The Research Path to Tuberculosis Control: An NIH Perspective

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National Institutes of Health
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The AIDS Research Model
Implications for Other Infectious Diseases of Global Health Importance

Gregory K. Folkers, MS, MPH and Anthony S. Fauci, MD
Infectious Diseases Cause ~24% of All Deaths Worldwide

- Cardiovascular Diseases: 17.1 Million
- Infectious Diseases: 14.2 Million
- Neoplastic Diseases: 7.6 Million
- Injuries: 5.8 Million
- Asthma and COPD: 4.0 Million
- Digestive Diseases: 2.0 Million
- All Other Causes of Death

Total Deaths: ~58.8 Million

Source: WHO, 10/2008
## Selected Established Infectious Diseases of Global Public Health Importance

<table>
<thead>
<tr>
<th>Disease</th>
<th>Annual Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Infections</td>
<td>4.3 million</td>
</tr>
<tr>
<td>Diarrheal Diseases</td>
<td>2.2 million</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>2.0 million</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>1.7 million</td>
</tr>
<tr>
<td>Malaria</td>
<td>881,000</td>
</tr>
<tr>
<td>Vaccine Preventable Childhood Diseases (measles, pertussis, tetanus, etc.)</td>
<td>847,000</td>
</tr>
<tr>
<td>“Neglected” Tropical Diseases (schistosomiasis, hookworm infection, leishmaniasis, trypanosomiasis, etc.)</td>
<td>530,000</td>
</tr>
</tbody>
</table>

**Sources:** WHO, 2008; NEJM 357:1018, 2007.
June 5, 1981

Pneumocystis Pneumonia - Los Angeles

July 4, 1981

Kaposi’s Sarcoma and
Pneumocystis Pneumonia Among Homosexual Men - New York City and California
Adults and Children Estimated to be Living with HIV, 2007

Global Total: ~33 million

Source: UNAIDS, 7/2008

>$210 Billion Cumulative Federal Funding for HIV/AIDS (through FY 2007)
NIH HIV/AIDS Research Funding

$36 Billion in Cumulative Funding (through FY 2007)
Advances in AIDS Research, 1981-2008

- Etiology
- Diagnosis
- Molecular Virology and Epidemiology
- Pathogenesis
- Natural History
- Treatment
- Prevention
- Vaccine Development
Advances in AIDS Research, 1981-2008

- Etiology
- Diagnosis
- Molecular Virology and Epidemiology
- Pathogenesis
- Natural History
- **Treatment**
- Prevention
- Vaccine Development
FDA-Approved Antiretroviral Drugs

NRTI
- Zidovudine
- Didanosine
- Zalcitabine
- Stavudine
- Lamivudine
- Abacavir
- Tenofovir
- Emtricitabine

NNRTI
- Nevirapine
- Delavirdine
- Efavirenz
- Etravirine

PI
- Saquinavir
- Ritonavir
- Indinavir
- Nelfinavir
- Amprenavir
- Lopinavir
- Atazanavir
- Fosamprenavir
- Tipranavir
- Darunavir

Entry Inhibitor
- Maraviroc

Integrase Inhibitor
- Raltegravir

Combinations
- 6 available, combining 2 or 3 drugs

Fusion Inhibitor
- Enfuvirtide (T-20)
AIDS Drugs Have Saved 3 Million Years of Life in the United States

The Journal of Infectious Diseases

July 1, 2006 Volume 194

The Survival Benefits of AIDS Treatment in the United States

RP Walensky et al.
Examples of Programs Providing HIV/AIDS Prevention, Treatment and Care to Developing Nations

- President's Emergency Plan for AIDS Relief (PEPFAR)
- Global Fund to Fight AIDS, Tuberculosis and Malaria
- Philanthropies and NGOs (e.g. Gates Fdtn., Clinton Fdtn., MSF)
Number of People Receiving Antiretrovirals in Low- and Middle-Income Countries, 2002-2007

Advances in AIDS Research, 1981-2008

- Etiology
- Diagnosis
- Molecular Virology and Epidemiology
- Pathogenesis
- Natural History
- Treatment
- Prevention
- Vaccine Development
NIAID AIDS Vaccine Funding
1988, 1998, 2008 (est.)

1988
Total AIDS: $223M
Vaccine: $22M

1998
Total AIDS: $703M
Vaccine: $115M

2008
Total AIDS: $1.5B
Vaccine: $491M
Lessons Learned from HIV/AIDS

- Commit substantial financial and human resources
- Enlist the “best and the brightest” investigators in basic and clinical research, domestically and internationally
- Engage the affected community
- Foster cross-sector collaboration with industry, academia, global organizations, philanthropies, NGOs
- Garner support of leaders and policymakers
The Global Burden of Tuberculosis

- One-third of the world's population is infected with *Mycobacterium tuberculosis*

- In 2006
  - 9.2 million new TB cases, incl. 700,000 among HIV-infected people
  - 1.7 million deaths, incl. 200,000 among HIV-infected people
  - Est. 490,000 new cases of MDR TB, incl. 40,000 XDR TB cases

Source: WHO, 2008
TB Patient is Isolated After Taking Two Flights

By LAWRENCE K. ALTMAN

Federal and international officials are tracking down passengers and crew members on two trans-Atlantic flights earlier this month who may have been exposed to a man infected with an exceptionally dangerous form of tuberculosis.

The male passenger flew to Paris from his home in Atlanta on May 12 on Air France 385 and arrived in Paris on May 13. He returned to the United States on May 24 after taking Czech Air 104 to Montreal from Prague. The man drove into the United States that day and entered a hospital in New York City on May 25.
Major Challenges in the Control of Tuberculosis

- Available diagnostics are antiquated, insensitive and slow
- Current drug regimens are complex and lengthy
- Available vaccine not effective in preventing adult pulmonary TB
NIH HIV/AIDS Research Funding

$36 Billion in Cumulative Funding
(through FY 2007)
Inflation Eroded Gains in NIH Funding
Real and Nominal NIH Funding Levels Since 2003

![Graph showing nominal and adjusted NIH funding levels from FY2003 to FY2009.](Image)

Notes: BRDPI is the Biomedical Research and Development Price Index.
Tuberculosis: NIH and NIAID Funding

Fiscal Year

Dollars in Millions

$170
$150
$130
$110
$90
$70
$50
$30
$10

(est.)

NIH
NIAID
NIAID TB Funding - FY 2007

- Basic: $60.6M
- Drugs: $47M
- Diagnostics: $8.5M
- Vaccines: $14.9M

Total TB: $131.1 Million
NIAID’s TB Program

- **Fundamental Science**
  - Host - Pathogen Interactions

- **Immunology, Microbiology, -omics**

- **Translational Science**
  - Drug, Vaccine, Diagnostic Candidates

- **Discovery, preclinical validation, candidate selection**

- **Clinical Studies**
  - Pathogenesis, Disease and Immune Markers, HIV/TB
  - Clinical Trials of New Candidates and Regimens

- **Research Support**
  - TB specific and “generic” contract support across NIAID

- **Research reagents, product testing, models, preclinical support, training**
Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis: The National Institute of Allergy and Infectious Diseases Research Agenda and Recommendations for Priority Research

AS Fauci and the NIAID Tuberculosis Working Group
NIAID Research Agenda for MDR/XDR TB

- **Diagnostics:** Develop reliable technologies to rapidly diagnose drug resistant TB
- **Drugs:** Determine effective use of existing second-line TB therapies and develop new chemotherapeutic agents
- **Basic studies:** Understand the basic biology and immunology of host and pathogen that underlie development and spread of drug resistant *Mtb*
- **Epidemiology:** Understand the epidemiology that contributes to the spread of drug-resistant *Mtb* among HIV+ and HIV- patients
- **HIV/AIDS:** Understand the influence of HIV co-infection on drug-resistance and TB chemotherapy
- **Prevention:** Develop effective vaccines and chemoprevention strategies for all forms of TB
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Sophisticated Molecular Diagnosis/ Monitoring is Needed at the Point of Care
International Partnership to Develop MDR/XDR TB Test

- Expansion of GeneXpert TB test
- Identification of gene markers associated with XDR TB
- Partners
  - NIAID
  - UMDNJ (David Alland)
  - Cepheid
  - FIND/Bill and Melinda Gates Foundation
NIAID Tuberculosis Clinical Diagnostics Research Consortium

- Establishes consortium of clinical study sites in TB-endemic countries
- Goal: to assess the performance of novel, early stage TB diagnostics in the context of existing clinical diagnostic algorithms
- RFP issued July 2008
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Selected Approaches to TB Drug Discovery

- Genetic Approaches to Target Identification
- High-Throughput Screening
- Structural Biology and Virtual Screening

Convergent Technologies Have Revolutionized High-Throughput Screening

- Genomics and Other "-omics"
- High-Throughput Organic Synthesis
- Compound Libraries
- Robotic Technology
- Assay Technology

- Availability of Targets
- Availability of Compounds
- Availability of Screening

High-Throughput Screening 100,000 to 1 Million Compounds/Day

Source: C. Austin, NIH Chemical Genomics Center
Examples of TB Drug Candidates Identified with High-Throughput Screening

A Diarylquinoline Drug Active on the ATP Synthase of *Mycobacterium tuberculosis*

K Andries, V Jarlier et al.

**TMC207**

Combinatorial Lead Optimization of [1,2]-Diamines Based on Ethambutol as Potential Antituberculosis Preclinical Candidates

RE Lee, CE Barry et al.

**SQ109**
FOR IMMEDIATE RELEASE
Wednesday, October 24, 2007

Promising New TB Drug Given Special Status by U.S. and European Regulators

- SQ109 discovered by NIAID intramural scientists in 1999
- Developed through a partnership between NIAID, and the biotech company Sequella, Inc.
- Granted “orphan drug” status by the U.S. FDA and the European Medicines Agency
NIH-NMTH Center of Excellence in TB Research - Masan, South Korea

- Joint US-Korea center for rapid, Phase II evaluation of new antituberculosis drugs
- Established 2003
- National referral center for TB treatment failures
- 50% of inpatients are MDR
- DOT for all inpatients
- Very low HIV+
Re-Evaluating/Re-Formulating Existing Drugs for TB Therapy

- Clinical trials at South Korea site
  - Metronidazole in MDR-TB patients
  - Linezolid in XDR-TB patients
  - >700 patients on study, most M(X)DR
  - Partnership with Gates Foundations and Wellcome Trust

- TB Grants awarded under RFA “Pharmacological Approaches to Combating Antimicrobial Resistance”
  - Pharmacological studies to improve use of existing 1st and 2nd line TB drugs

- Other projects
  - e.g. aerosol delivery of capreomycin, rifampin
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“The first genome analysis of an extensively drug-resistant tuberculosis (XDR-TB) strain has found that only a small number of mutations distinguish it from a less drug-resistant strain and a drug-sensitive one.”
Mechanistic Studies

Ongoing studies at NIAID to determine the mechanism of action of drugs – informs target discovery and validation

- PA-824
  - Novel mechanism of action- kills latent bacteria
  - NIAID Partnership with Novartis Institute for Tropical Diseases in Singapore to develop improved analogs
  - Currently in phase II trials
Genetic Association and Expression Studies Indicate a Role of Toll-like Receptor 8 in Pulmonary Tuberculosis

S Davila, ML Hibberd, et al.
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Harvard Researchers Receive $14 Million TB Study Grant

Harvard researchers at Brigham and Women’s Hospital, Harvard School of Public Health, Harvard Medical School and Partners In Health have received a grant of $14 million over five years from the National Institutes of Health to study multidrug-resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB). The goal of the project is to better understand the development and transmission of drug resistant tuberculosis and to identify practical approaches to reduce the public health burden created by this disease.
Extensively Drug-resistant Tuberculosis in South Korea: Risk Factors and Treatment Outcomes Among Patients at a Tertiary Referral Hospital

CY Jeon, CE Barry, LE Via, et al.
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Integrating Antiretroviral Therapy with TB Treatment for Co-Infections Reduces Mortality

October 16, 2008 -- A South African treatment study conducted by researchers in the Department of Epidemiology at the Mailman School of Public Health shows that mortality among TB-HIV co-infected patients can be reduced by a remarkable 55%, if antiretroviral therapy (ART) is provided simultaneously with TB treatment.
Research on HIV/TB Co-infections: Optimizing HIV and TB Treatment

ACTG 5221
- randomized, open-label study
- determine whether immediate versus deferred ART reduces mortality in HIV+ patients being treated for TB

CAMELIA
- multi-center prospective, randomized, open-label study
- determine timing for the introduction of the HAART in HIV-infected adult patients with TB in Cambodia

PART
- randomized study of HIV-infected patients with active pulmonary TB
- determine whether a punctuated six-month course of ARV therapy during treatment of active TB delays HIV disease progression
Immune Reconstitution and "Unmasking" of Tuberculosis During Antiretroviral Therapy

Stephen D. Lawn, Robert J. Wilkinson, Marc C. I. Lipman and Robin Wood
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Vaccinology: Applying New Science to an Old Discipline

- Genomics
- Structure-based vaccine design
- Biotechnology (e.g. nanotechnology, high-throughput protein production and crystallography, systems biology, bioinformatics)
- Delivery (e.g. viral vectors and mechanism-based adjuvants)
- Production technology (e.g. cell culture-based manufacturing)
Developing Pipeline of New Adjuvants

- CpG - (TLR 9 ligand) in clinical trials
- Lipid A mimics - (TLR 4) safe in humans
- RNA-based - (TLR 3,7,8) in development; may mimic viral infection
- Peptide-based - (TLR 2, 5) in development, example, bacterial flagellin
- Carbohydrate-based - (probably non-TLR; potentially DC SIGN, surfactant D, other lectins) Th2-promoting in laboratory testing
- Small molecule activators of TLR signaling – early discovery
Four of Eight TB Vaccine Candidates in Clinical Trials have Moved into Phase II Studies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Type</th>
<th>Description</th>
<th>Sponsor</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVA85A</td>
<td>Prime boost</td>
<td>MVA vector</td>
<td>Oxford University</td>
<td>Phase II</td>
</tr>
<tr>
<td>GSK M72</td>
<td>Prime boost</td>
<td>Recombinant protein</td>
<td>GlaxoSmithKline</td>
<td>Phase II</td>
</tr>
<tr>
<td>Mycobacterium vaccae</td>
<td>Prime boost</td>
<td>Heat killed NTM</td>
<td>Silence Therapeutics</td>
<td>Phase II</td>
</tr>
<tr>
<td>AERAS-402/ Crucell Ad35</td>
<td>Prime boost</td>
<td>Adenovirus vector</td>
<td>Aeras/Crucell NV</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

Source: TAG 2008 Pipeline Report
Global Partners in Tuberculosis Research and Development

Drug and Biotechnology Companies

Government Agencies

International Development Agencies

Public-Private Partnerships and Research Consortia

TB Diagnostics, Drugs and Vaccines

Philanthropies
Tuberculosis Research and Development: The Way Forward

- Do not “silo” TB – study in context of other diseases, as co-morbidities and "polyparasitism" are common
- Balance basic science with product development
- Integrate multiple scientific disciplines, technologies, and partners
- Invest in -- and sustain -- human capital