



World TB Day Panel Discussion


Tuberculosis Research: State of the Science




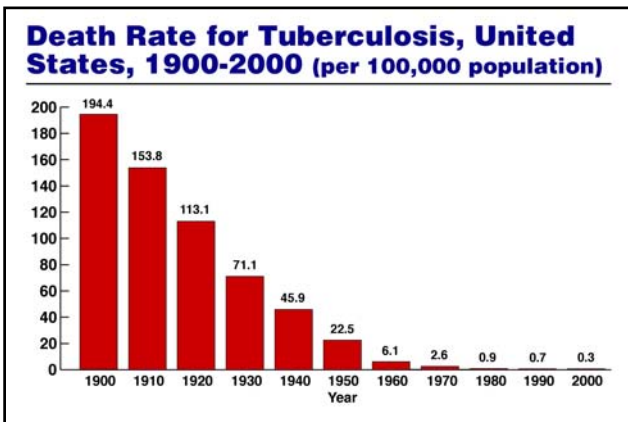
Anthony S. Fauci, M.D.
Director
National Institute of Allergy and
Infectious Diseases
National Institutes of Health
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**Research to Develop and Optimize
Interventions Against Tuberculosis**



**Implementation: Delivery of
Proven Interventions to
Patients and Populations**


Widespread Complacency: Perception That We Had an Adequate Tuberculosis Armamentarium

- Skin test
- Sputum for diagnosis
- Curative drugs
- No domestic demand for vaccine

A Failure to Look Beyond our Borders

The Global Burden of Tuberculosis

- One-third of the world's population is infected with *Mycobacterium tuberculosis* (Mtb)
- In 2010
 - 8.8 million new cases, incl. 1.1 million among HIV+
 - 1.45 million deaths, incl. 350,000 among HIV+
 - 650,000 prevalent cases of MDR-TB
 - XDR-TB reported in ~70 countries



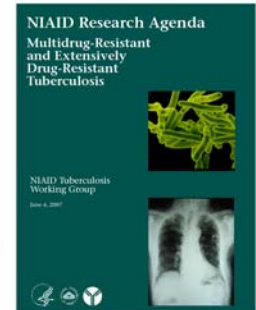
Source: WHO, 10/2011 Image: CDC

Major Challenges in the Control of Tuberculosis

- Standard **diagnostics** are antiquated, insensitive and slow
- Our understanding of TB **pathogenesis** is limited
- Current **drug regimens** are complex and lengthy
- Available **vaccine** not effective in preventing adult pulmonary TB

NIAID Tuberculosis Research

- Basic research
- Epidemiology and natural history
- Drug, vaccine, diagnostics development
- Implementation of NIAID Research Agenda for MDR- and XDR-TB



Selected TB Research Areas

- Diagnosis
- Pathogenesis
- Treatment
- Prevention



Selected TB Research Areas

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Despite Progress in TB Diagnostics, Severe Limitations

- In community settings, only antiquated diagnostics are available; newer methodologies are confined to referral or reference laboratories
- We still await truly transformative diagnostics
 - Point-of-care
 - Simple, accurate, safe, inexpensive
 - Amenable to readily available clinical specimens
 - Can detect TB anywhere in the body




Sensitive Detection of Tuberculosis and Rifampin Resistance in < 2 hours with Minimal Hands-on Time

Rapid Molecular Detection of Tuberculosis and Rifampin Resistance

CC Boehme, DA Alland, MD Perkins, et al.


Selected TB Research Areas

- Diagnosis
- **Pathogenesis**
- Treatment
- Prevention



TB Pathogenesis

- Bridge basic and clinical research to understand fundamental questions, eg mechanisms of latency, correlates of immunity
- A better understanding of TB pathogenesis will inform the development of new interventions
- Need for TB biomarkers
- Need to understand the host, the pathogen and their complex interactions -- **systems biology**




Tuberculosis: the Need for a Systems Biology Approach

A new way of thinking to understand:

- Pathogenesis and immunity – integrated approach to biosignature discovery
- Treatments – illuminate biochemical pathways to guide identification of new drug targets
- Vaccines – define host/pathogen systems to guide antigen discovery and interpret immune responses


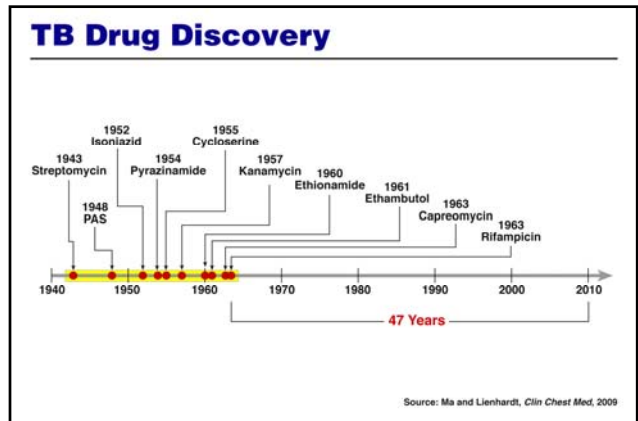
Selected TB Research Areas

- Diagnosis
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TB Therapeutics

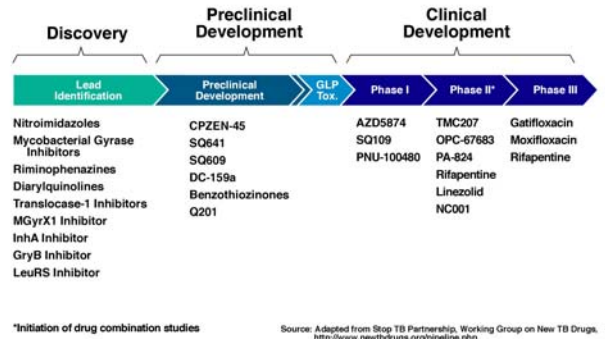
- Current regimens require 6-9 months treatment with multiple drugs
- Plagued by patient noncompliance and insufficient medical monitoring
- Various levels of drug resistance complicate treatment

Transforming TB Therapeutics

- Increase understanding of current regimens
- “Grow” pipeline
- Develop and test new combination regimens
- Explore sensitive and specific surrogate markers
- Explore new areas – e.g., combining drugs with biologics such as synthetic vaccines or immune stimulants
- Increase clinical trials capacity

Global TB Drug Pipeline



“In the foreseeable future, the development of new and novel TB drugs and regimens could be impeded by a lack of adequate clinical trial capacity.....”

Clinical TB Research Expansion

- HIV/AIDS Networks –
 - Expanded TB agenda/capabilities
 - New sites
 - Labs – routine, specialized, and translational
 - Global TB clinical research expansion
 - Prospective cohorts
 - Clinical trials consortia
 - Key countries include: India, Brazil, South Africa, China
- “I am in the process of exploring the possibility...of utilizing our HIV/AIDS clinical trials networks for the implementation of similar clinical trial capacities for TB as well as other infectious diseases.”*
- AS Fauci
Pacific Health Summit, June 17, 2009

Selected TB Research Areas

- Diagnosis
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- Treatment
- Prevention

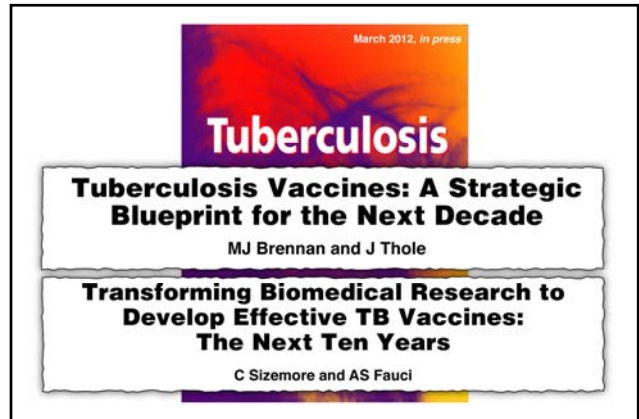


Tuberculosis Vaccine

- BCG not effective in preventing adult pulmonary TB, the most transmissible form of the disease
- BCG no longer recommended in HIV co-infected children
- New safe and effective vaccines against all forms of TB are urgently needed

Selected Barriers to TB Vaccine Development

- Correlates of protective immunity not known
- Vaccine needed to prevent different stages of disease and pathologic lesions
- Placebo-controlled clinical trials difficult
- Animal models may not predict most effective human vaccines

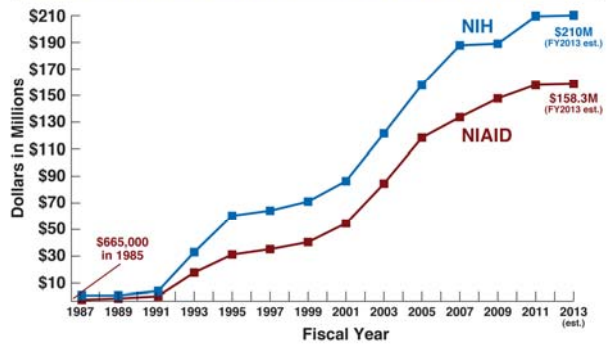


TB Vaccine Development

- ~14 novel TB vaccine candidates tested in clinical trials
- ~6 candidates in preclinical development
- 30 “next-generation” candidates in the vaccine discovery phase
- To overcome lack of knowledge about markers of protective immunity, diverse vaccine candidates and platforms are being developed

Source: Stop TB Partnership Working Group on New TB Vaccines, 2012

Tuberculosis: NIH and NIAID Funding



Key Advances in TB Research

- Sequencing of drug sensitive and M/XDR TB
- Surveillance informed by clade evolution
- Differentiation between treatment failure & reinfection
- Molecular markers of drug resistance used in diagnostics
- Targeted mutations for drug discovery
- Bioinformatics to identify vaccine epitopes
- Identify strains with increased virulence and/or drug resistance



The State of TB Research: Reasons for Optimism

- Commitment to funding
- Forging new/stronger partnerships – e.g., clinical trial capacity, translational research
- Robust pipelines
- Progress in HIV-TB management
- Powerful new tools – e.g. “omics” approaches, high-throughput screening, integrative “systems biology”