A standard protocol for the murine pneumonia model to evaluate treatments for AMR lung infections

Jon Ulf Hansen[1], Rakel Arrazuria[2], Bernhard Kerscher[2], Jennifer L. Hoover[3], Carina Vingsbo Lundberg[1], Sylvie Sordello[4], Vincent Aranzana-Climent[5], Isabelle Bekeredjian-Ding[2,8], Diarmaid Hughes[6], Philip Gribbon[7], Lena E. Friberg[5]

[1] Bacteria, Parasites & Fungi, Statens Serum Institut, Copenhagen, Denmark.
[2] Division of Microbiology, Paul-Ehrlich-Institut, Langen, Germany
[3] Infectious Diseases Research Unit, GSK, Collegeville, Pennsylvania, USA
[4] Infectious Diseases, Evotec, Toulouse, France
[5] Department of Pharmacy, Uppsala University, Uppsala, Sweden
[6] Department of Medical Biochemistry and Microbiology, Uppsala University, Uppsala, Sweden
[7] Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Discovery Research ScreeningPort, Hamburg, Germany
[8] Institute of Medical Microbiology, Immunology and Parasitology, University Hospital Bonn, Bonn, Germany

BACKGROUND

Preclinical *in vivo* PK/PD models play a crucial role in antimicrobial efficacy investigations and provide the basis for the selection of dosing regimens in clinical applications. Differences in the methodology in the preclinical *in vivo* models used are extensive, thus limiting the results' comparability and reproducibility and possibly impeding successful translation to the clinic. To facilitate bench-to-bedside translation, and to accelerate and support the development of new antibiotics, the COMBINE consortium aims to establish a reliable and globally harmonized preclinical *in vivo* mouse pneumonia model.

METHOD

Through a systematic literature review, we identified important experimental variables and confirmed the relevance of these parameters through a workshop with experts in the field. Using a small panel of reference and clinical *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* isolates, we report a first test of the application of the standard mouse lung infection protocol.

RESULTS

A standard protocol was developed focused on the following variables: neutropenic female CD-1 mice 6-8 weeks of age and 5-6 mice per group; intranasal inoculation with 50 µl with an inoculum in log-phase growth resulting in a bacterial burden of 6-7 log CFU at start of treatment; treatment initiated 2 h post inoculation; a primary endpoint of bacterial load in the lungs 26 h after inoculation; a minimum of 1 log growth during this time frame and untreated controls should not meet the humane endpoint prior to 12 hrs post inoculation. The standard mouse pneumonia protocol has been applied to test susceptible as well as AMR isolates of species *K. pneumoniae* and *P. aeruginosa* to identify strains that meet the virulence targets for use in the COMBINE standard protocol.

CONCLUSION

The COMBINE consortium has established a standard protocol for murine gram-negative pneumonia and initiated the characterization of reference and clinical *K. pneumoniae and P. aeruginosa* isolates. Ultimately, a selection of isolates together with PK/PD data of reference antibiotics vs. these isolates will be made available to the community for benchmarking new small molecule antibiotics in preclinical development.

KEYWORDS (3) preclinical, murine, pneumonia

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