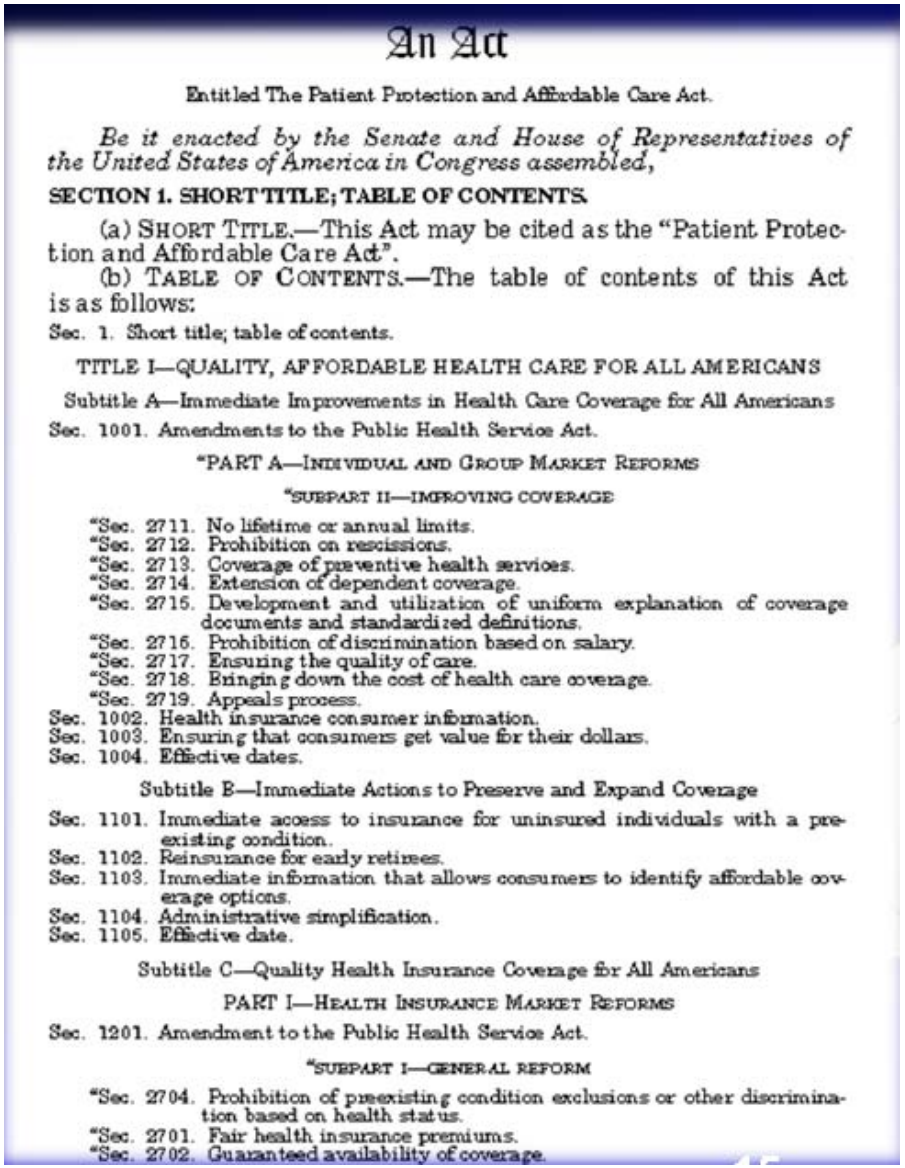
Opportunities to Study Rare Diseases at the NIH Clinical Center

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 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

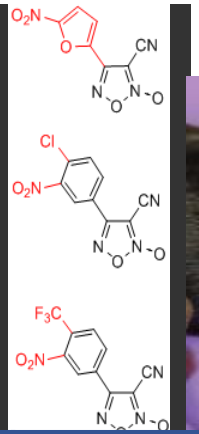
Sec. 1201. Amendment to the Public Health Service Act.

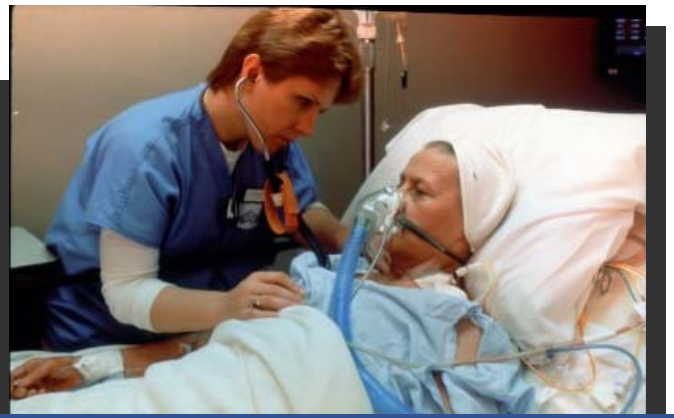
"SUBPART I—GENERAL REFORM

"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





Disease	Target ID	Assay Dev.	HTS	Probe to Lead	Pre-Clinical	FDA IND	Ph. 0	Ph. I	Ph. II	Ph. III	FDA Re-view

NIH Molecular Libraries Initiative

NIH TRND

NIH RAID

Pharma, Biotech, NIH Clinical Center, CTSAs

New NIH FDA Partnerships


NIH Clinical Center

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

Patient Care

Training

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 capabili
- Imaging equipmen
  - 3 cyclotrons
  - MRI center
- Biomechanics laborato
- Blood products; stem c
- 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

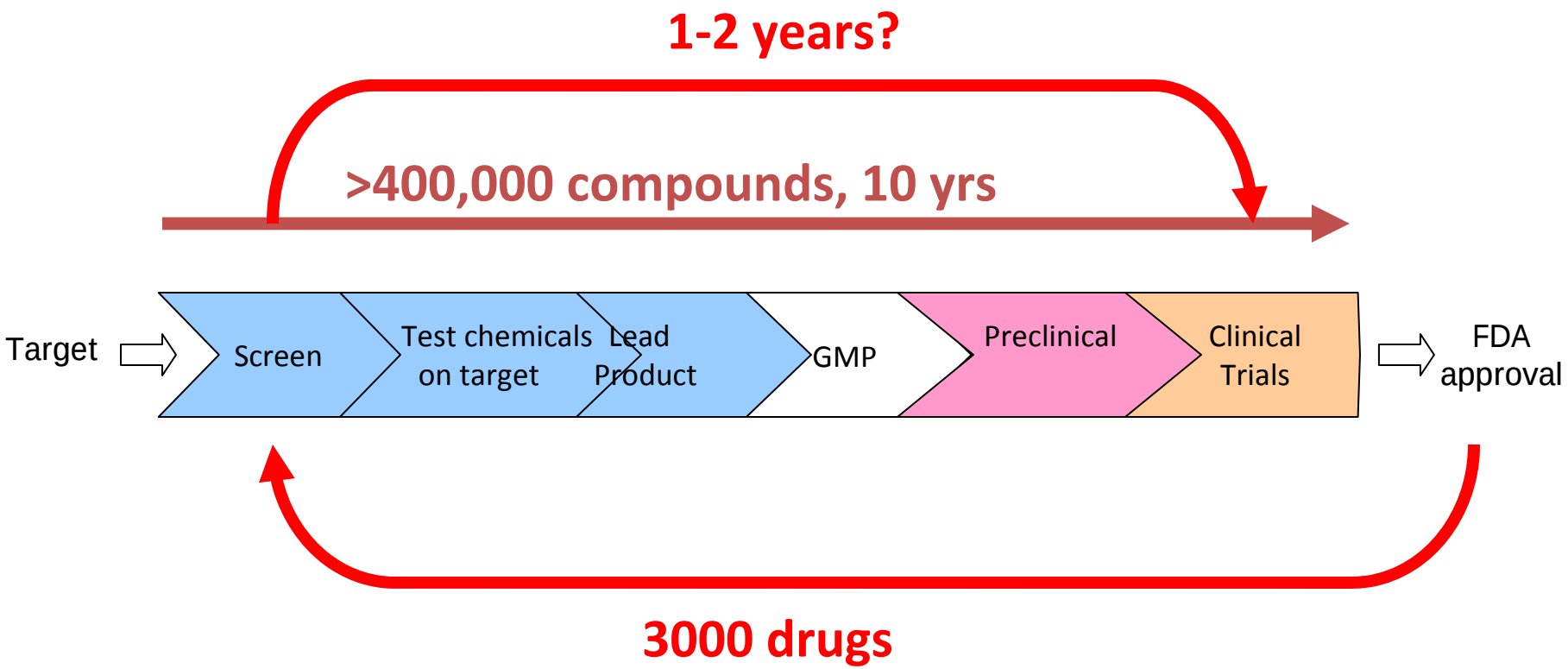
Interventional/Clinical Trials by Phase

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



Modified from C. Austin, NHGRI

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**.

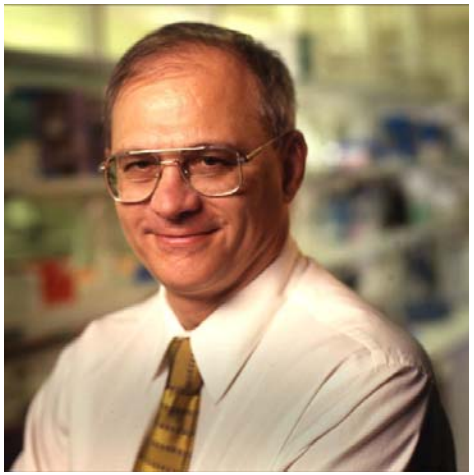
Rare Diseases at the NIH Clinical Center*

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)

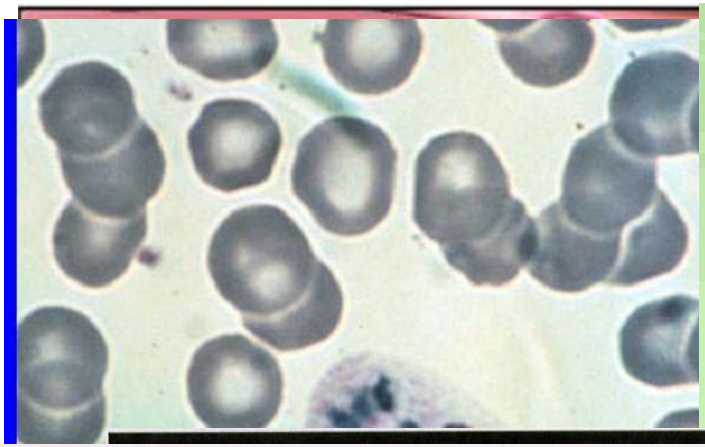
- A call for undiagnosed diseases with no phenotype restrictions
- A multi-disciplinary approach to each patient
- ~45 NIH senior consultants participate
- About 50% UDP patients have neurodegenerative diseases
- Total # of patients: ~4,000 screened; 350 admissions

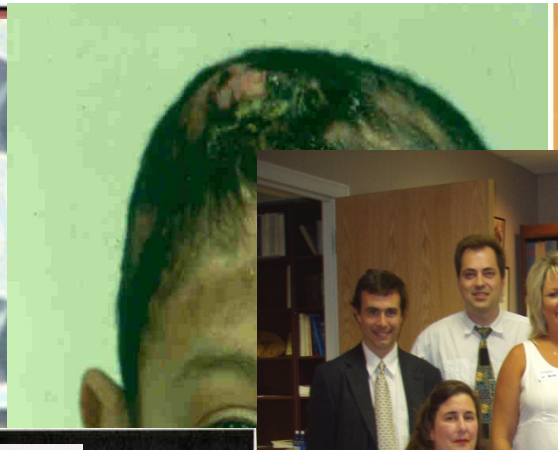


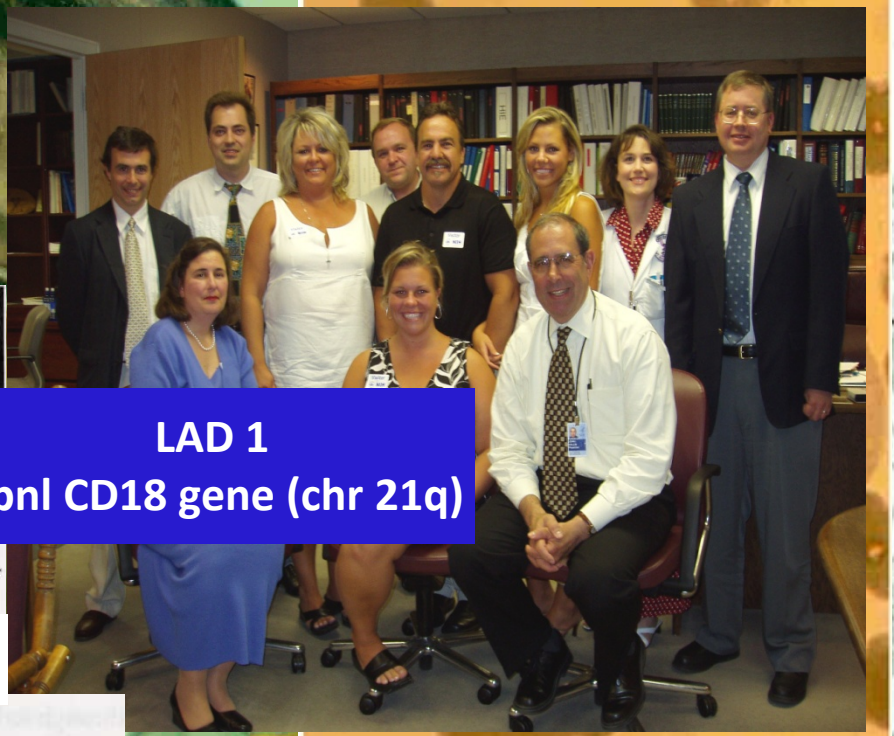
William Gahl, MD, PhD
Clinical Director, NHGRI

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, Piroska 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

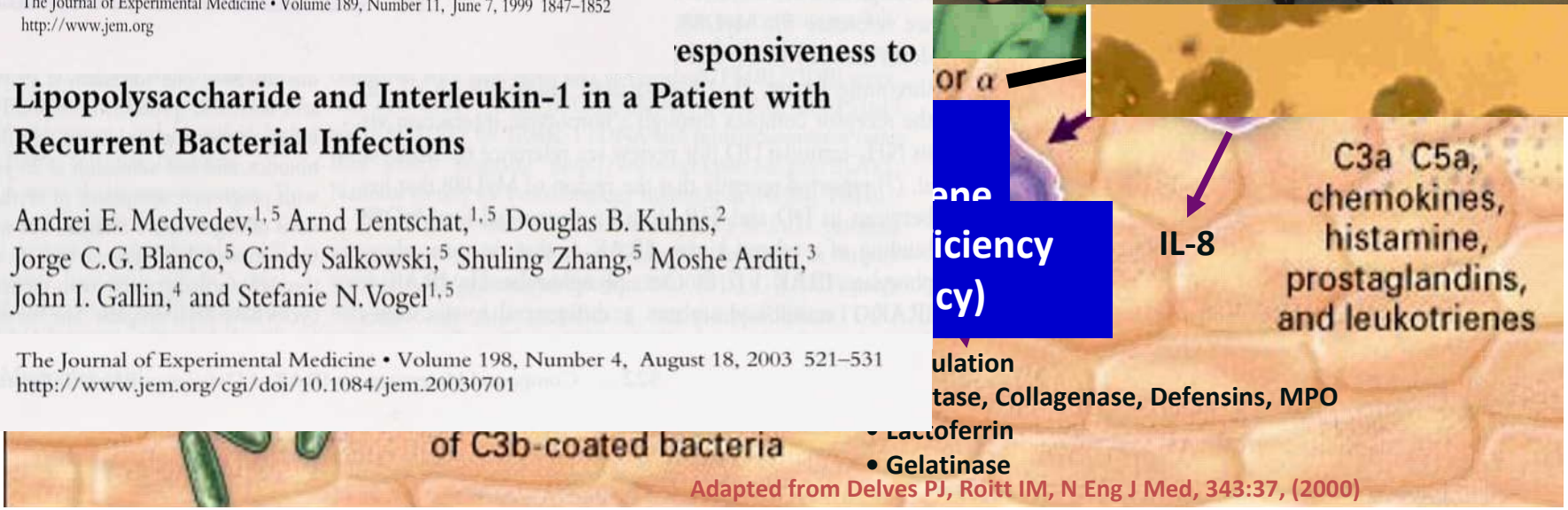
1847 The Journal of Experimental Medicine • Volume 189, Number 11, June 7, 1999 1847–1852
http://www.jem.org

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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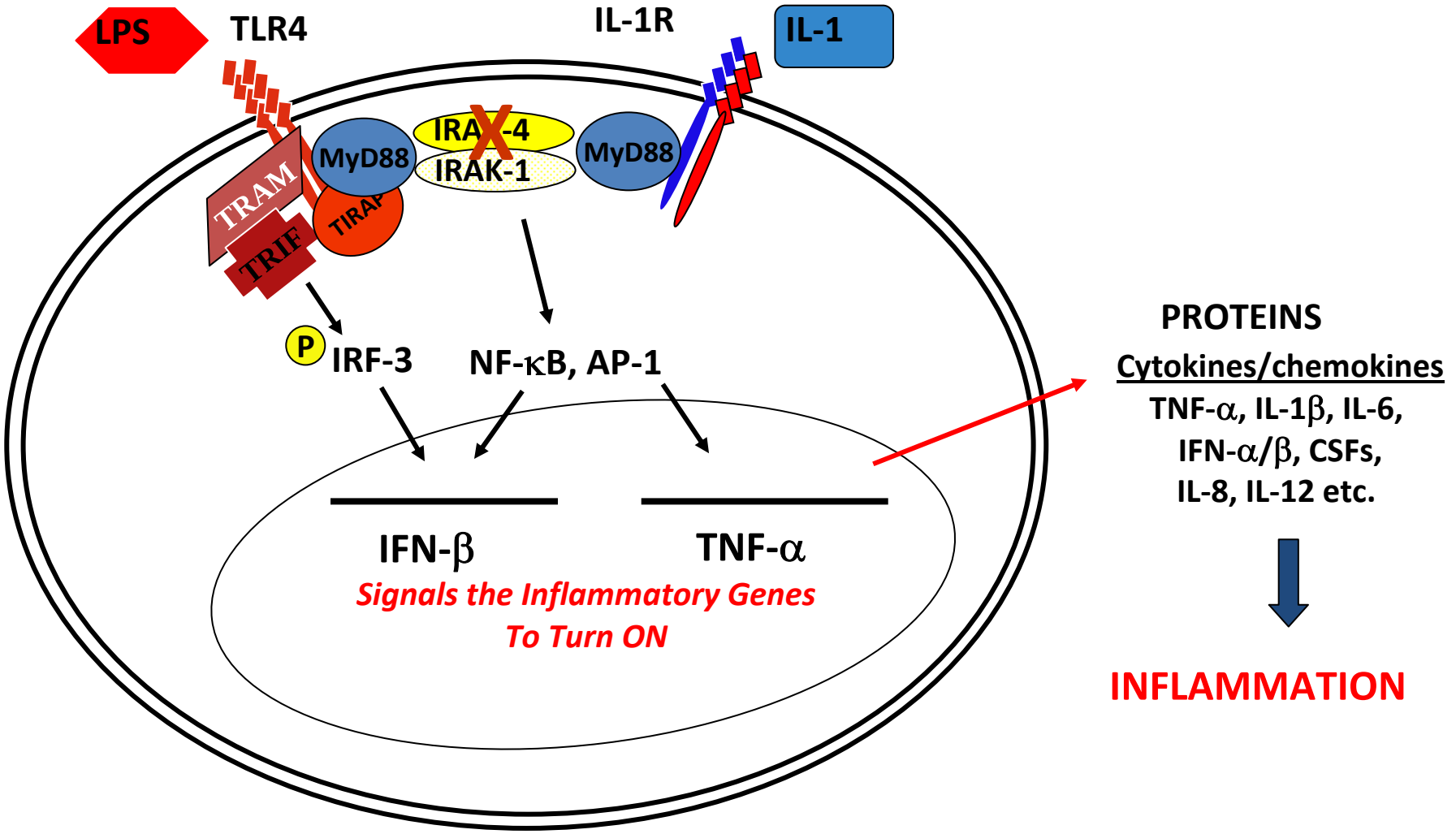
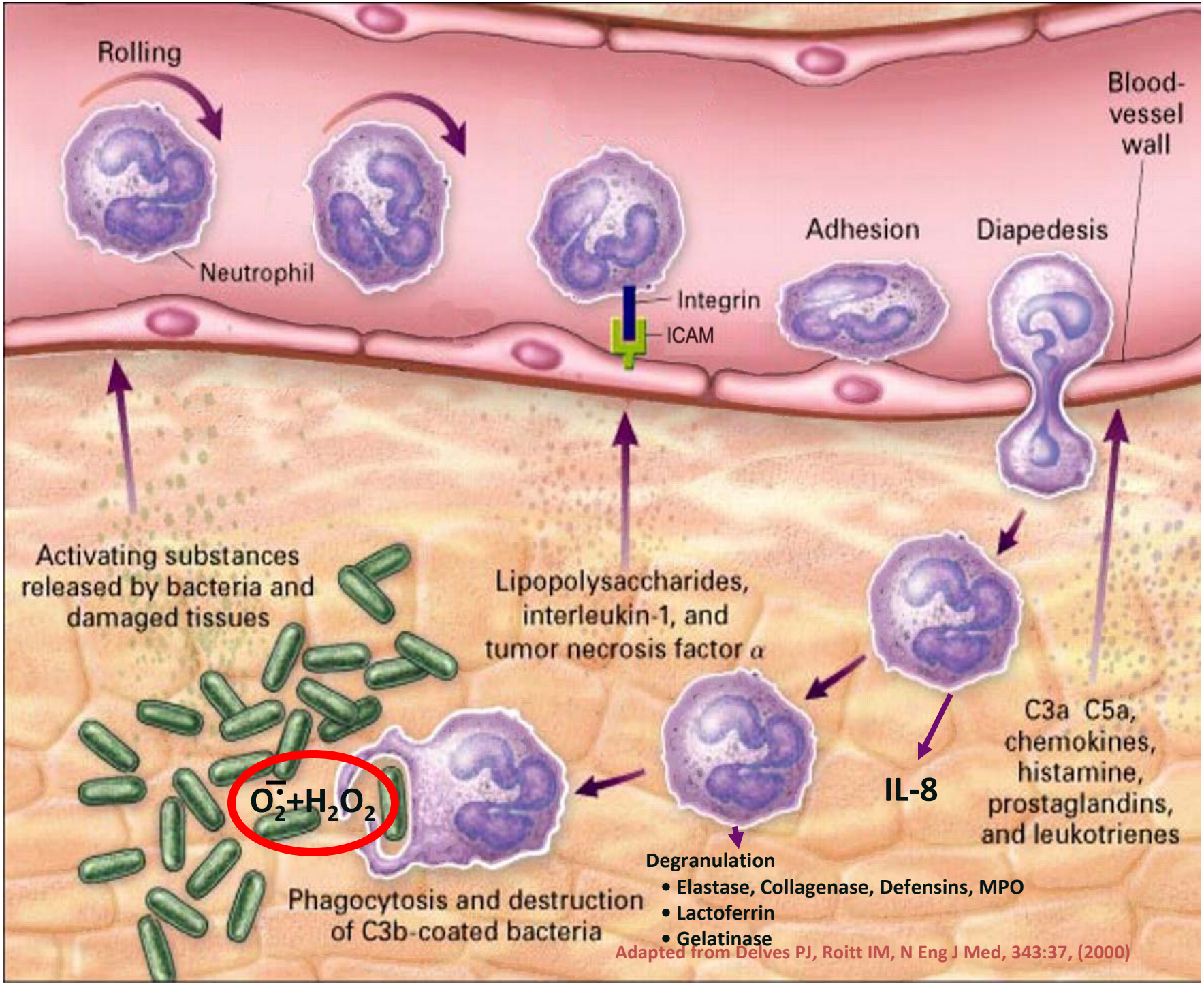
tase, Collagenase, Defensins, MPO
• Lactoferrin
• Gelatinase

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

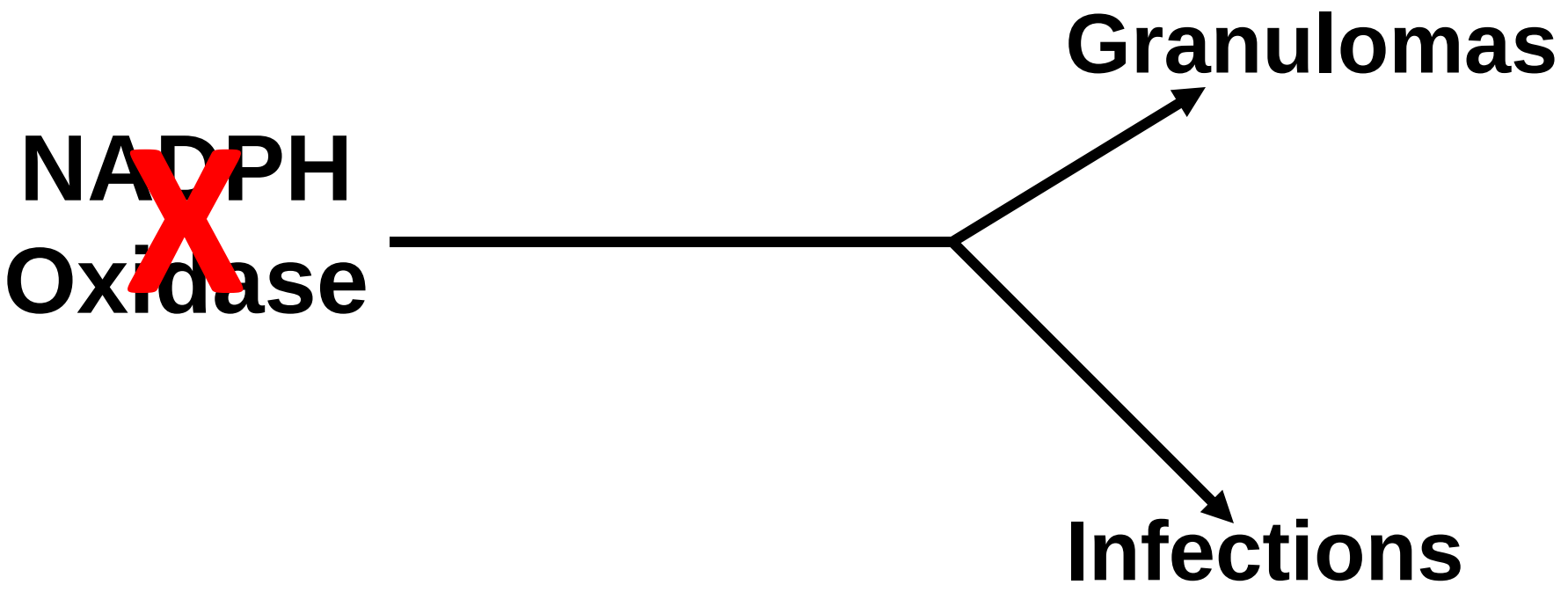


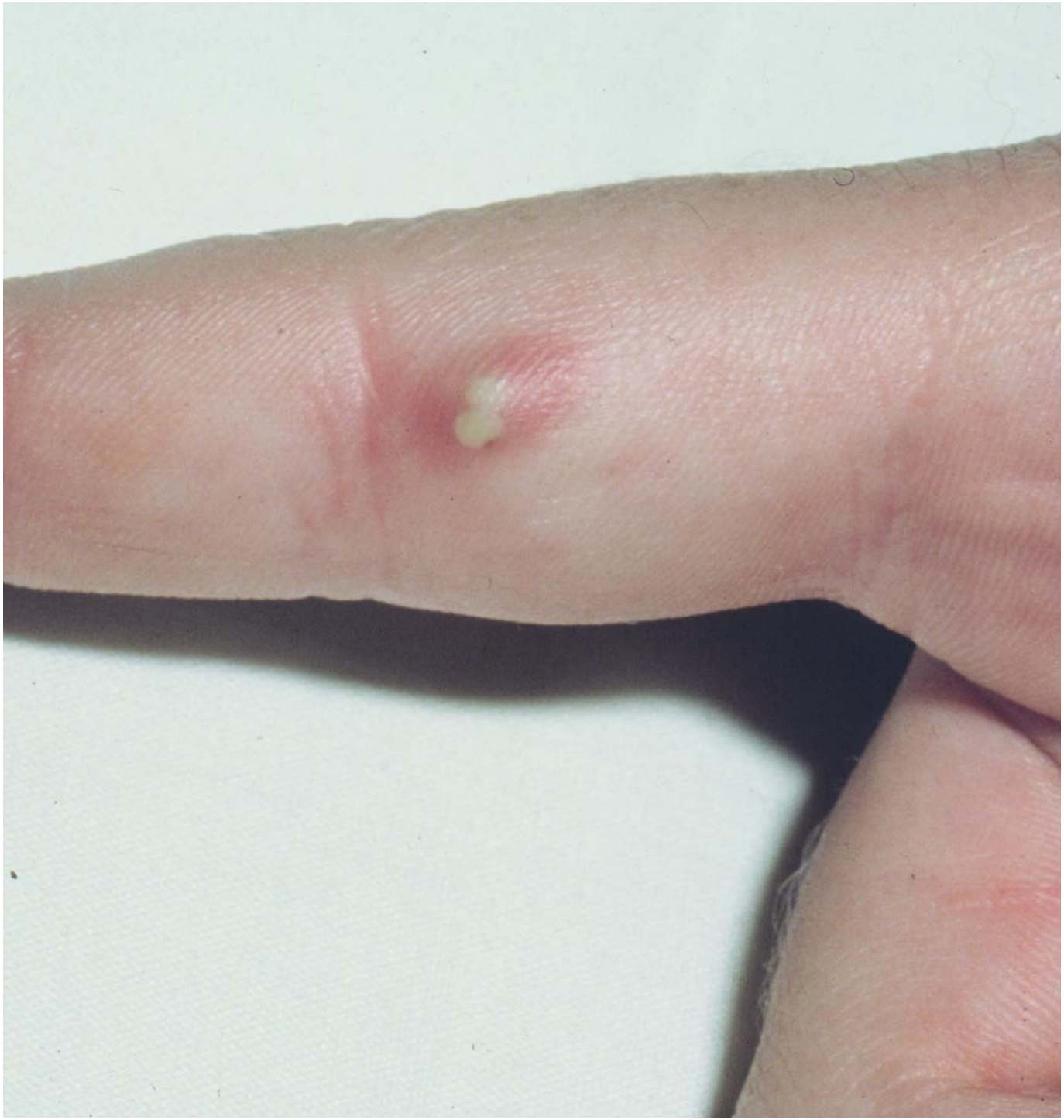
Adapted from Delves PJ, Roitt IM, N Eng J Med, 343:37, (2000)

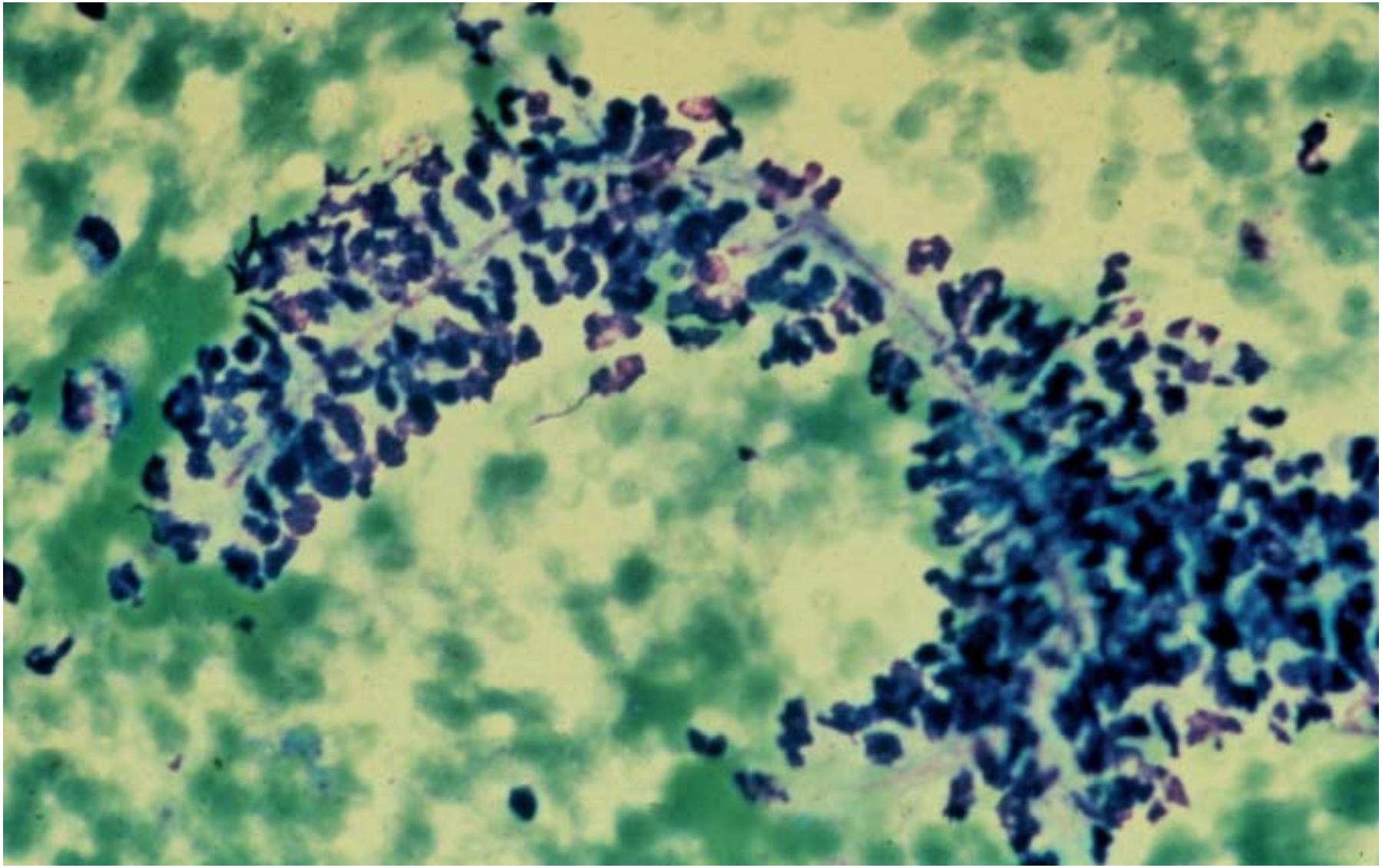
Chronic Granulomatous Disease (CGD)

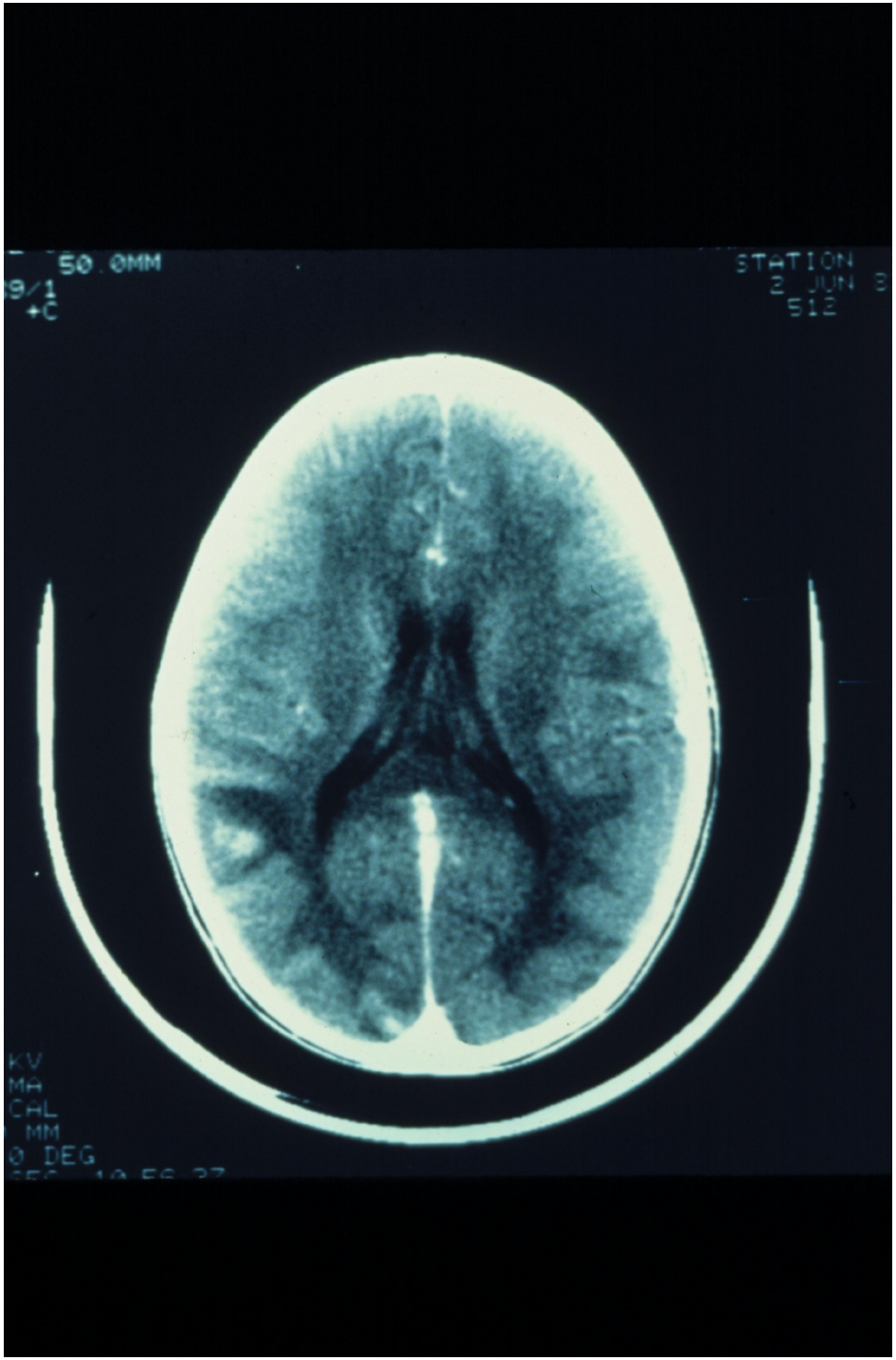
- ~1:200,000 live births in US
- Mortality 2%/yr
- 1/3 CGD deaths caused by *Aspergillus*
- Abnormal NADPH Oxidase

Chronic Granulomatous Disease





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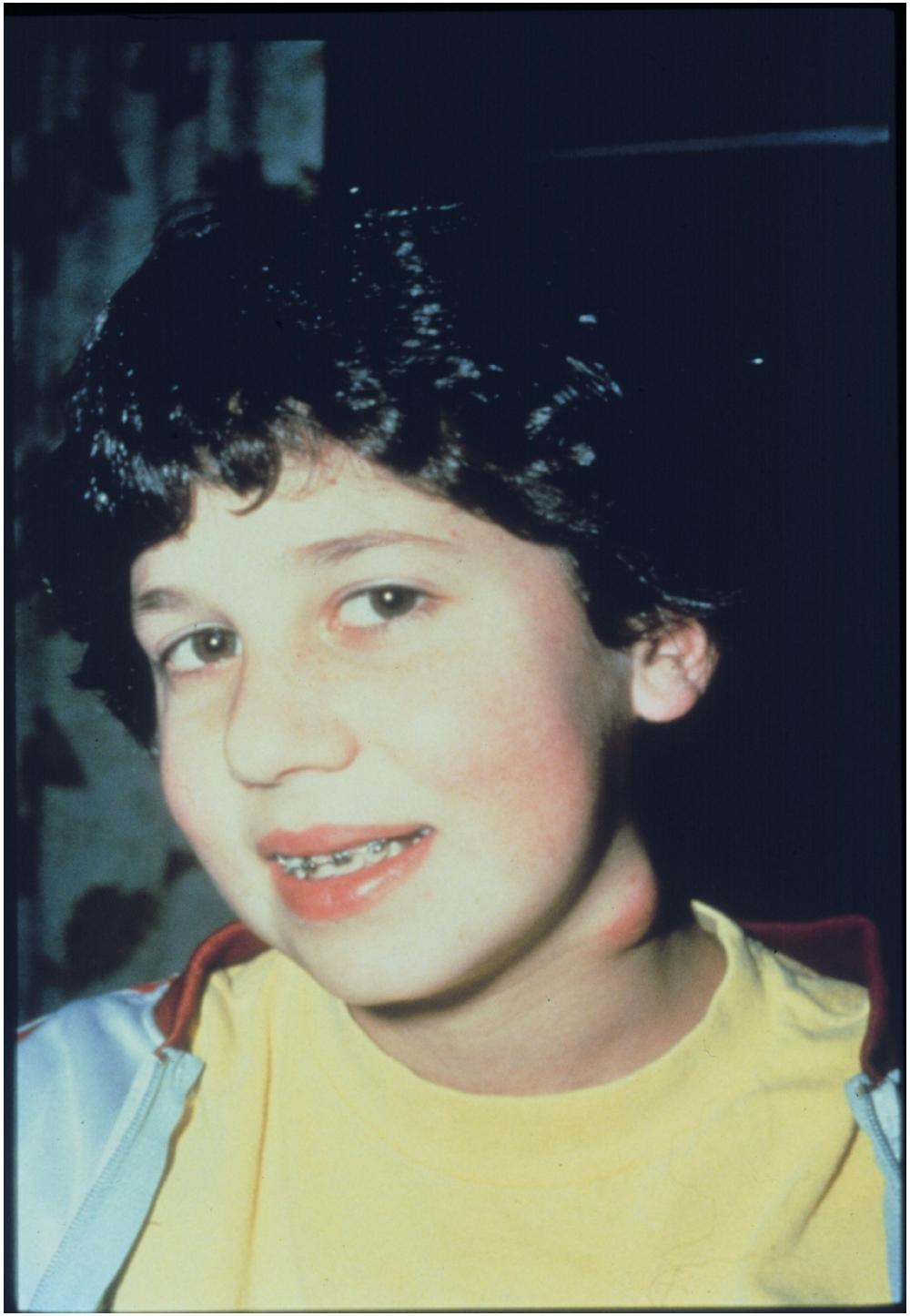
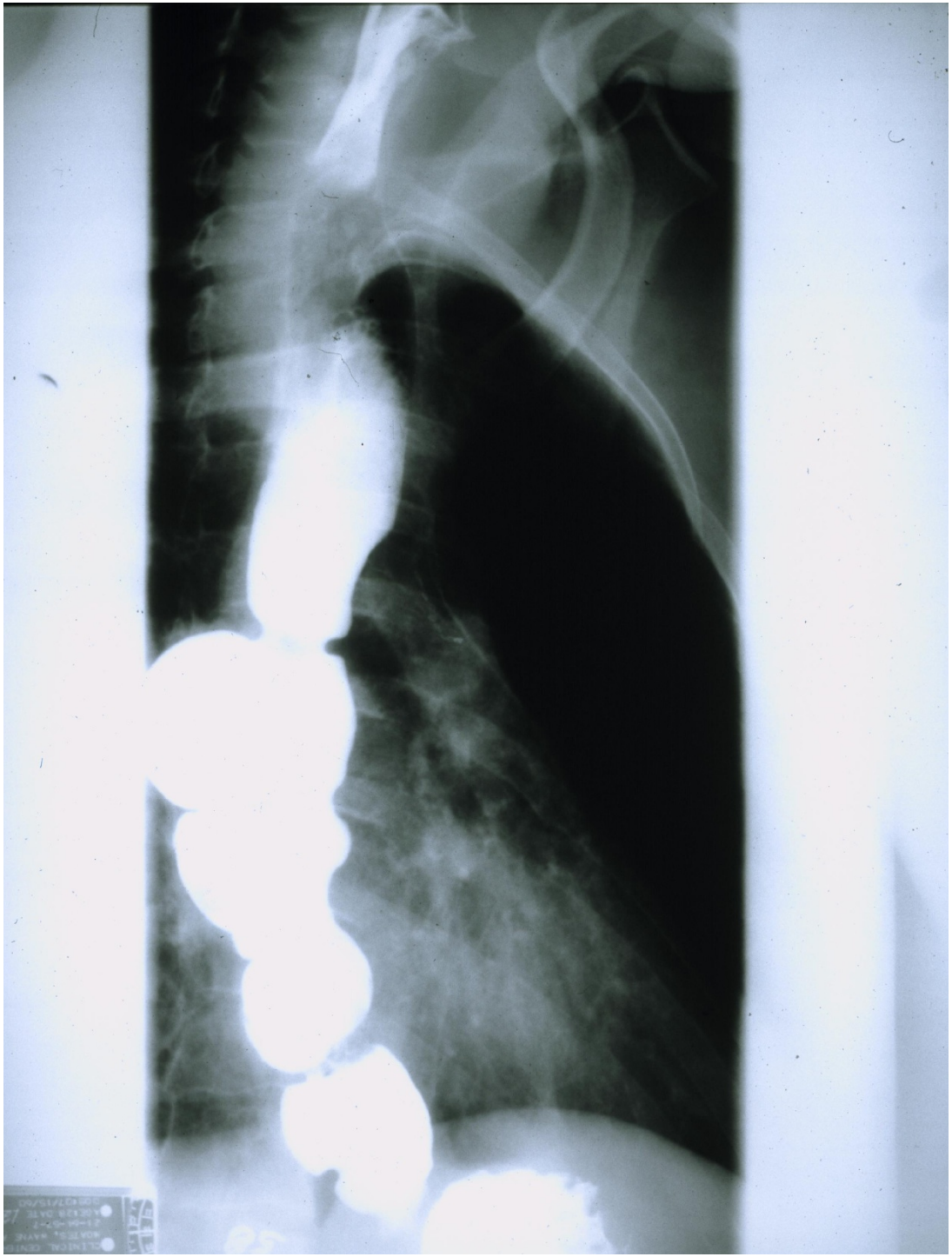
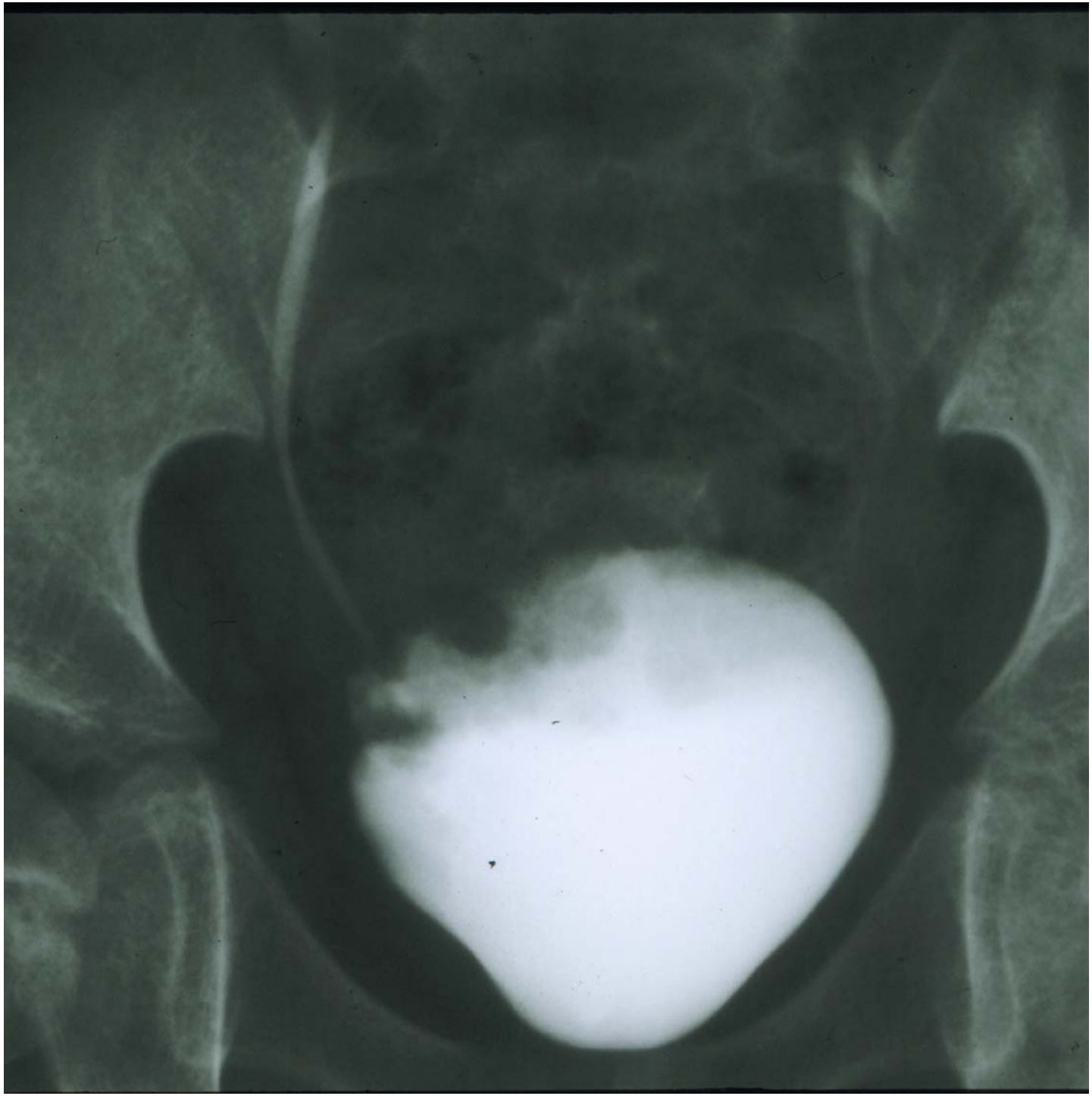
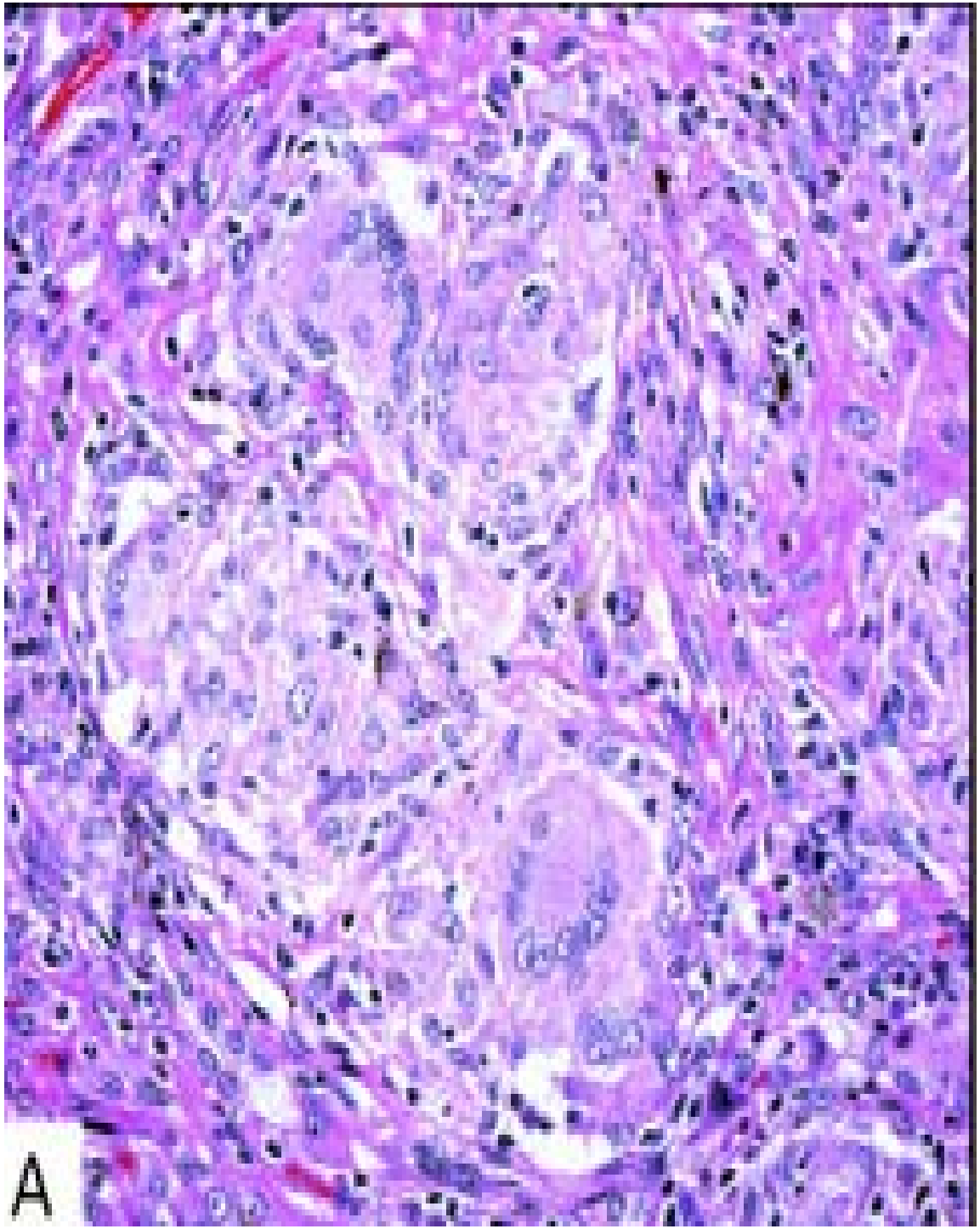







A

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

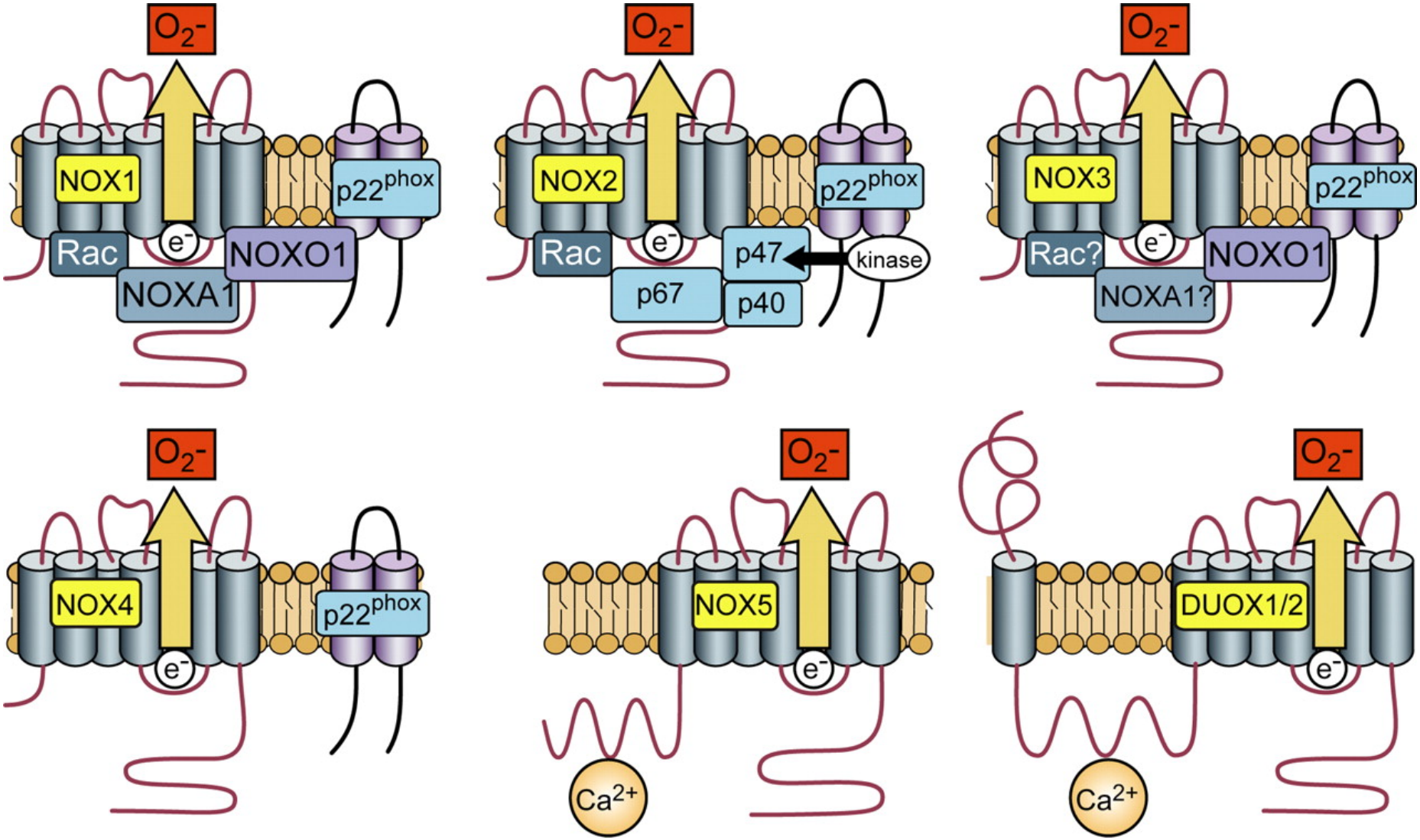
Residual NADPH Oxidase and Survival in Chronic Granulomatous Disease

Douglas B. Kuhns, Ph.D., W. Gregory Alvord, Ph.D., Theo Heller, M.B., Ch.B., Jordan J. Feld, M.D., M.P.H., Kristen M. Pike, M.S., Beatriz E. Marciano, M.D., Gulbu Uzel, M.D., Suk See DeRavin, M.D., Ph.D., Debra A. Long Priel, M.S., Benjamin P. Soule, M.D., Kol A. Zarember, Ph.D., Harry L. Malech, M.D., Steven M. Holland, M.D., and John I. Gallin, M.D.

N ENGL J MED 363;27 NEJM.ORG DECEMBER 30, 2010

Broad relevance of the NADPH oxidase?

NADPH Oxidase Isoforms



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

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

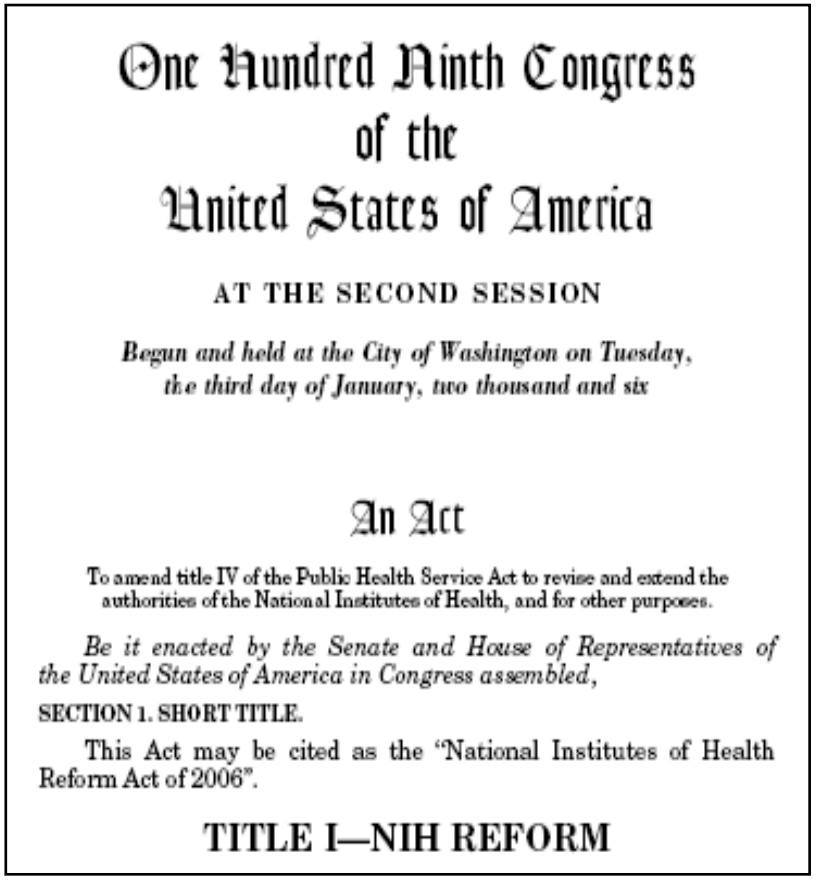
- Atherosclerosis
- Ischemia/Reperfusion Injury
- Heart Failure
- Hypertension
- Cancer
- Chronic Pancreatitis
- Thyroid Disease
- Retinal Vascular Disease

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

Begun 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,

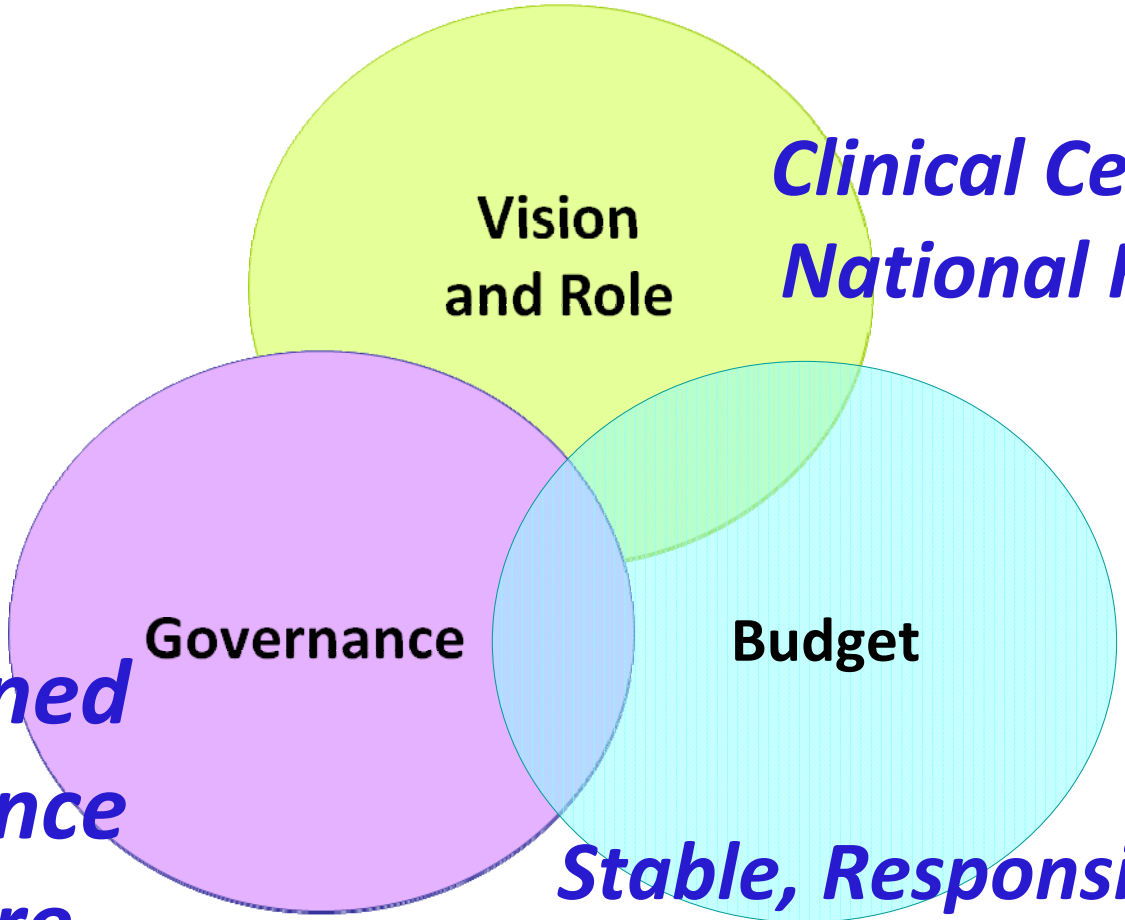
SECTION 1. SHORT TITLE.

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

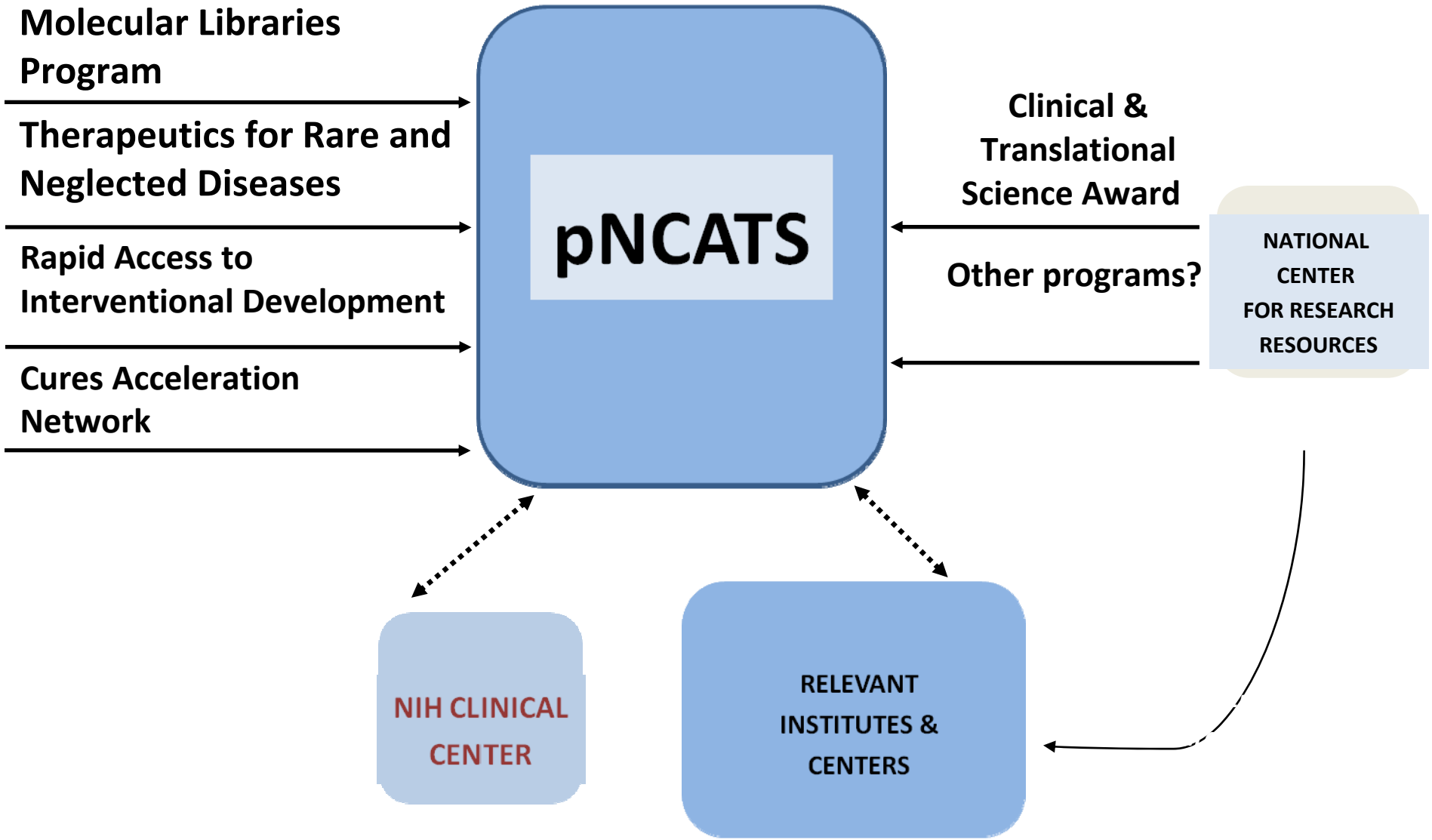


Clinical Center as a National Resource

Streamlined Governance Structure

Stable, Responsive Budget Underpinned by Priority Setting

SMRB Proposed
National Center for Advancing Translational Science



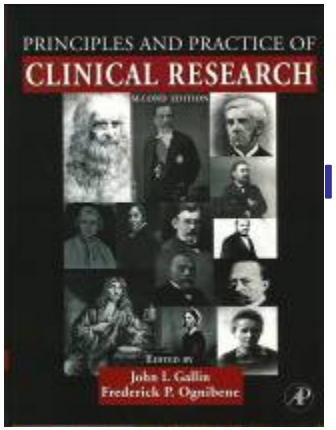
What will the Clinical Center Contribute?

- 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

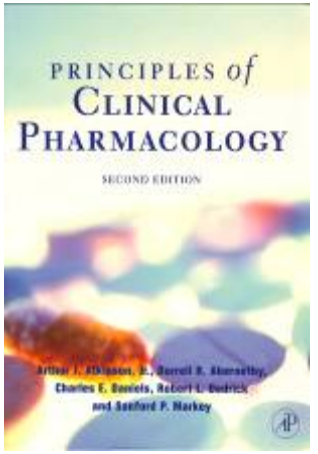
The Clinical Center has trained many of the leaders of academic medicine throughout the United States and abroad.

NIH Curriculum In Clinical Research



Introduction to the Principles & Practice of Clinical Research

>10,300 participants since course introduced in 1995



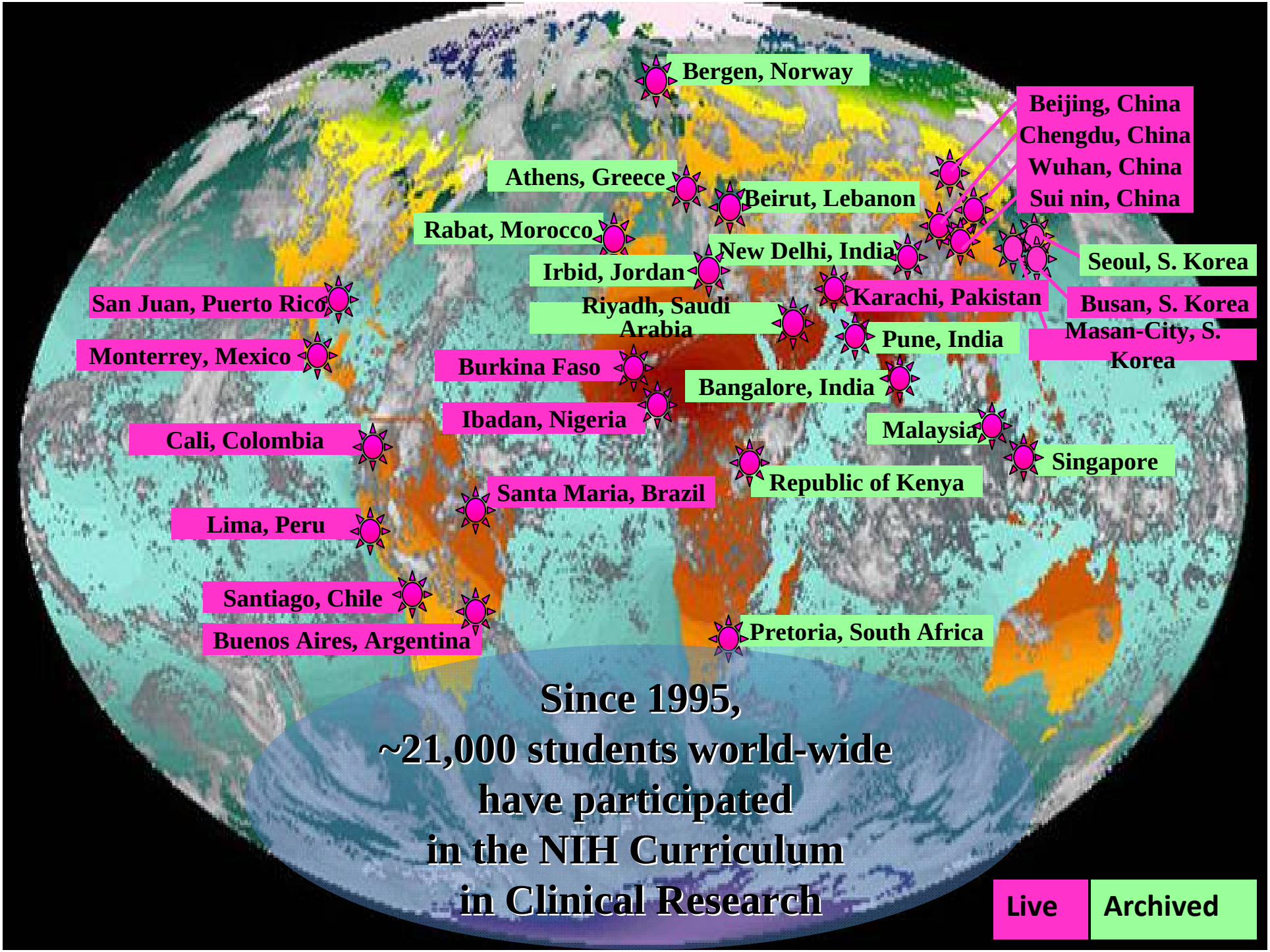
Principles of Clinical Pharmacology

>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


Bergen, Norway
Beijing, China
Chengdu, China
Wuhan, China
Sui nin, China
Athens, Greece
Beirut, Lebanon
Rabat, Morocco
New Delhi, India
Seoul, S. Korea
Irbid, Jordan
San Juan, Puerto Rico
Karachi, Pakistan
Busan, S. Korea
Riyadh, Saudi Arabia
Masan-City, S. Korea
Pune, India
Monterrey, Mexico
Burkina Faso
Bangalore, India
Ibadan, Nigeria
Malaysia
Cali, Colombia
Singapore
Republic of Kenya
Santa Maria, Brazil
Lima, Peru
Santiago, Chile
Buenos Aires, Argentina
Pretoria, South Africa
Since 1995,
~21,000 students world-wide
have participated
in the NIH Curriculum
in Clinical Research
Live
Archived

New Sabbatical
Clinical Research Management

Elective Modules

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

U.S. Department of Health and Human Services

NIH News

National Institutes of Health

NIH Clinical Center (CC)

For Immediate Release
Wednesday, September 29, 2010

Contact:
Bill Schmalfeldt
301-917-5507

NIH Clinical Center offers sabbatical in clinical research management

The National Institutes of Health Clinical Center is accepting applications for a sabbatical program in clinical research management. After a successful pilot, during which three experienced researchers completed their sabbaticals, the Clinical Center is seeking more professionals for this training to help ensure that medical research programs are safe, ethical, and efficient.

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

Bench-to-Bedside Awards

- A program to promote new partnerships between basic science and clinical investigators

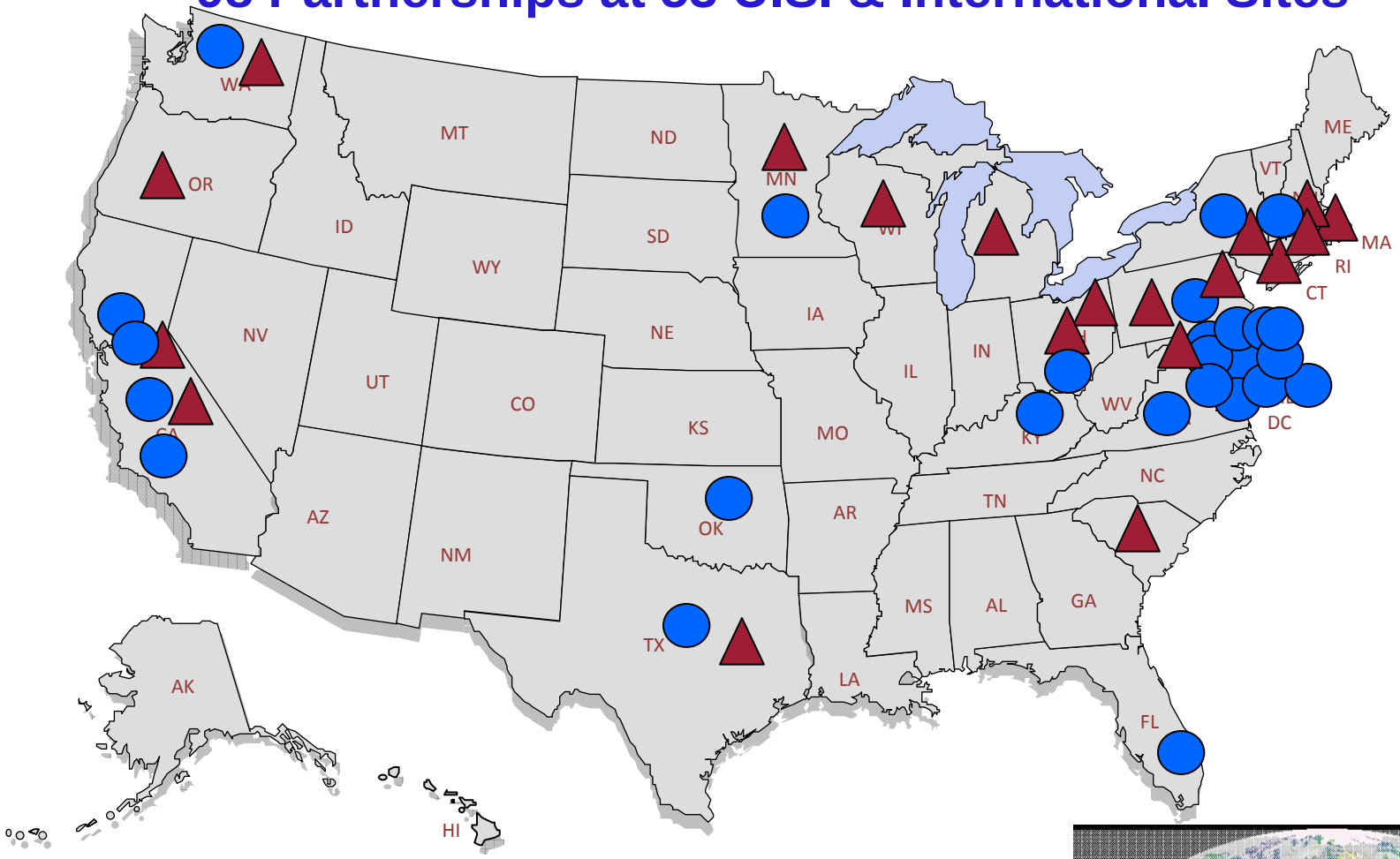
- Goals:
- Develop new clinical protocols
- Discover new therapeutics and devices
- Foster long standing collaborations

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

B2B Partnerships 2006 – 2010
98 Partnerships at 53 U.S. & International Sites



Participating Institutions

- CTSA site
- Non-CTSA partnership

The Gulf War Syndrome

Are there opportunities at the NIH Clinical Center?