

A standardized murine pneumonia model to evaluate antibiotic treatments



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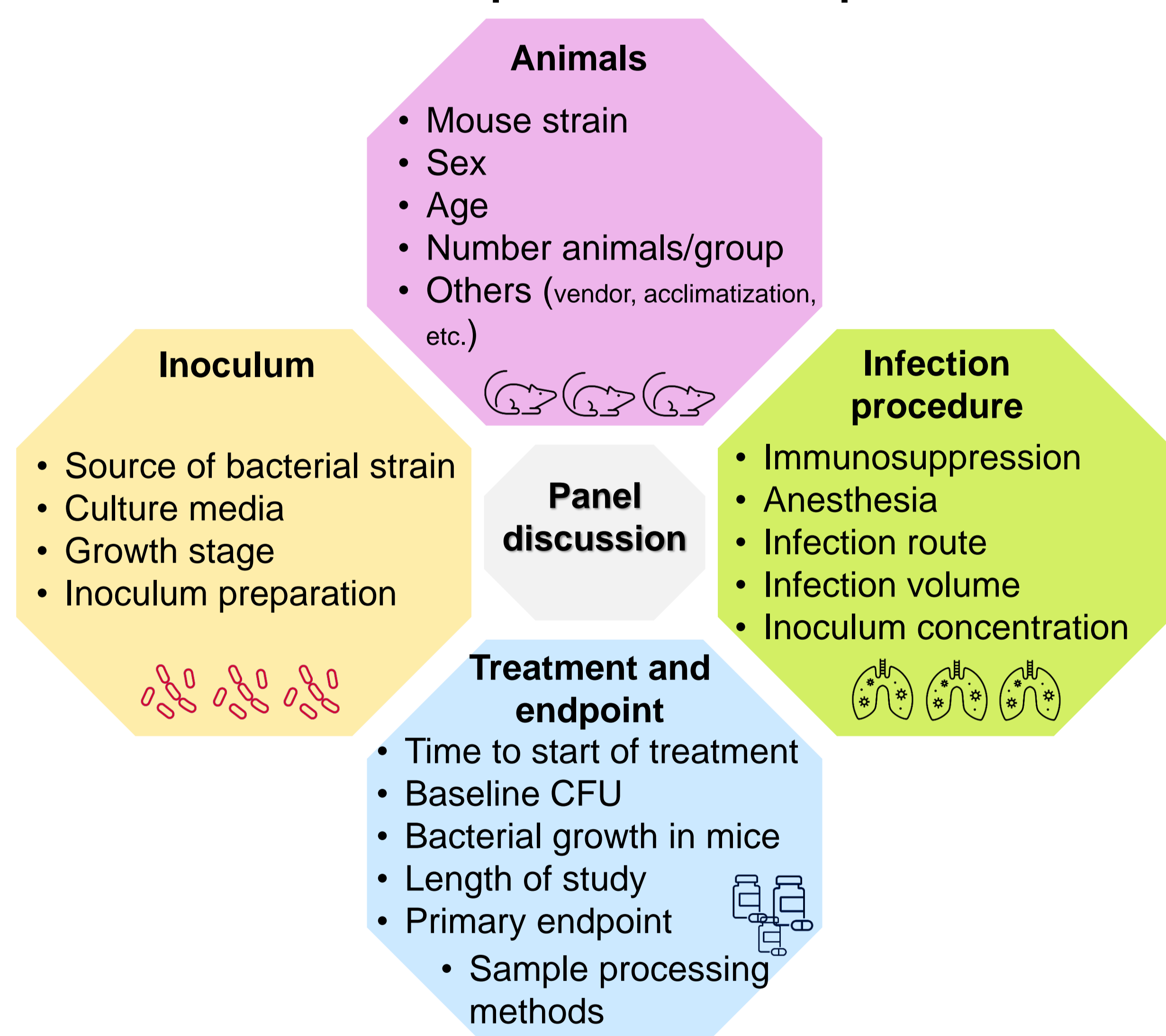
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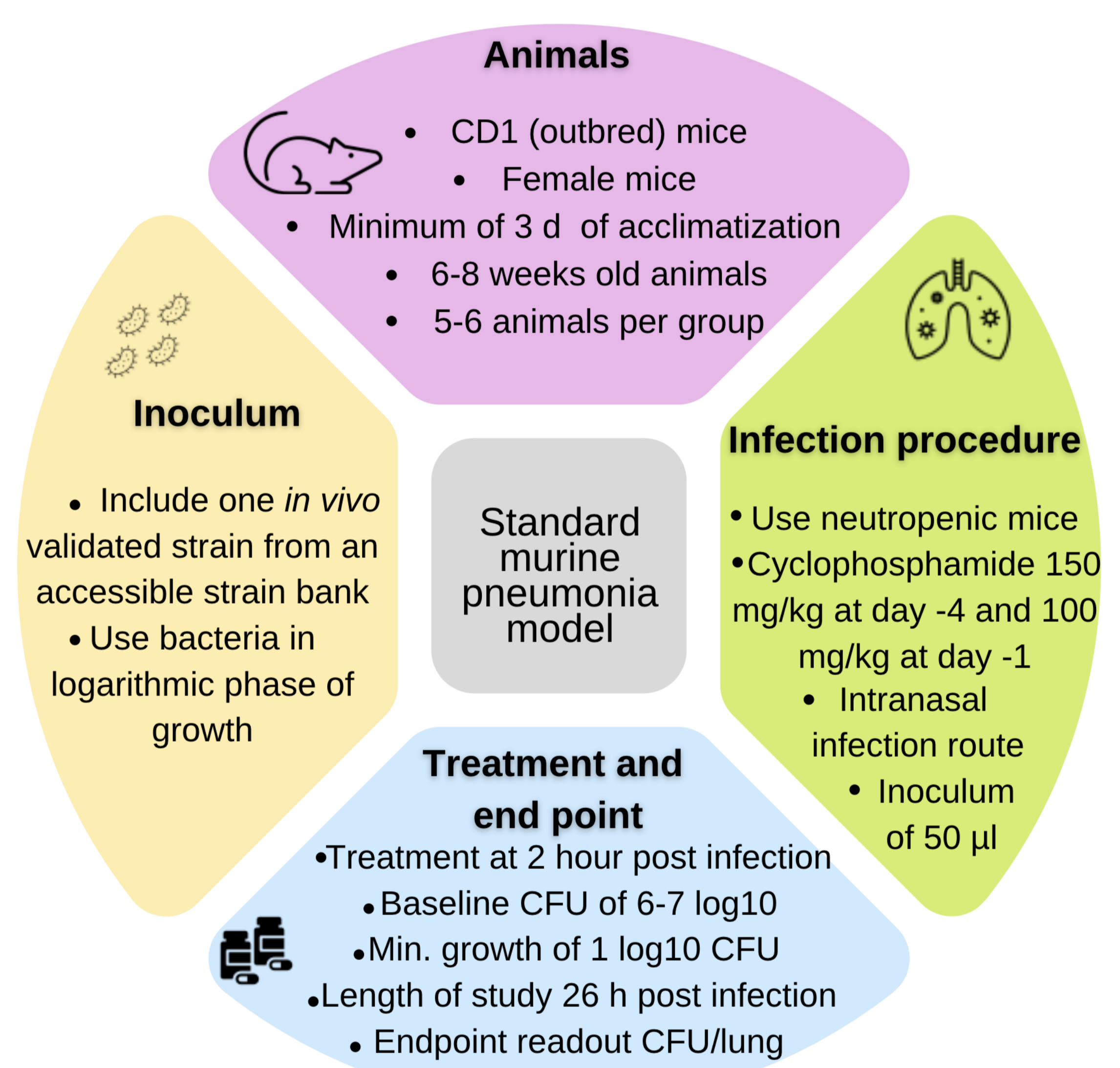
Preclinical in vivo pharmacokinetic and pharmacodynamic models play a crucial role in assessing antimicrobial efficacy and provide the basis for the selection of dosing regimens in clinical applications. Differences in the methodology used to conduct preclinical in vivo models are extensive, thus limiting 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, it is advantageous to establish reliable and globally harmonized preclinical in vivo models.

The murine lung infection model is commonly used in proof-of-concept studies as well as PK/PD evaluation of antimicrobials against the major Gram-negative AMR pathogens *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Acinetobacter baumannii*. With the goal of developing a standard protocol for this model, experimental variables that may have a significant impact on the results were identified, as detailed in a complementary poster by Arrazuria *et al.* An expert workshop, "Advancing towards a standardized murine model to evaluate treatments for AMR lung infections", was held to discuss and explore the conduct and interpretation of these mouse lung infection models and the impact of each of the experimental variables.

Parameters with potential impact

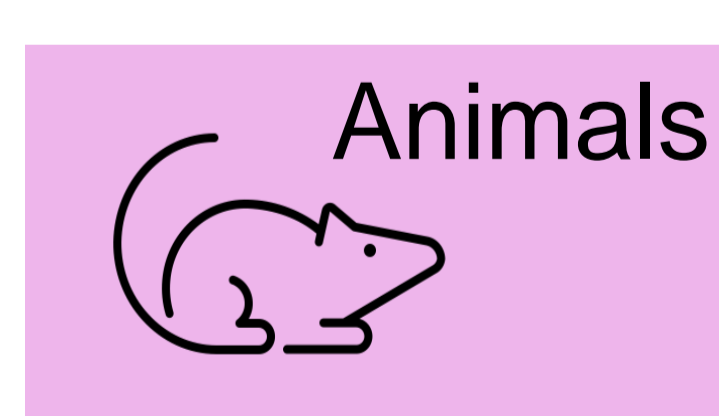


Recommendations for standard parameters

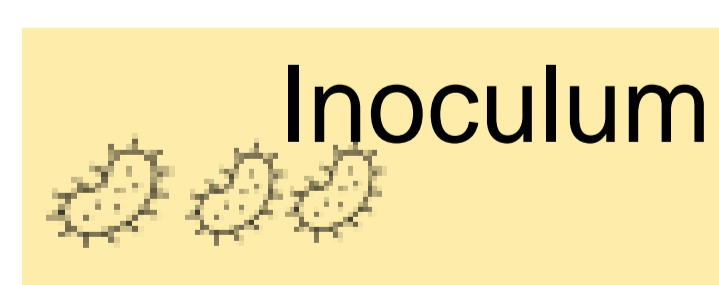


A survey at the end of the workshop confirmed a consensus in favour of these recommendations among the participants. **Future perspective:** A standard murine lung infection protocol using these recommended parameters has been developed and is being validated with *P. aeruginosa*, *K. pneumoniae* and *A. baumannii* for the purpose of characterizing PK/PD of small molecule antibiotics in pre-clinical development.

Good practice recommendations



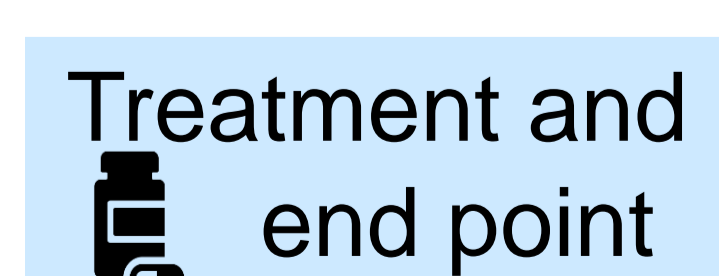
- Use animals of the same sex consistently in the same study. After preliminary study consider testing the effect in the other gender.
- Use animals from the same vendor.
- Adjust the number of animals to the power analysis if necessary.
- A minimum of acclimatization period is required.
- Animal randomization is encouraged.



- Time between inoculum preparation and its use in vivo should be short.
- Ensure inoculum viability and growth consistency in the whole experiment.



- Anesthesia should be deep enough to allow the inoculum to settle in the lungs.
- Intra tracheal route should be considered for less pathogenic strains.
- If a lower inoculum is required, 20 µl is the recommended minimum.



- If longer experimental endpoint (26 h) are needed for additional outputs (3-4 d), take several time points including 26 h.
- Blinding the CFU counts if possible.

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