Evaluation of a Standard Protocol for the Murine Pneumonia Model to Investigate Antibiotic Treatment Effect of Infections with MDR Gram Negative Bacteria

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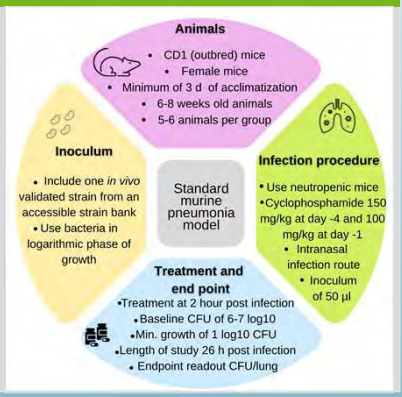
Introduction

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 translation, and to accelerate the development of new antibiotics, the COMBINE consortium is validating a mouse pneumonia model that could serve as a globally harmonized standard pre-clinical model for the AMR community.

Methods

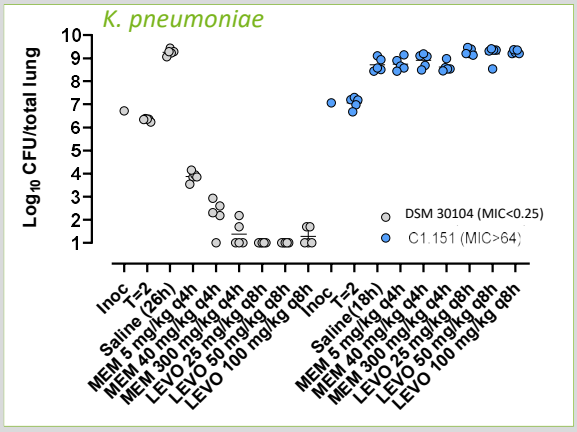
Supported by literature review, we identified important experimental variables and discussed the relevance of these parameters through a workshop with experts in the field. A survey at the end of the workshop confirmed a consensus in favor of these recommendations among the participants. Using a small panel of reference and clinical *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* isolates we identified a set of strains with suitable virulence that met the endpoint criteria set up. These strains proceeded to treatment studies with meropenem and levofloxacin.

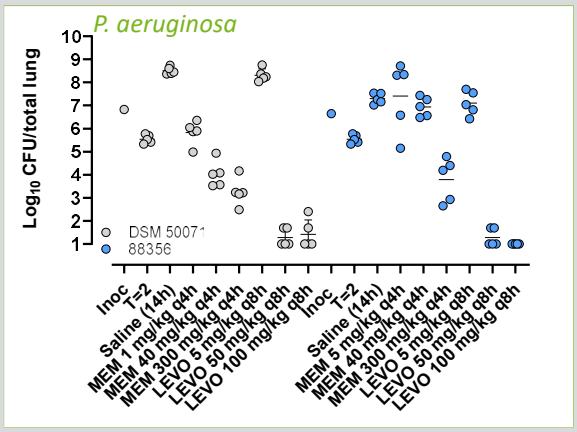


Results: Treatment efficacy in the murine pneumonia model

- Historic data was used to build population PK models to guide dose selection.
- The selection criteria for selected dosing regimens were:
  1. attainment of either human or preclinical PK/PD index targets (% *f*T>MIC, *f*AUC/MIC) in the simulated mouse population and
  2. matching the same drug exposure (*f*AUC) as in humans.
- For **MEM**, 150 mg/kg q4h was predicted to result in a drug exposure close to the expected *f*AUC (198 mg*h*L-1) in humans for a dose of 1g q8h IV. Higher and lower doses, 5 to 300 mg/kg q4h, were also added to the experimental design.
- For **LEVO**, 50 mg/kg q8h was predicted to result in a drug exposure close to the expected *f*AUC24h in humans (76 mg*h*L-1) after a standard human dose (750 mg IV). Higher and lower doses, 5 to 100 mg/kg q8h, were also added to the experimental design.

Strain	Meropenem (MEM) 1, 5, 40, 300 mg/kg q4h			Levofloxacin (LEVO) 5, 25, 50, 100 mg/kg q8h		
	MIC (mg/L)	mg/kg	Δ Log CFU	MIC (mg/L)	mg/kg	Δ Log CFU
***K.Pneumoniae* DSM 30104**	<0.25	5 mg/kg	- 2.4	<0.125	25 mg/kg	- 5.3
		40 mg/kg	- 4.4		50 mg/kg	
		300 mg/kg	- 4.96		100 mg/kg	
***K.Pneumoniae* C1.151**	1024	5 mg/kg	+ 1.7	64	25 mg/kg	+ 2.2
		40 mg/kg			50 mg/kg	
		300 mg/kg			100 mg/kg	
***P. aeruginosa* DSM 50071**	0.5	1 mg/kg	+ 0.29	<0.125	5 mg/kg	+ 2.78
		40 mg/kg	- 1.53		50 mg/kg	- 4.26
		300 mg/kg	-2.29		100 mg/kg	- 4.12
***P. aeruginosa* 88356**	16-32	5 mg/kg	+ 1.87	4	5 mg/kg	+ 1.56
		40 mg/kg	+ 1.39		50 mg/kg	- 4.26
		300 mg/kg	- 2.15		100 mg/kg	- 4.54





Conclusion

- Initial studies with MEM and LEVO indicate appropriate responses of the *K. pneumoniae* and *P. aeruginosa* strains tested in the COMBINE standard model based on in vitro susceptibility.

Future Perspective

- Further studies are in progress to fully characterize the model with additional isolates and additional antibiotics.
- Both isolates, and the PK/PD data of reference antibiotics, will be made available to the AMR community for benchmarking new small molecule antibiotics in preclinical development.

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All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EEC and the GSK Policy on the Care, Welfare and Treatment of Animals.

References

1. Rakel Arrazuria et.al. Variability of murine bacterial pneumonia models used to evaluate antimicrobial agents. Front. Microbiol. 2022
2. Rakel Arrazuria et.al. Expert Workshop Summary: Advancing towards a standardized murine model to evaluate treatments for AMR lung infections. Front. Microbiol. 2022
3. Abdul-Aziz et al, *Intensive Care Med*, 2020:

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