Anti-Tuberculosis Activity of Pyrazinamide Varies by Lesion Type in C3HeB/FeJ Mice

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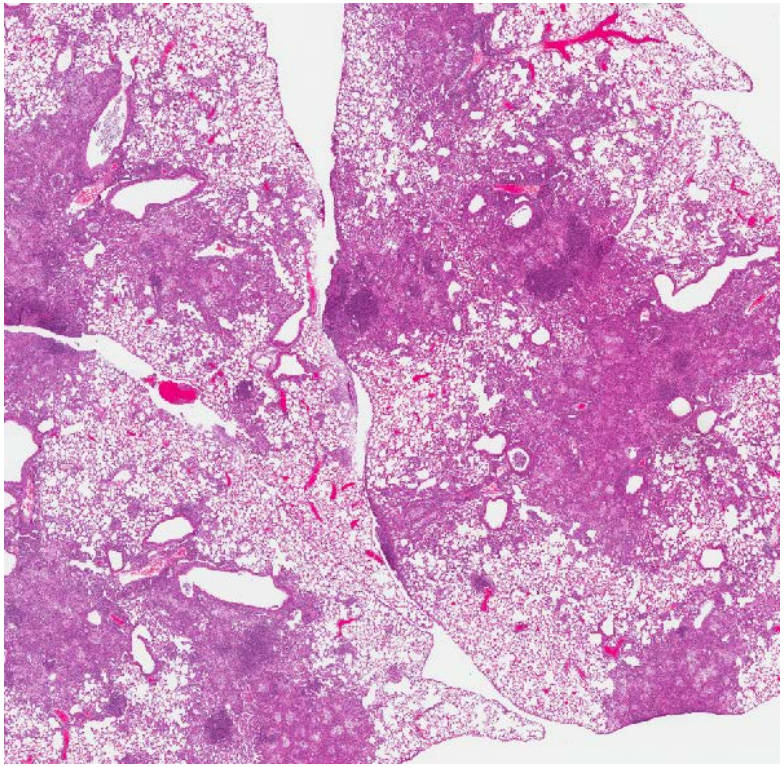
Introduction

- Humans develop a wide variety of lesion types when infected with *M. tuberculosis.*
- Commonly used mouse models develop only intracellular lesions.



Introduction

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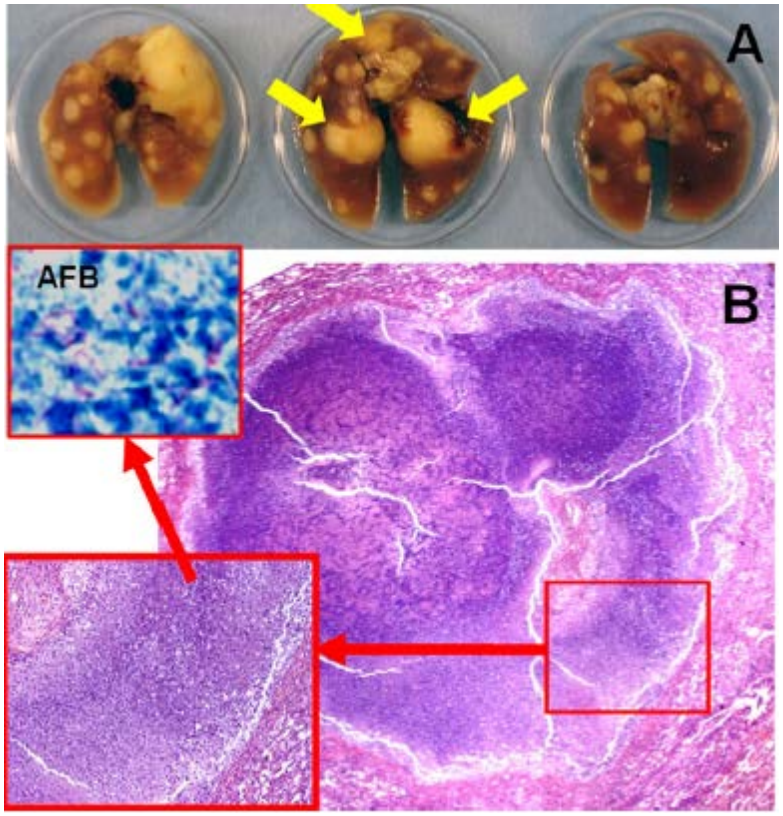
- Commonly used mouse models develop only intracellular lesions.
- Like humans, C3HeB/FeJ mice develop necrotic granulomas, caseous pneumonia and, occasionally, cavities.



Davis et al, 2009

Introduction

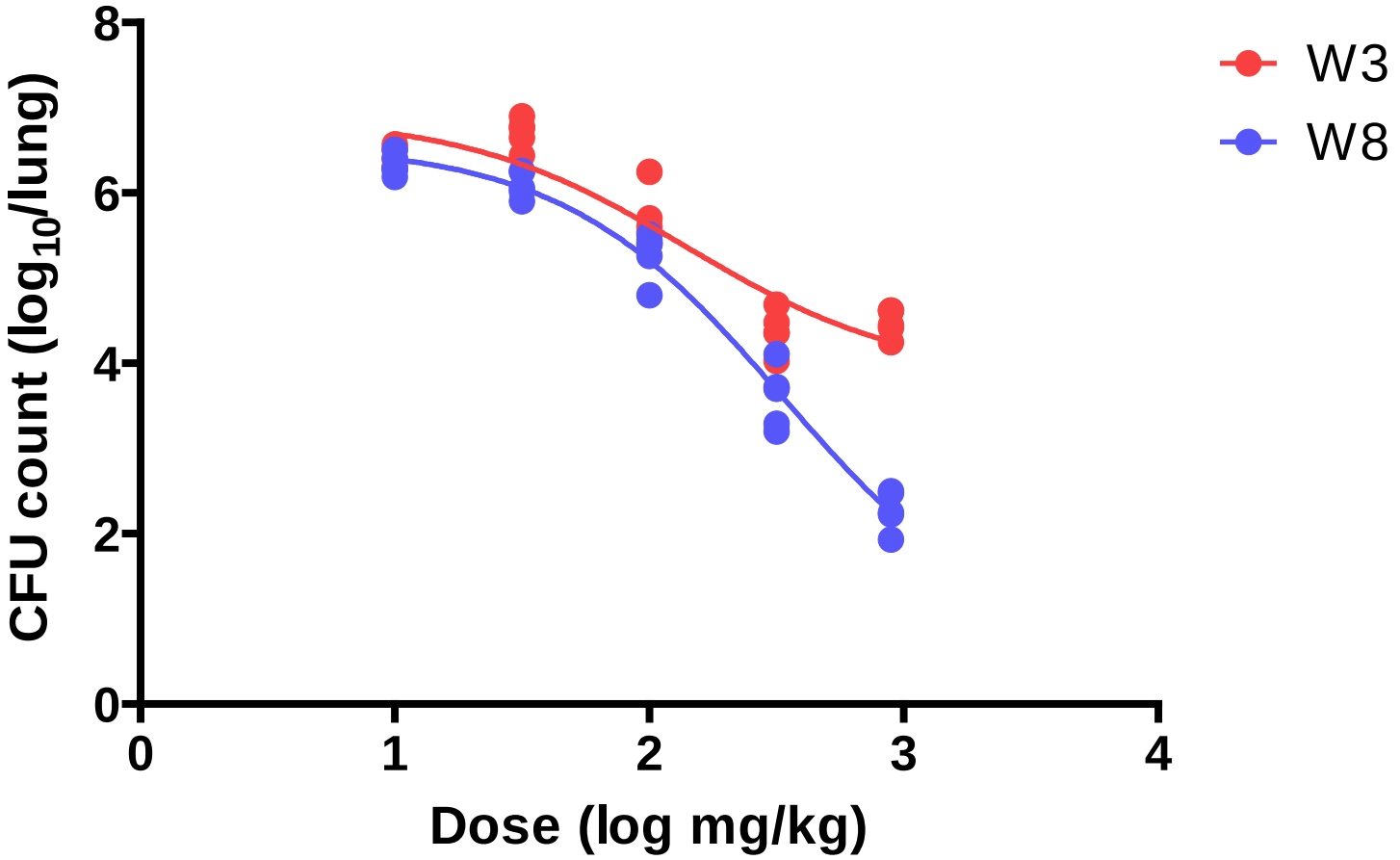
- If caseous necrosis is a determinant of drug effect, then C3HeB/FeJ mice may be more representative of a drug's activity in humans.
- Pyrazinamide (PZA) is an interesting drug to study in C3HeB/FeJ mice because:
  - It requires a unique environmental condition (low pH) to be active at achievable concentrations
  - It is 1 of only 2 drugs with sterilizing activity
  - It has no sterilizing activity beyond the first 2 months of treatment with the 1st-line regimen

- These curious characteristics suggest **PZA acts against a specific sub-population** of persisting bacteria residing in an acidic milieu which is not as susceptible to other anti-TB drugs.
- To better understand the relationship between lesion type and PZA activity, we investigated the pharmacodynamics of PZA in C3HeB/FeJ and BALB/c mice.

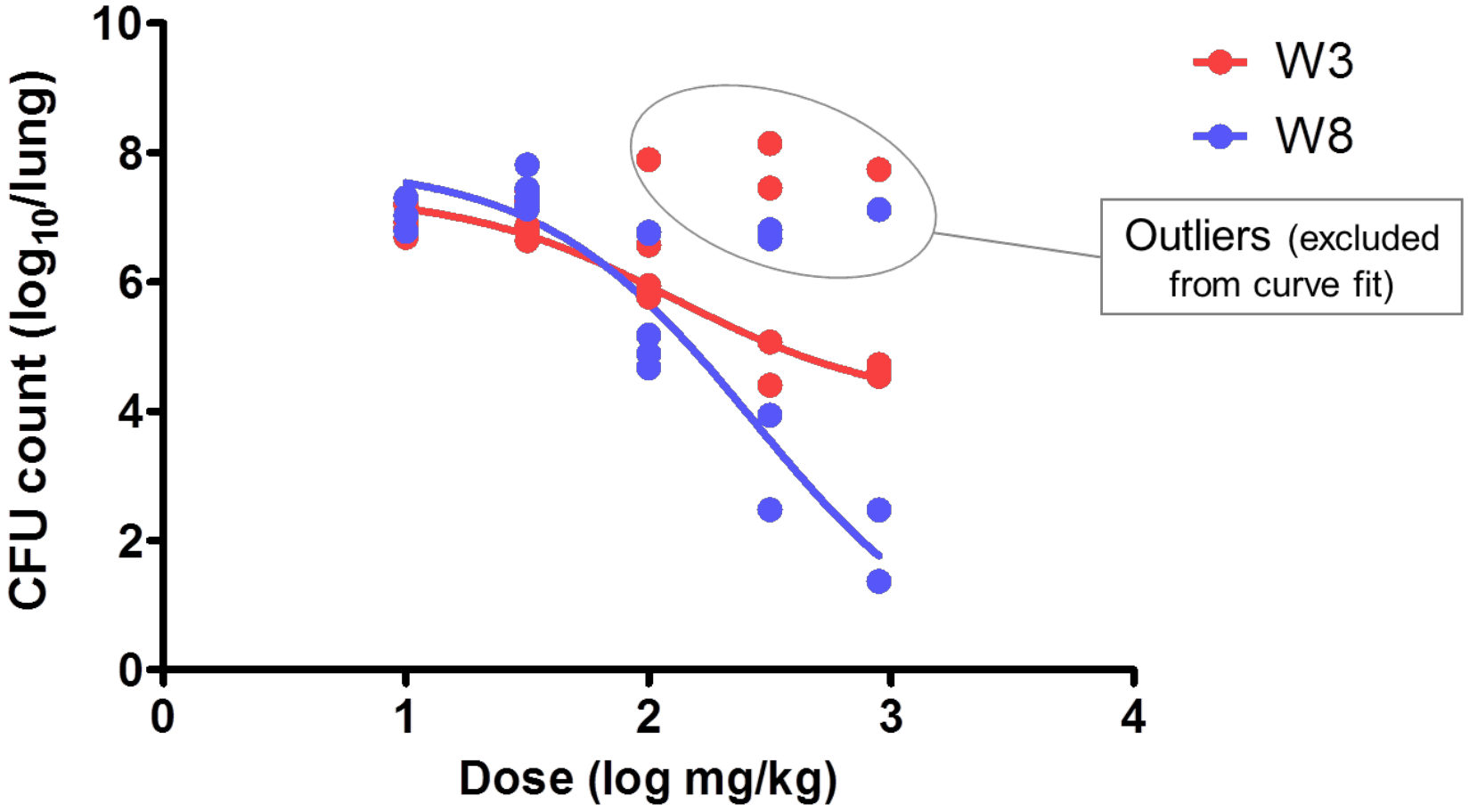
Objectives

- Compare the dose-ranging activity of PZA against established Mtb infection in both strains
- Describe the pharmacokinetics of PZA in plasma, epithelial lining fluid and lung lesions of C3HeB/FeJ mice
- Measure the pH of liquefied caseum in the lung lesions of C3HeB/FeJ mice

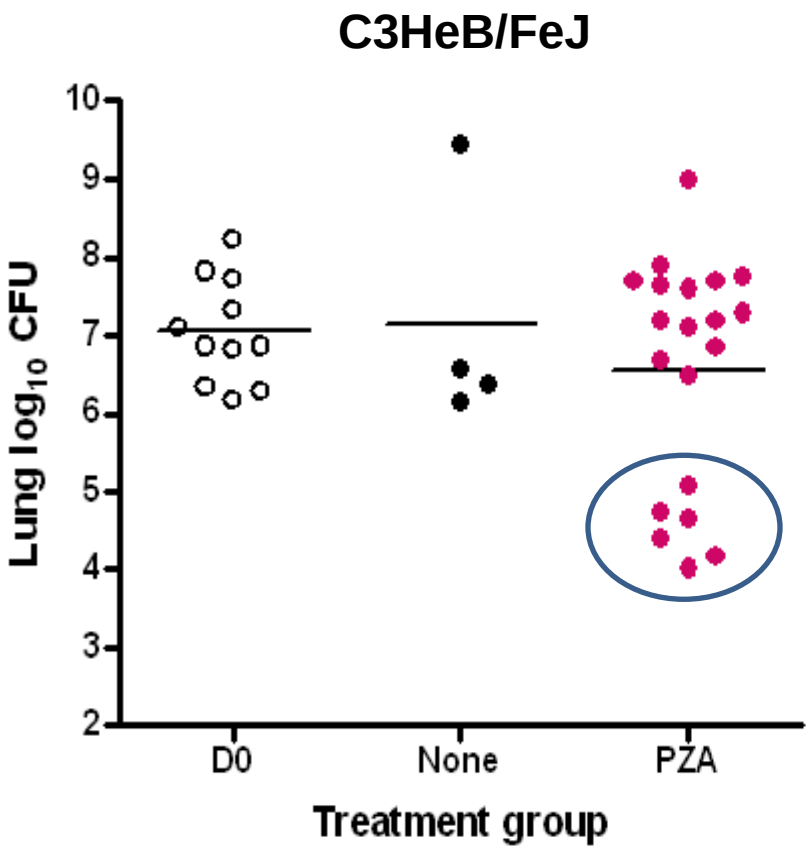
Dose-dependent activity of PZA in BALB/c mice

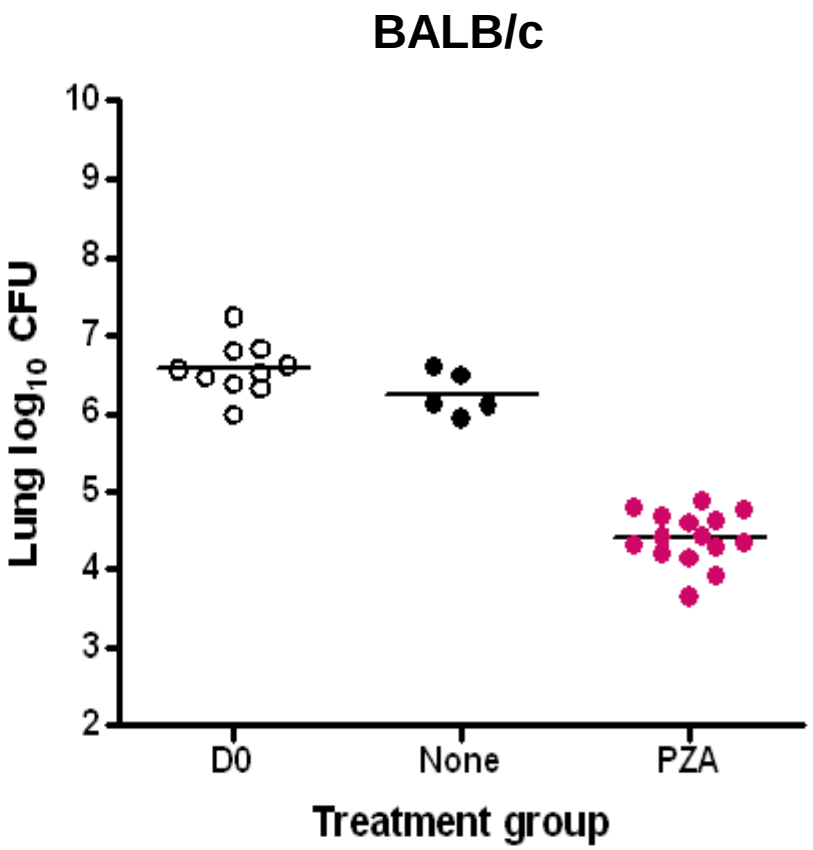


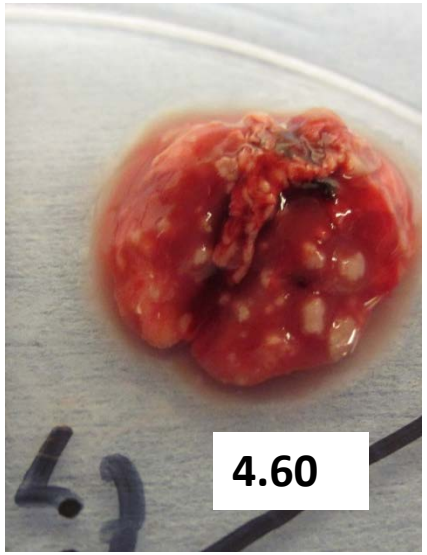
Dose-dependent activity of PZA in *some* C3HeB/FeJ mice



“Dichotomous” activity of PZA in C3HeB/FeJ mice



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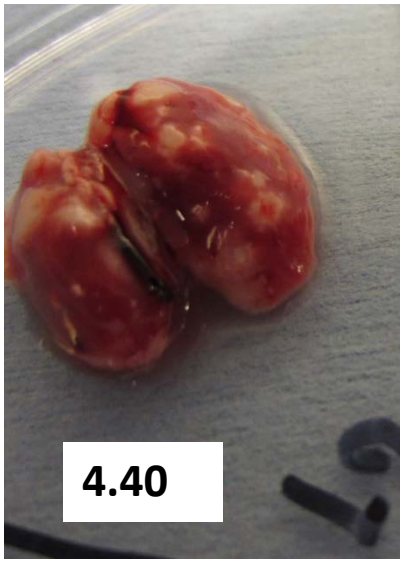
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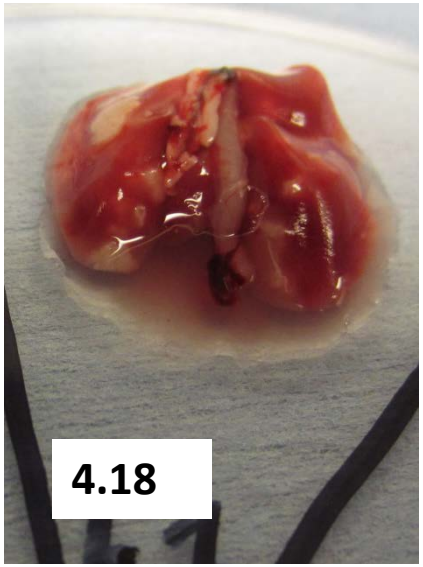
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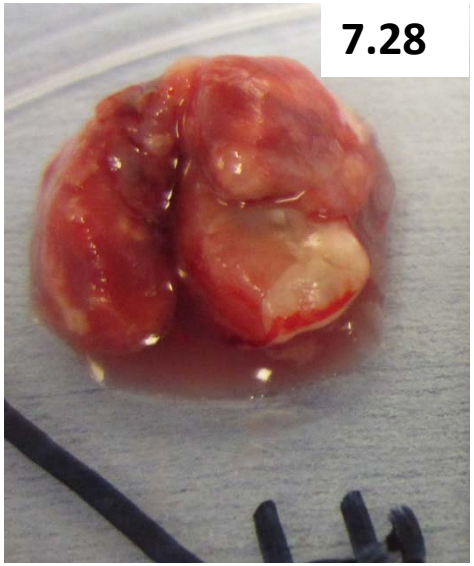
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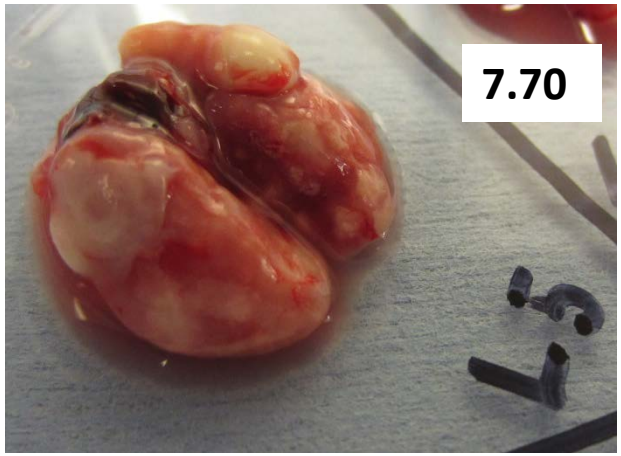
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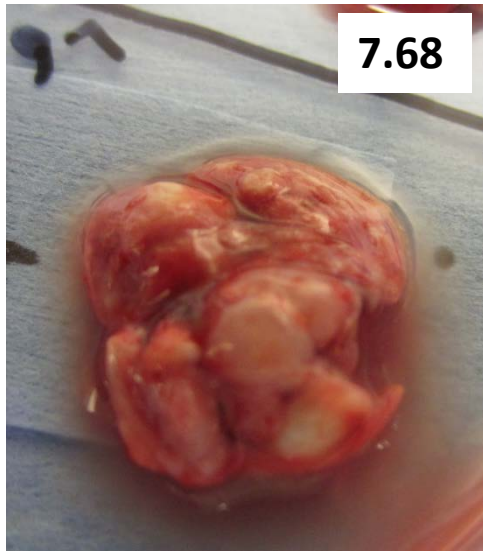
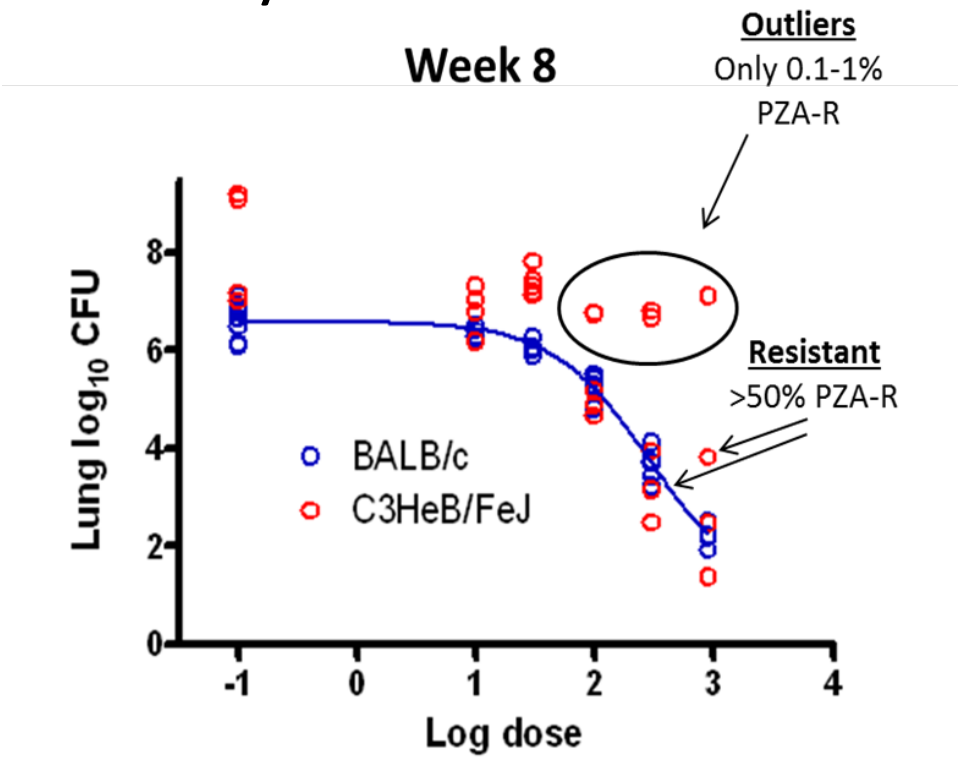

7.68

Why does PZA exhibit no dose-response in large, caseous lesions?

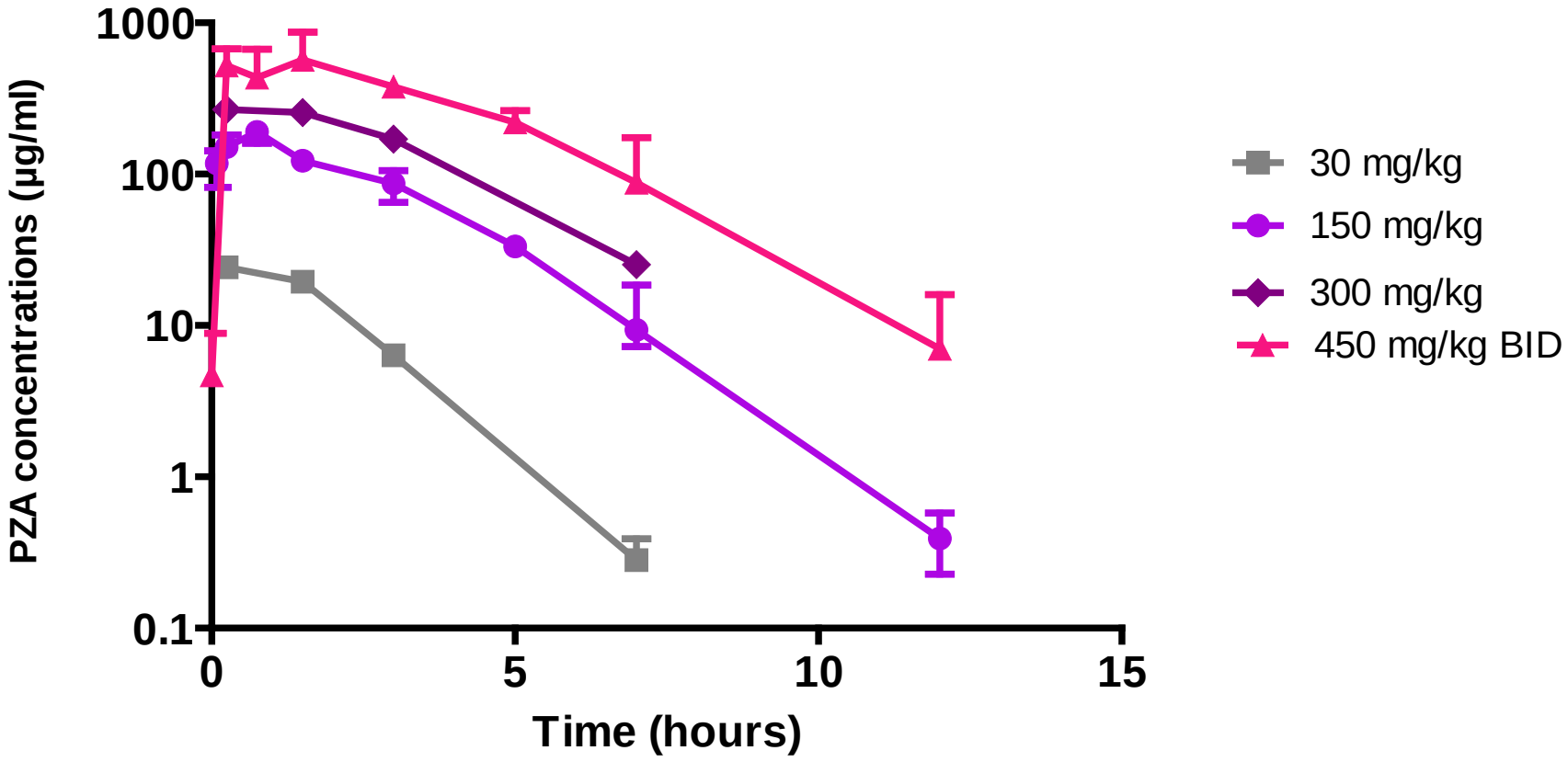
- Selection of PZA-resistant mutants ?
- Lack of dose-proportional PK in plasma? In epithelial lining fluid (ELF)?
- Lack of penetration into caseous lesions?
- Lack of sufficiently acidic conditions in caseum?

Resistance?

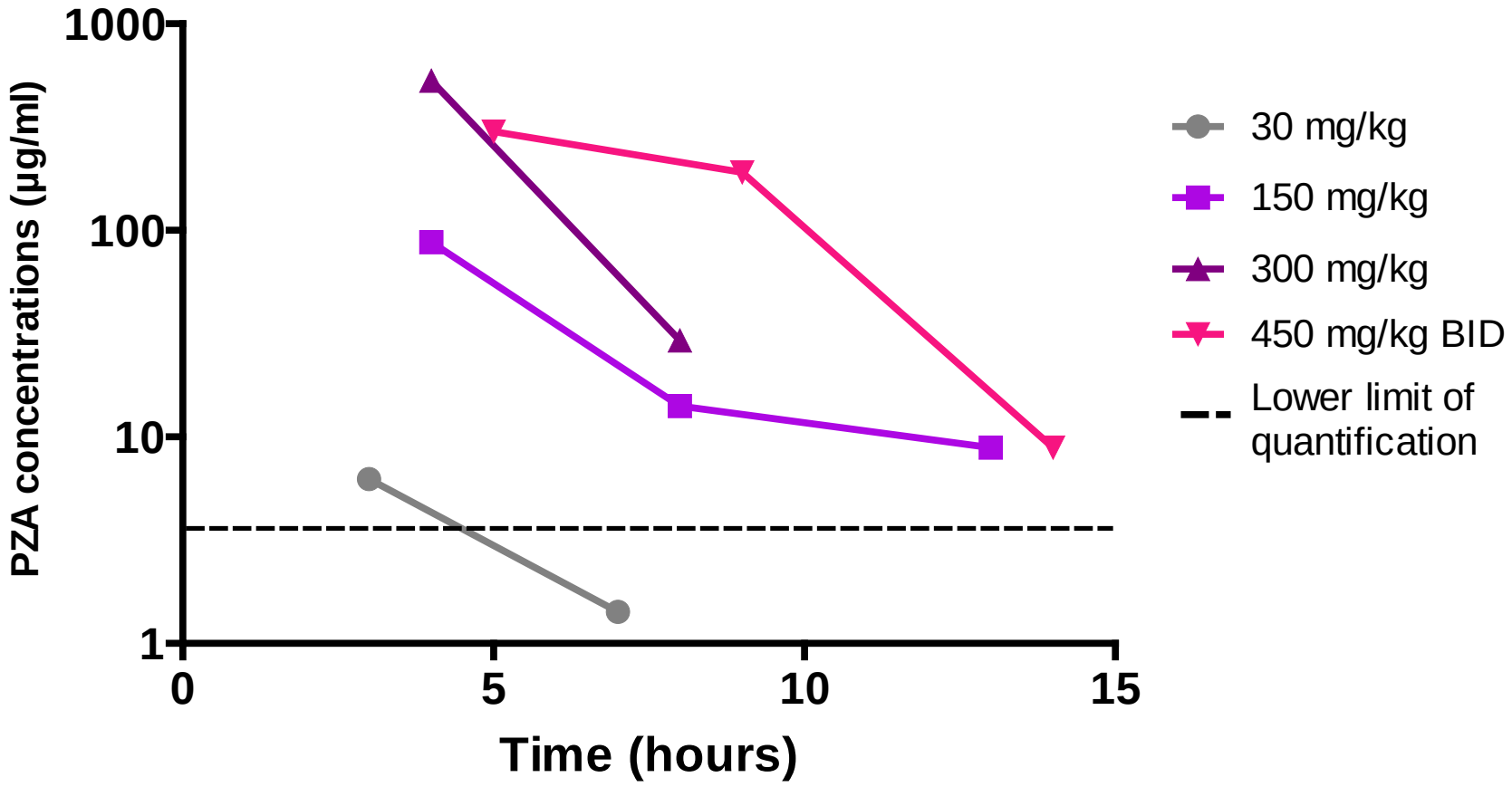
- "Breakthrough" of PZA-resistant mutants was not found in the outliers but in mice where PZA had bactericidal activity.



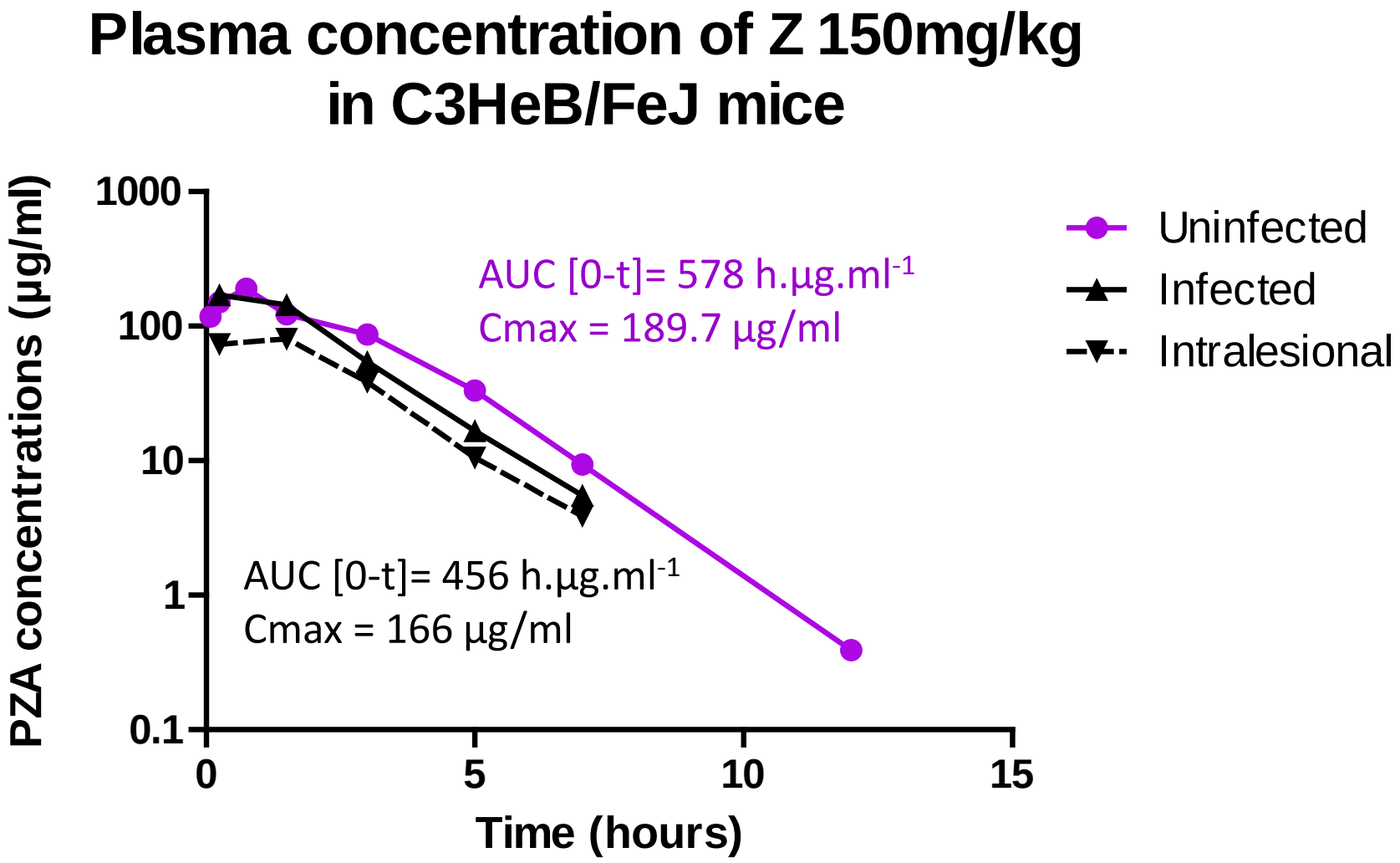
Dose-proportional PK in plasma?



Dose-proportional PK in ELF?



Penetration in lesions?



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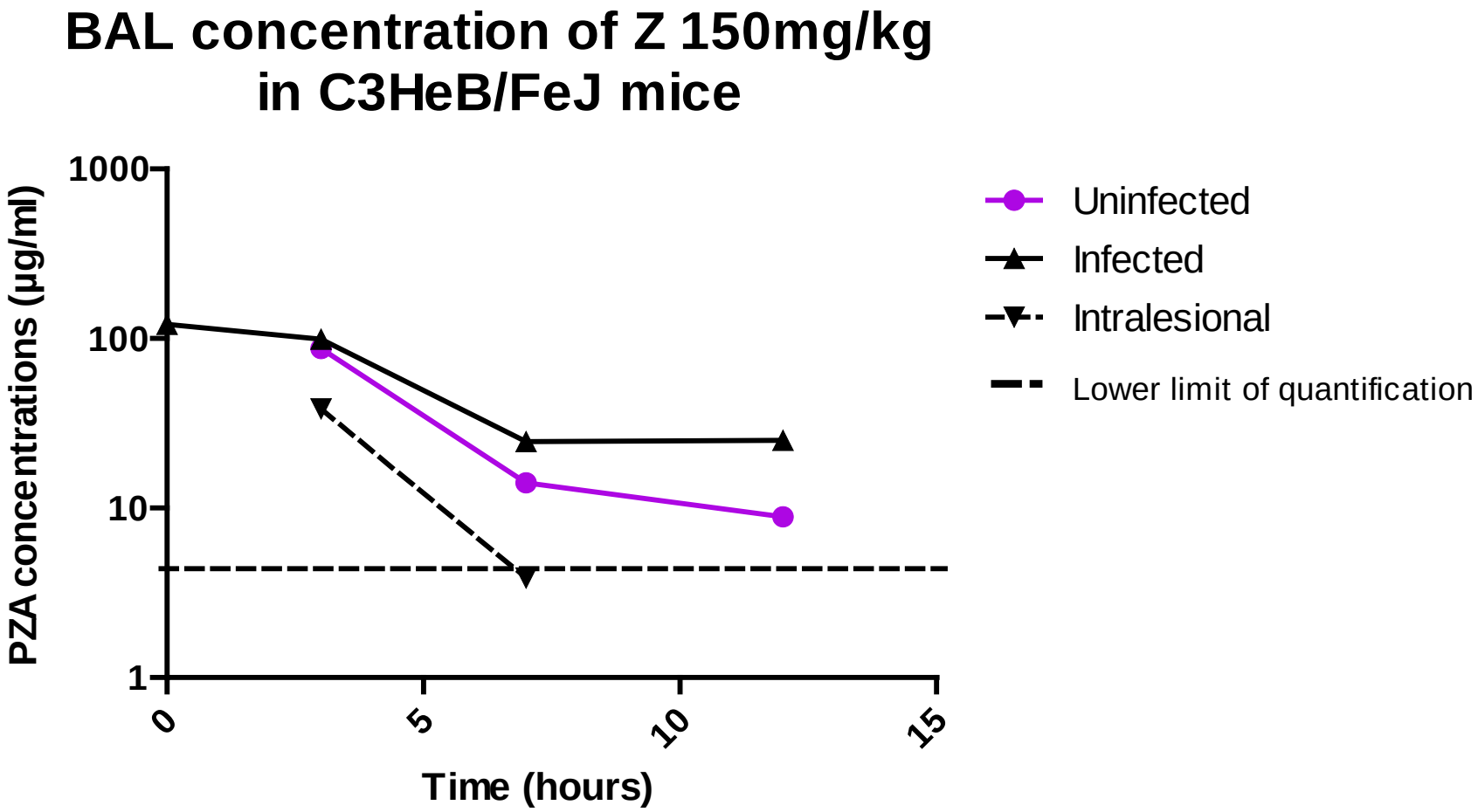
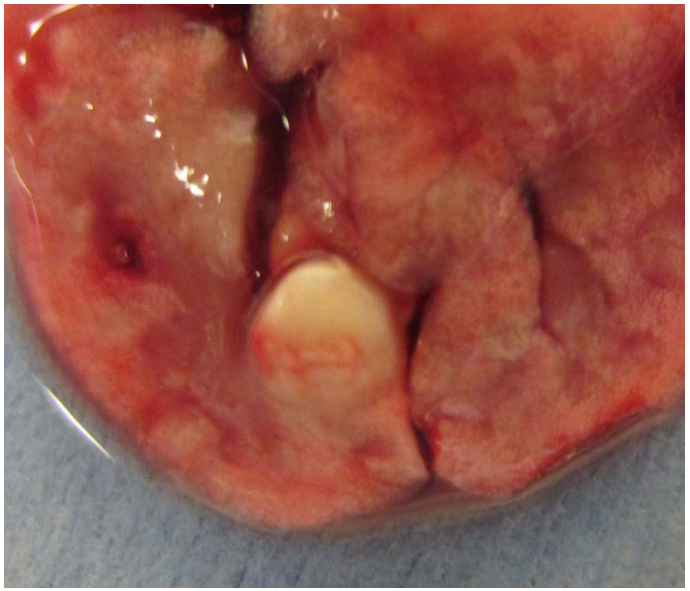
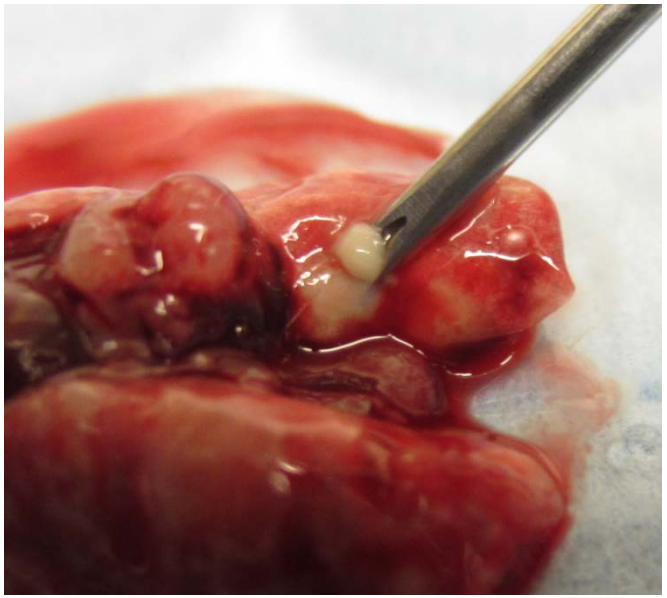


pH of caseum?

- 13 liquefied lesions tested with needle probe:
  - pH=7.39 ± 0.096 (range [7.19 - 7.54])





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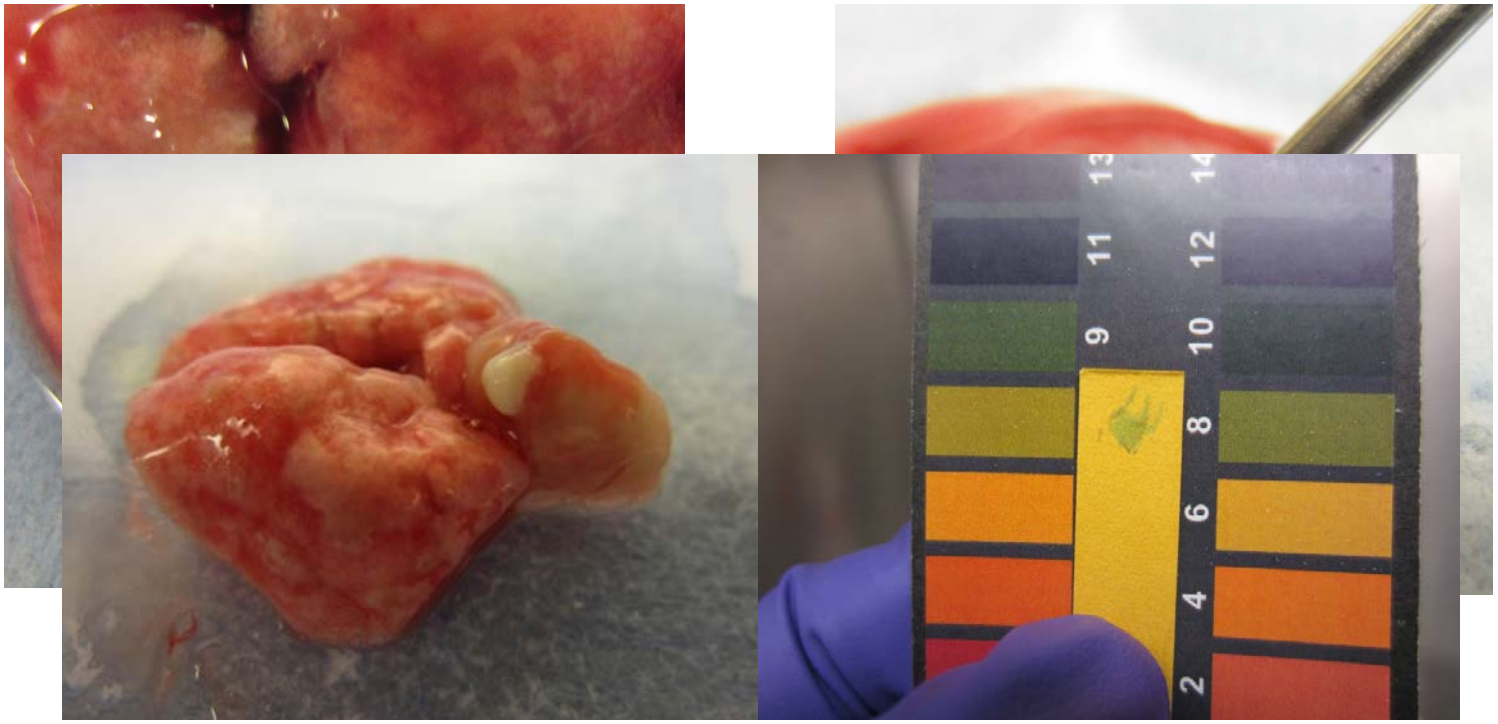

Conclusions

- PZA has lesion-dependent activity in a C3HeB/FeJ mouse model TB
- The pH of liquefied caseum in this model is not sufficiently acidic to enable PZA activity, even at drug exposures exceeding maximal human exposures
- Z most likely exerts its unique sterilizing activity inside activated macrophages, where pH can be ≤ 5, and not in acellular caseum, where the pH is neutral

Ongoing study

- Assess the contribution of PZA to the first-line regimen in C3HeB/FeJ mice

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