Bundesinstitut für Impfstoffe und biomedizinische Arzneimittel
Federal Institute for Vaccines and Biomedicines

Paul-Ehrlich-Institut

The COMBINE Preclinical Bacterial Strain Repository (PBSR)

A new resource for preclinical lung infection models to assess antibiotic efficacy

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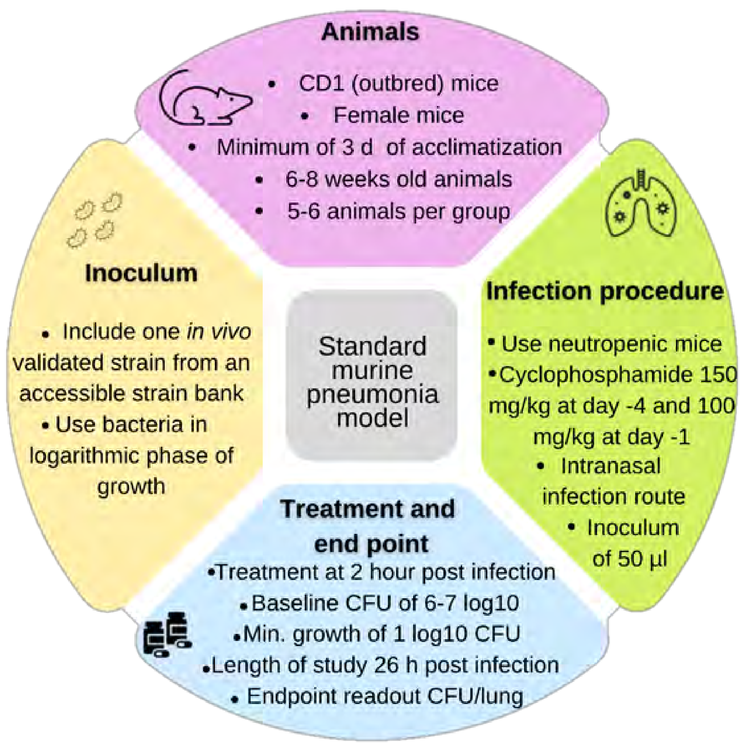
Background

The rise in antimicrobial resistance (AMR) and increase in treatment-refractory AMR infections, generates an urgent need to accelerate the discovery and development of novel anti-infectives. Preclinical animal models play a crucial role in assessing the efficacy of novel drugs, informing human dosing regimens and progressing drug candidates into the clinic. The Innovative Medicines Initiative-funded "Collaboration for prevention and treatment of MDR bacterial infections" (COMBINE; https://amr-accelerator.eu/project/combine/) consortium is establishing a validated and globally harmonized murine lung infection model to increase comparability and reproducibility of preclinical efficacy studies and more reliably translate results from animals to humans.

Development of the COMBINE standard pneumonia model

We recently reviewed the literature on commonly used antibiotics efficacy models [1] and developed a consensus mouse lung infection model based on our findings and a public stakeholder workshop with experts from industry, academia and medicines regulation [2].



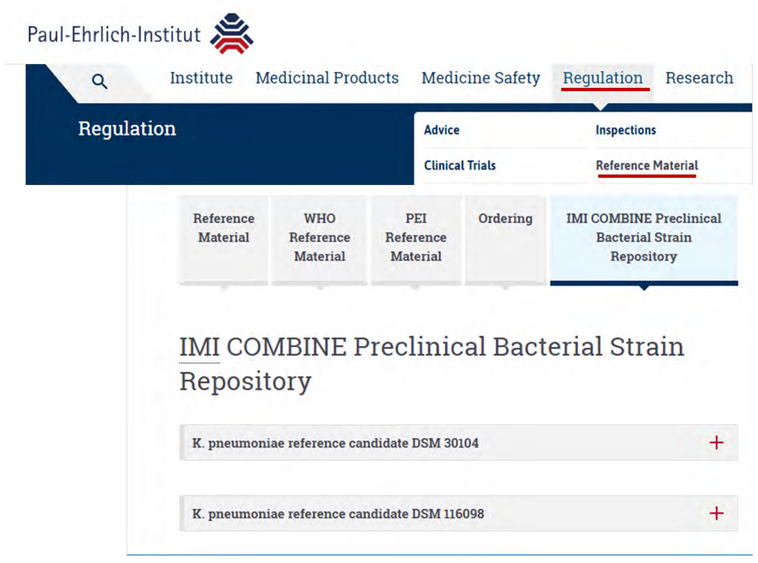
Virulence screening

To date, we have screened 33 bacterial isolates for virulence in our proposed standard lung infection model and 5 isolates each of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were assessed for inter-laboratory reproducibility of virulence. Strains meeting our COMBINE criteria, i.e. at least a ten-fold increase in lung bacterial burden between 2 hours post infection and the experimental endpoint (26 hours post infection or the humane endpoint) and an endpoint not earlier than 12 hours post infection, were included as potential reference strains. Additional isolate characterization and *in vivo* validation studies are currently ongoing and data will be made available as part of the PBSR.

Launch of the PBSR with virulent candidate strains

Here, we report the launch of our COMBINE Preclinical Bacterial Strain Repository (PBSR) which will provide Gram-negative bacterial isolates to interested investigators.

Strain information is being made available via the PEI website:
https://www.pei.de/EN/regulation/reference-material/reference-material-node

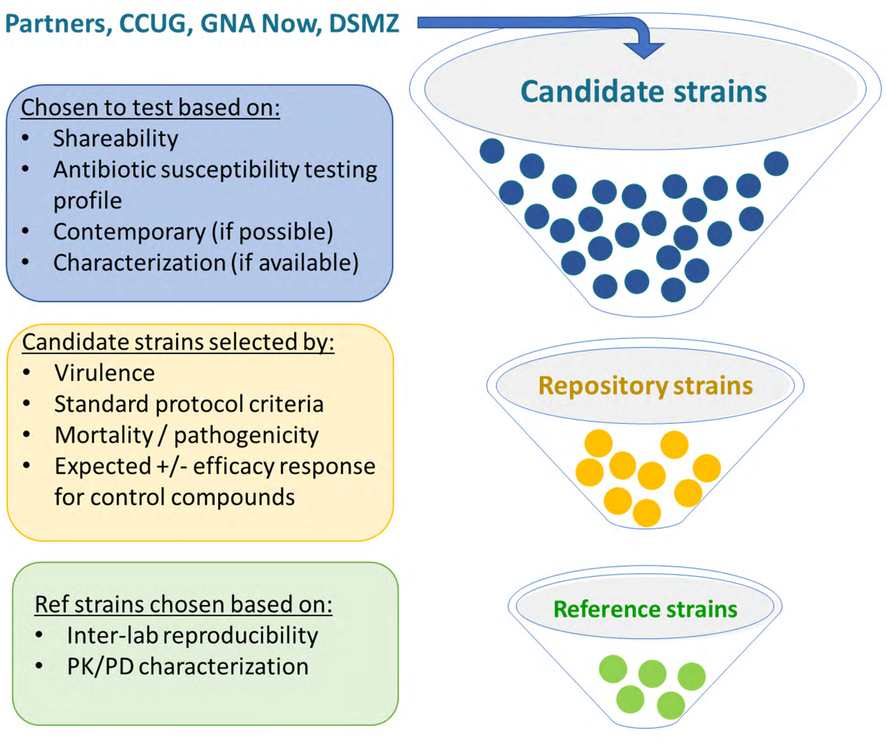


DSMZ
Leibniz Institute
DSMZ-German Collection of Microorganisms and Cell Cultures GmbH

Strains have been deposited to the German Collection of Microorganisms and Cell Cultures (DSMZ) for maintenance and distribution.

Reference strain selection workflow

COMBINE acquired bacterial isolates based on shareability, clinical relevance and molecular characteristics, which are being further characterised, assessed for *in vivo* virulence and validated in dosing studies with reference treatments.



Outlook

- Protocol and strain validation with antibiotics dose-ranging studies.
- Model validation in ring studies.
- Publication of strain and model characterization data.

The PBSR in combination with the COMBINE standard protocol and our validation data will provide an important resource to investigators to facilitate model validation and enhance the comparability of preclinical antibiotics efficacy data.

References

1. Arrazuria et al. Variability of murine bacterial pneumonia models used to evaluate antimicrobial agents. *Frontiers in Microbiology* 2022, *13*, 988728.
2. Arrazuria et al. Expert workshop summary: Advancing toward a standardized murine model to evaluate treatments for antimicrobial resistance lung infections. *Frontiers in Microbiology* 2022, *13*, 988725.

COMBINE Part of IMI AMR Accelerator

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