Cancer immunotherapy has proven to be a highly effective therapeutic option for cancer patients. However, the overall response rate with check-point inhibitors and other related modalities has been modest due to various factors. Targeting innate immune signaling pathways that induce type I IFN production to re-program tumor microenvironment and restore anti-tumor immunity represents a novel immunotherapeutic approach. In this regard, agonists that activate the Stimulator of Interferon Genes (STING) pathway have emerged as an attractive strategy. We have previously reported that SB 11285 is a novel cyclic dinucleotide STING agonist, which has demonstrated highly potent antitumor activity, when used alone or in combination with other anti-tumor agents, in several syngeneic mouse tumor models when administered by intratumoral, intravenous or intraperitoneal routes. Presented here are recent studies that provide additional insights into the mechanism of action of SB 11285.

RESULTS

EVALUATION OF BINDING AFFINITY OF WT-STING-CTD (AA138-379) TO BIOTINYLATED SB 11285 ANALOG (SB 11416) BY SURFACE PLASMON RESONANCE (SPR)

SB 11416 retains STING agonist activity in THP1-Dual-WT cells

SB 11285 (SB 11146) directly binds human wild-type STING

The equilibrium dissociation constant (KD) Value was 1.22 X 10^-12 M (122 nM)

The ligand was covalently conjugated to PlexaNan Capture Strep Tag and STING protein was injected into the flow cell. SPR measurements were performed at 4°C and signal changes after binding were recorded as the assay value. Real-time binding signals were recorded and kinetic analysis was performed using Plexera Analysis.

PHARMACODYNAMIC STUDY OF SB 11285 IN NORMAL BALB/C MICE

Groups of 4-5 Balb/c mice (female, 6 weeks of age) were intraperitoneally injected via tail vein with saline control or SB 11285 at 9 mg/kg. Serum, spleen, and liver samples were collected at 2 and 24 hrs post-treatment. (Top panels) Levels of Rantes (top) and Tnf-a (bottom) were measured using ELISA and results are shown as light for serum samples and log2 of tissue for spleen and liver samples. (Bottom panels) The expression levels of representative ISGs in spleen samples were quantified using Q-PCR. p<0.05 for all ISGs tested in SB 11285 treated mice as compared to mock-treated mice.

CONCLUSIONS

• SB 11285 is a potent systemically bioavailable STING agonist.
• SB 11285 directly binds human wild-type STING.
• Key residues in STING binding pocket play an essential role in SB 11285 induction of type I IFN signaling.
• SB 11285 induces type I IFN and other cytokines in human PBMCs and PBMC-derived monocytes.
• SB 11285 administered by i.v. route in normal BALB/c mice induces type I IFN response.
• During early incubation, SB 11285 is predominately taken up by monocytes and other innate immune cells.
• Previous pharmacodynamic studies (ref 3-5) in multiple syngeneic mouse tumor models have shown that SB 11285 has potent and durable anti-tumor activity.
• SB 11285 is being advanced to clinical trials.

REFERENCES

2. O. Illmensee et al., "Characterizing the Agonistic Activity of SB 11285 on Monocytes and Tumors," Cancer Immunology and Immunotherapy, October 2015.

For additional information, please contact: szhou@springbankpharm.com and beyer@springbankpharm.com