Porcine Animal Model of Ventilator-Associated Bacterial Pneumonia Caused by *Pseudomonas aeruginosa* or *Acinetobacter baumannii*

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March 5th, 2020

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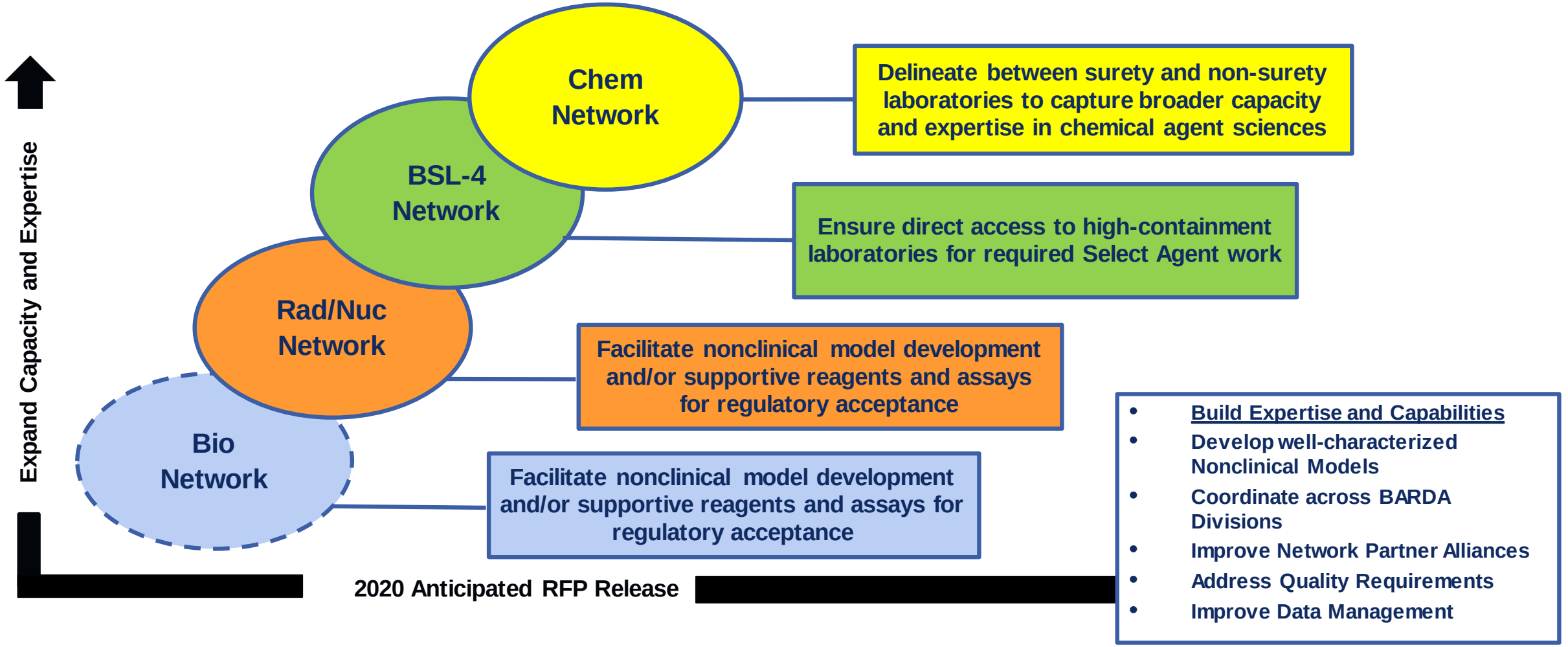
BARDA Nonclinical Division



Application of Animal Models in Drug Development

- …"When human efficacy studies are not ethical and field trials are not feasible"
- Well-understood disease mechanism and prevention/reduction by the product
- Action within animal model(s) should be predictive of human response
- Endpoints related to the desired benefit in humans
- PD/PK data for translation of an effective dose to humans

Development of Large Animal Models for Antibacterial Drug Development

Obtain efficacy data from adequately characterized animal model(s)

- Could be supplemented with clinical data from patients with a variety of infections caused by *P. aeruginosa* in one or more descriptive studies
- There are currently no adequately characterized animal models for the indications being considered
- Unlike trials for biothreat agents, it is ethical to conduct human efficacy trials; however, feasibility of conducting such trials is the issue

Advantages of Porcine Model

- Anatomical, physiological and biochemical similarities to humans
- Gross and microscopic anatomy of the porcine lung is similar to human lungs
- Similar array of innate immune function in the lungs
- Large size amenable to the use of equipment typically used for humans in critical care scenarios
- Previous VABP studies using swine have also demonstrated that they can be mechanically ventilated for 3-4 days after bacterial inoculation, which allows sufficient time for development of disease, initiation of therapy, and monitoring the response to therapy (LiBassi et al., 2014)

Study Plan

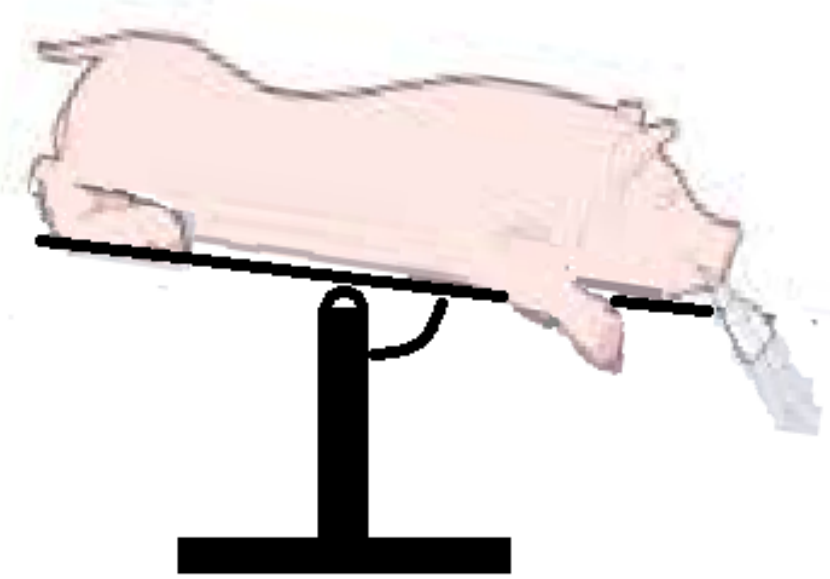
- √ Create and characterize strains of ceftriaxone-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa*
- √ Pilot to establish prolonged ventilation in the porcine model
  - Female Yorkshire-Landrace crossbred juvenile pigs
  - Anesthetized and ventilated for 96 hours
  - Antibiotic treatment to minimize spontaneous pneumonia
- Establish bronchoscopic challenge and dose ranging for each strain
- Characterize the natural history of VABP disease in the porcine model
  - Monitor disease development and progression
  - Establish euthanasia criteria
- Utilize the developed model to evaluate the efficacy of antibacterial drugs to which the strains are susceptible and resistant

Challenges and Considerations

- Catheterization
  - Venous & arterial
  - Urinary
- Intubation
  - Endotracheal tube
  - Mechanical ventilation
- Maintenance & Support
  - Continuous rate infusion anesthesia
  - IV fluids
  - Vital sign monitoring
  - Hematology, clinical chemistry
- Euthanasia
  - Necropsy
  - Bacteriology

Positioning

- Trendelenburg position at -15 degree angle relative to the horizontal plane
  - Ventral Recumbency
  - Restraints
  - Foam padding
- Pressure sores
  - Sternum
  - Hind limbs
  - Forelimbs

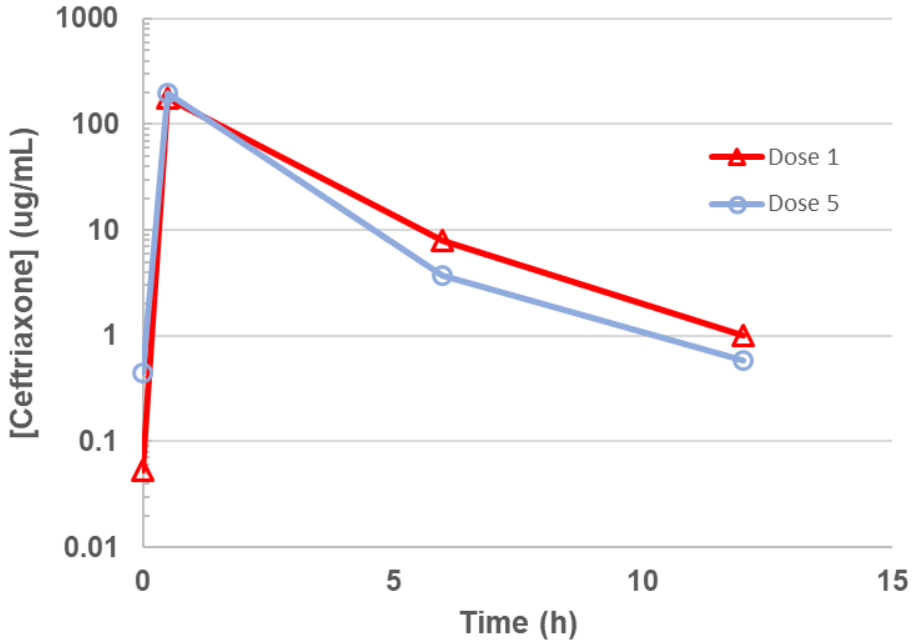


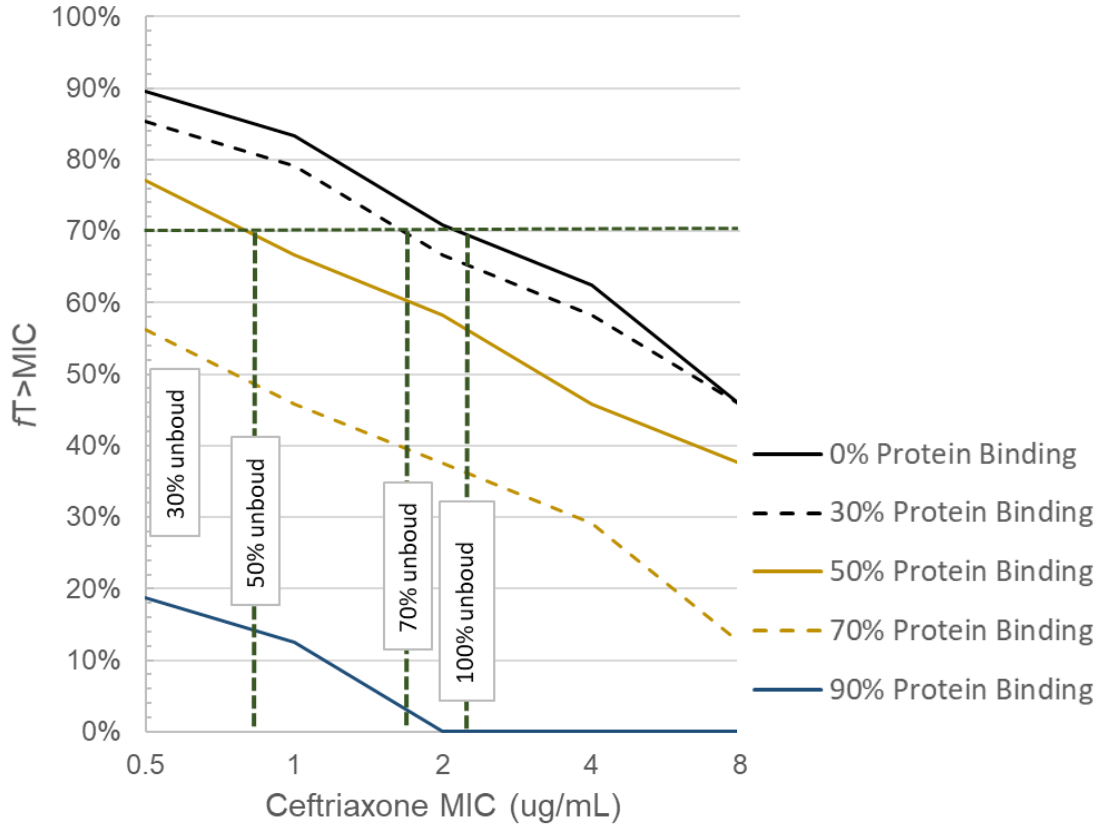
Monitoring

- Heart rate
- Mean arterial pressure (MAP)
- Core body temperature
- SpO_2 (pulse oximeter)
- ECG
- Urine output
- Arterial blood gas
- Respiratory rate
- Spontaneous respiration rate
- Total minute volume
- End tidal CO_2
- FiO_2
- P_{aw} plateau
- Peak inspiratory pressure
- Compliance
- Resistance
- PO_2/FiO_2 (calculated)
- ETT Cuff Pressure
- Tracheal secretion quantity (estimated)
- Tracheal secretion quality
- Hematology (every 24 hours)
- Clinical chemistry (every 24 hours)
- Porcine CRP
- Porcine procalcitonin

Ceftriaxone

- Intravenous dose of 50 mg/kg q12h
- 30 minute infusion
- Start within two hours of mechanical ventilation





Note: If we assume that the unbound fraction is between 50-60%, then a dose of 50 mg/kg q12h should provide coverage for organisms with a ceftriaxone MIC ≤ 2 ug/mL

Bacteriology

- Blood culture at time of euthanasia
  - Ideally 100 mL
- Culture of lung tissue samples (quantitative)
  - Ideally 8 to 10 samples with a pre-specified tissue sampling plan
- Identification (MALDI-TOF)
- Antibiotic susceptibility testing

Proposed Euthanasia Criteria

Parameter	Potential Humane Endpoint
• Technical	• Any adverse mechanical event that cannot be remedied
• Severe Hypoxia	• < 40 mm of PaO_2 twice, 5 minutes apart with FiO_2 of 100%
• Mean Arterial Blood Pressure	• Persistent hypotension, < 30 mm Hg for > 30 minutes
• Electrocardiography	• Asystole for > 3 minutes

Necropsy

- Gross necropsy findings
- Sterile collection of tissues for bacteriology
- Collection of lung samples for histopathology
- Grading of pathologic lesions (Marquette, 1999)
- Collection of a limited set of tissues for histopathology

Conclusions

- Pilot studies demonstrate feasibility of mechanical ventilation for 96h in the Yorkshire-Landrace pigs
- Large animal model is amenable to physiologic and microbiologic characterization of the natural history of disease
- Large animal studies are challenging to establish and conduct

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