Acinetobacter baumannii

- MDR infections tend to occur in immunosuppressed patients, in patients with serious underlying diseases, and in those subjected to invasive procedures and treated with broad-spectrum antibiotics.
- Infections are frequently found in intensive care units (ICUs), where they are implicated as the cause of ventilator-associated pneumonia (VAP), urinary tract infections, and bacteremia.
- Resistance to β-lactams, (β-lactamases: Class A (TEM, SHV, CTX-M), Class B (IMP), Class C and Class D (OXA-23), aminoglycosides, fluoroquinolones (gyrA / parC), tetracyclines (efflux) and polymixins.

Pseudomonas aeruginosa

- Problematic for seriously ill patients - Responsible for 21% of pneumonias, 10% of urinary tract infections, 3% of bloodstream infections, and 13% of eye, ear, nose, and throat infections within ICUs.
- Most commonly isolated bacterium colonizing severe burns and wound infections.
- Wound infections caused by multidrug resistant (MDR) P. aeruginosa have been associated with high morbidity and mortality rates worldwide.
Based on the clinical issues faced due to both *A. baumannii* and *P. aeruginosa* infections, there exists the need for specific experimental animal models to be developed and used to screen and evaluate efficacy of new treatment options for these infections.

To be relevant for the evaluation of new therapies to combat MDR *A. baumannii* and *P. aeruginosa* animal models:

- Need to be representative of current clinical needs
  - Pneumonia, urinary tract infections, wounds/burns, bacteremia
- Need to make use of relevant bacteria strains
  - Clinical isolates based on indication or site of isolation/infection
- Need to utilize current strains of concern
  - Based on resistance phenotypes
- Need to involve proper doses and dosing regimens
  - Treatment of established chronic infections
- Need to define the measure of efficacy
  - Reduction of bacterial titers at the site(s) of infection
- Murine Lung Infection Model (Bacterial pneumonia)
  - Normal / Neutropenic mice (CD-1, Balb/c, C57Bl/6)
  - Intranasal inoculation
  - Treatment delayed 4 - 24 hrs post-infection (single/multiple dose regimens and routes – parenteral, oral and aerosol delivery)
  - Lung titer / Survival endpoints / PK-PD estimates (plasma & ELF)
  - Established for *A. baumannii* & *P. aeruginosa* endotracheal clinical isolates of various resistance phenotypes

- Murine Ascending Pyelonephritis (Urinary Tract Infection)
  - Normal / diabetic mice (C3H/HeJ)
  - Transurethral inoculation
  - Treatment initiated 4 days post-infection (established ascending model)
  - Kidney / Bladder / Urine titer endpoints
  - Established for multiple *P. aeruginosa* urine clinical isolates
- Murine Skin Infection Models (Skin & Skin Structure Infection)
  - Normal / Partial neutropenic mice (CD-1)
  - Intradermal (superficial) or subcutaneous (abscess) infection types
  - Treatment initiated 4 - 24 hrs post-infection, single/multiple dose regimens, both topical and parenteral
  - Bacterial titer / wound healing endpoints
  - Established for *A. baumannii* & *P. aeruginosa* wound clinical isolates (including mixed infection with *S. aureus*)

- Murine Septicemia (Systemic Bacteremia)
  - Normal mice (CD-1)
  - Intraperitoneal or intravenous inoculation
  - Treatment initiated 1 - 4 hrs post-infection (single/multiple dose regimens)
  - Survival (ED$_{50}$) / Blood & Spleen titer endpoints (time course)
  - Established for *A. baumannii* & *P. aeruginosa* bloodstream clinical isolates, including characterized resistant strains (IMP-4, OXA, TEM, SHV, KPC, NDM)