Poster abstract submission

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Poster title

A human lung infection model for pharmacokinetics and –dynamics studies

Poster abstract

The discovery of novel antibiotic compounds has stagnated for many years. As this is in part due to the nature of the currently used in vitro and in vivo models, there is an urgent need for new technologies that accommodate better precision in the selection for antimicrobial efficacy in patients. We have recently developed a stem cell-based human lung tissue infection model that closely mimics the architecture, cellular composition, and barrier function of the human bronchial epithelium, including air exposure, mucus production, and cilia beating. This tool could offer a physiologically relevant, time- and cost-efficient system for assessing the efficacy of novel antimicrobial compounds, while addressing the translational challenges associated with conventional in vitro and in vivo models in pre-clinical development.

We conduct a comprehensive assessment of tissue-level pharmacokinetics and pharmacodynamics (PK/PD) for three critical priority Gram-negative lung pathogens. We have established standardized infection conditions and robust tissue-based PK/PD assays, including compound permeability, MIC and time–kill kinetics assays (TKK). We have determined the distribution kinetics for selected marketed compounds, including the front-line fluoroquinolone levofloxacin, the carbapenem meropenem, and the glycylcycline tigecycline. To mimic intravenous bolus administration, antibiotics were applied to the basal compartment of air–liquid interface cultures, and their concentrations in the apical mucus were quantified over time to assess epithelial barrier penetration. When assessing PD through TKK assays, we observed a strong tendency of reduced antibiotic susceptibility in the tissue model, indicated by slower killing and overall lack of complete tissue clearance.

We are currently integrating killing kinetics data in broth and on tissue into computational PK/PD modeling and benchmarking the results against in vivo and clinical datasets. This work will to provide a clear

assessment of the capacity of the human lung tissue model to characterize exposure–response relationships, define PK/PD indices and exposure targets, and predict clinical epithelial lining fluid penetration. Through this approach, we aim to establish the Transwell lung model as a novel, highly predictive in vitro tool for the rapid and reliable evaluation of antibiotic PK/PD, thereby supporting more cost-effective antibiotic discovery.

Research topic

PK/PD