Development of a Probody Drug Conjugate (PDC) Targeting CD71 **for the Treatment of Cancer**

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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.

Outline

Overview of Probody® technology and CytomX pipeline

Development of a CX-2029, a Probody Drug Conjugate (PDC) targeting CD71 (Transferrin Receptor)

Development and validation of a diagnostic assay for CD71

Evaluation of target distribution in a patient population

Probody Therapeutics Are Designed to Be Activated in the Tumor Microenvironment (TME)

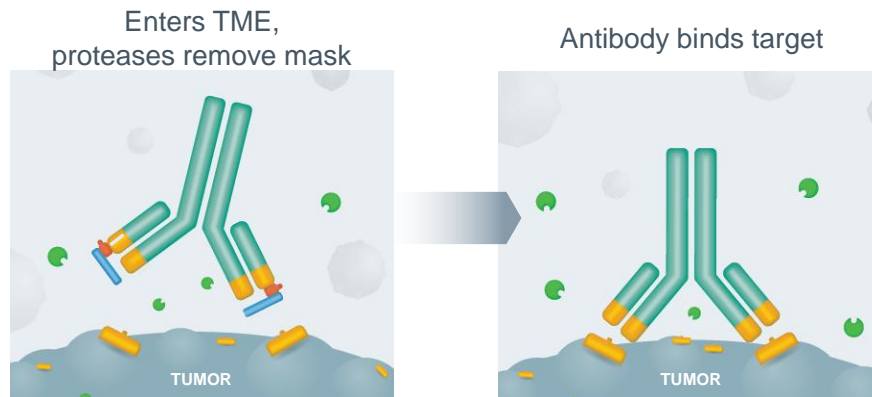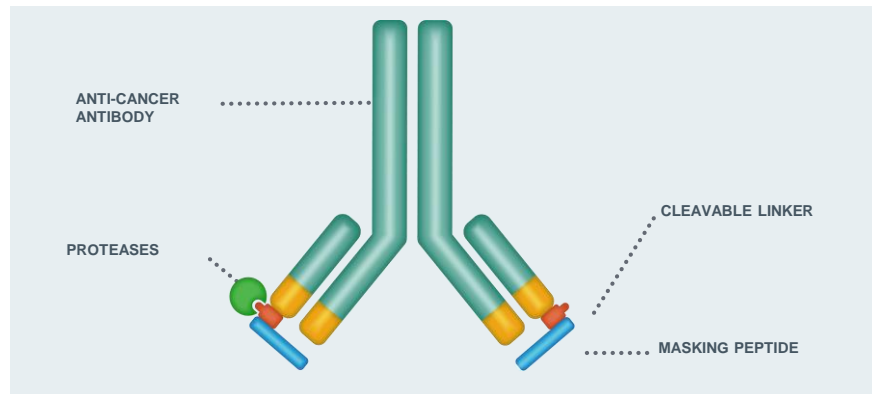**ON TARGET TOXICITY LIMITS THE DEVELOPMENT OF POTENTIALLY ATTRACTIVE ANTIBODY THERAPEUTICS**

- "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
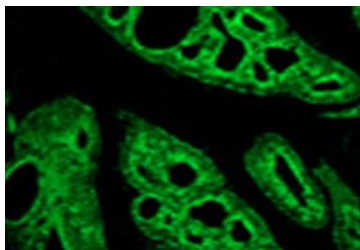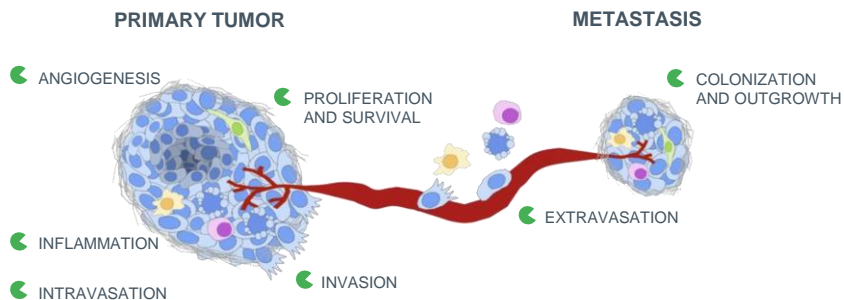- Enabling new target opportunities

PROBODY PLATFORM IS APPLICABLE ACROSS MULTIPLE TARGETS AND MODALITIES

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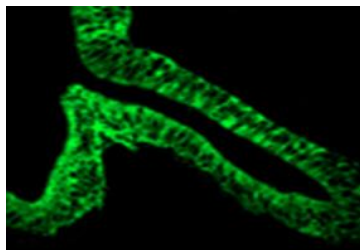- Applicable to multiple binding modalities

ANTI-CANCER ANTIBODY

PROTEASES

CLEAVABLE LINKER

MASKING PEPTIDE

Enters TME, proteases remove mask

Antibody binds target

TUMOR

TUMOR

Activated Proteases Are Prevalent in Tumors But Not in Healthy Tissue

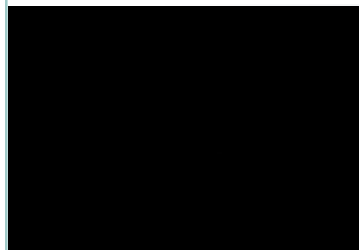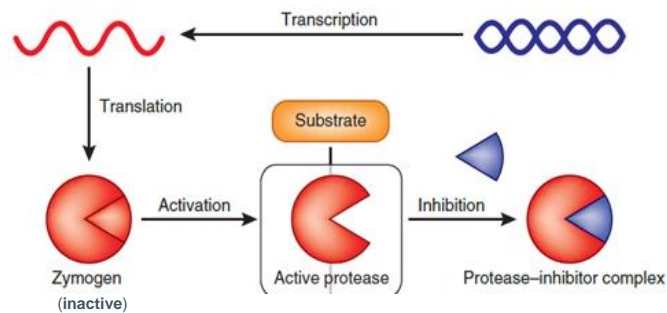## UPREGULATED PROTEASE ACTIVITY IS A HALLMARK OF ALL CANCERS[1]

PRIMARY TUMOR

METASTASIS

- ANGIOGENESIS
- PROLIFERATION AND SURVIVAL
- COLONIZATION AND OUTGROWTH
- EXTRAVASATION
- INFLAMMATION
- INVASION
- INTRAVASATION

Primary Colon Cancer

Metastatic Colon Cancer

PROTEASE ACTIVITY IS TIGHTLY CONTROLLED IN HEALTHY TISSUES[2]

Transcription

Translation

Substrate

Activation

Inhibition

Zymogen (inactive)
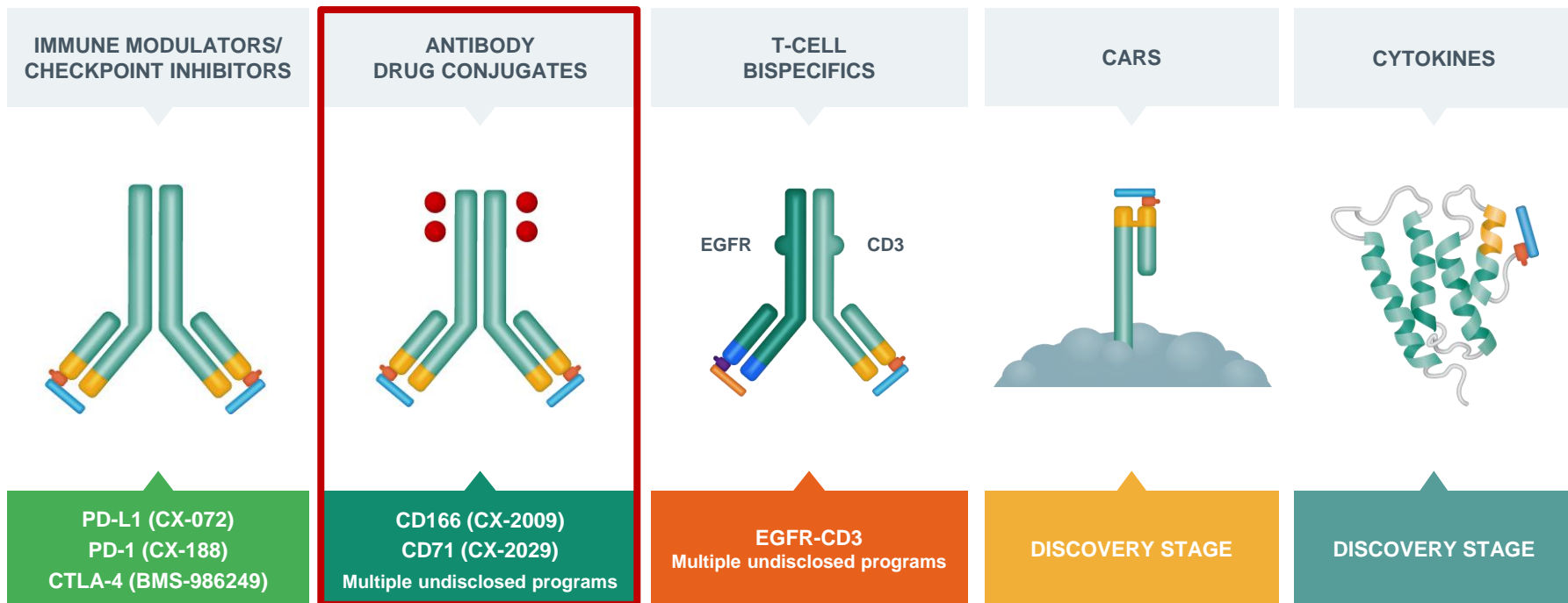
Active protease

Protease–inhibitor complex

Normal Colon

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	CARS	CYTOKINES

EGFR — CD3

PD-L1 (CX-072) PD-1 (CX-188) CTLA-4 (BMS-986249)	CD166 (CX-2009) CD71 (CX-2029) Multiple undisclosed programs	EGFR-CD3 Multiple undisclosed programs	DISCOVERY STAGE	DISCOVERY STAGE

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The Probody Platform Potentially Enables an Attractive Class of ADC Target
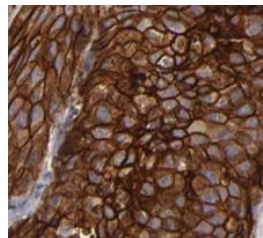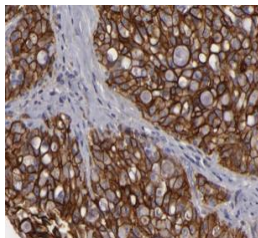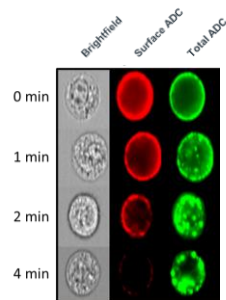

Efficiently Internalizing

High Membrane expression

Uniform Tumor Expression

Majority of Patients Express at High Level

Highly Expressed in Multiple Common Cancers

CD166 Staining Intensity

% Tumor Cells

IHC 0   IHC 1   IHC 2   IHC 3

LUNG CANCER   OVARIAN CANCER

BREAST CANCER
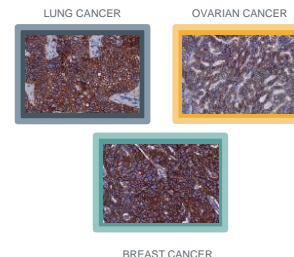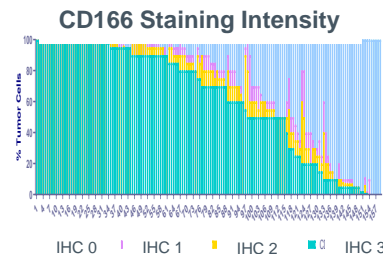
These targets are typically expressed highly in normal tissues = not suitable for traditional ADC

CD71 (TfR1):

An Undruggable ADC Target

CD71 (TfR1) Transferrin Receptor

- Transmembrane glycoprotein that efficiently internalizes iron-bound transferrin

- Highly expressed in malignant cells

- 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

  - Collaboration with AbbVie
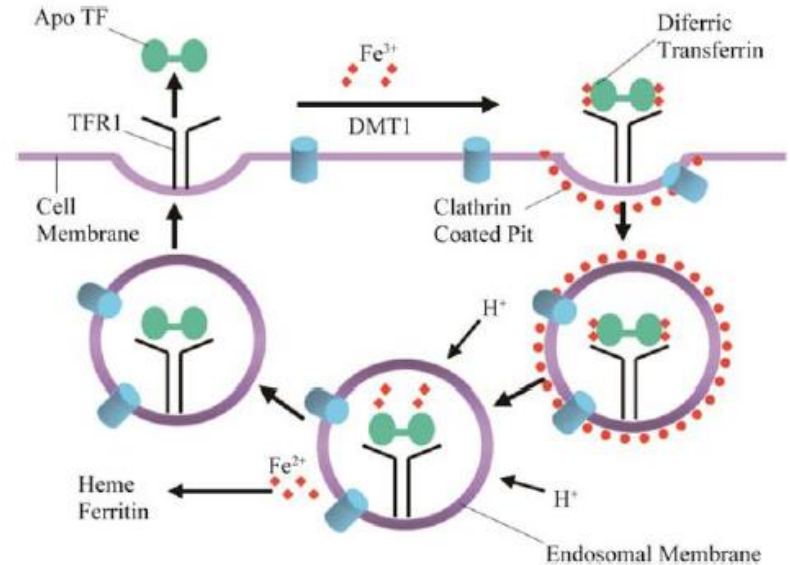
Elliott & Head, J Cancer Therapy, 3: 278-311 (2012)

CD71 Expression Is High and Prevalent in Multiple Cancer Types
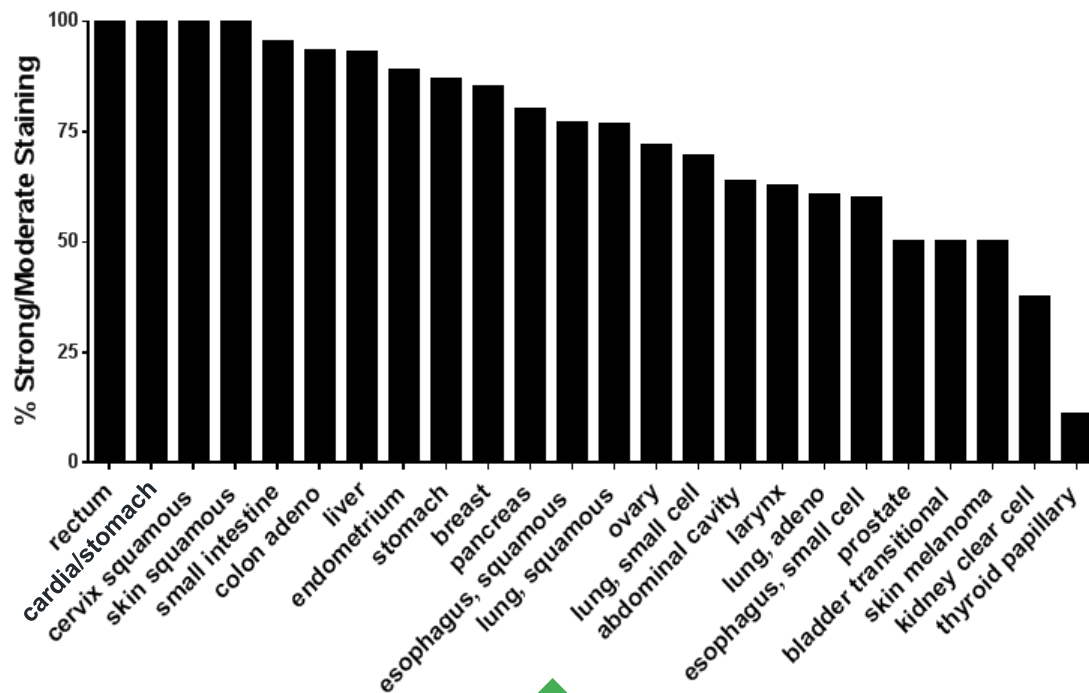
Expression evaluated by IHC using commercial Ab and cancer TMAs

CD71 Is Expressed in Many Normal Tissues

Tissue Type	Human
Bone	++
Breast	-
Brain	+
Colon	-
Esophagus	-
Heart	-
Kidney	-/+
Liver	-
Lung	++ (few cells)
Nerve	++
Ovary	+
Pancreas	-
Prostate	-
Skin	-/+
Small Intestine	-
Spleen	-
Stomach	+
Skeletal Muscle	-
Testis	+
Uterus	+/++

Peripheral Nerve

Bone Marrow
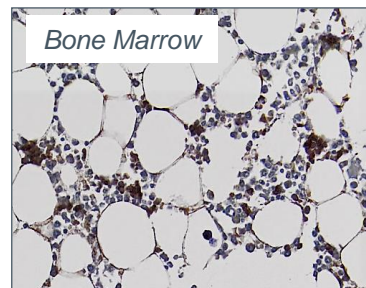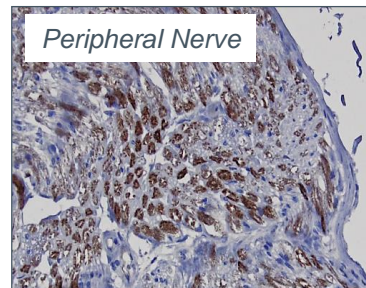
High CD71 expression in normal tissues suggests it is not a suitable ADC target
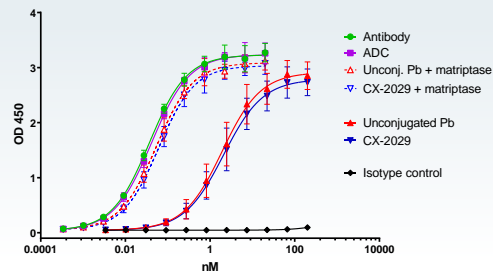
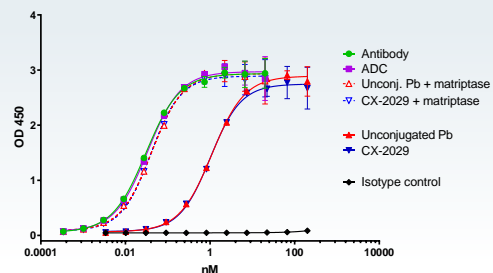CX-2029:

A Probody Drug Conjugate (PDC) Targeting CD71

CX-2029 Is Active in Cell line-Derived and Patient-Derived Tumor Models in Mice

HUMAN CD71

Legend:
- Antibody
- ADC
- Unconj. Pb + matriptase
- CX-2029 + matriptase
- Unconjugated Pb
- CX-2029
- Isotype control

CYNOMOLGUS CD71

Legend:
- Antibody
- ADC
- Unconj. Pb + matriptase
- CX-2029 + matriptase
- Unconjugated Pb
- CX-2029
- Isotype control

CDX - cell line derived xenograft
PDX - patient derived xenograft

- Parental anti-CD71 antibody binds equivalently to human and monkey CD71 (ELISA)

- 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
Cell line- derived (unselected)	15/21 (71%)
Patient-derived (high expressing)	30/36 (83%)

EFFICACY IN PDX MODELS

DLBCL, Breast, Head and Neck, Pancreatic, NSCLC, Gastric, Esophageal
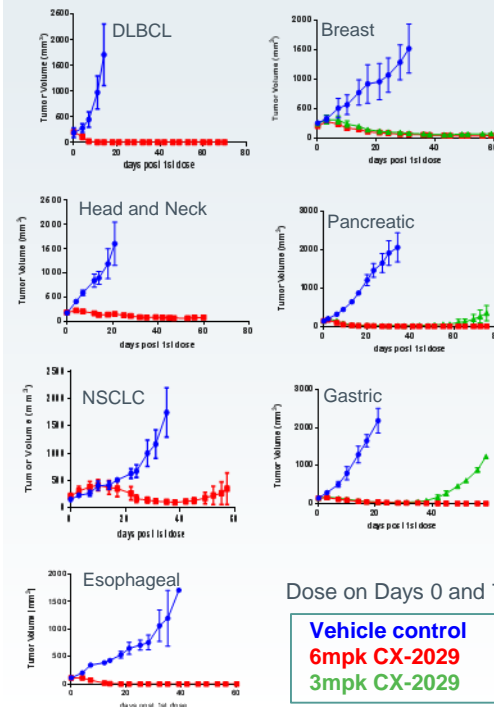
Dose on Days 0 and 7

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

CX-2029 Was Tolerated at 10x Higher Dose Than CD71 ADC
Cynomolgus monkeys, DAR2

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

- Toxicity is hematologic: anemia and neutropenia
  - 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

CX-2029 Summary and Conclusions

CX-2029 is a protease-activatable PDC, targeting the transferrin receptor CD71

Robust efficacy is observed in mouse CDX and PDX models representing multiple cancer indications

PDC to CD71 (CX-2029) was tolerable at doses projected to be consistent with efficacy in humans whereas the ADC to CD71 (CX-2030) was not

Preclinical results are consistent with CX-2029 behaving as designed for PDC

Development and Validation of an IHC Assay for CD71

Diagnostics Strategy for ADCs

The Efficacy of ADCs requires:

- Sensitivity to payload:
  - Indication specific
  - Prior evidence of sensitivity/resistance to toxin class (e.g. acquired taxane-resistance)

- Target expression:
  - Selection of patients based on homogeneity and intensity of target expression above a predetermined threshold
  - Fresh tissue preferred, archival accepted provided expression is maintained over time and regardless of intervening treatments

Development of a Clinical Trial Test CTA

Generation of a specific Anti-CD71 IHC Antibody

Mouse monoclonal antibodies generated using standard hybridoma technology

- Immunization with peptide unique to CD71

- Primary screening by ELISA

- Secondary screening by IHC

- Selection based on:
    - Cell line IHC staining specificity
    - Human tissues IHC staining specificity
    - Western blot
    - IHC staining on CD71 knock-down cells
    - IHC performance on accepted platforms

HCC1806 parental

HCC1806 knock down
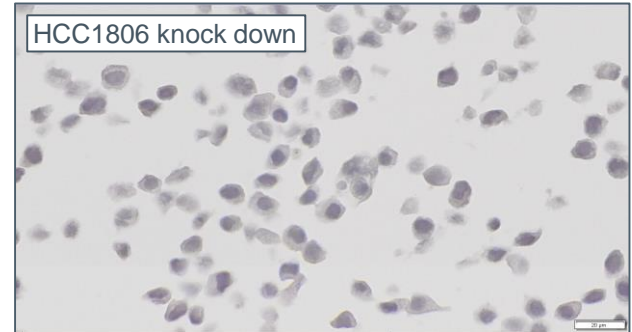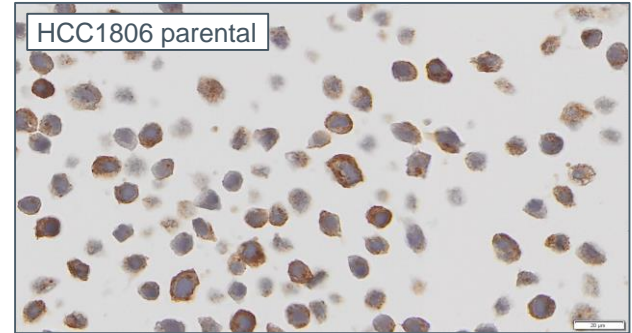
CD71 IHC Assay Was Validated in 7 Tumor Types

Tumor Type	Tissue	Number Blocks
Breast Cancer	Breast Tumor	20
	Normal Breast	10
Esophageal Cancer	Esophageal carcinoma	20
	Normal esophagus	10
Pancreatic Cancer	Pancreatic carcinoma	20
	Normal pancreas	10
Non Small Cell Lung Cancer	NSCLC	20
	Normal Lung	10
Non- Hodgkin Lymphoma	Non-Hodgkin Lymphoma	20
	Normal lymph node	10
Gastric Cancer	Gastric tumor	20
	Normal stomach	10
Head and Neck Squamous Cell Carcinoma	Head and Neck tumor	20
	Normal larynx, pharynx, etc	10

Validation done at Molecular MD

Specificity:
- No/low background in cell pellets/ tissues negative for CD71

Sensitivity
- Able to detect CD71 in tissues known to be weakly positive
- Adequate dynamic range to distinguish cells with low, medium and high CD71 levels in tissues

Precision
- Comparable intensity and percentage of positive cells in five specimens from each indication:
  - On the same day (intra-assay)
  - On non consecutive days (inter-assay)
  - By two separate lots of reagent

CytomX
THERAPEUTICS

Development of a Scoring Method Based on Staining Intensity and Tumor Cell Content
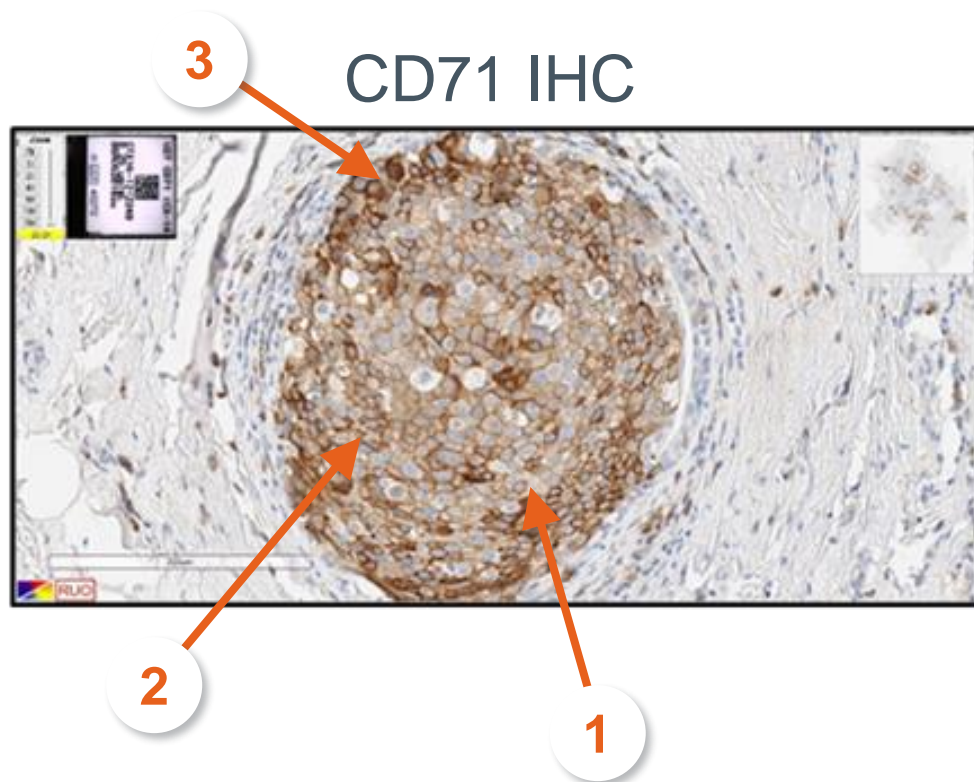
CD71 IHC

Intensity Score	Percentage of Cells
Strong (3+)	5
Moderate (2+)	90
Weak (1+)	5
Negative (0)	0

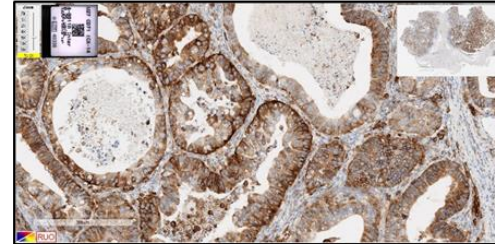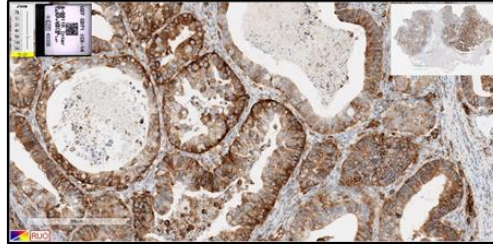Example of staining of Breast Cancer on Ventana platform

CD71 IHC Assay

- CAP/CLIA validation completed at Molecular MD

- Membrane-associated and total staining scored separately

- Staining in non-tumor cells (normal epithelium, immune, etc.) is excluded from analysis

- Scoring is attributed following pathologist's visual assessment of the staining intensity on tumor cells:

  0 = no staining

  1 = weak staining

  2 = moderate staining

  3 = strong staining

- A minimum of 100 tumor cells is required for the assessment to be valid

CD71 IHC Demonstrates a Robust Inter-Assay Precision

Operator 1 **Operator 2**

Esophageal cancer
Sample 1

Esophageal cancer
Sample 2

Example of staining of esophageal cancer on Ventana platform
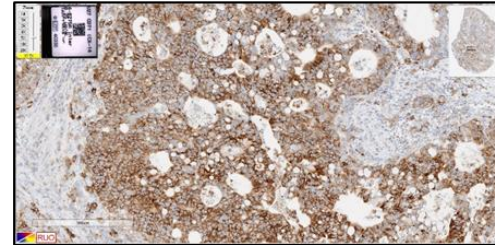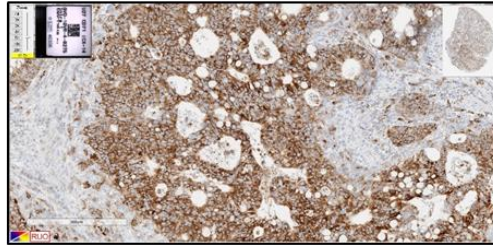
Assay precision evaluated on 5 samples for all indications with similar results

		% cells 3+	% cells 2+	% cells 1+	% cells 0
Sample 1	Operator 1	80	10	10	0
	Operator 2	70	20	10	0
Sample 2	Operator 1	80	10	10	0
	Operator 2	80	10	10	0

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CD71 IHC Demonstrates Robust Lot-to-Lot Assay Precision

Lot 02272018 **Lot INH-01J1**

Pancreatic cancer Sample 1
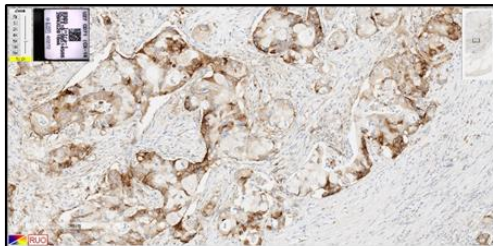
Pancreatic cancer Sample 2
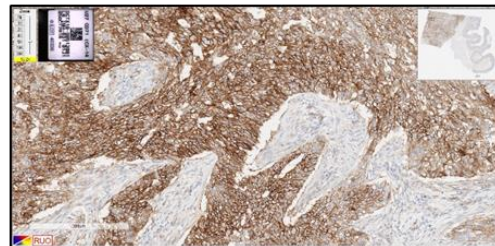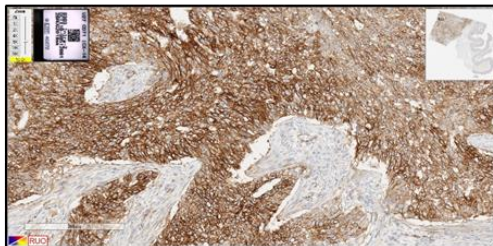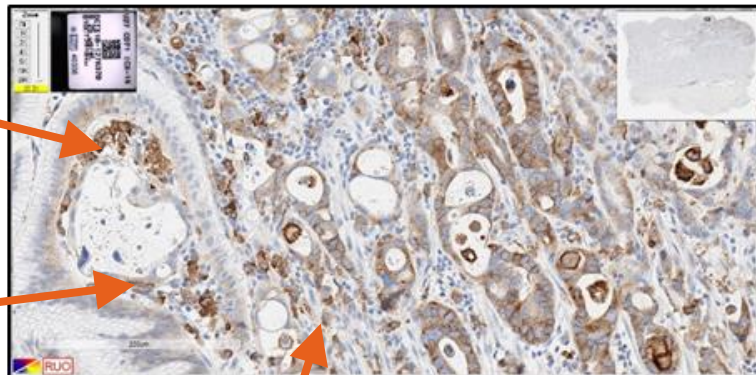
Example of staining of pancreatic cancer on Ventana platform
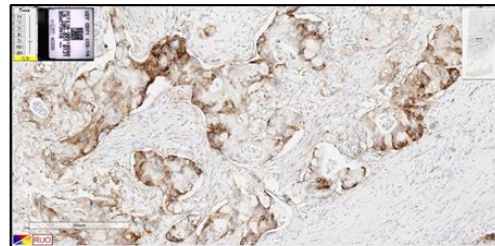
Assay precision evaluated on 5 samples for all indications with similar results

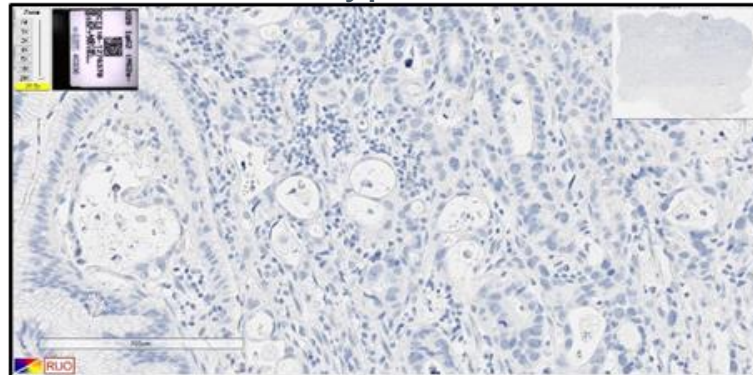|		% cells 3+	% cells 2+	% cells 1+	% cells 0
Sample 1	Lot 02272018	70	30	0	0
	Lot INH-01J1	70	30	0	0
Sample 2	Lot 02272018	90	10	0	0
	Lot INH-01J1	80	20	0	0

Example of CD71 Heterogenous Staining

CD71 IHC

Isotype Control

Intensity Score	Percentage of Cells
Strong (3+)	50
Moderate (2+)	10
Weak (1+)	5
Negative (0)	35

Example of staining in gastric cancer sample

Example of CD71 Homogenous Staining

CD71 IHC
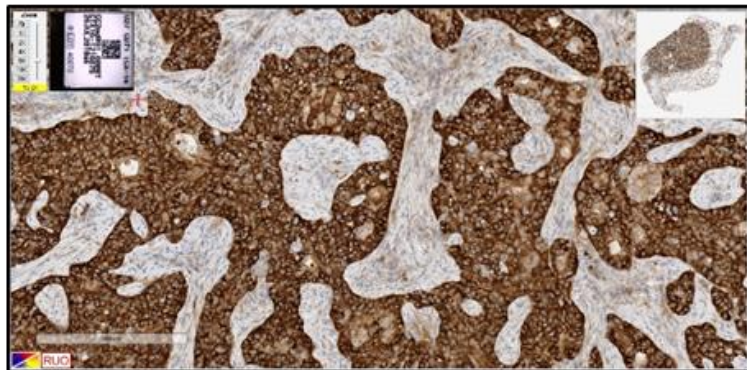
Isotype Control
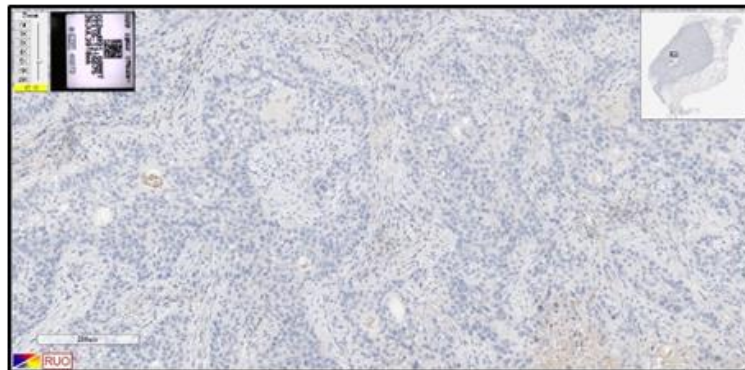
Intensity Score	Percentage of Cells
Strong (3+)	100
Moderate (2+)	0
Weak (1+)	0
Negative (0)	0

Example of staining in squamous cell carcinoma of the lung sample

CX-2029 Summary and Conclusions

CX-2029 is a protease-activatable PDC, targeting the transferrin receptor CD71

Robust efficacy is observed in mouse CDX and PDX models representing multiple cancer indications

PDC to CD71 (CX-2029) was tolerable at doses projected to be consistent with efficacy in humans whereas the ADC to CD71 (CX-2030) was not

A robust IHC assay for the detection of CD71 expression in archival tumor tissue was developed and validated for 7 tumor types (Breast, Esophageal, Pancreas, NSCLC, NHL, Gastric, HNSCC)

CX-2029 FIH trial was initiated in June 2018 (NCT03543813)
- Dose escalation is on-going
- CD71 expression in patient tumor is being assessed