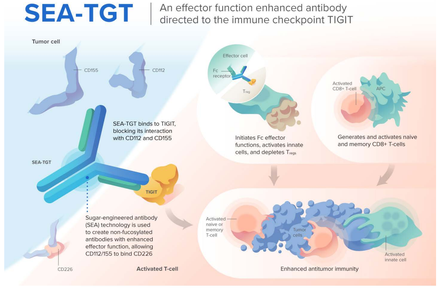
SEA-TGT is a nonfucosylated antibody with distinct and amplified effector function activity that leverages the dependencies of anti-TIGIT anti-tumor activity upon FcγR engagement

Alyson J. Smith, Weiping Zeng, Bryan Grogan, Serena Wo, Sasha Lucas, Will Siegall, Amber Blackmarr, Scott Peterson, Shyra J. Gardai
Research Department, Seattle Genetics Inc., Bothell, WA

Background

- TIGIT is an inhibitory immune receptor expressed on memory and regulatory T cells that is emerging as a clinically relevant immuno-oncology target
- TIGIT targeting can elicit multiple mechanisms of action (MOAs) including:
  - Depletion of TIGIT+ Treg
  - Amplifying naïve and memory CD8 T cell responses
  - Activation of innate cells
  - Activation of NK cells
- Here in we describe the activity of SEA-TGT, our investigational anti-TIGIT antibody which has been sugar engineered to be nonfucosylated and shows enhanced backbone effector function across all preclinical MOAs



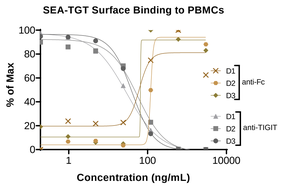
mAb	Description
SEA-TGT	Non-fucosylated backbone
TIGIT IgG1	Wild type backbone
TIGIT LALA IgG1	Inactive backbone (L234A L235A P329G)

SEA-TGT binds TIGIT with high affinity and restores CD155 signaling

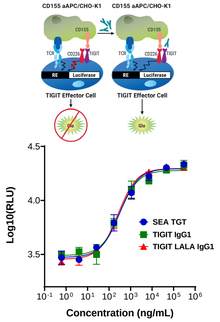
Monovalent BLI Binding Affinity

Human TIGIT K_D (nM)	Cyno TIGIT K_D (nM)	Murine TIGIT K_D (nM)
8.50	52.60	13.4

Cell Binding and Receptor Saturation



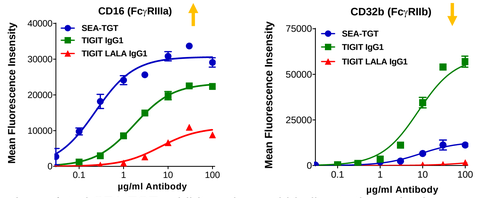
CD155/TIGIT Human Signaling assay



SEA-TGT binds human, cyno and mouse TIGIT with similar nM affinity and saturates TIGIT on human PBCMs with an EC50 of 62 ng/ml. Strong restoration of CD155 signaling, regardless of FcγR engagement of the backbone, occurred.

SEA-TGT has amplified effector function that results in superior anti-tumor activity

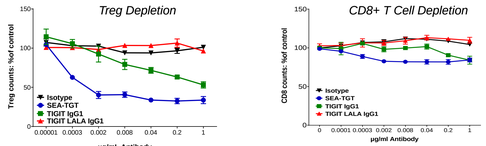
SEA-TGT binds differentially to activating and inhibitor FcγRs



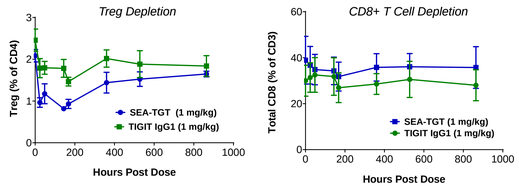
Nonfucosylated SEA-TGT exhibits enhanced binding to the activating receptor FcγRIIIa/CD16 with concomitant decreased binding to the inhibitory receptor FcγRIIb/CD32 compared to the IgG1 backbone.

SEA-TGT effectively depletes T regs with limited CD8+ T cell changes

In Vitro (Human PBMCs)

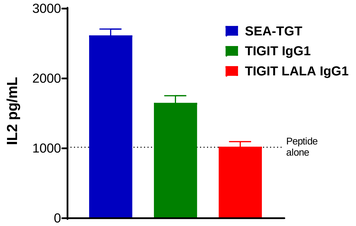


In Vivo (NHP)



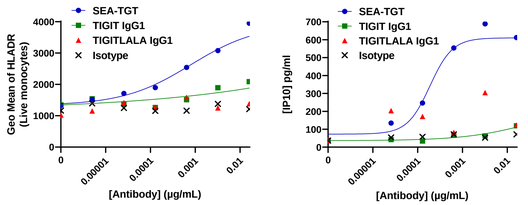
SEA-TGT was superior at depleting TIGIT+ Tregs in human PBMCs and in vivo in NHPs compared to the IgG1 or LALA backbone, which was totally inactive. SEA-TGT-mediated loss of CD8+ T cells was minimal both in vitro and in vivo.

SEA-TGT increases antigen-specific CD8+ T cell responses



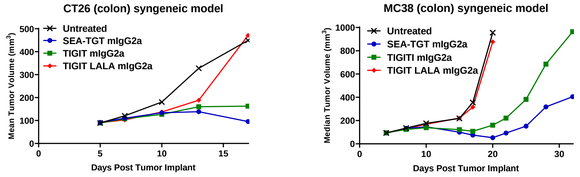
Intact FcγR engagement is required for driving T cell activation in response to staphylococcal enterotoxin A (SEA) peptide. SEA-TGT exhibited superior activity at driving T cell activation measured by IL2 production.

SEA-TGT is distinct at activating antigen presenting cells



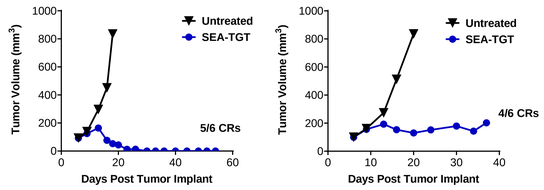
SEA-TGT drives robust innate cell activation, monitored by increased HLA-DR (MHCII) on the surface of CD14+ cells and production of the type I interferon related cytokine CXLC10. The IgG1 or LALA backbones had muted or no APC activation.

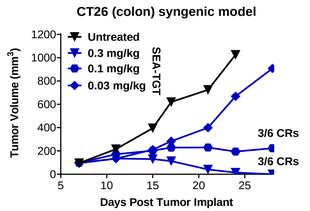
SEA-TGT drives more robust curative single agent anti-tumor activity



FcγR engagement was critical for anti-tumor activity with strength of this interaction being associated with increased cure rates, from 50% with IgG1 to 66% with SEA-TGT in CT26 at 1 mg/kg. This dependence on FcγR engagement to drive activity was also seen in the MC38 model treated with 0.1 mg/kg of the therapies.

SEA-TGT elicits curative activity across tumor models

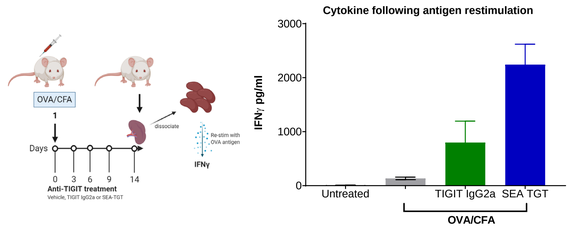




The A20 and Renca syngeneic tumor models were treated with SEA-TGT (1 mg/kg) and potent tumor growth delay and curative responses were seen. This strong anti-tumor activity of SEA-TGT was seen in the CT26 model even at doses as low as 0.1 mg/kg.

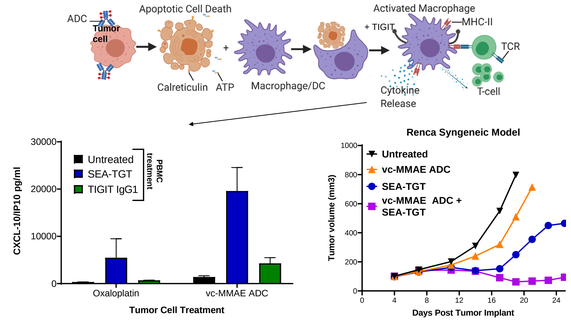
SEA-TGT enhances antigen specific T cells

SEA-TGT enhances generation of antigen specific T cells in a vaccination model



Vaccination in concert with SEA-TGT treatment generated superior antigen specific T cell responses seen by IFNγ induction post antigen re-stimulation.

SEA-TGT synergizes with vc-MMAE ADCs



Concomitant with SEA-TGT's ability to enhance antigen-specific T cell generation, there is significant synergy between SEA-TGT and immunogenic cell death (ICD) induced by MMAE ADC treatment both in vitro and in vivo.

Conclusions

	CD155	T reg depletion	CD8 T cell response	APC activation	Curative anti-tumor activity
SEA-TGT	++	++++	+++	+++	++++
TIGIT IgG1	++	++	++	+	++
TIGIT LALA IgG1	++	-	-	-	-

- SEA-TGT is an investigational human monoclonal antibody that binds to human, murine, and cynomolgus TIGIT with nM monovalent affinity
- The SEA-TGT nonfucosylated backbone preferentially increases binding to activating but not inhibitory Fcγ receptors
- SEA-TGT treatment drives robust depletion of T regulatory cells, activation of APCs and amplifies antigen specific T cell responses
- SEA-TGT has potent, curative single agent activity in several syngeneic tumor models
- A phase I trial of SEA-TGT is currently enrolling patients with solid tumors and lymphomas in sites across North America and Europe (NCT04254107)

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DISCLOSURES: All authors are employees of and hold stock in Seattle Genetics Inc.

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