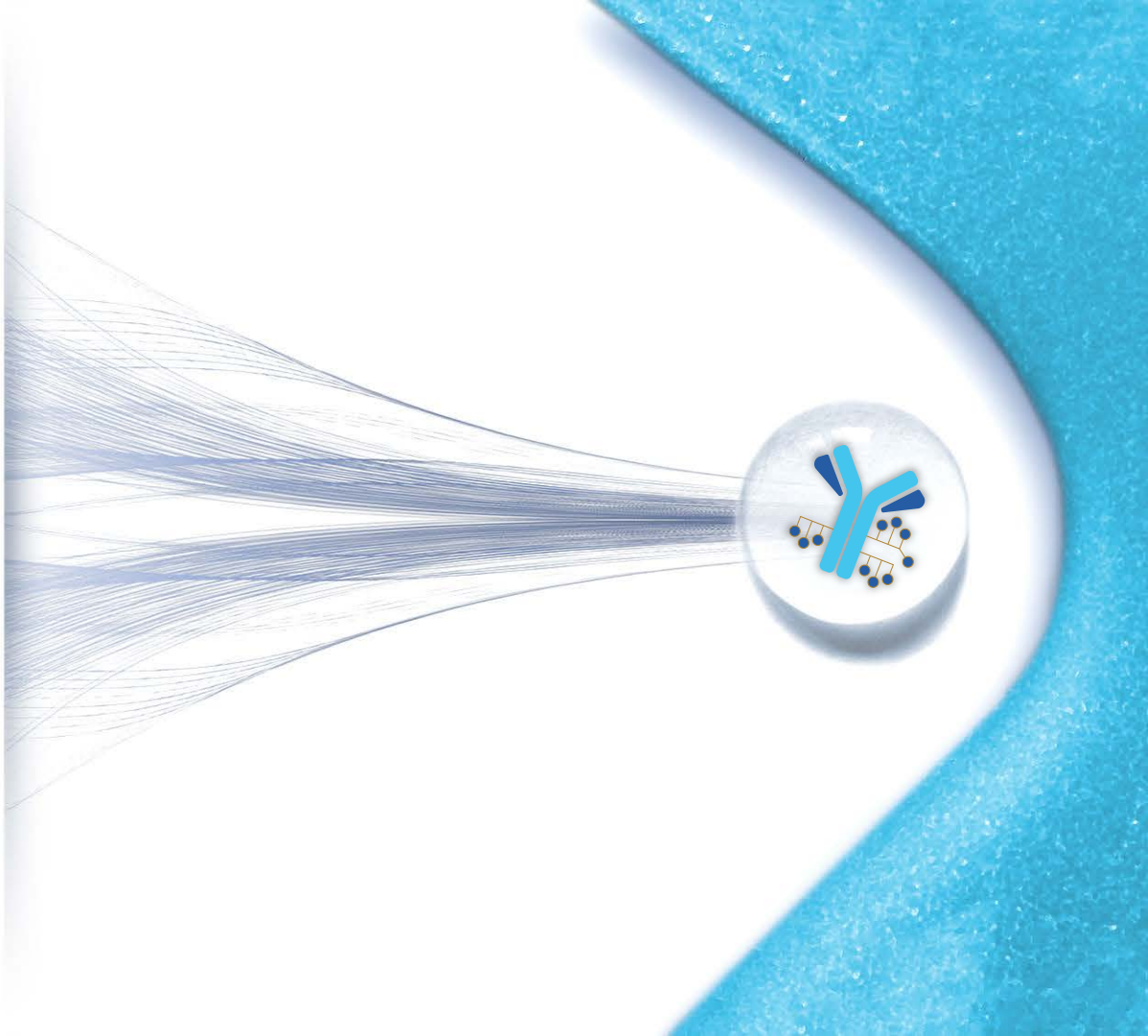
Mersana THERAPEUTICS

Tumor Targeting of a STING Agonist by Means of an Antibody-Drug Conjugate Induces Potent Anti-Tumor Immune Responses

Marc Damelin, Ph.D.

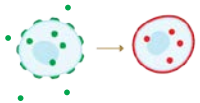
Innate Immunity Stimulating Therapies Summit
Digital Event – July 22, 2020



Innovative and Highly Differentiated ADC Technologies and Platforms

DolaLock

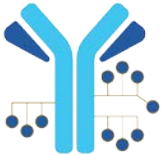
Efficacy without severe neutropenia, neuropathy, or ocular toxicity



- Controlled bystander effect
- Selectively toxic to rapidly dividing cells
- Not a PgP substrate
- Induces immunogenic cell death

Dolaflexin

Improved therapeutic index vs. other platforms



- DolaLock payload
- Polymer scaffold
- DAR ~10-12
- Excellent drug like properties

Dolasynthen

Homogenous & Customizable Platform

- DolaLock payload
- Synthetic scaffold
- Site-specific
- Precise DAR (2-24)

Immunosynthen

Systemic administration with targeted immuno-stimulatory effect

- Novel STING agonist
- Complete regression with one dose in multiple preclinical models
- Limited effect on systemic cytokines

DAR = Drug-to-antibody ratio
STING = Stimulator of Interferon Genes

Why We Invested in STING over other Innate Immunity Pathways

- **Preclinical evidence** that STING activation induces prolonged anti-tumor activity and generates immune memory
  - Other agonists, including TLR7/8, have not shown similar activity in reported studies
  - STING activation is more specific to potent Type I interferon gene activation, while TLR activation is associated with general inflammation
- Emerging **clinical evidence** that STING agonists (intratumoral injection) activate the pathway and do not have significant tolerability concerns
- STING agonists are highly **compatible with bioconjugation** through the platform technology as they have favorable physicochemical properties
  - Oligonucleotides are less compatible (i.e. TLR9, RIG-1)
  - Mersana has focused on non-CDN agonists

Strong Rationale for a STING ADC Approach

ADCs are suited to overcome limitations of free agonist (intratumoral or IV)

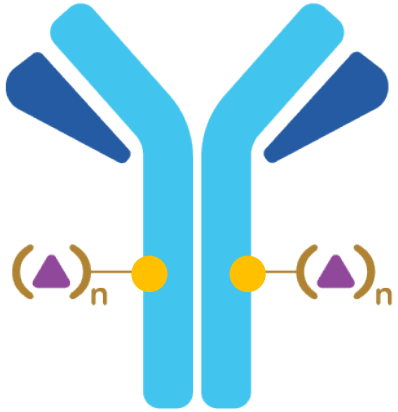
- Targeted delivery reduces toxicity liabilities
  - Minimize toxicity to T and B cells by selective targeting of ADCs (T cell intrinsic function)
  - Minimize systemic inflammation
- Improved pharmacokinetics
- Accessibility to metastatic sites
- No restriction on tumor type, location or size

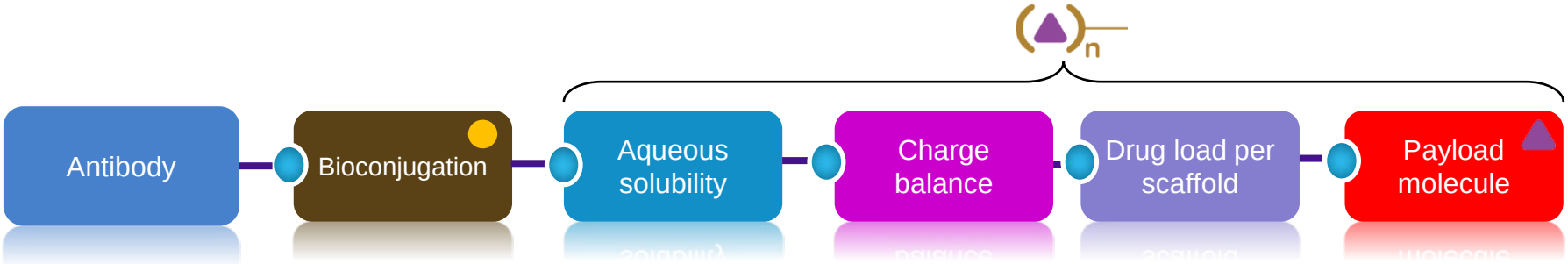
Holistic Approach to Build the Optimal STING ADC

Evaluation included:

- Analytical
- *In vitro* characterization
- *In vivo* characterization
- Developability

1. **Platform**
   - Payload
   - Linker
   - Scaffold
   - Drug-to-Antibody Ratio (DAR)
2. **Target and Antibody**
   - Immune cell antigens
   - Tumor cell antigens
   - Tumor-associated antigens

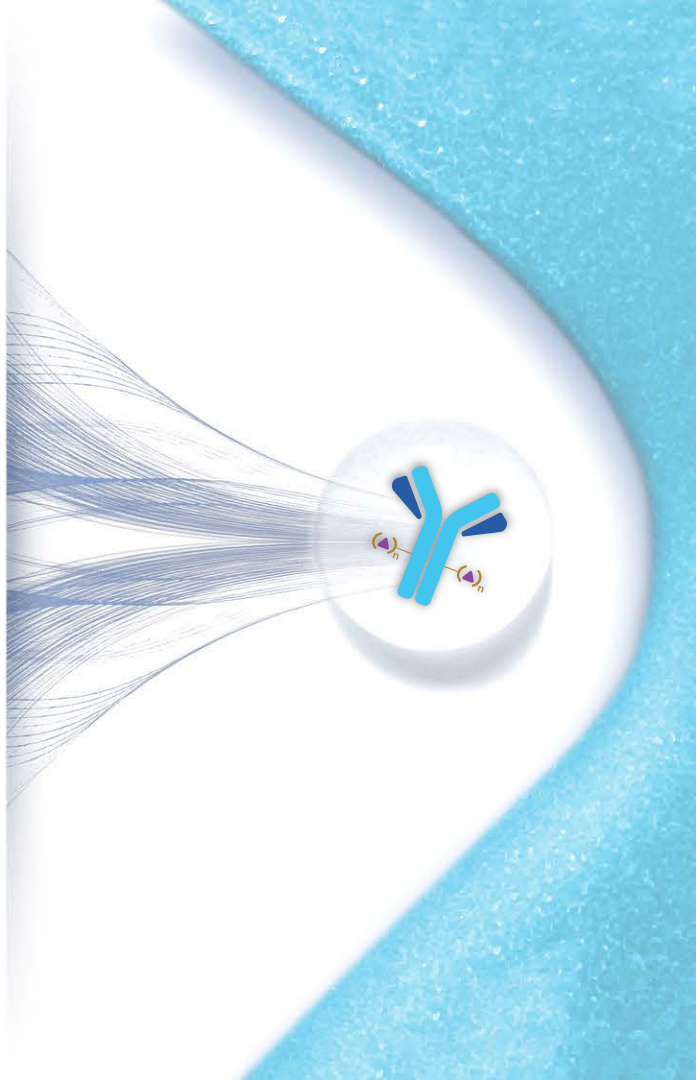




Immunostimulatory ADC Platform Development Cannot Be Based Solely on Cytotoxic ADC Experience

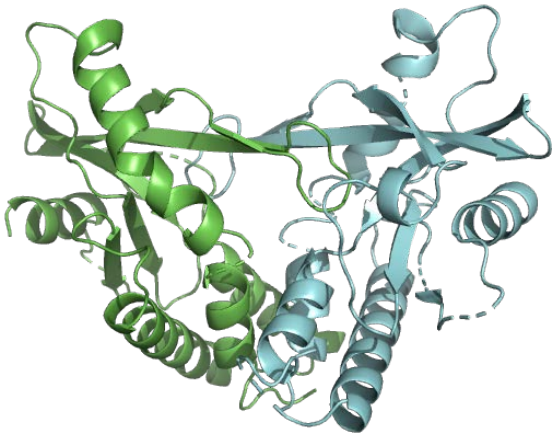
- The target cell is not necessarily a tumor cell
  - Potential for new mechanisms for payload delivery
  - Implications for choice of targets and antibodies
- Optimal payload requirements are not known
  - Potency
  - Membrane permeability & efflux properties
  - Metabolism rate (once released)
- Special considerations for I-O *in vivo* studies
  - Xenograft models are grown in immune-compromised mice
  - Syngeneic models are not compatible with certain targets and antibodies

Platform Development

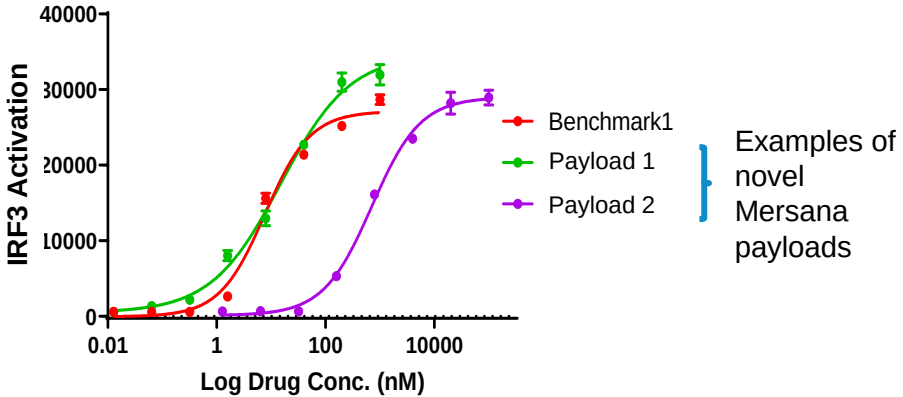


Novel STING Agonists Designed for ADCs

- Identified novel compounds representing multiple series
  - Compounds have a range of biological activity & diverse physicochemical properties
- Leveraged structure-based drug design (SBDD) and crystallography
  - Crystal structure solved with novel ligand bound to STING
- Filed IP

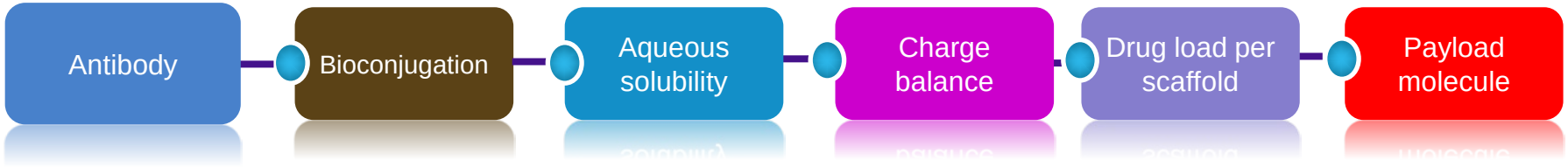


*Ligand has been removed from structure

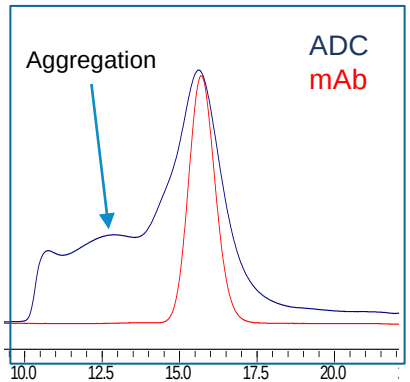


Leveraging Our ADC Expertise and Proprietary Technologies

Modular Synthemer Approach Enables ADC Optimization

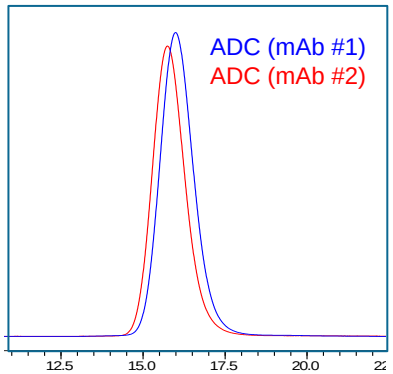


Aggregation in Initial STING ADC



Optimization

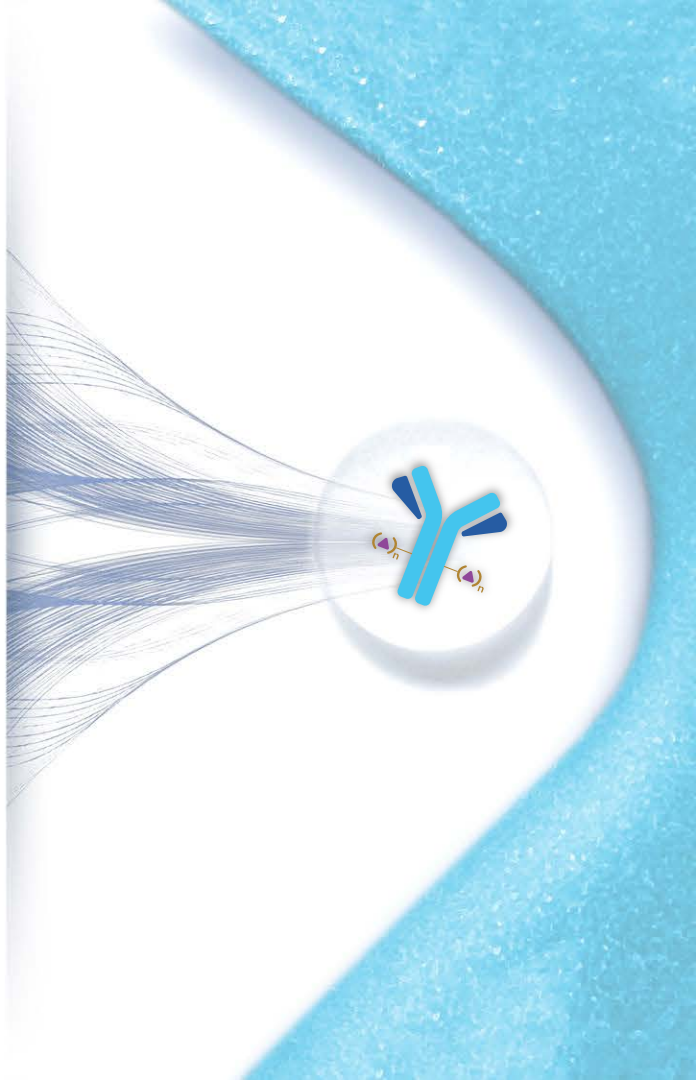
No Aggregation after Optimization
(STING ADCs from 2 different mAbs)



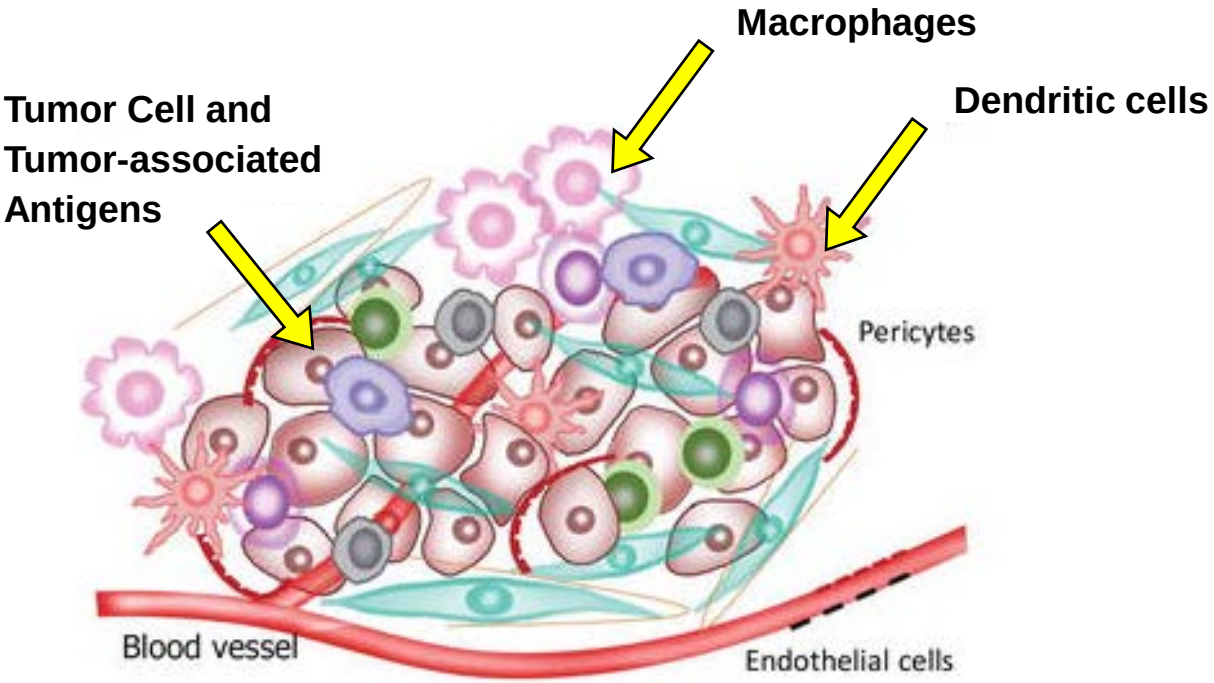
Summary of Exploratory Toxicology in NHP

- Evaluated ADCs based on 3 antibodies
- Dosed up to 9 mg/kg antibody (~0.3 mg/kg STING agonist)
- Repeat-dose and single-dose cohorts
- Clinical observations
  - All animals appeared normal throughout study
  - No changes in body temperature
  - No mortality or unscheduled euthanasia
- Toxicokinetics
  - High exposure after both administrations; 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

Targets and Antibodies



Comprehensive Approach to Target Validation and Selection



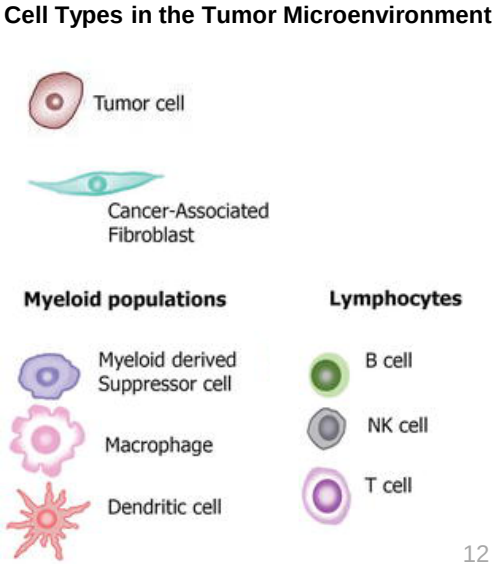
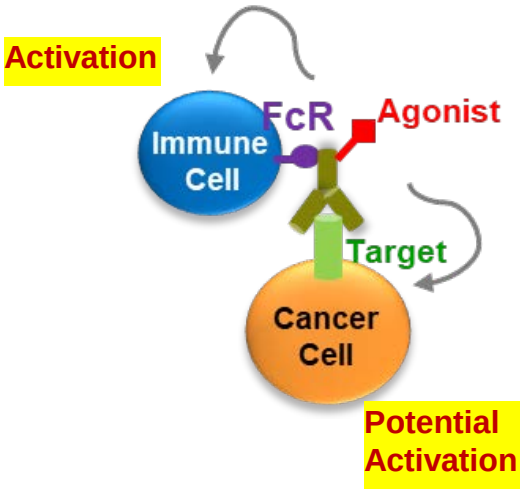


Image based on DOI: 10.5772/intechopen.72648

STING Agonist ADCs with Complementary Therapeutic Rationales Based on Antigens and Target Cells

Target Category	Rationale
Immune Cell	• Direct activation of immune cells
Tumor Cell	• Delivery to tumor and immune cells • Tumor-targeted delivery
Tumor-Associated	• Proximity of antigen to immune cells • Tumor-targeted delivery

Delivery to 2 Cell Types



Tumor-Targeted ADC Activates STING in Immune Cells

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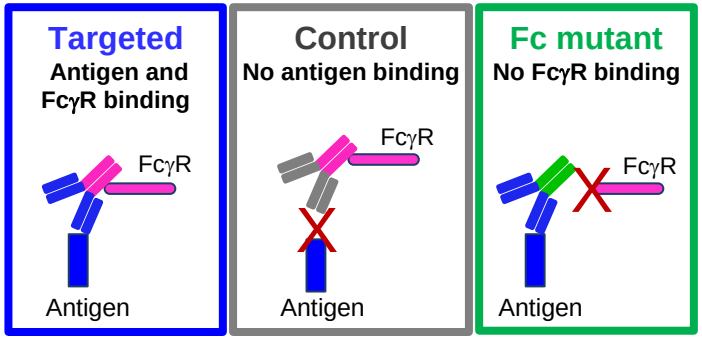
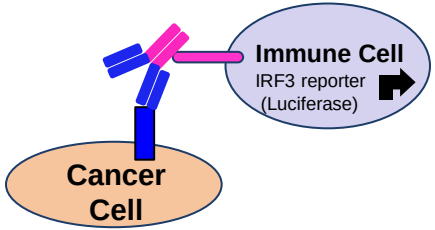
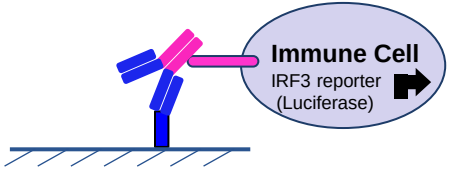
Antibody variants



Co-culture assay

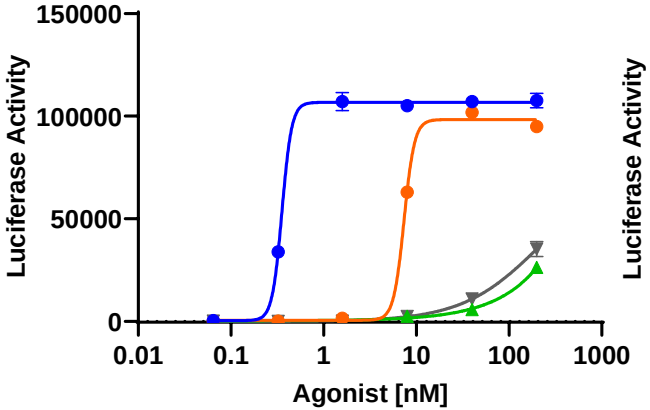


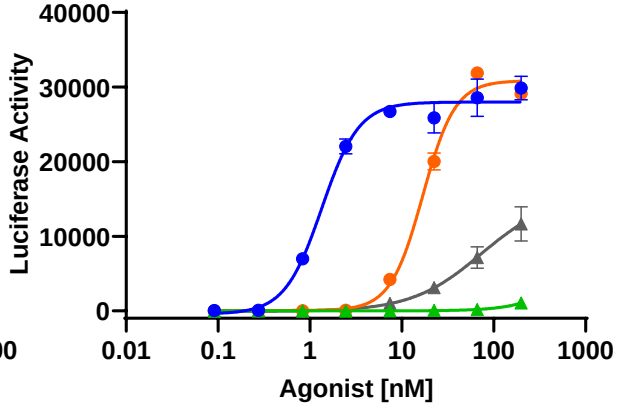
Recombinant antigen assay



Legend

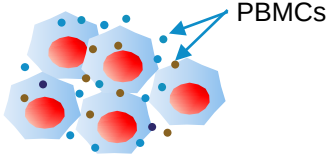
- Targeted ADC
- Targeted ADC – Fc Mutant
- Control ADC
- Free Payload



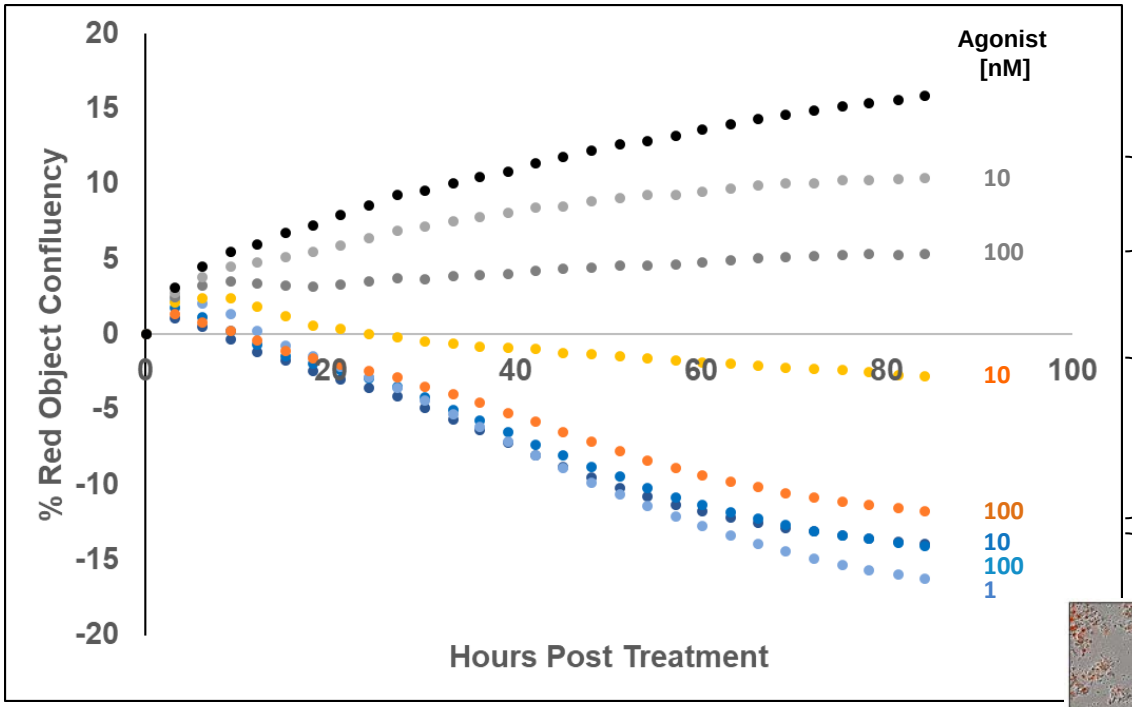


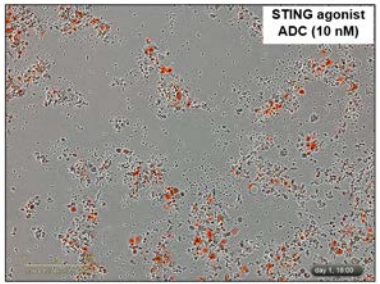
Tumor-Targeted STING Agonist ADC Induces Killing of Cancer Cells by PBMCs

Co-culture:
Cancer cells & PBMCs



- Cancer cells have stable expression of a red fluorescent protein in the nucleus
- These cancer cells have minimal STING activity

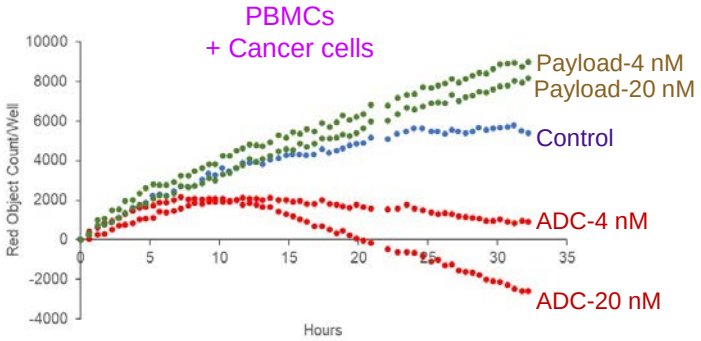


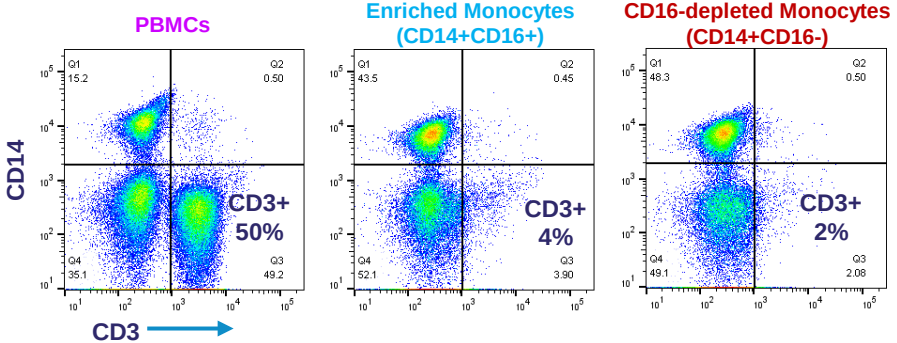


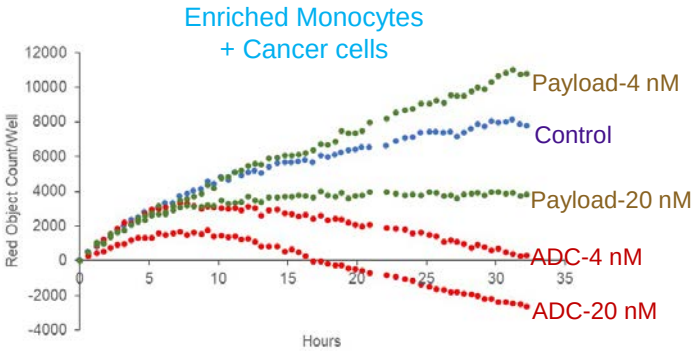
100-Fold Increased Potency of ADC over Free Agonist

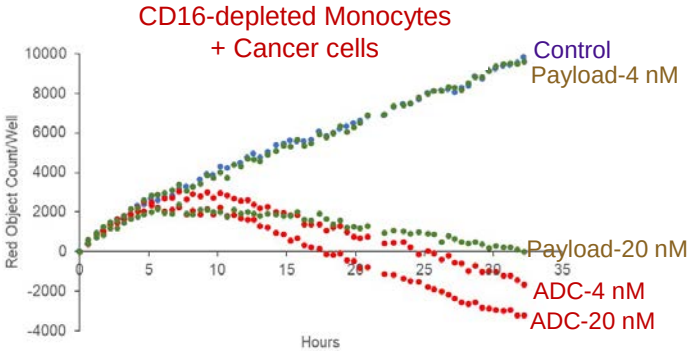
T Cells are Dispensable for Cancer Cell Killing

Supports the hypothesized mechanism of action

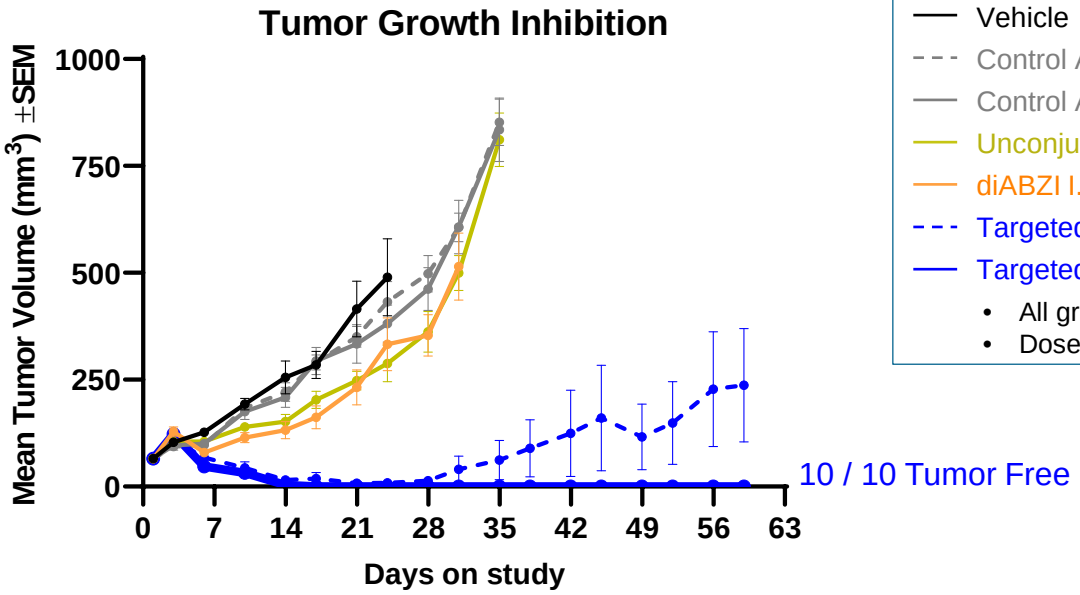








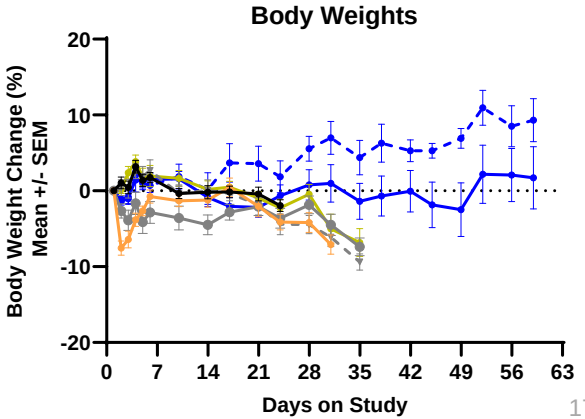
Sustained Tumor Regressions Induced by a Single Administration of STING ADC



Legend

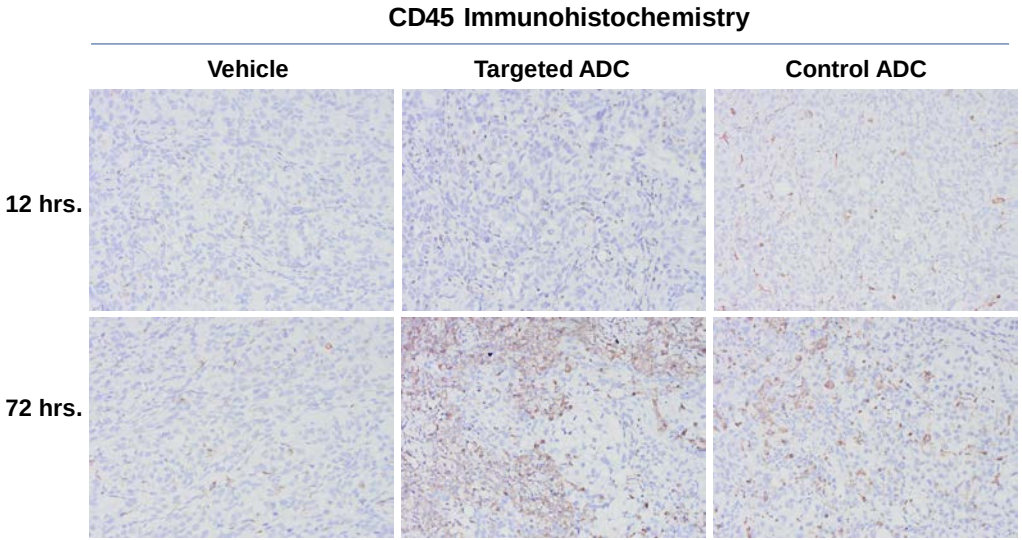
- Vehicle
- Control ADC (1 / 0.04 mg/kg)
- Control ADC (3 / 0.12 mg/kg)
- Unconjugated Antibody (3 / 0 mg/kg)
- diABZI I.V. agonist (0 / 5 mg/kg)
- Targeted ADC (1 / 0.03 mg/kg)
- Targeted ADC (3 / 0.09 mg/kg)

• All groups dosed IV
• Doses in (mAb [mg/kg] / Payload [mg/kg])



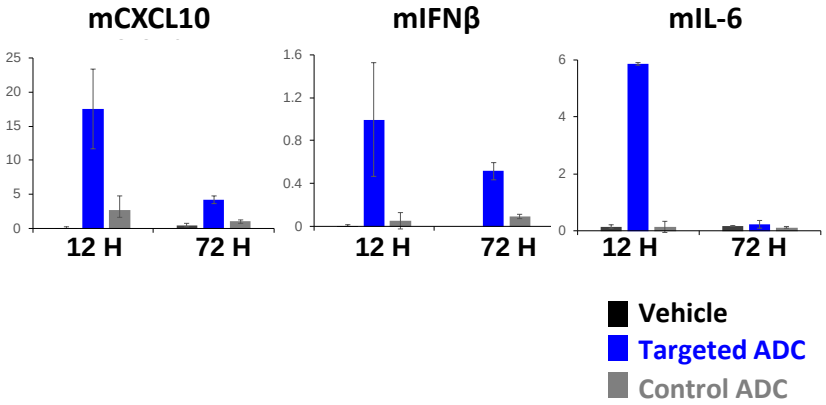
Target-Dependent Immune Cell Infiltration and Cytokine Induction in Tumors

- ADC single dose
- Tumors harvested 12 or 72 hrs post dose

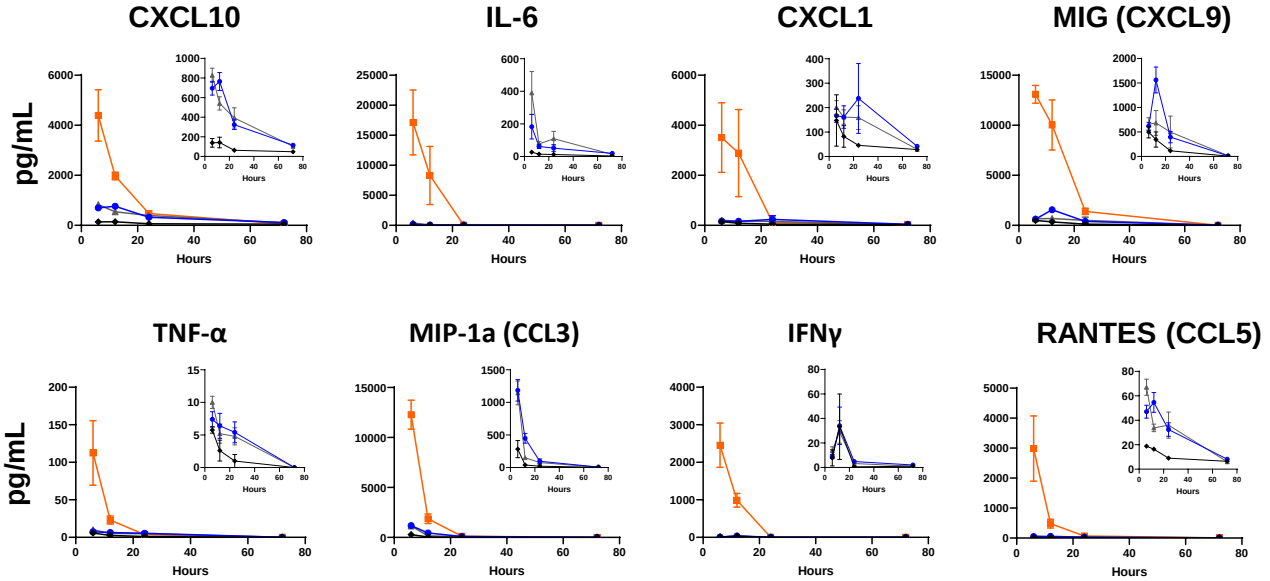


Murine cytokine expression

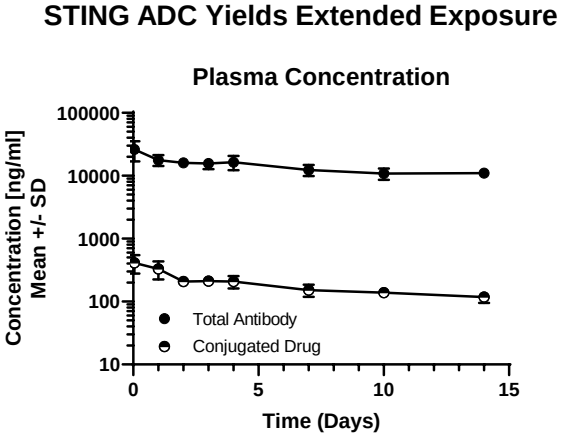
(qPCR on FFPE samples)



Dramatically Lower Induction of Serum Cytokines in Mice by STING ADC Compared to Free STING Agonist

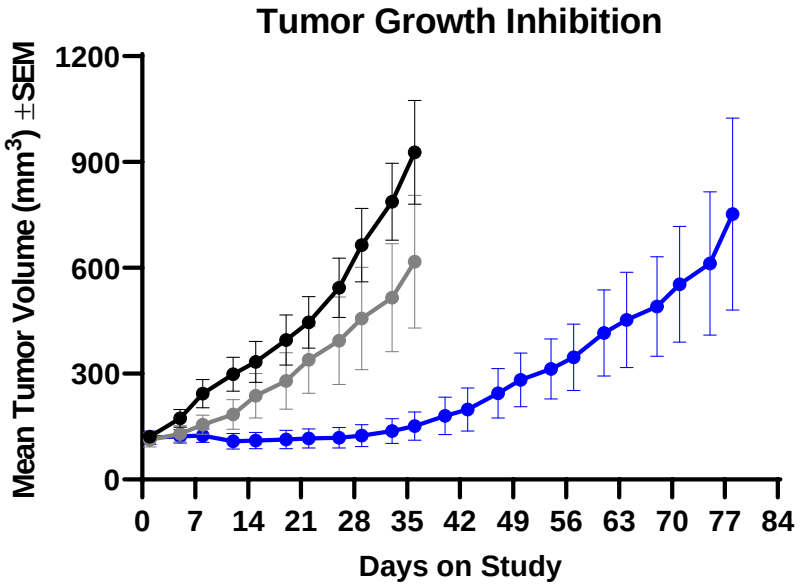


Luminex assay



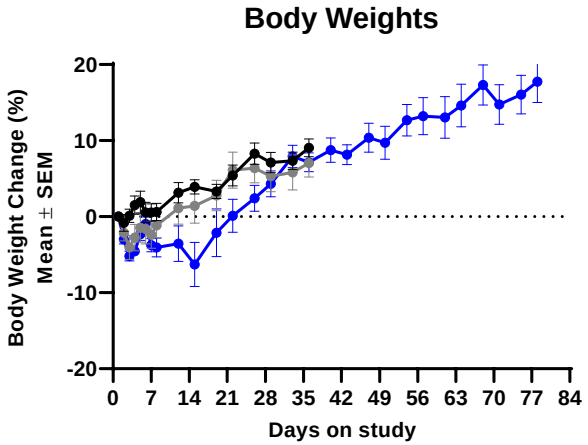
- Vehicle control
- Targeted ADC (0.09 mg/kg payload = dose for complete tumor regression)
- Control ADC (0.09 mg/kg payload)
- STING diABZI I.V. agonist (5 mg/kg payload = maximum tolerated dose; 37% tumor growth inhibition)

Another Target and Tumor Model: STING Agonist ADC Inhibits Tumor Growth After a Single Dose



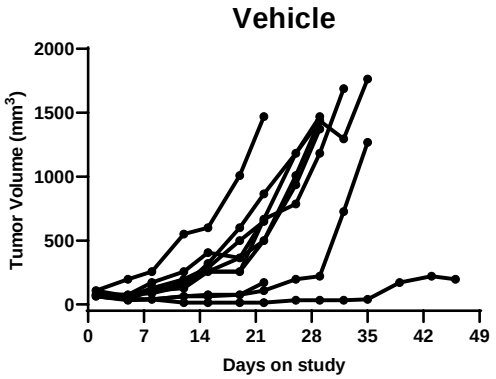
Legend

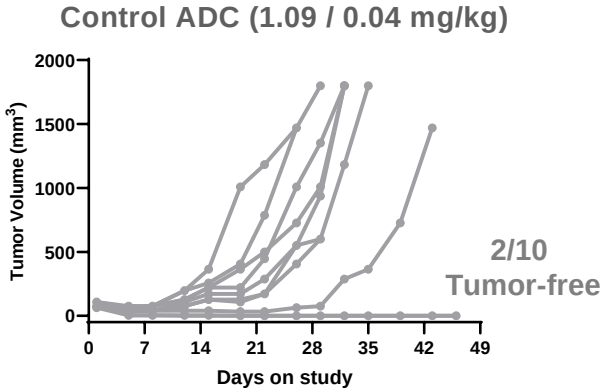
- Vehicle
- Control ADC (3 / 0.1 mg/kg)
- Targeted ADC (3 / 0.1 mg/kg)
  - All groups dosed IV
  - Doses in (mAb [mg/kg] / Payload [mg/kg])

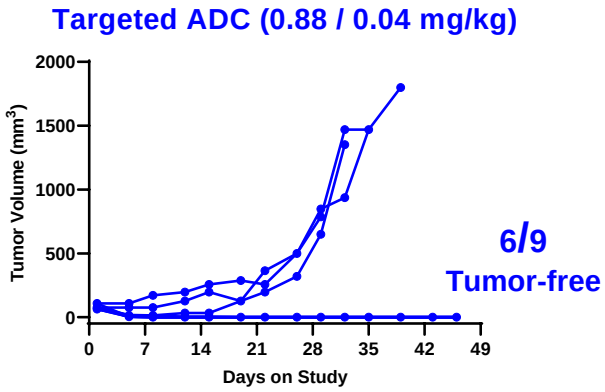


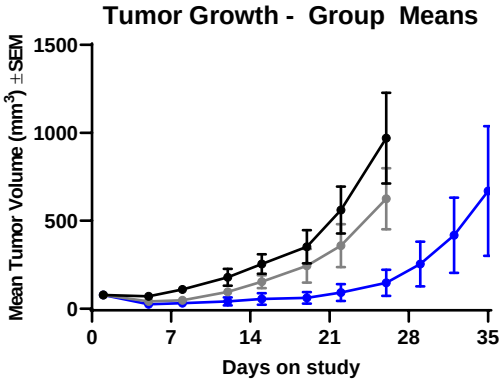
Sustained Tumor Regressions After a Single Dose in a Syngeneic Model

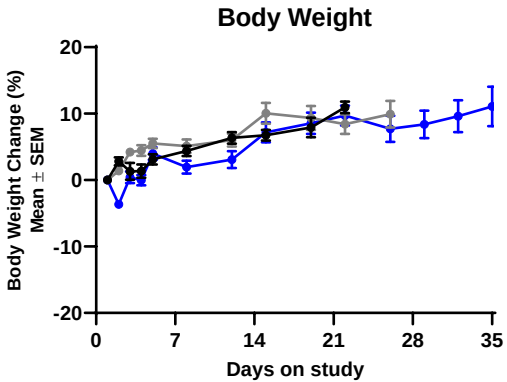
Dose: mAb / payload (mg/kg)





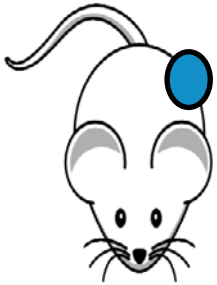






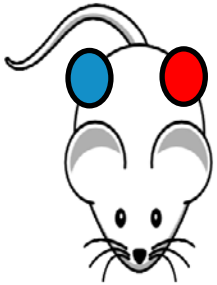
Immunological Memory Induced by STING Agonist ADC

Efficacy Study

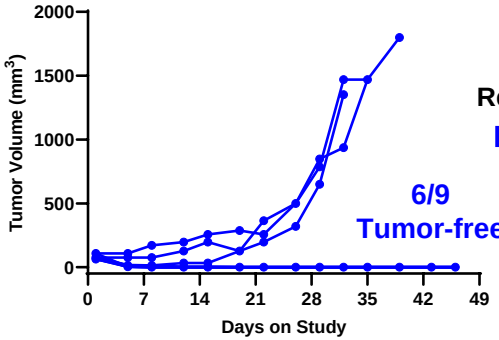


- **Tumor free mice** re-implanted with:
  - Original targeted tumor on the opposite flank (blue), and
  - Non-targeted tumor on the other flank (red).
- Untreated age matched mice also implanted as a control (black line).

Rechallenge Study (Dual Flank)



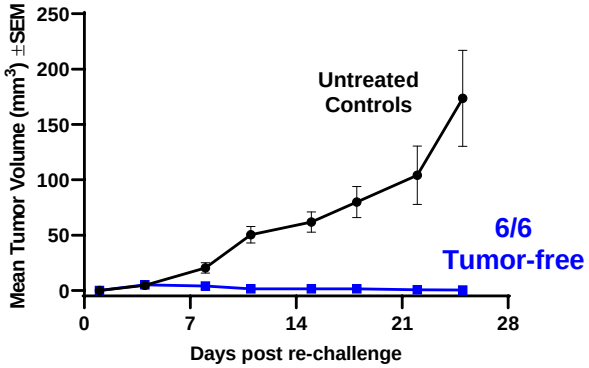
Targeted ADC (0.88 / 0.04 mg/kg)



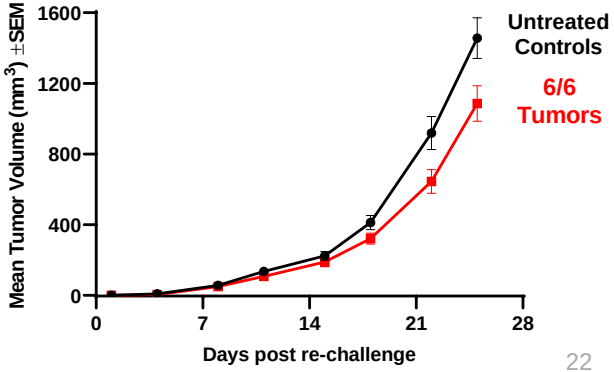
Dose: mAb/ payload mg/kg)

Re-challenge

Targeted tumor



Non-targeted tumor



Conclusions

1. STING agonist ADC platform
    - Novel agonist payload optimized for ADC
    - Linker & scaffold designed to maximize therapeutic index
    - Well-tolerated in non-human primates
2. *In vivo* activity in multiple targets, tumor models and mouse strains
3. Differentiation from IV agonist: activity and tolerability
4. Immunological memory
5. On track to nominate 1st Development Candidate in 2020

Mersana's STING ADC Research Team

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Eoin Kelleher
Liping Yang
Radha Iyengar
Dorin Toader

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Alex Uttard
Anouk Dirksen
Dorin Toader

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Tyler Carter
Susan Clardy
Mark Nazzaro
Elena Ter-Ovanseyan
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