comprising as heavy chain CDRs CDR1H of SEQ ID NO:21, CDR2H of SEQ ID NO:24, and CDR3H selected from the group consisting of SEQ ID NO: 27, 119, 121, 123, 125, 127, and 129.

Preferably an antibody according to the invention comprises within the first light chain of a first antibody specifically binding to BCMA a variable light chain domain VL of SEQ ID NO:18 and within the first heavy chain of a first antibody specifically binding to BCMA a variable heavy chain domain VH selected from the group consisting of SEQ ID NO: 15, 120, 122, 124, 126, 128, and 130.

The invention relates further to a bispecific antibody specifically binding to the extracellular domain of BCMA and to CD3ε, characterized in comprising as heavy and light chains the polypeptides of SEQ ID NO: 45, 50, 51, and 52 wherein one or more CDRs are replaced by the respective CDRs of the "BCMA antibody variants". The invention relates further to a bispecific antibody specifically binding to the extracellular domain of BCMA and to CD3ε, characterized in comprising as heavy and light chains the polypeptides of SEQ ID NO: 45, 50, 51, and 52 wherein one or more VHs and/or VLs are replaced by the respective VHs and/or VLs of the "BCMA antibody variants". The invention relates further to a bispecific antibody specifically binding to the extracellular domain of BCMA and to CD3ε, characterized in comprising as heavy and light chains the polypeptides of SEQ ID NO: 43, 44, 45, and 46 wherein one or more CDRs are replaced by the respective CDRs of the "BCMA antibody variants". The invention relates further to a bispecific antibody specifically binding to the extracellular domain of BCMA and to CD3ε, characterized in comprising as heavy and light chains the polypeptides of SEQ ID NO: 43, 44, 45, and 46 wherein one or more VHs and/or VLs are replaced by the respective VHs and/or VLs of the "BCMA antibody variants". Preferably an antibody according to the invention shows high affinity to BCMA and low aggregation.

The invention further relates to a nucleic acid set encoding a respective heavy and light chain set.

Preferably the bispecific antibody according to the invention comprising constant heavy regions CH2/CH3 of IgG1 subclass is characterized in comprising the mutations L234A, L235A and P329G (numbering according to EU index of Kabat) to avoid FcR and C1q binding and minimizing ADCC/CDC. The advantage is that such an antibody of the invention mediates its tumor cell killing efficacy purely by the powerful mechanism of T-cell redirection/activation. Additional mechanisms of action like effects on complement system and on effector cells expressing FcR are avoided and the risk of side-effects is decreased.

The invention comprises preferably a heavy chain of an antibody according to the invention consisting of (from N-to-C-terminus) VH(BCMA)-CH1(BCMA)-VL(CD3)-CH1(CD3)-CH2-CH3 of SEQ ID NO: 43, 47, or 50, as well as the respective encoding nucleic acids. These polypeptides and respective nucleic acids are useful for the production of a bispecific antibody according to the invention.

Claims

1. A bispecific bi- or trivalent antibody specifically binding to the extracellular domain of human B cell maturation antigen (BCMA) and to human CD3ε (CD3) wherein variable domains VL and VH in a light chain and a respective heavy chain of said antibody are replaced by each other, wherein the antibody comprises a constant domain CL wherein the amino acid at position 124 of the CL (numbering according to Kabat) is substituted independently by lysine (K), arginine (R) or histidine (H), and in a respective constant domain CH1 the amino acid at position 147 of the CH1 and the amino acid at position 213 of the CH1 (numbering according to EU index of Kabat) is substituted independently by glutamic acid (E), or aspartic acid (D).

2. A bispecific antibody specifically binding to the extracellular domain of human BCMA and to human CD3, wherein the antibody comprises
    a) a first light chain and a first heavy chain of a first antibody which specifically binds to BCMA; and
    b) a second light chain and a second heavy chain of a second antibody which specifically binds to CD3, and wherein variable domains VL and VH in the second light chain and second heavy chain of the second antibody are replaced by each other; and wherein
    c) the amino acid at position 124 of a constant domain CL of the first light chain (numbering according to Kabat) is substituted independently by lysine (K), arginine (R) or histidine (H), and wherein the amino acid at position 147 and the amino acid at position 213 of a constant domain CH1 of the first heavy chain (numbering according to EU index of Kabat) are each substituted independently by glutamic acid (E), or aspartic acid (D).

3. A bispecific antibody specifically binding to the extracellular domain of human BCMA and to human CD3, wherein the antibody comprises
    a) a first light chain and a first heavy chain of a first antibody which specifically binds to BCMA; and
    b) a second light chain and a second heavy chain of a second antibody which specifically binds to CD3, and wherein variable domains VL and VH in the second light chain and second heavy chain of the second antibody are replaced by each other; and wherein
    c) the amino acid at position 124 of a constant domain CL of the second light chain (numbering according to Kabat) is substituted independently by lysine (K), arginine (R) or histidine (H), and wherein the amino acid at positions 147 and the amino acid at position 213 of a constant domain CH1 of the second heavy chain (numbering according to EU index of Kabat) are each substituted independently by glutamic acid (E), or aspartic acid (D).

4. A bispecific antibody according to claim 2, wherein said bispecific antibody additionally comprises a Fab fragment of said first antibody (BCMA-Fab), wherein the amino acid at position 124 of a constant domain CL of said Fab fragment (numbering according to Kabat) is substituted independently by lysine (K), arginine (R) or

histidine (H), and the amino acid at position 147 and the amino acid at position 213 of a constant domain CH of said Fab fragment (numbering according to EU index of Kabat) are each substituted independently by glutamic acid (E), or aspartic acid (D).

5. A bispecific antibody according to claim 3, wherein said bispecific antibody additionally comprises a second BCMA- Fab.

6. A bispecific antibody according to claim 2, wherein the amino acid at position 123 in the constant domain CL (numbering according to Kabat) is substituted independently by lysine (K), arginine (R) or histidine (H).

7. A bispecific antibody according to claim 6, wherein said amino acid at position 124 in the CL is K, said amino acid at position 147 in the CH1 is E, said amino acid at position 213 in the CH1 is E, and said amino acid at position 123 in the CL is R.

8. A bispecific antibody specifically binding to the extracellular domain of human BCMA and to human CD3, characterized in comprising a heavy and light chain set selected from the group consisting of polypeptides having the amino acid sequence of:
   i) SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45, and SEQ ID NO:46 (set 1),
   ii) SEQ ID NO:45, SEQ ID NO:47, SEQ ID NO:48, and SEQ ID NO:49 (set 2), and
   iii) SEQ ID NO:45, SEQ ID NO:50, SEQ ID NO:51, and SEQ ID NO:52 (set 3).

9. A bispecific antibody according to claim 2, wherein in the antibody portion specifically binding to human CD3 the variable domain VH comprises the heavy chain CDRs having the amino acid sequences of SEQ ID NO: 1, 2 and 3 as respectively heavy chain CDR1, CDR2 and CDR3 and the variable domain VL comprises the light chain CDRs having the amino acid sequences of SEQ ID NO: 4, 5 and 6 as respectively light chain CDR1, CDR2 and CDR3.

10. An antibody according to claim 2 wherein the CH3 domain of one heavy chain and the CH3 domain of the other heavy chain each meet at an interface which comprises an original interface between the antibody CH3 domains; wherein said interface is altered to promote the formation of the bispecific antibody, wherein the alteration is characterized in that:
    a) the CH3 domain of one heavy chain is altered, so that within the original interface the CH3 domain of one heavy chain that meets the original interface of the CH3 domain of the other heavy chain within the bispecific antibody, an amino acid residue is replaced with an amino acid residue having a larger side chain volume, thereby generating a protuberance within the interface of the CH3 domain of one heavy chain which is positionable in a cavity within the interface of the CH3 domain of the other heavy chain and
    b) the CH3 domain of the other heavy chain is altered, so that within the original interface of the second CH3 domain that meets the original interface of the first CH3 domain within the bispecific antibody an amino acid residue is replaced with an amino acid residue having a smaller side chain volume, thereby generating a cavity within the interface of the second CH3 domain

within which a protuberance within the interface of the first CH3 domain is positionable.

11. A method for the preparation of a bispecific antibody according to claim 1 comprising the steps of
    a) transforming a host cell with vectors comprising nucleic acid molecules encoding said light chain and heavy chain,
    b) culturing the host cell under conditions that allow synthesis of said antibody molecule; and
    c) recovering said antibody molecule from said culture.

12. A host cell comprising vectors comprising nucleic acid molecules encoding light and heavy chains of an antibody according to claim 1.

13. A pharmaceutical composition comprising an antibody according to claim 1 and a pharmaceutically acceptable excipient.

14. The pharmaceutical composition according to claim 13, for use in the treatment of a plasma cell disorder in a subject.

15. The pharmaceutical composition for use according to claim 14, wherein the plasma cell disorder is multiple myeloma.

16. A bispecific antibody according to claim 2 wherein an antibody portion specifically binding to BCMA comprises a variable domain VH comprising the heavy chain CDRs of SEQ ID NO: 21, 24 and 27 as respectively heavy chain CDR1, CDR2 and CDR3 and a variable domain VL comprising the light chain CDRs of SEQ ID NO: 30, 33 and 36 as respectively light chain CDR1, CDR2 and CDR3.