Anti-PD1 x anti-ICOS bispecific antibody XmAb23104 brings together PD1 blockade and ICOS costimulation to promote human T cell activation and proliferation

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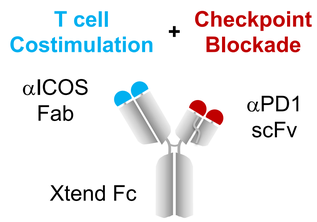
Introduction

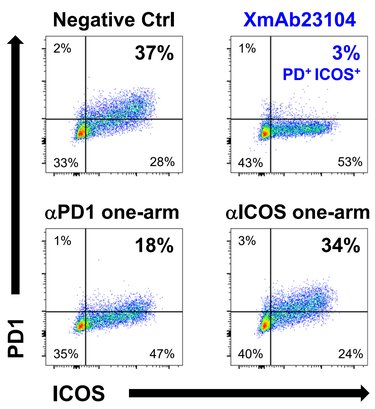
- Tumor infiltrating lymphocytes (TILs) often express multiple immune checkpoints and costimulatory receptors (Matsuzaki *et al* PNAS 2010, Fourcade *et al* Cancer Res 2012, Gros *et al* JCI 2014).
- We sought to identify an additional therapeutic modality to stack with checkpoint blockade that could 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 together with PD1 blockade could further increase activation and proliferation of tumor-reactive TILs.
- Activity screens for multiple PD1/costimulatory combinations demonstrated compelling activity for a PD1 and ICOS pairing.
- We engineered XmAb23104, a highly active anti-PD1 × anti-ICOS bispecific antibody, and characterized its T cell activation activity *in vitro* and *in vivo*.

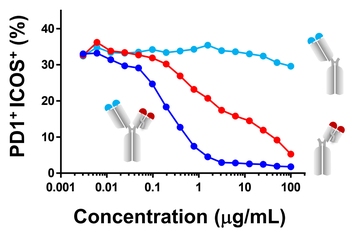


XmAb23104
Anti-PD1 × Anti-ICOS
Bispecific Antibody

- Fab-scFv-Fc format enables monovalent binding of both PD1 and ICOS
- 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
- Component PD1 scFv blocks PDL1 and PDL2 interactions and has high stability

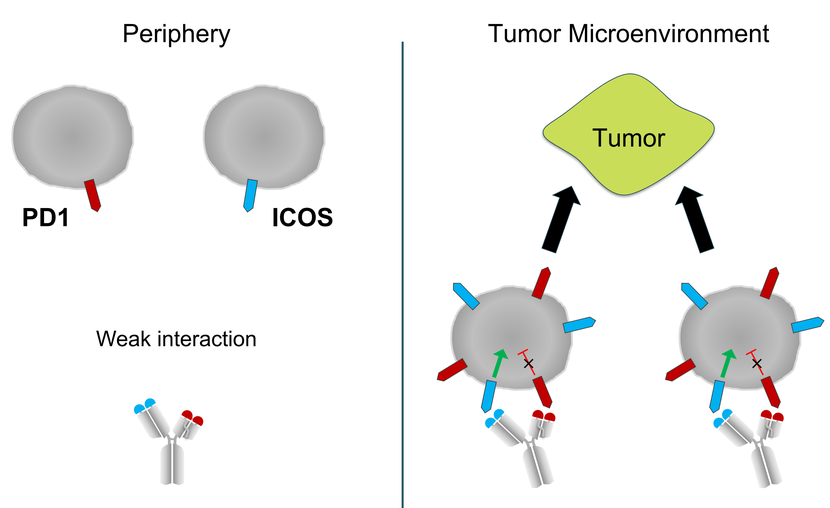
A Monovalent engagement of PD1 and ICOS enables avid targeting of double-positive T cells





Receptor occupancy of PD1 and ICOS on human CD3$^+$ T cells stimulated with SEB
Scatterplots shown for 3 μg/mL concentration

Selective TIL activation with bispecific antibodies

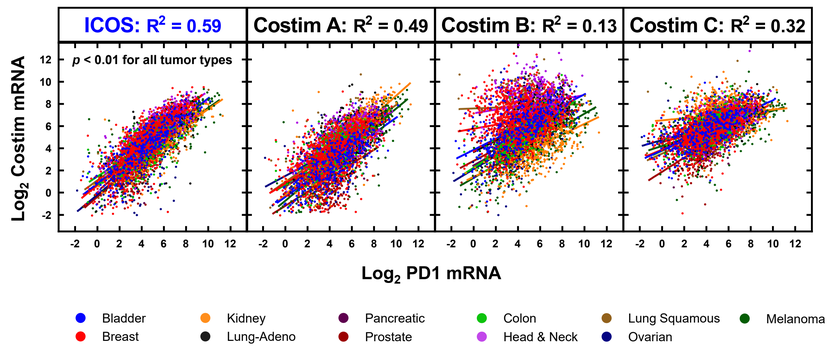


Peripheral T cells
Limited tumor reactivity
Weak binding
No T cell activation

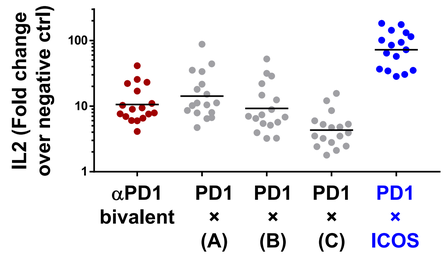
Double positive TILs
Enriched for tumor reactivity
Avid binding
Enhanced TIL activation

B PD1 × ICOS pairing is motivated by tumor mRNA co-expression data and activity screens

TILs co-express PD1 and ICOS



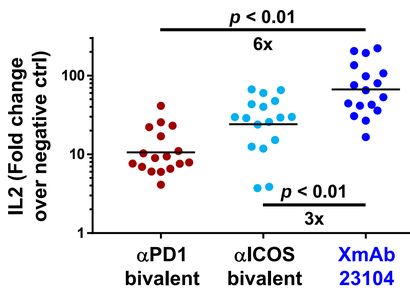
PD1 × ICOS pairing enhances T cell activation versus PD1 × other costimulatory receptors



SEB-stimulated human PBMCs (multiple healthy donors)
* Data shown is for an anti-PD1 × anti-ICOS prototype bispecific

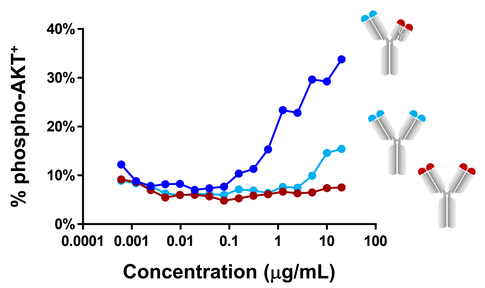
C XmAb23104 significantly enhances T cell activation *in vitro*

IL2 production is significantly increased by XmAb23104 versus bivalent antibodies



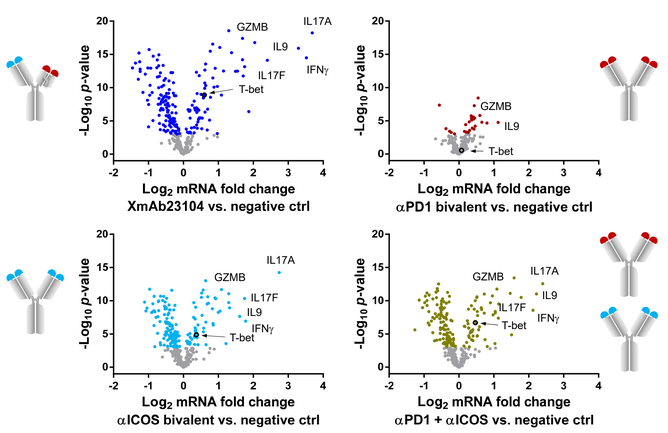
SEB-stimulated human PBMCs (multiple healthy donors)

PD1 × ICOS bispecific induces ICOS signaling via AKT phosphorylation



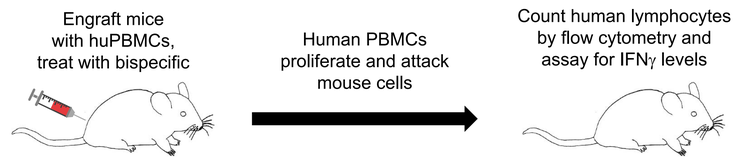
Purified T cells isolated from SEB-stimulated human PBMCs
With plate-bound anti-CD3, assay by MSD Phospho(Ser473)/Total Akt Whole Cell Lysate Kit
* Data shown is for an anti-PD1 × anti-ICOS prototype bispecific

XmAb23104 exhibits a multi-gene expression signature consistent with ICOS costimulation



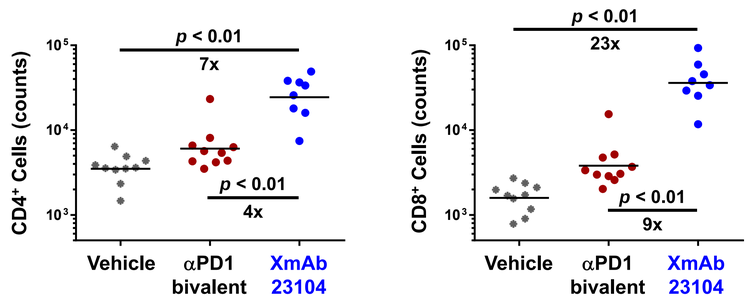
SEB-stimulated human PBMCs (multiple healthy donors)
RNA analyzed on a NanoString platform using the nCounter PanCancer Immune Profiling Panel

D XmAb23104 enhances T cell activation and exacerbates GVHD in huPBMC-NSG mice



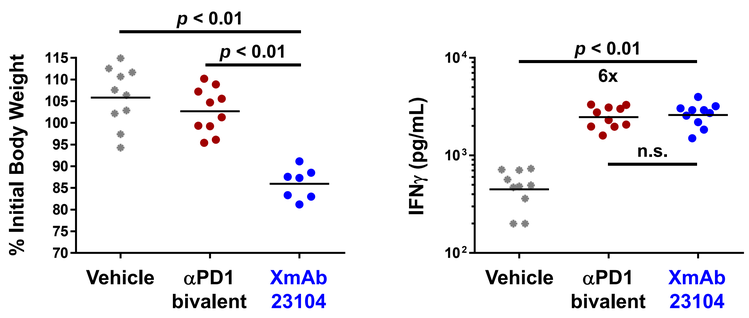
T cells are significantly increased by XmAb23104 versus anti-PD1

- XmAb23104 promotes survival/proliferation of both CD4$^+$ and CD8$^+$ T cells



GVHD is significantly exacerbated by XmAb23104 versus anti-PD1

- Decreases in body weight result from T cell expansion, IFNγ production



Summary

XmAb23104 anti-PD1 × anti-ICOS bispecific antibody:

- Is humanized and includes optimized component antibodies
- Contains a modified Fc domain with Xtend technology for long serum half-life
- Selectively targets double-positive T cells
- Enhances T cell activation more than anti-PD1 or anti-ICOS antibodies
- Is well tolerated in cynomolgus monkeys with antibody-like pharmacokinetics
- Is efficiently manufactured using standard production methods

XmAb23104 is currently under preclinical development with an expected IND filing in 2018.

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