Trispecific Antibodies for Selective CD16A-directed NK-Cell Engagement in Multiple Myeloma

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Abstract
Development of antibody scaffolds to directly engage cytotoxic effector cells for therapeutic applications is limited by the scarcity of surface antigens which are expressed exclusively on tumor cells and show limited or no expression on non-malignant cells. We have therefore designed a novel antibody format to selectively retarget effector cell cytotoxicity to tumor cells co-expressing two surface antigens. NK-cells play an important role in the innate immune response to multiple myeloma (MM) and are known to contribute to the efficacy of novel therapeutics. We, therefore, utilized a MM-based model system to generate proof-of-concept data demonstrating antibody-mediated NK-cell retargeting to cell lines co-expressing two MM-expressed surface antigens with increased selectivity (‘dual-targeting’).

Key results
1. A novel trispecific CD16A-directed antibody format was developed to selectively retarget NK-cell cytotoxicity to two tumor expressed surface antigens
2. In vitro proof-of-concept data suggest increased selectivity of NK-cell-mediated target cell lysis using dual-targeting trispecifics
3. Trispecific antibodies may allow novel targeting approaches in multiple myeloma

Dual-targeting: Concept and MoA
1) Bivalent NK-cell engagement via CD16A (FcγRIIIa)
2) Monovalent, low affinity binding to antigen single-positive cells
3) Increased avidity upon bivalent target cell interaction

Selective targeting of BCMA+/CD200+ cells in vitro
• Dual-targeting of BCMA and CD200 increased aTriFlex avidity on antigen double-positive cells
• Up to 20-fold increased cytotoxic in vitro potency towards BCMA+/CD200+ cells

Disclosures
• T.G., M.W., C.H., U.R., K.E., I.F. and M.T. are full-time employees of Affimed GmbH.
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