SEA-TGT is an Empowered Anti-TIGIT Antibody that Displays Superior Combinatorial Activity with Several Therapeutic Agents

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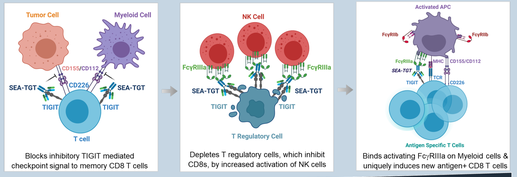
SEA-TGT Proposed Mechanisms of Action

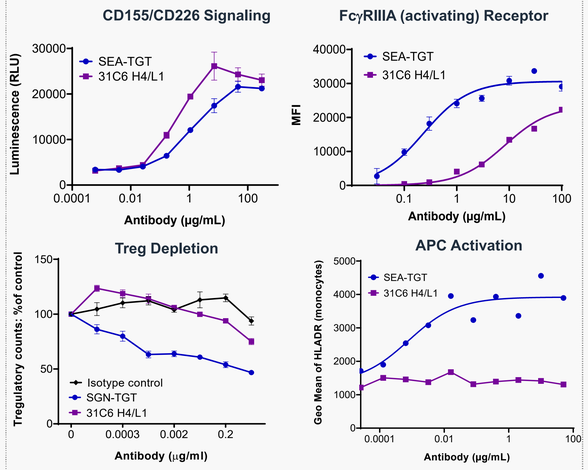


TIGIT is a receptor expressed on a subset of activated memory CD8+ T cells and immunosuppressive T regulatory cells (Tregs). TIGIT binds CD155 and CD112, which are overexpressed on tumor cells and inhibits signals to CD8+ T cells. TIGIT targeting can drive CD8+ T cell activation critical for anti-tumor responses.

SEA-TGT is an investigational empowered human IgG1 antibody that employs sugar engineering technology to create a nonfucosylated antibody with increased effector function. SEA-TGT binds human, cynomolgus, and murine TIGIT with equal affinity and prevents TIGIT binding to CD155/112 to restore CD226 signaling.

The SEA-TGT backbone is distinct as it increases binding to activating FcγRIIIa with minimal binding to inhibitory FcγRIIb. Amplified binding to FcγRIIIa results in increased depletion of TIGIT+ Tregs as well as confers distinct activation of innate cells and generation of memory CD8 T cell responses.

SEA-TGT Backbone Confers Enhanced Activity

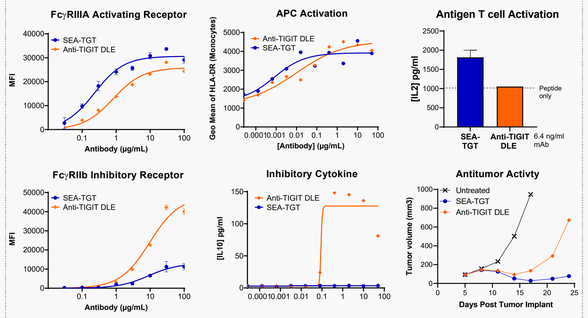


* 31C6 H4/L1 is a TIGIT mAb similar to M-7684 based on the patent US2018/0066055A1

SEA-TGT is a differentiated TIGIT targeted mAb. SEA-TGT restores CD226 signaling similar to competitor mAbs but has enhanced binding to activating FcγRIIIa with limited binding to inhibitory FcγRIIb. SEA-TGT's effector function enhanced backbone amplified depletion of Tregs and exclusively activated APCs.

Results

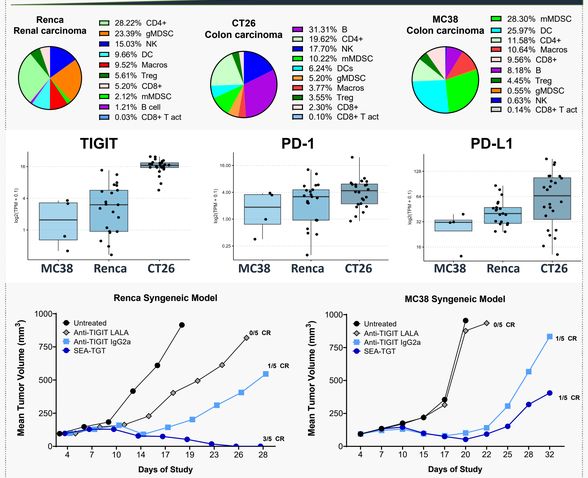
SEA-TGT Preferentially Binds Activating FcγRs



SEA-TGT selectively drives stimulatory FcγR signaling. Mutation of the TGT backbone, S239D/A330L/I332E (DLE), enhances FcγR binding for both activating and inhibitory receptors opposed to the selective IIIa binding of SEA-TGT. Unbiased binding of the DLE backbone led to production of inhibitory cytokines, limited T cell activation, and had muted anti-tumor activity compared to SEA-TGT. These data exemplify the importance of solely engaging activating Fc receptors.

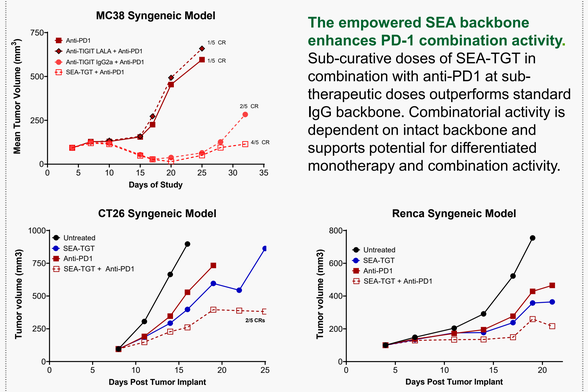
SEA-TGT is Active in Diverse Immune TMEs

Innate Enriched Microenvironment



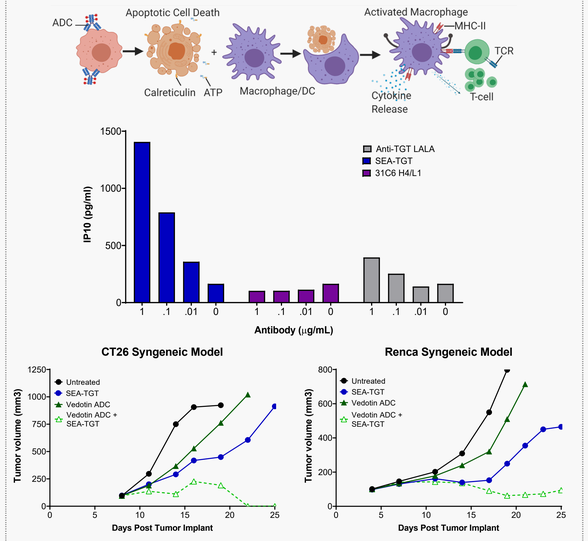
SEA-TGT drives strong activity across a diverse range of TMEs. Immuno-phenotyping of syngeneic models demonstrate disparate baseline immune repertoires across the models, and differential TIGIT, PD-1 and PD-L1 expression via RNAseq. Regardless of these differences SEA-TGT drove superior single agent activity in all models vs. the standard IgG2a or IgG2a FC inactive LALA L234A/L235A TIGIT mAbs.

SEA-TGT has Greater PD-1 Combination Activity



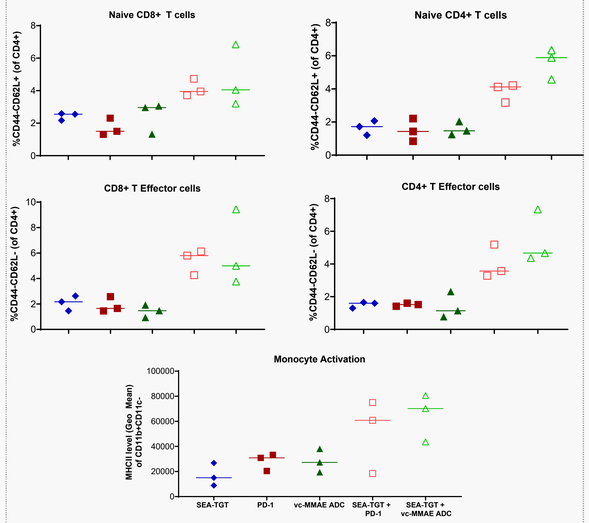
The empowered SEA backbone enhances PD-1 combination activity. Sub-curative doses of SEA-TGT in combination with anti-PD1 at sub-therapeutic doses outperforms standard IgG backbone. Combinatorial activity is dependent on intact backbone and supports potential for differentiated monotherapy and combination activity.

SEA-TGT MOA Synergizes with Vedotin ADCs



SEA-TGT combines with ADC therapy across targets and models. SEA-TGT synergizes with the immunogenic tumor cell death (ICD) driven by vedotin ADCs to drive substantial APC activation *in vitro*. This *in vitro* data translates into significant combinatorial activity between SEA-TGT and tumor targeted vedotin ADCs *in vivo* in disparate models using different tumor targeting antigens.

SEA-TGT Combinations Enrich the Immune TME



SEA-TGT and PD-1 were dosed q3dx3, ADC was dosed once concurrent with first SEA-TGT dose

Combination treatment with SEA-TGT and anti-PD-1 or vedotin ADC drives intratumoral immune remodeling. The immune microenvironment in Renca tumors 1 day post 3rd treatment was evaluated in response to single agent or the indicated combinations. The combinations were more robust at driving T cell infiltration as well as antigen presenting cell activation in the tumor microenvironment.

Conclusions

Anti-TIGIT treatments have recently emerged as an active cancer therapeutic modality. We evaluated the activity of SEA-TGT compared to TIGIT mAbs with different effector function backbones including the DLE effector function mutation. Nonfucosylated SEA-TGT had the greatest therapeutic properties *in vitro* and *in vivo*.

SEA-TGT had superior single agent and anti-PD1 combination anti-tumor activity and produced curative activity when combined with an ICD inducing vedotin antibody-drug conjugate. Collectively, these data strengthen our findings that the nonfucosylated effector function enhanced backbone of SEA-TGT and its preferential binding to activating FcγRIIIa receptor confers superior preclinical anti-tumor activity as a monotherapy agent and in combination with anti-PD-1 mAbs.

A Phase 1 trial of SEA-TGT is ongoing to evaluate the safety and activity of SEA-TGT alone and in combination with anti-PD-1 therapy in patients with advanced solid tumors and select lymphomas (NCT04254107).

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DISCLOSURES: All authors are employees of and have equity ownership in Seagen, Inc.

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