# Dual Blockade of PD-1 and CTLA-4 with Bispecific Antibodies Promotes Human T cell Activation and Proliferation

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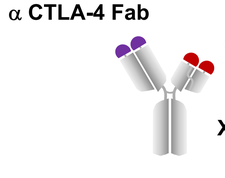
## Introduction

- Tumor infiltrating lymphocytes (TILs) co-express multiple checkpoint receptors in contrast to lymphocytes found in the periphery
- TILs that co-express multiple checkpoint receptors may be resistant to single checkpoint blockade (Matsuzaki et al PNAS 2010, Fourcade et al Cancer Res 2012, Gros et al JCI 2014)
- Treatment of advanced melanoma patients with nivolumab plus ipilimumab significantly increases progression-free survival compared to each monotherapy alone
- Targeting of PD-1$^{+}$CTLA-4$^{+}$ TILs with a bispecific antibody may reproduce the efficacy of the combination of nivolumab and ipilimumab therapy with reduced treatment-associated toxicities

## Summary


- Dual blockade of PD-1 and CTLA-4 promotes superior T cell activation, proliferation and T cell mediated anti-tumor efficacy compared to anti-PD-1 alone
- XmAb20717 is a PD-1 x CTLA-4 bispecific antibody currently under pre-clinical development at Xencor

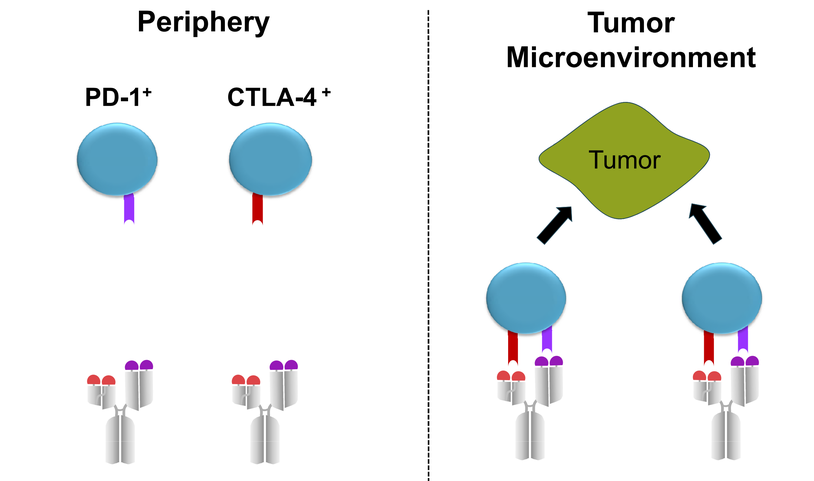

## Dual-checkpoint bispecific antibody design




- High yielding stable cell lines
- Protein A + Ion exchange chromatography

- Modified Fc domain eliminates FcγR interactions
- Modified Fc domain with Xtend technology to promote long half-life
- Fc substitutions promote heterodimer formation and facilitate purification by standard methods
- Optimized Anti-PD-1 and CTLA-4 antibodies were plugged into the platform without further reformatting

## TIL activation with bispecific antibodies



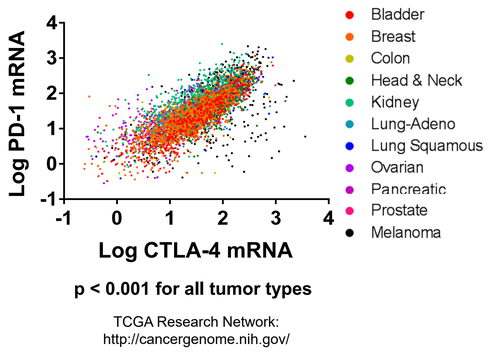

**Peripheral T cells**

Weak bispecific-antibody interactions
No T cell activation

**Dual-checkpoint positive TILs**

Avid bispecific antibody binding
TIL activation

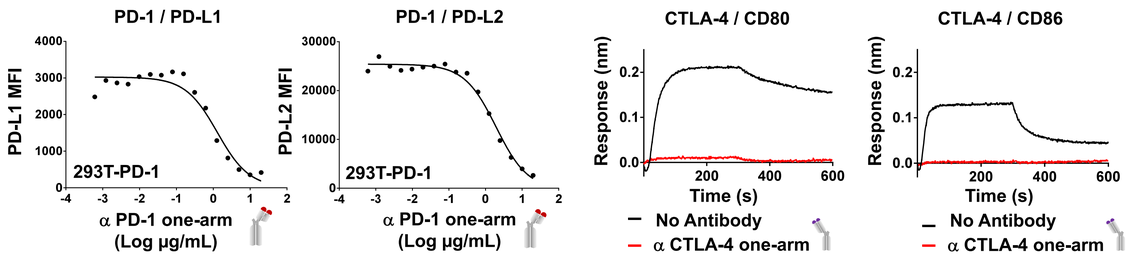
## TILs co-express PD-1 and CTLA-4



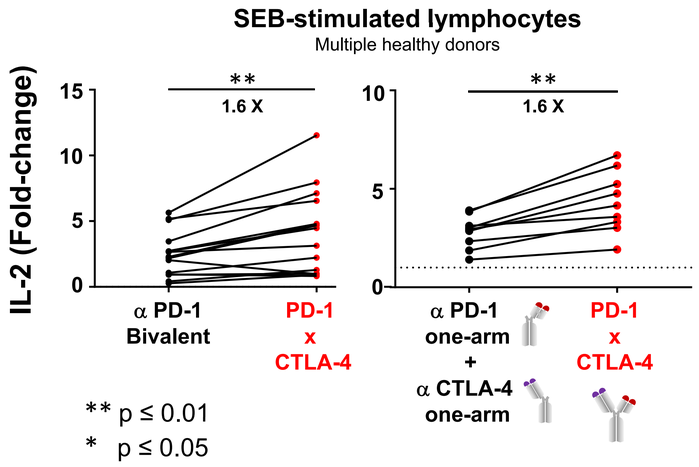

$p < 0.001$ for all tumor types

TCGA Research Network:
http://cancergenome.nih.gov/

## Component antibody domains block checkpoint receptor / ligand interactions

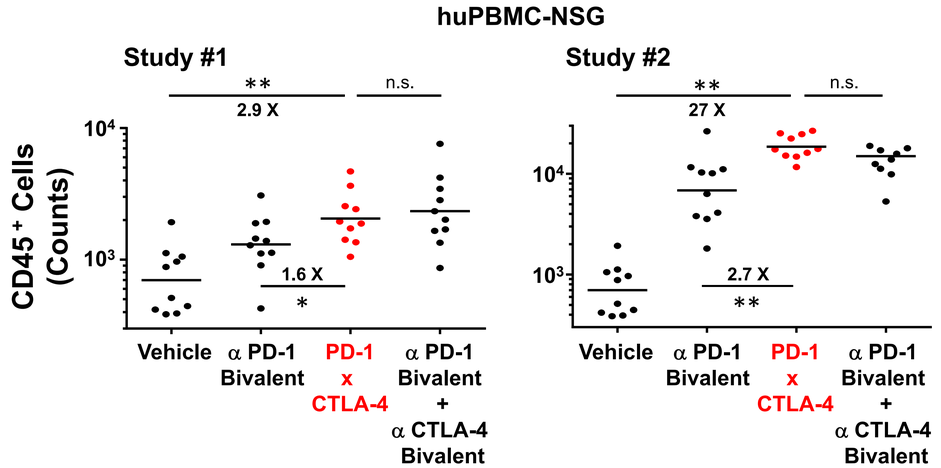



## PD-1 x CTLA-4 bispecific antibodies promote T cell activation *in vitro*

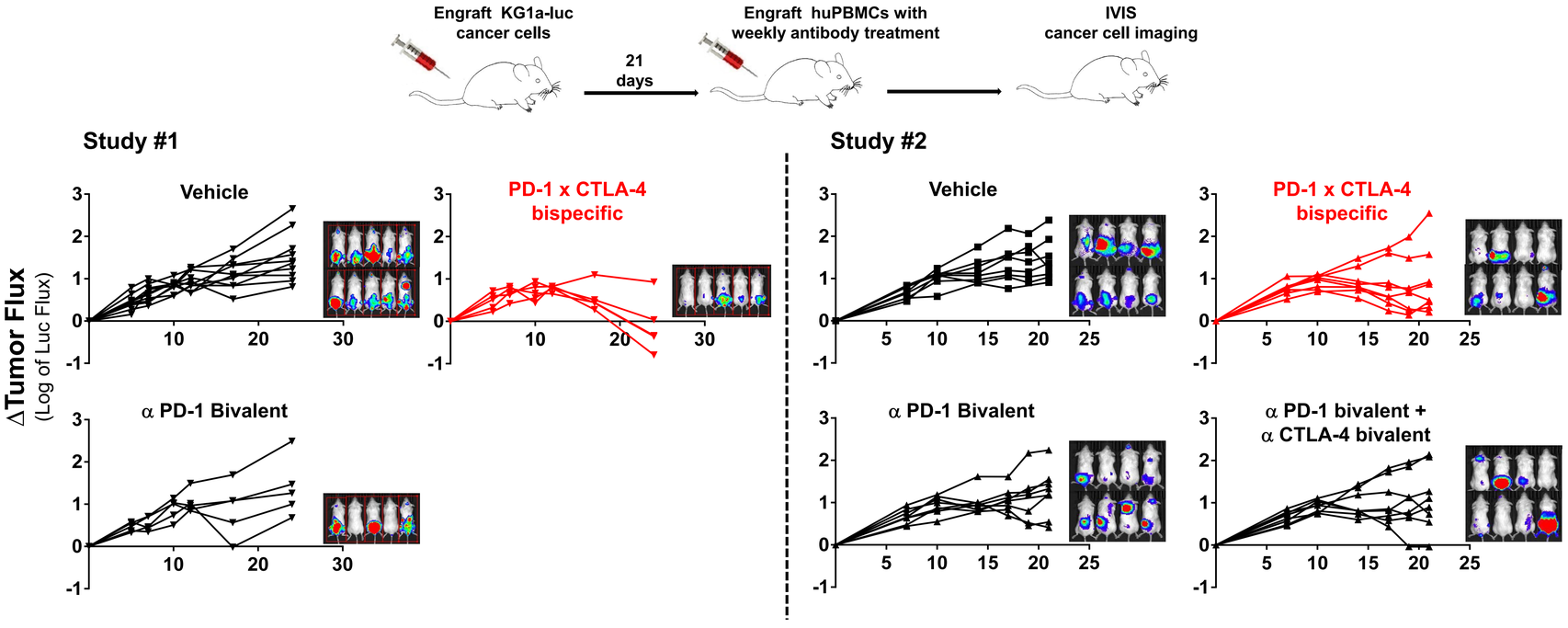



** $p \le 0.01$
* $p \le 0.05$

## PD-1 x CTLA-4 bispecific antibodies promote human T cell proliferation *in vivo*




## PD-1 x CTLA-4 bispecific antibodies promote *in vivo* T cell mediated anti-tumor efficacy

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