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

Bivalent Vhh Antibodies Are Protective Against Lethal Venezuelan Equine Encephalitis Challenge In Mice

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Venezuelan equine encephalitis virus (VEEV) is an arbovirus that causes periodic epizootic and epidemic outbreaks in the Americas. In humans, VEEV causes a biphasic disease; the initial phase is lymphotropic causing flu-like symptoms and the second phase is encephalitic. The human fatality rate for VEEV infection is low, less than 1%, with most individuals presenting with a self-limiting febrile illness. However, 4-14% of people can develop neurological disease and long-term sequalae. During the Cold War, VEEV was developed as a biological threat agent due to the high rate of morbidity with a subclinical to clinical symptom ratio of 1:1. Currently there are no FDA licensed vaccines or therapeutics for VEEV. To date, the only therapeutic with demonstrated efficacy in the VEEV non-human primate model is a monoclonal antibody (IgG). Given this, variable domain of heavy-chain antibodies (VHHs, also known as nanobodies) may provide another therapeutic option. VHHs offer better tissue penetration compared to traditional IgGs potentially enabling crossing of the blood-brain-barrier to provide protection within the central nervous system. Previously, we demonstrated that bivalent VHHs were potent neutralizers of VEEV in vitro. In this study, we evaluated two bivalent VHHs linked to an albumin binding domain for efficacy in vivo against both epizootic and enzootic subtypes of VEEV. All subtypes of VEEV can cause disease in humans. The VEEV IAB and IC subtypes are epizootic strains capable of causing epidemics, while VEEV ID and IE subtypes are enzootic strains mainly transmitted between the mosquito vector and the rodent reservoir host. Both VHHs tested were able to protect the mice from a lethal VEEV challenge against the epizootic and enzootic subtypes of VEEV. This study is the first to demonstrate efficacy of VHHs against VEEV in vivo. Lastly the bivalent VHHs have the potential to be a broad-spectrum anti-alphavirus therapeutic as they also cross-neutralize arthritogenic alphaviruses.