SUMMARY OF THE INVENTION

[0010] The present invention meets the needs presented above by providing a bispecific construct that specifically binds to an immune effector cell, i.e. a cytotoxic effector T (Tc) cell and, simultaneously, to a IL-23 receptor expressing target cell, e.g. a pathogenic IL-17-producing helper T cell (Th17 cell), in order to kill the IL-23 receptor expressing target cell.

[0010a] In one aspect, there is provided a bispecific construct comprising at least one first binding moiety and at least one second binding moiety for use in the treatment of cancer comprising IL23R-expressing tumor cells, wherein said first binding moiety specifically binds to a first antigen present on a cytotoxic effector T (Tc) cell, wherein said first antigen is selected from CD3, and said second binding moiety specifically binds to the p19-specific subunit of the IL-23 receptor (IL23R).

[0010b] In one aspect, there is provided a bispecific construct comprising at least one first binding moiety and at least one second binding moiety, wherein said first binding moiety specifically binds to a first antigen present on a cytotoxic effector T (Tc) cell, wherein said first antigen is selected from CD3, and said second binding moiety specifically binds to the IL-23 receptor (IL23R) specific p19 subunit present on the surface of a target cell, particularly wherein the target cell is a pathogenic cell, particularly a cell selected from the group consisting of an IL-17 producing T cell (Th17 cell), a γδ T cell, a natural killer T (NKT) cell, an invariant natural killer (iNK) cell and an IL23R expressing tumor cell, more particularly a Th17 cell or a γδ T cell or an IL23R expressing tumor cell.

[0011] In ~~a first~~one aspect, the present invention provides a bispecific construct comprising at least one first binding moiety and at least one second binding moiety for use in the treatment of cancer comprising IL23R-expressing tumor cells, wherein said first binding moiety specifically binds to a first antigen present on a cytotoxic

[0012] effector T (Tc) cell, and said second binding moiety specifically binds to the IL-23 receptor specific subunit (IL23R).

[0013] In ~~a second~~another aspect, the present invention provides a bispecific construct comprising at least one first binding moiety and at least one second binding moiety, wherein said first binding moiety specifically binds to a first antigen present on a cytotoxic effector T (Tc) cell, and said second binding moiety specifically binds to the IL-23 receptor specific subunit (IL23R) present on the surface of a target cell.

[0014] The present invention also provides, in further aspects, a nucleic acid or nucleic acids encoding the bispecific construct of the present invention, as well as a vector or vectors comprising said nucleic acid or nucleic acids, and a host cell or host cells comprising said vector or vectors.

[0015] Another aspect the present invention relates to a method for producing the bispecific construct of the present invention, comprising (i) providing a nucleic acid or nucleic acids according to the present invention, or a vector or vectors according to

CLAIMS

1. A bispecific construct comprising at least one first binding moiety and at least one second binding moiety for use in the treatment of cancer comprising IL23R-expressing tumor cells, wherein said first binding moiety specifically binds to a first antigen present on a cytotoxic effector T (Tc) cell, and said second binding moiety specifically binds to the IL-23 receptor specific subunit (IL23R).

2. A bispecific construct comprising at least one first binding moiety and at least one second binding moiety, wherein said first binding moiety specifically binds to a first antigen present on a cytotoxic effector T (Tc) cell, and said second binding moiety specifically binds to the IL-23 receptor specific subunit (IL23R) present on the surface of a target cell, particularly wherein the target cell is a pathogenic cell, particularly a cell selected from the group consisting of an IL-17 producing T cell (Th17 cell), a γδ T cell, a natural killer T (NKT) cell, an invariant natural killer (iNK) cell and an IL23R expressing tumor cell, more particularly a Th17 cell or a γδ T cell or an IL23R expressing tumor cell

3. The bispecific construct of claim 1 or 2, wherein said first binding moiety specifically binds to an antigen selected from CD3 and CD28.

4. The bispecific construct of any one or claims 1 to 3, wherein said first binding moiety specifically binds to CD3, particularly to the epsilon chain of CD3 (CD3ε), more particularly to an agonistic epitope of CD3ε.

5. The bispecific construct of any one of claims 1 to 4, wherein the construct allows for efficient killing of said target cell by the Tc cell and/or wherein said Tc cell is a stimulated or an unstimulated Tc cell.

6. The bispecific construct of any one of claims 1 to 5, wherein said first and second binding moieties are arranged relative to each other in such a manner that the part of the first binding moiety recognizing the first antigen and the part of the second binding moiety recognizing IL23R project, relative to the center of the bispecific construct, outward in essentially opposite directions.

7. The bispecific construct of any one of claims 1 to 6, wherein said first binding moiety and/or said second binding moiety is an antibody-based binding moiety, particularly an antibody-based binding moiety comprising a heavy chain variable domain (V_H) or binding fragment thereof, more particularly an antibody-based binding moiety comprising a heavy chain variable domain (V_H) or binding fragment thereof, and a light chain variable domain (V_L) or binding fragment thereof.

8. The bispecific construct of claim 7, which is an antibody format selected from the group consisting of a single-chain diabody (scDb), a tandem scDb (Tandab), a linear dimeric scDb (LD-scDb), a circular dimeric scDb (CD-scDb), a bispecific T-cell engager (BiTE; tandem di-scFv), a tandem tri-scFv, a tri(a)body, bispecific Fab_2, di-miniantibody, tetrabody, scFv-Fc-scFv fusion, di-diabody, DVD-Ig, IgG-scFab, scFab-dsscFv, Fv2-Fc, IgG-scFv fusions, including bsAb, Bs1Ab, Bs2Ab, Bs3Ab, Ts1Ab, Ts2Ab, and Knob-into-Holes (KiHs) and DuoBodies, particularly a single-chain diabody (scDb), and more particularly a bispecific monomeric scDb.

9. The bispecific construct of claim 8, wherein the bispecific scDb comprises two variable heavy chain domains (V_H) or fragments thereof and two variable light chain domains (V_L) or fragments thereof connected by linkers L1, L2 and L3 in

the order V_HA-L1-V_LB-L2-V_HB-L3-V_LA, V_HA-L1-V_HB-L2-V_LB-L3-V_LA, V_LA-L1-V_LB-L2-V_HB-L3-V_HA, V_LA-L1-V_HB-L2-V_LB-L3-V_HA, V_HB-L1-V_LA-L2-V_HA-L3-V_LB, V_HB-L1-V_HA-L2-V_LA-L3-V_LB, V_LB-L1-V_LA-L2-V_HA-L3-V_HB or V_LB-L1-V_HA-L2-V_LA-L3-V_HB, wherein the V_LA and V_HA domains jointly form the antigen binding site for the first antigen, and V_LB and V_HB jointly form the antigen binding site for IL23R, particularly wherein linker L1 is a peptide of 2-10 amino acids, linker L3 is a peptide of 1-10 amino acids, and the linker L2 is a peptide of 10-40 amino acids.

10. The bispecific construct of any one of claims 1 to 9, wherein the bispecific construct is PRO165 (SEQ ID NO: 7), or a functionally active variant of PRO165.

11. A nucleic acid or nucleic acids encoding the bispecific construct according to any one of claims 1 to 10.

12. A vector or vectors comprising the nucleic acid or nucleic acids according to claim 11.

13. A host cell or host cells comprising the vector or vectors according to claim 12.

14. A method for producing the bispecific construct according to any one of claims 1 to 10, comprising (i) providing a nucleic acid or nucleic acids according to claim 11, or a vector or vectors according to claim 12, expressing said nucleic acid or nucleic acids or said vector or vectors and collecting said bispecific construct from the expression system, or (ii) providing a host cell or host cells according to claim 13, culturing said host cell or said host cells; and collecting said bispecific construct from the cell culture.

15. A pharmaceutical composition comprising the bispecific construct according to any one of claims 1 to 10 and a pharmaceutically acceptable carrier.

16. Use of a bispecific construct according to any one of claims 2 to 10 in the manufacture of a medicament for the treatment of an inflammatory and/or autoimmune disease, particularly in the treatment of a human patient, particularly wherein the inflammatory and/or autoimmune disease is selected from the group consisting of rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, juvenile diabetes, autoimmune uveitis, and multiple sclerosis, Parkinson´s disease, Alzheimer´s disease, and ischemia-reperfusion injury.

17. Use of a bispecific construct according to claim 1 in the manufacture of a medicament for treatment of a human patient, particularly wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, breast cancer, nasopharyngeal cancer, oral cancer, esophageal cancer, pancreatic cancer, B-cell lymphomas, and T-cell lymphomas, including adult T-cell lymphoma leukemia (ATLL), acute myeloid lymphoma (AML), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), pediatric acute lymphoblastic lymphoma (B-ALL), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large-cell lymphoma (ALCL), T-/natural killer-cell lymphomas, and peripheral T-cell lymphoma (PTCL).

18. The bispecific construct according to claim 17, wherein said human patient is a patient, which has a high Th17 response.

CLAIMS

1. A bispecific construct comprising at least one first binding moiety and at least one second binding moiety for use in the treatment of cancer comprising IL23R-expressing tumor cells, wherein said first binding moiety specifically binds to a first antigen present on a cytotoxic effector T (Tc) cell, wherein said first antigen is selected from CD3, and said second binding moiety specifically binds to the p19-specific subunit of the IL-23 receptor (IL23R).

2. A bispecific construct comprising at least one first binding moiety and at least one second binding moiety, wherein said first binding moiety specifically binds to a first antigen present on a cytotoxic effector T (Tc) cell, wherein said first antigen is selected from CD3, and said second binding moiety specifically binds to the IL-23 receptor (IL23R) specific p19 subunit present on the surface of a target cell, particularly wherein the target cell is a pathogenic cell, particularly a cell selected from the group consisting of an IL-17 producing T cell (Th17 cell), a γδ T cell, a natural killer T (NKT) cell, an invariant natural killer (iNK) cell and an IL23R expressing tumor cell, more particularly a Th17 cell or a γδ T cell or an IL23R expressing tumor cell.

3. The bispecific construct of claim 1 or 2, wherein said first binding moiety specifically binds to the epsilon chain of CD3 (CD3ε), more particularly to an agonistic epitope of CD3ε.

4. The bispecific construct of any one of claims 1 to 3, wherein the construct allows for efficient killing of said target cell by the Tc cell and/or wherein said Tc cell is a stimulated or an unstimulated Tc cell.

5. The bispecific construct of any one of claims 1 to 4, wherein said first and second binding moieties are arranged relative to each other in such a manner

that the part of the first binding moiety recognizing the first antigen and the part of the second binding moiety recognizing IL23R project, relative to the center of the bispecific construct, outward in essentially opposite directions.

6. The bispecific construct of any one of claims 1 to 5, wherein said first binding moiety and/or said second binding moiety is an antibody-based binding moiety, particularly an antibody-based binding moiety comprising a heavy chain variable domain (V_H) or binding fragment thereof, more particularly an antibody-based binding moiety comprising a heavy chain variable domain (V_H) or binding fragment thereof, and a light chain variable domain (V_L) or binding fragment thereof.

7. The bispecific construct of claim 6, which is an antibody format selected from the group consisting of a single-chain diabody (scDb), a tandem scDb (Tandab), a linear dimeric scDb (LD-scDb), a circular dimeric scDb (CD-scDb), a bispecific T-cell engager (BiTE; tandem di-scFv), a tandem tri-scFv, a tri(a)body, bispecific Fab_2, di-miniantibody, tetrabody, scFv-Fc-scFv fusion, di-diabody, DVD-Ig, IgG-scFab, scFab-dsscFv, Fv2-Fc, IgG-scFv fusions, including bsAb, Bs1Ab, Bs2Ab, Bs3Ab, Ts1Ab, Ts2Ab, and Knob-into-Holes (KiHs) and DuoBodies, particularly a single-chain diabody (scDb), and more particularly a bispecific monomeric scDb,

particularly, wherein the bispecific scDb comprises two variable heavy chain domains (V_H) or fragments thereof and two variable light chain domains (V_L) or fragments thereof connected by linkers L1, L2 and L3 in the order V_HA-L1-V_LB-L2-V_HB-L3-V_LA, V_HA-L1-V_HB-L2-V_LB-L3-V_LA, V_LA-L1-V_LB-L2-V_HB-L3-V_HA, V_LA-L1-V_HB-L2-V_LB-L3-V_HA, V_HB-L1-V_LA-L2-V_HA-L3-V_LB, V_HB-L1-V_HA-L2-V_LA-L3-V_LB, V_LB-L1-V_LA-L2-V_HA-L3-V_HB or V_LB-L1-V_HA-L2-V_LA-L3-V_HB, wherein the V_LA and V_HA domains jointly form the antigen binding site for the first antigen, and V_LB and V_HB jointly form the antigen binding site for IL23R, particularly wherein linker L1 is a peptide of 2-10 amino acids, linker L3 is a

peptide of 1-10 amino acids, and the linker L2 is a peptide of 10-40 amino acids.

8. The bispecific construct of any one of claims 1 to 7, wherein the bispecific construct is PRO165 (SEQ ID NO: 7), or a functionally active variant of PRO165.

9. A nucleic acid or nucleic acids encoding the bispecific construct according to any one of claims 1 to 8.

10. A vector or vectors comprising the nucleic acid or nucleic acids according to claim 9.

11. A host cell or host cells comprising the vector or vectors according to claim 10.

12. A method for producing the bispecific construct according to any one of claims 1 to 8, comprising (i) providing a nucleic acid or nucleic acids according to claim 9, or a vector or vectors according to claim 10, expressing said nucleic acid or nucleic acids or said vector or vectors and collecting said bispecific construct from the expression system, or (ii) providing a host cell or host cells according to claim 11, culturing said host cell or said host cells; and collecting said bispecific construct from the cell culture.

13. A pharmaceutical composition comprising the bispecific construct according to any one of claims 1 to 8 and a pharmaceutically acceptable carrier.

14. The bispecific construct according to any one of claims 2 to 8 for use in the treatment of an inflammatory and/or autoimmune disease, particularly in the treatment of a human patient, particularly wherein the inflammatory and/or autoimmune disease is selected from the group consisting of rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, ulcerative colitis, Crohn's disease, systemic lupus erythematosus, juvenile diabetes,

autoimmune uveitis, and multiple sclerosis, Parkinson´s disease, Alzheimer´s disease, and ischemia-reperfusion injury.

15. The bispecific construct according to claim 1 for use in the treatment of a human patient, particularly wherein the cancer is selected from the group consisting of colorectal cancer, lung cancer, breast cancer, nasopharyngeal cancer, oral cancer, esophageal cancer, pancreatic cancer, B-cell lymphomas, and T-cell lymphomas, including adult T-cell lymphoma leukemia (ATLL), acute myeloid lymphoma (AML), diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), pediatric acute lymphoblastic lymphoma (B-ALL), angioimmunoblastic T-cell lymphoma (AITL), anaplastic large-cell lymphoma (ALCL), T-/natural killer-cell lymphomas, and peripheral T-cell lymphoma (PTCL), particularly wherein said human patient is a patient, which has a high Th17 response.