Novel Dinucleotides that Activate cGAS-STING Signaling for Immuno-oncology

**INTRODUCTION**

Immune therapy has matured as a transformative approach for the treatment of cancer; nevertheless, many patients remain unresponsive to treatment. It is being recognized that Induction of type I interferon (IFN) and interferon-stimulated genes (ISGs) in tumor cells and within the tumor microenvironment (TME) is essential for modulating the host immune response and inducing apoptosis of tumor cells. Furthermore, the antigen-presenting cells within TME can cause induction of adaptive immune responses by priming of CD8+ T cells and tumor killing. Importantly, the DNA disabled from released damaged cells and cancer cells can be sensed by cyclic GMP-AMP synthase (cGAS) leading to the synthesis of cyclic GMP-AMP (cGAMP), a second messenger that activates Stimulator of Interferon Genes (STING) pathway resulting in the production of type I IFN and ISGs. The cumulative effects of activation of innate and adaptive immune response result in a powerful anti-cancer strategy. Therefore therapeutic agents that activate the cGAS-STING signaling pathway in tumor cells and TME are urgently needed. Here we describe discovery of novel potent, first-in-class small molecules for application in immuno-oncology.

**RESULTS**

**SB 9003-6 induces IFN in monocytic cells**

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- **SB 9003-6 induces expression of IFN-β and IFN-γ in monocytic cells**
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- **The cGAS pathway is essential for 9003-6-induced type I IFN responses**

**ACKNOWLEDGEMENTS**

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**REFERENCE**


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**Poster # 836**

**AACC 2016 - Tumor Immunology and Immunotherapy**

**RESULTS**

- **Screening of nucleic acid sequences for induction of STING activity and activation of IFN expression**
- **SB 9003-6 and SB 11285-treated THP1-conditioned medium significantly inhibits the growth of multiple tumor-derived cell lines**

**CONCLUSIONS**

- **The analog SB 9006 appears to be an agonist of cGAS whereas SB 11285 is a STING agonist**
- **Residues K384 and K411 in cGAS play critical roles in SB 9003-6-induced activation of type I IFN response**
- **SB 9003-6 induces IFN-β and ISGs, including multiple pattern recognition receptors in human monocytic cells**
- **Both SB 9003-6 and SB 11285 suppress tumor cell growth in conditioned media**

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