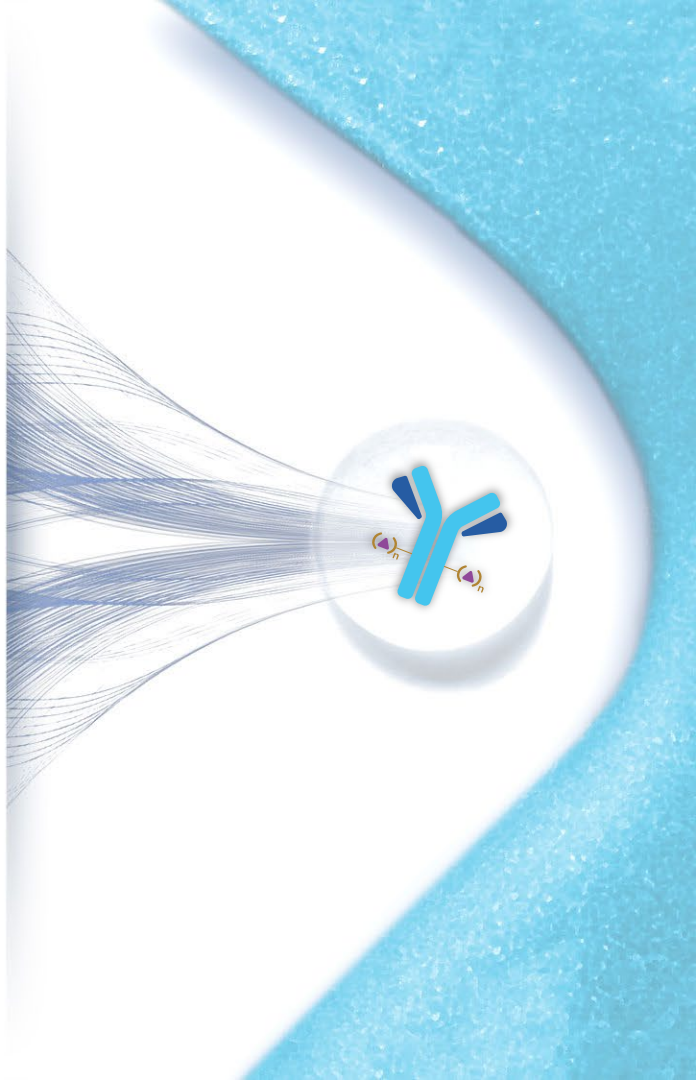
Mersana THERAPEUTICS

Immunosynthen: STING-Agonist ADC Platform

November 16, 2020



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Forward-looking statements generally can be identified by terms such as “aims,” “anticipates,” “believes,” “contemplates,” “continues,” “could,” “estimates,” “expects,” “goal,” “intends,” “may,” “on track,” “plans,” “possible,” “potential,” “predicts,” “projects,” “seeks,” “should,” “target,” “will,” “would” or similar expressions and the negatives of those terms. Forward-looking statements represent management’s beliefs and assumptions only as of the date of this presentation. The Company’s operations involve risks and uncertainties, many of which are outside its control, and any one of which, or combination of which, could materially affect its results of operations and whether the forward-looking statements ultimately prove to be correct. Factors that may materially affect the Company’s results of operations and whether these forward-looking statements prove to be correct include, among other things, that preclinical testing or early clinical results may not be predictive of the results or success of ongoing or later clinical trials, and that the development and testing of the Company’s product candidates will take longer and/or cost more than planned, as well as those listed in the Company’s Annual Report on Form 10-K filed with the Securities and Exchange Commission (“SEC”) on February 28, 2020, the Company’s Quarterly Report on Form 10-Q filed with the SEC on May 8, 2020 and subsequent SEC filings. In addition, while we expect that the COVID-19 pandemic might adversely affect the Company’s preclinical and clinical development efforts, business operations and financial results, the extent of the impact on the Company’s operations and the value of and market for the Company’s common stock will depend on future developments that are highly uncertain and cannot be predicted with confidence at this time, such as the ultimate duration of the pandemic, travel restrictions, quarantines, physical distancing and business closure requirements in the U.S. and in other countries, and the effectiveness of actions taken globally to contain and treat the disease. Except as required by law, the Company assumes no obligation to update these forward-looking statements publicly, or to update the reasons actual results could differ materially from those anticipated in the forward-looking statements, even if new information becomes available in the future.

Copies of the Company’s Annual Report on Form 10-K and our other SEC filings are available by visiting EDGAR on the SEC website at http://www.sec.gov.

Agenda

- **Anna Protopapas, President & Chief Executive Officer**
  - Opening remarks & introductions
- **Tim Lowinger, PhD, Chief Science & Technology Officer**
  - Therapeutic rationale for a STING-agonist ADC
  - Development & optimization of Immunosynthen platform
- **Marc Damelin, PhD, Executive Director & Head of Biology**
  - Preclinical data supporting Immunosynthen ADC pipeline
- **Tim Lowinger, PhD, Chief Science & Technology Officer**
  - Potential of the Immunosynthen ADC pipeline and next steps
- **Q&A**

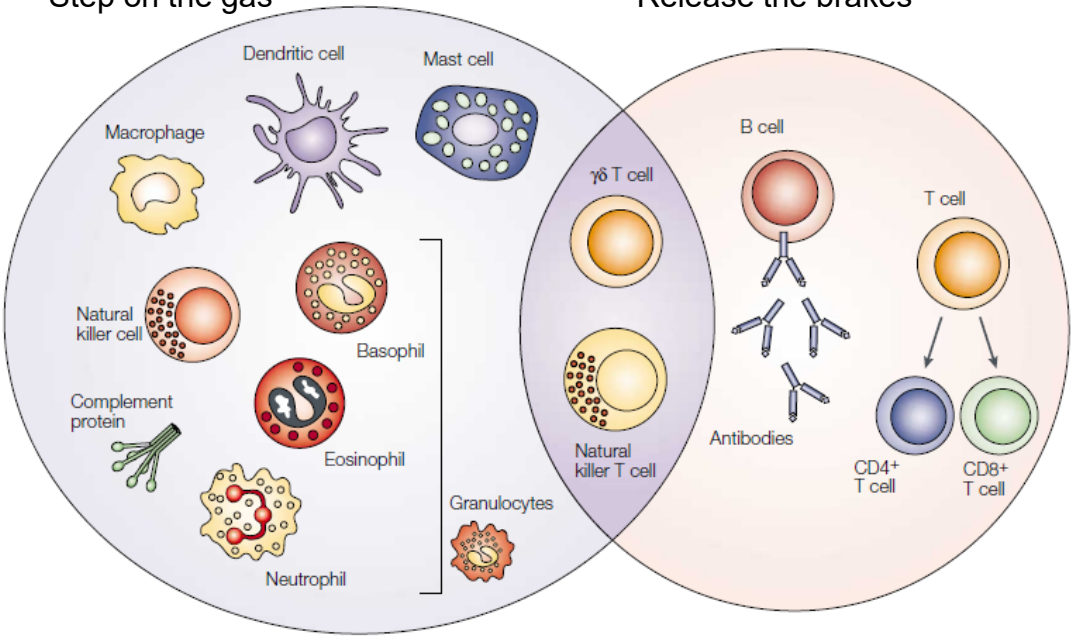
We Intend to Answer Key Questions Today

- Why activate innate immunity with a STING-Agonist ADC?
- How is Immunosynthen different than other approaches to stimulate innate immunity (SITC 2020, Abstract #620)?
- How did Mersana build and optimize the Immunosynthen platform?
- How deep is the pipeline of Immunosynthen ADCs, and which indications might be addressable?
- When will we reach the clinic?

Targeted Stimulation of Innate Immunity has the Potential to Deliver Breakthroughs

Innate Immunity
- Includes STING
- "Step on the gas"

Adaptive Immunity
- Includes CTLA4, PD1/PD-L1
- "Release the brakes"

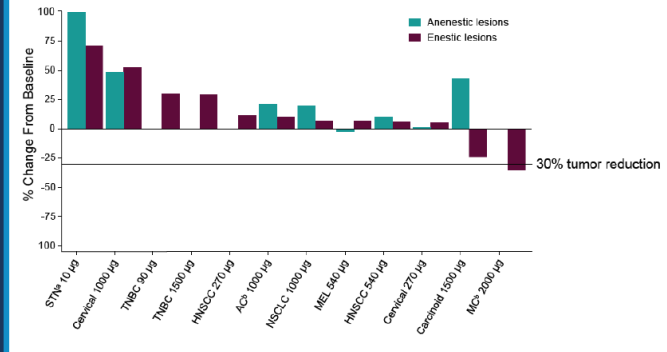


- The immunotherapy revolution has focused on adaptive immunity and serves only a fraction of patients
- Innate immune stimulation could address unmet medical needs in
  - Checkpoint refractory tumors
  - Checkpoint relapsed tumors
  - Tumor types where checkpoints have minimal activity

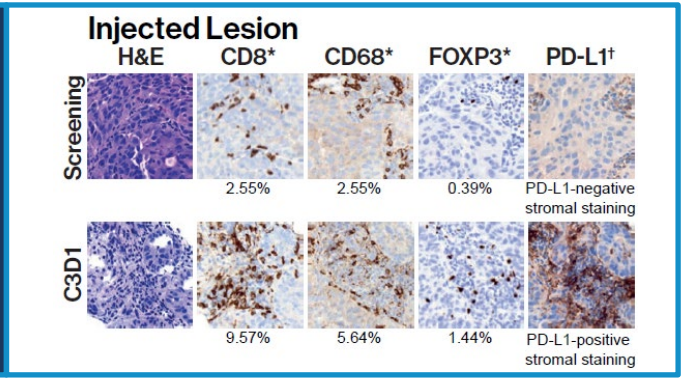
Nature Reviews Cancer 4, 11–22 (2004)

STING Pathway Activation has Shown Intriguing Signs of Activity

RECIST Clinical Response



Immune Cell Infiltrates

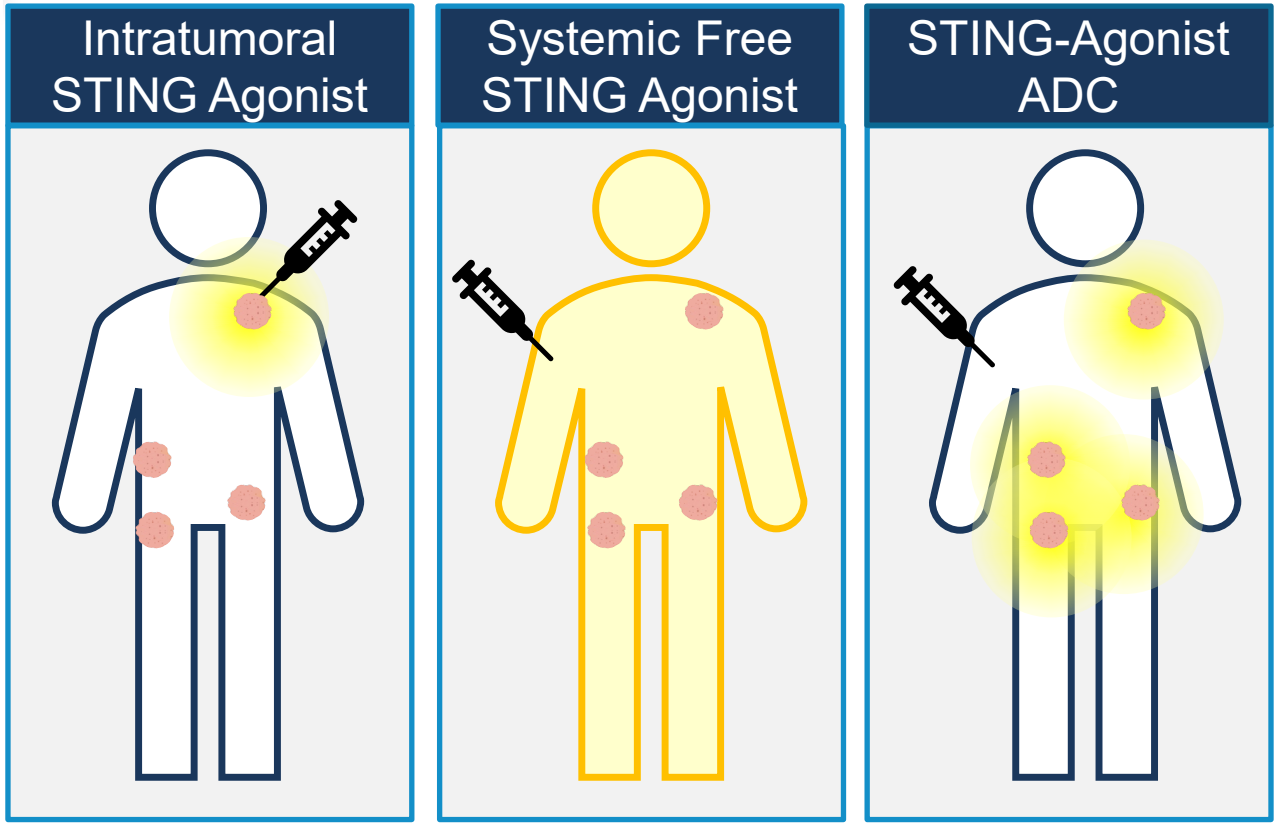


Top panel: Harrington et al. (2018) ESMO 2018 Congress. LBA15.
Bottom panel: Meric-Bernstam et al. (2018) SITC 33rd Annual Meeting. P10763.

- In clinical trials, intratumoral injection of STING agonists has induced:
  - Tumor shrinkage (top panel)
  - Immune cell infiltrates (bottom panel)
- In preclinical studies, compelling genetic and pharmacological evidence for anti-tumor potential of STING activation
- STING activation leads to a potent Type I interferon response without general inflammation

Selected preclinical references:
Woo *et al.* (2014) *Immunity*; Corrales *et al.* (2015) *Cell Reports*; Barber (2015) *Nature Reviews Immunology*.

Hypothesis: An ADC Approach Could Address Administration Issues, Systemic Tolerability, and Activity



- Systemic administration with targeted delivery to the tumor
- Improved anti-tumor activity compared to free agonist
- Improved tolerability compared to free agonist

Systemic immune activation

Tumor, no immune activation

Tumor with STING-Mediated Innate Immune Activation

Immunosynthen ADCs Activate STING in Immune and Tumor Cells
Presented at SITC 2020

What We Thought

- STING pathway is silenced in tumor cells
- The STING mechanism of action is limited to immune cells

What We Now Know

- Tumor cells activate STING in the presence of immune cues
  - Field has been misled by standard monoculture conditions
- Our studies employed:
  - CRISPR-mediated STING knockout cancer cells
  - Fc mutant ADCs
  - Co-cultures of tumor cells and immune cells
  - Conditioned media from immune cells

The ADC Modality Is Ideally Suited

- Immunosynthen ADCs enable target-dependent activation of STING in tumor-resident immune cells ***and*** tumor cells
  - Active internalization into both cell types in the tumor (via FcγR and via tumor antigen)
- Immunosynthen ADCs avoid STING activation in undesired cell types (e.g., T and B cells)

STING: The One-Two Punch
Presented at SITC 2020

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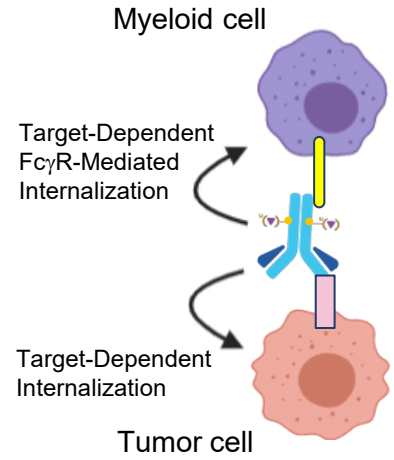
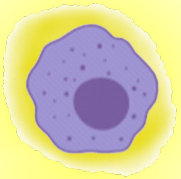
Tumor



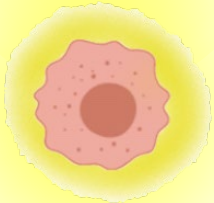
No internalization into undesired immune cells (T, B)

Hit the tumor-resident immune cells

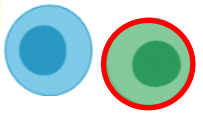
Hit the tumor cells



STING Activated in Myeloid Cell



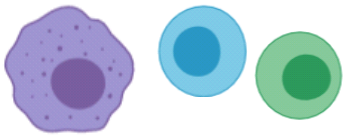
STING Activated in Tumor Cell



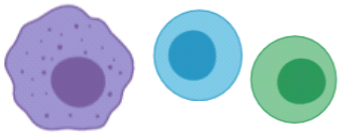
Stimulated T Cells

Periphery

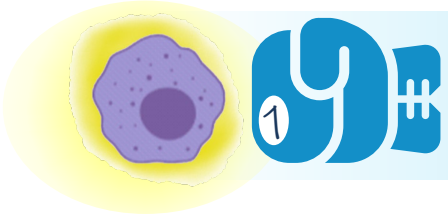
No internalization into immune cells



No stimulation of immune cells



Punch One: Fc-Mediated Delivery to Immune Cells is Target Dependent



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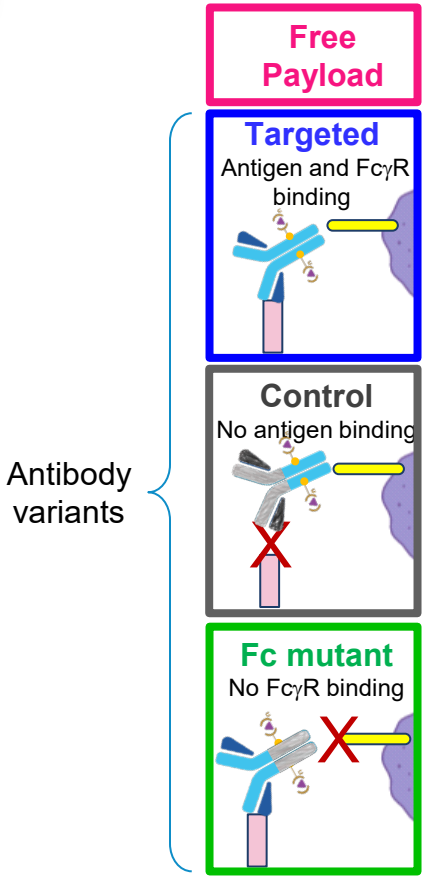
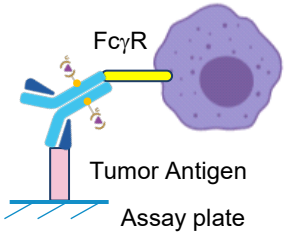
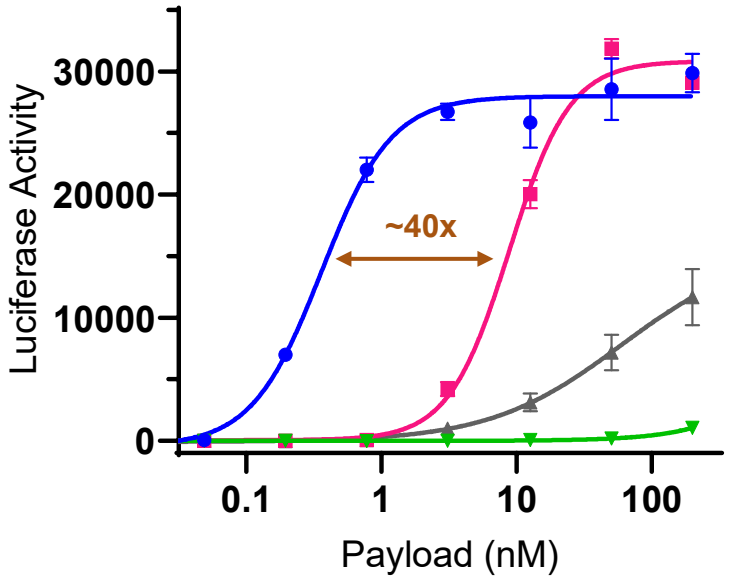




Human immune cell
STING pathway activation
(Luciferase reporter)

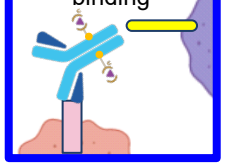


- Specific tumor antigen binding provides high local concentration, which promotes FcγR binding on tumor-resident immune cells
- FcγR binding results in internalization into tumor-resident immune cells and STING activation
- STING activation by ADC is ~40-100x more potent than free agonist

Punch Two: STING Activation in the Tumor Cell Also Contributes to Efficacy

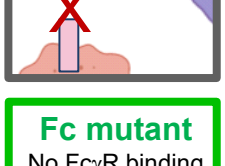
Antibody Variants

Targeted
Antigen and FcγR binding



Control
No antigen binding

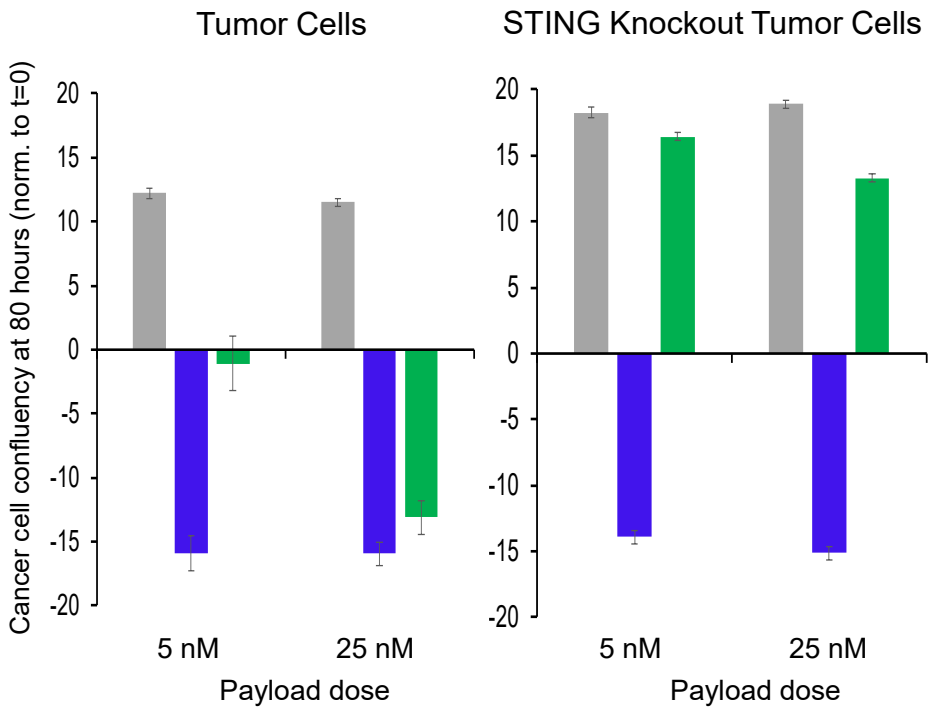
Fc mutant
No FcγR binding



Growth

Killing

Tumor Cell Killing in Immune Cell (PBMC) Co-Culture

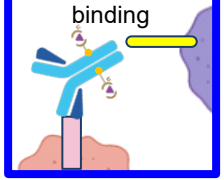


- Surprising observation that Fc-mutant ADCs are active in co-culture – which indicates tumor intrinsic STING activation
- Previously believed that STING pathway is silenced in tumor cells
- Co-cultures with STING knockout cancer cells demonstrate the direct contribution of tumor intrinsic STING

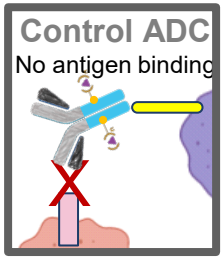
The One-Two Punch: *In Vivo* Data Consistent and Differentiated

Vehicle

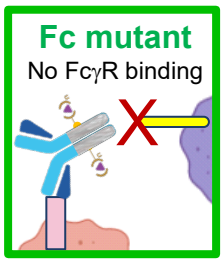
Targeted
Antigen and FcγR binding

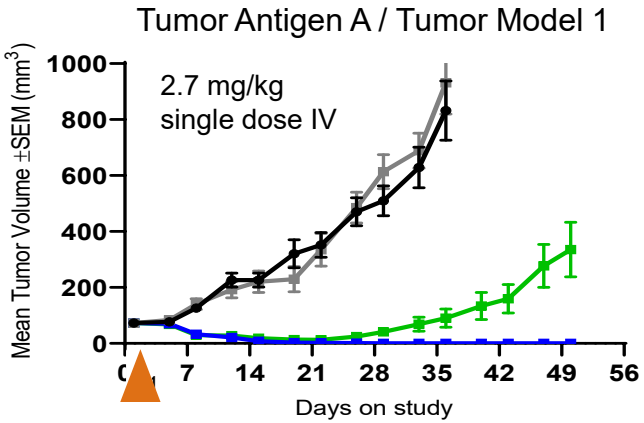


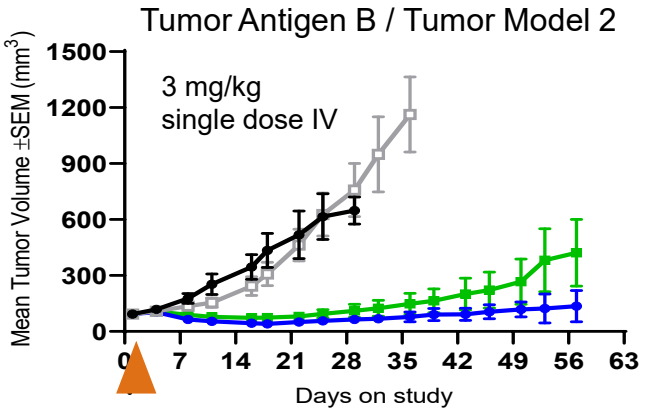
Control ADC
No antigen binding



Fc mutant
No FcγR binding

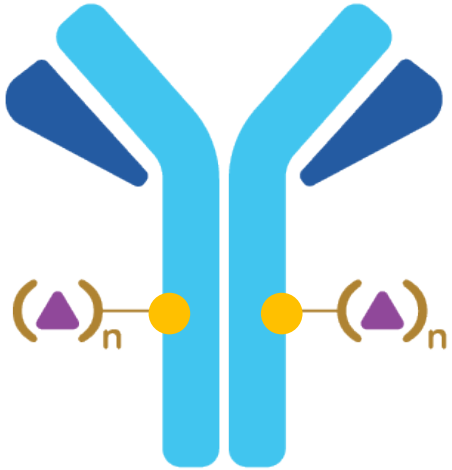


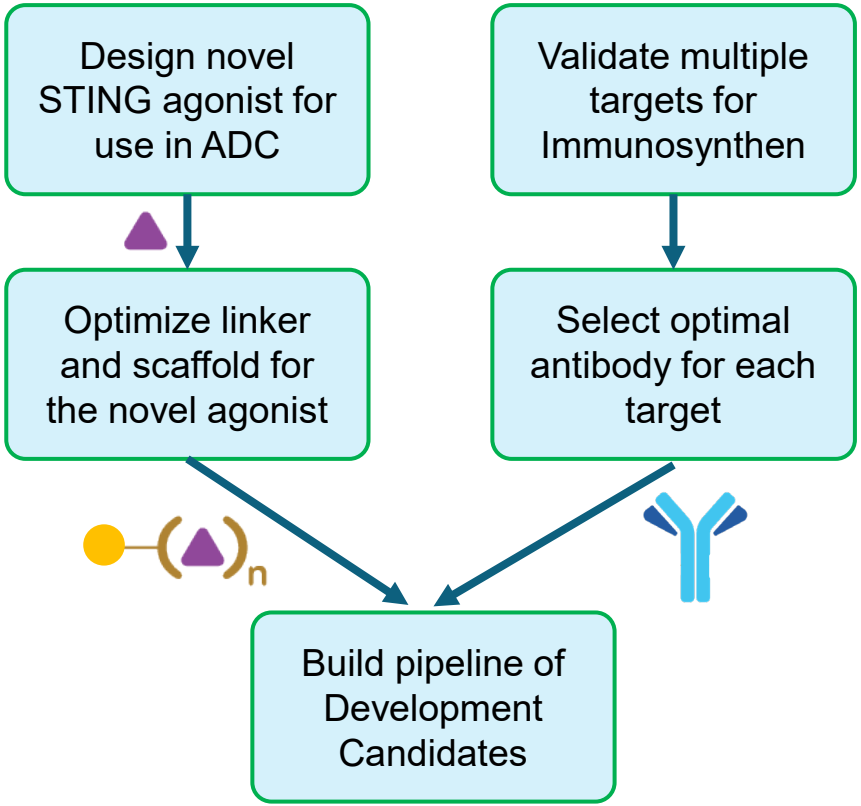




- Significant anti-tumor activity is maintained by the Fc-mutant ADC, which cannot internalize into the immune cells
  - Demonstrates the contribution of tumor cell STING to anti-tumor activity
  - Demonstrates the contribution of immune cell STING to activity
  - The One-Two Punch

Holistic Approach to Building a STING-Agonist ADC





Mersana's ADC Expertise Drives Platform Optimization

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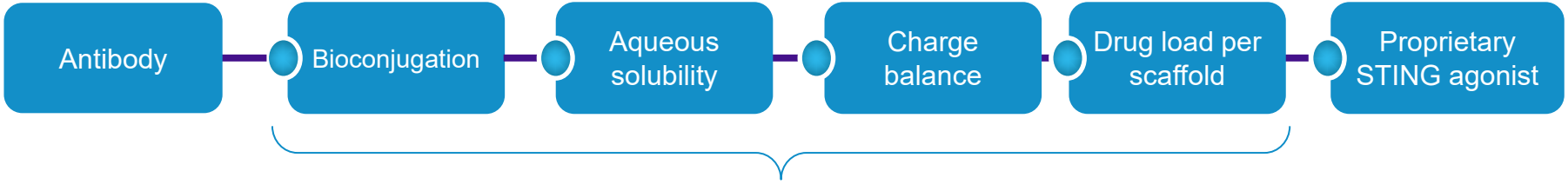
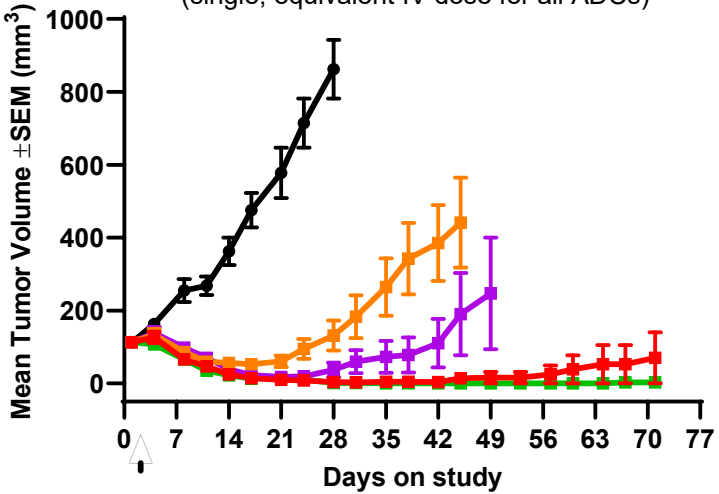
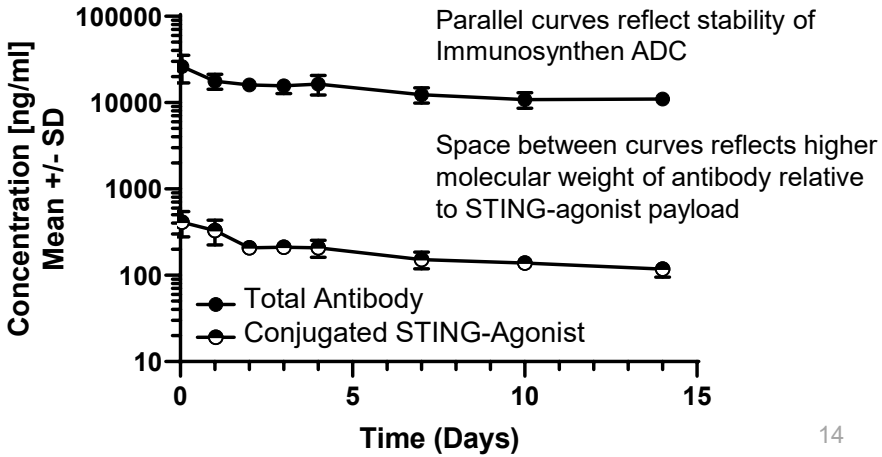


Optimizing Activity With the Same Antibody and Same STING agonist
(single, equivalent IV dose for all ADCs)



High Stability and Extended Exposure of Immunosynthen ADC



Defined Success Criteria Have Been Achieved

- ✓ Antigen-dependent targeted delivery to the tumor
- ✓ Sustained tumor regressions
  - Consistent results across tumor models and mouse strains
- ✓ Proof of mechanism
  - Induction of STING pathway cytokines in the tumor
  - Induction of STING genes in the cancer cell
  - Immune memory
- ✓ Well-tolerated; minimal systemic inflammation; favorable NHP
- ✓ Compatible with many antigens
  - Enables a portfolio to address many clinical indications

Comprehensive Approach to Target Selection

- Innate immune activation with STING enables many target classes
  - Immune cells
  - Tumor cell antigens
  - Tumor-associated antigens
- Potential broad target space encompasses multiple indications of high unmet medical need

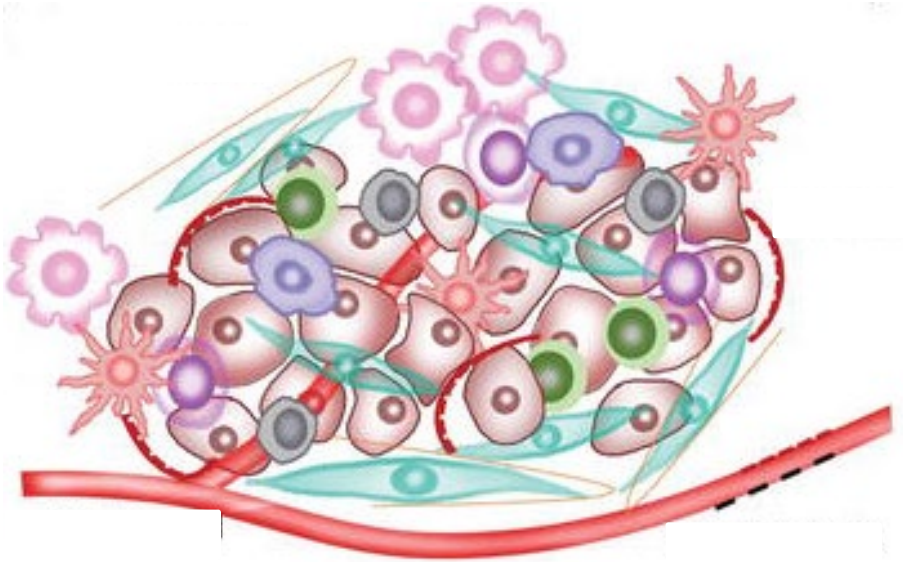
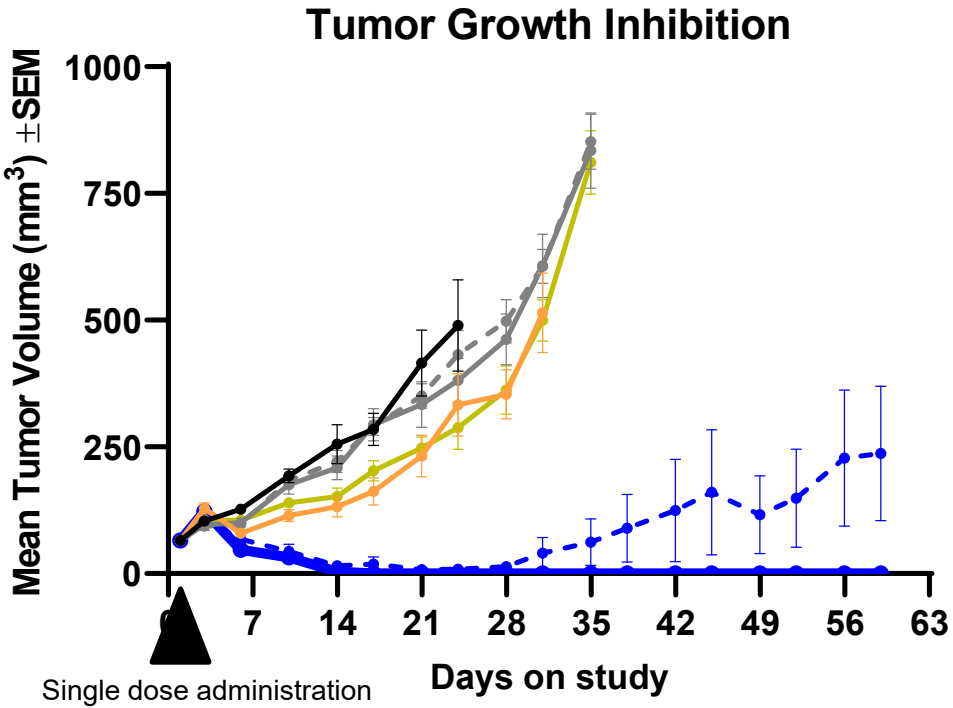


Image based on DOI: 10.5772/intechopen.72648

Single, Low Dose of Immunosynthen ADC Dramatically Outperforms Benchmark

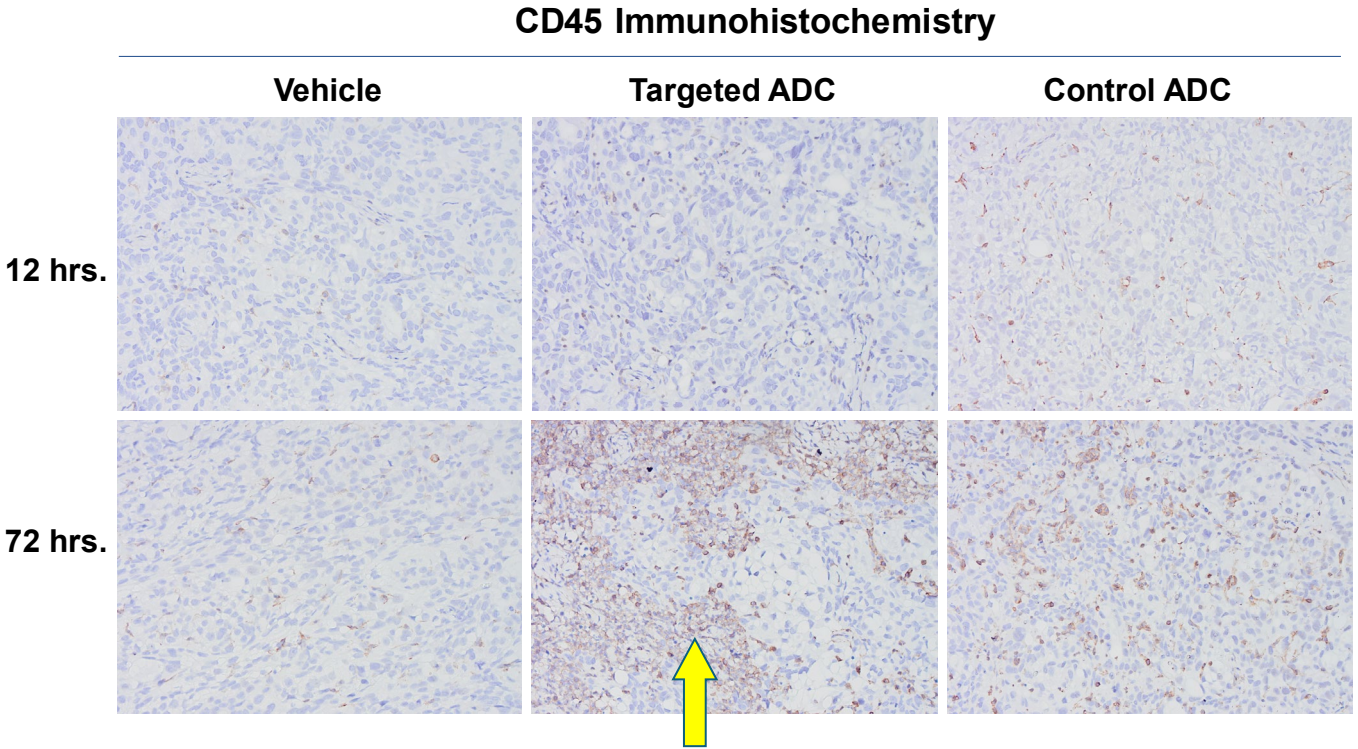


Legend

- Vehicle
- Control ADC (1 mg/kg)
- Control ADC (3 mg/kg)
- Unconjugated Antibody (3 mg/kg)
- *Benchmark IV agonist (5 mg/kg)
- Targeted ADC (1 mg/kg)#
- Targeted ADC (3 mg/kg)#
  - All groups dosed IV
  - ADC Doses by mAb [mg/kg]

*Benchmark described in J.M. Ramanjulu *et al.* (2018) *Nature*
#1 mg/kg by mAb = 0.03 mg/kg by STING-agonist payload

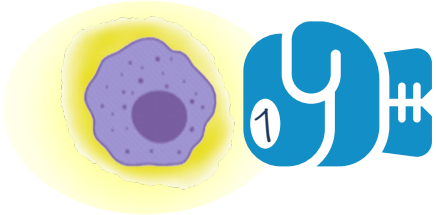
Target-Dependent Immune Cell Infiltration into Tumor

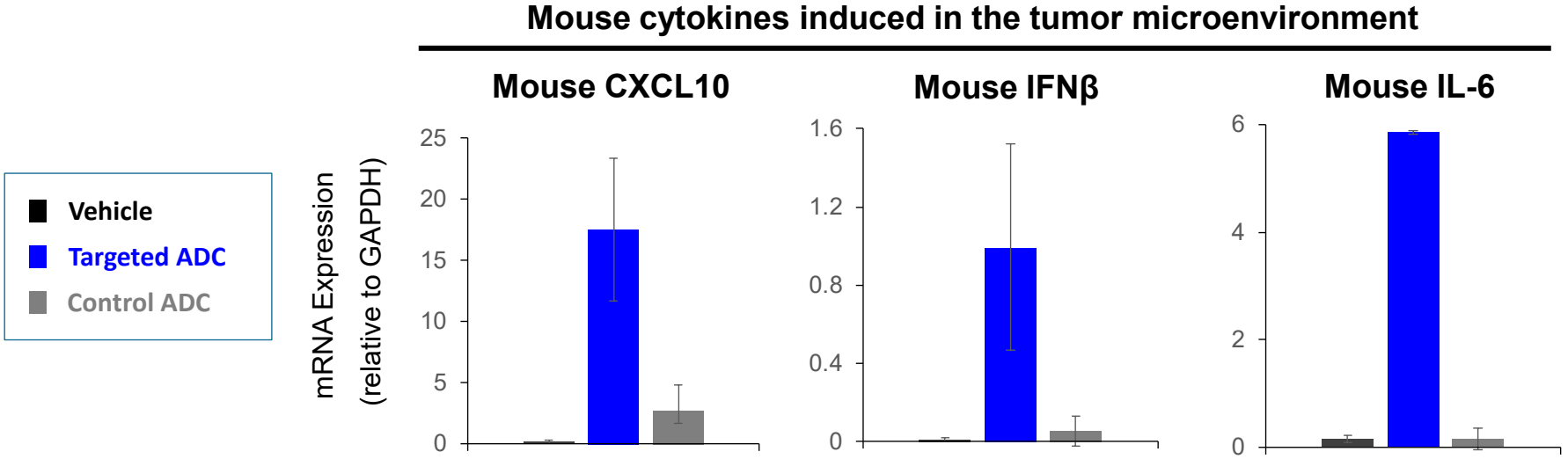


Brown staining indicates immune cells (CD45+)

Punch One: Immunosynthen ADC Induces STING Pathway Cytokines in the Tumor-Resident Mouse Immune Cells *In Vivo*

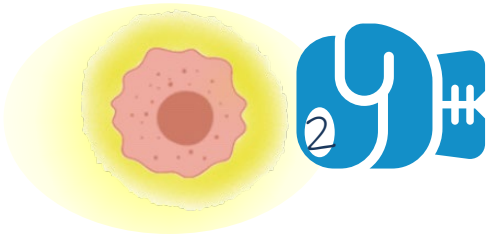
- ***Mouse*** cytokines in tumor microenvironment measured by qPCR
- ADC targets the human tumor cells

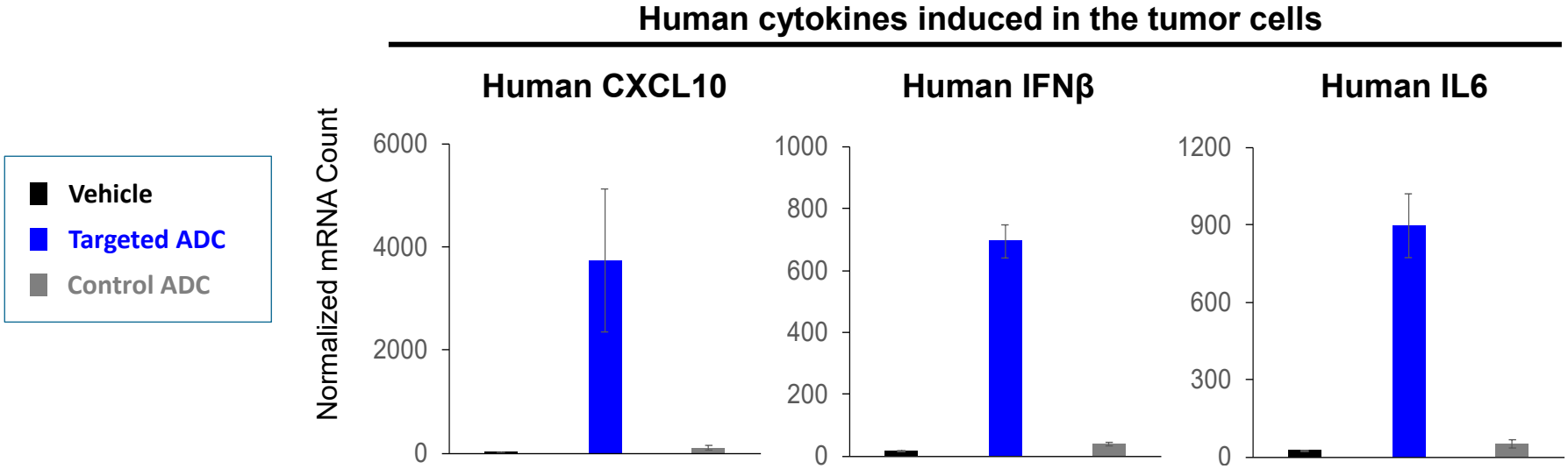




Punch Two: Immunosynthen ADC Induces STING Pathway in Human Tumor Cells *In Vivo*

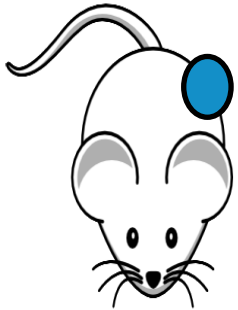
- ***Human*** cytokines in tumor microenvironment measured by Nanostring





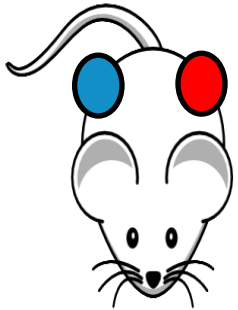
Down for the Count: Immunosynthen ADC Triggers Tumor-Specific Immunological Memory

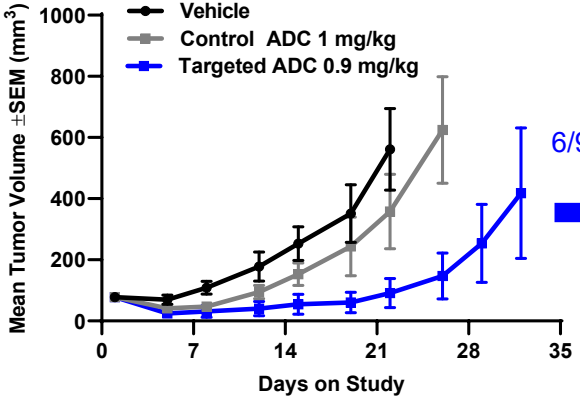
Tumor Growth Inhibition Study



- Tumor free mice re-implanted with targeted tumor on one flank (blue) and a non targeted tumor on the other flank (red).
- Untreated age matched mice also implanted as a control (black line).

Tumor Rechallenge Study (Dual Flank)

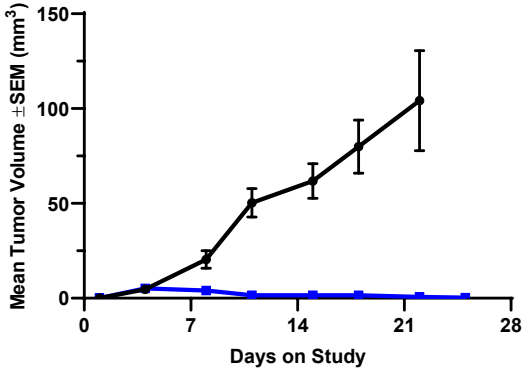




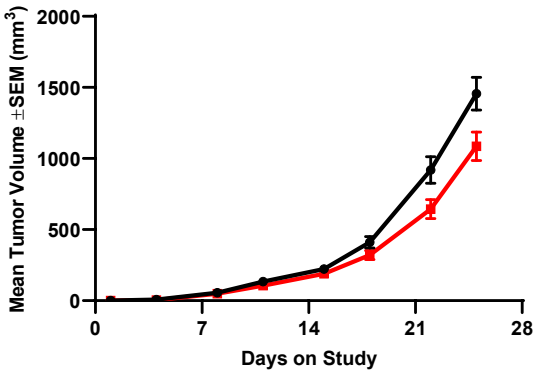
single IV dose

6/9 tumor-free animals

Targeted-tumor



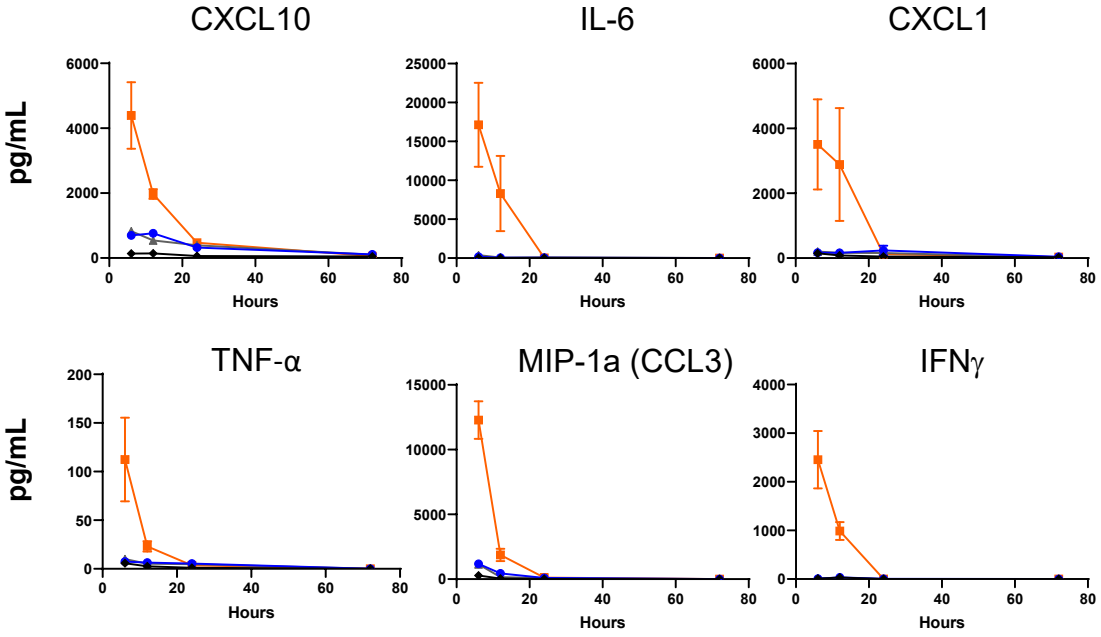
Non-targeted tumor



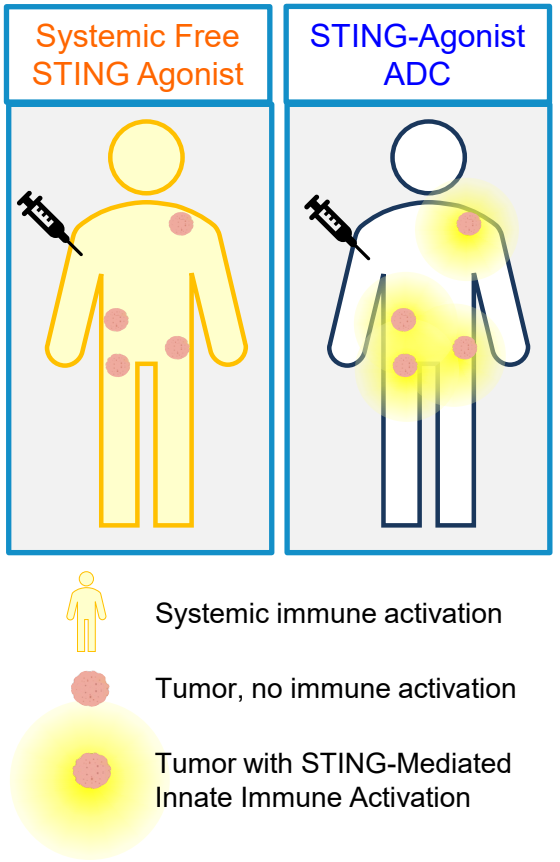
Untreated Control Mouse (age matched)
Previously Treated with Targeted ADC

Untreated Control Mouse (age matched)
Previously Treated with Targeted ADC

Dramatically Lower Systemic Cytokine Levels After Immunosynthen ADC Compared to Benchmark IV Agonist



Serum cytokines measured with Luminex assay



Immunosynthen ADCs Well-Tolerated in Non-Human Primate Studies After Repeat IV Dosing

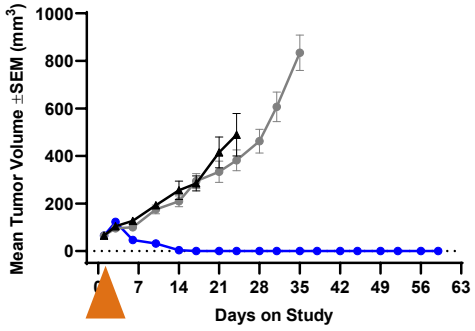
- NHP studies with Immunosynthen ADCs based on 5 antibodies
  - 4 fully cross-reactive antibodies for 4 therapeutic targets
  - 1 non-reactive antibody to assess platform safety profile
- Intravenous administration; single-dose and repeat-dose studies
- Pharmacokinetics
  - High exposure; dose dependent; overall profile similar to non-STING ADCs
  - ADC highly stable in circulation; minimal free payload in plasma
- Serum Cytokines
  - Transient, modest elevation of 5 cytokines out of 24 tested; similar to results in mouse
- No adverse changes in hematology or clinical chemistry
- No adverse findings in histopathology to date

Immunosynthen ADCs Active Against Diverse Tumor Antigens and Tumor-Associated Antigens in Multiple Models After Single, Low IV Dose

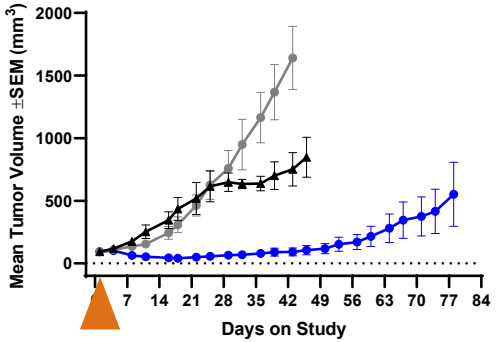
Legend

Vehicle
Control ADC
Targeted ADC

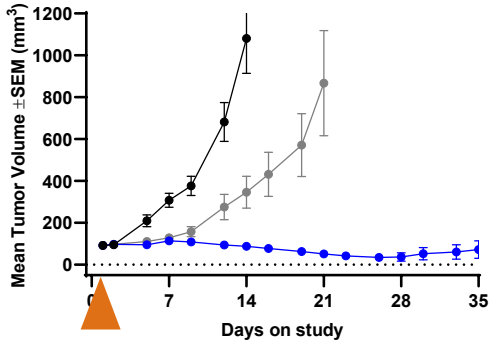
Tumor Antigen A
3.0 mg/kg



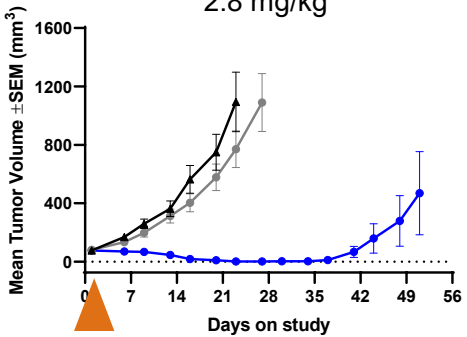
Tumor Antigen B
3.0 mg/kg



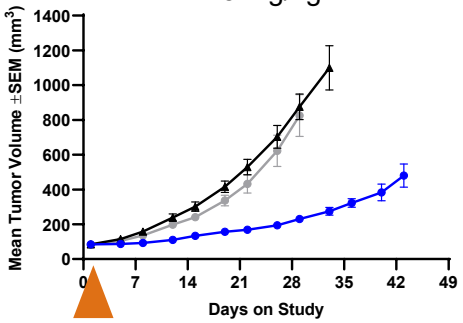
Tumor-Associated Antigen A
2.2 mg/kg



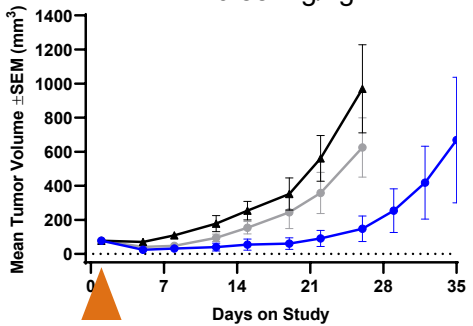
Tumor Antigen C
2.8 mg/kg



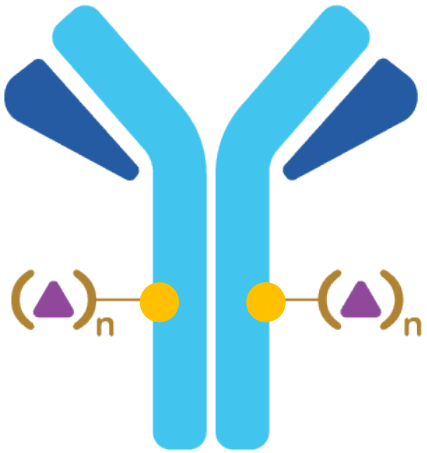
Tumor Antigen D
2.5 mg/kg



Tumor-Associated Antigen B
0.88 mg/kg



Opportunity to Build a Robust Pipeline to Treat a Broad Range of Cancers



- Bladder Cancer
- Breast cancer
- Colorectal cancer
- Endometrial Cancer
- Gastric cancer
- Head & Neck Squamous Carcinoma
- Lung cancer
- Melanoma
- Ovarian cancer
- Pancreatic cancer

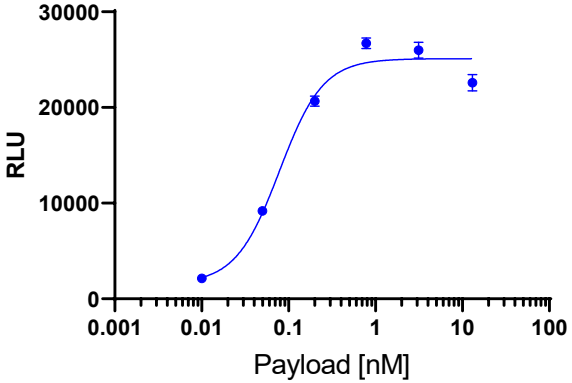
XMT-2056: First Immunosynthen Development Candidate

Summary of Data

Fc-mediated uptake and THP1 cell activation

IRF3 Reporter (THP1)

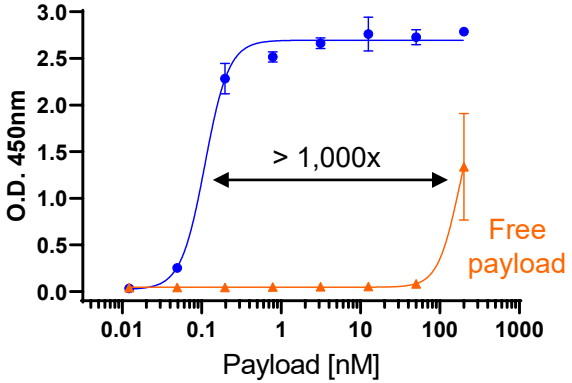
EC_{50} = 0.08 nM



Tumor cells with PBMCs

CXCL10 ELISA

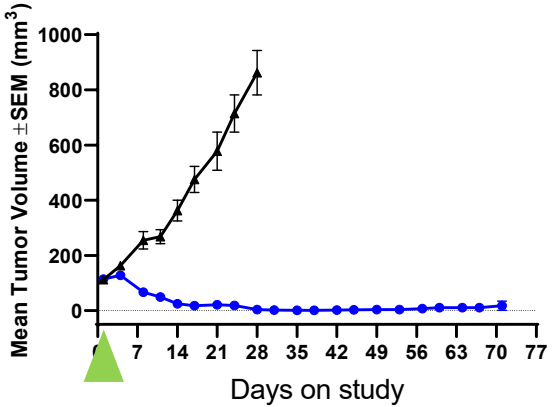
EC_{50} = 0.11 nM



***In vivo* Activity**

0.96 mg/kg antibody / 0.033 mg/kg STING

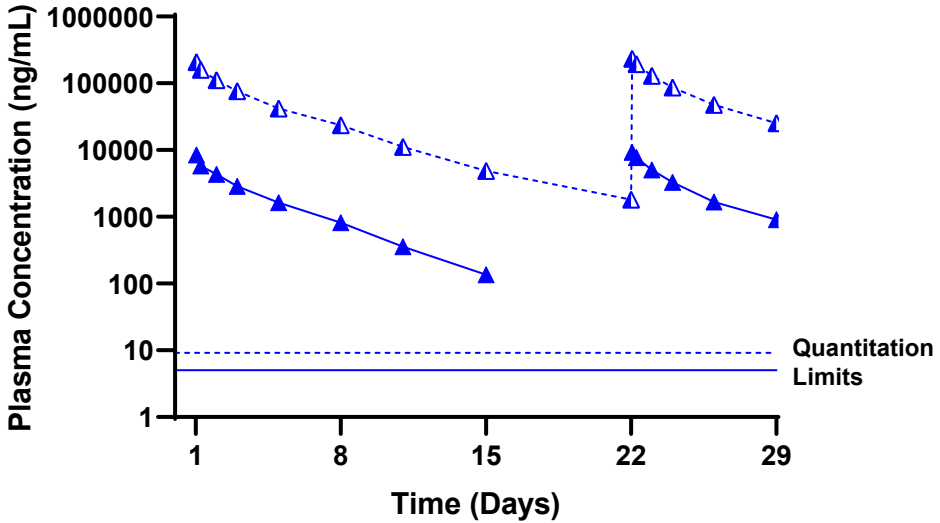
Single dose IV



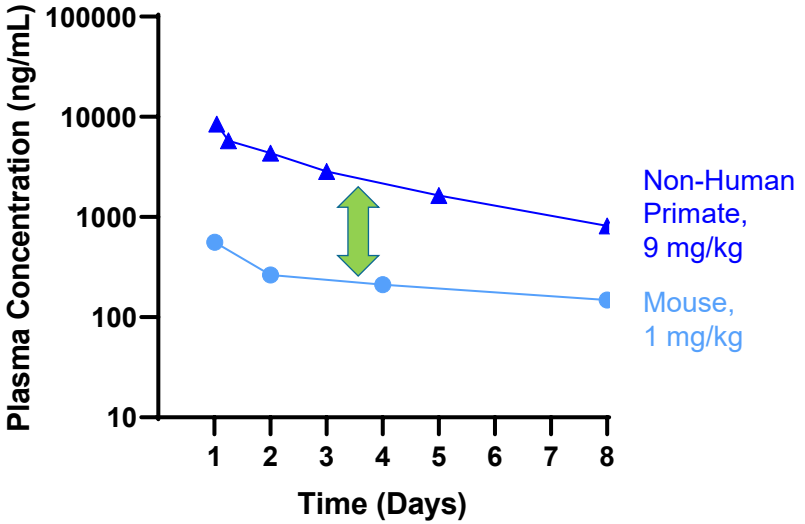
NHP Results	
Single-dose and repeat-dose studies at 9 mg/kg antibody Intravenous administration	• No clinical signs, no mortality • High exposure, high ADC stability in circulation • Transient elevation of 5 cytokines out of 24 tested • No adverse changes in clinical pathology • No adverse findings in histopathology

XMT-2056 Shows Excellent PK after Repeat IV Dosing and a Wide Therapeutic Index

Plasma Concentrations in Non-Human Primate
(Total Antibody ◭ and Conjugated STING agonist ▲)



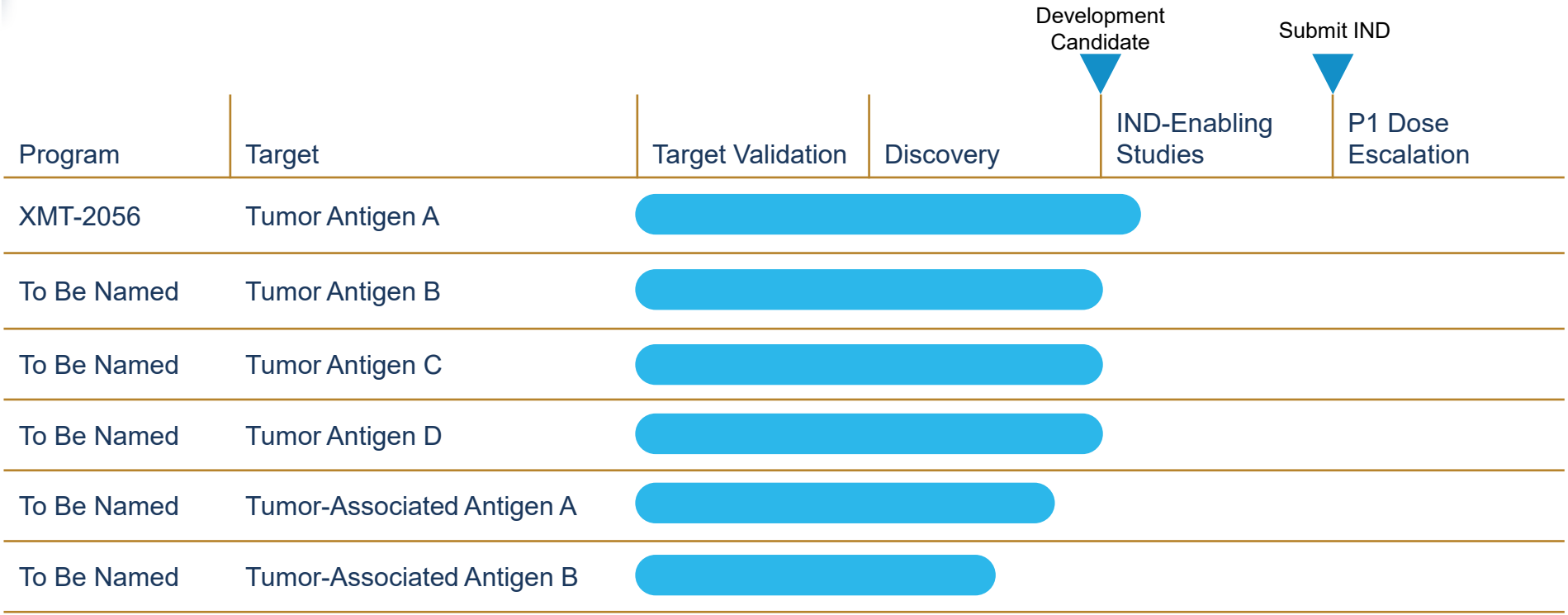
Plasma Concentrations in Non-Human Primate vs. Mouse
(Conjugated STING agonist)



- High stability as indicated by parallel curves of antibody and conjugated drug
  - Space between curves reflects higher molecular weight of antibody relative to STING-agonist payload
- Comparable PK profiles after 1st and 2nd dose

Exposure of XMT-2056 at well-tolerated dose in non-human primate is **~10-fold higher** than the exposure required for sustained tumor regression in mouse

The Immunosynthen Platform is Already Delivering Multiple Product Candidates



Summary

- Immunosynthen ADCs have the potential to address the limitations of current approaches to activate innate immunity / STING
- Immunosynthen ADCs deliver One-Two knockout punch from STING activation in tumor cells and tumor-resident immune cells (SITC 2020)
- We have optimized the platform using our ADC expertise
- We are building a deep pipeline of Immunosynthen ADCs with a broad range of clinical indications and potential for value-creating partnerships
- XMT-2056 has been selected as the first Immunosynthen ADC with initiation of Phase I Dose Escalation expected in Q1 2022

Q&A