Introduction

- Tumor infiltrating lymphocytes (TILs) co-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 produced PD-1 x CTLA-4, PD-1 x LAG-3, CTLA-4 x LAG-3, and PD-1 x BTLA bispecific antibodies and characterized their T cell activation activity in vitro and in vivo (huPBMC-engrafted NSG mice)

Summary

- Bispecific antibodies selectively target T cells co-expressing multiple checkpoint receptors
- All bispecific antibody pairs enhanced IL-2 production in an in vitro SEB stimulation assay relative to control, indicating functional checkpoint blockade
- Bispecific antibodies promote human T cell proliferation in mice engrafted with human PBMCs
- CTLA-4 x LAG-3 bispecific combines productively with anti-PD-1 to promote triple checkpoint blockade and strong T cell stimulation

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 checkpoint receptor antibodies were plugged into the platform without further reformating

TIL activation with bispecific antibodies

- Peripheral T cells
- Weak bispecific-antibody interactions
- No T cell activation
- Microenvironment
- Checkpoint X
- Checkpoint Y
- Tumor
- Multi-checkpoint positive TILs
- Avid bispecific antibody binding
- TIL activation

Component antibody domains block checkpoint receptor / ligand interactions

- PD-1 / PD-L1
- PD-1 / PD-L2
- LAG-3 / MHC II
- CTLA-4 / CD80
- CTLA-4 / CD86
- BTLA / HVEM

Bispecific antibodies selectively target dual-checkpoint positive T cells

Receptor occupancy of PD-1 and LAG-3 on human CD3+ T cells stimulated with SEB

Bispecific antibody blockade promotes T cell activation in vitro

SEB-stimulated human lymphocytes (multiple healthy donors)

Bispecific antibody blockade promotes human T cell proliferation in huPBMC-NSG mice

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