COMBINE WP5:
Improving animal models and preclinical-to-clinical translation

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AMR Accelerator: Public-Private collaboration with the shared goal of progressing the development of new medicines to treat or prevent resistant bacterial infections (www.amr-accelerator.eu)
Who are we?
3 topics within the AMR Accelerator

**TUBERCULOSIS & NTM**
Accelerating scientific discoveries and advancing the R&D pipeline of new and innovative agents to treat TB and NTM lung disease.

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

**CAPABILITY BUILDING**
Accelerating and validating scientific discoveries in AMR. Coordinating and supporting projects across the AMR Accelerator.
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
- B IOCOM (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 understanding of 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 standardised animal infection model protocol
- 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
Two main workstreams

Establish Reference Strain Bank

- Identify candidate strains that perform well in the standard model
- Evaluate performance of selected strains across labs and studies
- Provide benchmark data for the selected strain-antibiotic combinations
- Ensure reference strains and data are available to AMR community

Improve Preclinical-to-Clinical Translation

- Investigate how response in our standard model translates to the clinic
- Learn how to appropriately interpret the data from our standard model
- Explore variability in drug response across strains and between labs
- Demonstrate how to best use the data for PK/PD modeling
- Provide preclinical data for further translational analyses
Selection of model and assessment of methods in literature

**AMR Animal Models Webinar**
- Presentations on models to study antibiotics vs. Gram-neg pathogens
- Survey of participants to identify greatest need for model improvement

**Results of Literature Review**
- Substantial differences in study methods
  - Mouse strain, sex, age, etc.
  - Bacterial strains/inoculum
  - Infection procedure
  - Treatment time, route, etc.
  - Study endpoints and timing

![Bar chart showing model with greatest translational gap](chart.png)

*Model with greatest translational gap (% of survey participants)*
Identification of key variables and selection of standards

**EXPERT WORKSHOP:** Develop standardized murine model to evaluate treatments for AMR lung infections

- **Day 1 (Tuesday, April 27th 2021): 15:00-19:00 CEST**
  - Developing a standardized murine pneumonia model to characterize PK/PD of antibiotics

- **Day 2 (Wednesday, April 28th 2021): 15:00-19:00 CEST**
  - Standard protocols for murine pneumonia models - beyond PK/PD

**Variables discussed/standardized**

- **Inoculum**
  - Source of bacteria
  - Culture media
  - Growth stage
  - Inoculum preparation

- **Animals**
  - Mouse strain
  - Sex
  - Age
  - Number animals/group
  - Others

- **Infection procedure**
  - Immunosuppression
  - Anesthesia
  - Infection route
  - Infection volume
  - Inoculum concentration

- **Treatment and endpoint**
  - Start of treatment
  - Baseline CFU
  - Bacterial growth in mice
  - Length of study
  - Primary endpoint
  - Sample processing methods

**Watch for our upcoming publications!**
1. Select bacterial strains
   - Characterized for resistance profile
   - That are shareable via an accessible repository

2. Validate strains in model
   - To ensure consistent growth

3. Choose reference compounds
   - Examples of different classes
   - Reasonable to work with in vivo
   - Maximize collaborative efforts

4. Generate in vivo data
   - PK from infected mice
   - PD for ≥3 strains of P. aeruginosa and K. pneumoniae

5. Analyses/reporting

**Standard lung model established for PK/PD**

- **Animals**
  - CD1 (outbred) mice
  - Female mice
  - Minimum of 3 days of acclimatization
  - 6-8 weeks old animals
  - 5-6 animals per group

- **Inoculum**
  - Include one in vivo validated strain from an accessible strain bank
  - Use bacteria in logarithmic phase of growth

- **Infection procedure**
  - Use neutropenic mice
  - Cyclophosphamide 150 mg/kg at day -4 and 100 mg/kg at day -1
  - Intranasal infection route
  - Inoculum of 50 μl

- **Treatment and end point**
  - Treatment at 2 hour post infection
  - Baseline CFU of 6-7 log10
  - Min. growth of 1 log10 CFU
  - Length of study 26 h post infection
  - Endpoint readout CFU/lung

**What’s next?**
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. Benchmarked in vivo reference strains
3. More informed interpretation
4. Clear PK/PD modeling framework
5. Greater confidence moving to clinic with new antibacterials
COMBINE aims to identify better ways to translate preclinical know-how into clinical predictions.

Let’s collaborate! Can you...

- **Share expertise** and strains
  
  *Contact us: IMI-COMBINE@pei.de*

- **Support our data quest**
  
  *Share your preclinical and/or clinical pneumonia data*

- **Combine effort** on common interests
  
  *Conduct validation studies in your lab or CRO*
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