Novel Peptide-Based Immunomodulators for Infectious Disease Vaccines and Therapy

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Abstract

Similar to cancers, pathogens avoid immune detection by the inappropriate expression of checkpoint receptors on T-cells in patients with chronic infections (e.g. HIV, HBV, malaria). Indeed, immune checkpoint mAb-based inhibitors have been shown to enhance T cell responses in patients with chronic infections; however, from a cost and safety profile, mAbs are not ideal for delivering with vaccines. Therefore, Leidos set out to create safe and cost-effective peptide-based checkpoint inhibitors that would be more suitable for infectious disease vaccines. Inspiration for this new class of immunomodulators came from the human microbiome, where we have mined microbial-derived peptide libraries. We discovered a series of small linear peptides with bi-specific activity against PD1 and CTLA4. These peptides have been shown to activate the immune response and enhance vaccine efficacy (i.e. T-cell immunomodulatory adjuvant). They induce dramatic increases in effector T-cell responses in ex vivo human PBMC assays and mouse models of vaccination. Further, they provide survival benefit in lethal mouse models of sepsis and malaria. In addition to being as effective as the FDA approved PD1 mAb in enhancing T-cell response, our peptides are expected to have better safety profiles due to their ability to only transiently effect their immunomodulatory activity when compared to mAbs that circulate for weeks to months which, in part, contributes to their immune-related adverse effects. Importantly, our peptides can be encoded and delivered in as DNA, RNA, and viral vectors, which would allow for cost effective co-delivery with vaccines against challenging infectious diseases of the developing world.