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Short Linear and Microbe-Derived Peptides Enhance T-Cells and Anti-Tumor Activity

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Monoclonal antibody inhibitors of checkpoint receptors, particularly PD1 and CTLA4, have proved to be powerful tools for treating cancer. Additionally, the combination of these checkpoint inhibitors could be advantageous and many such combination trials of monoclonal antibodies are underway (1). However, inhibition of PD1 and CTLA4 through therapeutic antibodies also comes with a cost of increased safety issues related primarily to autoimmune adverse reactions (2, 3). Moreover, combination therapies will add to the cost of these already expensive modalities. We have created a platform, Microtide™, for discovering short peptides that bind the checkpoint receptors by screening peptide libraries and rapidly evolving the peptide scaffolds by in silico design. Here, we report the discovery, invitro characterization, and invivo proof of concept of our lead peptide-based checkpoint immunomodulators (LD-series). These peptides appear to have the polypharmacological properties of simultaneously antagonizing at least two of the CD28 family of receptors, namely PD1 and CTLA4. We demonstrated that the LD peptides induce T cell proliferation, enhance T cell activity in PBMCs, have potent antitumor activity in mouse models, and promote vaccine-induced T cells with as little as a single LD peptide administration. In addition, we have generated RNA, DNA, and virus constructs encoding the LD peptides to demonstrate the feasibility and advantage of our peptides to be effectively delivered locally in the tumor microenvironment. Our peptides have shown great potential as a novel, polypharmacological immunotherapies that can be cost effectively incorporated into, and combined with, other modalities such as cellular therapies, oncolytic viruses, and cancer vaccines to safely deliver antitumor efficacy.

References:

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