Evaluating New TB Drugs in Mice: Relevance to Humans, especially with HIV

Eric Nuermberger, M.D.
Center for TB Research
Johns Hopkins University School of Medicine
Baltimore, MD

February 27, 2011
Disclosures

• Active research grants:
  – Pfizer, sanofi-aventis, Global Alliance for TB Drug Development
What would we like to see from new TB drugs and regimens?

• Improved sterilizing activity to shorten the duration of treatment (active and latent TB)
• Activity against isolates resistant to existing drugs (M/XDR-TB)
• Lower risk of resistance emerging (HIV-TB)
• No interactions with anti-retroviral agents (HIV-TB)
Role of animal models in drug development

Provides critical bridge between *in vitro* studies and human trials

- embodies dynamic interaction b/w host, drug and microbe
- enables testing of a wide range of drug doses and dosing schedules
- enables testing of novel drug combinations and abbreviated treatment durations

Nuernberger, Semin Respir Crit Care Med (2008); 29:542
“All models are wrong, some are useful.”

George Box
Histological comparison of TB in the mouse and guinea pig

Mouse

Guinea pig
The mouse model of TB chemotherapy

Aerosol Infection

Log_{10} CFU in lungs

Weeks

Rx Onset
Treatment
Rx Offset
Follow-up

0 2 10 26 38

0 1 2 3 4 5 6 7 8 9

The diagram shows the logarithmic concentration of CFUs in the lungs over weeks, with specific markers for aerosol infection, Rx Onset, Treatment, Rx Offset, and Follow-up.
Recapitulation of the short-course regimen in the mouse...as in humans

Log$_{10}$ cfu in lungs

- **INH + SM**
- **INH + RIF**

20% relapse (human: 7%)

0% relapse (human: 1-3%)

75% relapse (human 10%)

Recapitulation of the short-course regimen in the mouse…as in humans

![Graph showing Log_{10} cfu in lungs over months for different regimens: INH + SM, INH + RIF, and INH + RIF + PZA. The graph illustrates the effectiveness of the regimens in reducing bacterial counts.](image-url)

Pharmacodynamics of INH activity

Jayaram et al, AAC 2004

Donald et al, AJRCCM 1997

Mouse

Human

Jayaram et al, AAC 2004
Pharmacodynamics of rifampin in the mouse model

Jayaram et al, AAC (2003); 47:2118

Range of mean values after 10 mg/kg oral dose in humans

Jayaram et al, AAC 2003
Dose-ranging activity of rifampin

Early bactericidal activity

<table>
<thead>
<tr>
<th>RIF dose</th>
<th>n</th>
<th>EBA_{0.2} (log CFU/ml/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>300 mg</td>
<td>3</td>
<td>0.06</td>
</tr>
<tr>
<td>600 mg</td>
<td>8</td>
<td>0.19</td>
</tr>
<tr>
<td>1200 mg</td>
<td>8</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Jindani et al, ARRD 1980; 121:939

Combination therapy in mice

Rosenthal et al, unpublished
The maximum predicted effect was a 0.11 log CFU/day reduction. Activity correlated best with free drug $T_{\text{MIC}}$, followed by AUC/MIC and then Cmax/MIC. The free drug $T_{\text{MIC}}$ value associated with 90% of the maximal predicted effect was 53%.

The maximum observed effect was a 0.1 log CFU/day reduction, like the extended EBA observed in humans. Activity correlated best with free drug $T_{\text{MIC}}$, followed by AUC/MIC and then Cmax/MIC. Free drug $T_{\text{MIC}}$ values associated with a bacteriostatic effect, a 1 log kill and 80% of the maximal observed effect were 22%, 48% and 77%, respectively.

The maximum predicted effect was a 0.11 log CFU/day reduction. Again, activity correlated best with free drug $T_{\text{MIC}}$, followed by AUC/MIC and then Cmax/MIC. The free drug $T_{\text{MIC}}$ value associated with 90% of the maximal predicted effect was 53%.
## Summary Data from PA-824 EBA Studies

### First Study

<table>
<thead>
<tr>
<th></th>
<th>PA-824 200 mg</th>
<th>PA-824 600 mg</th>
<th>PA-824 1000 mg</th>
<th>PA-824 1200 mg</th>
<th>Rifafour® e-275</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>12</td>
<td>14</td>
<td>15</td>
<td>11</td>
<td>7</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>0.106</td>
<td>0.107</td>
<td>0.091</td>
<td>0.088</td>
<td>0.148</td>
</tr>
<tr>
<td><strong>Standard Error</strong></td>
<td>0.014</td>
<td>0.014</td>
<td>0.021</td>
<td>0.025</td>
<td>0.021</td>
</tr>
</tbody>
</table>

### Second Study

<table>
<thead>
<tr>
<th></th>
<th>PA-824 200 mg</th>
<th>PA-824 150 mg</th>
<th>PA-824 100 mg</th>
<th>PA-824 50 mg</th>
<th>Rifafour® e-275</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>0.111</td>
<td>0.106</td>
<td>0.099</td>
<td>0.060</td>
<td>0.141</td>
</tr>
<tr>
<td><strong>Standard Error</strong></td>
<td>0.019</td>
<td>0.018</td>
<td>0.022</td>
<td>0.019</td>
<td>0.019</td>
</tr>
</tbody>
</table>
Mouse models of LTBI therapy

- Small mammals (e.g., mice & GPs) do not develop LTBI after *M. tb* infection

- Mouse models of LTBI have sought:
  - low burden of infection (ideally < 10^4 CFU)
  - limited or no multiplication

- Methods have included:
  - Low-dose aerosol infection
  - Pre-treatment with antibiotics
  - Infection with replication-deficient strains
  - Immunization prior to *M. tb* challenge
A paucibacillary model for the experimental chemotherapy of LTBI in mice

Zhang et al., *Am J Respir Crit Care Med* (2009); 180:1151
Sterilizing activity of RH and RZ

<table>
<thead>
<tr>
<th></th>
<th>Proportion (%) with positive lung cultures 3 months after treatment for:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 wks</td>
</tr>
<tr>
<td>RH</td>
<td>15/15 (100%)</td>
</tr>
<tr>
<td>RZ</td>
<td>8/15 (55%)*</td>
</tr>
</tbody>
</table>

*p<0.01 vs. RH

Sterilizing activity of daily and once-weekly PH regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>W2</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M6</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15/15</td>
<td>15/15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(100%)</td>
<td>(100%)</td>
</tr>
<tr>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15/15</td>
<td>13/15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(100%)</td>
<td>(87%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6/13</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(46%)</td>
<td></td>
</tr>
<tr>
<td>RH</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14/15</td>
<td>7/13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(93%)</td>
<td>(54%)</td>
</tr>
<tr>
<td>P_{15H} (1/7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>13/15</td>
<td>7/15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(87%)</td>
<td>(47%)</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10/15</td>
<td>0/15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(67%)</td>
<td>(0%)</td>
</tr>
<tr>
<td>P_{10H} (5/7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9/15</td>
<td>0/15</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(60%)</td>
<td>(0%)</td>
</tr>
</tbody>
</table>
Sterilizing activity of daily and once-weekly PH regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>W2</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M6</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>15/15 (100%)</td>
<td>15/15 (100%)</td>
</tr>
<tr>
<td>R</td>
<td></td>
<td></td>
<td>15/15 (100%)</td>
<td>13/15 (87%)</td>
<td>6/13 (46%)</td>
<td></td>
</tr>
<tr>
<td>RH</td>
<td></td>
<td></td>
<td>14/15 (93%)</td>
<td>7/13 (54%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P&lt;sub&gt;15&lt;/sub&gt;H (1/7)</td>
<td></td>
<td></td>
<td>13/15 (87%)</td>
<td>7/15 (47%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P&lt;sub&gt;10&lt;/sub&gt;H (5/7)</td>
<td></td>
<td></td>
<td>9/15 (60%)</td>
<td>0/15 (0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J (5/7)</td>
<td></td>
<td></td>
<td>13/15 (87%)</td>
<td>2/14 (14%)</td>
<td>4/14 (29%)</td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• This paucibacillary model represents the activity of existing LTBI regimens very well
  – RZ > RH = PH\(_{1/7}\) > R > H

• 1PH has efficacy similar to 4R, 3RH and 3PH\(_{1/7}\)

• 3-4 months of TMC207 also has efficacy similar to 4R, 3RH and 3PH\(_{1/7}\)
Acquired rifamycin resistance (ARR) in HIV-TB co-infection

- ARR is thankfully rare among clinical isolates, but is strongly associated with advanced AIDS and intermittent treatment regimens.
- ARR occurred with unusually high frequency in clinical trials of AIDS pts receiving:
  - H+RPT (1/7) in the continuation phase,\(^1\) and
  - H+RBT (2/7) after 2 wks of daily treatment\(^2\)
- This resistance emergence was not foreseen by expts in conventional mouse models.

\(^1\) Vernon et al, *Lancet* (1999); 353:1843
Treatment failure in nude mice treated with 2RHZ/RH for 8 months

Can we recapitulate ARR in nude mice?

• ARR requires 2 things:
  – Sufficient rifamycin pressure to select for spontaneous R-resistant mutants
  – Companion agent exposures insufficient to provide counterselection

• ARR should be recapitulated by:
  – increasing rifamycin exposures to a level sufficient for selection, while
  – decreasing companion drug exposures to a level which no longer provides counterselection
Of mice and men

- Do features specific to necrotic granulomas influence the treatment response?

BALB/c mice

Guinea pigs

C3HeB/FeJ mice
Conclusions

• Mouse models represent the activity of existing TB drugs well; their careful use can (and should!) inform TB drug development

• However, pathological differences between mice and humans have raised concerns about the “predictiveness” of mouse models

• Existing new drugs offer a new “validation set” for comparing mouse and human results
Important considerations for animal models

• Use a well-characterized bacterial strain
• Use a relevant bacterial burden
• Use drug dosages that match human PK/PD
• Select relevant outcomes
  – Bactericidal activity
  – Sterilizing activity
  – Selection / suppression of resistant mutants
  – PK/PD relationships for the above outcomes
• Understand that manipulation of experimental variables may have a profound effect on results
Conclusions

• RHZ (5/7) readily selects H-resistant mutants in immunodeficient nude mice

• Emergence of resistance on RHZ
  – is prevented by
    • substitution of P for R
    • addition of ethambutol during the intensive phase
  – is NOT prevented by
    • true daily (7/7) administration of 2RHZ/RH

• Nude mice may represent a permissive model for resistance emergence, not unlike HIV/AIDS