Pharmacokinetics and pharmacodynamics of pyrazinoic acid in murine models of tuberculosis

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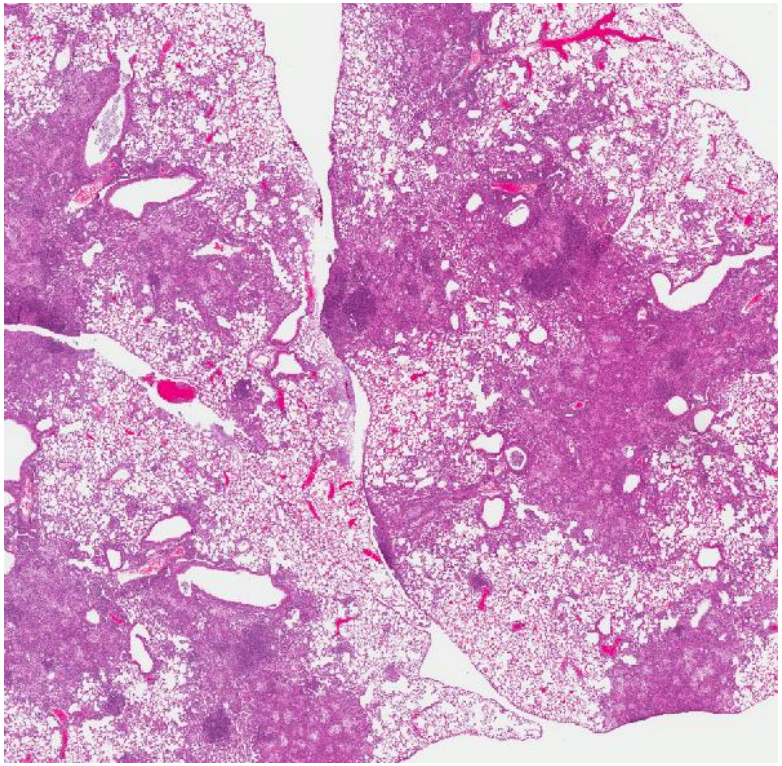
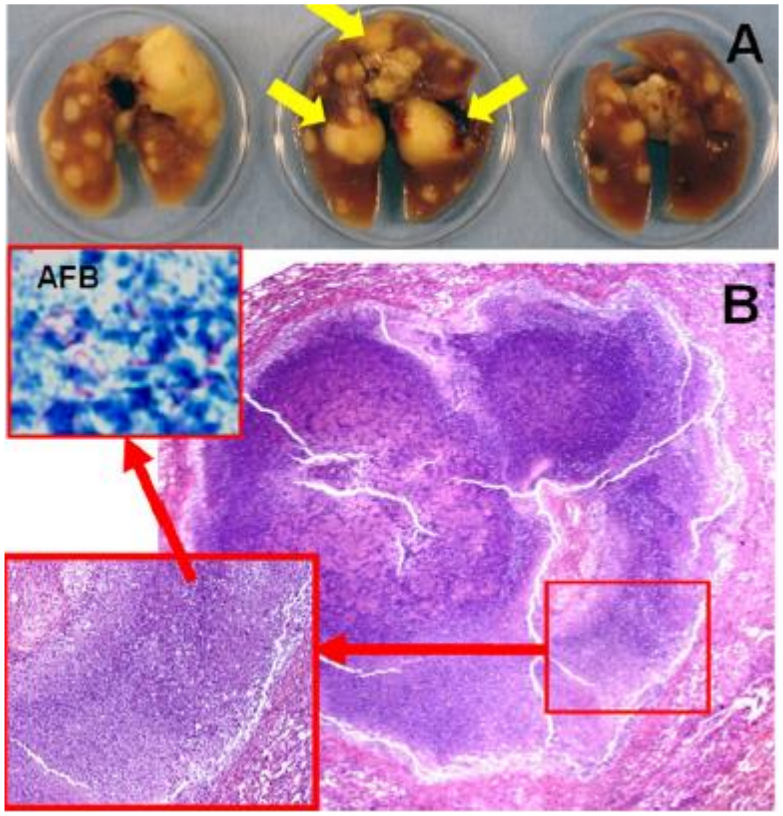
Introduction

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



Introduction

- Humans develop a wide variety of lesion types when infected with *M. tuberculosis.*
- 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

Pyrazinoic acid (POA)

- POA is the active metabolite of PZA, produced through the action of the bacterial pyrazinamidase, PncA
- POA is also produced during metabolism of PZA by humans and other mammals
- A past study attributed poor *in vivo* activity in acute mouse infection to poor oral bioavailability

Via et al, *ACS ID 2015*
Zhang et al, *IJTLD 2003*
Konno et al, *AJRCCM 1967*

Pyrazinoic acid (POA)

- Would systemic administration of POA be useful to treat TB caused by *pncA* mutants?
- Could POA concentrations produced by humans contribute to activity against *pncA* mutants?
- Is POA orally bioavailable?

- Objectives:
  - Describe the PK of POA in plasma, epithelial lining fluid (ELF) and lung lesions of C3HeB/FeJ mice after PZA administration (POA metabolite)
  - Describe the PK of POA in plasma and ELF after oral administration of POA (POA dosed)
  - Describe the activity of POA after oral administration

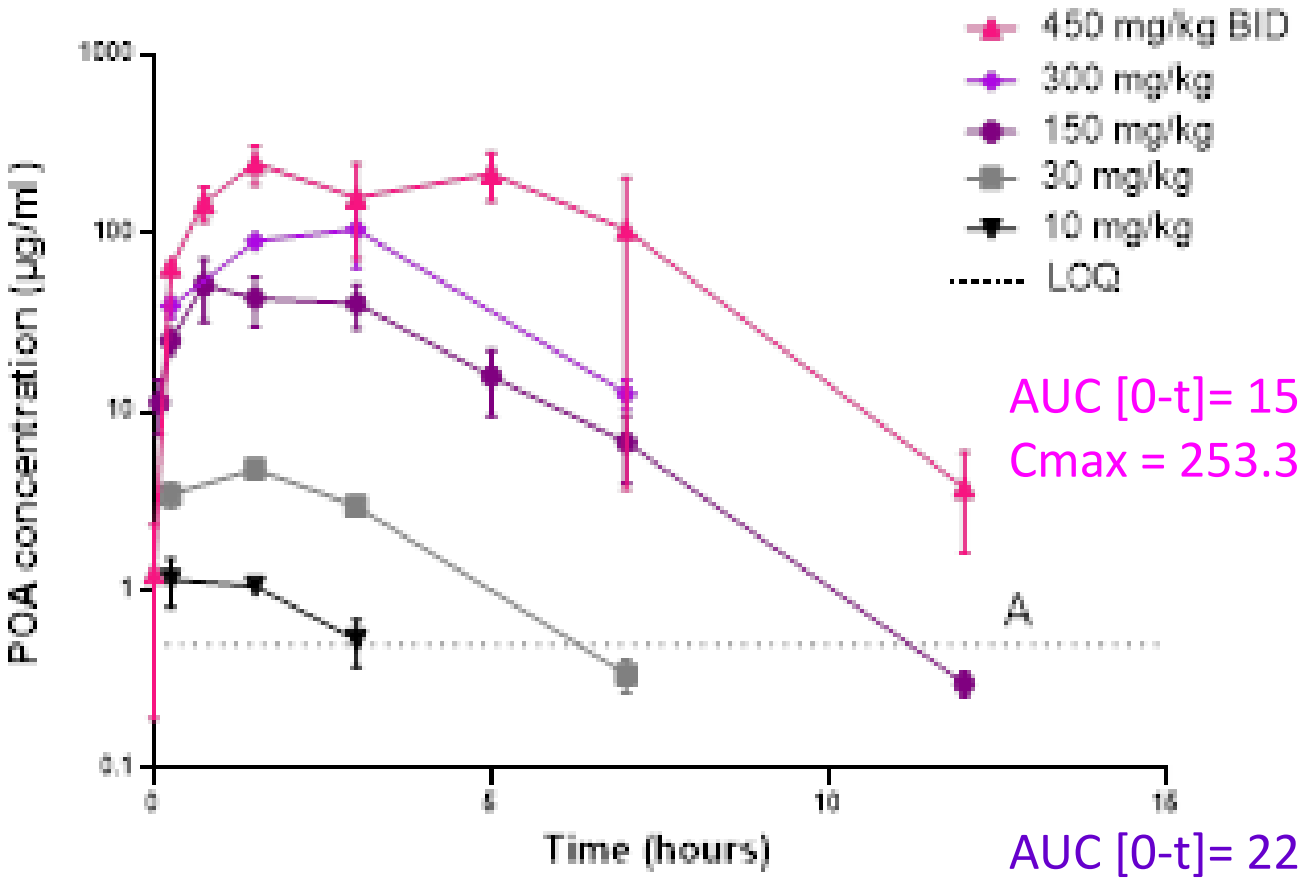
POA MIC against H37Rv

7H9 pH 6.8	POA concentrations µg/ml											
	0	30	45	60	90	120	180	240	360	480	720	960
H37Rv	+++	++	++	++	+	-	-	-	-	-	-	-

- 16-32µg/ml in 7H10 media at pH 5.8,
- 62-496 µg/ml at pH 6.5 in 7H9 or 7H11

Speirs et al, *AAC 1995*
Via et al, *ACS ID 2015*

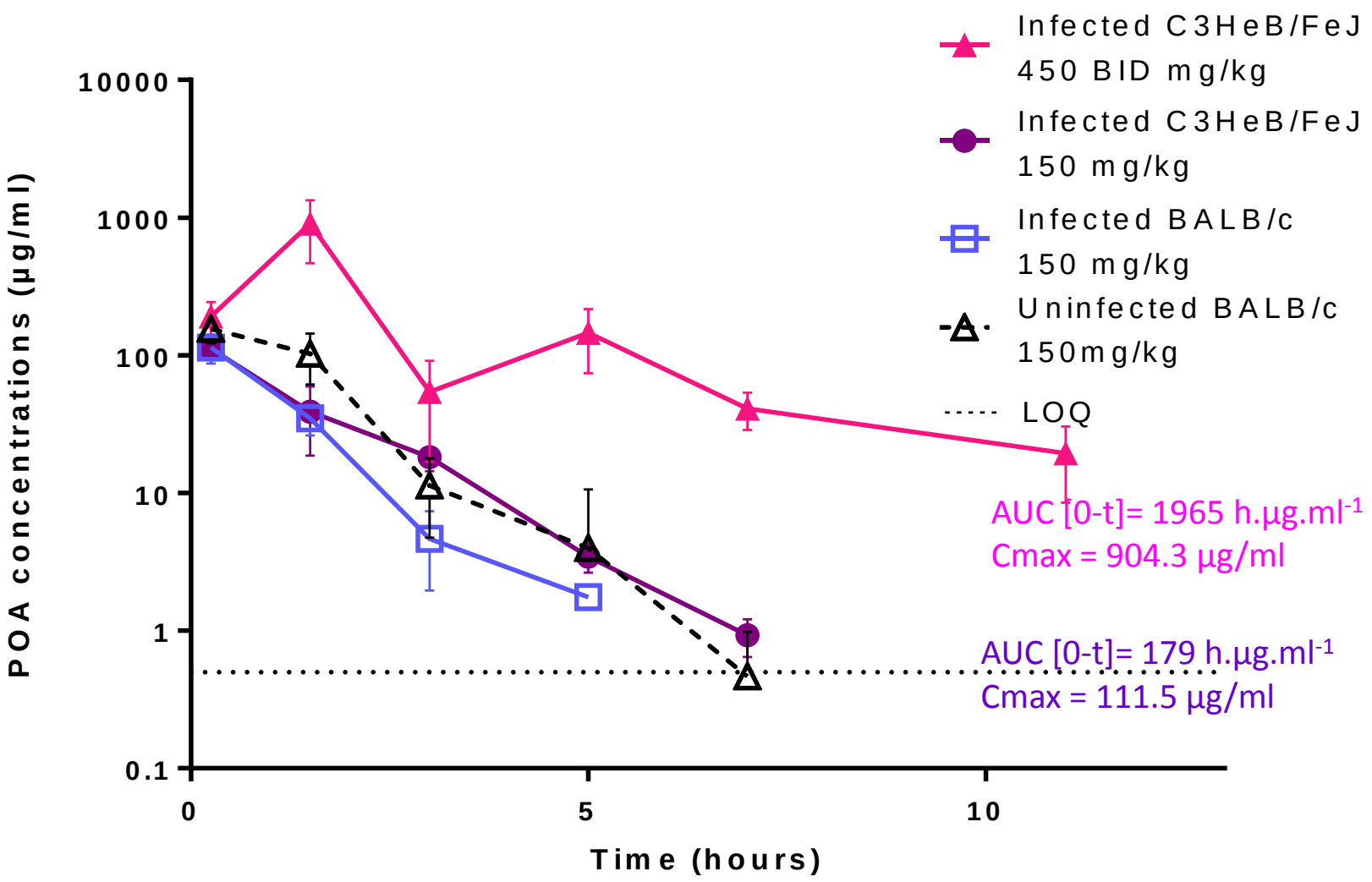
Dose-proportional PK in plasma after administration of PZA



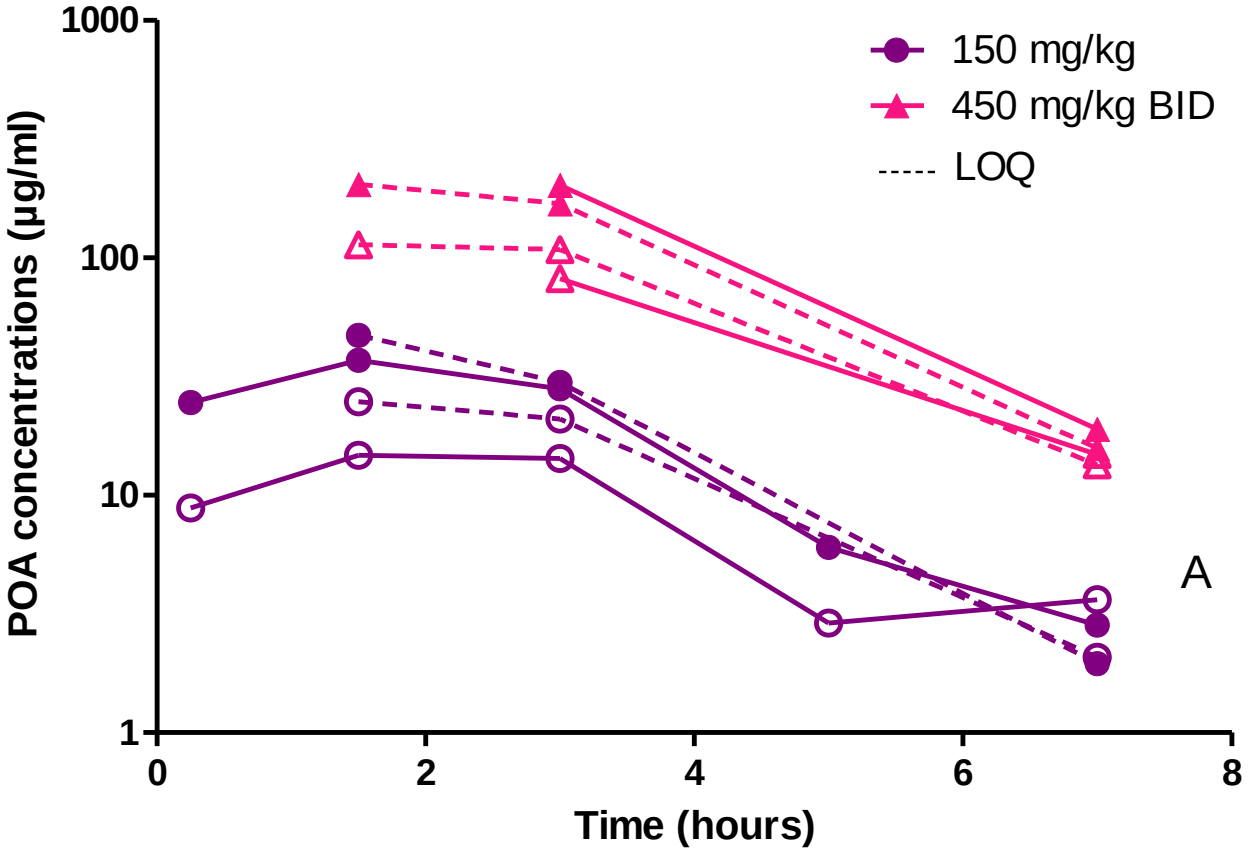
AUC [0-t]= 1511 h.µg.ml^{-1}
Cmax = 253.3 µg/ml

AUC [0-t]= 221 h.µg.ml^{-1}
Cmax = 52.6 µg/ml

Dose-proportional PK in plasma after administration of POA

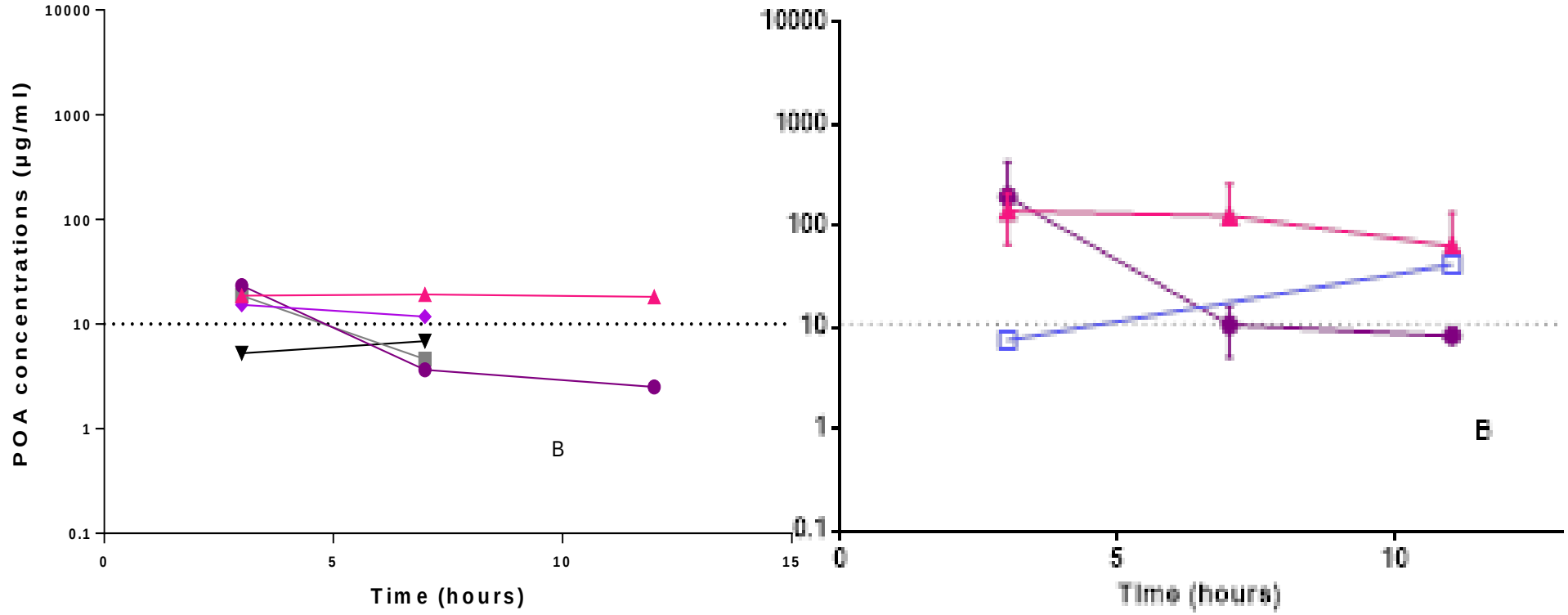


Dose-proportional PK in lesions after administration of PZA



Open symbols are intralesional concentrations
Solid and dotted lines are duplicates

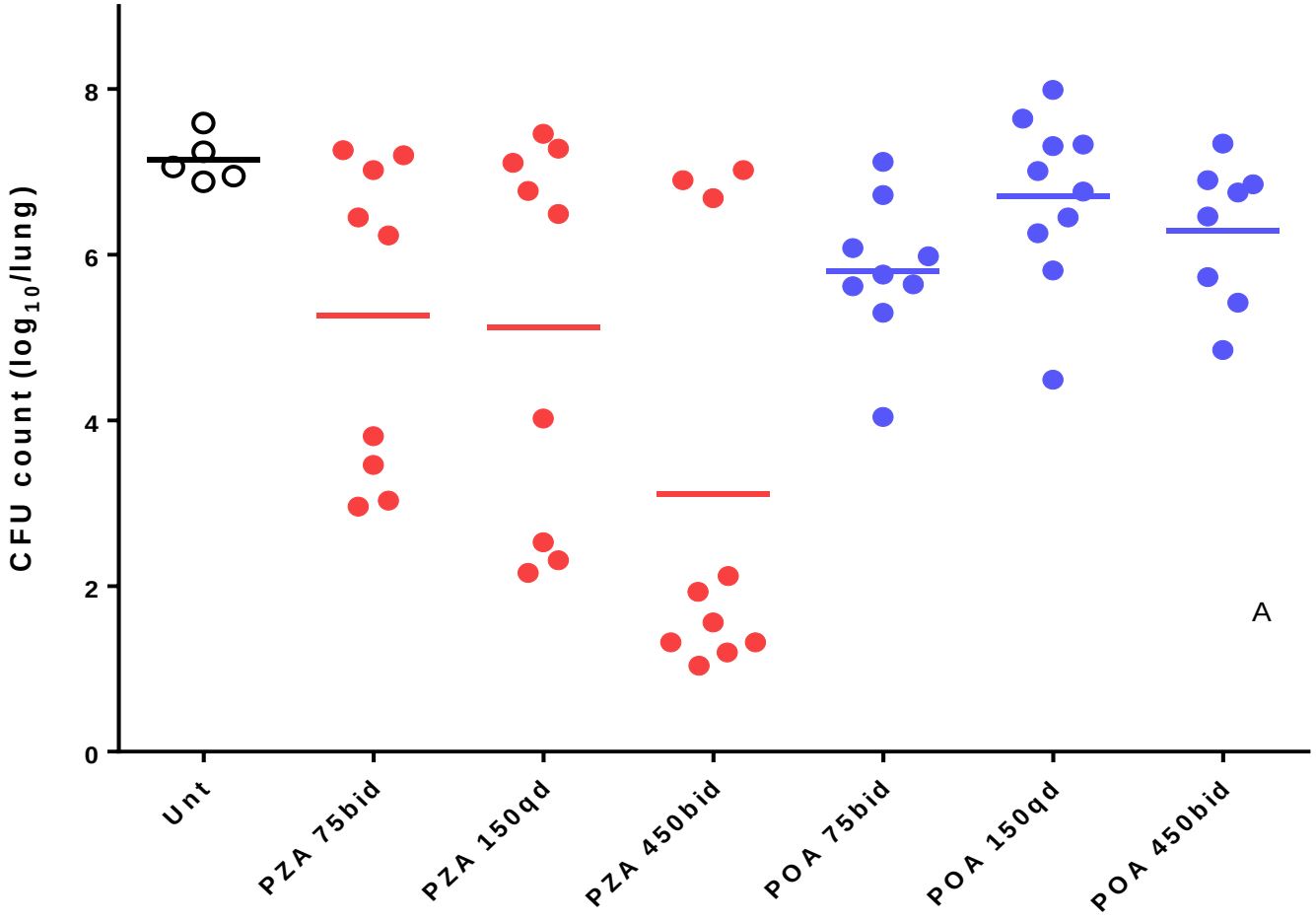
ELF PK of POA



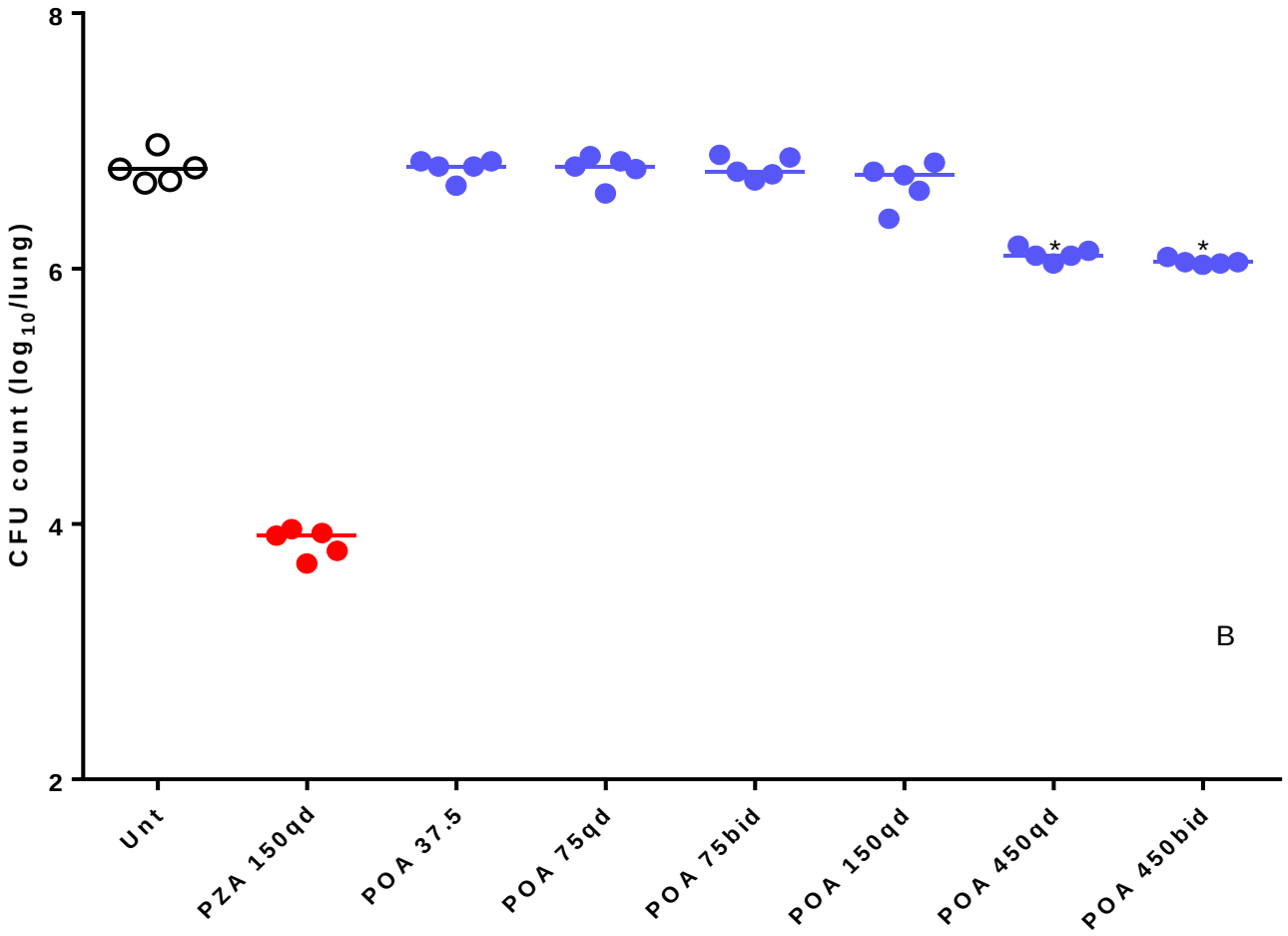
No dose-proportional PK in ELF

POA activity in C3HeB/FeJ mice

POA activity in C3HeB/FeJ mice



POA activity in BALB/c mice



Conclusion

- POA has good bioavailability, good dose proportional exposures in plasma, comparable to those produced by PZA administration
- Possibly a saturable secretion in ELF
- No dose proportional activity

Conclusion

- Future direction to improve POA efficacy:
  - more efficient delivery of POA into (or near to) bacilli at the site of infection
  - through new pro-drugs metabolized by *M. tuberculosis*,
  - novel vehicles to deliver a POA payload to infected macrophages,
  - intrapulmonary administration

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