Materials and Methods

- Focused libraries of CDNs were synthesized using phosphoramidite chemistry
- Binding affinity with human STING CTD was determined by SPR
- STING-dependent Induction of IRF and NF-κB was assayed as % fold change in luminometric units using cells, with reporter constructs
- Self-assembly to nanostuctures was determined by SEM
- In vivo efficacy was assessed by measurement of mean tumor volumes following administration of compounds by i.v. or i.p. in the A20 lymphoma, CT26 carcinoma, B16 melanoma, and 4T1 breast cancer models
- Flow cytometry, multiplexing assays and immuno-histochemistry of blood and tissues were carried out to assess MDA

Results

Lead compounds that induce IRF induction in reporter assays (EC50 to 10 mM) were found to self-assemble into nanostuctures. The lead analog, SB 11285, showed highly potent and durable anti-tumor response in multiple tumor models with M.E.D 10 μg (i.l.) and 1 mg/kg (s.c.).

Uptake by Immune Cells

Significant uptake of SB 11285 by myeloid dendritic cells and monocytes

PAMCs were treated with Bio-ID SB 11285 at various time points to evaluate uptake of SB 11285 in PAMCs. Cells were then harvested for starting with various surface markers such as CD14 (monocytes), CD11c (myeloid dendritic cells) before performing immunofluorescence staining with streptavidin probe for Bio-ID SB 11285. Cells were analyzed by flow cytometry. A representative plot is shown.

In Vivo Efficacy

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

Durable anti-tumor response

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

Induction of immune memory

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

IP and IV administered SB 11285 shows highly potent anti-tumor activity in the B16 melanoma mouse model

Conclusions

We have discovered next generation CDNs as highly potent first-in-class STING agonists. These CDNs self-assemble into nanostuctures that enable system administration reticulo-endothelial cellular delivery. Administration of the lead compound SB 11285 by I.V., I.P. or i.7 routes in syngeneic models of A20 lymphoma, CT26 colon cancer, B16 melanoma, 4T1 breast cancer models resulted in potent dose-dependent and durable anti-tumor response with the induction of immune memory and anti-tumor effect. Anti-tumor activity was associated with induction of Type I IFN and CD8+ T cells in the tumor and periphery. The lead compound is being advanced into further clinical trials.

References


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