Tumor-specific CD28 costimulatory bispecific antibodies enhance T cell activation in solid tumors


Introduction
- T cells in the tumor microenvironment require TCR/peptide MHC (pMHC; Signal 1) and costimulatory receptor (Signal 2) engagement to achieve optimal activation
- Tumor cells do not typically express CD28 ligands (CD80/86); this lack of costimulation may compromise the activity of CD3 engagers or anti-PD1 therapies in the clinic
- Therefore, we generated bispecific antibodies that conditionally provide CD28 costimulation only in the presence of tumor-associated antigen (TAA) and TCR engagement using Xencor’s XmAb® bispecific platform

CD28 x TAA bispecific antibodies may expand the utility of checkpoint blockade and CD3 T cell engagers

In combination with anti-PD1
In combination with CD3 T cell engagers

- T cell
- Tumor
- Anti-PD1

The XmAb heterodimeric Fc platform allows for well-behaved CD28 bispecific antibodies

- Non-superagonist anti-CD28
- No cytokine release in dry cell assay*

1+1 format (monovalent CD28)

- CEACAM5 x CD28
- Trop-2 x CD28
- MSLN x CD28

- FcR interactions silenced
- XmAb™ (LS) half-life extension
- Highly stable scFv (TdN > 70°C)

CEACAM5 x CD28: Colorectal and other GI tract cancers

- CEACAM5 x CD28 promotes T cell activation by TCR-pMHC recognition
- CEACAM5 x CD28 tolerates high concentrations of soluble CEACAM5

TROP-2 x CD28: Broad applicability across solid tumors

- Trop-2 x CD28 enhances alloreactivity alone and in combination with anti-PD1
- Trop-2 x CD28 enhances T cell activation in combination with a CD3 T cell engager

Summary
- The XmAb bispecific antibody platform uses a modular, non-superagonist anti-CD28 domain to rapidly produce TAA x CD28 bispecific antibodies that conditionally provide T cell costimulation dependent upon TCR engagement and TAA expression
- TAA x CD28 bispecific antibodies can be used as a single agent, or in combination with anti-PD1 or TAA x CD3 T cell engagers
- TAA x CD28 bispecific antibodies show compelling preclinical activity and warrant further exploration for clinical development

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