Novel Drug Combinations for TB Therapy

Khisi Mdluli, PhD
TB Alliance
New York, NY
The TB Alliance

- Not-for-profit, public private product development partnership (PDP) based in New York, Pretoria and Brussels
- Established in 2000 by international stakeholders
- Funded by foundations and bilateral government donors
- Scientific collaboration with public, private and not-for-profit research organizations
- Operations in many developing countries worldwide
- Developed the largest new TB drug portfolio in history; on the verge of delivering dramatically improved TB therapies
TB Product Development Partnerships
TB Alliance Mission

• Develop new, better treatments for TB that are:
  ▪ Faster-acting and less complex
  ▪ Effective against MDR/XDR-TB
  ▪ Compatible with anti-retrovirals for TB/HIV co-infection

• Coordinate and act as catalyst for global TB drug development activities

• Ensure that new regimens are Affordable, made widely Available, and are Adopted
TB Alliance Vision

Success will require novel multi-drug combinations
TB Alliance Therapeutic Objectives

Short-Term: 1st Wave of Innovation
Oral, 4-month or less daily (or better) regimen for drug sensitive TB

Mid-Term: 2nd Wave of Innovation
Oral, 2-month or less daily (or better) regimen which can be administered with ARVs and also has activity against drug-resistant TB and ability to reduce the length of MDR-TB treatment

Long-Term: 3rd Wave of Innovation
Oral, 2-week or less once daily (or better) dose regimen and also has activity against drug-resistant TB

New regimen
Approach to Novel Regimen Development (CPTR)
# Current TB Therapy and Unmet Needs

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Current Therapy</th>
<th>Unmet Needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-Susceptible DS-TB</td>
<td>4 drugs; ≥6 month therapy (2RHZE + 4RH)</td>
<td>Shorter, simpler therapy</td>
</tr>
<tr>
<td>Drug-Resistant M(X)DR-TB</td>
<td>Few good drugs (including injectables); ≥18 months; toxicities; cost</td>
<td>Totally oral, shorter, more efficacious, safer, affordable therapy</td>
</tr>
<tr>
<td>TB/HIV Co-Infection</td>
<td>Drug-drug interactions (DDI) with ARVs</td>
<td>No or low DDI, co-administration with ARVs</td>
</tr>
<tr>
<td>Latent TB Infection</td>
<td>6-9 months H</td>
<td>Shorter, safer therapy</td>
</tr>
</tbody>
</table>

* Rifampin (R), Isoniazid (H), Pyrazinamide (Z), Ethambutol (E)

- Need shorter, simpler therapies against both DS and DR-TB
- To accomplish, will need to replace all or most current drugs
TB Drug/Regimen Discovery and Development Process

- **Discovery**
  - Compound 1
  - Compound 2
  - Compound 3
  - Compound 4
  - Compound 5

- **Drug Candidate Pool**

- **Regimen Identification**
  - Regimen A
  - Regimen B
  - Regimen C

- **Identification of New Drug Candidates**

- **Selection of Potential New Regimens**

- **Single Compound Preclinical Development → Phase I → EBA**

- **Phase II → Phase III**

Presented at the 4th International Workshop on Clinical Pharmacology of TB Drugs, 16 September 2011, Chicago, IL, USA
Process for Regimen Discovery

An unbiased, empirical approach:

1. Single Drug PK in Mouse
2. Combination Efficacy (Mouse Acute Model)
3. Combination Efficacy (Mouse Relapse Model)
4. PK/Chemical Interaction
5. Confirmation of Efficacy
6. Secondary Species Infection Model
7. Combination Safety (if needed)
8. Clinical Studies

- Appropriate Dose Selection in Mice
- Bactericidal Activity: Initial Screening
- Sterilizing Activity: Duration of Therapy
- Combination Specific Safety
Novel Pre-Clinical Drug Combination Testing Study

Collaborators:
TB Drugs
Currently in Clinical Development

Repurposed or Redeveloped Drugs
- Rifapentine
- Gatifloxacin
- Moxifloxacin

New Drugs
- TMC207
- OPC67683
- PA-824
- SQ109
- PNU-100480
- PNU-100480
- AZD5847

A historic opportunity to identify and develop novel regimens that are effective against both drug-susceptible and resistant (MDR- and XDR-TB) organisms
Paradigm Change in TB Drug Development

- Current TB drug development replaces one drug at a time, requiring decades to introduce a new regimen that consists of multiple novel agents.
- Under the new paradigm, the regimen, not an individual drug, is the unit of development. New drugs are tested in combinations in clinical trials simultaneously, rather than successively.

![Diagram showing current and novel combination testing paradigms for TB drug development.](image-url)
Drug Classes for Regimen Discovery and Development

(Orally bioavailable compounds only)

<table>
<thead>
<tr>
<th>Current Drugs</th>
<th>Drugs in Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin/Rifapentine</td>
<td>Moxifloxacin/Gatifloxacin</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>TMC207</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>PA-824/OPC-67683</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>PNU-100480/AZD5847</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>SQ-109</td>
</tr>
</tbody>
</table>

Potential 3-drug combinations: 120
Potential 4-drug combinations: 210
(without even varying dose)

The need for prioritization using preclinical models
# Drugs in the Pre-Clinical Combo Study

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Drug Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Rifampicin</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Isoniazid</td>
<td></td>
</tr>
<tr>
<td>Z</td>
<td>Pyrazinamide</td>
<td></td>
</tr>
<tr>
<td>Pa</td>
<td>PA-824</td>
<td></td>
</tr>
<tr>
<td>J</td>
<td>TMC207</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>Rifapentine</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>Moxifloxacin</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>Clofazimine</td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>Linezolid</td>
<td></td>
</tr>
<tr>
<td>U</td>
<td>PNU-100480</td>
<td></td>
</tr>
</tbody>
</table>
Best Combinations that Deserve Clinical Evaluation

1. JZ-based combinations with known treatment durations
   - JZC - ≤ 2 months
   - JZP - ≤ 2 months
   - JZMC - ≤ 2 months
   - JZPa - 3 months
   - JMZ – 4 months

2. JZ-based combinations not yet evaluated earlier than 3 months (evaluation pending)
   - JZ, JZM, JZR, and JZL

3. Combinations with no pre-existing resistance (evaluation in progress)
   - JCU
   - JPaU
   - JPaC
   - CPaU
   - JPaUC
Clinical Regimen Testing
Powerful Bactericidal and Sterilizing Activity of a Regimen Containing PA-824, Moxifloxacin, and Pyrazinamide in a Murine Model of Tuberculosis

Eric Nuermberger,* Sandeep Tyagi, Rokeya Tasneen, Kathy N. Williams, Deepak Almeida, Ian Rosenthal, and Jacques H. Grosset

TABLE 3. Outcomes of test-of-cure assessments in the second experiment

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Treatment</th>
<th>Proportion (%) of mice cured after treatment for:</th>
<th>4 mos</th>
<th>5 mos</th>
<th>6 mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 mos of RIF-INH-PZA plus 4 mos of RIF-INH</td>
<td>10 of 20 (50)</td>
<td>20 of 20 (100)</td>
<td>20 of 20 (100)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 mos of RIF-MXF-PZA plus 3 mos of RIF-MXF</td>
<td>19 of 20 (95)</td>
<td>20 of 20 (100)</td>
<td>20 of 20 (100)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2 mos of Pa-MXF-PZA plus 4 mos of Pa-MXF</td>
<td>20 of 20 (100)</td>
<td>20 of 20 (100)</td>
<td>20 of 20 (100)</td>
<td></td>
</tr>
</tbody>
</table>

*Drug doses were as given in Table 2, footnote a.
*P < 0.01 versus regimen 1.
Early Bactericidal Activity (EBA) Study

• EBA Definition:
  – The fall in viable colony forming units of *Mycobacterium tuberculosis* in sputum early in therapy (14-day duration)
    • Calculated as the rate of fall over the period \((t_x, t_y)\) using the formula:
      \[
      EBA(t_x - t_y) = \left( \frac{\text{mean } \log \text{CFU(Day } t_x) - \log \text{CFU(Day } t_y)}{(t_y - t_x)} \right)
      \]
    – A measure of the ability of a drug to kill the bacilli found in the sputum of patients with smear-positive pulmonary TB
    – TTP may be able to substitute

• Uses:
  – POC & dose ranging
  – Testing principles learned from pre-clinical models:
    • Synergy/enhanced bactericidal activity or antagonism of 2-drug combos
  – Begin clinical development of novel regimens
CFU vs TTP as Readout in EBA Studies - Background

• EBA clinical studies provide a quantitative measure of bacterial killing in sputum
• Quantitative colony counting (CFU), the traditional readout in EBA studies, can be performed at only a few centers around the world
• TTP, an alternative readout, is automated and can be performed more widely
• Competition for EBA sites is increasing; EBA capacity could become rate-limiting to TB drug development
Use of EBA to Test Principles Learned From Animal Models and to Begin Clinical Development of Novel Regimens: NC-001

- NC-001 (first novel combination EBA study)
  - JZ synergy observed in the mouse
  - PaZ additive effect observed in the mouse
  - PaJ antagonism observed in the mouse
  - PaMZ an enhanced novel regimen in the mouse
First Novel Combo EBA: NC-001

Pa = PA-824: M = moxifloxacin; Z = pyrazinamide; J = TMC207
All Treatment Groups: Bi-linear regression mean of logCFU over day; Change from baseline (Day X – Day 0)
All Treatment Groups: Bi-linear regression mean of TTP over day; Change from baseline (Day X – Day 0)
Post NC-001 Study: Next Steps

• 2-month “SSCC” study (NC-002)
  – PaMZ
• Develop for both DS- and DR-TB (in setting of appropriate resistance testing)
Additional Planned EBA Arms

- PNU 100480 (Pfizer)
- JPaZ
- JCZ
- JPaC
- PaCZ
- JPaCZ
- Z
Many Thanks