

2017/102830 (UCB Biopharma) discloses a multispecific antibody, which is capable of inhibiting TNF α , IL-17A and IL-17F, in particular, comprising a binding domain specific to human TNF α and a binding domain specific to human IL-17A and human IL-17F. Xu et al., Oncotarget, 8 (2017) 81860-81872, generated an IgG-like bispecific antibody (bsAb), wherein the two arms of the IgG-like molecules are directed against TNF α and IL-17A, respectively. Interestingly, WO 2015/014979 (Roche, see also Fischer et al., Arthritis & Rheumatology 67 (2015) 51–62) discloses bispecific tetravalent IL-17AxTNF antibody constructs, which are either bivalent (“2 +2” construct) or monovalent (“2 +2” construct) for each of the two antigens. According to WO 2015/014979, the bivalent construct is to be preferred over the monovalent alternative.

However, there still remains a need for improved anti-inflammatory drugs that can effectively neutralize the activity of both IL-17A and TNF α for the treatment of disorders such as inflammatory and autoimmune disease, for example rheumatoid arthritis, in which a significant portion of patients still do not respond adequately to therapy. There is still a need for the development of improved therapeutic antibodies effectively neutralizing the activity of both IL-17A and TNF α , having beneficial affinity and efficacy, and improved safety profile, e.g., lower immunogenicity. Furthermore, the therapeutic antibodies should have improved biophysical properties leading to better developability, producibility in high yields and superior antibody stability.

SUMMARY OF THE INVENTION

It is an object of the present ~~invention~~disclosure to provide a medicament to improve treatment of inflammatory and autoimmune disorders.

The antibody of the ~~invention~~present disclosure provides a new treatment option for patients with an unmet medical need. The present invention ~~provides~~describes a novel multispecific antibody, which is capable of simultaneously inhibiting IL-17A and TNF α , and which has further improved properties beneficial for use in therapies, such as higher affinity, improved efficacy, selectivity, safety, e.g., low immunogenicity, and improved biophysical properties, such as developability, and stability.

In one aspect, the present disclosure refers to an isolated multispecific antibody comprising a first domain specifically binding IL-17A, a second domain specifically binding TNF α , and, optionally, a third domain specifically binding to human serum albumin (HSA), wherein (a) said first domain comprises (i) a set of CDRs: HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 1, 2, and 3, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 12, 13, and 14, respectively, or (ii) a set of CDRs: HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 39, 40, and 41, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 50, 51, and 52, respectively,; wherein said first domain selectively binds to human IL-17A over human IL-17B, IL-17C, IL-17D, IL-17E and IL-17F as measured by ELISA; and (b) said second domain comprises a set of CDRs: HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 63, 64, and 65, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 76, 77, and 78, respectively; and (c) said third domain, when present, comprises a set of CDRs: (i) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 90, 91, and 92, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 100, 101, and 102, respectively; or (ii) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 111, 112, and 113, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 121, 122, and 123, respectively. In one example, the present disclosure ~~relates~~ refers to isolated multispecific antibody comprising a first domain specifically binding IL-17A and a second domain specifically binding TNF α , and, optionally, a third domain specifically binding human serum albumin.

In one aspect, the present disclosure ~~relates~~ refers to a pharmaceutical composition comprising the multispecific antibody ~~of the invention~~ as disclosed herein and a pharmaceutically acceptable carrier.

In a further aspect, the present disclosure ~~provides~~ refers to the multispecific antibody ~~of the invention~~ as disclosed herein or the pharmaceutical composition ~~of the invention~~ as disclosed herein for use as a medicament.

In a further ~~aspect~~ example, the present disclosure ~~provides~~ describes the multispecific antibody of the invention or the pharmaceutical composition of the ~~invention~~ disclosure for use in treatment of a disorder mediated by IL-17A and/or TNF α or a disorder that can be treated by inhibiting Gro- α secretion, in particular for use in the treatment of an inflammatory condition or an autoimmune disease.

In one ~~aspect~~ example, the present disclosure ~~provides~~ describes the use of the multispecific antibody of the invention or the pharmaceutical composition of the ~~invention~~ disclosure for the treatment of a disorder mediated by IL-17A and/or TNF α or a disorder that

can be treated by inhibiting Gro- α secretion, in particular for use in the treatment of an inflammatory condition or an autoimmune disease.

5 In one ~~aspect~~example, the present disclosure ~~provides~~describes the use of the multispecific antibody of the ~~invention~~disclosure or the pharmaceutical composition of the ~~invention~~disclosure in the manufacture of a medicament for treatment of a disorder mediated by IL-17A and/or TNF α or a disorder that can be treated by inhibiting Gro- α secretion, in particular for use in the treatment of an inflammatory condition or an autoimmune disease.

10 In yet another ~~aspect~~example, the present disclosure ~~provides~~describes a method of treating a disorder mediated by IL-17A and/or TNF α , said method comprising administering an effective amount of the multispecific antibody of the ~~invention~~disclosure or the pharmaceutical composition of the invention to a subject in need thereof.

In one aspect, the present disclosure ~~provides~~refers to a kit comprising the multispecific antibody of the invention, or the pharmaceutical composition of the invention.

In a further ~~aspect~~example, the present disclosure ~~describes~~ provides a nucleic acid comprising a nucleotide sequence encoding the multispecific antibody of the ~~disclosure~~invention. In a further aspect, the present disclosure ~~describes~~ provides a vector comprising said nucleic acid. In a further aspect, the present disclosure ~~describes~~ provides a host cell comprising said nucleic acid or said vector.

In yet another ~~example~~aspect, the present disclosure ~~provides~~ describes a method of producing the multispecific antibody of the ~~inve~~disclosure ~~ntion~~ or a binding domain thereof or a fragment thereof, the method comprising the step of culturing a host cell comprising a nucleic acid or a vector encoding the multispecific antibody of the ~~disclosure~~ invention or a binding domain thereof or a fragment thereof.

The aspects, advantageous features and preferred ~~embodiments~~ examples of the present disclosure, summarized in the following items, respectively alone or in combination, further contribute to solving the object of the invention:

1. An isolated multispecific antibody comprising a first domain specifically binding IL-17A and a second domain specifically binding TNF α .
2. The multispecific antibody of item 1, wherein said antibody comprises only one domain specifically binding IL-17A and/or only one domain specifically binding TNF α .
3. The multispecific antibody of item 1 or item 2, wherein said antibody is capable of neutralizing the biological activity of human TNF α and human IL-17A.
4. The multispecific antibody of any one of the preceding items, wherein said antibody selectively binds to human IL-17A over human IL-17B, IL-17C, IL-17D, IL-17E and IL-17F as measured by ELISA.
5. The multispecific antibody of any one of the preceding items further comprising a third domain having a specificity against an antigen other than IL-17A or TNF α .
6. The multispecific antibody of item 5, wherein said antibody comprises a third domain specifically binding to human serum albumin (HSA), preferably said antibody comprising only one domain specifically binding human serum albumin.
7. The multispecific antibody of any one of the preceding items, wherein said domains are capable of binding to their respective antigen or receptor simultaneously.
8. The multispecific antibody of any one of the preceding items, wherein said first domain and said second domain, and, optionally said third domain, are independently

CLAIMS

1. An isolated multispecific antibody comprising a first domain specifically binding IL-17A, a second domain specifically binding TNF α , and, optionally, a third domain specifically binding to human serum albumin (HSA), wherein
 - (a) said first domain comprises (i) a set of CDRs: HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 1, 2, and 3, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 12, 13, and 14, respectively, or (ii) a set of CDRs: HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 39, 40, and 41, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 50, 51, and 52, respectively; wherein said first domain selectively binds to human IL-17A over human IL-17B, IL-17C, IL-17D, IL-17E and IL-17F as measured by ELISA; and
 - (b) said second domain comprises a set of CDRs: HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 63, 64, and 65, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 76, 77, and 78, respectively; and
 - (c) said third domain, when present, comprises a set of CDRs: (i) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 90, 91, and 92, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 100, 101, and 102, respectively; or (ii) HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 111, 112, and 113, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 121, 122, and 123, respectively.
2. The multispecific antibody of claim 1, wherein said antibody comprises only one domain specifically binding IL-17A and/or only one domain specifically binding TNF α , and/or, optionally, comprises only one domain specifically binding human serum albumin.
3. The multispecific antibody of claim 1 or claim 2, wherein said first domain specifically binding IL-17A, said second domain specifically binding TNF α , and, when present, said third domain specifically binding to HSA domains are capable of binding to their respective antigens or receptor IL-17A, TNF α and HSA simultaneously.

4. The multispecific antibody of any one of the preceding claims, wherein said antibody has the following properties

(a) has the ability to neutralize IL-17A with a potency relative to that of secukinumab (relative potency), determined by measuring Gro- α secretion in an HT-29 assay, greater than 2, e.g. greater than 5, greater than 10, greater than 15, greater than 20, greater than 25, greater than 30, greater than 35, greater than 40, greater than 45, preferably greater than 50, and wherein said relative potency is the ratio of the IC₅₀ value in ng/mL of secukinumab as measured in the HT-29 assay to the IC₅₀ value in ng/mL of said multispecific antibody as measured in the HT-29 assay; and

(b) has the ability to neutralize TNF α with a potency relative to that of an scDb according to SEQ ID NO: 149 (A13) (relative potency), determined by measuring Gro- α secretion in an HT-29 assay, of at least 1, e.g., greater than 1, greater than 1.5, greater than 2, greater than 2.5, greater than 3, greater than 3.5, preferably greater than 4, more preferably greater than 4.5, and wherein said relative potency is the ratio of the IC₅₀ value in nM of said scDb according to SEQ ID NO: 149 as measured in the HT-29 assay to the IC₅₀ value in nM of said multispecific antibody as measured in the HT-29 assay; and

(c) optionally, has the ability to block interaction between IL-17A and IL-17RA with a potency relative to that of secukinumab (relative potency), determined in ELISA assay, greater than 2, e.g., greater than 3, greater than 4, greater than 5, greater than 6, greater than 7, greater than 8, greater than 9, preferably greater than 10, and wherein said relative potency is the ratio of the IC₅₀ value in ng/mL of secukinumab as measured by ELISA to the IC₅₀ value in ng/mL of said multispecific antibody as measured by ELISA; and

(d) optionally, has the ability to neutralize TNF α with a potency relative to that of an scDb according to SEQ ID NO: 149 (A13) (relative potency), determined in L929 assay, of at least 0.4, e.g., at least 0.5, preferably at least 1, and wherein said relative potency is the ratio of the IC₅₀ value in nM of said scDb according to SEQ ID NO: 125 as measured in the L929 assay to the IC₅₀ value in nM of said multispecific antibody as measured in the L929 assay; and/or

(e) binds to human IL-17A with a dissociation constant (K_D) of less than 5 nM, e.g., less than 4 nM, less than 3 nM, less than 2 nM, than 1 nM, preferably less than 0.5 nM, as measured by surface plasmon resonance; and optionally, binds to cynomolgus IL-17A with a K_D of less than 5 nM, e.g., less than 4 nM, less than 3 nM, less than 2 nM, than 1 nM, preferably less than 0.5 nM as measured by surface plasmon resonance;

(f) binds to human TNF α with a dissociation constant (K_D) of less than 5 nM, e.g., less than 4 nM, less than 3 nM, less than 2 nM, less than 1 nM, preferably less than 0.5 nM, more preferably less than 0.25 nM, as measured by surface plasmon resonance; and (g) optionally, binds to human serum albumin with a dissociation constant (K_D) of less than 5 nM, e.g., less than 4 nM, less than 3 nM, preferably less than 2 nM, as measured by surface plasmon resonance, and optionally, binds to cynomolgus serum albumin with a dissociation constant (K_D) of less than 5 nM, e.g., less than 4 nM, less than 3 nM, preferably less than 2 nM as measured by surface plasmon resonance.

54. The multispecific antibody of any one of the preceding claims, wherein said antibody has the following properties

(a) has a melting temperature (T_m), determined by differential scanning fluorimetry, of at least 55°C, preferably of at least 58°C, more preferably at least 60°C in phosphate-citrate buffer at pH 6.4, 150 mM NaCl;

(b) has a loss in monomer content, after five consecutive freeze-thaw cycles, of less than 5%, e.g., less than 4%, less than 3%, less than 2%, preferably 1% or less, when said multispecific antibody is at a starting concentration of 10 mg/ml in phosphate buffered saline (PBS), pH 7.4;

(c) has a loss in monomer content, after storage for at least two weeks, particularly for at least four weeks, at 4°C, of less than 10%, preferably less than 5%, when said multispecific antibody is at a starting concentration of 10 mg/ml in phosphate buffered saline (PBS), pH 7.4; and/or

(d) has a loss in monomer content, after storage for at least two weeks, particularly for at least four weeks, at 37°C, of less than 20%, preferably less than 15%, when said multispecific antibody is at a starting concentration of 10 mg/ml in phosphate buffered saline (PBS), pH 7.4.

65. The multispecific antibody of any one of the preceding claims, wherein said first domain and/or said second domain, and/or, optionally said third domain, comprise(s) a heavy chain variable region VH and wherein said VH is VH3 or VH4, preferably VH3.

76. The multispecific antibody of any one of the preceding claims, wherein said first domain and/or said second domain, and/or, optionally said third domain, comprise(s) a

light chain variable region VL and wherein said VL comprises V κ frameworks FR1, FR2 and FR3, particularly V κ 1 or V κ 3 FR1 to FR3, preferably V κ 1 FR1 to FR3, and a framework FR4, which is selected from a V κ FR4, particularly V κ 1 FR4, V κ 3 FR4, and V λ FR4, particularly V λ FR4 comprising the amino acid sequence having at least 60, 70, 80, 90 percent identity to an amino acid sequence selected from any of SEQ ID NO: 26 to SEQ ID NO: 32, preferably V λ FR4 as set forth in any of SEQ ID NO: 26 to SEQ ID NO: 32, preferably V λ FR4 as set forth in SEQ ID NO: 26 or 27, more preferably V λ FR4 as set forth in SEQ ID NO: 27.

87. The multispecific antibody of ~~any one of claims 6-5 or 6 to 7~~, wherein said VH of the first domain comprises an amino acid sequence that is at least 90 percent identical to the amino acid sequence SEQ ID NO: 10; and/or said VL of the first domain comprises an amino acid sequence that is at least 90 percent identical to the amino acid sequence SEQ ID NO: 21, preferably wherein said VH of the first domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 10 and 11; and/or said VL of the first domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 21 and 22, more preferably wherein said VH of the first domain is as set forth in SEQ ID NO: 10 and/or said VL of the first domain is as set forth in of SEQ ID NO: 21.

98. The multispecific antibody of any one of claims 6-5 to 87, wherein said VH of the second domain comprises an amino acid sequence that is at least 90 percent identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 72, 73, 74 or 75, preferably SEQ ID NO: 72; and/or said VL of the second domain comprises an amino acid sequence that is at least 90 percent identical to the amino acid sequence selected from the group consisting of SEQ ID NOs: 85, 86, 87, 88 and 89, preferably SEQ ID NO: 85, preferably wherein said VH of the second domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 72, 73, 74 or 75; and/or said VL of the second domain comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 85, 86, 87, 88 and 89, more preferably wherein said VH of the second domain is as set forth in SEQ ID NO: 72 and/or said VL of the second domain is as set forth SEQ ID NO: 85.

~~109.~~ The multispecific antibody of any one of claims ~~6-5~~ to ~~98~~, wherein the third domain is present and

(i) said VH of the third domain comprises an amino acid sequence that is at least 90 percent identical to the amino acid sequence SEQ ID NO: 99; and/or said VL of the third domain comprises an amino acid sequence that is at least 90 percent identical to the amino acid sequence SEQ ID NO: 108, preferably wherein said VH of the third domain is as set forth in sequence of SEQ ID NO: 99 and/or a VL of the third domain is as set forth in SEQ ID NO: 108; or

(ii) said VH of the third domain comprises an amino acid sequence that is at least 90 percent identical to the amino acid sequence SEQ ID NO: 120; and/or said VL comprises an amino acid sequence that is at least 90 percent identical to the amino acid sequence SEQ ID NO: 130, preferably wherein said VH of the third domain is as set forth in SEQ ID NO: 120 and/or said VL of the third domain is as set forth in SEQ ID NO: 130.

~~110.~~ The multispecific antibody of any one of the preceding claims, wherein said multispecific antibody is in a 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 tribody (Fab-(scFv)₂) or bibody (Fab-(scFv)₁), Fab, γ -Fab-Fv₂, Morrison (IgG CH3-scFv fusion (Morrison L) or IgG CL-scFv fusion (Morrison H)), triabody, scDb-scFv, bispecific Fab₂, di-miniantibody, tetrabody, scFv-Fc-scFv fusion, scFv-HSA-scFv fusion, di-diabody, DVD-Ig, COVD, IgG-scFab, scFab-dsscFv, Fv₂-Fc, IgG-scFv fusions, such as bsAb (scFv linked to C-terminus of light chain), Bs1Ab (scFv linked to N-terminus of light chain), Bs2Ab (scFv linked to N-terminus of heavy chain), Bs3Ab (scFv linked to C-terminus of heavy chain), Ts1Ab (scFv linked to N-terminus of both heavy chain and light chain), Ts2Ab (dsscFv linked to C-terminus of heavy chain), Bispecific antibodies based on heterodimeric Fc domains, such as Knob-into-Hole antibodies (KiHs); an Fv, scFv, scDb, tandem-di-scFv, tandem tri-scFv, Fab-(scFv)₂, Fab-(scFv)₁, Fab, Fab-Fv₂, COVD fused to the N- and/or the C-terminus of either chain of a heterodimeric Fc domain or any other heterodimerization domain, a MATCH and DuoBodies, preferably is tribody or scDb-scFv.

~~111.~~ The multispecific antibody of any of the preceding claims, wherein the antibody comprises an amino acid sequence having at least 80% identity, preferably at

least 90% identity, to the sequence selected from any of SEQ ID NOs: 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, and 148, preferably to the sequence of SEQ ID NO: 143, and wherein the antibody comprises

(i) a first domain specifically binding IL-17A comprising HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 1, 2, and 3, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 12, 13, and 14, respectively, and

(ii) a second domain specifically binding TNF α comprising HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 63, 64, and 65, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 76, 77, and 78, respectively, and

(iii) a third domain specifically binding HSA comprising HCDR1, HCDR2, and HCDR3 sequences of SEQ ID NOs: 90, 91, and 92, respectively, and LCDR1, LCDR2, and LCDR3 sequences of SEQ ID NOs: 100, 101, and 102, respectively.

12. The multispecific antibody of claim 11, preferably wherein the antibody comprises an amino acid sequence selected from any of SEQ ID NOs: 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, and 148.

13. The multispecific antibody of claim 12, wherein the antibody comprises the amino acid sequence of SEQ ID NO: 143.

~~13~~14. A pharmaceutical composition comprising the multispecific antibody of any one of the preceding claims and a pharmaceutically acceptable carrier.

~~14~~15. The multispecific antibody of any one of claims 1 to ~~12~~13, or the pharmaceutical composition of claim ~~13~~14, for use as a medicament.

~~15~~16. A kit comprising the multispecific antibody of any one of claims 1 to ~~13~~13, or the pharmaceutical composition of claim ~~14~~14.