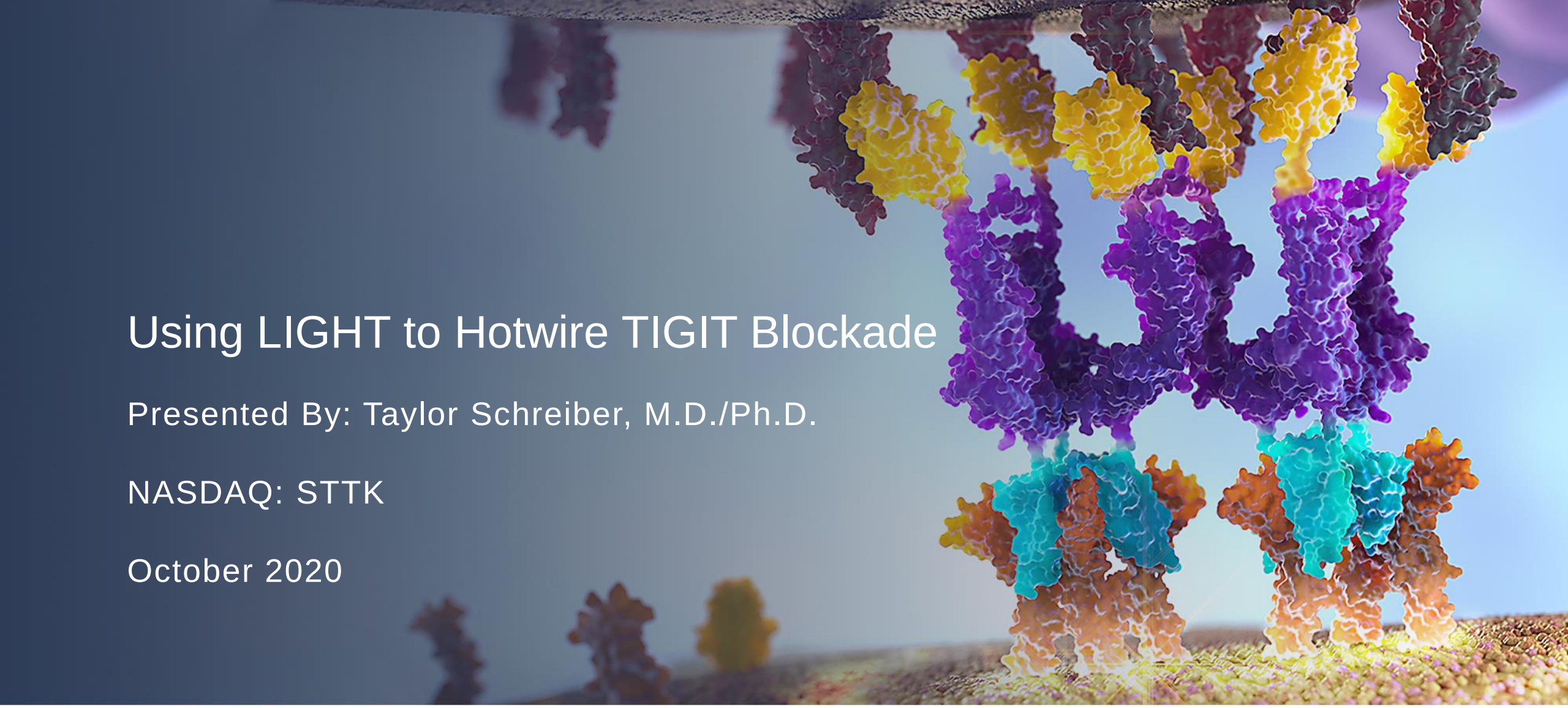

Using LIGHT to Hotwire TIGIT Blockade

Presented By: Taylor Schreiber, M.D./Ph.D.

NASDAQ: STTK

October 2020

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 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 anticipated timing of our planned clinical trials, 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 and our liquidity and capital resources and business trends are 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, including those described in “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations” in our Registration Statement on Form S-1 (File. No. 333-248918), as amended, and elsewhere in such filing and other 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 disclaim any intent to publicly update or revise any forward-looking statements to reflect subsequent events or circumstances, except as required by law.

We obtained the industry, market and competitive position data used throughout this presentation from our own internal estimates and research, as well as from industry and general publications, and research, surveys and studies conducted by third parties. Internal estimates are derived from publicly available information released by industry analysts and third-party sources, our internal research and our industry experience, and are based on assumptions made by us based on such data and our knowledge of the industry and market, which we believe to be reasonable. In addition, while we believe the industry, market and competitive position 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.

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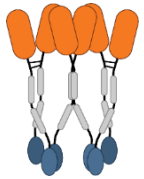
Shattuck Labs Overview

Shattuck Labs (NASDAQ: STTK)

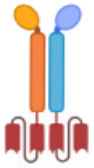
Clinical-stage biotechnology company pioneering the development of bi-functional fusion proteins designed to fundamentally transform therapeutic immune modulation

Next-Generation Fusion Protein Platforms



ARC Platform

Over 300 unique dual function fusion proteins
Checkpoint inhibition + Costimulatory molecule activation
High binding affinity / avidity to targets
Rapid *Concept to Compound to Clinic*



GADLEN Platform

Clinical Pipeline Against Validated Targets

SL-172154: CD47/SIRPα Inhibitor ⊕ CD40 Agonist

Lead independent product candidate
- Ovarian cancer: Phase 1 ongoing
- CSCC and HNSCC: Phase 1 initiating

SL-279252: PD-1/PD-L1 Inhibitor ⊕ OX40 Agonist

In collaboration with Takeda
- Phase 1 ongoing for patients with advanced solid tumors and lymphoma

Experienced Team and Strong Cash Position

Assembled a world-class management team, board of directors, and scientific advisory board
Closed Initial Public Offering in October 2020 with gross proceeds of $232.3 million
Cash, cash equivalents and short-term investments, with net IPO proceeds, expected to fund operations through 2024

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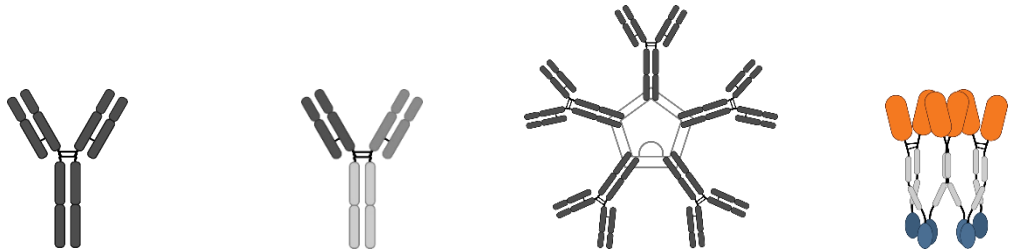
Properties of IgG, IgM and ARC Therapeutics

Structural Differentiation Allows for New Therapeutic Approach



	IgG	Bispecifics	IgM	ARC
Binding Domains	2	2	10	12
Unique Binding Targets	1	2	1	2
Binding Valency	Bivalent	Monovalent	Multivalent	Multivalent
Affinity	Low	Low	Medium	High
Avidity	Low	None	High	High
Dual Functionality	No	Yes	No	Yes
TNF Receptor Agonist Properties	Weak	Weak	Strong	Strong
Protein Construct	Heavy Chains Light Chains	Multiple Heavy & Light Chains	Heavy Chains Light Chains Jchain	Single Peptide Chain
Molecular Weight	150 kDa	150 kDa	≥ 960 kDa	~ 400-700 kDa

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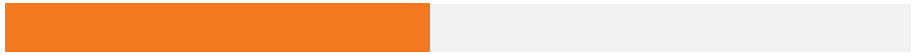
Clinical Stage Pipeline

Wholly Owned and Partnered Programs

	Program	Domains: Domain 1	Domains: Domain 2	Indications	Stage of Development	Anticipated Milestones	Collaborator
ARC Platform	**SL-172154**	SIRPα	CD40L	Ovarian Cancer		Initial Dose Escalation Data 2H'2021	SHATTUCK LABS Worldwide Rights
				CSCC and HNSCC		IND Open Initiating Q4'2020	SHATTUCK LABS Worldwide Rights
	SL-279252	PD-1	OX40L	Advanced Solid Tumors and Lymphoma		Dose Escalation Data 2H'2021	Takeda

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Select Preclinical Programs

Numerous Programs to Support Future Clinical Pipeline

Platform	Program	Domains		Indication	Status	Collaborator
		Domain 1	Domain 2			
ARC	**SL-115154**	CSF1R	CD40L	Advanced Solid Tumors	Manufacturing	Takeda
	SL-9258	TIGIT	LIGHT	Oncology	Manufacturing	SHATTUCK LABS Worldwide Rights
	SL-279137	PD-1	4-1BBL	Oncology	Non-Clinical Development	SHATTUCK LABS Worldwide Rights
	SL-6159	CD86	NKG2a	Oncology	Lead Selection	SHATTUCK LABS Worldwide Rights
	Multiple	Undisclosed		Autoimmune	Lead Selection	SHATTUCK LABS Worldwide Rights
GADLEN	**Multiple**	γδ TCR	Tumor Antigen	Oncology	Lead Selection	SHATTUCK LABS Worldwide Rights

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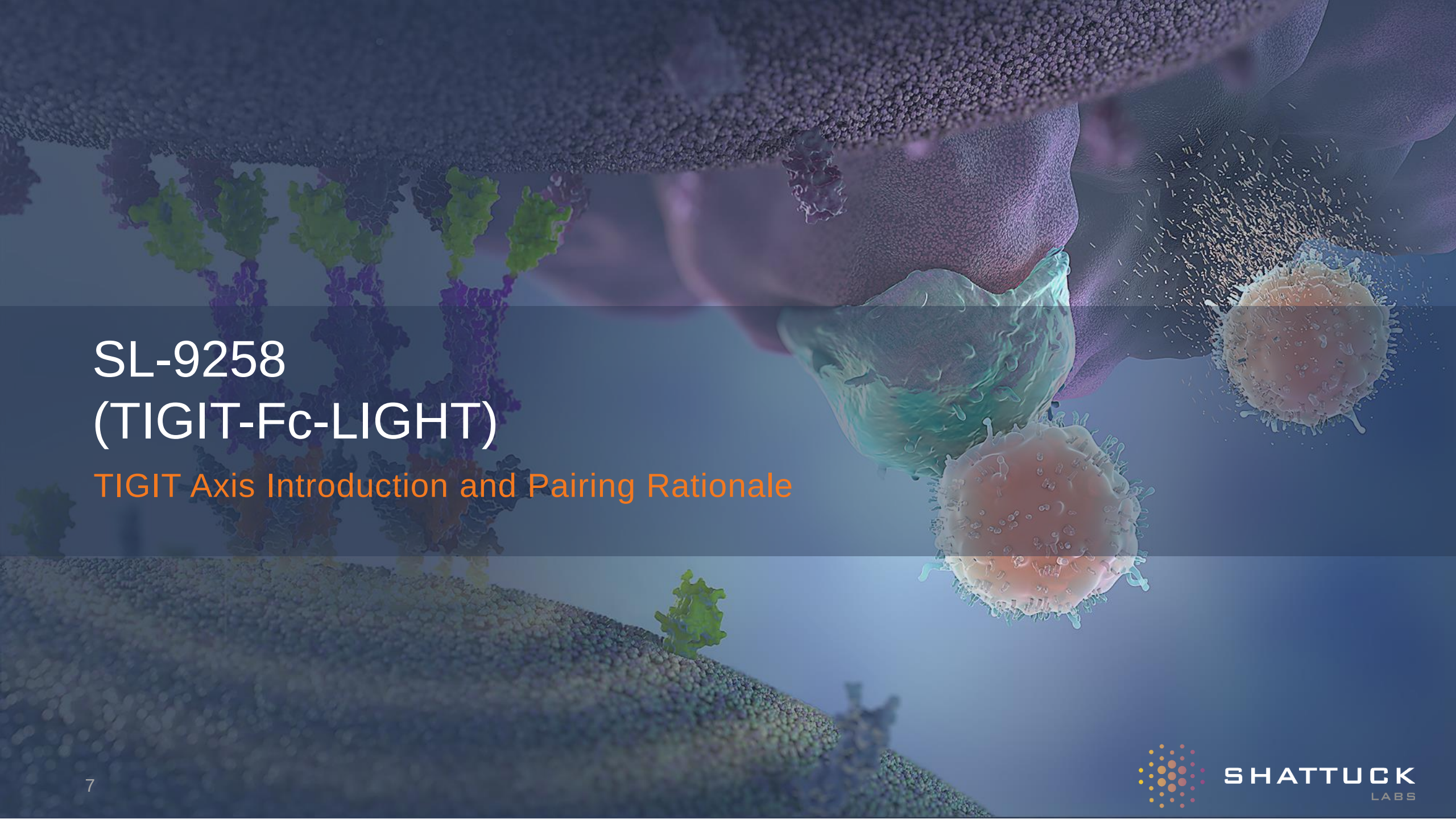

SL-9258 (TIGIT-Fc-LIGHT)

TIGIT Axis Introduction and Pairing Rationale

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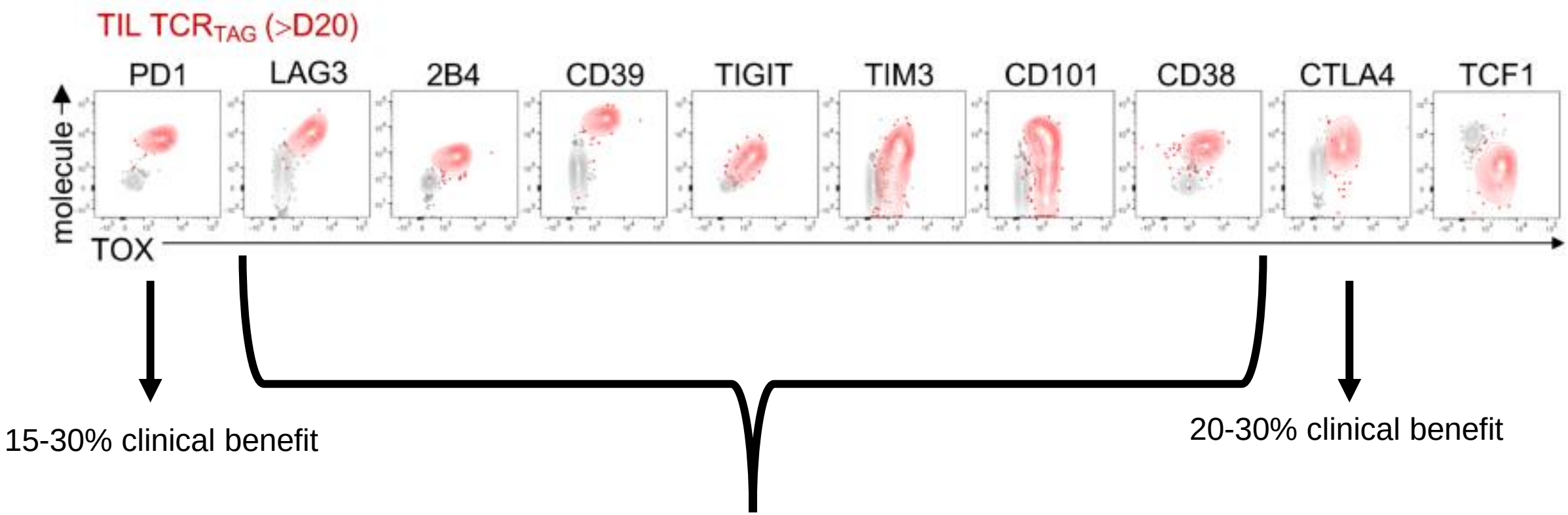
Many Checkpoint Receptors Exist, But Few Beyond PD-1 Show Clinical Activity



Scott AC, *et* al. *Nature* 2019 571;270-274

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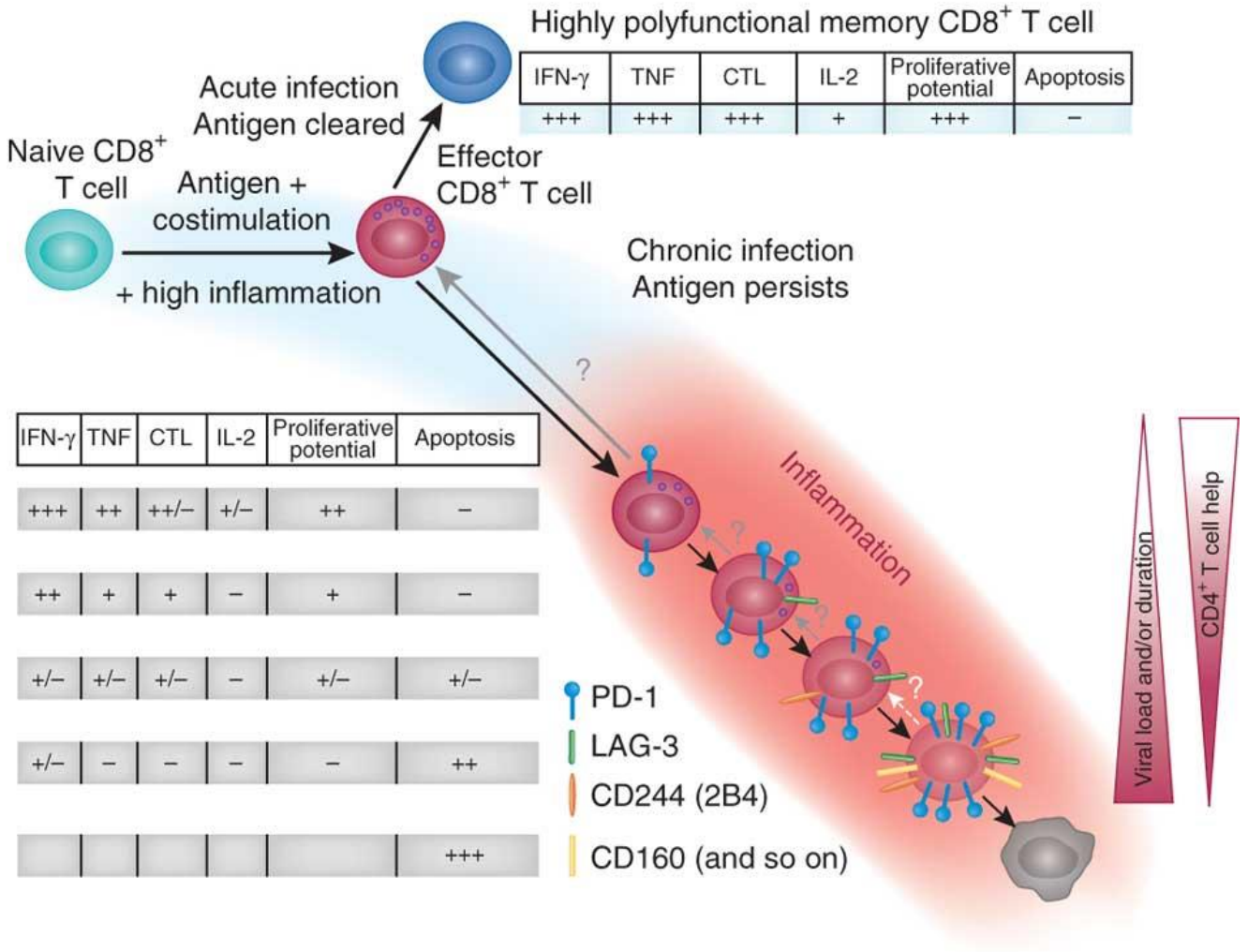
PD-1 Sits Atop An Immune Exhaustion Cascade



Wherry JE. *Nature Immunology* 2011 12;492-499

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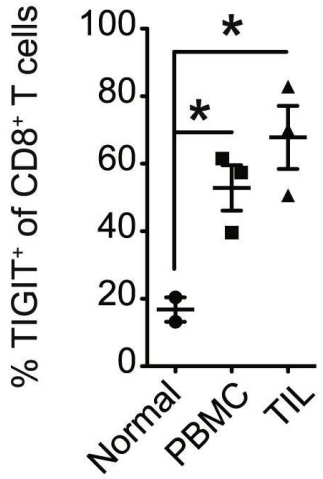
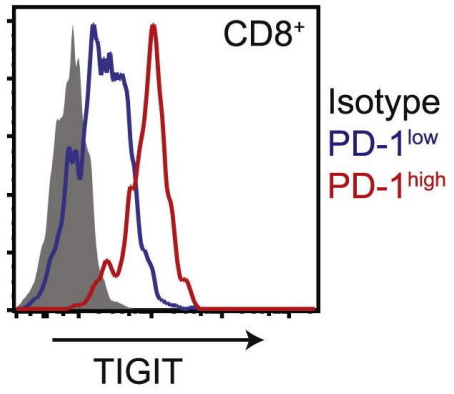
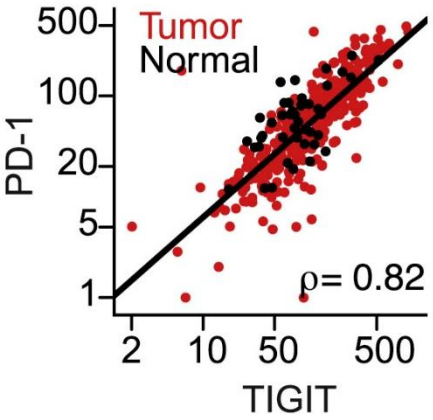
TIGIT Is Likely a Sub-Dominant Checkpoint to PD-1

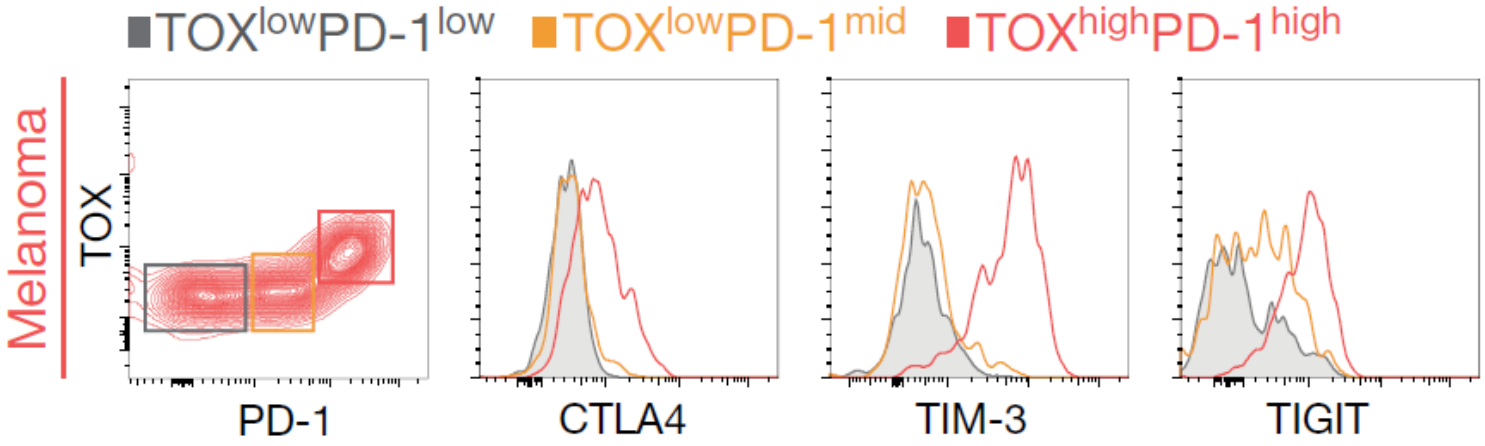
- **In human NSCLC samples:**
  - TIGIT is upregulated on TIL
  - All TIGIT positive TIL are PD-1 positive
  - The density of TIGIT expression correlates with the density of PD-1 expression







- **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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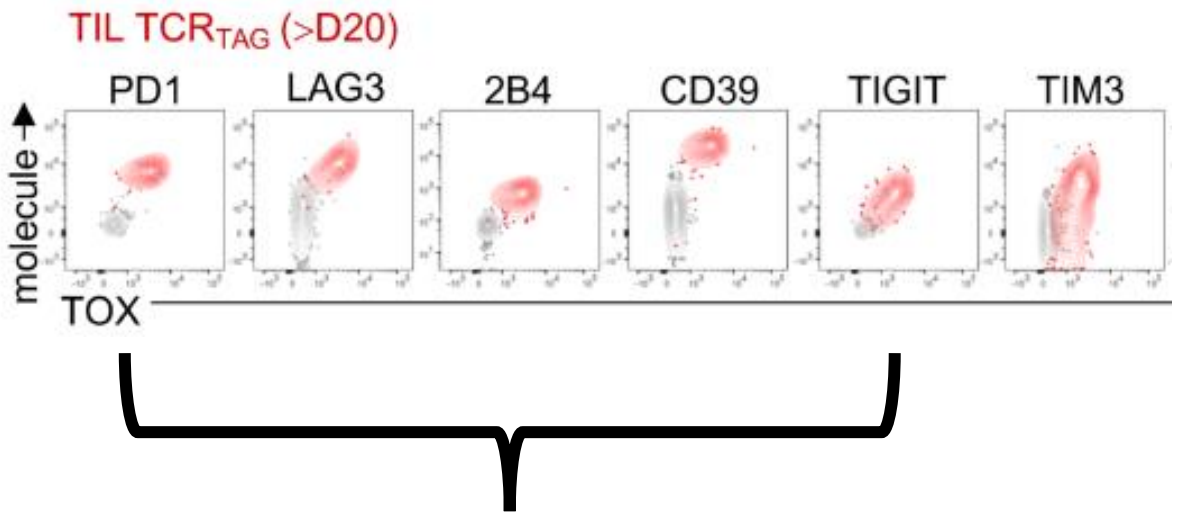
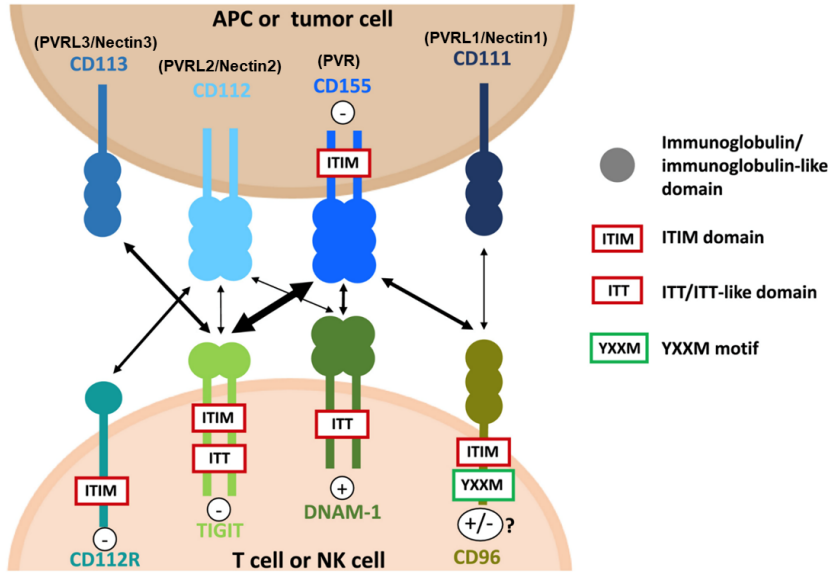
TIGIT Functions as More Than Just an Inhibitory Checkpoint



- **Combinations of PD-1/L1 and TIGIT blocking antibodies (Roche/Merck) have shown encouraging clinical activity in third-party Phase 2 studies**
- **What makes TIGIT different from other checkpoint receptors (LAG3, TIM3, etc.)?**

- **TIGIT Is More Than Just an Immune Checkpoint**



Scott AC, *et* al. *Nature* 2019 571;270-274

Harjunpaa H. *Clin Exp Immunol.* 2019 200;108-119

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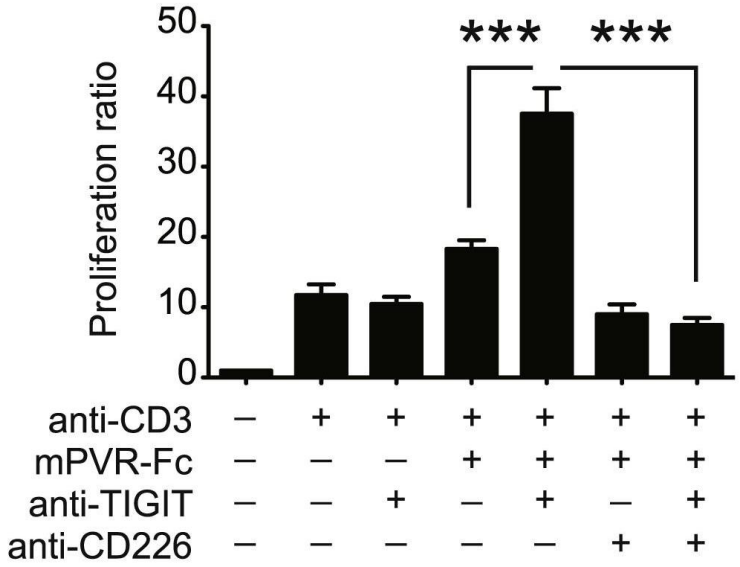
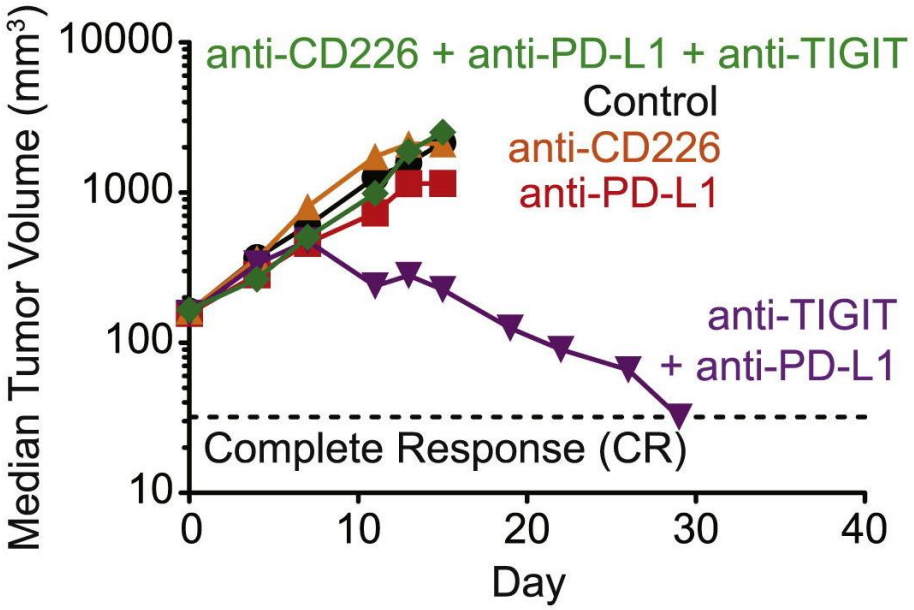
Antitumor Activity of TIGIT Blockade Depends Upon DNAM-1 Activation

- **DNAM-1 (CD226) is a T cell costimulator**



- **However DNAM-1 costimulation is essential for tumor rejection downstream of TIGIT blockade**



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

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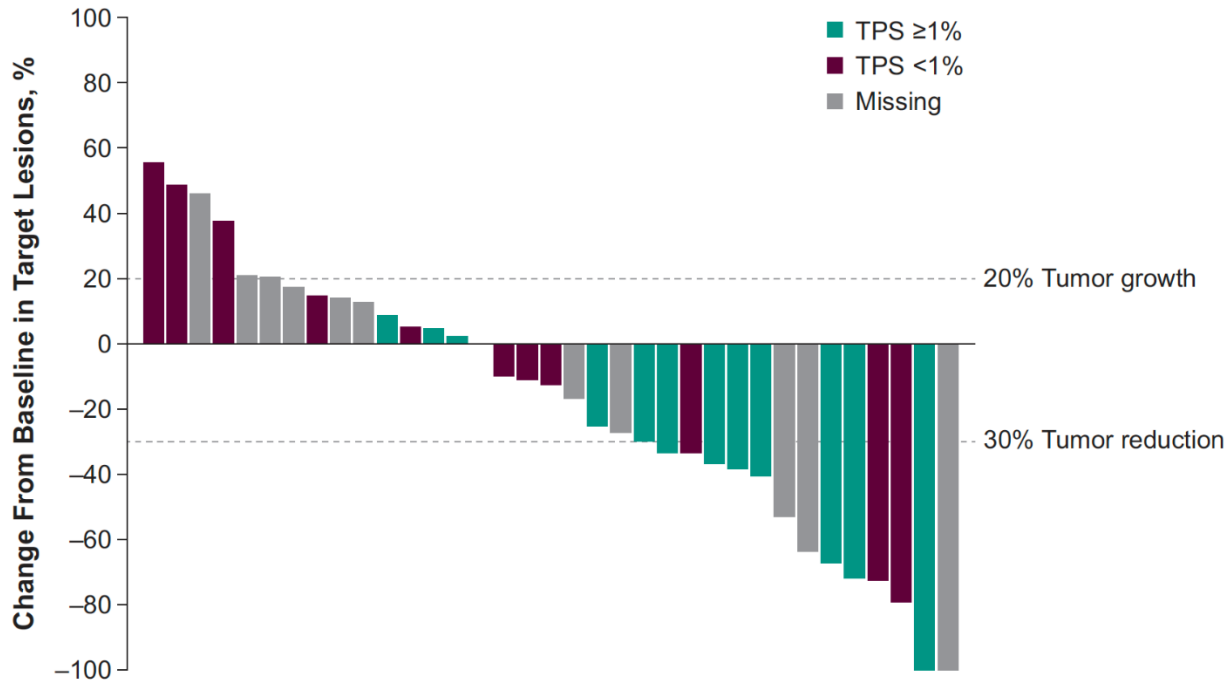
Clinical Benefit of PD-1/TIGIT Blockade is Related to PD-L1 Expression in Checkpoint Naïve NSCLC

Figure 1. Best Change From Baseline in Target Lesions Based on Investigator Assessment per RECIST v1.1 in Patients With Anti-PD-1/PD-L1-Naive NSCLC[a]



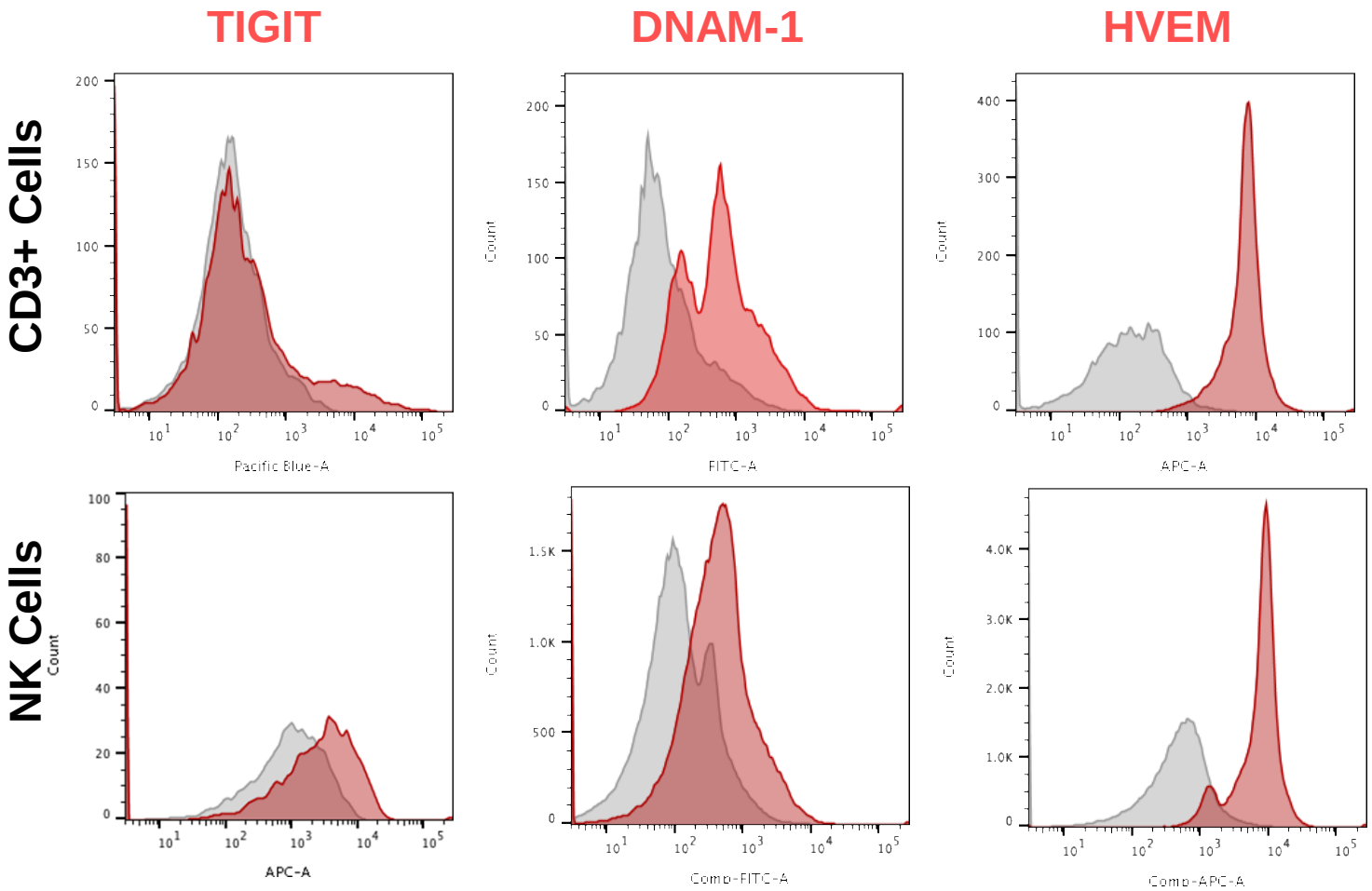
[a]Includes all patients with at least one postbaseline target lesion measurement (n = 35).

- Vibostolimab (IgG1 αTIGIT) in combination with Pembrolizumab demonstrated an ORR of 24% (41 patients) in checkpoint-naïve NSCLC patients (Niu J. ESMO 2020)
- Responses were noted in both PD-L1 positive and negative patients, however PD-L1 was only reported above and below a 1% TPS threshold
- Tiragolumab (IgG1 αTIGIT) demonstrated an ORR of 37% (135 patients) in patients with PD-L1 TPS >1% and an ORR of 66% in patients with PD-L1 TPS >50% (Rodriguez-Abreu D. ASCO 2020)

Niu J *et al*. *Presented at ESMO* 2020

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

- Murine T cells were sub-optimally activated with CD3/28 beads to initiate a T cell exhaustion program
- TIGIT & DNAM-1 were partially induced in T cells
- Freshly isolated murine NK cells express low levels of TIGIT, moderate DNAM-1, and high levels of HVEM



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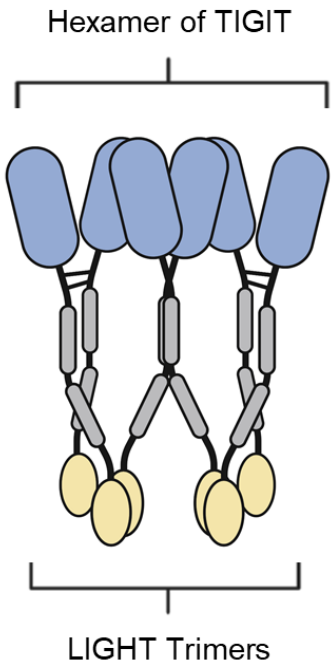
Initial Characterization of TIGIT-Fc-LIGHT

Extracellular Domains of TIGIT (VSIG9)

Flexible Fc Domain Optionality

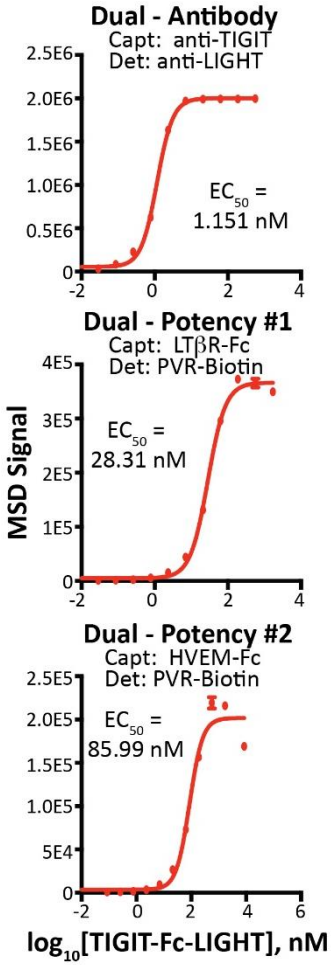
Extracellular Domains of LIGHT (TNFSF14)



→ High avidity binding blocks not only PVR, but also PVR-L2, PVR-L3, and Nectin4 on cancer cells

→ IgG1: Retain Fc gamma receptor binding
IgG4: Effector silent Fc

→ Dual Mechanisms of Action
(1) Direct activation of CD8 T and NK cells via HVEM
(2) LTβR induction of chemokine gradient attracts immune cells to the tumor environment



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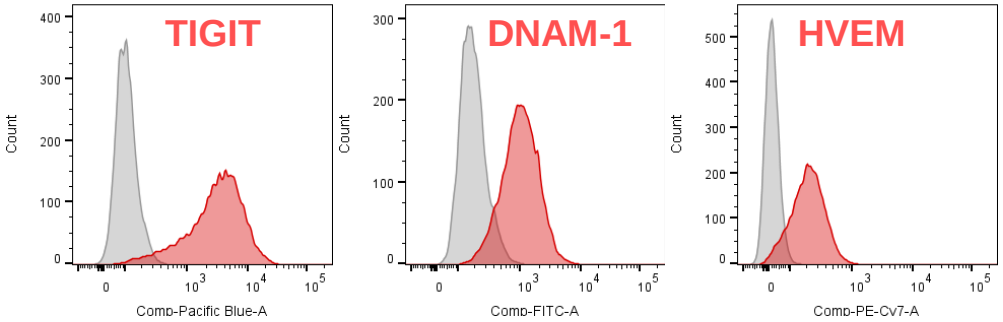
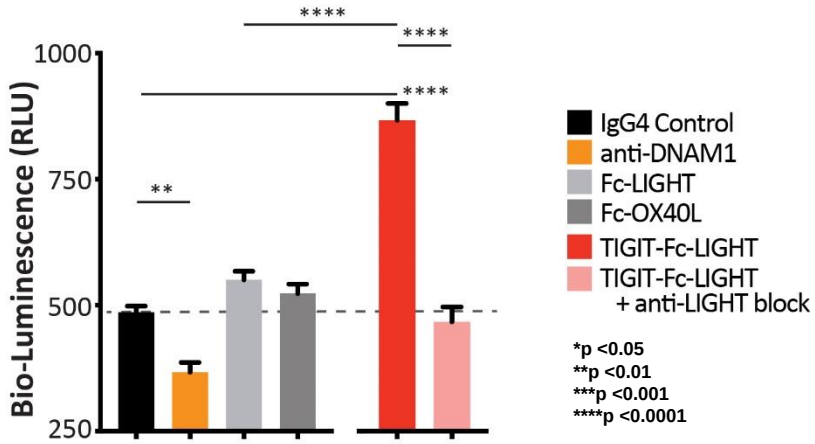
LIGHT/HVEM Provides Overlapping, but Broader Signaling Than PVR/DNAM-1

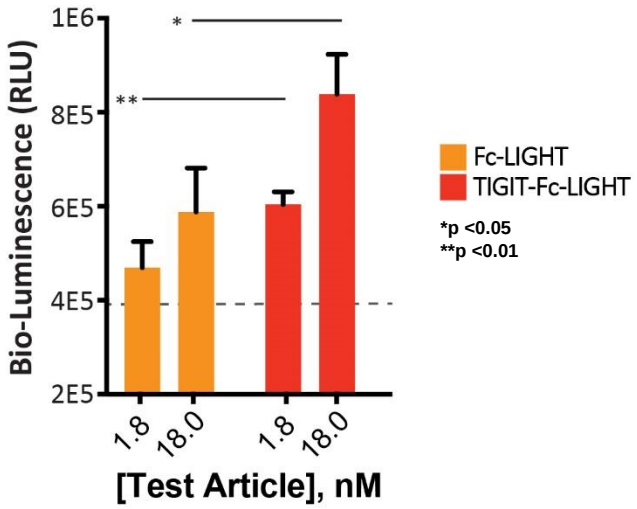


- Promega developed a two-cell reporter assay that indicates the TCR-dependent signaling activity of DNAM-1 expressed by Jurkat cells following co-culture with PVR-expressing CHO cells
- LIGHT also activates the NFκB pathway via LTβR

TIGIT/PVR/DNAM1 Blocking Assay
Jurkat/TIGIT/DNAM1 + CHO/PVR



Non-Canonical NFκB Signaling Assay
U2OS/NIK-NFκB



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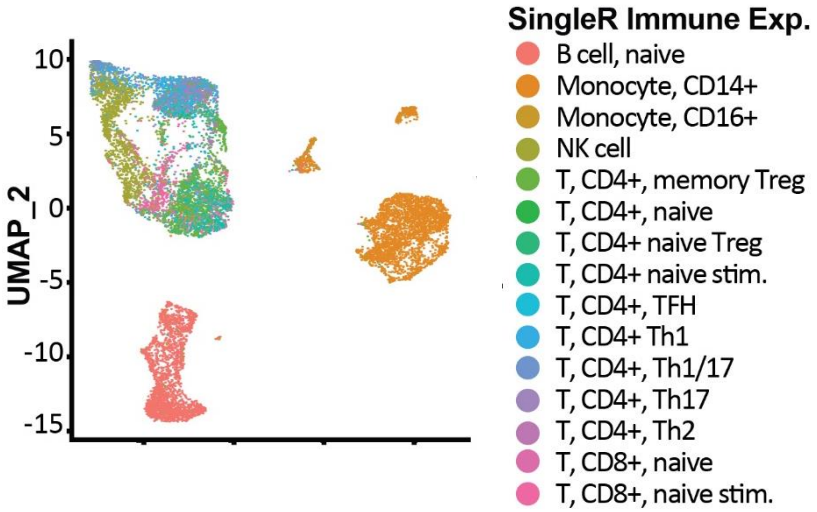
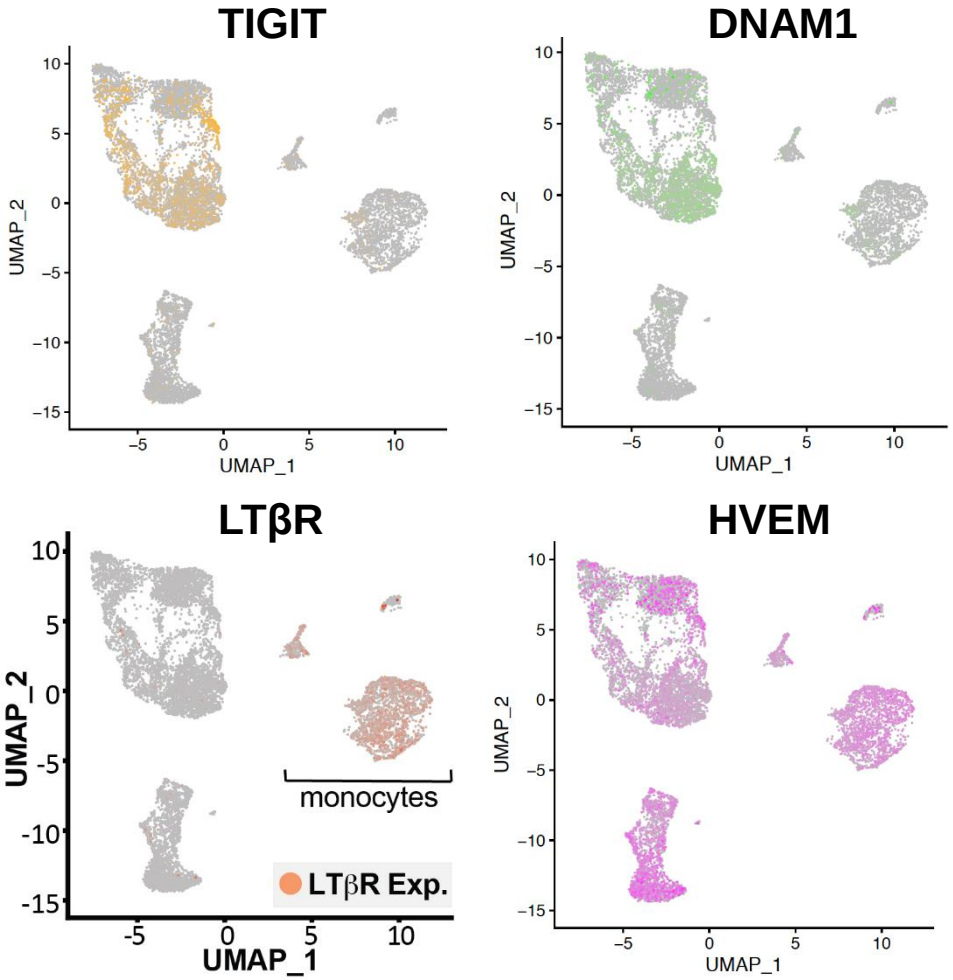
LTβR/HVEM Have Overlapping But Broader Expression Than TIGIT/DNAM-1

- Single-Cell RNA Sequencing of Human PBMC





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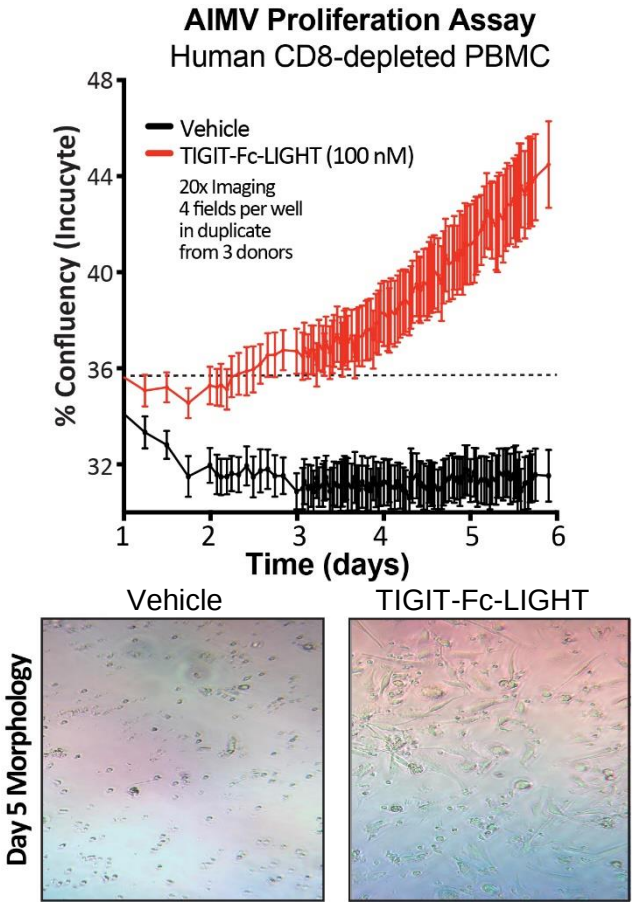
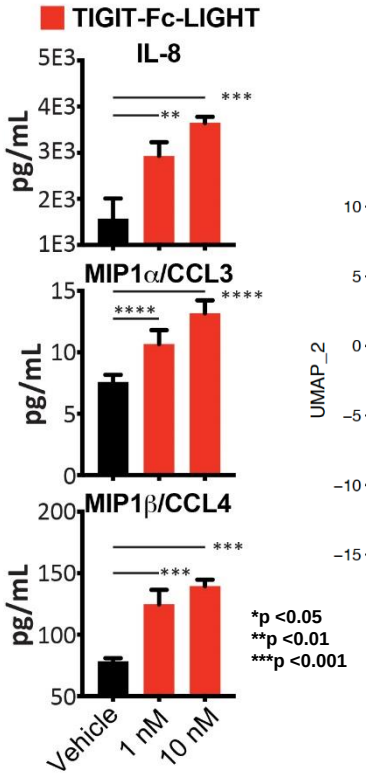
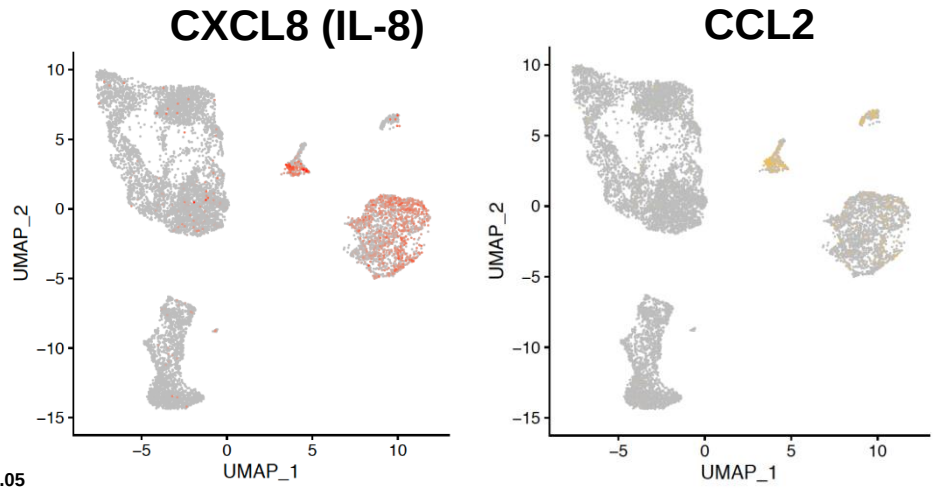
LTβR/HVEM Signaling Activates both Myeloid and Lymphoid Lineages







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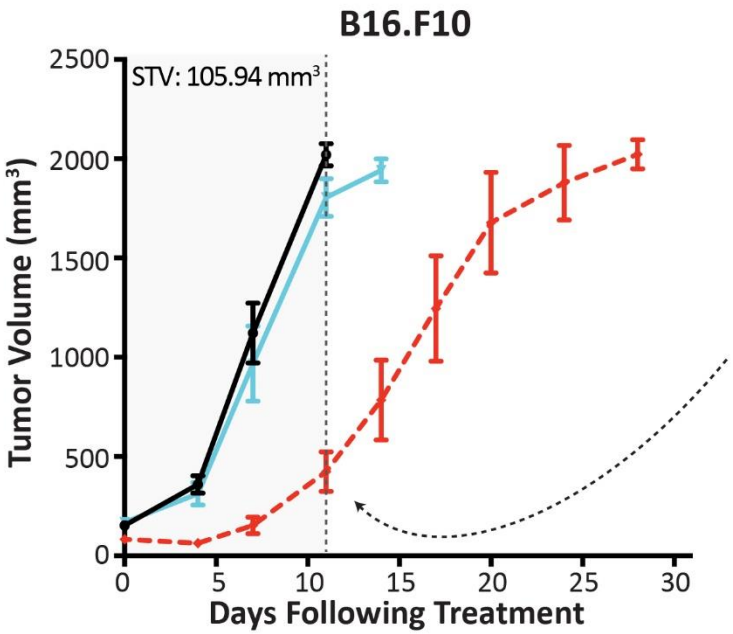
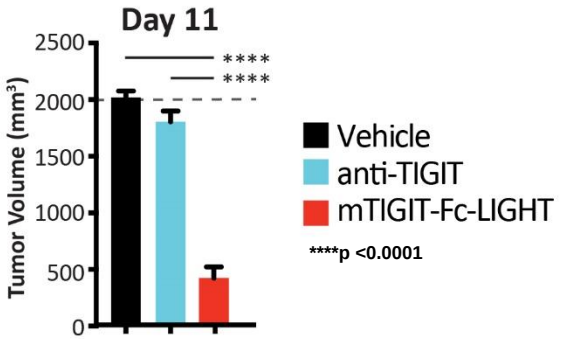
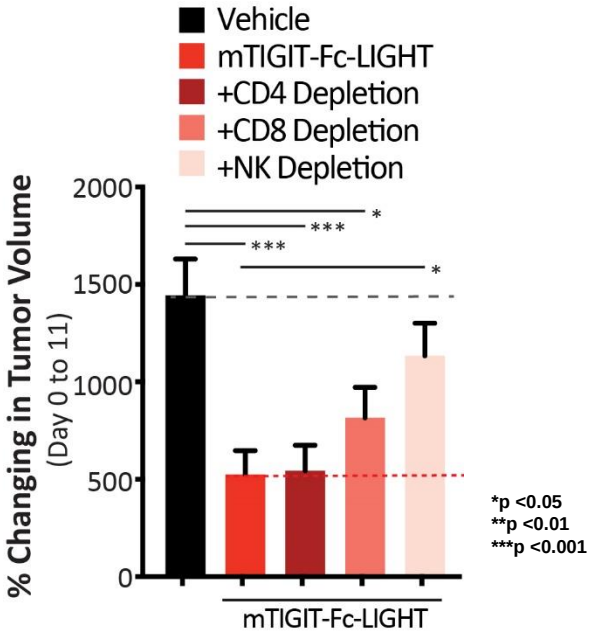
TIGIT-Fc-LIGHT Demonstrates Lower Tumor Volume Growth of Established Tumors Compared to TIGIT Blocking Antibodies







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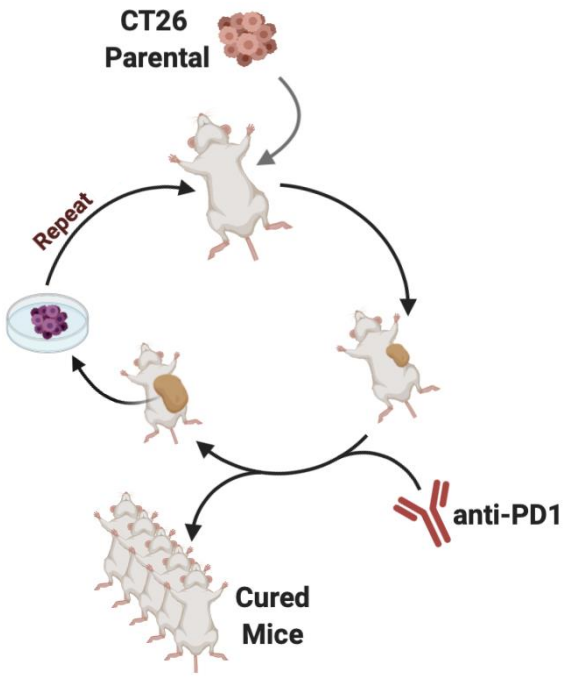
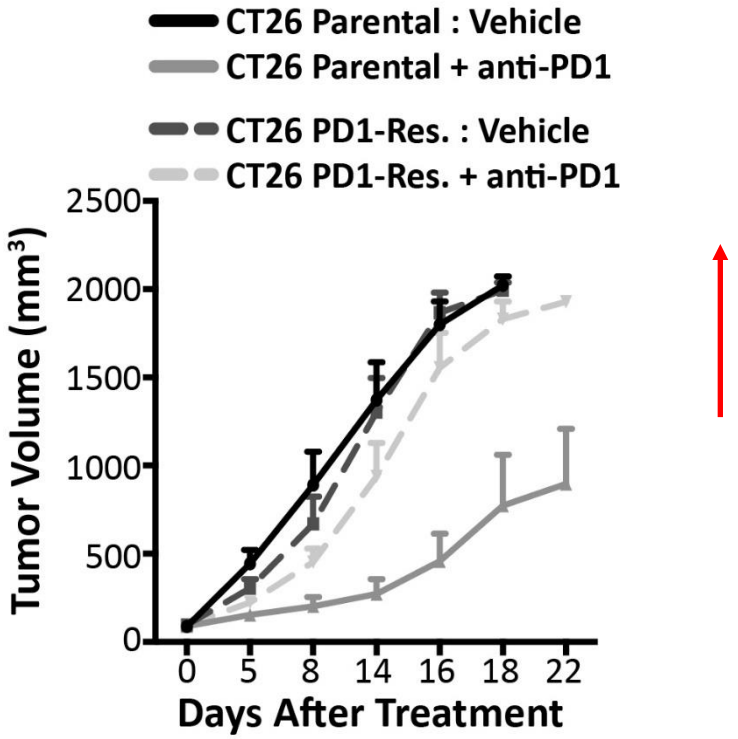
Development of PD-1 Antibody-Resistant CT26 Tumor Model





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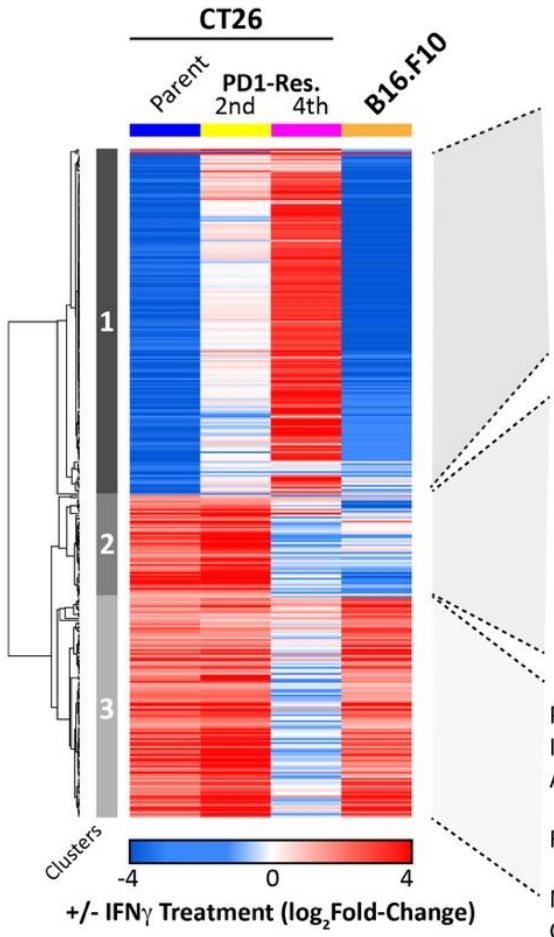
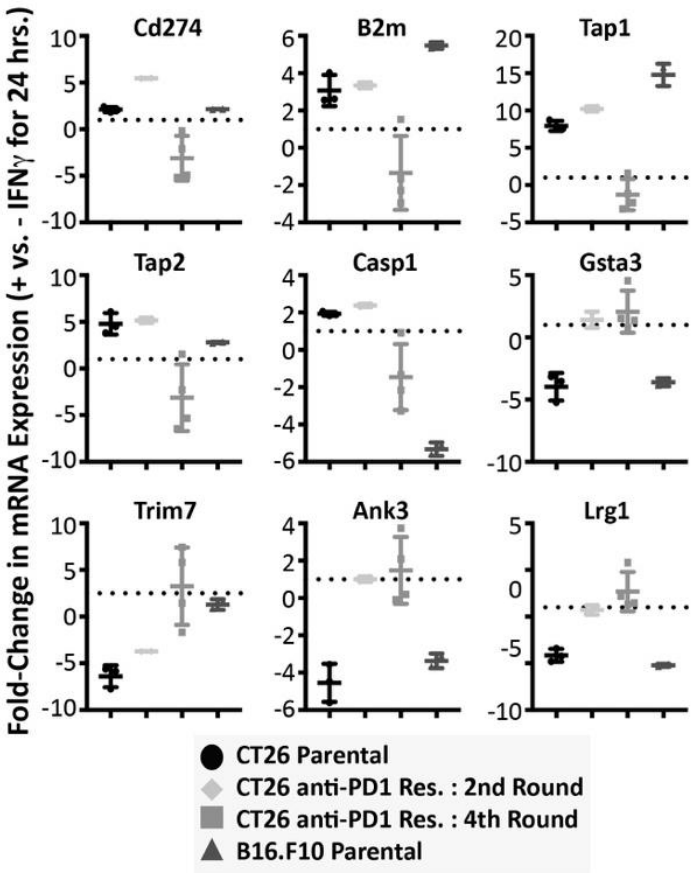
PD-1 Resistant CT26 Tumors Lost IFN Responsiveness



Enriched GO Pathway	p-value
L-phenylalanine catabolic process	6.46E-7
Phospholipid efflux	2.62E-6
Phospholipid homeostasis	4.51E-6
Tyrosine catabolic process	1.67E-5
Pos. reg. of transcription from RNA pol II promoter in response to acidic pH	2.72E-4
Drug export	2.72E-4

Enriched GO Pathway	p-value
Pos. reg. of IκB kinase/NFκB signaling	7.04E-6
Type I IFN signaling pathway	1.23E-5
Pos. reg. of IFNα production	2.06E-5
Pos. reg. of defense response	2.32E-5
Pos. reg. of IFNβ production	6.07E-5
Reg. of inflammatory response	1.12E-4

Enriched GO Pathway	p-value
Protection from NK cell mediated cytotoxicity	1.07E-7
ISG15-protein conjugation	4.36E-6
Antigen processing/presentation of endog. peptide antigen via MHC class 1b, TAP-dependent	1.11E-4
Reg. of antigen processing/presentation via MHC class I	1.85E-4
MHC protein complex assembly	2.76E-4
Cytosol to ER transport	2.76E-4



Internally Derived Shattuck Data

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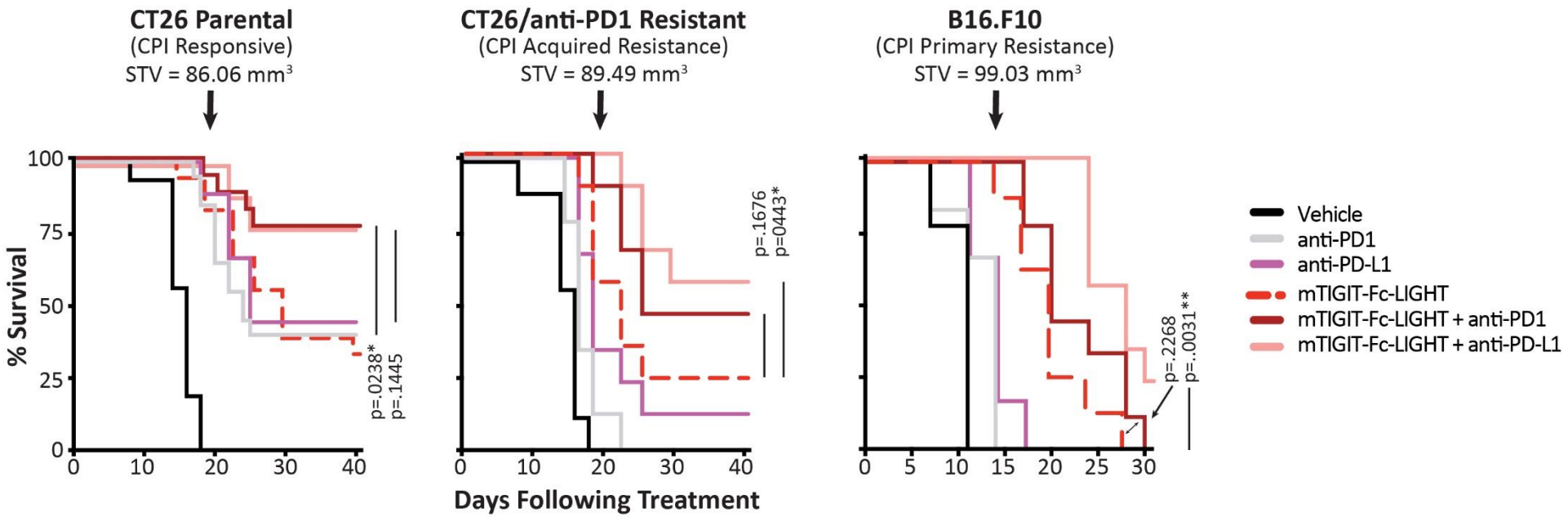
PD-1 Resistant Tumors Responded to TIGIT-Fc-LIGHT Treatment



Internally Derived Shattuck Data

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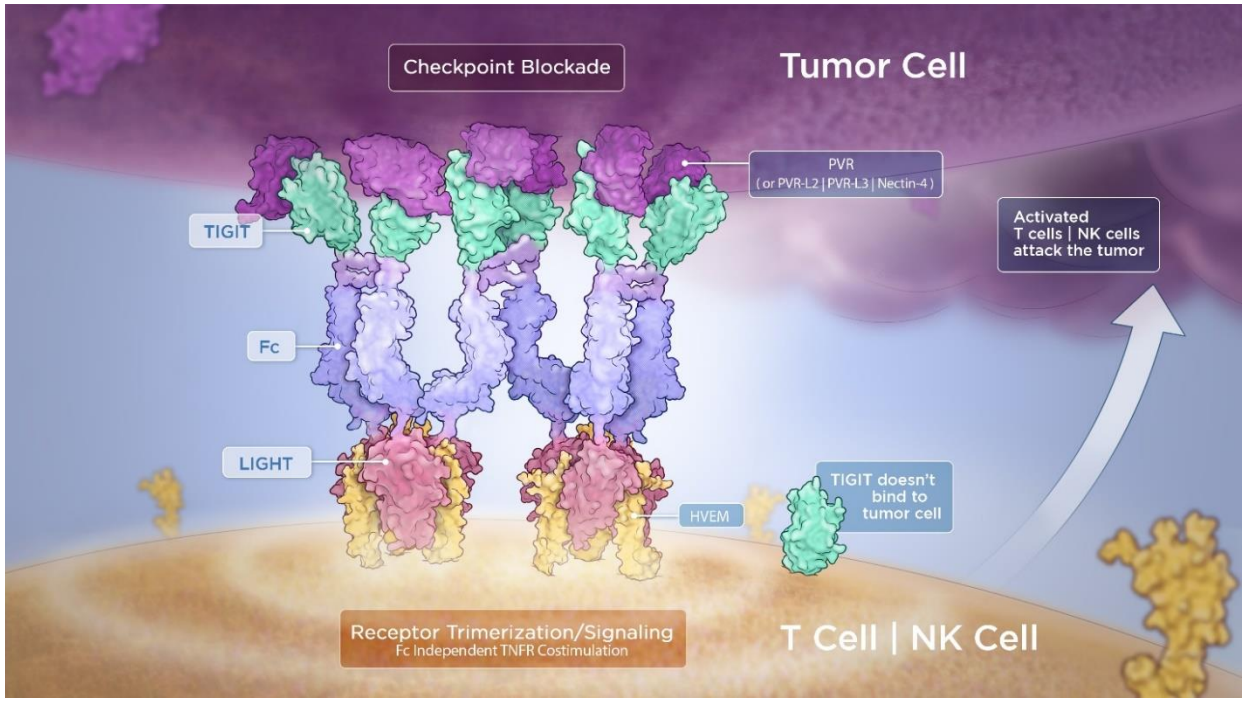
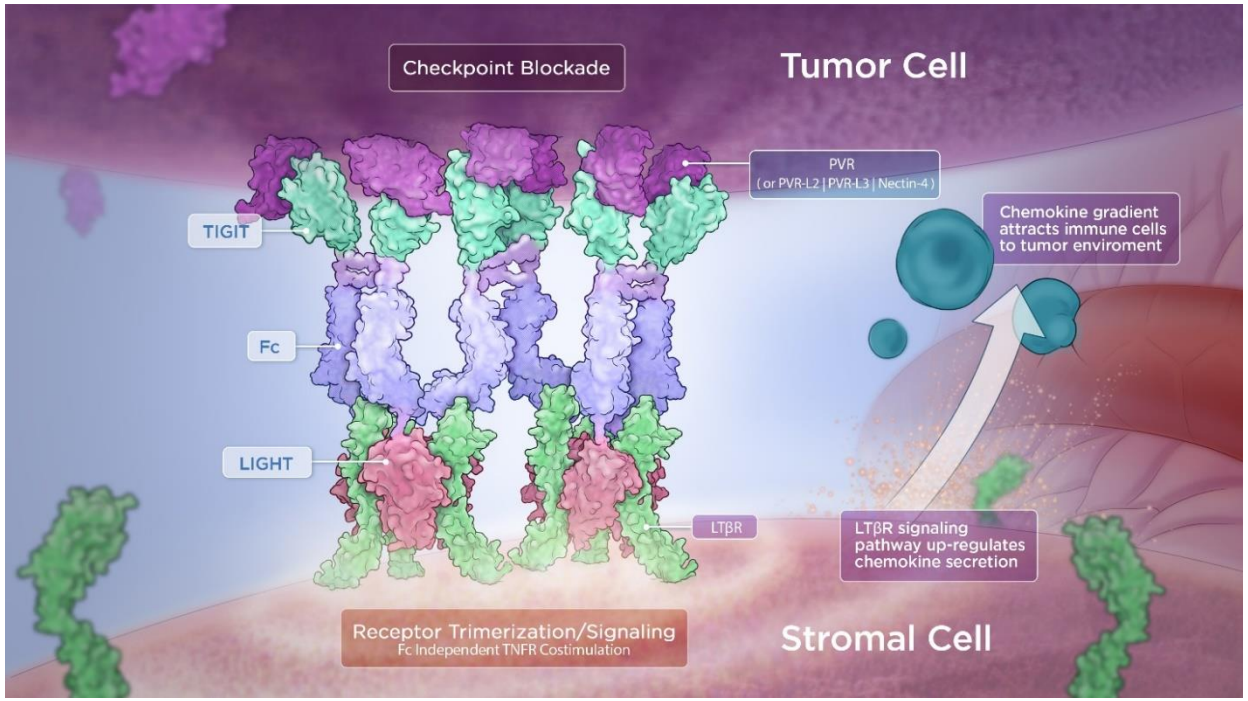
Dual Mechanism of Action of TIGIT-Fc-LIGHT

HVEM Co-Stimulation



LTβR Activation



- ✓ **TIGIT / PVR Checkpoint Blockade**
- ✓ **LIGHT Co-Stimulation 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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TIGIT-Fc-LIGHT Summary

Blocks All Known TIGIT Ligands	Native TIGIT domain binds and competitively inhibits PVR, PVR-L1, PVR-L2, PVR-L3 & Nectin-4
Costimulation Via LIGHT	LIGHT signaling through HVEM and LTβR provide activation of both hematopoietic and non-hematopoietic cell lineages
Reduced Tumor Volume Growth in Pre-Clinical Studies	TIGIT-Fc-LIGHT led to enhanced control of PD-1/TIGIT resistant tumors in comparison to TIGIT blocking antibodies
Non-Human Toxicology Completed	Non-GLP studies established initial safety and pharmacodynamic activity

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Acknowledgements

George Fromm
Suresh de Silva
Kyung Jin Yoo
Arpita Patel
Casey Shuptrine
Kellsey Johannes
Zach Opheim
Louis Gonzalez
Thuy-Ai Nguyen
Fatima Rangwala




Thank you
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