

Opportunities to Study Rare Diseases at the NIH Clinical Center

Research Advisory Committee on Gulf War Veterans' Illnesses

John I. Gallin, MD
Director NIH Clinical Center
February 28, 2011



Rare Disease Day is an annual, awareness-raising event coordinated by [EURORDIS](http://eurordis.org) at the international level and National Alliances of Patient Organizations at the national

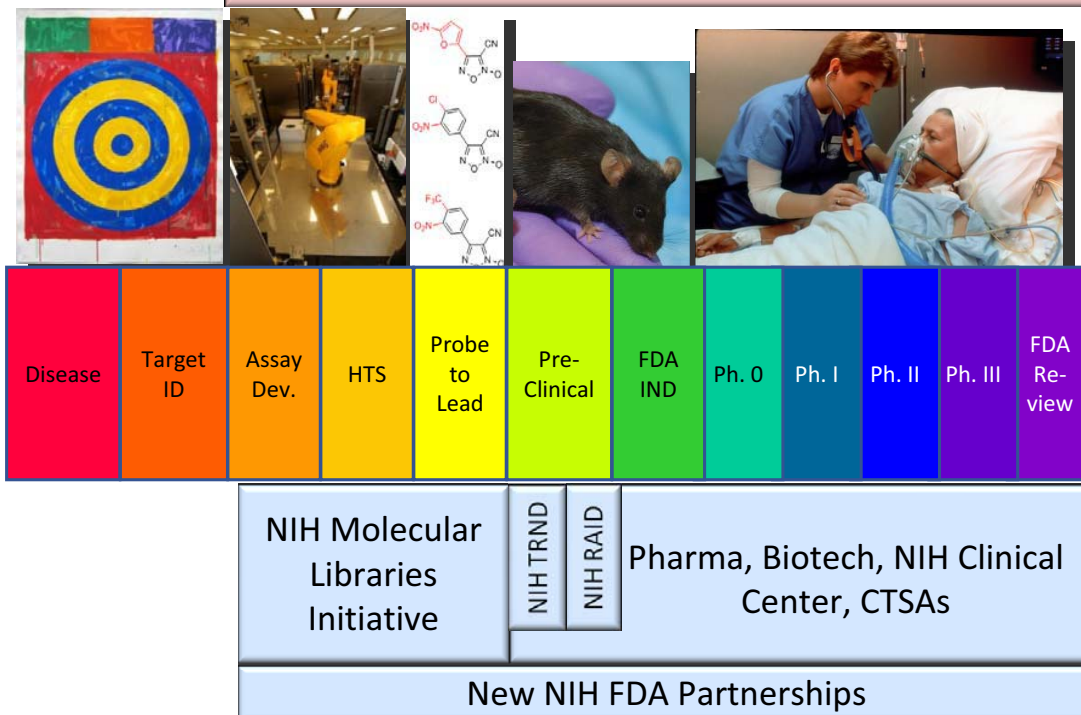
A Role for NIH: Health Care Reform

An Act
 Entitled The Patient Protection and Affordable Care Act.
Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,
SECTION 1. SHORT TITLE; TABLE OF CONTENTS.
 (a) **SHORT TITLE.**—This Act may be cited as the “Patient Protection and Affordable Care Act.”
 (b) **TABLE OF CONTENTS.**—The table of contents of this Act is as follows:
 Sec. 1. Short title; table of contents.
TITLE I—QUALITY, AFFORDABLE HEALTH CARE FOR ALL AMERICANS
 Subtitle A—Immediate Improvements in Health Care Coverage for All Americans
 Sec. 1001. Amendments to the Public Health Service Act.
***PART A—INDIVIDUAL AND GROUP MARKET REFORMS**
***SUBPART II—IMPROVING COVERAGE**
 *Sec. 2711. No lifetime or annual limits.
 *Sec. 2712. Prohibition on rescissions.
 *Sec. 2713. Coverage of preventive health services.
 *Sec. 2714. Extension of dependent coverage.
 *Sec. 2715. Development and utilization of uniform explanation of coverage documents and standardized definitions.
 *Sec. 2716. Prohibition of discrimination based on salary.
 *Sec. 2717. Ensuring the quality of care.
 *Sec. 2718. Bringing down the cost of health care coverage.
 *Sec. 2719. Appeals process.
 Sec. 1002. Health insurance consumer information.
 Sec. 1003. Ensuring that consumers get value for their dollars.
 Sec. 1004. Effective dates.
 Subtitle B—Immediate Actions to Preserve and Expand Coverage
 Sec. 1101. Immediate access to insurance for uninsured individuals with a pre-existing condition.
 Sec. 1102. Reinsurance for early retirees.
 Sec. 1103. Immediate information that allows consumers to identify affordable coverage options.
 Sec. 1104. Administrative simplification.
 Sec. 1105. Effective date.
 Subtitle C—Quality Health Insurance Coverage for All Americans
PART I—HEALTH INSURANCE MARKET REFORMS
 Sec. 1201. Amendment to the Public Health Service Act.
***SUBPART I—GENERAL REFORM**
 *Sec. 2704. Prohibition of preexisting condition exclusions or other discrimination based on health status.
 *Sec. 2701. Fair health insurance premiums.
 *Sec. 2702. Guaranteed availability of coverage.

The Patient Protection and Affordability Act authorizes the NIH to establish a Cures Acceleration Network



Cures Acceleration Network





CC Vision

**As America's research hospital,
we will lead the global effort
in training today's investigators and
discovering tomorrow's cures.**

Mission

Science



Training



Patient Care

Clinical Center Profile



- 17 NIH Institutes use the CC
- More than 400,000 patients since opening in 1953
- 240 beds
- FY 2010
 - 70% occupancy
 - 52,109 inpatient days
 - 9.4 days average length of stay
- 1,918 CC and ~4,000 IC employees
- 1,255 credentialed physicians
- 1,428 active protocols
- Budget 2010: \$377.5M

“There’s No Other Hospital Like It” So What Makes Us Different?



- **Every patient is enrolled on a protocol**
- **Patients are partners on research teams**
- **Care is free**
- **Highly educated nurses familiar with clinical research**
- **A hospital surrounded by research labs with gifted investigators**
- **Long term and high intellectual/economic risk studies**
- **Rapid response to public health emergencies and scientific opportunities**

– CC Accomplishments –



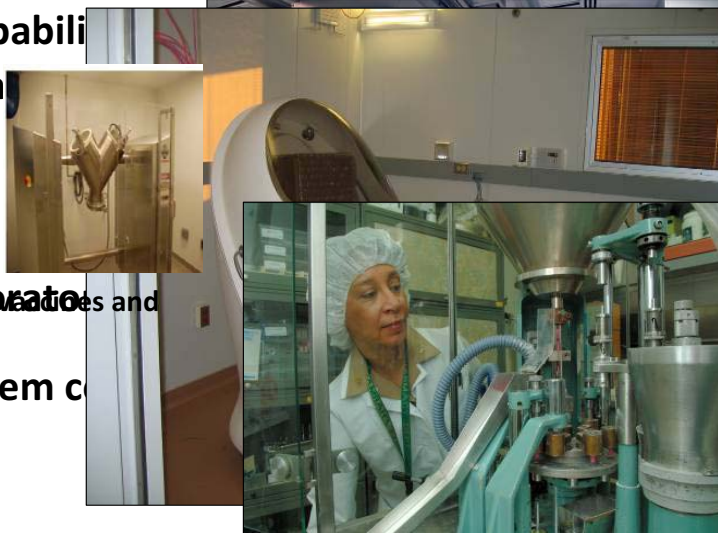
- **Chemotherapy for cancer**
- **1st platelet and granulocyte transfusions; 1st continuous flow blood cell separator**
- **Lithium for bipolar disorders**
- **Blood tests for AIDS, hepatitis**
- **1st gene therapy (ADA Deficiency)**
- **Pathogenesis and treatment of AIDS**
- **1st successful artificial mitral heart valve**
- **Immunosuppressive therapy for nonmalignant diseases**
- **1st fluoride gels to treat dental caries as an infectious disease**

– Recent Accomplishments –

- Cardiac MRI in patients with chest pain to identify high-risk versus low-risk individuals
- Use of adoptive transfer as immunotherapy for metastatic melanoma
- First use of an immunotoxin to treat malignancy (hairy cell leukemia)
- Identification of the genetic basis of kidney cancer which led to new therapeutic approaches
- Use of PET scans to identify abnormalities in schizophrenia
- Discovery of autoinflammatory diseases

Specialized Services and Facilities

- GMP facility for producing candidate drugs
- Manufacturing capabilities
- Imaging equipment
 - 75,000 capsules
 - 150,000 tablets
 - 3 cyclotrons
 - 220 liters
 - MRI center
 - 5,000 syringes
- Biomechanics laboratory (cell lines and biologics)
- Blood products; stem cells
- Phenotyping
- Information Technology
 - BTRIS
 - ProtoType



CC Pharmaceutical Development Section
producing capsules of green tea for a study

Protocols by Research Type

Interventional/Clinical Trials	645 (45%)
Natural History	695 (49%)
Screening	67 (5%)
Training	21 (1%)
Total	1,428

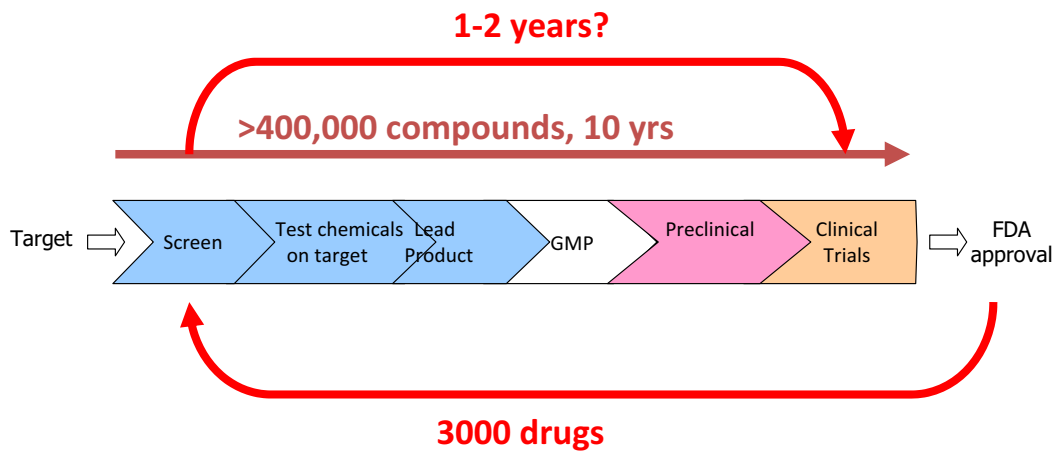
Interventional/Clinical Trials by Phase

Phase I (toxicity)	221	(34%)
Phase II (activity)	370	(57%)
Phase III (efficacy)	38	(6%)
Phase IV (safety)	16	(3%)
Total	645	

Major Emphasis

- **First in human with new therapeutics**

Two Approaches to Develop New Therapeutics



Drug Repurposing NIH Contributions

A shelved nucleoside analogue with poor anticancer activity is rediscovered and becomes an effective antiretroviral drug:

Zidovudine (AZT) for HIV/AIDS

Yarchoan R et al. *Lancet* 1986;1(8481):575-80

Drug Repurposing Research at the NIH Clinical Center

Drug:	Repurposed for:
Atorvastatin	Pulmonary Sarcoidosis
Rituximab	Autoimmune Retinopathy Cryoglobulinemic Vasculitis- Hep. C
Anakinra	Severe Atopic Dermatitis
Scopolamine	Severe Depression
Cladribine	High-Grade Glioma
Nitric Oxide	Sickle Cell Anemia
Pioglitazone	Allergic Asthma Hepatic Steatosis

Drug Repurposing Research at the NIH Clinical Center (continued)

Drug:	Repurposed for:
Tamoxifen	Bipolar Disorder
Pioglitazone	NSC Lung Cancer
Montelukast	Bronchiolitis Obliterans
Interferon gamma 1-b	Cystoid Macular Edema
Hydroxyurea	Sickle Cell Disease
Linezolid	MDR and XDR M. Tuberculosis
Bevacizumab	Glioblastoma Multiforme

*Currently over 65 protocols testing the value of
“old” drugs for new indications.*

Major Emphasis

- **First in human with new therapeutics**
- **Study of patients with rare diseases**

Why Study Rare Diseases at the Clinical Center?

1. Understanding the **pathophysiology and genetics of rare diseases** provides **hope** to patients and may **provide insights to understanding common diseases**.
2. **Ability to assemble cohorts of patients with rare diseases**.

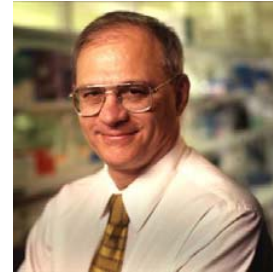
Rare Diseases at the NIH Clinical Center*

Number of Rare Diseases	758
Number of Patients	8,268
Number of Protocols	608
• Clinical Trials	342
• Natural History	266

*May 2008 – October 2010

Undiagnosed Diseases Program (UDP)

-  A call for undiagnosed diseases with no phenotype restrictions
- A multi-disciplinary approach to each patient
-  ~45 NIH senior consultants participate
- About 50% UDP patients have neurodegenerative diseases
-  Total # of patients ~4,000 screened; 350 accepted



William Gahl, MD, PhD
Clinical Director, NHGRI

The New York Times Magazine

UDP Successes

- **Enhances specialty clinic admissions**
 - Bolsters protocols
 - Assists training programs
- **Accepted patients' satisfaction (very high)**
- **Public relations benefits for NIH Intramural Program and NIH Clinical Center**
- **Establishment of new clinical protocols**
- **Science: Discovery of new diseases**

Brief Definitive Report

Neutrophil-specific Granule Deficiency Results from a Novel Mutation with Loss of Function of the Transcription Factor CCAAT/Enhancer Binding Protein ϵ

By Julie A. Lekstrom-Himes, Susan E. Dorman, Pirooska Kopar, Steven M. Holland, and John I. Gallin

From the Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892

1847 The Journal of Experimental Medicine • Volume 189, Number 11, June 7, 1999 1847-1852
<http://www.jem.org>

LAD 1 Abnl CD18 gene (chr 21q)

Lipopolysaccharide and Interleukin-1 in a Patient with Recurrent Bacterial Infections

Andrei E. Medvedev,^{1,5} Arnd Lentschat,^{1,5} Douglas B. Kuhns,² Jorge C.G. Blanco,⁵ Cindy Salkowski,⁵ Shuling Zhang,⁵ Moshe Arditi,³ John I. Gallin,⁴ and Stefanie N. Vogel^{1,5}

The Journal of Experimental Medicine • Volume 198, Number 4, August 18, 2003 521-531
<http://www.jem.org/cgi/doi/10.1084/jem.20030701>

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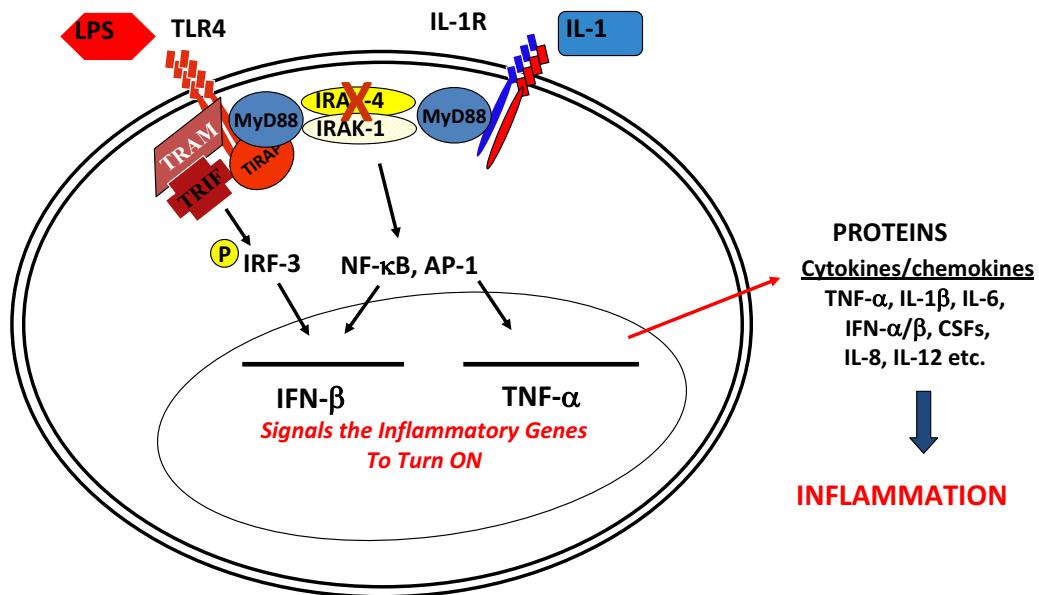
IL-8
 C3a C5a,
 chemokines,
 histamine,
 prostaglandins,
 and leukotrienes

ulation
 tase, Collagenase, Defensins, MPO
 • Lactoferrin
 • Gelatinase

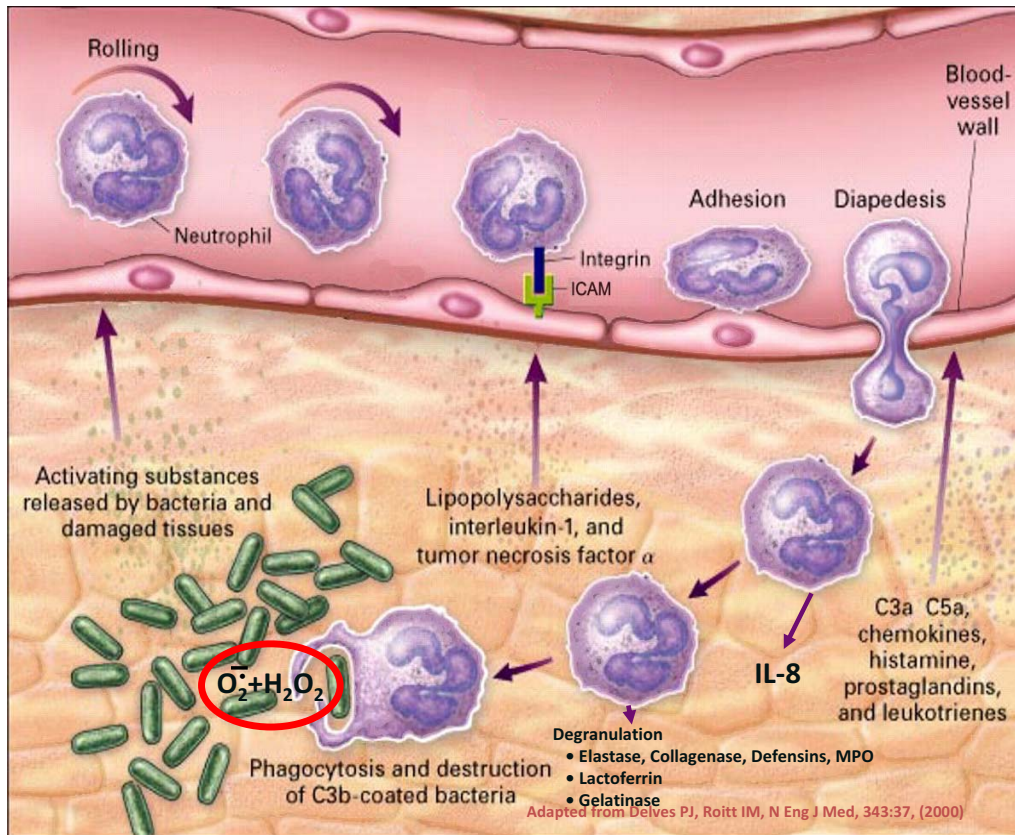
of C3b-coated bacteria

Adapted from Delves PJ, Roitt IM, N Eng J Med, 343:37, (2000)

LPS and IL-1 Activate a Shared Signaling Pathway



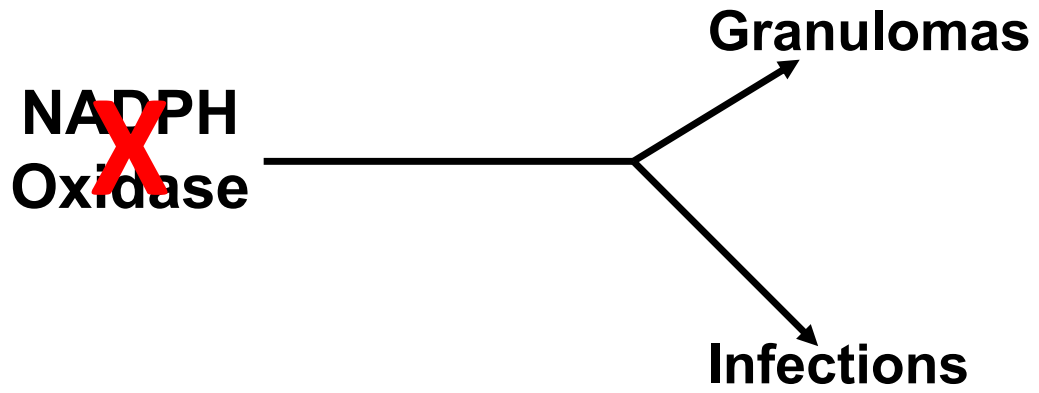
S.Vogel, 2005

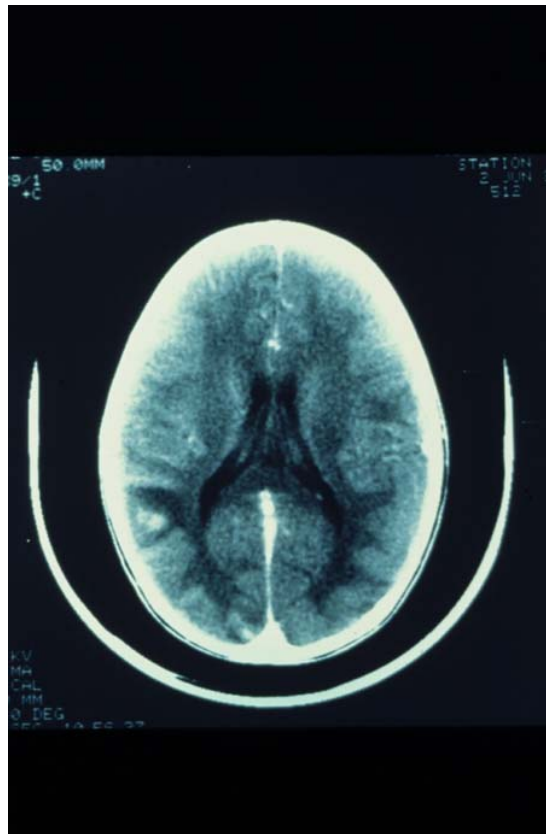
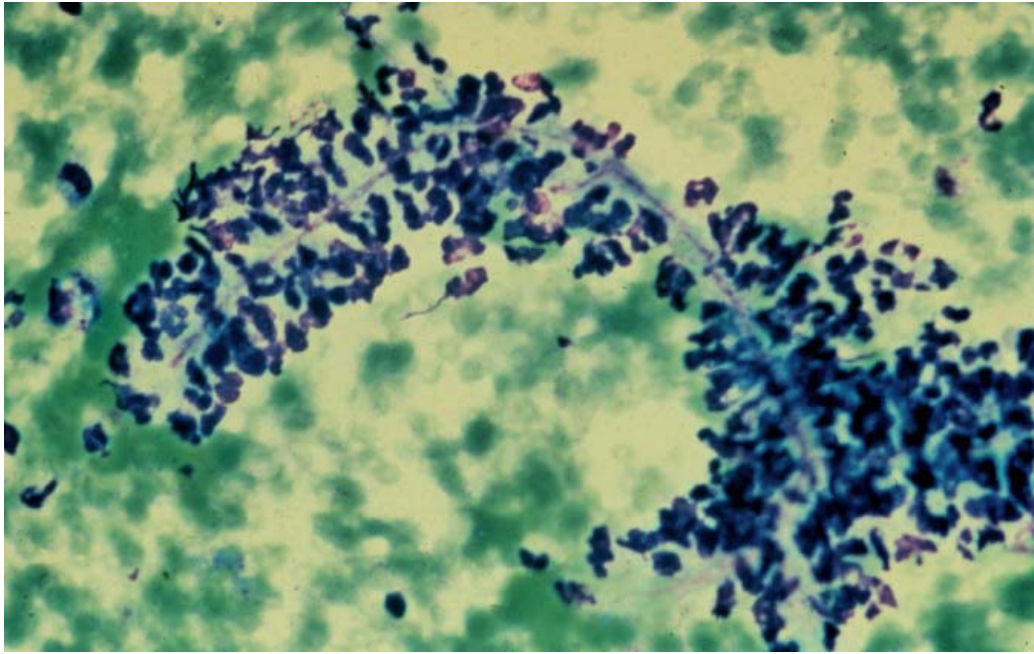


Chronic Granulomatous Disease (CGD)

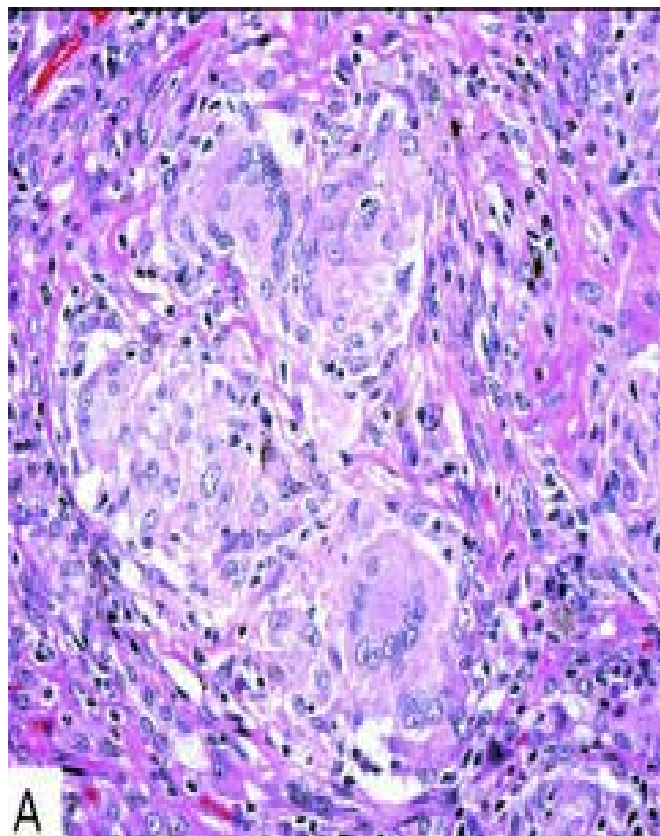
- ~1:200,000 live births in US
- Mortality 2%/yr
- 1/3 CGD deaths caused by *Aspergillus*
- Abnormal NADPH Oxidase

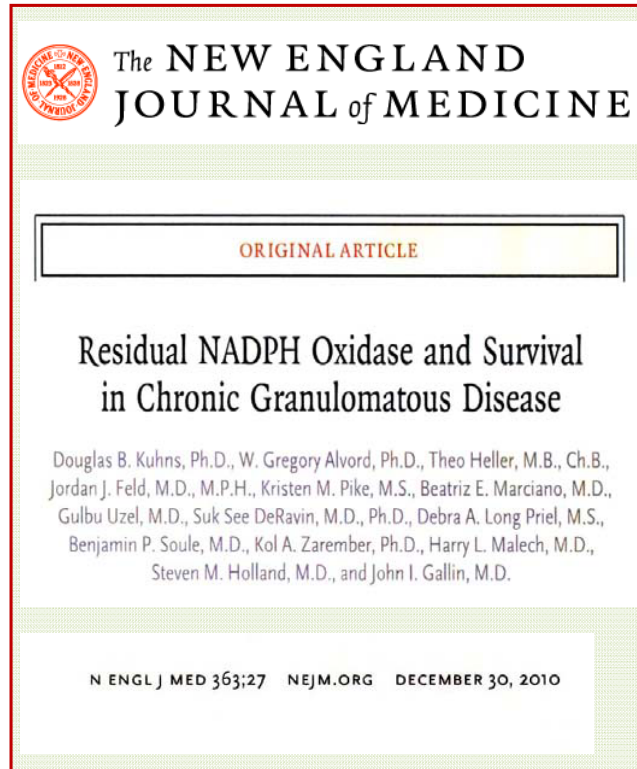
Chronic Granulomatous Disease





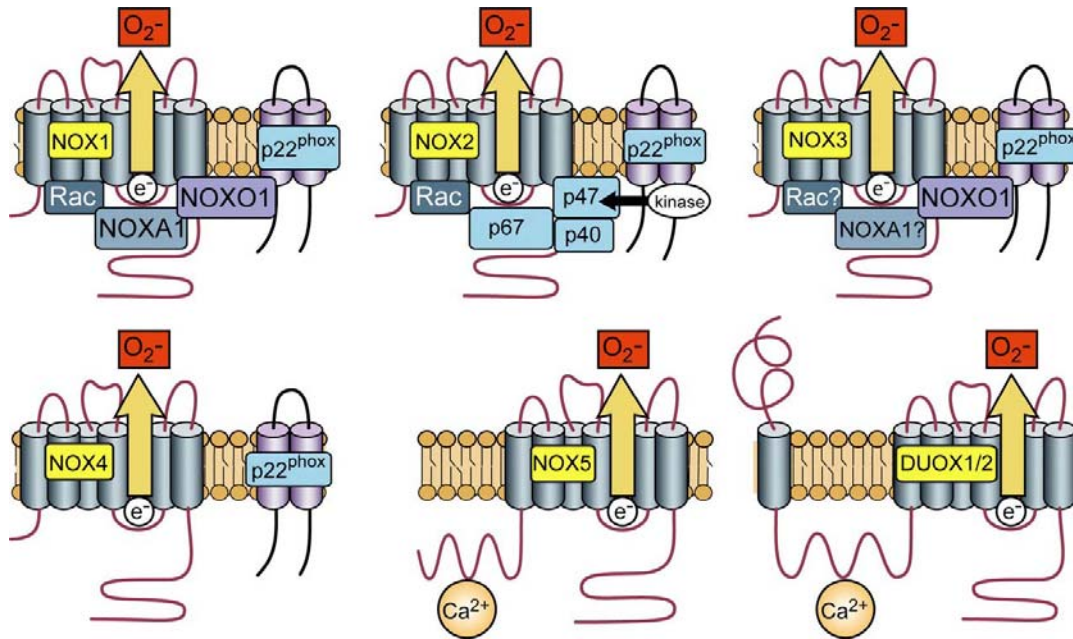






Broad relevance of the NADPH oxidase?

NADPH Oxidase Isoforms



Source: Bedard, K. et al. *Physiol. Rev.* 2007. 87: 245-313

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The NADPH Oxidase Family -NOX Isoforms- Tissue Distribution

NOX Enzyme	High-Level Expression
NOX 1	Colon
NOX 2	Phagocytes, Salivary glands
NOX 3	Inner ear
NOX 4	Kidney, Blood vessels
NOX 5	Lymphoid tissue, Testis
DUOX 1	Thyroid
DUOX 2	Thyroid

Adapted from Bedard, K. and Krause, K.H. 2007. *Physiol Rev* 87: 245-313.

The NOX Proteins in Disease

- **Atherosclerosis**
- **Ischemia/Reperfusion Injury**
- **Heart Failure**
- **Hypertension**
- **Cancer**
- **Chronic Pancreatitis**
- **Thyroid Disease**
- **Retinal Vascular Disease**

The Future
A New Vision
for the Clinical Center

SMRB Legislation

The Scientific Management Review Board (SMRB) was established by the NIH Reform Act of 2006 to advise the NIH Director through reports to Congress regarding the use of certain organizational authorities

One Hundred Ninth Congress
of the
United States of America

AT THE SECOND SESSION

*Began and held at the City of Washington on Tuesday,
the third day of January, two thousand and six*

An Act

To amend title IV of the Public Health Service Act to revise and extend the authorities of the National Institutes of Health, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

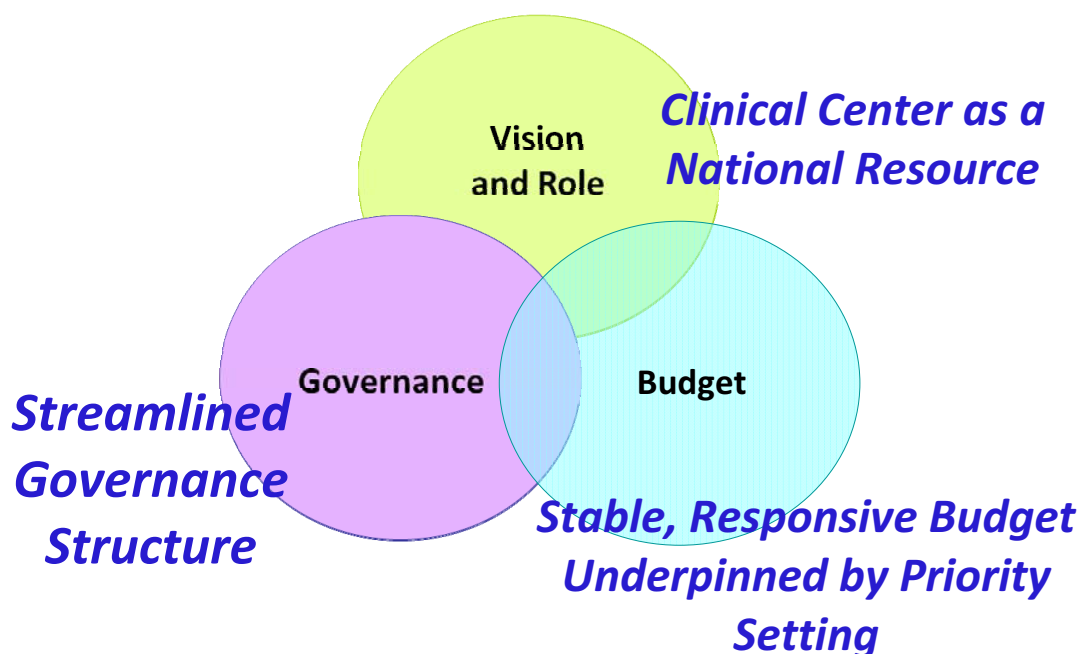
SECTION 1. SHORT TITLE.

This Act may be cited as the "National Institutes of Health Reform Act of 2006".

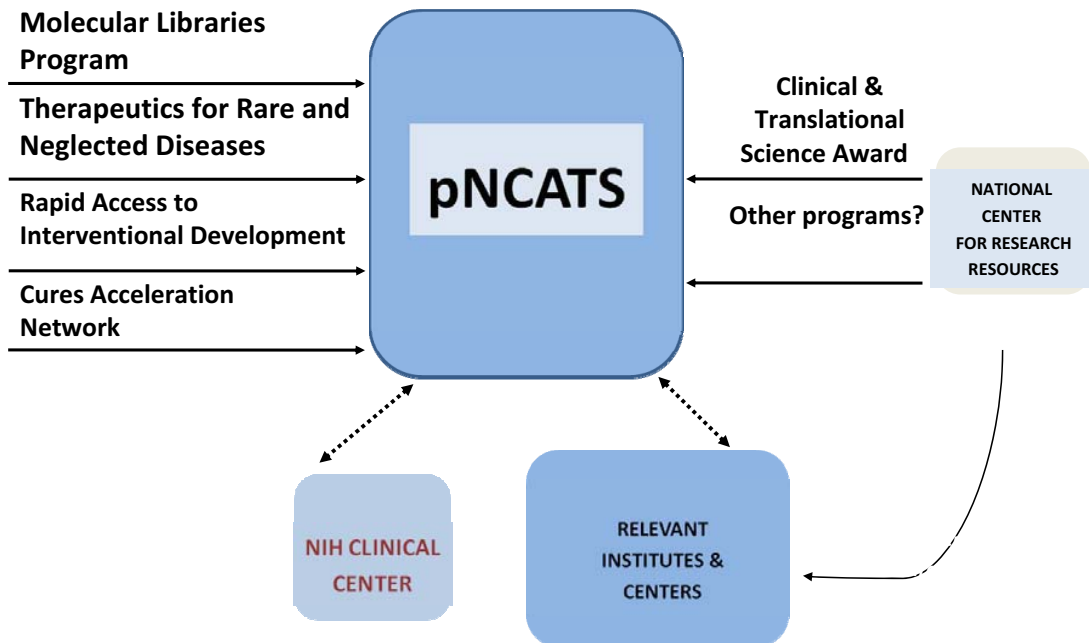
TITLE I—NIH REFORM

***Per P.L. 109-482**

SMRB Recommendations



SMRB Proposed National Center for Advancing Translational Science



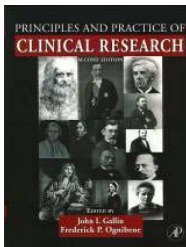
What will the Clinical Center Contribute?

- Access to special services
- Access to patients with rare diseases
- Opportunity to bring cohorts of patients to the CC for study (under discussion)
- Training

Training Clinical Investigators

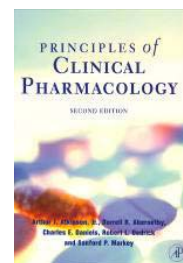
**The Clinical Center has trained
many of the leaders of academic
medicine throughout the United
States and abroad.**

NIH Curriculum In Clinical Research



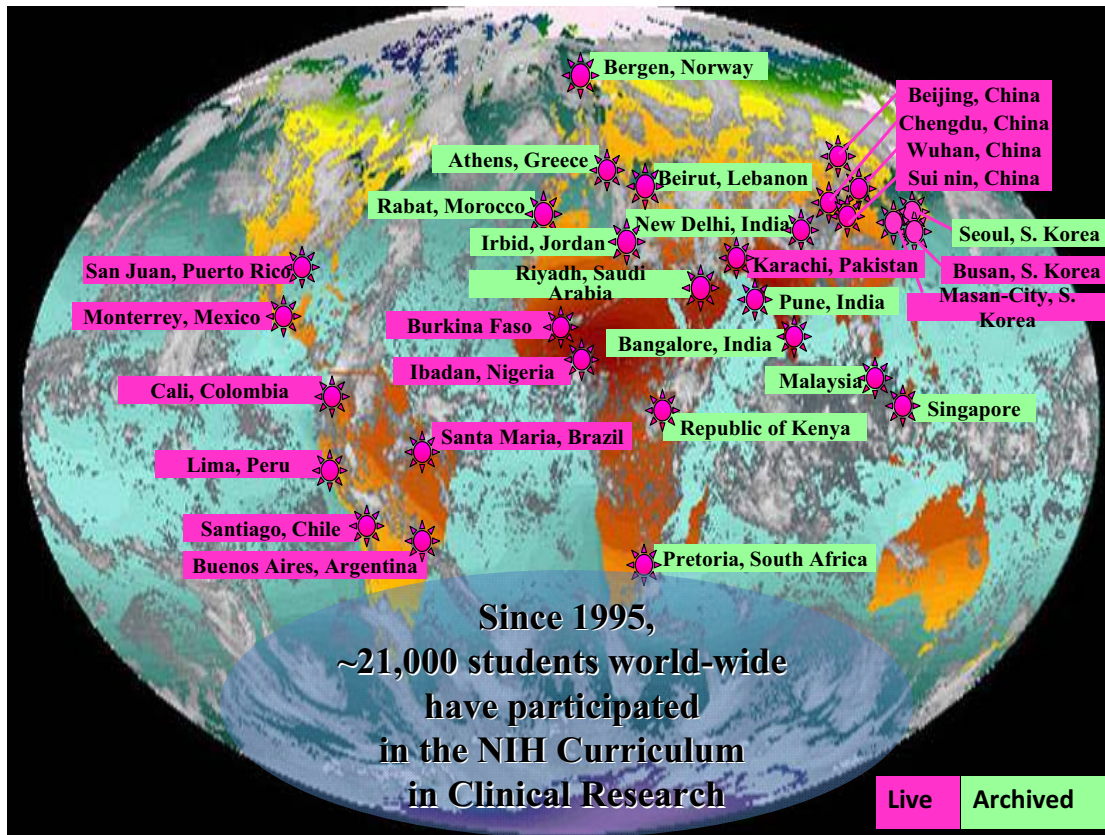
Introduction to the Principles & Practice of Clinical Research
>10,300 participants since course introduced in 1995

Principles of Clinical Pharmacology
>6,500 registrants since course began in 1998



Ethical and Regulatory Aspects of Human Subjects Research
>4,200 participants since course began in 1999

<http://clinicalcenter.nih.gov/training/training/ippcr.html>



New Sabbatical Clinical Research Management

Elective Modules

- CC
- ICs
- FDA
- OTT
- OHRP
- OHSR
- NLM
- FIC
- OGC



<http://clinicalcenter.nih.gov/training/sabbatical/index.html>

Bench-to-Bedside Awards

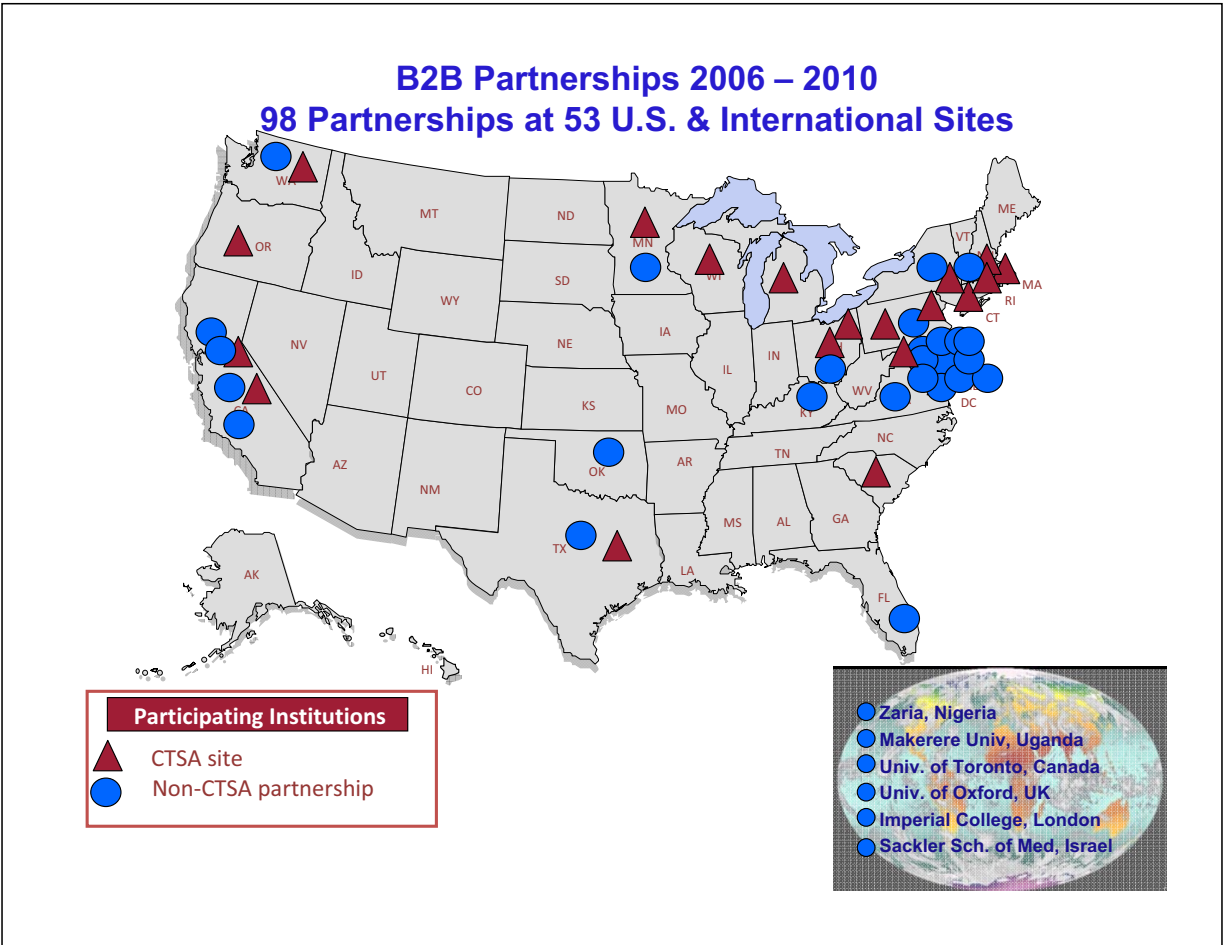
- **A program to promote new partnerships between basic science and clinical investigators**
- **Goals:**
 - **Develop new clinical protocols**
 - **Discover new therapeutics and devices**
 - **Foster long standing collaborations**



NIH Bench-to-Bedside Program

- **Started in 1999**
- **175 projects funded to date; ~\$40M investment**
- **Today \$135K per year X 2 years**
- **In 2006 established intramural/extramural partnerships (currently ~ 90%)**

[www. http://clinicalcenter.nih.gov/ccc/btb/index.html](http://clinicalcenter.nih.gov/ccc/btb/index.html)



The Gulf War Syndrome

**Are there opportunities at the
NIH Clinical Center?**