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### SBT6290, A SYSTEMICALLY ADMINISTERED NECTIN-4-DIRECTED TLR8 IMMUNOTAC (TM) THERAPEUTIC, IS A POTENT HUMAN MYELOID CELL AGONIST FOR THE TREATMENT OF NECTIN-4-EXPRESSING TUMORS

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**Background** SBT6290 is a novel therapeutic comprised of a selective TLR8 agonist conjugated to a Nectin-4-specific monoclonal antibody, designed for systemic delivery and tumor-localized activation of myeloid cells. Nectin-4 is a cell surface adhesion molecule that is overexpressed in multiple solid tumor types including triple negative breast, head and neck, lung, and urothelial cancers, with limited expression in normal tissues. Many solid tumors, including those expressing Nectin-4, are resistant to immunotherapy due to immune-suppressive mechanisms, loss of HLA, low neoantigen availability, and/or minimal T cell infiltrates. These tumors, however, are often replete with myeloid cells. Activation of these cells has emerged as a promising approach in overcoming resistance mechanisms to current cancer immunotherapies. TLR8 is highly expressed in myeloid cell types prevalent in human tumors, including conventional DCs and macrophages. Agonism of TLR8 in human myeloid cells activates a broad spectrum of anti-tumor immune mechanisms, including proinflammatory cytokine production, repolarization of suppressive myeloid cells, and the priming of CTL responses. Here, we show that SBT6290 potently activates human myeloid cells in a Nectin-4-dependent manner and that a mouse surrogate confers single agent anti-tumor activity in preclinical studies. These data support the development of SBT6290 for the treatment of patients with Nectin-4-expressing tumors.

**Methods** SBT6290 activity was characterized in vitro using co-culture systems consisting of human immune cells and Nectin-4-expressing tumor cells. The in vivo efficacy of the SBT6290 surrogate was evaluated as a single agent in mouse tumor models expressing Nectin-4.

**Results** Studies with human immune cells show that SBT6290 potently induces multiple anti-tumor immune activities including proinflammatory cytokine and chemokine production, inflammasome activation, direct activation of DCs and indirect T and NK cell cytolytic activity. This activity requires the presence of Nectin-4 expressing tumor cells and the engagement of Fc gamma receptors on the surface of the myeloid cells by the conjugate to facilitate delivery of SBT6290 into myeloid cells. Notably, SBT6290 is >100 fold more potent than the free, unconjugated TLR8 agonist. Systemic administration of a SBT6290 surrogate in mice results in robust single agent efficacy in tumor models intrinsically resistant to checkpoint blockade, including the EMT6 model engineered to express human Nectin-4.

**Conclusions** The preclinical data described here show the potential for SBT6290 to drive robust, single agent anti-tumor responses and support the clinical development of SBT6290 for patients with Nectin-4 expressing tumors.

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### ANTIBODY-BASED APPROACH OF MT1-MMP METALLOPROTEASE INHIBITION RESULTS IN DECREASED INVASIVE PROPERTIES OF PANCREATIC CANCER CELLS

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**Background** Pancreatic cancer (PC) is one of the most aggressive types of malignant tumors due to the fact, that early stages of the disease are asymptomatic and difficult to diagnose. Matrix metalloproteinases (MMP) play a key role in progression of early PC stages through proteolysis of collagen and a range of regulators that promotes tumor invasion and angiogenesis. MMPs are considered as promising therapeutic targets, but MMP inhibitors exhibit significant efficacy exclusively in a narrow time window, that makes it difficult to use them for prevention of local relapses. That is why MMP inhibitors and blocking antibodies demonstrated moderate results in clinical trials – progressive tumor stages could not be effectively treated with these agents, while their use in the early stages still looks very promising. The aim of the present work was to study the effects of longterm and preventive suppression of the activity of MT1MMP (a key initiator of tumor proliferation and invasion) in pancreatic cancer using the approach of active immunization.

**Methods** We performed active immunization of SPF C57BL/6 mice using different variants of the vaccine: peptide fragments of MT1-MMP protein or DNA expression vectors coding these peptide fragments. 2-fold vaccine administration and serums collection were performed according to the previously published protocol.<sup>1</sup> The serums were collected on the 21 day of the experiment. We applied ELISA to estimate the levels of anti-MT1-MMP antibodies. The functional activity of the serums was tested using enzymatic assay and in vitro metastatic assay according to previously described protocols.<sup>2</sup>

**Results** We selected the serum containing high titers of anti-MT1-MMP antibodies which effectively suppressed MT1-MMP activity in the absence of the effect on MMP9. This feature of the serum is fundamental due to the fact, that MMP9 is currently regarded as an undesirable target of anti-cancer therapy. The functional activity of selected serum and its ability to inhibit pancreatic cancer cell invasion was shown in an in vitro metastatic assay using the PC mouse cell line. In addition, we demonstrated the ability of this serum to inhibit the activity of MMP2 and TGFβ in conditioned mediums and lysates of PC cells, that suggests its additional anticancer properties associated with the suppression of the ability of MT1-MMP to proteolytic activation of a number of tumor modulators.

**Conclusions** The selected mode could be used for effective immunization against MT1-MMP.

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