Standardization of the murine pneumonia model

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On behalf of the AMR Accelerator and COMBINE Consortium
Accelerating scientific discoveries and advancing the R&D pipeline of new and innovative agents to treat TB and NTM lung disease.

Advancing the R&D pipeline of new and innovative agents to address AMR in Gram-negative bacteria.

Accelerating and validating scientific discoveries in AMR. Coordinating and supporting projects across the AMR Accelerator.

Who are we?

WP1: Coordination and support
WP2: IT infrastructure and Data Management
WP3: Communication and Networking
WP4: Clinical Trial Design
WP5: Animal models

IMI AMR Accelerator: Tackling antibiotic resistance together

Participants: 98
ME Budget: 489
Projects: 9
Programmes in the Portfolio: 15
Collaboration for prevention and treatment of MDR bacterial infections (COMBINE)

- 6 year project from Nov 2019 – Nov 2025

Universities, research organisations, public bodies, non-profit groups:
- Uppsala University (UU) Sweden Coordinator
- Paul-Ehrlich-Institut (PEI) Germany
- Fraunhofer Gesellschaft (FRAUNHOFER) Germany
- Statens Serum Institut (SSI) Denmark
- BEAM Alliance (BA) France

Small and medium-sized enterprises (SMEs) and mid-sized companies (<€500 m turnover):
- Asclepia (AC) Belgium
- GRIT42 (G42) Denmark
- BIOCOM (BC) Germany

EFPIA companies:
- GlaxoSmithKline (GSK) United Kingdom Project Lead
- Evotec (EVT) Germany
- Janssen (JNJ) Belgium

https://amr-accelerator.eu/project/combine
WP5: Animal Models & PK/PD

**Improve animal infection model reproducibility and translation to clinical efficacy**

**Problem:**
- Animal infection models are excellent tools, yet translational gaps remain
- Methods used for study conduct & analyses impact results
- Lack of standardization hinders interpretation & comparison

**Our ambitious goals:**
- Develop a standardized animal infection model
- Benchmark standard model using relevant control compounds
- Establish *in vivo* reference strain bank supported by data from the model
- Provide framework for PK/PD analysis & mathematical modelling
- Improve understanding of preclinical-to-clinical translation
Establish Reference Strain Bank

- Identify strains that can be made available to the AMR community
- Select candidate strains that perform well in a standard model across labs

Improve Preclinical-to-Clinical Translation

- Demonstrate how to best interpret and use the data for PK/PD modeling
- Evaluate how response in our standard model translates to the clinic

Generate & Validate a standardized infection model

- Select appropriate model and parameters to standardize
- Generate efficacy data for control antibiotics using candidate strains

Selection of Isolates

Chosen to test based on:
• Shareability
• Antibiogram
• Contemporary
• Characterization (if available)

Candidate strains filtered by:
• Virulence
• Standard protocol criteria
• Mortality
• Expected +/- efficacy response

Ref strains chosen for:
• Standard protocol criteria
• PK/PD characterization

Candidate strains

Repository strains

Reference strains
1. **Validate strains in model**
   - To ensure consistent virulence in the model at multiple labs (SSI, PEI, GSK)

2. **Choose reference compounds**
   - Examples of different classes (Meropenem and Levofloxacin)
   - Reasonable to work with *in vivo*
   - Maximize given resources (collaborations)

3. **Generate in vivo data**
   - PK from infected mice
   - PD for \( \geq 3 \) strains of *P. aeruginosa* and *K. pneumoniae*
Our goal in WP5 is to move the AMR community

FROM:
1. Variability in animal models employed for pneumonia
2. Inconsistent strain use
3. Lack of consensus on interpretation
4. Varying application of mathematical modeling
5. Greater translational risk

TO:
1. Standardized & validated pneumonia model
2. (At least some) reference strains
3. More informed interpretation
4. Clear PK/PD modeling framework
5. Greater confidence moving to clinic with new antibacterials
Outreach and collaborations with other organizations

Strains

In vivo studies

- Input and advice on both our general strategy and the chosen parameters in to standardize pneumonia model
- Exchange ideas on study design for validation/benchmarking studies
- Highlight insights and discuss challenges
Would you like to collaborate with COMBINE?

Share expertise

Contact us: IMI-COMBINE@pei.de

Support our data quest

Share your preclinical and clinical pneumonia data

Combine effort on common interests

Conduct validation studies in your lab
Share isolates for repository
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All animal experiments were ethically reviewed as per local requirements prior to commencement of work.

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