Optimising tb treatment: what choices can we take?

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Overview

- The challenge
- How therapeutics can help
- Developing new treatments
  - optimising existing tb drugs
  - adapting other antibiotics
  - developing new anti-tb drugs
- Improving the pipeline
- Conclusions
Figure: Distribution of multidrug-resistant tuberculosis among new cases, 1994-2007

Subnational coverage in China, India, Indonesia, and Brazil. Source: WHO, 2000. "The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city, or area, or of its authorities, or concerning the delimitation of its frontiers or boundaries."
<table>
<thead>
<tr>
<th>Region</th>
<th>Cases</th>
<th>95% CI</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established market economies</td>
<td>105795</td>
<td>1317 (1147-1557)</td>
<td>1.2% (1.1-1.5)</td>
</tr>
<tr>
<td>Central Europe</td>
<td>50502</td>
<td>1201 (623-3694)</td>
<td>2.4% (1.3-7.2)</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>416 316</td>
<td>80057 (71,893-97,623)</td>
<td>19.2% (18.0-22.2)</td>
</tr>
<tr>
<td>Latin America</td>
<td>349 278</td>
<td>12070 (10,523-15,526)</td>
<td>3.5% (3.0-4.4)</td>
</tr>
<tr>
<td>Eastern Mediterranean region</td>
<td>601 225</td>
<td>25,475 (15,737-73,132)</td>
<td>4.2% (2.6-11.9)</td>
</tr>
<tr>
<td>Africa, low HIV incidence</td>
<td>375 801</td>
<td>8415 (6889-18,758)</td>
<td>2.2% (1.9-5.0)</td>
</tr>
<tr>
<td>Africa, high HIV incidence</td>
<td>2656 422</td>
<td>58,296 (48,718-118,506)</td>
<td>2.2% (1.9-4.5)</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>3464 313</td>
<td>149,615 (114,780-217,921)</td>
<td>4.3% (3.5-6.2)</td>
</tr>
<tr>
<td>Western Pacific region</td>
<td>2173 333</td>
<td>152,694 (119,886-188,014)</td>
<td>7.0% (6.1-8.1)</td>
</tr>
<tr>
<td>Surveyed countries (n=115)</td>
<td>7953 603</td>
<td>408,325 (361,264-464,069)</td>
<td>5.1% (4.7-5.7)</td>
</tr>
<tr>
<td>Non-surveyed countries (n=70)</td>
<td>2239 383</td>
<td>80,814 (71,684-188,605)</td>
<td>3.6% (3.2-8.4)</td>
</tr>
<tr>
<td>All countries (n=185)</td>
<td>10192 986</td>
<td>489,139 (455,093-614,215)</td>
<td>4.8% (4.6-6.0)</td>
</tr>
</tbody>
</table>

The total number of estimated cases includes estimated re-treatment cases; see Methods section for details of calculations.
Reducing resistance and controlling TB

• Rapid diagnosis
• Effective treatment
• Higher completion rates
• Shorter regimens
TB Treatment Trials

- **1950**: 1st Regimen: Streptomycin, PAS, Isoniazid
- **1952**: Rifampin synthesized
- **1954**: Pyrazinamide synthesized – liver toxicity
- **1957**: BMRC Trials - Addition of Rifampin
- **1966**: Trials add Lower Dosage Pyrazinimide.
- **1980s**: Trials Substitute Moxifloxacin into Regimen
- **2005**: Current Treatment
  - **2 Months**: Rifampin, Isoniazid, Pyrazinamide, Ethambutol +
  - **4 Months**: Rifampin, Isoniazid

- **Rx Lasts Up to 24 Months**
- **Rx Shortened to 9 Months**
- **Rx Shortened to 6 Months**
- **Rx Shortened to 3 Months**
- **Rx Target: 3 - 4 Months**
Study R – the design

- Four regimens of 6 months duration:
  - 6SHR
  - 6SHZ
  - 6SHT
  - 6SH
- The control: 2STH/16TH

S streptomycin, H isoniazid, R rifampicin Z pyrazinamide, T thiacetazone
Study R – the results

• The results were the first signs of a new era in the treatment of TB.
• In patients with fully sensitive organisms relapse rates were:

  – 6SHR  3%
  – 6SHZ  8%
  – 6SHT  22%
  – 6SH   29%
  – 2STH/16TH 3%

Even at 5 years the 6SHR relapse rate was only 3%
‘Standard’ treatment

- Subsequent trials explored variations on the successful 6SHR regimen, adding Z, pyrazinamide to the initial intensive phase and giving two drugs in the continuation phase, either HR or TH (the cheaper alternative which required continuing treatment for up to 8 months).

- Streptomycin was replaced by ethambutol and 2EHRZ/4HR eventually became standard treatment in many developed country settings and ultimately in many developing country settings.
If 6 months works why not 4?

• Study X explored the possibility that treatment could be shortened still further to 4 months.

• The regimens were:
  – 2SHRZ/2HRZ
  – 2SHRZ/2HR
  – 2SHRZ/2HZ
  – 2SHRZ/2H
  – 2HRZ/2H

S Streptomycin, H isoniazid, R rifampicin, Z pyrazinamide
Study X - results

• Relapse rates:
  – 2SHRZ/2HRZ 16%
  – 2SHRZ/2HR 11%
  – 2SHRZ/2HZ 32%
  – 2SHRZ/2H 30%
  – 2HRZ/2H 40%

S streptomycin, H isoniazid, R rifampicin
Z pyrazinamide, T thiacetazone

Unacceptably high relapses rates
No benefit from Z after 2 months
What can we do?

• Utilise existing anti-tb drugs better
• Adapt antibiotics from other indications
• Develop new anti-tuberculosis agents
Adapt existing tb-drugs

- Pyrazinamide
  - dosage optimised in 1970s
  - engineer the molecule to avoid resistance
- Ethambutol
- Isoniazid
- Improve performance of existing drugs
- Rifampicin
Improving performance with efflux inhibitors

- Adding verapamil?
- Adding thioridizine?
- Anecdotal evidence of benefit but no clinical trials planned
Optimising rifamycin dosage 1

- Kreis and Pretit 1976
- H 900mg/R 1200mg/S 1000mg
- Three month regimen
- near 100% culture conversion
- 16% relapse rate
FIG. 1. Two-hour plasma rifampin concentrations after 4 weeks of TB treatment in Indonesian patients randomized to standard-dose (450 mg) or high-dose (600 mg) rifampin daily. Rifampin doses were combined with standard-dose isoniazid, pyrazinamide, and ethambutol. Depicted are data for individual patients (bullets) and means for both groups (horizontal bars).
Moxifloxacin – Chemical Structure

- Minimizes efflux (*S. pneumoniae, S. aureus*)
- Enhances Gram-positive activity

![Chemical structure of Moxifloxacin]

- Minimizes development of resistance
- Enhances anaerobic activity

Increased overall bactericidal activity

\[ \text{NH} \quad \text{F} \quad \text{O} \quad \text{H}\]
Moxifloxacin: Metabolism and Elimination

LIVER
Metabolites
Sulfo-compound (inactive), M-1, Acyl-glucuronide (inactive), M-2

BILE
Parent + M-1, M-2

No dose adjustments necessary in patients with renal or hepatic impairment

Hepatic ~ 60%
Renal ~ 40%

Enterohepatic cycling:
Parent + M-2

Faecal excretion:
M-1 (35% of dose)

Faecal excretion:
26% of dose unchanged

Urine:
M-1 (2.5% of dose)
M-2 (14% of dose)

Urine:
~20% of dose unchanged
Moxifloxacin: Appropriate PK/PD Profile

Steady-State Plasma Concentrations of Moxifloxacin 400 mg QD (mean; SD) (n =10)

The Bactericidal Activity of Moxifloxacin in Patients with Pulmonary Tuberculosis*

### TABLE 3. MEAN EARLY BACTERICIDAL ACTIVITY OF ISONIAZID, MOXIFLOXACIN, AND RIFAMPIN GROUPS

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>Mean EBA</th>
<th>SD</th>
<th>Lower Bound</th>
<th>Upper Bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin</td>
<td>8</td>
<td>0.53</td>
<td>0.31</td>
<td>0.28</td>
<td>0.79</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>12</td>
<td>0.77</td>
<td>0.37</td>
<td>0.54</td>
<td>1.00</td>
</tr>
<tr>
<td>Rifampin</td>
<td>12</td>
<td>0.28*</td>
<td>0.21</td>
<td>0.15</td>
<td>0.41</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

95% CI for Mean

**Definition of abbreviations:** CI = confidence interval; EBA = early bactericidal activity.

* Mean EBA of rifampin is significantly lower than that of isoniazid (asymptotic p < 0.01) using the Kruskal–Wallis analysis of variance.


Moxifloxacin-containing Regimen Greatly Reduces Time to Culture Conversion in Murine Tuberculosis*

![Graph showing log CFU in lungs versus duration of treatment months for different regimens: Untreated, 2HRZ/4HR, 2HRZM/4HRM, 2HRM/4HR, 2HZM/4HM, and 2RZM/4RM.]

H = isoniazid
R = rifampin
Z = pyrazinamide
M = moxifloxacin
[M for H]

Nuermberger et al AJRCCM 2004;169:421
Moxifloxacin-containing Regimens of Reduced Duration Produce a Stable Cure in Murine TB

H = isoniazid
R = rifampin
Z = pyrazinamide
[M for H]
M = moxifloxacin

Nuermerber et al AJRCCM 2004;170:1131
TBTC Study 27 - Design

- Double-blind, multi-centre
- African and North American sites
- Treatment arms
  - HRZM x 8 weeks
  - HRZE x 8 weeks

H = Isoniazid (INH); R = Rifampicin; Z = Pyrazinamide; E = Ethambutol; M = Moxifloxacin; DOT = direct observed therapy
TBTC Study 27 - End Points

• Primary
  – Efficacy: Proportion of patients culture negative at 8 weeks
  – Tolerability: Proportion of subjects who completed 2 months of study regimen

• Key secondary endpoints
  – Compare efficacy, safety and tolerability of 5 days/week versus 3 days per week regimens
  – Compare adverse events among HIV-infected patients vs. HIV-uninfected patients
TBTC Study 27 - Patients with Negative Sputum Culture Results at 8 Weeks

Burman et. al. AJRCCM 2006;174:331-338
Figure 2: Proportion of patients with negative sputum cultures during 8 weeks of treatment
Data are for patients with 8-week culture data available at each timepoint.
Study 28 - Endpoints

• Primary
  – Proportion of individuals with negative sputum cultures after 8 weeks

• Secondary
  – Safety and tolerability
  – Time to culture conversion
Figure 2. Time to stable sputum culture conversion for the protocol-correct analysis group, by treatment group, using (1) the combined result for both liquid and solid culture medium, and (2) separate results for liquid and solid culture medium.

TABLE 4. FINAL MULTIVARIATE LOGISTIC REGRESSION MODEL FOR SPUTUM CULTURE NEGATIVITY AT COMPLETION OF 8 WEEKS OF TREATMENT IN THE PROTOCOL CORRECT ANALYSIS GROUP

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moxifloxacin vs. Isoniazid</td>
<td>1.30</td>
<td>0.80, 2.12</td>
<td>0.29</td>
</tr>
<tr>
<td>Assignment stratum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-African, noncavitary</td>
<td>1.00</td>
<td>(ref)</td>
<td></td>
</tr>
<tr>
<td>Non-African, cavitary</td>
<td>0.11</td>
<td>0.02, 0.49</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>African, noncavitary</td>
<td>0.06</td>
<td>0.01, 0.31</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>African, cavitary</td>
<td>0.05</td>
<td>0.01, 0.21</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age at enrollment (per year)</td>
<td>0.97</td>
<td>0.95, 1.00</td>
<td>0.03</td>
</tr>
<tr>
<td>High bacillary burden on</td>
<td>0.45</td>
<td>0.26, 0.79</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>baseline sputum smear*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days to detection in liquid culture</td>
<td>1.04</td>
<td>1.00, 1.07</td>
<td>0.03</td>
</tr>
<tr>
<td>system for baseline sputum*</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

See Table 3 for abbreviations.

* Defined as one or greater acid fast bacilli/field at ×1000.

† For 322 participants with a baseline liquid culture positive for M. tuberculosis.
Study objective

• To assess whether substituting moxifloxacin for individual drugs (isoniazid OR ethambutol) in the existing 6 month regimen and stopping treatment at 4 months will be as effective as the standard 6 month regimen.
Hypothesis

In treatment naïve adults with smear positive pulmonary TB treatment with a 4 month regimen is not inferior to standard 6 month therapy

Non-inferiority is being assessed in terms of efficacy and safety
Study design

Fig. 1 REMox Trial Design

Regimen 1
- EHRZ + M placebo
- HR + M placebo
- HR

Regimen 2
- MHRZ + E placebo
- MHR
- H placebo

Regimen 3
- EMRZ + H placebo
- MR + H placebo
- H placebo

Comparison 1
M subst for E (4 vs 8 mos.) Non-inferior Failure/relapse rate

Comparison 2
M subst for H (4 vs 8 mos.) Non-inferior Failure/relapse rate

Screening Phase | Intensive Treatment Phase | Continuation Treatment Phase | Follow-Up Phase

<table>
<thead>
<tr>
<th>Months</th>
<th>Weeks</th>
<th>Visit #</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>-1</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>52</td>
<td>3</td>
</tr>
<tr>
<td>18</td>
<td>78</td>
<td>4</td>
</tr>
</tbody>
</table>

Combination
Drug packaging II

- Intensive Active Phase Weekly Blister Pack
- Monthly Continuation Phase Box
- Continuation Phase Weekly Blister Pack
- Patient drug shipping box (6 months supply)
Visits

<table>
<thead>
<tr>
<th>Months (wks)</th>
<th>0</th>
<th>2 (8)</th>
<th>4 (17)</th>
<th>6 (26)</th>
<th>12</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Screening</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Intensive</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td><strong>Continuation</strong></td>
<td></td>
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<tr>
<td><strong>Follow-Up</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BASELINE**
Consent; Clinical, Samples, Labs

**INTENSIVE**
Eight weekly visits
Clinical, Samples

**CONTINUATION**
Four monthly visits
Clinical, Samples

**FOLLOW-UP**
Four 3-monthly visits
Relapse

Adverse Events
Major challenges

- First TB regulatory trial
- Laboratory standardisation
- Drug supply
- Capacity Development and training
- Funding support
- Languages and translation
- Co-ordinating large teams: the central team exceeds 100
<table>
<thead>
<tr>
<th>Sites Approved</th>
<th>Per Country</th>
<th>Sites active</th>
<th>Pts screened</th>
<th>Scr. Failure</th>
<th>Rand</th>
<th>Active</th>
<th>W/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>9</td>
<td>6</td>
<td>631</td>
<td>174</td>
<td>451</td>
<td>346</td>
<td>105</td>
</tr>
<tr>
<td>China</td>
<td>4</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>20</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Korea</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Latin America</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL As at 02 Oct 09</td>
<td>18 + India</td>
<td>6</td>
<td>625</td>
<td>170</td>
<td>448</td>
<td>346</td>
<td>102</td>
</tr>
<tr>
<td>As at 23 OCT 09</td>
<td>18 + India</td>
<td>6</td>
<td>631</td>
<td>174</td>
<td>451</td>
<td>346</td>
<td>105</td>
</tr>
</tbody>
</table>
Learning in REMoxTB

- Regulatory studies of TB not performed previously
- Developing and implementing consistent standard operating procedures is challenging
- Laboratory practice is a particular problem
  - for developing countries
  - for experienced clinical trialists
- There is a world shortage of GCP compliant sites
Novel drugs 1

- Fluoroquinolones
- PA 824
- Carboxylates
- Novel fluoroquinolones
- Novel macrolides
- Pleuromutalins
- Nitroimidazo-oxazole
- TMC 207
- SQ 109
- Pyrrole
- Iso-citrate lyase inhibitors
- Phase IIb/III
- Phase IIb
- Discovery
- Pre-clinical
- Discovery
- Pre-clinical
- Phase I/IIb
- Phase IIb
- Phase Ila
- Phase I
- Discovery
Novel drugs 2

- Diarylquinolines
- Imidizoles
- SQ109
### TMC 207 Diaryquinoline

**Table 1.** MICs of R207910 that inhibited 99% of the growth of different mycobacterial species.

<table>
<thead>
<tr>
<th>Mycobacterial species</th>
<th>Number of strains</th>
<th>Range of MICs for multiple strains (µg/ml)</th>
<th>Median MIC (µg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>M. tuberculosis</em>, H37Rv</td>
<td>1</td>
<td>—</td>
<td>0.030</td>
</tr>
<tr>
<td><em>M. tuberculosis</em>, fully susceptible clinical isolates</td>
<td>6</td>
<td>0.030–0.120</td>
<td>0.050</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> resistant to isoniazid</td>
<td>7</td>
<td>0.003–0.050</td>
<td>0.010</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> resistant to rifampin</td>
<td>1</td>
<td>—</td>
<td>0.030</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> resistant to isoniazid and rifampin</td>
<td>2</td>
<td>0.030–0.030</td>
<td>0.030</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> resistant to isoniazid and streptomycin</td>
<td>1</td>
<td>—</td>
<td>0.010</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> resistant to ethambutol</td>
<td>1</td>
<td>—</td>
<td>0.010</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> resistant to pyrazinamide</td>
<td>1</td>
<td>—</td>
<td>0.050</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> resistant to fluoroquinolone</td>
<td>2</td>
<td>0.050–0.120</td>
<td>0.090</td>
</tr>
<tr>
<td><em>M. bovis</em></td>
<td>1</td>
<td>—</td>
<td>0.003</td>
</tr>
<tr>
<td><em>M. avium/M. intracellulare</em> (MAC)</td>
<td>7</td>
<td>0.007–0.010</td>
<td>0.010</td>
</tr>
<tr>
<td><em>M. kansasii</em></td>
<td>1</td>
<td>—</td>
<td>0.003</td>
</tr>
<tr>
<td><em>M. marinum</em></td>
<td>1</td>
<td>—</td>
<td>0.003</td>
</tr>
<tr>
<td><em>M. fortuitum</em></td>
<td>5</td>
<td>0.007–0.010</td>
<td>0.010</td>
</tr>
<tr>
<td><em>M. abscessus</em></td>
<td>1</td>
<td>—</td>
<td>0.250</td>
</tr>
<tr>
<td><em>M. smeagnatis</em></td>
<td>7</td>
<td>0.003–0.010</td>
<td>0.007</td>
</tr>
<tr>
<td><em>M. ulcerans</em></td>
<td>1</td>
<td>—</td>
<td>0.500</td>
</tr>
</tbody>
</table>

Andreis Science 2005;223
Mechanism of action identified by whole genome sequencing

Diaryquinolones act by inhibiting an ATP synthase specific to mycobacteria

Andreis Science 2005;223
TMC-207 activity in mouse model
TMC-207 human pharmacokinetics

Andreis Science 2005;223
FIG. 2. Bactericidal activities for days 0 to 7 by treatment. The activities of 300 mg isoniazid and 600 mg rifampin are diate onset and continuous over 7 days. TMC207 shows de of activity from day 4. The values are means. Log Fall, cha CFU/ml sputum from baseline to day 7. The error bar confidence intervals.

FIG. 3. Decline in CFU from baseline to day 7 for individual subjects by treatment group. Log Fall, change in $\log_{10}$ CFU/ml sputum from baseline to day 7.
Study design

- Proven MDR
- Multi-centre
- Placebo controlled
- Standard MDR regimen +/- TMC 207 for 8 weeks
- Pharmacokinetics
- Culture conversion
Figure 1. Mean (±SD) Plasma Concentration–Time Profiles for TMC207 at Week 2 and Week 8.

Dosing was selected to maintain plasma TMC207 concentrations above a target average steady-state plasma concentration of 600 ng per milliliter. Error bars indicate standard deviations.

Figure 2. The Proportion of Patients with Positive Sputum Cultures and Time to Conversion.
• EBA study completed in South Africa
• Shows evidence of concentration dependant effect
• Further studies are planned
Table 1

<table>
<thead>
<tr>
<th>Species</th>
<th>Half-life (h)</th>
<th>AUC (mg·h/l)</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/ml)</th>
<th>Volume distribution (l/kg)</th>
<th>Clearance (ml/h)</th>
<th>PK methodology</th>
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<tr>
<td>Mouse</td>
<td>5.2 ±1.1 *</td>
<td>0.254 ±0.184 *</td>
<td>0.135 ±0.01 *</td>
<td>11.83 ±1.49 **</td>
<td>3788 ±1768 ml/kg/h**</td>
<td>*Oral dose of 25 mg/kg, *<em>i.v. dose of 3 mg/kg</em></td>
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<tr>
<td>Rat</td>
<td>8.2 *</td>
<td>0.99 *</td>
<td>0.64 *</td>
<td>9.96 **</td>
<td>1575 ml/kg/h**</td>
<td>*13 mg/kg single oral, *<em>1.5 mg/kg i.v. dose</em></td>
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<tr>
<td>Dog</td>
<td>19.6 ±4.8 *</td>
<td>0.087 ±0.016 *</td>
<td>0.011 ±0.002 *</td>
<td>29.2 ±6.9 **</td>
<td>2471 ±319 ml/kg/h**</td>
<td>*3.75 mg/kg single oral, *<em>4.5 mg/kg i.v. dose</em></td>
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Tuberculosis Drug Development – UK consortium

- A consortium of Academics and industry
- UCL, Strathclyde, Birmingham, Oxford, School of Pharmacy, St Georges, Birkbeck
- Funded by MRC
- Aims to bring together the drug development process from drug discovery to clinical trials
- To support the development and evaluation of novel compounds
Figure 1. The chemical structures of thiolactomycin 1, its analogue 4, and inhibitors 2 and 3.

doi:10.1371/journal.pone.0005617.g001

Figure 2. The modeling studies of the 2-aminothiazole-4-carboxylate analogues with mtFabH. (A) The hypothetical template of the 2-aminothiazole-4-carboxylates for mtFabH inhibitor development. This illustrates the key H-bonding interactions with the catalytic triad amino acid residues. (B) The binding pose of methyl 2-amino-5-methylthiazole-4-carboxylate in the active site of mtFabH showing the NH₂ group proximal to His 244 and directed towards the lateral channel, with the 5-methyl group directed towards the longitudinal channel. (C) The binding pose of methyl 2-(2-bromoacetamido)-5-(3-chlorophenyl)thiazole-4-carboxylate with the bromomethylene portion in the vicinity of the Cys112 thiol group.
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<th>R&lt;sub&gt;2&lt;/sub&gt;</th>
<th>R&lt;sub&gt;3&lt;/sub&gt;</th>
<th>mtFabH IC&lt;sub&gt;50&lt;/sub&gt; (µM)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>TB MIC (µM)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>FAS-I&lt;sup&gt;c&lt;/sup&gt;</th>
<th>FAS-II&lt;sup&gt;c&lt;/sup&gt;</th>
<th>AlogP&lt;sup&gt;d&lt;/sup&gt; (logD)&lt;sup&gt;e&lt;/sup&gt;</th>
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<td>(TLM)</td>
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<td></td>
<td></td>
<td>16 (75)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>13 (62.5)&lt;sup&gt;f&lt;/sup&gt;</td>
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<td>N/A</td>
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<td>N/A</td>
<td>N/A</td>
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<td>NHCOCH&lt;sub&gt;2&lt;/sub&gt;Br</td>
<td>0.95±0.05 (2.42±0.13)</td>
<td>N/A</td>
<td>N/A</td>
<td>Active</td>
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<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
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<td>N/A</td>
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<td>N/A</td>
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<td>NHCOCH&lt;sub&gt;2&lt;/sub&gt;Br</td>
<td>1.1±0.1 (3.22±0.29)</td>
<td>N/A</td>
<td>N/A</td>
<td>Active</td>
<td>2.72 (2.72)</td>
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<td>Active</td>
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<td>N/A</td>
<td>Active</td>
<td>Active</td>
<td>3.16 (3.13)</td>
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<td>19</td>
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<td>H</td>
<td>NHCOCH&lt;sub&gt;2&lt;/sub&gt;Br</td>
<td>225±2.81 (718±8.97)</td>
<td>N/A</td>
<td>Active</td>
<td>Active</td>
<td>2.56 (1.38)</td>
</tr>
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</table>

Figure 4. The in vitro activity and molecular properties of the 2-aminothiazole-4-carboxylates. <sup>a</sup> Compounds regarded as not active (N/A) if no inhibition is observed at 200 µg/ml. <sup>b</sup> FAS-II assay conducted at 200 µg/ml and compounds regarded as not active is <50% inhibition observed. <sup>c</sup> AlogP and logD calculated using Pipeline Pilot (SciTegic) software. <sup>d</sup> From reference [18]. <sup>e</sup> From reference [22].
TB-DUK portfolio developments

• Two grants for target based drug discovery
• Evaluating a compound series targeting drug delivery
• Four series of new compounds under evaluation in vitro
• Developing new clinical trials protocols for TB meningitis
Conclusion

- The landscape has transformed from the Cape Town Declaration 2000
- TB Drug development has risen in the public health and research agendas
- Studies are addressing optimising current drugs and developing registered antibiotics for the tb indication
- Many consortia now are developing new compounds
- In future the challenge may be how to trial combination regimens
Trials evaluating impact of fluoroquinolones

ReMox TB
- 2HRZE → 4HR
- 2MRZE → 2MR
- 2HRZM → 2HRM
800 per arm

Ofloxph 3
- 2HRZE → 4HR
- 2HRZG → 2HRG
1035 per arm

Rifaquin
- 2HRZE → 4HR
- 2MRZE → 2(MP)_{2-800mg}
- 2MRZE → 4(MP)_{1-1200mg}
1250 in total
Trials evaluating use of higher dose rifamycins

TBTC

Study 29: phase 2 RPT 600mg 5/7 days
Study 31: ?phase 3 vs dose escalation

Hopkins

Brazil: phase 2 Moxi-Rpt 450mg 7/7 days
Cape Town: phase 2/3 RPT 450 or 600mg 5/7 days

PANACEA

APRIORI

Tanzania/Indonesia: phased PK and phase 2 studies of high dose rifampicin
Trials evaluating use of new drugs (1)

**TMC207**
- Phase 2 MDR trial (ongoing)
- Open label study
- EBA study (completed)
- Bioavailability of 3 formulations
- PK with lopinavir/ritonavir
- PK with nevirapine

**PA-824**
- EBA high-dose (completed)
- EBA low-dose (underway)

**OPC 67,683**
- Phase 2 MDR trial (ongoing)
- EBA study (completed)
Trials evaluating use of new drugs (2)

SQ-109 Phase 1 dose escalation

Oxazolidinones
PNU 100,480 Phase 1 PK, healthy vol’s

Linezolid Phase 2 in MDR, Korea
Phase 2 in MDR, Durban