BISPECIFIC DEATH RECEPTOR AGONISTIC ANTIBODIES

The present invention relates to bispecific antibodies comprising a first antigen binding site specific for a death receptor and a second antigen binding site specific for a second antigen, methods for their production, pharmaceutical compositions containing said antibodies, and uses thereof.

Monoclonal antibodies are proving to be powerful therapeutic agents in the treatment of cancer owing to the selective targeting of antigens which are differentially expressed on cancer cells. The therapeutic strategies of most currently developed monoclonal antibodies include the targeting of tumor-associated antigens to modify tumor-cell biology, inhibition of growth factor receptors, inhibition of angiogenesis, apoptosis induction and cytotoxicity via complement fixation or antibody-dependent cellular cytotoxicity. Some antibodies target the growth factor receptors that are crucial for cancer cell survival, such as trastuzumab (Herceptin®) and cetuximab (Erbitux®). Targeting of the TRAIL death receptors on cancer cells with agonistic monoclonal antibodies represents a new generation of monoclonal antibody therapy, as they are able to directly induce apoptosis of targeted cells. The use of an agonistic monoclonal antibody against the death receptors instead of TRAIL may be advantageous: TRAIL targets multiple receptors including both the death receptors and decoy receptors and, therefore, selectivity is a concern. In addition, TRAIL has a much shorter blood half-life compared with monoclonal antibodies, a factor which affects dose and schedule parameters. The very short blood half-life of TRAIL would require large and frequent doses compared with monoclonal antibodies. In addition recombinant TRAIL is very difficult and tedious to produce.

Michaelson J.S. et al. (mAbs, Vol 1, Issue 2, p:128 – 141; March/April 2009) describe engineered IgG like biscpecific antibodies targeting two TNF family member receptors, namely TRAIL-R2 (TNF related Apoptosis Inducing Ligand Receptor-2) and LTβR (Lymphotoxin-beta Receptor).

Herrmann T. et al. (Cancer Res 2008; 68: (4); p: 1221 – 1227) describe bispecific monovalent chemically combined Fab molecules directed to CD95/Fas/Apo-1 cell surface receptor and three target antigens on glioblastoma cells: NG2, EGFR and CD40.

The present disclosure~~invention~~ relates to antibodies combining a death receptor targeting antigen binding site with a second antigen binding site that targets a second antigen. By that the death receptors become cross linked and apoptosis of the target cell is induced. The advantage of these

bispecific death receptor agonistic antibodies over conventional death receptor targeting antibodies is the specificity of induction of apoptosis only at the site where the second antigen is expressed.

TIn a first object, the present invention relates todisclosure provides for a bispecific antibody comprising a first antigen binding site specific for a death receptor antigen and a second antigen binding site specific for a second antigen.

In a preferred embodiment of the bispecific antibody, the death receptor is selected from death receptor 4 polypeptide (DR4), death receptor 5 polypeptide (DR5) or FAS polypeptide, preferably human DR4 polypeptide (Seq. Id. No. 1), human DR5 polypeptide (Seq. Id. No. 2) or human FAS polypeptide (Seq. Id. No. 3).

In a further preferred embodiment of the bispecific antibody, the second antigen is associated with an oncological disease or rheumatoid arthrithis.

In a further preferred embodiment of the bispecific antibody, the second antigen is selected from,carcinoembryonic antigen (CEA) polypeptide, CRIPTO protein, magic roundabout homolog 4 (ROBO4) polypeptide, melanoma-associated chondroitin sulfate proteoglycan (MCSP) polypeptide, tenascin C polypeptide and fibroblast activation protein (FAP) polypeptide, preferably human CEA polypeptide (Seq. Id. No. 4), human CRIPTO polypeptide (Seq. Id. No. 5), human ROBO4 polypeptide (Seq. Id. No. 6), human MCSP polypeptide (Seq. Id. No. 7), human tenascin C polypeptide (Seq. Id. No. 8) and human FAP polypeptide (Seq. Id. No. 9).

In a first aspect, there is provided a bispecific antibody comprising a first antigen binding site specific for DR5 and a second antigen binding site specific for FAP.

In a further preferred embodiment of the bispecific antibody, the bispecific antibody is a dimeric molecule comprising a first antibody comprising the first antigen binding site and a second antibody comprising the second antigen binding site.

In a preferred embodiment of the dimeric bispecific antibody of the present invention, the first and second antibody comprise an Fc part of an antibody heavy chain, wherein the Fc part of the first antibody comprises a first dimerization module and the Fc part of the second antibody comprises a second dimerization module allowing a heterodimerization of the two antibodies.

In a further preferred embodiment of the dimeric bispecific antibody, the first dimerization module comprises knobs and the second dimerization module comprises holes according to the knobs into holes strategy (see Carter P.; Ridgway J.B.B.; Presta L.G.: Immunotechnology, Volume 2, Number 1, February 1996 , pp. 73-73(1)).

In a further preferred embodiment of the dimeric bispecific antibody, the first antibody is an Immunoglobulin (Ig) molecule comprising a light chain and a heavy chain and the second antibody is selected from the group consisting of scFv, scFab, Fab or Fv.

In a further preferred embodiment the bispecific antibody comprises a modified Fc part having a reduced binding affinity for the Fcγ receptors compared to a wildtpye Fc part e.g. a LALA modification.

In yet a further preferred embodiment of the dimeric bispecific antibody, the Ig molecule comprises the first antigen binding site specific for the death receptor and the second antibody comprises the second antigen binding site specific for the second antigen.

In a further preferred embodiment of the bispecific antibody, the Ig molecule comprises the second antigen binding site specific for the second antigen and the second antibody comprises the antigen binding site specific for the death receptor.

In a further preferred embodiment of the dimeric bispecific antibody, the second antibody is fused to the N- or C- terminus of the heavy chain of the Ig molecule.

In a further preferred embodiment of the dimeric bispecific antibody, the second antibody is fused to the N- or C-terminus of the light chain of the Ig molecule.

In yet another preferred embodiment of the dimeric bispecific antibody, the Ig molecule is an IgG. In a further preferred embodiment of the dimeric bispecific antibody, the second molecule is fused to the Ig molecule by a peptide linker, preferably a peptide linker having a length of about 10 – 30 amino acids.

In a further preferred embodiment of the dimeric bispecific antibody, the second antibody comprises additional cysteine residues to form disulfide bonds.

The bispecific antibodies according to the invention are at least bivalent and can be trivalent or multivalent e.g. tetravalent or hexavalent.

In a second aspect~~object~~ the present disclosure~~invention~~ relates to a pharmaceutical composition comprising a bispecific antibody of the present disclosure~~invention~~.

There is also provided~~In a third object the present invention relates to~~ a bispecific antibody of the present disclosure~~invention~~ for the treatment of cancer or rheumatoid arthritis.

In a third aspect, there is provided the bispecific antibody as defined above for use in the treatment of cancer.

In a fourth aspect, there is provided the use of the bispecific antibody as defined above in the manufacture of a medicament for the treatment of cancer.

There is also provided~~In further objects the present invention relates to~~ a nucleic acid sequence comprising a sequence encoding a heavy chain of a bispecific antibody of the present ~~invention~~disclosure, a nucleic acid sequence comprising a sequence encoding a light chain of a bispecific antibody of the present ~~invention~~disclosure, an expression vector comprising a nucleic acid sequence of the present ~~invention~~disclosure and to a prokaryotic or eukaryotic host cell comprising a vector of the present ~~invention~~disclosure.