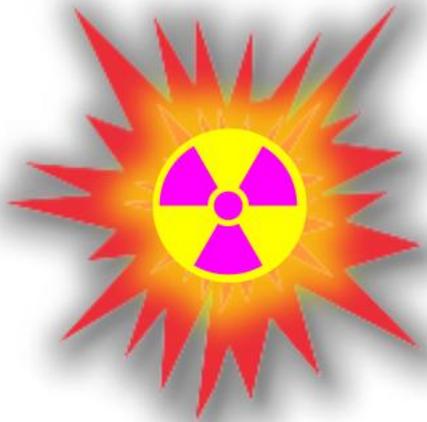
Pre-exposure



## Protectants

Amifostine  
Phosphonol  
Vitamin E  
Genistein  
5-AED

Radiation  
Exposure



## Assessment

Cytogenetic assays  
Protein markers

Post-exposure



## Therapeutics

G-CSF and Cytokines  
Antimicrobials  
Immune System Recovery

# **Immune System Recovery Following Radiation Exposure**

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- **Acceleration of immune system recovery is critical for survival**
- **Bone marrow transplantation is impractical following large number of radiation injuries**
- **Experimental stem cell technologies need to be pursued**

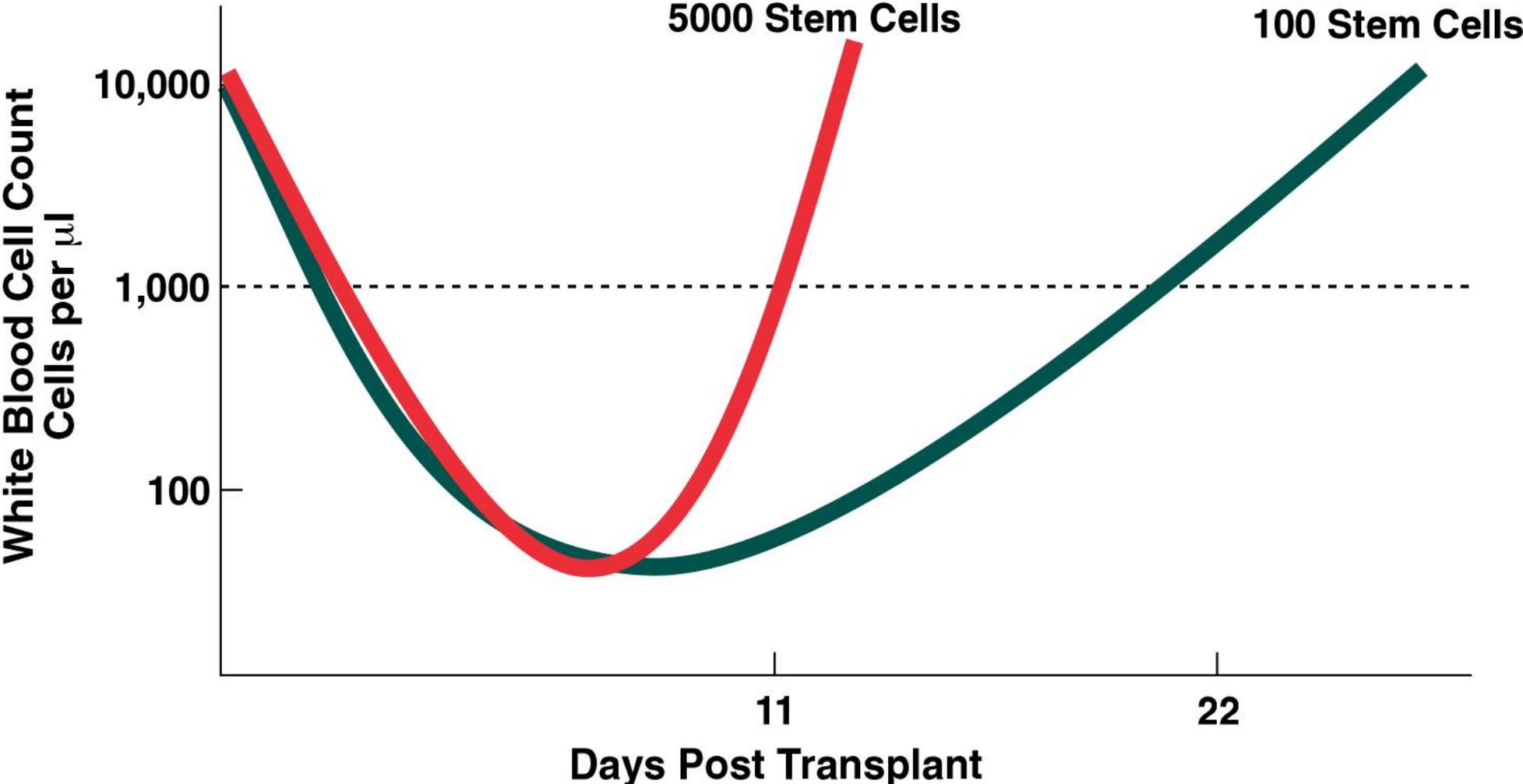
# **Novel Approach to Immune System Recovery: Stem Cell Transfusion**

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- **Dramatically increase purity of stem cells**
- **Greatly expand cell numbers *in vitro* with novel growth factors**
- **Maintain pluripotency of stem cells during expansion**

# Stem Cell Dose vs. Days to Recovery

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# Human Adult Stem Cells

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- **Long Range Goal: establish a national bank of human adult stem cells**
- **Applications extend beyond radiation, e.g. cancer, transplantation**

# **NIAID and AFRRI Partnership**

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## **■ FY03 Interagency Agreement**

- \$1.5M provided to procure cobalt-60 gamma radiation source for radiation studies**

## **■ FY04 Interagency Agreement**

- ~ \$5M**
- Will fund further development of radioprotectants, e.g., 5-AED and genestein**
- Validate a lab-based biodosimetry tool**
- Explore molecular biodosimetry tools**
- Evaluate antimicrobial drugs currently in SNS in treatment and prevention of post-radiation-associated infections**

# **Infectious Diseases Preparedness: Vision for the Future**

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- **“Universal” antibiotics, antivirals, antitoxins against all classes of biological pathogens**
- **Safe and effective vaccines against all classes of biological pathogens, and “platforms” to quickly develop vaccines against new threats**
- **Safe and effective approaches for modulating innate immunity to induce broad protection against biological pathogens**
- **Simple and rapid diagnostics to detect, characterize and quantify any infectious threat**

**These advances hold the promise of transforming our capability to effectively defend the Nation and the world against virtually any infectious diseases threat, either naturally occurring or deliberately released.**