State of the Art: TB drug pharmacokinetics at the site of disease

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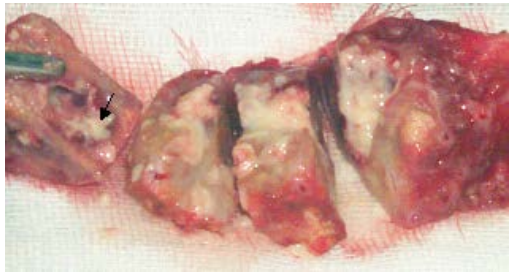
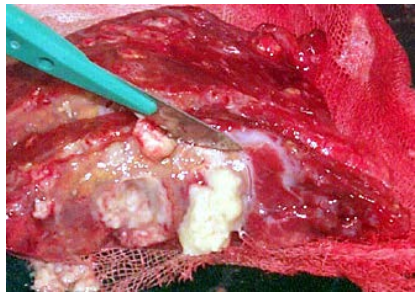
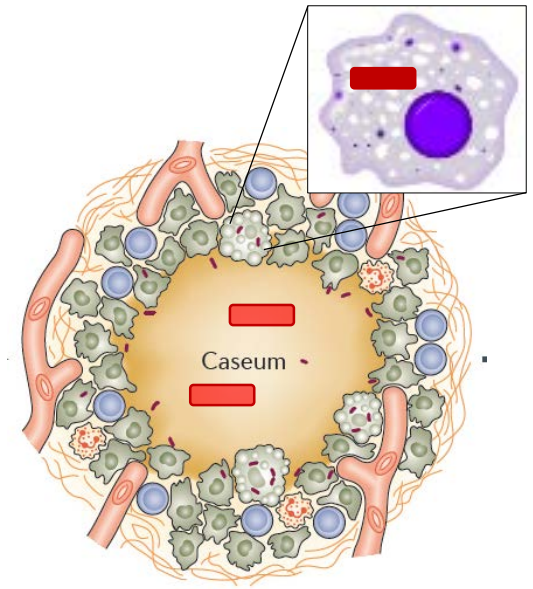
TB Steering Committee IMPAACT, June 2018

HYPOTHESIS

If TB drugs reach all bacterial populations at sufficient concentration in lesions, cure rates will increase and treatment duration will decrease

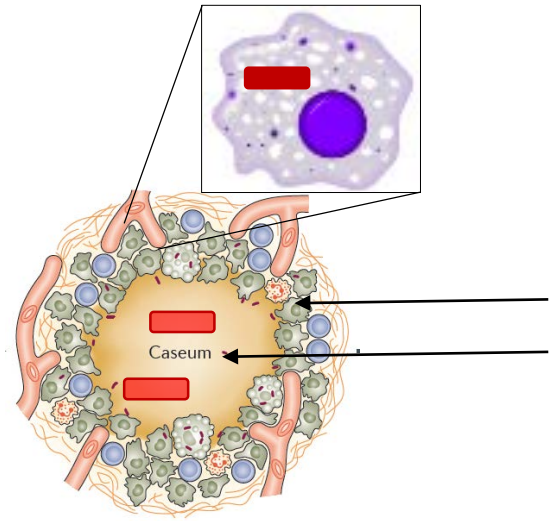






What do we need to know to test this hypothesis?

1. Measure the concentrations of all TB drugs in cellular and necrotic lesion compartments
2. Measure the activity of all TB drugs against Mtb populations residing in each compartment
3. Use lesion-centric efficacy read-outs in human-like animal models to correlate lesion PK, lesion PD and efficacy



1. How much drug reaches each compartment?

PK

2. How much drug does it take to kill the resident bugs?

PD

3. How does that translate into lesion sterilization in an in vivo model?

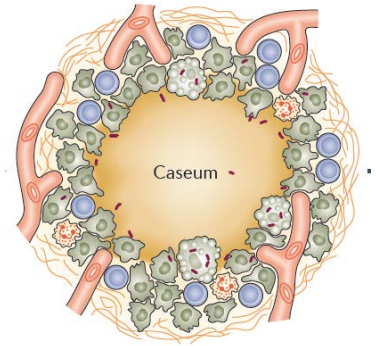
PK-PD

↓ log CFU?
Sterilization?

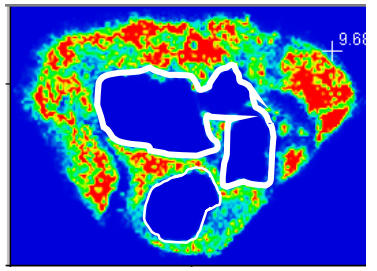
Lesion PK- PD methods

LC/MS/MS
Quantify

Homogenize
Extract



MALDI MS imaging



100%

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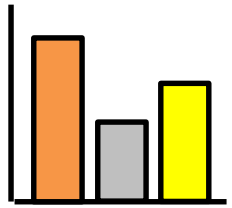
Laser capture microdissection

LC/MS/MS
Quantify

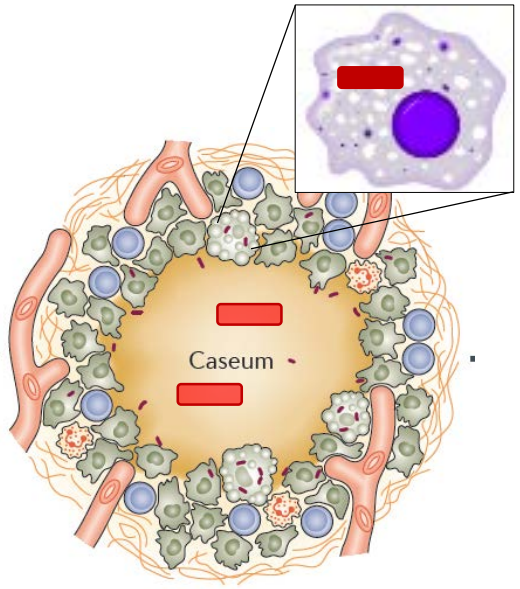


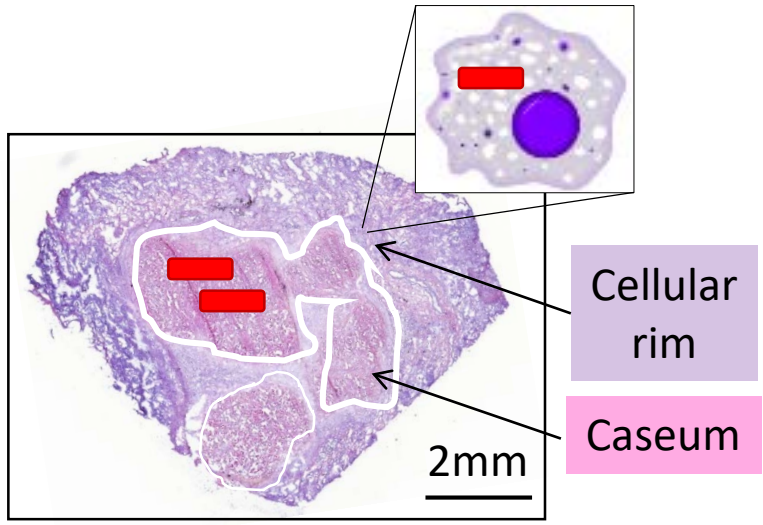
PK

PD

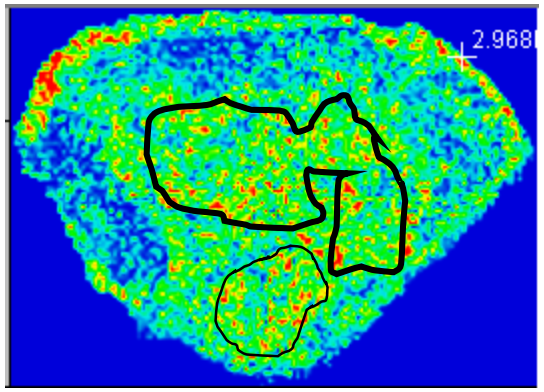
Drug activity in caseum

MALDI Imaging of multiple drugs in a single section

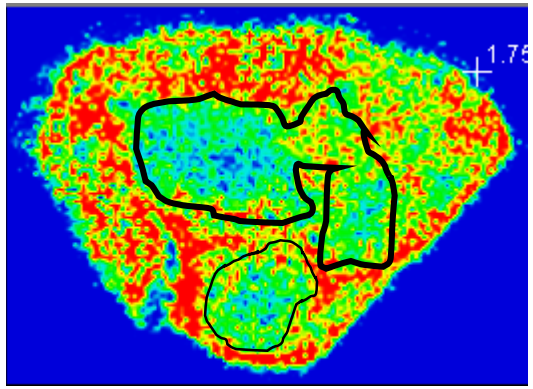




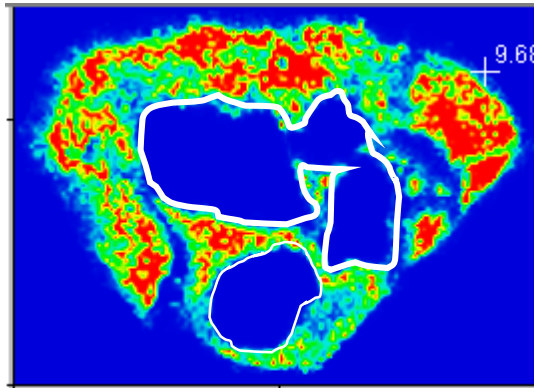
Pyrazinamide



Moxifloxacin



Clofazimine



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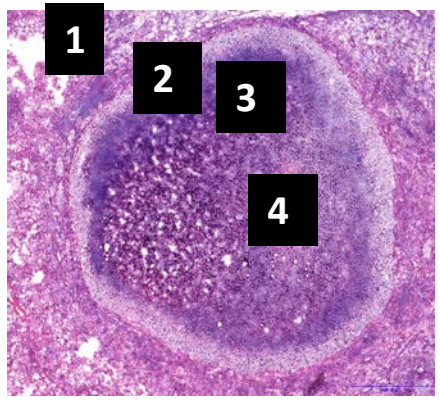
Limit of detection

Laser-capture microdissection / LCMS

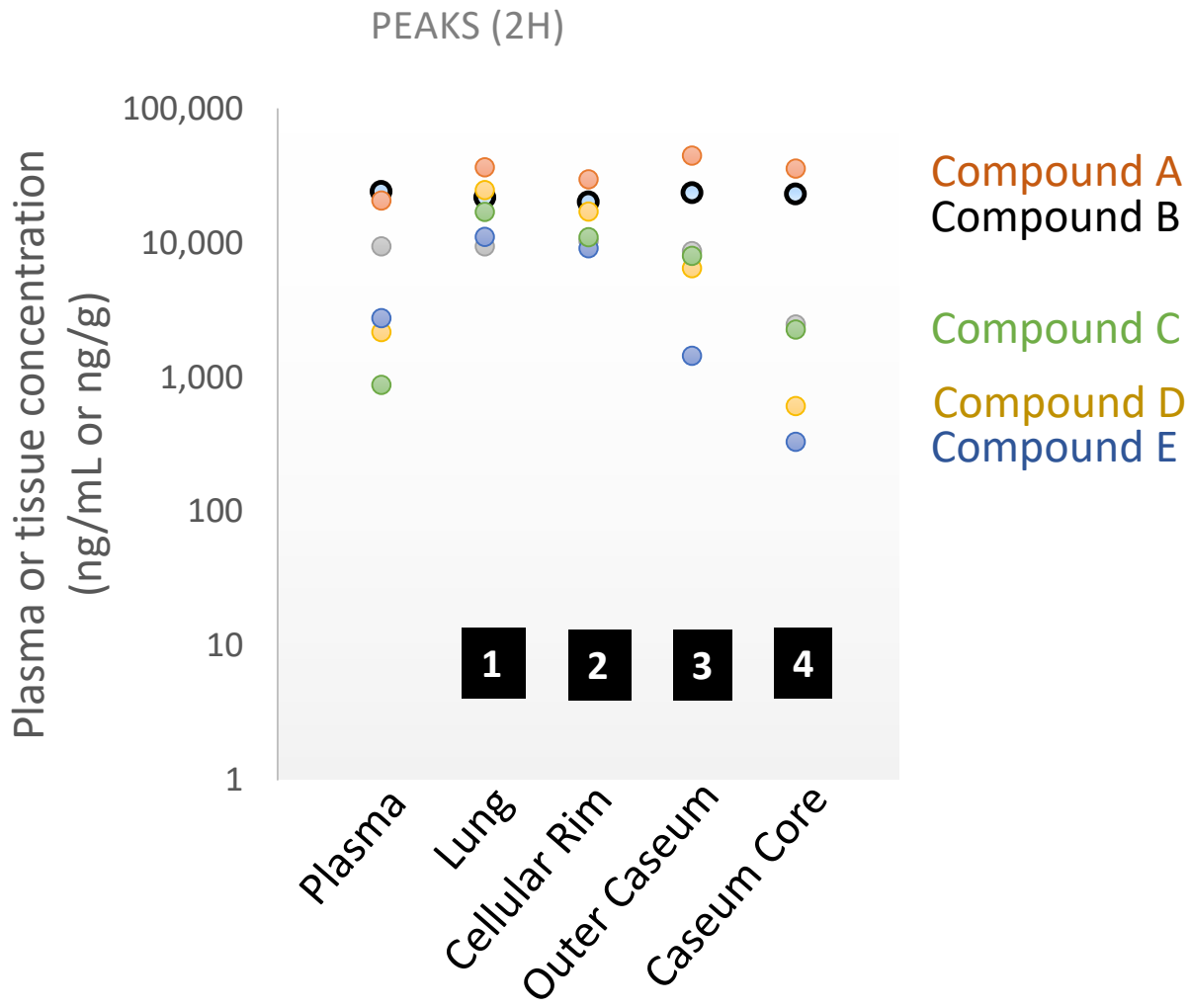


1 Uninvolved lung

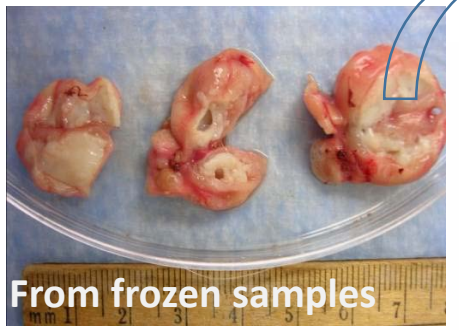
2 Cellular rim

3 Outer caseum ring

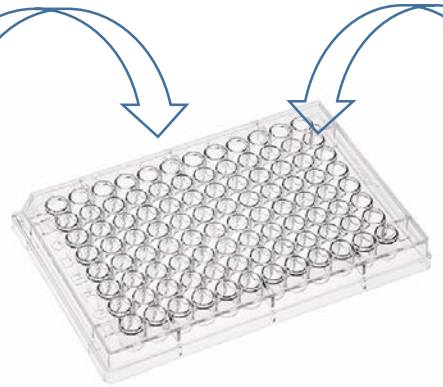
4 Inner caseum



An assay to measure the drug susceptibility of caseum Mtb



(NIH & PHRI rabbits)



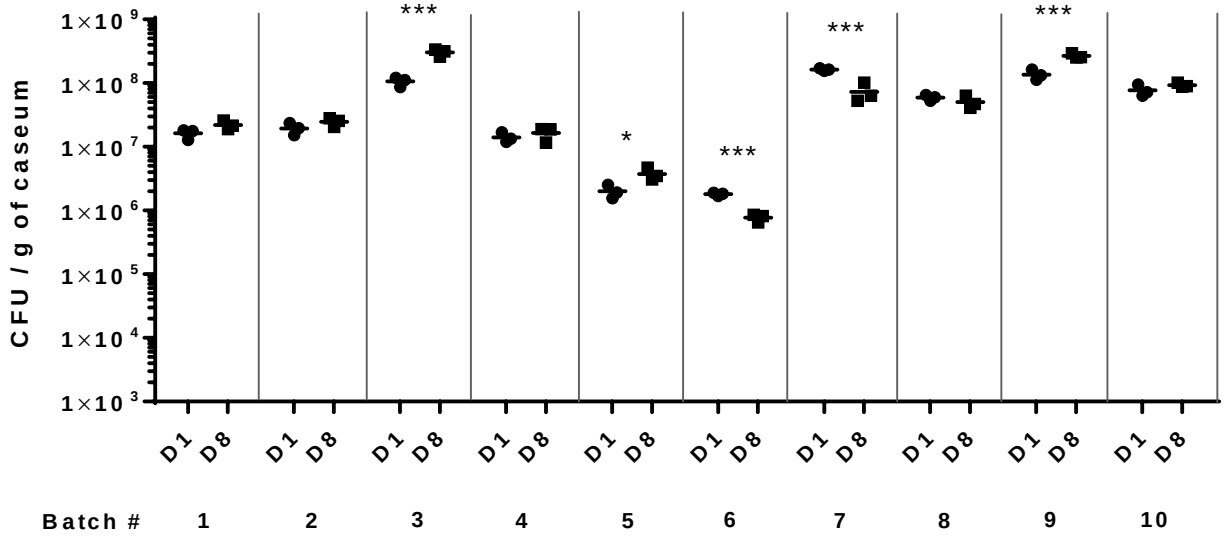
\+
DRUG

seal

7 days @ 37°C
Plate

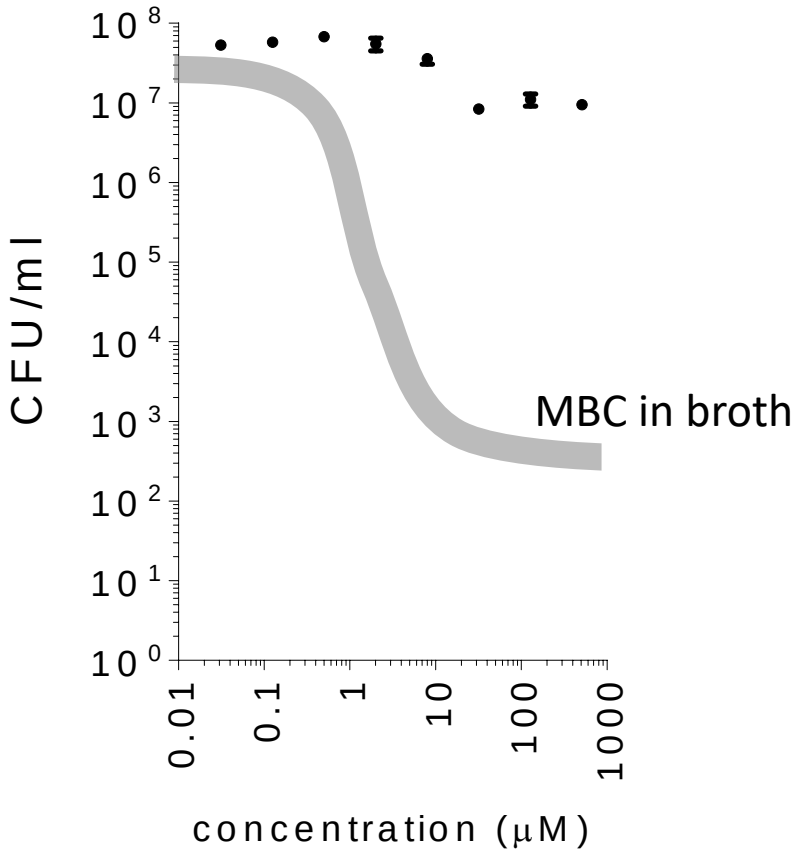
NO DRUG control

Growth kinetics in 10 caseum batches from D0 to D7

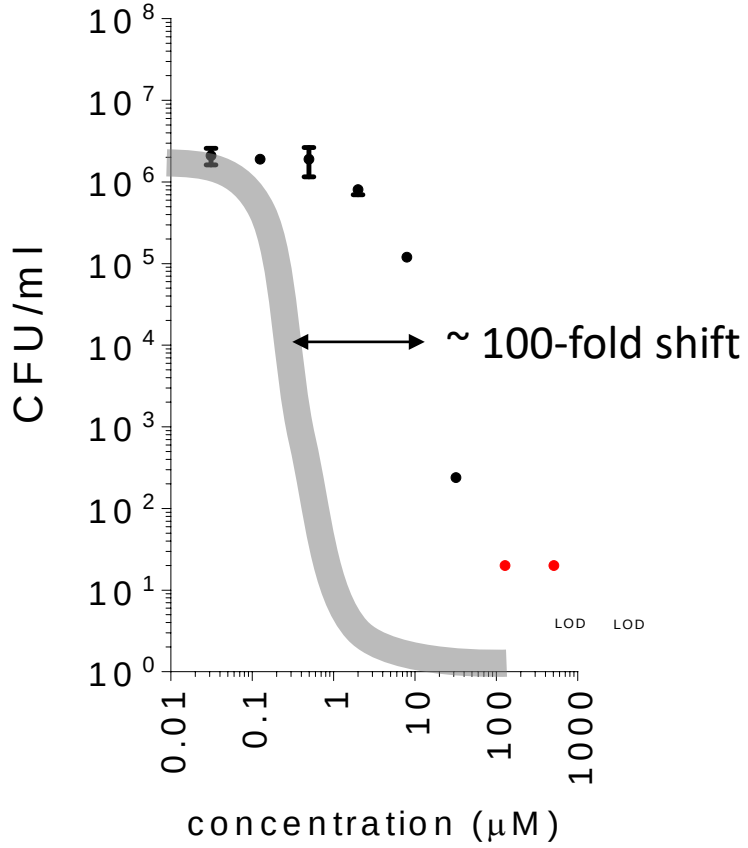


Caseum Mtb is highly drug tolerant

isoniazid

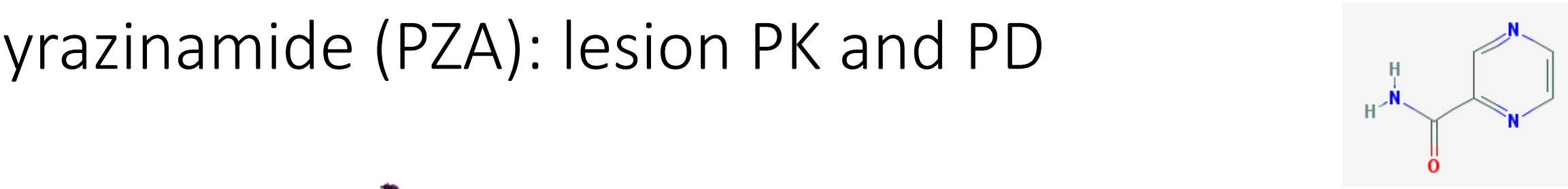


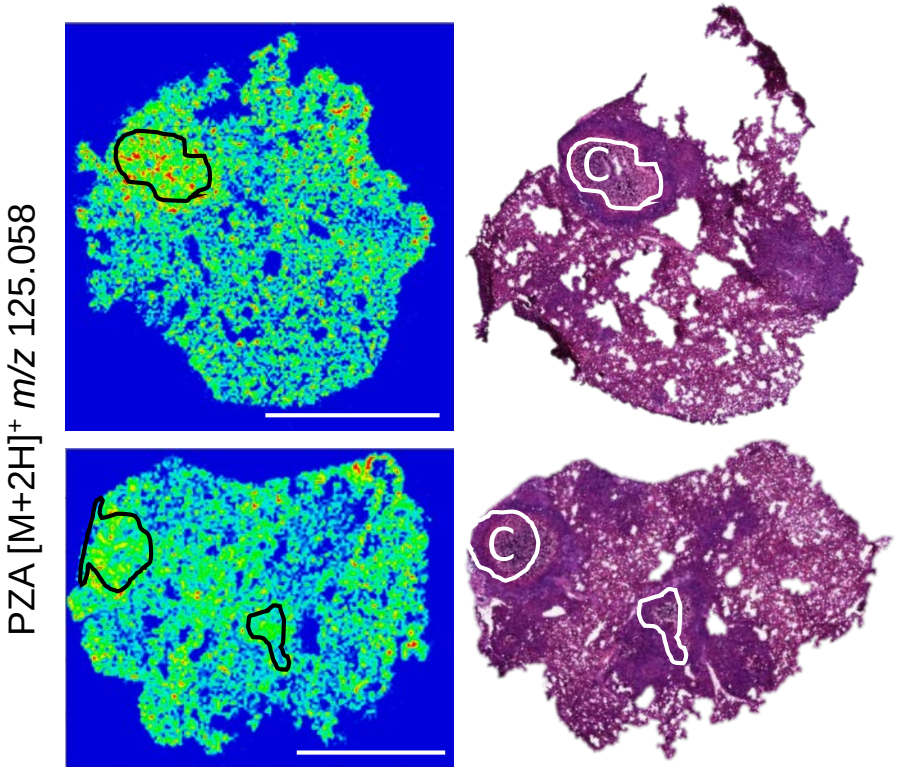
rifampicin



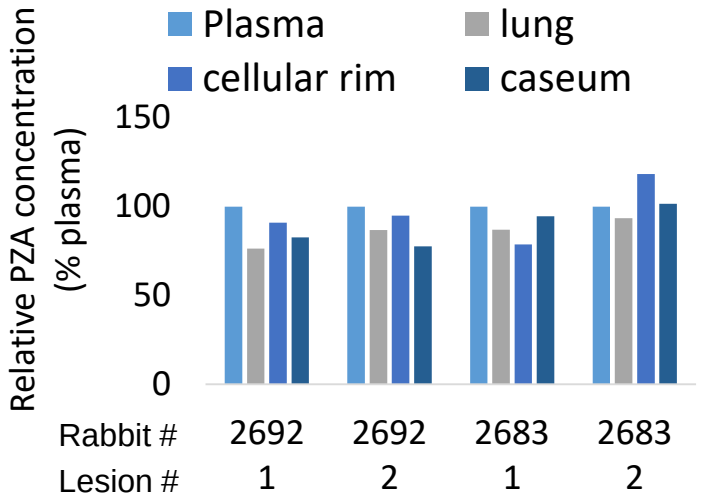
Antimicrob Agents Chemother. 2018 Jan 25;62(2)

Pyrazinamide (PZA): lesion PK and PD

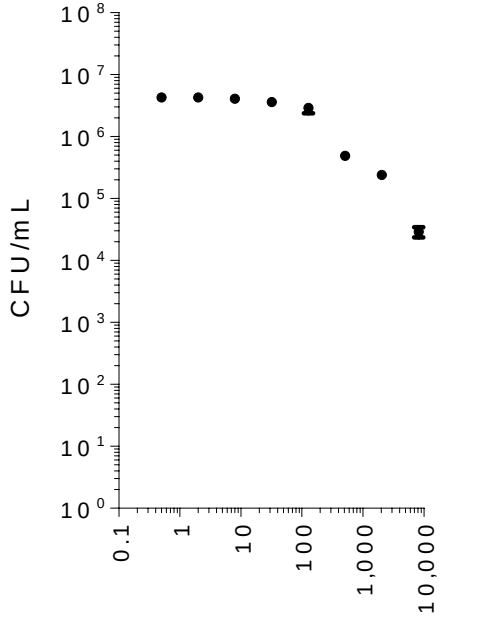




Laser-capture in lesions



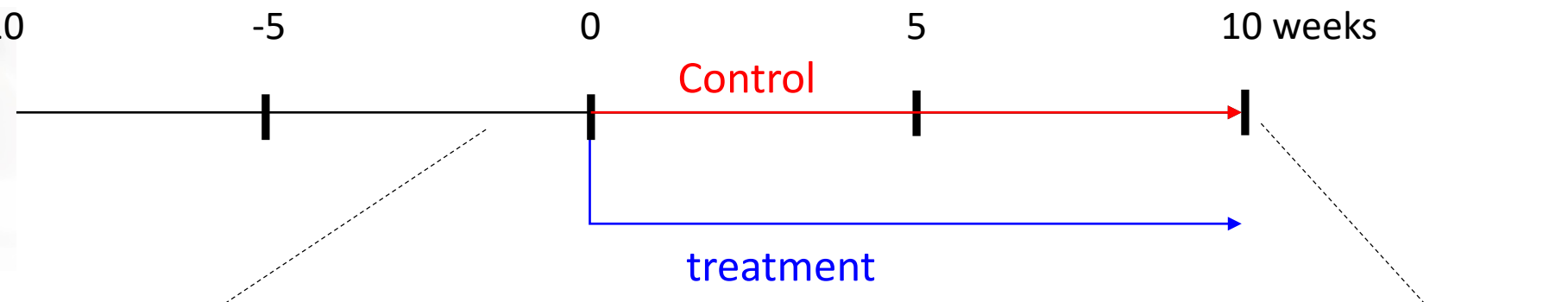
Cidal activity in caseum



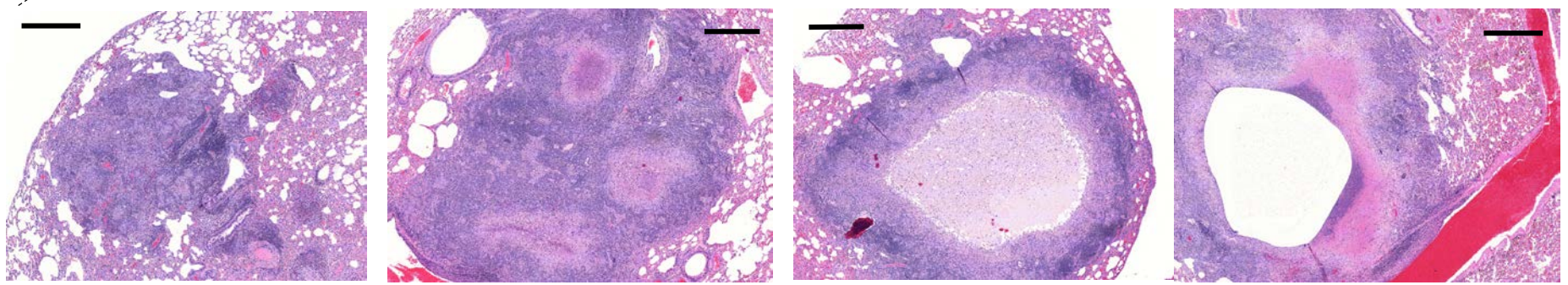
PZA penetrates all lesion compartments and kills Mtb in caseum

The rabbit model of active Tuberculosis

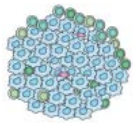
Infection
Mtb HN878 (Beijing)



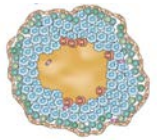
Scale bar: 500 μm



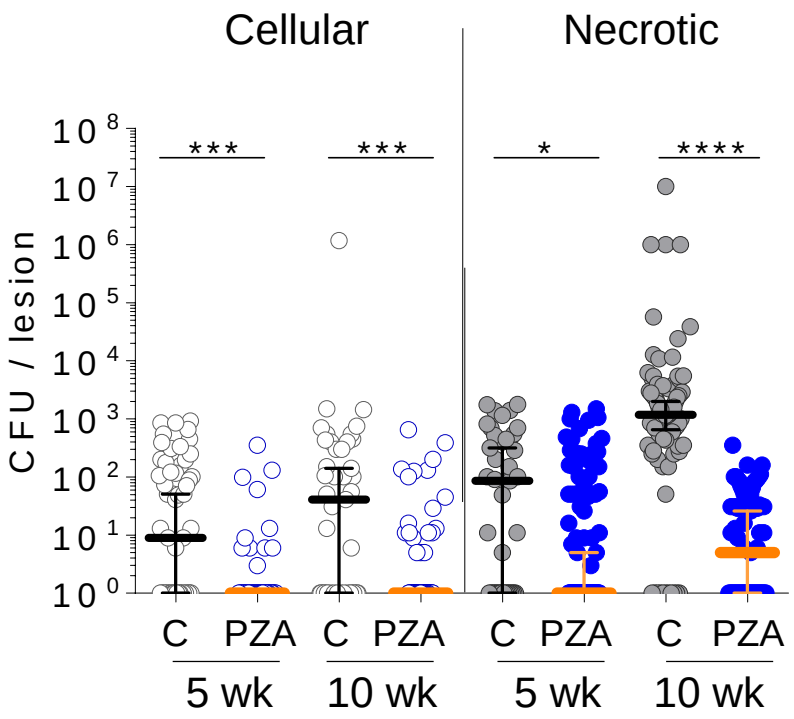
Cellular lesion

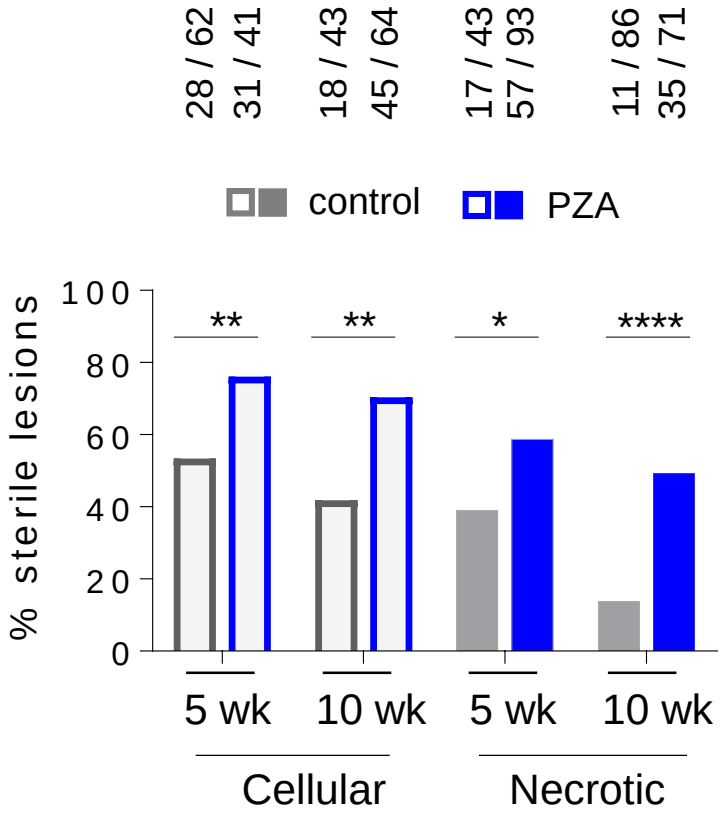


Necrotic (caseous) lesions



Pyrazinamide (PZA): in vivo efficacy in rabbits

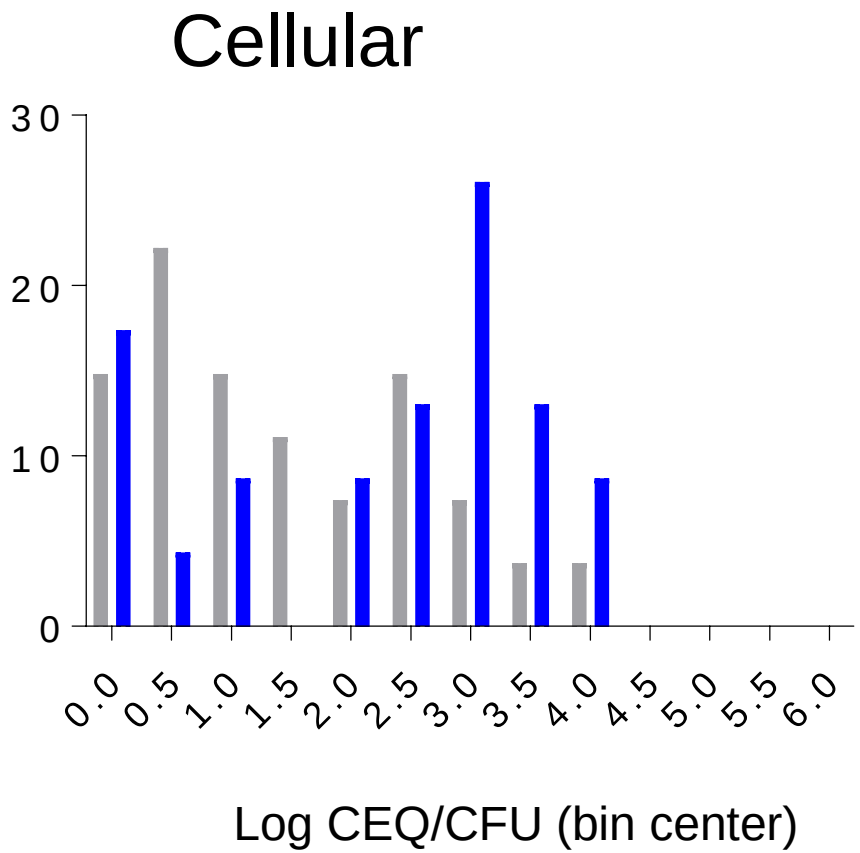


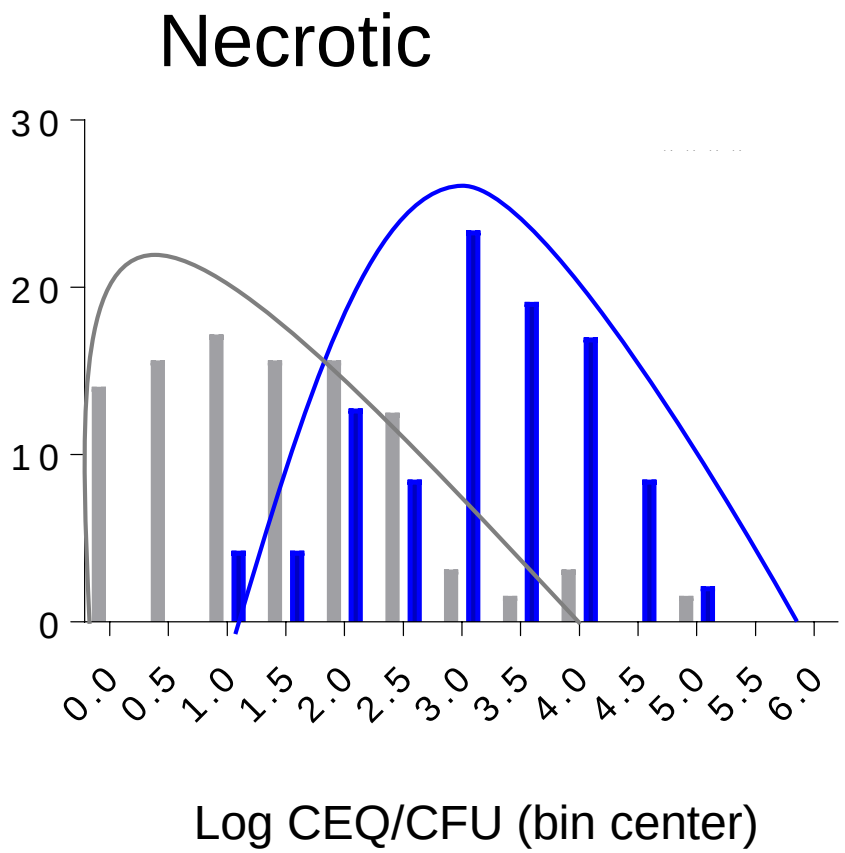


PZA sterilizes cellular and necrotic lesions in rabbits

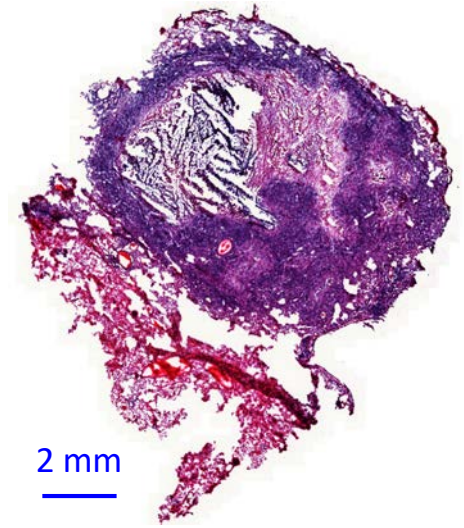
How much kill has happened in a lesion

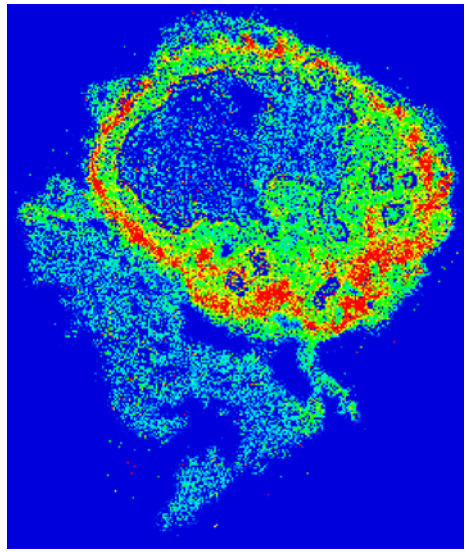
Landry
Blanc

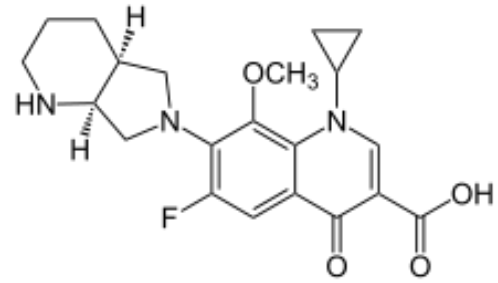




Moxifloxacin (MXF): lesion PK and PD







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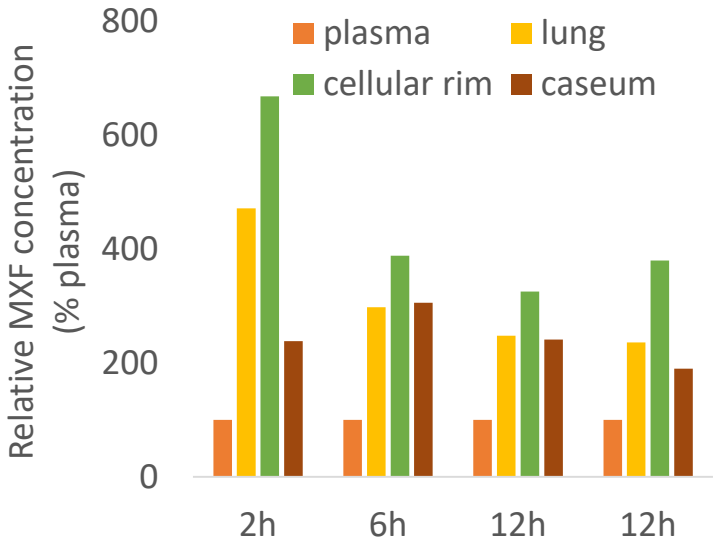
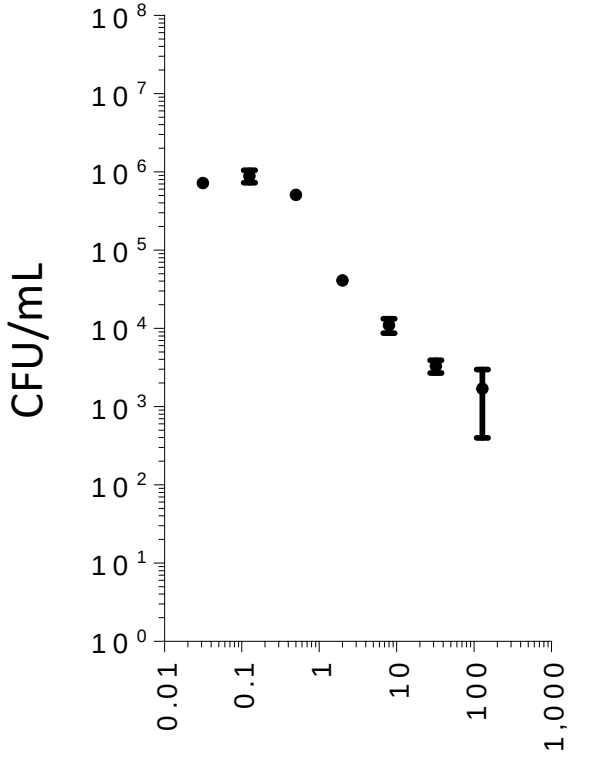
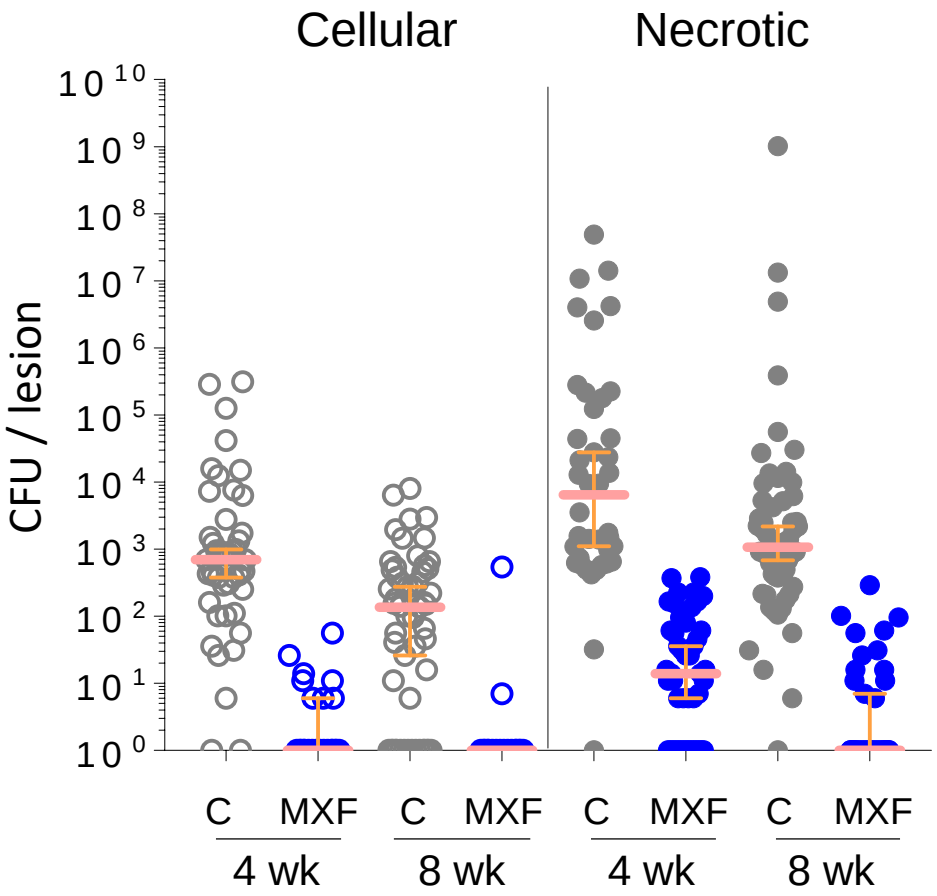
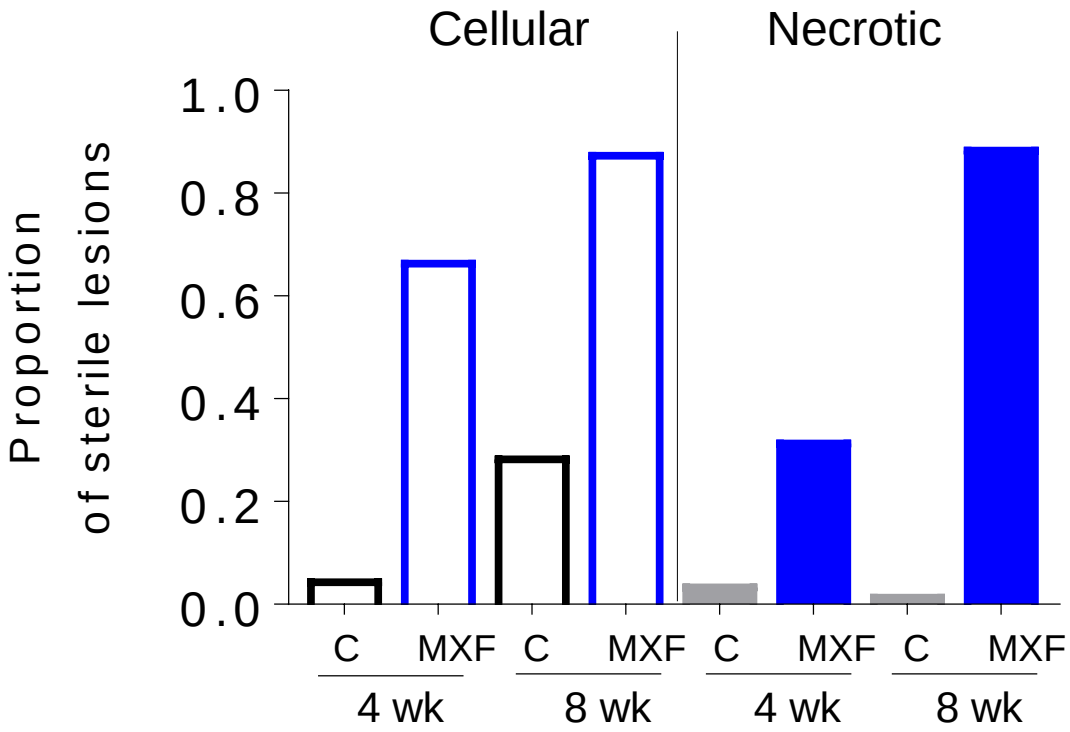


Cidal activity in caseum



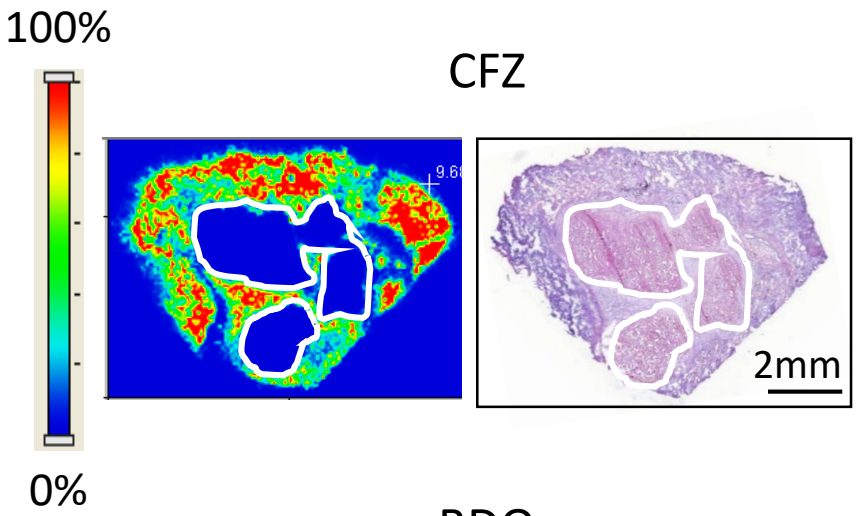
Moxifloxacin (MXF): in vivo efficacy

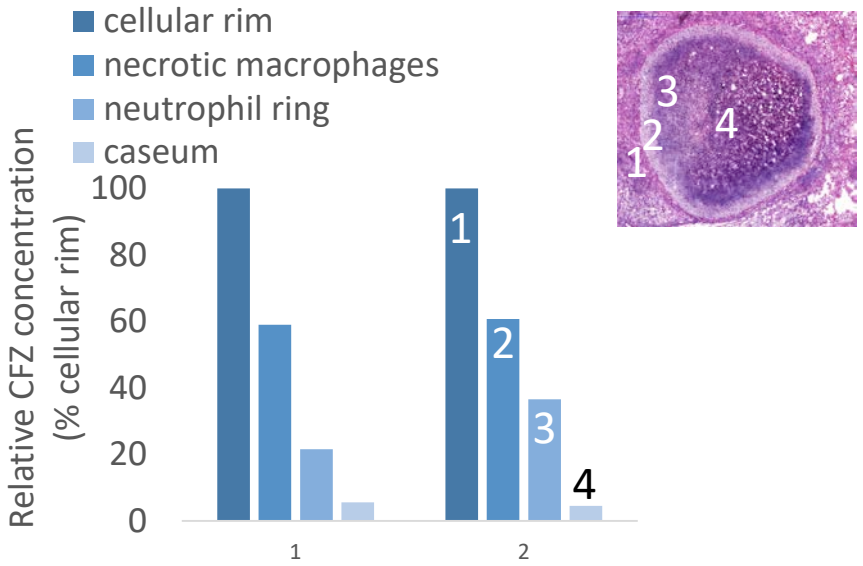


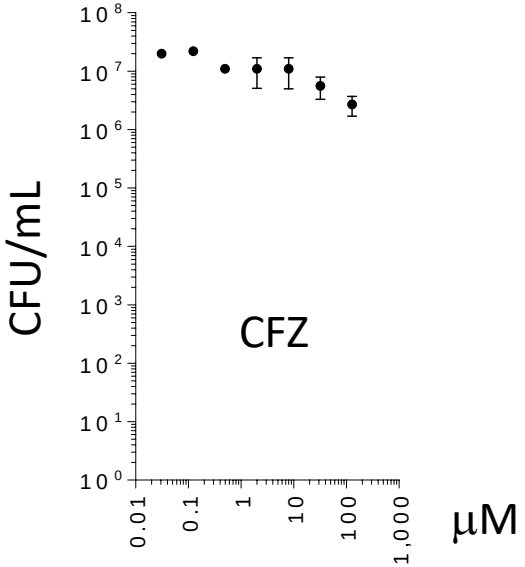


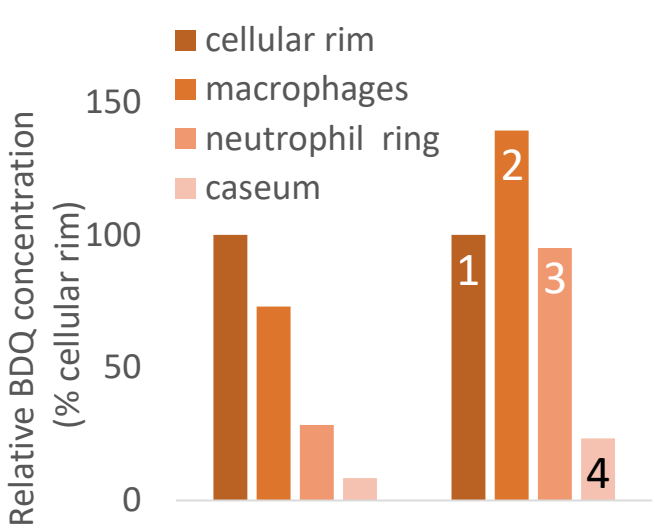
MXF sterilizes cellular and necrotic lesions in rabbits

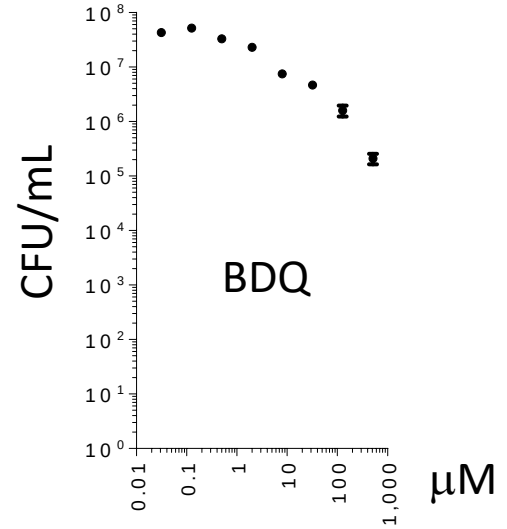
Clofazimine (CFZ) and Bedaquiline (BDQ)



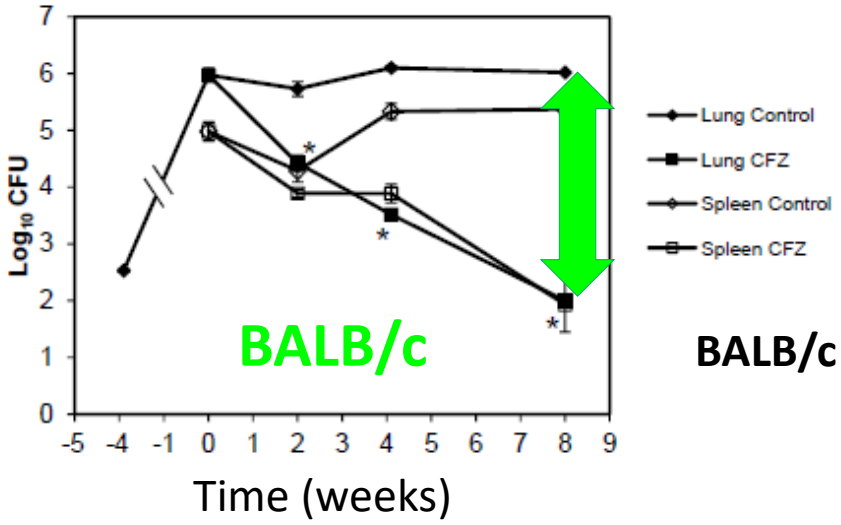




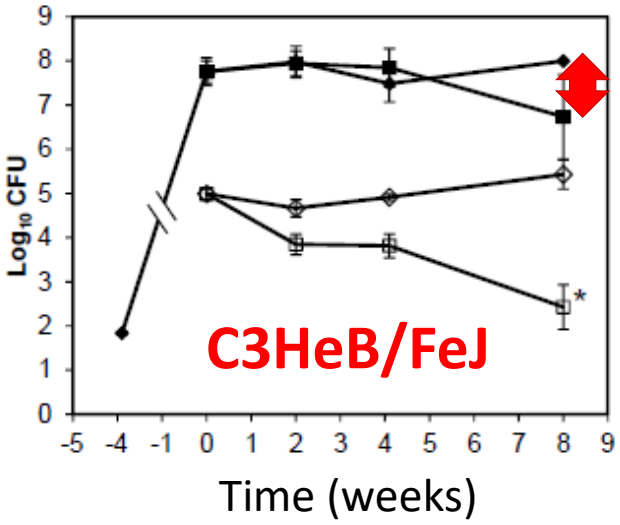


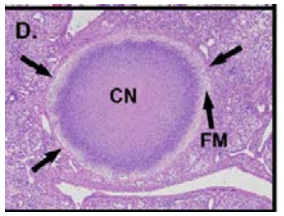


BDQ and CFZ: in vivo efficacy



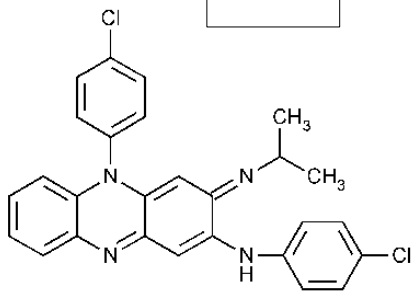
BALB/c

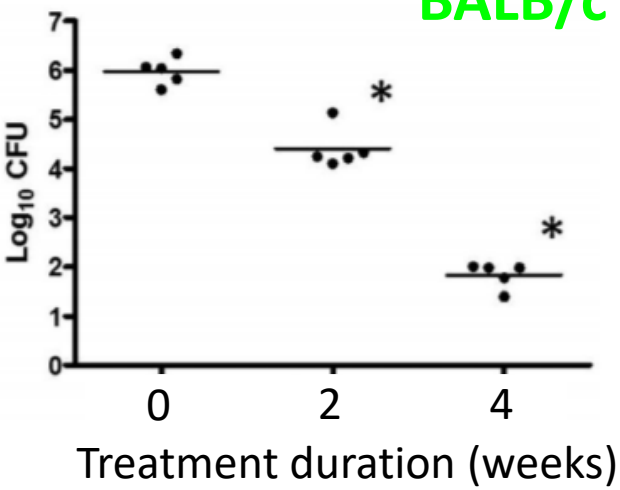


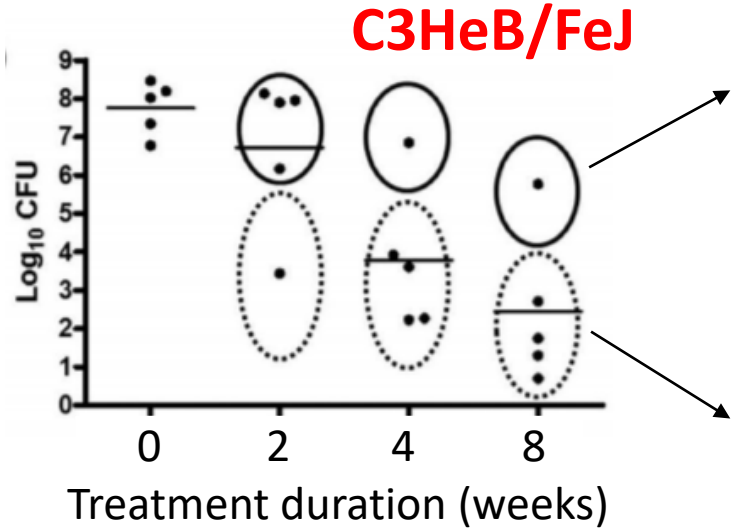


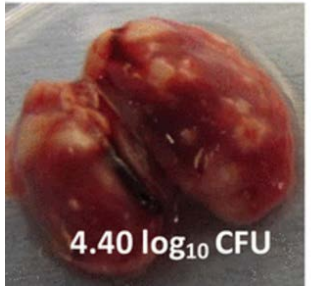
C3HeB/FeJ

CFZ

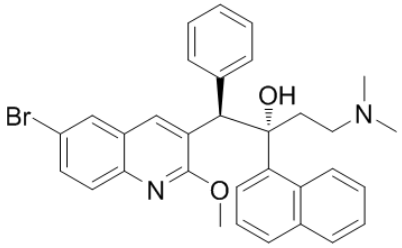




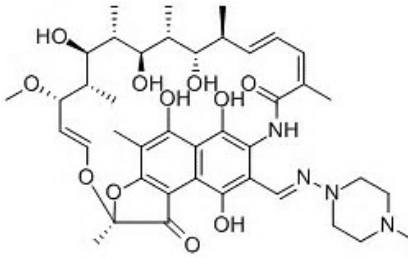


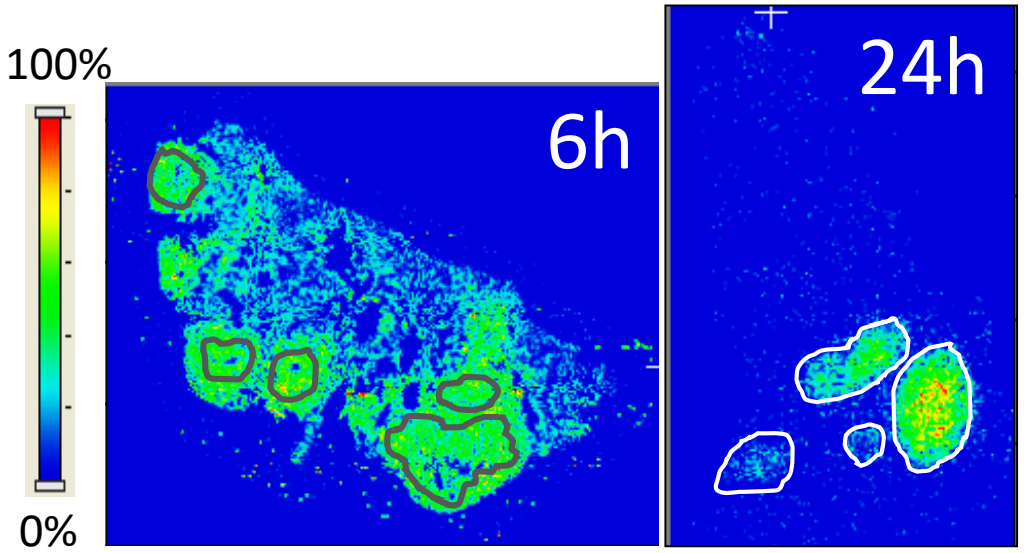


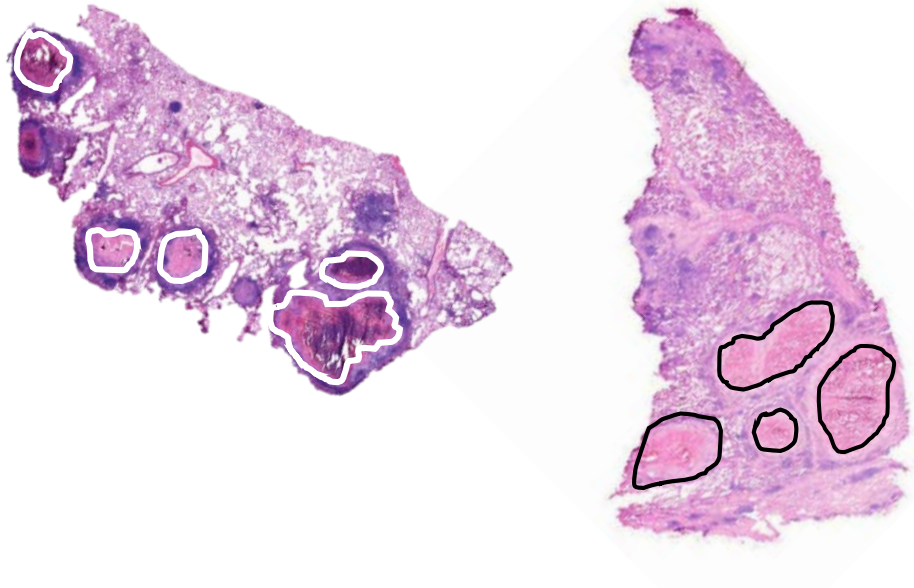
BDQ



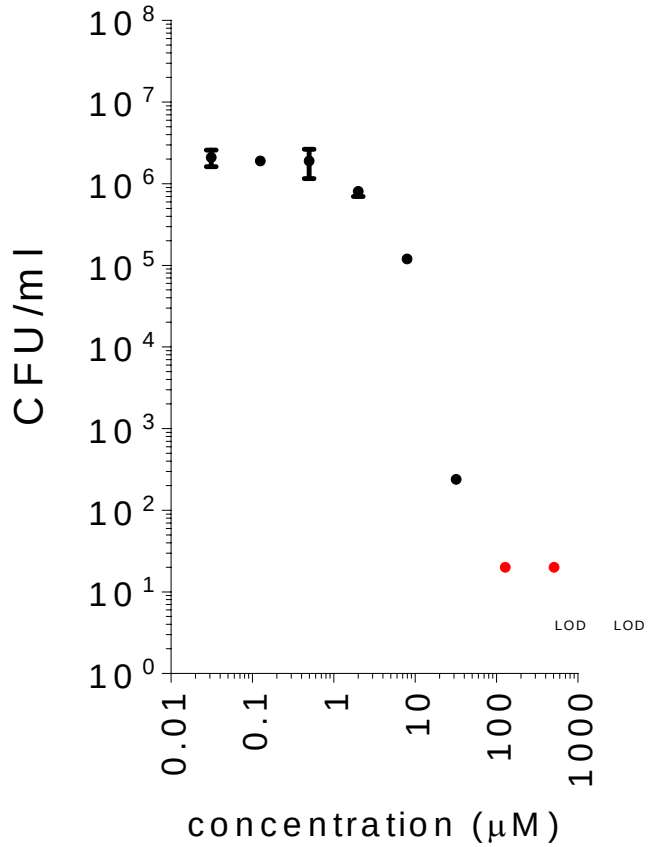
RIF accumulates in caseum… … and kills the resident bugs





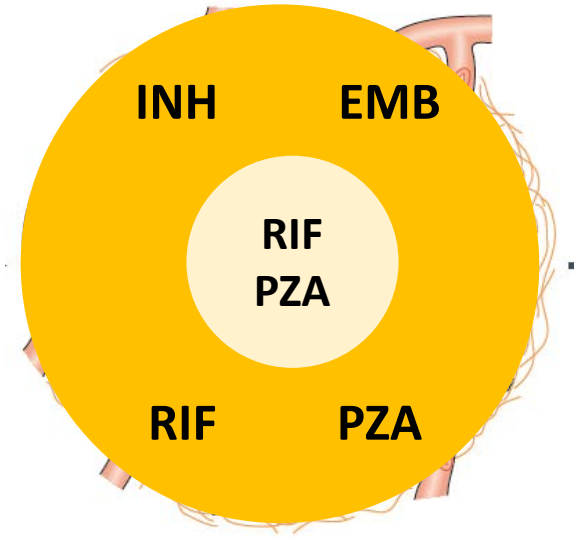


rifampicin

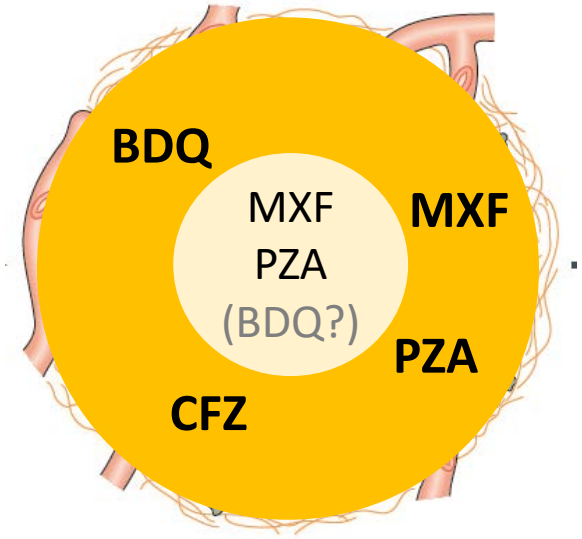


Clinical regimens: plug-and-play

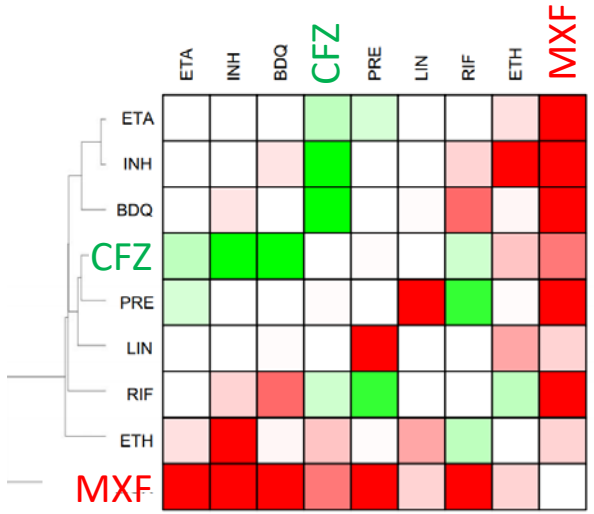
DS-TB



MDR-TB



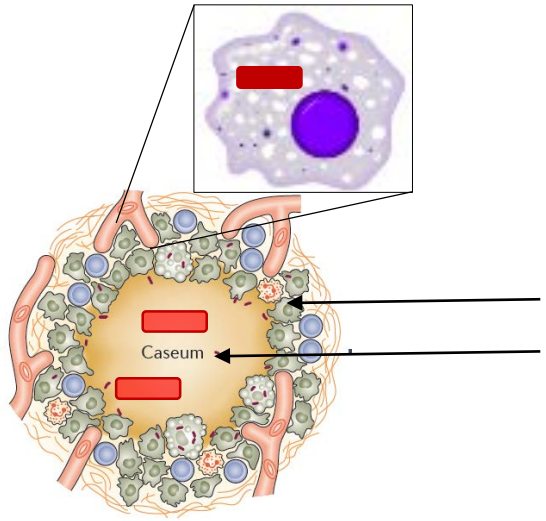
Prideaux et al., Nat Med 21(10):1223-7 (2015)
Zimmerman et al., AAC 61(9) (2017)



But why does it take 6 to 24 months?

HYPOTHESIS

If TB drugs reach all bacterial populations at sufficient concentration in lesions, cure rates will increase and treatment duration will decrease



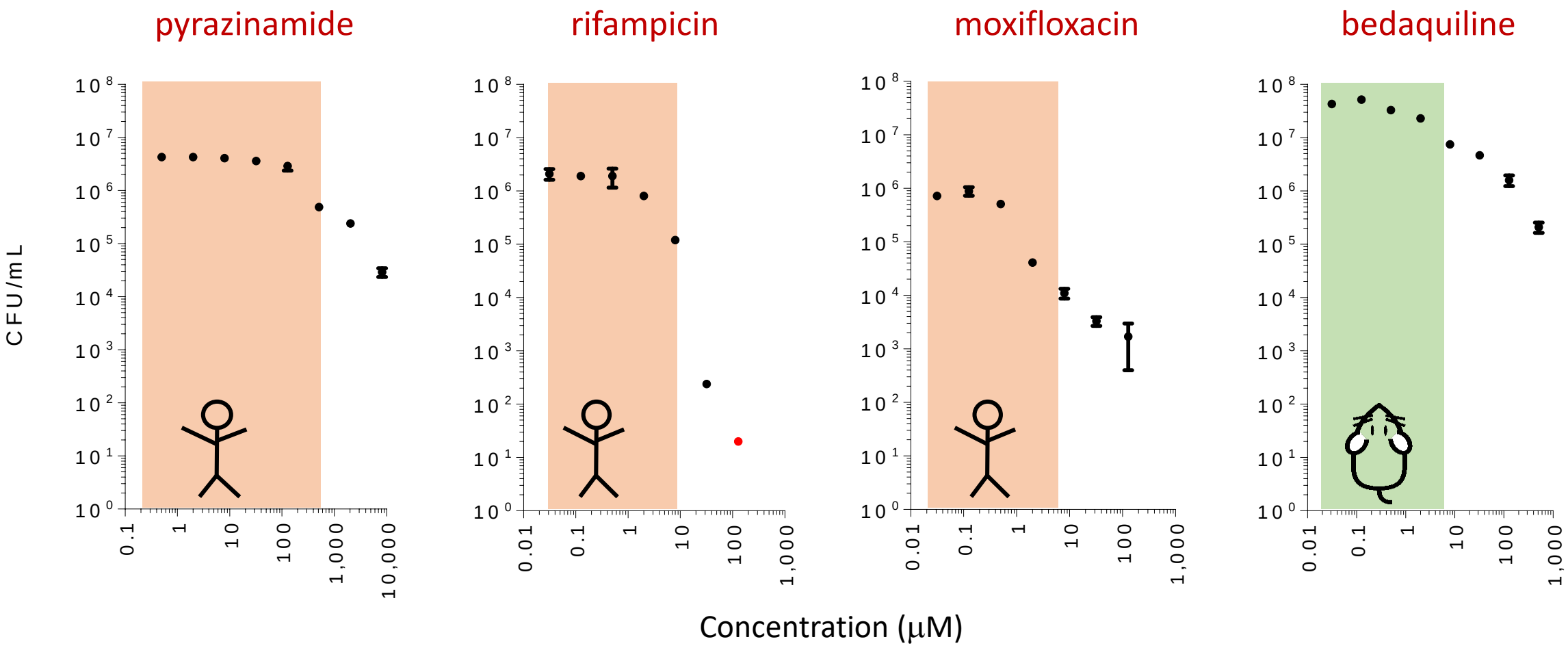
1. How much drug reaches each compartment?

2. How much drug does it take to kill the resident bugs?

3. How does that translate in the clinic?

PK-PD without the equations ☺

Concentrations achieved in caseum of man and C3H mice at steady state



Even the best TB drugs come short of ideal target attainment in caseum

Take Home

- MALDI mass spectrometry imaging combined with laser capture microdissection and LC-MS provides full drug quantitation at high spatial resolution
- Lesion-centric PK-PD helps understand the relative inefficiency of TB therapy
- Developing new PZA, MXF, RIF and BDQ derivatives that are more potent, less toxic, and/or higher in lesions is almost guaranteed to shorten therapy duration

Thank you!

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