Status of the TB Drug Pipeline

Chair: Dr. Barbara Laughon, NIAID, NIH

- Discovery/Preclinical - Dr. Tanjore Balganesh, AstraZeneca*

- Clinical Development - Dr. Ngozi Erondu, TB Alliance

- Community Perspective on Need for a Robust Pipeline and Challenges with Current Regimens - Francis George Alpina, patient representative
The Global Discovery / Preclinical Pipeline for New TB Drugs

Barbara E Laughon, PhD
Senior Scientist for TB Drug Development Partnerships
Division of Microbiology and Infectious Diseases
NIAID, NIH, DHHS
Discovery of TB Drugs


1943
Streptomycin (S)
1948
PAS
1952
Isoniazid (H)
1954
Pyrazinamide (Z)
1955
Cycloserine
1961
Ethambutol (E)
1963
Capreomycin
1963
Ethionamide
1963
Rifampicin (R)
1992
Gatifloxacin
1996
Moxifloxacin
2000
PA-824
2005
TMC-207
2006
OPC-67683

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT
Tuberculosis: NIH and NIAID Funding

- NIH
- NIAID

Dollars in Millions

Fiscal Year

- 1988
- 1990
- 1992
- 1994
- 1996
- 1998
- 2000
- 2002
- 2004
- 2006
- 2008 (est.)
## 2008 TB R&D Funders

<table>
<thead>
<tr>
<th>2008 Rank</th>
<th>Institute</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Bill &amp; Melinda Gates Foundation (BMGF)</td>
<td>147,827,264</td>
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<tr>
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<td>US NIAID, NIH</td>
<td>104,645,069</td>
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<td>3</td>
<td>Otsuka Pharmaceutical Company</td>
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<td>4</td>
<td>European Commission Framework 6/7</td>
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<td>5</td>
<td>US other institutes &amp; centers, NIH</td>
<td>26,472,839</td>
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<td>6</td>
<td>US Centers for Disease Control &amp; Prevention (CDC)</td>
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<td>7</td>
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<td>USAID</td>
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<td>AstraZeneca</td>
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<td>12</td>
<td>Company Z</td>
<td>7,050,000</td>
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<td>13</td>
<td>Institut Pasteur</td>
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<td>Sequella, Inc</td>
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<td>17</td>
<td>Netherlands Ministry of Foreign Affairs (DGIS)</td>
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<td>18</td>
<td>Brazil (aggregate)</td>
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<tr>
<td>19</td>
<td>India (aggregate)</td>
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<tr>
<td>20</td>
<td>Canadian Institute of Health Research</td>
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Global TB Research Partnerships

- Governments
- Academic Consortia
- Global Alliance for TB Drug Development
- STOP TB Partnership / WHO
- Multinational Research Organizations
- Philanthropic Efforts
- Pharmaceutical Companies
Global TB Drug Pipeline, 2010

Discovery

Preclinical Development

Clinical Development

Screening

-- InhA Inhibitor
-- Tryptanthrins
-- LeuRS Inhibitor
-- Protein Kinase Inhibitors
-- Actinomycete Metabolites
-- Fungal Metabolites
-- DNA metabolism
-- Novel compound evaluations

Phenotypic screens

Combinatorial Biosynthetic Compounds

Lead Identification

-- Nitroimidazoles
-- Mycobacterial Gyrase Inhibitors
-- Riminophenazines
-- Diarylquinoline
-- Translocase-1 Inhibitor

Preclinical Development

-- CPZEN-45
-- AZD5847
-- SQ641
-- SQ-109
-- SQ609
-- PNU-100480
-- DC-159a
-- Benzothiazinones

Preclinical Development Discovery Clinical Development

Phase I

-- TMC-207
-- OPC-67683
-- PA-824
-- Rifapentine
-- Linezolid

Phase II*

Phase III

Follow the link below for more information:

www.newtbdrugs.org
Tuberculosis drug discovery- a decade of learning

Tanjore S Balganesh
Vice President Discovery
Head of Research
AstraZeneca India Pvt Ltd.
AstraZeneca India in Bangalore

- Unit devoted to the discovery of novel molecules for the treatment of Tuberculosis
- Mandate given in 2002
- 110 researchers
- Integrated into the global R and D of AZ
- Access to all the technologies, compound libraries of AZ corporate
- Delivered first compound for development in 2009
The Need

- Multiple drugs / compounds are needed to allow new combinations
  - Introducing one new drug at a time into the existing regimen is the worst possible scenario and thus the challenge for MDR regimen.
  - Compounds with different attributes needed to treat the heterogeneity in the infecting microbial population.
  - Need a portfolio of projects to deliver this.
Based on the most recent success rate data, major pharmas must enter 11.1 FGLPs in order to achieve one new drug approval.
AZI 2006-07 Portfolio

Screening

Pre-HI
- MtCoaE
- Alr
- FolB
- MtGlmU
- Ask
- MtrB
- CoaA
- CoaD

HI
- MtLigA
- FtsZ
- MEP
- MtIPan
- UMPK2
- MtSK2

LI

LO
- MtSK
- ALS

Genomic targets
- Most programmes genome target based
- No validated (clinically proven) targets in portfolio

• pmolar inhibitors
  • No MIC
    • Lig A, Umpk
  • + MIC no MBC
    • ALS, Mtsk
Diversity of approaches

Class 1: Macromolecular synthesis and repair
Class 2: Energy metabolism
Class 3: Cell wall
Class 4: Whole cell screening

SCREENING
- Genomic targets
- Validated targets
- Whole cells

LEAD GENERATION
- CHEMICALLY VALIDATED
- COMPOUNDS WITH MIC

DEVELOPMENT

MTS: Medium through-put screening
HCS: High concentration screening
WCS: Whole cell screen
HTS: High through-put screening
Leads from other projects
# TB Alliance Portfolio

## TB ALLIANCE PROGRAMS

### DISCOVERY

<table>
<thead>
<tr>
<th>Lead Identification</th>
<th>Lead Optimization</th>
<th>Preclinical</th>
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<tbody>
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<td>Moxifloxacin</td>
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<tr>
<td>TMC-207</td>
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<td>PA-824</td>
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<tr>
<td>Nitroimidazoles</td>
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<tr>
<td>Mycobact. Gyrase Inhibitors</td>
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<tr>
<td>Riminophenazines</td>
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<tr>
<td>InhA Inhibitors</td>
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<tr>
<td>Diarylquinolines</td>
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<td>Tryptanthrins</td>
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<td>LeuRS Inhibitors</td>
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<td>Phenotypic Screening (H2L)</td>
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<td>Folate Biosynthesis Inhibitors</td>
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<td>Menaquinone Syn Inhibitors</td>
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<td>Natural Products</td>
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<td>RNA Polymerase Inhibitors</td>
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<td>Energy Metabolism Inhibitors</td>
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<td>Protease Inhibitors</td>
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<td>Topoisomerase I Inhibitors</td>
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<td>NITD Portfolio</td>
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### CLINICAL DEVELOPMENT

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<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<tbody>
<tr>
<td>University of Auckland</td>
<td>GlaxoSmithKline</td>
<td>Inst. of Materia Medica, Chinese Academy of Medical Sciences</td>
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<tr>
<td>Novartis</td>
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<td>Tibotec</td>
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<tr>
<td>Bayer</td>
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</table>

- **TMC-207**
- **PA-824**
- **Nitroimidazoles**
- **Mycobact. Gyrase Inhibitors**
- **Riminophenazines**
- **InhA Inhibitors**
- **Diarylquinolines**
- **Tryptanthrins**
- **LeuRS Inhibitors**
- **Phenotypic Screening (H2L)**
- **GyrB Inhibitors**
- **Folate Biosynthesis Inhibitors**
- **AZ Whole-Cell Screening (H2L)**
- **GSK Whole-Cell Screening (H2L)**
- **Malate Synthase Inhibitors**
- **Menaquinone Syn Inhibitors**
- **Natural Products**
- **RNA Polymerase Inhibitors**
- **Energy Metabolism Inhibitors**
- **Protease Inhibitors**
- **Topoisomerase I Inhibitors**
- **NITD Portfolio**

---

*H2L – Hit-to-Lead*
Aligning the portfolio

SCRENNING

LEAD GENERATION

Genomic targets

Protease

Malate synthesis inhibitors

Topo 1

Validated targets

Menaquinone inhibitors

RNA pol.

Energy metabolism

GyrB

Folate synthesis inhibitors

Diarylquinolines

Whole cells

Tryptanthrins

Phenotypic screening

Riminophenazines

WCS

MTS: Medium through-put screening

HCS: High concentration screening

WCS: Whole cell screen

HTS: High through-put screening

Leads from other projects
In 2007, Lilly announced the **The Lilly TB Drug Discovery Initiative**.

A not-for-profit, public-private partnership focused on accelerating early-stage drug discovery in TB.

Lilly grants access to its library of 800,000 compounds and contributes drug discovery technology and expertise.

Founding members include the Infectious Disease Research Institute in Seattle, the U.S. National Institutes of Health, and Lilly.

New members include Jubilant Biosys and Academia Sinica.

Together, the MDR partnership and the Drug Discovery initiatives represent Lilly’s comprehensive approach and a $135 million commitment.

www.tbdrugdiscovery.org
STOP TB Partnership
Working Group on New Drugs
TB Drug R&D Portfolio, 2009

www.newTBdrugs.org

Barbara Laughon
Candidates Subgroup Leader
## Global TB Drugs Pipeline 2009

**Hit To Lead**

<table>
<thead>
<tr>
<th>Category</th>
<th>Project Information</th>
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<tbody>
<tr>
<td>Tryptanthrins</td>
<td>TB Alliance, Korea Institute of Chemical Technology and Yonsei University</td>
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<tr>
<td>M. tuberculosis Protein Kinase Inhibitors</td>
<td>Vertex Pharmaceuticals, Incorporated</td>
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<tr>
<td>Actinomycete metabolites</td>
<td>University of Illinois at Chicago, Myongji University</td>
</tr>
<tr>
<td>Phenotype screening</td>
<td>AstraZeneca R and D Bangalore</td>
</tr>
<tr>
<td>Phenotypic Screening</td>
<td>TB Alliance, University of Illinois</td>
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<tr>
<td>LeuRS inhibitors</td>
<td>TB Alliance, Anacor Pharmaceuticals</td>
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<tr>
<td>DNA metabolism</td>
<td>AstraZeneca R and D Bangalore</td>
</tr>
<tr>
<td>InhA Inhibitors</td>
<td>TB Alliance, GlaxoSmithKline</td>
</tr>
<tr>
<td>Fungal metabolites</td>
<td>Mycosynthetix, University of Illinois at Chicago</td>
</tr>
<tr>
<td>Hit to Lead Evaluation of novel compounds</td>
<td>The Lilly TB Drug Discovery Initiative</td>
</tr>
</tbody>
</table>

## Lead Optimization

<table>
<thead>
<tr>
<th>Category</th>
<th>Project Information</th>
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<tbody>
<tr>
<td>Nitroimidazoles</td>
<td>TB Alliance, University of Auckland, University of Illinois</td>
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<tr>
<td>Mycobacterial Gyrase Inhibitors</td>
<td>TB Alliance, GlaxoSmithKline</td>
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<td>MTopo</td>
<td>AstraZeneca R and D Bangalore</td>
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<tr>
<td>New Generation Diaryquinoline</td>
<td>TB Alliance, Tibotec</td>
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<td>Bi-functional Molecules</td>
<td>TB Alliance, University of Auckland and Colorado State University</td>
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<tr>
<td>Riminophenazines</td>
<td>TB Alliance, Institute of Materia Medica, The Beijing Tuberculosis an...</td>
</tr>
<tr>
<td>TL1 Inhibitors</td>
<td>Sequella</td>
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