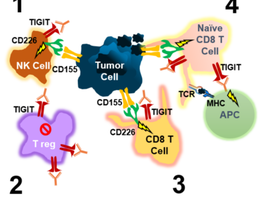
TIGIT Directed Human Antibody Modulates T-regulatory and Effector Cell Function

Alyson J. Smith, Weiping Zeng, Bryan Grogan, Jane Haass, Amber Blackmarr, Robert Thurman, Scott Peterson, Shyra J. Gardai
Research Department, Seattle Genetics Inc., Bothell, WA

Background

- TIGIT inhibits T and NK cell function by binding CD155 and CD112, which are upregulated on tumor cells
- SGN-TIGIT is fully human anti-TIGIT monoclonal antibody (mAb) that has equivalent affinity for human, murine and cynomolgus TIGIT and blocks TIGIT ligand binding
- SGN-TIGIT mediates ADCC to preferentially deplete Tregs in ex-vivo PBMC cultures
- SGN-TIGIT amplifies naïve and memory CD8 T cell responses
- SGN-TIGIT can result in curative single agent anti-tumor responses in several preclinical models, though its MOA appears distinct from PD-(L)1
- Models enriched for activated and/or memory CD8 T cell transcripts were positively correlated with curative response

TIGIT blockade drives multiple MOAs



Targeting TIGIT is believed to drive/restore 4 key functions

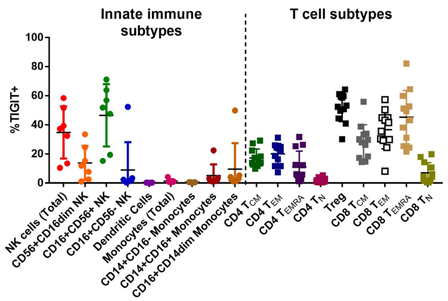
1. Restoration of NK Function

2. Depletion of T regs

3. Increased antigen-specific CD8 memory response

4. Induction of new antigen-specific CD8 T cells

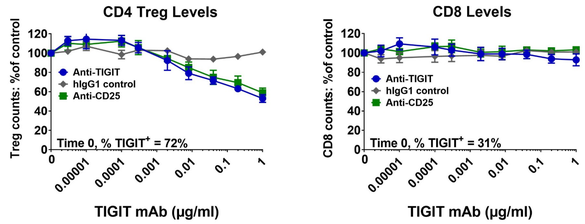
TIGIT expression on healthy PBMCs



- TIGIT was found to be most highly expressed on T regulatory cells, memory CD8+ T cell subsets and NK cells in the PBMCs of normal healthy donors

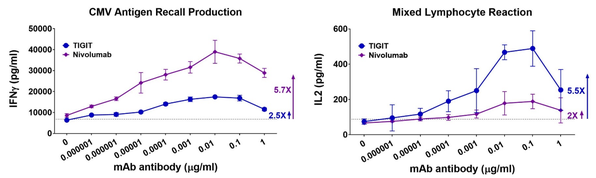
TIGIT-mediated T cell modulation

SGN-TIGIT treatment depletes TIGIT+ cells in vitro



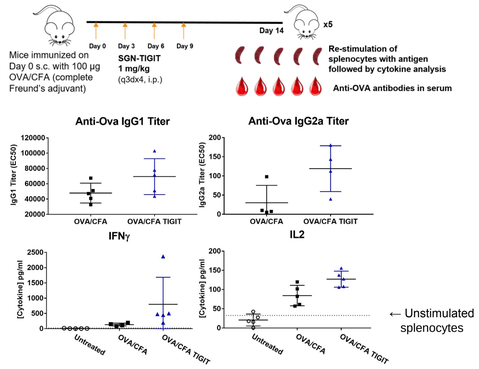
- PBMCs treated with increasing concentrations of SGN-TIGIT had decreased Treg numbers with no profound loss of CD4+ (not shown) or CD8+ T cells.
- Treg:NK co-cultures demonstrate TIGIT+ Treg loss is due to ADCC activity (not shown).

SGN-TIGIT enhances antigen-specific T cell responses



- SGN-TIGIT treatment enhanced IFNγ production from CMV-specific memory CD8 T cells. PD1 blockade (Nivo) demonstrated superior memory CD8 re-activation over TIGIT blockade in this system.
- SGN-TIGIT treatment in a mixed lymphocyte reaction (MLR) enhanced T cell activation as monitored by IL-2 production. TIGIT blockade outperformed PD1 blockade in this system.

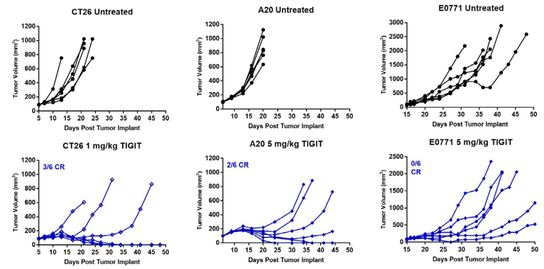
SGN-TIGIT boosts naïve antigen-specific responses



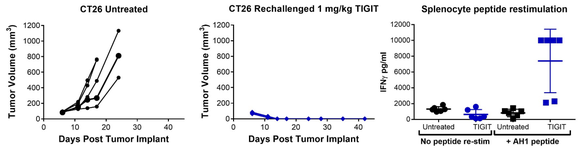
- Antibody titers increased in animals immunized in concert with SGN-TIGIT
- Vaccination in concert with SGN-TIGIT treatment enhanced antigen-specific CD8 T-cell priming seen by IL-2 and IFNγ following antigen re-stimulation.

TIGIT-mediated anti-tumor response

SGN-TIGIT displays strong anti-tumor efficacy

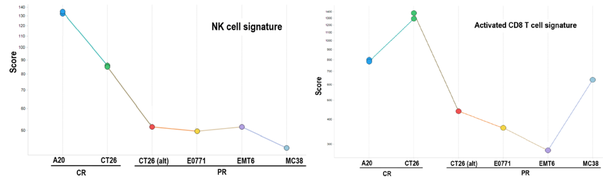


- SGN-TIGIT treatment in CT26 and A20 syngeneic models cured 50% and 33% of animals, respectively. SGN-TIGIT in the MC38, E0771, EMT6, and an alternative CT26 model, run by MI Bioresearch, resulted in partial responses (PR), seen as tumor growth delay.



- Mice cured in the CT26 study generated long-lasting anti-tumor memory CD8 T cells capable of rejecting re-challenged tumor cells.

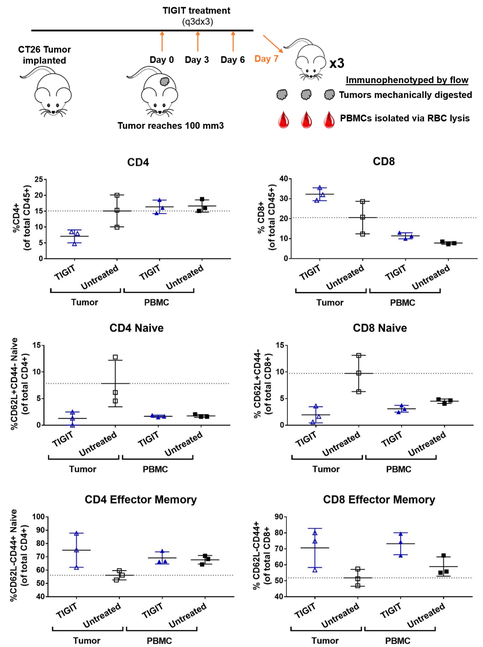
SGN-TIGIT responses correlate with baseline NK and CD8 T cell gene signatures



Gene Signature	Correlation	P value
Gamma delta T cell	0.9262	0.0009
NK cell	0.9200	0.0012
Activated CD8 T cell	0.8535	0.0070
Activated DC	-0.8437	0.0085
Immature B cell	0.7875	0.0203
CD96	0.7569	0.0297
CD8 T cell	0.7569	0.0297
CD56^{bright} NK cell	0.7319	0.0390
T helper 17 cell	0.7139	0.0467
Activated CD4 T cell	0.7092	0.0488

- SGN-TIGIT responses were classified as curative = A20, CT26 or partial response = CT26 (alt), EMT-6, E0771, MC38.
- Immune system gene signatures from Mosely et al. and The Cancer Immunome Atlas were scored using RNA-seq FPKM values (log transformed sum). Scores were correlated to a response vector, 0 for partial response and 1 for curative (Pearson correlation). Correlation tested for non-zero significance.

SGN-TIGIT treatment skews the TME towards a memory T cell response



- Within the TME, SGN-TIGIT decreased CD4+ T cells, increased CD8+ T cells, and increased the ratio of effector memory:naive CD4+ and CD8+ T cells.
- Minimal loss of CD4+CD25+CD127- Tregs in the tumor were seen (not shown).
- T cell changes were more prominent in or constrained to the TME.

Conclusions

- TIGIT is enriched on CD4+ Treg, memory CD8s and NK cells in healthy human PBMC populations
- SGN-TIGIT treatment induced dose dependent Treg depletion
- In vitro and in vivo data suggest that SGN-TIGIT re-activates memory T cells *and* primes new antigen-specific T cells
- Tumor efficacy studies in several syngeneic models demonstrate clear anti-tumor activity of SGN-TIGIT
- SGN-TIGIT treatment either delayed tumor growth or cured. Curative activity correlated to activated and memory CD8 T cell and NK cell gene signatures in the tumors at baseline
- Collectively these studies suggest SGN-TIGIT has pleiotropic anti-tumor mechanisms of action

* *Mosely et al, Cancer Immunol Res* 2017;5:29-41

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