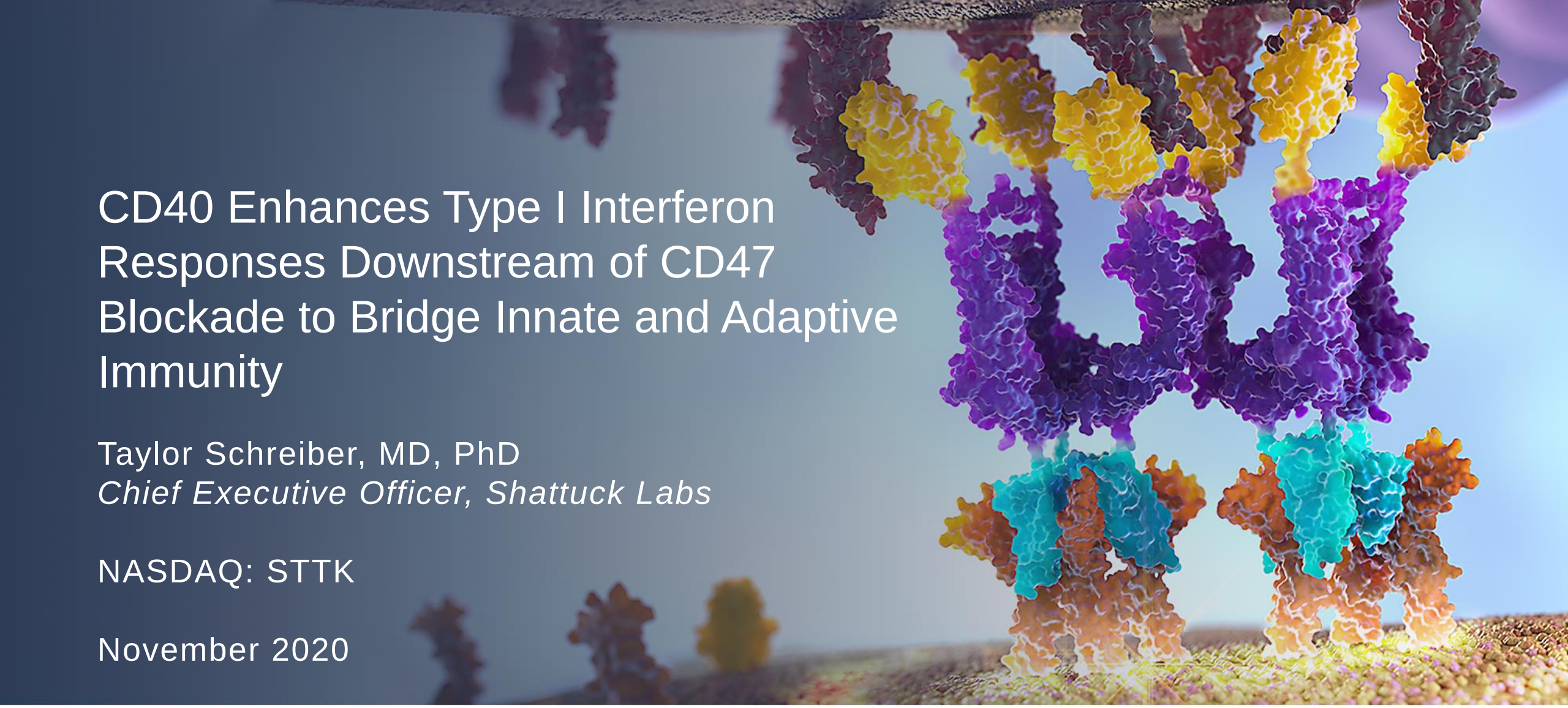

CD40 Enhances Type I Interferon Responses Downstream of CD47 Blockade to Bridge Innate and Adaptive Immunity

Taylor Schreiber, MD, PhD
Chief Executive Officer, Shattuck Labs

NASDAQ: STTK

November 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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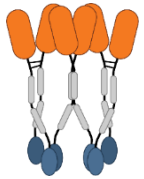
Shattuck Labs Overview

Shattuck Labs (NASDAQ: STTK)

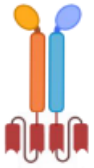
Clinical-stage biotechnology company pioneering the development of bi-functional fusion proteins designed to fundamentally transform therapeutic immune modulation

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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Shattuck's Pipeline

Clinical and Pre-Clinical Programs

Platform	Program	Domains		Indications	Stage of Development					Anticipated Milestones/ Status	Rights
		Domain 1	Domain 2		Discovery	Preclinical	Phase 1	Phase 2	Phase 3		
	Clinical Stage Pipeline										
ARC	**SL-172154**	SIRPα	CD40L	Ovarian Cancer						Initial Dose Escalation Data 2H'2021	SHATTUCK LABS
				CSCC and HNSCC						IND Open Initiating Q4'2020	SHATTUCK LABS
	SL-279252	PD-1	OX40L	Advanced Solid Tumors and Lymphoma						Dose Escalation Data 2H'2021	Takeda (1)
	Select Preclinical Pipeline										
ARC	**SL-115154**	CSF1R	CD40L	Advanced Solid Tumors						Manufacturing	Takeda (1)
	SL-9258	TIGIT	LIGHT	Oncology						Manufacturing	SHATTUCK LABS
	SL-279137	PD-1	4-1BBL	Oncology						Non-Clinical Dev.	SHATTUCK LABS
	SL-6159	CD86	NKG2a	Oncology						Lead Selection	SHATTUCK LABS
	Multiple	Undisclosed		Autoimmune						Lead Selection	SHATTUCK LABS
GADLEN	**Multiple**	γδ TCR	Tumor Antigen	Oncology						Lead Selection	SHATTUCK LABS

(1) Takeda holds an exclusive option to license SL-279252 and SL-115154

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ARC Platform Technology

Structural Advantages Allow for Plug and Play

Type 1 Membrane Proteins

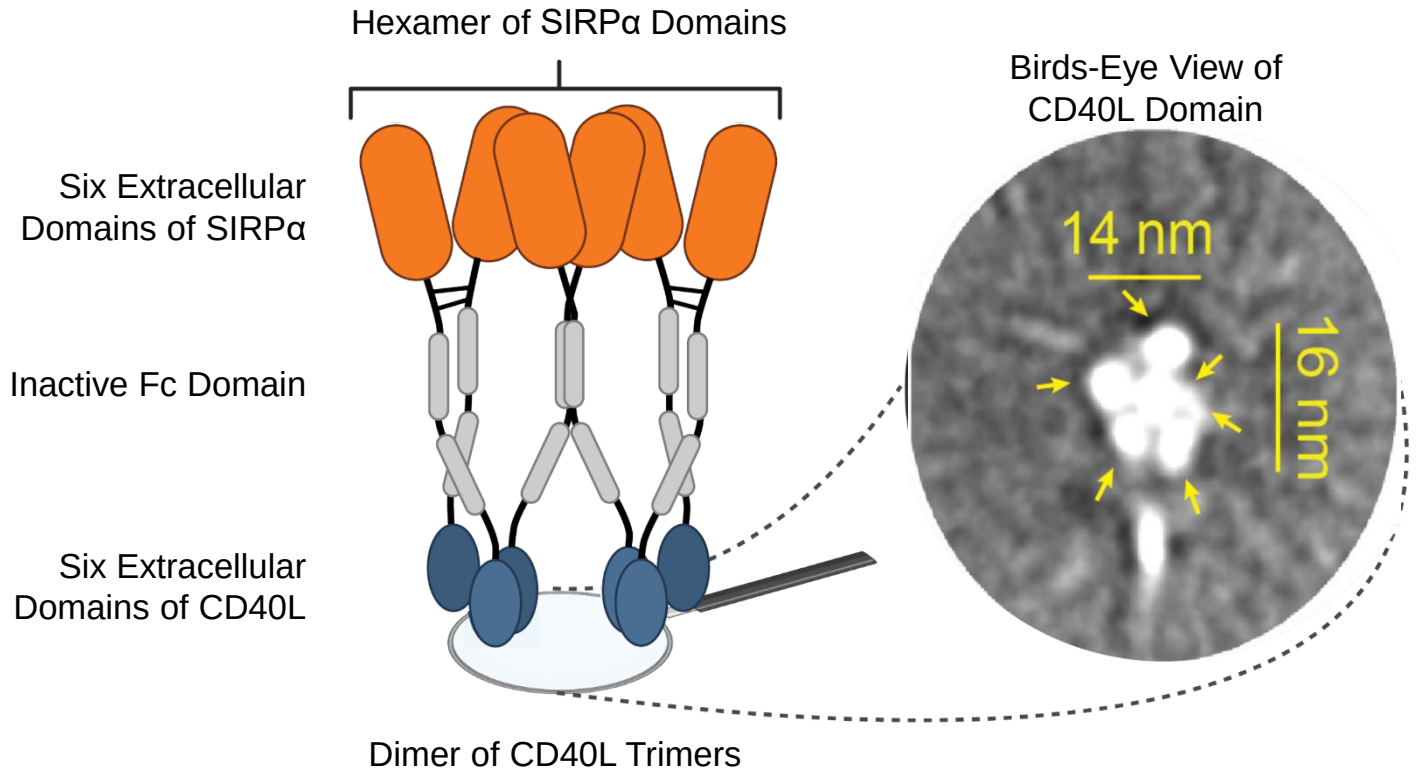
(>1,400 POTENTIAL TARGETS)

Checkpoint Molecules	Cytokine Receptors
SIRPα	CSF1R
PD-1	TGFβR1
TIGIT	FLT3L
VSIG8	Others....

Type 2 Membrane and Soluble Proteins

(>450 POTENTIAL TARGETS)

TNFSF Ligands	Cytokines
CD40L	IL-2
OX40L	IL-12
LIGHT	IL-15
4-1BBL	Others....



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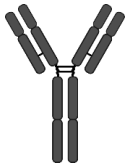
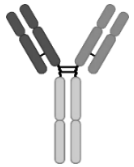
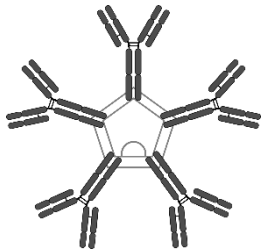
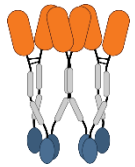
Properties of IgG, IgM and ARC Therapeutics

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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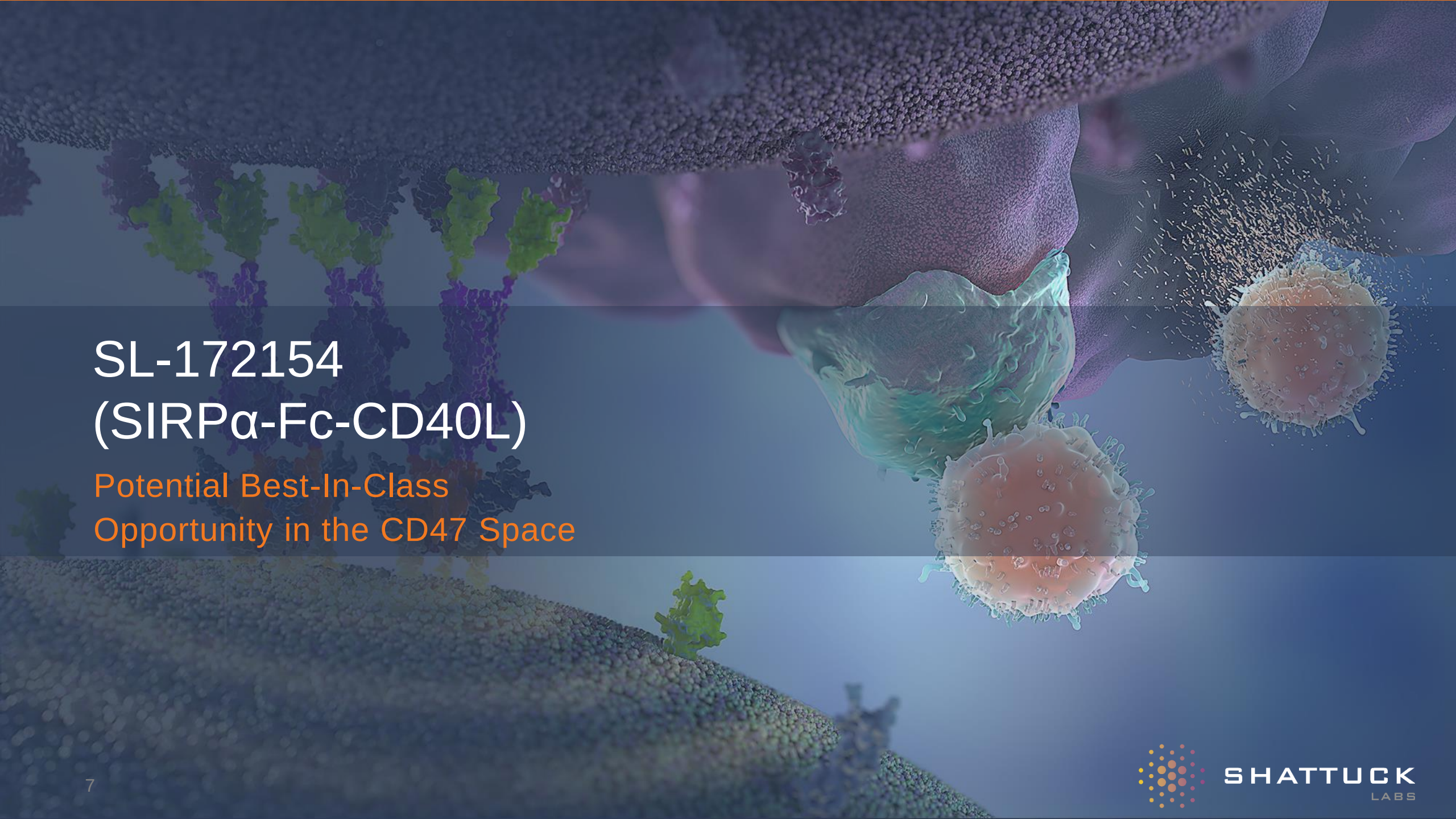

SL-172154 (SIRPα-Fc-CD40L)

Potential Best-In-Class Opportunity in the CD47 Space

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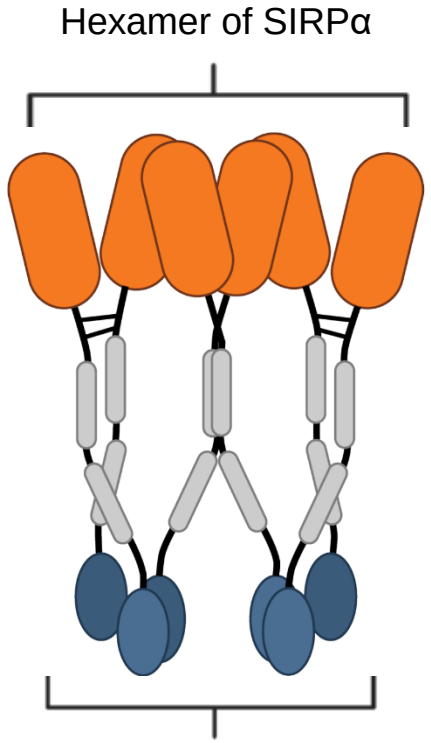
Design and Structure of SL-172154

Extracellular Domains of SIRPα (CD172)

Inactive Fc Domains

Extracellular Domains of CD40L (CD154)



→ High avidity binding potently blocks CD47 on cancer cells with durable receptor occupancy

→ No anemia or thrombocytopenia

→ Direct activation on CD40 on macrophages enhances activation and tumor antigen presentation

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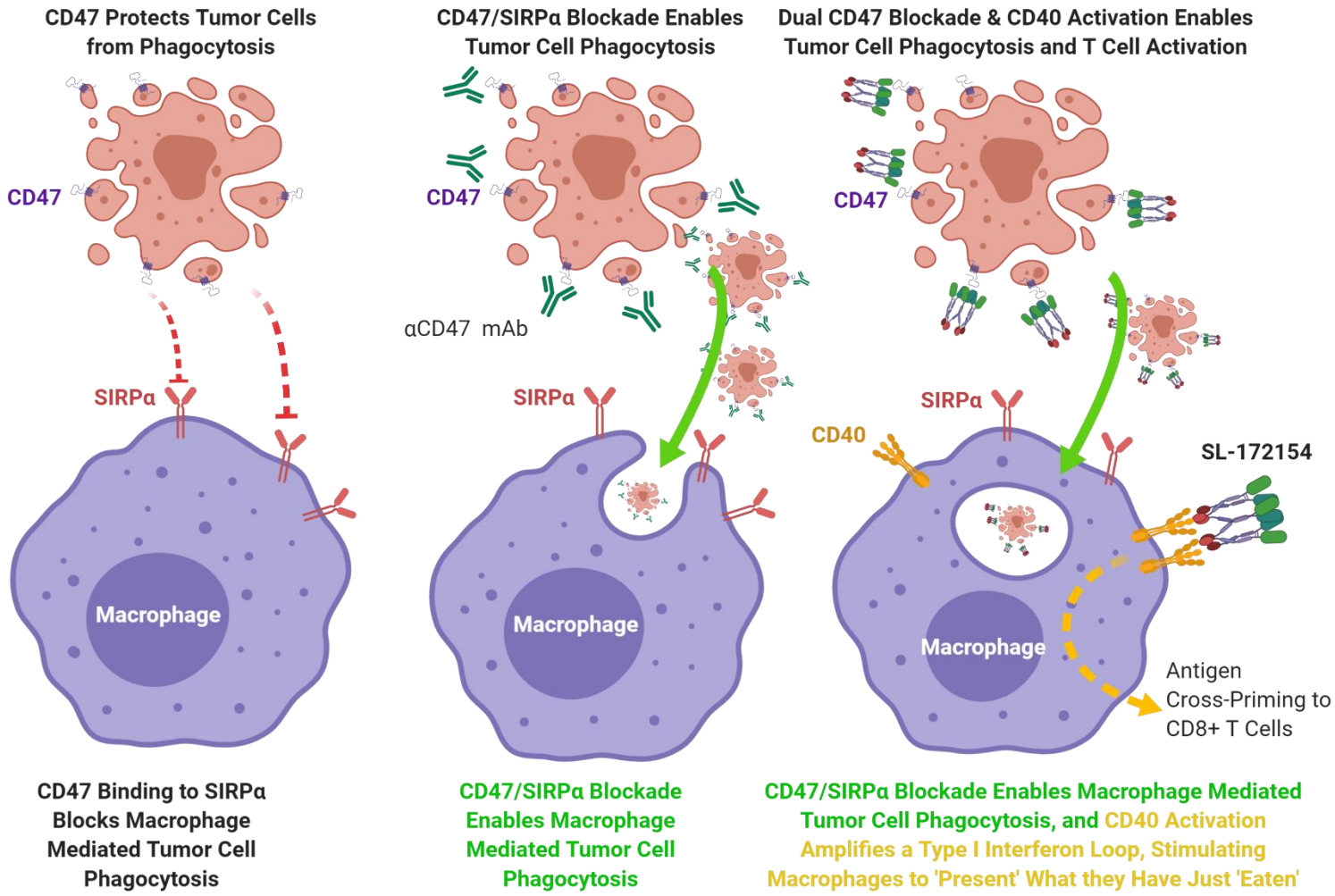
Pairing Rationale: SIRPα-Fc-CD40L

Dual Mechanism: Checkpoint Blockade and TNF Activation



- Tumor cell phagocytosis requires an ‘eat me’ signal, which can be provided by either:
  - ADCP-competent antibodies (rituximab, trastuzumab, cetuximab, etc.)
  - Upregulating natural “eat me” signals (i.e., calreticulin) by immunogenic cell-death inducing chemotherapy

de Silva et al, Cancer Immunology Research, 2020

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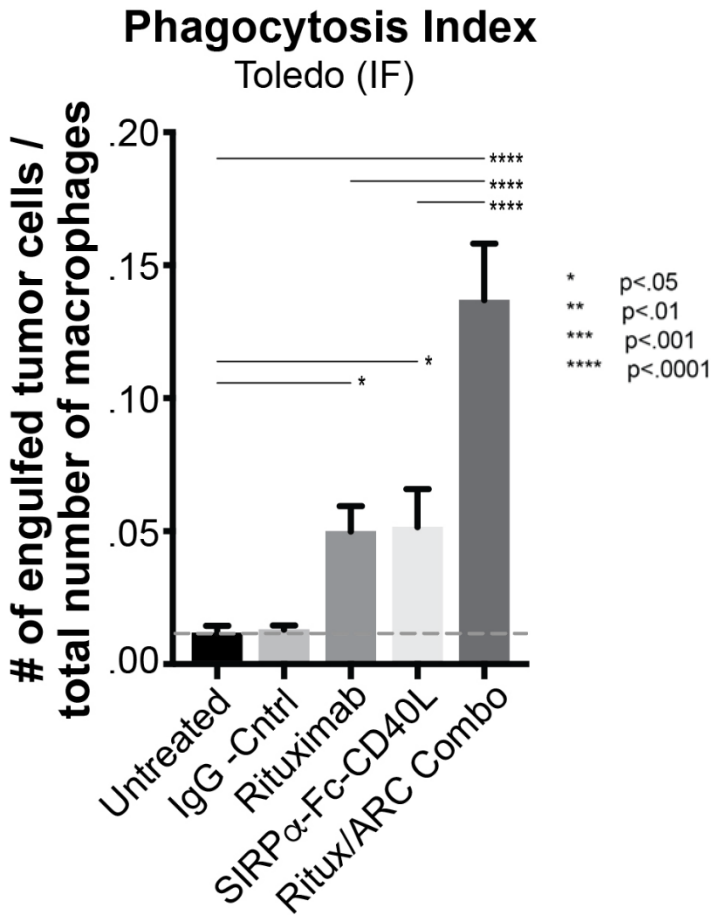
SL-172154 Potentiated Tumor Cell Phagocytosis



- Phagocytosis of the CD20+ Toledo DLBCL tumor cell line is observed with either Rituximab or SL-172154, and enhanced when both are combined
- SL-172154 potentiated the phagocytic activity of Rituximab to a greater degree than CD47 antibodies

de Silva et al, Cancer Immunology Research, 2020

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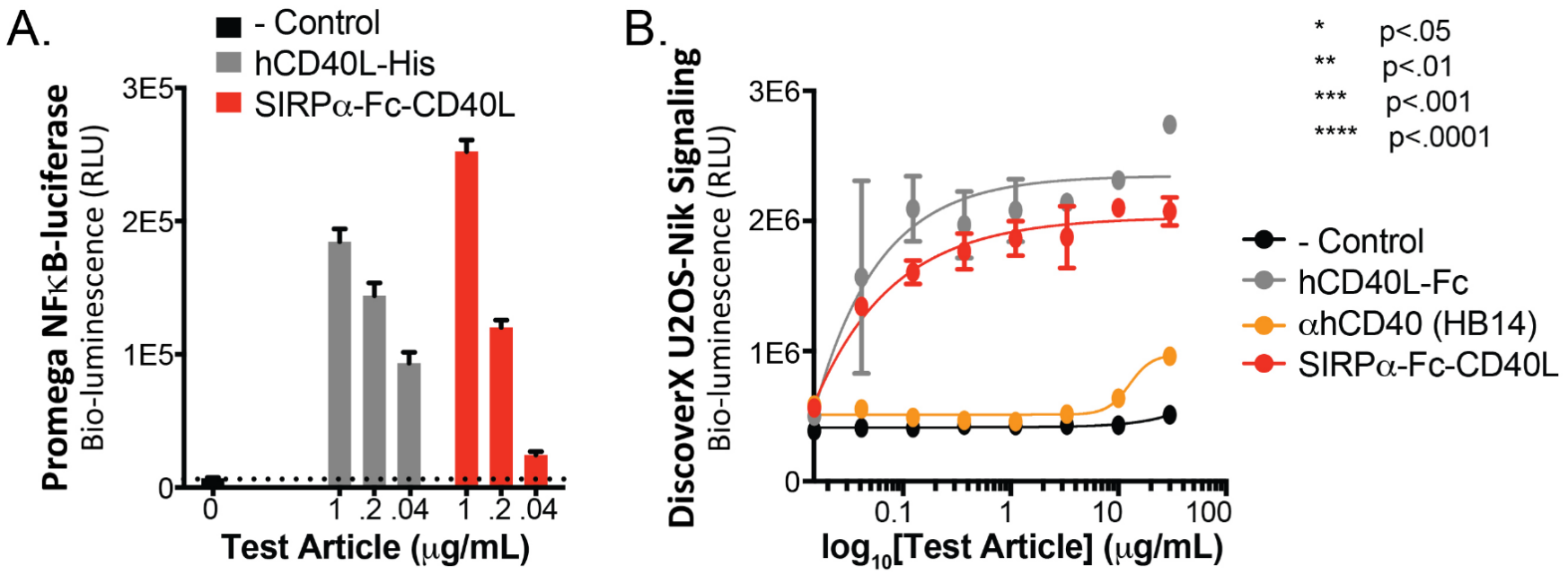
SL-172154 Potently Stimulated CD40 Signaling



- A) Both recombinant CD40L and SL-172154 stimulated dose-dependent activation of the canonical NFκB pathway
- B) Recombinant CD40L and SL-172154, but not CD40 antibodies, stimulated dose-dependent activation of the non-canonical NFκB pathway

de Silva et al, Cancer Immunology Research, 2020

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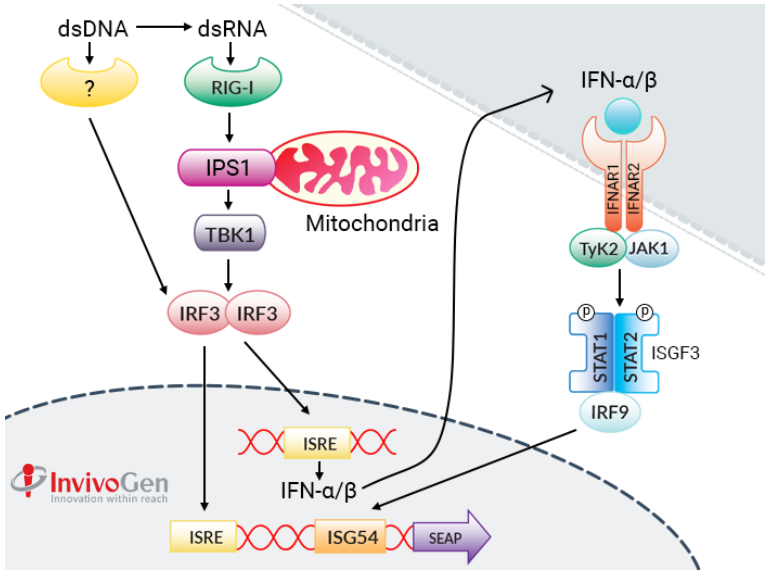
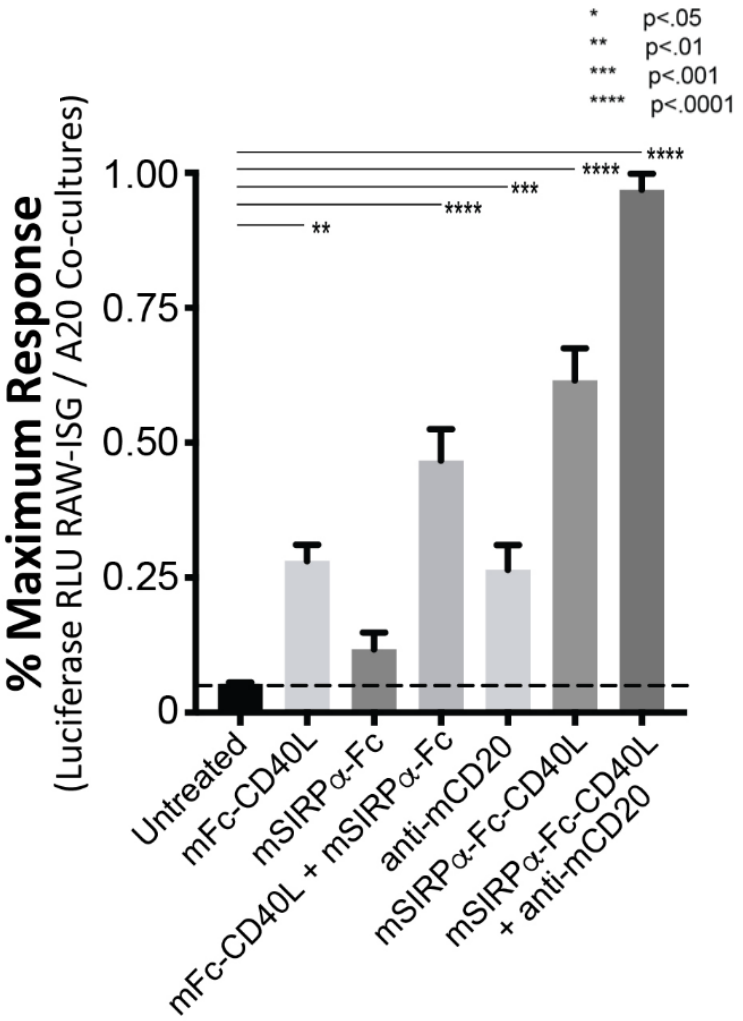
SL-172154 Amplified Type I Interferon Signaling



- Anti-tumor immunity following CD47/SIRPα blockade is reported to be dependent upon Type I interferon signaling in antigen presenting cells (Xu M *et al.* Immunity 2017)
- Type I interferon signaling is activated by cytosolic sensing of tumor cell DNA and STING pathway activation
- CD40L was shown to significantly amplify Type I interferon signaling in macrophages



de Silva et al, Cancer Immunology Research, 2020

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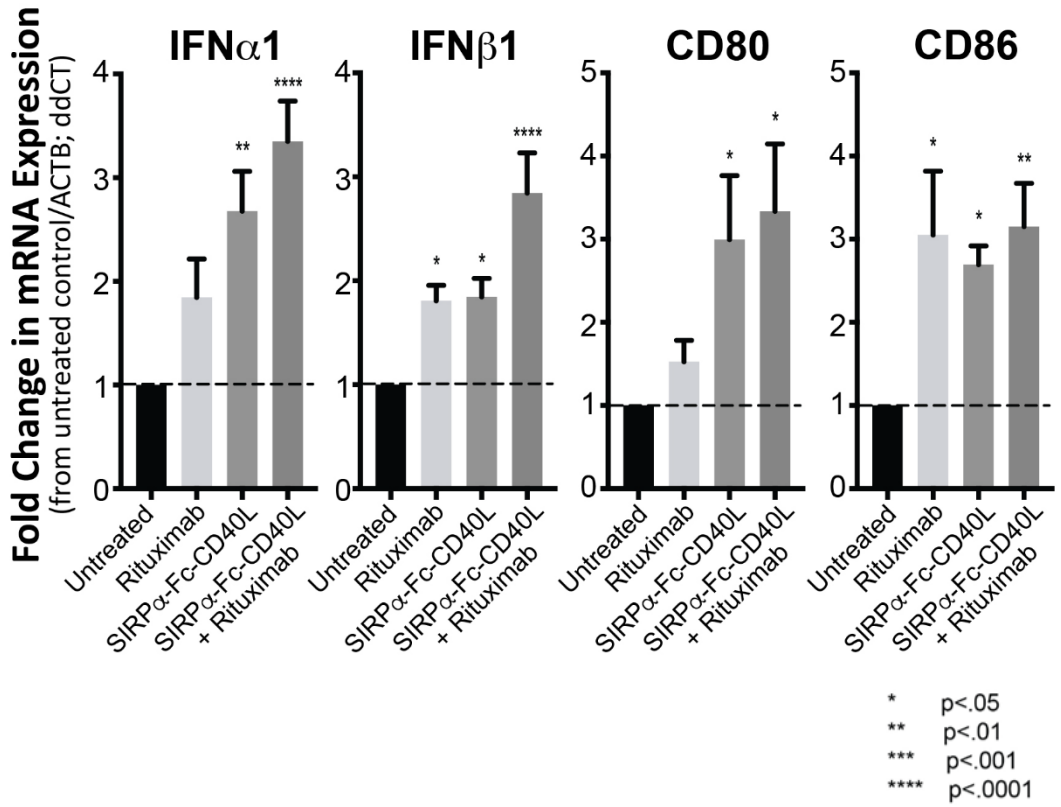
SL-172154 Stimulated Human Macrophage Activation



- Human macrophages were co-cultured with human Toledo DLBCL tumor cells and the indicated treatments
- 2 hours into the co-culture, macrophages were sorted and RNA was extracted for RT-PCR analysis for the indicated transcripts

de Silva et al, Cancer Immunology Research, 2020

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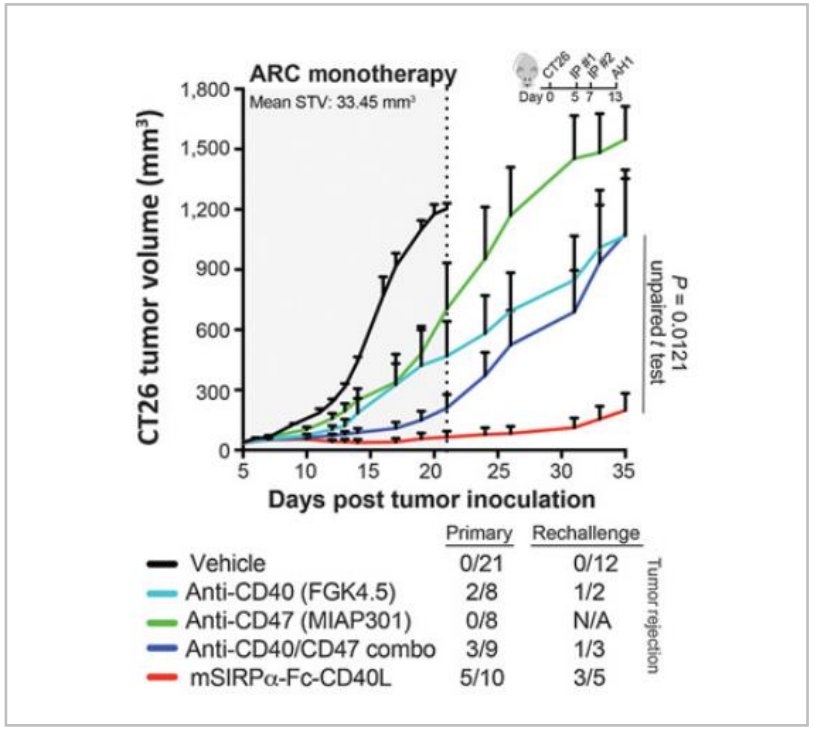
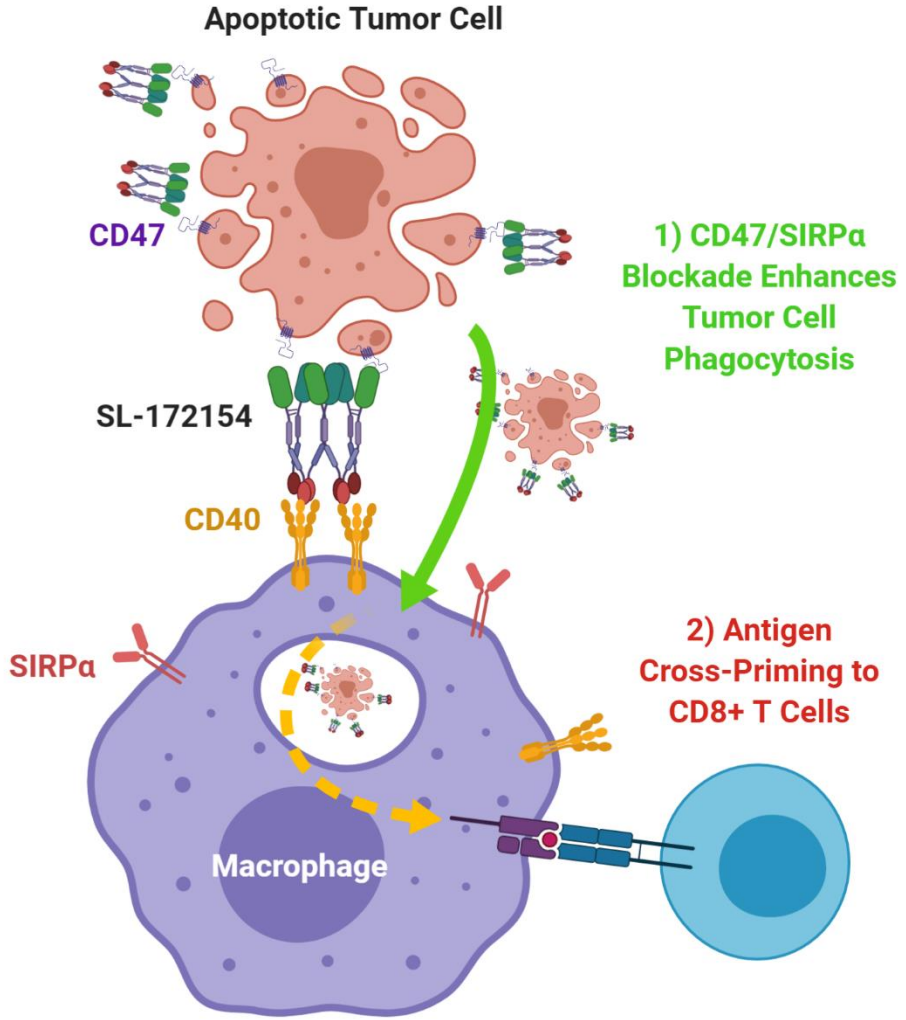
SIRPα-Fc-CD40L Outperformed CD47-Blocking and CD40-Activating Antibody Combinations in Vivo

CANCER IMMUNOLOGY RESEARCH

CD40 Enhances Type I Interferon Responses Downstream of CD47 Blockade, Bridging Innate and Adaptive Immunity

Suresh de Silva, George Fromm, Casey W. Shuptrine, Kellsey Johannes, Arpita Patel, Kyung Jin Yoo, Kaiwen Huang, and Taylor H. Schreiber





de Silva et al, Cancer Immunology Research, 2020

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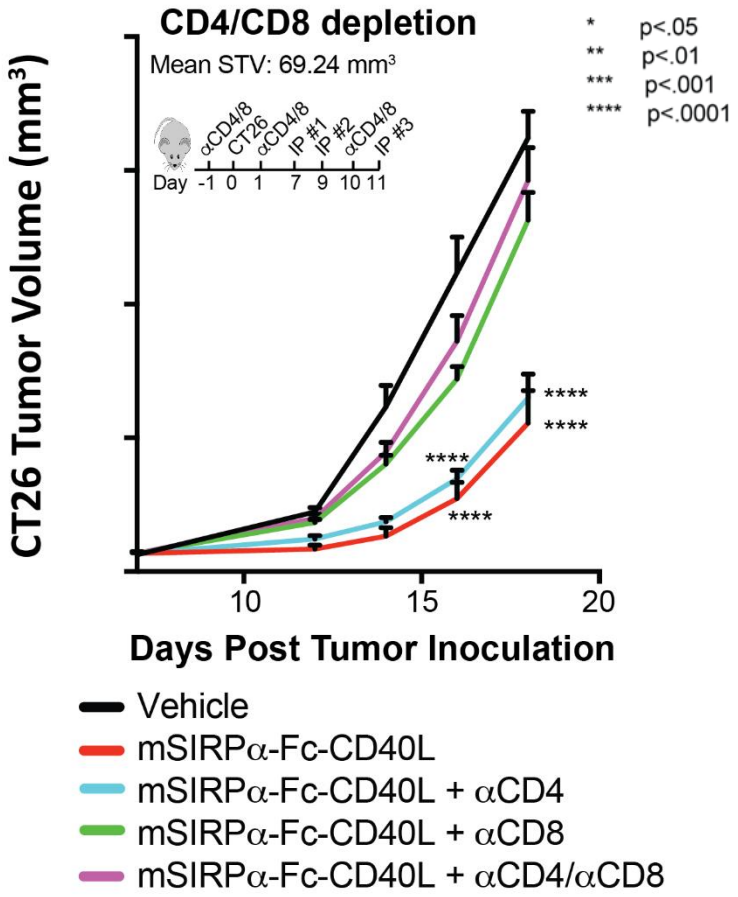
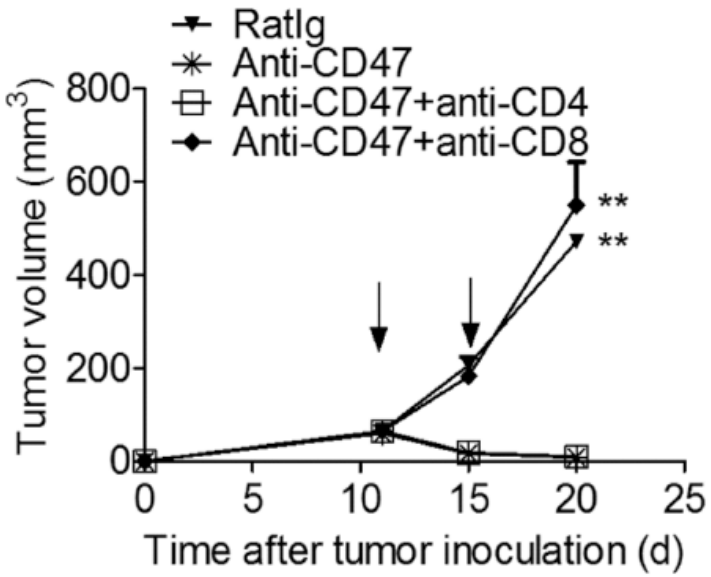
Anti-Tumor Activity of CD47 Blockade Depends on CD8+ T Cells



de Silva et al, Cancer Immunology Research, 2020

- CD47/SIRPα blockade is essential to increase macrophage-mediated phagocytosis of tumor cells
- However, macrophages must then process and present tumor antigens to CD8+ T cells
- In the absence of CD8+ T cells, CD47/SIRPα blockade did not reduce tumor growth in pre-clinical studies



Liu J *et al*. Nature Medicine 2015

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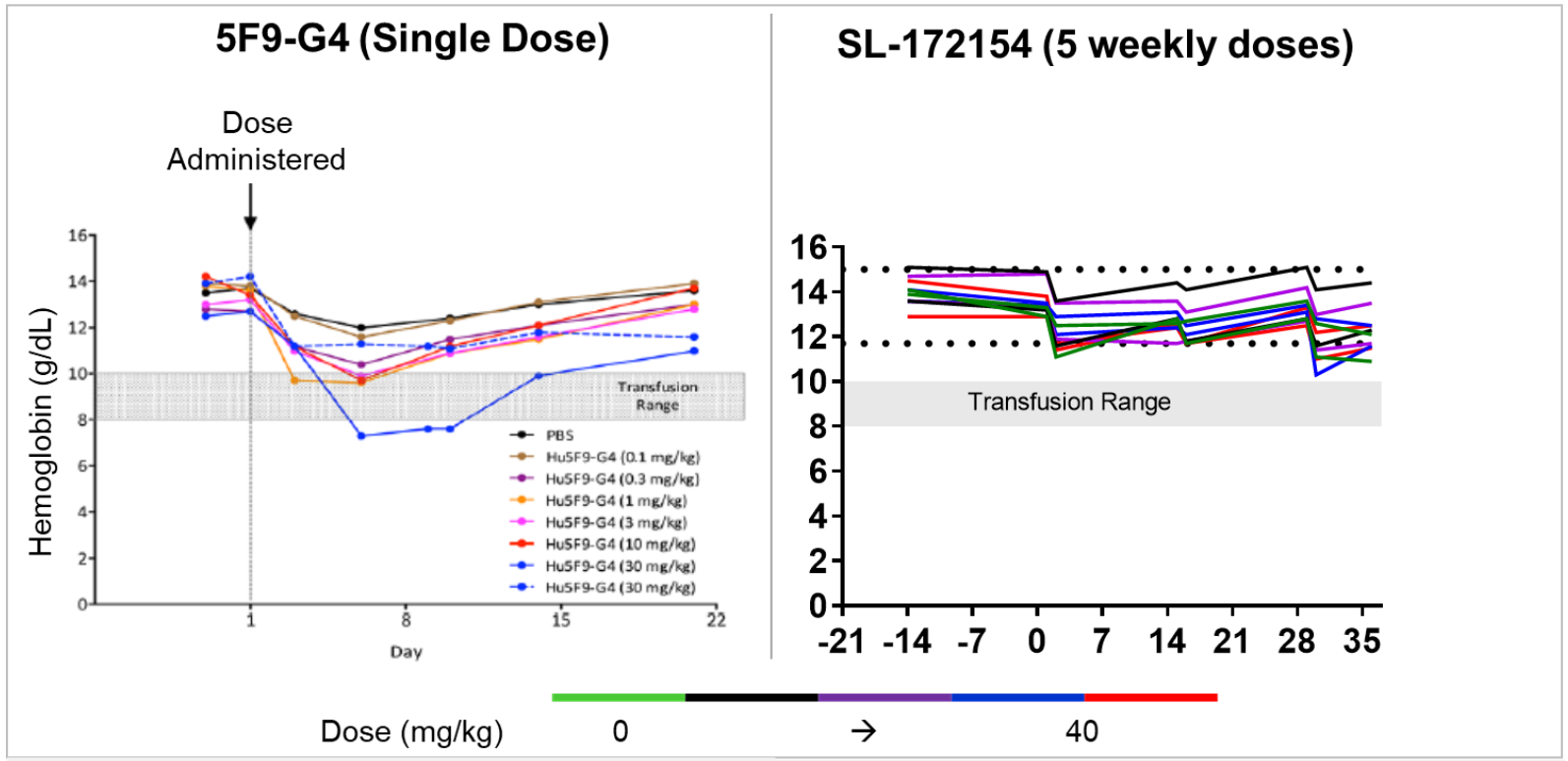
SL-172154 Demonstrated No Occurrence of Anemia in Preclinical Studies in Nonhuman Primates



FcR-competent CD47/SIRPα therapeutics can cause hemolysis/thrombocytopenia

With SL-172154, no evidence of hemolysis, thrombocytopenia, or liver enzyme elevation was observed

Note: The safety and tolerability of SL-172154 in preclinical studies in nonhuman primates appears to be comparable or better than data reported to date in preclinical studies in nonhuman primates of 5F9-54, despite more frequent dosing, although no head-to-head studies have been conducted.

NHP, Non-Human Primate

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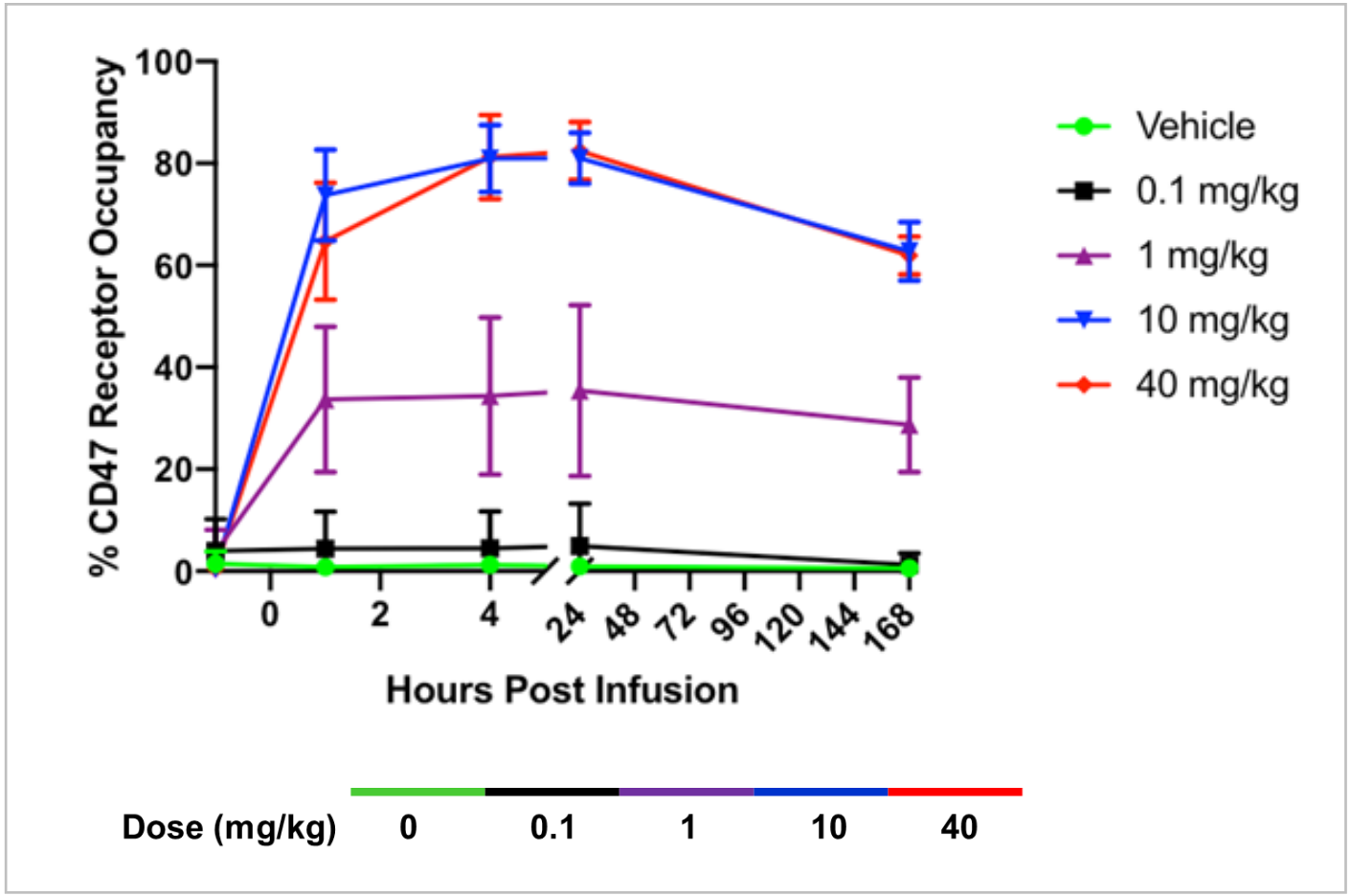
SL-172154 Demonstrated Durable CD47 Receptor Occupancy in Nonhuman Primates



- Durable receptor occupancy on RBC for >7 days post infusion
- Data are supportive of ≥ Q7D dosing

RBC, Red Blood Cell; Q7D, Every 7 Days

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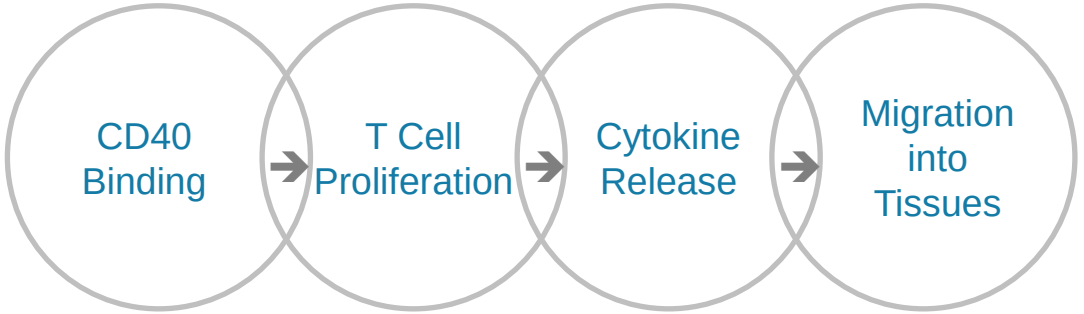
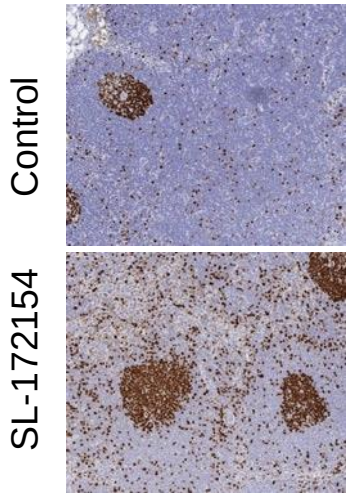
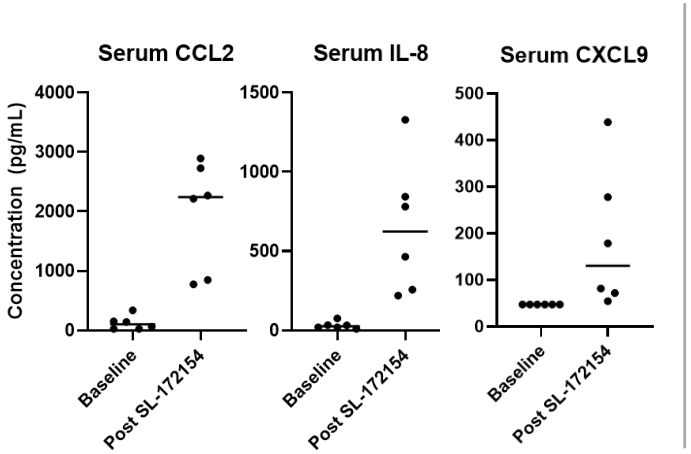
Evidence for Bridging Innate and Adaptive Immunity

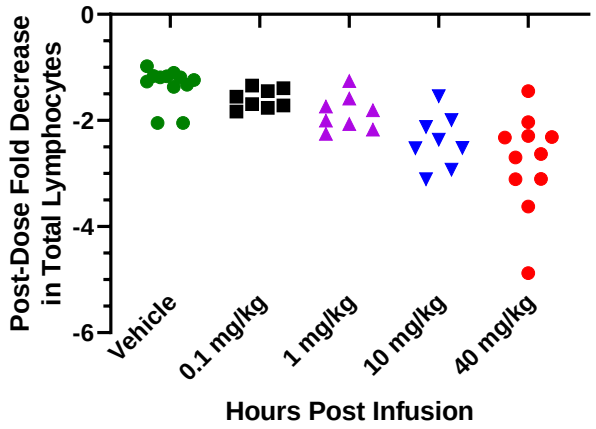
Preclinical Studies of SL-172154 (SIRPα-Fc-CD40L) in Nonhuman Primates



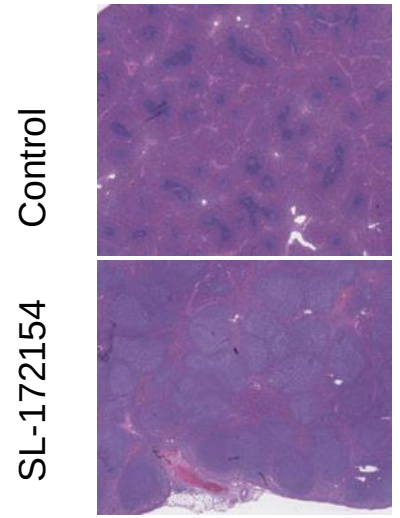


Brown (Ki67) Indicates Proliferation of Lymphocytes in Lymph Nodes





Dose-Dependent Serum Cytokine Release and Post-Dose Lymphocyte Decrease in the Blood



Expansion of Lymphoid Follicles in the Spleen

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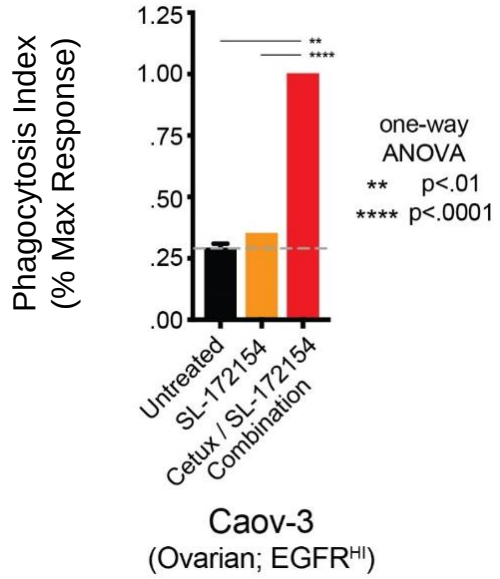
Rationale for SL-172154 In Ovarian Cancer

First-to-Market Opportunity in Ovarian

- Ovarian cancer has the highest expression of CD47 amongst solid tumors
- Pre-clinical studies showed SL-172154 significantly potentiated the activity of cetuximab in macrophage phagocytosis assays
- The lack of activity of cetuximab in ovarian cancer was possibly restrained by high expression of CD47
- Doxil is standard of care in ovarian cancer and stimulates upregulation of calreticulin on ovarian cancer

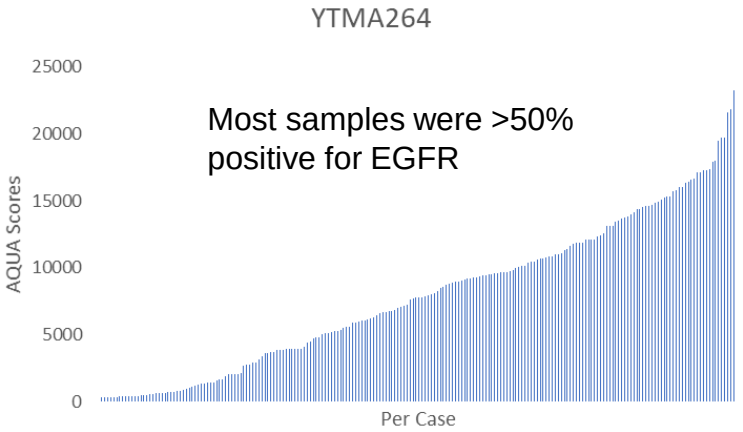
Synergy Observed Between SL-172154 and Targeted Antibodies

SL-172154 + anti-EGFR



Distribution of EGFR Expression in the Ovarian Cancer Tissue Microarrays

Array	Patient Samples (n)	Positive in Tumor (%)
OV20811a	199	155/198 (78)
OV20813	189	83/186 (44.6)
YTMA264	210	158/210 (75)



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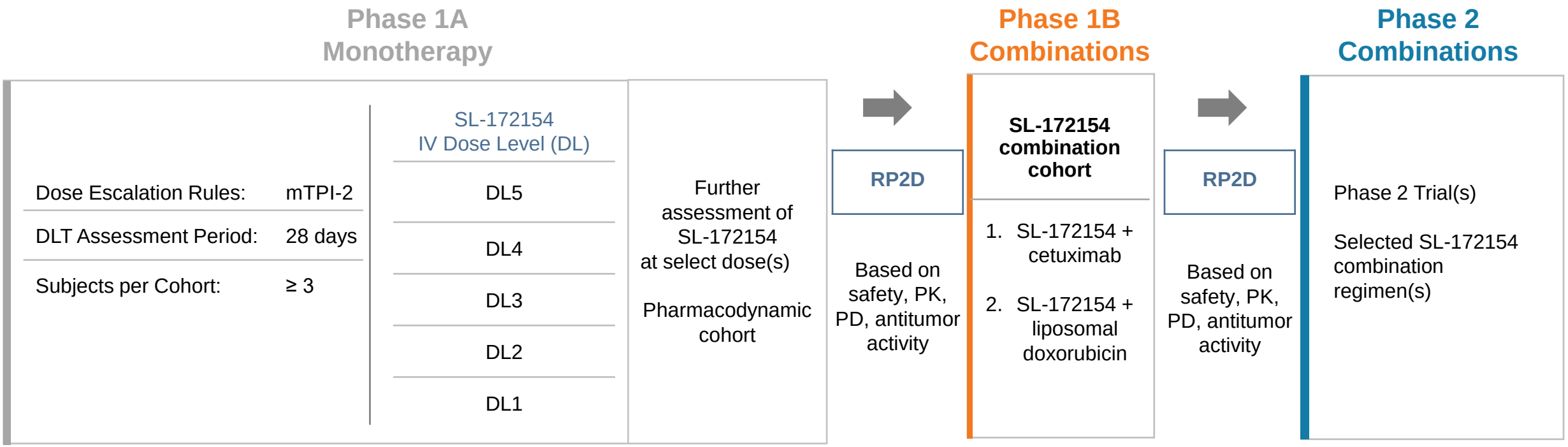
Initial Clinical Development Strategy for SL-172154 in Ovarian Cancer

Phase 1 Objectives and Tumor Types:

- **Primary:** Safety and tolerability of SL-172154 administered intravenously
- **Secondary:** RP2D, PK, immunogenicity and anti-tumor activity
- **Exploratory:** PD markers in blood and tumor
- **Tumor types:** Ovarian, fallopian tube, and primary peritoneal cancers



mTPI: modified toxicity probability interval method
DLT: Dose Limiting Toxicity

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SL-172154 Development Summary

SL-172154 Has Best-In-Class Potential Amongst CD47 Inhibitors

- Bridges both innate and adaptive immunity via CD40 activation
- Superior tumor rejection in pre-clinical models compared to combinations of CD47 and CD40 antibodies
- High affinity binding to CD47
- Durable receptor occupancy supportive of ≥ weekly dosing
- Effector-silent Fc domain significantly reduces the risk of anemias or thrombocytopenias

Two Active Phase 1 Clinical Trials

Ovarian Cancer

Intravenous infusion study

- High unmet medical need population
- Near-term combinations with ADCP-competent Abs
- Near-term combination with immunogenic chemotherapy

CSCC and HNSCC

Intra-tumoral injection study

- Path to clinical proof of concept
- Near-term combinations with ADCP-competent Abs
- Serial biopsies to define mechanism of action

Phase 2 Development Plan

- Development in hematological malignancy planned following dose-escalation study in ovarian cancer
- Parallel Phase 1 programs in multiple indications expected to provide comprehensive data package to inform registrational pathway for SL-172154

SHATTUCK LABS

Acknowledgements

George Fromm
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Thuy-Ai Nguyen
Fatima Rangwala




Thank you
SHATTUCK
LABS