

Preclinical Development of SL-172154 Demonstrates Translatable On-Target Pharmacodynamic Activity

Dr. George Fromm, PhD
Vice President of Research and Development, Shattuck Labs

NASDAQ: STTK

Macrophage-Directed Summit Company Presentation
September 29, 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 anticipated timing of our planned clinical trials, including timing of regulatory filings and initiation of additional cohorts, 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.

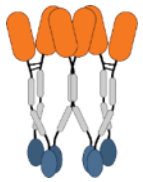
SHATTUCK LABS

Shattuck Labs Overview

Shattuck Labs (NASDAQ: STTK)

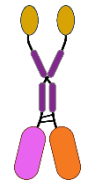
Clinical-stage biotechnology company pioneering the development of **bi-functional fusion proteins** designed to fundamentally **transform therapeutic immune modulation**

Next-Generation Fusion Protein Platforms



ARC Platform

- **> 400** unique bi-functional fusion proteins
- Checkpoint inhibition + Costimulatory pathway 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 WHOLLY OWNED PRODUCT CANDIDATE

Phase 1 trial ongoing for patients with Ovarian cancer
Phase 1 trial ongoing for patients with HNSCC/CSCC
Phase 1 trial planned for patients with AML/HR-MDS

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

- Highly experienced management team, board of directors, and scientific advisory board
- $304.8 million in cash, cash equivalents, and marketable securities as of June 30, 2021
- Expected cash runway through 2024 with multiple key clinical data readouts

Disclosure: George Fromm is an employee and shareholder of Shattuck Labs, Inc.

SHATTUCK LABS

Goal of the ARC Platform

Address the Structural Limitations of Antibody-Based Therapeutics

ARC Compounds Yield Structural Advantages

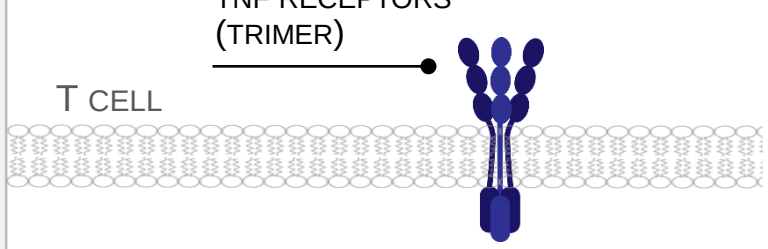
- Immune Checkpoint Blockade (e.g., PD-1, CD47, TIGIT)
- Costimulation of TNF Receptors (e.g., OX40, CD40, LIGHT, 4-1BB)
- Colocalization Within a Single Therapeutic

SHATTUCK LABS

Current Antibody Therapy Approaches Have Limitations

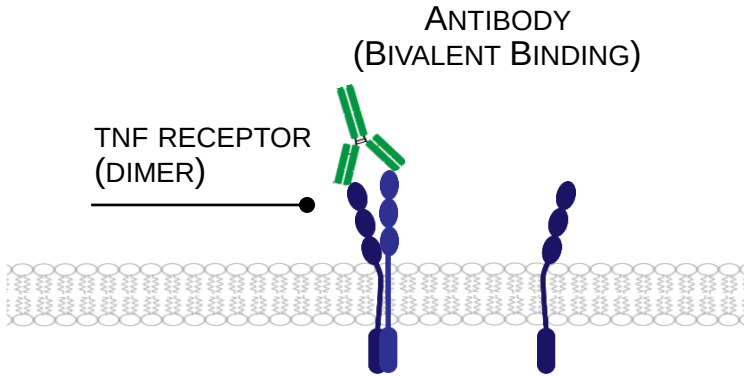
Bivalent Antibodies Cannot Efficiently Activate Trimeric Receptors

A.



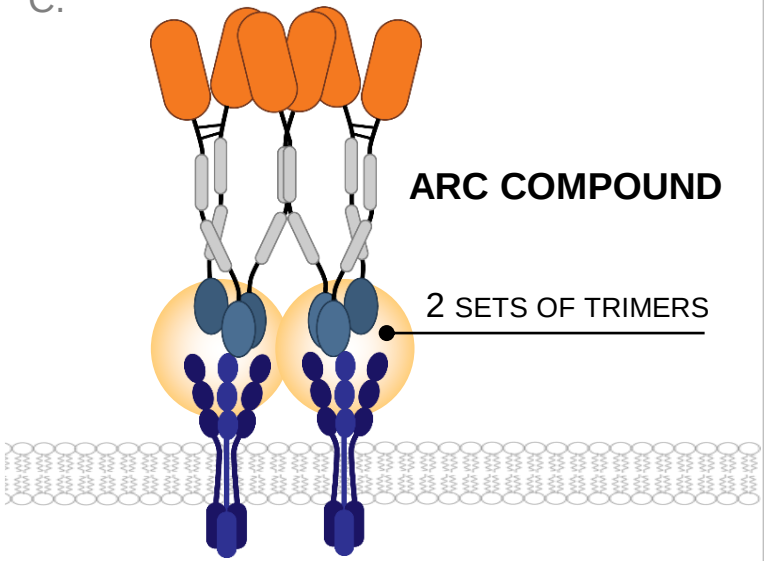
TNF receptors require trimerization for effective activation, and hexamers signal even more effectively than trimers[1]

B.



Bivalent antibodies cannot bring together TNF receptors to form a trimer due to a **structural mismatch**

C.



ARCs contain two preformed TNF ligand trimers, which match the requisite structure to efficiently **activate TNF receptor signaling**

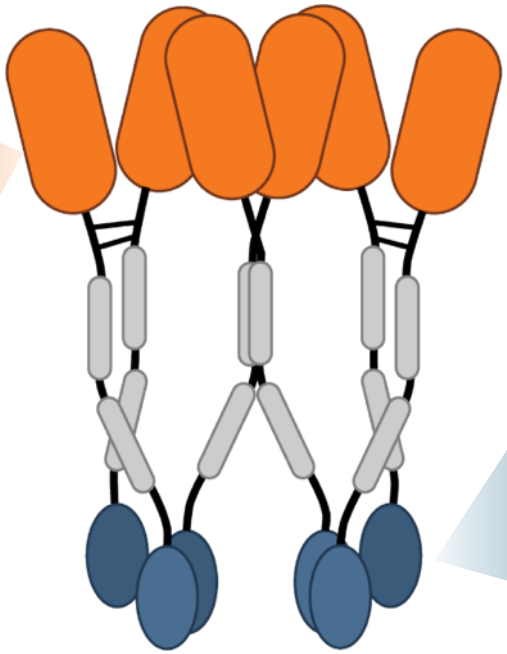
1. Vanamee E et al. *Science Signaling* Jan 2018

SHATTUCK LABS

ARC Platform Technology

Structural Advantages Allow for Unparalleled Modularity

Type 1 Membrane Proteins (>1,400 POTENTIAL TARGETS)	
Checkpoint Molecules + Cytokine Receptors	
SIRPα	TIM3
PD-1	KIR3DL3
TIGIT	FLT3L
VSIG8	Others....



Type 2 Membrane & Soluble Proteins (>450 POTENTIAL TARGETS)	
TNFSF Ligands + Cytokines	
CD40L	IL-2
OX40L	IL-12
LIGHT	IL-15
4-1BBL	Others....

➔ Shattuck has **produced over 400 bi-functional fusion proteins** to date

SHATTUCK LABS

Shattuck's Development Pipeline

Deep Pipeline of Scientifically Validated and Novel Targets

PLATFORM	PROGRAM	DOMAINS: DOMAIN 1	DOMAINS: DOMAIN 2	INDICATIONS	STAGE OF DEVELOPMENT	ANTICIPATED MILESTONES / STATUS	RIGHTS
CLINICAL-STAGE PIPELINE							
ARC	SL-172154	SIRPα	CD40L	Ovarian Cancer	Discovery / Preclinical / Phase 1	Initial Dose Escalation Data Q4'2021	SHATTUCK LABS
				CSCC and HNSCC (1)	Discovery / Preclinical / Phase 1	Initial Dose Escalation Data 1H'2022	SHATTUCK LABS
				AML and HR-MDS (2)	Discovery / Preclinical / Phase 1	IND Filing Expected Q4'2021	SHATTUCK LABS
	SL-279252	PD-1	OX40L	Advanced Solid Tumors and Lymphoma	Discovery / Preclinical / Phase 1 / Phase 2	Initial Dose Escalation Data Q4'2021	Takeda (3)
SELECT PRECLINICAL-STAGE PIPELINE							
ARC (4)	SL-9258	TIGIT	LIGHT	Oncology	Discovery / Preclinical	Manufacturing	SHATTUCK LABS
	SL-279137	PD-1	4-1BBL	Oncology	Discovery / Preclinical	Manufacturing	SHATTUCK LABS
	Multiple	Undisclosed		Autoimmune	Discovery / Preclinical	Non-Clinical Dev.	SHATTUCK LABS
GADLEN	Multiple	γδ TCR	Tumor Antigen	Oncology	Discovery / Preclinical	Lead Candidate Selection 2021	SHATTUCK LABS

(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
(3) Takeda holds an exclusive option to license SL-279252
(4) Nomination of 3rd ARC compound to clinical-stage pipeline anticipated in 2H'2021

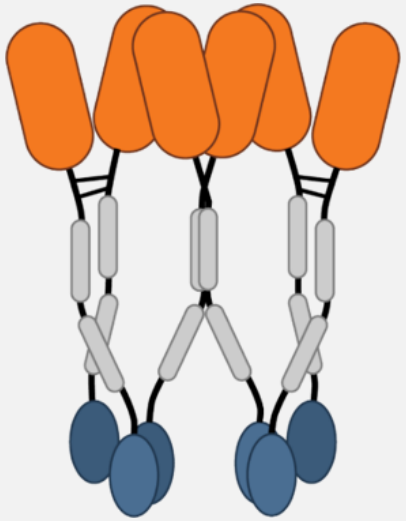
SHATTUCK LABS

SL-172154: Novel CD47 Inhibitor + CD40 Agonist

Rationally Designed to Maximize the Benefits of CD47 Blockade

1. High Affinity and Avidity CD47 Binding	Inhibition of CD47/SIRPα interaction**, potentiates phagocytosis of tumor cells**
2. Inert Fc Domain	Designed to reduce binding activity, **no hemolysis or thrombocytopenia in NHP**
3. Activation of CD40 pathway	Enhances antigen cross presentation, **leads to T cell activation, bridging innate and adaptive immunity**
4. Combination Opportunities	**May be combined** with targeted antibodies or immunogenic chemotherapy

SL-172154
(SIRPα-Fc-CD40L)



6 SIRPα Binding Domains:
Blocks “Don’t Eat Me” CD47 Signal

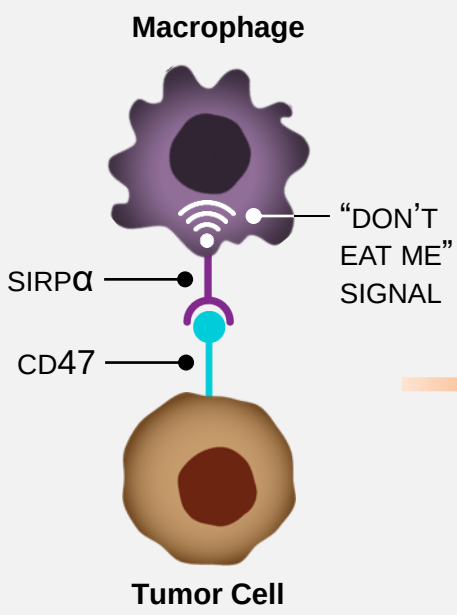
Inert IgG4 Fc

2 CD40L Trimers:
Provides CD40 Stimulation to Antigen Presenting Cells

SHATTUCK LABS

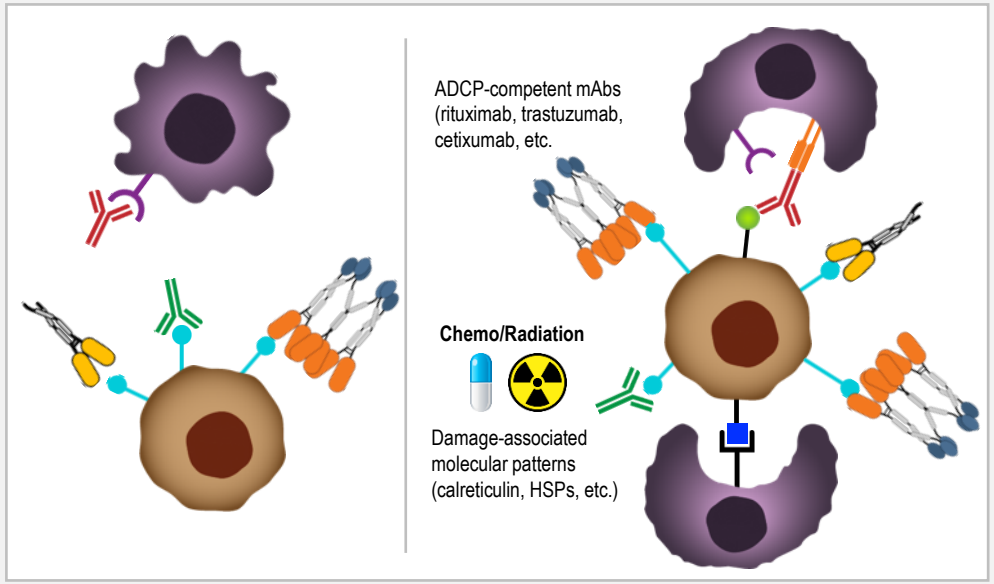
Pairing Rationale For SL-172154

Dual Mechanism: CD47 Checkpoint Blockade and CD40 TNF Activation



Tumor cells ward off macrophages using CD47

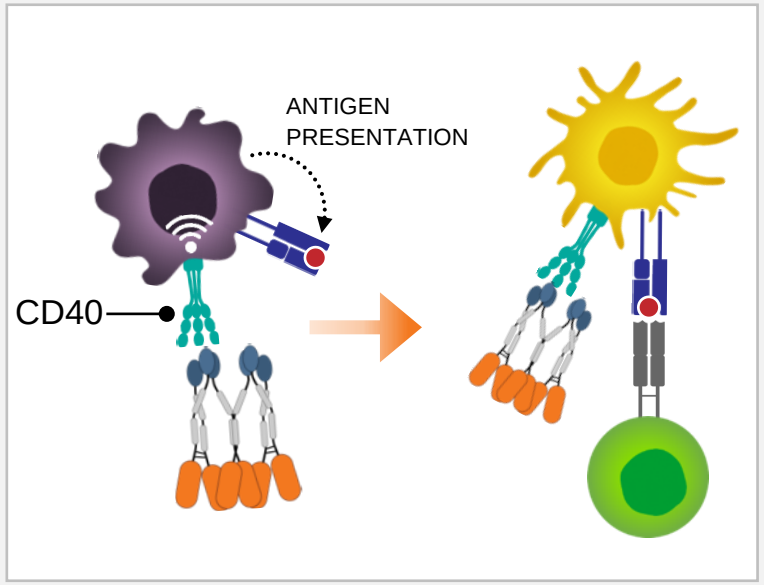
All CD47/SIRPα inhibitors



CD47/SIRPα inhibitors block the CD47 "don't eat me" signal

Phagocytic signals (induced by chemo/radiation or provided by tumor-targeted mAbs) are required to stimulate phagocytosis

Only SL-172154



CD40 stimulation facilitates antigen processing and presentation following phagocytosis of tumor cells

CD40-activated macrophages cross-present phagocytosed tumor antigens to T cells

CD47 inhibitors with active FC domains:

✗ Sporadic monotherapy activity

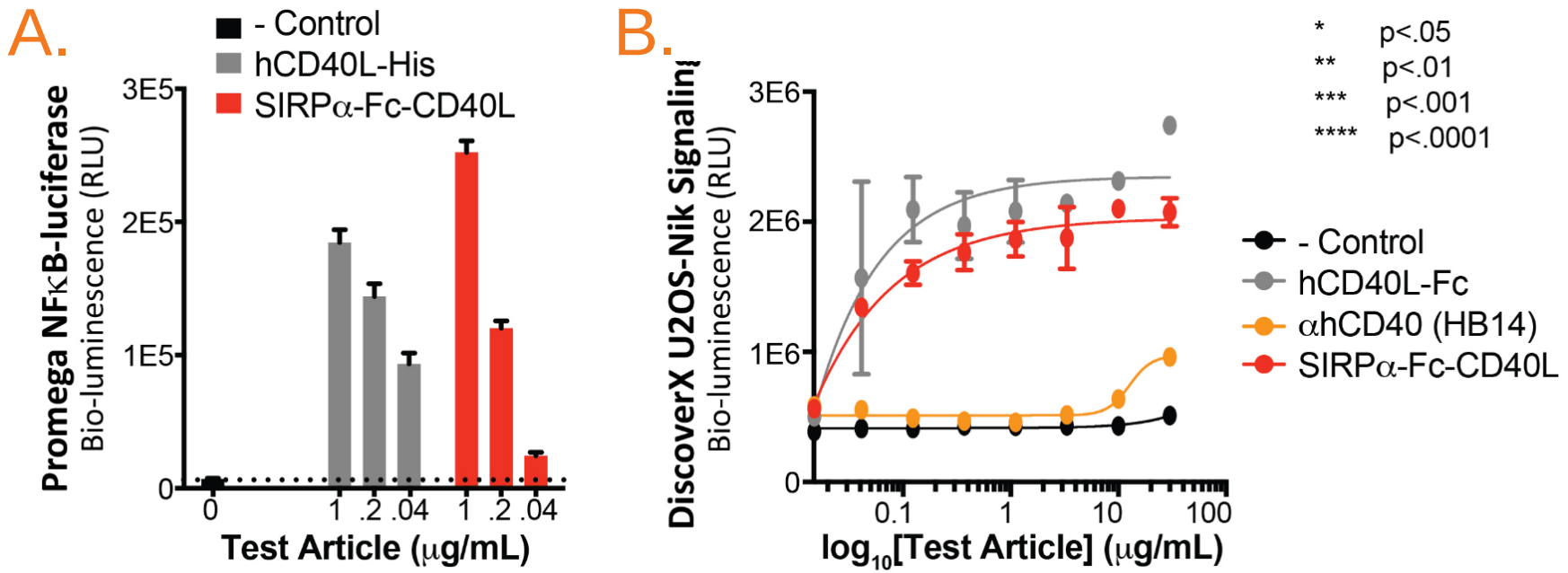
✗ Consistent toxicity & cytopenias

CD47 / SIRPα Inhibitors						
CD 47 mAb (i.e. magrolimab, lemzoparlimab)	SL-172154	SIRPα	DAMP receptor (i.e. Calreticulin receptor)	Fc receptor	CD40	Tumor antigen (i.e. CD20)
SIRPα-Fc (i.e. TTI-662, ALX-148)	Tumor-targeted mAb (i.e. rituximab, etc.)	CD47	DAMP (i.e. Calreticulin)	MHC1		TCR /antigen

de Silva et al, *Cancer Immunology Research*, 2020

SHATTUCK LABS

SL-172154 Potently Stimulated CD40 Signaling

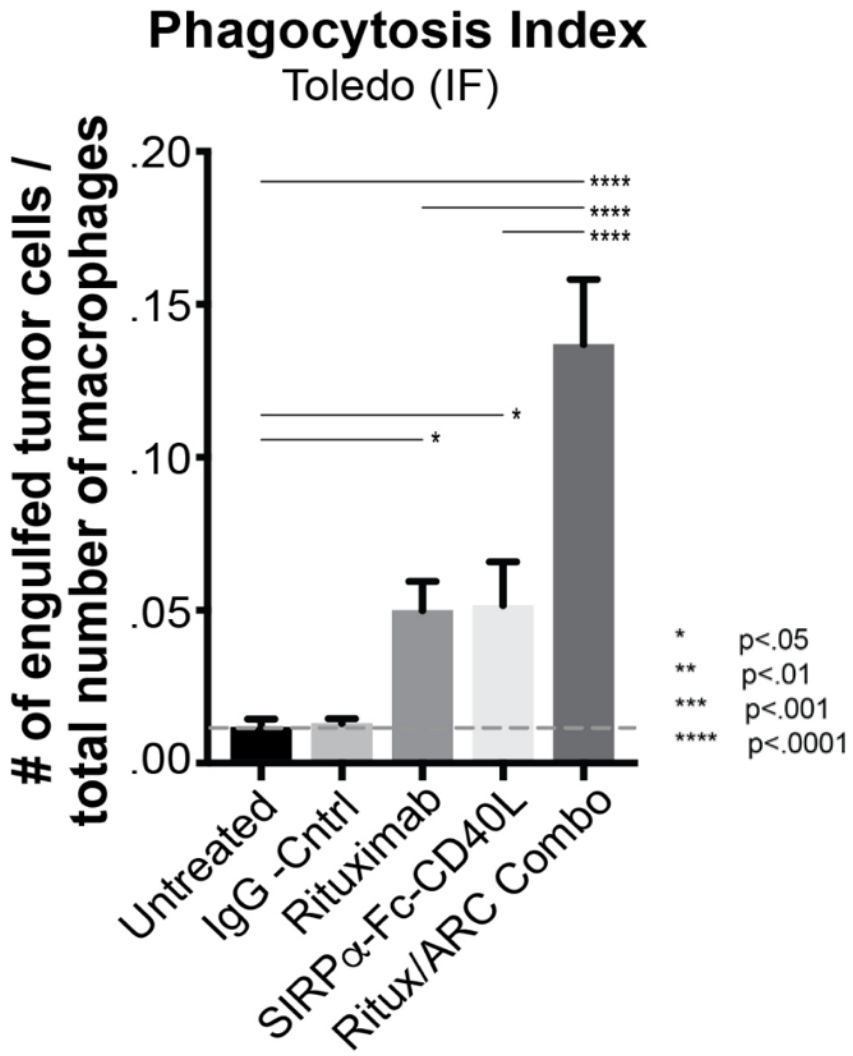


A. Both recombinant CD40L and SL-172154 stimulated dose-dependent **activation of the canonical NFκB pathway**

B. Recombinant CD40L and SL-172154, but not CD40 antibodies, stimulated dose-dependent **activation of the non-canonical NFκB pathway**

SHATTUCK LABS

SL-172154 Potentiated Tumor Phagocytosis and Macrophage Activation

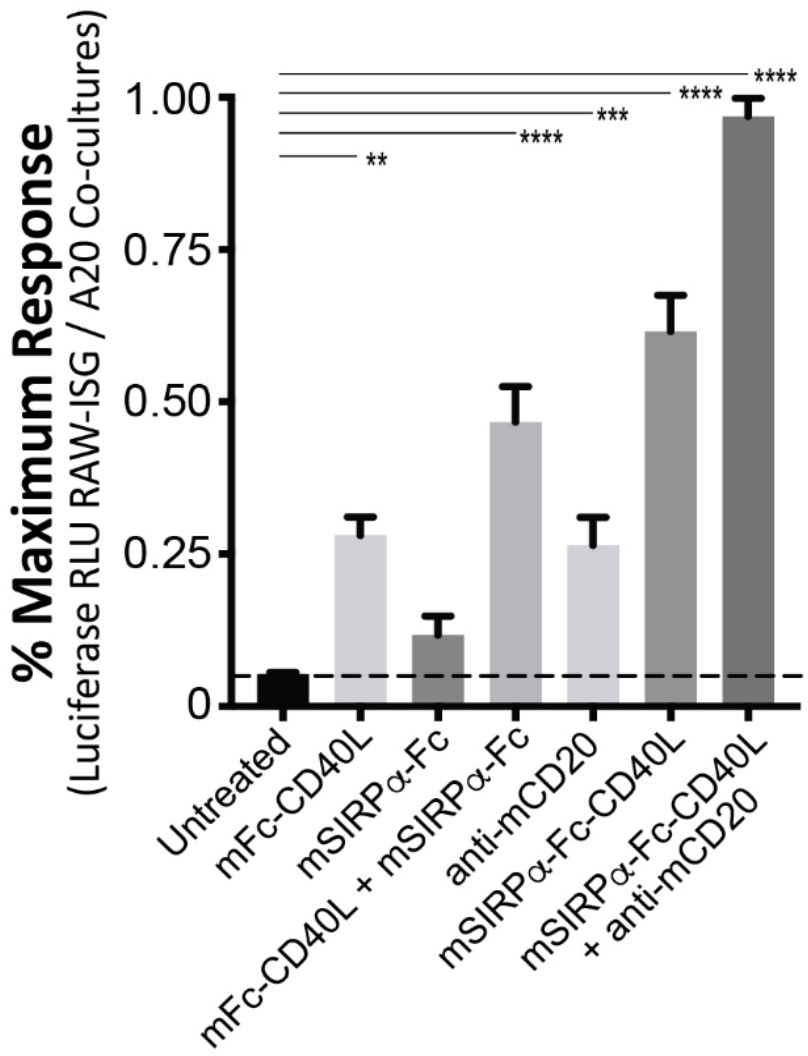


- SL-172154 induces phagocytosis of solid and hematological tumors and is potentiated with other targeted agents (i.e. Rituximab, Cetuximab, and Trastuzumab

de Silva et al, Cancer Immunology Research, 2020

SHATTUCK LABS

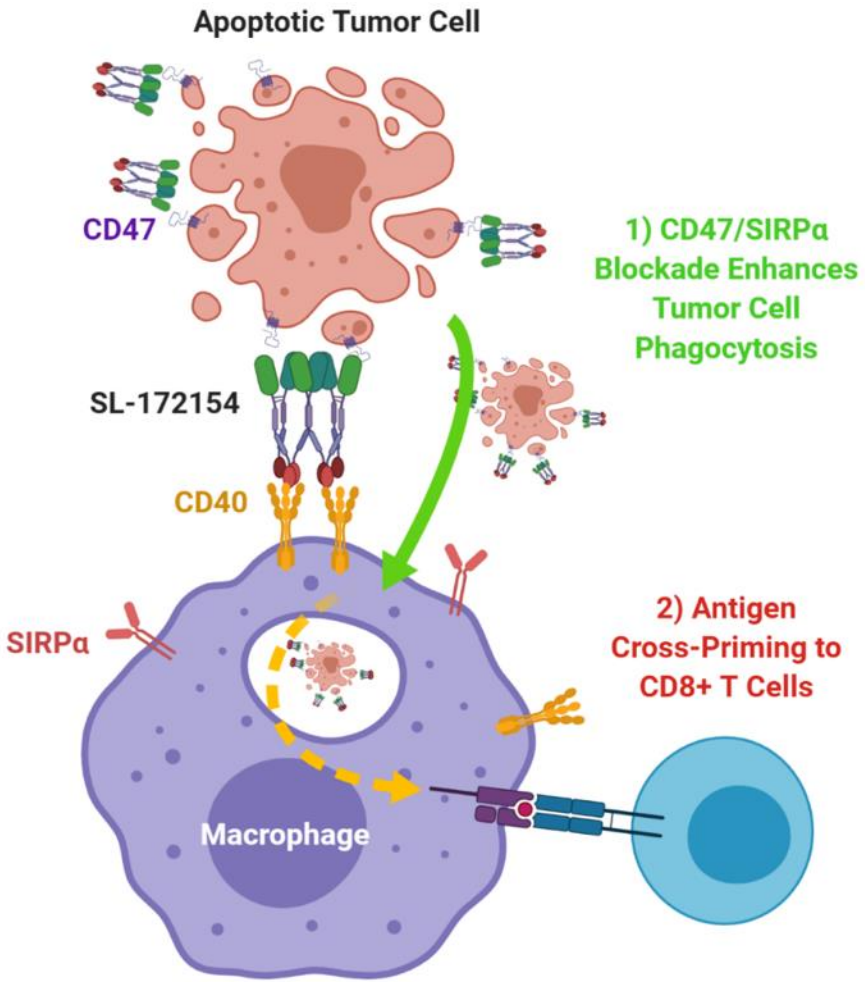
SL-172154 Amplified Type I Interferon Signaling



- 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

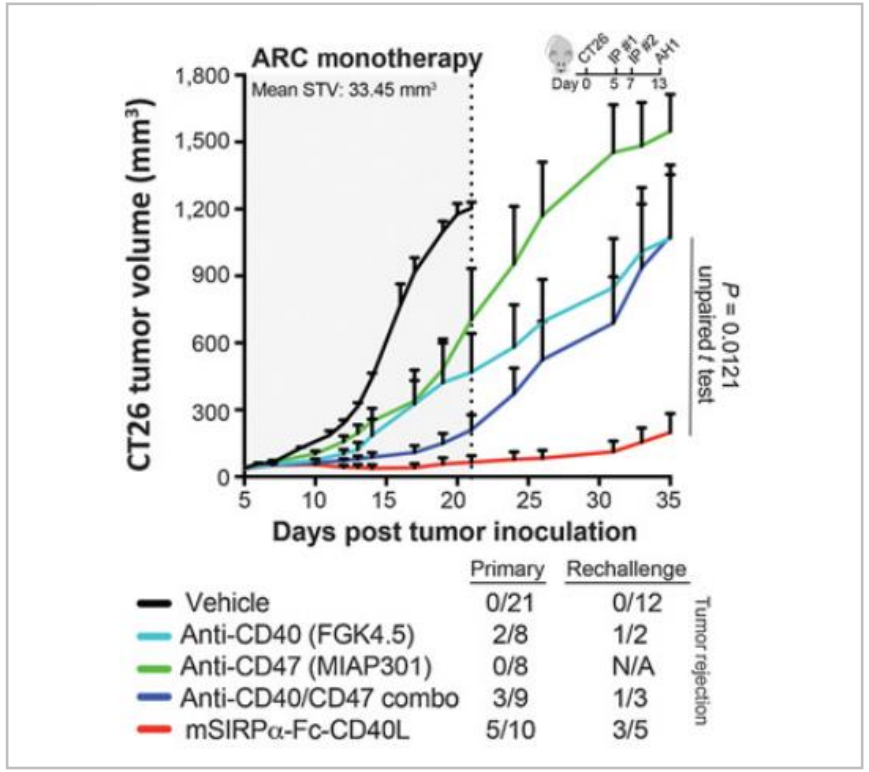
SHATTUCK LABS

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



CANCER IMMUNOLOGY RESEARCH

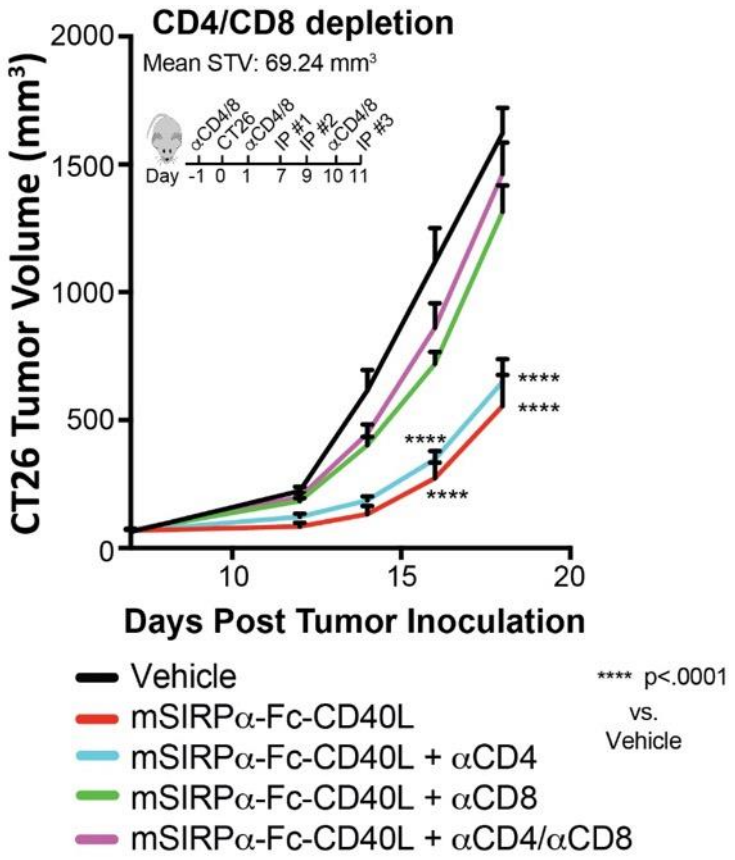
CD40 Enhances Type I Interferon Responses Downstream of CD47 Blockade, Bridging Innate and Adaptive Immunity



de Silva et al, Cancer Immunology Research, 2020

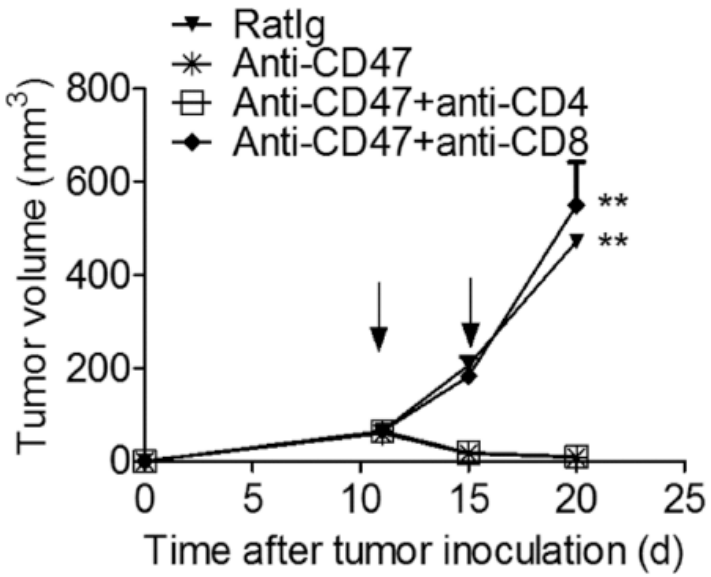
SHATTUCK LABS

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



de Silva S *et al*. Cancer Immunology Research 2020

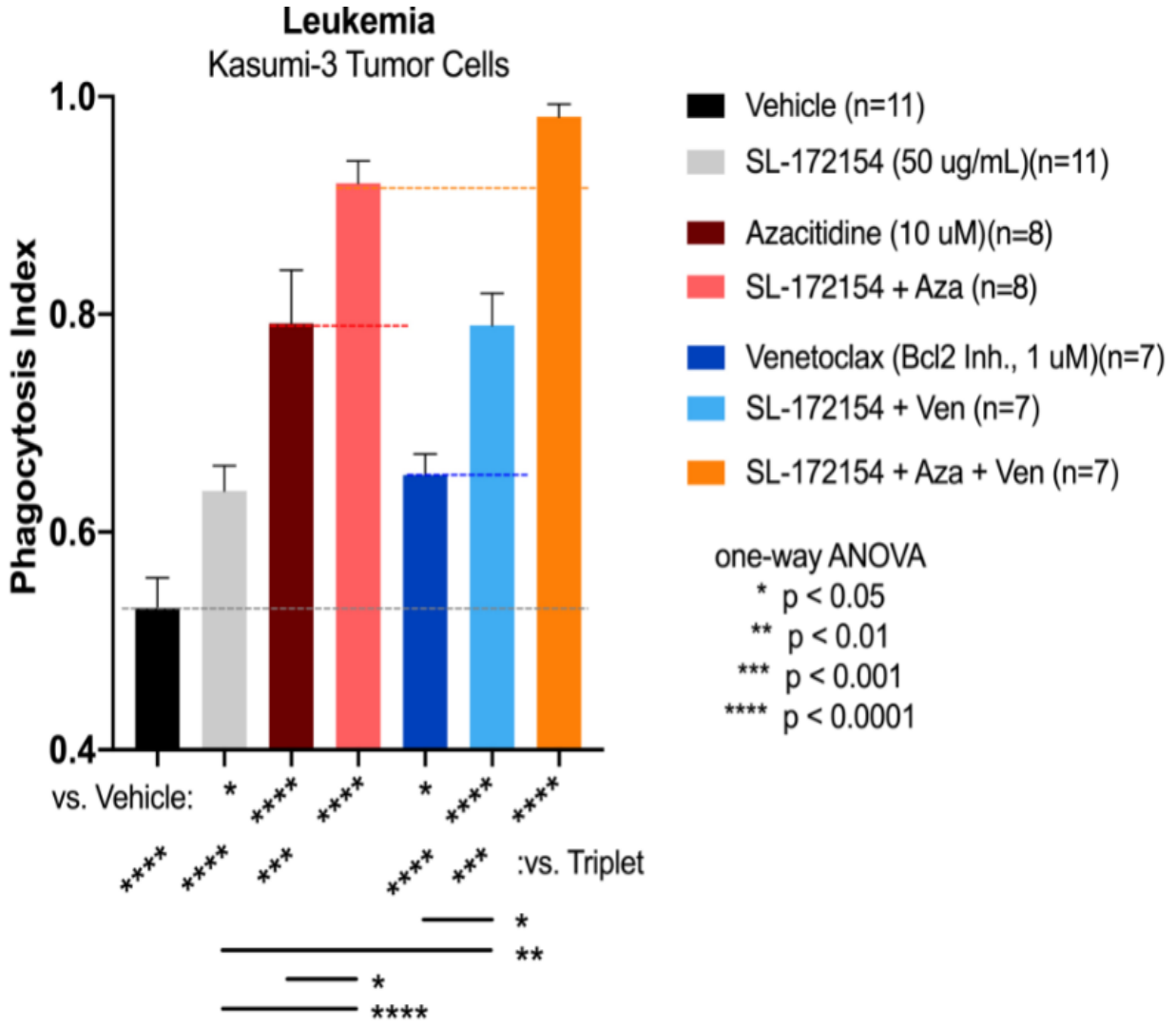
- CD47/SIRPα blockade is essential to increase macrophage-mediate phagocytosis of tumor cells
- However, macrophages must then process and present tumor antigens to CD8+ T cells
- In the absence of CD8+ T cells, CD47/SIRPα blockade did not reduce tumor growth in pre-clinical studies



Liu J *et al*. Nature Medicine 2015

SHATTUCK LABS

Pre-Clinical Data Confirmed CD47 Inhibition

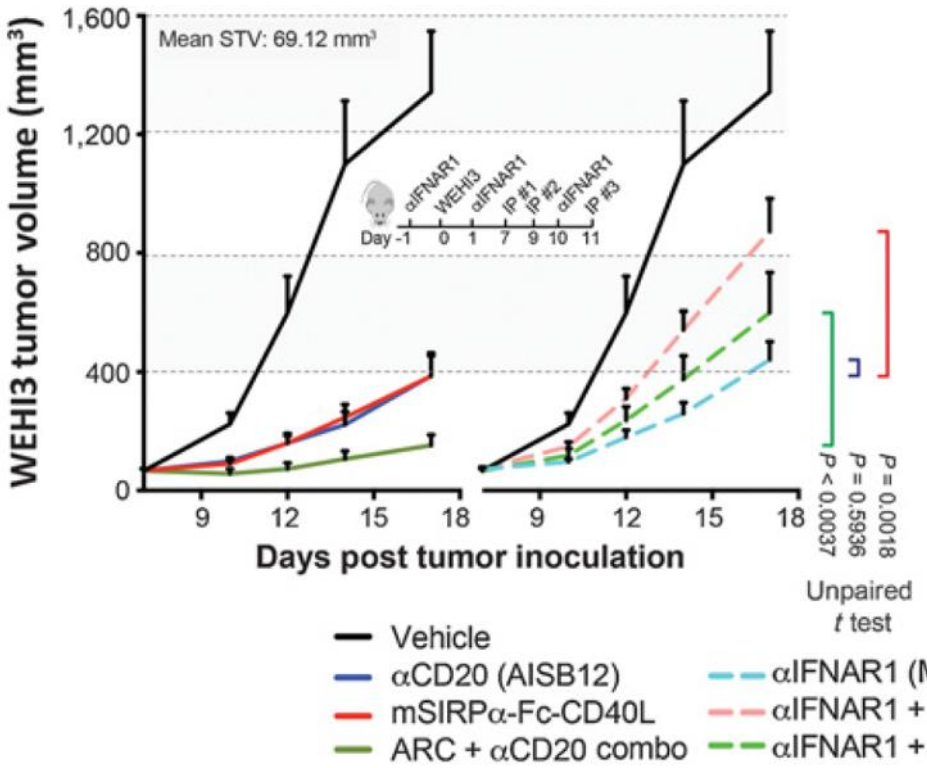


- SL-172154 potentiated macrophage phagocytosis of tumor cell lines alone and in combination with azacitidine and/or venetoclax

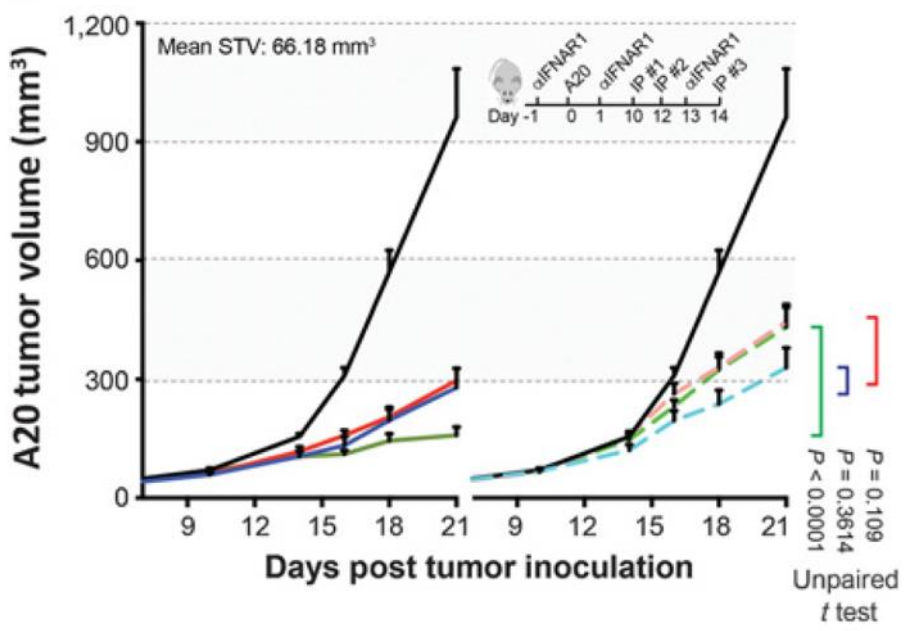
SHATTUCK LABS

SIRPα-Fc-CD40L *in vivo* Activity in Preclinical Models of Leukemia and Lymphoma

WEHI3 Leukemia



A20 Lymphoma



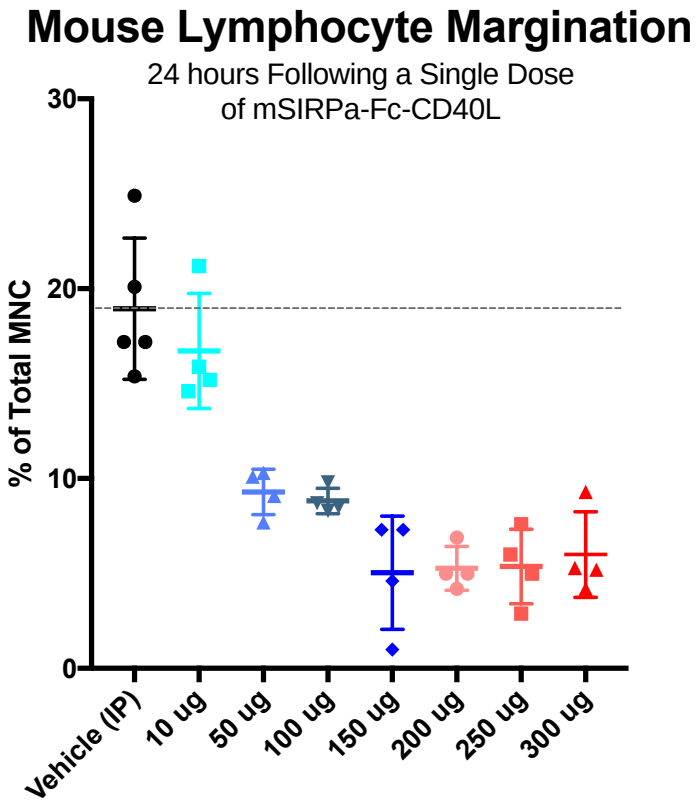
- Vehicle
- αCD20 (AISB12)
- mSIRPα-Fc-CD40L
- ARC + αCD20 combo
- αIFNAR1 (MAR1-5A3) + αCD20
- αIFNAR1 + mSIRPα-Fc-CD40L
- αIFNAR1 + ARC + αCD20 combo

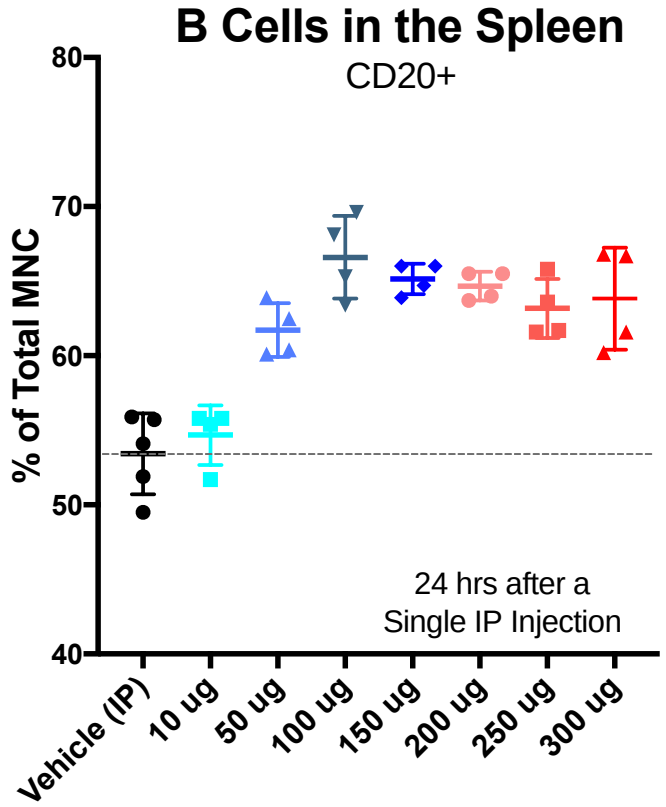
➔ SIRPα-Fc-CD40L controls leukemia/lymphoma tumor growth alone and in combination with anti-CD20

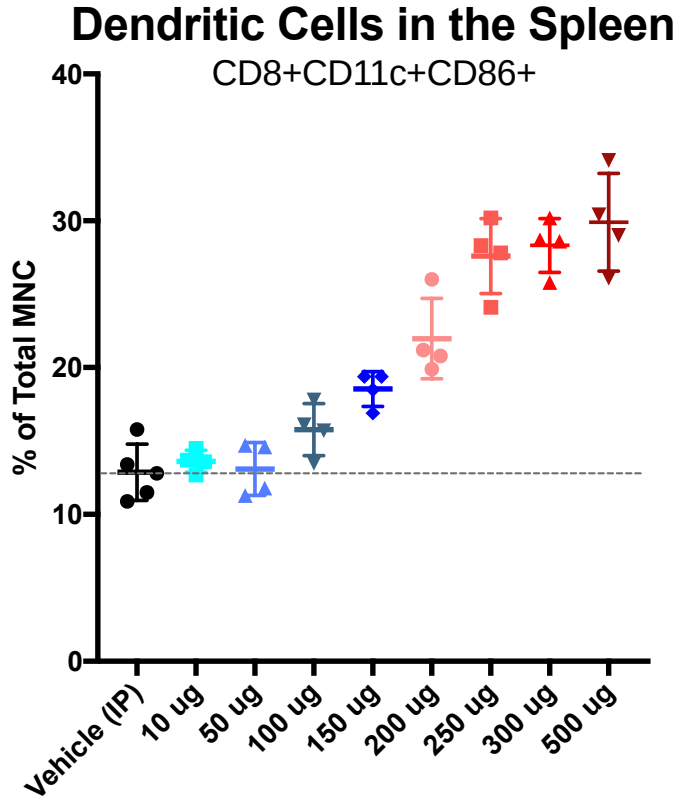
➔ SIRPα-Fc-CD40L activity is dependent on type I interferon response (IFNAR1)

SHATTUCK LABS

Leukocyte Margination





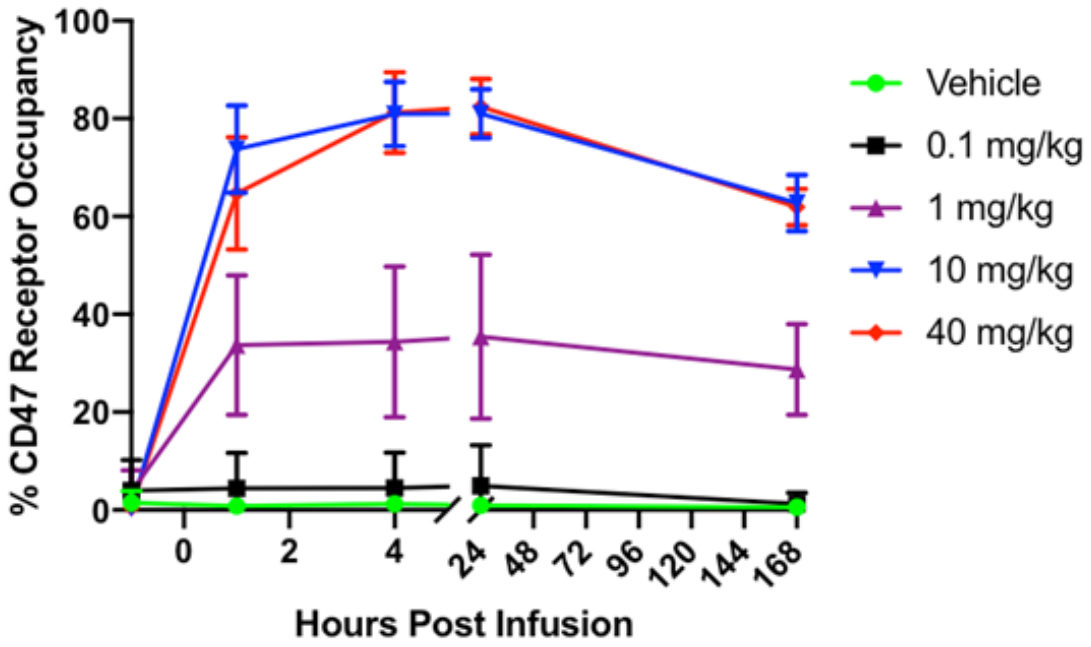


➔ Activated CD40+ leukocytes marginate from the periphery to secondary lymphoid tissues

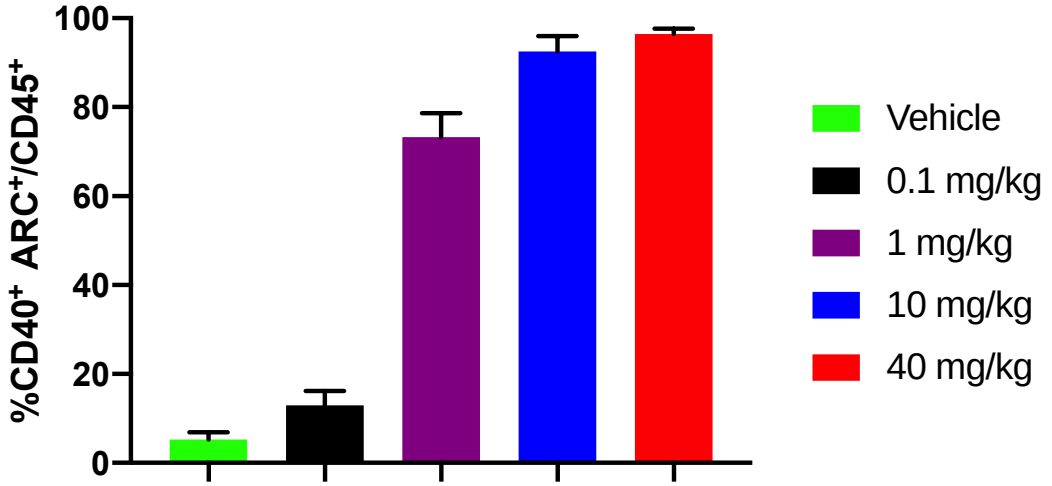
SHATTUCK LABS

Non-Human Primate Receptor Occupancy

% CD47 Receptor Occupancy



Peak CD40 Receptor Occupancy



➔ Dose-dependent saturation of CD40 and CD47 receptors

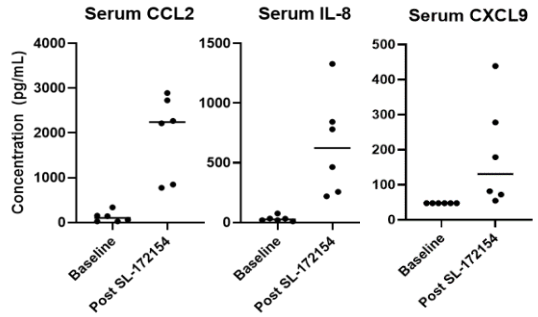
NHP, Non-Human Primate

SHATTUCK LABS

Evidence for Bridging Innate and Adaptive Immunity

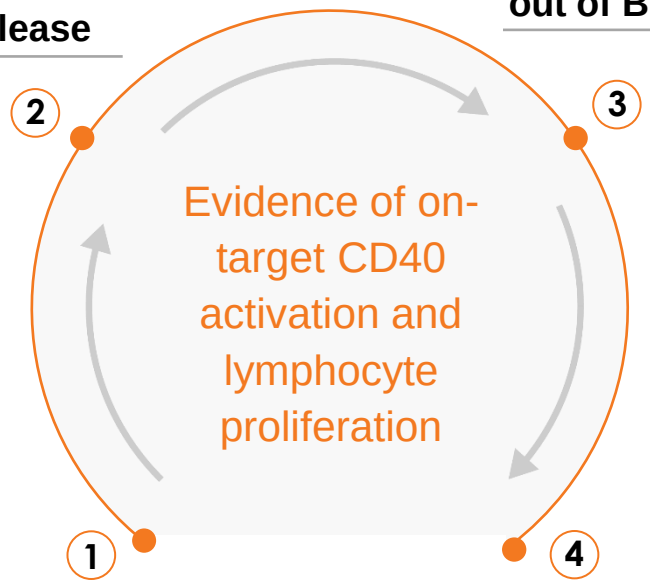
Preclinical Studies of SL-172154 (SIRPα-Fc-CD40L) in Nonhuman Primates

Dose-Dependent Serum Cytokine Release

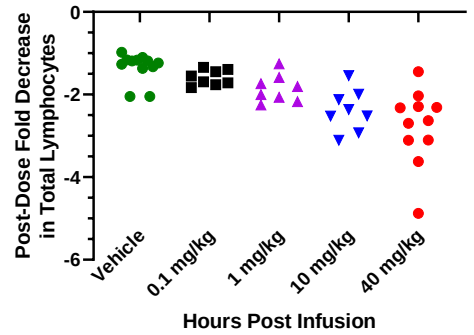


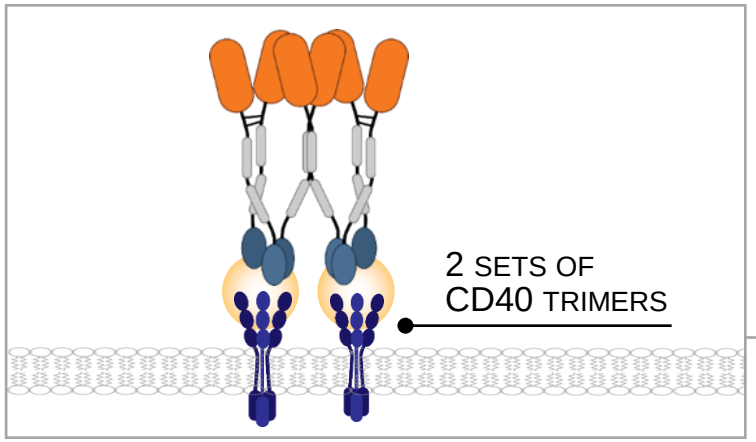
Cytokine Release

Migration out of Blood



Lymphocyte Decrease in the Blood



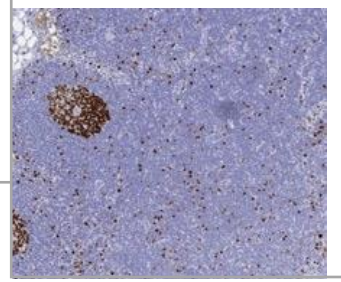


CD40 Binding

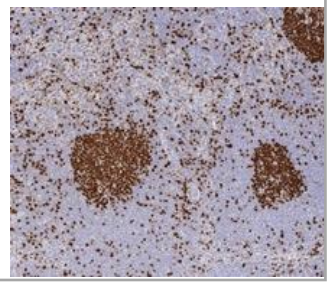
Accumulation & Proliferation in Specific Tissues

Brown (Ki67) Indicates Proliferation of Lymphocytes in Lymph Nodes (below) and Spleen (not shown)

Control



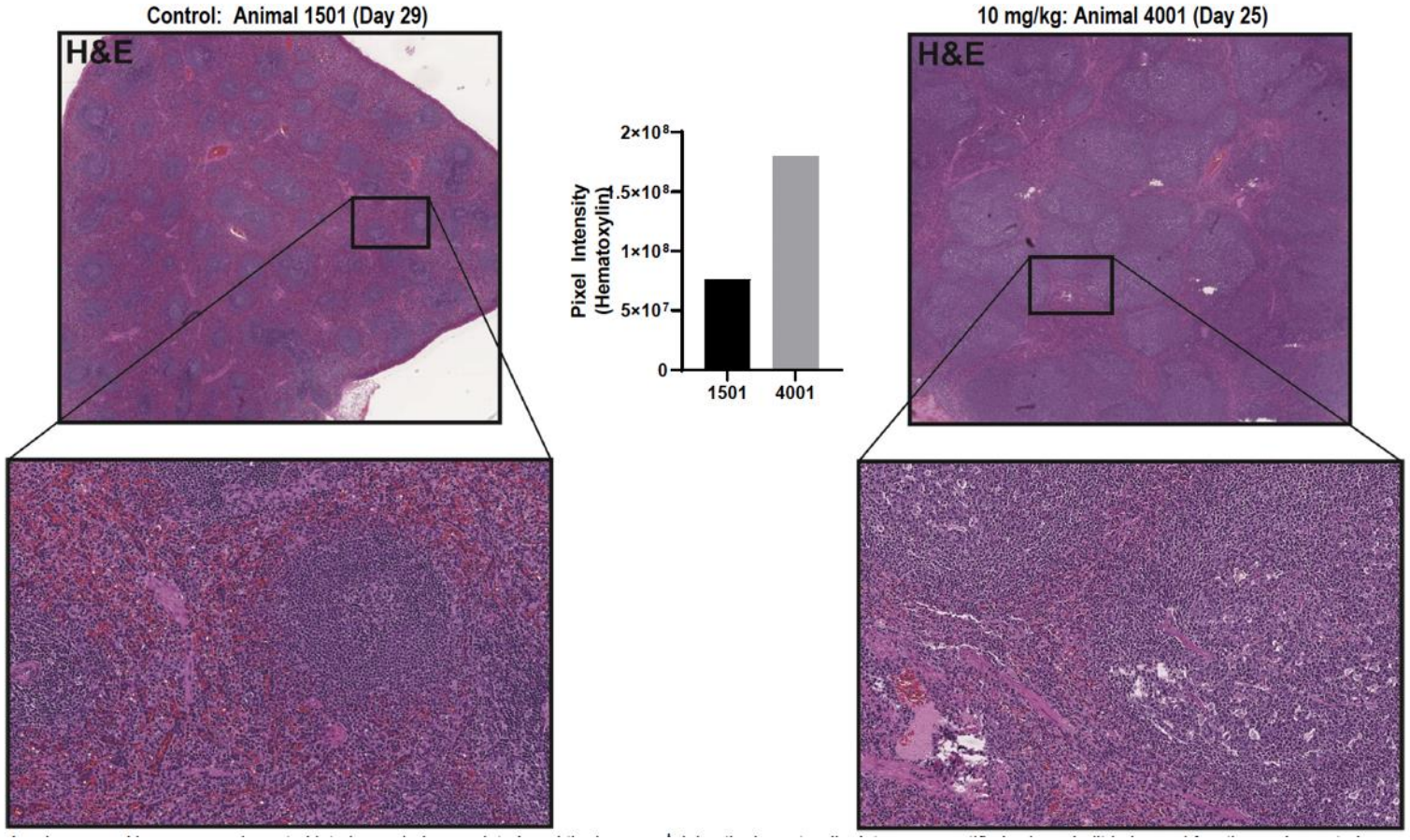
SL-172154



SHATTUCK LABS

Non-Human Primate Lymphocyte Margination

Accumulation of proliferating lymphocytes in secondary lymphoid tissues



Photomicrographs of the Spleen (H&E Stained) at Necropsy

NHP, Non-Human Primate

SHATTUCK LABS

SL-172154 Clinical Development Strategy

Multiple Shots on Goal in Combination

PHASE 1A Monotherapy (IV)
Platinum resistant ovarian, fallopian tube and primary peritoneal cancers

Dose Escalation Rules:	**mTPI-2**
DLT Assessment Period:	**28 days**
Subjects per Cohort:	**≥ 3**
PD Cohort	**~ 6**

SL-172154
IV Dose Level (DL)

- DL5 - 10.0 mg/kg
- DL4 - 3.0 mg/kg
- DL3 - 1.0 mg/kg
- DL2 - 0.3 mg/kg
- DL1 - 0.1 mg/kg

Immunologically active dose

PHASE 1B
Combinations

- **Ovarian Cancer** → SL-172154 Combos (Disclosed 4Q 2021)
- **MDS / TP53 AML AML** → SL-172154 + azacitidine; SL-172154 + azacitidine + venetoclax
- **Other Indications** → SL-172154 Combos

PHASE 1A Monotherapy (ITI)
Cutaneous squamous cell carcinoma (CSCC), head and neck SCC (HNSCC)

SHATTUCK LABS

SL-172154: Differentiation in Emerging Safety Profile

Avoidance of Traditional CD47 Inhibition and CD40 Agonism Toxicities

Candidate	SL-172154	Common CD47 Toxicities	Common CD40 Toxicities
Infusion Related Reactions (chills, rigors, rash, nausea, fever, etc.)	✓ (Grade 1-2 through 3 mg/kg*)	✓ (Grade 1-2 through > 10 mg/kg)	✓ (Grade ≥3 at ≥0.6 mg/kg)
Cytokine Release Syndrome	✗	✗	✓
Anemia	✗	✓	✗
Thrombocytopenia	✗	✓	✓
Liver Dysfunction (AST/ALT/bilirubin elevations)	✗	✗	✓

➔ Dosing 10-fold higher than CD40 antibodies due to hexameric structure of ARC, technology allows for clinical exploration of CD40 with fundamentally new approach

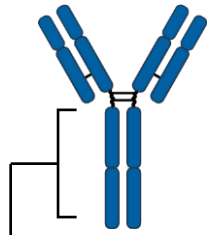
*Shattuck is currently enrolling patients in the DL3, or 3 mg/kg, cohort
Emerging profile of SL-172154 supports continued dose escalation

SHATTUCK LABS

CD47/SIRPα Development Landscape

All Current Competitor Registrational Strategies Are in Combination

CD47 Inhibitors



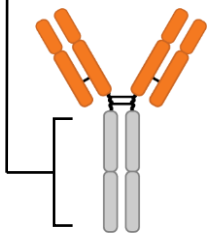
GILEAD	TRILLIUM THERAPEUTICS INC.	I-MAB BIOPHARMA	arch oncology
IgG4	IgG1 / IgG4	IgG4	IgG2
Magrolimab	TTI 622/621	TJC4	AO-176

1 Competent Fc

2 approaches;
1 development track

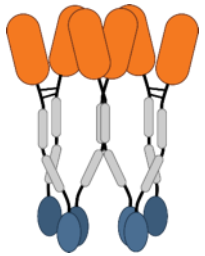
2 Inert Fc

REGISTRATION IN COMBINATION



CD47 Inhibitors

ALX ONCOLOGY	SHATTUCK LABS
Inert IgG1	Inert IgG4
ALX148	



SL-172154
(SIRPα-Fc-CD40L)

CD47 Axis Registrational Strategies are in Combination		
ADCP and/or ChemoTx		
Doxorubicin	Azacitidine	Venetoclax
Rituximab	Carfilzomib	Cetuximab
Trastuzumab	Others…	

SHATTUCK LABS

SL-172154 Development Summary

Potential Best-In-Class CD47 Inhibitor

- 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

Squamous Cell Carcinoma of the Head & Neck
Intra-tumoral injection study

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

Phase 2 Development Plan

- IND filing in AML/HR-MDS expected Q4’2021
- Expansion into combinations in ovarian, HNSCC, and CSCC
- Multiple parallel phase 1 programs in several indications expected to inform registrational pathway

SHATTUCK LABS



Acknowledgements

Jaya Miriyala
Kyung Jin Yoo
Arpita Patel
Casey Shuptrine
Kellsey Johannes
Zach Opheim
Louis Gonzalez
Thuy-Ai Nguyen
Karen Lenz
Suresh de Silva
Conor Richardson
Fatima Rangwala
Lini Pandite
Taylor Schreiber


Thank you
SHATTUCK
LABS