Standardization of the murine pneumonia model

Rakel Arrazuria - Paul Ehrlich Institut (German Federal Institute for Vaccines and Biomedicines)
On behalf of the AMR Accelerator and COMBINE Consortium

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?

IMI AMR Accelerator

Tackling antibiotic resistance together

98	489	9	15
Participants	M€ Budget	Projects	Programmes in the Portfolio

TUBERCULOSIS & NTM

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

TRIC-TB

UNITE 4TB

RESPIRI TB

RESPIRI NTM

ERA 4TB EUROPEAN REGIMEN ACCELERATOR FOR TUBERCULOSIS

GRAM-NEGATIVES

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

AB-Direct Antibiotic Distribution & Recovery

GNA NOW

CAPABILITY BUILDING

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

COMBINE

PrIMAVeRa

COMBINE Part of IMI AMR Accelerator

WP1: Coordination and support

WP2: IT infrastructure and Data Management.

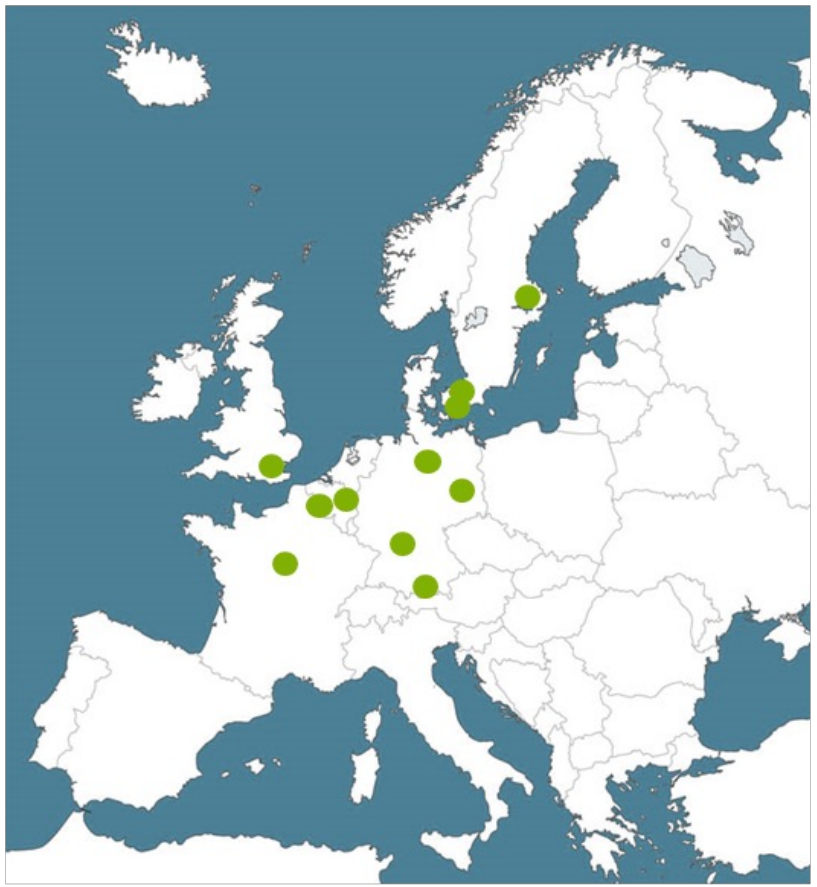
WP3: Communication and Networking

WP4: Clinical Trial Design

WP5: Animal models

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

Three main activities

Generate & Validate a standardized infection model

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

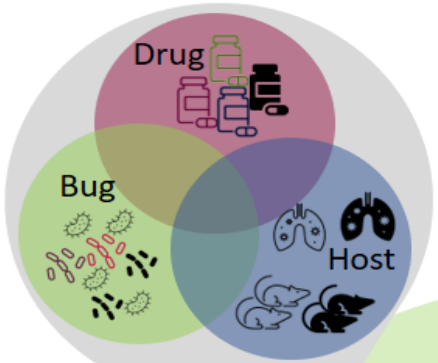
Establish Reference Strain Bank

- 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

Standardization Process



Rakel Arrazuria et.al. Expert Workshop Summary:
Advancing towards a standardized murine model to evaluate treatments for AMR lung infections. Front. Microbiol., 08 September 2022 Sec. Antimicrobials, Resistance and Chemotherapy: https://doi.org/10.3389/fmicb.2022.988725

Rakel Arrazuria et.al. Variability of murine bacterial pneumonia models used to evaluate antimicrobial agents. Front. Microbiol., 08 September 2022 Sec. Antimicrobials, Resistance and Chemotherapy: https://doi.org/10.3389/fmicb.2022.988728

Institutional protocols review

Identification of variables

Literature review

Expert Workshop

Panel Discussion

Survey

Combine WP5 team

Standard murine pneumonia model

Model validation

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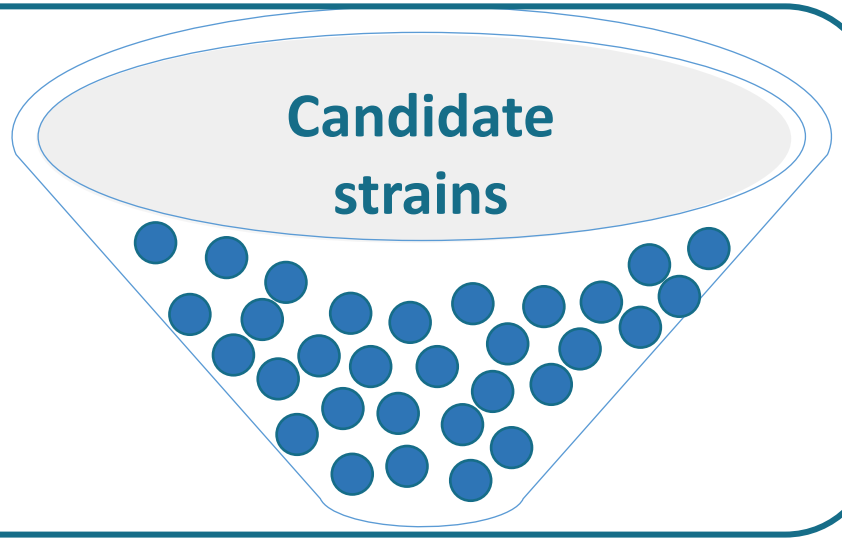
Selection of Isolates

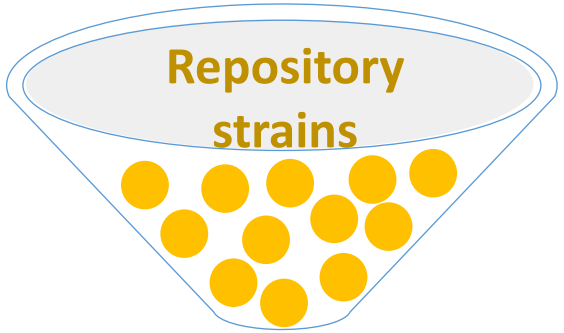
Chosen to test based on:

- Shareability
- Antibiogram
- Contemporary
- Characterization (if available)



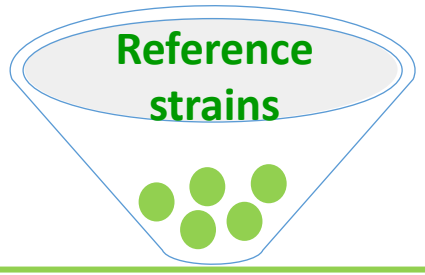
Candidate strains filtered by:

- Virulence
- Standard protocol criteria
- Mortality
- Expected +/- efficacy response



Ref strains chosen for:

- Standard protocol criteria
- PK/PD characterization



DSMZ

Leibniz-Institut
DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH

COMBINE
IMI AMR Accelerator

IMI AMR Accelerator
Tackling antibiotic resistance together

Work in progress

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 ≥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

NHS North Bristol NHS Trust

DSMZ Leibniz-Institut DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH

In vivo studies

CARB-X Combating Antibiotic Resistant Bacteria

iiCON infection innovation consortium

University of Liverpool

INFEX THERAPEUTICS

Pharmacology Discovery Services A Eurofins Discovery Partner Lab

- 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

Acknowledgement

COMBINE WP5 Members

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All animal experiments were ethically reviewed as per local requirements prior to commencement of work.