Challenges in finding new treatments for TB

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Professor of Infectious Diseases
National University of Singapore
TUBERCULOSIS (TB)

• 2014:
  • 8.6 million new cases
  • 1.3 million deaths annually
Top causes of death worldwide in 2012. Deaths from TB among HIV-positive people are shown in grey.

- Ischaemic heart disease: 7 million
- Stroke: 6.5 million
- Lower respiratory infections: 3.5 million
- Chronic obstructive pulmonary disease: 3 million
- TB: 1.5 million
- Tracheal, bronchus, lung cancers: 1 million
- Diarrheal diseases: 0.7 million
- Diabetes mellitus: 0.5 million
- HIV/AIDS: 0.3 million
- Road injury: 0.2 million
Standard TB treatment

2 months induction
• RIF, INH, PZA, EMB

4 months continuation
• RIF & INH
3 approaches to shorten treatment for TB

• New drug regimens with improved activity against dormant / persistent bacteria - “sterilising activity”

• Improve the immune response to clear persistent bacteria

• Innovative treatment strategies
3 approaches to shorten treatment for TB

• New drug regimens with improved activity against dormant / persistent bacteria - “sterilising activity”

• Improve the immune response to clear persistent bacteria

• Innovative treatment strategies
Discovery of drugs for tuberculosis

1940
1943 Streptomycin
1948 PAS
1951 Thiacetazone
1952 Isoniazid
1954 Pyrazinamide
1955 Cycloserine
1957 Kanamycin
1960 Ethionamide
1961 Ethambutol
1963 Capreomycin
1963 Rifampicin
1982 Ofloxacin
1992 Gatifloxacin
1996 Moxifloxacin
2000 PA-824
2005 TMC-207
2006 OPC-67683

1946 First randomised trial: streptomycin monotherapy led to streptomycin resistance

1952 First regimen: streptomycin, aminosalicylic acid, and isoniazid 24 months of treatment

1960s Aminosalicylic acid replaced with ethambutol: streptomycin, isoniazid, and ethambutol 18 months of treatment

1960s Streptomycin replaced with pyrazinamide: isoniazid, rifampicin, pyrazinamide, ethambutol 6–8 months, oral treatment

1970s Addition of rifampicin: streptomycin, isoniazid, rifampicin and ethambutol 9–12 months of treatment

Development of regimens

2010s Potential new regimen 2–4 months, oral treatment?
Re-purposed drugs for TB

- Meropenem, imipenem,
- Linezolid
- Clofazimine
Testing combinations

• Many possible combinations of…..
  – old drugs
  – old drugs with modified doses
  – re-purposed drugs
  – new drugs
Testing new drugs / combinations

**Phase I (healthy volunteers)**
- Dose finding / tolerability
- PK / Drug interactions

**Phase II (TB patients)**
- EBA (2 wks.) and SSCC (8 wks.)
- Quantitative Cultures / time to conversion + PK/PD

**Phase III (TB patients)**
- Large scale clinical trials
- Treatment failure / relapse
- Tolerability / safety
Phase IIa: Early Bactericidal Activity (EBA) trials

Figure 2: Bilinear regression showing the fall in mean log$_{10}$CFU from baseline
CFU= colony forming unit.
EBA ≠ sterilizing activity

Diacon et al, Am J Respir Crit Care Med 2015
Testing new drugs / combinations

**Phase I (healthy volunteers)**
Dose finding / tolerability
PK / Drug interactions

**Phase II (TB patients)**
EBA (2 wks.) and SSCC (8 wks.)
Quantitative Cultures / time to conversion + PK/PD

**Phase III (TB patients)**
Large scale clinical trials
Treatment failure / relapse
Tolerability / safety
Phase IIb: Serial sputum colony count (SSCC) trial
2m culture conversion is a “reasonable predictor of sterilization in trials” but not individuals

Wallis Lancet 2010
Phase II SSCC trial: quinolones

Table 5  Cox regression estimates for the speed of sputum conversion

<table>
<thead>
<tr>
<th>Treatment series</th>
<th>Hazard ratio</th>
<th>P vs. control</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before adjustment for covariates*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>GFX</td>
<td>1.257</td>
<td>0.3</td>
<td>0.835–1.890</td>
</tr>
<tr>
<td>MXF</td>
<td>1.726</td>
<td>0.009</td>
<td>1.145–2.601</td>
</tr>
<tr>
<td>OFX</td>
<td>0.887</td>
<td>0.6</td>
<td>0.584–1.348</td>
</tr>
<tr>
<td>After adjustment for covariates*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>GFX</td>
<td>1.519</td>
<td>0.054</td>
<td>0.993–2.324</td>
</tr>
<tr>
<td>MXF</td>
<td>1.683</td>
<td>0.017</td>
<td>1.098–2.578</td>
</tr>
<tr>
<td>OFX</td>
<td>0.830</td>
<td>0.4</td>
<td>0.542–1.271</td>
</tr>
</tbody>
</table>

* Covariates were age, sex, HIV status and radiographic extent of disease. CI = confidence interval; GFX = gatifloxacin; MXF = moxifloxacin; OFX = ofloxacin.
Quinolone trials in DS-TB

![Graph showing time to unfavorable outcome](graph.png)

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>600</th>
<th>563</th>
<th>533</th>
<th>493</th>
<th>472</th>
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</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>617</td>
<td>570</td>
<td>522</td>
<td>459</td>
<td>439</td>
<td></td>
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<tr>
<td>Ethambutol</td>
<td>604</td>
<td>568</td>
<td>523</td>
<td>445</td>
<td>425</td>
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</tbody>
</table>

Gillespie NEJM 2014
SINGAPORE PROGRAMME OF RESEARCH INVESTIGATING NEW APPROACHES TO TREATMENT OF TUBERCULOSIS
**SPRINT-TB RESEARCH THEMES**

**Theme 1**
**BACTERIAL TARGET DISCOVERY**
Lead: A/Prof. Thomas Dick
Department of Microbiology, NUS
Using genetic and chemical approaches to identify new mycobacterial targets.

**Theme 2**
**DRUG DISCOVERY**
Lead: Prof. Alex Matter
Experimental Therapeutics Centre, A*STAR
Screening, medicinal chemistry and pharmacology studies to develop new TB drug candidates. Preclinical development/animal models.

**Theme 3**
**CLINICAL DEVELOPMENT**
Lead: Prof. Nick Paton
Department of Medicine, NUS
Conducting clinical trials to evaluate safety and efficacy of new drugs with the focus on novel treatment regimens for TB.

**Theme 4**
**TREATMENT DELIVERY**
Lead: Prof. Richard Coker
School of Public Health, NUS
Studying individual and systemic barriers that hinder successful provision of effective combination therapy and develops solutions to these problems.
“Improving” Phase II TB trials

• Principle of testing drugs individually and in combination for a short period is valuable

• Problem is the outcome parameters .....
New outcomes in Phase II

- Whole blood bactericidal activity
- Cultures with resuscitation promotion factors
- Transcriptomics (bacterial and host)
- Imaging
Pharmacokinetics data

Rifampicin Conc (nmol/L)

Time of blood collection (Hours)
Whole Blood Bactericidal activity of Rifampicin against *M. tuberculosis* H37Rv

**WBA or Bacillary Killing:**

\[
\Delta \log_{10} \text{CFU} = \log_{10} (\text{final}) - \log_{10} (\text{initial})
\]
TB vs Pneumonia

Pneumonia

Tuberculosis

5 days

6 weeks
De-risking Phase III

- Adaptive designs
- Observational trials
## Multi arm, Multi stage trial design (MAMS)

<table>
<thead>
<tr>
<th>Start of Recruitment</th>
<th>1(^{st}) Interim Analysis</th>
<th>2(^{nd}) Interim Analysis</th>
<th>End of Recruitment</th>
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</thead>
<tbody>
<tr>
<td>Control Regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novel regimen 1</td>
<td></td>
<td>Stop</td>
<td></td>
</tr>
<tr>
<td>Novel regimen 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novel regimen 3</td>
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<td>Stop</td>
<td></td>
</tr>
<tr>
<td>Novel regimen 4</td>
<td></td>
<td>Stop</td>
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</tbody>
</table>

Stage 1 | Stage 2 | Stage 3
CORE DELIVERABLE: SHORTER TB TREATMENT REGIMEN

TRUNCATE-TB Trial

Standard Regimen
Arm A: 8 weeks rifampicin (10mg/kg), isoniazid, pyrazinamide, ethambutol, then 16 weeks rifampicin, isoniazid

Experimental Regimens
Arm B: 8 weeks rifampicin (35mg/kg), isoniazid, pyrazinamide, ethambutol, linezolid
Arm C: 8 weeks rifampicin (35mg/kg), isoniazid, pyrazinamide, ethambutol, clofazimine
Arm D: 8 weeks rifapentine, isoniazid, pyrazinamide, linezolid, levofloxacin
Arm E: 8 weeks isoniazid, pyrazinamide, ethambutol, linezolid, bedaquiline

Conducted in 4 countries in Asia
Recruitment starting Q1/2017
Number of subjects 900
Design Muti-arm, multi-stage
Short, Highly Effective, and Inexpensive Standardized Treatment of Multidrug-resistant Tuberculosis

Armand Van Deun¹,², Aung Kya Jai Maug³, Md Abdul Hamid Salim³, Pankaj Kumar Das³, Mihir Ranjan Sarker³, Paul Daru³, and Hans L. Rieder¹,⁴

¹International Union Against Tuberculosis and Lung Disease, Paris, France; ²Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium; ³Damien Foundation Bangladesh, Dhaka, Bangladesh; and ⁴Institute of Social and Preventive Medicine, University of Zurich, Switzerland

TABLE 1. REGIMENS SEQUENTIALLY USED IN THE TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS, BANGLADESH DAMIEN FOUNDATION PROJECTS

<table>
<thead>
<tr>
<th>Regimen (sequence)</th>
<th>Intensive Phase</th>
<th>Continuation Phase 1</th>
<th>Continuation Phase 2</th>
<th>Patients Enrolled</th>
<th>Col %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3* KCOEHZP</td>
<td>12 OEHZP</td>
<td>6 EP</td>
<td>59</td>
<td>13.8</td>
</tr>
<tr>
<td>2</td>
<td>3(+) KCOEHZP</td>
<td>12 OHEZP</td>
<td></td>
<td>44</td>
<td>10.3</td>
</tr>
<tr>
<td>3</td>
<td>3(4) KCOEZP</td>
<td>12 OEZP</td>
<td></td>
<td>35</td>
<td>8.2</td>
</tr>
<tr>
<td>4</td>
<td>3(+) KCOEHZP</td>
<td>12 OHEZ</td>
<td></td>
<td>45</td>
<td>10.5</td>
</tr>
<tr>
<td>5</td>
<td>3(+) KCOEHZP</td>
<td>12 OHEZC</td>
<td></td>
<td>38</td>
<td>8.9</td>
</tr>
<tr>
<td>6</td>
<td>4(+) KCGHEZP</td>
<td>5 GEZC</td>
<td></td>
<td>206</td>
<td>48.2</td>
</tr>
<tr>
<td>Total number of patients enrolled</td>
<td></td>
<td></td>
<td></td>
<td>427</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Definition of abbreviations: C = clofazimine; Col % = column percent; E = ethambutol; G = gatifloxacin; H = isoniazid; K = kanamycin; O = ofloxacin; P = prothionamide; Z = pyrazinamide.
# Results from the initial 9m regimen cohorts

<table>
<thead>
<tr>
<th></th>
<th>Original cohort (206 pts)</th>
<th>Updated cohort (515 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure</td>
<td>82.5%</td>
<td>81.2%</td>
</tr>
<tr>
<td>Completion</td>
<td>5.3%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Default</td>
<td>5.8%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Death</td>
<td>5.3%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Failure</td>
<td>0.5%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Relapse</td>
<td>0.5%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Overall success rate</td>
<td>87.9% (95% CI 82.7, 92.6)</td>
<td>84.5% (95% CI 0.81, 0.88)</td>
</tr>
</tbody>
</table>

Am J Respir Crit Care Med Vol 182. 684–692, 2010

Countries using the shorter MDR-TB regimen

(in addition, Ethiopia, South Africa, Viet Nam and Mongolia are participating in the clinical trial)

Bangladesh
Benin
Burkina Faso
Burundi
Cameroon
Central African Republic
Côte d’Ivoire
DR Congo
Guinea
Niger
Rwanda
Senegal
Swaziland
Uzbekistan

WHO May 2016
THE SHORTER MDR-TB REGIMEN
SINGAPORE PROGRAMME OF RESEARCH INVESTIGATING NEW APPROACHES TO TREATMENT OF TUBERCULOSIS

www.sprinttb.org