TB Drug Development: 
*pipeline realities*

Ann M. Ginsberg, M.D., Ph.D.  
Global Alliance for TB Drug Development

IOM Planning Summit on MDRTB, XDRTB, and Totally Drug Resistant TB  
Washington D.C.  
November 5, 2008
Discovery of Current TB Drugs

1st line TB drugs (Drug-Sensitive TB)

- 1940: Streptomycin (S)
- 1944: Isoniazid (H)
- 1948: PAS
- 1950: Cycloserine
- 1952: Pyrazinamide (Z)
- 1954: Ethionamide
- 1955: Ethambutol (E)
- 1957: Kanamycin
- 1961: Rifampin (R)
- 1963: FQ-Ofloxacin
- 1970: Rifapentine
- 1972: Amkicin
- 1975: Rifabutin
- 1980: Levofloxacin
- 1992: Rifapentine

2nd line TB drugs (Drug-Resistant TB)
Current TB Therapy

- **Active, drug-sensitive TB**
  4 Drugs, ≥6 months: 2RHZE + 4RH

- **M(X)DR-TB**
  Individualized therapy for ≥2 years, few available drugs, poorly tolerated, expensive

- **TB/HIV co-infection**
  Drug-drug interactions with ARVs - simultaneous therapy difficult

- **Latent TB Infection**
  9 Month H
  Rifampin (R), Isoniazid (H), Pyrazinamide (Z), Ethambutol (E)
Optimal Target Profile

- **Shortens and simplifies treatment**
  Active against drug persistent *Mtb* populations

- **Equally effective against M(X)DR-TB**
  Novel mechanism of action

- **Easy, safe, co-administration with ARVs**
  No P450 mediated drug-drug interactions

- **Excellent safety/tolerability**

- **Oral, ≤ once daily dosing**

- **Low cost of goods**
Distribution of TB Drug Targets

Cell Wall Synthesis
- Isoniazid
- Cycloserine
- Ethambutol
- Ethionamide/Prothioamide
- Ethylene diamine SQ-109
- Novel InhA inhibitors

Energy Production
- Malate synthase inhibitors
- Energy metabolism inhibitors
- Isocitrate lyase inhibitors
- Menaquinone synthesis
- Riminophenazones
- Pyrazinamide
- ATP Synthase
  - Diarylquinoline TMC-207

Folic Acid Metabolism
- p-Aminosalicylic acid

Multiple Targets
- OPC-67683
- PA-824
- Nitroimidazoles

Replication & Transcription
- Rifamycins
- Novel RNAP inhibitors

DNA Gyrase
- Moxifloxacin
- Gatifloxacin
- TBK-613
- Novel DNA gyrase inhibitors

RNA Polymerase
- PNU-100480
- Macrolides
- Pleuromutilins

Ribosome (50S)
- Streptomycin
- Kanamycin/Amikacin
- Capreomycin/Viomycin

Ribosome (30S)
- Streptomycin
- Kanamycin/Amikacin
- Capreomycin/Viomycin

Others/Unknown
- Pyrrole LL3858
- Bifunctional molecules
- Protease inhibitors
- Phenotypic screening

ATP Synthase
- Diarylquinoline TMC-207

Energy Metabolism
- Malate synthase inhibitors
- Energy metabolism inhibitors
- Isocitrate lyase inhibitors
- Menaquinone synthesis
- Riminophenazones
- Pyrazinamide

DNA Synthesis
- DHFA
- PABA

Translation
- rRNA synthetase inhibitors
- tRNA Synthetase
- rRNA synthetase inhibitors
- Peptide Deformylase
- PDF inhibitors

Current drugs: Black
Compounds in Clinical: Blue
Compounds in preclinical: Green
Discovery projects: Red

TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

IOM 5 November 2008
New Trends in TB Drug R&D

Active TB

Drug Resistance Targets

Drug Persistence Targets

Treatment of M(X)DR-TB

Ideal Drug Targets
- DNA gyrase
- ATP synthesis
- RNA polymerase
- Others

Treatment Shortening
Why shouldn't malate synthase inhibitors, for example, work on M(X)DR and therefore also belong in the "ideal Drug Targets" list? PDF inhibitors?

aginsberg, 10/15/2008
TB Drug R&D Process

Drug Discovery
- Identify drug candidates that can meet the drug target profiles
  ~2-5 Years

Preclinical Development
- Study safety and efficacy in preclinical models
  ~1-2 Years

Clinical Development
- Demonstrate safety and efficacy in TB patients
  ~6-10 Years

TOTAL DURATION: 10 to >15 years
a2  OFLOTUB rather than OFLUTUB
aginsberg. 10/15/2008
Probability of Success for a Drug Candidate

- Preclinical: 10.30%
- Phase I: 18.40%
- Phase II: 28.10%
- Phase III: 65.80%
- Submission: 90.60%

Source: The Pharmaceutical R&D Companion.
Global Clinical Portfolio – Registration Programs

- **Gatifloxacin**: Phase III - Oflotub, TDR
- **Moxifloxacin**: Phase III - Bayer, TB Alliance
- **TMC207**: Phase III - J&J/Tibotec
- **OPC67683**: Phase II - Otsuka
- **PA-824**: Phase II - TB Alliance
- **SQ109**: Phase I - Sequella
- **LL-3858**: Phase I - Lupin

**TB ALLIANCE**
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT
Key Challenges

- Multidrug therapy
  - need *regimens*, not single drugs

- Long clinical development timelines;
  to streamline, need:
  - validated biomarkers of drug effect
  - validated animal model that reliably predicts
    human dose range and treatment duration
  - validated “proof of concept” trial design for
    treatment-shortening
  - adequate clinical trial capacity (GCP/GLP)
  - harmonized, TB-specific regulatory guidances
Current TB Alliance Portfolio

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Clinical Preclinical Discovery
Key Challenges (2)

- High costs of clinical development and global registration
  - Parallel programs for DS and M(X)DR
- Affordability
- Accessibility
- Adoption

NTPs and private sector
Conclusions

- Multiple new TB drugs and regimens are needed to address the challenges in TB, including M(X)DR-TB.

- A resurgence in TB drug R&D is ongoing; 2-3 new drugs may reach registration before 2015.

- Improved understanding of *M. tb* biology may lead to better, smarter drugs to tackle drug resistance, shorten treatment, and eliminate latent infection.

- A much more robust pipeline is needed.
1st bullet: not sure the challenges are "new"
aginsberg, 10/15/2008
“TB claims 1.7 million lives each year, and eliminating it will be a global challenge - but it's a challenge we must take on....”

Thank you