Selection of a Bispecific Trivalent HER2 x CD137 TRIDENT™ Format Providing Optimal Tumor-anchored Immune Co-stimulation

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Abstract

Introduction: CD73 (4-1BB) signaling provides co-stimulation of CD8 or NK cells following anti-HER2 engagement, respectively. Efforts to leverage CD73 co-stimulation via monoclonal antibodies (mAbs) have been thwarted by limited clinical efficacy on unscorable toxicity. Bispecific targeting strategies linking CD137 activation to a tumor-targeting moiety provides an approach to localize CD137 activation to the tumor microenvironment. Here we evaluate a panel of Fc-bearing HER2 x CD137 bispecific molecules incorporating different valency and geometry to define the format providing optimal CD137 co-stimulation in a tumor-cell anchor-dependent manner.

Methods: An anti-HER2 mAb that does not cross compete with margetuximab, trastuzumab or pertuzumab and a proprietary anti-CD137 mAb were utilized to assemble a set of HER2 x CD137 bispecific molecules in bivalent and trivalent DARt™ or TRIDENT™ configurations. The resulting molecules were compared for binding, signaling and co-stimulation activity in the presence or absence of tumor cells expressed B7-H3. Combination studies were performed in vitro and in immune deficient mice reconstituted with human PBMCs.

Results: TRIDENT molecules bearing B7-H3 and monovalent HER2 binding achieve optimal HER2-dependent tumor-cell anchored CD137 immune cell co-stimulation. CD137 co-stimulation increases proportionally with the level of HER2 expression as observed with HER2 1+ (MCF7 breast), HER2 x CD137 Bi-specific: Desired Molecule Profile

 HER2 x CD137 TRIDENT molecule enhances activity mediated by an anti-HER2 antibody (margetuximab) – strickly dependent on HER2 and TNF-α. HER2 x CD137 TRIDENT molecule enhances the potency of T-cells primed with B7-H3 x CD3 DART molecule to sustain redirected tumor killing.

CD137 x CD137 expression is up-regulated in T cells following TCR engagement with cognate MHC, peptide complex

Expresed on a tumor reacting T cell lineage

Mode of action of CD137 agonistic antibodies blockchain

Monoclonal antibodies can further induce CD137 expression on NK cells upon cognate activation

Mode of action of CD137 agonistic antibodies trilexicon

Agonistic CD137 mAbs can be programmed to induce co-stimulation activity in specific TCR-T cell receptor-molecules

Goal: Develop optimal bispecific conditional CD137 pathway activation of tumor immune infiltrates

HER2 x CD137 Bi-specific: Desired Molecule Profile

Properties of anti-CD137 Arm

The HER2 (Y) mAb (M4-22) mAb selected for incorporation into HER2 x CD137 bispecifics binds to a monovalent epitope on HER2 as transduced on various cell lines including PDAC primary cells. The HER2 x CD137 TRIDENT molecule enhances activity mediated by an anti-HER2 antibody (margetuximab) – strictly dependent on HER2 and TNF-α.

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Results

HER2 x CD137 TRIDENT Molecule: Combinatorial Activity with Redirected T-cell Killing

Conclusions

References

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