Targeting the CXCR3 pathway with a novel peptide drug candidate mobilizes the immune system to enhance anti-tumor immunity

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ABSTRACT

Immune checkpoint inhibitor (ICI) therapy releases the molecular “brakes” on the immune system thereby promoting robust anti-tumor immune responses. However, many patients do not respond to ICI therapy due to development of primary and secondary resistance, and this population represents a large unmet medical need. The critical role of CX-3-C motif chemokine receptor 3 (CXCR3) signaling in eliciting an effective response to anti-ICD-1 therapy has been recently demonstrated. The CXCR3 chemokine system is instrumental in immune effector cell recruitment to the tumor and augments intratumoral CD8+ T-cell proliferation and function, which are key mechanisms driving anti-tumor immunity and responses to ICI therapy.

We used our proprietary drug discovery platform to identify a unique microbe-derived peptide, SG-3-00802, from bacterial strains associated with response to anti-ICI inhibitors in patients with melanoma. We subsequently determined that CXCR3 is the target receptor for SG-3-00802 and demonstrated that SG-3-00802 enhanced the activity of CXCR3 in the presence of its endogenous ligands CXCL9/CXCL10/CXCL11. Optimization of SG-3-00802 pharmacological properties led to the selection of a novel drug development candidate SG-3-00802 with improved potency and PK properties. Mechanistically, it increases CXCR3 expression on monocytes, though with different fold increases on T cells. We demonstrated that this drug candidate can activate mouse CD8 T cells to migrate to tumor microenvironment (TME) and stimulates beta-lactamase transcription. The beta-lactamase then cleaves the substrate to provide a quantitative FRET-based readout of CXCR3 activity.

In vitro migration assays showed anti-tumor activity in pre-clinical models. T cells primed with SG-3-00802 and SG-3-00802 in combination with anti-PD-1 or chemotherapeutic agents in preclinical models. The CXCR3 chemokine system is instrumental in immune effector cell recruitment to the tumor and augments intratumoral CD8+ T-cell proliferation and function, which are key mechanisms driving anti-tumor immunity and responses to ICI therapy. Our proprietary drug discovery platform identified a peptide, SG-3-00802, which shows anti-tumor activity in pre-clinical models. T cells primed with SG-3-00802 and SG-3-00802 in combination with anti-PD-1 or chemotherapeutic agents in preclinical models.