CAMO (COMPARING ANIMAL MODELS TO ORGANOIDS) - TESTING MEDICAL COUNTERMEASURES WITH MICROPHYSIOLOGICAL SYSTEMS AND COMPARING TO TRADITIONAL ANIMAL MODELS AND CLINICAL TRAILS

Establishing Pk/pd Drivers Of Therapeutic Efficacy For Bacterial Threats: Bridging In Vitro And In Vivo Results Using Neutropenic Mouse And Hollow-fibre Infection Models

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Effective dosing of anti-infective therapeutics is dependent on understanding the pharmacokinetic/pharmacodynamic (PK/PD) relationship that drives antimicrobial activity. While robust in vivo PK/PD models are routinely used for pathogens in the public health space, appropriate models have not been reported for bacterial infections of biodefense concern. Here, we describe the use of both in vivo and in vitro models specifically to describe PK/PD parameters of the bacterial biothreat agent Burkholderia pseudomallei. As the etiological agent of melioidosis, novel countermeasures are needed to protect the Warfighter and the public against both endemic disease and misuse by adversaries. The murine neutropenic thigh infection (NTI) model is considered a gold-standard for deriving PK/PD targets and commonly evaluated by regulatory agencies for indications involving common public health pathogens. The PK/PD results from the murine NTI study can go on to inform clinical dosing decisions. We have stood up capabilities to test virulent B. pseudomallei infection in an NTI model and have validated the model using ceftazidime, the standard-of-care antibiotic for melioidosis. From this study, we have derived in vivo PK/PD drivers specific for ceftazidime and B. pseudomallei for the first time. Additionally, the hollow-fibre infection model (HFIM) has been utilized to derive PK/PD parameters for Burkhodleria spp. in vitro. The HFIM utilizes bacteria loading into an extra-capillary compartment and antibiotic concentration is controlled via fluidics systems in order to mimic human pharmacokinetics. Changes in bacterial load and emergence of resistance can then be examined over a full human treatment regimen. Results from the HFIM with surrogates of B. pseudomallei correlated well with the outcomes of the murine NTI model. Importantly, these results together suggest that prior assumption on PK/PD targets for melioidosis based on other gram-negative pathogens may underestimate required PK/PD drivers leading to underdosing in future studies or trials. This highlights the need to develop and utilize biodefense specific PK/PD models to inform dosing decisions for novel medical countermeasures. Using consensus data from the models, a probability of target attainment (PTA) analysis was performed using Monte Carlo simulations of human population PK (popPK). These results suggest a high probability (>90%) of a successful bacteriological outcome for infections with B. pseudomallei strains with ceftazidime minimum inhibitory concentrations (MICs) ≤ 4 µg/mL. These results are in good agreement with empirical observations from melioidosis patients. Going forward, incorporating PK/PD models such as these into the biodefense development pipeline for new antimicrobials could help bridge regulatory review between public health and biodefense indications and assist decision makers in prepositioning the right countermeasures for biological threats.

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