Patent Claims

1. A biparatopic 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 biparatopic 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 $GX^1IX^2IFX^3TANYAQKFQG$ 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, 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 sequence 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.

2. The biparatopic antibody 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 QVQLVQSGAEVKKPGSSVKVSCKASGGTF 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 RVTITADESTSTAYMELSSLRSEDTAVY YCAR of SEQ ID NO:65, and (g) a FR-H4 comprising the amino acid sequence WGQGTLVTVSS of SEQ ID NO:66;
and
a VL domain comprising (h) a CDR-L1 comprising the amino acid sequence RASQHVSDAYLA of SEQ ID NO: 60; (i) a CDR-L2 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 ID NO:68, (m) a FR-L3 comprising the amino acid sequence GVPARFSGSGSGTDFTLTISSLEPEDFAVYYC of SEQ ID NO:69, and (n) a FR-L4 comprising the amino acid sequence GQGTKVEIK of SEQ ID NO:70;
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, (c) a CDR-H3 comprising the amino acid sequence GVFGFFXH of SEQ ID NO:78 wherein X is D or E, (d) a FR-H1 comprising the amino acid sequence QVQLVQSGAEVKKPGSSVKVSCKASGLTIS 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 RVTITADTSTSTAYMELSSLRSEDTAVYYCAR of SEQ ID NO:84, and (g) a FR-H4 comprising the amino acid sequence WGQGTTVTVSS of SEQ ID NO:85;
and
a VL domain comprising (h) a CDR-L1 comprising the amino acid sequence KAX^{1}EDIYNRX^{2}A of SEQ ID NO: 79 wherein X^1 is F or T and X^2 is R or L, (i) a CDR-L2 comprising the amino acid sequence 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.

3. The biparatopic antibody according to claim 1 or 2, 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:91; 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:90; and a VL domain comprising the amino acid sequence of SEQ ID NO:94.

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

5. The biparatopic antibody according to anyone of the preceding claims, wherein the biparatopic 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.

6. Isolated nucleic acid encoding the antibody according to any one of the preceding claims.

7. A host cell comprising the nucleic acid of claim 6.

8. A method of producing an antibody comprising culturing the host cell of claim 7 so that the antibody is produced.

9. The method of claim 8, further comprising recovering the antibody from the host cell.

10. A pharmaceutical formulation comprising the biparatopic antibody according any one of claims 1 to 5 and a pharmaceutically acceptable carrier.

11. The biparatopic antibody according any one of claims 1 to 5 for use as a medicament.

12. Use of the biparatopic antibody according any one of claims 1 to 5 in the manufacture of a medicament for treating cancer.