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

Development Of Broad Spectrum Affinity Matured Monoclonal Antibodies Against New World Hantavirus

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Hantaviruses are enveloped, negative-stranded RNA viruses that are members of the Bunyaviridae order. They are typically transmitted to humans through aerosolized rodent droppings and are responsible for more than 150,000 infections every year. These viruses have a large geographical footprint and are separated into two clades, Old World Hantaviruses (OWH) and New World Hantaviruses (NWH), found in Eurasia and the Americas, respectively. OWH cause hemorrhagic fever with renal syndrome and NWH are responsible for hantavirus pulmonary syndrome, which has a 40% case-fatality rate. There is currently no FDA-approved treatment or vaccine for hantavirus infections, resulting in a dire need for the development of novel therapeutics. The hantavirus glycoprotein is a heterotetramer composed of (Gn/Gc)4 subunits. Monoclonal antibodies (mAbs) targeting the Gn/Gc lattice were developed from Puumala virus (OWH) experienced donors and found to confer cross-clade neutralization. Despite 100 % protection in an Andes Virus (NWH) hamster model, in vitro analyses revealed that the lead candidate, ADI-42898, left an un-neutralized Andes virus fraction. Consequently, this mAb was selected for further affinity maturation against the Andes Virus glycoprotein. Affinity matured antibodies maintained their neutralizing ability against OWH while exhibiting enhanced neutralization against ANDV. Top affinity matured antibodies were down-selected and engineered as fucosylated and afucosylated variants. Here, we report that afucosylated affinity matured antibodies provide 100% protection in hamsters against Andes Virus when administered three days post-challenge with doses as low as 0.5 mg/kg. These results highlight the therapeutic potential of the described affinity matured antibodies and provide a foundation for future studies that will focus on delaying the treatment window, to better reflect real-life infections and treatment regiments.