BROAD-SPECTRUM THERAPEUTICS FOR VIRAL DISEASES: A MEDICAL COUNTERMEASURE PLATFORM FOR EMERGING THREATS

Towards Immunotherapy Against Alphaviral Encephalitis

Thomas Laws DSTL **Amanda Phelps** DSTL **Javier Salguero** UKHSA **Alexander Stoll** DSTL **Dominic Jenner** DSTL
Diane Williamson DSTL **Steve Lever** DSTL

Similar to most infections, much of the pathology driven by alpha virus infections is primarily caused by inflammation of the brain (encephalitis) and this is also typical for human alphavirus infection. Despite being an immune-privileged organ, the blood brain barrier is known to lower and allow conventional inflammation to occur. While the inflammation process is undoubtedly complex, there are a spectrum of pharmacological interventions to modulate it, both at a general level and at the specific pathway level. Treating disease-associated pathology using these drugs has recently been thrown into sharp relief during the SARS-CoV-2 pandemic. Both dexamethasone and tocilizumab were used to alleviate the most severe cases of COVID-19. Specific knowledge concerning the nature of alphavirus-driven inflammation is scant.

In this study, we used the subcutaneous mouse model of Venezuelan Equine Encephalitis Virus (VEEV) disease to characterise the nature of the brain inflammation and relate this to the observed pathology. We found substantial upregulation of multiple specific targets for immunomodulatory drugs and general Th1- biased inflammation. These correlated well with the levels of pathology within the mouse brains. Specifically, the brain pathology coincided with increased numbers of CD45 positive leukocytes isolated from the brains and raised titres of Tumour Necrosis Factor-alpha, Interferon-gamma, Interleukins 1alpha, 6 and 10 and multiple chemokines (CCL2, CCL5 and CXCL1). Brain disease occurred after systemic disease peaked and was most severe immediately prior to the lethal endpoint for these animals.

Immunomodulatory drugs will be explored in future studies. The hope is that these inflammatory regulating strategies can be used to reduce the debilitating effects that this family of biothreat agents have on the war fighter. Moreover, by repurposing pharmacological interventions that are already in clinical use to treat other unrelated disease conditions, these drugs can brought into rapid use.

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