SBT6050, a HER2-Directed TL8 ImmunoTAC™ Therapeutic, is a Potent Human Myeloid Cell Agonist that Provides Opportunity for Single Agent Clinical Activity

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Introduction

Many solid tumors, including those expressing HER2, are resistant to immunotherapy due to immune-suppressive microenvironment, lack of human immune response (AIC), low tumour antigen availability, and/or minimal T cell infiltration. These tumors frequently contain abundant populations of tumor-associated myeloid cells. Activation of these cells through TLR agonists has emerged as a promising approach in restoring immune mechanisms to current cancer immunotherapies. TLR8 is highly expressed in human myeloid cells known to be present in human tumors such as conventional DCs and macrophages. Agonists of TLR8 in human myeloid cells activate a broad spectrum of anti-tumor immune mechanisms, including proinflammatory cytokine production, repolarization of suppressive myeloid cells and the priming of cytotoxic T cells. TLR8 agonists such as SBT6050 is a tumor innervated TLR8-specific therapeutic comprised of a HER2-directed monoclonal antibody conjugated to a potent and specific TLR8 agonist, allowing for systemic delivery of an activated cell with activity localized to HER2-expressing tumor sites. Here we present data demonstrating the superiority of SBT6050 at activating human myeloid cells compared to HER2-specific conjugates that use either a selective TLR7 agonist or reprogrammed

The data presented here demonstrate the following:

• SBT6050, but not TLR7 agonist or reprogrammed HER2 conjugates, drives a broad spectrum of anti-tumor immune mechanisms in vitro.
• SBT6050, but not TLR7 reprogrammed HER2 conjugates, activates pro-inflammatory cytokine production from polarized human macrophages.
• SBT6050 potently activates human myeloid cells only in the presence of HER2-expressing tumor cells.
• SBT6050 induction of IL-12 and IL-18 from human myeloid cells results in the secondary activation of Granzyme-B and IFN-γ production by conventional killer T cells.
• SBT6050 mouse surrogate (SBT6050-S) is efficacious as a single agent in a HER2-expressing xenograft model with low T cell infiltration.

Figure 1: SBT6050 is an ImmunoTAC™ Therapeutic Designed for Systemic Administration with TLR-Localized Activity

Table 1: Human Myeloid-Restricted Expression Profile Supports Development of a TLR-Selective Payload

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<th>Cell Type</th>
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<th>TLR11</th>
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Table 1: Expression levels determined using publically available RNA-seq datasets.

Figure 2: Her2 and TLR8 are Adjacent in Tumor, Consistent with Activation Requirements of SBT6050

Figure 3: SBT6050, a TLR8 Agonist Conjugate, Potently Activates Human Myeloid Cells

Figure 4: SBT6050, But Not TLR7 Agonist or Reprogrammed Conjugates, Drives a Broad Spectrum of Human Anti-Tumor Immune Mechanisms

Figure 5: SBT6050-Induced Myeloid Cell Production of IL-12, IL-18 and TNF-α Leads to T, NK Cell Effector Responses

Figure 6: SBT6050 is Equi-Potent on Differentially Skewed Human Macrophages

Figure 7: SBT6050 Mouse Surrogate (SBT6050-S) Matches the Functional Profile of SBT6050 on Myeloid Cells

Figure 8: SBT6050-S Induces Durable Single Agent Efficacy in a T Cell Excluded Syngeneic Model

Figure 9: SBT6050-S Induces Robust Single Agent Tumor Clearance in T, B and NK Cell Deficient Mice

Conclusions

• SBT6050, an ImmunoTAC™ Therapeutic, is a HER2-directed monoclonal antibody conjugated to a TLR8-specific agonist which potently activates multiple human anti-tumor immune mechanisms in a HER2-dependent manner, enabling tumor-localized activity via systemic delivery.
• The activity of SBT6050 on human myeloid cells cannot be activated with TLR8-specific or reprogrammed antibody conjugates, despite these agents activating murine myeloid cells.
• SBT6050 conjugates demonstrate potent single agent activity and durable anti-tumor responses upon re-challenge in tumor models with low tumor infiltrating lymphocytes, highlighting the potential for clinical activity in tumors with low tumor-infiltrating lymphocytes (TIL).
• SBT6050 mouse surrogate (SBT6050-S) is suitable as a single agent in a xenograft model lacking T, B and NK cells, demonstrating the potential of myeloid cells to mediate robust efficacy.
• SBT6050 is currently in preclinical development for patients with moderate or high HER2-expressing tumors and is projected to enter the clinic later this year.


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