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

Evaluation Of Protective Antibodies From Human Survivors Of Crimean-congo Hemorrhagic Fever

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Antibody-based therapeutics have grown increasingly important in the medical countermeasure sector following the development of the highly efficacious Ebola-specific antibody cocktail. ZmappTM. In response to a growing need for antibody therapeutics that are cross-reactive against multiple ebolaviruses, our group at USAMRIID established an antibody development platform that efficiently generated filovirus-specific mAb libraries from survivor B-cell repertoires that enrich antigen-specific B-cells from whole peripheral blood mononuclear cell (PBMC) populations. Utilizing this platform, two mAbs were identified which target conserved epitopes on the viral glycoprotein, which together neutralize all five members of the Ebolavirus genus. Our objective for the project described herin was to utilize this platform to generate Crimean-Congo hemorrhagic fever virus (CCHFV)-specific mAb libraries from which mAb cocktails could be developed. CCHFV is the most prevalent tick-borne virus, causing severe human disease throughout Europe, Asia, and Africa and posing a significant threat to the warfighter. Despite its high lethality and widespread distribution, no vaccines or specific treatments are currently available. Evidence suggests that antibodies can protect humans against lethal CCHFV disease, but thus far, only non-neutralizing monoclonal antibodies (mAbs) isolated from immunized mice and targeting the nonstructural glycoprotein GP38 have shown limited protection in mice. To identify potent neutralizing antibodies (nAbs) targeting the viral glycoprotein, we mined the B cell repertoires of four CCHF-convalescent donors from Uganda. From this, broadly active nAbs (bnAbs) that recognize six antigenically distinct epitopes in Gc, as well as a subset targeting GP38 were identified. In a prophylactic setting, these antibodies could protect mice from a lethal CCHFV challenge. However, neither these bnAbs nor GP38-specific mAbs from this or previous work afforded therapeutic protection, either alone or in combination. We postulated that the neutralization breadth and potency of synergistic nAb pairs could be further amplified by engineering a bispecific antibody (bsAb) physically linking variable domains from each nAb. One bsAb, DVD-121-801, was identified that could provide significant therapeutic protection against CCHFV with a single dose. Ongoing work is evaluating the therapeutic efficacy of DVD -121-801 and variants of this bsAb, which exhibit improved developability properties, against genetically divergent CCHFV clades. Moreover, our work has uncovered a set of GP38-specific mAbs that map to 12 different epitope bins. Efforts to test the efficacy of these GP38-specific mAbs in vivo, individually and in combination with the Gc-specific bsAb are underway. The work described herin was funded by NIAID and with recent funding support from DTRA, collection activities were expanded to include sample collections from CCHFV survivors in Georgia, expanding the repertoire of antibodies to include the Crimea clades of CCHFV. This work is critical for the discovery and clinical development of potent and broadly-reactive CCHFV therapeutic candidates to mitigate the risk of this important human pathogen to the warfighter.