Combination of PD1 blockade and T cell costimulation by bispecific antibodies promotes human T cell activation and proliferation

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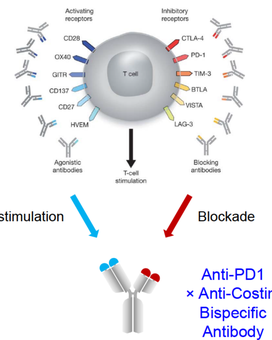
Introduction

- Tumor infiltrating lymphocytes (TILs) express multiple checkpoint receptors, in contrast to lymphocytes found in the periphery (Matsuzaki et al PNAS 2010, Fourcade et al Cancer Res 2012, Gros et al JCI 2014). TILs that co-express multiple checkpoint receptors may be resistant to single-checkpoint blockade.
- We sought to identify an additional therapeutic modality to stack with checkpoint blockade that could increase patient response rate.
- The PD1$^+$ TIL population is likely enriched for tumor-reactivity (Gros et al JCI 2014).
- Engagement of T cell costimulatory receptors with PD1 blockade could further increase T cell activation and proliferation of tumor-reactive TILs.
- We engineered a highly active anti-PD1 × anti-Costim bispecific antibody and characterized its T cell activation activity *in vitro* and *in vivo*.

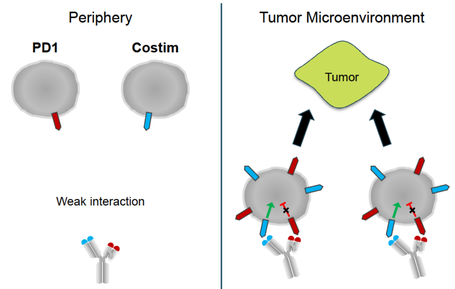
Potential immunoregulatory T cell targets
(Mellman et al Nature 2011)



Costimulation | Blockade

Anti-PD1 × Anti-Costim Bispecific Antibody

TIL activation with bispecific antibodies

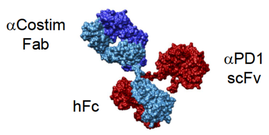


Peripheral T cells
Limited tumor reactivity
Weak bispecific antibody interactions
No T cell activation

Double positive TILs
Enriched for tumor reactivity
Avid bispecific antibody binding
Enhancement of TIL activation

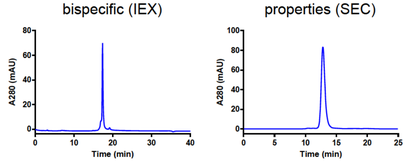
A PD1 × Costim Fab-scFv-Fc bispecifics are readily produced and purified

- 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 antibodies were plugged into the platform without further reformatting
- Component PD1 scFv blocks PDL1 and PDL2 interactions and has high thermal stability



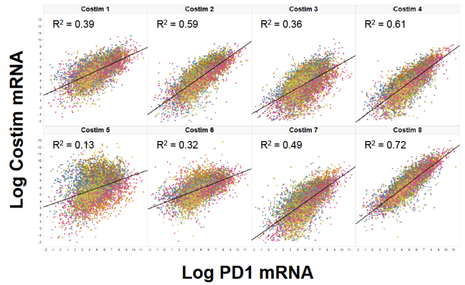
Fab-scFv-Fc

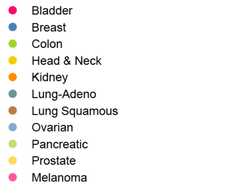
High purity bispecific (IEX) | Favorable solution properties (SEC)



Analytical chromatography

B TILs co-express PD1 and T cell costimulatory receptors

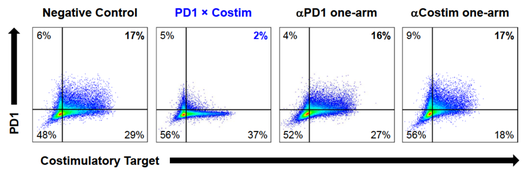


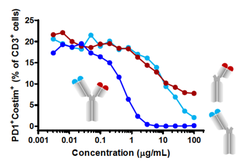


The results shown are based upon data generated by the TCGA Research Network: http://cancergenome.nih.gov/

C PD1 × Costim bispecific selectively targets double-positive T cells

- Double-positive cells are selectively occupied by PD1 × Costim bispecific

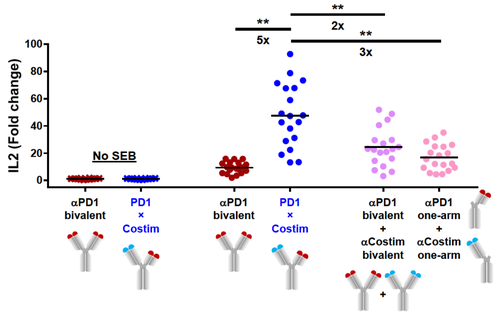




Receptor occupancy of PD1 and Costim on human CD3$^+$ T cells stimulated with SEB

D PD1 × Costim bispecific significantly enhances T cell activation *in vitro*

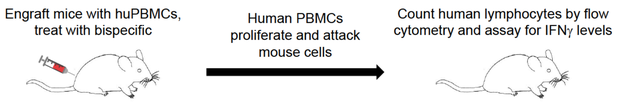
- IL2 production by SEB-stimulated human PBMCs is significantly increased by PD1 × Costim bispecific versus controls (** $p \leq 0.01$)



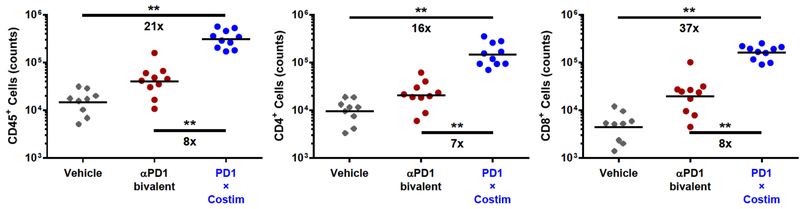
- ✓ Bispecific does not activate naive cells
- ✓ Bispecific enhances T cell activation more than anti-PD1 bivalent antibody alone
- ✓ Bispecific enhances T cell activation more than combination of bivalents

SEB-stimulated human PBMCs (multiple healthy donors)

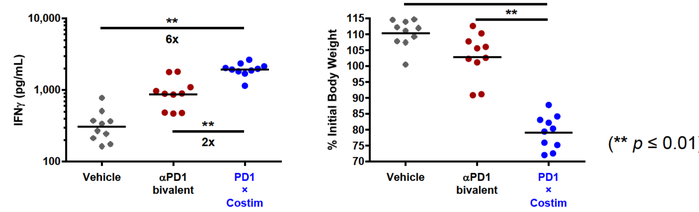
E PD1 × Costim bispecific enhances T cell activation and exacerbates GVHD in huPBMC-engrafted NSG mice



- Human T cell counts are significantly increased by PD1 × Costim bispecific versus anti-PD1
  - Bispecific promotes survival/proliferation of both CD4$^+$ and CD8$^+$ T cells



- Human IFNγ production is significantly increased by PD1 × Costim bispecific versus anti-PD1
  - Decreases in body weight result from exacerbation of GVHD due to T cell expansion, IFNγ production



(** $p \leq 0.01$)

Summary

Anti-PD1 × anti-Costim bispecific antibody:

- Is humanized and includes optimized component antibodies with high thermal stability
- Contains a modified Fc domain with Xtend technology for long serum half-life
- Selectively targets double-positive T cells
- Enhances T cell activation *in vitro* and *in vivo*
- Is well tolerated in cynomolgus monkeys with antibody-like pharmacokinetics
- Is efficiently manufactured using standard antibody production methods

These results support clinical testing of an anti-PD1 × anti-Costim bispecific in cancer.

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