Designing Conditionally Activated Probody® Cytokines to Localize Antitumor Activity to Cancers

International Cytokine and Interferon Society (ICIS) Symposium: Understanding and Modulating Cytokine Activity through Structural Knowledge

American Association of Immunologists Annual Meeting

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CytomX Therapeutics, Inc., South San Francisco, CA

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Disclosures

- Dylan Daniel is an employee and stockholder at CytomX Therapeutics, Inc.

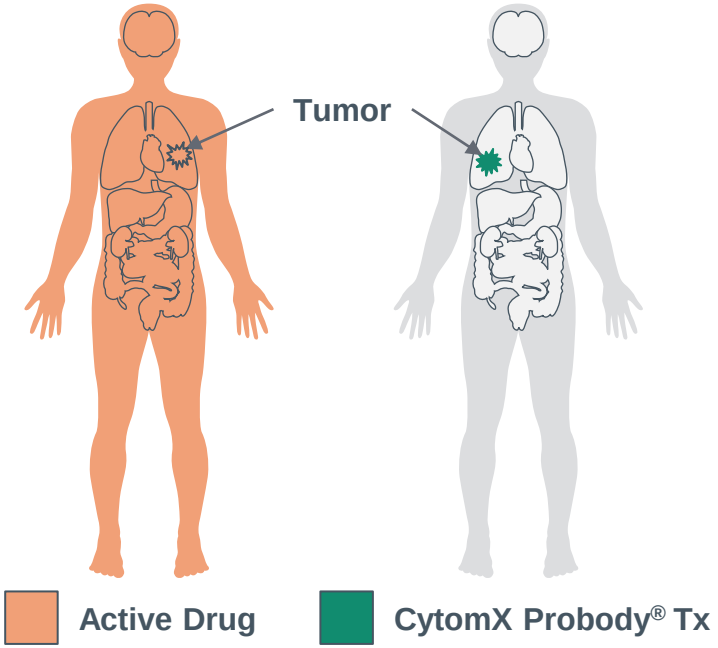
The Promise of Conditionally Active, Localized Biologic Therapies
Addressing Major Challenges in Today's Cancer R&D Landscape

CytomX Therapeutics

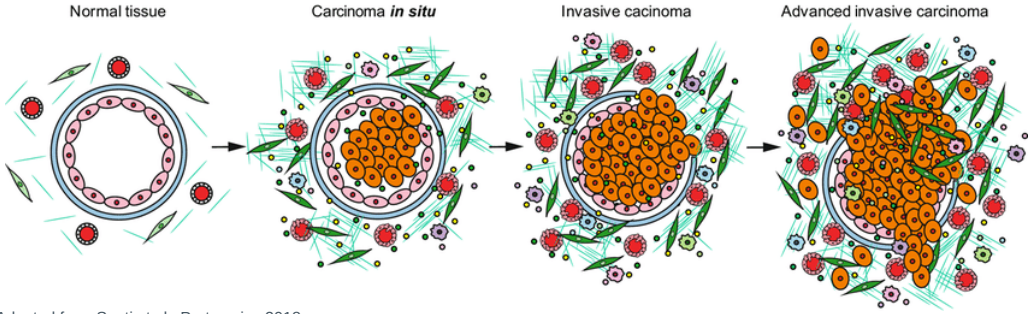
Probody® Therapeutics
Designed to **localize anti-cancer efficacy** and **decrease systemic toxicities**

R&D Challenge

- **Next Generation Biologic Therapies have evolved to highly potent formats including:**
  - Antibody Drug Conjugates (ADCs)
  - T-Cell Engagers (TCBs)
  - Immunotherapies
  - **Cytokines**
- **Separating potency from toxicity is a key challenge for optimizing therapeutic effectiveness**



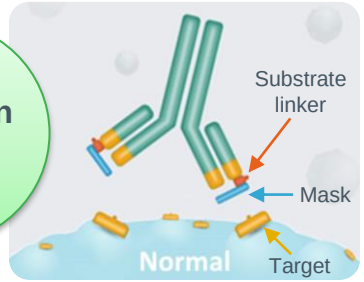
The Probody® Therapeutic Platform – Exploiting Cancer's Achilles' Heel



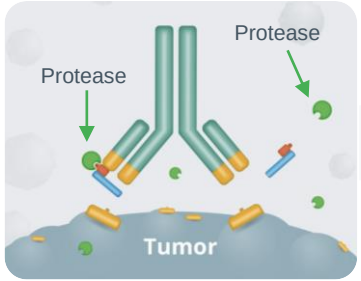
Adapted from Santi et al., Proteomics 2018

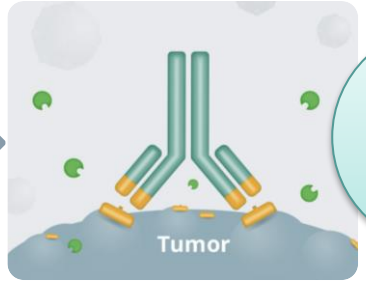
Upregulated protease activity is a hallmark of cancer

Less Binding in Normal Tissues



"Masking" limits ability of Probody therapeutics to bind to healthy tissues





More Binding in Tumors

Proteases in tumor microenvironment "unmask" Probody therapeutics, allowing more binding to tumor cells

Unmasked Cytokine Therapeutics Are Potent, But Associated With Safety Issues

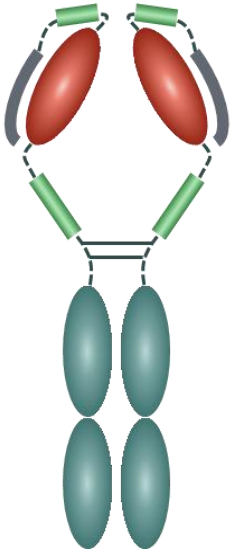
Cytokines and Cytokine Therapeutics

- Major regulators of innate and adaptive immune system
- Antitumor activity demonstrated clinically by IFNα and IL-2 in melanoma and RCC
- ***Clinical successes to date limited by systemic toxicity and/or poor exposure***

Potential Advantages for Conditional Cytokine Therapeutics

- ✓ **Less systemic toxicity**
- ✓ **Better exposure** (reduced TMDD)
- ✓ **Systemic delivery** (versus IT injection)
- ✓ **Increased therapeutic index**
- ✓ **Improved combination therapies**

Probody® Cytokines



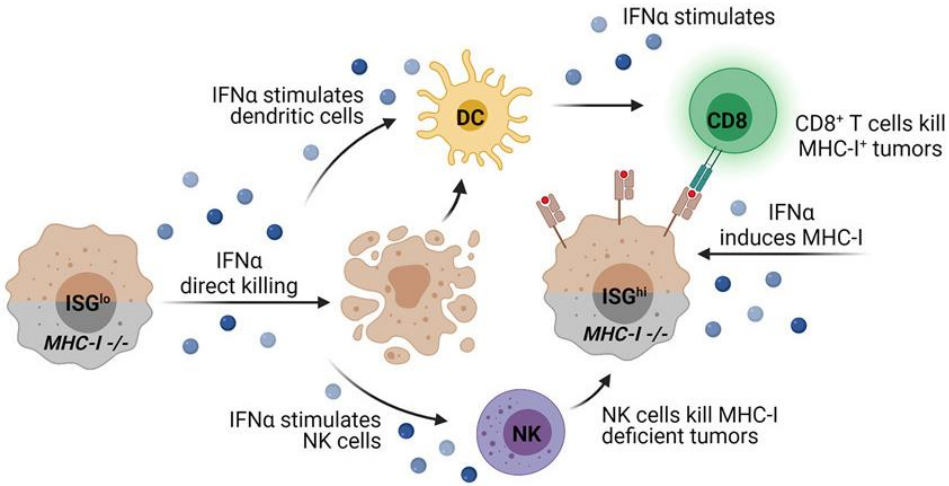
Conditionally Activated IFNα-2b: CX-801

IFNα-2b is a Powerful Mediator of Immune Activation with Ideal Properties for Cancer Immunotherapy

Why IFNα-2b?

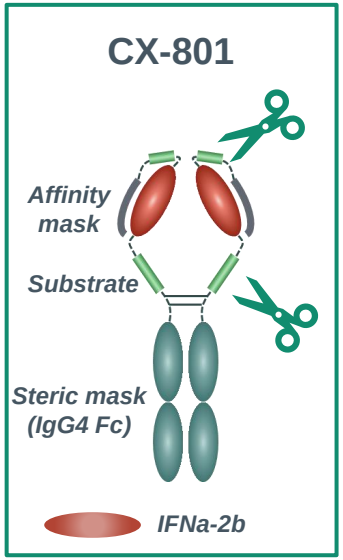
Mechanism of Action

- IFNα-2b provides an **orthogonal activity to IL-12, IL-2 and IL-15** in the cancer immunity cycle
  - IFNα-2b can **kill cancer cells directly** leading to immunogenic cell death, and
  - IFNα-2b **stimulates antigen presenting cells to activate T cells** – *distinct from IL-2, IL-12, and IL-15 that are restricted to proliferative effects*
- Potential to **unlock classically CPI-resistant indications**

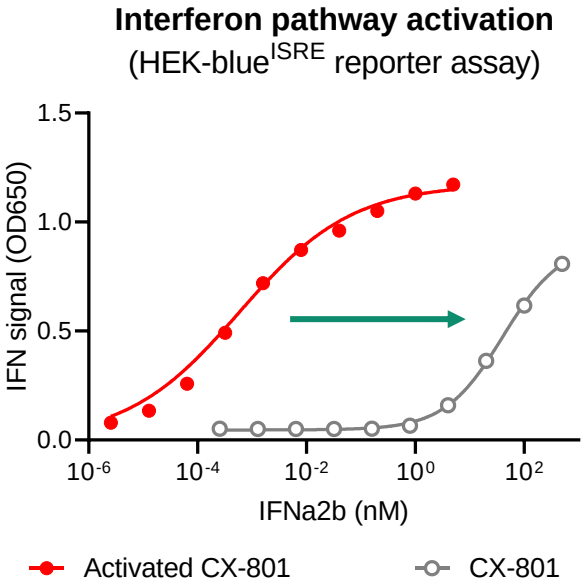


Adapted from Green et al., Mol. Ther. Onc. 2021

CX-801 is a Highly Masked, Conditionally Active IFNα-2b



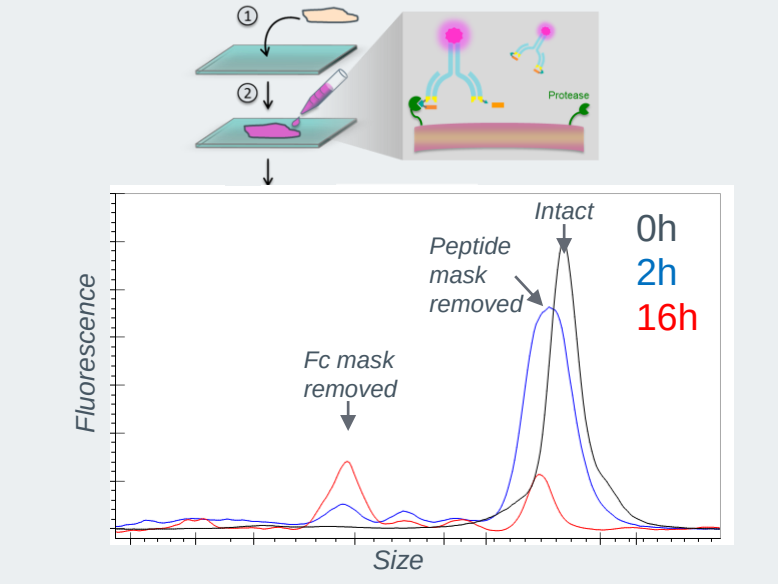
- Multiplicative masking from two masking approaches
- Leads to >1,000x masking in IFNa reporter assay
- Proteolytic activation releases active, short half-life IFN



	Avg. EC50 (nM)
CX-801	42.44
Act. CX-801	0.03

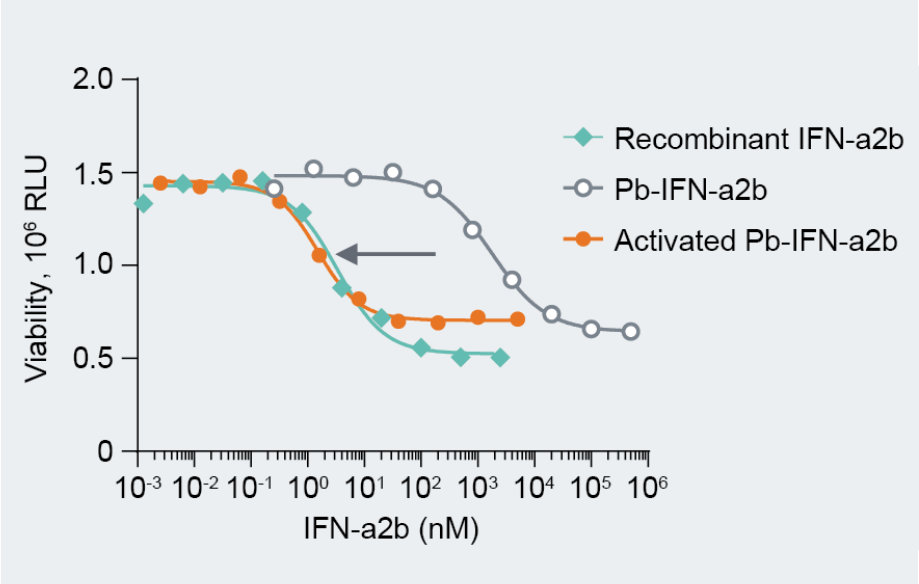
Activation of CX-801 by Tumor Proteases Fully Restores IFNα-2b Activity

Activation by tumor tissues



- Exposure to tumor tissues removes masks

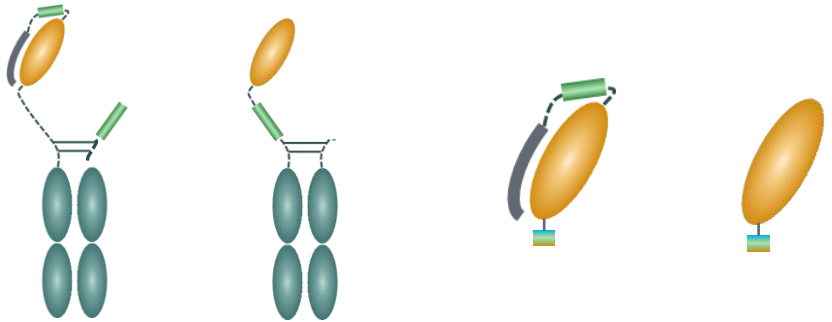
Antiproliferative effect



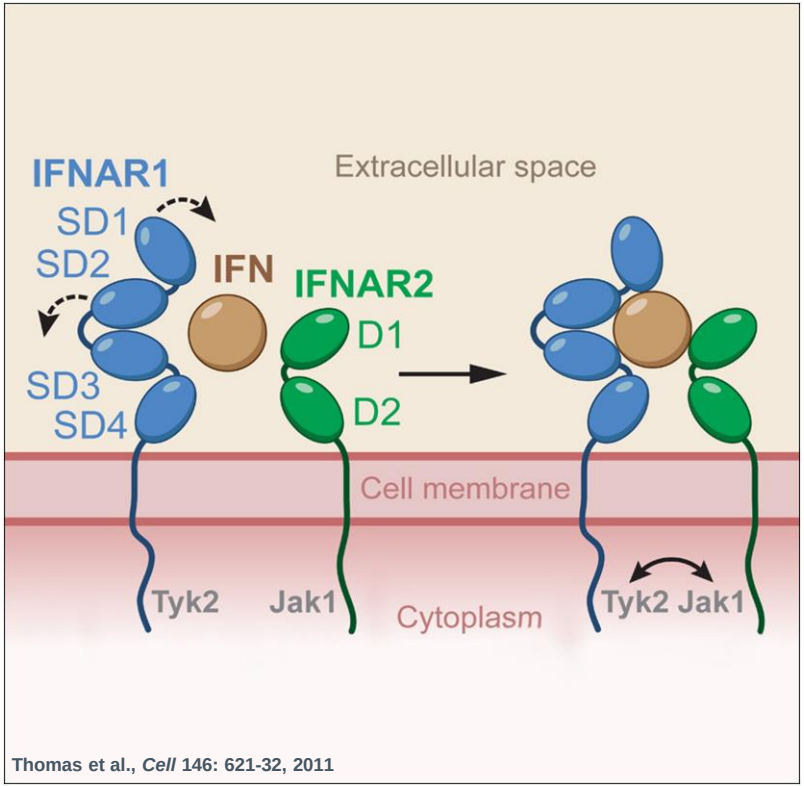
- Unmasked CX-801 is as potent as recombinant IFN

What is the Structural Basis for Steric and Peptide Masking of IFNα-2b?

- Type 1 IFN receptor is a heterodimer composed of:
  - IFNαR1 – Low affinity receptor
  - IFNαR2 – High affinity receptor
- Both receptors must be engaged for IFNα signaling to occur
- Monomeric test molecules used to probe masking mechanisms:



Dual Masked **Steric Masked** **Affinity Masked** **Unmasked**



Thomas et al., *Cell* 146: 621-32, 2011

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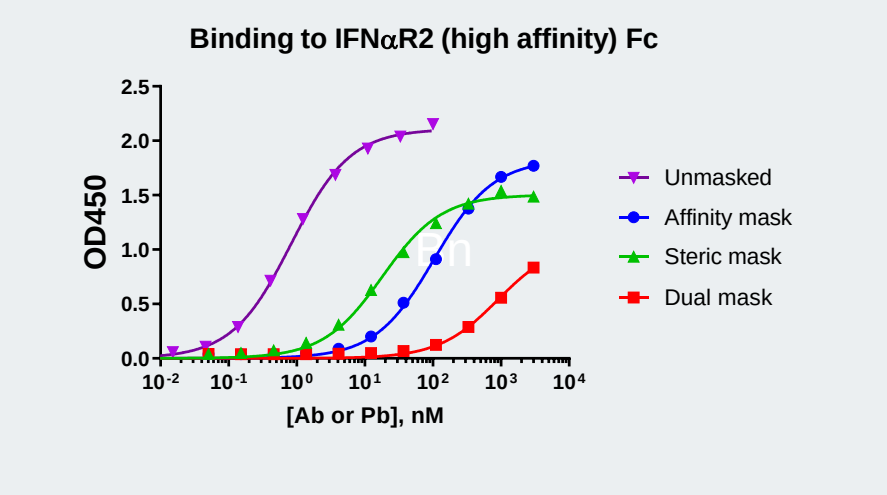
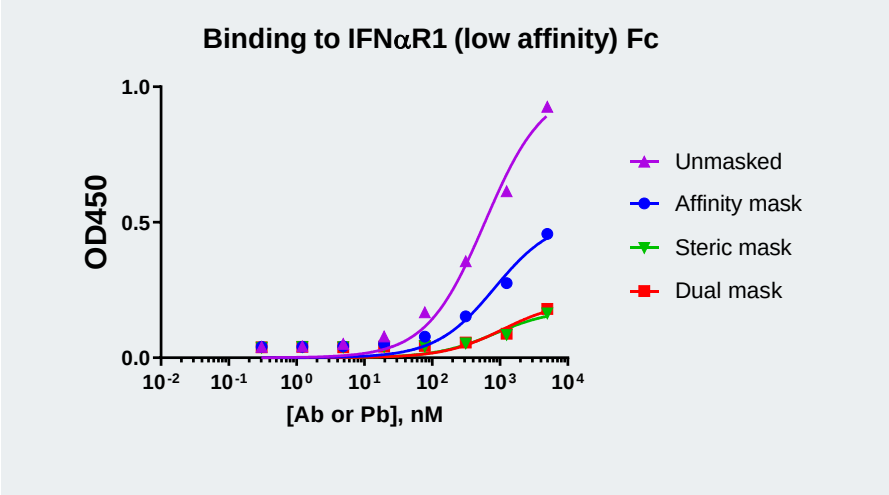
Modes of Masking Differentially Affect IFNα-2b Interaction with R1 and R2

ELISA measurements of binding to Type I interferon receptors

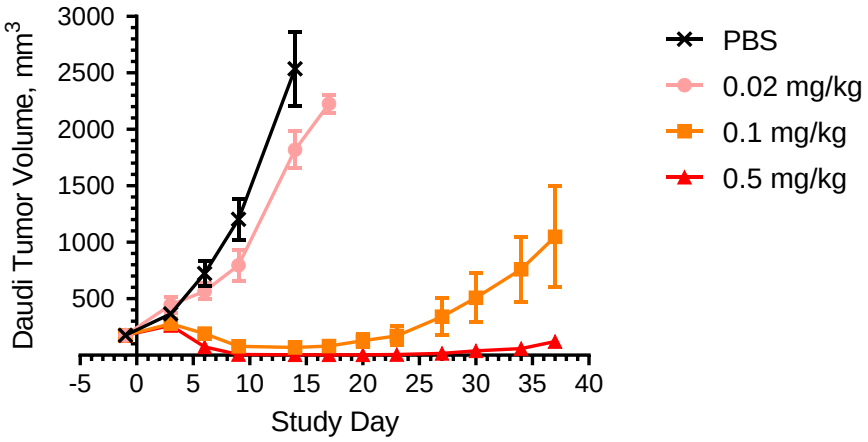




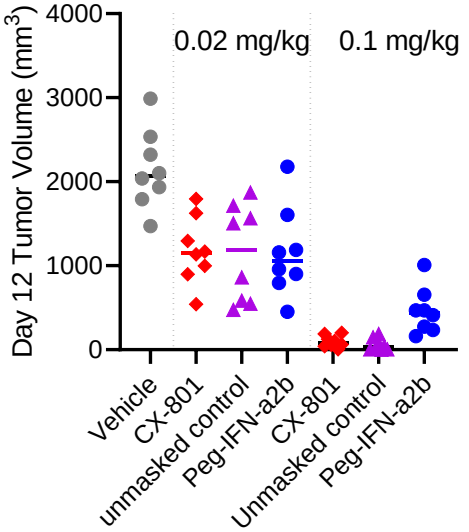
- Affinity masking and steric masking act multiplicatively to increase overall masking efficiency

CX-801 Induces Dose Dependent Tumor Regression in Human Xenograft Model

CX-801 Efficacy in Daudi Tumor Model



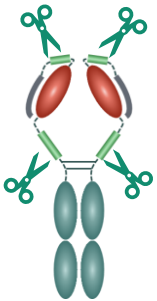
CX-801 vs. Unmasked Controls



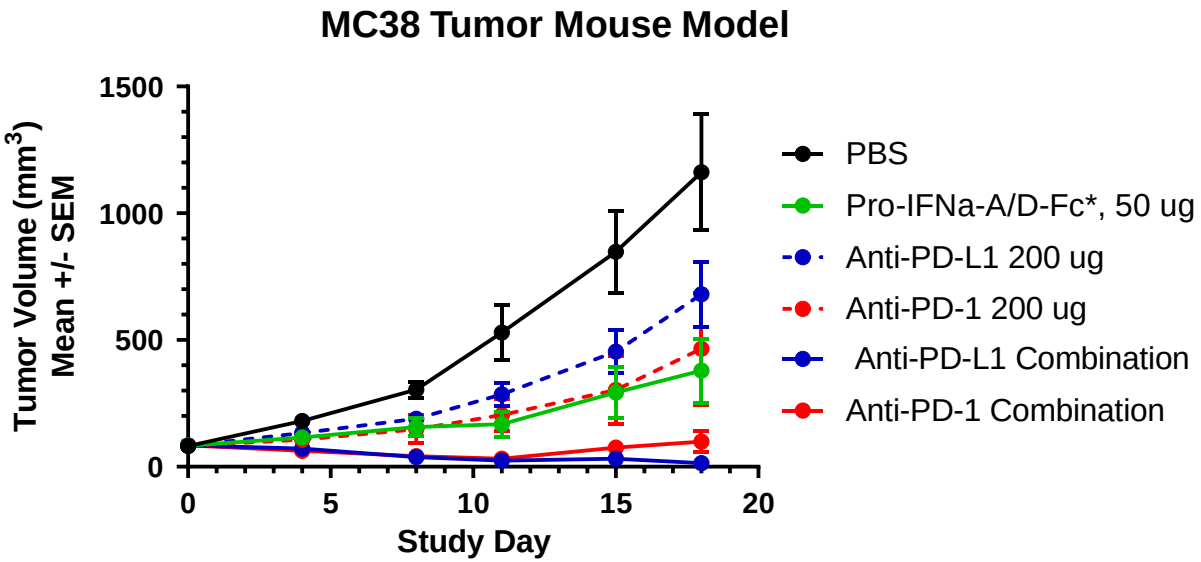
- CX-801 induces tumor regression at dose as low as 0.1 mg/kg
- CX-801 is as active as peginterferon and unmasked IFN-a2b-Fc fusion protein

CX-801 Surrogate* Shows Potent Single Agent Tumor Growth Inhibition

Combination with immune checkpoint inhibitor shows enhanced efficacy



Pb-IFNa-A/D-Fc



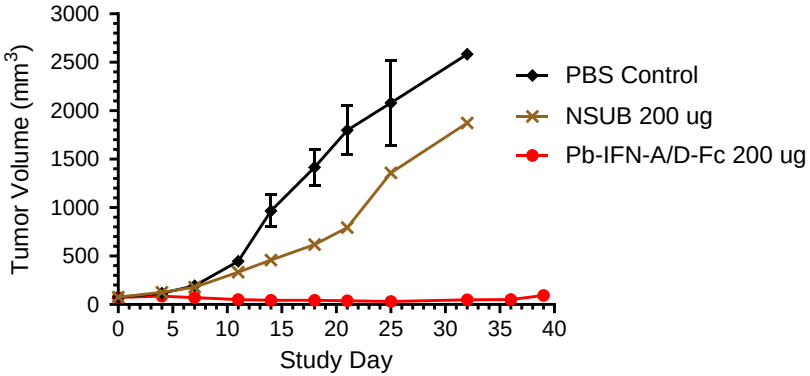
Doses
PBS, ProC1023: d0, d4, d8, d11, d15
Anti-PD-L1, Anti-PD-1: d0,d8, d15

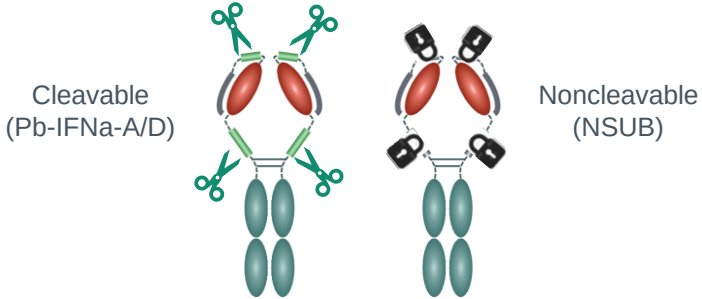
* Surrogate is IFNa-A/D is a mouse cross-reactive human IFN-a2a/IFN-a1 fusion protein enabling evaluation in immune competent mouse models to understand ability of INFa to sensitize tumor to checkpoint inhibition

CX-801 Surrogate Activity is Protease-Dependent

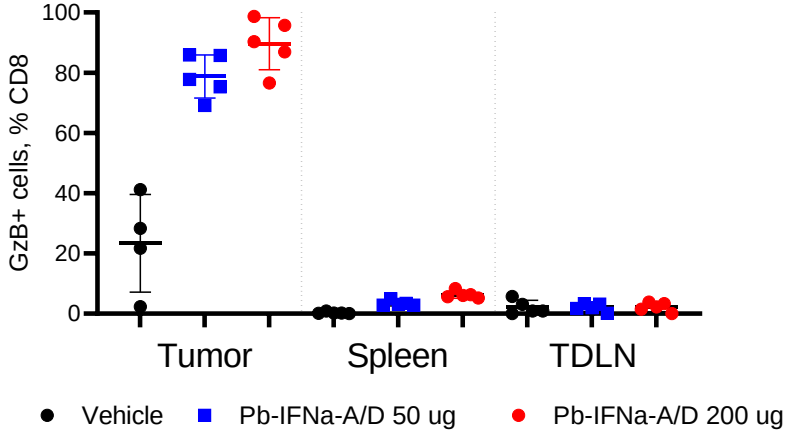
Activates T cells in tumors, but not in periphery

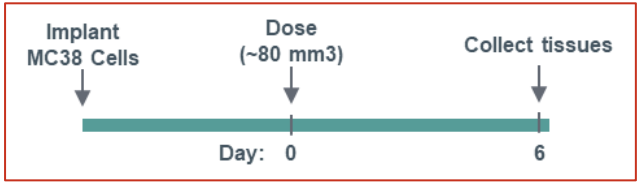
Protease-dependent activity





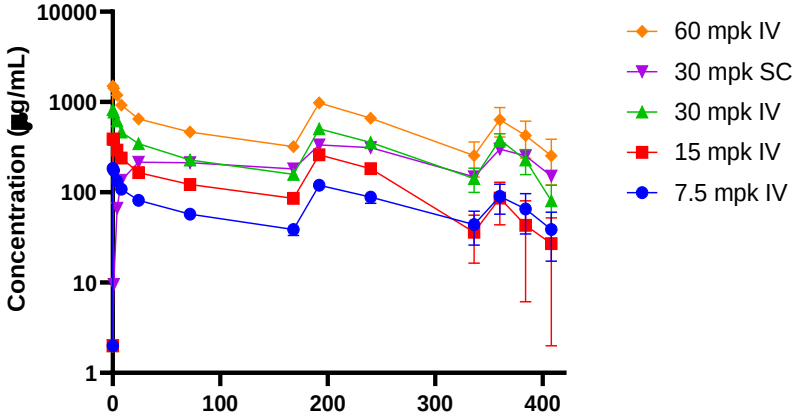
Tumor-specific immune activation



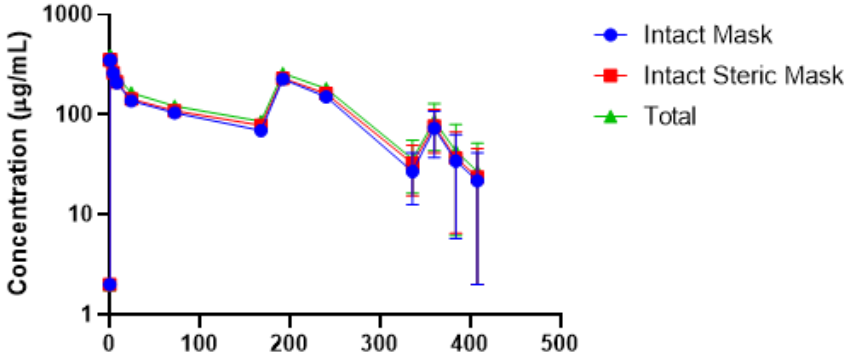


CX-801 Displays Linear Pharmacokinetics and High Stability in Circulation in Cynomolgus Monkey

Dose Linear Pharmacokinetics



High Stability in Circulation



CX-801 has Significantly Improved Tolerability

Compared to unmasked interferon in non-human primates

Protection in multi-dose tolerability study is ≥ 30x

Historical Peginterferon Data

Dosing (mpk/w)	Peginterferon (SQ)
0.35	Tolerated (6/6)
1.05	Tolerated (6/6)
3.5	Not Tolerated (5/6)

Probody® IFNα-2b Tolerability Study

Dosing (mpk/w) (3 x QW)	CX-801 (IV)
-	-
-	-
-	-
7.5	Tolerated (4/4)
15	Tolerated (4/4)
30	Tolerated (4/4)
60	Tolerated (4/4)

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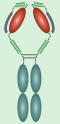
CX-801: Expanding the Reach of I/O Therapy



CX-801
Potential Best in Class

1 **Best-in-Class Profile**

- Differentiated molecule with attractive preclinical efficacy and tolerability profile
- Well tolerated in multi-dose pilot NHP tox study up to 60 mg/kg
- Estimate predicted therapeutic index of ~3-7

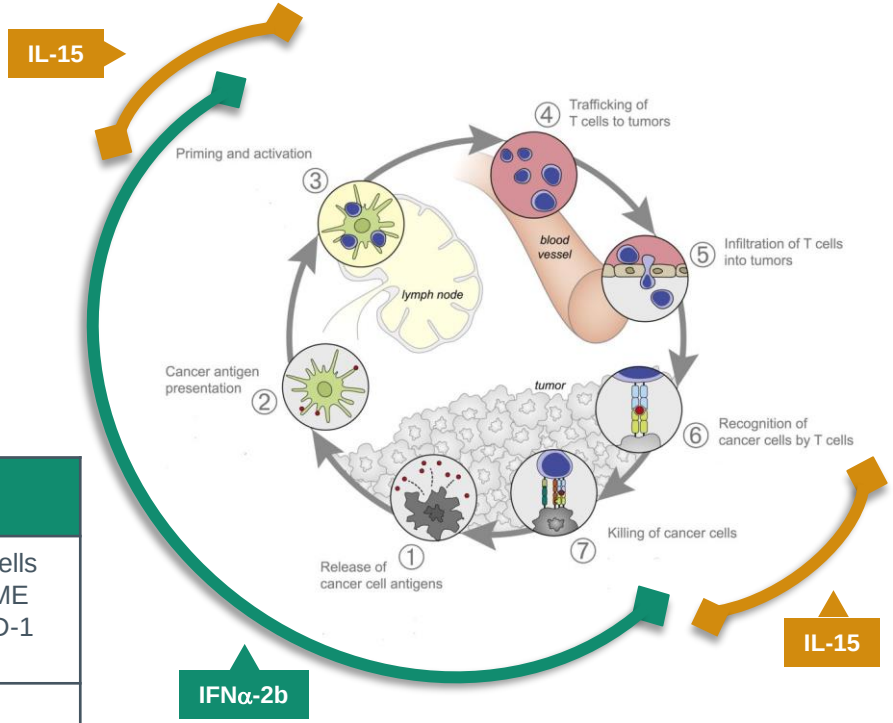
Broad Therapeutic Applications

- Enhance IO therapy and expand the reach of IO agents to more patients

2023 **CX-801 IND planned in 2H 2023**

Applying Probody® Platform Across Cytokines

Expanding Masking to IL-15



IFNα-2b

- Activate antigen presenting cells
- Promote pro-inflammatory TME
- Complementary biology to PD-1
- Broad combination potential

- IND 2H23

IL-15

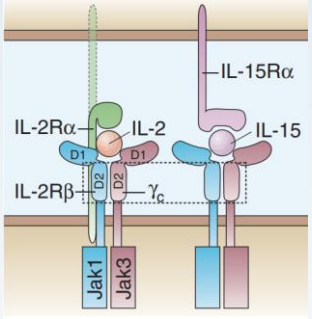
- Strong agonist of immune effector cells – CD8+ T cells and NK cells

Chen, Immunity 39, July 25, 2013.

Designing an IL-15 Cytokine Probody® Therapeutic

Target Background

- IL-15 is essential for NK, NKT, CD8+ T cell development and function
- Unique mode of trans-presentation of IL-15 by its producing cells



- Anti-tumor activity mediated by:
  - NK cells – direct tumor cell killing and enhancement of ADCC efficacy of tumor targeting antibodies
  - CD8+ cells – promotion of proliferation and memory formation

Key Challenges/Opportunity

Challenges

- Clinical activity is limited by short half-life and Cmax related toxicity (e.g. fevers, rigors, and hypotension)

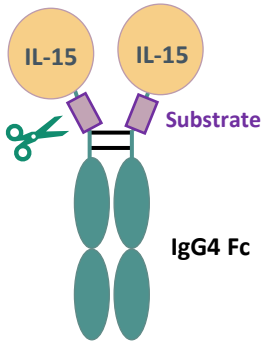
Opportunity

- Explore masking strategies to improve the safety profile of IL-15 therapeutics
- Potential activity in hematological and solid cancers

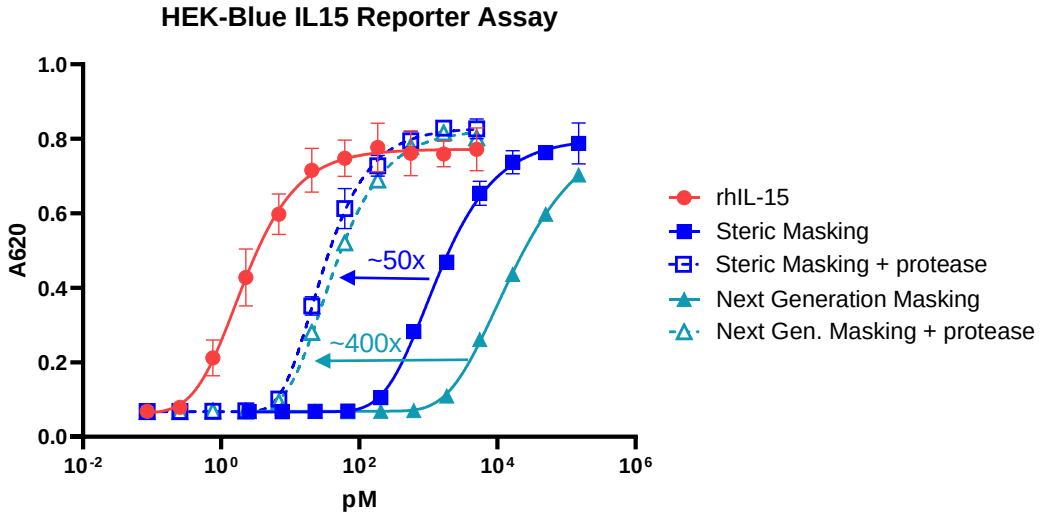
Exploring Probody® Tx Technology for Steric Masking of IL-15

IgG Fc Provides Steric Masking of IL-15

Steric Masked IL-15



IL-15
Strong agonist of NK and CD8⁺ T cells



Format	ME * (vs IL-15)	ME (vs Act.)
Steric Masking	~600X	~50X
Next Gen. Masking	~5,000X	~400X

- CytomX is exploring next generation masking strategies for IL-15

Probody® Cytokines Summary

- Affinity peptide masking and steric masking act multiplicatively to increase the masking of conditionally activated IFNα-2b
- Dual masked IFNα-2b CX-801 surrogate demonstrates protease-dependent, tumor localized $CD8^+$ T cells activating activity
- CX-801 shows a significant safety improvement in non-human primate
- Steric masking is applicable to IL-15
- CytomX is exploring next generation masking strategies for IL-15

Thank you!