Development and PK Challenges of a Murine Model for *Acinetobacter baumannii* infection

Brian Luna, PhD, and Jürgen Bulitta, PhD
Team Effort

University of Southern California
• Brian Luna, PhD
• Brad Spellberg, MD

University of Florida
• Jürgen Bulitta, PhD
• George Drusano, MD
• Arnold Louie, MD

Case Western
• Robert Bonomo, MD
Rationale behind animal chosen

• Mouse model
• Murine models have proven useful historically for the study of host/pathogen interactions and preclinical drug efficacy studies.

**Study Design**

**TWA** = Temperature, Weight, and Activity Scores  
**CFUs** = Blood (and lung homogenate for OA model)  
**iStat** = blood pH, serum bicarbonate, lactate, and base deficit  
**Cytokines** = Measure blood, lung and ELF compartments.  
  proinflammatory IL-1B, IL-6, and TNF and the anti-inflammatory IL-10.

Mice are euthanized for sample collection.
Hypotheses

• Treatment of mice with FDA-approved antibiotics that are active *in vitro* against the infecting isolate will result in clinical success
  • Survival, clinical endpoints, decrease in CFU burden, inflammatory and physiological endpoints

• In contrast, treatment of mice infected with strains that are resistant to the FDA approved antibiotics will result in clinical failure.
A. baumannii virulence

Integrated Overview of A. baumannii virulence. A) Early clearance of the microbe by the three primary innate effectors—(1) complement, (2) neutrophils, and (3) macrophages—prevents sustained LPS-TLR4 activation and subsequent cytokine storm. B) If the organism can resist initial innate effector clearance and replicate, it triggers sustained LPS activation of TLR4, resulting in cytokine storm and sepsis syndrome.

### Table 1. Antibiotic MICs for Clinical *A. baumannii* isolates.

<table>
<thead>
<tr>
<th><em>A. baumannii</em> Strain</th>
<th>MIC (µg/ml)</th>
<th>AMK</th>
<th>MER</th>
<th>PMB</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>HUMC1</em></td>
<td>128</td>
<td>128</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td><em>VA-AB41</em></td>
<td>8</td>
<td>64</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>LAC-4</td>
<td>128</td>
<td>4</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td><em>LAC-4 ColR</em></td>
<td>64</td>
<td>1</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>ATCC 17978</td>
<td>8</td>
<td>0.25</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>C-14</td>
<td>2</td>
<td>1</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>C-8</td>
<td>8</td>
<td>8</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. LD100s of *A. baumannii* Isolates.1

<table>
<thead>
<tr>
<th></th>
<th>IV bacteremia model</th>
<th>OA pneumonia model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sublethal CFU</td>
<td>LD₁₀₀ CFU</td>
</tr>
<tr>
<td><em>HUMC1</em></td>
<td>5.4x10⁶</td>
<td>2.0x10⁷</td>
</tr>
<tr>
<td>LAC-4</td>
<td>1.0x10⁷</td>
<td>2.5x10⁷</td>
</tr>
<tr>
<td><em>LAC-4 ColR</em></td>
<td>5.7x10⁷</td>
<td>9.7x10⁷</td>
</tr>
<tr>
<td><em>VA-AB41</em></td>
<td>1.0x10⁷</td>
<td>4.3x10⁷</td>
</tr>
<tr>
<td>ATCC 17978</td>
<td>5.0x10⁸</td>
<td>9.0x10⁸</td>
</tr>
<tr>
<td>C-14</td>
<td>5.0x10⁸</td>
<td>N/A</td>
</tr>
<tr>
<td>C-8</td>
<td>8.6x10⁸</td>
<td>9.6x10⁸</td>
</tr>
</tbody>
</table>

1The number shown reflect the highest sublethal inocula or lowest lethal inocula identified.
Temperature and Activity Scores

• Blood infection model: The physiology and host response indicates that the mice die due to sepsis.

• Oral aspiration pneumonia: The physiology and host response indicates that the mice die due to respiratory failure.
**Sepsis Biomarkers**

- **Blood infection model:** The physiology and host response indicates that the mice die due to sepsis.
- **Oral aspiration pneumonia:** The physiology and host response indicates that the mice die due to respiratory failure.
Cytokines

- Blood infection model: The physiology and host response indicates that the mice die due to sepsis.
- Oral aspiration pneumonia: The physiology and host response indicates that the mice die due to respiratory failure.
- Mice in the bacteremia model tend to be sicker than those in the OA model.
Mouse model summary

• *A. baumannii* Isolates
  • Available upon request.
  • Isolates will be deposited to CDC & FDA Antibiotic Resistance Isolate Bank

• Trigger to treat
  • Treatment is initiated 2 hrs post infection.
    • Decrease in activity score.
    • Increase in proinflammatory cytokines
Mouse model summary

To validate the mouse models by testing the efficacy of FDA-approved antibiotics, which have been confirmed by FDA to be effective for treating clinical infections based on adequate and well-controlled clinical trials.

Our goal is to further characterize their validity for predicting efficacy of proven antibiotics that will or will not be effective at treating *A. baumannii* infections.
Projected use of animal model in future drug development

• Useful for testing novel therapeutic agents or novel therapeutic combinations
  • Academia and Industry
• No other validated mouse model for the study of *A. baumannii* infection
  • Immune competent infection models
  • Characterized host/pathogen interaction
  • Humanized PK regimens
    • PK modeling in sick mice
  • Validated clinical endpoints
Projected use of animal model in future drug development (cont.)

• **Mouse ≠ Human**

• **Limitations**
  - Comparatively higher inoculum to cause disease
  - Not all human clinical isolates are virulent in the mice (for *A. baumannii*, hypervirulent strains differ from non-hypervirulent strains; this is important to consider for PK/PD studies)
  - Differences in mouse vs human PK
Efficacy (IV Model)

- HUMC1 (AMK^R)
- VA-AB41 (AMKS)

- Response to therapy (humanized PK) reflects predicted clinical outcomes
**Efficacy (Lung Model)**

- **HUMC1 (AMK<sup>R</sup>)**
- **VA-AB41 (AMK<sup>S</sup>)**

- Response to therapy (humanized PK) reflects predicted clinical outcomes

---

**In vitro susceptibility: Resistant**

- *A. baumannii OA HUMC1 + Amikacin (96.72 mg/kg) Blood CFUs*
- *A. baumannii OA HUMC1 + Amikacin (96.72 mg/kg) BAL CFUs*

---

**In vitro susceptibility: Sensitive**

- *A. baumannii OA VA-AB41 + Amikacin (96.72 mg/kg) Blood CFUs*
- *A. baumannii OA VA-AB41 + Amikacin (96.72 mg/kg) BAL CFUs*
PK- Amikacin
Amikacin dose range study: visual predictive check – IV challenge

Plasma conc. (mg/L) vs. Time (h) for 1.37 mg/kg, 13.7 mg/kg, and 137 mg/kg doses.

- 90th percentile
- 75th percentile
- 50th percentile
- 25th percentile
- 10th percentile
- Observations
Amikacin dose range study: visual predictive check – OA challenge

Plasma conc. (mg/L)

Lung ELF conc. (mg/L)

Time (h)
### Population PK estimates for amikacin dose range studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Unit</th>
<th>Mean (SE)</th>
<th>BSV (SE)</th>
<th>Parameter</th>
<th>Symbol</th>
<th>Unit</th>
<th>Mean (SE)</th>
<th>BSV (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance</td>
<td>CL</td>
<td>mL/h</td>
<td>9.93 (7.9%)</td>
<td>0.185 (54.8%)</td>
<td>Clearance</td>
<td>CL</td>
<td>mL/h</td>
<td>9.93 (7.9%)</td>
<td>0.185 (54.8%)</td>
</tr>
<tr>
<td>Absorption half-life</td>
<td>T1/2abs</td>
<td>min</td>
<td>1.75 (12.1%)</td>
<td>0.1 (fixed)</td>
<td>Absorption half-life</td>
<td>T1/2abs</td>
<td>min</td>
<td>1.01 (34.9%)</td>
<td>0.1 (fixed)</td>
</tr>
<tr>
<td>Volume of central compartment</td>
<td>V1</td>
<td>mL</td>
<td>11.4 (14.1%)</td>
<td>0.1 (fixed)</td>
<td>Volume of central compartment</td>
<td>V1</td>
<td>mL</td>
<td>8.56 (10.6%)</td>
<td>0.1 (fixed)</td>
</tr>
<tr>
<td>Ratio of AUC(elf) by AUC(plasma)</td>
<td>Felf</td>
<td></td>
<td>0.727 (16.9%)</td>
<td>0.1 (fixed)</td>
<td>Ratio of AUC(elf) by AUC(plasma)</td>
<td>Felf</td>
<td></td>
<td>0.727 (16.9%)</td>
<td>0.1 (fixed)</td>
</tr>
<tr>
<td>ELF to plasma equil. half-life</td>
<td>T1/2elf</td>
<td>min</td>
<td>21.9 (8.2%)</td>
<td>0.1 (fixed)</td>
<td>ELF to plasma equil. half-life</td>
<td>T1/2elf</td>
<td>min</td>
<td>21.9 (8.2%)</td>
<td>0.1 (fixed)</td>
</tr>
<tr>
<td>Volume of ELF</td>
<td>Velf</td>
<td>mL</td>
<td>0.1 (fixed)</td>
<td></td>
<td>Volume of ELF</td>
<td>Velf</td>
<td>mL</td>
<td>0.1 (fixed)</td>
<td></td>
</tr>
</tbody>
</table>

- Same clearance after IV and OA challenge.
- Slightly larger volume of distribution for IV vs. OA.
- Terminal half-life: 48 min for IV and 36 min for OA.
- AUC(ELF) 72.7% of the AUC(plasma).
Clinical datasets used as input for the humanization

Avg. dose in humans:
20 to 25 mg/kg amikacin
Amikacin humanized dosing **IV method** (4 doses every 6 h) – Plasma

Daily Dose – 117 mg/kg/day
Fractions of daily doses 61.8% at 0 h, 18.6% at 6 h, 11.3% at 12 h, and 8.2% at 18 h.

![Graph showing plasma concentration over time](image)

**Log Scale**

**Linear Scale**

- **AUC**<sub>0-24h</sub>(plasma)
  - 851 mg·h/L
  - 296 mg·h/L
  - 179 mg·h/L

**Plasma concentration (mg/L)**

- 90<sup>th</sup> percentile (clinical)
- Simulated humanized conc.
- 10<sup>th</sup> percentile (clinical)

**Time (h)**

- 0
- 6
- 12
- 18
- 24
Amikacin humanized dosing **OA method** (4 doses every 6 h) – Plasma

Daily Dose – 96.7 mg/kg/day
Fractions of daily doses 65.0% at 0 h, 16.9% at 6 h, 10.5% at 12 h, and 7.4% at 18 h.

**Linear Scale - PLASMA**

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Concentration (mg·h/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90th percentile</td>
<td>851 mg·h/L</td>
</tr>
<tr>
<td>Sim. Human. plasms</td>
<td>244 mg·h/L</td>
</tr>
<tr>
<td>10th percentile</td>
<td>179 mg·h/L</td>
</tr>
</tbody>
</table>

**Linear Scale - ELF**

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Concentration (mg·h/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>90th percentile</td>
<td>851 mg·h/L</td>
</tr>
<tr>
<td>Sim. humanized ELF</td>
<td>244 mg·h/L</td>
</tr>
<tr>
<td>10th percentile</td>
<td>179 mg·h/L</td>
</tr>
</tbody>
</table>
Amikacin PK validation: visual predictive checks

IV model

OA model

Plasma conc. (mg/L)

Lung ELF conc. (mg/L)

→ Large variability from 18 to 24 h
### Population PK estimates for amikacin from humanized PK validation

#### IV Model - Amikacin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Mean (SE)</th>
<th>BSV (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL_0-6h</td>
<td>mL/h</td>
<td>7.35 (6.8%)</td>
<td>0.1 (fixed)</td>
</tr>
<tr>
<td>CL_6-12h</td>
<td>mL/h</td>
<td>3.81 (6.5%)</td>
<td>0.155 (68.5%)</td>
</tr>
<tr>
<td>CL_12-18h</td>
<td>mL/h</td>
<td>1.39 (25.1%)</td>
<td>1.07 (29.9%)</td>
</tr>
<tr>
<td>CL_18-24h</td>
<td>mL/h</td>
<td>1.60 (23.5%)</td>
<td>0.779 (47.4%)</td>
</tr>
<tr>
<td>T1/2abs</td>
<td>min</td>
<td>1.00 (21.2%)</td>
<td>0.115 (146%)</td>
</tr>
<tr>
<td>V1_0-6h</td>
<td>mL</td>
<td>9.75 (14.7%)</td>
<td>0.1 (fixed)</td>
</tr>
<tr>
<td>V1_6-12h</td>
<td>mL</td>
<td>5.24 (10.4%)</td>
<td>0.250 (72.4%)</td>
</tr>
<tr>
<td>V1_12-18h</td>
<td>mL</td>
<td>3.50 (28.3%)</td>
<td>0.430 (80.9%)</td>
</tr>
<tr>
<td>V1_18-24h</td>
<td>mL</td>
<td>1.51 (18.6%)</td>
<td>0.195 (147%)</td>
</tr>
</tbody>
</table>

#### OA Model - Amikacin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Mean (SE)</th>
<th>BSV (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL_0-6h</td>
<td>mL/h</td>
<td>7.44 (5.5%)</td>
<td>0.1 (fixed)</td>
</tr>
<tr>
<td>CL_6-12h</td>
<td>mL/h</td>
<td>7.69 (4.9%)</td>
<td>0.1 (fixed)</td>
</tr>
<tr>
<td>CL_12-18h</td>
<td>mL/h</td>
<td>5.92 (13.1%)</td>
<td>0.500 (42.3%)</td>
</tr>
<tr>
<td>CL_18-24h</td>
<td>mL/h</td>
<td>4.39 (17.6%)</td>
<td>0.656 (39.7%)</td>
</tr>
<tr>
<td>T1/2abs</td>
<td>min</td>
<td>1.12 (24.7%)</td>
<td>0.1 (fixed)</td>
</tr>
<tr>
<td>V1</td>
<td>mL</td>
<td>7.69 (6.4%)</td>
<td>0.1 (fixed)</td>
</tr>
<tr>
<td>Felf</td>
<td>-</td>
<td>0.604 (4.9%)</td>
<td>0.1 (fixed)</td>
</tr>
<tr>
<td>T1/2elf</td>
<td>min</td>
<td>36.4 (4.4%)</td>
<td>0.1 (fixed)</td>
</tr>
<tr>
<td>Velf</td>
<td>mL</td>
<td>0.10 (fixed)</td>
<td></td>
</tr>
</tbody>
</table>

- Clearance decreased over time in both models (more pronounced for IV model).
- Volume of distribution also decrease for IV model.
- Large between subject variability (BSV) for clearance after 12 h.
- ELF penetration results comparable to those in the dose range study.
Conclusions of dosing simulations – Amikacin

- PK model in mice was used to simulate human-like drug exposures.
- We targeted the 90\textsuperscript{th} percentile of concentrations in VABP patients.
- The AUCs for amikacin associated with the 10\textsuperscript{th} and 90\textsuperscript{th} percentiles were approximately 179 and 851 mg\cdot h/L
- The AUC in patients for a dose of 30 mg/kg is \(~308\) mg\cdot h/L.
- Peaks in critically-ill patient are typically 60 to 100 mg/L (medians).
- Humanized concentrations were similar to the targeted conc. range.
- Clearances decreased and became more variable after 12 h, potentially due to bacterial damage to the kidneys.
PK- Polymyxin B
Polymyxin B concentrations in mice for IV challenge model

DVID 1 = polymyxin B1
DVID 2 = polymyxin B1-Ile
DVID 3 = polymyxin B2
DVID 4 = polymyxin B3
DVID 5 = All 4 components

Polymyxin B1 was the predominant component.
Polymyxin B3 was the lowest abundancy component.
Relative bioavailability (F) estimated during modeling.
Structural model for all 5 dependent variables in IV challenge mice

**Structure:** One-compartment model for each component, sum of four $F$ equal to 1

- **ASC PB1**
- **ASC PB1-ILe**
- **ASC PB2**
- **ASC PB3**

Total polymyxin B concentration modeled as the sum of all 4 components.

V1 and CL were shared across all four components of polymyxin B.

Other modeling choices and estimation algorithms were thoroughly tested at this stage.
Polymyxin B dose range study: VPC for 16 mg/kg – IV challenge

Polymyxin B1

Polymyxin B2

Polymyxin B (sum)

Polymyxin B1-ILe

Polymyxin B3

Plasma concentration (mg/L)

Time (h)

90th percentile
75th percentile
50th percentile
25th percentile
10th percentile
Observations
### Parameter estimates for polymyxin B for IV model

*(importance sampling in S-ADAPT; Luna et al. dataset)*

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Parameter</th>
<th>Unit</th>
<th>Population Mean (relative standard error, SE%)</th>
<th>Between Subject Variability, CV (SE%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2abs(L)</td>
<td>Absorption half-life at 8 and 12 mg/kg</td>
<td>min</td>
<td>7.20 (9.2%)</td>
<td>0.109 (77.5%)</td>
</tr>
<tr>
<td>T1/2abs(H)</td>
<td>Absorption half-life at 16 mg/kg</td>
<td>min</td>
<td>11.7 (54.7%)</td>
<td>0.125 (105%)</td>
</tr>
<tr>
<td>CL</td>
<td>Clearance</td>
<td>mL/h</td>
<td>5.60 (6.0%)</td>
<td>0.471 (26.2%)</td>
</tr>
<tr>
<td>V1</td>
<td>Volume of distribution for central compartment</td>
<td>mL</td>
<td>26.3 (6.2%)</td>
<td>0.308 (26.1%)</td>
</tr>
<tr>
<td>F(PB1)</td>
<td>Bioavailability of PB1</td>
<td>-</td>
<td>72.4% (2.7%)</td>
<td>small</td>
</tr>
<tr>
<td>F(PB1-ILe)</td>
<td>Bioavailability of PB1-ILe</td>
<td>-</td>
<td>12.0% (3.3%)</td>
<td>small</td>
</tr>
<tr>
<td>F(PB2)</td>
<td>Bioavailability of PB2</td>
<td>-</td>
<td>12.8% (3.2%)</td>
<td>small</td>
</tr>
<tr>
<td>F(PB3)</td>
<td>Bioavailability of PB3</td>
<td>-</td>
<td>2.83%</td>
<td>small</td>
</tr>
</tbody>
</table>

Estimating the same volume of distribution for all components stabilized the model and allowed us to estimate the BSV for both CL and V1.

All additive residual error standard deviations were fixed to 0.025 mg/L.
All proportional residual errors were fixed to a 10% coefficient of variation.
Humanized dosing for polymyxin B for IV model

Polymyxin B in critically ill patients
2 mg/kg load, 1.5 mg/kg Q12h maintenance dose;
IV: Mouse: 11 mg/kg at 0 h and 10 mg/kg at 12h
Mouse_b: 9.5 @ 0h, 1.5 @ 6h, 8.5 @ 12h, 1.5 @ 18h

AUC (mg*h/L)

- 90%: 116
- 50%: 80
- 10%: 52
- Mouse: 83
- Mouse_b: 81

We recommend 11 mg/kg at 0 h and 10 mg/kg at 12 h option

Total concentrations were matched. This assumes that the protein binding in plasma was similar between infected mice and patients.
Polymyxin B dose range study: VPC for validation – IV challenge

Polymyxin B1

Polymyxin B2

Polymyxin B (sum)

Polymyxin B1-ILe

Polymyxin B3

Sandri AM, Landersdorfer CB et al. CID 2013; 57:524-31

Patients
Conclusions for humanizing PMB

• For the IV model: we recommend 11 mg/kg (0 h) & 10 mg/kg (12 h)
  • Match the total drug AUC in plasma from 0 to 24 h between patients and mice
  • Mouse values stay between the 10th and 90th percentile in humans

• For the OA model, we recommend 7 mg/kg (0 h) & 6 mg/kg (12 h)
  • This matches the total drug AUC from 0 to 24 h in patient plasma with the unbound AUC in mouse ELF. The mouse plasma AUC are slightly higher.

• The IV vs. OA challenge considerably affected total clearance.

• It seems important to validate the PK in the mouse model using the same isolates and pathogens that are used in efficacy studies.
PK- Meropenem
Meropenem peak and trough concentrations for bolus and short-term infusion regimens in critically ill patients

• We sought to mirror the PK in critically ill patients with normal renal function by humanizing the mouse dosage regimens.
• Targeted dosage regimen in humans: 2g short-term (30min) infusions every 8h.

For this dosage regimen:
• The average peak concentrations ~60 to 100 mg/L.
• The average trough concentrations ~1 to 10 mg/L.
• Meropenem is minimally protein bound in human plasma.
Monte Carlo simulated meropenem concentrations in humans for 2g q8h as 30 min infusion in critically ill patients

Linear scale

Meropenem concentrations in critically ill patients

Log-scale

Meropenem concentrations in critically ill patients
Monte Carlo simulated meropenem concentrations in humans for 2g q8h as **30 min** infusion in critically ill patients

![Graph showing meropenem concentrations in critically ill patients](image)

- **Humanized mouse regimen**
- **Linear scale**
- **Log-scale**

Meropenem concentrations in critically ill patients

- **50 mg/kg**
- **30 mg/kg**
- **18 mg/kg**
- **11 mg/kg**

**Best capture of the human concentration time profile. However, this would result in 12 (=4 x 3) doses per day.**
Monte Carlo simulated meropenem concentrations in humans for 2g q8h as 30 min infusion in critically ill patients

Linear scale

Humanized mouse regimen

Log-scale

Meropenem concentrations in critically ill patients

If we use the criterion not to over-shoot the 90% percentile in patients, 2 doses every 8 h (i.e. 6 doses per day) do likely not well capture the time-course of plasma concentrations in humans.
Free time above MIC (fT>MIC) for different humanized regimens in mouse (OA model) using 4, 3 or 2 doses every 8 h

Carbapenem targets in mice:
- Stasis: ~20% fT>MIC
- Near-max killing: ~40% fT>MIC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>MIC (mg/L)</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4 doses Q8h</strong></td>
<td>Plasma</td>
<td>50 mg/kg @ 0h</td>
<td>87%</td>
<td>76%</td>
<td>65%</td>
<td>52%</td>
<td>37%</td>
</tr>
<tr>
<td></td>
<td>ELF</td>
<td>30 mg/kg @ 1.5h</td>
<td>75%</td>
<td>63%</td>
<td>47%</td>
<td>25%</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18 mg/kg @ 3.5h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>11 mg/kg @ 5.5h</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2 doses Q8h</strong></td>
<td>Plasma</td>
<td>50 mg/kg @ 0h</td>
<td>51%</td>
<td>43%</td>
<td>36%</td>
<td>28%</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>ELF</td>
<td>17 mg/kg @ 3.5h</td>
<td>43%</td>
<td>35%</td>
<td>26%</td>
<td>14%</td>
<td>7%</td>
</tr>
</tbody>
</table>

2 doses Q8h would only achieve fT>MIC >35% for MICs up to 2 mg/L in plasma. The covered MICs in ELF were approximately 2-fold lower than those in plasma.
Meropenem in mice

• Very short half-life relative to that in humans.
• Limited to 6 daily SC injections

• The addition of *cilastatin* or *probenecid* may reduce meropenem clearance and improve murine model.

• Uranyl nitrate likely no option, since this compound is toxic and is becoming increasingly hard to purchase.
Summary

- Immune competent mouse model
- Humanized PK
  - AMK and PMB
  - MERO in progress
- Therapeutic outcomes
  - Amikacin- outcomes reflect *in vitro* antimicrobial sensitivity data.
  - Polymyxin B & Meropenem- In progress
- Each drug to be studied has its own unique problems for developing a humanized dosing strategy
Acknowledgements

USC
- Brad Spellberg
- Jun Yan
- Peggy Lu
- Zeferino Reyna
- Juan Ruiz-Delgado
- Rosemary She

University of Florida
- George Drusano
- Arnold Louie
- Dhruvit Sutaria
- Yuanyuan Jiao
- Nirav Shah
- David Brown

Case Western
- Robert Bonomo
- Kristine Hujer
- Funding: FDA Contract HHSF2230110199C