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New standardised lung infection model to evaluate the efficacy of novel antibiotics

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Drug-resistant pneumonia kills more than 400,000 people every year. The COMBINE project has published a lung infection model offering a reproducible and well-characterised experimental framework to evaluate new antibiotics.

Developing new antibiotics relies on well-characterised *in vivo* models that deliver reproducible results with selected bacterial strains as bridges between *in vitro* preclinical testing and clinical development, and provide the data that regulators require before any drug is tested on humans in clinical trials.

According to Jon Ulf Hansen, preclinical researcher focused on antibiotic resistance at SSI in Copenhagen, "reliable animal data is essential to accelerate antibiotic development, and standardised *in vivo* infection models improve reproducibility and comparability across laboratories, which is key for clinical translation".

One of the goals of the COMBINE project has been to improve our understanding of animal infection model reproducibility and translation to clinical efficacy. The result, just published in the ASM Journal Microbiology Spectrum, is a standardised lung infection model and a bacterial strain repository that is open and available for anyone to use: academics, CROs, and companies alike.

The IMI COMBINE Preclinical Bacterial Strain Repository consists of well-characterised and virulent strains of Gram-negative bacteria *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, now available for order through DSMZ. Infections caused by Gram-negative bacteria are more difficult to treat because they have a protective membrane that acts as a barrier to antibiotics. In addition, the global spread of multidrug resistance is accelerating among these pathogens, now listed as critical priority pathogens for drug discovery by WHO.

Animal infection models have always played a crucial role in the development and efficacy evaluation of new antimicrobial agents. According to Jon Ulf Hansen and colleagues, the choice of model should be both feasible and ethical, and driven by the clinical indication. Lung infection is a common target in development programmes for novel antibiotics, leading the COMBINE project to focus on a mouse lung infection model. Mouse models are commonly used to evaluate compounds that target bacterial pneumonia because they, to some extent, mimic the changes in function and symptoms that humans experience from pneumonia. More importantly, by offering a reproducible and well-characterised model with improved reliability and consistency of preclinical efficacy assessments, we will be able to reduce the number of animals required in new studies, in line with the 3R principles for animal research: to reduce, refine, and replace.

A reproducible model is essential for generating high-quality efficacy data and enabling translation from preclinical to clinical studies. The next step is led by Professor Lena Friberg's team at Uppsala University, using the model to define PK/PD parameters for key antibiotics. An effort that will help advance the development of drugs to treat multidrug-resistant pathogens.

About the study

The COMBINE project (Collaboration for Prevention and Treatment of MDR Bacterial Infection) aims to standardize murine bacterial infection models and improve quality and consistency in preclinical efficacy studies. COMBINE researchers developed a consensus lung infection protocol, where researchers at Statens Serum Institut (SSI) in Denmark, GSK in the USA and the Paul-Ehrlich-Institut in Germany tested *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* isolates against predefined virulence criteria, followed up by independent sites to confirm virulence with minimal variability in bacterial growth. A total of 7 isolates are now available through the German Collection of Microorganisms and Cell Cultures GmbH (DSMZ) through the COMBINE Preclinical Bacterial Strain Repository (PBSR). Based on this effort COMBINE has proposed a standardized experimental framework using this panel of isolates for robust preclinical testing of new antibiotics.

The protocol has standardised key methodological procedures that can influence study outcomes: The use of consistently available virulent bacterial isolates; mice of same sex, breed, immune status and age; and inoculation techniques. The parameters have been discussed with the scientific community before proposing a consensus protocol.

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