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

Andrew Phipps, DVM, PhD, DACVM
Contractor in support of the Biomedical Advanced Research and Development Authority

March 5th, 2020

UNCLASSIFIED
BARDA Nonclinical Division

Delineate between surety and non-surety laboratories to capture broader capacity and expertise in chemical agent sciences

Ensure direct access to high-containment laboratories for required Select Agent work

Facilitate nonclinical model development and/or supportive reagents and assays for regulatory acceptance

Facilitate nonclinical model development and/or supportive reagents and assays for regulatory acceptance

• Build Expertise and Capabilities
• Develop well-characterized Nonclinical Models
• Coordinate across BARDA Divisions
• Improve Network Partner Alliances
• Address Quality Requirements
• Improve Data Management

Expand Capacity and Expertise

Bio Network

BSL-4 Network

Rad/Nuc Network

Chem Network

2020 Anticipated RFP Release
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
- $\text{SpO}_2$ (pulse oximeter)
- ECG
- Urine output
- Arterial blood gas
- Respiratory rate
- Spontaneous respiration rate
- Total minute volume
- End tidal $\text{CO}_2$
- $\text{FiO}_2$
- $P_{aw}$ plateau
- Peak inspiratory pressure
- Compliance
- Resistance
- $\text{PO}_2/\text{FiO}_2$ (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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Potential Humane Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical</td>
<td>Any adverse mechanical event that cannot be remedied</td>
</tr>
<tr>
<td>Severe Hypoxia</td>
<td>&lt; 40 mm of PaO$_2$ twice, 5 minutes apart with FiO$_2$ of 100%</td>
</tr>
<tr>
<td>Mean Arterial Blood Pressure</td>
<td>Persistent hypotension, &lt; 30 mm Hg for &gt; 30 minutes</td>
</tr>
<tr>
<td>Electrocardiography</td>
<td>Asystole for &gt; 3 minutes</td>
</tr>
</tbody>
</table>
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
How to Contact BARDA

phe.gov/BARDA
Program description, information, news, announcements, connect to TechWatch

medicalcountermeasures.gov
Portal to BARDA: Register to request a TechWatch meeting!

beta.sam.gov/
Official announcements and info for all government contract solicitations

drive.hhs.gov
Learn about DRIVE, including our Accelerator Network and EZ BAA

www.usajobs.gov
Join the team!