AACR-NCI-EORTC Virtual International Conference on
MOLECULAR TARGETS AND CANCER THERAPEUTICS
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XMT-2056: Tumor-targeted Innate Immune Activation via a STING-agonist Antibody Drug Conjugate

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Disclosures

Timothy B. Lowinger, PhD

I have the following financial relationships to disclose:

- Stockholder in and Employee of Mersana Therapeutics, Inc.
- I will not discuss off label use and/or investigational use in my presentation.

Targeted Stimulation of Innate Immunity has the Potential to Deliver Breakthroughs

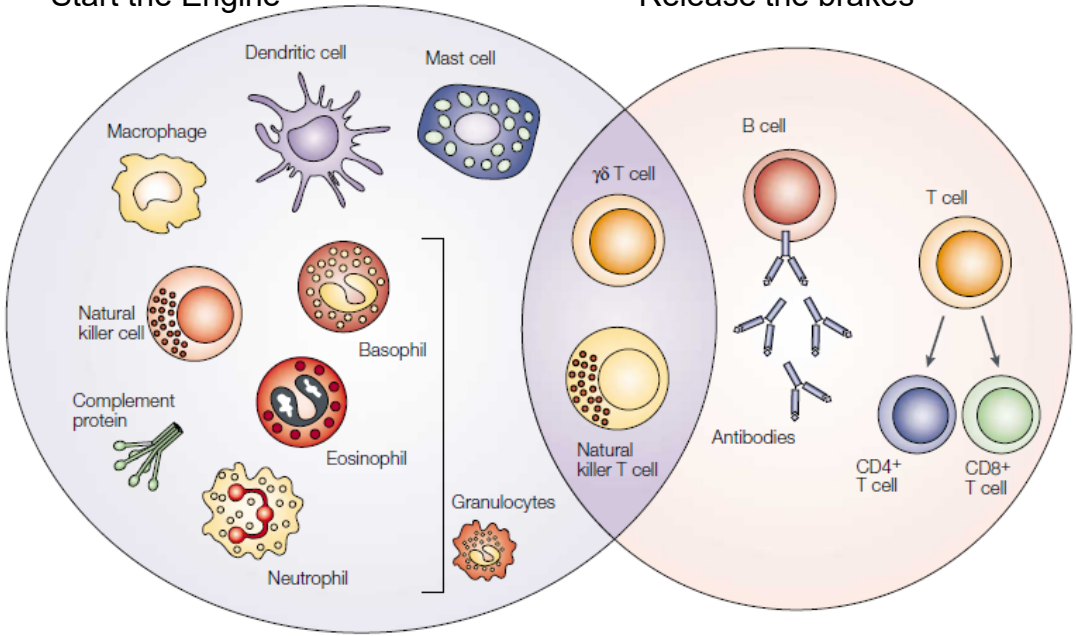
AACR American Association for Cancer Research FINDING CURES TOGETHER | NIH NATIONAL CANCER INSTITUTE | EORTC European Organisation for Research and Treatment of Cancer — The future of cancer therapy

Innate Immunity

- Includes STING
- "Start the Engine"

Adaptive Immunity

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

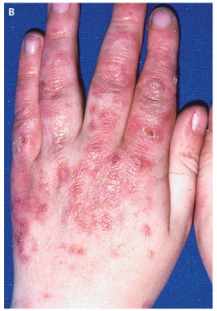


Nature Reviews Cancer 4, 11–22 (2004)

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

STING Is a Fundamental Immune Pathway In Health & Disease

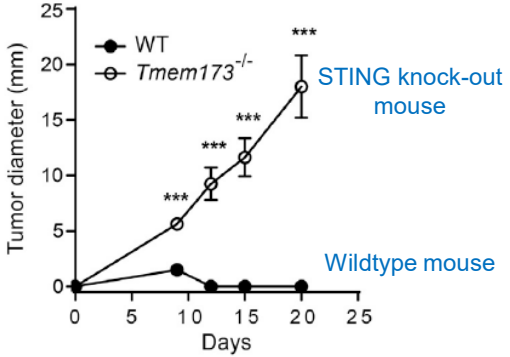
Human Genetics



Liu et al, NEJM, 2014

Ligand-independent gain-of-function mutation in STING leading to pediatric STING-associated vasculopathy with onset in infancy (SAVI) - severe auto-inflammatory disease

Mouse Genetics

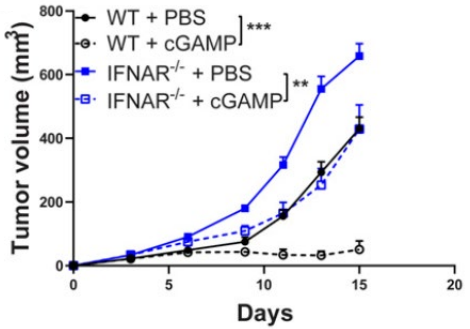


Woo et al, Immunity, 2014

STING knock-out (KO) mouse (*Tmem173*$^{-/-}$)

- Unable to mount immune-mediated anti-tumor response
- Sensitivity to HSV-1 virus infection
  (*Ishikawa et al, 2009, Nature*)

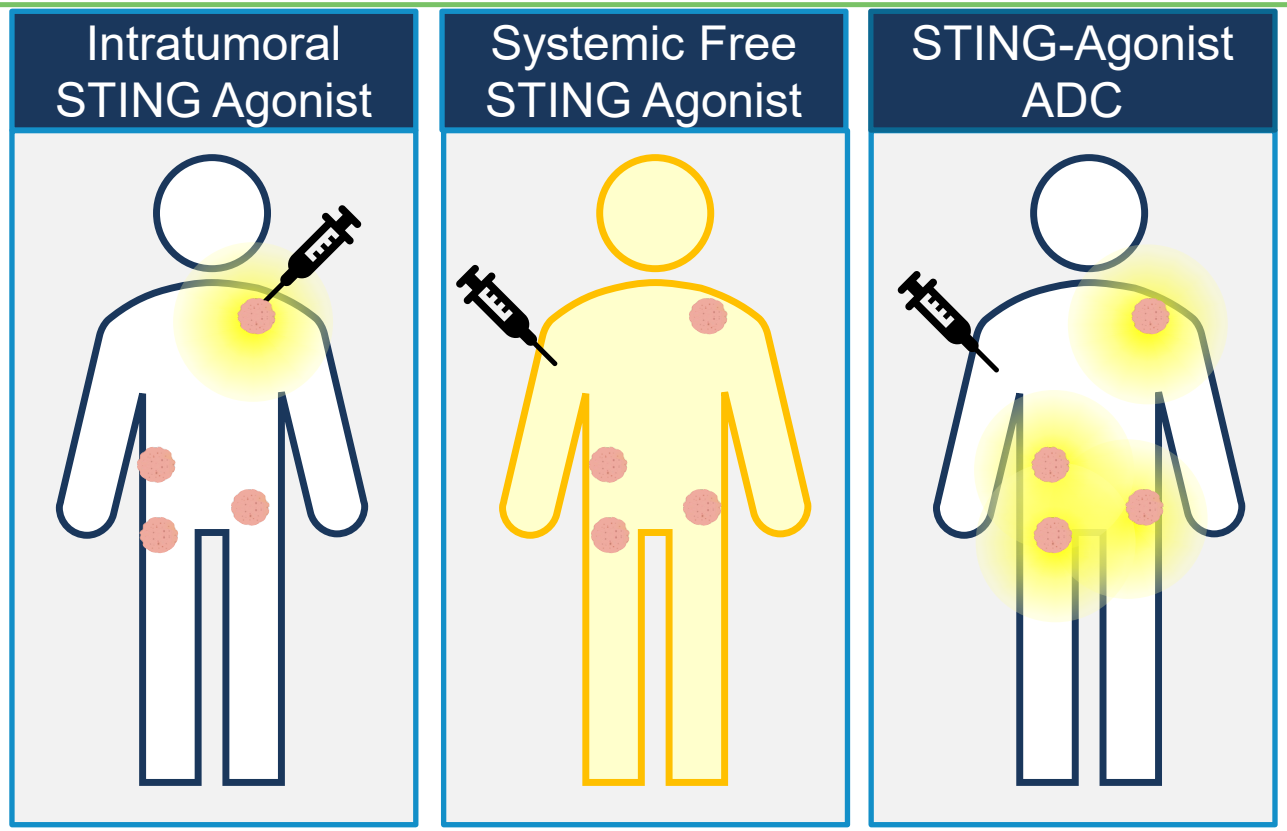
Cancer Pharmacology



Yum et al, PNAS, 2021

STING agonist (cGAMP) inhibits tumor growth via an interferon response

An ADC is an Ideal Approach for Targeted Innate Immune Activation with STING



- Systemic administration with targeted delivery to all tumor lesions while avoiding healthy tissues
- Improved anti-tumor activity compared to free agonist
- Improved tolerability compared to free agonist

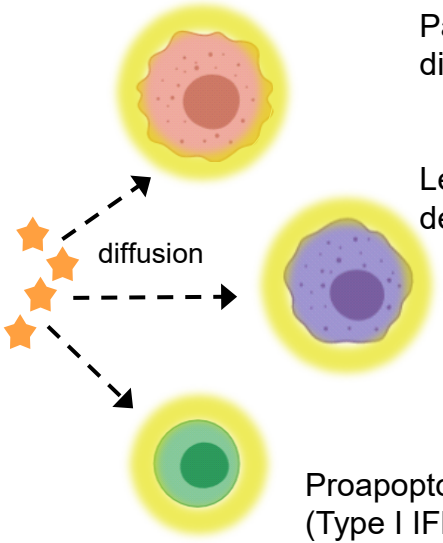
Systemic immune activation

Tumor, no immune activation

Tumor with STING-Mediated Innate Immune Activation

How and Where You Deliver STING is Key to Maximizing the Therapeutic Index – a Major Advantage of an ADC

Free STING Agonist



Passive, indiscriminate diffusion

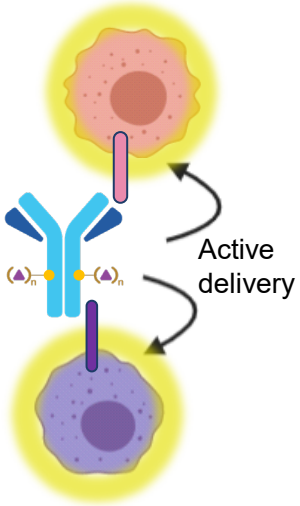
Less efficient delivery to desired cell types

Proapoptotic activation of T cells (Type I IFN independent)

Gulen et al. *Nature Comm.* 2017
Wu et al. *Immunity* 2020

Immunosynthen ADC

✓ Antigen-dependent, active delivery into tumor cells



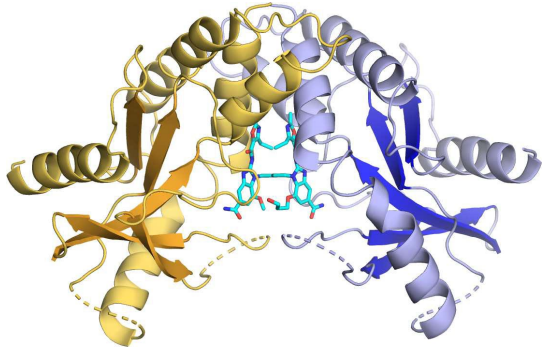
✓ FcγR-mediated, active delivery into tumor-resident myeloid and dendritic cells

✓ No delivery to T cells

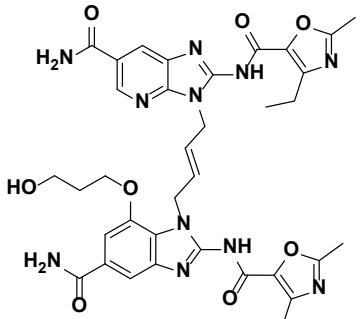
Proprietary STING Payload Specifically Designed for an ADC

Extensive Structure-based Medicinal Chemistry Effort

- Highly potent STING agonist
  - K_D = 271 pM (SPR)
  - EC_{50} = 4.4 nM (IRF3 reporter, WT haplotype)
  - Active against all major haplotypes
  - Active vs. mouse, rat, NHP, human
- Very low cell permeability
  - P_{app} < 0.1 x 10^{-6} cm/s
  - ADC >100-fold more active than free payload
- Short half-life
  - In vitro ½ life (human microsomes) = 28 minutes
  - In vivo ½ life (mouse) < 0.5 hour
- Physicochemical properties suitable for an ADC
  - Low cLogP, high tPSA



Co-crystal structure confirms agonist binds in an active, “closed” conformation of the protein

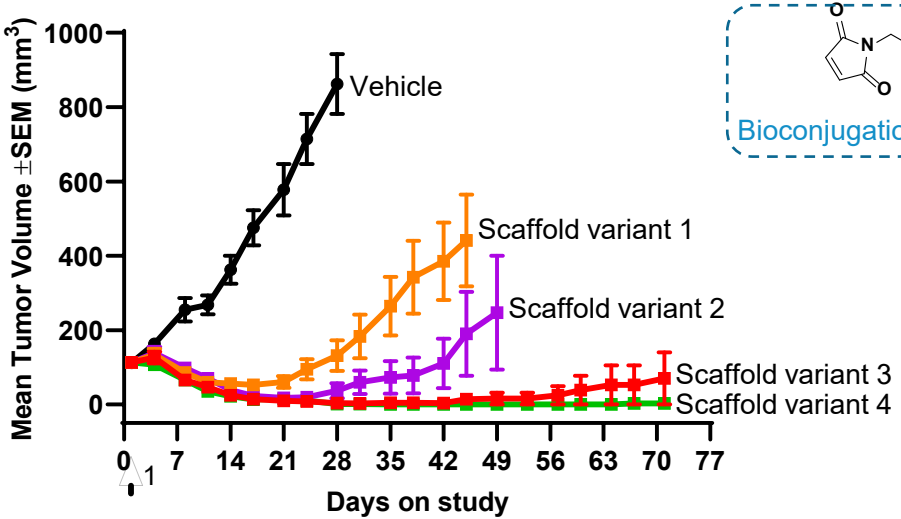


XMT-1616

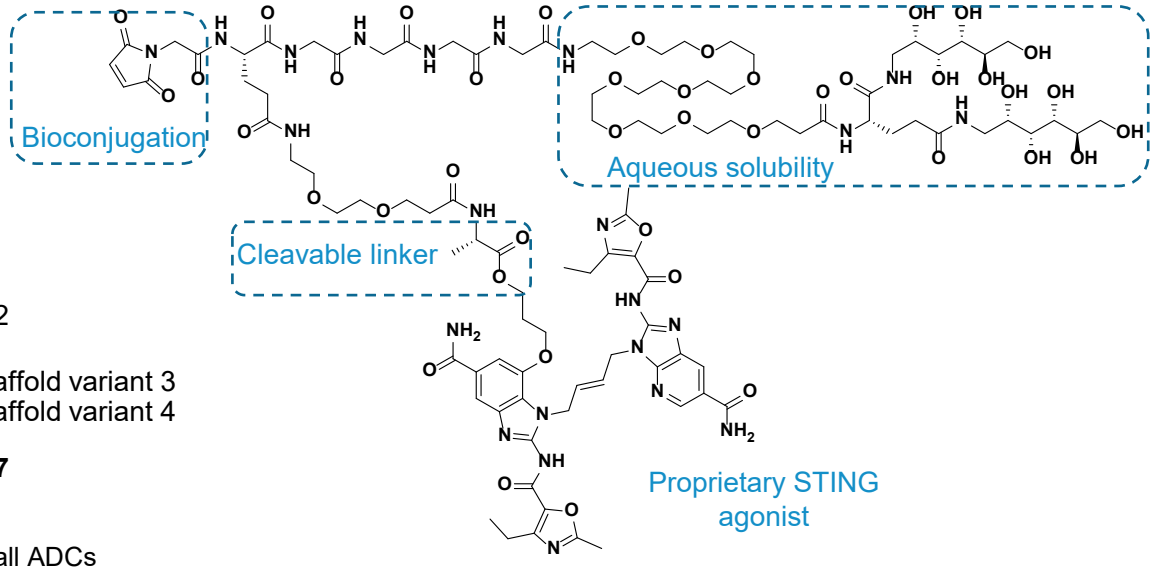
Linker-Scaffold Specifically Optimized for the STING Agonist

Antibody — Bioconjugation — Aqueous solubility — Charge balance — Drug load per scaffold — Proprietary STING agonist

ADC Optimization via Modular Approach



- Used same antibody and same STING agonist for all ADCs
- Single, equivalent IV dose for all ADCs

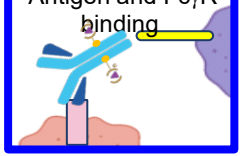


Immunosynthen Platform (XMT-1621)

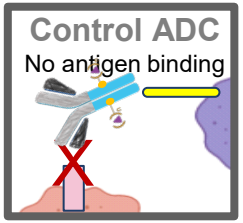
Single, Low Dose of Prototype Trastuzumab-STING ADC Outperforms Comparators

Vehicle

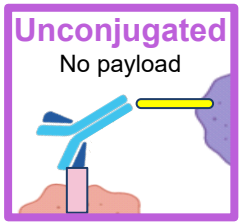
Targeted ADC
Antigen and FcγR binding



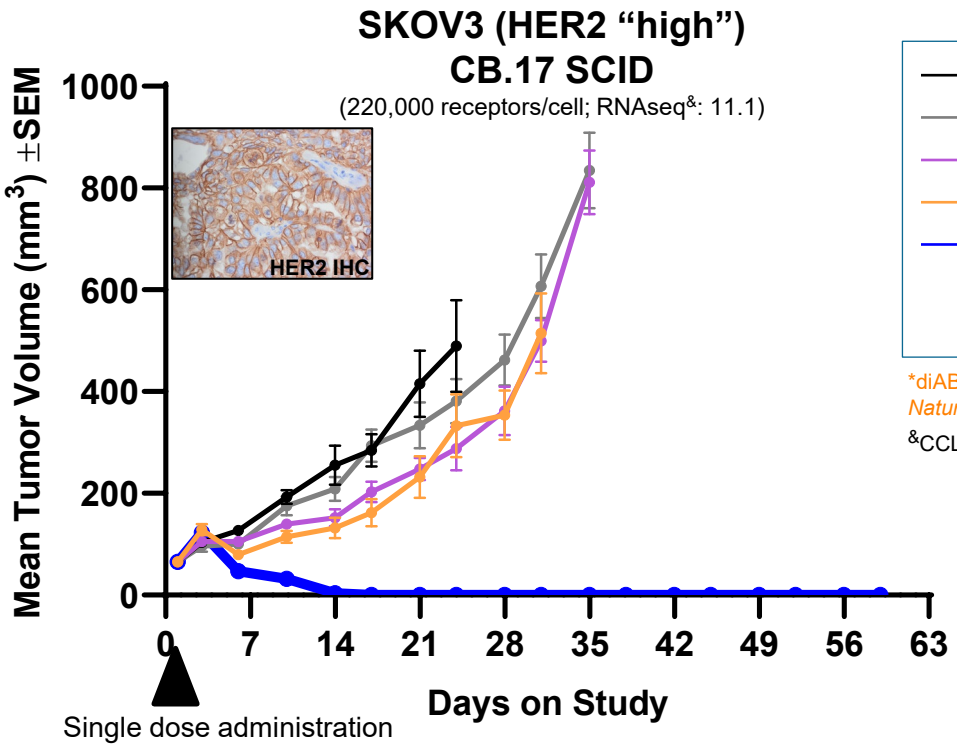
Control ADC
No antigen binding



Unconjugated
No payload



Free IV Agonist



Legend

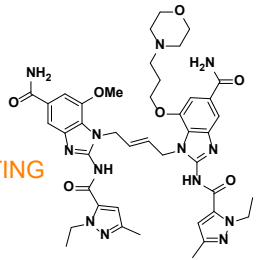
- Vehicle
- Non-binding Control STING ADC (3 / 0.09 mg/kg)
- Trastuzumab (3 mg/kg)
- diABZI IV STING agonist (5 mg/kg)*
- Trastuzumab-STING ADC (3 / 0.09 mg/kg)

  - All groups dosed IV
  - ADC doses reflect mAb / payload mg/kg

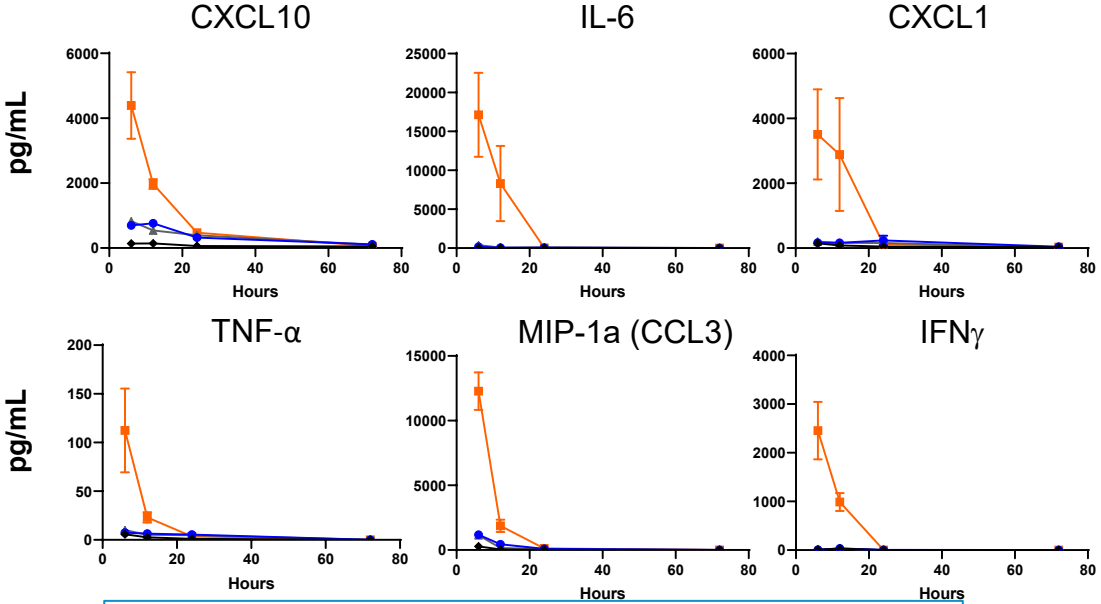
*diABZI IV STING agonist described in J.M. Ramanjulu *et al.* (2018) *Nature* (compound 3 in reference)

&CCLE RNAseq data from DepMap, Broad (2021): DepMap 21Q3 Public

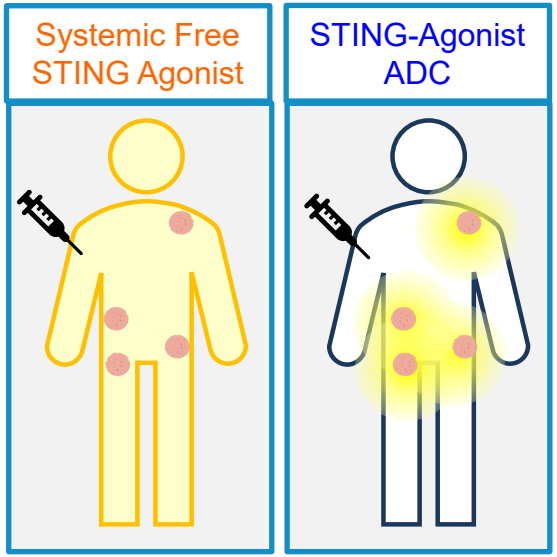
diABZI IV STING agonist*



Dramatically Lower Systemic Cytokine Levels After IV Dosing of Prototype Trastuzumab–STING ADC Compared to diABZI Small Molecule STING Agonist



Serum cytokines measured with Luminex assay

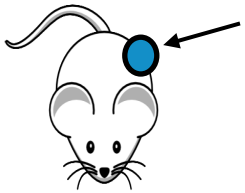


Systemic immune activation

Tumor, no immune activation

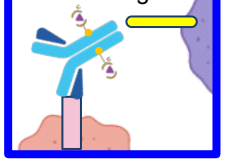
Tumor with STING-Mediated Innate Immune Activation

Prototype Trastuzumab-STING ADC Induces STING Pathway Cytokines in Tumor-Resident Mouse Cells and Human Tumor Cells *In Vivo* in a Target-Dependent Manner

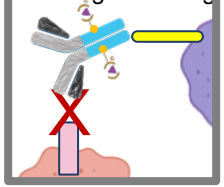


Vehicle

Targeted ADC
Antigen and FcγR binding

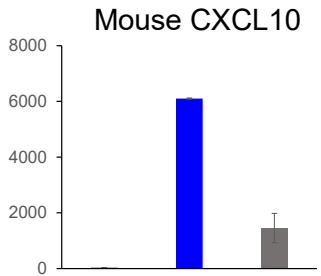


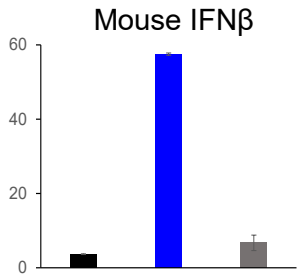
Control ADC
No antigen binding

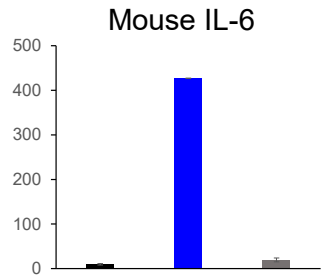


Cytokine Induction in the Tumor Microenvironment

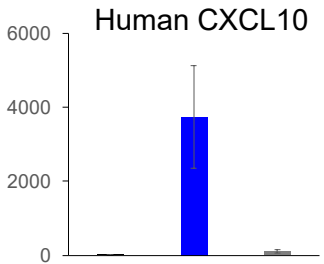
Murine Cytokines

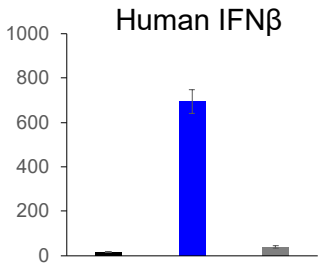


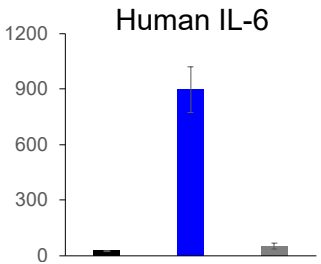




Human Cytokines (produced by human tumor cells)





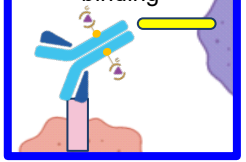


Normalized mRNA Counts by Nanostring

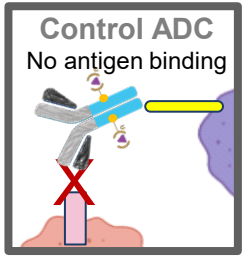
Fc-Blocking Experiment Further Confirms Tumor Cell Contribution and Fc-mediated Uptake to Immune cells

Vehicle

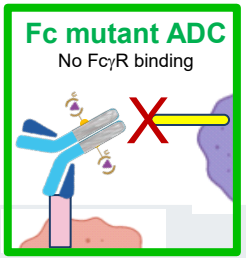
Targeted ADC
Antigen and FcγR binding



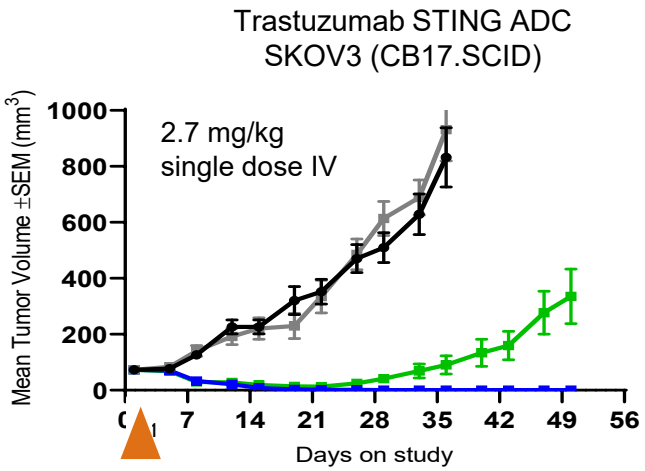
Control ADC
No antigen binding



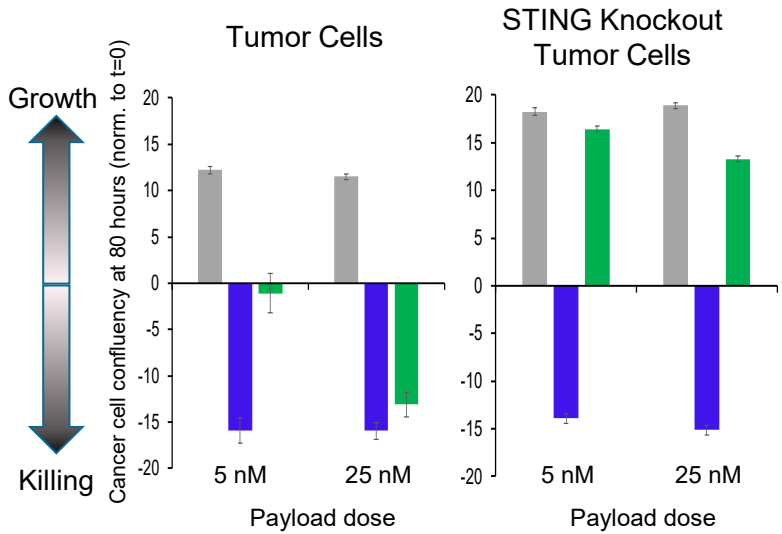
Fc mutant ADC
No FcγR binding



In Vivo Efficacy



Tumor Cell Killing in PBMC Co-Culture



Significant anti-tumor activity in vivo & tumor cell killing in vitro is maintained by the Fc-mutant ADC, which cannot internalize into the immune cells

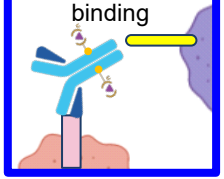
- Demonstrates the contribution of immune cell STING to activity
- Demonstrates the direct contribution of tumor-intrinsic STING activation

Mersana Therapeutics, SITC 2020 & AACR 2021

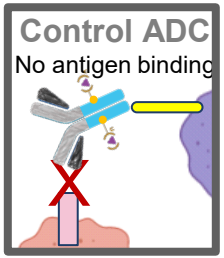
Immunosynthen ADCs Active Against Diverse Tumor Antigens and Tumor-Associated Antigens in Multiple Models After Single, Low IV Dose

Vehicle

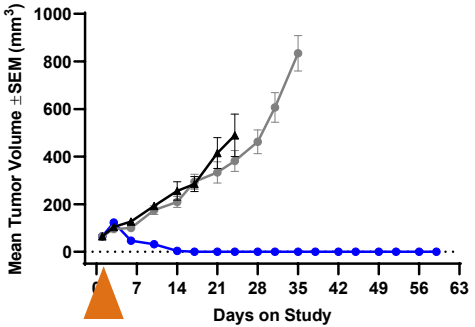
Targeted
Antigen and FcγR binding



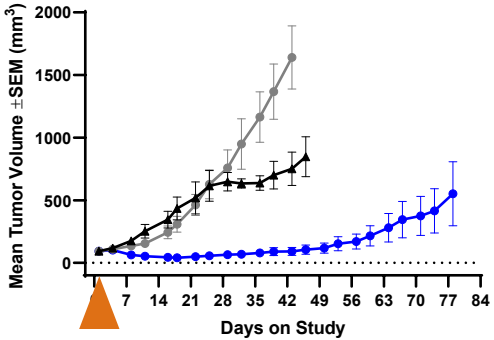
Control ADC
No antigen binding



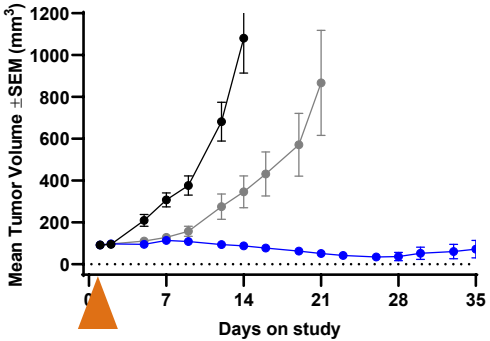
Tumor Antigen A
3.0 mg/kg



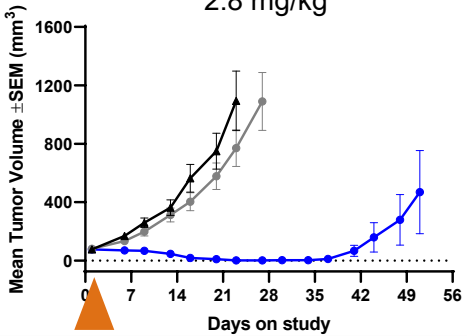
Tumor Antigen B
3.0 mg/kg



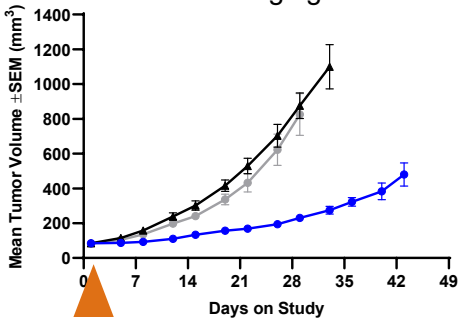
Tumor-Associated Antigen A
2.2 mg/kg



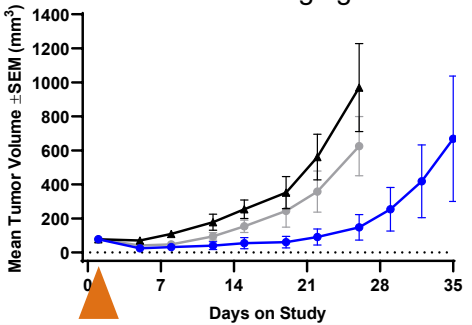
Tumor Antigen C
2.8 mg/kg



Tumor Antigen D
2.5 mg/kg



Tumor-Associated Antigen B
0.88 mg/kg



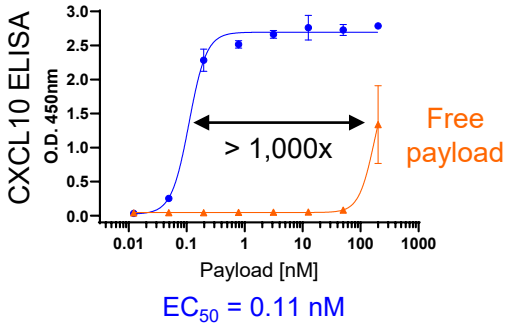
Targeting HER2:
XMT-2056 Provides a Differentiated Approach to a Well-validated Target

- HER2 is a well-validated target with multiple potential indications
  - Breast cancer, gastric cancer, NSCLC, colorectal cancer
  - Patient selection assays readily available
- Mersana developed a differentiated anti-HER2 antibody with Adimab
  - Specifically optimized for use in an ADC
  - Does not compete with trastuzumab or pertuzumab for HER2 binding
    - Rationale and opportunity for therapeutic combinations
- STING pathway is differentiated from other innate immune pathways
  - Activation in tumor cells and tumor-resident immune cells

XMT-2056: Mersana's First Immunosynthen Development Candidate

In Vitro – Tumor cells with PBMCs

Greater than 1000 fold increase in potency of ADC vs. free payload

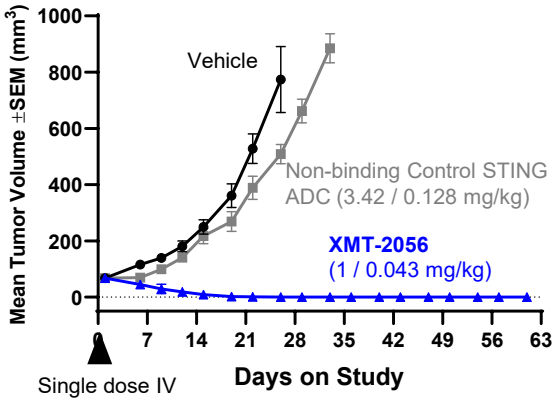


EC_{50} = 0.11 nM

- ADC-mediated active delivery of STING payload to HER2 expressing tumor cells and PBMCs

In Vivo – Mouse

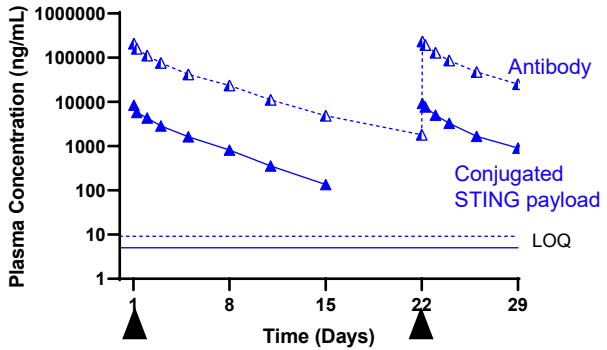
Highly efficacious in various human xenograft models



- Target dependent anti-tumor activity after a single dose of 1 mg/kg ADC

In Vivo – Non-Human Primate (NHP)

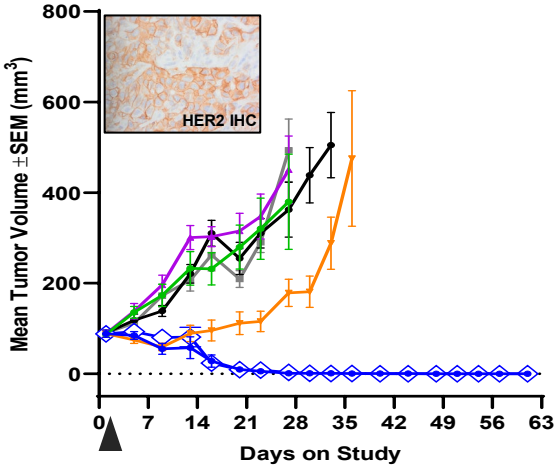
High, consistent exposures after repeat IV doses



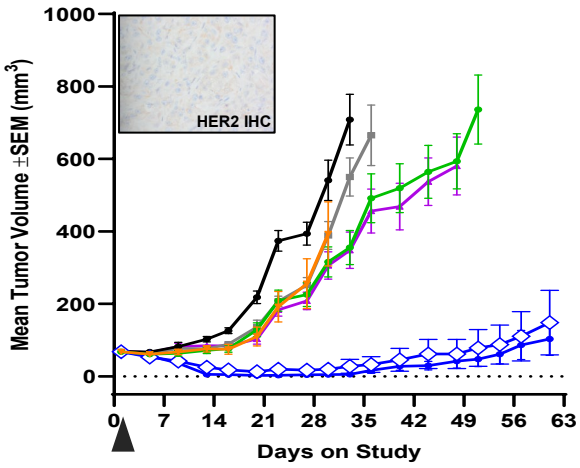
- High stability as indicated by parallel curves of antibody and conjugated drug
- Comparable PK profiles after 1st and 2nd dose

XMT-2056 Outperforms diABZI IV STING Agonist and Trastuzumab TLR7/8 ISAC in Her2^{high} and HER2^{low} Models

HCC1954 (HER2 "high")
SCID Beige
(RNAseq[&]: 11.90)



SNU-5 (HER2 "low")
CB.17 SCID
(~22,000 receptors/cell; RNAseq[&]: 5.30)



Vehicle

diABZI IV STING agonist (1.5 mg/kg; q3dx3, IV)*

Trastuzumab (10 mg/kg; qdx1, IP)

Non-binding Control STING ADC (3 / 0.112 mg/kg; qdx1, IV)

Trastuzumab TLR7/8 ISAC (5 / 0.033 mg/kg; q5dx6, IP)#

XMT-2056

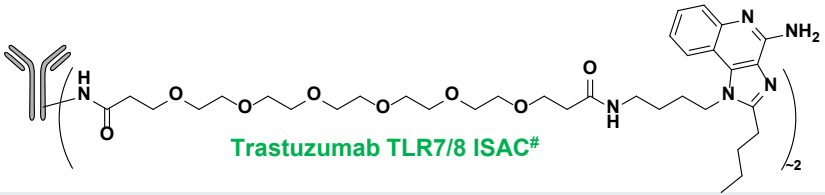
- **(1 / 0.043 mg/kg; qdx1, IV)**
- **◇ (0.3 / 0.013 mg/kg; q5dx6, IP)**

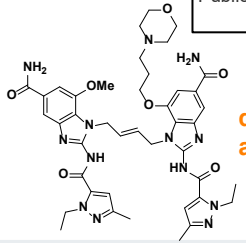
(Doses reflect mAb / payload mg/kg)

*agonist described in Ramanjulu *et al.* (2018) *Nature* (compd 3 in reference)

#TLR7/8 ISAC described in Ackerman *et al*, (2020) *Nature Cancer*

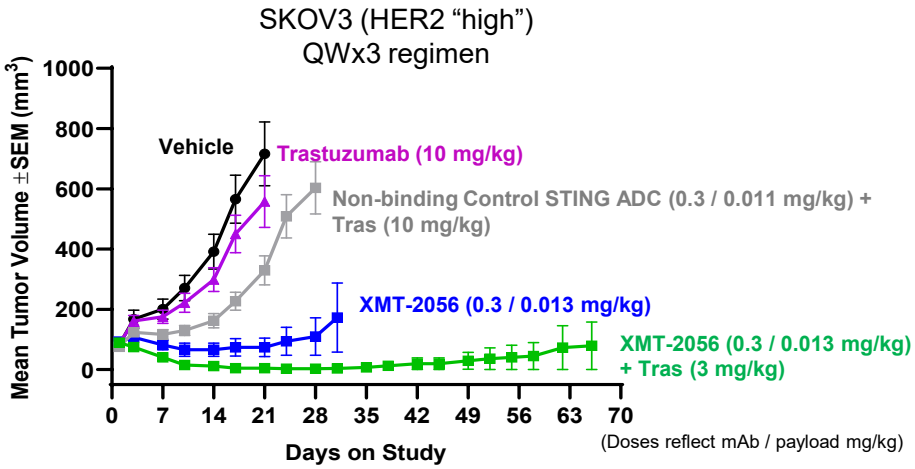
[&]CCLE RNAseq data from DepMap, Broad (2021): DepMap 21Q3 Public

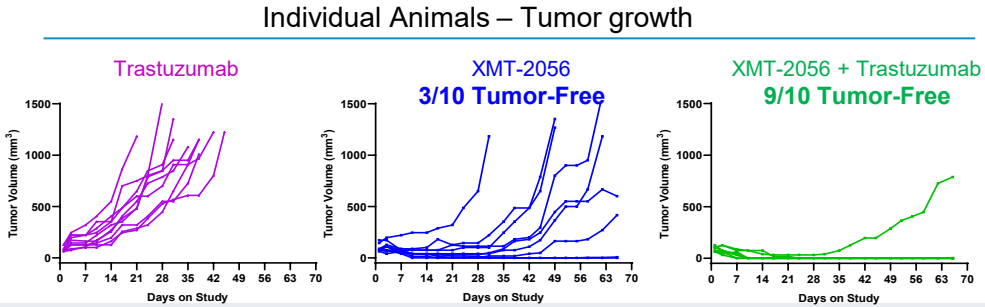


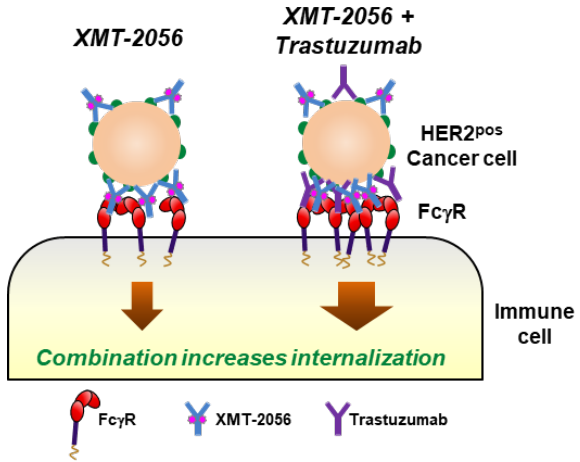


diABZI IV STING agonist*

XMT-2056 plus Trastuzumab Combination Shows Benefit *In Vivo*







XMT-2056 and trastuzumab have non-overlapping epitopes

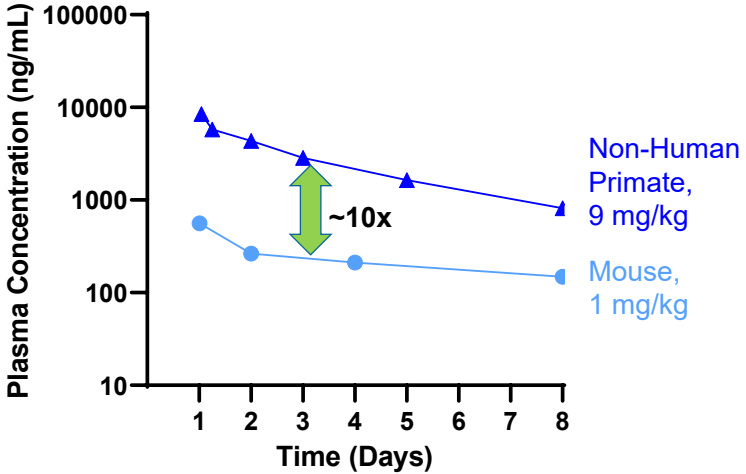
XMT-2056 Displays a Therapeutic Index Based on Exposure in Relevant Pre-clinical Species

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

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



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

XMT-2056 - Summary

- XMT-2056 offers a novel approach to the treatment of HER2-expressing tumors. Preclinical data to date shows it:
  - Utilizes a novel antibody that is non-competitive with trastuzumab and pertuzumab
  - Demonstrates target-dependent STING activation of tumor cells and tumor-resident immune cells, both of which can contribute to the anti-tumor effect
  - Is highly efficacious as single agent and in combination with trastuzumab
  - Is well-tolerated with no adverse events in NHPs after repeat doses at exposures far exceeding those required for efficacy in mouse

IND-enabling studies on-going with Ph1 study planned for early 2022

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