



Conditional Cytokine Therapeutics for Tumor-Selective Biological Activity

Preclinical characterization of a dual-masked IFN α -2b

Erwan Le Scolan, Ph.D.

CytomX Therapeutics, Inc



Cytokine-Based Cancer Immunotherapies Summit

March 24th, 2021

Forward Looking Statements

This presentation may contain projections and other forward-looking statements regarding future events. All statements other than statements of historical facts contained in this presentation, including statements regarding our future financial condition, technology platform, development strategy, prospective products, preclinical and clinical pipeline and milestones, regulatory objectives, expected payments from and outcomes of collaborations, and likelihood of success, are forward-looking statements. Such statements are predictions only and involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. These risks and uncertainties include, among others, the costs, timing and results of preclinical studies and clinical trials and other development activities; the uncertainties inherent in the initiation and enrollment of clinical trials; expectations of expanding on-going clinical trials; availability and timing of data from clinical trials; the unpredictability of the duration and results of regulatory review; market acceptance for approved products and innovative therapeutic treatments; competition; the potential not to receive partnership milestone, profit sharing or royalty payments; the possible impairment of, inability to obtain and costs of obtaining intellectual property rights; and possible safety or efficacy concerns, general business, financial and accounting risks and litigation. Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. More information concerning us and such risks and uncertainties is available on our website and in our press releases and in our public filings with the U.S. Securities and Exchange Commission. We are providing this information as of its date and do not undertake any obligation to update or revise it, whether as a result of new information, future events or circumstances or otherwise. Additional information may be available in press releases or other public announcements and public filings made after the date of this presentation.

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



Promise of Conditional Cytokines



Overview of Probody[®] Therapeutic Technology Platform



In vitro Characterization of a Conditional IFN α -2b With a Dual Masking Strategy



Preclinical Activity and Tolerability

Cytokine Therapeutics Are Potent, But Associated With Safety Issues

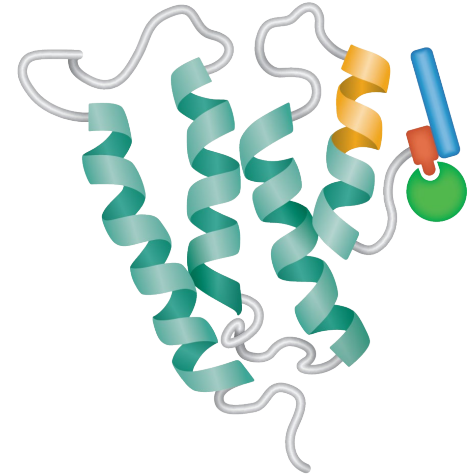
Cytokines and Cytokine Therapeutics

- Major regulators of innate and adaptive immune system
- Broad anti-tumor activity in preclinical models
- Clinical success to date limited by systemic toxicity or poor exposure

Potential advantages for Conditional Cytokine Therapeutics

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

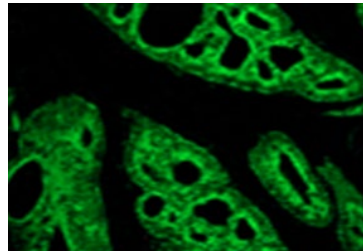
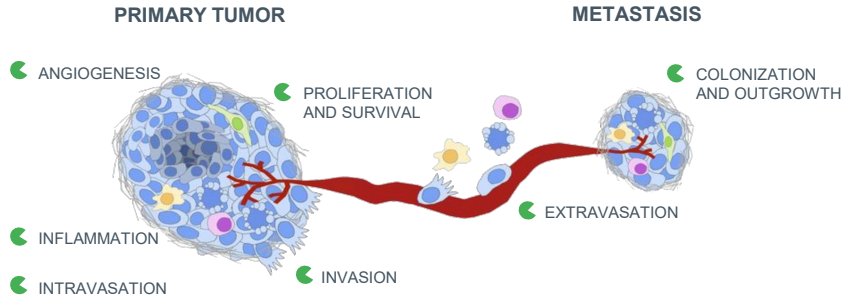
Conditional-Cytokines



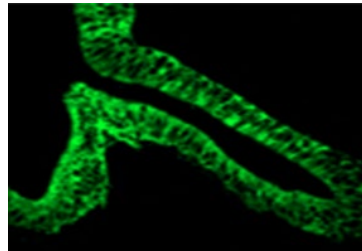
Activated Proteases Are Prevalent in Tumors but not in Healthy Tissue

UPREGULATED PROTEASE ACTIVITY IS A HALLMARK OF ALL CANCERS¹

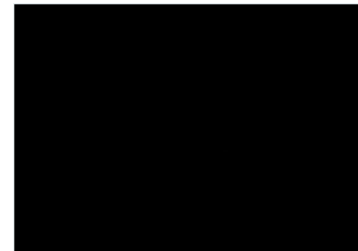
PROTEASE ACTIVITY IS TIGHTLY CONTROLLED IN HEALTHY TISSUES²



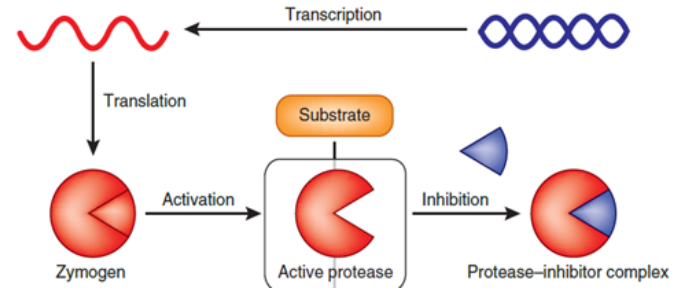
Primary Colon Cancer



Metastatic Colon Cancer



Normal Colon³



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

The Probody Therapeutic Platform Localizes Biologics to the Tumor Microenvironment (TME)

ON TARGET TOXICITY LIMITS THE DEVELOPMENT OF POTENTIALLY ATTRACTIVE ANTIBODY THERAPEUTICS

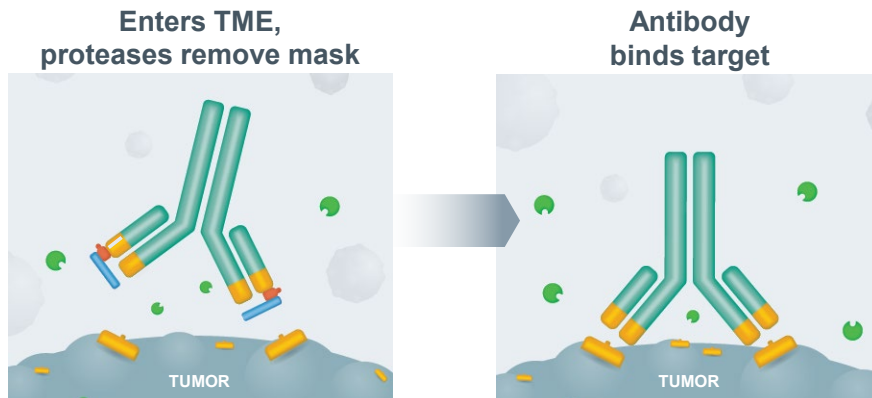
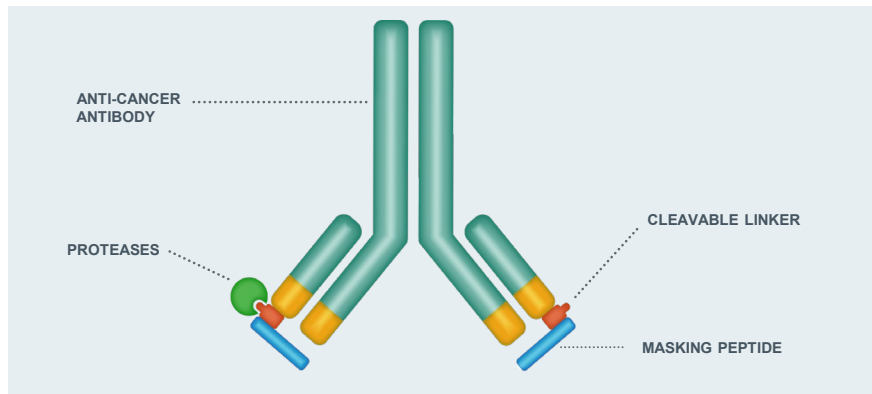
- “Masked” to limit binding to normal tissue
- “Un-masked” by tumor-associated proteases
- Linkers cleaved by multiple proteases for utility across tumor types

CYTOMX PROBODY PLATFORM IS DESIGNED TO LOCALIZE TARGET BINDING TO TUMOR

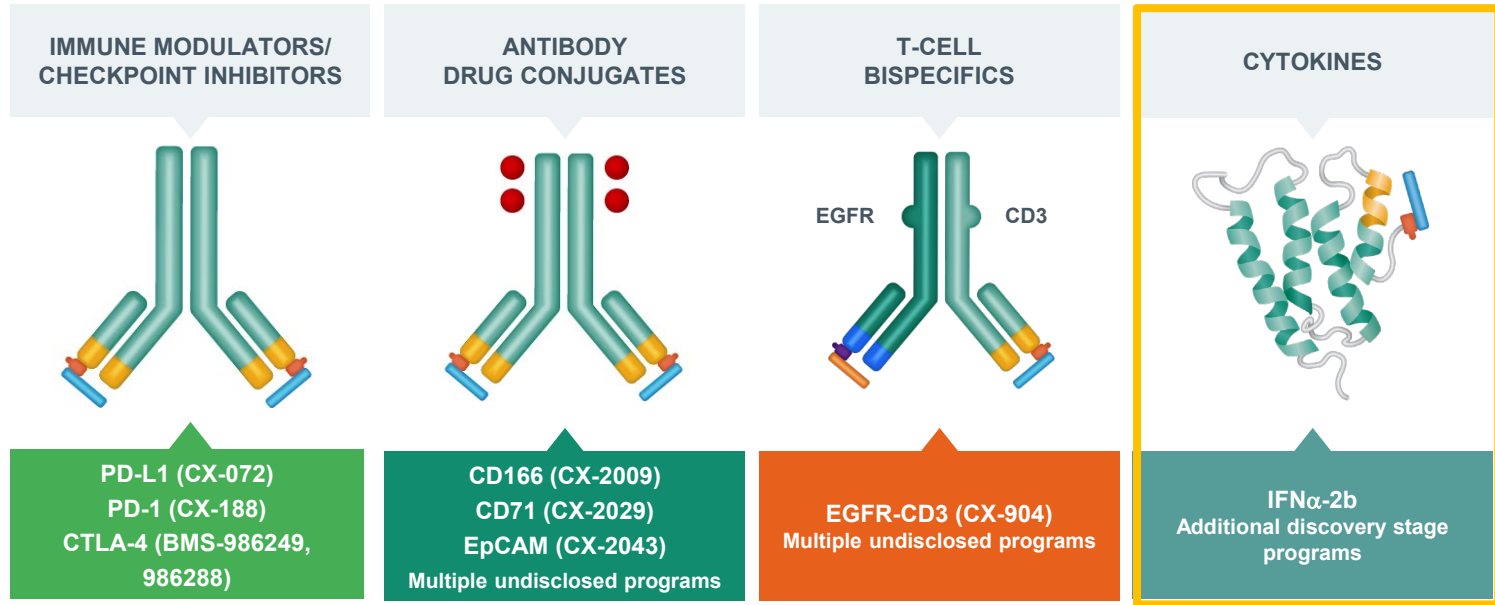
- Maintaining potency
- Reducing side effects
- Enabling new target opportunities

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



The Probody Platform is Applicable Across Multiple Modalities



Applying Probody Technology Beyond Antibody Formats

- Affinity peptide mask used for Probody Antibody-based formats
- Conditional Cytokines may require novel masking approaches
- Opportunity for multiple strategies

Pre-Clinical Proof of Concept With Conditional IFN α -2b

Target Biology and Opportunity

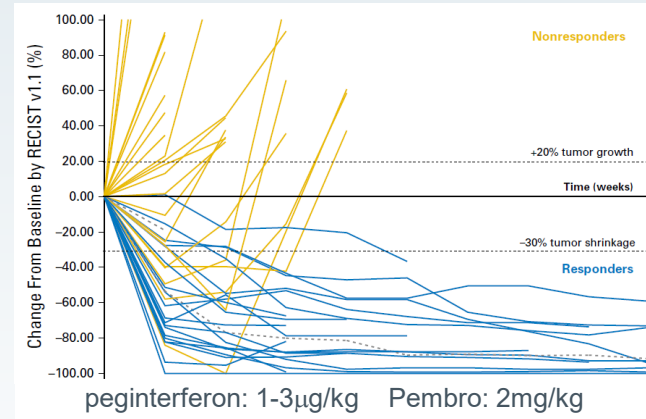
TARGET BACKGROUND

- Single chain polypeptide of Type I IFN
- Virtually all nucleated cells express receptors for IFN α/β
- Pleiotropic activities:
 - Antiviral activity
 - Immunomodulatory
 - Antiproliferative/Pro-apoptotic activity
- Approved for use for antiviral and cancer therapy
- Systemic administration is accompanied by dose dependent toxicities
- Local delivery is safe and effective in BCG unresponsive bladder cancer

CONDITIONAL IFN α -2b OPPORTUNITY

peginterferon + PD-1 in Melanoma

(Davar et al., J Clin. Onc., 2018)



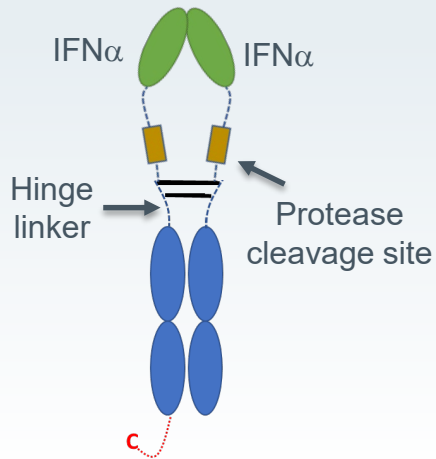
- ORR: 60.5%
- 49% G3/4 AEs

- Room to improve therapeutic index
- Potential for tumor localized activity

Exploring Probody Technology for Steric Masking of IFN α 2b

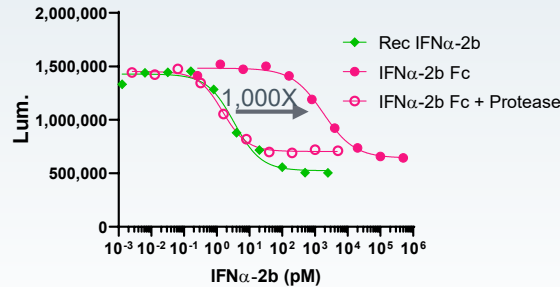
IFN α 2b-Fc fusion is masked compared to monomeric IFN α 2b

IFN α 2b-Fc engineered with protease-cleavage site

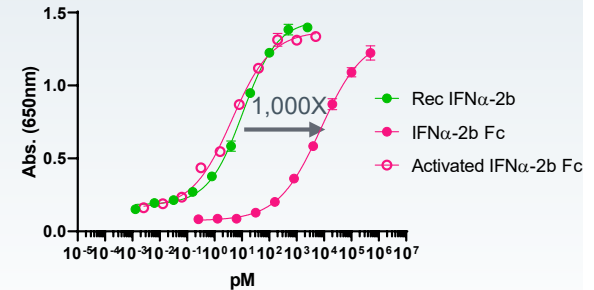


Optimized IFN α 2b-Fc construct to maximize cleavability and minimize IFN α -2b toxicity

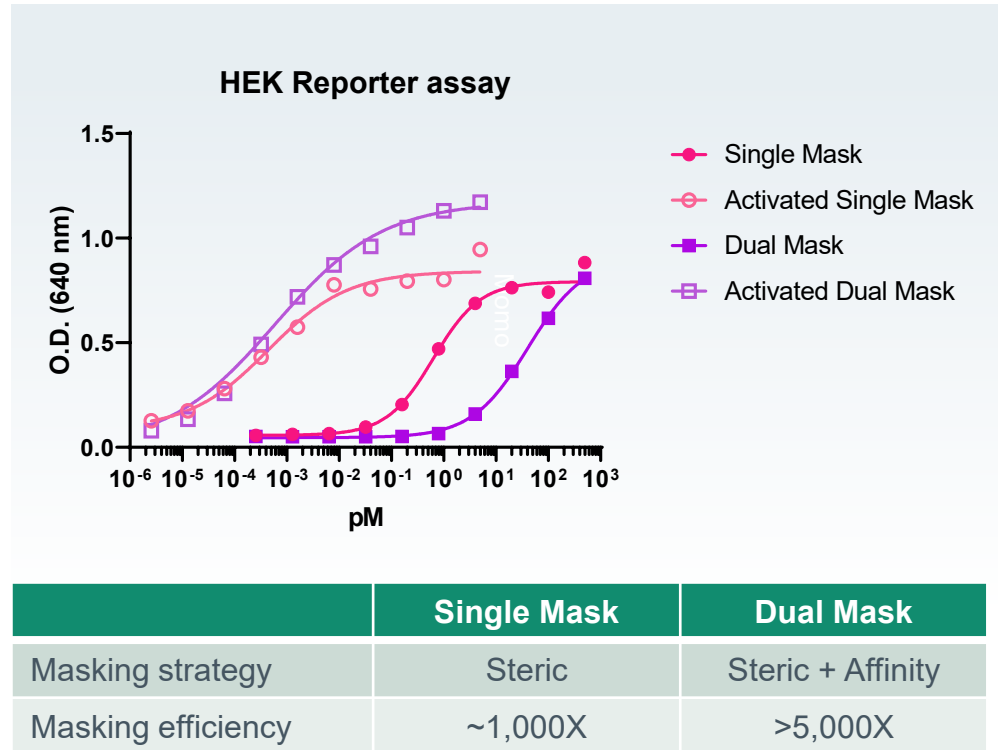
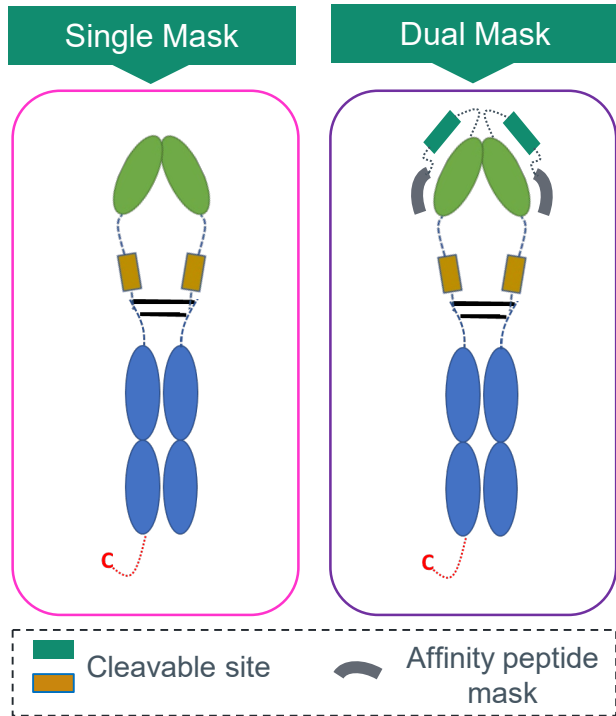
Daudi Proliferation Assay



HEK reporter assay

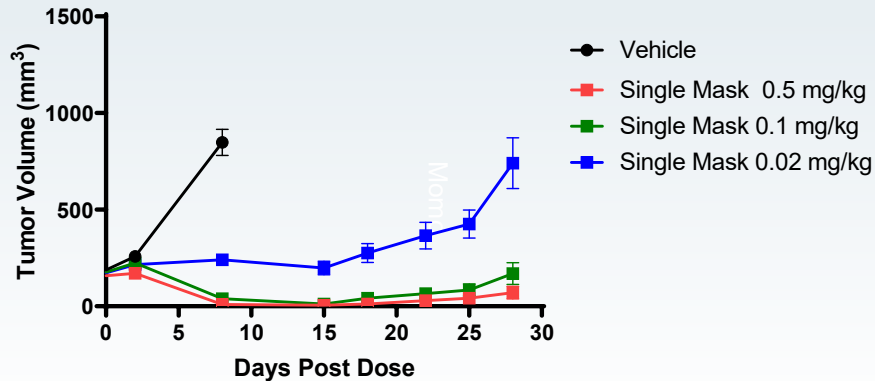


Exploring Probody Technology for Dual Masking of IFN α 2b

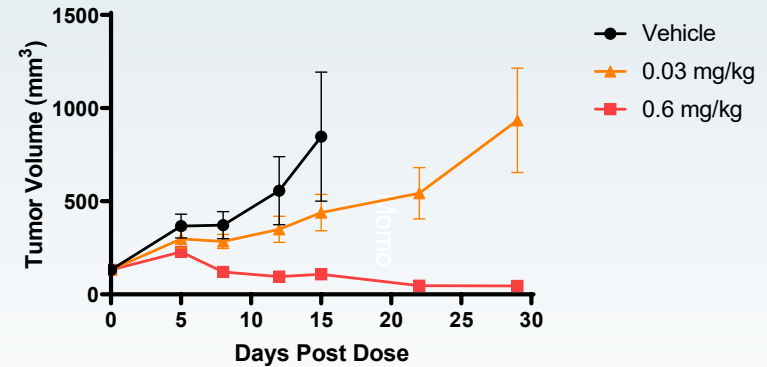


Single Masked IFN α -2b/Fc is Active in Daudi Tumor Mouse Model

Single Masked IFN α -2b/Fc



peginterferon



- Single Masked IFN α -2b/Fc induces tumor regression at dose as low as 0.1 mg/kg
- Single Masked IFN α -2b/Fc is as active as peginterferon

Pilot Tolerability Study in Hamster

Goal

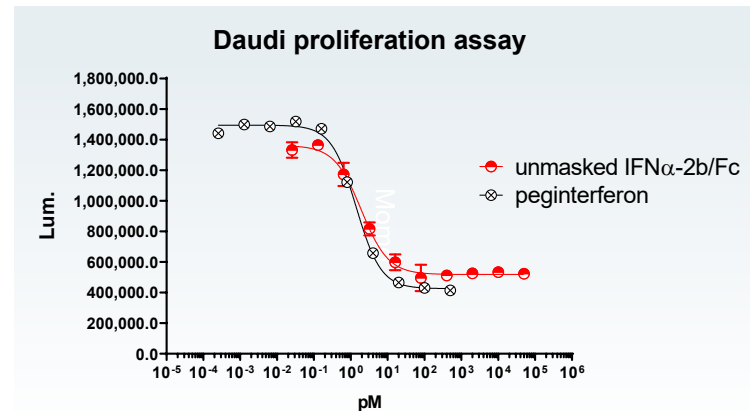
- Characterize toxicities of masked and non-masked IFN α -2b after single dose administration to Syrian hamster

Rationale

- Syrian hamster is sensitive to human IFN α

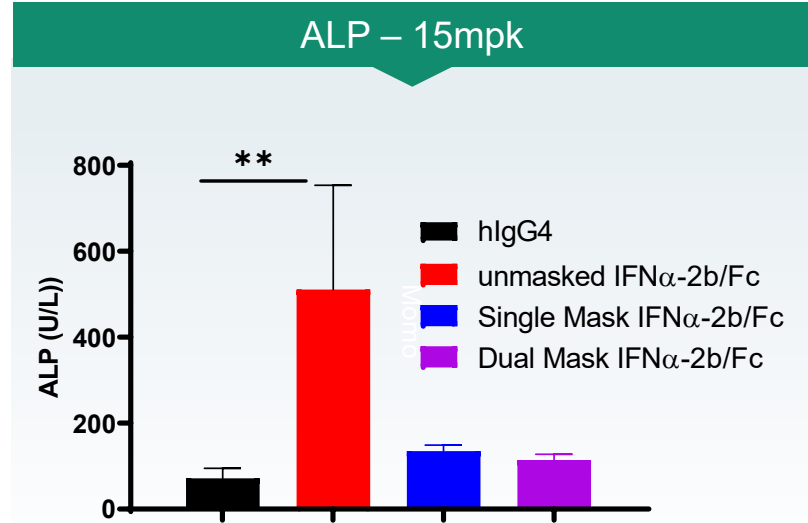
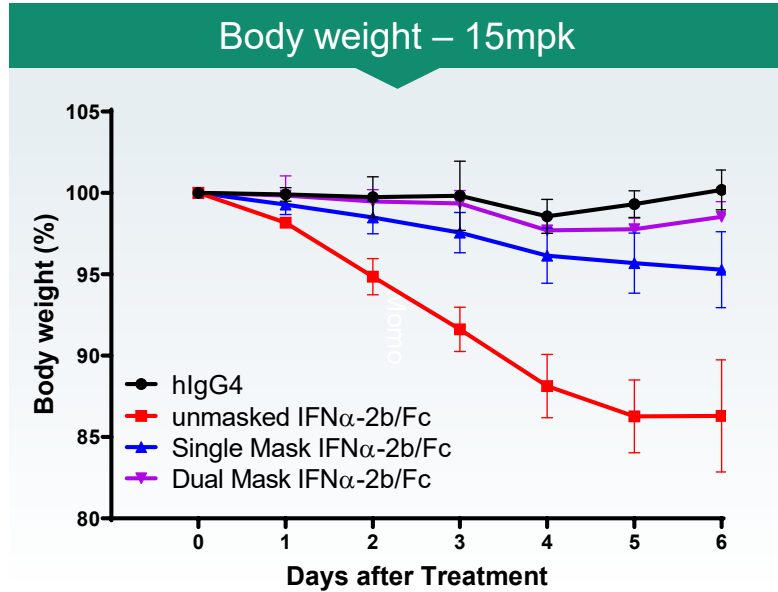
Test Articles:

- Single Mask IFN α -2b/Fc
- Dual Mask IFN α -2b/Fc
- Unmasked IFN α 2b/Fc (peginterferon)
- IgG4



Masked IFN α -2b/Fc are Well Tolerated in Hamster up to 15 mg/kg

Single dose escalation study



- Evidence of IFN α -2b mediated toxicity in animals dosed with unmasked IFN α -2b/Fc (Increased ALP detected at 0.4mpk)
- Increased therapeutic index for dual and single masked IFN α -2b/Fc

Summary: The Probody Platform can be Applied to Create Conditionally Active Cytokine Therapeutics

Probody Technology

- Designed to be minimally active systemically, until activated in the protease-enriched diseased microenvironment

Conditional IFN α -2b characteristics

- Conditionally active dual mask strategy reduces IFN α -2b activity in vitro (>5,000X)
- Highly potent in xenograft in vivo studies – comparable to peginterferon
- Reduced systemic IFN α -2b mediated toxicity in Hamster

Conditional Cytokine opportunities

- Broad opportunity for Probody platform to create conditional cytokines leveraging deep expertise in protease biology and masking strategies