COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Implementation Of A Post-exposure Tularemia Treatment Model For Pneumonic Challenged Fischer Rats

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Francisella tularensis is the etiological agent of the potentially fatal disease tularemia. Due to the low infectious dose, ability to be aerosolized, lack of an approved vaccine, and historical interest in its use as a biological weapon, F. tularensis still poses a threat to both the public and military forces. Fortunately, F. tularensis is sensitive to several antibiotic classes, two of which are aminoglycosides and fluoroquinolones. However, the ability to derive antibiotic resistant Francsisella strains has been well documented, therefore, there is a need for new antimicrobials to be developed which requires animal models suitable to recapitulate critical inpatient therapy. To address this need, a proof-of-concept study was performed in venous catheterized rats that can be implemented to test future therapeutics. Using gentamicin and levofloxacin as representative antibiotics, it was first determined the pharmacokinetics (PK) from IV infusions of these drugs in rats to establish human-equivalent doses. Next, catheterized Fischer rats were aerosol challenged with F. tularensis. Three days after challenge, the rats were delivered gentamicin or levofloxacin via intravenous infusion using an optimal dose regime informed by PK studies. The control for this study was naïve rats which only received saline. Antibiotics or saline was delivered twice daily for 14 days and survival was followed for an additional 21 days post-treatment. All challenged rats provided antibiotic treatment survived to the end of the study. In contrast, the rats provided only saline succumbed by day 7 post-challenge. This study was performed in two iterations purposely to allow optimization. In the first iteration of this study, catheter patency pre- and post- exposure was difficult to maintain leading to adverse clotting events. In the second iteration, animals were provided a continuous flow of saline (drip) which maintained patency for most of the rats throughout the study. Overall, the study demonstrated the ability of delivering a humanized antibiotic treatment in the preferred small animal model of tularemia which can be used to test future therapeutics against F. tularensis. In addition, this treatment and aerosol challenge model could be adapted to additional diseases for the development of medical countermeasures for the protection of the warfighter.

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