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

Characterization Of SnI Identified Bbb-penetrating Moieties (bbb Pms) For Delivery Of Therapeutic Cargo To The Cns

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Viral diseases causing encephalic inflammation, including new world alphaviruses (NWA) which can be spread by aerosol transmission, present a significant threat to national security as potential bioterrorism agents. While biologics such as monoclonal antibodies are increasingly popular as rapidly deployable therapeutics, especially targeting emerging viral pathogens, a major challenge complicating the treatment of neurotropic pathogens such as new world alphaviruses is the transport of therapeutic molecules across the blood brain barrier (BBB). Although there are multiple published examples of strongly neutralizing antibodies which show some promise prophylactically against alphaviruses such as Venezuelan Equine Encephalitis virus (VEEV) or Eastern Equine Encephalitis virus (EEEV), there are currently no effective post-exposure treatment strategies available for these pathogens. This is most likely because available therapeutics are excluded from the central nervous system and cannot prevent virus replication in this privileged environment. Receptor mediated transcytosis (RMT) has been identified as a potential method of cargo delivery across the BBB, however approaches targeting previously known BBB RMT pathways, including antibodies binding transferrin receptor and insulin receptor, have demonstrated modest transport efficiency, requiring high peripheral concentration to achieve therapeutic levels within the CNS.

At Sandia, we have utilized a phage-display bio-panning approach to identify several novel nanobody candidates which can cross the BBB and are enriched in the brain after IP injection. These novel nanobodies, or BBB penetrating moieties (BBB PMs), present the opportunity to develop a brain delivery platform for biologic therapy. Given that our BBB PM candidates were selected agnostic of previously identified RMT pathways in a mouse in vivo model system, we are currently working to 1) validate that these BBB PMs are also functional in human endothelial systems and 2) characterize the cellular transport pathways utilized by top candidates to cross the BBB endothelial layer. Our findings will advance our understanding of the mechanisms utilized by these novel nanobodies to cross the BBB and will inform their development as shuttles for therapeutic antibodies targeting encephalitic new world alphaviruses as well as a platform which can be adapted to transport therapeutics targeting other diseases affecting the CNS.

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