BSI-060T, a High Affinity, Fully Human Anti-Siglec-15 Antibody as an Alternative Immune Checkpoint Blocker

Zeyu Peng[a], Xiaodong F. Liu[b], Shukai Xia[a], Jinyu Liu[a], Hongyan Li[a], Yuxiang Liu[a], Hugh M. Davis[b], Mingjiu Chen[a], Mark Z. Ma[a]

[a]Biosion, Inc., Nanjing, Jiangsu, China [b]Biosion USA, Inc., Newark, DE, USA

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Abstract

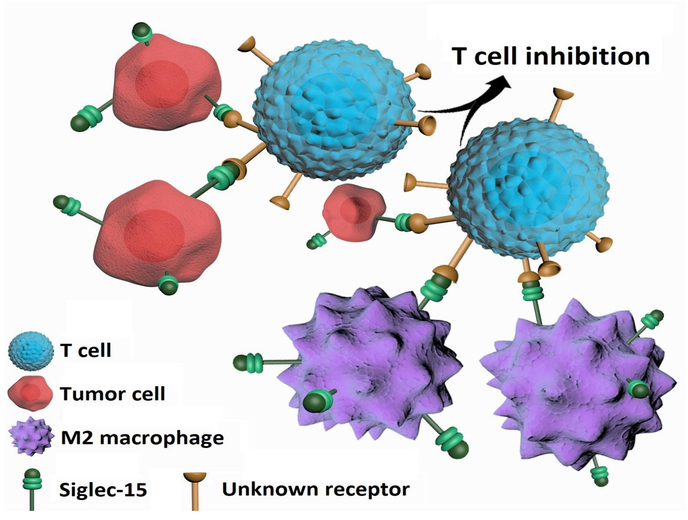
Background: Siglec-15 is a single-pass type I membrane protein that plays an important role in the immune-suppressive tumor microenvironment (TME). Siglec-15 has low expression levels in most normal human tissues but it is highly expressed in a subset of myeloid cells of the TME and over-expressed in some solid tumors. Siglec-15 on tumor associated macrophages and tumor cells inhibits T cell proliferation and pro-inflammatory cytokine release. Therefore, targeting Siglec-15 may overcome a suppressive TME and enhance the anti-tumor activity of other immune checkpoint inhibitors.

Experimental procedures: Humanized mice were immunized with recombinant Siglec-15-ECD-Fc. The Biosion proprietary H^3 (High-throughput, High-content and High-efficiency) antibody screening platform was used to identify a lead anti-Siglec-15 mAb candidate-BSI-060T. Siglec-15 expression in different cancer types was assessed by immunohistochemistry (IHC) in conjunction with PD-L1. The *ex vivo* reverse of T cell suppression was determined by stimulating human peripheral blood mononuclear cells (PBMCs) with a suboptimal dose of immobilized OKT3 in the presence of recombinant human Siglec-15-Fc with and without BSI-060T. A pharmacokinetic study was carried out in cynomolgus monkeys to determine the exposure of BSI-060T over time. Tumor inhibitory activity of BSI-060T was evaluated in Siglec-15 humanized mice that were inoculated with MC38 cells overexpressing human Siglec-15.

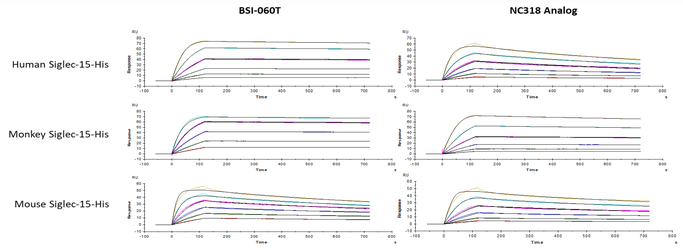
Results: BSI-060T is a fully human IgG1κ monoclonal antibody that binds to Siglec-15 protein with high affinity and blocks the interaction between Siglec-15 and its putative receptor LRRC4C. BSI-060T shows cross-reactivity to monkey and mouse Siglec-15. In *ex vivo* T cell response assays, BSI-060T exhibits strong activity on reversing Siglec-15-mediated inhibition of $CD8^+$ and $CD4^+$ T cell proliferation and interferon-γ release. In a humanized Siglec-15 mouse syngeneic tumor model, BSI-060T induces significant inhibition of tumor growth. BSI-060T exhibits a favorable PK profile and dose-dependent exposure in monkey.

Conclusion: BSI-060T exhibits best-in-class biophysical properties and functional activities, supporting the initiation of clinical development in solid tumors.

Siglec-15 is Immunosuppressive in the TME

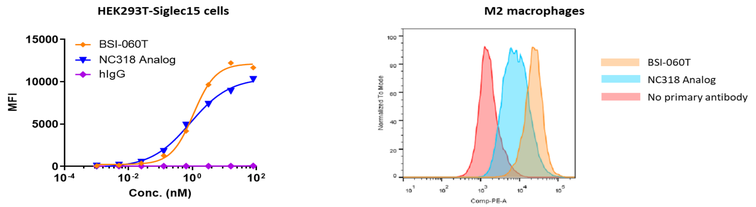


BSI-060T Shows Higher Binding Affinity to Siglec-15 Than NC318 Analog

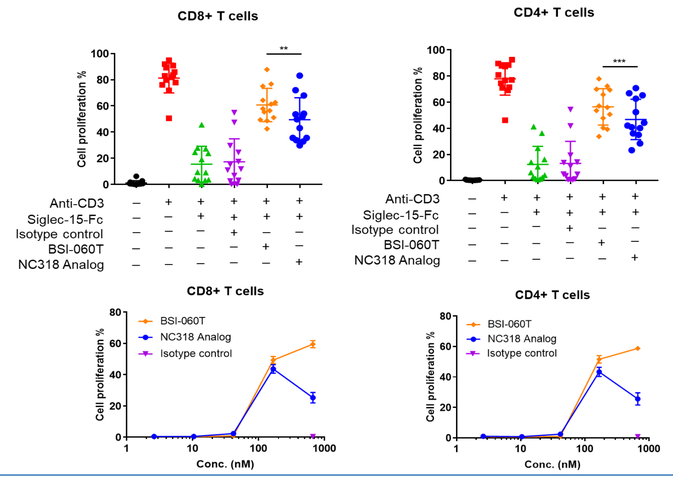


Antibody	Human Siglec-15			Monkey Siglec-15			Mouse Siglec-15		
	ka (1/Ms)	kd (1/s)	K_D (M)	ka (1/Ms)	kd (1/s)	K_D (M)	ka (1/Ms)	kd (1/s)	K_D (M)
BSI-060T	1.88E+06	7.46E-05	**3.96E-11**	7.08E+05	5.32E-05	**7.51E-11**	2.24E+06	1.65E-04	**7.37E-11**
NC318 Analog	2.27E+06	9.55E-04	4.22E-10	1.13E+06	7.81E-04	4.48E-10	5.47E+06	9.31E-04	1.70E-10

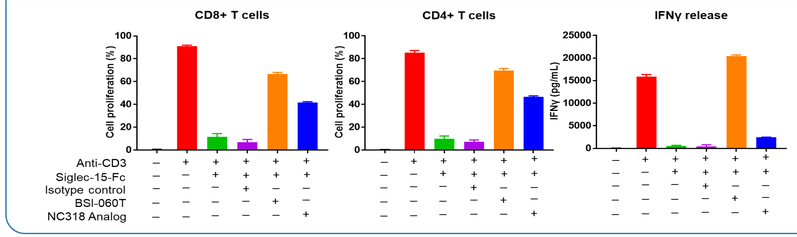
BSI-060T Binds to Cell Surface Siglec-15



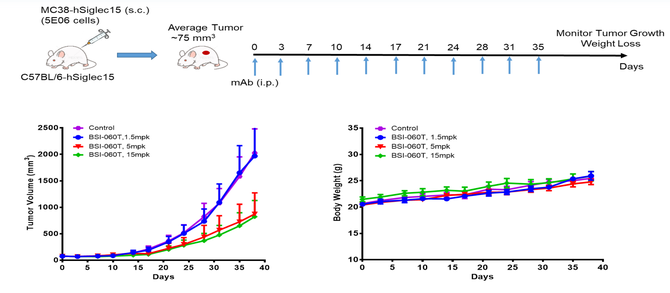
BSI-060T Reverses Siglec-15-Mediated T Cell Suppression Better Than NC318 Analog



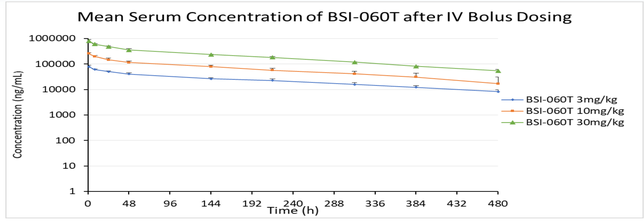
BSI-060T Reverses Siglec-15-Mediated Inhibition of IFNγ Secretion from PBMCs Significantly Better Than NC318 Analog



BSI-060T Exhibits Anti-Tumor Activity *in vivo*



BSI-060T Exhibits a Favorable Pharmacokinetic Profile in Cynomolgus Monkeys



Parameter	Unit	BSI-060T Low Dosage (3 mg/kg)	BSI-060T Medium Dosage (10 mg/kg)	BSI-060T High Dosage (30 mg/kg)
$T_{1/2}$	h	177±11.1	151±61.0	151±20.8

Summary

- BSI-060T is a fully human anti-Siglec-15 therapeutic antibody, exhibiting higher affinity and higher *ex vivo* bioactivity;
- BSI-060T induces significant inhibition of tumor growth *in vivo* with a favorable PK profile in cynomolgus monkeys;
- BSI-060T is an IND-ready asset with an IND submission and phase 1 initiation planned for 2022.