Research Week 2020

Characterization of single-domain antibodies against Zika virus structural and non-structural proteins

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Keywords

Zika virus

Abstract

The flavivirus Zika virus (ZIKV) has extensive human health impact yet lacks vaccines and antiviral treatments in part due to gaps in understanding of the its infectious cycle. To gain further insight into the infectious cycle without complete ablation of host or viral proteins we designed alpaca derived variable-heavy-chain antibody fragments (VHHs) against ZIKV. VHHs are encoded on a single gene, can be expressed in mammalian cells, and bind cognates in cytoplasm. Therefore, an entire alpaca VHH repertoire can be screened for ZIKV inhibitory function intracellularly. To obtain a library with ZIKV activity, we first immunized alpacas with whole inactivated ZIKV virions alongside recombinant ZIKV structural and non-structural proteins. We then isolated a library of VHH genes representative of the alpaca's immune repertoire from the peripheral blood. Currently we are isolating VHHs capable of disrupting ZIKV infection through two complementary screens: 1) Phage display and iterative panning against ZIKV antigens and 2) lethal ZIKV challenge of VHH expressing stable cell lines. From phage display we have evidence of individual VHHs with structural protein (capsid and envelope) and non-structural protein (NS5, NS3) binding activity. We expect to isolate VHHs capable of disrupting viral entry, genome replication, and assembly. We will then use inhibitory VHHs alongside mutated ZIKV proteins to better characterize functions and binding partners of ZIKV proteins during viral replication. An example is the unknown role of ZIKV capsid protein on host lipid manipulation.