Utilizing Probody® Technology to Develop Therapeutics to Undruggable Targets

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CytomX Therapeutics, Inc.

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This presentation concerns products that have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). No representation is made as to their safety or effectiveness for the purposes for which they are being investigated.

Presentation Outline

Overview of Probody® technology

CX-2029: A Probody Drug Conjugate (PDC) Targeting Transferrin Receptor (CD71)

- Target rationale (rapid internalization, ubiquitous tumor expression)
- Preclinical efficacy and nonclinical safety

CX-2043: A PDC targeting EpCAM (CD326)

- Target rationale (high tumor expression)
- Preclinical efficacy and nonclinical safety

Probody Therapeutics are Designed to be Activated in the Tumor Microenvironment (TME)

ON TARGET TOXICITY LIMITS THE DEVELOPMENT OF POTENTIALLY ATTRACTIVE ANTIBODY THERAPEUTICS

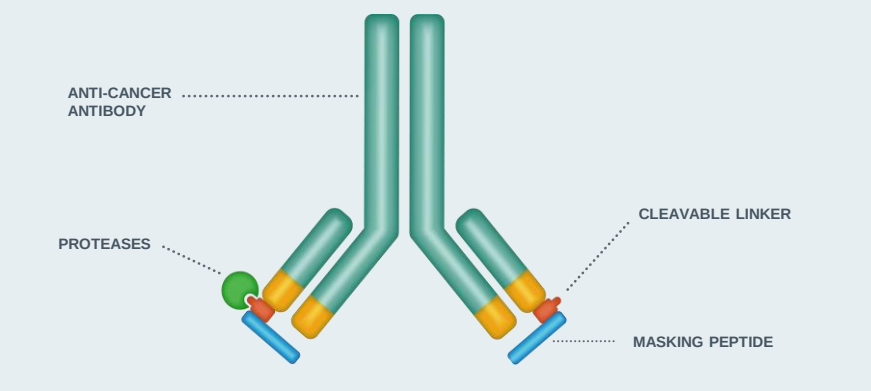
- "Masked" to limit binding to normal tissue
- "Un-masked" by tumor-associated proteases
- Linkers cleaved by multiple proteases for utility across tumor types

CYTOMX PROBODY PLATFORM IS DESIGNED TO LOCALIZE TARGET BINDING TO TUMOR

- Maintaining potency
- Reducing side effects
- Enabling new target opportunities

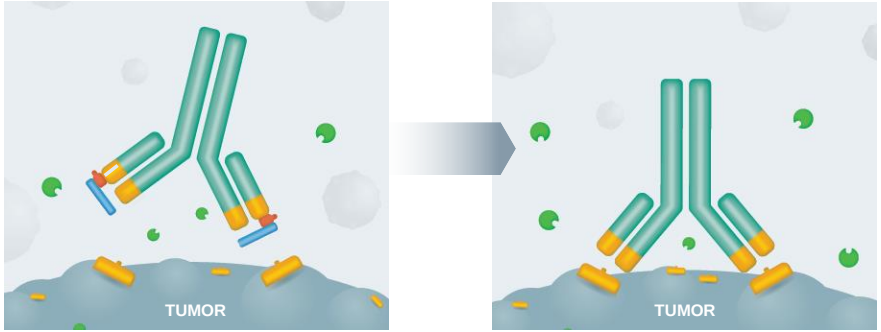
PROBODY PLATFORM IS APPLICABLE ACROSS MULTIPLE TARGETS AND MODALITIES

- Improve therapeutic window for validated targets
- Create therapeutic window for undruggable targets
- Applicable to multiple binding modalities



Enters TME, proteases remove mask

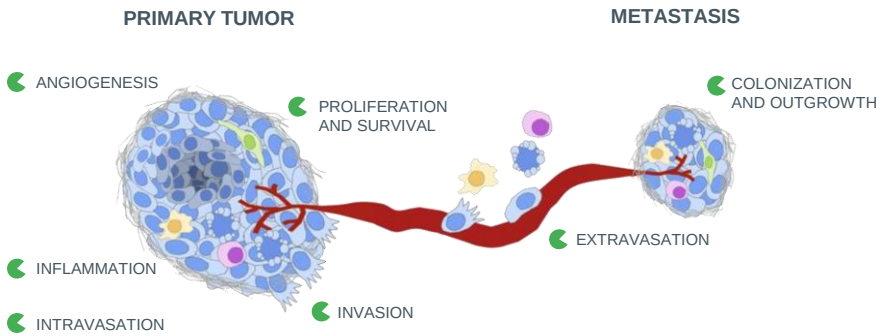
Antibody binds target



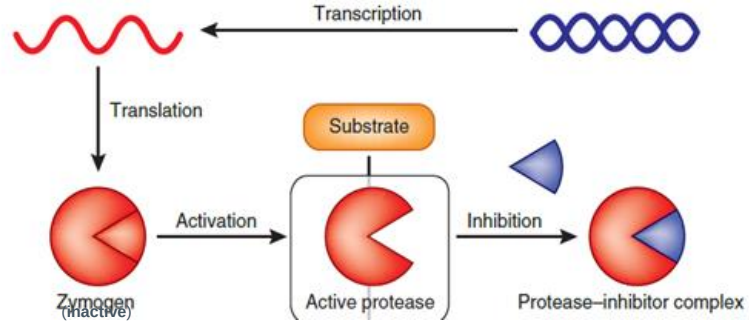
CytomX Therapeutics

Activated Proteases are Prevalent in Tumors but Not in Healthy Tissue

UPREGULATED PROTEASE ACTIVITY IS A HALLMARK OF ALL CANCERS[1]



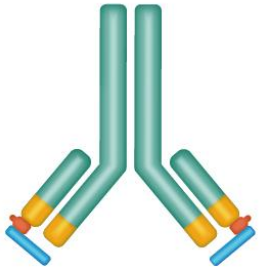
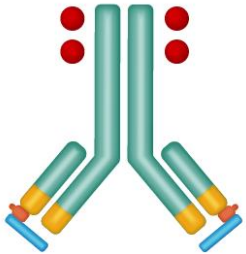
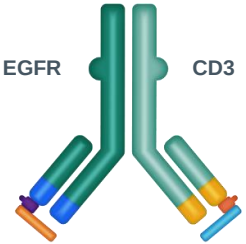
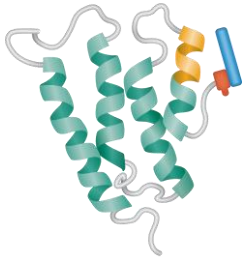
PROTEASE ACTIVITY IS TIGHTLY CONTROLLED IN HEALTHY TISSUES[2]



IMAGING OF ACTIVE PROTEASE[3]

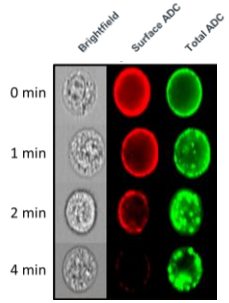
1. Sevenich, et. al. Gene & Dev., 2014; 2. Deu, et.al., Nature Struct Mol Biol 2012; 3. Matriptase: LeBeau, et al., PNAS 2013

Probody Platform is Applicable Across Multiple Modalities

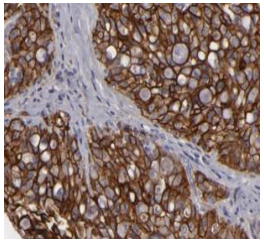
IMMUNE MODULATORS/ CHECKPOINT INHIBITORS	ANTIBODY DRUG CONJUGATES	T-CELL BISPECIFICS	CYTOKINES
			
PD-L1 (CX-072) PD-1 (CX-188) CTLA-4 (BMS-986249, 986288)	CD166 (CX-2009) CD71 (CX-2029) EpCAM (CX-2043) Multiple undisclosed programs	EGFR-CD3 (CX-904) Multiple undisclosed programs	DISCOVERY STAGE

Probody Platform Expands Target Landscape; Converting Undruggable to Druggable

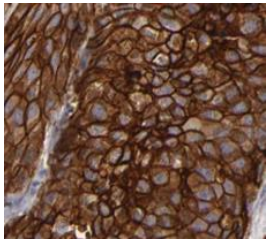
Efficiently Internalizing



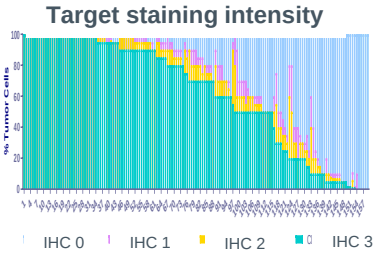
High Membrane Expression



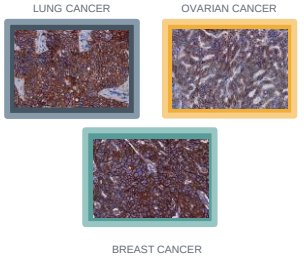
Uniform Tumor Expression



Majority of Patients Express at High Level



Highly Expressed in Multiple Common Cancers



These targets are typically expressed highly in normal tissues → not suitable for traditional ADC

CytomX Therapeutics

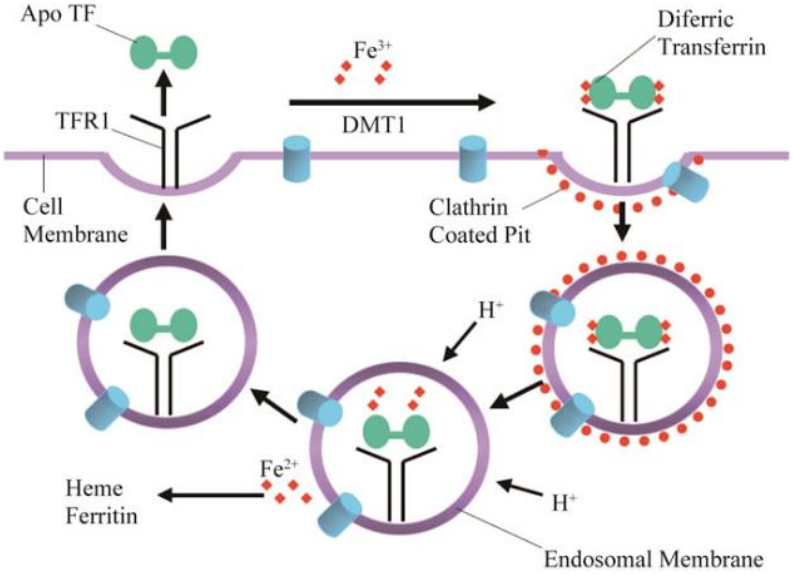
CX-2029:
A Probody Drug Conjugate (PDC) Targeting CD71, Transferrin Receptor

Clinical Presentation: Dr. Alison Hannah, CMO

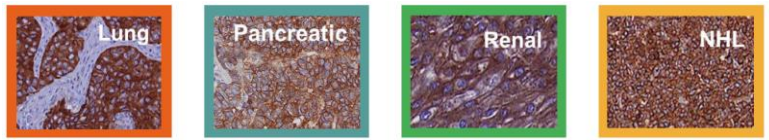
12:10pm Sept. 16th, Clinical Stream

CD71 (TfR1) Transferrin Receptor

- Transmembrane glycoprotein that efficiently internalizes iron-bound transferrin
- Ubiquitously expressed on malignant cells, i.e. NSCLC-SCC, CRC, esophageal
- ‘Professional’ internalizing antigen
- Also expressed in healthy tissues with high iron requirement, notably
  - Dividing cells
  - Erythrocyte precursors
- Considered ‘undruggable’ with traditional ADC technology
- CX-2029 is a masked form of a proprietary anti-CD71 antibody conjugated to MMAE (DAR = 2)
  - Partnership with AbbVie

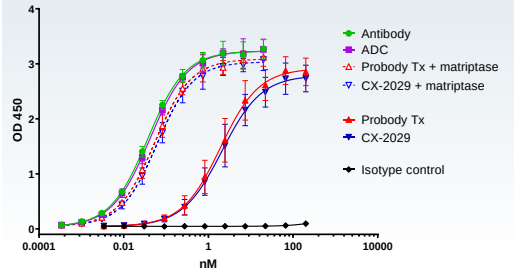


Elliott & Head, *J Cancer Therapy*, 3: 278-311 (2012)

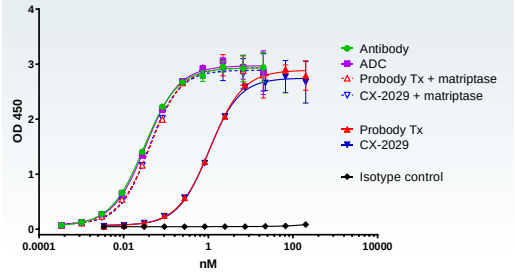


CX-2029 is Active in CDX and PDX Tumor Models in Mice

HUMAN CD71



CYNOMOLGUS CD71

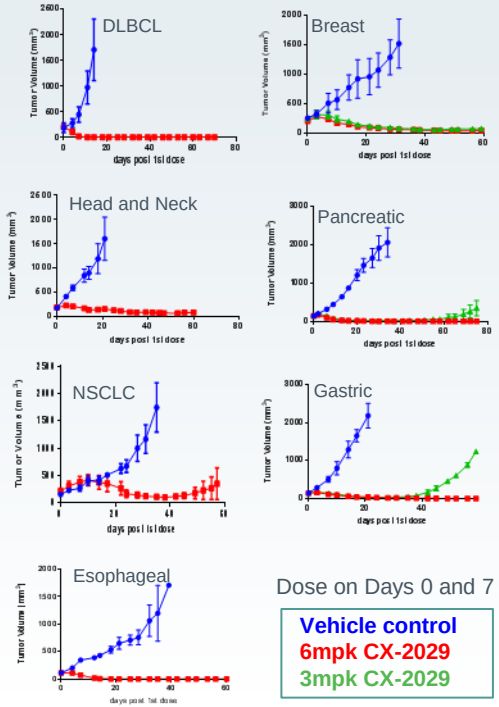


CDX - cell line derived xenograft
PDX - patient derived xenograft

- Parental anti-CD71 antibody binds equivalently to human and monkey CD71 (ELISA)
- Intact Probody therapeutic shows reduced binding to CD71
- Protease activation of PDC restores binding activity
- Broad, potent activity in mouse tumor models

Model Type	Regressions or Stasis
CDX (unselected)	15/21 (71%)
PDX (high expressing)	30/36 (83%)

EFFICACY IN PDX MODELS



Dose on Days 0 and 7

Vehicle control
6mpk CX-2029
3mpk CX-2029

CX-2029 Was Tolerated at a Higher Dose Than CD71 ADC in *Cynomolgus monkeys, DAR = 2*

Test Article	Dose (mg/kg)	Outcome	Hemoglobin*	Neutrophil count*
Vehicle	NA	--	13.1	4,693
CX-2029 (PDC)	6	Tolerated	10.1	347
CX-2029 (PDC)	12	Not tolerated	9.0	87
CX-2030 (ADC)	6	Not tolerated	6.6 (d10)	20 (d10)
CX-2030 (ADC)	2	Not tolerated	9.3 (d7)	70 (d7)
CX-2030 (ADC)	0.6	Tolerated	12.2	280

*Average HGB (g/dL), d15 or as indicated; average neutrophil count (per ul) on Day 11 or as indicated

- Primary toxicities are hematologic: Neutropenia and anemia
  - Consistent with either on-target (CD71-mediated) and/or off-target toxicity of MMAE
- Mortality at non-tolerated dose levels was attributed to bacterial infection

In clinical trial, phase I/II: NCT03543813 in collaboration with AbbVie

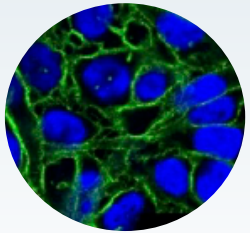
CytomX Therapeutics

CX-2043:
A Probody Drug Conjugate (PDC) Targeting EpCAM

EpCAM Target Biology and Opportunity for Probody Technology

TARGET BACKGROUND

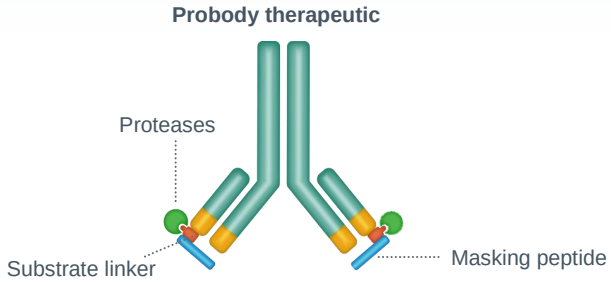
- Discovered via immunization of cancers in mice in 1979
- Epithelial cell marker
  - Widely used for delivery of toxins and immune stimulatory agents for epithelial cancers



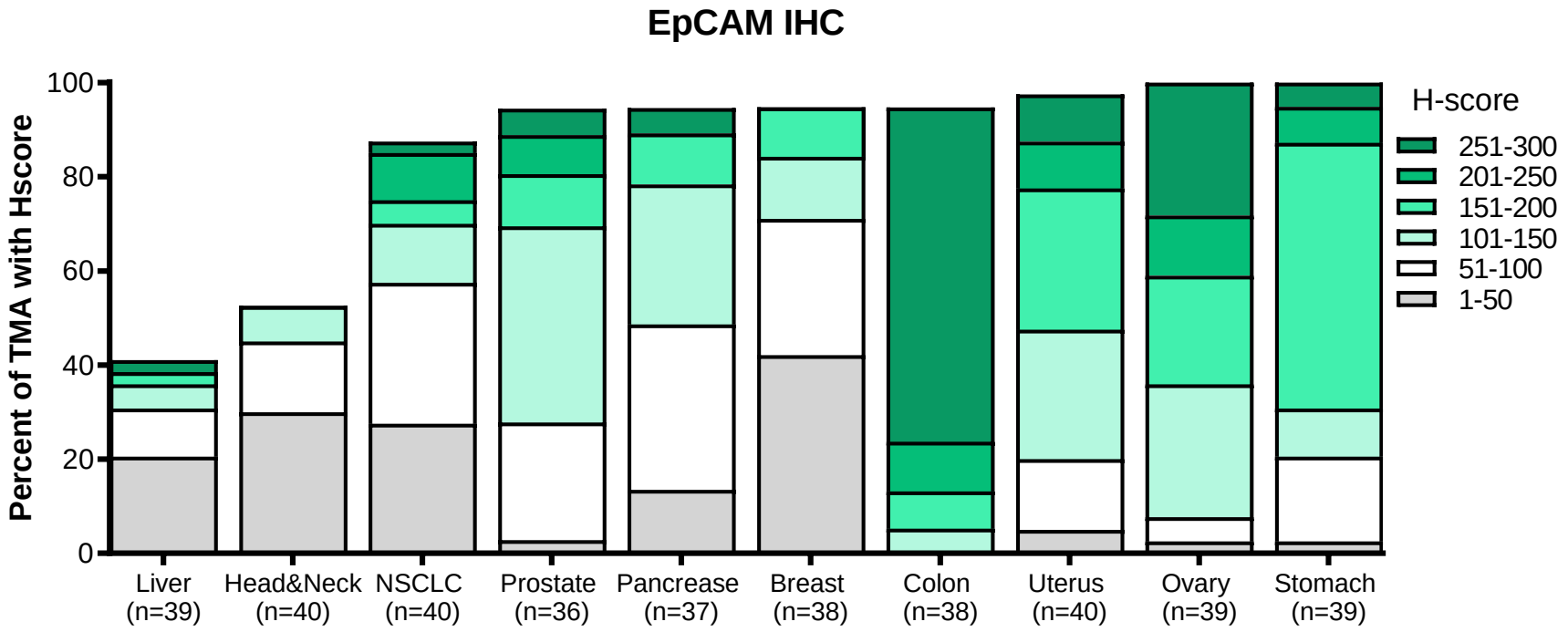
- Target with previously approved therapy (Catumaxomab: EpCAM-CD3 TCB)
  - Usage limited to local injection due to toxicity, discontinued in 2017
- Development of EpCAM-targeting therapeutics hindered by ON-target/OFF-tumor toxicity
  - Pancreatitis with α-EpCAM Ab
  - GI tox with EpCAM-CD3 BiTE

PDC OPPORTUNITY

- Alleviate ON-target/OFF-tumor toxicity (pancreatitis, GI tox)
- Retain potent efficacy
- Improve exposure by reducing target mediated clearance (TMDD)
- Expanded therapeutic index

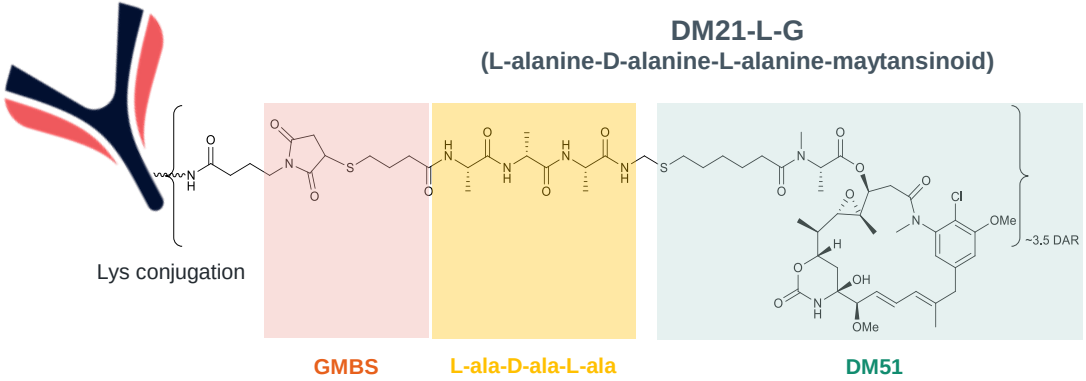


EpCAM Expression in Multiple Indications

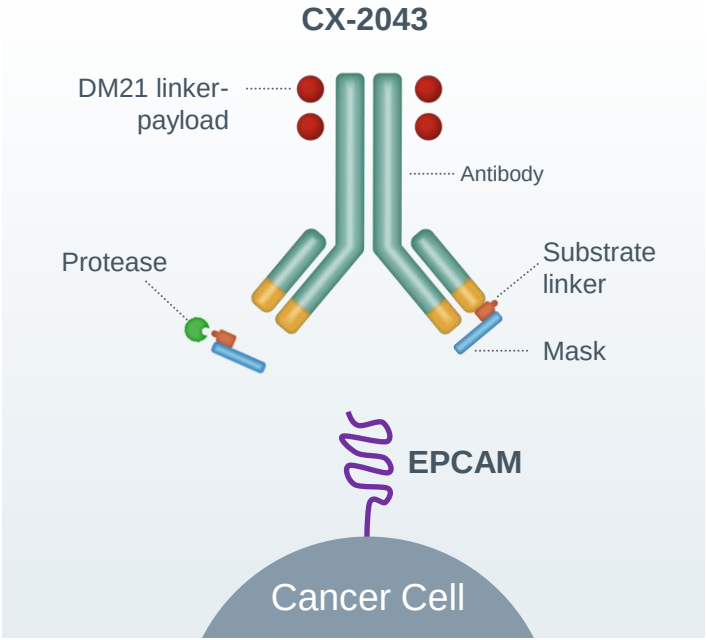


EpCAM expression is also present in corresponding normal tissues, and high in colon and GI tissues

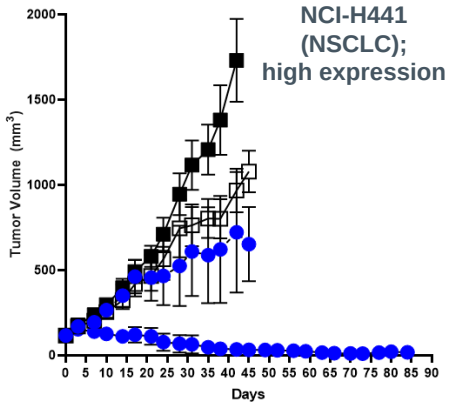
CX-2043: A Probody Drug Conjugate (PDC) Targeting EpCAM

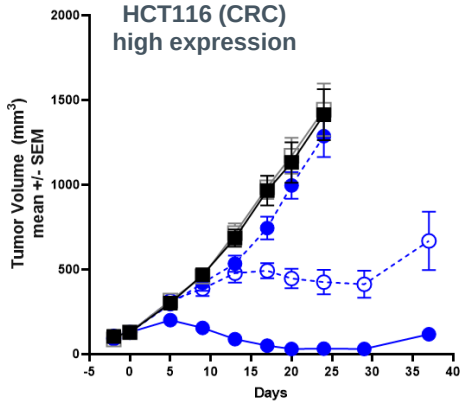


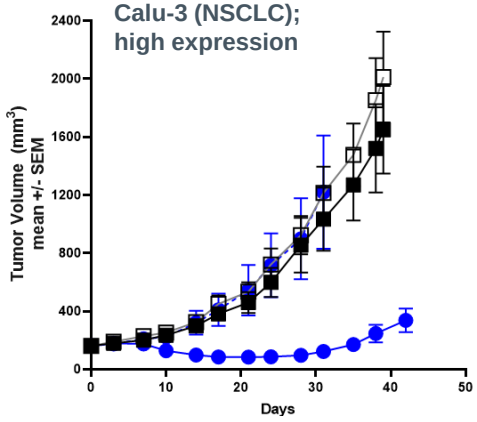
- Stochastic lysine conjugation, DAR 3.5 – 4
- Optimized stability with tripeptide linker, cleavable by intracellular lysosomal proteases
- Provides improved bystander activity

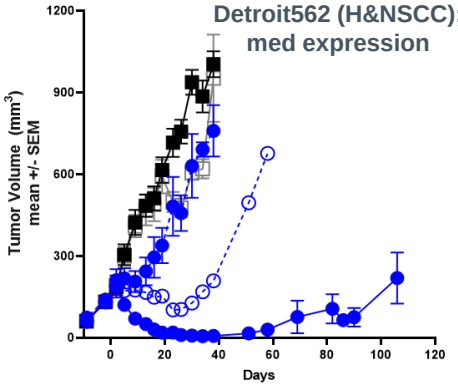


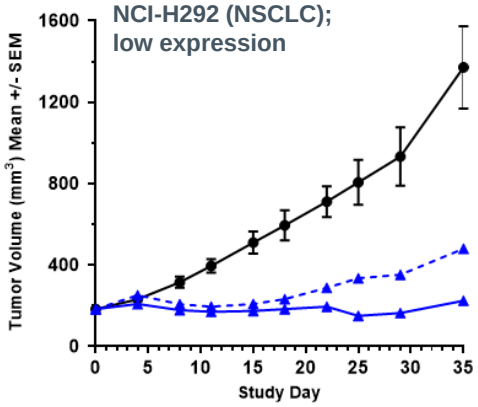
Single Dose of CX-2043 is Efficacious, Particularly in High Target Expression Models

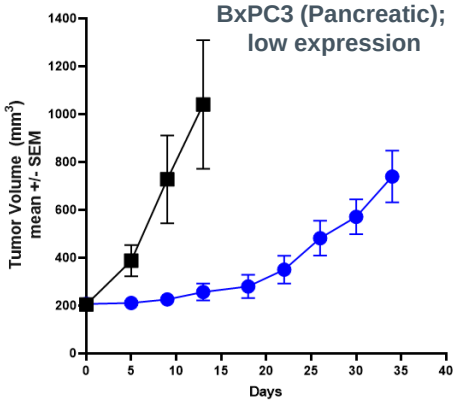












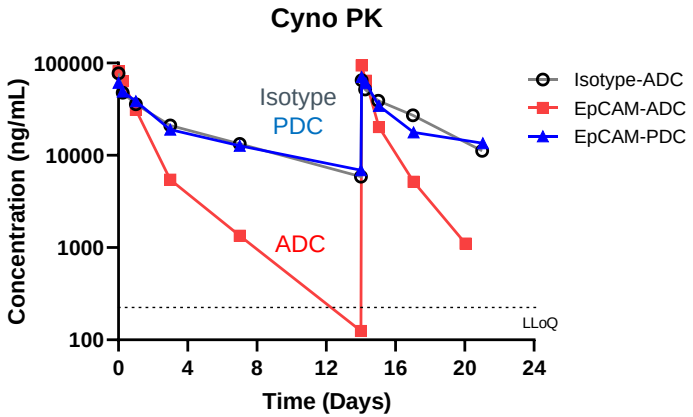
Single dose or fractionated

- CX-2043 low (0.9-2.5 mpk)
- CX-2043 high (3-5 mpk)
- CX-2043 fractionate (QWX3)
- IgG-DM21 high (3-5 mpk)
- Vehicle

CytomX Therapeutics

CX-2043 is Well Tolerated in Cyno up to 9 mg/kg; Q2WX2 Dosing

Dosing (Q2WX2)	ADC	PDC	Isotype
3 mpk	Not tolerated	Tolerated	Tolerated
6 mpk	Not tolerated		
9 mpk		Tolerated	
12 mpk			Tolerated



TOXICITY

- **Isotype-DM21-L-G ADC** at 12 mg/kg:
  - Dry, discolored skin; abrasion
  - Liquid feces, mild dehydration
  - ↓ albumin, electrolytes (Na^+, Cl^-), RBC
- **EpCAM-DM21-L-G PDC** at 9 mg/kg:
  - Dry skin, slight abrasion
  - Mild dehydration
- **EpCAM-DM21-L-G ADC** at 3 and/or 6 mg/kg:
  - > 10% weight loss, liquid feces
  - Early euthanasia required
  - ↓ albumin, Na^+, Cl^-, RBC; ↑ AST, BUN, CRN

PHARMACOKINETICS

- Increased PDC exposure relative to ADC suggests mitigation of target mediated clearance (TMDD) and effective masking

Summary: Utilizing Probody Technology for PDC Development

Probody Technology	• Designed to be minimally active systemically, until activated in the protease-enriched diseased microenvironment
Probody Advantages	• Mitigation of ON-target/OFF-tumor toxicity • Allows expansion of target landscape and development of therapeutics to traditionally undruggable targets, i.e. CD71 and EpCAM
PDC Opportunities	• Probody technology combined with next generation of linker-payloads for CX-2043 (EpCAM-PDC) has the potential to realize a therapeutic index
Advancing Clinical PDC Programs	• CytomX PDC programs, CX-2009 (CD166) and CX-2029 (CD71), demonstrated promising results and are proceeding to phase II clinical trials. CX-2043 (EpCAM) is in IND enabling studies