World TB Day Panel Discussion

Tuberculosis Research: State of the Science

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Research to Develop and Optimize Interventions Against Tuberculosis

Implementation: Delivery of Proven Interventions to Patients and Populations

Death Rate for Tuberculosis, United States, 1900-2000 (per 100,000 population)

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, 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

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- Diagnosis
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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
Selected TB Research Areas

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

TB Pathogenesis

- Bridge basic and clinical research to understand fundamental questions, e.g., 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
- **Pathogenesis**
- Treatment
- Prevention

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

TB Drug Discovery

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

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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

Selected TB Research Areas

- Diagnosis
- Pathogenesis
- 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


Tuberculosis: NIH and NIAID Funding

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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”