1. A polypeptide comprising an antibody single domain, or antigen-binding fragment thereof, that binds TNF-alpha, said domain comprising a light chain variable domain (VL),

wherein said variable domain comprises at least one amino acid sequence selected from the group consisting of SEQ ID NOs:1-18, or a TNF-alpha-binding fragment or derivative thereof.

2. The polypeptide according to claim 1 wherein said variable domain comprises SEQ ID NO:1 (VL18) or SEQ ID NO:2 (VL11) and/or wherein said variable domain antagonizes binding of human TNF-alpha to a TNF-alpha receptor; and/or wherein said variable domain further cross-reacts with at least one other mammalian TNF-alpha, wherein said mammal is not a primate.

3. The polypeptide according to claim 1 or 2 wherein said mammal is a rat or a mouse and/or wherein said variable domain cross-reacts with TNF-alpha of at least two other mammals, said at least two other mammals being a rodent and a non-rodent species.

4. The polypeptide according to any one of the above claims wherein said variable domain

(i) is de-immunized by eliminating at least one T_H epitope of said variable domain;

(ii) comprises a sequence corresponding to SEQ ID NO:1 (VL18), which is de-immunized by at least one amino acid substitution selected from the group consisting of T7Q, V15P, (A51V-L54R/A51V-L54E), K63S, E79K, (C80S), T91A, and L111K, said substitutions referring to amino acid positions in SEQ ID NO:1;

(iii) comprises a sequence corresponding to SEQ ID NO:2 (VL11), which is de-immunized by at least one amino acid substitution selected from the group consisting of T7Q, V15P, R31S, (A51V-L54R /A51V-L54E), K63S, E79K, (C80S), T91A, A100S, and E106K, said substitutions referring to amino acid positions in SEQ ID NO:2; or

(iv) comprises at least one sequence selected from the group consisting of SEQ ID NOs:19-23 (five VL18 variants), SEQ ID NOs: 24-28 (five VL11 variants), and a TNF-alpha-binding fragment or derivative thereof.

5. The polypeptide according to any one of the above claims, further comprising an albumin-binding domain linked thereto,

preferably wherein said albumin-binding domain is linked to said polypeptide as a fusion;

preferably wherein said fusion is via a linker; and

preferably wherein said linker is a peptide linker comprising an amino acid sequence corresponding to SEQ ID NO:29 (3L).

6. The polypeptide according to claim 5 wherein said albumin-binding domain enhances the half-life of said polypeptide by five fold, and/or

wherein said albumin-binding domain corresponds to an albumin-binding domain isolated from *S. zooepidemicus* Z5,

preferably comprising a sequence corresponding to SEQ ID NO:30 (PEP), or an albumin-binding fragment or derivative thereof,

preferably wherein said albumin-binding domain is de-immunized by at least one amino acid substitution selected from the group consisting of E12D, T29H-K35D, and A45D, said substitutions referring to amino acid positions in SEQ ID NO:30,

preferably wherein said albumin-binding domain comprises an amino acid sequence corresponding to SEQ ID NO:31; and/or

wherein said polypeptide is de-immunized by eliminating at least one T_H epitope in said variable domain and/or in said albumin-binding domain.

7. The polypeptide according to any one of the above claims, further comprising a second antibody single domain, or antigen-binding fragment thereof, that binds TNF-alpha, wherein said second domain comprises a second light chain variable domain and wherein said single domains together form a dimer,

preferably wherein wherein said dimer comprises sequences corresponding to SEQ ID NO:1 (VL18) and SEQ ID NO:2 (VL11), or a TNF-alpha-binding fragment or derivative thereof for one or both sequences,

preferably wherein said dimer comprises a sequence corresponding to SEQ ID NO:32 (VL18-3L-VL11), or a TNF-alpha-binding fragment or derivative thereof.

8. The polypeptide according to any one of claims 4-7 wherein said dimer is de-immunized by eliminating at least one T_H epitope of in at least one of said variable domains,

preferably wherein said polypeptide comprises at least one sequence selected from the group consisting of SEQ ID NOs: 35-39 (VL18-3L-VL11 variants), or a TNF-alpha-binding fragment or derivative thereof.

9. The polypeptide according to claim 7 or 8 wherein said dimer further comprises an albumin-binding domain linked to at least one of said variable domains,

preferably wherein said said albumin-binding domain comprises a sequence corresponding to SEQ ID NO:30 (PEP), or an albumin-binding fragment or derivative thereof,

preferably wherein said polypeptide comprises a sequence corresponding to SEQ ID NO: 33 (VL18-3L-VL11-PEP) or a TNF-alpha-binding fragment or derivative thereof.

10. The polypeptide according to any one of claims 5-9 wherein said polypeptide is de-immunized by eliminating at least one T_H epitope in at least one of said variable domains and/or in said albumin-binding domain,

preferably wherein said polypeptide comprises at least one sequence selected from the group consisting of SEQ ID NOs: 34 and 40-44 (VL18-3L-VL11-PEP variants), or a TNF-alpha-binding fragment or derivative thereof.

11. Use of an effective amount of the polypeptide according to any one of the above claims for the preparation of a medicament for treating and/or delaying a TNF-alpha-related condition in a subject suffering therefrom and/or pre-disposed thereto,

preferably wherein said TNF-alpha-related condition is an inflammatory disorder, and

preferably wherein said inflammatory disorder is rheumatoid arthritis.

12. The use of claim 11 wherein said medicament is administered no more than twice a month,

preferably wherein said medicament is administered no more than once a month.

13. A pharmaceutical composition comprising an effective amount of the polypeptide according to any one of claims 1-12 and a pharmaceutically acceptable carrier.

14. A nucleic acid comprising a nucleotide sequence encoding the polypeptide according to any one of claims 1-12; or

~~a vector comprising the nucleic acid; or~~

a host cell comprising the vector.

15. A method of making the polypeptide according to any one of claims 1-12 comprising:

(i) providing a host cell comprising a vector encoding said polypeptide;

(ii) culturing said cell under conditions allowing expression of said polypeptide; and

(iii) recovering said polypeptide from said culture.

Claims

1. A polypeptide comprising

a first antibody single domain, or antigen-binding fragment thereof, that binds TNF-alpha, said first domain comprising a first light chain variable domain (VL),

wherein said first light chain variable domain comprises the amino acid sequence of SEQ ID NO:1 (VL18), or a TNF-alpha-binding fragment or derivative thereof; and

a second antibody single domain, or antigen-binding fragment thereof, that binds TNF-alpha, said second domain comprises a second light chain variable domain; and

wherein said first and said second single domains together form a dimer.

2. The polypeptide according to claim 1, wherein said second variable domain comprises at least one amino acid sequence selected from the group consisting of SEQ ID NOs:1-18, or a TNF-alpha-binding fragment or derivative thereof;

preferably wherein said second variable domain comprises a sequence corresponding to SEQ ID NO:2 (VL11), or a TNF-alpha-binding fragment or derivative thereof,

preferably wherein said dimer comprises a sequence corresponding to SEQ ID NO:32 (VL18-3L-VL11), or a TNF-alpha-binding fragment or derivative thereof.

3. The polypeptide according to claim 1

wherein said first and/or second variable domain antagonizes binding of human TNF-alpha to a TNF-alpha receptor; and/or

wherein said first and/or second variable domain further cross-reacts with at least one other mammalian TNF-alpha, wherein said mammal is not a primate.

4. The polypeptide according to claim 3 wherein said mammal is a rat or a mouse and/or

wherein said first and/or second variable domain cross-reacts with TNF-alpha of at least two other mammals, said at least two other mammals being a rodent and a non-rodent species.

5. The polypeptide according to any one of the above claims wherein said first and/or second variable domain

(i) is de-immunized by eliminating at least one T_H epitope of said first and/or second variable domain;

(ii) comprises a sequence corresponding to SEQ ID NO:1 (VL18), which is de-immunized by at least one amino acid substitution selected from the group consisting of T7Q, V15P, (A51V-L54R/A51V-L54E), K63S, E79K, (C80S), T91A, and L111K, said substitutions referring to amino acid positions in SEQ ID NO:1;

(iii) comprises a sequence corresponding to SEQ ID NO:2 (VL11), which is de-immunized by at least one amino acid substitution selected from the group consisting of T7Q, V15P, R31S, (A51V-L54R /A51V-L54E), K63S, E79K, (C80S), T91A, A100S, and E106K, said substitutions referring to amino acid positions in SEQ ID NO:2; and/or

(iv) comprises at least one sequence selected from the group consisting of SEQ ID NOs:19-23 (five VL18 variants), SEQ ID NOs: 24-28 (five VL11 variants), and a TNF-alpha-binding fragment or derivative thereof.

6. The polypeptide according to claim 5, wherein said dimer comprises at least one sequence selected from the group consisting of SEQ ID NOs: 35-39 (VL18-3L-VL11 variants), or a TNF-alpha-binding fragment or derivative thereof.

7. The polypeptide according to any one of the above claims, further comprising an albumin-binding domain linked to at least one of said first or second variable domains,

preferably wherein said albumin-binding domain is linked to said polypeptide as a fusion;

preferably wherein said fusion is via a linker; and

preferably wherein said linker is a peptide linker comprising an amino acid sequence corresponding to SEQ ID NO:29 (3L).

8. The polypeptide according to claim 7 wherein said albumin-binding domain enhances the half-life of said polypeptide by fivefold, and/or

wherein said albumin-binding domain corresponds to an albumin-binding domain isolated from *S. zooepidemicus* Z5,

preferably comprising a sequence corresponding to SEQ ID NO:30 (PEP), or an albumin-binding fragment or derivative thereof,

preferably wherein said albumin-binding domain is de-immunized by at least one amino acid substitution selected from the group consisting of E12D, T29H-K35D, and A45D, said substitutions referring to amino acid positions in SEQ ID NO:30,

preferably wherein said albumin-binding domain comprises an amino acid sequence corresponding to SEQ ID NO:31.

9. The polypeptide according to claim 8, wherein said polypeptide comprises a sequence corresponding to SEQ ID NO:33 (VL18-3L-VL11-PEP) or a TNF-alpha-binding fragment or derivative thereof.

10. The polypeptide according to any one of claims 7-9 wherein said polypeptide is de-immunized by eliminating at least one T_H epitope in at least one of said variable domains and/or in said albumin-binding domain,

preferably wherein said polypeptide comprises at least one sequence selected from the group consisting of SEQ ID NOs:34 and 40-44 (VL18-3L-VL11-PEP variants), or a TNF-alpha-binding fragment or derivative thereof.

11. Use of an effective amount of the polypeptide according to any one of the above claims for the preparation of a medicament for treating and/or delaying a TNF-alpha-related condition in a subject suffering therefrom and/or pre-disposed thereto,

preferably wherein said TNF-alpha-related condition is an inflammatory disorder, and

preferably wherein said inflammatory disorder is rheumatoid arthritis.

12. The use of claim 11 wherein said medicament is administered no more than twice a month,

preferably wherein said medicament is administered no more than once a month.

13. A pharmaceutical composition comprising an effective amount of the polypeptide according to any one of claims 1-10 and a pharmaceutically acceptable carrier.

14. A nucleic acid comprising a nucleotide sequence encoding the polypeptide according to any one of claims 1-10; or

a vector comprising the nucleic acid; or

a host cell comprising the vector.

15. A method of making the polypeptide according to any one of claims 1-10 comprising:

(i) providing a host cell comprising a vector encoding said polypeptide;

(ii) culturing said cell under conditions allowing expression of said polypeptide; and

(iii) recovering said polypeptide from said culture.

16. The polypeptide according to claim 9, wherein said polypeptide comprises a sequence corresponding to SEQ ID NO:33 (VL18-3L-VL11-PEP).

17. A pharmaceutical composition comprising an effective amount of the polypeptide according to claims 16 and a pharmaceutically acceptable carrier.