Establishment and validation of rodent pneumonia models with *P. aeruginosa* and *A. baumannii* at GSK

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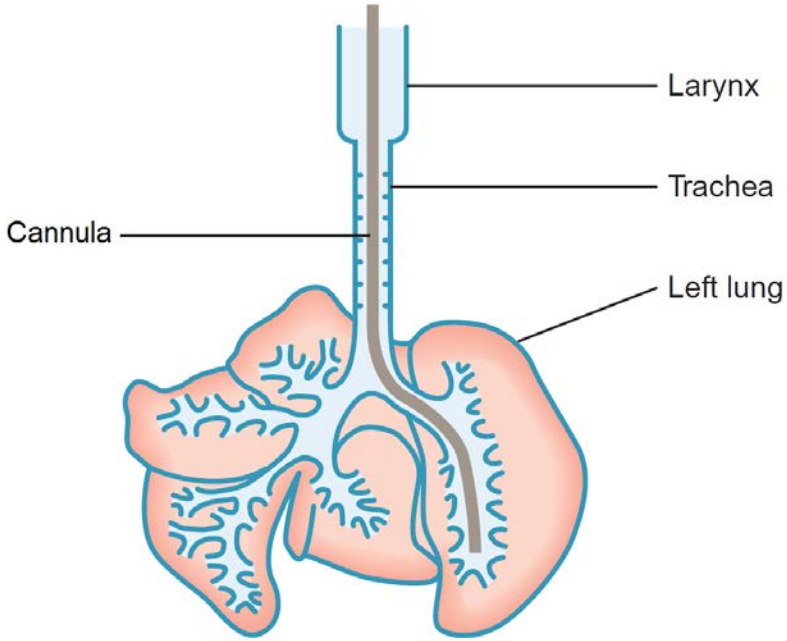
Induction of pneumonia in immunocompetent mice and rats

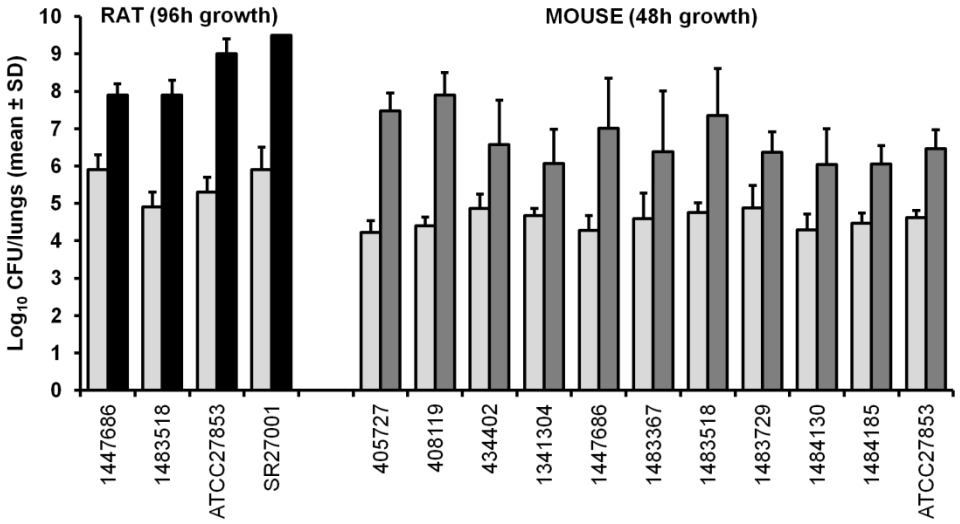
- Animals are briefly anesthetized by inhalation of isoflurane
- Deep lung is accessed via nonsurgical intratracheal intubation
- Agar suspension inoculum (not beads) is deposited deep into lung
- Procedure can be performed rapidly by skilled personnel
- Refer to our recent article in JoVE for detailed methods and video demonstration

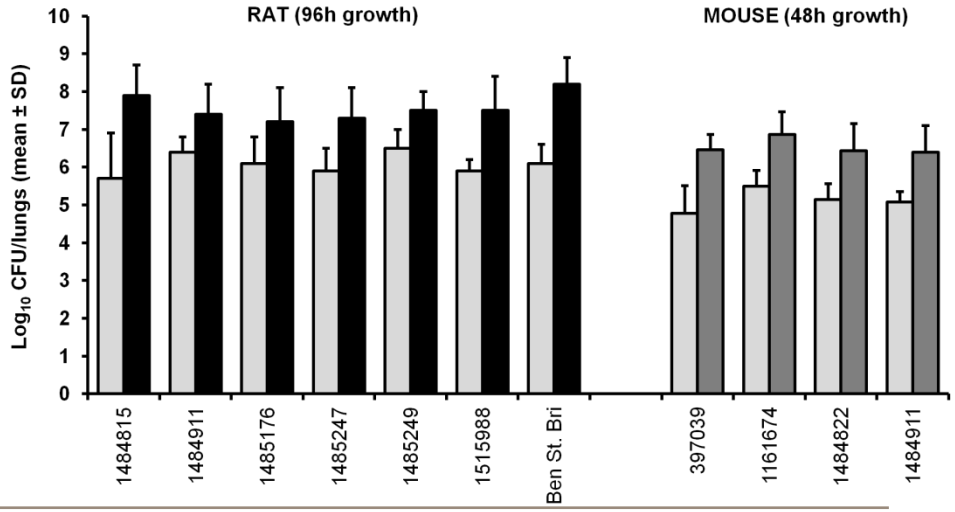


Hoover, J. L., Lewandowski, T. F., Mininger, C. L., Singley, C. M., Sucoloski, S., Rittenhouse, S. **A Robust Pneumonia Model in Immunocompetent Rodents to Evaluate Antibacterial Efficacy against *S. pneumoniae*, *H. influenzae*, *K. pneumoniae*, *P. aeruginosa* or *A. baumannii*.** J. Vis. Exp. (119), e55068, doi:10.3791/55068 (2017).

Infection can be established with many isolates across a range of pathogens

- Example strains of *P. aeruginosa* (top) and *A. baumannii* (bottom)
  - Light bars = Baseline CFU
  - Dark bars = End-of-study CFU
- Spontaneous clearance of bacteria not observed over 48h or 96h study period
- Amenable to many different strains with varying resistance profiles
- Flexibility in strain choice
- Neutropenia not required





J. Vis. Exp. (doi:10.3791/55068)

Models are validated based on isolate susceptibility and relevance to human disease

- Relevant doses of commercially available antibiotics are ineffective against resistant isolates
- Efficacy at relevant doses is observed against isolates considered susceptible
- Pathology similar to human disease was noted in a limited histology examination of rat lungs infected with *P. aeruginosa* via this method
  - bronchopneumonia with multifocal inflammation, perivascular edema, localized congestion, thickening of the interstitium, infiltrates of neutrophils and macrophages, fibrin, necrotic and apoptotic cell debris

"Wish List" for additional validation to confirm translation to clinic

- PK/PD validation
  - Based on clinically accepted targets for stasis, 1-log and/or 2-log reduction in CFU for at least one exemplar of most commonly used antibiotics
- Expanded investigation of pathology
  - Include mice
  - Evaluate time course of disease progression
  - Understand impact of agar (if any)

Summary and Next Steps

– In summary, this model offers another approach for preclinical evaluation of novel antibacterials against *P. aeruginosa* and *A. baumannii* and has advantages over some existing models

– Goals from this presentation are to:

1. Raise awareness of this model
2. Seek collaboration with other scientists
3. Offer GSK's expertise to support establishment of animal models which best translate to the clinic