

# Development and PK Challenges of a Rabbit Meningoencephalitis Model

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# The principal problem...

- Antimicrobial pharmacokinetics-pharmacodynamics (PK-PD) bridging studies require several fundamental assumptions
  - Invading pathogen is the pharmacological target in experimental systems and patients
  - [more subtlety] assume the pharmacodynamics are the same
  - [this last point generally lost]

# Neonatal Meningoencephalitis

- CNS involvement may occur because of an immature Blood-Brain-Barrier in neonates
  - CNS involvement results in poor neurodevelopmental outcomes
  - But CNS involvement is often assumed and very difficult to definitively demonstrate.
- Direct involvement of the CNS [potentially] changes the pharmacodynamics
  - Some antimicrobial agents/ antimicrobial classes are ineffective
  - Altered dose-exposure-response relationships (i.e. more drug may be required for the same effect for treatment of CNS infections)

Predictive models that explicitly define the pharmacodynamics of new antimicrobials in the neonatal brain and can be used to identify candidate dosages for clinical use for neonates

# A new rabbit model of bacterial meningoenzephalitis was developed

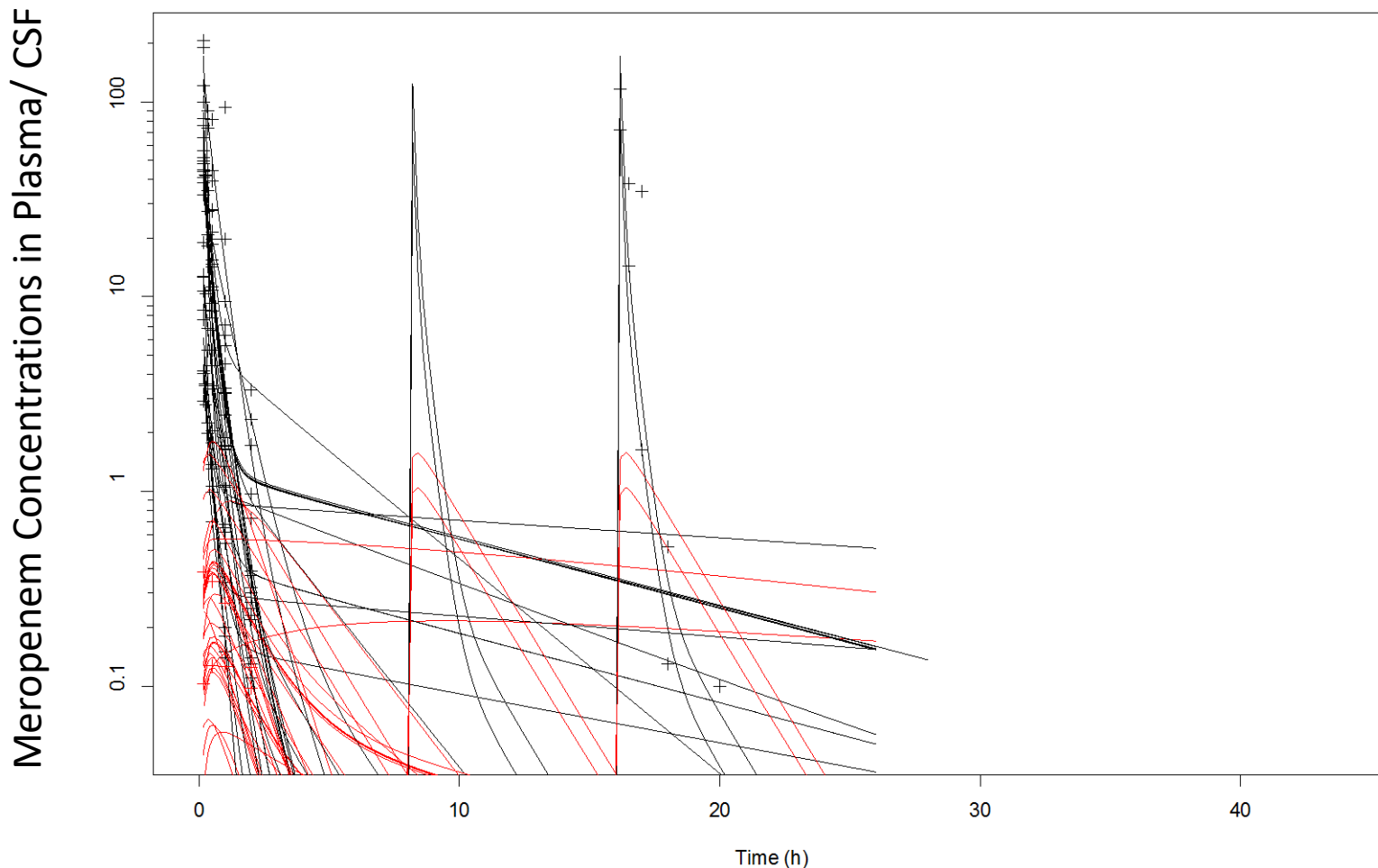
- The rabbit enables clinically relevant CNS sub-compartments to be modelled (i.e. cerebrum and CSF)
  - Both PK and PD can be established here
- It [potentially] enables serial sampling
  - As might occur clinically
- Track record of using the rabbit to model *Candida* meningoenzephalitis and assess the pharmacodynamics of micafungin and anidulafungin

# Experimental details of this model

- Immunocompetent model
- Intrathecal inoculation of *Pseudomonas aeruginosa* ATCC 27853 under general anesthesia
- 6-hour delay in initiation of antimicrobial treatment
- Meropenem and tobramycin administered q8h i.v.
- 30-hour model
- We could not serially sample CSF because rabbits too sick and could not tolerate repeated anesthesia
- Quantified bacterial burden in CSF and cerebrum

Meropenem

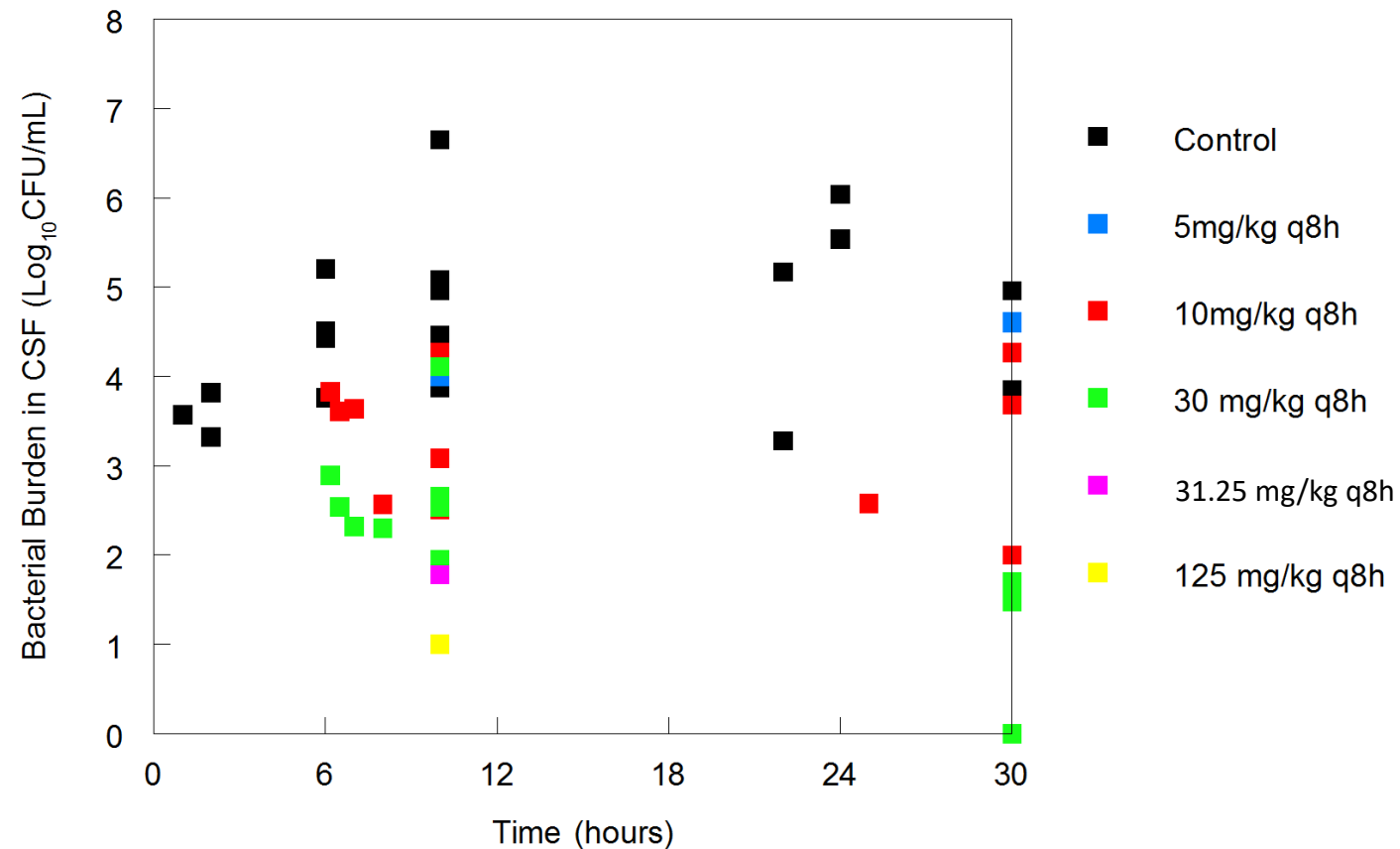
# Meropenem partitioning into CSF: plasma=black; CSF=red]



Partition ratio  
calculated as  
 $AUC_{CSF}/AUC_{plasma}$   
in 7 rabbits where  
PK measured in  
both matrices  
was 14.3%



Meropenem: pooled raw data from CSF from multiple expts. Treatment starts at time=6 hours



# Meropenem

$$XP(1) = \text{RATEIV}(1) - (\text{SCL}/V_c) * X(1) - K_{12} * X(1) + k_{21} * X(2) + K_{31} * X(3) - K_{13} * X(1)$$

$$XP(2) = K_{12} * X(1) - K_{21} * X(2)$$

$$XP(3) = K_{13} * X(1) - K_{31} * X(3)$$

PK

$$XP(4) = K_{gmax} * (1 - D_0 - (X(4)/\text{popmax})) * X(4) - k_{kmax} * (X(3)/V_{csf})^{**} Hk / (C_{50k}^{**} Hk + (X(3)/V_{csf})^{**} Hk) * X(4)$$

PD

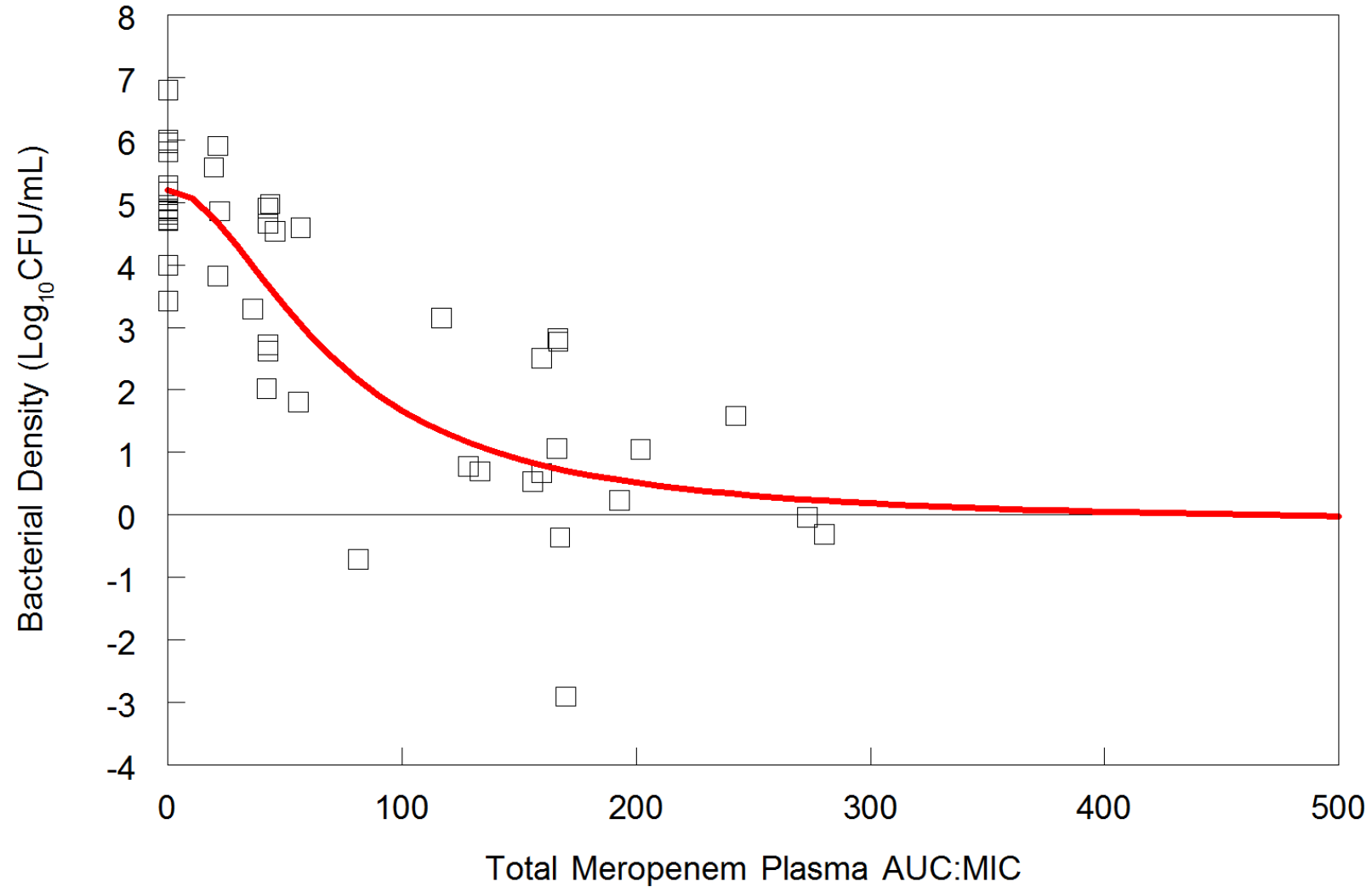
The time course of the antibacterial effect is modeled as growth minus drug induced killing

Drug concentrations in CSF are linked to effect

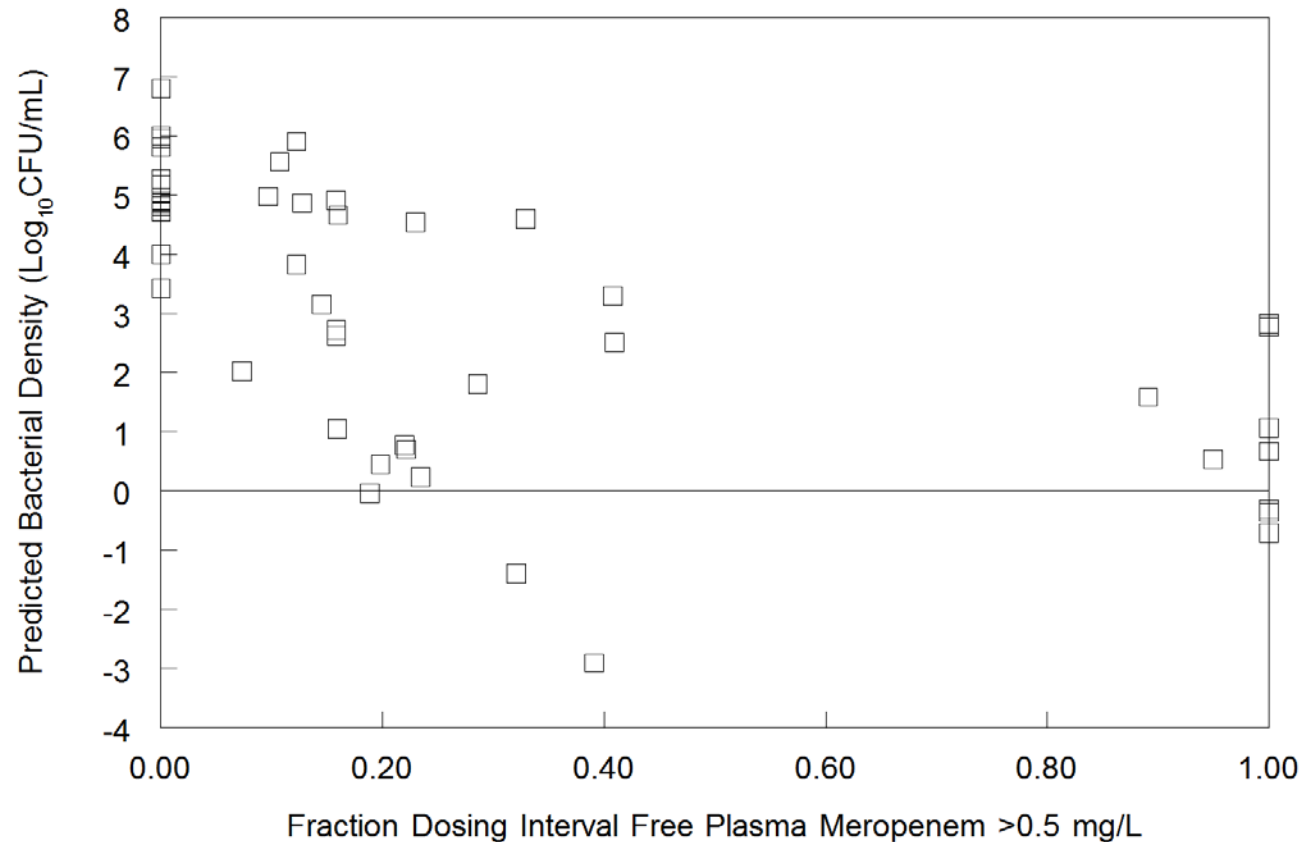
# Establishing Dose-Exposure-Response Relationships for Meropenem

- Posteriors for each rabbit used to estimate  $\text{Log}_{10}\text{CFU/mL}$  at the end of therapy in CSF
  - Area under  $\text{Log}_{10}\text{CFU/mL}$  vs. time curve also examined, but proved to be quite insensitive
  - Each rabbit assumed to receive a full course of meropenem (i.e. dose mg/kg q8h) in these calculations
- [NB brain PD data also available, but was not modelled]
  - Consistent with CSF data
  - The driving compartment less clear. Perhaps plasma more appropriate?
- Total drug measured in plasma and CSF
  - Consider CSF meropenem as “free” even though that may not be true

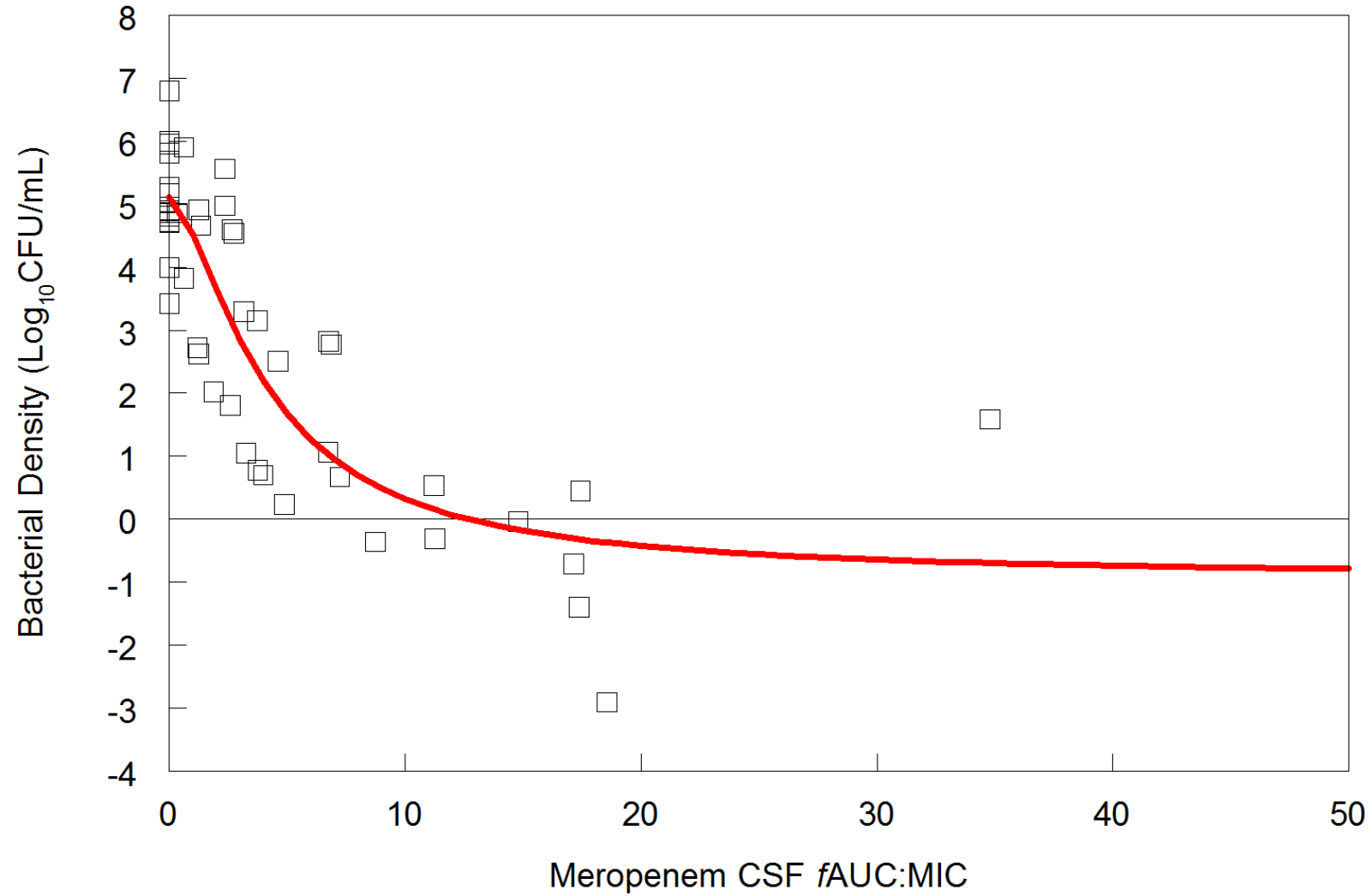
# Meropenem Plasma vs. CSF Effect



[Just for comparison with  $fT > MIC$  in plasma, which is not as tight]

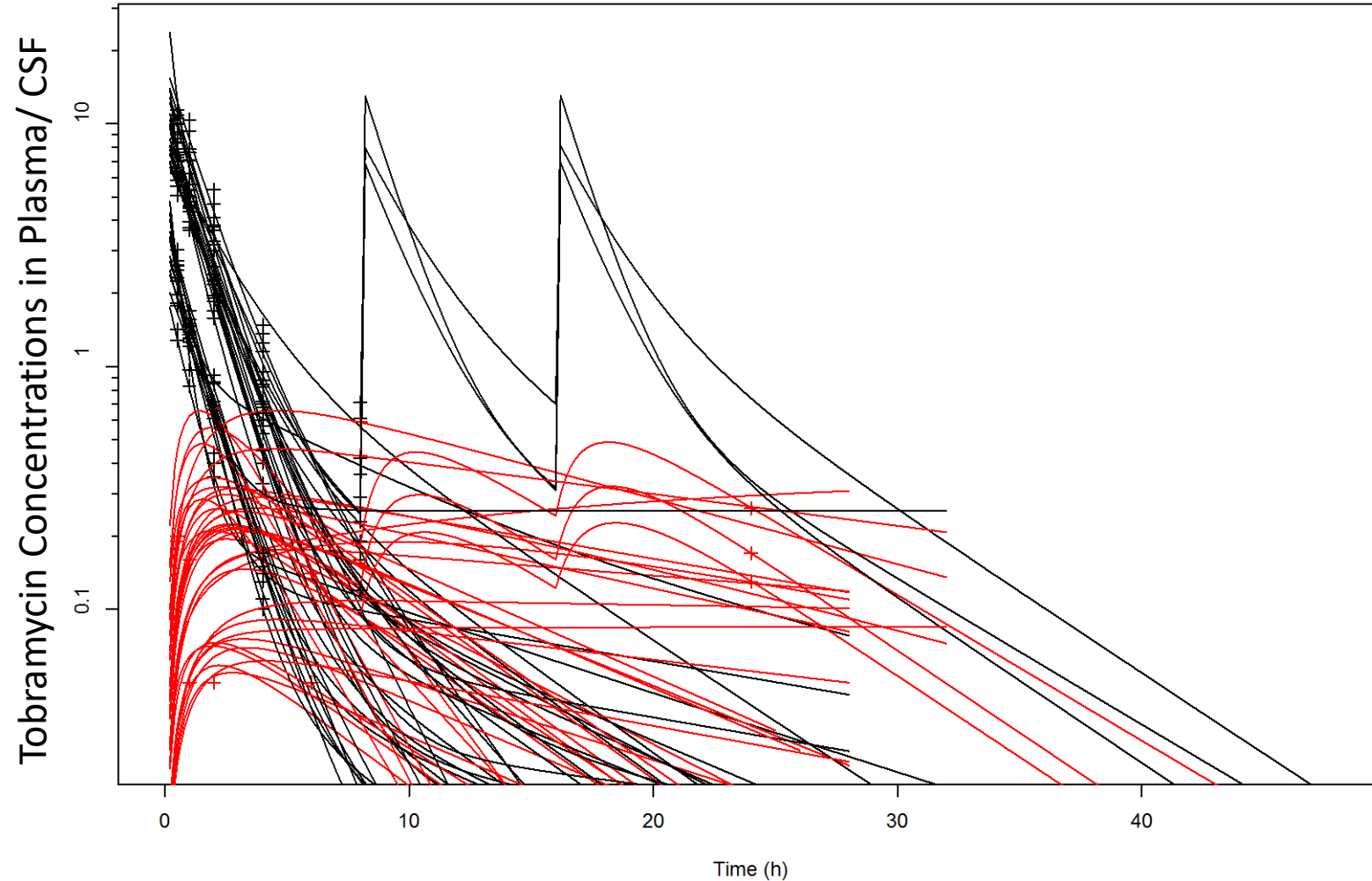


# Meropenem CSF vs. CSF Effect



Compare these findings to  
tobramycin

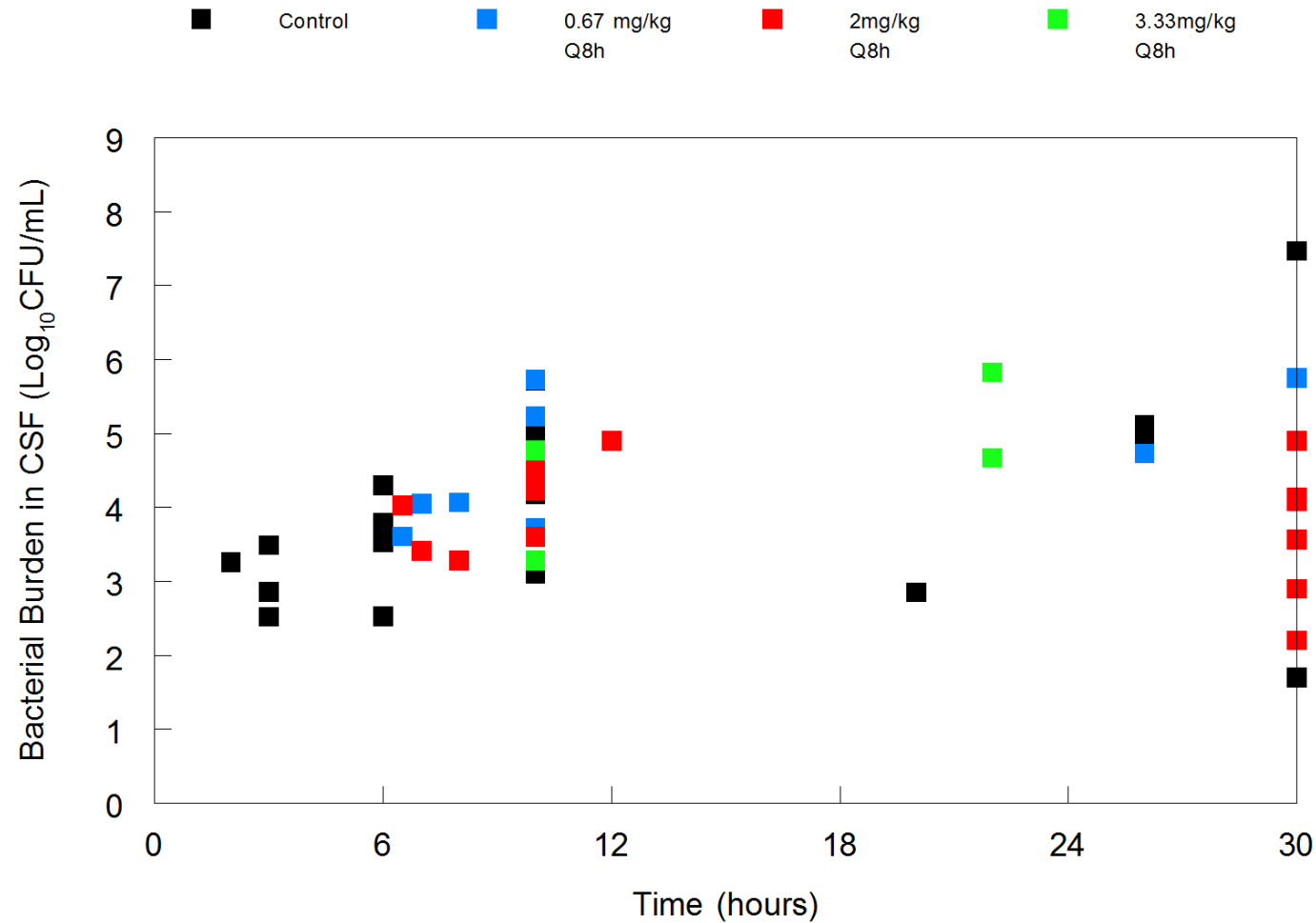
# Tobramycin PK in plasma and CSF



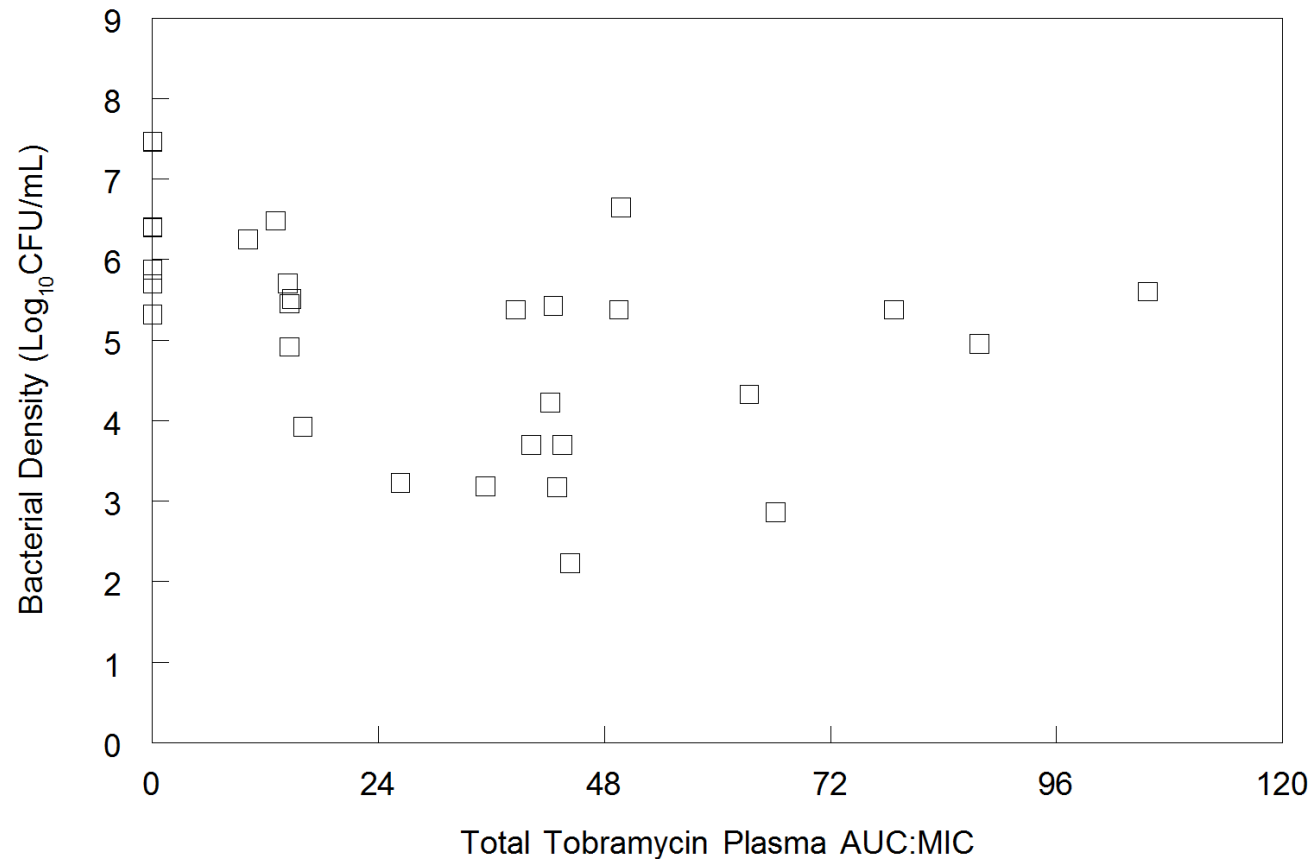
Partition ratio  
calculated as  
 $AUC_{CSF}/AUC_{plasma}$   
in 12 rabbits  
where PK  
measured in  
both matrices  
was 13.7%



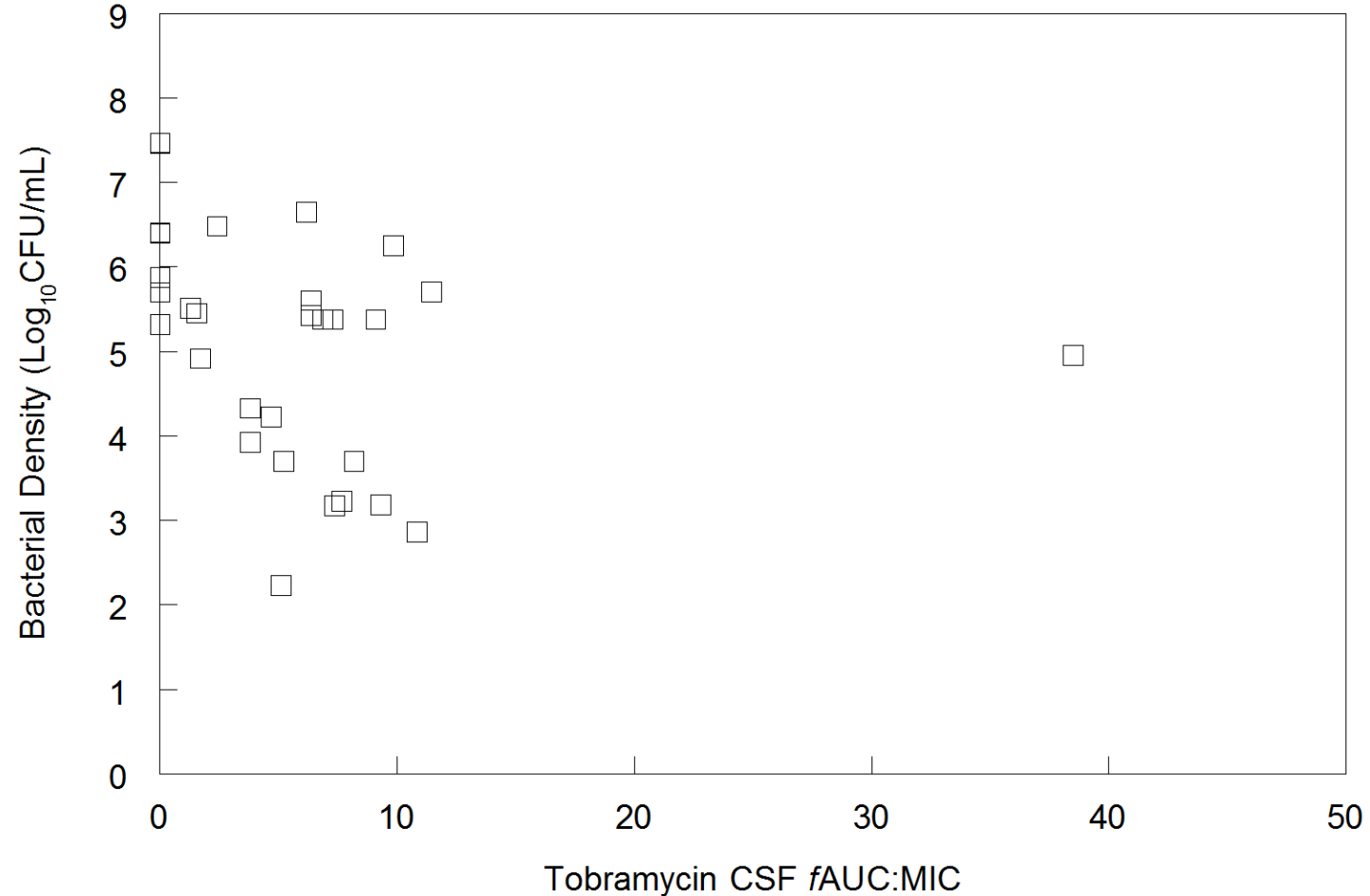
# Tobramycin: pooled raw data from multiple expts.



Pharmacodynamics: Tobramycin plasma exposure vs. CSF  $\text{Log}_{10}\text{CFU/mL}$  (perhaps minimal effect but highly variable and no attempts at regression)



# Pharmacodynamics: Tobramycin CSF exposure vs. CSF $\text{Log}_{10}\text{CFU/mL}$ (no clear effect)



How can these models and this approach be used for neonatal drug development?

# Several observations

- Demonstration of drug in CSF does not necessarily mean there is meaningful clinical activity
  - Compare meropenem and tobramycin in these studies
- The use of MEM in neonates under 3 months of age is not FDA approved. Whether that matters for its use as a benchmark for regulatory purpose is a matter of debate
- However, the pharmacodynamics of new agents (and their potential use for neonatal meningoencephalitis) could be assessed in this model.
- The PK-PD de-risks the subsequent clinical development program by blocking agents that have no CNS activity

# Several observations (cont.)

- A further point of debate is what to do with the information
- Clinical efficacy data with proven/ probable disease is unlikely, which is what everyone ultimately cares about
  - [come to hear Laura Kovanda's talk at ASM-ESCMID Dublin 2020]
- Also, worth reviewing the agency's recent assessment of micafungin for neonatal meningoen­cephalitis
  - [Micafungin was not approved by FDA for treatment of neonatal meningoen­cephalitis due to the absence of clinical data]
- Interesting issues related what to do if dosage escalation is predicted by PK-PD modelling, but if there is no opportunity for clinical correlation.
  - [what to do about clinical PK studies, safety etc.]

# Conclusions

- The experimental-to-clinical bridge seems the only realistic way new antibiotics can be developed for neonates
  - But it does not solve the problem of acquiring definitive clinical data
  - And the current experimental tools are limited
  - The PK-PD approach is “necessary but insufficient”
- The experimental PK-PD assessment and bridging may
  - At least block the progression of compounds that are not safe to use in CNS disease
  - Provide a foundation for justification of dosage
  - Give some reassurance that underpins subsequent clinical studies even if those studies are not likely to be definitive

# Acknowledgements

- Project supported by FDA



