An *in vivo*-like lung infection model for pharmacokinetics and –dynamics studies

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The discovery of novel antibiotic compounds has been 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 developed a Transwell-based air-interface lung model from human bronchial epithelial stem cells from healthy individuals. Using this fully differentiated and pseudo-stratified tissue model, we have established standard infection conditions and have gained insight into the distinct infection kinetics of *P. aeruginosa*, *K. pneumonia* and *A. baumannii* using CFU assessment and confocal microscopy of live and fixed samples. We have determined the pharmacokinetics for selected marketed compounds, including front-line fluoroquinolone (levofloxacin), carbapenem (meropenem) and glycylcycline (tigecycline) antibiotics, by mimicking intravenous drug administration in the air-liquid interface. Next, we have determined the minimal inhibitory and bactericidal concentrations, as well as time kill kinetics, for the three species and compound combinations in broth and in the lung tissue model. We observed a strong tendency of reduced antibiotic susceptibility in the tissue model, indicated by slower killing and overall lack of complete tissue clearance even when treated with antibiotic concentrations up to 32-fold the MIC.

In a next step, we will use data from killing kinetics in broth and on tissue for PK/PD modeling and compare the outcome to existing *in vivo* and clinical data. With this approach, we aim to evaluate and establish the Transwell lung model as a novel and highly predictive *in vitro* tool to rapidly assess pharmacokinetics and pharmacodynamics of antibiotics, thereby facilitating the discovery of novel antimicrobial compounds with high translational potential to clinical efficacy.