

The COMBINE Preclinical Bacterial Strain Repository

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

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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.

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 (Figure 1A) [2]. 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 (Figure 1B). Both our data and the bacterial isolates are being made available to the scientific community.

Here, we report the launch of our COMBINE Preclinical Bacterial Strain Repository (PBSR; <https://www.pei.de/EN/regulation/reference-material/reference-material-node>), which will provide Gram-negative bacterial isolates to interested investigators via the German Collection of Microorganisms and Cell Cultures (DSMZ). 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.

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.

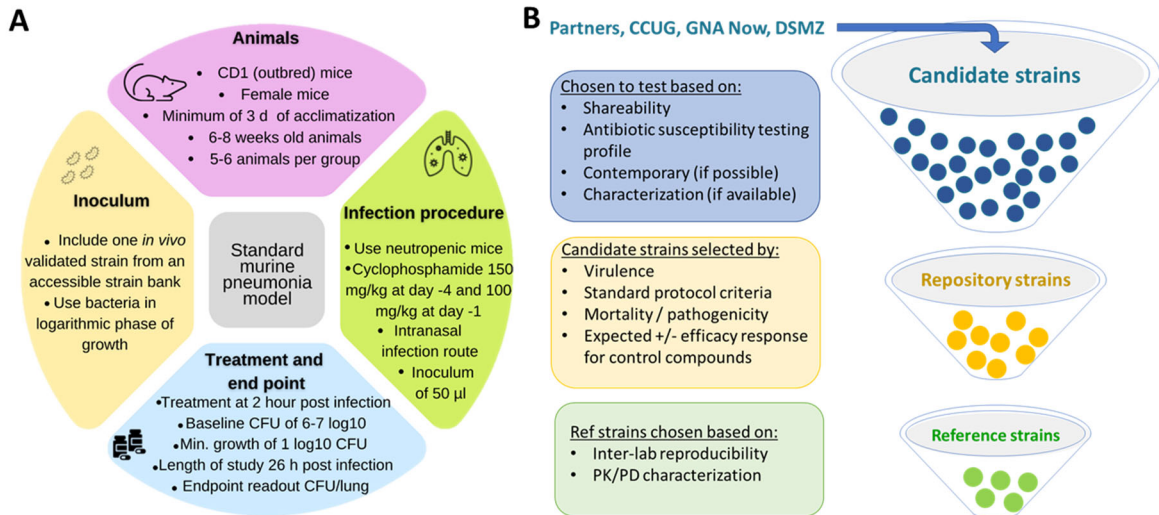


Figure 1: COMBINE Preclinical Bacterial Strain Repository; **(A)** Summary of COMBINE developed standard murine infection protocol variables and **(B)** Schematic of the selection of candidate and reference strains.

- [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.