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, wherein said first binding moiety specifically binds to a first antigen present on a cytotoxic effector T (Tc) cell, wherein said first antigen is CD3, and said second binding moiety specifically binds to the p19-specific subunit of the IL-23 receptor (IL23R) present on the surface of a target cell, and wherein said first binding moiety and/or said second binding moiety is an antibody-based binding moiety.

[0011] In 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

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

[0012] In 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.

[0013] 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.

[0014] 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

fucosyltransferase (FUT8) in the antibody-producing cell (the Potelligent technology from Kyowa Hakko Kirin). Specific examples of enhancing mutations in the Fc part include those described in Shields et al., J. Biol. Chem. 276:6591-6604 (2001).

[0052] In accordance with the present invention, the bispecific construct is particularly designed in such a way that the killing of IL23R-expressing target cells by Tc cells is highly efficient. Such efficient killing generally involves the ability of the bispecific construct to effectively redirect Tc cells to lyse IL23R-expressing target cells. The term "efficient", as used herein, means that the bispecific construct of the present invention typically shows an *in vitro* EC_{50} ranging from 10 to 500 ng/ml, and is able to induce redirected lysis of about 50% of the target cells through Tc cells at a ratio of Tc cells to target cells of from 1:1 to 50:1, particularly from 1:1 to 15:1, more particularly from 2:1 to 10:1. As used herein above and below, the terms "about" and "approximately" refer to ±10% of the indicated value or range.

[0053] Furthermore, the bispecific construct of the present invention is particularly capable of cross-linking a stimulated or an (otherwise) unstimulated Tc cell and the target cell in such a way that the target cell is lysed. This offers the advantage that no generation of target-specific T cell clones or common antigen presentation by dendritic cells is required for the bispecific construct to exert its desired activity. In fact, the bispecific construct of the present invention is particularly capable of redirecting Tc cells to lyse the target cells in the absence of other activating signals. More particularly, if the first binding moiety of the bispecific construct specifically binds to CD3, particularly to CD3ε, signaling through CD28 and/or IL-2 is not required for redirecting Tc cells to lyse the target cells. The high potential to activate non-target specific and/or unstimulated Tc cells is considered to be an important feature of the bispecific construct of the present invention and is believed to contribute to the efficient killing of target cells.

Sequences for PRO165: VLA-L1-VHB-L2-VLB-L3-VHA

SEQ ID	Type	Sequence
1	Linker L1	GGGGS
2	Linker L2	GGGGS GGGGS GGGGS GGGGS
	Linker L3	GGGGS
3	VL anti-IL23R 14-11-D07-sc01	DIQMTQSPSSLSASVGDRVTITCQASENIYSFLA WYQQKPGKAPKLLIYSASKLAAGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQTNRYSNPDIYN VFGQGTKLTVLG
4	VH anti-IL23R 14-11-D07-sc01	EVQLVESGGGLVQPGGSLRLSCAASGIDFNSNY YMCWVRQAPGKGLEWIGCIYVGSHVNTYYANW AKGRFTISRDNSKNTVYLQMNSLRAEDTAVYYC ATSGSSVLYFKFWGQGTLVTVSS
5	VL anti-CD3 clone 6	DIQMTQSPSSLSASVGDRVTITCQSSESVYNNKR LSWYQQKPGKAPKLLIYTASSLASGVPSRFSGS GSGTDFTLTISSLQPEDFATYYCQGEFTCSNADC FTFGQGTKLTVLG
6	VH anti-CD3 clone 6	EVQLVESGGGLVQPGGSLRLSCAASGFPLSSYA MIWVRQAPGKGLEWIGMILRAGNIYYASWVKGR FTISRDNSKNTVYLQMNSLRAEDTAVYYCARRH YNREGYPIGIGDLWGQGTLVTVSS
7	PRO165	DIQMTQSPSSLSASVGDRVTITCQASENIYSFLA WYQQKPGKAPKLLIYSASKLAAGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQQTNRYSNPDIYN VFGQGTKLTVLGGGGGSEVQLVESGGGLVQPG GSLRLSCAASGFPLSSYAMIWVRQAPGKGLEWI GMILRAGNIYYASWVKGRFTISRDNSKNTVYLQM NSLRAEDTAVYYCARRHYNREGYPIGIGDLWGQ GTLVTVSSGGGGSGGGGSGGGGSGGGGSDIQ MTQSPSSLSASVGDRVTITCQSSESVYNNKRLS WYQQKPGKAPKLLIYTASSLASGVPSRFSGSGS GTDFTLTISSLQPEDFATYYCQGEFTCSNADCFT FGQGTKLTVLGGGGGSEVQLVESGGGLVQPGG SLRLSCAASGIDFNSNYYMCWVRQAPGKGLEWI GCIYVGSHVNTYYANWAKGRFTISRDNSKNTVYL QMNSLRAEDTAVYYCATSGSSVLYFKFWGQGTL VTVSS

CLAIMS

1. 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 CD3, and said second binding moiety specifically binds to the p19-specific subunit of the IL-23 receptor (IL23R) present on the surface of a target cell, and wherein said first binding moiety and/or said second binding moiety is an antibody-based binding moiety.

2. The bispecific construct of claim 1, wherein said antibody-based binding moiety comprises a heavy chain variable domain (V_H) or binding fragment thereof.

3. The bispecific construct of claim 2, wherein said antibody-based binding moiety further comprises a light chain variable domain (V_L) or binding fragment thereof.

4. The bispecific construct of any one of claims 1 to 3, wherein the target cell is a pathogenic cell.

5. The bispecific construct of claim 4, wherein said target cell is 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, and an invariant natural killer (iNK) cell.

6. The bispecific construct of claim 5, wherein said target cell isa Th17 cell or a γδ T cell.

7. The bispecific construct of any one of claims 1 to 6, wherein said first binding moiety specifically binds to the epsilon chain of CD3 (CD3□).

8. The bispecific construct of claim 7, wherein said first binding moiety specifically binds to an agonistic epitope of CD3□.

9. The bispecific construct of any one of claims 1 to 8, 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.

10. The bispecific construct of any one of claims 1 to 9, 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.

11. The bispecific construct of any one of claims 1 to 10, 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.

12. The bispecific construct of claim 11, which is a single-chain diabody (scDb).

13. The bispecific construct of claim 12, which is a bispecific monomeric scDb.

14. The bispecific construct of claim 13, 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.

15. The bispecific construct of claim 14, 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.

16. The bispecific construct of any one of claims 1 to 15, wherein the bispecific construct is the construct according to SEQ ID NO: 7, or a functionally active variant of the construct according to SEQ ID NO: 7.

17. A nucleic acid or nucleic acids encoding the bispecific construct according to any one of claims 1 to 16.

18. A vector or vectors comprising the nucleic acid or nucleic acids according to claim 17.

19. A host cell or host cells comprising the vector or vectors according to claim 18.

20. A method for producing the bispecific construct according to any one of claims 1 to 16, comprising (i) providing a nucleic acid or nucleic acids according to claim 17, or a vector or vectors according to claim 18, 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 19, culturing said host cell or said host cells; and collecting said bispecific construct from the cell culture.

21. A pharmaceutical composition comprising the bispecific construct according to any one of claims 1 to 16 and a pharmaceutically acceptable carrier.

22. The bispecific construct according to any one of claims 1 to 16 for use in the treatment of an inflammatory and/or autoimmune disease.

23. The bispecific construct for use in the treatment of an inflammatory and/or autoimmune disease according to claim 22, which is for use in the treatment of a human patient.

24. The bispecific construct for use in the treatment of an inflammatory and/or autoimmune disease according to claim 22 or 23, 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.