Abstract

Bi-specific Antibodies Targeting Signal Pathway Crosstalk are a New Breast Cancer Immunotherapeutic Strategy

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Characterization of scFv-Fc Knob-into-Hole BsAb

Analysis of the scFv-Fc BsAb BA-0702

Characterization of Chemical Conjugation BsAb

Introduction

To overcome dose limiting toxicities and to increase efficacy of immunotherapy, cancer-specific strategies have been developed for selectively redirecting effector cells/molecules towards tumor cells. Many of these strategies exploit the specificity of tumor associated antigen recognition by monoclonal antibodies. Using either hybridoma fusion, chemical derivatization or molecular biology technology, antibodies with dual specificity can be constructed. These so called bispecific antibodies have been used to redirect the cytolytic activity of a variety of immune effector cells such as cytotoxic T lymphocytes, natural killer cells, neutrophils and monocytes/macrophages to tumor cells. Several clinically available therapeutic monoclonal antibodies (mAbs) can induce immunomediated tumor cell killing through mechanisms that include complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC). In clinical studies, ADCC has been demonstrated to significantly enhance the efficacy of various mAbs, including rituximab (anti-CD20), trastuzumab (anti-human-epidermal-growth-factor receptor 2 (Her2)) and cetuximab (anti-epidermal-growth-factor receptor (EGFR)) 1. In order to enhance cell-mediated cytotoxicity, bispecific antibodies have recently been developed as new agents for immunotherapy 2, 3.

Most of the currently approved therapeutic anti-cancer antibodies are monospecific and therefore only capable of interfering with the biological function of a single molecule. However, breast cancers mostly involve crosstalk of often synergistic signal transduction pathways, and thus, isolated blockade of a single signal transduction pathway is frequently met by escape mechanisms, such as upregulation of redundant pathways, rendering the monospecific immunotherapy less effective.

Using both chemical and molecular biology techniques, Sorrento has developed new approaches to generate IgG-like bi-specific antibodies (BsAbs) targeting either two compensating signal transduction pathways, such as HER family members, or a breast cancer specific antigen and an immuno-regulatory molecule such as PD-L1 or PD1. The chemical biology method, which involves specific hetero-dimerization of two half antibody molecules using bio-orthogonal chemistry, was used to generate an anti-c-Met and anti-PD-1 chemical bi-specific antibody (CBA). Lastly, employing a molecular biology approach, an anti-c-Met and ErbB3 scFv-scFv bi-specific antibody was produced. Progresses on in vitro characterization and cell-based functional assays of these BsAbs are presented.

Conclusions

- Bi-specific antibodies of many different formats have been developed with superior anti cancer activities, and one of the major obstacles in producing BsAbs is the so-called chain association issue 4. We have shown here that scFv fragment based approach and conjugation based method are promising solutions for this issue.
- Anti-c-Met/Erbb3 BsAbs BA-0702 in scFv-Fc format demonstrated superior binding activity towards tumor cell lines MDA-MA-468 and MCF7 to each parental monospecific IgG1s. Also, BA-072 showed activity in suppressing HGF induced c-Met phosphorylation in cancer cell line MDA-MB-231 and showed much higher cell killing activity (HS578T) than each parental IgGs when they are all were complexed with MAFF-conjugated Protein-D, indicating its potential application in ADC. Similarly, Anti-Met/PD-L1 chemical BsAb CBA-0710 retained excellent affinity for their respective cellular target and demonstrated potent in vitro activities in cell-based functional assays.

References