Pharmacodynamic and preclinical studies of SB 11285, a highly potent, and systemically bioavailable STING agonist as a novel immuno-therapeutic agent

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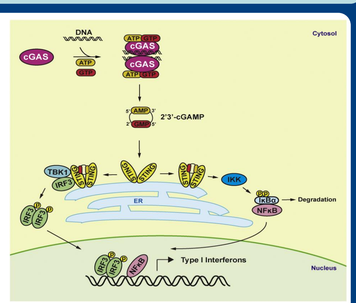
INTRODUCTION

Immunotherapy has emerged as a transformative approach for the treatment of cancer. Recent work has highlighted a major role for Stimulator of Interferon Genes (**STING**) agonists in immunotherapy. Conceptually, the activation of STING pathway in immune cells and tumor cells in the tumor microenvironment could result in the induction of innate and adaptive immunity through the activation of cytotoxic T cells and NK cells for profound and durable anti-tumor response. We recently reported the discovery of SB 11285 as a potent, first-in-class, STING agonist. Reported here are the pharmacodynamic studies of SB 11285, in multiple syngeneic mouse tumor models, when administered by intravenous **(IV)**, intraperitoneal (**IP**) and intratumoral (**IT**) routes.



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RESULTS

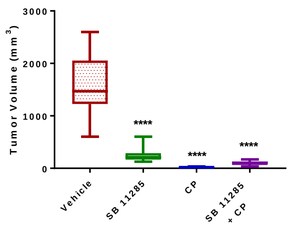
General Study Design

Tumor implant → 2-3 weeks → MTV 100 mm3 → Treatment phase (Day 1 of dosing) → TGI phase (Monitor until Vehicle MTV reaches 2000 mm3) → TGD phase

P.S. All anti-tumor data plots are shown as days post start of dosing

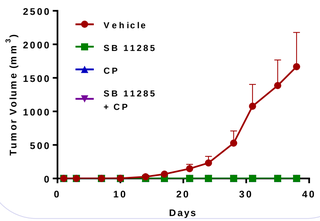
IT administration of SB 11285 results in potent and durable anti-tumor activity and induces immune memory in the A20 lymphoma mouse model

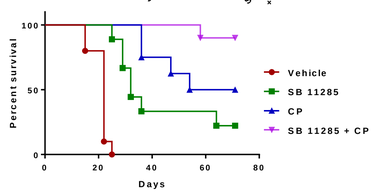
Group	Dose	Route	Schedule (days)
Vehicle	50µl Saline	IT	3, 4, 6, 8, 10
SB 11285	100µg/animal	IT	3, 4, 6, 8, 10
Cyclophosphamide	100mg/kg	IP	1 & 2
Cyclophosphamide + (SB 11285)	100mg/kg + (100µg/animal)	IP + (IT)	1 & 2 3, 4, 6, 8, 10



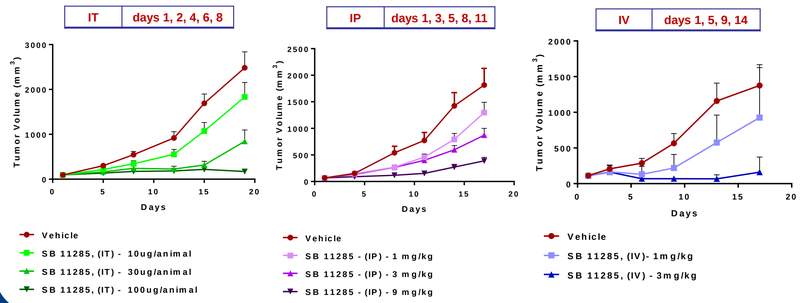
Re-Challenge Study

Complete responders along with a new vehicle group mice were challenged with A20 cells on opposite Flank

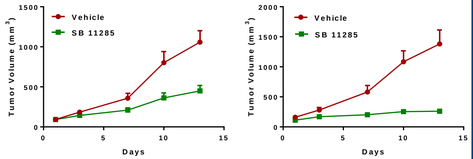




IT, IP, and IV administered SB 11285 shows dose-dependent and highly potent anti-tumor activity In the CT26 colon carcinoma mouse model

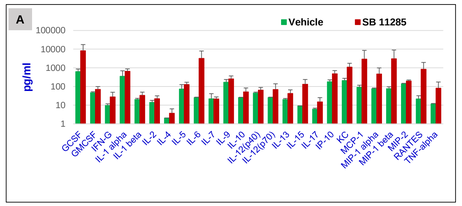


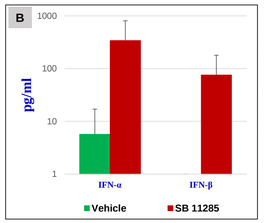
SB 11285 displayed significant abscopal effect after IT administration in CT26 mouse model



Tumor Implantation	Dose	Route	Schedule (days)
Right flank	None	None	None
Left Flank	100µg/animal	IT	1, 2, 4, 6, 8

Cytokine expression profile after IP administration of SB 11285 in mice



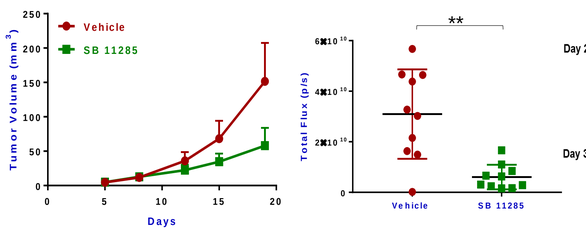


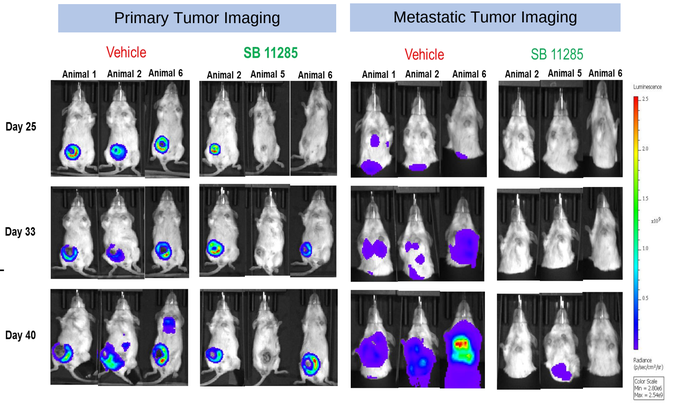
Evaluation of cytokine expression after IP administration of SB 11285: A group of five, C57BL/6 mice were given IP dosing of either saline or 10mg/kg SB 11285. Four hours after injection, serum was collected to investigate cytokine secretion by Luminex assays. (A) MCYTOMAG-70K-PMX MILLIPLEX MAP Mouse Cytokine/Chemokine Magnetic Bead Panel and (B) Procartaplex Luminex IFNα-β Mouse Cytokine Magnetic Bead Panel were used.

RESULTS

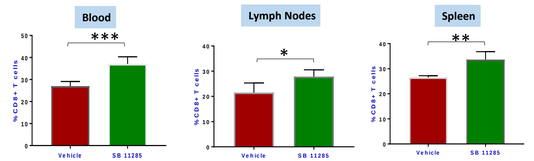
SB 11285 inhibits tumor growth and metastasis in orthotopic 4T1 breast cancer model after IP administration. Significant induction of CD8+ T cells in Spleen, Blood and Lymph nodes was also observed

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





% CD8+ T cells



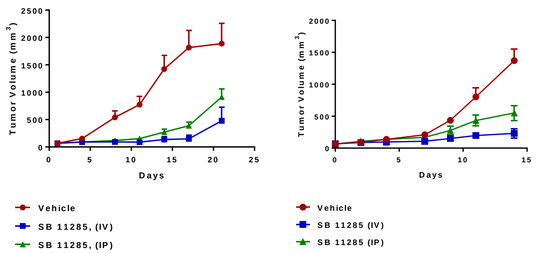
IV administration of SB 11285 is more efficacious than IP administration

CT26 Colon Carcinoma

Group	Dose	Route	Schedule (days)
Vehicle	100µl Saline	IV	1, 3, 5, 8
SB 11285	9mg/kg	IP	1, 3, 8
SB 11285	9mg/kg	IV	1, 3, 8

B16 Melanoma

Group	Dose	Route	Schedule (days)
Vehicle	100µl Saline	IV	1, 3, 8
SB 11285	9mg/kg	IP	1, 3, 8
SB 11285	9mg/kg	IV	1, 3, 8



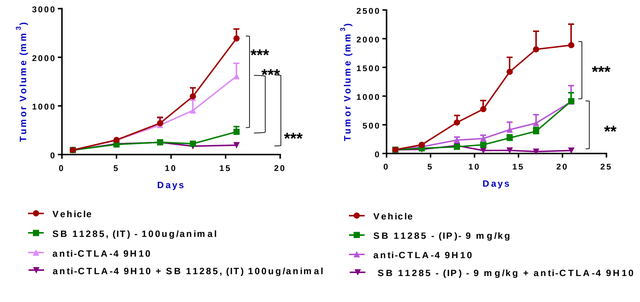
SB 11285 shows synergistic anti-tumoral activity when combined with the Immune Check Point Inhibitor - anti-CTLA Antibody

Intratumoral (IT) Study

Group	Dose	Route	Schedule (days)
Vehicle	50µl Saline	IT	1, 4, 7, 10, 17
SB 11285	50µg/animal	IT	1, 4, 7, 10, 17
Anti-CTLA4-9H10	5mg/kg 2.5mg/kg	IP IP	1 4, 7
Anti-CTLA4-9H10 + (SB 11285)	5mg/kg 2.5mg/kg + (50µg/animal)	IP IP + (IT)	1 4, 7 1, 4, 7, 10, 17

Intraperitoneal (IP) Study

Group	Dose	Route	Schedule (days)
Vehicle	100µl Saline	IP	1, 3, 5, 8
SB 11285	9mg/kg	IP	1, 3, 5, 8
Anti-CTLA4-9H10	5mg/kg 2.5mg/kg	IP IP	1 4, 7
Anti-CTLA4-9H10 + (SB 11285)	5mg/kg 2.5mg/kg + (9mg/kg)	IP IP + (IP)	1 4, 7 1, 3, 5, 8



SUMMARY

We have discovered highly potent first-in-class STING agonists that cause induction of IFN, NF-κB, ISGs, and cytokines. The lead STING agonist SB 11285 administered by IT, IP and IV routes has demonstrated potent anti-tumor activity in multiple subcutaneous and orthotopic tumor models, and is synergistic with anti-cancer agents. As a novel STING agonist, SB 11285 induces anti-tumor immune memory, shows abscopal anti-tumor activity and inhibits tumor metastasis. SB 11285 is being advanced for IND-enabling studies for the initiation of clinical trials.

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