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

Developing Human Monoclonal Antibody-based Therapies For Venezuelan Equine Encephalitis Virus.

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Antibody-based therapeutics have gained increased prominence in the medical countermeasure arena following the development and assessment of antibody cocktails specific for Ebola virus (EBOV). The efficacy of EBOV-specific antibody cocktails paved the way for the development of antibody cocktails against other pathogens of interest to the Department of Defense (DoD). USAMRIID and our collaborative partners from academia and industry established an antibody discovery platform focused on developing fully human monoclonal antibody (mAbs) cocktails derived from survivors of emerging infectious diseases. Utilizing this antibody discovery platform, we are actively working toward the development of mAb-based therapies for several hemorrhagic fever viruses and encephalitic viruses. The overall goal of these efforts is to develop broadly-reactive human mAb cocktails that confer protection across divergent viral species by targeting conserved epitopes within viral targets. Here, we will discuss our efforts to source sera and peripheral blood mononuclear (PBMCs) from survivors of Venezuelan equine encephalitis virus (VEEV) and Madariaga virus (MADV, previously South American EEEV) from Panama for the purposes of antibody discovery. VEEV is considered a Category A pathogen due to its low infectious dose, ease of production and transmissibility via aerosol, and is the cause of periodic outbreaks in South and Central America. A member of the Togaviridae family, VEEV infection causes a debilitating febrile disease that sometimes leads to encephalitis and fatality. Currently, our survivor cohort is composed of 51 individuals, and enrollment continues in association with additional epidemiological efforts at Gorgas Memorial in Panama City, Panama. Sera samples are initially screened at USAMRIID for reactivity via ELISA and neutralization activity against authentic VEEV. We determined that several individuals were highly seroreactive and able to neutralize against multiple VEEV subtypes (VEEV IA/B, VEEV IC, VEEV ID, VEEV IE). Some VEEV survivors even demonstrated circulating antibodies that neutralized other encephalitic alphaviruses (EEEV, MADV). This data was utilized to prioritize PBMC samples for sorting VEEV antigen-specific B cells and mAb production. Anti-VEEV mAb candidates are currently being screened for in vitro neutralization, and will be down-selected for in vivo studies. Rodent studies to evaluate efficacy against lethal aerosolized VEEV challenge are scheduled for the fall. In a previously funded effort, we characterized anti-VEEV mAbs derived from a single VEEV survivor that demonstrated comparable in vivo efficacy to one of the current best-in-class murine candidate (1A4A). However, these mAbs all shared a common binding epitope on the VEEV glycoprotein. We hope that by panning from a larger donor pool, we will isolate additional mAb candidates with increased breadth and/or epitope diversity, thereby providing the DoD with a potent, human-derived anti-VEEV mAb cocktail with cross-protective activity.