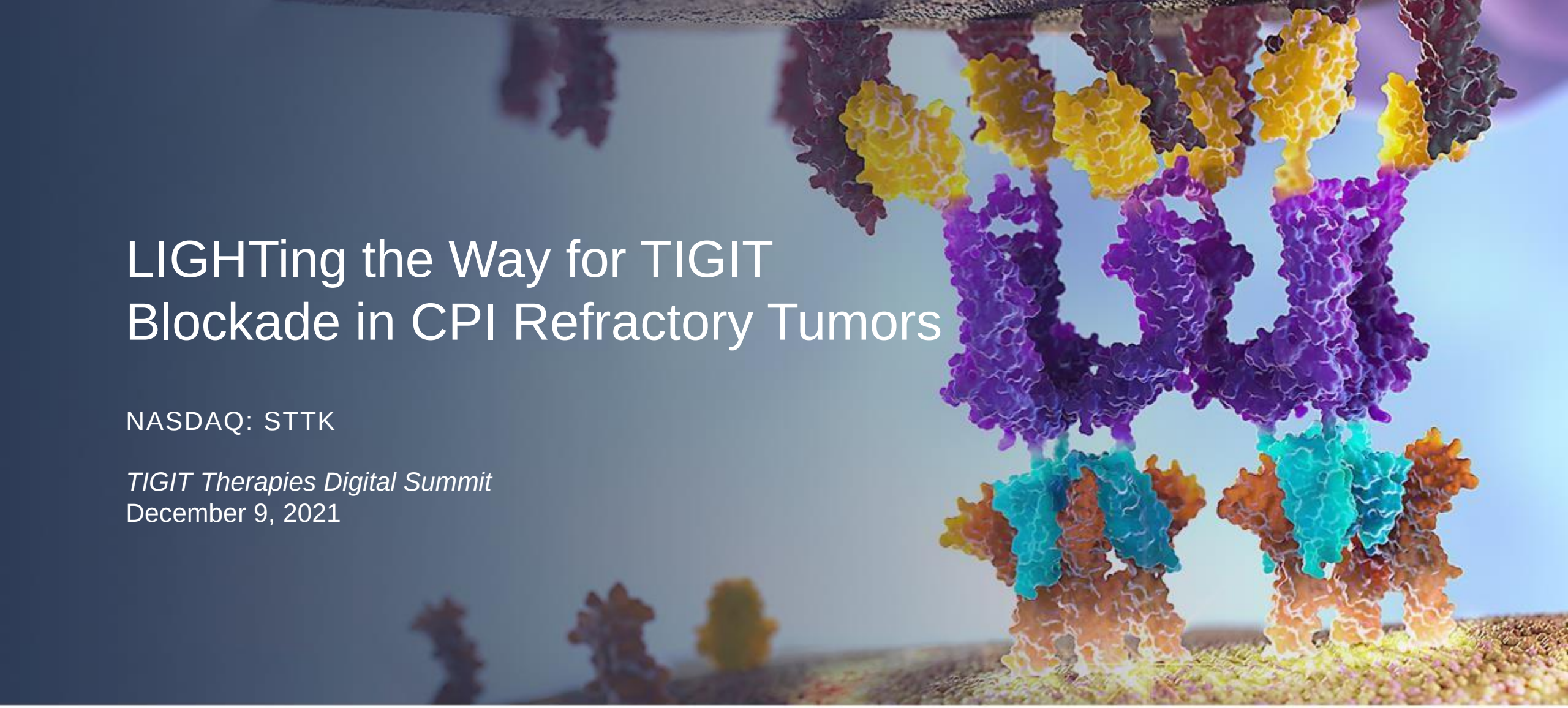


LIGHTing the Way for TIGIT Blockade in CPI Refractory Tumors

NASDAQ: STTK

TIGIT Therapies Digital Summit
December 9, 2021

SHATTUCK LABS

PIONEERING NOVEL BI-FUNCTIONAL FUSION PROTEINS
EXPANDING THE BOUNDARIES OF BIOLOGIC MEDICINES

Forward-Looking Statements

This presentation contains “forward-looking statements” within the meaning of the federal securities laws, which statements are subject to substantial risks and uncertainties and are based on our estimates and assumptions. All statements, other than statements of historical facts included in this presentation, including statements concerning our plans, objectives, goals, strategies, future events, plans or intentions relating to products and markets, the safety, efficacy and clinical benefits of our product candidates, the anticipated timing of our planned clinical trials, including initiation of additional cohorts, the anticipated timing for data, the association of preclinical data with potential clinical benefit, the timing of anticipated milestones, plans and objectives of management for future operations and future results of anticipated product development efforts, the timing of expected announcements, and our liquidity and capital resources and business trends are all forward-looking statements. In some cases, you can identify forward-looking statements by terms such as “may,” “might,” “will,” “objective,” “intend,” “should,” “could,” “can,” “would,” “expect,” “believe,” “design,” “estimate,” “predict,” “potential,” “plan,” or the negative of these terms, and similar expressions intended to identify forward-looking statements. These statements involve known and unknown risks, uncertainties and other factors that could cause our actual results to differ materially from the forward-looking statements expressed or implied in this presentation, in addition to those risks and uncertainties, such as the effects from the COVID-19 pandemic on our clinical trial activities, the uncertainties inherent in the clinical drug development process, such as the regulatory approval process, the timing of our regulatory filings, the potential for substantial delays, and the risk that earlier study results may not be predictive of future study results, manufacturing risks, and competition from other therapies or products, described in “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in our Annual Report on Form 10-K (File No. 001-39593) for the fiscal year ended December 31, 2020 and elsewhere in such filing and in our other periodic reports and subsequent disclosure documents filed with the U.S. Securities and Exchange Commission.

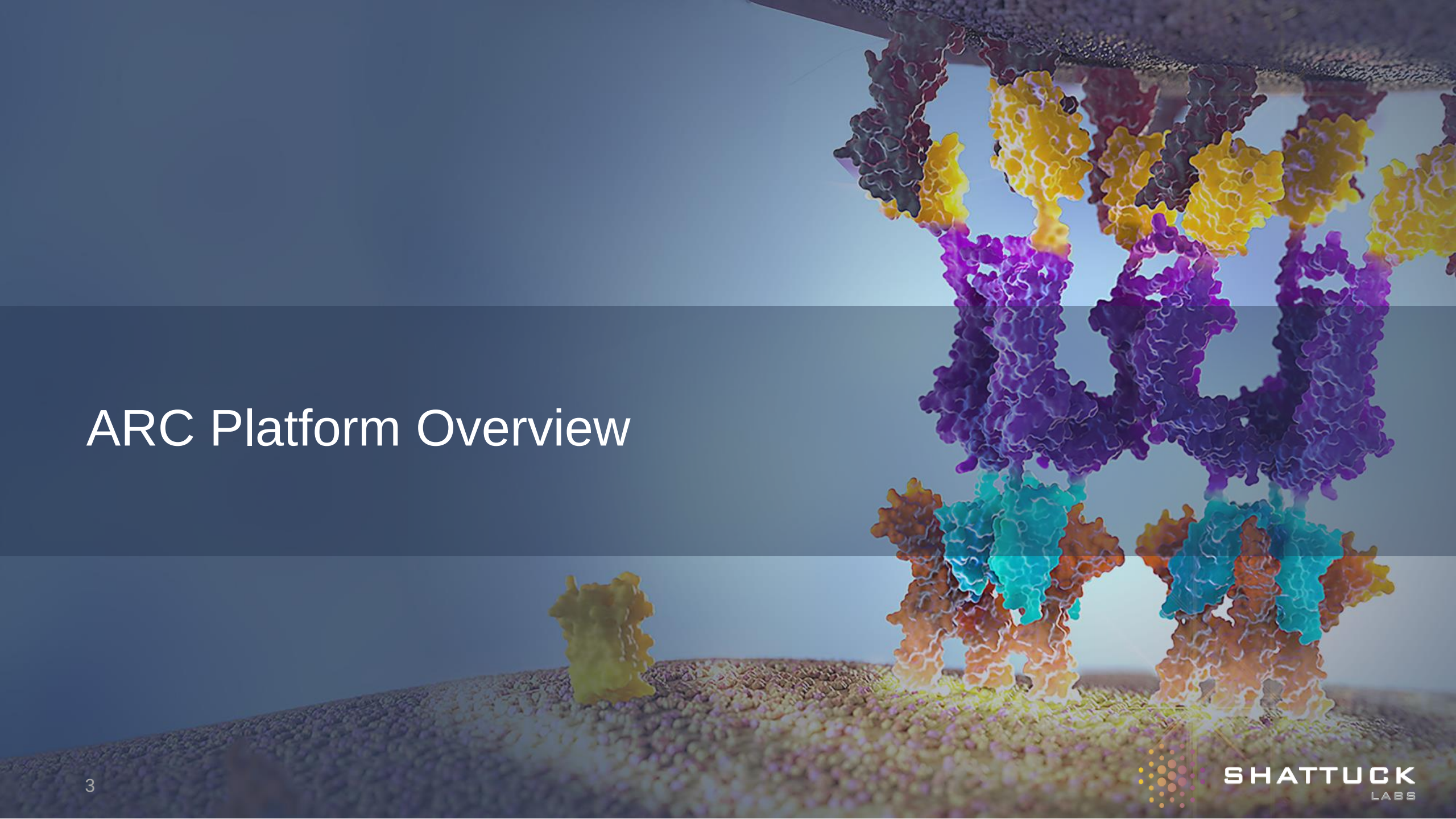
We cannot assure you that we will realize the results, benefits or developments that we expect or anticipate or, even if substantially realized, that they will result in the consequences or affect us or our business in the way expected. Forward-looking statements are not historical facts, and reflect our current views with respect to future events. Given the significant uncertainties, you should evaluate all forward-looking statements made in this presentation in the context of these risks and uncertainties and not place undue reliance on these forward-looking statements as predictions of future events. All forward-looking statements in this presentation apply only as of the date made and are expressly qualified in their entirety by the cautionary statements included in this presentation. We have no intention to publicly update or revise any forward-looking statements to reflect subsequent events or circumstances, except as required by law.

We obtained the data used throughout this presentation from our own internal estimates and research, as well as from research, surveys and studies conducted by third parties. Internal estimates are derived from publicly available information released and our own internal research and experience, and are based on assumptions made by us based on such data and our knowledge, which we believe to be reasonable. In addition, while we believe the data included in this presentation is reliable and based on reasonable assumptions, we have not independently verified any third-party information, and all such data involve risks and uncertainties and are subject to change based on various factors.

This presentation concerns a discussion of investigational drugs that are under preclinical and/or clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration. They are currently limited by Federal law to investigational use, and no representations are made as to their safety or effectiveness for the purposes for which they are being investigated.

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ARC Platform Overview

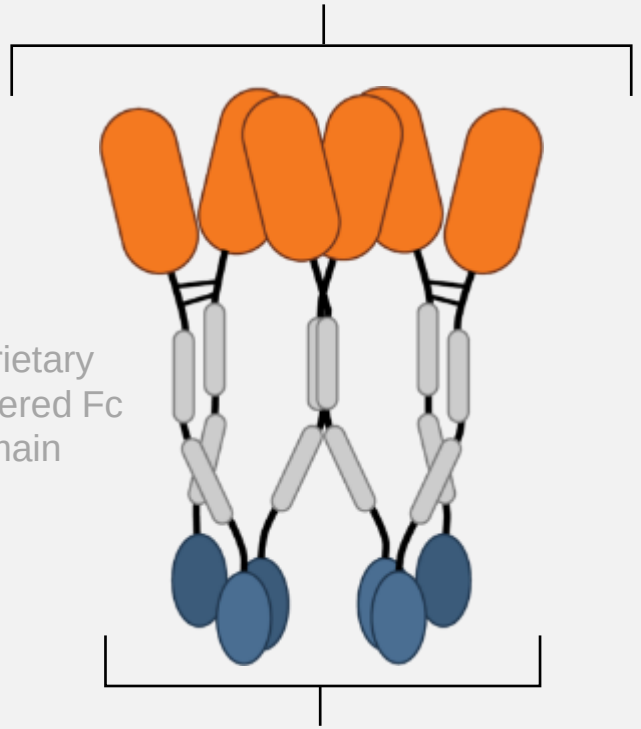


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ARC Platform Technology

Designed to Simultaneously Block Immune Checkpoints and Activate TNF Receptors

6 Checkpoint Binding Domains



6 TNF Receptor Binding Domains
(Two Sets of TNF Ligand Trimers)

ARC Platform Structure and Mechanistic Design

✓ **Checkpoint Inhibition**
Removes the "Brakes" From the Immune System

✓ **TNF Superfamily Agonism**
Structural Properties of ARCs Match TNF Receptor Biology to Properly Activate

✓ **Colocalization of Multiple Mechanisms**
Within a Single Therapeutic

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Shattuck's Development Pipeline

Deep Pipeline of Scientifically Validated and Novel Targets

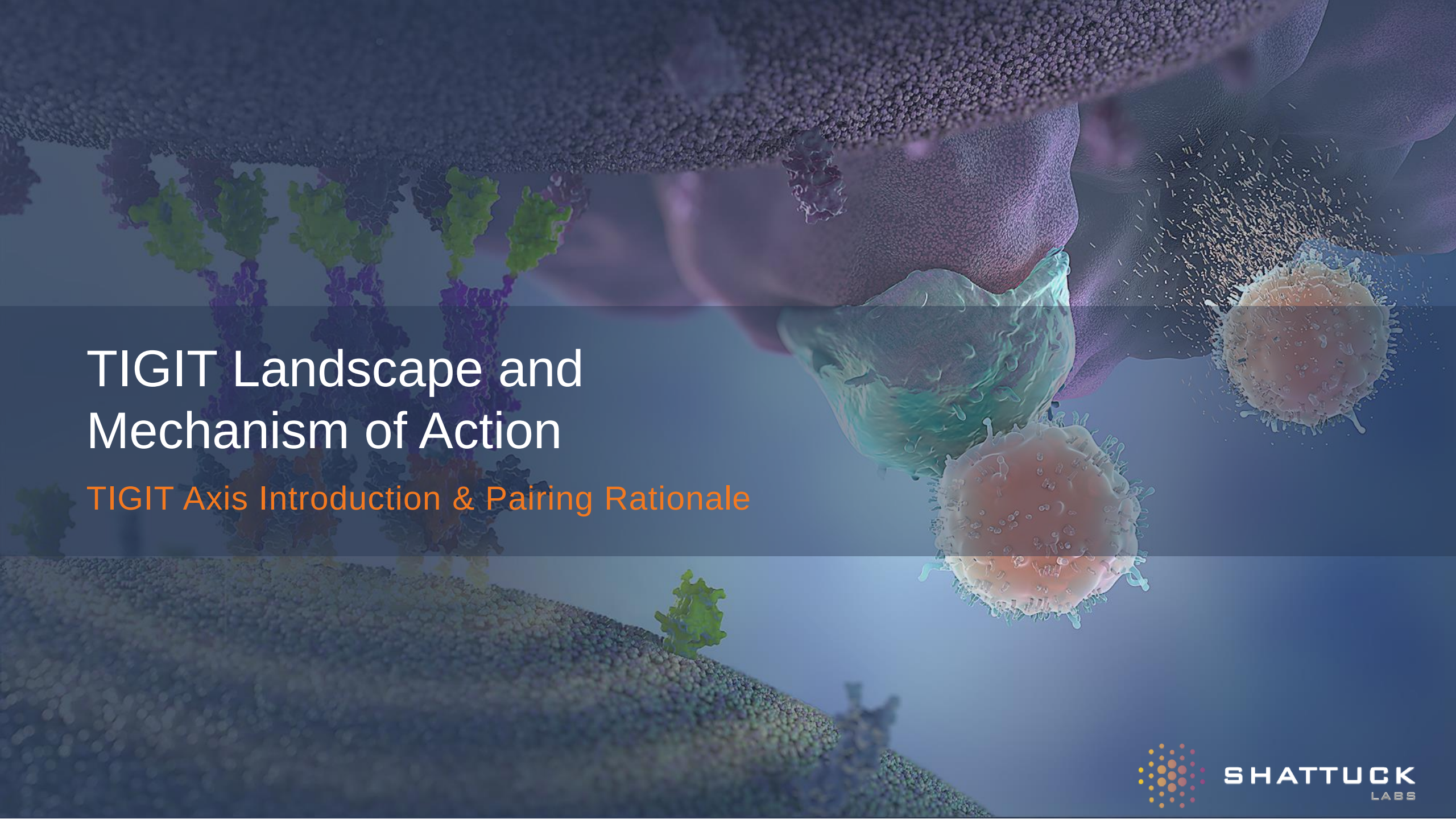
PLATFORM	PROGRAM	DOMAINS: DOMAIN 1	DOMAINS: DOMAIN 2	INDICATIONS	STAGE OF DEVELOPMENT
CLINICAL-STAGE PIPELINE					
ARC	SL-172154	SIRPα	CD40L	Ovarian Cancer	
				CSCC and HNSCC[1]	
				AML and HR-MDS[2]	
	SL-279252	PD-1	OX40L	Advanced Solid Tumors and Lymphoma	
SELECT PRECLINICAL-STAGE PIPELINE					
ARC	SL-9258	TIGIT	LIGHT	Oncology	
	SL-279137	PD-1	4-1BBL	Oncology	
	Multiple	Undisclosed		Autoimmune	
GADLEN	Multiple	γδ TCR	Tumor Antigen	Oncology	

STAGE OF DEVELOPMENT: DISCOVERY | PRECLINICAL | PHASE 1 | PHASE 2 | PHASE 3

(1) Cutaneous Squamous Cell Carcinoma (CSCC) and Head and Neck Squamous Cell Carcinoma (HNSCC)

(2) Acute Myeloid Leukemia (AML) in combination with Azacitidine and Higher-Risk Myelodysplastic Syndromes (HR-MDS) in combination with Azacitidine + Venetoclax

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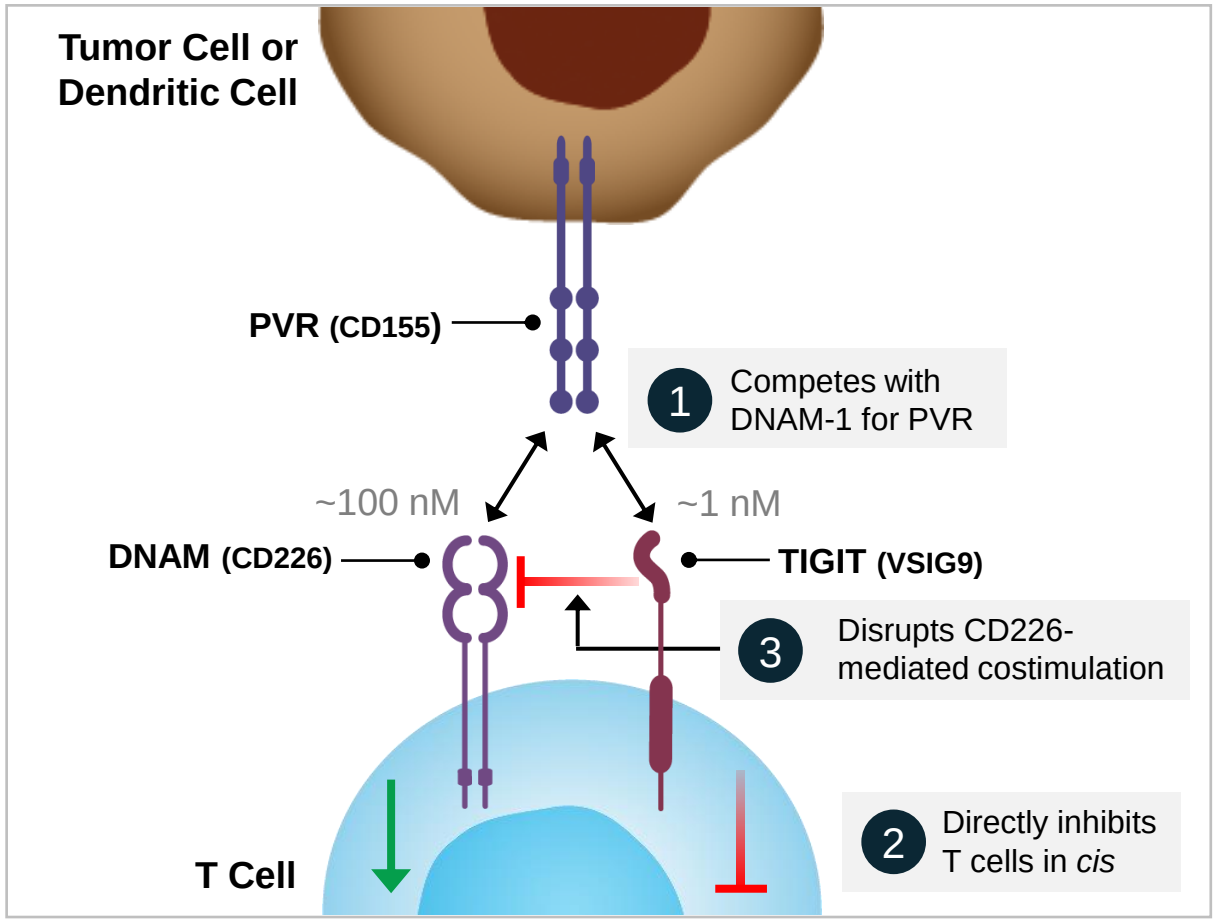
TIGIT Landscape and Mechanism of Action

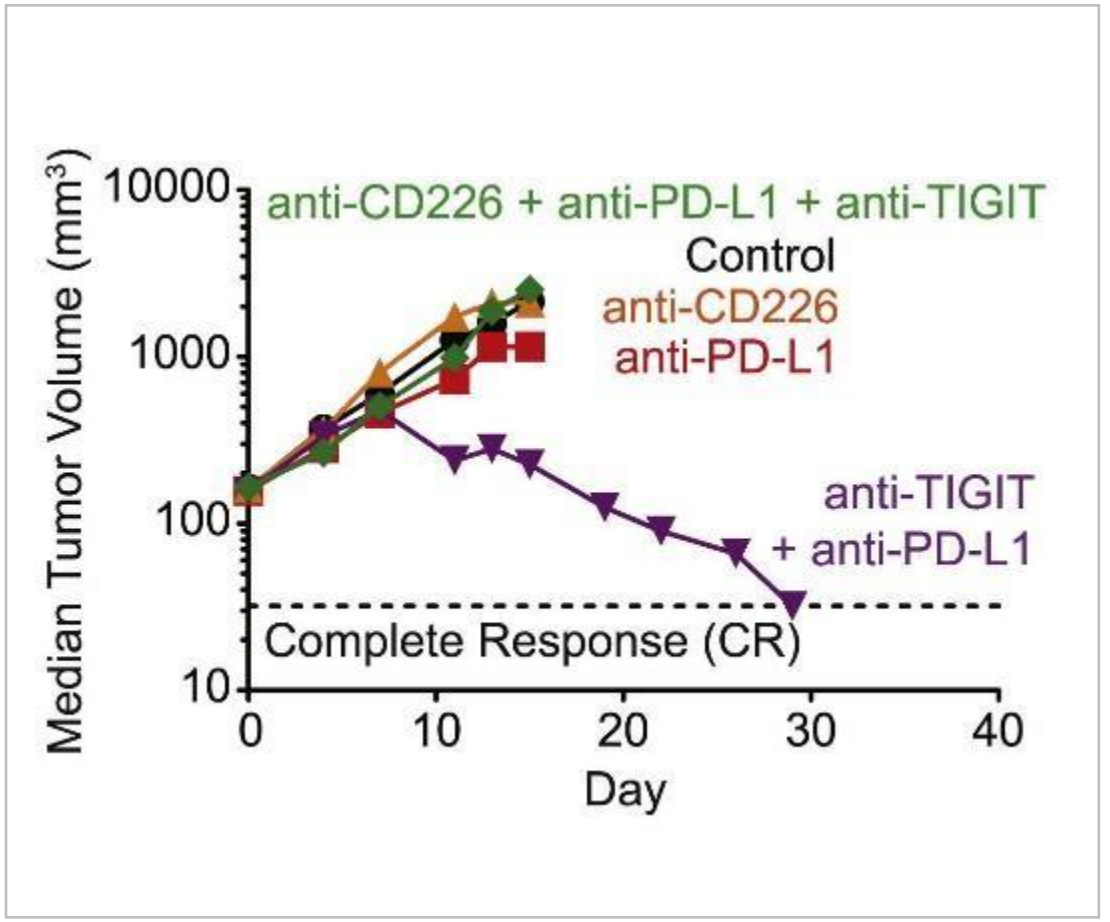
TIGIT Axis Introduction & Pairing Rationale

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Pre-Clinical and Clinical Validation of TIGIT

TIGIT Blockade Enables PVR Costimulation of DNAM-1 (CD226)

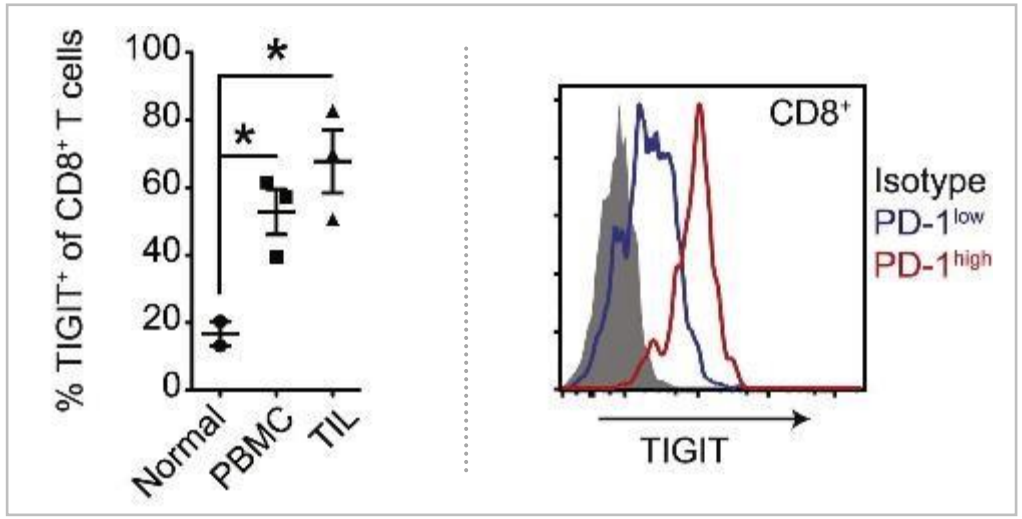


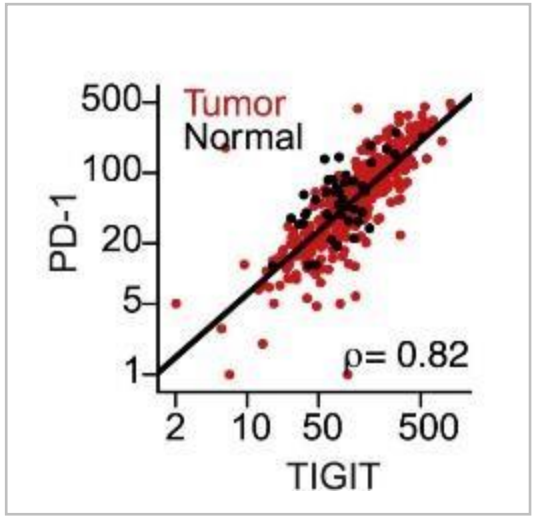


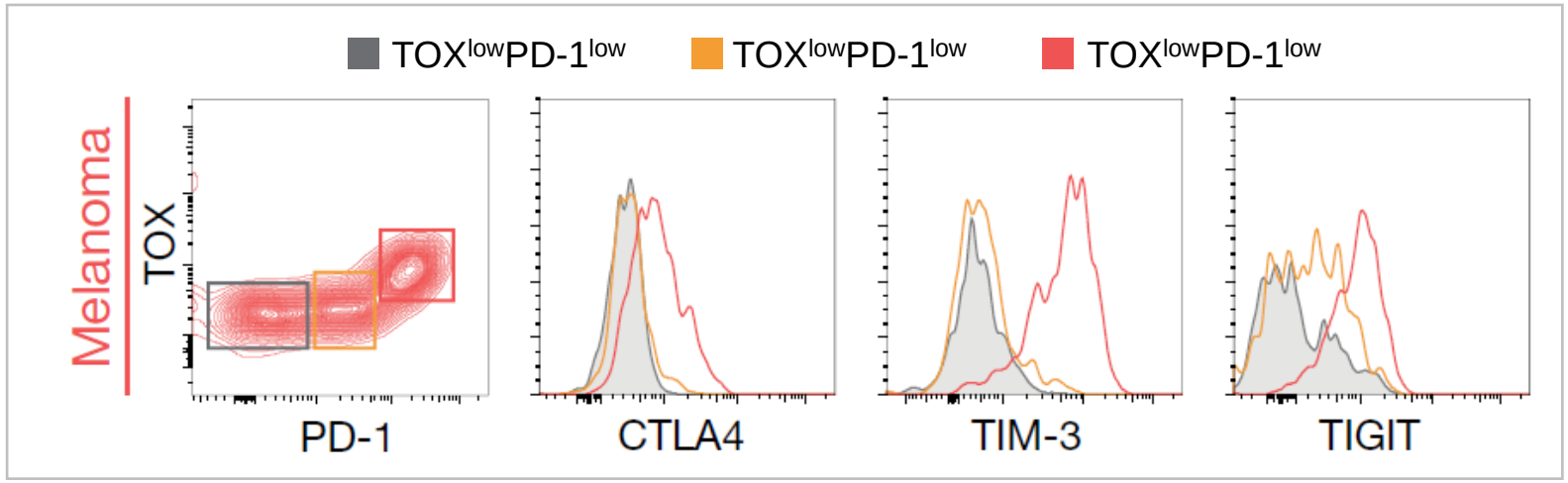
Johnston RJ, et al., *Cancer Cell,* 2014 26923-937

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TIGIT is Likely a Sub-Dominant Checkpoint to PD-1







In human NSCLC samples

- TIGIT is upregulated on TIL
- All TIGIT positive TIL are PD-1 positive
- The density of TIGIT expression correlates with the density of PD-1 expression

In human melanoma samples

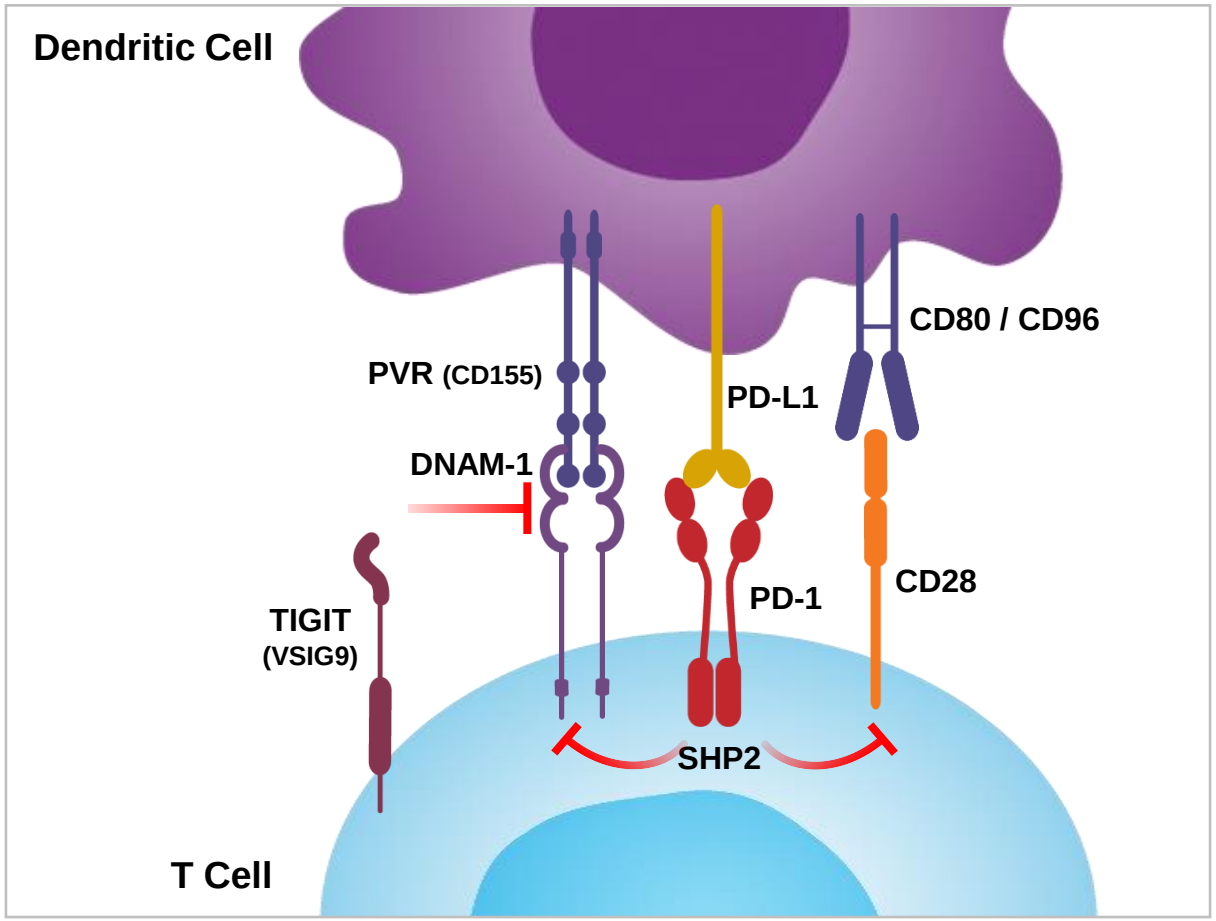
- TIGIT is expressed on TIL
- TIGIT expression is upregulated in a coordinated manner with PD-1 expression
- TIGIT appears to be expressed at an earlier state of exhaustion than TIM3

Johnston RJ, et al., *Cancer Cell,* 2014 26923-937
Khan O, et al., *Nature,* 2019 57;211-218

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Inhibition of DNAM-1 by PD-1 Signaling

TIGIT Requires Co-Blockade of PD-1 Because PD-1 Inhibits DNAM-1



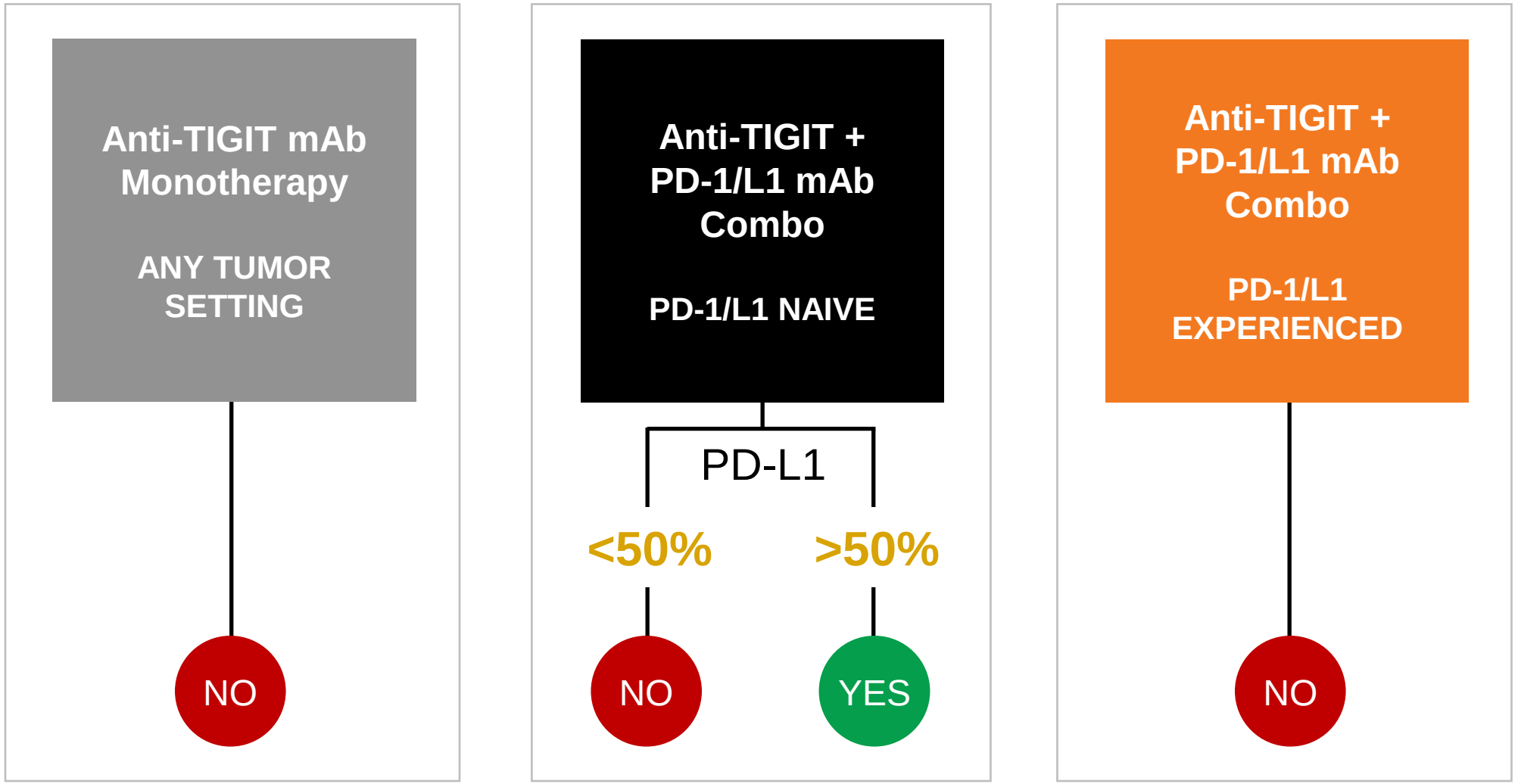
- PD-1 mediated SHP-2 activation directly dephosphorylates DNAM-1, in a similar manner to CD28
- This mechanism explains why anti-tumor activity of TIGIT blockade is dependent upon concurrent PD-1/L1 blockade in PD-L1 positive tumors

Modified from Genentech presentation – Xu X et al – SITC 2021 'The TIGIT Pathway Meeting'

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Pre-Clinical and Clinical Validation of TIGIT

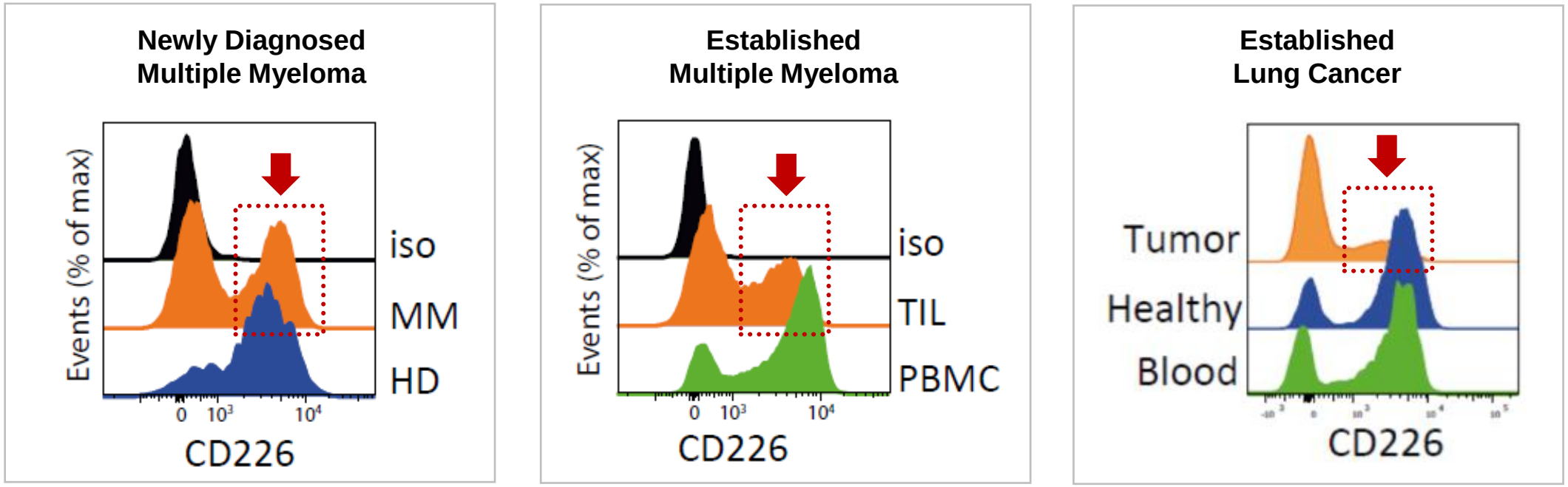
Potential Clinical Benefit Emerging in PD-1/L1 Naïve Low Expressing Tumors



Data inclusive of: tiragolumab, vibostolimab, etigilimab, EOS-448, domvanalimab, COM-902, BGB-A1217, PTZ-201

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Why Doesn't TIGIT/PD-1 Blockade Work in PD-1 Experienced Patients?

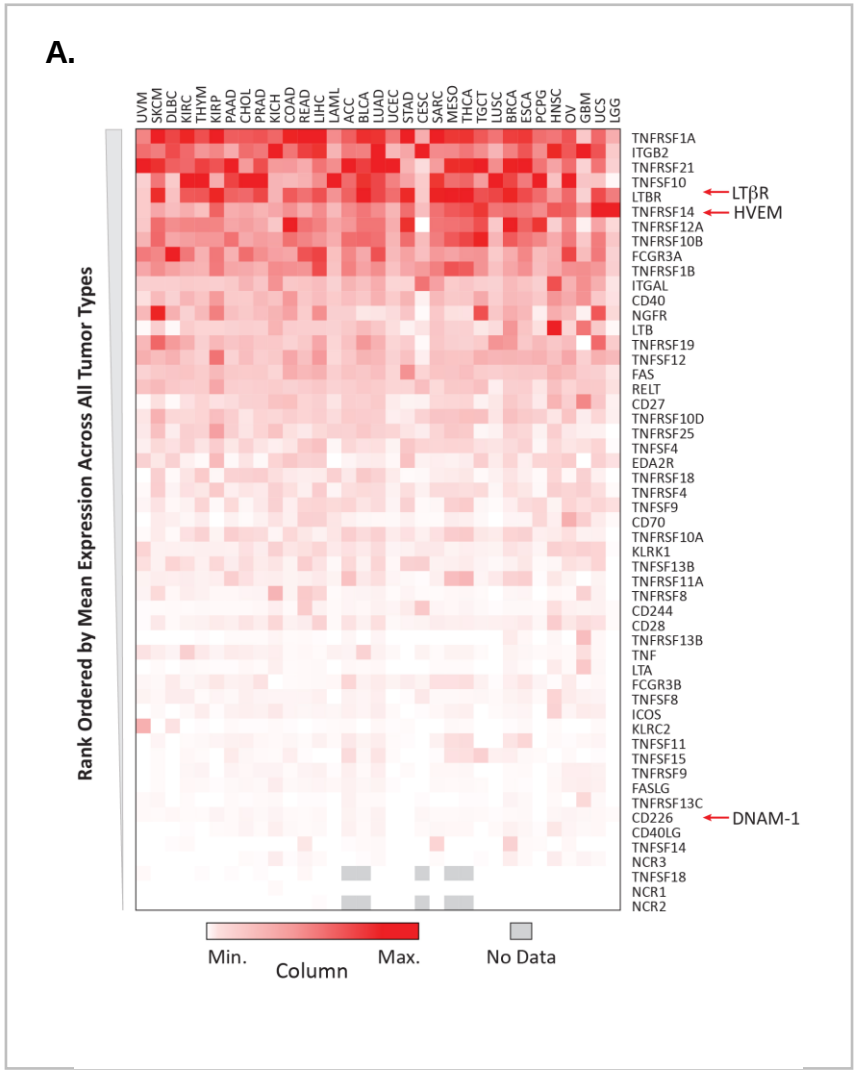


- Intratumoral CD8+ T cells express DNAM-1 at reasonable levels immediately following diagnosis; however, DNAM-1 is rapidly downregulated as tumors progress and CD8+ T cells become exhausted
  - Because the anti-tumor activity of TIGIT blockade is dependent upon DNAM-1 activation, the probability of clinical benefit will decline as tumors progress and DNAM-1 is downregulated

Weulersse M. et al., Immunity 2020;53:824-839

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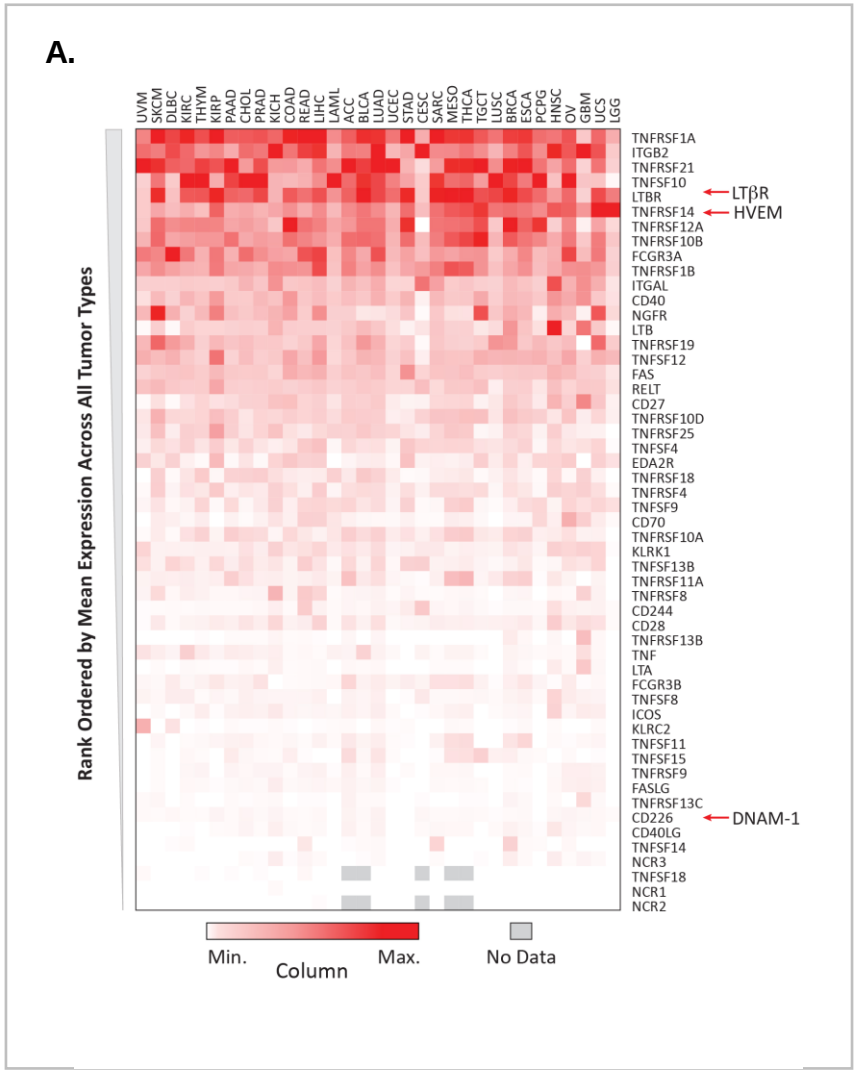
HVEM & LTβR Are Highly Expressed in TIL Across Tumor Types

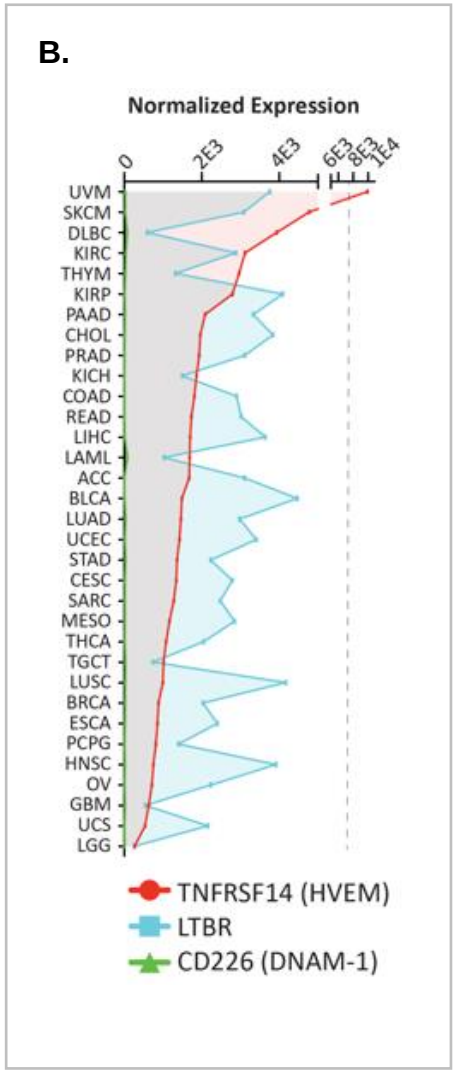


Yoo KJ, 2021, Under Review

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HVEM & LTβR Are Highly Expressed in TIL Across Tumor Types

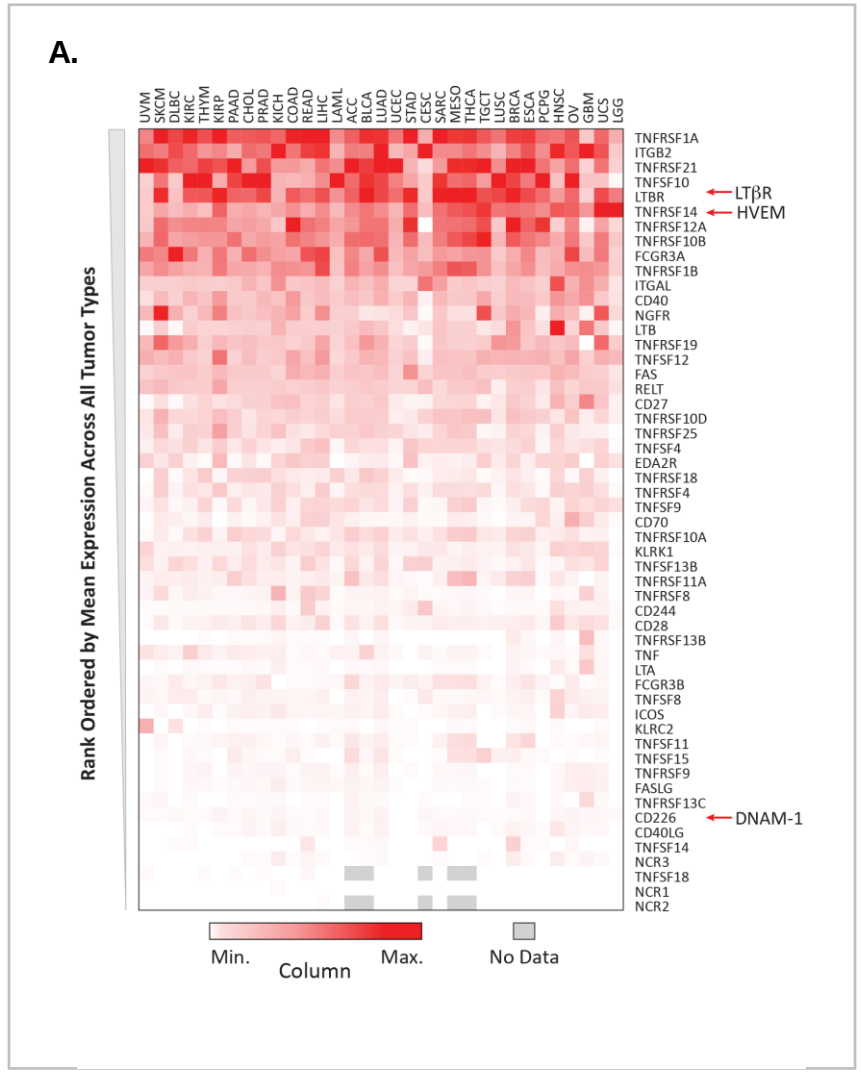


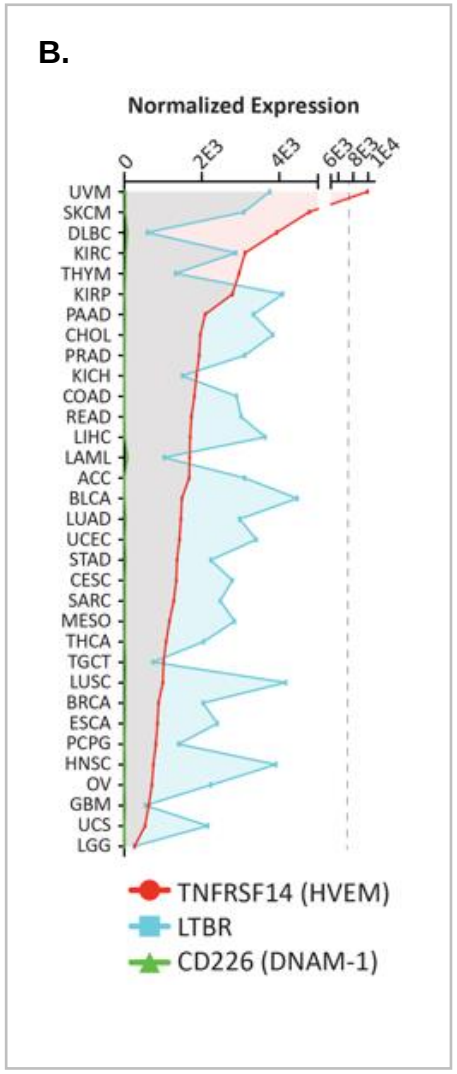


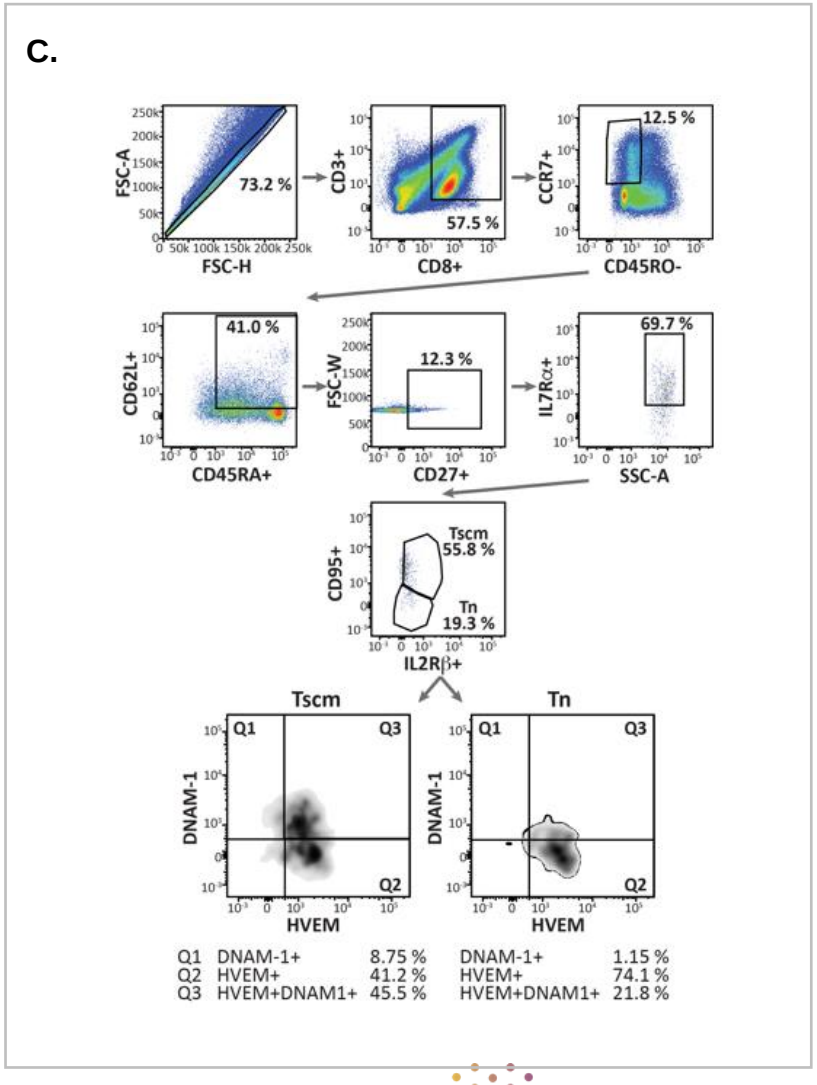
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HVEM & LTβR Are Highly Expressed in TIL Across Tumor Types



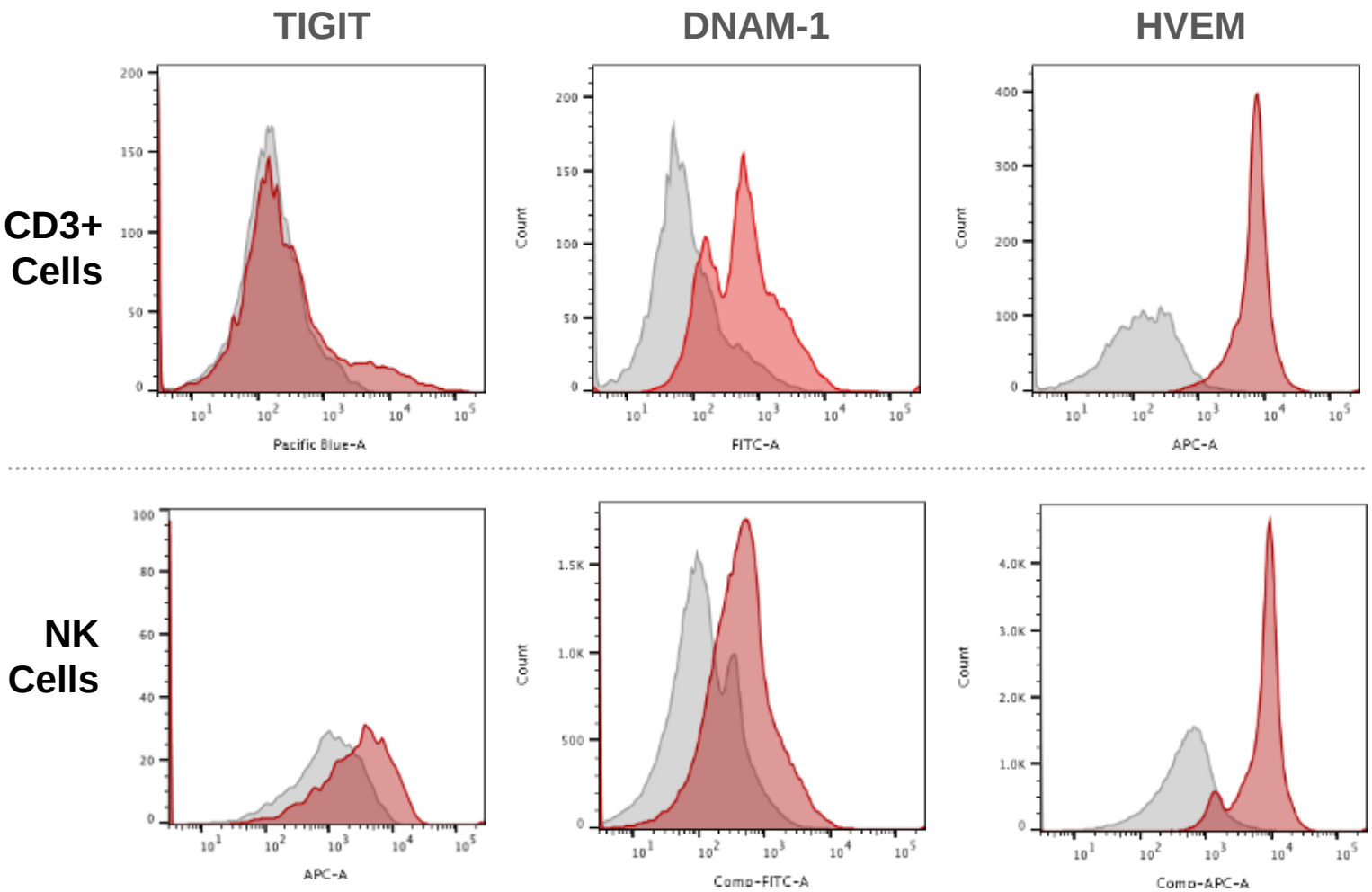




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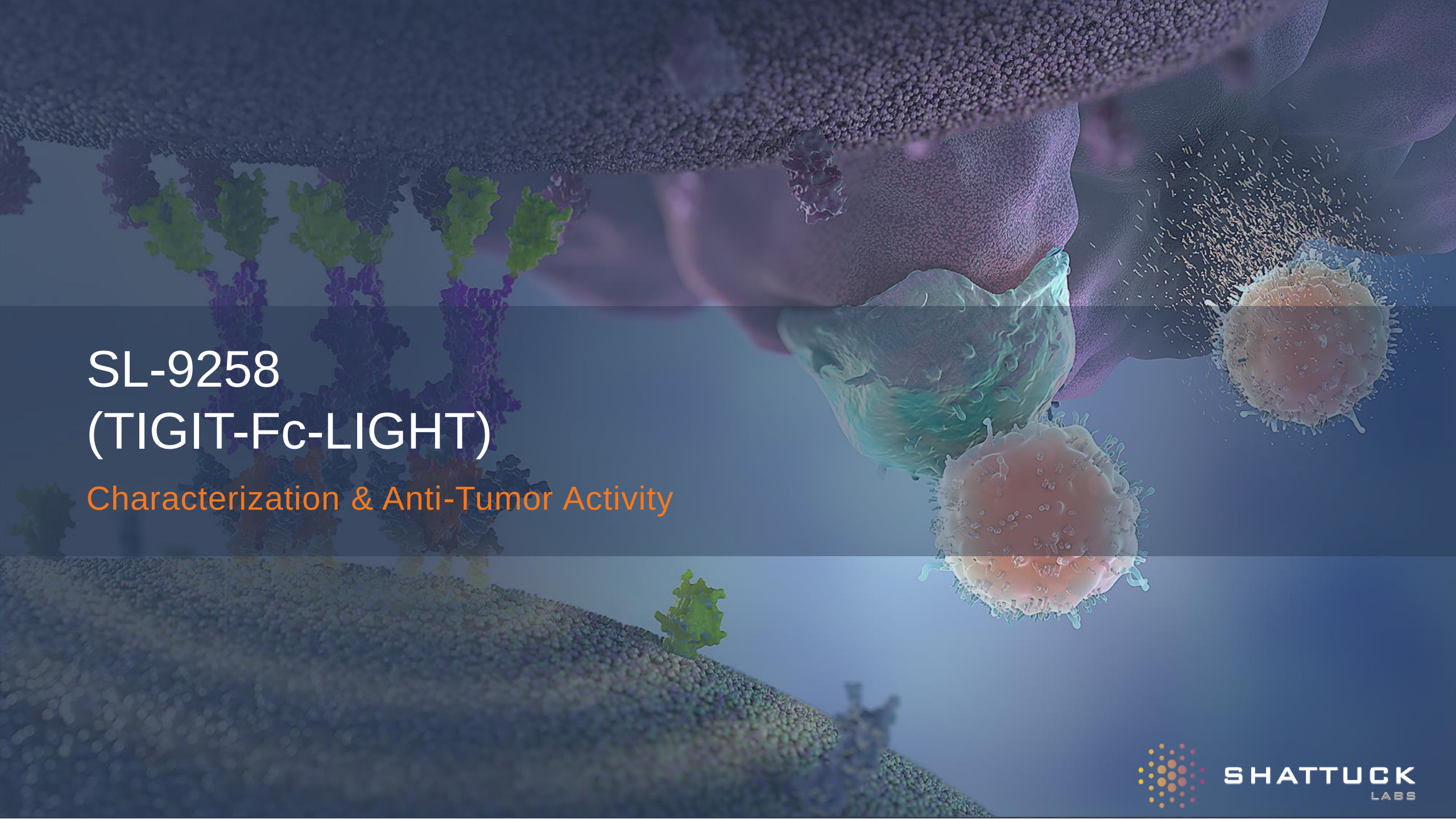
Co-Expression of TIGIT, DNAM-1 & HVEM on T and NK Cells



- Murine T cells were activated with CD3/28 beads, and the relative induction of TIGIT & DNAM-1 was assessed
- Freshly isolated murine NK cells express low levels of TIGIT, moderate DNAM-1, and high levels of HVEM

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SL-9258 (TIGIT-Fc-LIGHT)

Characterization & Anti-Tumor Activity

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SL-9258: Novel TIGIT Inhibitor + LTβR/HVEM Agonist

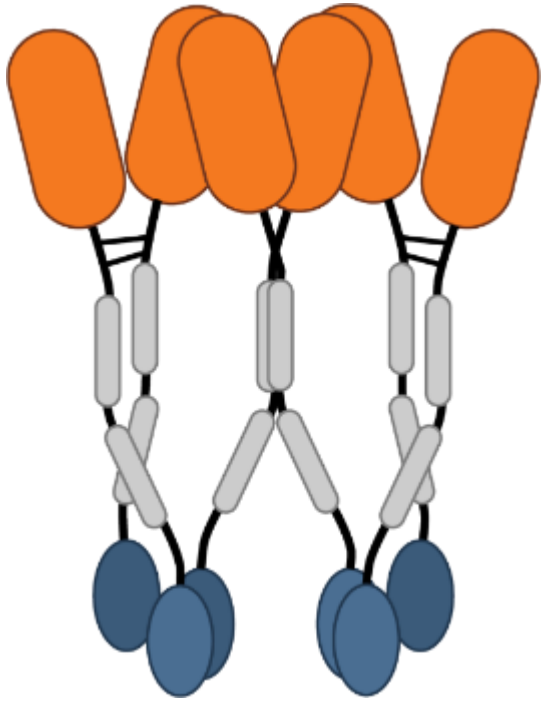
Rationally Designed to Increase Efficacy of TIGIT Blockade

Highly Differentiated
PVR/PVRL2/PVRL3 &
Nectin-4 Inhibitor

Potential First-In-Class
LTβR & HVEM Agonist

Dual Mechanism
of Action

SL-9258
(TIGIT-Fc-LIGHT)



6 TIGIT Binding Domains:
Blocks All TIGIT Ligands

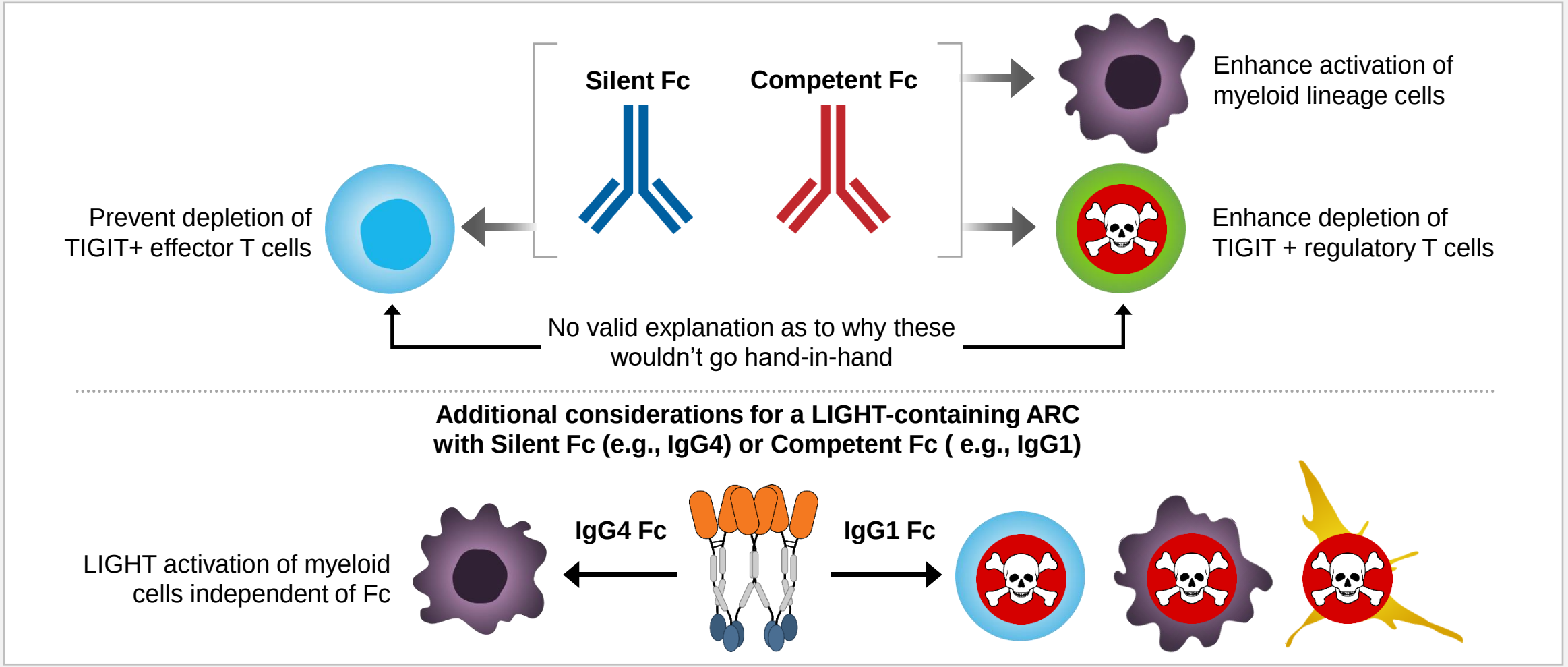
Inert IgG4 Fc

2 LIGHT Trimers:
Provides LTβR Stimulation to
Stromal/Myeloid Cells & HVEM
Stimulation to CD8+ T Cells and NK Cells

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Fc Domain Considerations

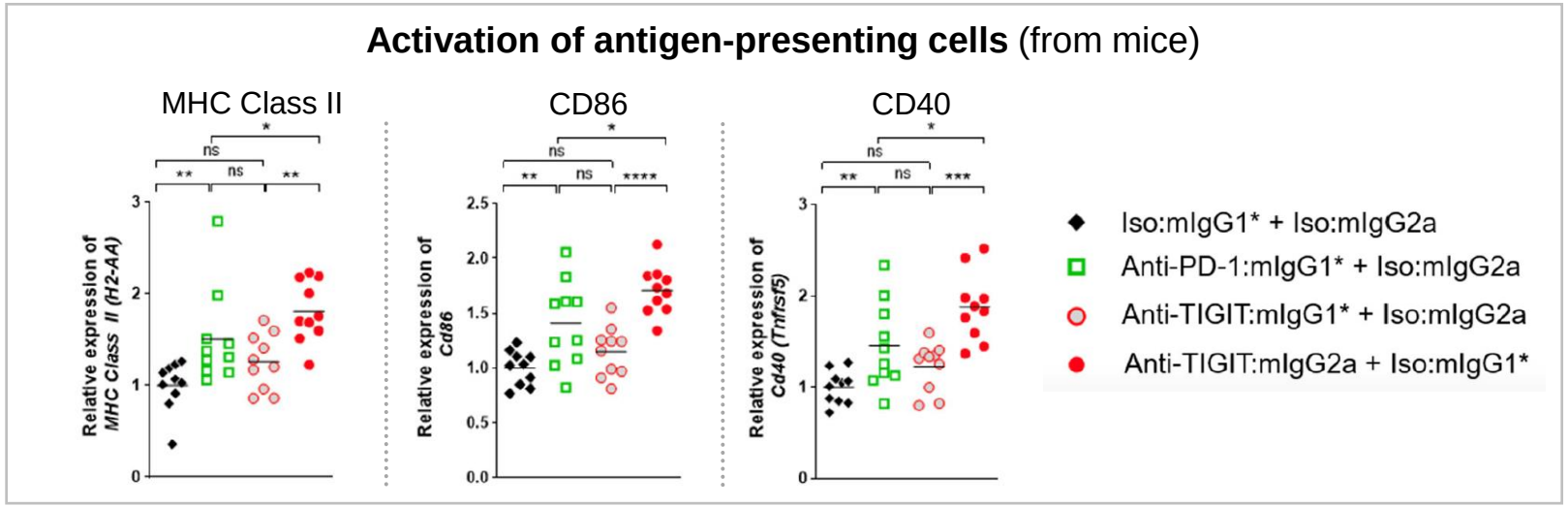
Advantages to Fc Silent ARC Paired with LIGHT Costimulation



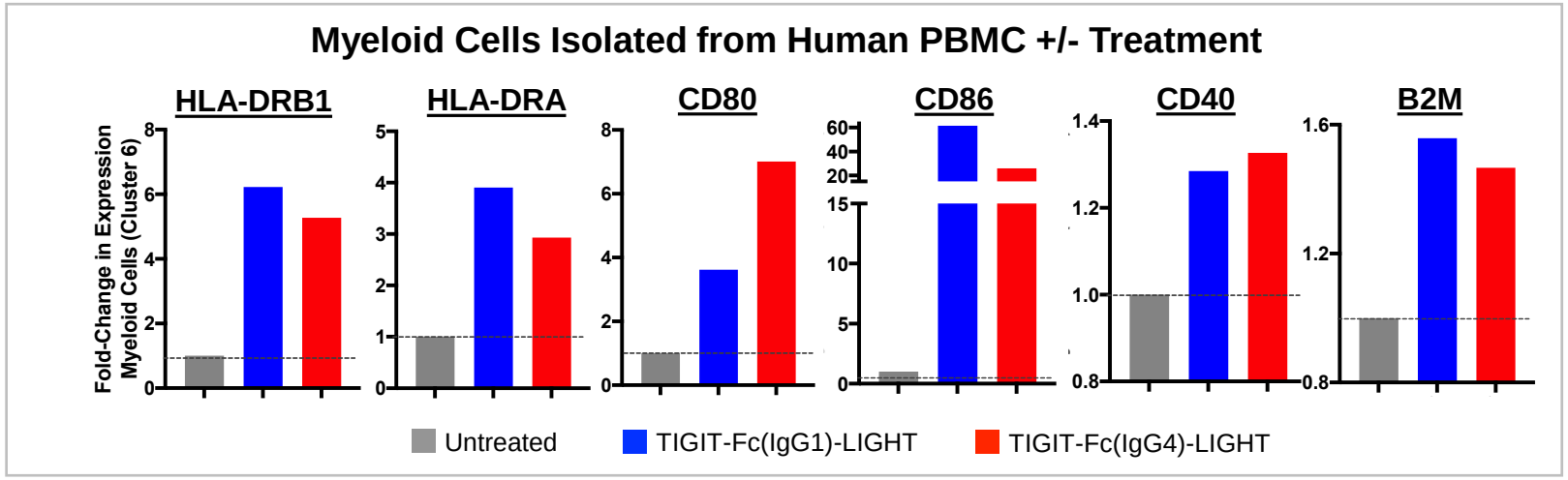
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Activation of LTβR on Myeloid Cells Supersedes Role of Fc Domain in TIGIT Blockade

Merck



Shattuck



- TIGIT-Fc-LIGHT induces the up-regulation of MHC Class II and other myeloid cell activation genes.
- Fold-induction is greater than what has been observed with an Fc-competent murine antibody.
- TIGIT-Fc-LIGHT activates myeloid cells through LIGHT:LTbR interactions and does not depend upon the composition of the Fc domain

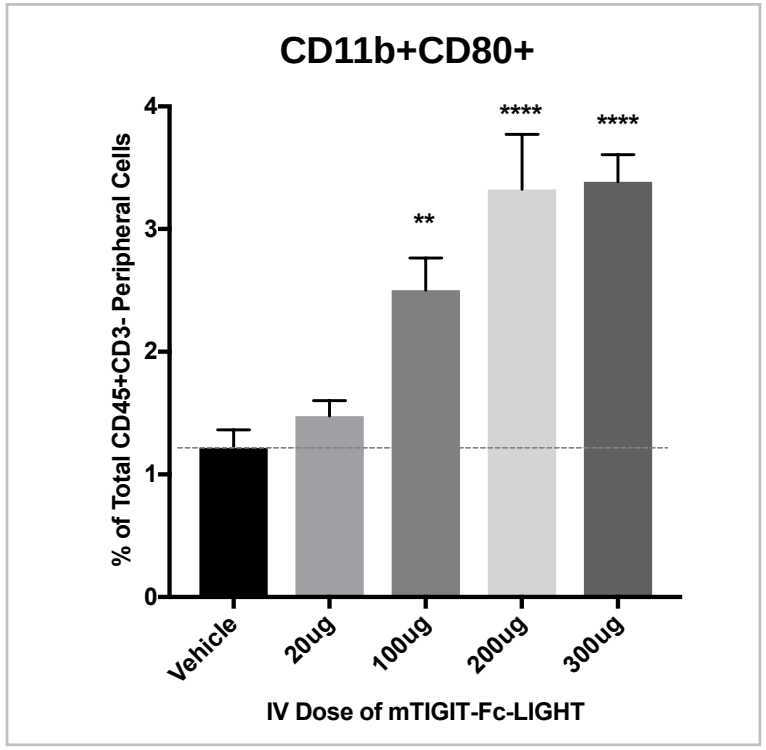
Han JH, *Frontiers in Immunology*, 2020
Yoo KJ, 2021, Under Review

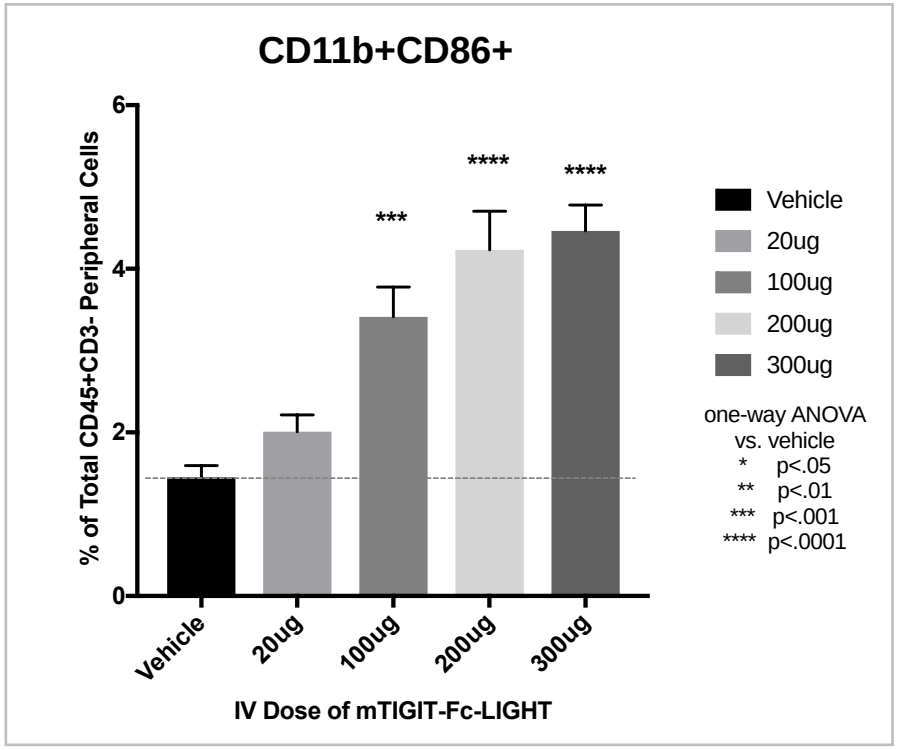
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In vivo: Immune Activation and Anti-Tumor Efficacy

24 Hours Following a Single Intravenous Injection

Myeloid Cells





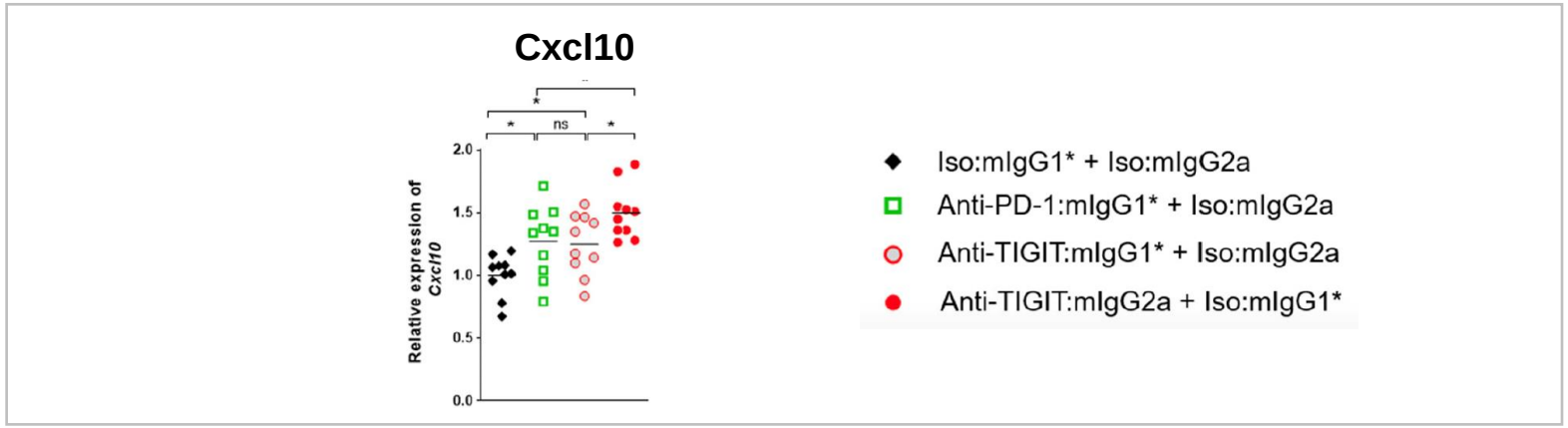
➔ TIGIT-Fc-LIGHT induces a dose-dependent increase in total and activated myeloid cells in the peripheral blood

 Internally Derived Shattuck Data

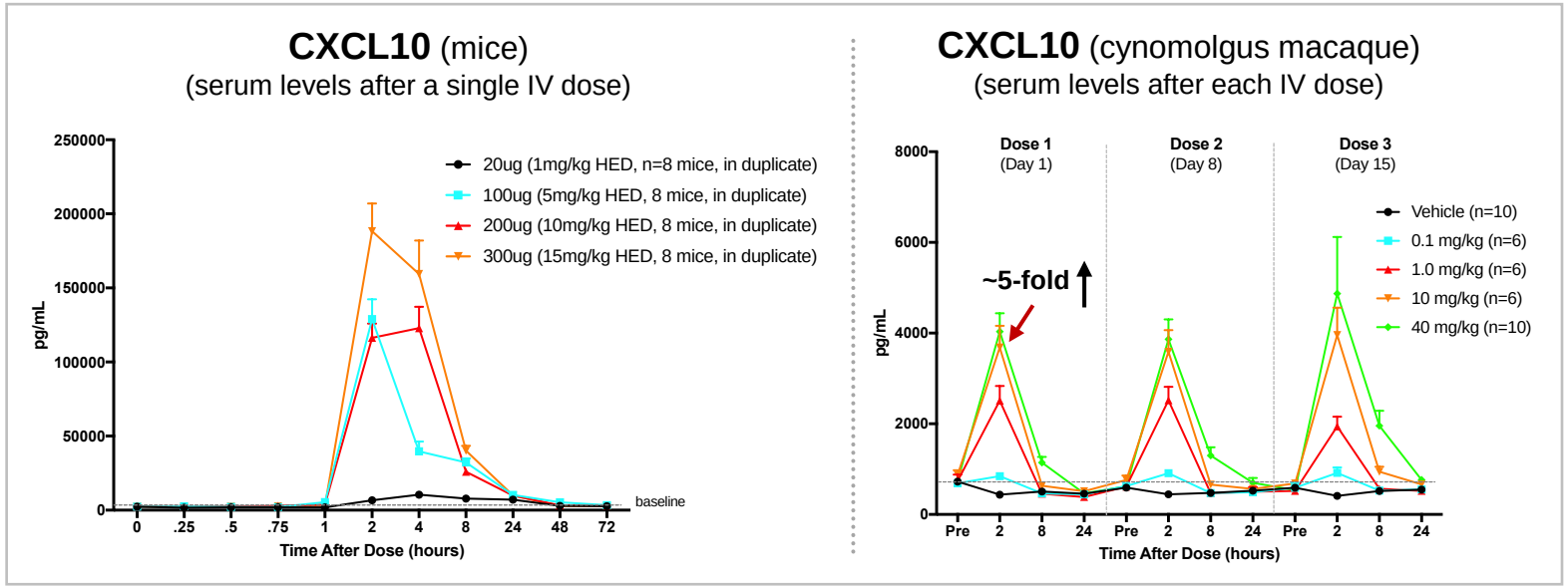
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Activation of LTβR on Myeloid Cells Supersedes Role of Fc Domain in TIGIT Blockade

Merck



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- TIGIT-Fc-LIGHT increases chemokine/cytokine production in vivo, in both mice and NHP
- The kinetics of chemokine induction by TIGIT-Fc-LIGHT translates from mouse to NHP studies and is observed at a greater magnitude than an Fc-competent mouse antibody
- A range of adaptive immune and proinflammatory cytokines demonstrate the same profile between species, including IL-2, CCL2, CCL4, and CCL17

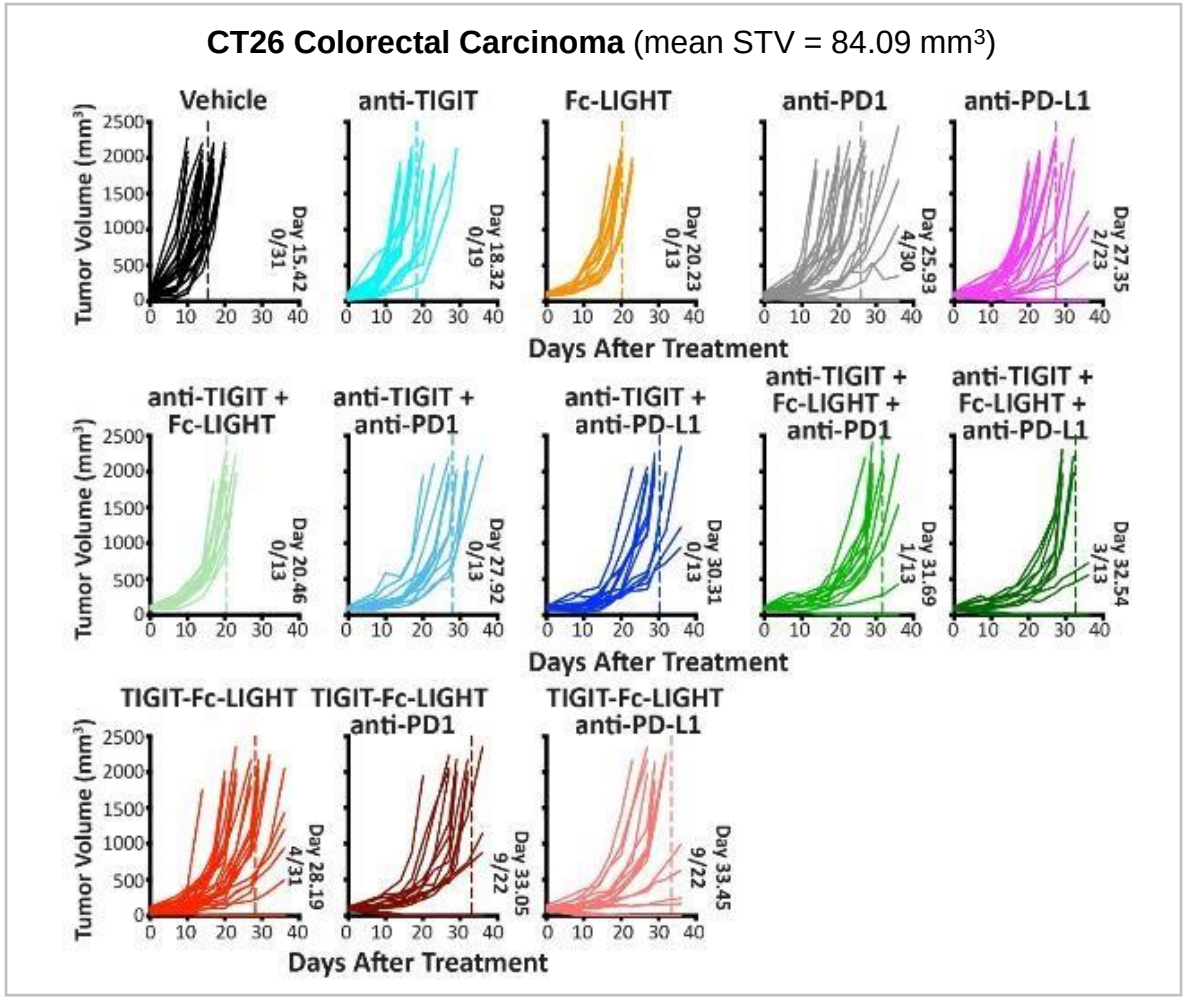
Han JH, *Frontiers in Immunology*, 2020
Yoo KJ, 2021, Under Review

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Assessing *in vivo* Activity & Combinations with Anti-PD(L)1

PD-1 Sensitive CT26 Tumor Model

Internally Derived Shattuck Data

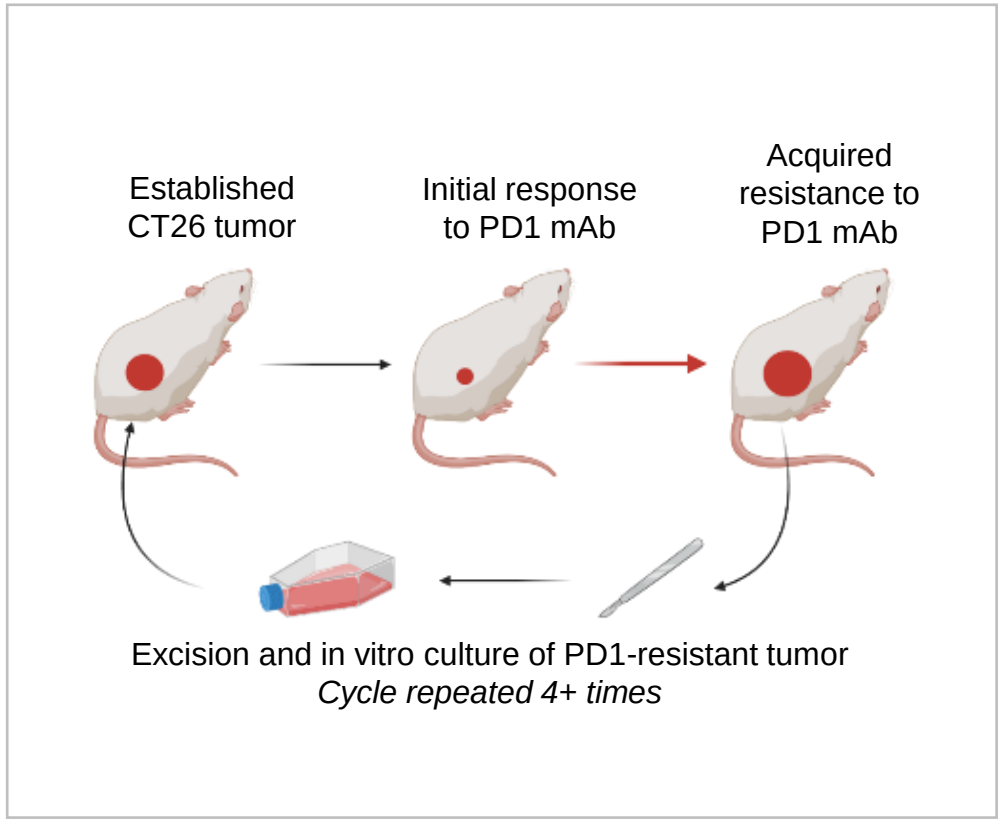


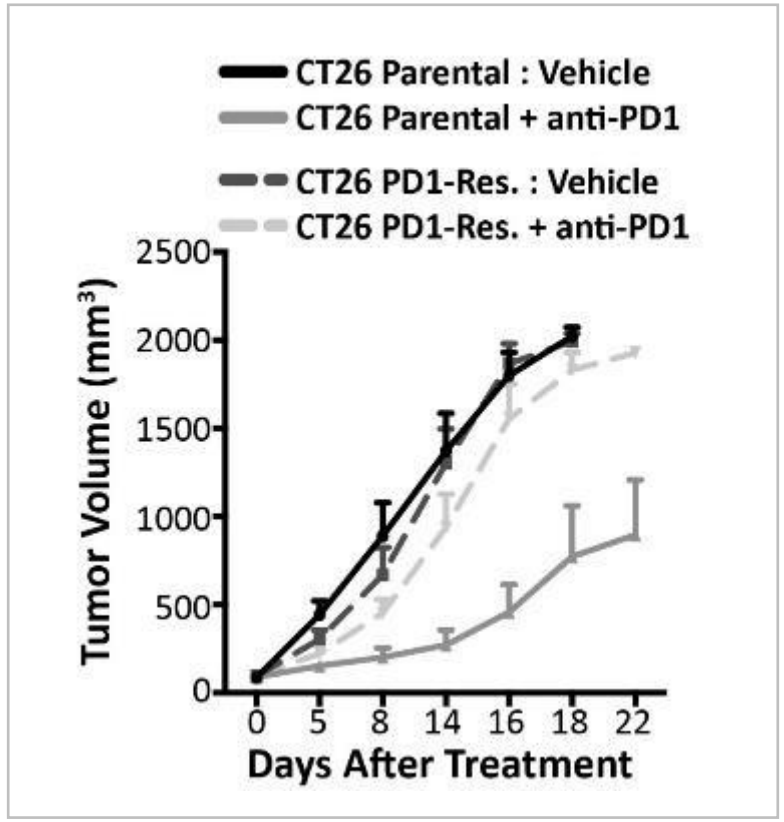
- CT26 colorectal carcinoma tumors are usually responsive to checkpoint blockade of PD1 and PD-L1/
- Pre-clinical mouse models show that TIGIT-Fc-LIGHT induces a more potent and durable anti-tumor response when compared to the combination of all relevant benchmark controls.
- TIGIT-Fc-LIGHT also induces an immune memory response in mice that are rechallenged with a secondary tumor on day 29
- Individual mouse tumor growth curves are shown
- Also shown is the average day at which each group reached tumor burden (i.e. vehicle Day 15.42), the experimental replicate number (i.e. vehicle = 31), and the number of mice that completely rejected the tumor (i.e. vehicle = 0/31)

Yoo KJ, 2021, Under Review

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Development of Anti-PD1 Acquired Resistant CT26 Tumor Model





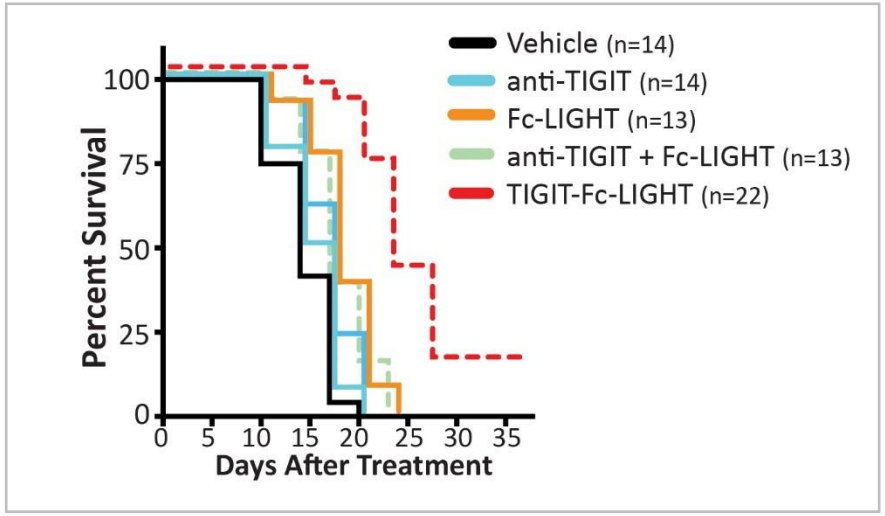
➔ The CT26-AR model pheno-copies CPI acquired resistant NSCLC tumors, and may be used to provide pre-clinical rationale to support development of novel agents in CPI acquired resistant tumors

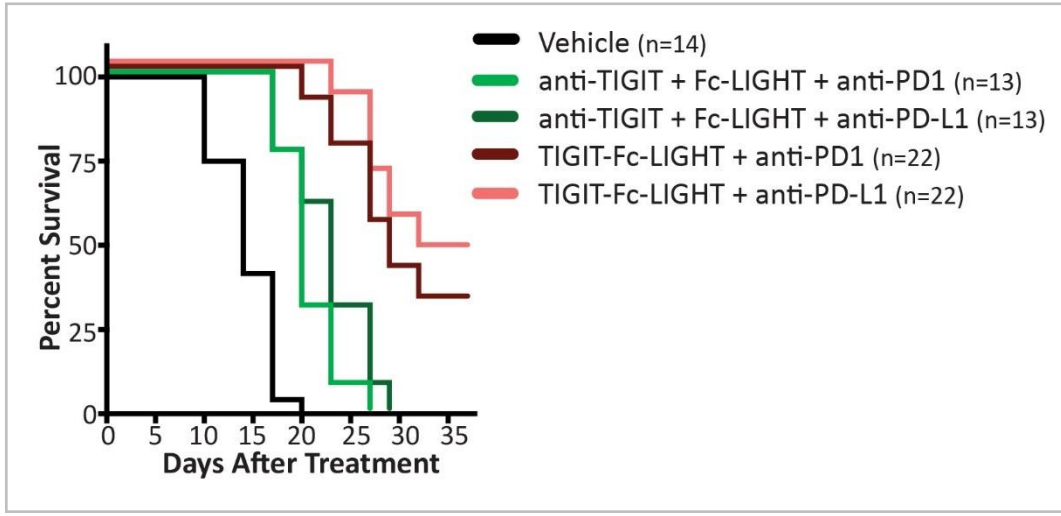
Fromm, et al., AACR, 2021

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Assessing *in vivo* Activity & Combinations with Anti-PD(L)1

PD-1 Acquired Resistant Tumor Model





Group	Comparator	Mantel Cox p-value
anti-TIGIT + Fc-LIGHT + anti-PD1	TIGIT-Fc-LIGHT	0.0082
	TIGIT-Fc-LIGHT + anti-PD1	<0.0001
anti-TIGIT + Fc-LIGHT + anti-PD-L1	TIGIT-Fc-LIGHT	0.2502
	TIGIT-Fc-LIGHT + anti-PD-L1	<0.0001

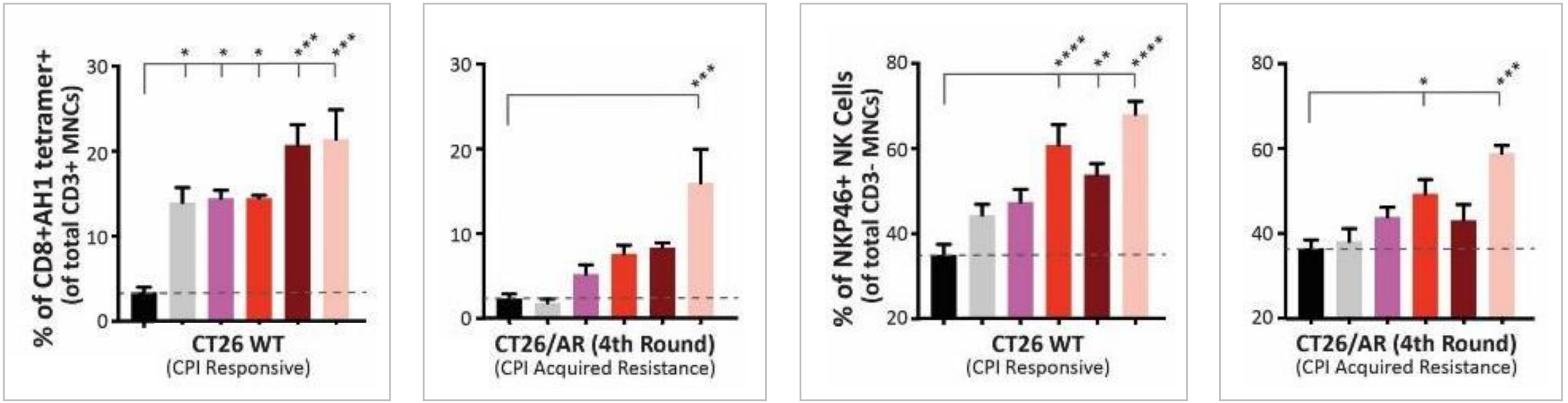
➔ Only TIGIT-Fc-LIGHT induced monotherapy activity in the aggressive CPI acquired resistance model

➔ TIGIT-Fc-LIGHT broadens the activity of anti-PD(L)1 in AR model where they lack single-agent activity

Yoo KJ, 2021, Under Review

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TIGIT-Fc-LIGHT Activates Both Innate and Adaptive Immunity in Tumors



➔ Anti-tumor activity is accompanied by the tumor infiltration of antigen-specific CD8+ T cells and NK cells

➔ Activity of TIGIT-Fc-LIGHT in the setting of CPI acquired resistance may be due to the broad immune simulating activity of LIGHT

Yoo KJ, 2021, Under Review

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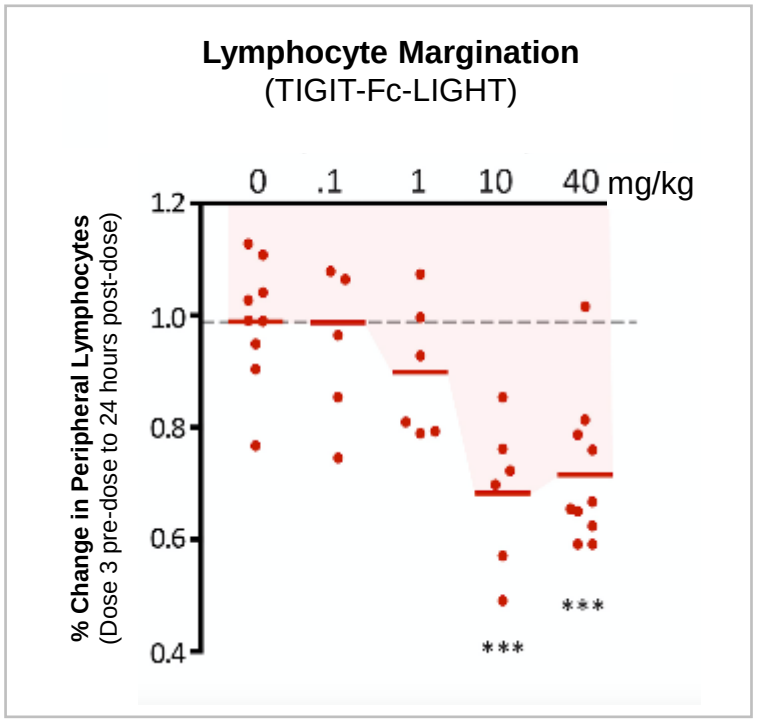


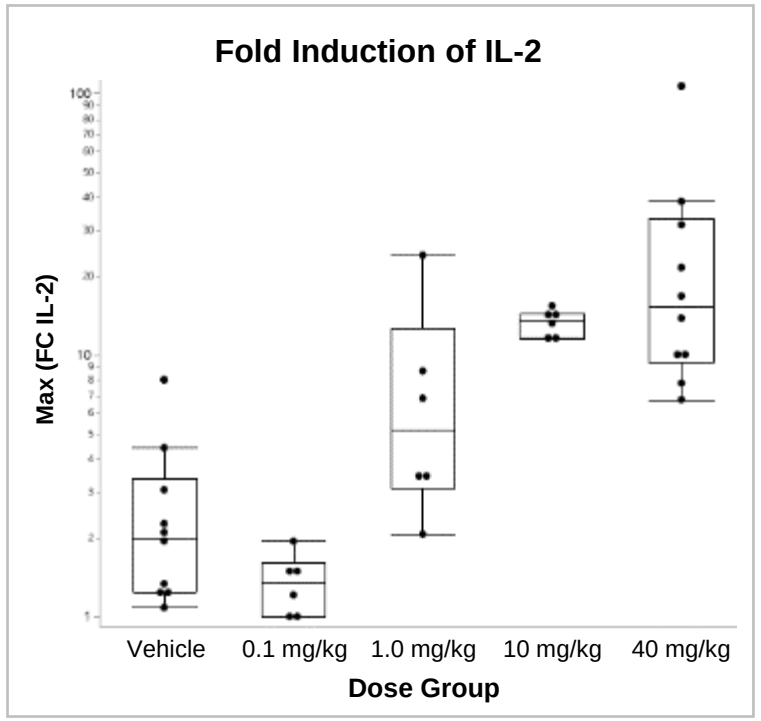
SL-9258 (TIGIT-Fc-LIGHT)

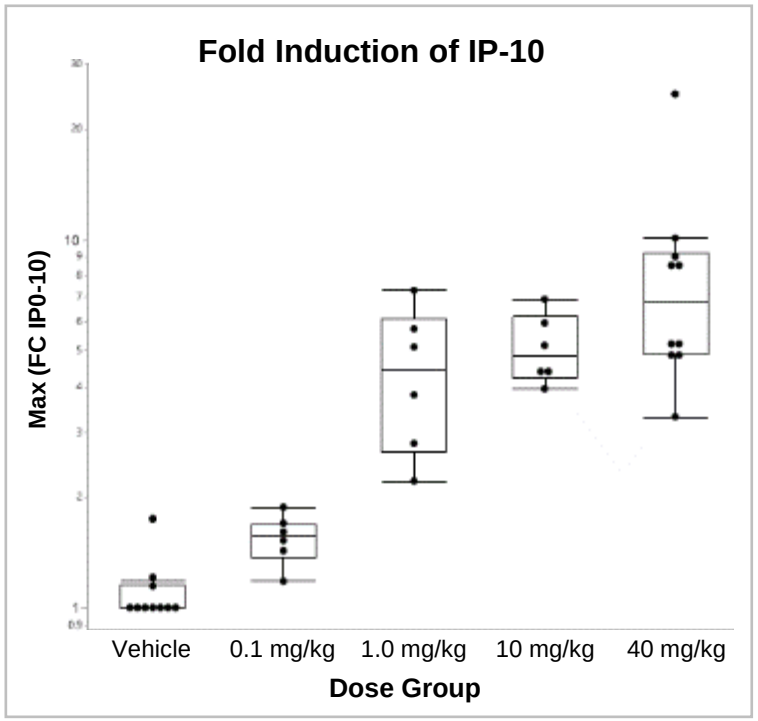
Differentiated Mechanism of Action

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SL-9258 Stimulated Dose-Dependent Lymphocyte Migration and Cytokine Production in Non-Human Primates







- A repeat-dose GLP toxicology study demonstrated SL-9258 was well tolerated through a total of 4 weekly doses up to 40 mg/kg
  - Rapid post-infusion margination of HVEM+ lymphocytes was observed post infusion
  - A distinct profile of serum cytokines including IL-2 and IP-10 (above) was observed in a dose-dependent manner

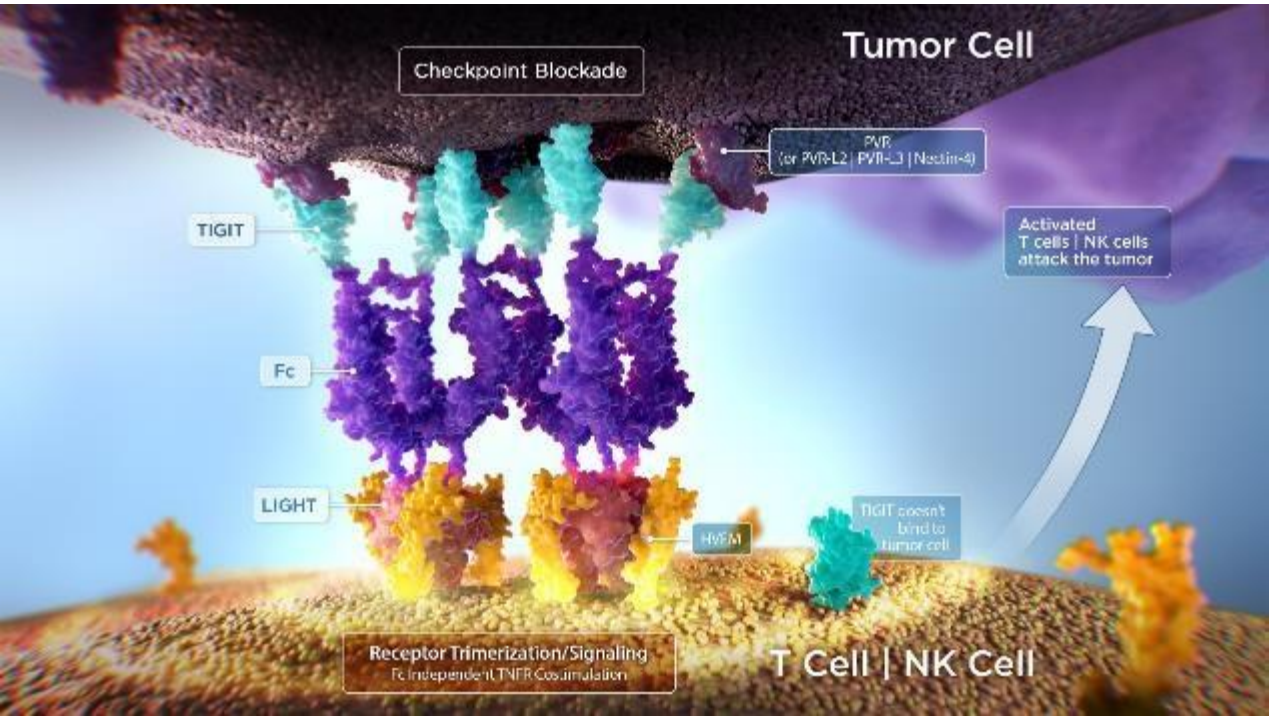
Yoo KJ, 2021, Under Review

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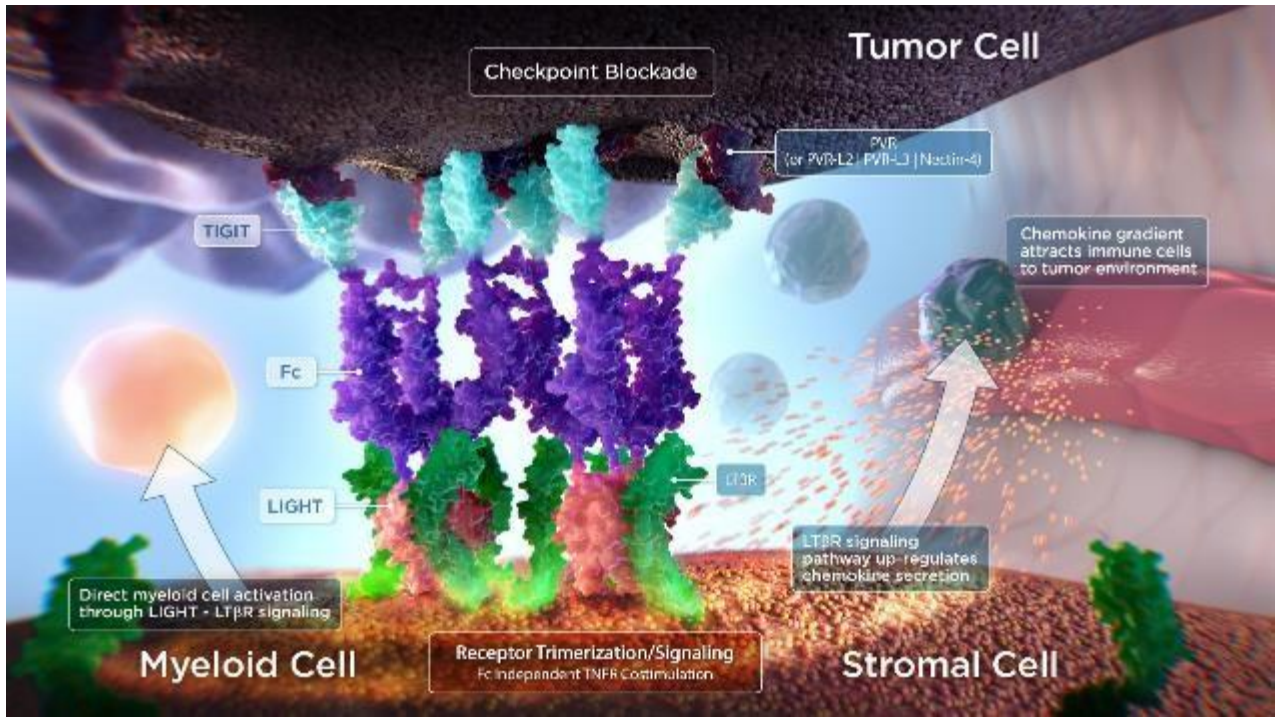
SL-9258 (TIGIT-Fc-LIGHT): Dual Mechanism of Action

Differentiated TIGIT Inhibitor and LIGHT Costimulation

HVEM Co-Stimulation



LTβR Activation



- ✓ TIGIT / PVR checkpoint blockade
- ✓ LIGHT costimulation of HVEM on T and NK Cells
- ✓ LIGHT activation of LTβR + stromal, tumor, and myeloid cells to chemo-attract immune cells and induce tumor death

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SL-9258 (TIGIT-Fc-LIGHT) has Potential to be Highly Differentiated

Triple MOA differentiates from other in-class agents	✓ Checkpoint blockade (PVR) ✓ T/NK cell activation (HVEM) ✓ Myeloid cell activation and pro-inflammatory signaling in TME (LTβR)
Potential best-in-class activity	✓ Pre-clinical development demonstrates monotherapy activity in models of primary and acquired resistance to checkpoint blockade ✓ Combinations may position TIGIT-Fc-LIGHT for success in patients who fail to receive benefit from other checkpoint targeting agents
Differentiated clinical pathway	✓ Potential to provide benefit in the PD-1/L1 acquired resistant setting

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Thank you
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