Hollow Fiber Model of Tuberculosis for Predictive Accuracy

Jotam Pasipanodya MD, DrPH,¹
Tawanda Gumbo, MD¹*

University of Texas Southwestern Medical Center, Dallas, Texas
The Hollow fiber model of TB

• Hollow fiber PK systems for gram negative and gram positive bacteria by Blaser, Stone & Zinner in 1985.

• We adapted it to *Mycobacterium tuberculosis* with first presentation on rifampin and log-phase growth at 43rd ICAAC (Chicago, Ill)
  
  — Abstract #A-1156; Gumbo T, A Louie, M Deziel and G. Drusano: “Pharmacodynamic (PD) driven dosing of rifampin (RIF) in a hollow fiber system (HFS) model of tuberculosis.
Hollow fiber model of TB (HFM-TB)

- *M. tuberculosis* has complex metabolic phenotypes relevant to therapeutics, and thus the HFM-TB is actually several models
  - Log-phase growth bacteria in ambient air
  - Semi-dormant bacteria under acidic conditions
  - Non-replicating bacteria under hypoxia
  - Intracellular bacteria in macrophages
  - Intracellular bacteria in neutrophils
Integrated HFS-TB Model Components

- Inoculation Device (Syringe)
- Hollow Fiber Cartridge
- Cross Section Hollow Fiber Cartridge
- Pump
- Fresh Media
- Central Compartment (Pharmacokinetic PK)
- Waste Media
- Pump-controlled Syringe (Drug Delivery)
- Hollow Fiber Lumen
- Hollow Fiber Wall
- Drug
- Peripheral Compartment (Pharmacodynamic PD)
- Bacteria
Myths & conspiracy theories on the HFM-TB

• It does not take into account drug penetration into the lesion X
• Kill rates in the system are exaggerated compared to patients X
• Some drugs are too sticky to be studied X
• Output and modeling from it can not be reproduced X
• Too prone to contamination ?
Critical Path/CPTR initiative

• The Critical Path to TB Regimens (CPTR):
  – The CPTR Preclinical and Clinical Sciences Working Group (PCS-WG) strives to identify, develop consensus around, and build the evidence base to support potential new drug development tools (DDTs) for TB medical product development.

• PCS-WG formed a sub-team (co-led by Dr. Debra Hanna) to identify the predictive accuracy of the HFM-TB as a drug development tool (DDT)
PREDICTION, FORECASTING & ACCURACY
Prediction

• Prediction, via Latin
  – præ-, "before,“
  – dicere, "to tell or to say“
  – **To predict is to declare or say before the event**

• Forecasting:
  – A specific form of prediction
  – Information transferred from time 1 to time 2 in the future (t₂>t₁)
Accuracy of a quantitative measure is the degree of closeness of measure to the quantity's actual (true) value: HOW CLOSE TO THE BULLSEYE
AIM

To identify the accuracy of the HFM-TB, and Monte Carlo simulations based on HFM-TB output, in forecasting:

- (a) therapeutic concepts and hypotheses
- (b) quantitative therapeutic parameters
Step #1: Literature search on HFM-TB

- **AIM:** To identify all experiments performed with the HFM-TB and Monte Carlo experiments based on HFM-TB output.
- **Data sources:** PubMed, EMBASE, ISI Web of Science, and the Cochrane Library, ICAAC, IDSA, the Gordon Research Conferences (Tuberculosis Drug Development), International Workshops on Clinical Pharmacology of Tuberculosis Drugs, Inside Conferences, and Open Grey.
- **Medical subject heading terms and strategy used:** “hollow fiber” OR “hollow fibre” AND either “tuberculosis” OR “mycobacterium” OR “mycobacteria.”
- **Time period:** January 1, 2000 to December 31, 2012.
HFM-TB search findings

• Total of 26 HFM-TB experiments
• More PK/PD studies in HFM-TB than with mice and Guinea pigs combined
• Monotherapy:
  – 10 studies, mainly from 3 research groups; several in tandem with MCS
• Combination therapy:
  – 12 studies, mainly from 2 groups; several in tandem with MCS
• MCS stand alone: 4 studies
STEP#2:

HOW ACCURATE WERE THESE HFM-TB EXPERIMENTS IN FORECASTING?
DEFINITION OF FORECASTING

• HFM-TB publication or conference presentation followed 6 months later by clinical findings

HFM-TB >6 months ± MCS Clinical study publication

“In forecasting information is transferred from time 1 to a future time 2 ”
• The HFM-TB±MCS is the prediction model
  – From the HFM-TB comes forecasting quantity (F)
• The truth is from Clinical study findings
  – From clinical studies come the truth quantity (T)
• NB: Since animal models are themselves pre-clinical models, they do not define the truth but can only lead to predictions (F)
The quality of the clinical study from which the truth is defined matters!

- We utilized quality of evidence criteria based on currently accepted evidence based medicine decision making:
  - GRADE criteria
  - Infectious Diseases of America-US Public Health Service Grading System (USPHS)
<table>
<thead>
<tr>
<th>Quality Of Evidence Score</th>
<th>Criteria</th>
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<tbody>
<tr>
<td></td>
<td>Evidence from $\geq 1$ properly randomized, controlled trial; meta-analysis of randomized, controlled trials that followed PRISMA recommendations</td>
</tr>
<tr>
<td>1</td>
<td>Evidence from $\geq 1$ well-designed <em>prospective</em> clinical trial, without randomization; from prospective cohort or case-controlled analytic studies; Dramatic experimental study results of uncontrolled clinical studies</td>
</tr>
<tr>
<td>2</td>
<td>Evidence from multiple time-series; Evidence from dramatic epidemiological data</td>
</tr>
<tr>
<td>3</td>
<td>Evidence from a large retrospective case series in single center; Examination of clinical isolates from case series</td>
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Estimates from key opinion leaders based on clinical experience, or reports of expert committees, or historical precedence, considered NOT to be evidence, but mere opinion.
Literature search for clinical studies

• Time period of clinical search similar to that for HFM-TB experiments
• Data sources as in HFM-TB searches, but this time also including www.clinicaltrials.gov
• **Steps for minimizing bias and for reporting systematic reviews** outlined by the Cochrane collaboration, PRISMA, & the GRADE
OVERTURNING ACCEPTED DOGMAS AND PREDICTION OF NEW THERAPEUTIC CONCEPTS
<table>
<thead>
<tr>
<th>HFM-TB and MCS Predictions</th>
<th>Type Of Clinical Study Or Experiment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOXI and CIPRO standard doses biphasic kill pattern due to dislinkage of efficacy and</td>
<td>Biphasic kill, and emergence of ADR with &gt;10 days of monotherapy with MOXI, levofloxacin, and CIPRO.</td>
</tr>
<tr>
<td>ii. Biphasic kill of MOXI administered for ≥10 days. (2010)</td>
<td></td>
</tr>
<tr>
<td>CIPRO (and ofloxacin) used at standard doses with second line agents in MDR-TB will lead</td>
<td>Emergence of what was later termed XDR-TB when quinolones used with 2nd line drugs in MDR-TB. (2006,</td>
</tr>
<tr>
<td>to further ADR within weeks (2005)</td>
<td>2007).</td>
</tr>
<tr>
<td>Efflux pump derived multiple drug resistance to monotherapy as an early event leading to</td>
<td>i. Transcriptional profile of sequential sputum isolates in patients who developed MDR-TB from</td>
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<tr>
<td>high level resistance chromosomal mutations; The “antibiotic resistance arrow of time”</td>
<td>initially susceptible isolates, despite DOTS. (2013)</td>
</tr>
<tr>
<td>ADR and most microbiological failure is not due to poor compliance (2011)</td>
<td>(2011, 2012)</td>
</tr>
<tr>
<td></td>
<td>Meta-analysis of 10 prospective trials of patients on DOT (n=8774) versus SAT (n=3708):</td>
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<tr>
<td>ADR and therapy failure is driven by pharmacokinetic variability (2011)</td>
<td>• 1.5 vs. 1.7% for microbiological failure</td>
</tr>
<tr>
<td></td>
<td>• 3.7% vs. 2.3% for relapse</td>
</tr>
<tr>
<td></td>
<td>• 1.5% vs. 0.9% for ADR. (2013)</td>
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<tr>
<td></td>
<td>i. Meta-analysis of 13 randomized studies. Rapid versus slow acetylator relative risk was 2.0 for</td>
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<td>microbiological failure and 2.0 for ADR. (2012)</td>
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<td>ii. Prospective clinical cohort of 142 patients demonstrated that &gt;91% of therapy failure and</td>
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<td>relapse, and 100% ADR due to PK variability. (2013)</td>
</tr>
<tr>
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<td>iii. RCT of 56 pts rates of sterilizing effect. (2013)</td>
</tr>
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QUANTITATIVE PREDICTIVE ACCURACY
What is quantitative predictive accuracy?
Examples

• Type #1: Direct output of the HFM-TB
  – In Year 2009, the HFM-TB predicted pyrazinamide $AUC_{0-24}/MIC$ of 209 at site of infection was optimal for sterilizing effect (translates to 11.7 in serum/plasma)

• Type #2: HFM-TB output followed by Monte Carlo simulations.
  – MIC resistance breakpoints (Year 2009)

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<th></th>
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<th>INH</th>
<th>PZA</th>
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<td>Standard/accepted (mg/L):</td>
<td>1.0</td>
<td>2.0/0.2</td>
<td>100</td>
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<tr>
<td>Prediction (mg/L):</td>
<td>0.0625</td>
<td>0.0313/0.125</td>
<td>25-50</td>
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Predictive accuracy is how well these predicted quantities were to what was found in future in clinical studies: how close to the bullseye.
0% accuracy or 100% error

100% accuracy or 0% error
Accuracy

- P = HFM-TB predicted value
- T = true value (from clinical study)
- FE = Forecasting Error
- T-P = Error
- For a number of trials or experiments i of up to n, this takes the form of the mean absolute percentage error, which is given by:

\[ \text{MAPE} = \frac{1}{n} \sum_{i=1}^{n} \left| \frac{T_i - P_i}{T_i} \right| \times 100 \]

- If the MAPE is the FE, then accuracy (A) is defined by:

\[ A = 100\% - \text{FE} \]

- Weighting was based on the size of the study population in a given clinical study (i.e., number of patients), divided by the quality of evidence score (i.e., the lower the quality of study, the less weighty the prediction)

- Bias (B) is the tendency of the forecasting method to overstate or understate the true value.
DIRECT OUTPUT OF HFM-TB: PYRAZINAMIDE STERILIZING EFFECT

• Sterilizing effect found to be driven by AUC/MIC (prediction #1)

• Optimal plasma AUC/MIC in patients was **11.3 compared to 11.7** in HFM-TB (or **201 versus 209** in the lung)

• FE = (T-P)*100/T

• FE = (|11.3-11.7|)*100/11.3

• FE = 3.54%

• Accuracy = 100-FE

• Accuracy = 96.46%
Example #2: HFM-TB output followed by Monte Carlo simulations

- **MIC Breakpoints:**

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<tr>
<td>Prospective clinical study (mg/L)</td>
<td>0.125</td>
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</tbody>
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- **FE:**
  - 50%
  - 0%
  - 0%

- **ACCURACY:**
  - 50%
  - 100%
  - 100%
HFM-TB quantitative predictions

- Eight prospective studies that examined 14 parameters/quantitative predictions:
  - Quality of evidence for 7 studies: 1 or 2
  - 8th was 3
  - used together with sample size in weighting

- Predictive accuracy = 94.4% (CI, 84.3-99.9%)

- Bias = 1.8% (CI, -13.7 to 6.2%) – crossed zero.
BULLSEYE!
Acknowledgements

• CPTR PCS-WG & hollow fiber system sub-team:
  – Dr Eric Nuermbeger (Johns Hopkins)
  – Dr. Debra Hanna (C-Path/CPTR)

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  – Sandirai Musuka
  – Carleton Sherman
  – Crystal Norton
  – Dr. Aurelia Schmalsteig
  – Dr. Devyani Deshpande

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  – Dr. Emmanuel Chigutsa (PK/PD datasets)
  – Dr. Frederick Sirgel (MIC determination)
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