Discovery of peptide-inspired orally bioavailable drugs for cancer immunotherapy

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Pioneering success of antibodies targeting immune checkpoints such as PD-1 and CTLA4 has changed the outlook of cancer therapy. Along with durable clinical responses, severe immune-related adverse events are becoming increasingly evident in antibody-based approaches. As a strategy to better manage severe adverse effects, we set out to discover and develop an orally available PDL1 antagonist. We envisaged an oral agent could potentially offer the convenience and flexibility to adjust the dose and schedule to address any emergent adverse events and ease of combination therapy.

In this pursuit we discovered the first rationally designed peptide therapeutic, 29 amino acid peptide (NP-12), behaving as a PD-1 decoy generated from the selected portions of the human PD-1 receptor. NP-12 displayed equipotent antagonism towards PD-L1 and PD-L2 in rescue of lymphocyte proliferation and effector functions and showed significant anti-tumor efficacy in various syngeneic mouse tumor models upon subcutaneous route of dosing. In order to develop an orally bioavailable agent, we took a reductionist approach by truncating high-affinity peptides or critical peptide sequences covering the hotspots from the interface to arrive at the shortest pharmacophore. The shortest pharmacophore was further transformed into druggable molecules either by converting it into a peptidomimetic or as a peptide inspired agent with good oral bioavailability.

Our strategy was based on the hypothesis that minimum pharmacophore derived from protein-protein interacting interfaces of PD-L1 and PD-1 also has the potential to interact with other proteins belonging to the same immunoglobulin superfamily (such as VISTA). A focused library of compounds mimicking the interaction of checkpoint proteins was designed and synthesized. Further optimization for potency and drug like properties resulted in compounds targeting either single or spectrum-selective immune checkpoint pathways. The first compound from this approach CA-170, a first-in-class orally bioavailable dual antagonist targeting PD-L1 and VISTA, is undergoing clinical trials with encouraging results.