CLAIMS:

1. A protein comprising an antigen binding site of an antibody, wherein the antigen binding site binds to human granulocyte-colony stimulating factor receptor (hG-CSFR) and neutralizes granulocyte-colony stimulating factor (G-CSF) signaling, and wherein the protein inhibits growth of colony forming units – granulocytes (CFU-G) from $CD34^+$ bone marrow cells grown in the presence of G-CSF with an $IC_{50}$ of at least about 0.2nM.

2. A protein comprising an antigen binding site of an antibody, wherein the antigen binding site binds to both human and cynomolgus monkey granulocyte-colony stimulating factor receptor (G-CSFR) with a similar affinity and neutralizes granulocyte-colony stimulating factor (G-CSF) signaling.

3. A protein comprising an antigen binding site of an antibody wherein the antigen binding site binds specifically to the same epitope in human granulocyte-colony stimulating factor receptor (hG-CSFR) as that bound by C1.2 (comprising a heavy chain variable region ($V_H$) comprising a sequence set forth in SEQ ID NO: 2 and a light chain variable region ($V_L$) comprising a sequence set forth in SEQ ID NO: 3) or C1.2G (comprising a $V_H$ comprising a sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising a sequence set forth in SEQ ID NO: 5).

4. A protein comprising an antigen binding site of an antibody, wherein (i) the protein competitively inhibits binding of C1.2 (comprising a heavy chain variable region ($V_H$) comprising a sequence set forth in SEQ ID NO: 2 and a light chain variable region ($V_L$) comprising a sequence set forth in SEQ ID NO: 3) or C1.2G (comprising a $V_H$ comprising a sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising a sequence set forth in SEQ ID NO: 5) to human granulocyte-colony stimulating factor receptor (hG-CSFR); (ii) the protein neutralizes granulocyte colony stimulating factor (G-CSF) signaling; and (iii) the level of binding of the protein to a polypeptide of SEQ ID NO: 1 in which an alanine is substituted for any one of:

(a) the arginine at position 287 of SEQ ID NO:1;
(b) the histidine at position 237 of SEQ ID NO:1;
(c) the methionine at position 198 of SEQ ID NO:1;
(d) the tyrosine at position 172 of SEQ ID NO:1;
(e) the leucine at position 171 of SEQ ID NO:1; or
(f) the leucine at position 111 of SEQ ID NO:1:

is lower than the level of binding of the protein to a polypeptide of SEQ ID NO: 1.

5. The protein of claim 4, wherein the antigen binding site does not detectably bind to the polypeptide comprising the alanine substitution position 287 of SEQ ID NO: 1.

6. A protein comprising an antigen binding site of an antibody, wherein (i) the protein binds to human granulocyte colony stimulating factor receptor (hG-CSFR); (ii) the protein neutralizes granulocyte colony stimulating factor (G-CSF) signaling; and (iii) the level of binding of the protein to a polypeptide of SEQ ID NO: 1 in which an alanine is substituted for any one of:

(a) the arginine at position 287 of SEQ ID NO:1;

(b) the histidine at position 237 of SEQ ID NO:1;

(c) the methionine at position 198 of SEQ ID NO:1;

(d) the tyrosine at position 172 of SEQ ID NO:1;

(e) the leucine at position 171 of SEQ ID NO:1; or

(f) the leucine at position 111 of SEQ ID NO:1:

is lower than the level of binding of the protein to a polypeptide of SEQ ID NO: 1.

7. The protein of any one of claims 4 to 6, wherein the polypeptide to which the protein binds at a reduced level additionally comprises one or more of the following:

(i) an alanine at a position 111 of SEQ ID NO: 1;

(ii) an alanine at a position 171 of SEQ ID NO: 1;

(iii) an alanine at a position 172 of SEQ ID NO: 1; and

(iv) an alanine at a position 198 of SEQ ID NO: 1.

8. The protein of any one of claims 1 to 7, wherein the antigen binding site cross-reacts with:

(i) a polypeptide of SEQ ID NO: 1 in which an alanine is substituted for the lysine at position 167 of SEQ ID NO: 1; and/or

(ii) a polypeptide of SEQ ID NO: 1 in which an alanine is substituted for the histidine at position 168 of SEQ ID NO: 1.

9. The protein of any one of claims 1 to 8, which competitively inhibits the binding of C1.2 (comprising a heavy chain variable region ($V_H$) comprising a sequence set forth in SEQ ID NO: 2 and a light chain variable region ($V_L$) comprising a sequence set forth in SEQ ID NO: 3) or C1.2G (comprising a $V_H$ comprising a sequence set forth in SEQ

ID NO: 4 and a $V_L$ comprising a sequence set forth in SEQ ID NO: 5) to one or more of:

(i) a polypeptide of SEQ ID NO: 1 in which an alanine is substituted for the lysine at position 167 of SEQ ID NO: 1; and/or

(ii) a polypeptide of SEQ ID NO: 1 in which an alanine is substituted for the histidine at position 168 of SEQ ID NO: 1.

10. A protein that binds to human granulocyte-colony stimulating factor receptor (hG-CSFR) and neutralizes granulocyte-colony stimulating factor (G-CSF) signaling, the protein comprising at least one of:

(i) a $V_H$ comprising a complementarity determining region (CDR) 1 comprising a sequence set forth in SEQ ID NO: 6, a CDR2 comprising a sequence set forth in SEQ ID NO: 7 and a CDR3 comprising a sequence at least about 55% identity to the sequence set forth in SEQ ID NO: 8;

(ii) a $V_H$ comprising a sequence at least about 80% identical to a sequence set forth in SEQ ID NO: 2 and/or 4;

(iii) a $V_L$ comprising a CDR1 comprising a sequence set forth in SEQ ID NO: 9, a CDR2 comprising a sequence set forth in SEQ ID NO: 10 and a CDR3 comprising a sequence at least about 33% identity to the sequence set forth in SEQ ID NO: 11; and

(iv) a $V_L$ comprising a sequence at least about 80% identical to a sequence set forth in SEQ ID NO: 3 and/or 5.

11. The protein of claim 10, the $V_H$ comprises a CDR3 comprising a sequence $LGELGX_1X_2X_3X_4$ (SEQ ID NO: 12), wherein:

$X_1$ is an amino acid selected from the group consisting of tryptophan, glutamine, methionine, serine, phenylalanine, glutamic acid and histidine;

$X_2$ is an amino acid selected from the group consisting of phenylalanine, tyrosine, methionine, serine, glycine and isoleucine;

$X_3$ is an amino acid selected from the group consisting of aspartic acid, methionine, glutamine, serine, leucine, valine, arginine and histidine; and

$X_4$ is an amino acid selected from the group consisting of proline, glutamic acid, alanine, leucine, phenylalanine, tyrosine, threonine, asparagine, aspartic acid, serine, glycine, arginine, and lysine.

12. The protein of claim 11, wherein:

$X_1$ is a neutral amino acid;

$X_2$ is phenylalanine, tyrosine, methionine or serine;
$X_3$ is aspartic acid, methionine, glutamine, serine or leucine; and
$X_4$ is proline, glutamic acid, alanine, leucine, phenylalanine or tyrosine.

13. The protein of claim 10, wherein the $V_L$ comprising a CDR3 comprising a sequence $X_1X_2X_3X_4X_5X_6X_7X_8X_9$ (SEQ ID NO: 13), wherein:
$X_1$ is an amino acid selected from the group consisting of glutamine, glutamic acid, histidine, alanine and serine;
$X_2$ is an amino acid selected from the group consisting of glutamine, valine, phenylalanine, asparagine and glutamic acid;
$X_3$ is an amino acid selected from the group consisting of serine and glycine;
$X_4$ is an amino acid selected from the group consisting of tryptophan, methionine, phenylalanine, tyrosine, isoleucine and leucine;
$X_5$ is an amino acid selected from the group consisting of glutamic acid, methionine, glutamine, tryptophan, serine, valine, asparagine, glycine, alanine, arganine, histidine, tyrosine, lysine and threonine;
$X_6$ is an amino acid selected from the group consisting of tyrosine, methionine, isoleucine and threonine;
$X_7$ is an amino acid selected from the group consisting of proline, alanine, histidine, glycine and lysine;
$X_8$ is an amino acid selected from the group consisting of leucine, glutamine, methionine, alanine, phenylalanine, isoleucine, lysine, histidine and glycine;
$X_9$ is an amino acid selected from the group consisting of threonine, phenylalanine, tyrosine, methionine, lysine, serine, histidine, proline, tryptophan, isoleucine, glutamine, glycine and valine.

14. The protein of claim 13, wherein:
$X_1$ is a hydrophobic amino acid, such as glutamine or glutamic acid;
$X_2$ is glutamine;
$X_3$ is an amino acid selected from the group consisting of serine and glycine;
$X_4$ is an amino acid selected from the group consisting of tryptophan, methionine, phenylalanine and tyrosine;
$X_5$ is an amino acid selected from the group consisting of glutamic acid, methionine, glutamine, tryptophan, serine, valine, asparagine, glycine and alanine;
$X_6$ is an amino acid selected from the group consisting of tyrosine, threonine and methionine;

$X_7$ is an amino acid selected from the group consisting of proline, alanine, histidine and glycine;

$X_8$ is an amino acid selected from the group consisting of leucine, glutamine, methionine, alanine, phenylalanine and isoleucine;

$X_9$ is an amino acid selected from the group consisting of threonine, phenylalanine, tyrosine, methionine, lysine, serine, histidine and phenylalanine.

15. A protein that binds to human granulocyte-colony stimulating factor receptor (hG-CSFR) and neutralizes granulocyte-colony stimulating factor (G-CSF) signaling, the protein comprising at least one variable region of an antibody selected from the group consisting of:

(i) a heavy chain variable region ($V_H$) comprising an amino acid sequence set forth in SEQ ID NO: 2;

(ii) a light chain variable region ($V_L$) comprising an amino acid sequence set forth in SEQ ID NO: 3;

(iii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4;

(iv) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 5;

(v) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 14;

(vi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 15;

(vii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 16;

(viii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 17;

(ix) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 18;

(x) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 19;

(xi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 20;

(xii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 21;

(xiii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 22;

(xiv) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 23;

(xv) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 24;

(xvi) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 25;

(xvii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 26;

(xviii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 27;

(xix) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 28;

(xx) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 29;

(xxi) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 30;

(xxii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 31;

(xxiii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 32;

(xxiv) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 33;
(xxv) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 34;
(xxvi) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 35;
(xxvii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 36;
(xxviii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 37;
(xxix) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 38;
(xxx) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 39;
(xxxi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 40;
(xxxii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 41;
(xxxiii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 42;
(xxxiv) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 43;
(xxxv) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 44;
(xxxvi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 45;
(xxxvii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 46;
(xxxviii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 47;
(xxix) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 48;
(xl) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 49;
(xli) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 50;
(xlii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 51;
(xliii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 52;
(xliv) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 53;
(xlv) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 54;
(xlvi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 55;
(xlvii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 56;
(xlviii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 57;
(xlix) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 58;
(l) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 59;
(li) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 60;
(lii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 61;
(liii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 62; and
(liv) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 63.

16. The protein of any one of claims 1 to 15 comprising at least a heavy chain variable region ($V_H$) and a light chain variable region ($V_L$), wherein the $V_H$ and $V_L$ bind to form a Fv comprising an antigen binding domain.

17. The protein of claim 16, wherein the $V_H$ and the $V_L$ are in a single polypeptide chain.

18. The protein of claim 17, which is:
(i) a single chain Fv fragment (scFv);
(ii) a dimeric scFv (di-scFv); or
(iii) at least one of (i) and/or (ii) linked to a constant region of an antibody, a Fc or a heavy chain constant domain ($C_H$) 2 and/or $C_H3$.

19. The protein of claim 16, wherein the $V_L$ and $V_H$ are in separate polypeptide chains.

20. The protein of claim 19, which is:
(i) a diabody;
(ii) a triabody;
(iii) a tetrabody;
(iv) a Fab;
(v) a $F(ab')_2$;
(vi) a Fv; or
(vii) one of (i) to (vi) linked to a constant region of an antibody, a Fc or a heavy chain constant domain ($C_H$) 2 and/or $C_H3$.

21. The protein of claim 19, which is an antibody.

22. The protein of any one of claims 1 to 21 which is chimeric, de-immunized, humanized, human or primatized.

23. An antibody to that binds to human granulocyte-colony stimulating factor receptor (hG-CSFR) and neutralizes granulocyte-colony stimulating factor (G-CSF) signaling, the antibody comprising:
(i) a heavy chain variable region ($V_H$) comprising an amino acid sequence set forth in SEQ ID NO: 2 and a light chain variable region ($V_L$) comprising an amino acid sequence set forth in SEQ ID NO: 3;
(ii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 5;

(iii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 15 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 14;

(iv) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 16;

(v) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 17;

(vi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 18;

(vii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 20 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 19;

(viii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 21;

(ix) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 22;

(x) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 24 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 23;

(ix) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 25;

(x) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 26;

(xi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 28 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 27;

(xii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 29;

(xiii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 31 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 30;

(xiv) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 33 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 32;

(xv) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 34;

(xvi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 36 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 35;

(xvii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 38 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 37;

(xviii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 40 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 39;

(xix) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 42 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 41;

(xx) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 43;

(xxi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 45 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 44;

(xxii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 46;

(xxiii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 47;

(xxiv) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 49 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 48;

(xxv) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 51 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 50;

(xxvi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 53 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 52;

(xxvii)a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 54;

(xxviii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 55 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 5;

(xxix) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 57 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 56;

(xxx) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 59 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 58;

(xxxi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 61 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 60;

(xxxii)a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 62;

(xxxiii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 63; and

(xxxiv) a $V_H$ comprising three CDRs of a $V_H$ set forth in any one or more of (i) to (xxxiii) and a $V_L$ comprising three CDRs of a $V_L$ set forth in any one or more of (i) to (xxxiii).

24. An antibody to that binds to human granulocyte-colony stimulating factor receptor (hG-CSFR) and neutralizes granulocyte-colony stimulating factor (G-CSF) signaling, the antibody comprising:

(i) a heavy chain variable region ($V_H$) comprising an amino acid sequence set forth in SEQ ID NO: 2 and a light chain variable region ($V_L$) comprising an amino acid sequence set forth in SEQ ID NO: 3; or

(ii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 5.

25. An antibody comprising:

(i) a heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 64 or 68 and a light chain comprising an amino acid sequence set forth in SEQ ID NO: 65; or

(ii) one heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 64 and one heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 68 and two light chains comprising an amino acid sequence set forth in SEQ ID NO: 65.

26. The protein or antibody of any one of claims 1 to 25, which inhibits G-CSF-induced proliferation of a BaF3 cell expressing hG-CSFR with an $IC_{50}$ of at least about 0.5nM.

27. The protein or antibody of any one of claims 1 to 26, which binds to a polypeptide comprising amino acids 1 to 311 of SEQ ID NO: 1 expressed as a fusion with an antibody Fc region with an affinity of at least about 0.5nM, wherein affinity is determined in an assay in which the polypeptide immobilized and the protein or antibody contacted to the immobilized polypeptide.

28. The protein or antibody of any one of claims 1 to 27, which binds to hG-CSFR expressed on the surface of a cell at an affinity of at least about 1nM.

29. The protein of any one of claims 1 to 28 conjugated to another compound.

30. A composition comprising the protein or antibody of any one of claims 1 to 29 and a pharmaceutically acceptable carrier.

31. A composition comprising:

(i) an antibody comprising a heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 64 and a light chain comprising an amino acid sequence set forth in SEQ ID NO: 65; and

(ii) (a) an antibody comprising a heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 64 and a light chain comprising an amino acid sequence set forth in SEQ ID NO: 65 and/or

(b) an antibody comprising one heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 64 and one heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 68 and two light chains comprising an amino acid sequence set forth in SEQ ID NO: 65,

and, optionally, a pharmaceutically acceptable carrier.

32. A method for treating or preventing a granulocyte-colony stimulating factor (G-CSF)-mediated condition in a subject, the method comprising administering the protein or antibody of any one of claims 1 to 29 or the composition of claim 30 or 31 to the subject.

33. The method of claim 32, wherein the G-CSF-mediated condition is an autoimmune disease, an inflammatory disease or cancer.

34. The method of claim 33, wherein the autoimmune disease or the inflammatory disease is arthritis, multiple sclerosis, pulmonary inflammation or chronic obstructive pulmonary disease.

35. The method of any one of claims 32 to 34 comprising administering an amount of the protein or antibody sufficient to reduce the number of neutrophils in a subject without inducing neutropenia.

36. The method of claim 35, wherein the amount of the protein is between about 0.05mg/kg and 30mg/kg.

**CLAIMS**

1. A protein comprising an antigen binding site of an antibody, in which:

(i) (a) the protein competitively inhibits binding of C1.2G (comprising a $V_H$ comprising a sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising a sequence set forth in SEQ ID NO: 5) or C1.2 (comprising a heavy chain variable region ($V_H$) comprising a sequence set forth in SEQ ID NO: 2 and a light chain variable region ($V_L$) comprising a sequence set forth in SEQ ID NO: 3) to human granulocyte-colony stimulating factor receptor (hG-CSFR); (b) the protein neutralizes granulocyte colony stimulating factor (G-CSF) signaling; and (c) the level of binding of the protein to a polypeptide of SEQ ID NO: 1 in which an alanine is substituted for any one of:

(a) the arginine at position 287 of SEQ ID NO:1;

(b) the histidine at position 237 of SEQ ID NO:1;

(c) the methionine at position 198 of SEQ ID NO:1;

(d) the tyrosine at position 172 of SEQ ID NO:1;

(e) the leucine at position 171 of SEQ ID NO:1; or

(f) the leucine at position 111 of SEQ ID NO:1

is lower than the level of binding of the protein to a polypeptide of SEQ ID NO: 1; and/or

(ii) (a) the protein binds to human granulocyte colony stimulating factor receptor (hG-CSFR); (b) the protein neutralizes granulocyte colony stimulating factor (G-CSF) signaling; and (c) the level of binding of the protein to a polypeptide of SEQ ID NO: 1 in which an alanine is substituted for any one of:

(a) the arginine at position 287 of SEQ ID NO:1;

(b) the histidine at position 237 of SEQ ID NO:1;

(c) the methionine at position 198 of SEQ ID NO:1;

(d) the tyrosine at position 172 of SEQ ID NO:1;

(e) the leucine at position 171 of SEQ ID NO:1; or

(f) the leucine at position 111 of SEQ ID NO:1

is lower than the level of binding of the protein to a polypeptide of SEQ ID NO: 1; and/or

(iii) the protein competitively inhibits the binding of C1.2 (comprising a $V_H$ comprising a sequence set forth in SEQ ID NO: 2 and a $V_L$ comprising a sequence set forth in SEQ ID NO: 3) or C1.2G (comprising a $V_H$ comprising a sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising a sequence set forth in SEQ ID NO: 5) to one or more of (a) a polypeptide of SEQ ID NO: 1 in which an alanine is substituted for the lysine at a position 167 of SEQ ID NO: 1; and/or a polypeptide of SEQ ID NO: 1 in which an alanine is substituted for the histidine at position 168 of SEQ ID NO: 1; and/or

(iv) the antigen binding site binds to human granulocyte-colony stimulating factor receptor (hG-CSFR) and neutralizes granulocyte-colony stimulating factor (G-CSF) signaling, and in which the protein inhibits growth of colony forming units – granulocytes (CFU-G) from $CD34^+$ bone marrow cells grown in the presence of G-CSF with an $IC_{50}$ of at least about 0.2nM; and/or

(v) the antigen binding site binds to both human and cynomolgus monkey granulocyte-colony stimulating factor receptor (G-CSFR) with a similar affinity and neutralizes granulocyte-colony stimulating factor (G-CSF) signaling; and/or

(vi) the antigen binding site binds specifically to the same epitope in human granulocyte-colony stimulating factor receptor (hG-CSFR) as that bound by C1.2 (comprising a heavy chain variable region ($V_H$) comprising a sequence set forth in SEQ ID NO: 2 and a light chain variable region ($V_L$) comprising a sequence set forth in SEQ ID NO: 3) or C1.2G (comprising a $V_H$ comprising a sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising a sequence set forth in SEQ ID NO: 5).

2. A protein according to Claim 1 (i), in which the antigen binding site does not detectably bind to the polypeptide comprising the alanine substitution position 287 of SEQ ID NO: 1.

3. A protein according to Claim 1 (i) or (ii), in which the polypeptide to which the protein binds at a reduced level additionally comprises one or more of the following:

(i) an alanine at a position 111 of SEQ ID NO: 1;

(ii) an alanine at a position 171 of SEQ ID NO: 1;

(iii) an alanine at a position 172 of SEQ ID NO: 1; and

(iv) an alanine at a position 198 of SEQ ID NO: 1.

4. A protein according to any of Claims 1 to 3, in which the antigen binding site cross-reacts with:

(i) a polypeptide of SEQ ID NO: 1 in which an alanine is substituted for the lysine at position 167 of SEQ ID NO: 1; and/or

(ii) a polypeptide of SEQ ID NO: 1 in which an alanine is substituted for the histidine at position 168 of SEQ ID NO: 1.

5. A protein according to any of Claims 1 to 4, which competitively inhibits the binding of C1.2 (comprising a heavy chain variable region ($V_H$) comprising a sequence set forth in SEQ ID NO: 2 and a light chain variable region ($V_L$) comprising a sequence set forth in SEQ ID NO: 3) or C1.2G (comprising a $V_H$ comprising a sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising a sequence set forth in SEQ ID NO: 5) to one or more of:

(i) a polypeptide of SEQ ID NO: 1 in which an alanine is substituted for the lysine at position 167 of SEQ ID NO: 1; and/or

(ii) a polypeptide of SEQ ID NO: 1 in which an alanine is substituted for the histidine at position 168 of SEQ ID NO: 1.

6. A protein that binds to human granulocyte-colony stimulating factor receptor (hG-CSFR) and neutralizes granulocyte-colony stimulating factor (G-CSF) signaling, the protein comprising at least one of:

(i) a $V_H$ comprising a complementarity determining region (CDR) 1 comprising a sequence set forth in SEQ ID NO: 6, a CDR2 comprising a sequence set forth in SEQ ID NO: 7 and a CDR3 comprising a sequence at least about 55% identity to the sequence set forth in SEQ ID NO: 8;

(ii) a $V_H$ comprising a sequence at least about 80% identical to a sequence set forth in SEQ ID NO: 2 and/or 4;

(iii) a $V_L$ comprising a CDR1 comprising a sequence set forth in SEQ ID NO: 9, a CDR2 comprising a sequence set forth in SEQ ID NO: 10 and a CDR3 comprising a sequence at least about 33% identity to the sequence set forth in SEQ ID NO: 11; and

(iv) a $V_L$ comprising a sequence at least about 80% identical to a sequence set forth in SEQ ID NO: 3 and/or 5.

7. A protein according to Claim 6 comprising at least one variable region of an antibody selected from the group consisting of:

(i) a heavy chain variable region ($V_H$) comprising an amino acid sequence set forth in SEQ ID NO: 4;

(ii) a light chain variable region ($V_L$) comprising an amino acid sequence set forth in SEQ ID NO: 5;

(iii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 2;

(iv) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 3;

(v) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 14;

(vi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 15;

(vii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 16;

(viii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 17;

(ix) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 18;

(x) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 19;

(xi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 20;

(xii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 21;

(xiii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 22;

(xiv) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 23;

(xv) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 24;

(xvi) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 25;

(xvii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 26;

(xviii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 27;

(xix) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 28;

(xx) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 29;

(xxi) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 30;

(xxii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 31;

(xxiii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 32;

(xxiv) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 33;

(xxv) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 34;

(xxvi) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 35;

(xxvii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 36;

(xxviii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 37;

(xxix) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 38;

(xxx) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 39;

(xxxi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 40;

(xxxii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 41;

(xxxiii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 42;

(xxxiv) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 43;

(xxxv) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 44;

(xxxvi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 45;

(xxxvii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 46;

(xxxviii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 47;

(xxix) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 48;

(xl) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 49;

(xli) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 50;

(xlii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 51;

(xliii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 52;

(xliv) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 53;

(xlv) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 54;

(xlvi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 55;

(xlvii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 56;

(xlviii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 57;

(xlix) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 58;

(l) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 59;

(li) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 60;

(lii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 61;

(liii) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 62; and

(liv) a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 63.

8. A protein according to any of Claims 1 to 7 comprising at least a heavy chain variable region ($V_H$) and a light chain variable region ($V_L$), in which the $V_H$ and $V_L$ bind to form a Fv comprising an antigen binding domain, for example, in which

(i) the $V_H$ and the $V_L$ are in a single polypeptide chain, for example, the protein is:

(a) a single chain Fv fragment (scFv);

(b) a dimeric scFv (di-scFv); or

(c) at least one of (i) and/or (ii) linked to a constant region of an antibody, a Fc or a heavy chain constant domain ($C_H$) 2 and/or $C_H3$; or

(ii) the $V_L$ and $V_H$ are in separate polypeptide chains, for example, the protein is:

(a) a diabody;

(b) a triabody;

(c) a tetrabody;

(d) a Fab;

(e) a F(ab')$_2$;

(f) a Fv;

(g) one of (i) to (vi) linked to a constant region of an antibody, a Fc or a heavy chain constant domain ($C_H$) 2 and/or $C_H3$; or

(h) an antibody.

9. A protein according to any of Claims 1 to 8 which is chimeric, de-immunized, humanized, human or primatized.

10. An antibody according to Claim 8 that binds to human granulocyte-colony stimulating factor receptor (hG-CSFR) and neutralizes granulocyte-colony stimulating factor (G-CSF) signaling, the antibody comprising:

(i) a heavy chain variable region ($V_H$) comprising an amino acid sequence set forth in SEQ ID NO: 4 and a light chain variable region ($V_L$) comprising an amino acid sequence set forth in SEQ ID NO: 5;

(ii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 2 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 3;

(iii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 15 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 14;

(iv) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 16;

(v) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 17;

(vi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 18;

(vii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 20 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 19;

(viii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 21;

(ix) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 22;

(x) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 24 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 23;

(ix) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 25;

(x) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 26;

(xi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 28 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 27;

(xii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 29;

(xiii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 31 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 30;

(xiv) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 33 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 32;

(xv) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 34;

(xvi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 36 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 35;

(xvii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 38 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 37;

(xviii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 40 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 39;

(xix) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 42 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 41;

(xx) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 43;

(xxi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 45 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 44;

(xxii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 46;

(xxiii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 47;

(xxiv) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 49 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 48;

(xxv) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 51 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 50;

(xxvi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 53 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 52;

(xxvii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 54;

(xxviii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 55 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 5;

(xxix) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 57 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 56;

(xxx) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 59 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 58;

(xxxi) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 61 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 60;

(xxxii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 62;

(xxxiii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 4 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 63; and

(xxxix) a $V_H$ comprising three CDRs of a $V_H$ set forth in any one or more of (i) to (xxxiii) and a $V_L$ comprising three CDRs of a $V_L$ set forth in any one or more of (i) to (xxxiii).

11. An antibody according to Claim 8 that binds to human granulocyte-colony stimulating factor receptor (hG-CSFR) and neutralizes granulocyte-colony stimulating factor (G-CSF) signaling, the antibody comprising:

(i) a heavy chain variable region ($V_H$) comprising an amino acid sequence set forth in SEQ ID NO: 4 and a light chain variable region ($V_L$) comprising an amino acid sequence set forth in SEQ ID NO: 5; or

(ii) a $V_H$ comprising an amino acid sequence set forth in SEQ ID NO: 2 and a $V_L$ comprising an amino acid sequence set forth in SEQ ID NO: 3.

12. An antibody comprising:

(i) a heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 64 or 68 and a light chain comprising an amino acid sequence set forth in SEQ ID NO: 65; or

(ii) one heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 64 and one heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 68 and two light chains comprising an amino acid sequence set forth in SEQ ID NO: 65.

13. A composition comprising a protein or antibody according to any of Claims 1 to 12 and a pharmaceutically acceptable carrier or comprising:

(i) an antibody comprising a heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 64 and a light chain comprising an amino acid sequence set forth in SEQ ID NO: 65; and

(ii) (a) an antibody comprising a heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 64 and a light chain comprising an amino acid sequence set forth in SEQ ID NO: 65 and/or (b) an antibody comprising one heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 64 and one heavy chain comprising an amino acid sequence set forth in SEQ ID NO: 68 and two light chains comprising an amino acid sequence set forth in SEQ ID NO: 65,

and, optionally, a pharmaceutically acceptable carrier.

14. Use of a protein or antibody according to any of Claims 1 to 12 or a composition according to Claim 13 in the manufacture of a medicament for treating or preventing a granulocyte-colony stimulating factor (G-CSF)-mediated condition in a subject.

15. Use according to Claim 14, in which the G-CSF-mediated condition is an autoimmune disease, an inflammatory disease or cancer.

16. Use according to Claim, in which the autoimmune disease or the inflammatory disease is arthritis, multiple sclerosis, pulmonary inflammation or chronic obstructive pulmonary disease.

17. Use according to any of Claims 14 to 16, comprising an amount of the protein or antibody sufficient to reduce the number of neutrophils in a subject without inducing neutropenia.

18. Use according to Claim 17, in which the amount of the protein is between about 0.05mg/kg and 30mg/kg.