A dynamic integrated drug, Mtb and host archetype for testing novel treatment interventions

International Workshop on Pharmacology of Tuberculosis Drugs
9 September 2013, Denver, USA
Background: Exploring New MtB Drug Therapy Options

- Current TB drug therapy guidelines are based on studies done long ago, even though various new drug options are available and/or planned.
- Need for a way to evaluate new therapy options to focus clinical trials likely to yield best results:
  - New drugs and drug combinations
  - New dose, schedule, and duration
- This project provides an integrated model to simulate MtB infection, drug therapy, and immune system response, considering overall patient outcome and risk of bacterial resistance.
### Project Expands on Previous Work

<table>
<thead>
<tr>
<th>Examples of Other Studies</th>
<th>Mtb Infection</th>
<th>Immune Response</th>
<th>Drug therapy (short term)</th>
<th>Long-term Outcome</th>
<th>Bacterial Resistance</th>
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<td>Peloquin et al. (1997)</td>
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Host-Mtb-Drug System

Image credit from: Max Planck Institute for Infection Biology /Volker Brinkmann
New Integrated Modeling Approach

METHOD

1. Bacterial Growth and Resistance

2. Immune System

3. Multi-Drug PK/PD

4. Patient Population Simulation

“Make everything as simple as possible, but not simpler…”
A Einstein
New Integrated Modeling Approach

1. Bacterial Growth and Resistance
   - Intra- and extra-macrophage bacterial growth and exchange
   - Bacterial growth rates per published experimental data
   - Wild-type and strains resistant per each drug
   - Bacterial mutation rate for each drug per research studies
   - Bacterial persistence effects
   - Fitness of mutated bacteria
   - Secondary mutation probability

2. Immune System*
   - Dynamic interaction of B-cells, T-cells, macrophages, and cytokines
   - Infection in resident macrophages
   - Multiple cytokine feedback signals, incl. IFN-γ, IL-10, IL-4 and IL-12
   - Th precursor cells migrate from lymph node to lung
   - Lymphocytes proliferate and differentiate to Th1 and Th2 cells
   - Bursting causes exchange of intra/extra-macrophage bacteria

* Based on publications by Marino & Kirschner (2004)
New Integrated Modeling Approach

3. Multi-Drug PK/PD
- Single-drug 1st order PK dynamics
- Therapy start time and duration
- Drug dose and frequency per drug
- Dose patterns, e.g., high/low
- Intra- and extra-macrophage concentration profiles
- Time varying kill rates, including EBA vs. long-term effectiveness
- Auto-induction index of RIF
- High-low INH acetylation rate
- Sustained antimicrobial effect

4. Patient Population Simulation
- PK/PD response variations (per patient and time period)
- Patient adherence (study based)
- Immune system variations
- Disease severity (initial infection)
- Adult vs. pediatric populations
- Genetic variability
- Degree of lung cavitations present
- Immune compromised, and other comorbidities, e.g., HIV
- Previous *Mtb* infection (latent TB)
High-Performance Computational Implementation

- Calculations done with C++ program
  - System of ODEs with 23 variables
  - Non-linear ODE parameters
  - Non-zero boundary conditions
  - Euler method for PK concentration (100 steps / hour)
- Immune system and drug parameters loaded from files for easy extension to new scenarios
- All key model parameters varied across patient population and per time step
- Solved in hourly increments, for 500-1000 days
- Visualizations done in MATLAB / R
- Simulation of 5000 patients < 5 min
Summary of Initial Results

• Simulation output consistent w/ previous work
• Intracellular bacterial killing governs overall time to clear patient’s infection
• Multi-drug therapy needed to avoid bacterial resistance, especially for RIF
• Immune system dynamics contributes directly and indirectly to overall bacterial clearing rate
• RIF/INH/PZA vs. RIF/INH -> 2-3 mo less time
• Earlier therapy start -> shorter treatment time
• Increased RIF dose -> shorter treatment time
Acute TB Infection w/o Treatment

Bacterial load (CFUs/mL) for intra- and extra macrophage compartments in lung tissue – reaches saturated level at around one year after infection. Adapted based on work by Marino & Kirschner (2004), and Goutelle (2011)
Intra-Macrophage Killing is Key

Intra- and extracellular bacteria count in lung tissue for acute TB infection with standard drug therapy (INH/RIF/PZA). The TB infection occurs on Day 0, and drug therapy is started on Day 180, triggering continued intracellular and extracellular bacterial growth. Bacteria residing inside chronically infected macrophages represent a continued reservoir thus sustaining the infection.
Effect of Drug Therapy Alternatives

Intracellular bacteria load over time in lung tissue for acute TB, with infection on Day 0 and drug therapy started on Day 180, for isoniazid (300mg/day), rifampin (600mg/day), isoniazid (300mg/day) and rifampin (600mg/day), and isoniazid (300mg/day), rifampin (600mg/day) and pyrazinamide (1500mg/day) combination therapy.
Effect of Different Drug Dose Levels

Intracellular bacteria load over time in lung tissue for acute TB, with infection at Day 0 and drug therapy started at Day 180, for isoniazid (300mg/day) + rifampin (300mg/day), isoniazid (300mg/day) + rifampin (600mg/day), isoniazid (300mg/day) + rifampin (900mg/day), and isoniazid (300mg/day) + rifampin (1200mg/day) combination therapy.
Impact of Immune System Effects

Intra- and extracellular bacteria count in lung tissue for acute TB infection with standard drug therapy (INH/RIF/PZA). The TB infection occurs on Day 0, and drug therapy is started on Day 180, triggering continued intracellular and extracellular bacterial growth. Comparing the cases of including vs. not including immune system bacterial killing and bursting in simulation model.
Value of Early Therapy Start

Intracellular bacteria load over time in lung tissue for acute TB, with infection at Day 0 and drug therapy started at Day 120 vs. at Day 180, for isoniazid (300mg/day), rifampin (600mg/day) and pyrazinamide (1500mg/day) combination therapy.
Planned Next Development

• Additional drugs and drug combinations, drug doses, schedules, and durations

• Attenuated drug PK effects due to granuloma in lung epithelium (multi-compartment model)

• Consider “cross-dependent” probability of resistance of bacteria to multiple drugs, i.e., INH resistant bacteria mutating to RMP resistant

• Explicit modeling of fast- vs. slow-growing bacteria populations (“persisting bacteria”) – each with distinct growth and drug kill rates

• Potentially consider including toxicity metrics of high-dose therapies
Areas of Further Investigation

• Drug PK/concentration profile inside of macrophages (vs. outside cells), in particular for RMP
• Long-term kill rate of key TB drugs – independent of any potential bacterial resistance and remaining number of bacteria
• Growth rate and drug kill rate for different bacterial populations in different metabolic and growth state, and at different time points during therapy