

CCL2 neutralization appears to be more obviously relevant in patients with elevated serum levels of CCL2, which has been observed in several types of cancers like breast cancer (BC), ovarian cancer (OvCa), colorectal cancer (CRC), pancreatic cancer and prostate cancer. However, even patients within these indications who do not present this serology but whose tumors are highly infiltrated with immune cells of the myeloid lineage might very well profit from this novel therapy due to the many roles that CCL2 plays in the tumor context as mentioned above.

Igawa et al, Immunological Reviews 270 (2016) 132–151 describes the Sweeping technology in which the generated antibody bears pH-dependent CDRs (for antibody-antigen dissociation within the acidic endosomes, leading to antigen degradation) and an engineered Fc moiety with an optimized isoelectric point (pI) and enhanced binding to FcγRIIb (favoring the cellular uptake of immune complexes), and a moderate affinity to the neonatal Fc receptor, to maintain an acceptable pharmacokinetic profile.

Summary of the invention

The present ~~invention~~disclosure relates to bispecific anti-CCL2 antibodies binding to two different epitopes on human CCL2, pharmaceutical compositions thereof, their manufacture, and use as medicaments for the treatment of cancers, inflammatory, autoimmune and ophthalmologic diseases.

One ~~embodiment~~example of the ~~invention~~disclosure is a bispecific antibody comprising a first antigen-binding site that (specifically) binds to a first epitope on human CCL2 and a second different antigen-binding site that (specifically) binds a second different epitope on human CCL2, wherein bispecific antibody comprises a Fc domain of human IgG isotype.

One ~~embodiment~~example of the ~~invention~~disclosure is a bispecific antibody comprising a first antigen-binding site that (specifically) binds to a first epitope on human CCL2 and a second different antigen-binding site that (specifically) binds a second epitope on human CCL2, wherein

- A) i) said first antigen-binding site comprises
a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 33, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 34, and (c) a CDR-H3 comprising the amino

and a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 12; (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 13, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 14; and

5 ii) said second antigen-binding site comprises
a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 25, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 26, and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 27;

10 and a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 28; (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 30;

or

15 I) i) said first antigen-binding site comprises
a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 1, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 2, and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 3;

20 and a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 4; (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 5, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 6; and

25 ii) said second antigen-binding site comprises
a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 25, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 26, and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 27;

30 and a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 28; (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 30.

| In one ~~embodiment~~example the bispecific antibody comprises a Fc domain of human IgG isotype.

In one embodimentexample the bispecific antibody comprises a Fc domain of human IgG1 isotype.

In one embodimentexample the bispecific antibody comprises constant heavy chain domain of human IgG isotype.

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In one embodimentexample the in vivo clearance rate for human CCL2 (ml/day/kg) after administration of the bispecific antibody comprising a constant heavy chain domain of human wild type IgG1 isotype (or the Fc domain thereof) is at least two fold higher (in one embodimentexample at least 5 fold higher, in one embodimentexample at least 10 fold higher, in one embodimentexample at least 20 fold higher) compared to the in vivo clearance rate for human CCL2 (ml/day/kg) after administration of a bispecific antibody comprising a Fc gamma receptor silenced constant heavy chain domain of human IgG1 isotype (or the Fc domain thereof) comprising the mutations L234A, L235A, P329G (Kabat EU numbering), when a pre-formed immune complex consisting of 20mg/kg of each bispecific antibody and 0.1mg/kg human CCL2 was administered at a single dose of 10 ml/kg into FcRn transgenic mice.

20 One embodimentexample of the inventiondisclosure is an (isolated) bispecific antibody comprising a first antigen-binding site that (specifically) binds to a first epitope on human CCL2 and a second antigen-binding site that (specifically) binds a second epitope on human CCL2, wherein

25 i) said first antigen-binding site binds to same epitope on CCL2 as an antibody comprising
a VH domain comprising the amino acid sequence of SEQ ID NO:39 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 33, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 34, and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 35;
30 and a VL domain comprising the amino acid sequence of SEQ ID NO:40 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 36; (e) a CDR-L2 comprising

the amino acid sequence of SEQ ID NO: 37, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 38; and

ii) said second antigen-binding site binds to same epitope on CCL2 as an antibody comprising

5 a VH domain comprising the amino acid sequence of SEQ ID NO:47 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 41, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 42, and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 43;

10 and a VL domain comprising the amino acid sequence of SEQ ID NO:48 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 44; (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 46.

15 In one ~~embodiment~~example the in vivo clearance rate for human CCL2 (ml/day/kg) after administration of the bispecific antibody comprising a constant heavy chain domain of human wild type IgG1 isotype (or the Fc domain thereof) is at least 15 fold higher, in particular at least 20 fold higher, compared to the in vivo clearance rate for human CCL2 (ml/day/kg) after administration of a bispecific antibody
20 comprising a Fc gamma receptor silenced constant heavy chain domain of human IgG1 isotype (or the Fc domain thereof) comprising the mutations L234A, L235A, P329G (Kabat EU numbering), when a pre-formed immune complex consisting of 20mg/kg of each bispecific antibody and 0.1mg/kg human CCL2 was administered at a single dose of 10 ml/kg into FcRn transgenic mice.

25 One ~~embodiment~~example of the ~~invention~~disclosure is an (isolated) bispecific antibody comprising a first antigen-binding site that (specifically) binds to a first epitope on human CCL2 and a second antigen-binding site that (specifically) binds a second epitope on human CCL2, wherein

30 i) said first antigen-binding site comprises a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H

or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;

and

a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62;

and

ii) said second antigen-binding site comprises a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E; and a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (e) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R.

Thus, in one aspect, the present disclosure relates to a bispecific antibody comprising a first antigen-binding site that binds to a first epitope on human CCL2 and a second different antigen-binding site that binds a second different epitope on human CCL2, wherein the bispecific antibody comprises a constant heavy chain domain of human IgG1 isotype

wherein

i) said first antigen-binding site comprises a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG

of SEQ ID NO: 58 wherein X^1 is V, I, or H, X^2 is P or H, and X^3 is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;

and

a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62;

and

ii) said second antigen-binding site comprises

a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;

and

a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence $KAX^1EDIYNRX^2A$ of SEQ ID NO: 79 wherein X^1 is F or T and X^2 is R or L, (e) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R.

One ~~embodiment~~ example of the ~~invention~~ disclosure is an (isolated) bispecific antibody comprising a first antigen-binding site that (specifically) binds to a first epitope on human CCL2 and a second antigen-binding site that (specifically) binds a second epitope on human CCL2, wherein

i) said first antigen-binding site comprises

a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence $GX^1IX^2IFX^3TANYAQKFQG$ of SEQ ID NO: 58 wherein X^1 is V, I, or H, X^2 is P or H, and X^3 is H or G, (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59, (d) a FR-H1 comprising the amino acid sequence QVQLVQSGAEVKKPGSSVKV SCKASGGTF

acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R,
(k) a FR-L1 comprising the amino acid sequence
DIQMTQSPSSLSASVGDRVTITC of SEQ ID NO:86, (l) a FR-L2
comprising the amino acid sequence WYQQKPGKAPKLLIH of SEQ
ID NO:87, (m) a FR-L3 comprising the amino acid sequence
GVPSRFSGSGSGTDYTLTISSLQPEDFATYYC of SEQ ID NO:88,
and (n) a FR-L4 comprising the amino acid sequence FGGGTKVEIK
of SEQ ID NO:89.

One ~~embodiment~~example of the ~~invention~~disclosure is an (isolated) bispecific
antibody comprising a first antigen-binding site that (specifically) binds to a
first epitope on human CCL2 and a second antigen-binding site that
(specifically) binds a second epitope on human CCL2,
wherein

A) i) said first antigen-binding site comprises

a VH domain comprising the amino acid sequence of SEQ ID NO:71;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75; and

ii) said second antigen-binding site comprises

a VH domain comprising the amino acid sequence of SEQ ID NO:90;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93;

or

B) i) said first antigen-binding site comprises

a VH domain comprising the amino acid sequence of SEQ ID NO:71;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75; and

ii) said second antigen-binding site comprises

a VH domain comprising the amino acid sequence of SEQ ID NO:91;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93;

or

ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:92;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93.

5 One ~~embodiment~~example of the ~~invention~~disclosure is an (isolated) bispecific
antibody comprising a first antigen-binding site that (specifically) binds to a
first epitope on human CCL2 and a second antigen-binding site that
(specifically) binds a second epitope on human CCL2,
wherein

10 A) i) said first antigen-binding site comprises
a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%,
95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino
acid sequence of SEQ ID NO:71 wherein the VH domain comprises (a)
a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID
15 NO: 57 wherein X is I, (b) a CDR-H2 comprising the amino acid
sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹
is V, X² is P, and X³ is H, and (c) a CDR-H3 comprising the amino acid
sequence YDAHYGELDF of SEQ ID NO: 59;
and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%,
20 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino
acid sequence of SEQ ID NO:75 wherein the VL domain comprises (d)
a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of
SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence
DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the
25 amino acid sequence HQYIHLHSFT of SEQ ID NO: 62; and

ii) said second antigen-binding site comprises
a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%,
95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino
acid sequence of SEQ ID NO:90 wherein the VH domain comprises (a)
30 a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID
NO: 76, (b) a CDR-H2 comprising the amino acid sequence
RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D, and (c)
a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ
ID NO:78 wherein X is D;
35 and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%,

5 acid sequence of SEQ ID NO:93 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (e) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R.

In one ~~embodiment~~example the bispecific antibody described herein

- i) blocks binding of CCL2 to its receptor CCR2 *in vitro* (reporter assay, IC₅₀=0.5nM); and/or
- 10 ii) inhibits CCL2-mediated chemotaxis of myeloid cells *in vitro* (IC₅₀=1.5nM); and/or
- iii) is cross-reactive to cynomolgus and human CCL2.

15 In one ~~embodiment~~example the bispecific antibody described herein is not cross-reactive to other CCL homologs in particular it shows 100 time less binding to other CCL homologs (as e.g. CCL8) compared to the binding to CCL2

In one ~~embodiment~~example the bispecific antibody described herein binds to the first and second epitope on human CCL2 in ion-dependent manner.

20 In one ~~embodiment~~example the bispecific antibody described herein binds to human CCL2 in pH dependent manner and wherein the first antigen binding site and the second antigen binding site both bind to CCL2 with a higher affinity at neutral pH than at acidic pH.

In one ~~embodiment~~example the bispecific antibody described herein binds to human CCL2 with a 10 times higher affinity at pH 7.4, than at pH 5.8.

25 In one ~~embodiment~~example the bispecific antibody described herein comprises a IgG1 heavy chain constant domain (or the Fc domain thereof) comprising one or more of the following mutations (Kabat EU numbering)

- i) Q311R and/or P343R (suitable for increasing pI for enhancing uptake of antigen); and/or

ii) L234Y, L235W, G236N, P238D, T250V, V264I, H268D, Q295L, T307P, K326T and/or A330K (suitable for increasing affinity to human FcγRIIb and decreasing affinity to other human FcγR); and/or

5 iii) M428L, N434A and/or Y436T (suitable for increasing affinity to FcRn for longer plasma half-life); and/or

iv) Q438R and/or S440E (suitable for suppressing rheumatoid factor binding).

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iii) Q438R and/ S440E (suitable for suppressing rheumatoid factor binding).

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iii) M428L, N434A and/or Y436T (suitable for increasing affinity to FcRn for longer plasma half-life); and/or

iv) Q438R and/or S440E (suitable for suppressing rheumatoid factor binding).

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ii) L234Y, P238D, T250V, V264I, T307P and A330K (suitable for increasing affinity to human FcγRIIb and decreasing affinity to other human FcγR); and

iii) M428L, N434A and Y436T (suitable for increasing affinity to FcRn for longer plasma half-life); and

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| In one ~~embodiment~~example the bispecific antibody described herein comprises a IgG1 heavy chain constant domain (or the Fc domain thereof) comprising one or more of the following mutations (Kabat EU numbering)

10 i) Q311R and P343R (suitable for increasing pI for enhancing uptake of antigen); and

ii) L234Y, P238D, T250V, V264I, T307P and A330K (suitable for increasing affinity to human FcγRIIb and decreasing affinity to other human FcγR); and

iii) N434A and (suitable for increasing affinity to FcRn for longer plasma half-life); and

15 iv) Q438R and S440E (suitable for suppressing rheumatoid factor binding).

| In one ~~embodiment~~example the bispecific antibody described herein comprises two IgG1 heavy chain constant domains (or the Fc domain thereof) comprising (independently or in addition to the above described mutations) the following mutations (EU numbering)

20 i) S354C and T366W in one of the heavy chain constant domains

ii) Y349C, T366S, L368A, Y407V in the other of the heavy chain constant domains

| One ~~embodiment~~example of the ~~invention~~disclosure is an (isolated) (monospecific) antibody that (specifically) binds to a human CCL2,
25 wherein the antibody comprises

A) a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H

or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;

and

5 a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62;

or

10 B) a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO:78 wherein X is D or E;
15 and
a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (e) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the
20 amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R.

| One embodimentexample of the inventiondisclosure is an (isolated) (monospecific) antibody that (specifically) binds to a human CCL2, wherein the antibody comprises

25 A) a VH domain comprising the amino acid sequence of SEQ ID NO:71; and a VL domain comprising the amino acid sequence of SEQ ID NO:75;

or

30 B) a VH domain comprising the amino acid sequence of SEQ ID NO:72; and a VL domain comprising the amino acid sequence of SEQ ID NO:75;

or

C) a VH domain comprising the amino acid sequence of SEQ ID NO:73;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75;

or

5 D) a VH domain comprising the amino acid sequence of SEQ ID NO:74;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75;

or

10 E) a VH domain comprising the amino acid sequence of SEQ ID NO:90;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93;

or

15 F) a VH domain comprising the amino acid sequence of SEQ ID NO:91;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93;

or

G) a VH domain comprising the amino acid sequence of SEQ ID NO:92;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93;

20 or

H) a VH domain comprising the amino acid sequence of SEQ ID NO:90;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:94;

25

~~One embodiment of the invention is~~The present disclosure relates to an isolated
nucleic acid encoding the (mono-or bispecific) antibody according to any one
of the preceding ~~embodiments~~examples. In another aspect, the present
disclosure relates to isolated nucleic acid encoding the antibody as described
herein.

~~One embodiment of the invention is~~The present disclosure relates to a host cell comprising such nucleic acid. In another aspect, the present disclosure relates to a host cell comprising the nucleic acid as described herein.

5

~~One embodiment of the invention is~~The present disclosure relates to a method of producing an antibody comprising culturing such host cell so that the antibody is produced. In another aspect, the present disclosure relates to a method of producing an antibody comprising culturing the host cell as described herein so that the antibody is produced.

In one ~~embodiment~~example of the ~~invention~~disclosure such method further comprises the step of recovering the antibody from the host cell.

~~One embodiment of the invention is~~In another aspect, the present disclosure relates to a pharmaceutical formulation comprising the bispecific antibody as described herein and a pharmaceutically acceptable carrier.

~~One embodiment of the invention is~~In another aspect, the present disclosure relates to the bispecific antibody as described herein for use as a medicament.

~~One embodiment of the invention is the~~In another aspect, the present disclosure relates to use of the bispecific antibody as described herein in the manufacture of a medicament.

In one ~~embodiment~~example such medicament is for the treatment of cancer.

In one ~~embodiment~~example such medicament is for the treatment of an inflammatory or autoimmune disease.

~~One embodiment of the invention is~~In another aspect, the present disclosure relates to the bispecific antibody as described herein for use in treating cancer.

~~One embodiment of the invention is~~In another aspect, the present disclosure relates to the bispecific antibody as described herein for use in treating an inflammatory or autoimmune disease.

One ~~embodiment~~example of the ~~invention~~disclosure is a method of treating an individual having cancer comprising administering to the individual an effective amount of the antibody as described herein.

One ~~embodiment~~example of the ~~invention~~disclosure is a method of treating an individual having an inflammatory or autoimmune disease comprising administering to the individual an effective amount of the antibody as described herein.

Description of the Figures

Figure 1: Surface plasmon resonance (Biacore®) sensorgrams showing binding of monospecific anti-CCL2 antibodies (CNTO888 (= CNTO), 1A5, 1G9 and humanized 11K2 (=11k2) to recombinant CCL2 and CCL2 homologs.

Figure 2a: Serum concentration of hCCL2 over time after i.v. injection of pre-formed immune complex consisting of a) solid line: 0.1mg/kg human

Patent Claims

1. A bispecific antibody comprising a first antigen-binding site that binds to a first epitope on human CCL2 and a second different antigen-binding site that binds a second different epitope on human CCL2, wherein the bispecific antibody comprises ~~a Fc domain of human IgG isotype~~ a constant heavy chain domain of human IgG1 isotype
- wherein
- i) said first antigen-binding site comprises
- a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;
- and
- a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62;
- and
- ii) said second antigen-binding site comprises
- a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;
- and
- a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (e) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R.

2. ~~The bispecific antibody according to claim 1,~~
~~wherein~~

~~A) i) said first antigen-binding site comprises~~

~~a VH domain comprising (a) a CDR-H1 comprising the amino acid
sequence of SEQ ID NO: 33, (b) a CDR-H2 comprising the amino acid
sequence of SEQ ID NO: 34, and (c) a CDR-H3 comprising the amino
acid sequence of SEQ ID NO: 35;~~

~~and a VL domain comprising (d) a CDR-L1 comprising the amino acid
sequence of SEQ ID NO: 36; (e) a CDR-L2 comprising the amino acid
sequence of SEQ ID NO: 37, and (f) a CDR-L3 comprising the amino
acid sequence of SEQ ID NO: 38; and~~

~~ii) said second antigen-binding site comprises~~

~~a VH domain comprising (a) a CDR-H1 comprising the amino acid
sequence of SEQ ID NO: 41, (b) a CDR-H2 comprising the amino acid
sequence of SEQ ID NO: 42, and (c) a CDR-H3 comprising the amino
acid sequence of SEQ ID NO: 43;~~

~~and a VL domain comprising (d) a CDR-L1 comprising the amino acid
sequence of SEQ ID NO: 44; (e) a CDR-L2 comprising the amino acid
sequence of SEQ ID NO: 45, and (f) a CDR-L3 comprising the amino
acid sequence of SEQ ID NO: 46;~~

~~or~~

~~B) i) said first antigen-binding site comprises~~

~~a VH domain comprising (a) a CDR-H1 comprising the amino acid
sequence of SEQ ID NO: 33, (b) a CDR-H2 comprising the amino acid
sequence of SEQ ID NO: 34, and (c) a CDR-H3 comprising the amino
acid sequence of SEQ ID NO: 35;~~

~~and a VL domain comprising (d) a CDR-L1 comprising the amino acid
sequence of SEQ ID NO: 36; (e) a CDR-L2 comprising the amino acid
sequence of SEQ ID NO: 37, and (f) a CDR-L3 comprising the amino
acid sequence of SEQ ID NO: 38; and~~

~~ii) said second antigen-binding site comprises~~

~~a VH domain comprising (a) a CDR-H1 comprising the amino acid
sequence of SEQ ID NO: 17, (b) a CDR-H2 comprising the amino acid
sequence of SEQ ID NO: 18, and (c) a CDR-H3 comprising the amino~~

acid-sequence of SEQ ID NO: 19;
and a VL domain comprising (d) a CDR-L1 comprising the amino acid
sequence of SEQ ID NO: 20; (e) a CDR-L2 comprising the amino acid
sequence of SEQ ID NO: 21, and (f) a CDR-L3 comprising the amino
acid-sequence of SEQ ID NO: 22;

or

~~C) i) said first antigen-binding site comprises~~
~~a VH domain comprising (a) a CDR-H1 comprising the amino acid~~
~~sequence of SEQ ID NO: 33, (b) a CDR-H2 comprising the amino acid~~
~~sequence of SEQ ID NO: 34, and (c) a CDR-H3 comprising the amino~~
~~acid-sequence of SEQ ID NO: 35;~~
~~and a VL domain comprising (d) a CDR-L1 comprising the amino acid~~
~~sequence of SEQ ID NO: 36; (e) a CDR-L2 comprising the amino acid~~
~~sequence of SEQ ID NO: 37, and (f) a CDR-L3 comprising the amino~~
~~acid-sequence of SEQ ID NO: 38; and~~

~~ii) said second antigen-binding site comprises~~
~~a VH domain comprising (a) a CDR-H1 comprising the amino acid~~
~~sequence of SEQ ID NO: 9, (b) a CDR-H2 comprising the amino acid~~
~~sequence of SEQ ID NO: 10, and (c) a CDR-H3 comprising the amino~~
~~acid-sequence of SEQ ID NO: 11;~~
~~and a VL domain comprising (d) a CDR-L1 comprising the amino acid~~
~~sequence of SEQ ID NO: 12; (e) a CDR-L2 comprising the amino acid~~
~~sequence of SEQ ID NO: 13, and (f) a CDR-L3 comprising the amino~~
~~acid-sequence of SEQ ID NO: 14;~~

or

~~D) i) said first antigen-binding site comprises~~
~~a VH domain comprising (a) a CDR-H1 comprising the amino acid~~
~~sequence of SEQ ID NO: 17, (b) a CDR-H2 comprising the amino acid~~
~~sequence of SEQ ID NO: 18, and (c) a CDR-H3 comprising the amino~~
~~acid-sequence of SEQ ID NO: 19;~~
~~and a VL domain comprising (d) a CDR-L1 comprising the amino acid~~
~~sequence of SEQ ID NO: 20; (e) a CDR-L2 comprising the amino acid~~
~~sequence of SEQ ID NO: 21, and (f) a CDR-L3 comprising the amino~~
~~acid-sequence of SEQ ID NO: 22; and~~

5 ~~ii) said second antigen-binding site comprises~~
a VH domain comprising (a) a CDR-H1 comprising the amino acid
sequence of SEQ ID NO: 41, (b) a CDR-H2 comprising the amino acid
sequence of SEQ ID NO: 42, and (c) a CDR-H3 comprising the amino
acid sequence of SEQ ID NO: 43;
and a VL domain comprising (d) a CDR-L1 comprising the amino acid
sequence of SEQ ID NO: 44; (e) a CDR-L2 comprising the amino acid
sequence of SEQ ID NO: 45, and (f) a CDR-L3 comprising the amino
acid sequence of SEQ ID NO: 46;

10 ~~or~~

E) ~~i) said first antigen-binding site comprises~~
a VH domain comprising (a) a CDR-H1 comprising the amino acid
sequence of SEQ ID NO: 25, (b) a CDR-H2 comprising the amino acid
sequence of SEQ ID NO: 26, and (c) a CDR-H3 comprising the amino
acid sequence of SEQ ID NO: 27;
and a VL domain comprising (d) a CDR-L1 comprising the amino acid
sequence of SEQ ID NO: 28; (e) a CDR-L2 comprising the amino acid
sequence of SEQ ID NO: 29, and (f) a CDR-L3 comprising the amino
acid sequence of SEQ ID NO: 30; and

20 ~~ii) said second antigen-binding site comprises~~
a VH domain comprising (a) a CDR-H1 comprising the amino acid
sequence of SEQ ID NO: 41, (b) a CDR-H2 comprising the amino acid
sequence of SEQ ID NO: 42, and (c) a CDR-H3 comprising the amino
acid sequence of SEQ ID NO: 43; and
25 a VL domain comprising (d) a CDR-L1 comprising the amino acid
sequence of SEQ ID NO: 44; (e) a CDR-L2 comprising the amino acid
sequence of SEQ ID NO: 45, and (f) a CDR-L3 comprising the amino
acid sequence of SEQ ID NO: 46;

~~or~~

30 F) ~~i) said first antigen-binding site comprises~~
a VH domain comprising (a) a CDR-H1 comprising the amino acid
sequence of SEQ ID NO: 49, (b) a CDR-H2 comprising the amino acid
sequence of SEQ ID NO: 50, and (c) a CDR-H3 comprising the amino
acid sequence of SEQ ID NO: 51;

and a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 52; (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 53, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 54; and

5

— ii) said second antigen binding site comprises
a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 41, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 42, and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 43; and

10

a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 44; (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 46;

or

15

G) i) said first antigen binding site comprises
a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 9, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 10, and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 11;

20

and a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 12; (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 13, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 14; and

25

— ii) said second antigen binding site comprises
a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 17, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 18, and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 19;

30

and a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 20; (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 21, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 22;

or

5 H) i) ~~said first antigen-binding site comprises~~
~~a VH domain comprising (a) a CDR-H1 comprising the amino acid~~
~~sequence of SEQ ID NO: 9, (b) a CDR-H2 comprising the amino acid~~
~~sequence of SEQ ID NO: 10, and (c) a CDR-H3 comprising the amino~~
~~acid sequence of SEQ ID NO: 11;~~
~~and a VL domain comprising (d) a CDR-L1 comprising the amino acid~~
~~sequence of SEQ ID NO: 12; (e) a CDR-L2 comprising the amino acid~~
~~sequence of SEQ ID NO: 13, and (f) a CDR-L3 comprising the amino~~
~~acid sequence of SEQ ID NO: 14; and~~

10 ~~ii) said second antigen-binding site comprises~~
~~a VH domain comprising (a) a CDR-H1 comprising the amino acid~~
~~sequence of SEQ ID NO: 25, (b) a CDR-H2 comprising the amino acid~~
~~sequence of SEQ ID NO: 26, and (c) a CDR-H3 comprising the amino~~
~~acid sequence of SEQ ID NO: 27;~~
15 ~~and a VL domain comprising (d) a CDR-L1 comprising the amino acid~~
~~sequence of SEQ ID NO: 28; (e) a CDR-L2 comprising the amino acid~~
~~sequence of SEQ ID NO: 29, and (f) a CDR-L3 comprising the amino~~
~~acid sequence of SEQ ID NO: 30;~~

~~or~~

20 I) i) ~~said first antigen-binding site comprises~~
~~a VH domain comprising (a) a CDR-H1 comprising the amino acid~~
~~sequence of SEQ ID NO: 1, (b) a CDR-H2 comprising the amino acid~~
~~sequence of SEQ ID NO: 2, and (c) a CDR-H3 comprising the amino~~
~~acid sequence of SEQ ID NO: 3;~~
25 ~~and a VL domain comprising (d) a CDR-L1 comprising the amino acid~~
~~sequence of SEQ ID NO: 4; (e) a CDR-L2 comprising the amino acid~~
~~sequence of SEQ ID NO: 5, and (f) a CDR-L3 comprising the amino~~
~~acid sequence of SEQ ID NO: 6; and~~

30 ~~ii) said second antigen-binding site comprises~~
~~a VH domain comprising (a) a CDR-H1 comprising the amino acid~~
~~sequence of SEQ ID NO: 25, (b) a CDR-H2 comprising the amino acid~~
~~sequence of SEQ ID NO: 26, and (c) a CDR-H3 comprising the amino~~
~~acid sequence of SEQ ID NO: 27;~~
~~and a VL domain comprising (d) a CDR-L1 comprising the amino acid~~

sequence of SEQ ID NO: 28; (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 29, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 30.

3. ~~The bispecific antibody according to claim 2,~~
wherein

A) i) ~~said first antigen-binding site comprises~~
a VH domain comprising the amino acid sequence of SEQ ID NO:39
wherein the VH domain comprises (a) a CDR-H1 comprising the
amino acid sequence of SEQ ID NO: 33, (b) a CDR-H2 comprising the
amino acid sequence of SEQ ID NO: 34, and (c) a CDR-H3 comprising
the amino acid sequence of SEQ ID NO: 35;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:40 wherein the VL domain comprises (d) a CDR-L1 comprising
the amino acid sequence of SEQ ID NO: 36; (e) a CDR-L2 comprising
the amino acid sequence of SEQ ID NO: 37, and (f) a CDR-L3
comprising the amino acid sequence of SEQ ID NO: 38; and

~~ii) said second antigen-binding site comprises~~
a VH domain comprising the amino acid sequence of SEQ ID NO:47
wherein the VH domain comprises (a) a CDR-H1 comprising the
amino acid sequence of SEQ ID NO: 41, (b) a CDR-H2 comprising the
amino acid sequence of SEQ ID NO: 42, and (c) a CDR-H3 comprising
the amino acid sequence of SEQ ID NO: 43;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:48 wherein the VL domain comprises (d) a CDR-L1 comprising
the amino acid sequence of SEQ ID NO: 44; (e) a CDR-L2 comprising
the amino acid sequence of SEQ ID NO: 45, and (f) a CDR-L3
comprising the amino acid sequence of SEQ ID NO: 46;

~~or~~

B) i) ~~said first antigen-binding site comprises~~
a VH domain comprising the amino acid sequence of SEQ ID NO:39
wherein the VH domain comprises (a) a CDR-H1 comprising the
amino acid sequence of SEQ ID NO: 33, (b) a CDR-H2 comprising the
amino acid sequence of SEQ ID NO: 34, and (c) a CDR-H3 comprising
the amino acid sequence of SEQ ID NO: 35;

and a VL domain comprising the amino acid sequence of SEQ ID NO:40 wherein the VL domain comprises (d) a CDR L1 comprising the amino acid sequence of SEQ ID NO: 36; (e) a CDR L2 comprising the amino acid sequence of SEQ ID NO: 37, and (f) a CDR L3 comprising the amino acid sequence of SEQ ID NO: 38; and

— ii) said second antigen-binding site comprises a VH domain comprising the amino acid sequence of SEQ ID NO:23 wherein the VH domain comprises (a) a CDR H1 comprising the amino acid sequence of SEQ ID NO: 17, (b) a CDR H2 comprising the amino acid sequence of SEQ ID NO: 18, and (c) a CDR H3 comprising the amino acid sequence of SEQ ID NO: 19; and a VL domain comprising the amino acid sequence of SEQ ID NO:24 wherein the VL domain comprises (d) a CDR L1 comprising the amino acid sequence of SEQ ID NO: 20; (e) a CDR L2 comprising the amino acid sequence of SEQ ID NO: 21, and (f) a CDR L3 comprising the amino acid sequence of SEQ ID NO: 22;

or

C) i) said first antigen-binding site comprises a VH domain comprising the amino acid sequence of SEQ ID NO:39 wherein the VH domain comprises (a) a CDR H1 comprising the amino acid sequence of SEQ ID NO: 33, (b) a CDR H2 comprising the amino acid sequence of SEQ ID NO: 34, and (c) a CDR H3 comprising the amino acid sequence of SEQ ID NO: 35; and a VL domain comprising the amino acid sequence of SEQ ID NO:40 wherein the VL domain comprises (d) a CDR L1 comprising the amino acid sequence of SEQ ID NO: 36; (e) a CDR L2 comprising the amino acid sequence of SEQ ID NO: 37, and (f) a CDR L3 comprising the amino acid sequence of SEQ ID NO: 38; and

— ii) said second antigen-binding site comprises a VH domain comprising the amino acid sequence of SEQ ID NO:15 wherein the VH domain comprises (a) a CDR H1 comprising the amino acid sequence of SEQ ID NO: 9, (b) a CDR H2 comprising the amino acid sequence of SEQ ID NO: 10, and (c) a CDR H3 comprising the amino acid sequence of SEQ ID NO: 11;

and a VL domain comprising the amino acid sequence of SEQ ID NO:16 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 12; (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 13, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 14;

or

~~D) i) said first antigen-binding site comprises~~

~~a VH domain comprising the amino acid sequence of SEQ ID NO:23 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 17, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 18, and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 19;~~

~~and a VL domain comprising the amino acid sequence of SEQ ID NO:24 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 20; (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 21, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 22; and~~

~~ii) said second antigen-binding site comprises~~

~~a VH domain comprising the amino acid sequence of SEQ ID NO:47 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 41, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 42, and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 43;~~

~~and a VL domain comprising the amino acid sequence of SEQ ID NO:48 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 44; (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 46;~~

or

E) i) said first antigen-binding site comprises

a VH domain comprising the amino acid sequence of SEQ ID NO:31 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 25, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 26, and (c) a CDR-H3 comprising

the amino acid sequence of SEQ ID NO: 27;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:32 wherein the VL domain comprises (d) a CDR L1 comprising
the amino acid sequence of SEQ ID NO: 28; (e) a CDR L2 comprising
the amino acid sequence of SEQ ID NO: 29, and (f) a CDR L3
comprising the amino acid sequence of SEQ ID NO: 30; and

— ii) said second antigen binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:47
wherein the VH domain comprises (a) a CDR H1 comprising the
amino acid sequence of SEQ ID NO: 41, (b) a CDR H2 comprising the
amino acid sequence of SEQ ID NO: 42, and (c) a CDR H3 comprising
the amino acid sequence of SEQ ID NO: 43;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:48 wherein the VL domain comprises (d) a CDR L1 comprising
the amino acid sequence of SEQ ID NO: 44; (e) a CDR L2 comprising
the amino acid sequence of SEQ ID NO: 45, and (f) a CDR L3
comprising the amino acid sequence of SEQ ID NO: 46;

or

F) i) said first antigen binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:55
wherein the VH domain comprises (a) a CDR H1 comprising the
amino acid sequence of SEQ ID NO: 49, (b) a CDR H2 comprising the
amino acid sequence of SEQ ID NO: 50, and (c) a CDR H3 comprising
the amino acid sequence of SEQ ID NO: 51;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:56 wherein the VL domain comprises (d) a CDR L1 comprising
the amino acid sequence of SEQ ID NO: 52; (e) a CDR L2 comprising
the amino acid sequence of SEQ ID NO: 53, and (f) a CDR L3
comprising the amino acid sequence of SEQ ID NO: 54; and

— ii) said second antigen binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:47
wherein the VH domain comprises (a) a CDR H1 comprising the
amino acid sequence of SEQ ID NO: 41, (b) a CDR H2 comprising the
amino acid sequence of SEQ ID NO: 42, and (c) a CDR H3 comprising

the amino acid sequence of SEQ ID NO: 43;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:48 wherein the VL domain comprises (d) a CDR L1 comprising
the amino acid sequence of SEQ ID NO: 44; (e) a CDR L2 comprising
the amino acid sequence of SEQ ID NO: 45, and (f) a CDR L3
comprising the amino acid sequence of SEQ ID NO: 46;

or

G) i) said first antigen binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:15
wherein the VH domain comprises (a) a CDR H1 comprising the
amino acid sequence of SEQ ID NO: 9, (b) a CDR H2 comprising the
amino acid sequence of SEQ ID NO: 10, and (c) a CDR H3 comprising
the amino acid sequence of SEQ ID NO: 11;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:16 wherein the VL domain comprises (d) a CDR L1 comprising
the amino acid sequence of SEQ ID NO: 12; (e) a CDR L2 comprising
the amino acid sequence of SEQ ID NO: 13, and (f) a CDR L3
comprising the amino acid sequence of SEQ ID NO: 14; and

— ii) said second antigen binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:23
wherein the VH domain comprises (a) a CDR H1 comprising the
amino acid sequence of SEQ ID NO: 17, (b) a CDR H2 comprising the
amino acid sequence of SEQ ID NO: 18, and (c) a CDR H3 comprising
the amino acid sequence of SEQ ID NO: 19;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:24 wherein the VL domain comprises a (d) CDR L1 comprising
the amino acid sequence of SEQ ID NO: 20; (e) a CDR L2 comprising
the amino acid sequence of SEQ ID NO: 21, and (f) a CDR L3
comprising the amino acid sequence of SEQ ID NO: 22;

or

H) i) said first antigen binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:15
wherein the VH domain comprises (a) a CDR H1 comprising the
amino acid sequence of SEQ ID NO: 9, (b) a CDR H2 comprising the

amino acid sequence of SEQ ID NO: 10, and (c) a CDR H3 comprising the amino acid sequence of SEQ ID NO: 11;
and a VL domain comprising the amino acid sequence of SEQ ID NO:16 wherein the VL domain comprises (d) a CDR L1 comprising the amino acid sequence of SEQ ID NO: 12; (e) a CDR L2 comprising the amino acid sequence of SEQ ID NO: 13, and (f) a CDR L3 comprising the amino acid sequence of SEQ ID NO: 14; and

ii) said second antigen binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:31 wherein the VH domain comprises (a) a CDR H1 comprising the amino acid sequence of SEQ ID NO: 25, (b) a CDR H2 comprising the amino acid sequence of SEQ ID NO: 26, and (c) a CDR H3 comprising the amino acid sequence of SEQ ID NO: 27;
and a VL domain comprising the amino acid sequence of SEQ ID NO:32 wherein the VL domain comprises (d) a CDR L1 comprising the amino acid sequence of SEQ ID NO: 28; (e) a CDR L2 comprising the amino acid sequence of SEQ ID NO: 29, and (f) a CDR L3 comprising the amino acid sequence of SEQ ID NO: 30;

or

i) i) said first antigen binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:7 wherein the VH domain comprises (a) a CDR H1 comprising the amino acid sequence of SEQ ID NO: 1, (b) a CDR H2 comprising the amino acid sequence of SEQ ID NO: 2, and (c) a CDR H3 comprising the amino acid sequence of SEQ ID NO: 3;
and a VL domain comprising the amino acid sequence of SEQ ID NO:8 wherein the VL domain comprises (d) a CDR L1 comprising the amino acid sequence of SEQ ID NO: 4; (e) a CDR L2 comprising the amino acid sequence of SEQ ID NO: 5, and (f) a CDR L3 comprising the amino acid sequence of SEQ ID NO: 6; and

ii) said second antigen binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:31 wherein the VH domain comprises (a) a CDR H1 comprising the amino acid sequence of SEQ ID NO: 25, (b) a CDR H2 comprising the

amino-acid sequence of SEQ ID NO: 26, and (c) a CDR-H3 comprising the amino-acid sequence of SEQ ID NO: 27;
and a VL domain comprising the amino-acid sequence of SEQ ID NO:32 wherein the VL domain comprises (d) a CDR-L1 comprising the amino-acid sequence of SEQ ID NO: 28; (e) a CDR-L2 comprising the amino-acid sequence of SEQ ID NO: 29, and (f) a CDR-L3 comprising the amino-acid sequence of SEQ ID NO: 30.

4. ~~The bispecific antibody according to any one of claims 1 to 3, wherein the bispecific antibody comprising a Fc domain of human IgG isotype is a bispecific antibody comprising a constant heavy chain domain of human IgG1 isotype.~~

5. ~~The bispecific antibody according to claim 4, wherein the in vivo clearance rate for human CCL2 (ml/day/kg) after administration of the bispecific antibody comprising a constant heavy chain domain of human wild type IgG1 isotype is at least two fold higher compared to the in vivo clearance rate for human CCL2 (ml/day/kg) after administration of a bispecific antibody comprising a Fc gamma receptor silenced constant heavy chain domain of human IgG1 isotype comprising the mutations L234A, L235A, P329G (Kabat EU numbering), when a pre-formed immune complex consisting of 20mg/kg of each bispecific antibody and 0.1mg/kg human CCL2 was administered at a single dose of 10 ml/kg into FcRn transgenic mice.~~

6. ~~An (isolated) bispecific antibody comprising a first antigen-binding site that (specifically) binds to a first epitope on human CCL2 and a second antigen-binding site that (specifically) binds a second epitope on human CCL2, wherein~~

i) ~~said first antigen-binding site binds to same epitope on CCL2 as an antibody comprising~~
~~a VH domain comprising the amino acid sequence of SEQ ID NO:39 wherein the VH domain comprises (a) a CDR-H1 comprising the amino-acid sequence of SEQ ID NO: 33, (b) a CDR-H2 comprising the amino-acid sequence of SEQ ID NO: 34, and (c) a CDR-H3 comprising the amino-acid sequence of SEQ ID NO: 35;~~
~~and a VL domain comprising the amino-acid sequence of SEQ ID NO:40 wherein the VL domain comprises (d) a CDR-L1 comprising~~

~~the amino acid sequence of SEQ ID NO: 36; (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 37, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 38; and~~

- 5 ii) ~~said second antigen-binding site binds to same epitope on CCL2 as an antibody comprising~~
 ~~a VH domain comprising the amino acid sequence of SEQ ID NO: 47 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 41, (b) a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 42, and (c) a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 43;~~
10 ~~and a VL domain comprising the amino acid sequence of SEQ ID NO: 48 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 44; (e) a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 45, and (f) a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 46.~~

7. ~~The bispecific antibody according to claim 6, wherein the in vivo clearance rate for human CCL2 (ml/day/kg) after administration of the bispecific antibody comprising a constant heavy chain domain of human wild type IgG1 isotype is at least 15 fold higher, in particular at least 20 fold higher, compared to the in vivo clearance rate for human CCL2 (ml/day/kg) after administration of a bispecific antibody comprising a Fc gamma receptor silenced constant heavy chain domain of human IgG1 isotype comprising the mutations L234A, L235A, P329G (Kabat EU numbering), when a pre-formed immune complex consisting of 20mg/kg of each bispecific antibody and 0.1mg/kg human CCL2 was administered at a single dose of 10 ml/kg into FcRn transgenic mice.~~

8. ~~An (isolated) bispecific antibody comprising a first antigen-binding site that (specifically) binds to a first epitope on human CCL2 and a second antigen-binding site that (specifically) binds a second epitope on human CCL2, wherein~~

- 30 i) ~~said first antigen-binding site comprises~~
 ~~a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG~~

of SEQ ID NO: 58 wherein X^1 is V, I, or H, X^2 is P or H, and X^3 is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;

and

a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62;

and

ii) — said second antigen binding site comprises

a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;

and

a VL domain comprising (d) a CDR-L1 comprising the amino acid sequence $KAX^1EDIYNRX^2A$ of SEQ ID NO: 79 wherein X^1 is F or T and X^2 is R or L, (e) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R.

92. ~~An (isolated)The~~ bispecific antibody comprising a first antigen binding site that (specifically) binds to a first epitope on human CCL2 and a second antigen binding site that (specifically) binds a second epitope on human CCL2 according to claim 1,

wherein

i) said first antigen-binding site comprises

a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence $GX^1IX^2IFX^3TANYAQKFQG$ of SEQ ID NO: 58 wherein X^1 is V, I, or H, X^2 is P or H, and X^3 is H or G, (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59, (d) a FR-H1 comprising the

amino acid sequence QVQLVQSGAEVKKPGSSVKVSCASGGTF of SEQ ID NO:63, (e) a FR-H2 comprising the amino acid sequence WVRQAPGQGLEWMG of SEQ ID NO:64, (f) a FR-H3 comprising the amino acid sequence RVTITADESTSTAYMELSSLRSED TAVY YCAR of SEQ ID NO:65, and (g) a FR-H4 comprising the amino acid sequence WGQGT LVT VSS of SEQ ID NO:66;

5 and

a VL domain comprising (h) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (i) a CDR-L2

10 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (j) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62, (k) a FR-L1 comprising the amino acid sequence EIVLTQSPATLSLSPGERATLSC of SEQ ID NO:67, (l) a FR-L2 comprising the amino acid sequence WYQQKPGQAPRLLIY of SEQ

15 ID NO:68, (m) a FR-L3 comprising the amino acid sequence GVPARFSGSGSGTDFTLTISSELPEDFAVYYC of SEQ ID NO:69, and (n) a FR-L4 comprising the amino acid sequence GQGTKVEIK of SEQ ID NO:70;

and

20 ii) said second antigen-binding site comprises

a VH domain comprising (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, (c) a CDR-H3 comprising the amino acid

25 sequences GVFGFFXH of SEQ ID NO:78 wherein X is D or E, (d) a FR-H1 comprising the amino acid sequence QVQLVQSGAEVKKPGSSVKVSCASGLTIS of SEQ ID NO:82, (e) a FR-H2 comprising the amino acid sequence WVRQAPGQGLEWMG of SEQ ID NO:83, (f) a FR-H3 comprising the amino acid sequence RVTITADTSTSTAYMELSSLRSED TAVYYCAR of SEQ ID NO:84,

30 and (g) a FR-H4 comprising the amino acid sequence WGQGTTVT VSS of SEQ ID NO:85;

and

a VL domain comprising (h) a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (i) a CDR-L2 comprising the amino acid sequence

35

GATSLEH of SEQ ID NO: 80, (j) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R, (k) a FR-L1 comprising the amino acid sequence DIQMTQSPSSLSASVGDRVTITC of SEQ ID NO:86, (l) a FR-L2 comprising the amino acid sequence WYQQKPGKAPKLLIH of SEQ ID NO:87, (m) a FR-L3 comprising the amino acid sequence GVPSRFSGSGSGTDYTLTISSLQPEDFATYYC of SEQ ID NO:88, and (n) a FR-L4 comprising the amino acid sequence FGGGTKVEIK of SEQ ID NO:89.

10 ~~103.~~ ~~An (isolated)The~~ bispecific antibody ~~comprising a first antigen-binding site that (specifically) binds to a first epitope on human CCL2 and a second antigen-binding site that (specifically) binds a second epitope on human CCL2~~according to claim 1 or 2,
wherein

15 A) i) said first antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:71;
and a VL domain comprising the amino acid sequence of SEQ ID NO:75; and

20 ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:90;
and a VL domain comprising the amino acid sequence of SEQ ID NO:93;

or

25 B) i) said first antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:71;
and a VL domain comprising the amino acid sequence of SEQ ID NO:75; and

30 ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:91;
and a VL domain comprising the amino acid sequence of SEQ ID NO:93;

or

C) i) said first antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:71;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75; and

5 ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:90;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:94;

or

10 D) i) said first antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:72;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75; and

15 ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:90;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:94;

or

20 E) i) said first antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:73;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75; and

25 ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:90;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93;

or

30 F) i) said first antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:73;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75; and

ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:90;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:94;

5 or

G) i) said first antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:73;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75; and

10 ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:92;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93;

or

15 H) i) said first antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:73;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75; and

20 ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:91;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93;

or

25 I) i) said first antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:72;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75; and

30 ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:90;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93;

or

J) i) said first antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:72;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75; and

ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:92;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93;

or

K) i) said first antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:72;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75; and

ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:91;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93;

or

L) i) said first antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:74;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75; and

ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:90;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93;

or

M) i) said first antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:74;

and a VL domain comprising the amino acid sequence of SEQ ID NO:75; and

ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:90;
and a VL domain comprising the amino acid sequence of SEQ ID NO:94;

or

N) i) said first antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:74;
and a VL domain comprising the amino acid sequence of SEQ ID NO:75; and

ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:92;
and a VL domain comprising the amino acid sequence of SEQ ID NO:93;

or

O) i) said first antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:74;
and a VL domain comprising the amino acid sequence of SEQ ID NO:75; and

ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:91;
and a VL domain comprising the amino acid sequence of SEQ ID NO:93;

or

P) i) said first antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:71;
and a VL domain comprising the amino acid sequence of SEQ ID NO:75; and

ii) said second antigen-binding site comprises
a VH domain comprising the amino acid sequence of SEQ ID NO:92;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93.

5 ~~11.— An (isolated) bispecific antibody comprising a first antigen-binding site that
(specifically) binds to a first epitope on human CCL2 and a second antigen-
binding site that (specifically) binds a second epitope on human CCL2,
wherein~~

10 ~~A) i) said first antigen-binding site comprises
a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%,
95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino
acid sequence of SEQ ID NO:71 wherein the VH domain comprises (a)
a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID
15 NO: 57 wherein X is I, (b) a CDR-H2 comprising the amino acid
sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹
is V, X² is P, and X³ is H, and (c) a CDR-H3 comprising the amino acid
sequence YDAHYGELDF of SEQ ID NO: 59;
and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%,
95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino
20 acid sequence of SEQ ID NO:75 wherein the VL domain comprises (d)
a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of
SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence
DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the
amino acid sequence HQYIHLHSFT of SEQ ID NO: 62; and~~

25 ~~— ii) said second antigen-binding site comprises
a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%,
95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino
acid sequence of SEQ ID NO:90 wherein the VH domain comprises (a)
a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID
30 NO: 76, (b) a CDR-H2 comprising the amino acid sequence
RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D, and (c)
a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ
ID NO:78 wherein X is D;
and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%,
35 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino~~

acid-sequence of SEQ ID NO:93 wherein the VL-domain comprises (d) a CDR-L1 comprising the amino-acid-sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F and X² is R, (e) a CDR-L2 comprising the amino-acid-sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino-acid-sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W;

or

B) i) ~~said first antigen-binding site comprises~~

~~a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid-sequence of SEQ ID NO:71 wherein the VH domain comprises (a) a CDR-H1 comprising the amino-acid-sequence SHYGXS of SEQ ID NO: 57 wherein X is I, (b) a CDR-H2 comprising the amino-acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, X² is P, and X³ is H, and (c) a CDR-H3 comprising the amino-acid sequence YDAHYGELDF of SEQ ID NO: 59; and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid-sequence of SEQ ID NO:75 wherein the VL-domain comprises (d) a CDR-L1 comprising the amino-acid-sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid-sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino-acid-sequence HQYIHLHSFT of SEQ ID NO: 62; and~~

~~ii) said second antigen-binding site comprises~~

~~a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid-sequence of SEQ ID NO:91 wherein the VH domain comprises (a) a CDR-H1 comprising the amino-acid-sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino-acid-sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D, and (c) a CDR-H3 comprising the amino-acid-sequences GVFGFFXH of SEQ ID NO:78 wherein X is E; and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid-sequence of SEQ ID NO:93 wherein the VL-domain comprises (d)~~

a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F and X² is R, (e) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W;

or

C) i) said first antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 71 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 75 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62; and

— ii) said second antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 90 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 94 wherein the VL domain comprises (d)

a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (c) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R;

or

D) i) said first antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 72 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 75 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62; and

— ii) said second antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 90 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 94 wherein the VL domain comprises (d)

a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (c) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R;

or

E) i) said first antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 73 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 75 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62; and

— ii) said second antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 90 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 93 wherein the VL domain comprises (d)

a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (c) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R;

or

~~F) i) said first antigen-binding site comprises~~

~~a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 73 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;~~

~~and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 75 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62; and~~

~~ii) said second antigen-binding site comprises~~

~~a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 90 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;~~

~~and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 94 wherein the VL domain comprises (d)~~

a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (c) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R;

or

G) i) said first antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 73 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 75 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62; and

— ii) said second antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 92 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 93 wherein the VL domain comprises (d)

a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (c) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R;

or

H) i) said first antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 73 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 75 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62; and

— ii) said second antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 91 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 93 wherein the VL domain comprises (d)

a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (c) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R;

or

i) i) said first antigen binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 72 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 75 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62; and

ii) said second antigen binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 90 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 93 wherein the VL domain comprises (d)

a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (c) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R;

or

J) i) ~~said first antigen binding site comprises~~

~~a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 72 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;~~

~~and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 75 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62; and~~

~~ii) said second antigen binding site comprises~~

~~a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 92 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;~~

~~and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 93 wherein the VL domain comprises (d)~~

a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (c) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R;

or

K) i) said first antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 72 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 75 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62; and

— ii) said second antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 91 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 93 wherein the VL domain comprises (d)

a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (c) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R;

or

L) i) said first antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 74 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 75 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62; and

— ii) said second antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 90 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 93 wherein the VL domain comprises (d)

a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (c) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R;

or

M) i) said first antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 74 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 75 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62; and

— ii) said second antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 90 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 94 wherein the VL domain comprises (d)

a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (c) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R;

or

N) i) said first antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 74 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 75 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62; and

— ii) said second antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 92 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 93 wherein the VL domain comprises (d)

a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (c) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R;

or

Θ) i) said first antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 74 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 75 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62; and

— ii) said second antigen-binding site comprises

a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 91 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;

and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 93 wherein the VL domain comprises (d)

a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (c) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R;

or

~~P) i) said first antigen-binding site comprises~~

~~a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 71 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H or G, and (c) a CDR-H3 comprising the amino acid sequence YDAHYGELDF of SEQ ID NO: 59;~~

~~and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 75 wherein the VL domain comprises (d) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2 comprising the amino acid sequence DASDRAE of SEQ ID NO: 61, and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT of SEQ ID NO: 62; and~~

~~ii) said second antigen-binding site comprises~~

~~a VH domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 92 wherein the VH domain comprises (a) a CDR-H1 comprising the amino acid sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77 wherein X is D or E, and (c) a CDR-H3 comprising the amino acid sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;~~

~~and a VL domain sequence having at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or 100% sequence identity to the amino acid sequence of SEQ ID NO: 93 wherein the VL domain comprises (d)~~

a CDR-L1 comprising the amino acid sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T and X² is R or L, (e) a CDR-L2 comprising the amino acid sequence GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W or R.

~~12. The bispecific antibody according to anyone of the claims 8 to 11, wherein the bispecific antibody comprises a Fc domain of human IgG isotype, preferably of human IgG1 isotype.~~

~~13. The bispecific antibody according to anyone of the claims 8 to 11, wherein the bispecific wherein comprises a constant domain of human IgG isotype, preferably of human IgG1 isotype.~~

~~14. The bispecific antibody according to anyone of the preceding claims, wherein the bispecific antibody~~

~~i) blocks binding of CCL2 to its receptor CCR2 *in vitro* (reporter assay, IC₅₀=0.5nM); and/or~~

~~ii) inhibits CCL2 mediated chemotaxis of myeloid cells *in vitro* (IC₅₀=1.5nM); and/or~~

~~iii) is cross-reactive to cyno and human CCL2.~~

~~15. The bispecific antibody according to anyone of the preceding claims, wherein the bispecific antibody is not cross-reactive to other CCL homologs.~~

~~164.~~ The bispecific antibody according to anyone of the preceding claims, wherein the bispecific antibody binds to human CCL2 with a 10 times higher affinity at pH 7.4, than at pH 5.8.

~~175.~~ The bispecific antibody according to anyone of the preceding claims, wherein the bispecific antibody, comprises a human IgG1 heavy chain constant domain comprising one or more of the following mutations (Kabat EU numbering)

i) Q311R and/or P343R; and/or

ii) L234Y, L235W, G236N, P238D, T250V, V264I, H268D, Q295L, T307P, K326T and/or A330K; and/or

iii) M428L, N434A and/or Y436T; and/or

iv) Q438R and/or S440E.

5 ~~18.—An (isolated) antibody that (specifically) binds to a human CCL2,
wherein the antibody comprises~~

10 ~~A)—a VH domain comprising (a) a CDR-H1 comprising the amino acid
sequence SHYGXS of SEQ ID NO: 57 wherein X is I or T, (b) a CDR-
H2 comprising the amino acid sequence GX¹IX²IFX³TANYAQKFQG
of SEQ ID NO: 58 wherein X¹ is V, I, or H, X² is P or H, and X³ is H
or G, and (c) a CDR-H3 comprising the amino acid sequence
YDAHYGELDF of SEQ ID NO: 59;~~

15 ~~and
a VL domain comprising (d) a CDR-L1 comprising the amino acid
sequence RASQHVSDAYLA of SEQ ID NO: 60; (e) a CDR-L2
comprising the amino acid sequence DASDRAE of SEQ ID NO: 61,
and (f) a CDR-L3 comprising the amino acid sequence HQYIHLHSFT
of SEQ ID NO: 62;~~

20 ~~or~~

25 ~~B)—a VH domain comprising (a) a CDR-H1 comprising the amino acid
sequence HTYMH of SEQ ID NO: 76, (b) a CDR-H2 comprising the
amino acid sequence RIDPXNHNTKFDPKFQG of SEQ ID NO: 77
wherein X is D or E, and (c) a CDR-H3 comprising the amino acid
sequences GVFGFFXH of SEQ ID NO: 78 wherein X is D or E;~~

30 ~~and
a VL domain comprising (d) a CDR-L1 comprising the amino acid
sequence KAX¹EDIYNRX²A of SEQ ID NO: 79 wherein X¹ is F or T
and X² is R or L, (e) a CDR-L2 comprising the amino acid sequence
GATSLEH of SEQ ID NO: 80, and (f) a CDR-L3 comprising the
amino acid sequence QQFXSAPYT of SEQ ID NO: 81 wherein X is W
or R.~~

19.—An (isolated) antibody that (specifically) binds to a human CCL2,

wherein the antibody comprises

A) — a VH domain comprising the amino acid sequence of SEQ ID NO:71;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75;

5

or

B) — a VH domain comprising the amino acid sequence of SEQ ID NO:72;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75;

or

10

C) — a VH domain comprising the amino acid sequence of SEQ ID NO:73;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75;

or

15

D) — a VH domain comprising the amino acid sequence of SEQ ID NO:74;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:75;

or

20

E) — a VH domain comprising the amino acid sequence of SEQ ID NO:90;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93;

or

25

F) — a VH domain comprising the amino acid sequence of SEQ ID NO:91;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93;

or

G) — a VH domain comprising the amino acid sequence of SEQ ID NO:92;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:93;

or

~~H) — a VH domain comprising the amino acid sequence of SEQ ID NO:90;
and a VL domain comprising the amino acid sequence of SEQ ID
NO:94;~~

5 ~~206.~~ Isolated nucleic acid encoding the antibody according to any one of the preceding claims.

~~217.~~ A host cell comprising the nucleic acid of claim ~~206~~.

~~228.~~ A method of producing an antibody comprising culturing the host cell of claim ~~217~~ so that the antibody is produced.

10 ~~239.~~ The method of claim ~~238~~, further comprising recovering the antibody from the host cell.

~~2410.~~ A pharmaceutical formulation comprising the bispecific antibody according any one of claims 1 to ~~175~~ and a pharmaceutically acceptable carrier.

15 ~~2511.~~ The bispecific antibody according any one of claims 1 to ~~175~~ for use as a medicament.

~~2612.~~ The bispecific antibody according any one of claims 1 to ~~175~~ for use in treating cancer.

~~2713.~~ The bispecific antibody according any one of claims 1 to ~~175~~ for use in treating an inflammatory or autoimmune disease.

20 ~~2814.~~ Use of the bispecific antibody according any one of claims 1 to ~~175~~ in the manufacture of a medicament.

~~2915.~~ The use of claim ~~2814~~, wherein the medicament is for treatment of cancer.

~~3016.~~ The use of claim ~~2814~~, wherein the medicament is for treatment of an inflammatory or autoimmune disease.

25 ~~31. — A method of treating an individual having cancer comprising administering to the individual an effective amount of the bispecific antibody according any one of embodiments 1 to 17.~~

32. ~~A method of treating an individual having an inflammatory or autoimmune disease comprising administering to the individual an effective amount of the bispecific antibody according any one of embodiments 1 to 17.~~