Pharmacodynamic studies of SB 11285, a systemically bioavailable STING agonist in orthotopic tumor models

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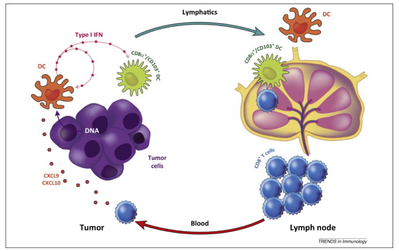
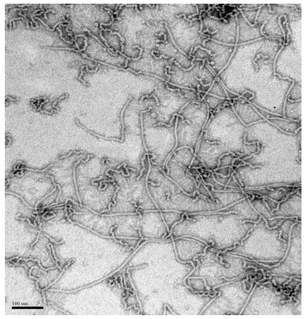
INTRODUCTION

The activation of innate and adaptive immunity via Stimulator of Interferon Genes (STING) signaling is a potentially transformative immuno-therapeutic strategy in cancer. We have previously reported that the cyclic dinucleotide SB 11285 administered by IT, IP and IV routes has demonstrated potent anti-tumor activity, immune memory, abscopal effect and is synergistic with other anti-cancer agents including checkpoint inhibitors. We report here the anti-tumor and pharmacodynamic studies of SB 11285 in multiple orthotopic and subcutaneous syngeneic mouse tumor models.



The STING pathway and the T cell-inflamed tumor microenvironment. Seng-Ryong Woo, Leticia Corrales, Thomas F. Gajewski. Trends in Immunology: Review special issue: IMMUNITY AND CANCER| VOLUME 36, ISSUE 4, P250-256, APRIL 01, 2015

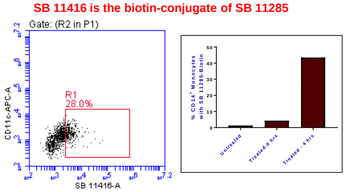
SB 11285 self-assembles to form nanostructures



SB 11285 was dissolved in saline @ 2mg/ml. The sample was then imaged by scanning electron microscopy

Significant uptake by myeloid dendritic cells and monocytes

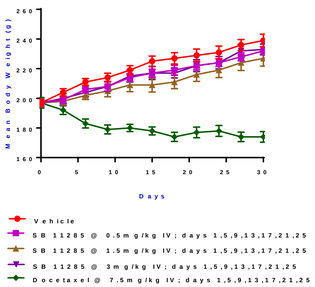
SB 11416 is the biotin-conjugate of SB 11285



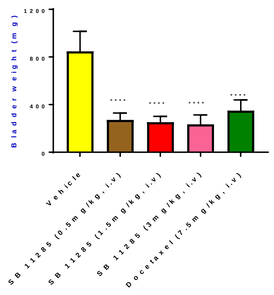
PBMCs were treated with SB 11416 (Biotin-SB 11285) at various time points to evaluate uptake of SB 11285 into cells. The cells were then harvested for staining with various surface markers such as CD14, CD 11c+ before performing intracellular cytokine staining with streptavidin probe for Biotin-SB 11285 by flow cytometry analysis. A representative plot is shown above.

IV administration of SB 11285 resulted in potent anti-tumor activity in Orthotopic NBT-II syngeneic rat bladder cancer model

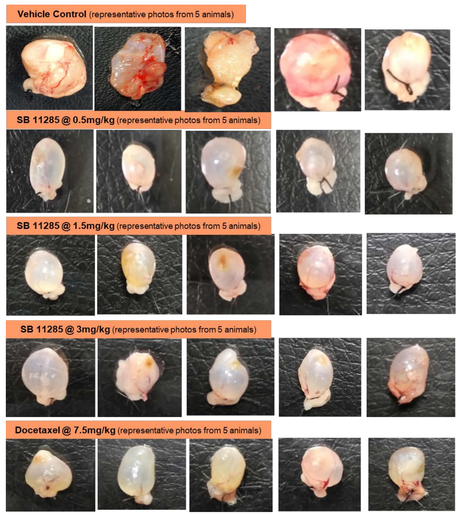
IV SB 11285 at the tested dose levels (0.5, 1.5 & 3 mg/kg) was well tolerated with no mortality.



Potent anti-tumor activity of IV SB 11285 against NBT-II bladder cancer



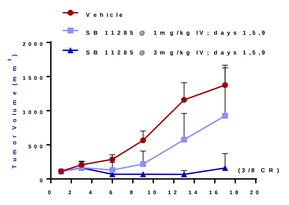
Gross Pathology evaluation of bladder revealed no visible tumor nodules in SB 11285 treated groups



NBT-II rat baldder carcinoma cells were implanted in bladder wall surgically. 6 days after implantation, SB 11285 treatment @ 0.5/1.5/3mg/kg was started on days 1,5,9,13,17,21&25. Animals were sacrificed on day 31 to measure bladder weight and to perform gross pathology evaluation of bladder. Body weights of rats were measured over the course of the study.

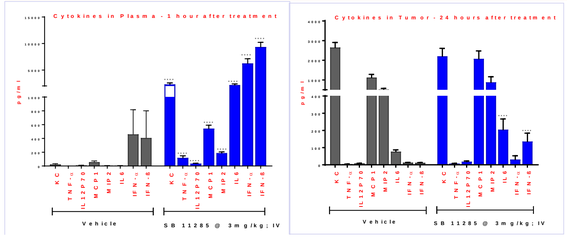
IV administration of SB 11285 resulted in durable Type I IFN and CD8+ T cell dependent anti-tumor activity in CT26 colon carcinoma mouse model

IV administered SB 11285 shows dose-dependent anti-tumor activity in the CT26 colon carcinoma model



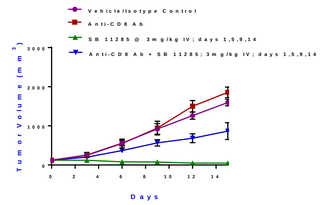
CT26 cells were implanted subcutaneously in right flank and SB 11285 treatment was started when mean tumor volume reached 100mm^3 . SB 11285 was given IV @ 1/3 mg/kg on days 1,5,9.

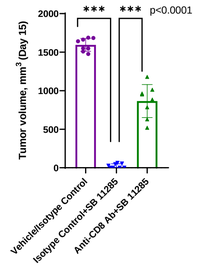
SB 11285 induced significant induction of cytokines associated with Type I IFN signature in both plasma and TME



Plasma samples were collected 1 hour after SB 11285 IV administration on day 1. Tumor tissues were collected on day 6 after SB 11285 administration on day 1 & 5 to obtain tumor tissue lysates. Both plasma and tissue lysates were tested for presence of cytokines by using mouse magnetic Luminex assay.

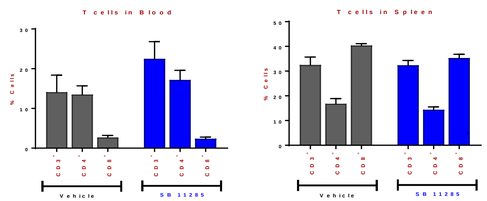
The potent anti-tumor activity of SB 11285 is mediated by CD8+ T cells





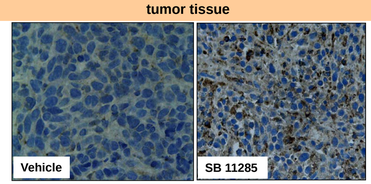
CT26 cells were implanted subcutaneously in right flank and SB 11285 treatment @ 3mg/kg was started when mean tumor volume reached 100mm^3 on days 1,5,9,14. 100μg Anti-CD8 Ab (53-5.8) was administered IP on days -3,-1,0,7,14,21.Mean tumor volumes were measured over the course of the study.

SB 11285-induced STING activation did not result in T cell cytotoxicity



Blood and spleen were on day 6 after SB 11285 administration on day 1 & 5 to obtain single cell suspension. The cells were then stained with anti-mouse CD3, CD4 and CD8a antibodies to enumerate cell population in vehicle and SB 11285 treated mice.

SB 11285 induced significant CD8+ T cells infiltration in tumor tissue

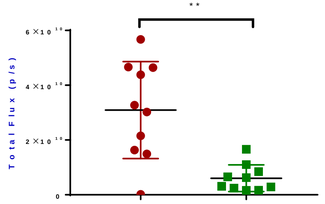


Tumor tissues on day 6 (after SB 11285 IV administration on day 1 & 5) were collected and fixed in 10% neutral buffered saline for further processing into paraffin embedded tissue sections. The sections were then stained with anti-CD8 antibody to detect CD8+ T cells. The images shown are a representative pictures from a group of 6

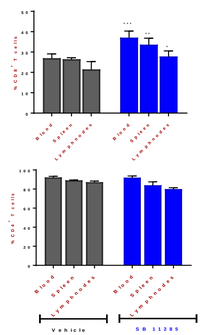
SB 11285 inhibits tumor growth and metastasis in orthotopic 4T1 breast cancer model after intraperitoneal (IP) administration

IP administered SB 11285 shows highly potent anti-tumor activity in 4T1 breast cancer mouse model

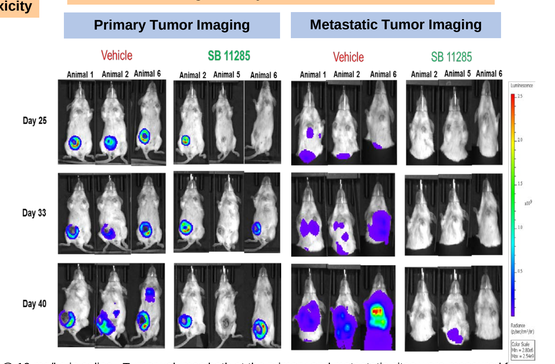
Group	Dose	Route	Schedule (days)
Vehicle	100 µl Saline	IP	5, 7, 9, 11, 13, 17, 19
SB 11285	10 mg/kg	IP	5, 7, 9, 11, 13, 17, 19



SB 11285-induced STING activation caused CD8+ T cell proliferation without cytotoxicity



SB 11285 significantly inhibited tumor metastasis



4T1 cells were implanted subcutaneously in mammary Fat Pad on day 1. SB 11285 was administered (IP) on days 5, 7, 9, 11, 13, 17 & 19 @ 10 mg/kg in saline. Tumor volumes both at the primary and metastatic sites were measured for the entire study by bioluminescence imaging. Blood, lymph nodes and spleen were collected on day 19 to obtain single cell suspension. The cells were then stained with anti mouse CD3, CD4 & CD8 antibodies to enumerate cell population.

Summary: We have discovered highly potent first-in-class STING agonists that can be administered by systemic routes. The lead STING agonist SB 11285 has demonstrated potent Type I IFN and CD8+ T cell-dependent anti-tumor activity in multiple subcutaneous and orthotopic tumor models. As a novel agonist, SB 11285 also showed inhibition of tumor metastasis. SB 11285 is being evaluated in IND-enabling studies for the initiation of clinical trials.