

# Translational quantitative systems pharmacology crossing borders between experimental and computational drug development using zebrafish as model organism

Rob van Wijk, Elke Krekels, Wanbin Hu, Astrid van der Sar, Sharka Dijkema, Dirk-Jan van den Berg, Rida Bahi, Jeremy Liu, Theo Verboom, Fons Verbeek, Ulrika Simonsson, Herman Spaink, Piet van der Graaf

PAGE Lewis Sheiner Student Session 2020

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# Learning versus confirming in (pre)clinical

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## CLINICAL PHARMACOLOGY & THERAPEUTICS

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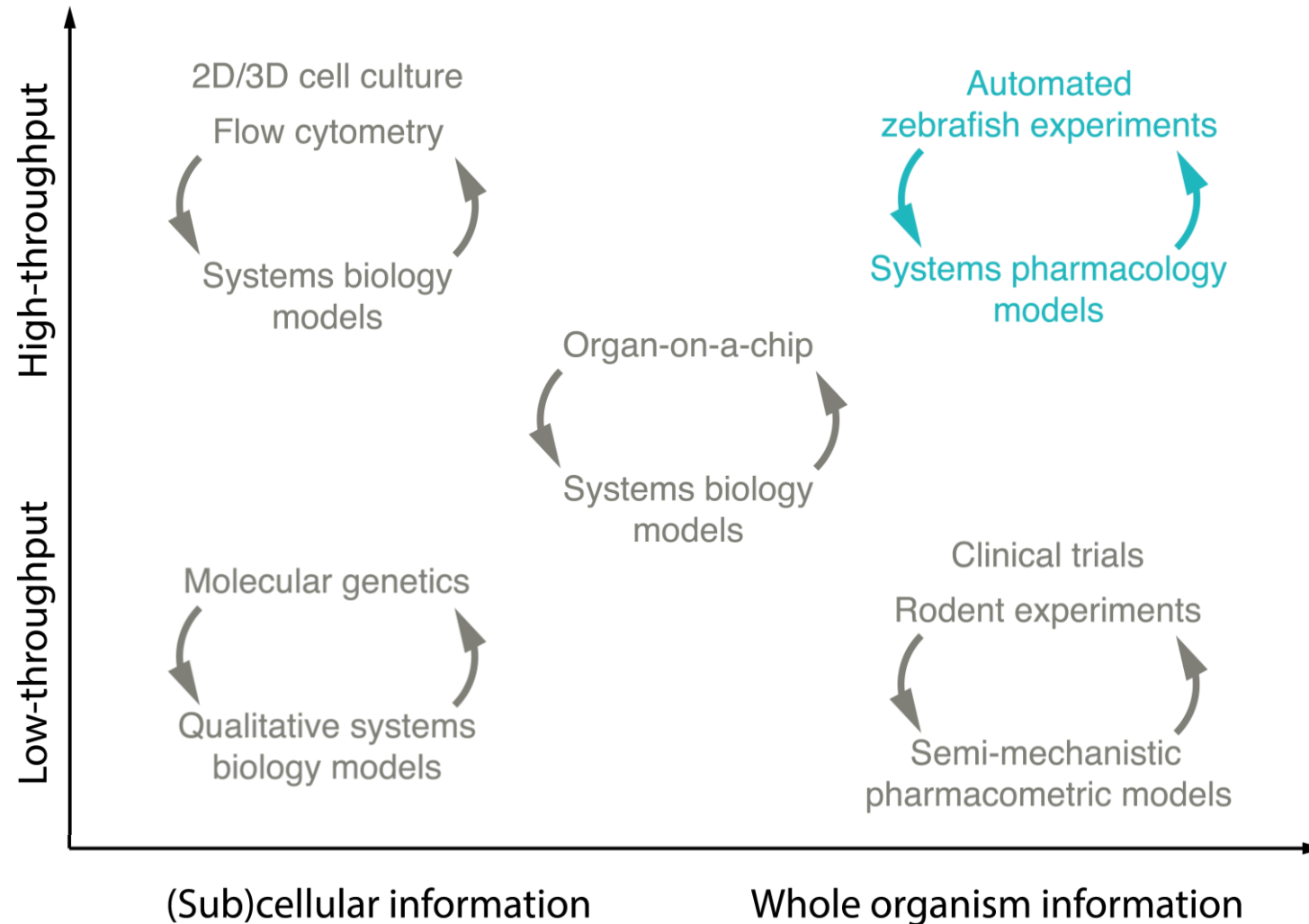
### COMMENTARY

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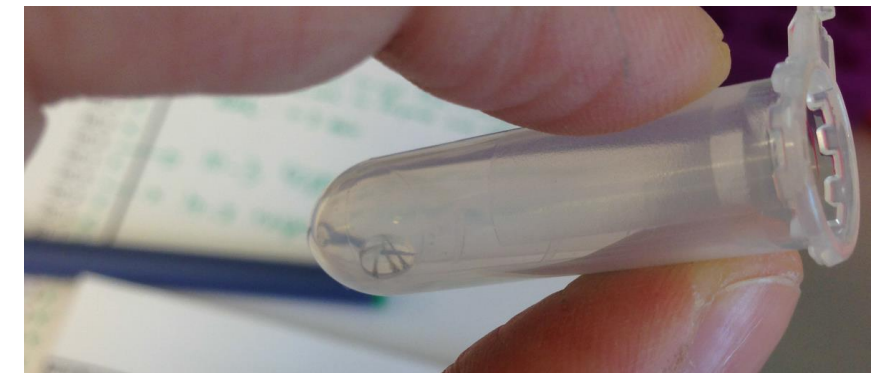
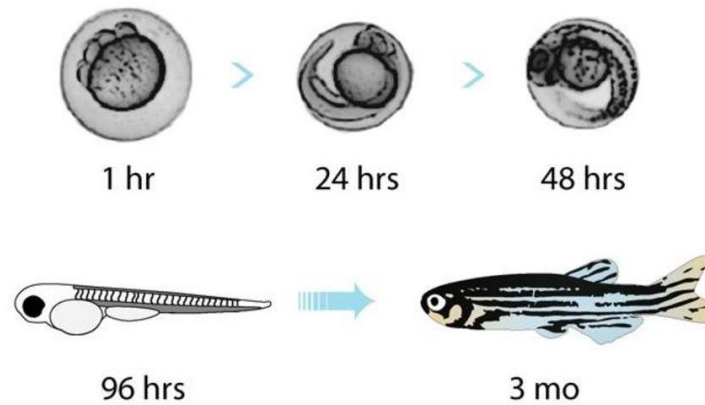
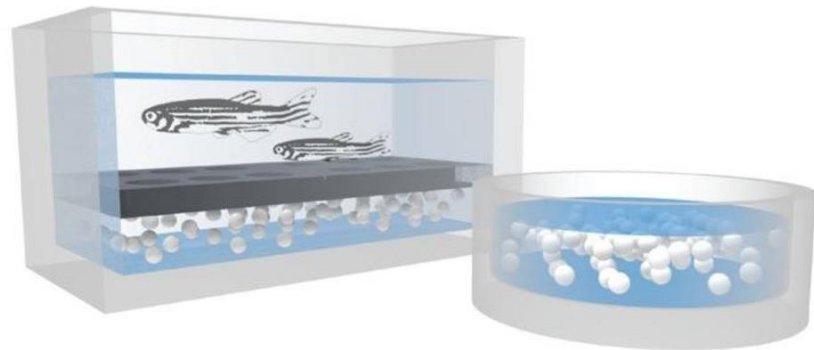
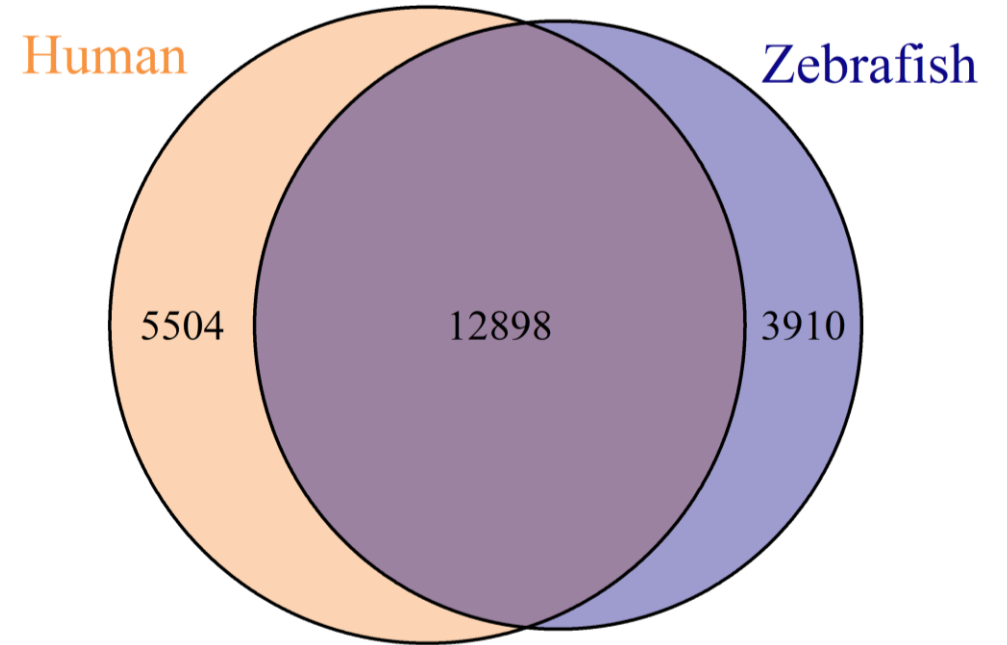
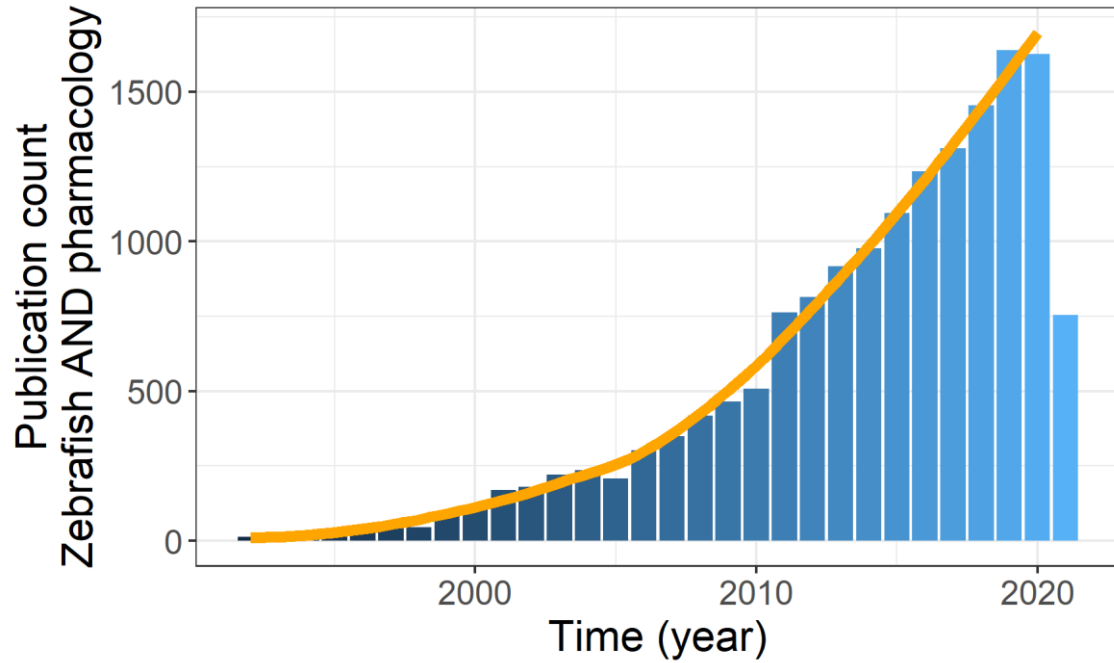
### Learning versus confirming in clinical drug development

Lewis B. Sheiner, MD *San Francisco, Calif.*

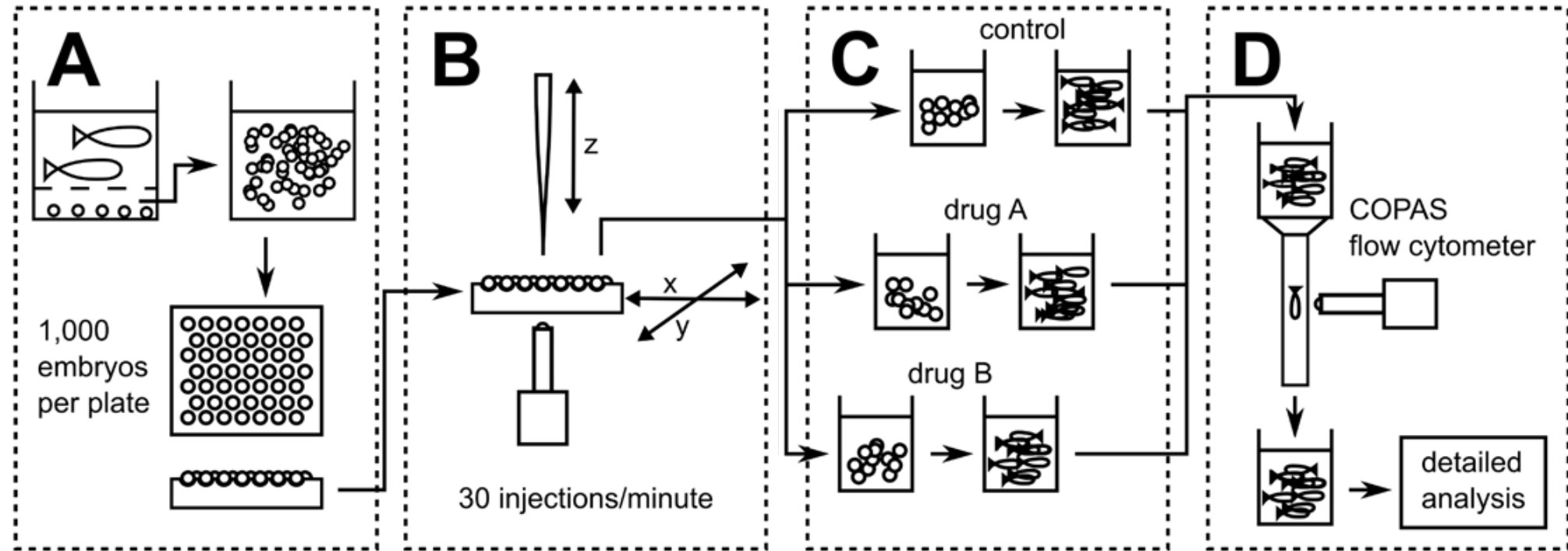
# Quantitative systems pharmacology requires high-throughput data



# Zebrafish as experimental vertebrate



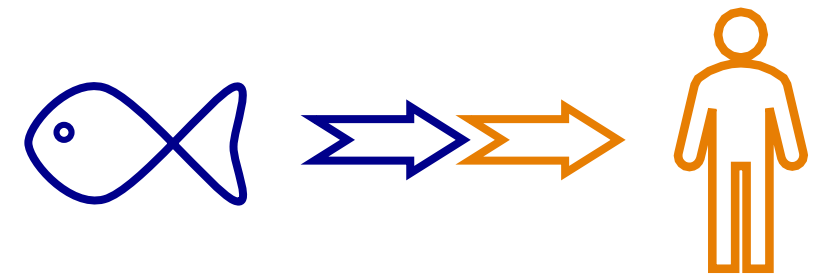
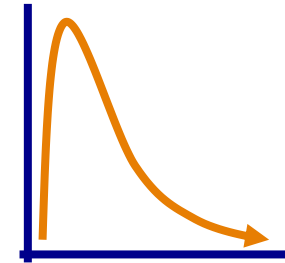
# Imaging based high throughput infection study



# Challenges for zebrafish in QSP

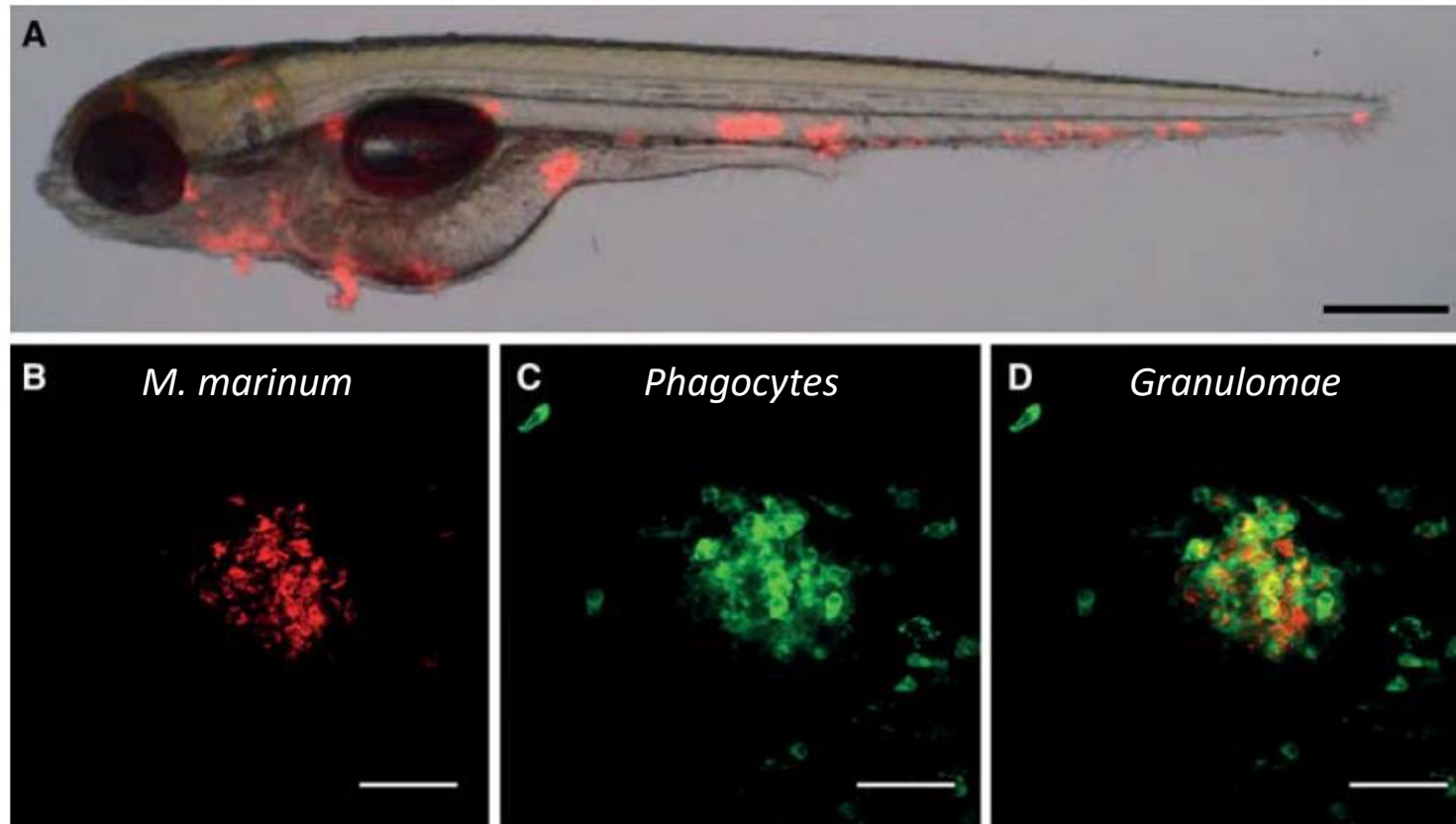
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- Quantification of internal drug exposure
- Quantification of between-species differences in disease and disease progression



# Zebrafish as disease model for tuberculosis

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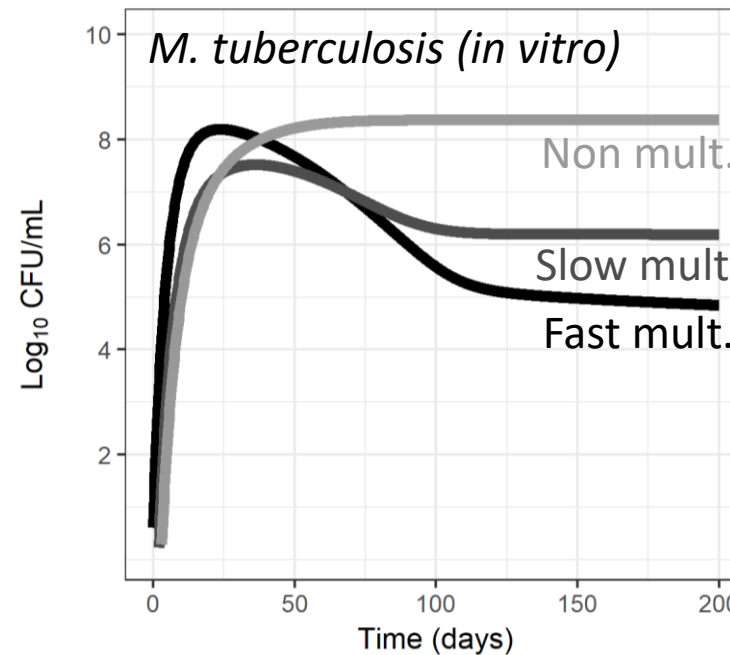
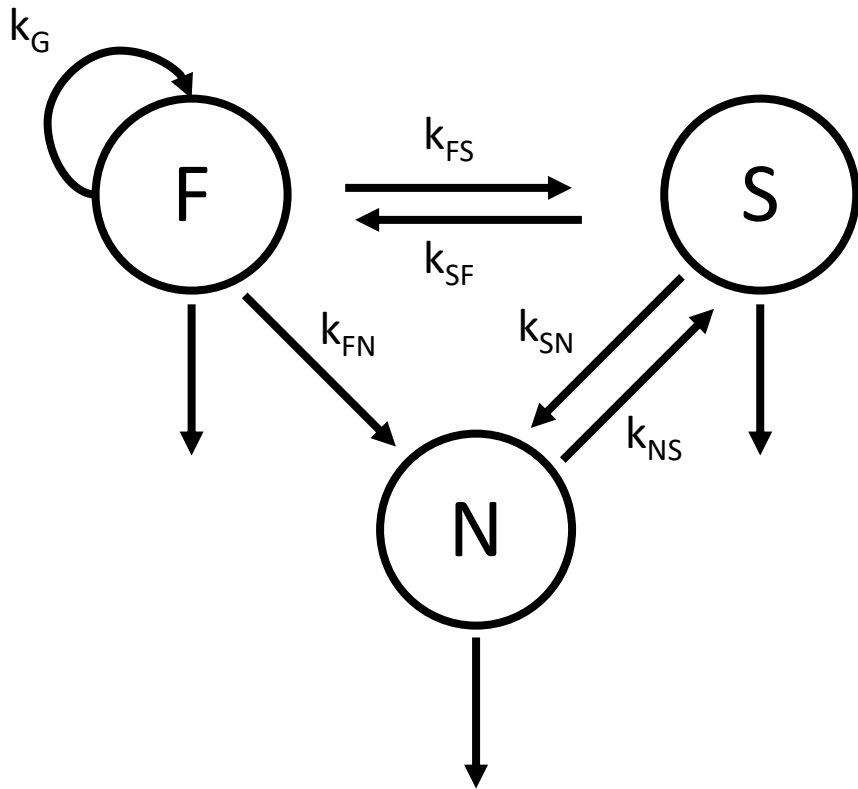


Zebrafish shows TB hallmark of granuloma formation after *Mycobacterium marinum* infection



# Quantify between-species differences in TB

*Mycobacterium tuberculosis*: fast, slow, or non multiplying state



Successful prediction:

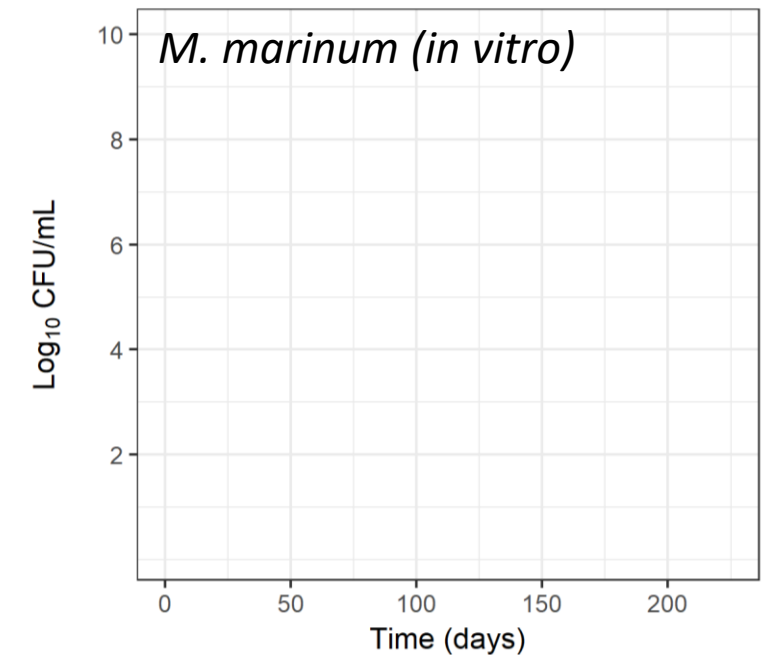
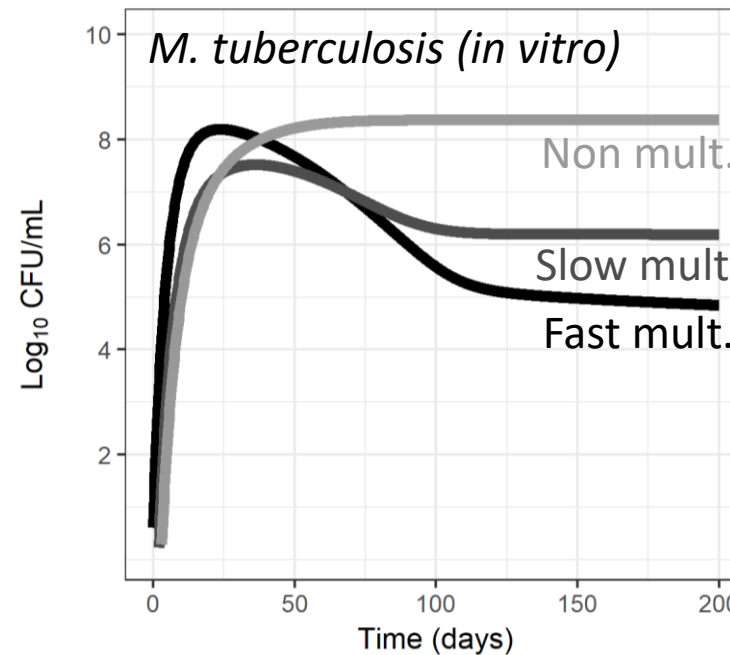
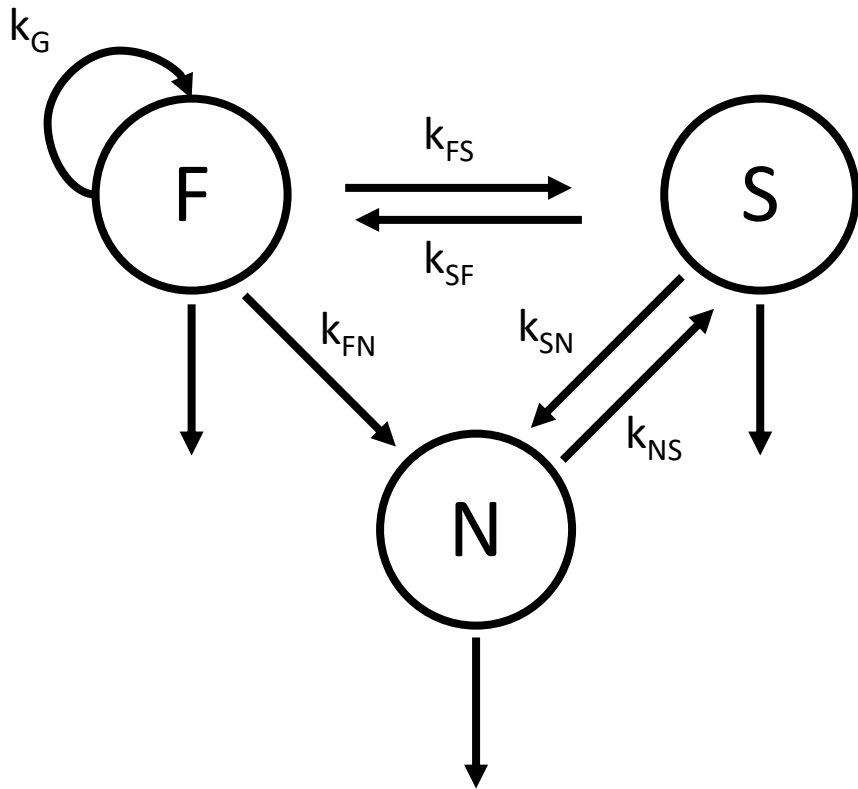
- *in vitro*
- Mice
- Patients

Multistate Tuberculosis Pharmacometric (MTP) model



# Quantify between-species differences in TB

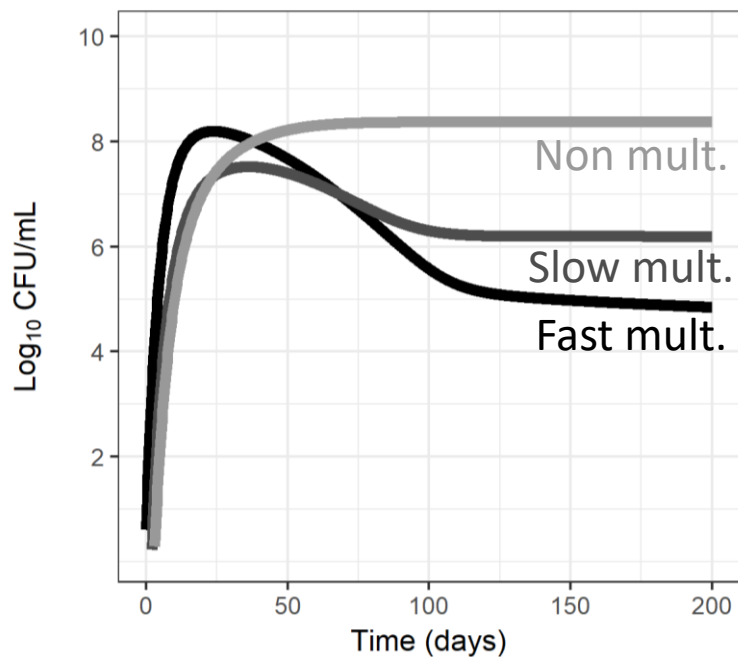
*Mycobacterium tuberculosis* compared to *Mycobacterium marinum*



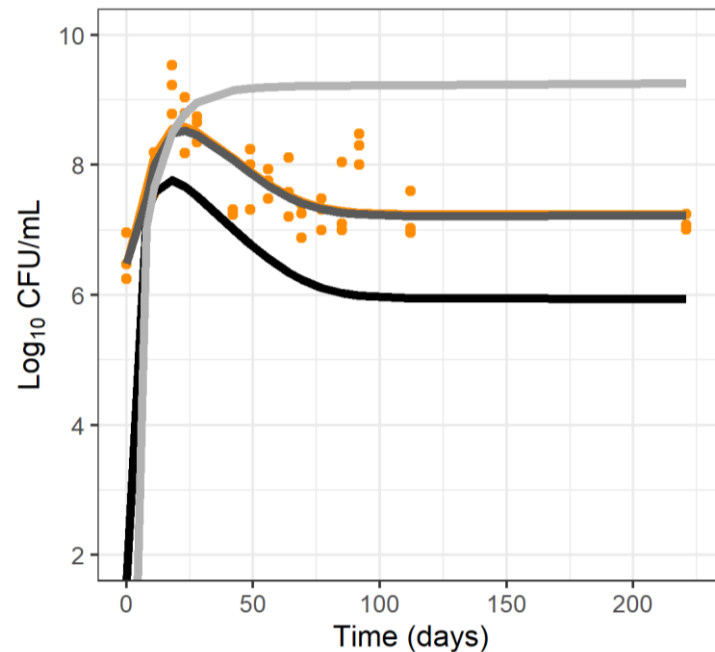
Multistate Tuberculosis Pharmacometric (MTP) model

# Quantify between-species differences in TB

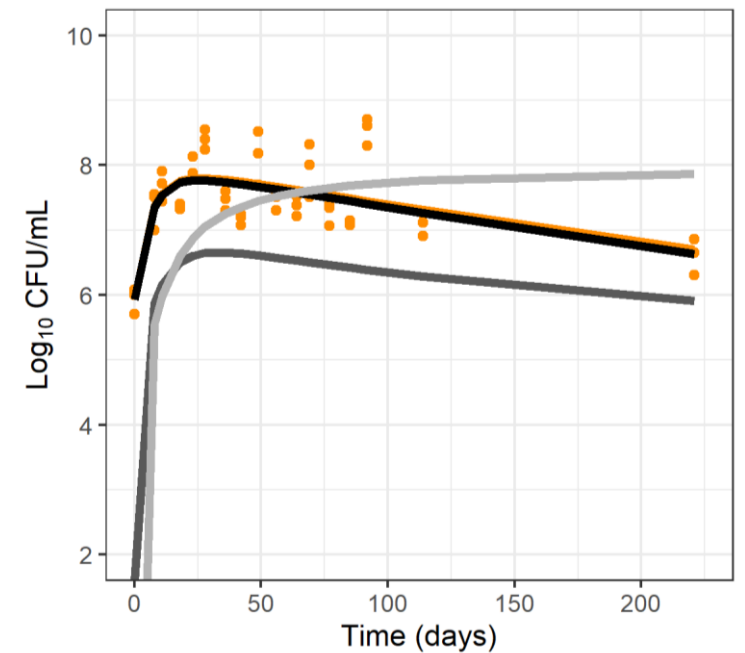
*Mycobacterium tuberculosis* compared to *Mycobacterium marinum*



*M. tuberculosis* (in vitro)



*M. marinum* (E11, in vitro)



*M. marinum* (M-USA, in vitro)

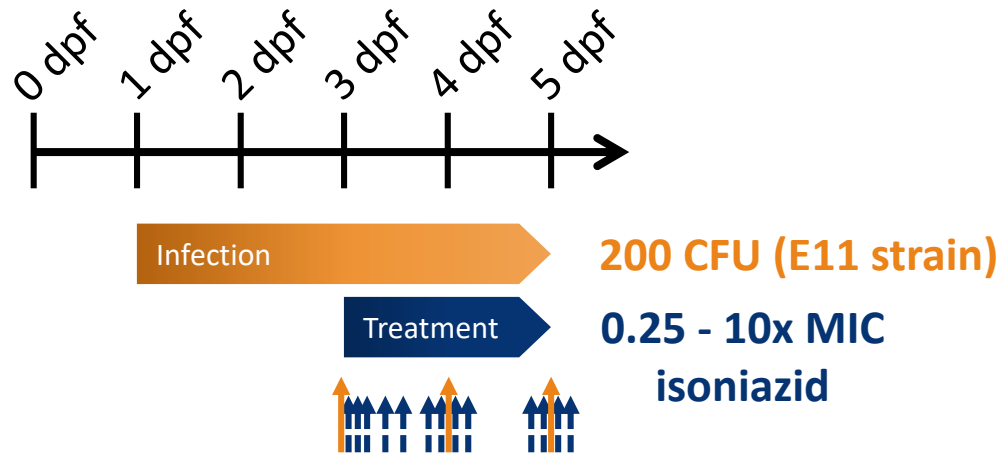
# Experimental design to quantify PKPD in zebrafish

## Sampling

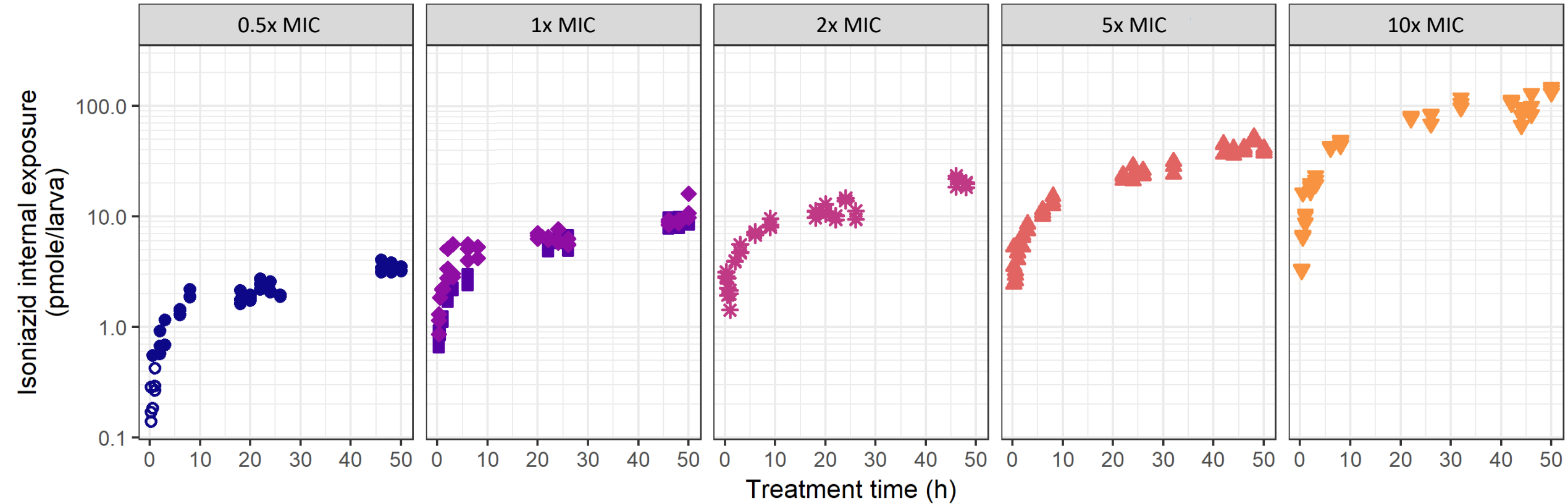
PK: Larval homogenate  
Blood



PD: Mycobacterial  
fluorescence



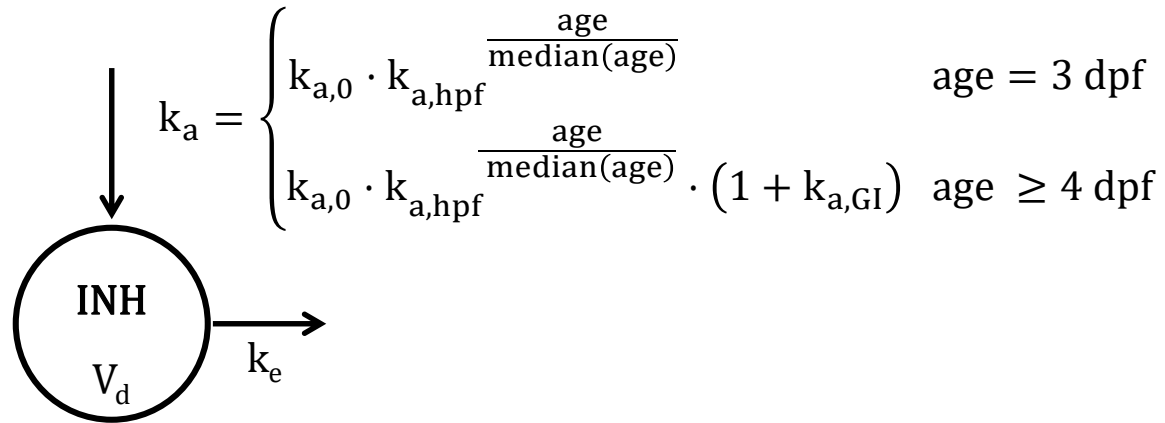
# Isoniazid exposure in larval homogenates



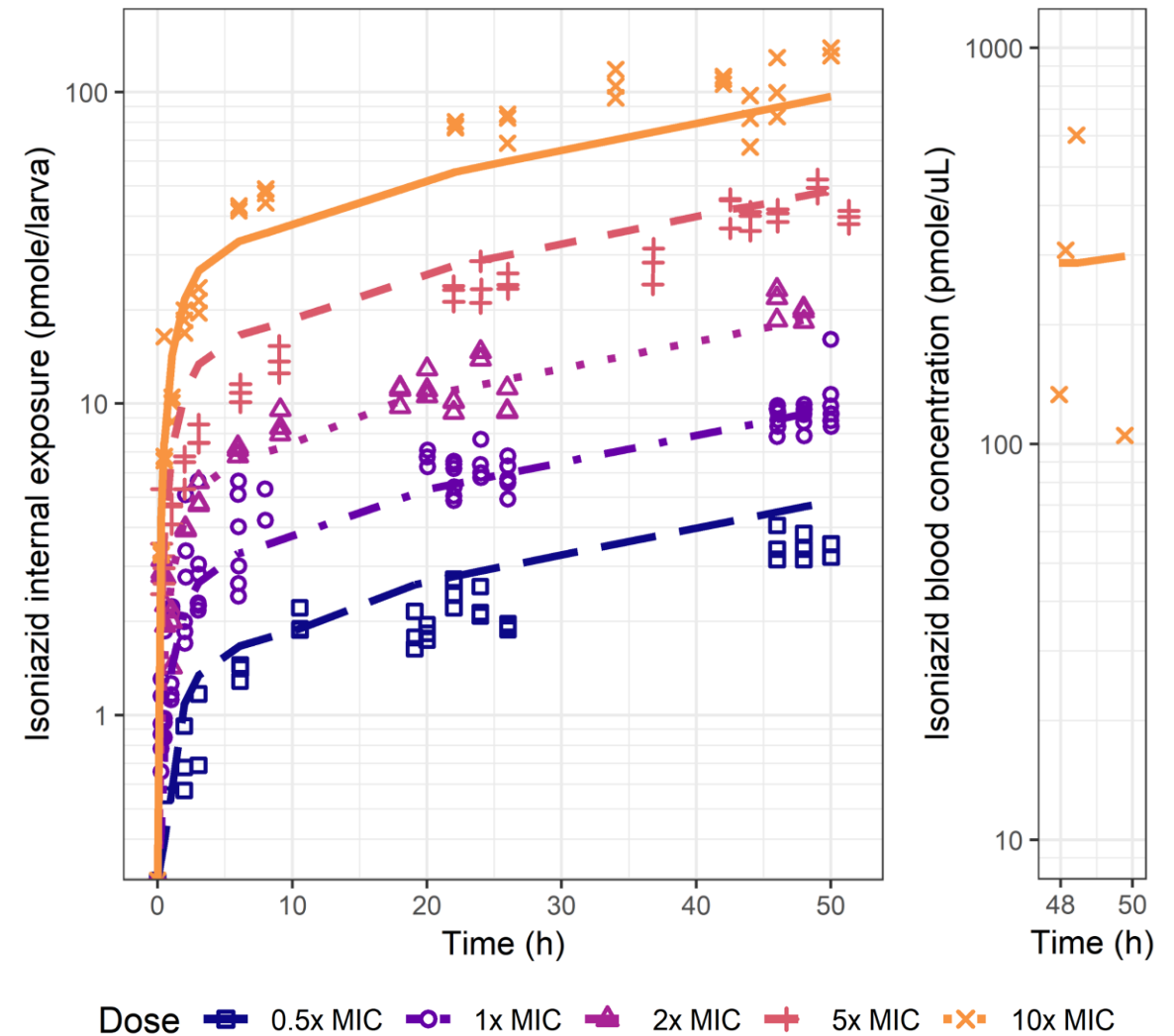
# Nanoscale blood sampling



# Integrated pharmacokinetics modelled

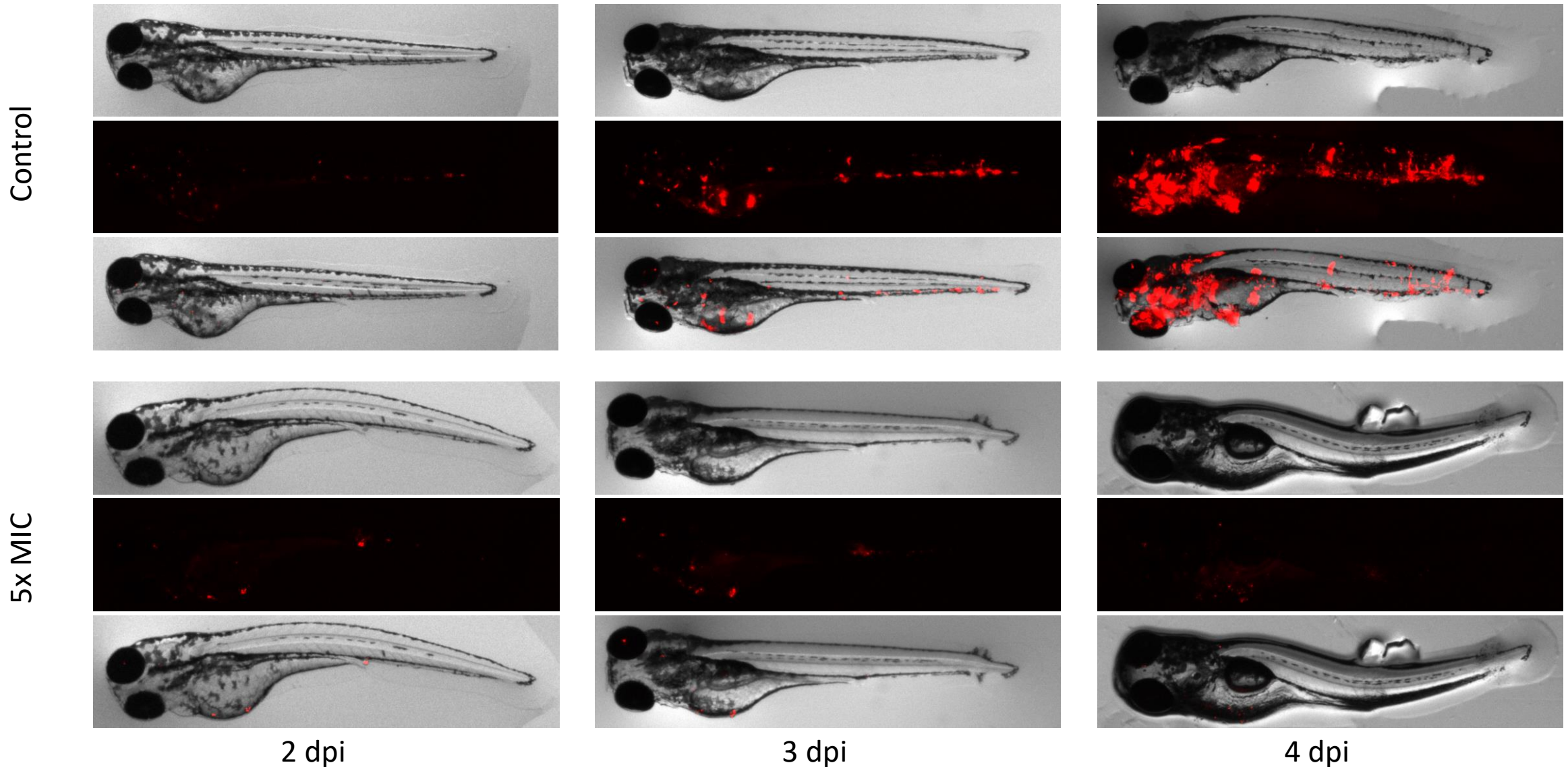


Parameter	Estimate	Relative standard error (%)
$k_{a,0}$ ( $\mu\text{L}/\text{h}$ )	0.00349	25
$k_{a,hpf}$	7.61	17
$k_{a,GI}$	0.171	51
$k_e$ (/h)	0.580	32
$V_d$ ( $\mu\text{L}$ )	0.325	36



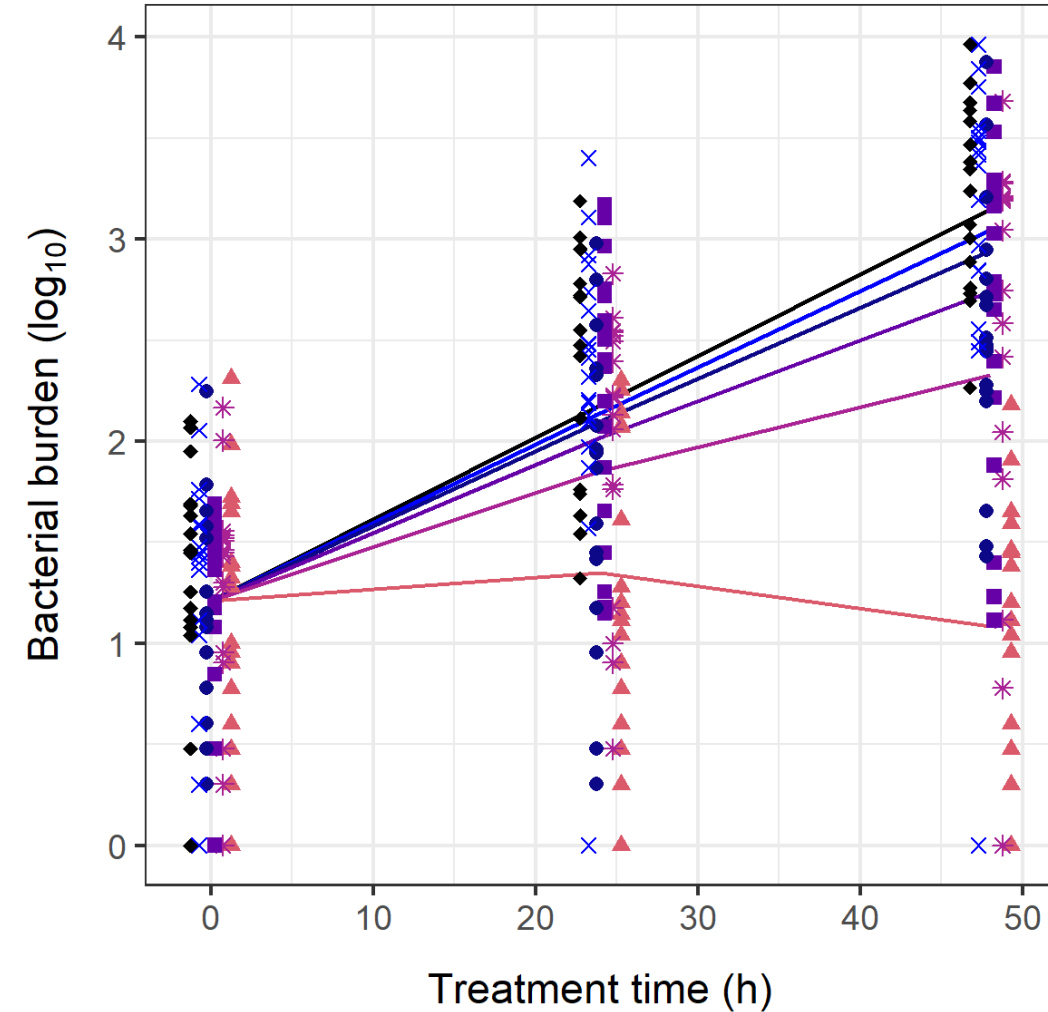
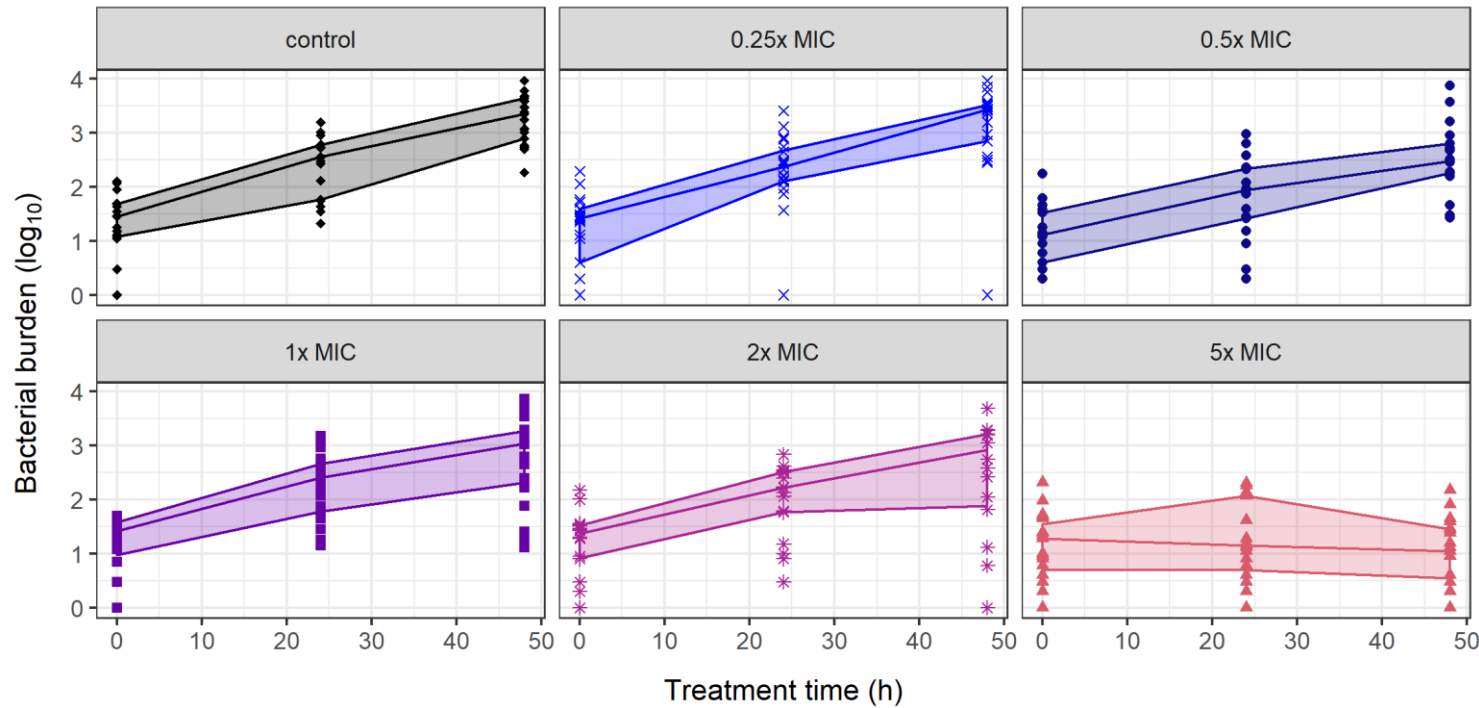


# Fluorescence microscopy shows infection

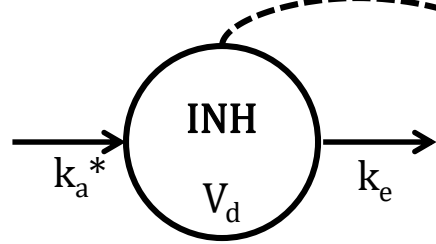




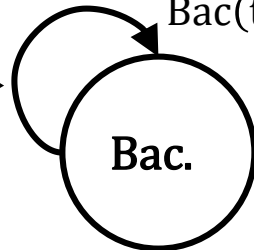
# Concentration-effect relationship quantified



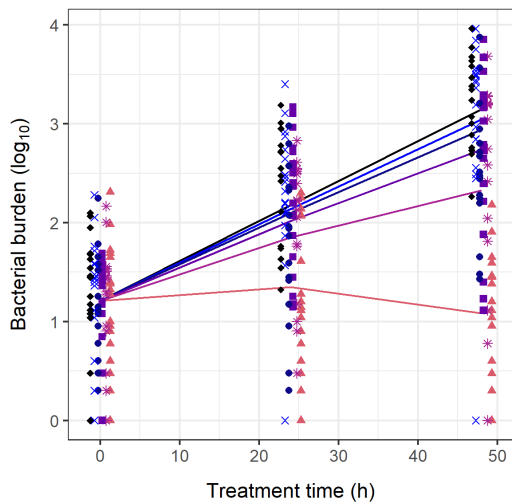
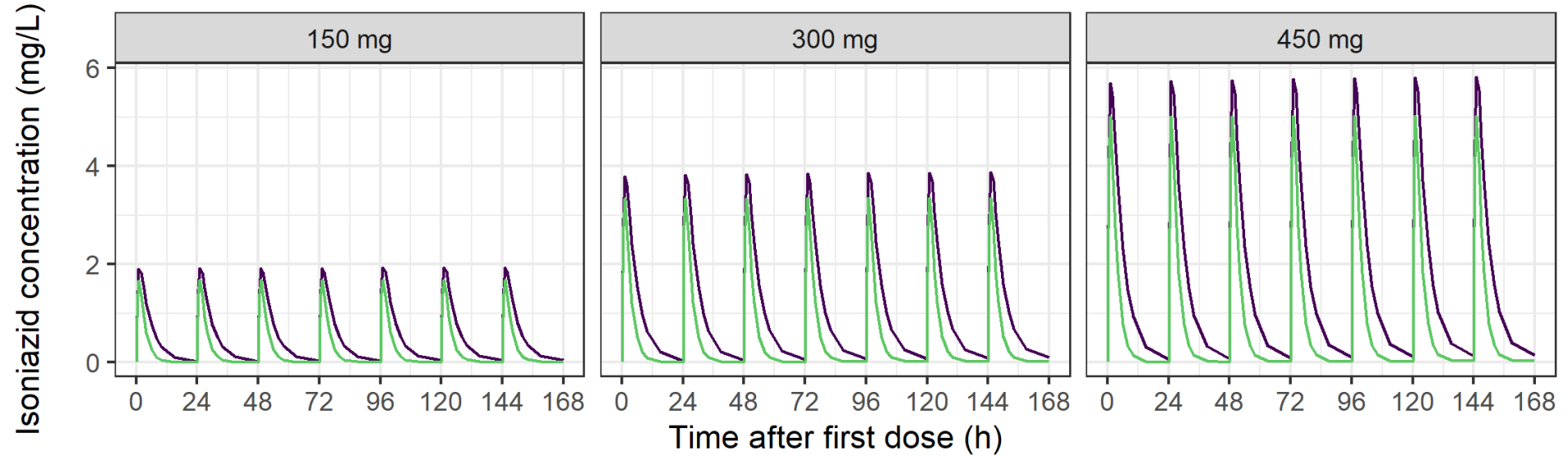
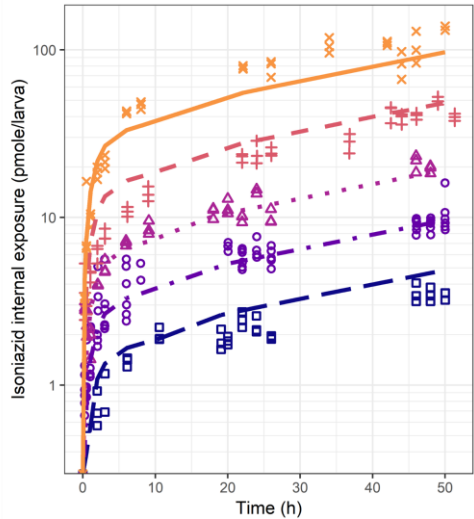
$$EFF = SLP * INH$$



$$Bac(t) = INOC \cdot e^{k_g \cdot t}$$

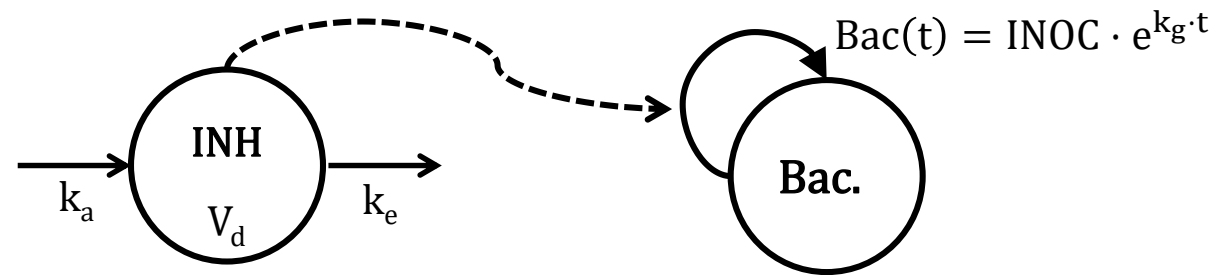


# Translate from zebrafish to human?

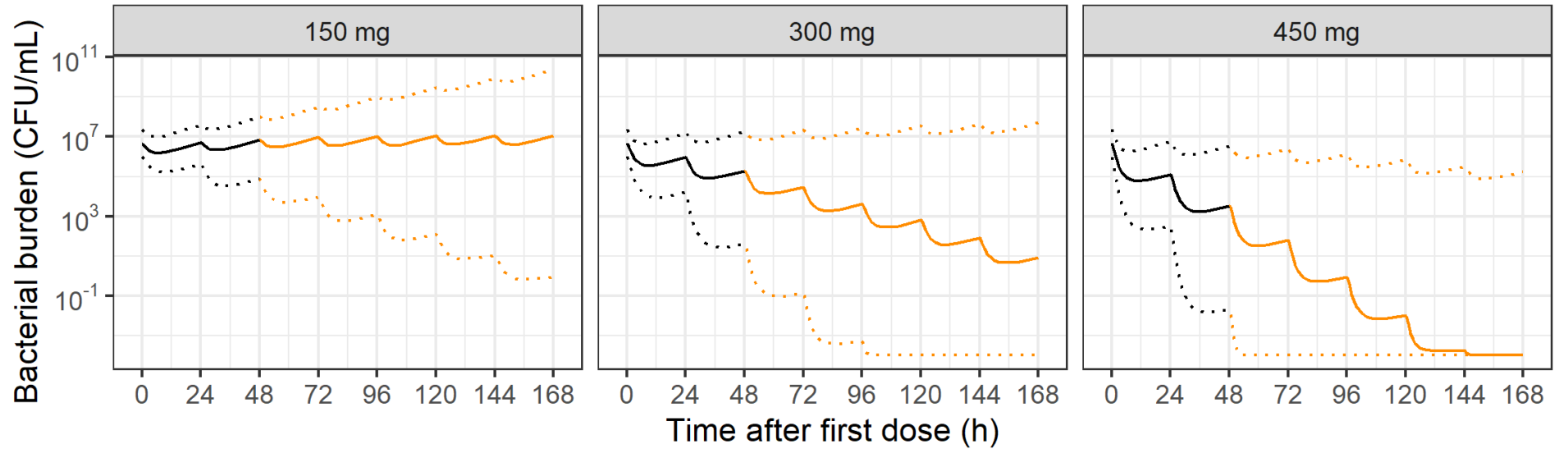
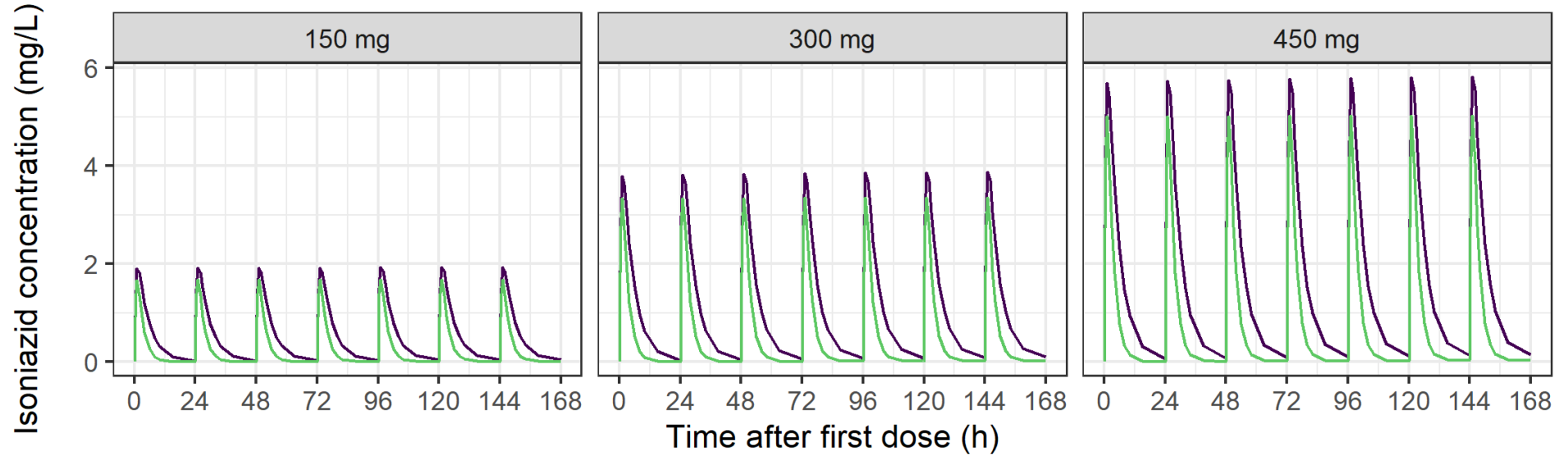
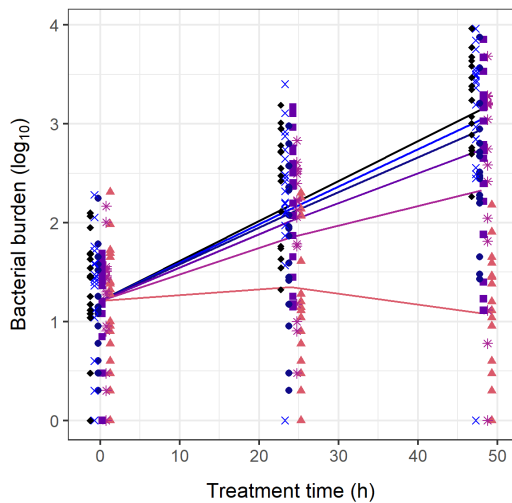
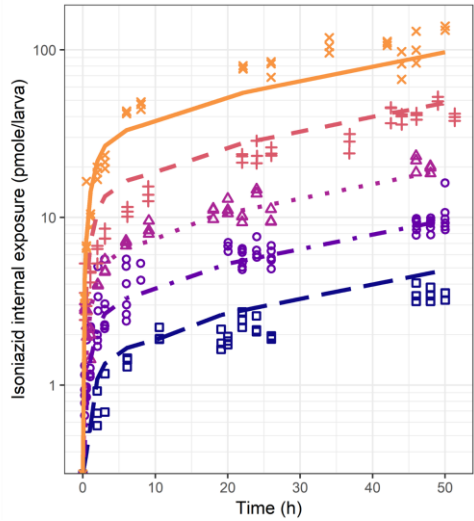


$EFF = SLP * INH$

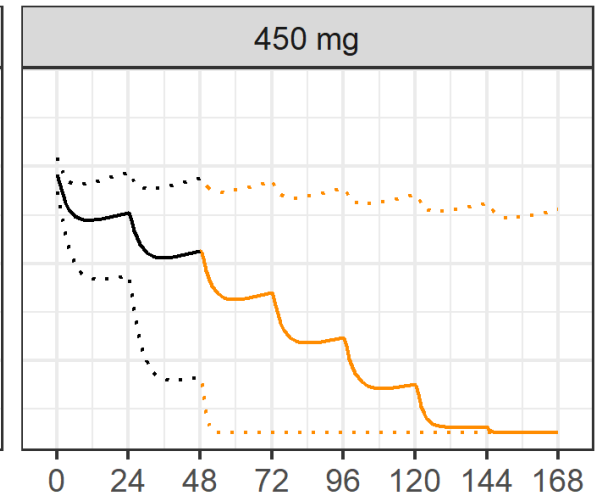
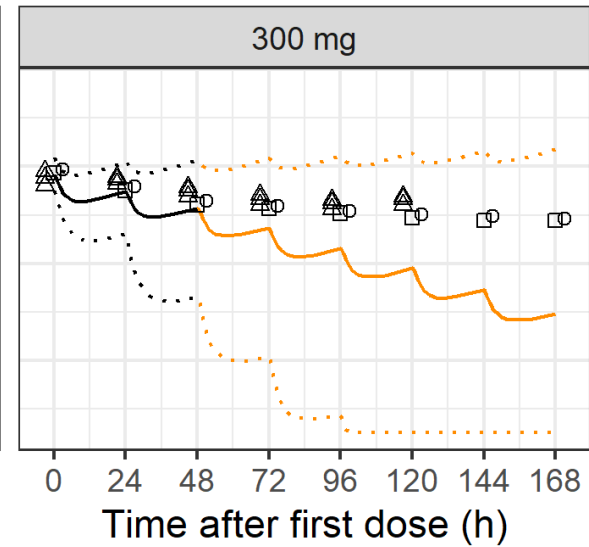
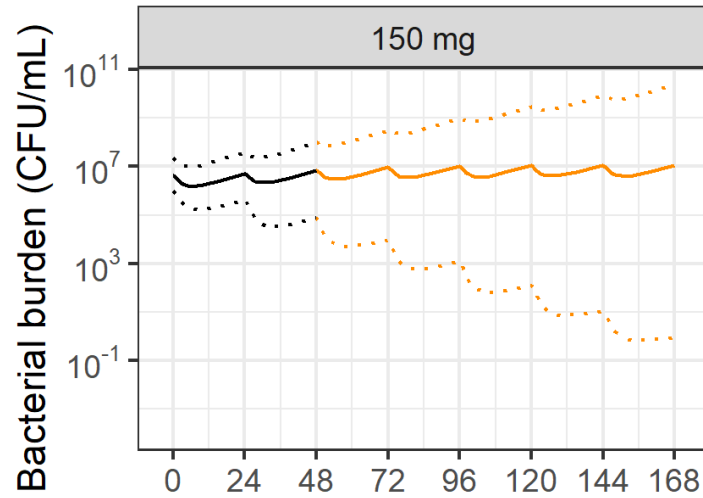
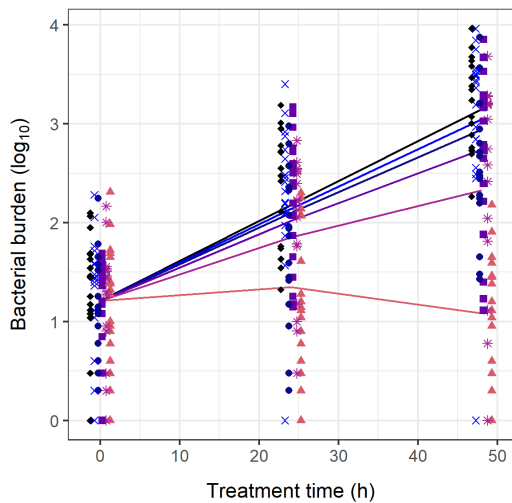
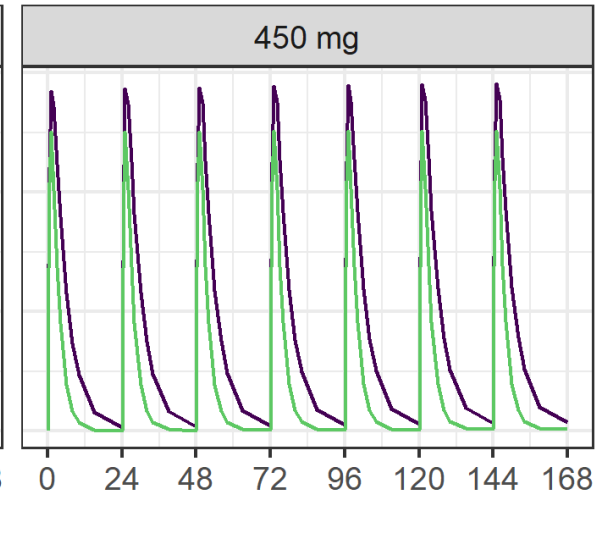
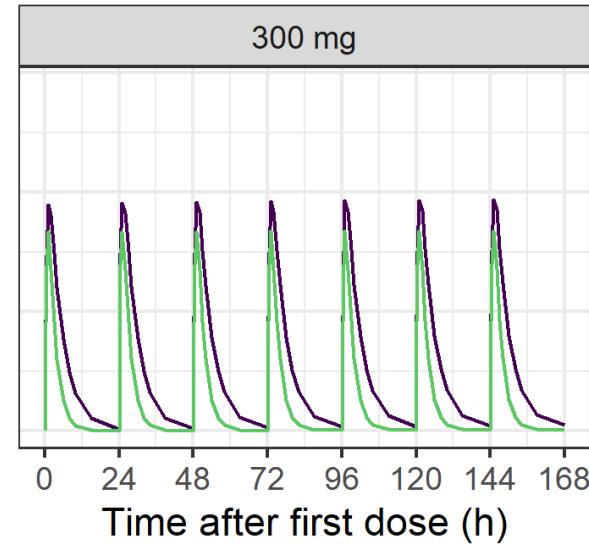
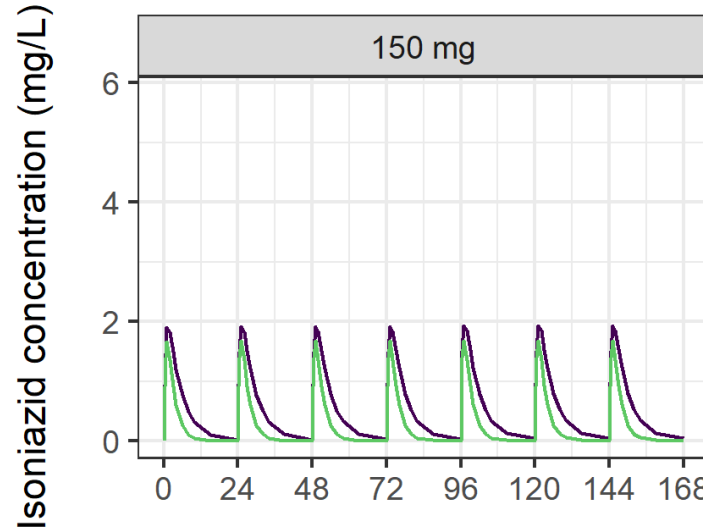
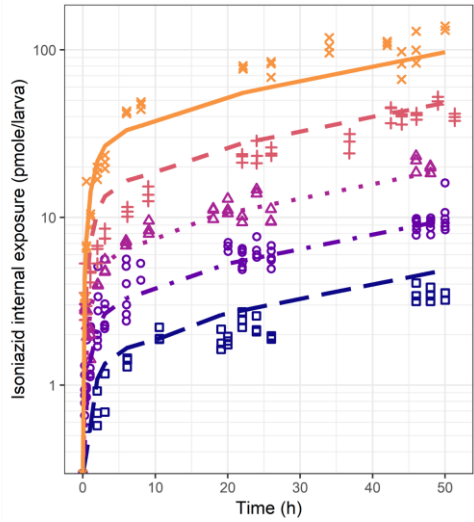
- 1. Mycobacterial sensitivity to isoniazid (MIC)
- 2. Stage of infection (logarithmic vs stationary)



# Translate from zebrafish to human?



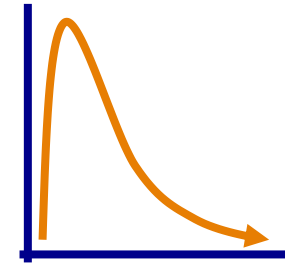
# Translate from zebrafish to human!



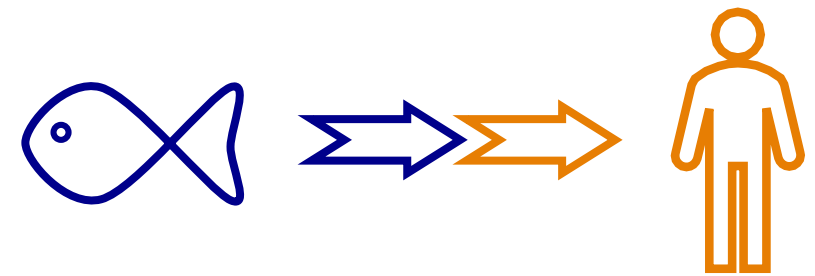
# Conclusion

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Internal drug exposure  
quantified to determine the  
exposure-response relationship



Promising translation from  
zebrafish to humans based on  
between-species differences



# Translational quantitative systems pharmacology crossing borders between experimental and computational drug development using zebrafish as model organism

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