A SYSTEMS PHARMACOLOGY MODEL FOR TB: Understanding Bug-Host-Regimen Interplay

Natasha Strydom
Connecting the Network

Regimen

Host

Bug
Current limit in measuring tuberculosis cure

Our current knowledge of tuberculosis treatment failure vs cure is limited by our assays.
Our current knowledge of tuberculosis treatment failure vs cure is limited by our assays. Through the use of **modelling**, **diagnostics** and emerging **biomarker data**, we can gain “depth” in understanding clearance of tuberculosis. Using this gained knowledge we’re able to better predict treatment outcome success and failure.
Model Overview

Input → Model → Output
TB progression

Infection

Mtb

Lung

Macrophage

Elimination

k_n_{growth} k_n_{mutation} k_{growth} k_{growth}
TB progression

Model Parameters;
Growth Rate
Natural resistance
Intracellular bacteria

Source
Mouse model - Ahmad Z, et al. (2011)

Median and quartiles for a population of 5000 patients

Spontaneous resistance
Intracellular
Extracellular

Total Tuberculosis Bacterial Growth Without Drug Therapy
-180 -120 -60 0 60 120 180 240 300 360 420
Time (days according to start of therapy)
Bacterial Load (CFU/mL)
10^{-1} 10^{0} 10^{1} 10^{2} 10^{3} 10^{4} 10^{5} 10^{6} 10^{7} 10^{8} 10^{9}
10^{-180} 10^{-120} 10^{-60} 10^{60} 10^{120} 10^{180} 10^{240} 10^{300} 10^{360} 10^{420}

Input → Model → Output
Model Parameters:
Maximal T-cell killing rate
Rate of Th1 differentiation
Rate of Th2 differentiation
Extracellular bacterial growth rate
Intracellular bacterial growth rate
Bacterial uptake by IDC in lung
Half-sat, Be on IDC activation

Source
Mono-therapy PK

Input → Model → Output

Lesion → Lesion → Lung → Lesion → Lesion

Macrophage → Plasma → Gut

Therapy introduced

kgrowth kgrowth
Elimination Elimination
knmutation
kdpmutation
Plasma
Gut
Lesion Lung
Lesion
Macrophage
Therapy
introduced
Multi-drug PD

Input → Model → Output
Multi-drug PK

Model Parameters & Sources
Absorption, clearance, elimination (human volunteers & patients)
Auto-induction & acetylation rate (human subjects)
Intra-macrophage accumulation (in-vitro, mouse, rabbit)

PK Concentration Profile per Drug
Lesion PK

Rutgers MALDI-MS data

Drug
Gut
Plasma

Sneha Gupta et al., Submission in progress
Full QSP model

Lesion → Lesion formation → Macrophage activation → Macrophage → Plasma

Gut

Lymph

Naive T-cells

Precursor T-cells

Helper T-cells

Full QSP model

Lesion formation

Macrophage activation

Macrophage

Lesion

Gut

Lymph

Naive T-cells

Precursor T-cells

Helper T-cells
Exploring drug therapies

- Increased RMP dose
- Start Tx earlier
- Standard Tx
- Shorter Tx
- Reduced Tx freq

% of population cured vs. Time (days after start of treatment)
Exploring drug therapies

% of population cured vs. Time (days after start of treatment)

- Standard Tx
- Lower immune system
- Lower adherance
Simulated Data vs Clinical Trials

<table>
<thead>
<tr>
<th>% Unfavorable Outcomes</th>
<th>Dosage Frequency</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>7/7 days</td>
<td>7/7 days</td>
<td>9 months</td>
</tr>
<tr>
<td>9-15</td>
<td>4-7</td>
<td></td>
</tr>
<tr>
<td>7-11</td>
<td>3-5</td>
<td></td>
</tr>
<tr>
<td>0-7</td>
<td>1-3</td>
<td></td>
</tr>
<tr>
<td>2/7 days</td>
<td>4-11</td>
<td></td>
</tr>
<tr>
<td>4-11</td>
<td>7-11</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Trial

Simulation
Simulation -> Estimation

![Graphs showing time vs. concentration and time vs. CFU](image-url)
Preclinical Translation
Scaling Limitations
Translating mouse data

Input → Model → Output

Imke Bartelink et al., Accepted submission, Clinical and Translational Science 2017
Regimen

Host
- HIV (+) and (-) included
- Hard to treat patients

Bug
- Mono-resist
- MDR
- XDR
- Strain diversity

Remedies:
- H
- R
- Z
- E
- M
- P
- Pa
- J
- L
- CFZ
- DLM
Please edit the chosen drug regimen below, if needed. Note that when clicking "Update", any changes to the regimen will only be used for the current simulation, and will not be saved persistently for the chosen regimen. If you want to store a particular regimen for later re-use, please "Save as new regimen".

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose (mg)</th>
<th>Start (days)</th>
<th>Duration (days)</th>
<th>Frequency</th>
<th>Include</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>RIF 600</td>
<td>0</td>
<td>182</td>
<td>Once daily</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>INH 300</td>
<td>0</td>
<td>182</td>
<td>Once daily</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>PZA 1500</td>
<td>0</td>
<td>56</td>
<td>Once daily</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>EMB 1200</td>
<td>0</td>
<td>56</td>
<td>Once daily</td>
<td></td>
</tr>
</tbody>
</table>

For initial empiric treatment of TB, start patients on a 4-drug regimen: isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin. Once the TB isolate is known to be fully susceptible, ethambutol (or streptomycin, if it is used as a fourth drug) can be discontinued.

Patients with TB who are receiving pyrazinamide should undergo baseline and periodic serum uric acid assessments, and patients with TB who are receiving long-term ethambutol therapy should undergo baseline and periodic visual acuity and red-green color perception testing. The latter can be performed with a standard test, such as the Ishihara test for color blindness.

After 2 months of therapy (for a fully susceptible isolate), pyrazinamide can be stopped. Isoniazid plus rifampin are continued as daily or intermittent therapy for 4 more months. If isolated isoniazid resistance is documented, discontinue isoniazid and continue treatment with rifampin, pyrazinamide, and ethambutol for the entire 6 months. Therapy must be extended if the patient has cavitary disease and remains culture-positive after 2 months of treatment.
Acknowledgements

UCSF, Rutgers, JHU

Insight Rx

CPTR
Gates foundation
NIH