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

Novel Antibody Based Therapies Have The Potential To Improve Medical Countermeasures For Pathogens Of Defense Concern

Adam Taylor Dstl **Izzy Norville** Dstl

Background:
Pathogens of defense concern can be difficult to treat successfully with current antibiotic therapies, together with the threat of anti-microbial resistance (AMR), this makes developing new medical countermeasures to pathogens crucial. Melioidosis is a neglected tropical disease caused by the bacterium Burkholderia pseudomallei, the bacterium is intrinsically resistant to antibiotics and survives in an intracellular niche, making this disease difficult to treat successfully. Plague is caused by the bacterium Yersinia pestis and is a concern from an AMR perspective, the ongoing outbreak in Madagascar with antibiotic resistant strains demonstrates the importance of developing new therapeutics.
Previous studies at Dstl have demonstrated that monoclonal antibodies offer a level of protection in vivo as a treatment/s for melioidosis and plague. A proof of concept antibody drug conjugate (ADC) has been developed at Dstl, consisting of an anti-Burkholderia monoclonal antibody conjugated to a fluoroquinolone antibiotic via a cathepsin cleavable linker.

Objective:
Building upon the proof of concept ADC data previously generated at Dstl, the objective of this research project is to further develop novel antibody based therapeutics for both melioidosis and plague. This includes the development of engineered antibodies, ADCs, and mesenchymal stromal cells (MSCs). ADCs have the potential to improve antibiotic therapies by directly targeting delivery of an antibiotic to the bacterial infection using antibodies. ADCs have advantages over antibiotic monotherapy including the fact that the antibiotic is only active when cleaved from the ADC at the site of infection. This reduces the likelihood of off target effects of the drug, potentially enabling a lower therapeutic dose to be used. Additionally, MSCs will be investigated as antibody delivery vectors, and to determine their intrinsic anti-microbial properties.

Methods:
Macrophage cell infection assays are the primary method used for analysing the intracellular action of antibody based therapies, together with confocal microscopy, imaging flow cytometry and bacterial enumeration. In vivo studies will also be performed to determine the pharmacokinetic properties of the novel antibody based therapies, together with in vivo efficacy studies for each pathogen.

Results:
Anti-Burkholderia monoclonal antibodies have been previously assessed in vitro for their opsonisation properties of B. pseudomallei, resulting in an anti-capsule antibody being selected for incorporation into an ADC. In addition to demonstrating effective opsonisation, this antibody also significantly reduced bacterial actin tail formation in vitro, a process essential for bacterial spread between cells. A fluoroquinolone antibiotic has been successfully chemically conjugated to an anti-capsule monoclonal antibody, via a cathepsin cleavable linker. The proof of concept ADC demonstrated the targeted delivery of antibiotic within macrophage cells.

Conclusion:
A proof of concept ADC has previously demonstrated targeted antibiotic delivery in vitro. This new antimicrobial project will build upon previous ADC data to further develop novel antibody based therapeutics, including ADCs and MSCs, for melioidosis and plague. Targeting antibiotic delivery is important for anti-microbial resistance concerns, and limiting off target effects of the antibiotic. Developing novel medical countermeasures is crucial to combat anti-microbial resistance, and improve upon current frontline antibiotic therapies for pathogens of defence concern.