Towards a new combination therapy for tuberculosis

The tuberculosis drug pipeline half-full or half-empty?

Stewart Cole

Global Health Institute

EPFL
History of TB drug discovery

First-line TB drugs (drug-sensitive TB)

Second-line TB drugs (drug-resistant TB)

Ginsberg Workshop on Addressing the Threat of Drug-Resistant Tuberculosis; November 5; Washington, DC. 2008.
History of clinical trials

MRC TB Unit Clinical Trials
Conducted from 1946 to 1986

- **1946**
  - The initial trial assessing the value of the addition of streptomycin to bed rest

- **1948**
  - Emergence of bacterial resistance to either streptomycin or \( p \)-aminosalicylic acid (PAS) alone was greatly decreased when combined treatment was given with both drugs.

- **1952-1955**
  - Exploration of isoniazid alone and in combination with PAS or streptomycin.

- **1958-1967**
  - Inclusion of rifampicin or pyrazinamide in a regimen of streptomycin and isoniazid substantially reduced the relapse rate

- **1970**
  - Period of treatment shortened to 6 months by the inclusion of rifampicin and pyrazinamide in the regimen.

- **1972-1974**
  - Affordable regimens for developing countries led to the substitution of thiacetazone for PAS.

- **1976**
  - Delineation of modern short-course chemotherapy by showing sterilizing activity of pyrazinamide in first 2 months of treatment.

- **1977- onwards**
  - Demonstration of the value of intermittency in short-course regimens as less expensive, less costly and as effective as daily therapy.
HIV prevalence in new TB cases 2011
MDR and XDR-TB

FIGURE 4.6 Number of MDR-TB cases estimated to occur among notified pulmonary TB cases, 2011
Short course chemotherapy

- Intensive phase: RHZE – 2 months
- Continuation phase: RH – 4 months
- Fully supervised – DOTS
- 95% cure rate for DS-TB

Surely this can be improved?

- But if DR-TB – ad hoc treatment
- Duration: 18 – 24 months, DOTS+
- Second line drugs – badly tolerated
- Cure rate <50%
Sterilizing, bactericidal activity

Oral delivery

Effective X persisters (extra/intracellular)

Novel MoA: active X MDR- & XDR-TB

No antagonism with DOTS & compatible with ART/T2D

Compatibility with ART/T2D - No Big ask!

Toxicologically acceptable for dosing >2 months

Therapy ideally results in cure within <6 (4, 2?) months
Repurposed drugs

Fluoroquinolones
- Gatifloxacin
- Moxifloxacin

Rifamycins
- Rifapentine
- Riminophenazine
- Clofazimine

Oxazolidinones
- Linezolid
- Sutezolid
- AZD5847

Beta-lactams
- Meropenem
- Clavulanate
- Faropenem

Zumla et al. 2013 Nat Rev Drug Dis
New chemical entities (NCE)

- Nitroimidazole derivatives: PA-824, TBA354, OPC67683 (delaminid)
- Diarylquinolines - TMC207 (bedaquiline)
- Ethylene diamines - SQ109
- Benzothiazinones - BTZ043, PBTZ169
- Imidazopyridine - Q203
Global TB Drug Pipeline

Preclinical Development

Early Stage Development
- CPZEN-45
- BTZ043
- DC-159a
- SQ609
- SQ641
- TBI-166

GLP Tox
- PBTZ169
- TBA-354
- Q203

Clinical Development

Phase I
- AZD5847 N
- Bedaquiline NC R
- (TMC-207) for DS-TB
- Linezolid
- Novel Regimens2
- PA-824 Nc
- Rifapentine for DS-TB
- SQ-109 N
- Sutezolid N
- (PNU-100480)

Phase II
- Delamanid N R
- (OPC-67683)
- Gatifloxacin†
- Moxifloxacin†
- Rifapentine N for LTBI
- Bedaquiline NC R
- (TMC-207) for MDR-TB

Phase III

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylmethane, benzothiazinone

1 Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php.

2 Combination regimens: NC-001-{I-M-Pa-2}, phase 2a, NCT01215851; NC-002-{M-Pa-2}, phase 2b, NCT01498419; NC-003-{C-J-Pa-2}, phase 2a, NCT01691534; PanACEAMAM1{-TB-01}-HR-Z-E{-C-M}, phase 2b, NCT01705186.

3 Drug candidate currently in combination regimen in clinical testing

4 Submitted for approval or approved by stringent regulatory authority (i.e., FDA, EMA, WHO Prequalification)

5 New chemical entity

* Projects that have been completed
New regimens in clinical trial

- Phase IIA trial, NC001-6, tests PA-824, MOXI & PZA in South Africa & elsewhere
- BDQ, PZA, CFM & PA-824
EBA evaluation of new combinations

Figure 2: Bilinear regression showing the fall in mean log_{10} CFU from baseline
CFU=colony forming unit.

Lancet 2012; 380: 986–93
Treatment shortening regimens

- Mouse models predicted FQ could reduce treatment duration by 1 – 2m (JHU)
- Prediction supported by observational study in humans (TRC-OFX)
- Further supported by 2m phase II studies with 4th generation FQ
- 3 phase III trials: REMoxTB, OFLOTUB, RIFAQUIN.
Treatment shortening regimens

• “Randomized, controlled trials to test non-inferiority” of 4m FQ-containing regimen v. 6m RHZE
• Primary endpoint – treatment failure or relapse within 18 – 24m
• Non-inferiority based on margin of 6% points (90% CI)
Failure and disappointment
Explaining failure and way forward

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIAL

Shortening Treatment for Tuberculosis — Back to Basics
Digby F. Warner, Ph.D., and Valerie Mizrahi, Ph.D.

• Murine models not predictive of human outcome
• 2m culture conversion not predictive of cure
• Better biomarkers needed
• Small phase II sample sizes have limitations
• Invest more in basic research

“Instead of relying on the results of 2m phase 2 trials to select candidate regimens for phase 3 studies, investigators might find that the most efficient approach is to conduct phase 3 trials as quickly as possible while establishing more feasible and less costly approaches to performing these studies.”

NEJM 371:1577-87
## Global TB drug pipeline 2015

### Drug Pipeline

#### Clinical Development

<table>
<thead>
<tr>
<th>Preclinical Development</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TBI-106</strong>&lt;br&gt; Raminophenazines antibiotic&lt;br&gt; Institute of Materia Medica, Tokyo, Japan.</td>
<td><strong>TBA-354</strong>&lt;br&gt; Nitroimidazole&lt;br&gt; TB Alliance</td>
<td><strong>Sutezolid (PNU-100480)</strong>&lt;br&gt; Oxazolidinone&lt;br&gt; Sequella</td>
<td><strong>Bedaquiline (TMC207)</strong>&lt;br&gt; with OBR for MDR-TB&lt;br&gt; Diaryquinoline OBR = Optimized Background Regimen&lt;br&gt; Janssen</td>
</tr>
<tr>
<td><strong>CPZEN-45</strong>&lt;br&gt; Caprazene nucleoside&lt;br&gt; Institute of Microbial Chemistry (BIAKEN), Tokyo, Japan. Lilly TB Drug Discovery Initiative, NIAID, IDR, Lilly, YourEncore.</td>
<td></td>
<td><strong>SQ108</strong>&lt;br&gt; Ethylisocrodamine&lt;br&gt; Sequella, NIH</td>
<td><strong>Delamanid (OPC-67683)</strong>&lt;br&gt; with OBR for MDR-TB&lt;br&gt; Nitro-dihydro-imidazooxazole&lt;br&gt; Otsuka Pharmaceutical Co., Ltd.</td>
</tr>
<tr>
<td><strong>SQ609</strong>&lt;br&gt; Dipiridamole&lt;br&gt; Sequella</td>
<td></td>
<td><strong>SQ109</strong>&lt;br&gt; Ethylisocrodamines&lt;br&gt; Sequella</td>
<td><strong>Rifapentine for LTBI</strong>&lt;br&gt; Rifamycin&lt;br&gt; CDC, Sanofi-aventis</td>
</tr>
<tr>
<td><strong>SQ641</strong>&lt;br&gt; Capramycin&lt;br&gt; Sequella</td>
<td></td>
<td></td>
<td><strong>Protoman - Moxifloxacin - Pyrazinamide</strong>&lt;br&gt; New chemical entity&lt;br&gt; TB Alliance, STAND Trial</td>
</tr>
<tr>
<td><strong>Q203-Novel anti-TB agent</strong>&lt;br&gt; Imidazopyridine&lt;br&gt; Quinent Co., Ltd.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PBTZ 169</strong>&lt;br&gt; Benzothiazinone&lt;br&gt; Innovative Medicines for Tuberculosis (IM4TB)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Additional Information

- **Login/Register** to add a Project
- **Download the PPT Slide**

J Antimicrob Chemother
doi:10.1093/jac/duv145

No activity in EBA; serum level < MIC
Global TB drug pipeline 2015

DRUG PIPELINE

PRECLINICAL DEVELOPMENT

- **TBI-106**
  - Rhamnolipid antibiotic
  - Institute of Materia Medica,

- **CPZEN-45**
  - Cephalosporin nucleoside
  - Institute of Micolbial Chemistry (Riken Kaken), Tokyo, Japan, Lilly TB Drug Discovery Initiative, NIAID, IDI, Lilly, YouEnCore

- **SQ909**
  - Diphenylamine
  - Sequella

- **SQ841**
  - Cephalosporin
  - Sequella

- **G203-Novel anti-TB agent**
  - Imidazopyridine
  - Querent Co. Ltd.

- **PBTZ 169**
  - Benzothiazinone
  - Innovative Medicines for Tuberculosis (IM4TB)

PHASE I

- **TBA-354**
  - Nitroimidazole
  - TB Alliance

- **SQ105**
  - Ethylenediamine
  - Sequella

- **SQ109**
  - Ethylenediamine
  - Sequella

- **Sutezolid (PNU-100480)**
  - Oxazolidinone
  - Sequella

PHASE II

- **Bedaquiline (TMC207)**
  - Diaryquinoline OBR = Optimized Background Regimen
  - Janssen

- **Delamanid (OPC-67683)**
  - Nitro-dihydro-imidazooxazole
  - Otsuka Pharmaceutical Co., Ltd.

- **Rifapentine for DS-TB**
  - Rifapentine
  - CDC, Sandhi-aventis

- **AZD5847**
  - Oxazolidinone
  - AstraZeneca

PHASE III

- **Protomanid - Moxifloxacin - Pyrazinamide**
  - New chemical entity
  - TB Alliance, STAND Trial

**CLINICAL DEVELOPMENT**

- **Login/Register to add a Project**
- **Download the PPT Slide**
Drug Development Funding Process

- Research
- Discovery
- Pre-clinical studies
- Phase I Clinical trials
- Phase II Clinical trials
- Phase III Clinical trials

Funding awarded

No Funding available

Funding available

Valley of Death
• Financial incentives are inadequate for most companies
  - market far less lucrative than for other diseases, which results in chronic underinvestment
  - reduced investment in TB drug R&D,
    • Pfizer withdrawal from TB R&D
    • AstraZeneca abandon TB R&D & close site
    • Novartis pull out
    • 4/22 Big Pharma producing antibacterials

• Limited financial support to progress preclinical drug candidates from public sector
Well - where are we?

- No TB drugs in Horizon 2020
- BMGF & TBDA
- Failing pipeline?
- BDQ/DMD approval MDR → DST
- Too much duplication; Not joined-up
- Long-term commitment from pharma?
Where are we going?

MUST CHANGE...OR ELSE!