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Novel CD74 Decoy Peptides for Treatment of Progressive Multiple Sclerosis

Arthur Vandenbark, Ph.D., Professor of Neurology and Molecular Microbiology & Immunology, Senior Research Career Scientist, VA.

Macrophage migration inhibitory factor (MIF) and D-dopachrome tautomerase (D-DT) are two chemokines that have been implicated in the pathogenesis of progressive multiple sclerosis (MS). Upon binding to a common receptor, CD74/CD44, these factors enhance T cell activation and survival, promote secretion of other pro-inflammatory factors and recruit additional leukocytes into the central nervous system. Given that there is only one approved drug on the market for primary progressive MS and none for secondary MS, additional new therapies are urgently needed. To this end, we propose to develop a decoy CD74 peptide with high affinity for MIF and D-DT to prevent their binding and signaling through cell-bound CD74. Our recent molecular modeling studies have identified two regions within the highly stable trimerization domain from each of three CD74 monomers that form the binding interface (hotspot) with MIF and D-DT trimers. Validity of these binding motifs has been confirmed using substitutions in full-length CD74 constructs that reduced MIF binding by >50% and ~30% respectively. We here propose to synthesize two CD74 decoy peptides containing the MIF/D-DT binding motifs, as well as a 30-mer peptide containing both motifs. These peptides would be predicted to cross the blood brain barrier and could be highly efficacious for inhibiting or reversing MS clinical progression in both male and female MS subjects. Support from the BIP program will be instrumental for demonstrating proof-of-concept of CD74 decoy peptides as the first step towards commercialization through additional grants and licensing agreements.