



CX-908, a PROBODY® T Cell Engager Targeting CDH3 and CD3, Induces Tumor Regressions and Improves the Therapeutic Window in Preclinical Studies

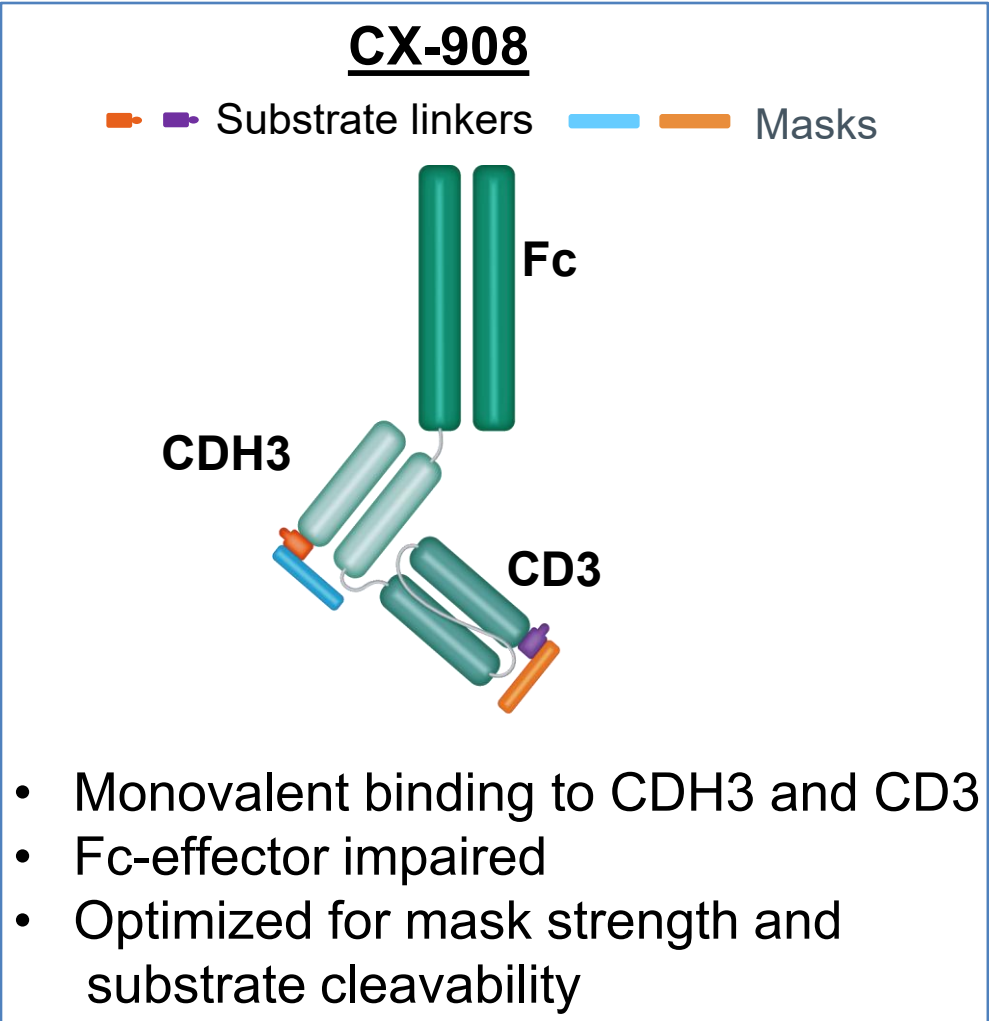
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Abstract

BACKGROUND

T cell-engaging bispecific antibodies (TCE) activate cytotoxic T cells to initiate a tumor antigen dependent anti-tumor response. The development of these highly potent therapeutics can be limited by on target toxicity in normal tissues and cytokine release syndrome. PROBODY® therapeutics (Pb-Tx) are recombinant protease activated prodrugs that are masked to reduce target engagement in normal tissues but are preferentially active in the tumor microenvironment upon protease-dependent activation. CDH3 (P-cadherin), a member of the cadherin family involved in cell-cell adhesion, is overexpressed in multiple solid tumors including lung and breast cancers making it an attractive tumor target. However, its development has been limited by toxicities due to its expression on normal tissue. Here we describe the preclinical efficacy and safety of CX-908, a masked PROBODY® T cell engager (Pb-TCE) targeting CDH3 and CD3.



METHODS

CX-908, a dually masked Pb-TCE targeting CDH3 and CD3, was engineered using PROBODY® platform technology. Masked and unmasked TCEs were evaluated for on-cell binding and T cell-dependent cellular cytotoxicity in vitro, efficacy in mouse xenograft models, and safety in non-human primate tolerability studies.

RESULTS

Compared to the unmasked TCE, CX-908 demonstrates at least a 500-fold decrease in target binding in vitro. Similarly, in vitro cytotoxic potency of CX-908 is reduced by at least 1000-fold. In contrast, in vivo, CX-908 potently induces tumor regressions in established breast and lung cancer cell line derived xenograft tumor models. Additionally, studies performed in non-human primates demonstrate that CX-908 is well tolerated with 100-fold improved tolerability compared to the unmasked form and shows significantly reduced cytokine release.

CONCLUSIONS

CX-908 shows strong anti-tumor efficacy and an improved tolerability profile compared to the unmasked TCE in preclinical studies. These data indicate that CX-908 has a wide predicted therapeutic window and support the potential to target CDH3 positive solid tumors clinically.

Background

Overview of the PROBODY® Therapeutic Platform

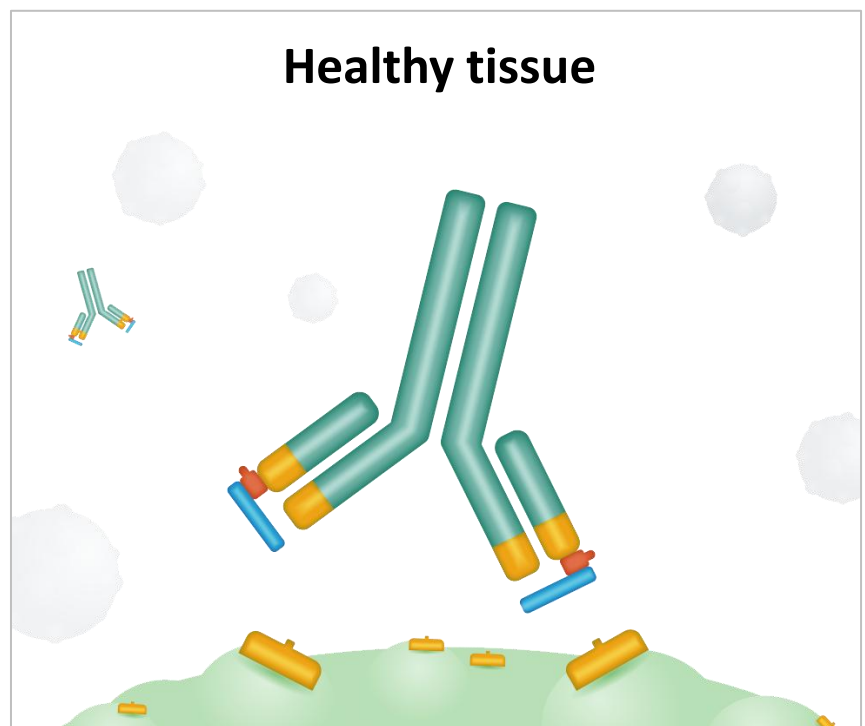


Figure 1. Masking limits ability of Pb-Tx to bind target in healthy tissues

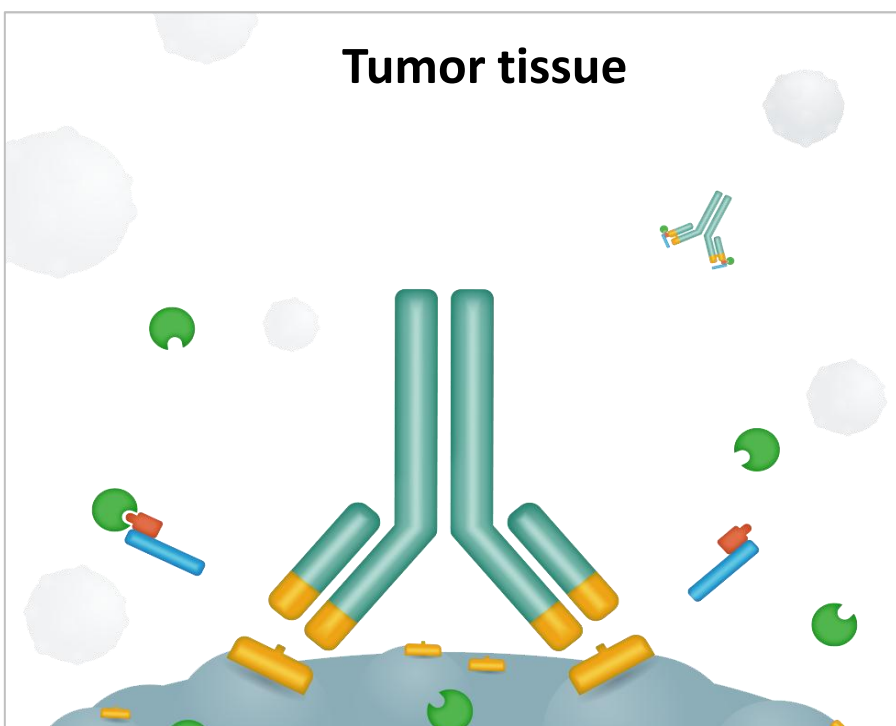


Figure 2. Tumor-associated proteases “unmask” Pb-Tx allowing more binding to target

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Results

CX-908 Demonstrates Attenuated Binding to CDH3 and CD3

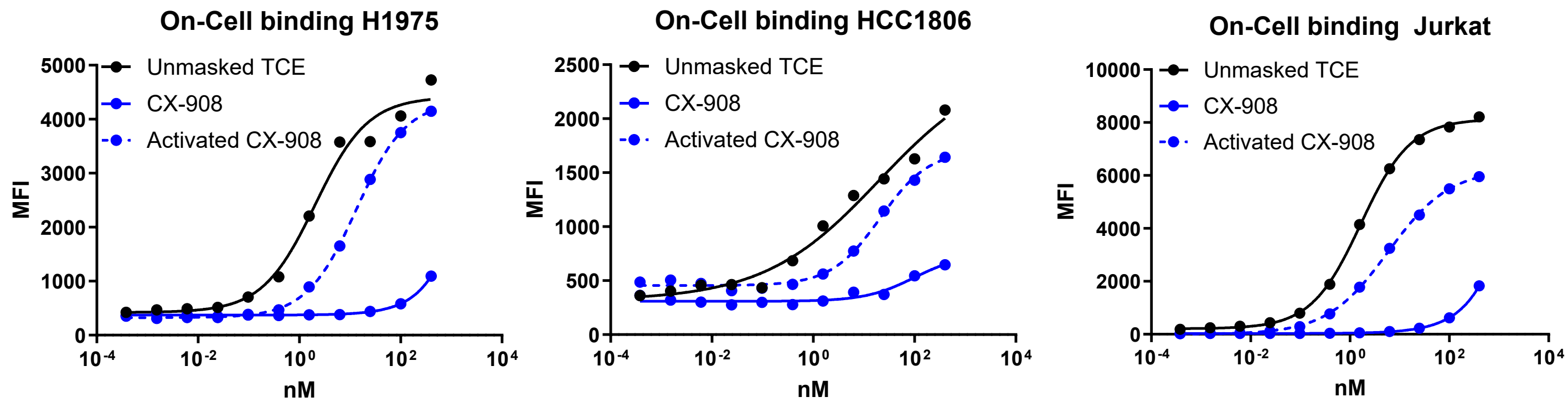


Figure 3. Binding of CX-908, protease activated CX-908, and unmasked TCE to cells expressing CDH3 or CD3 by flow cytometry. Left, NSCLC cell line H1975; Center, Breast cancer cell line HCC1806; Right, T-cell ALL cell line Jurkat. Binding of CX-908 is reduced compared to the unmasked TCE. Binding activity is restored when masks are removed through in vitro protease treatment. Mean fluorescence intensity (MFI) is plotted.

CX-908 Demonstrates Attenuation of in vitro Cytotoxicity

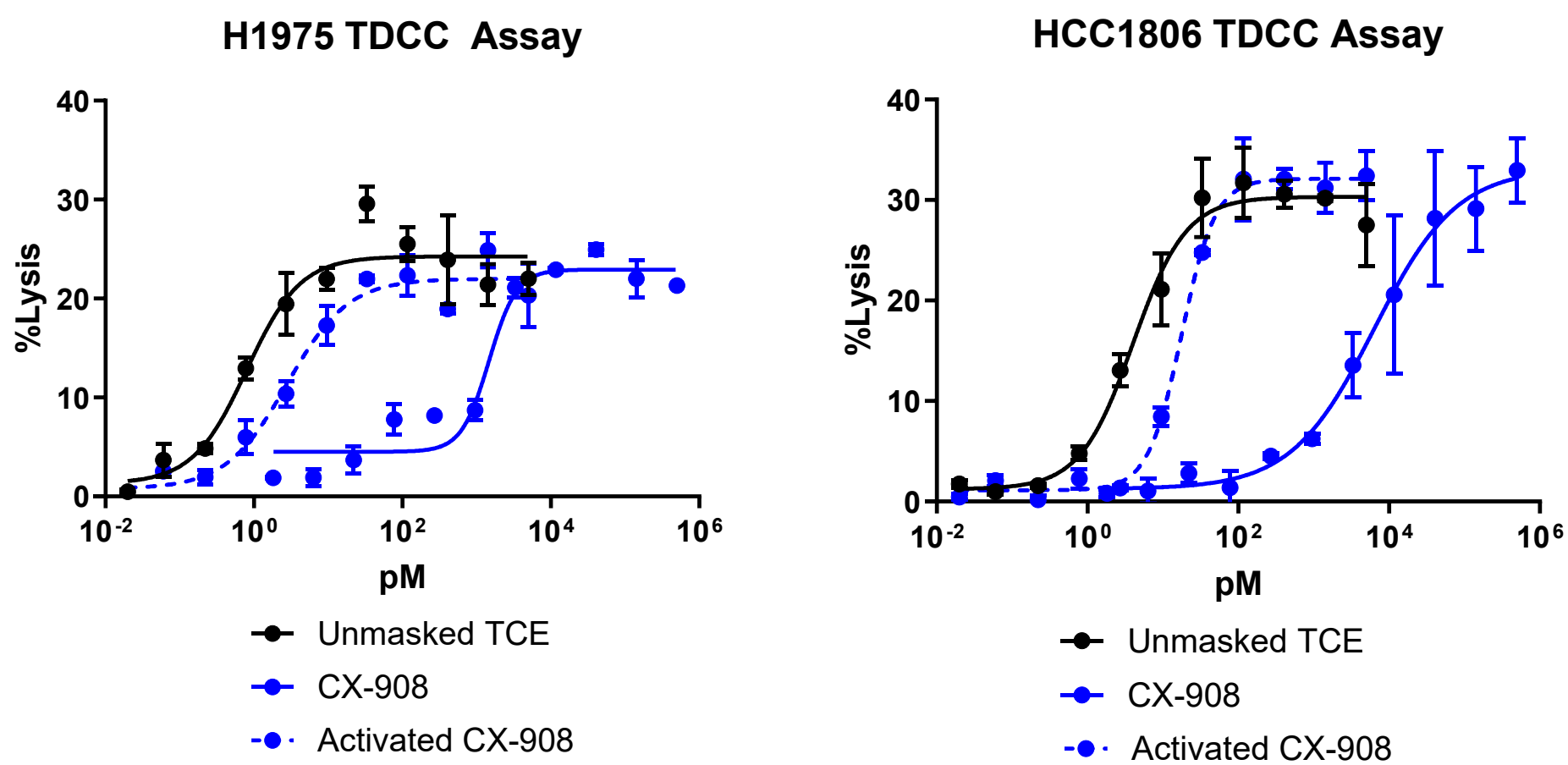


Figure 4. T cell dependent cytotoxic activity (TDCC) of CX-908, protease activated CX-908, and unmasked TCE. Masked CX-908 has reduced cytotoxic potency compared to unmasked TCE. Cytotoxic activity is restored when masks are removed through in vitro protease treatment. Left, H1975 target cells; Right, HCC1806 target cells. Cytotoxicity was quantified using CytoTox-Glo (Promega) following 48 hr co-culture of PBMC and target cells at a 10:1 ratio. Mean (n=2) +/- standard deviation is plotted.

CX-908 Induces Tumor Regressions in H1975 and HCC1806 Tumor Models

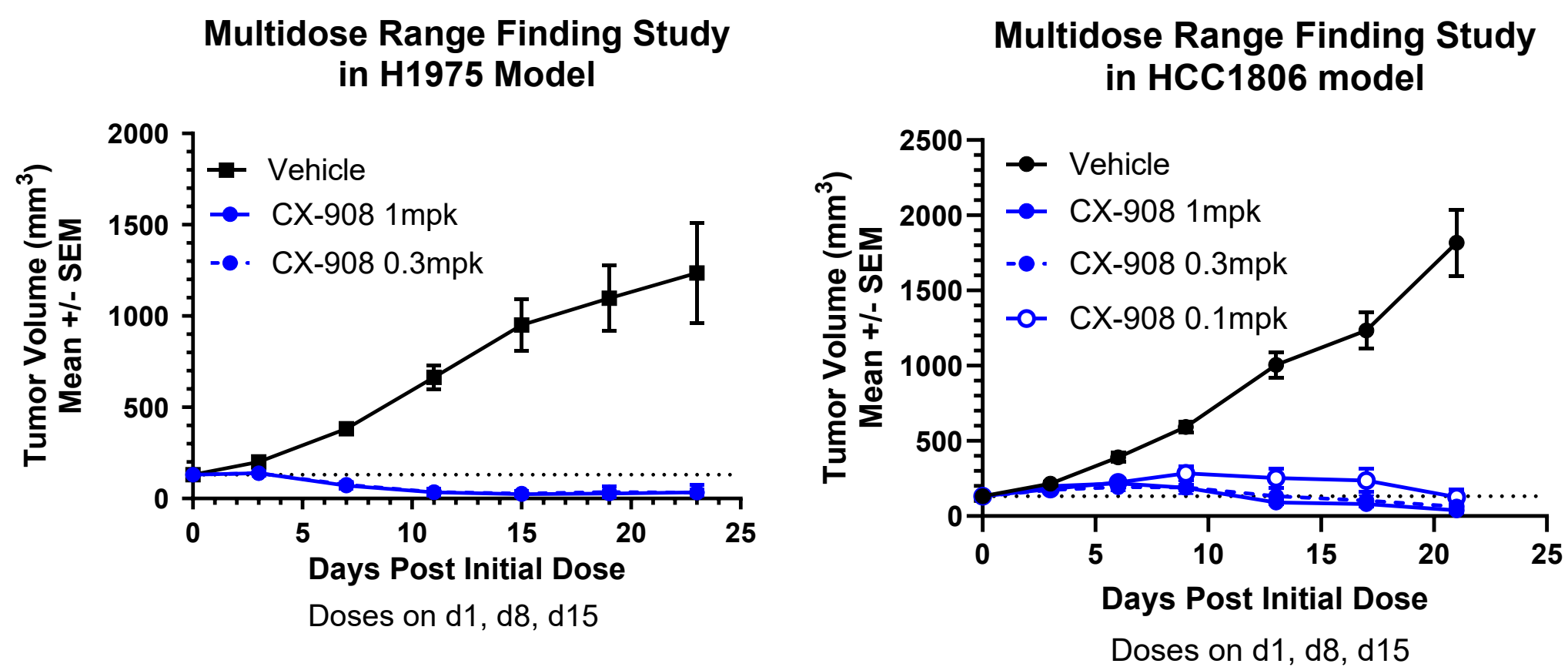


Figure 5. Efficacy of CX-908 in PBMC engrafted tumor intervention models. CX-908 induces tumor regressions at 0.3 mg/kg in the H1975 and HCC1806 tumor models. Female NSG mice (n=8) were implanted with tumor cells (s.c.) and subsequently engrafted with human PBMC. When tumors reached approximately 150 mm³, test articles were administered IV once weekly. Left, H1975 tumor model; Right, HCC1806 tumor model.

CX-908 Provides Increased Safety in Cynomolgus Monkey

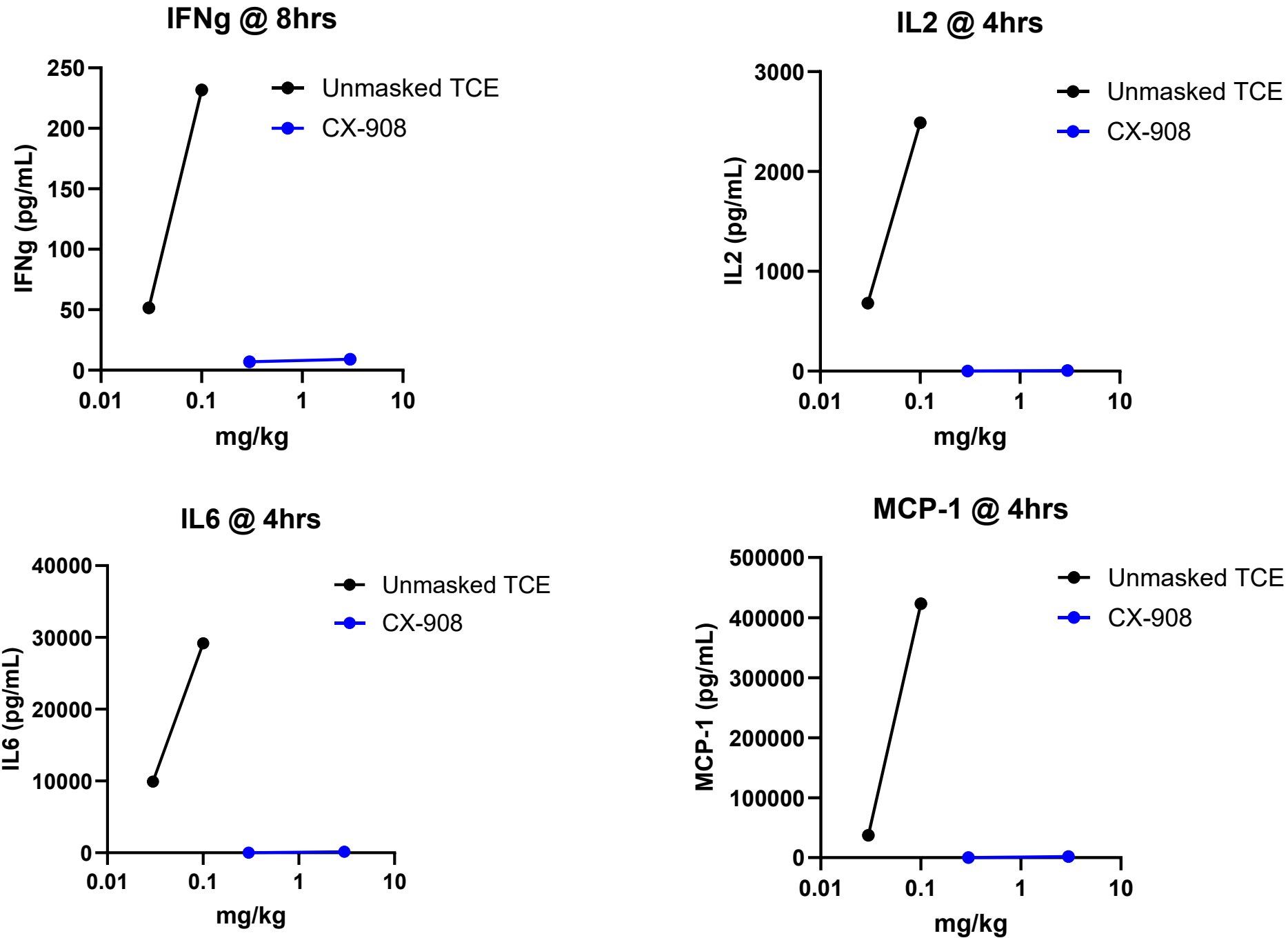


Figure 6. Cytokine release following a single dose of CX-908 or unmasked TCE in cynomolgus monkey. CX-908 greatly decreases the magnitude of cytokine release compared to unmasked TCE. Cytokine analysis was performed using a multiplex assay platform. Serum samples were obtained at 4 or 8 hr post dose as indicated.

	MTD (mg/kg)	Efficacy Benchmark	H1975 TI	HCC1806 TI
CX-908	3	70% tumor volume decrease	17	3
Unmasked TCE	0.03	Stable disease	28	11

Table 1. Maximum tolerated dose (MTD) and Therapeutic Index (TI) estimates. Left, Based on clinical observations in monkey, maximum tolerated dose of CX-908 was 3 mg/kg, while MTD of unmasked was 0.03 mg/kg, 100x lower. Right, PK/PD modeling was used to estimate TI of CX-908 using different efficacy benchmarks. PK parameters were estimated, and a minimal efficacious dose was projected for each model and benchmark. The TI was then calculated as Cyno AUC at maximum tolerated dose/Mouse AUC at minimum efficacious dose.

Conclusions

- CX-908 demonstrates attenuated target binding and cytotoxic activity relative to unmasked TCE in vitro in assay conditions where it remains in the masked form.
- CX-908 induces regressions of established CDH3+ tumors in human PBMC engrafted mice consistent with unmasking by tumor associated proteases.
- In cynomolgus monkey, CX-908 improves tolerability at least 100x relative to unmasked TCE and decreases the magnitude of cytokine release.
- These data along with a favorable predicted TI for the CX-908 clinical candidate, support the potential to target CDH3+ tumors clinically, including lung and breast cancers.