Conditional Cytokine Therapeutics for Tumor-Targeted Biological Activity: Preclinical Characterization of a Dual-Masked IFN-a2b

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**RESULTS**

**BACKGROUND**

Cytokines have been shown to elicit broad anti-tumor activity in preclinical models. These results have translated into the approval for clinical use of IFN-a and IFN-g. Therapeutic effects of IFN-a have been confirmed for many human cancers; however, the clinical success of cytokines has been limited by toxicity and poor systemic delivery.

CytomX Therapeutics has developed a new class of antibodies called Probody® therapeutics (Pb-Tx), designed to retain the therapeutic antibody by minimizing toxicity to healthy tissue while being preferentially activated in the tumor microenvironment (TME) by tumor-associated proteases. CytomX has applied the Pb-Tx platform across multiple modalities including traditional antibodies, antibody-drug conjugates, and T-cell engagers. Pb-Tx is a cleavable, conditionally active construct that is designed to widen the therapeutic window by minimizing binding to targets in healthy tissue while being preferentially activated in the TME by tumor-associated proteases.

**Methods**

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**Results**

The Pb-IFN-a2b construct was engineered with a dual masking strategy to improve the therapeutic index of IFN-a therapy and allow systemic delivery. IFN-a2b, and a cleavable affinity peptide mask at the other end. The construct was optimized to both have reduced systemic IFN-a2b mediated toxicity as compared to the unmasked cytokine.

hamster, which has been shown to be sensitive to IFN-a mediated toxicity in the liver and bone marrow. In highly potent in syngeneic mice in vivo efficacy studies. Finally, we established an in vivo safety model in an additional discovery.

**REFERENCES**


**CONCLUSIONS**

• Dual masked, conditionally active IFN-a2b demonstrated ~5000-fold reduced IFN-a2b signaling measured by reporter assay. Activation by tumor-associated proteases restores full function of the molecule.

• Pb-IFN-a2b directly activates primary immune cells, including immune infiltrate in dissociated human tumors.

• Pb-IFNa-A/D suppresses growth of syngeneic murine tumors in vivo. Co-administration of Pb-IFNa-A/D with PD-L1 mAb enhances the effect.

• Conditionally active IFN-a2b cytokine is well tolerated up to 15 mg/kg in hamsters compared with the unmasked cytokine.

• Pb-IFN-a2b cytokine is generally well tolerated in cynomolgus monkeys. Further preclinical evaluation of the in vivo pharmacology and toxicity for the conditionally IFN-a program is ongoing.

• The CytomX platform is being extended to additional cytokine families.

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