Conditional Cytokine Therapeutics for Tumor-Selective Biological Activity
Preclinical characterization of a dual-masked IFNα-2b

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Presentation Outline

1. Promise of Conditional Cytokines
2. Overview of Probody® Therapeutic Technology Platform
3. In vitro Characterization of a Conditional IFNα-2b With a Dual Masking Strategy
4. 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
Activated Proteases Are Prevalent in Tumors but not in Healthy Tissue

**UPREGULATED PROTEASE ACTIVITY IS A HALLMARK OF ALL CANCERS**


**PROTEASE ACTIVITY IS TIGHTLY CONTROLLED IN HEALTHY TISSUES**

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

**Immune Modulators/Checkpoint Inhibitors**
- PD-L1 (CX-072)
- PD-1 (CX-188)
- CTLA-4 (BMS-986249, 986288)

**Antibody Drug Conjugates**
- CD166 (CX-2009)
- CD71 (CX-2029)
- EpCAM (CX-2043)
- Multiple undisclosed programs

**T-Cell Bispecifics**
- EGFR-CD3 (CX-904)
- Multiple undisclosed programs

**Cytokines**
- IFNα-2b
  - Additional discovery stage programs

### 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 IFNα-2b
Target Biology and Opportunity

<table>
<thead>
<tr>
<th>TARGET BACKGROUND</th>
<th>CONDITIONAL IFNα-2b OPPORTUNITY</th>
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<tbody>
<tr>
<td>• Single chain polypeptide of Type I IFN</td>
<td>peginterferon + PD-1 in Melanoma (Davar et al., J Clin. Onc., 2018)</td>
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<tr>
<td>• Virtually all nucleated cells express receptors for IFNα/β</td>
<td>peginterferon: 1-3µg/kg Pembro: 2mg/kg</td>
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<td>• Pleiotropic activities:</td>
<td>• ORR: 60.5%</td>
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<td>• Antiviral activity</td>
<td>• 49% G3/4 AEs</td>
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<tr>
<td>• Immunomodulatory</td>
<td>• Room to improve therapeutic index</td>
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<tr>
<td>• Antiproliferative/Pro-apoptotic activity</td>
<td>• Potential for tumor localized activity</td>
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<tr>
<td>• Approved for use for antiviral and cancer therapy</td>
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<tr>
<td>• Systemic administration is accompanied by dose dependent toxicities</td>
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<tr>
<td>• Local delivery is safe and effective in BCG unresponsive bladder cancer</td>
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Exploring Probody Technology for Steric Masking of IFNα2b

IFNα2b-Fc fusion is masked compared to monomeric IFNα2b

IFNα2b-Fc engineered with protease-cleavage site

Optimized IFNα2b-Fc construct to maximize cleavability and minimize IFNα-2b toxicity

Daudi Proliferation Assay

HEK reporter assay
Exploring Probody Technology for Dual Masking of IFNα2b

<table>
<thead>
<tr>
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<th>Single Mask</th>
<th>Dual Mask</th>
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<tbody>
<tr>
<td>Masking strategy</td>
<td>Steric</td>
<td>Steric + Affinity</td>
</tr>
<tr>
<td>Masking efficiency</td>
<td>~1,000X</td>
<td>&gt;5,000X</td>
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**HEK Reporter assay**

- Single Mask
- Activated Single Mask
- Dual Mask
- Activated Dual Mask
Single Masked IFN$\alpha$-2b/Fc is Active in Daudi Tumor Mouse Model

- Single Masked IFN$\alpha$-2b/Fc induces tumor regression at dose as low as 0.1mg/kg
- Single Masked IFN$\alpha$-2b/Fc is as active as peginterferon
Pilot Tolerability Study in Hamster

Goal
• Characterize toxicities of masked and non-masked IFNα-2b after single dose administration to Syrian hamster

Rationale
• Syrian hamster is sensitive to human IFNα

Test Articles:
• Single Mask IFNα-2b/Fc
• Dual Mask IFNα-2b/Fc
• Unmasked IFNα2b/Fc (peginterferon)
• IgG4

Daudi proliferation assay
Masked IFNα-2b/Fc are Well Tolerated in Hamster up to 15 mg/kg

Single dose escalation study

- Evidence of INFα-2b mediated toxicity in animals dosed with unmasked IFNα-2b/Fc (Increased ALP detected at 0.4mpk)
- Increased therapeutic index for dual and single masked IFNα-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 IFNα-2b characteristics**
- Conditionally active dual mask strategy reduces IFNα-2b activity in vitro (>5,000X)
- Highly potent in xenograft in vivo studies – comparable to peginterferon
- Reduced systemic IFNα-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