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

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# Disclosures

- Active research grants:
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# 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

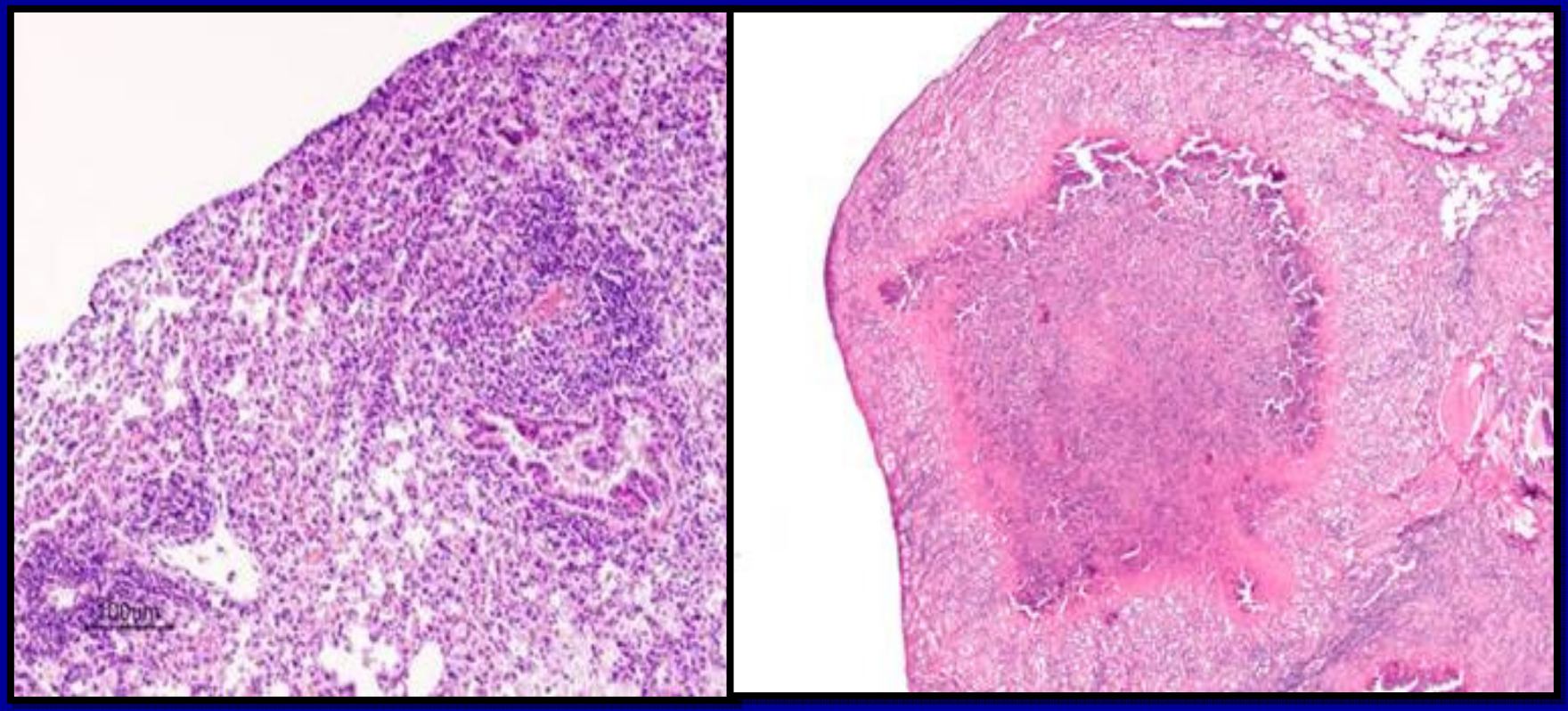
- embodies dynamic interaction b/w host, drug and microbe
- enables testing of a wide range of drug doses and dosing schedules
- enables testing of novel drug combinations and abbreviated treatment durations

Nuermberger, Semin Respir Crit Care Med (2008); 29:542

“All models are wrong,
some are useful.”

George Box

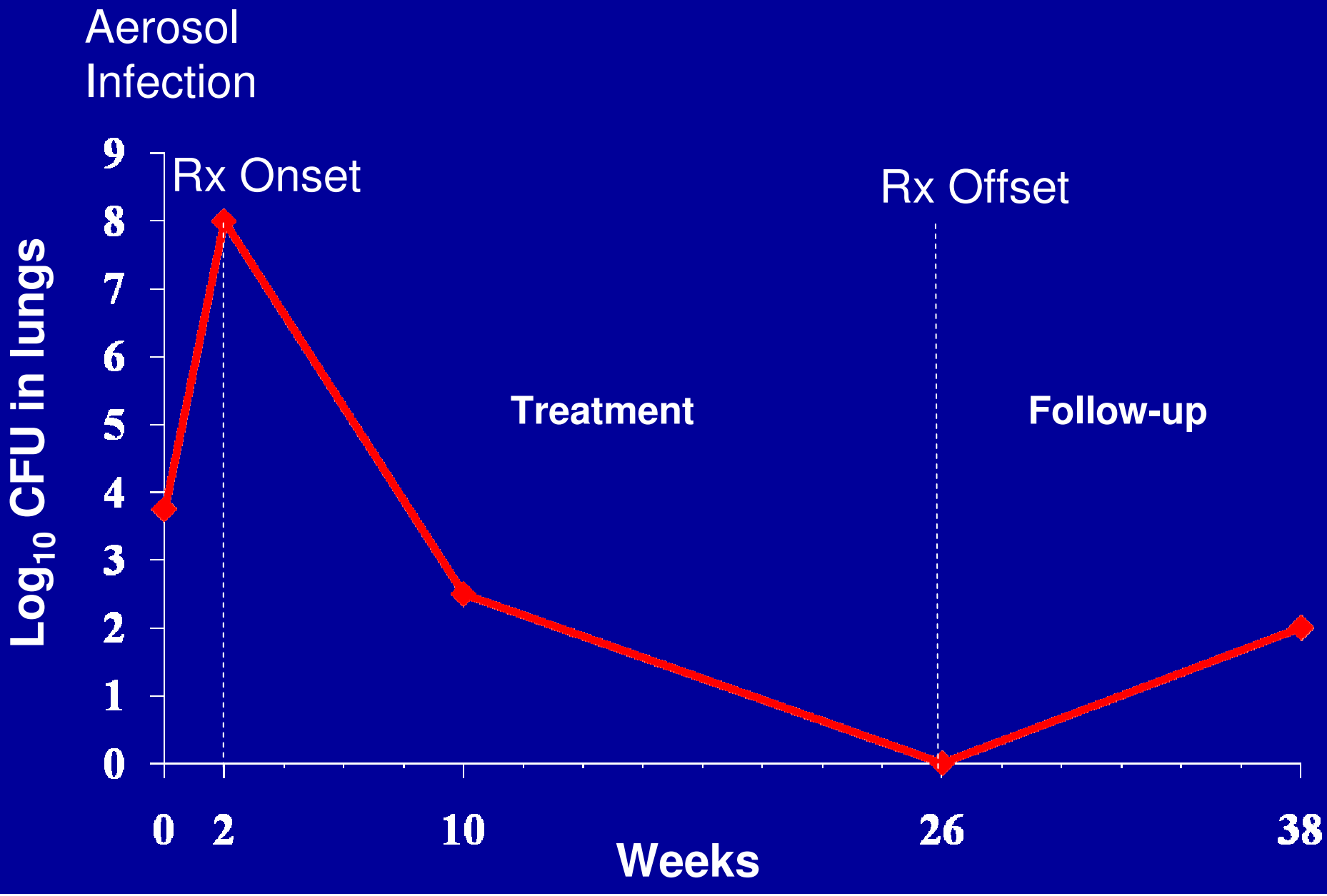
# Histological comparison of TB in the mouse and guinea pig



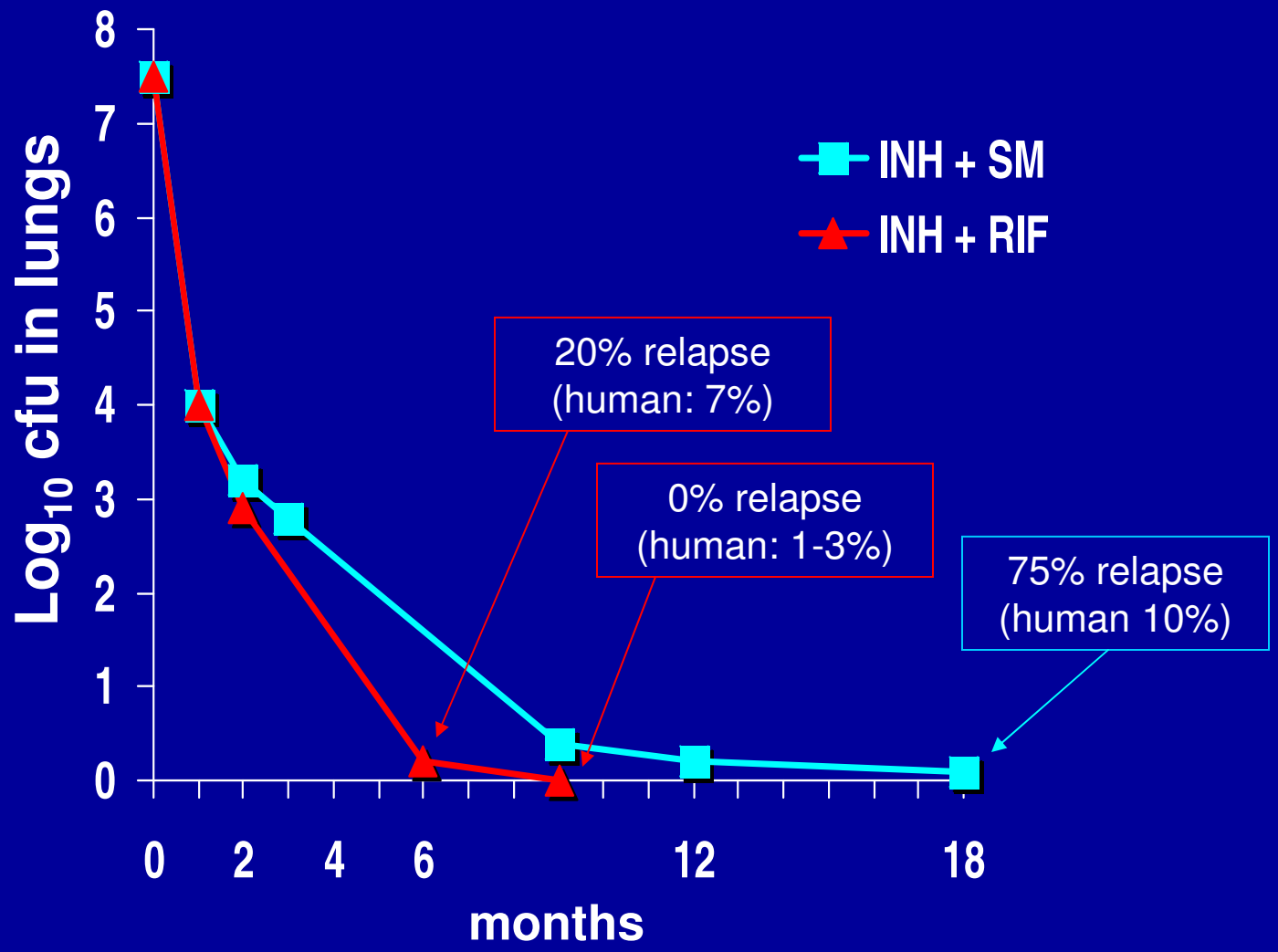
Mouse

Guinea pig

# The mouse model of TB chemotherapy



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




Tubercle 1978;59:287 & 1986;67:5

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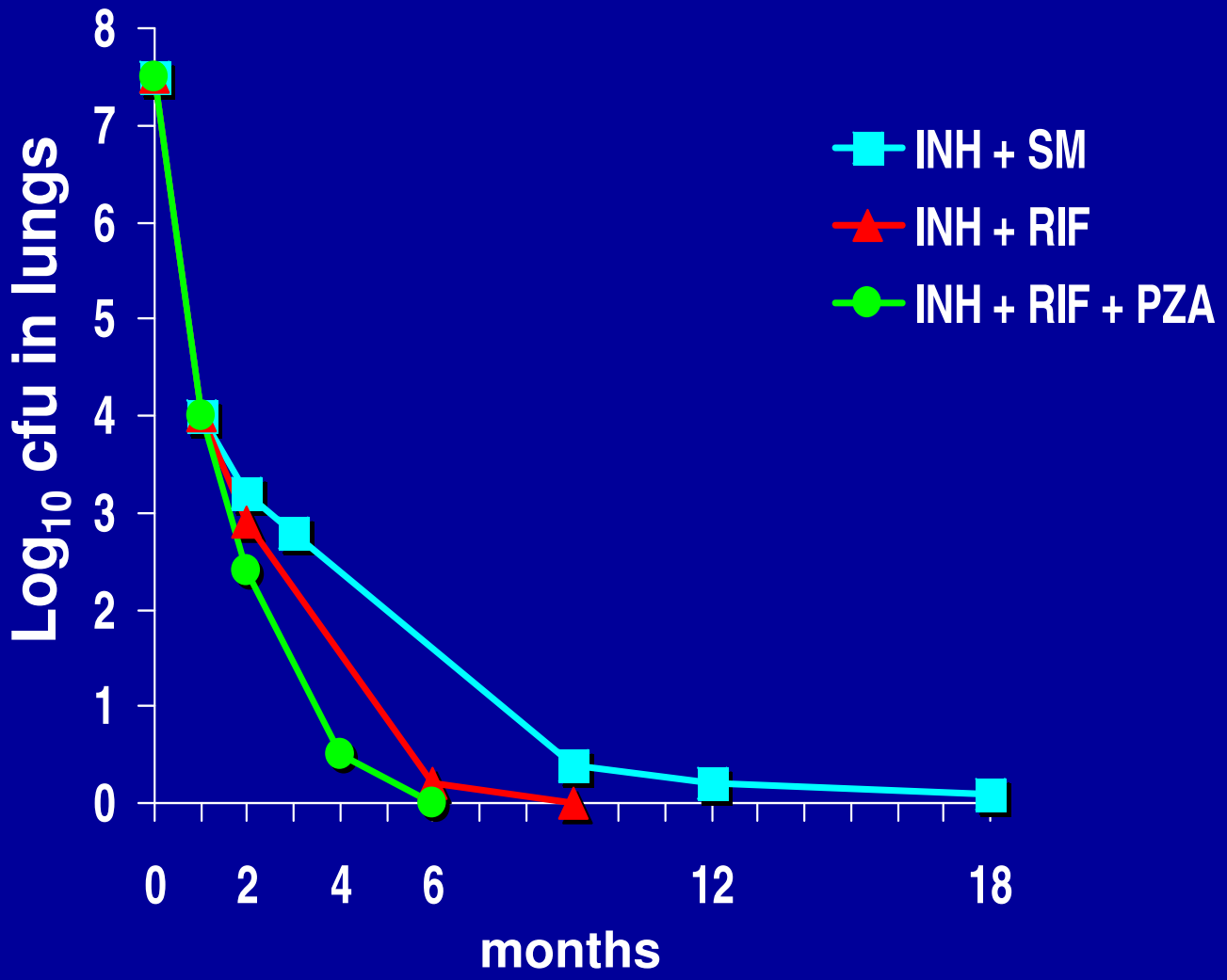
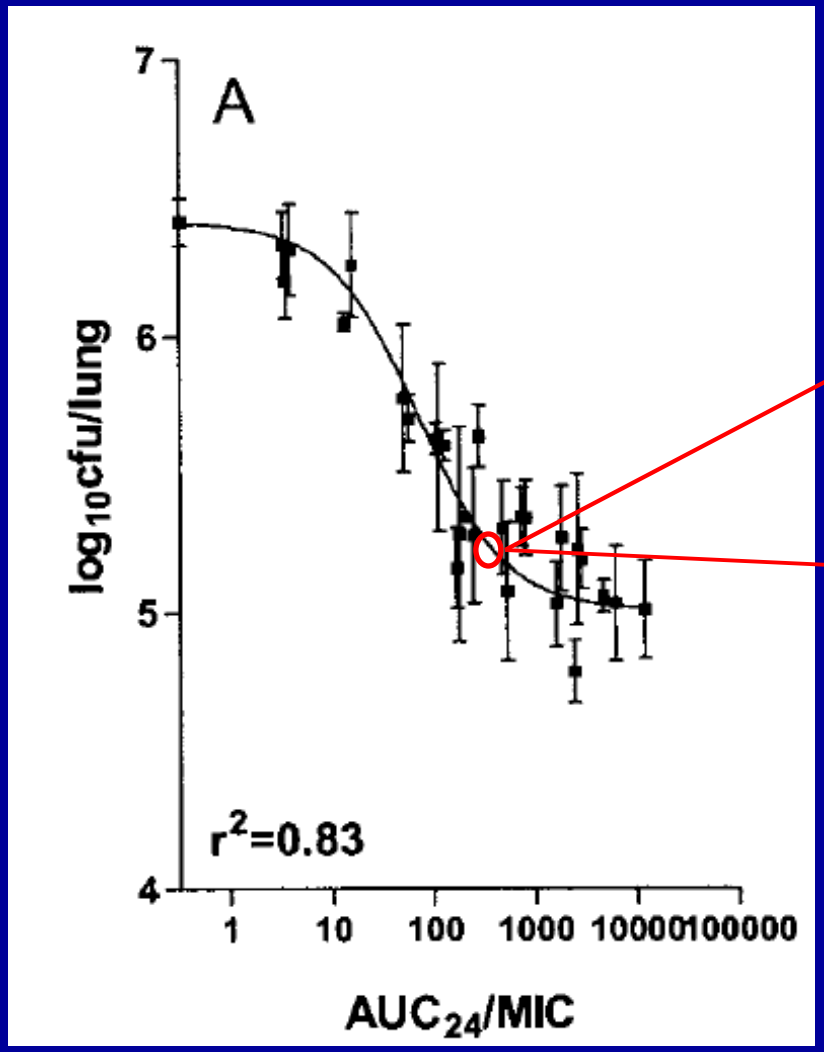
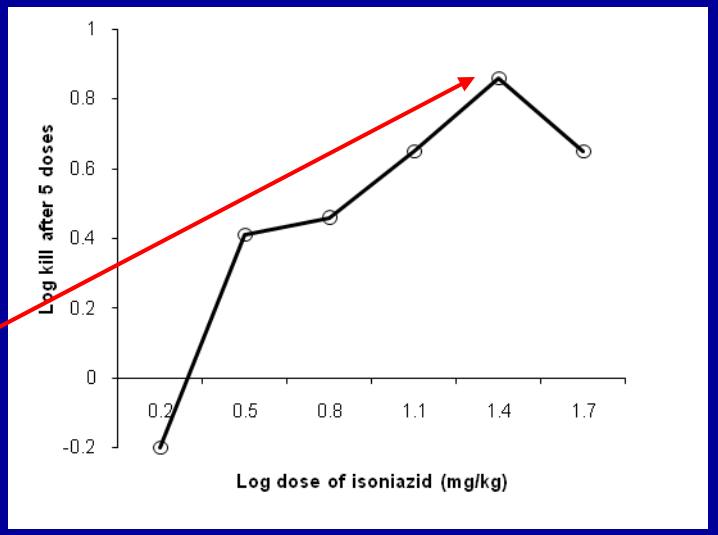



Tubercle 1978: 59:287 & 1986;67:5

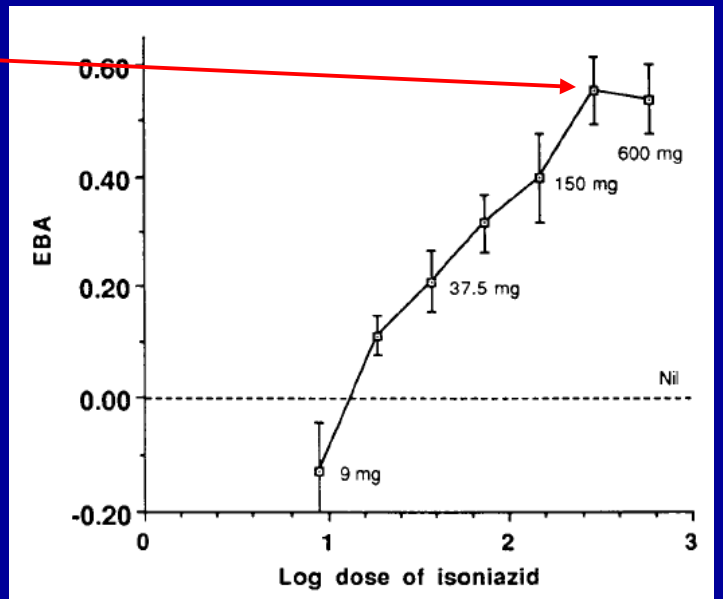
# Pharmacodynamics of INH activity




Jayaram et al, AAC 2004



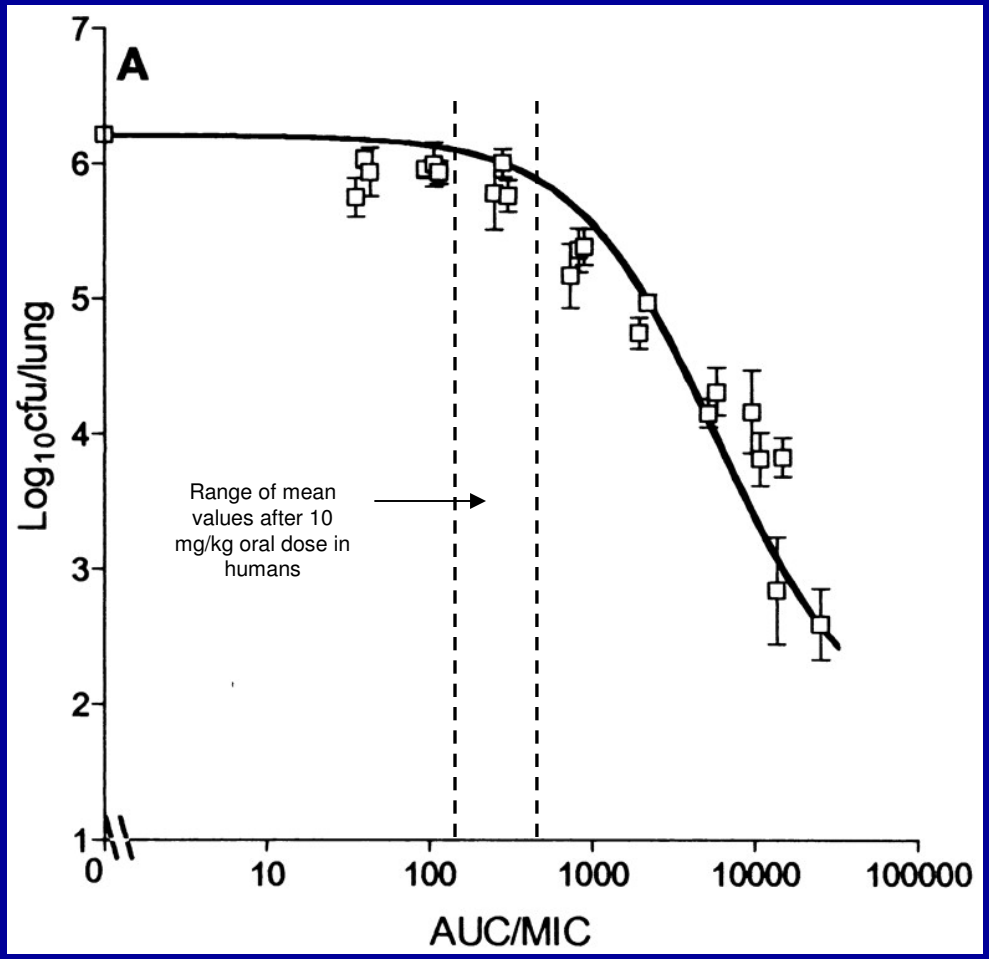

Mouse




Human

Donald et al, AJRCCM 1997

# Pharmacodynamics of rifampin in the mouse model




Jayaram et al, AAC 2003

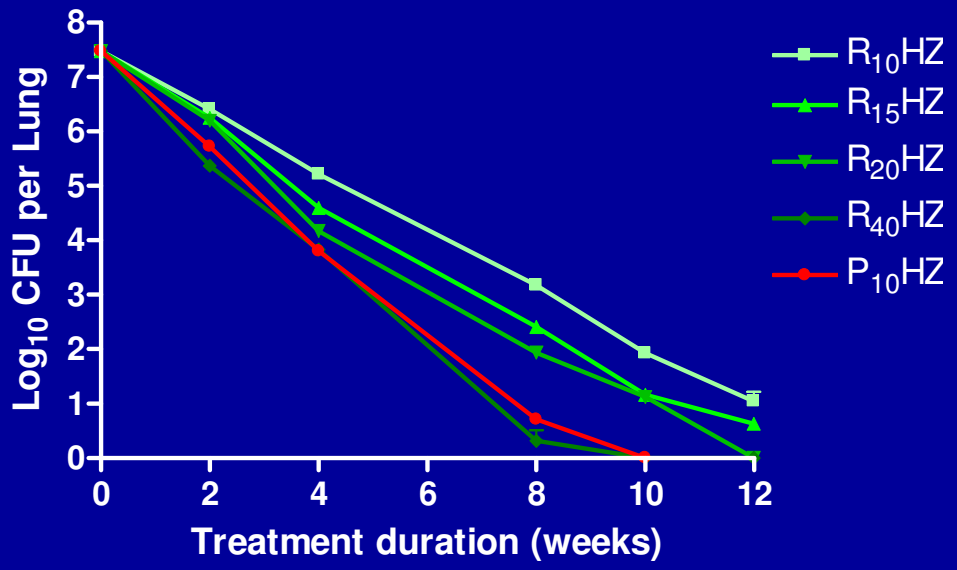
# Dose-ranging activity of rifampin

## Early bactericidal activity

| RIF dose | n | $EBA_{0-2}$ (log CFU/ml/day) |
|---|---|---|
| 300 mg | 3 | 0.06 |
| 600 mg | 8 | 0.19 |
| 1200 mg | 8 | 0.41 |

Jindani et al, ARRD 1980; 121:939

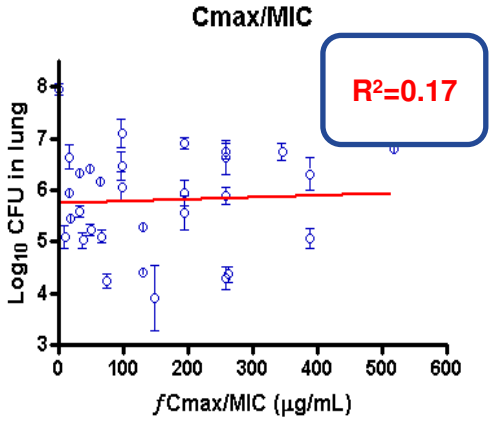
## Combination therapy in mice

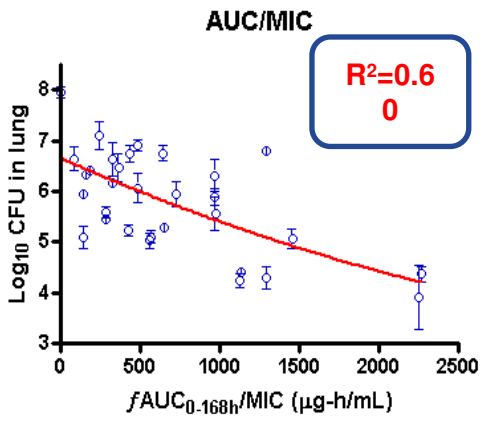


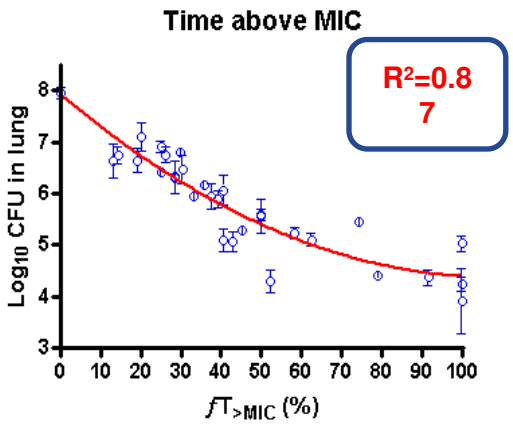

Rosenthal et al, unpublished

# Correlation of PA-824 PD parameters with effect

## Initial phase

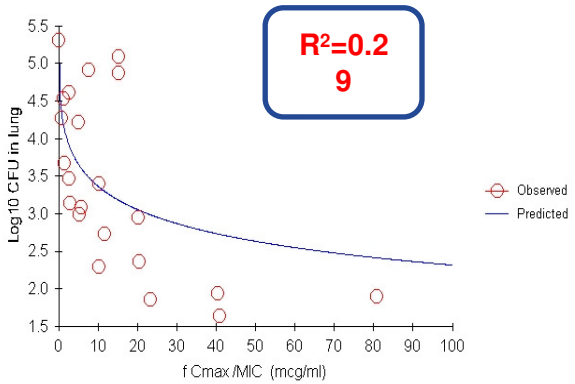


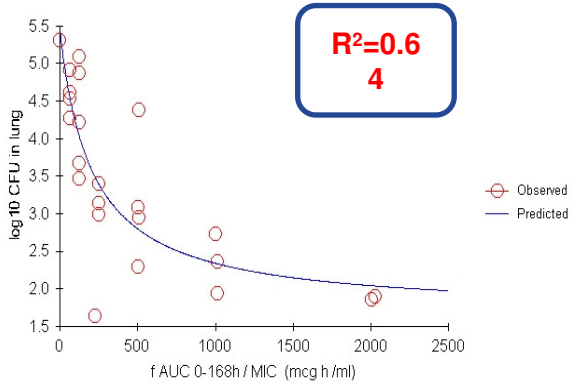



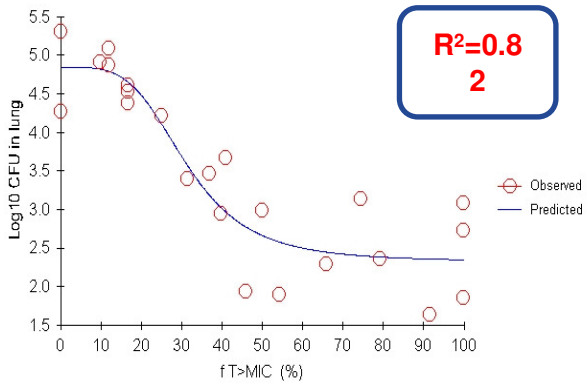




he maximum observed effect was a 0.1 log CFU/day reduction, like the extended EBA observed in humans. Activity correlated best with free drug $T_{>MIC}$, followed by AUC/MIC and then Cmax/MIC . Free drug $T_{>MIC}$ values associated with a bacteriostatic effect, a 1 log kill and 80% of the maximal observed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

## Continuation phase




he maximum predicted effect was a 0.11 log CFU/day reduction. Again, activity correlated best with free drug $T_{>MIC}$, followed by AUC/MIC and then Cmax/MIC . The free drug $T_{>MIC}$ value associated with 90% of the maximal predicted effect was 53%.

# Summary Data from PA-824 EBA Studies

## First Study

| | PA-824 200 mg | PA-824 600 mg | PA-824 1000 mg | PA-824 1200 mg | Rifafour® e-275 |
|---|---|---|---|---|---|
| **Number** | 12 | 14 | 15 | 11 | 7 |
| **Mean** | 0.106 | 0.107 | 0.091 | 0.088 | 0.148 |
| **Standard Error** | 0.014 | 0.014 | 0.021 | 0.025 | 0.021 |

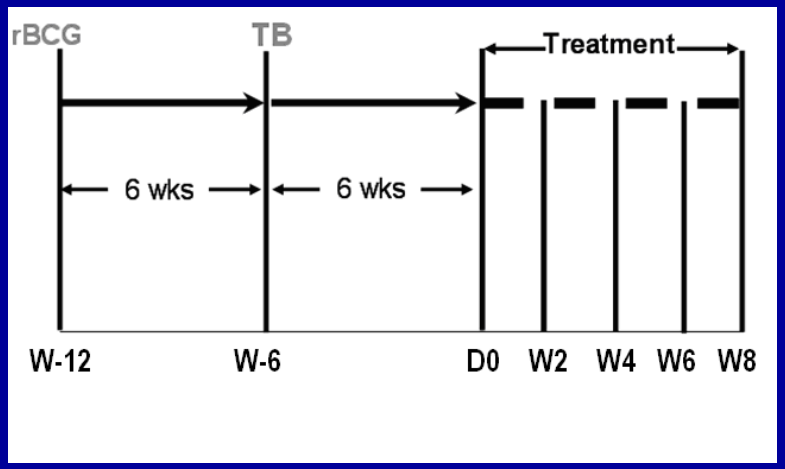
## Second Study

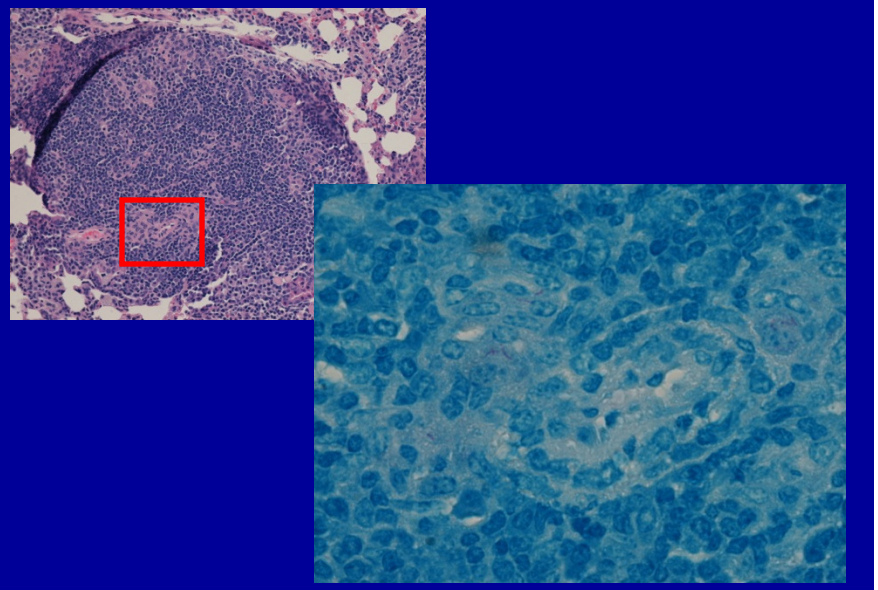
| | PA-824 200 mg | PA-824 150 mg | PA-824 100 mg | PA-824 50 mg | Rifafour® e-275 |
|---|---|---|---|---|---|
| **Number** | 15 | 15 | 15 | 13 | 8 |
| **Mean** | 0.111 | 0.106 | 0.099 | 0.060 | 0.141 |
| **Standard Error** | 0.019 | 0.018 | 0.022 | 0.019 | 0.019 |

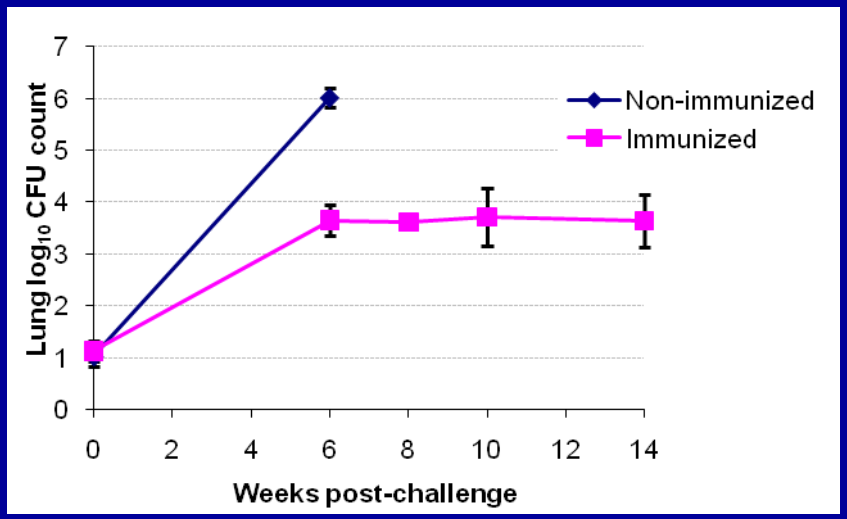
# Mouse models of LTBI therapy

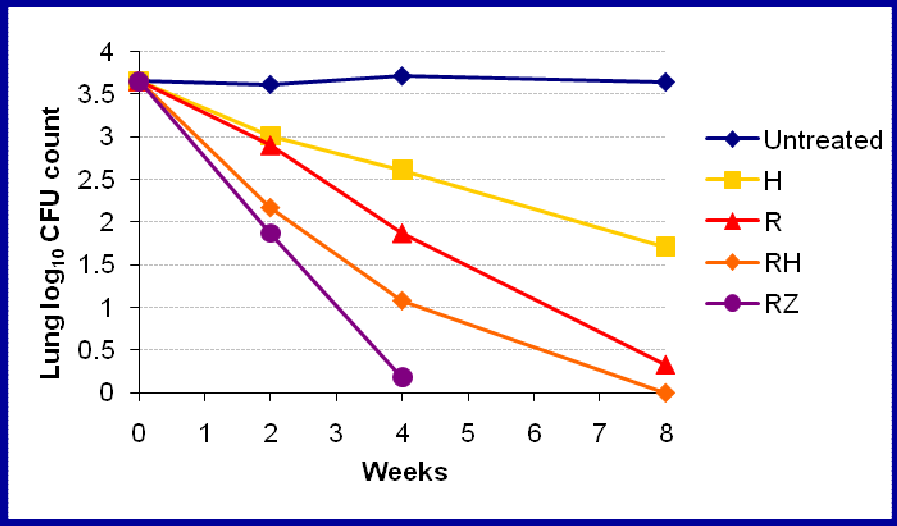
- Small mammals (eg, mice & GPs) do not develop LTBI after *M.tb* infection
- Mouse models of LTBI have sought:
  - low burden of infection (ideally < $10^4$ CFU)
  - limited or no multiplication
- Methods have included:
  - Low-dose aerosol infection
  - Pre-treatment with antibiotics
  - Infection 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

| | Proportion (%) with positive lung cultures 3 months after treatment for: | | |
|---|---|---|---|
| | 4 wks | 6 wks | 8 wks |
| RH | 15/15 (100%) | n/d | 7/15 (47%) |
| RZ | 8/15 (55%)* | n/d | 0/15 (0%)* |

*$p<0.01$ vs. RH

Zhang et al, *Am J Respir Crit Care Med* (2009); 180:1151

# Sterilizing activity of daily and once-weekly PH regimens

| | Proportion (%) relapsing after stopping treatment at: | | | | | |
|---|---|---|---|---|---|---|
| **Regimen** | W2 | M1 | M2 | M3 | M4 | M6 |
| **H** | | | | | 15/15 **(100%)** | 15/15 **(100%)** |
| **R** | | | 15/15 **(100%)** | 13/15 **(87%)** | 6/13 **(46%)** | |
| **RH** | | | 14/15 **(93%)** | 7/13 **(54%)** | | |
| **$P_{15}H$ (1/7)** | | | 13/15 **(87%)** | 7/15 **(47%)** | | |
| **P** | | 10/15 **(67%)** | 0/15 **(0%)** | | | |
| **$P_{10}H$ (5/7)** | | 9/15 **(60%)** | 0/15 **(0%)** | | | |

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| **J (5/7)** | | | 13/15 **(87%)** | 2/14 **(14%)** | 4/14 **(29%)** | |

# Conclusions

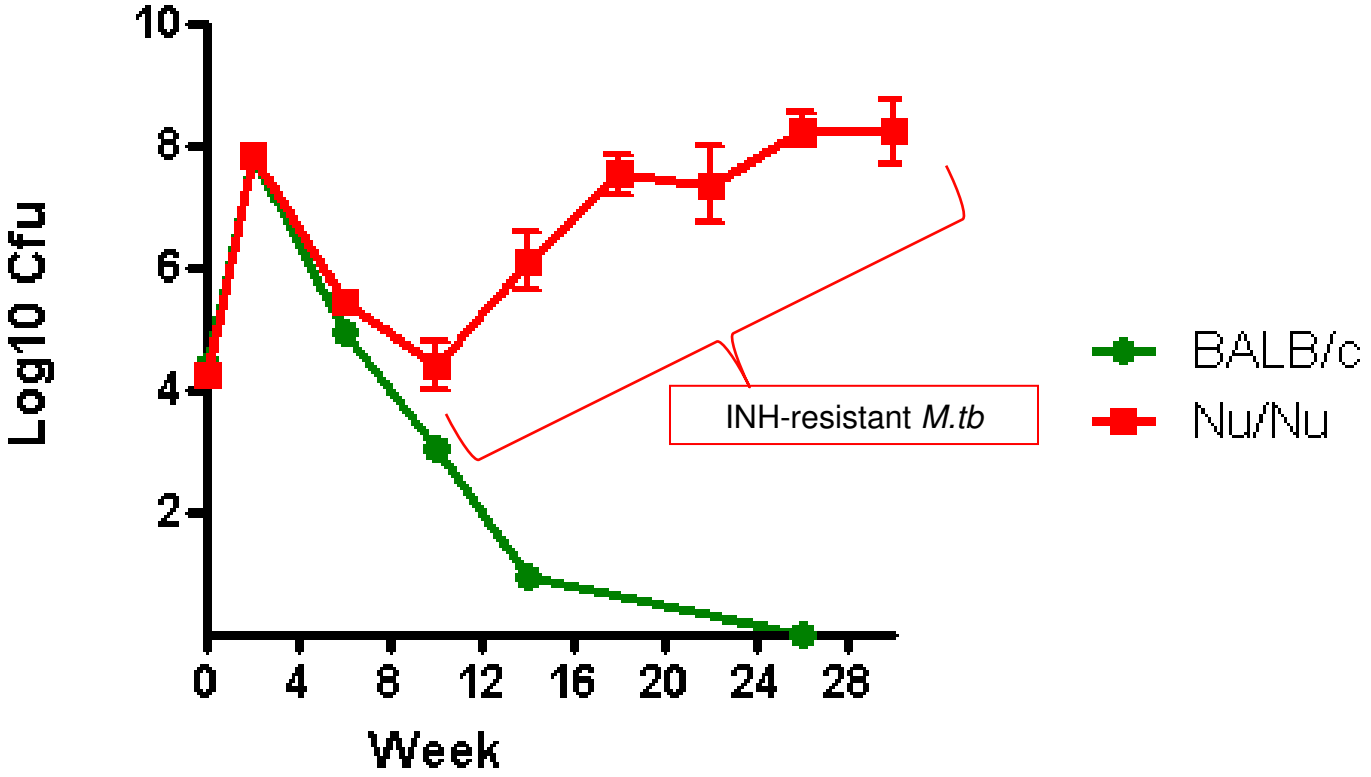
- This paucibacillary model represents the activity of existing LTBI regimens very well
  - RZ > RH = $PH_{1/7}$ > R > H
- 1PH has efficacy similar to 4R, 3RH and $3PH_{1/7}$
- 3-4 months of TMC207 also has efficacy similar to 4R, 3RH and $3PH_{1/7}$

# 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
[2] Burman et al, *Am J Respir Crit Care Med* (2006); 173:350

# Treatment failure in nude mice treated with 2RHZ/RH for 8 months



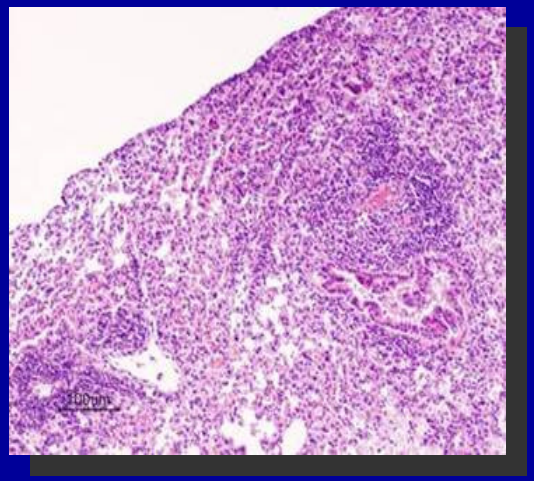

Zhang et al, *Am J Respir Crit Care Med* (2011), in press

# Can we recapitulate ARR in nude mice?

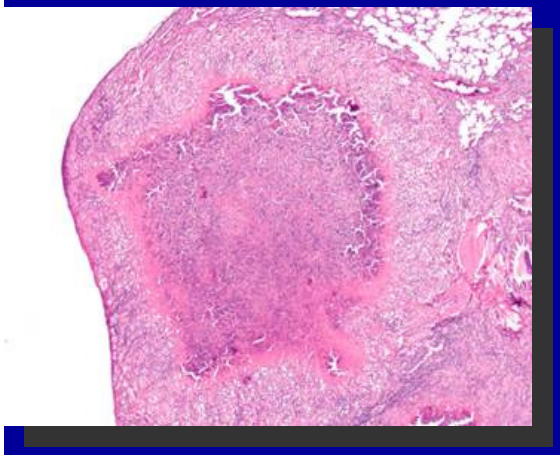
- ARR requires 2 things:
  - Sufficient rifamycin pressure to select for spontaneous R-resistant mutants
  - Companion agent exposures insufficient to provide counterselection
- ARR should be recapitulated by:
  - increasing rifamycin exposures to a level sufficient for selection, while
  - decreasing companion drug exposures to a level which no longer provides counterselection

# Of mice and men

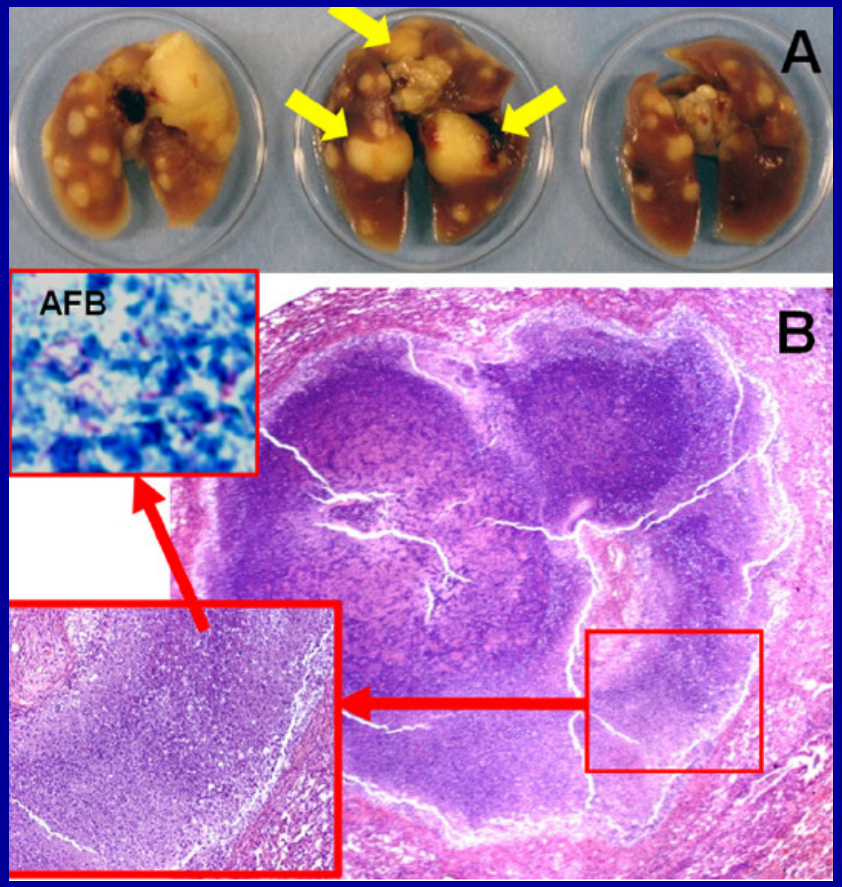
- Do features specific to necrotic granulomas influence the treatment response?



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