Summary ~~of the Invention~~

The ~~invention~~ disclosure provides antigen binding proteins which specifically bind to CD127. The antigen binding proteins can be used in therapeutic methods, in particular, in the treatment or prevention of diseases in which pathogenic T_H17 cells are implicated. The antigen binding proteins may bind to CD127 and inhibit, e.g. neutralize, the biological function of CD127.

In ~~a first aspect~~an embodiment, ~~the invention provides~~there is provided antigen binding proteins, such as antibodies, which comprise from one to six of the following complementarity determining regions, or variants thereof:

(i) CDRH1 as set out in SEQ ID NO:2
(ii) CDRH2 as set out in SEQ ID NO:3
(iii) CDRH3 as set out in SEQ ID NO:4 or in any of SEQ ID NO:132 – SEQ ID NO:137,
(iv) CDRL1 as set out in SEQ ID NO:5
(v) CDRL2 as set out in SEQ ID NO:6
(vi) CDRL3 as set out in SEQ ID NO:7.

In another ~~aspect~~embodiment, ~~the invention provides~~there is provided antigen binding proteins, such as antibodies, which comprise from one to six of the following complementarity determining regions, or variants thereof:

(i) CDRH1 as set out in SEQ ID NO:39
(ii) CDRH2 as set out in SEQ ID NO:40
(iii) CDRH3 as set out in SEQ ID NO:41
(iv) CDRL1 as set out in SEQ ID NO:42
(v) CDRL2 as set out in SEQ ID NO:43
(vi) CDRL3 as set out in SEQ ID NO:44.

In an embodiment the antigen binding protein is an antibody, optionally a chimeric, humanized or human antibody. The antibody may comprise the one or more CDR (of SEQ ID NO:2-7 or 39-44 from a donor antibody) in an acceptor antibody framework. The acceptor antibody framework may be a human antibody.

In ~~an aspect~~one embodiment, ~~the invention provides~~there is provided a humanised antibody which comprises a heavy chain variable region comprising one or more of the following complementarity determining regions:

(i) CDRH1 as set out in SEQ ID NO:2

(ii) CDRH2 as set out in SEQ ID NO:3

(iii) CDRH3 as set out in SEQ ID NO:4 or in any of SEQ ID NO:132 – SEQ ID NO:137,

wherein the antibody further comprises at least one of: a lysine residue at position 66, a phenyalanine, methionine, isoleucine, leucine or valine residue at position 69, and a valine, arginine, alanine or leucine residue at position 71 of the heavy chain variable region (numbering according to Kabat).

In an embodiment, the humanised antibody comprises a leucine at position 69. In an embodiment, the humanised antibody comprises a valine at position 71. In an embodiment, the humanised antibody comprises a leucine at position 69 and a valine at position 71. In an embodiment, the humanised antibody comprises a lysine at position 66, a leucine at position 69 and a valine at position 71. With the exception of the abovementioned point mutations, the heavy chain variable region may have the framework sequence of a human germline variable region. For instance, in an embodiment, the heavy chain variable region is derived from the IGHV1_2 human framework (SEQ ID NO:116).

In another ~~aspect~~embodiment, therefore, ~~the invention provides~~there is provided an antibody comprising one or more of the following complementarity determining regions:

(i) CDRH1 as set out in SEQ ID NO:2

(ii) CDRH2 as set out in SEQ ID NO:3

(iii) CDRH3 as set out in SEQ ID NO:4 or in any of SEQ ID NO:132 – SEQ ID NO:137,

in a V_H framework, wherein V_H framework is derived from a human germline V_H framework and comprises at least one of: a lysine residue at position 66, a phenyalanine, methionine, isoleucine, leucine or valine residue at position 69, and a valine, arginine, alanine or leucine residue at position 71 of the heavy chain variable region (numbering according to Kabat). In an embodiment, the human V_H framework is the IGHV1_2 human framework (SEQ ID NO:116).

The antibody of the ~~invention~~ disclosure may comprise a heavy chain variable region comprising CDRH1 (SEQ ID NO:2) and CDRH3 (SEQ ID NO:4); CDRH2 (SEQ ID NO:3) and CDRH3 (SEQ ID NO:4); CDRH1 (SEQ ID NO:2) and CDRH2 (SEQ ID NO:3); or CDRH1 (SEQ ID NO:2), CDRH2 (SEQ ID NO:3) and CDRH3 (SEQ ID NO:4). The antibody may comprise a heavy chain variable region of any of SEQ ID NOs:10-17 (1A11.H0 V_H to 1A11.H7 V_H). In an embodiment, the humanised antibody comprises a heavy chain variable region of SEQ ID NO:13 (1A11.H3 V_H). In any of these embodiments, CDRH3 of SEQ ID NO:4 may be substituted with CDRH3 as set out in any of SEQ ID NO:132 – SEQ ID NO:137. Alternatively, the heavy chain variable region of SEQ ID NO:13 may comprises one or more substitutions selected from N98D, N98E, F100bE, F100bH, F100bI and F100bV (Kabat). In another embodiment, the heavy chain variable domain has an amino acid sequence of SEQ ID NOs:121,123,125,127,129, or 131. In an embodiment, the heavy chain variable region is paired with a light chain variable region of SEQ ID NO:16.

The ~~invention~~ disclosure also provides an antibody which comprises a light chain variable region comprising one or more of the following complementarity determining regions:

(i) CDRL1 as set out in SEQ ID NO:5
(ii) CDRL2 as set out in SEQ ID NO:6
(iii) CDRL3 as set out in SEQ ID NO:7

wherein the antibody further comprises at least one of: a lysine residue at position 45, a proline residue at position 46, a tryptophan residue at position 47, a valine residue at position 58, a valine residue at position 60, a serine residue at position 70, and a tyrosine or phenylalanine residue at position 71 of the variable region light chain (numbering according to Kabat).

In an embodiment, the antibody comprises a proline residue at position 46. In an embodiment, the antibody comprises a tyrosine residue at position 71. In an embodiment, the antibody comprises a proline residue at position 46 and a tyrosine residue at position 71.

The antibody may comprise a light chain variable region comprising CDRL1 (SEQ ID NO:5) and CDRL3 (SEQ ID NO:7); CDRL2 (SEQ ID NO:6) and CDRL3 (SEQ ID NO:7); CDRL1 (SEQ ID NO:5) and CDRL2 (SEQ ID NO:6); or CDRL1 (SEQ ID NO:5), CDRL2 (SEQ ID NO:6) and CDRL3 (SEQ ID NO:7). The antibody may comprise a light chain

variable region of any of SEQ ID NOs:18-27 (1A11.L0 Vκ to 1A11.L9 Vκ). In an embodiment, the antibody comprises a light chain variable region of SEQ ID NO:22 (1A11.L4 Vκ).

In another ~~aspect~~embodiment, ~~the invention provides~~there is provided a antibody comprising:
a heavy chain variable region comprising one, two or three of the following complementarity determining regions:

(i) CDRH1 as set out in SEQ ID NO:2
(ii) CDRH2 as set out in SEQ ID NO:3
(iii) CDRH3 as set out in SEQ ID NO:4 or in any of SEQ ID NO:132 – SEQ ID NO:137,

wherein the antibody further comprises at least one of: a lysine residue at position 66, a phenyalanine, methionine, isoleucine, leucine or valine residue at position 69, and a valine, arginine, alanine or leucine at position 71 of the heavy chain variable region (numbering according to Kabat);
and a light chain variable region comprising one, two or three of the following complementarity determining regions:

(i) CDRL1 as set out in SEQ ID NO:5
(ii) CDRL2 as set out in SEQ ID NO:6
(iii) CDRL3 as set out in SEQ ID NO:7

wherein the antibody further comprises at least one of: a lysine residue at position 45, a proline residue at position 46, a tryptophan residue at position 47, a valine residue at position 58, a valine residue at position 60, a serine residue at position 70, and a tyrosine or phenylalanine residue at position 71 of the variable region light chain (numbering according to Kabat).

The antibody may comprise any combination of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, including from one heavy chain CDR and one light chain CDR, to all six of said CDRs (i.e. all 3 heavy chain and 3 light chain CDRs). In an embodiment, the antibody comprises all six of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3.

In one embodiment, the antibody comprises: a heavy chain variable region comprising the following complementarity determining regions:

(i) CDRH1 as set out in SEQ ID NO:2
(ii) CDRH2 as set out in SEQ ID NO:3

chain of SEQ ID NO:115. The heavy chain may further comprise any of the following substitutions: N98D, N98E, F100bE, F100bH, F100bI and F100bV (Kabat).

In another embodiment, the antigen binding protein comprises one or more point mutations within CDRH3, and wherein the antigen binding protein has a higher binding affinity for IL-7R than the antigen binding protein lacking said mutation. For example, in an embodiment, the antigen binding protein comprises a CDRH3 as set out in SEQ ID NOs:132-137. In an embodiment, the antigen binding protein comprises a heavy chain variable region as set out in SEQ ID NOs:121, 123, 125, 127, 129 or 131.

In another ~~aspect~~embodiment, ~~the invention provides~~there is provided an antigen binding protein comprising a heavy chain variable domain as set out in:

(a) SEQ ID NO:11
(b) SEQ ID NO:12
(c) SEQ ID NO:13
(d) SEQ ID NO:14
(e) SEQ ID NO:15
(f) SEQ ID NO:16
(g) SEQ ID NO:17
(h) SEQ ID NO:121
(i) SEQ ID NO:123
(j) SEQ ID NO:125
(k) SEQ ID NO:127
(l) SEQ ID NO:129
(m) SEQ ID NO:131,

or a heavy chain variable domain having 70% or more identity to one of SEQ ID NOs:11 to 17, wherein the antigen binding protein is capable of binding to CD127.

In an embodiment, the heavy chain variable domain has 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater identity to one of SEQ ID NOs:11 to 17.

In an embodiment, the antigen binding protein comprises a heavy chain variable domain as set out in SEQ ID NO:13, or a heavy chain variable domain having 70% or greater,

75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater identity to SEQ ID NO:13.

In an embodiment, the antigen binding protein has a heavy chain having 70% or greater, 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater identity to SEQ ID NO:115 or SEQ ID NO:118.
In an embodiment, the heavy chain, or heavy chain variable domain, is a variant of one of SEQ ID NOs: 11 to 17, 121, 123, 125, 127, 129, 131, and wherein the extent of variation consists of one or more of:

i. Val, Ile or Gly at position 2
ii. Leu or Val at position 4
iii. Leu, Ile, Met or Val at position 20
iv. Thr, Ala, Val, Gly or Ser at position 24
v. Trp or Tyr at position 47
vi. Ile, Met, Val or Leu at position 48
vii. Ile, Leu, Phe, Met or Val at position 69
viii. Arg, Val, Ala or Leu at position 71
ix. Ala, Leu, Val, Tyr or Phe at position 78
x. Leu or Met at position 80
xi. Tyr or Phe at position 90; and
xii. Arg, Lys, Gly, Ser, His or Asn at position 94.

In another ~~aspect~~embodiment, ~~the invention provides~~there is provided an antigen binding protein comprising a light chain variable domain as set out in:

(a) SEQ ID NO:19
(b) SEQ ID NO:20
(c) SEQ ID NO:21
(d) SEQ ID NO:22
(e) SEQ ID NO:23
(f) SEQ ID NO:24
(g) SEQ ID NO:25
(h) SEQ ID NO:26
(i) SEQ ID NO:27

or a light chain variable domain having 70% or more identity to one of SEQ ID NOs:19 to 27, wherein the antigen binding protein is capable of binding to CD127.

In an embodiment, the antigen binding protein comprises a light chain variable domain as set out in SEQ ID NO:22, or a light chain variable domain having 70% or more identity to SEQ ID NO:22.

In an embodiment, the light chain variable domain has 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater identity to one of SEQ ID NOs:19 to 27.

In an embodiment, the antigen binding protein has a light chain having 70% or greater, 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater identity to SEQ ID NO: 115.

The ~~invention~~ disclosure contemplates any pairing of the described heavy and light variable domains. In an embodiment, therefore, the ~~invention~~ disclosure also provides an antigen binding protein comprising any one of the following heavy and light chain variable domain combinations: a heavy chain variable domain of SEQ ID NO:11 (or a sequence having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater identity thereto), with a light chain variable domain of any one of SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, or SEQ ID NO:27 (or a sequence having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, or 99% or greater identity to any of SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, or SEQ ID NO:27);
a heavy chain variable domain of SEQ ID NO:12 (or a sequence having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater identity thereto), with a light chain variable domain of any one of SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, or SEQ ID NO:27 (or a sequence having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, or 99% or greater identity to any of SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, or SEQ ID NO:27);
a heavy chain variable domain of SEQ ID NO:13 (or a sequence having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater identity thereto), with a light chain variable domain of any one of SEQ ID NO:19,

a heavy chain variable domain of SEQ ID NO:129 (or a sequence having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater identity thereto), with a light chain variable domain of any one of SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, or SEQ ID NO:27 (or a sequence having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, or 99% or greater identity to any of SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, or SEQ ID NO:27); or,
a heavy chain variable domain of SEQ ID NO:131 (or a sequence having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater identity thereto), with a light chain variable domain of any one of SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, or SEQ ID NO:27 (or a sequence having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, or 99% or greater identity to any of SEQ ID NO:19, SEQ ID NO:20, SEQ ID NO:21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, or SEQ ID NO:27).

In one embodiment, the antigen binding protein comprises a heavy chain variable domain comprising an amino acid sequence having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater identity to the sequence set out in SEQ ID NO:13 and a light chain variable domain comprising an amino acid sequence having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater identity to the sequence set out in SEQ ID NO:22.

In one embodiment, the antigen binding protein comprises a heavy chain variable domain as set out in SEQ ID NO:13 and a light chain variable domain as set out in SEQ ID NO:22.

In another ~~aspect~~embodiment, the ~~invention provides~~there is provided an antigen binding protein comprising one or more of the following complementarity determining regions:

(i) CDRH1 as set out in SEQ ID NO:2 or a variant CDR thereof

(ii) CDRH2 as set out in SEQ ID NO:3 or a variant CDR thereof

(iii) CDRH3 as set out in SEQ ID NO:4 or a variant CDR thereof, or a CDRH3 as set out in any of SEQ ID NO:132 – SEQ ID NO:137,

(iv) CDRL1 as set out in SEQ ID NO:5 or a variant CDR thereof

(v) CDRL2 as set out in SEQ ID NO:6 or a variant CDR thereof

(vi) CDRL3 as set out in SEQ ID NO:7 or a variant CDR thereof

wherein at least one of said CDRs is a variant CDR, and wherein said antigen binding protein is capable of binding to CD127.

In an embodiment, the antigen binding protein comprises at least CDRL2 as set out in SEQ ID NO:6, or a variant thereof. In an embodiment, the antigen binding protein comprises at least CDRH3 as set out in SEQ ID NO:4, or a variant CDR thereof. The variant CDR of this ~~aspect of the invention~~embodiment may comprise:

(f) a variant of CDRH1 (SEQ ID NO:2), wherein:

i. the tyrosine residue at position 32 is substituted for isoleucine, histidine, phenylalanine, threonine, asparagine, cysteine, glutamic acid or aspartic acid;

ii. the threonine residue at position 33 is substituted for a tyrosine, alanine, tryptophan, glycine, leucine or valine,

iii. the methionine residue at position 34 is substituted for isoleucine, valine or tryptophan; and/or

iv. the asparagine residue at position 35 is substituted for histidine, glutamic acid, glutamine, serine, tyrosine or threonine;

(g) a variant of CDRH2 (SEQ ID NO:3) wherein:

i. the leucine residue at position 50 is substituted for arginine, glutamic acid, tryptophan, tyrosine, glycine, glutamine, valine, asparagine, lysine or alanine;

ii. the isoleucine residue at position 51 is substituted for leucine, valine, threonine, serine or asparagine;

iii. the asparagine residue at position 52 is substituted for asparagine, leucine, serine or tyrosine;

iv. the tyrosine residue at position 53 is substituted for alanine, glycine, serine, lysine, threonine or asparagine;

v. the asparagine at position 54 is substituted for serine, threonine, lysine, asparagine or glycine;

vi. the valine at position 56 is substituted for tyrosine, arginine, glutamic acid, aspartic acid, glycine, serine or alanine; and/or

vii. the serine at position 58 is substituted for lysine, asparagine, threonine, arginine, glycine, phenylalanine or tyrosine;

(h) a variant of CDRH3 (SEQ ID NO:4) wherein the valine at position 102 is substituted for tyrosine, histidine, isoleucine, serine, aspartic acid or glycine;

(i) a variant of CDRL1 (SEQ ID NO:5) wherein:

i. the serine at position 29 is substituted for a valine; and/or

ii. the methionine at position 33 is substituted for a leucine; and/or

(j) a variant of CDRL3 (SEQ ID NO:7) comprising one or more of the following substitutions:

i. the glutamine at position 89 is substituted for leucine;

ii. the glutamic acid at position 90 is substituted for glutamine;

iii. the tryptophan at position 91 is substituted for tyrosine; and/or

iv. the tyrosine at position 93 is substituted for serine or arginine.

In another ~~aspect~~embodiment, ~~the invention provides~~ there is provided an antigen binding protein comprising:

a heavy chain variable domain comprising:

(i) CDRH1 as set out in SEQ ID NO:2 or a variant CDR thereof

(ii) CDRH2 as set out in SEQ ID NO:3 or a variant CDR thereof

(iii) CDRH3 as set out in SEQ ID NO:4 or a variant CDR thereof, or a CDRH3 as set out in any of SEQ ID NO:132 – SEQ ID NO:137

in a heavy chain variable domain framework, which comprises at least one of:

(a) Val, Ile or Gly at position 2

(b) Leu or Val at position 4

(c) Leu, Ile, Met or Val at position 20

(d) Cys at position 22

(e) Thr, Ala, Val, Gly or Ser at position 24

(f) Gly at position 26

(g) Trp or Tyr at position 47

(h) Ile, Met, Val or Leu at position 48

(i) Ile, Leu, Phe, Met or Val at position 69

(j) Arg, Val, Ala or Leu at position 71

(k) Ala, Leu, Val, Tyr or Phe at position 78

(l) Leu or Met at position 80

(m) Tyr or Phe at position 90

(n) Cys at position 92

(o) Arg, Lys, Gly, Ser, His or Asn at position 94;

and a light chain variable domain comprising:

(iv) CDRL1 as set out in SEQ ID NO:5 or a variant CDR thereof

(v) CDRL2 as set out in SEQ ID NO:6 or a variant CDR thereof

(vi) CDRL3 as set out in SEQ ID NO:7 or a variant CDR thereof

in a light chain variable domain framework, which comprises at least one of:

(a) Ile at position 2

(b) Leu at position 4

(c) Cys at position 23

(d) Trp at position 35

(e) Tyr at position 36

(f) Tyr or Phe at position 71

(g) Cys at position 88

(h) Phe at position 98;

wherein the antigen binding protein is capable of binding to CD127.

The variant CDR of this ~~aspect of the invention~~embodiment may comprise:

(a) a variant of CDRH1 (SEQ ID NO:2), wherein:

i. the tyrosine residue at position 32 is substituted for isoleucine, histidine, phenylalanine, threonine, asparagine, cysteine, glutamic acid or aspartic acid;

ii. the threonine residue at position 33 is substituted for a tyrosine, alanine, tryptophan, glycine, leucine or valine,

iii. the methionine residue at position 34 is substituted for isoleucine, valine or tryptophan; and/or

iv. the asparagine residue at position 35 is substituted for histidine, glutamic acid, glutamine, serine, tyrosine or threonine;

(b) a variant of CDRH2 (SEQ ID NO:3) wherein:

i. the leucine residue at position 50 is substituted for arginine, glutamic acid, tryptophan, tyrosine, glycine, glutamine, valine, asparagine, lysine or alanine;

ii. the isoleucine residue at position 51 is substituted for leucine, valine, threonine, serine or asparagine;
iii. the asparagine residue at position 52 is substituted for asparagine, leucine, serine or tyrosine;
iv. the tyrosine residue at position 53 is substituted for alanine, glycine, serine, lysine, threonine or asparagine;
v. the asparagine at position 54 is substituted for serine, threonine, lysine, asparagine or glycine;
vi. the valine at position 56 is substituted for tyrosine, arginine, glutamic acid, aspartic acid, glycine, serine or alanine; and/or
vii. the serine at position 58 is substituted for lysine, asparagine, threonine, arginine, glycine, phenylalanine or tyrosine;

(c) a variant of CDRH3 (SEQ ID NO:4) wherein the valine at position 102 is substituted for tyrosine, histidine, isoleucine, serine, aspartic acid or glycine;

(d) a variant of CDRL1 (SEQ ID NO:5) wherein:
i. the serine at position 29 is substituted for a valine; and/or
ii. the methionine at position 33 is substituted for a leucine; and/or

(e) a variant of CDRL3 (SEQ ID NO:7) comprising one or more of the following substitutions:
i. the glutamine at position 89 is substituted for leucine;
ii. the glutamic acid at position 90 is substituted for glutamine;
iii. the tryptophan at position 91 is substituted for tyrosine; and/or
iv. the tyrosine at position 93 is substituted for serine or arginine.

In an embodiment, the antigen binding protein is an antibody, optionally a humanised or human antibody, or an antigen binding fragment thereof.

In another ~~aspect~~embodiment, ~~the invention provides~~there is provided an antibody which comprises a heavy chain variable region comprising one, two or three of the following complementarity determining regions:

(i) CDRH1 as set out in SEQ ID NO:39
(ii) CDRH2 as set out in SEQ ID NO:40
(iii) CDRH3 as set out in SEQ ID NO:41

wherein the antibody further comprises at least one of: a valine at position 24, a tyrosine at position 27, a serine at position 28, an isoleucine at position 29, a threonine at position

30, a methionine at position 48, a glycine at position 49, an isoleucine at position 67, an a serine at position 68, an arginine at position 71, a threonine at position 73 and a phenylalanine at position 78 of the heavy chain variable region (numbering according to Kabat).

In an embodiment, the antibody comprises at least one, two, three, four or all five of a tyrosine at position 27, a threonine at position 30, a methionine at position 48, an isoleucine at position 67 and an arginine at position 71.

The antibody may comprise a heavy chain variable region comprising CDRH1 (SEQ ID NO:39) and CDRH3 (SEQ ID NO:41); CDRH2 (SEQ ID NO:40) and CDRH3 (SEQ ID NO:41); CDRH1 (SEQ ID NO:39) and CDRH2 (SEQ ID NO:40); or CDRH1 (SEQ ID NO:39), CDRH2 (SEQ ID NO:40) and CDRH3 (SEQ ID NO:41). The antibody may comprise a heavy chain variable region of any of SEQ ID NOs:48-56 (6A3IGHV4_61.H1 V_H to 6A3IGHV4_61.H9) or SEQ ID NOs:58-68 (6A3IGHV3-33.H1 V_H to 6A3 IGHV3-33.H11).

The ~~invention~~ disclosure also provides an antibody which comprises a light chain variable region comprising one, two or three of the following complementarity determining regions:

(iv) CDRL1 as set out in SEQ ID NO:42

(v) CDRL2 as set out in SEQ ID NO:43

(vi) CDRL3 as set out in SEQ ID NO:44

wherein the antibody further comprises:

(a) one or both of a glutamine residue at position 45 and a lysine residue at position 70 of the variable region light chain, or

(b) one or more of a leucine at position 4, a tyrosine at position 31, a methionine at position 70, a threonine at position 85, a tyrosine at position 94, a glycine at position 100 and a valine at position 104 (numbering according to Kabat).

In an embodiment, the antibody comprises both a glutamine residue at position 45 and a lysine residue at position 70. In another embodiment, the antibody comprises each of a leucine at position 4, a tyrosine at position 31, a methionine at position 70, a threonine at position 85, a tyrosine at position 94, a glycine at position 100 and a valine at position 104.

The antibody may comprise a light chain variable region comprising CDRL1 (SEQ ID NO:42) and CDRL3 (SEQ ID NO:44); CDRL2 (SEQ ID NO:43) and CDRL3 (SEQ ID NO:44); or CDRL1 (SEQ ID NO:42) and CDRL2 (SEQ ID NO:43); or CDRL1 (SEQ ID NO:42), CDRL2 (SEQ ID NO:43) and CDRL3 (SEQ ID NO:44). The antibody may comprise a light chain variable region of any of SEQ ID NOs:70-72 and 138 (6A3.L1 Vκ, 6A3.L2 Vκ, 6A3.L3 Vκ and 6A3.L27 Vκ).

In another ~~aspect~~embodiment, the ~~invention provides~~there is provided an antibody which comprises a heavy chain variable region comprising one, two or three of the following complementarity determining regions:

(iv) CDRH1 as set out in SEQ ID NO:39

(v) CDRH2 as set out in SEQ ID NO:40

(vi) CDRH3 as set out in SEQ ID NO:41

wherein the antibody further comprises at least one of: a valine at position 24, a tyrosine at position 27, a serine at position 28, an isoleucine at position 29, a threonine at position 30, a methionine at position 48, a glycine at position 49, an isoleucine at position 67, an a serine at position 68, an arginine at position 71, a threonine at position 73 and a phenylalanine at position 78 of the heavy chain variable region, and

a light chain variable region comprising one, two or three of the following complementarity determining regions:

(i) CDRL1 as set out in SEQ ID NO:42

(ii) CDRL2 as set out in SEQ ID NO:43

(iii) CDRL3 as set out in SEQ ID NO:44

wherein the antibody further comprises:

(a) one or both of a glutamine residue at position 45 and a lysine residue at position 70 of the variable region light chain; or

(b) one or more of a leucine at position 4, a tyrosine at position 31, a methionine at position 70, a threonine at position 85, a tyrosine at position 94, a glycine at position 100 and a valine at position 104 (numbering according to Kabat).

The antibody may comprise any combination of CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3, including from one heavy chain and one light chain CDR, to all six of said CDRs.

In one embodiment, the antibody comprises: a heavy chain variable region comprising the following complementarity determining regions:

(i) CDRH1 as set out in SEQ ID NO:39

(ii) CDRH2 as set out in SEQ ID NO:40

(iii) CDRH3 as set out in SEQ ID NO:41

(iv) CDRL1 as set out in SEQ ID NO:42

(v) CDRL2 as set out in SEQ ID NO:43

(vi) CDRL3 as set out in SEQ ID NO:44

wherein the antibody further comprises at least one of:

(a) a valine at position 24, a tyrosine at position 27, a serine at position 28, an isoleucine at position 29, a threonine at position 30, a methionine at position 48, a glycine at position 49, an isoleucine at position 67, a serine at position 68, an arginine at position 71, a threonine at position 73 and a phenylalanine at position 78 of the heavy chain variable region; and/or

(b)

a. at least one of a glutamine residue at position 45 and a lysine residue at position 70 of the variable region light chain, or

b. one or more of a leucine at position 4, a tyrosine at position 31, a methionine at position 70, a threonine at position 85, a tyrosine at position 94, a glycine at position 100 and a valine at position 104 (numbering according to Kabat).

The ~~invention~~ disclosure contemplates any pairing of the described heavy and light variable domains. In an embodiment, therefore, the ~~invention~~ disclosure also provides an antigen binding protein comprising any one of the following heavy and light chain variable domain combinations: a heavy chain variable domain of SEQ ID NO:47 (or a sequence having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater identity thereto), with a light chain variable domain of any one of SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72 or SEQ ID NO:138 (or a sequence having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, or 99% or greater identity to any of SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72 or SEQ ID NO:138);

a heavy chain variable domain of SEQ ID NO:48 (or a sequence having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater identity thereto), with a light chain variable domain of any one of SEQ ID NO:69,

SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72 or SEQ ID NO:138 (or a sequence having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, or 99% or greater identity to any of SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72 or SEQ ID NO:138).

In a particular embodiment, there is provided an antigen binding protein comprising a heavy chain variable region having amino acid sequence as set out in a SEQ ID NO:53, 54 55 or 56, and a light chain variable region having an amino acid sequence as set out in SEQ ID NO:138.

The binding protein may be an antibody, in particular, a humanised or human antibody, or an antigen binding fragment thereof.

In another ~~aspect~~embodiment, the ~~invention provides~~there is provided a chimeric antibody, comprising a variable heavy chain domain of SEQ ID NO:28 and a variable light chain domain of SEQ ID NO:29, or a variable heavy chain domain of SEQ ID NO:73 and a variable light chain domain of SEQ ID NO:74.

The antigen binding protein of the ~~invention~~ disclosure may not inhibit TSLP signalling. In an embodiment, the antigen binding protein does not inhibit TSLP signalling.

The ~~invention~~ disclosure also provides a nucleic acid molecule encoding an antigen binding protein of the present ~~invention~~disclosure. In an embodiment, ~~the invention provides~~there is provided nucleic acid molecules of SEQ ID NO:30-38, SEQ ID NO:75-113, SEQ ID NO:119-120, and SEQ ID NOs:122, 124, 126, 128 and 130. The ~~invention~~ disclosure also provides an expression vector comprising a nucleic acid molecule as defined herein, and a recombinant host cell comprising an expression vector as defined herein. The expression vector may comprise a nucleic acid molecule of any one or more of SEQ ID NO:30-38, SEQ ID NO:75-113, and SEQ ID NO:119-120, and SEQ ID NOs:122, 124, 126, 128 and 130. In an embodiment, the expression vector comprises a nucleic acid molecule which encodes an antigen binding protein as hereinbefore described. In another embodiment, the ~~invention~~ disclosure provides a host cell comprising an expression vector as hereinbefore described. In a further embodiment, the ~~invention~~ disclosure provides an antibody expressed by host cell as hereinbefore described.

The ~~invention~~ disclosure also provides a method for the production of an antigen binding protein of the present ~~invention~~ disclosure which method comprises the step of culturing a host cell as defined above and recovering the antigen binding protein.

The ~~invention~~ disclosure also provides an antibody or antigen binding protein according to the invention which is expressed by a host cell comprising a nucleic acid sequence or sequence encoding an antibody or antigen binding fragment according to the ~~invention~~disclosure.

The ~~invention~~ disclosure also provides a pharmaceutical composition comprising an antigen binding protein of the present ~~invention~~ disclosure and a pharmaceutically acceptable carrier or excipient.

The ~~invention~~ disclosure also provides a method of treating a subject afflicted with an autoimmune or inflammatory disease, which method comprises the step of administering to the subject an antigen binding protein of the present ~~invention~~disclosure.

The ~~invention~~ disclosure also provides a method of treating a subject afflicted with a disease in which pathogenic T_H17 cells are implicated, which method comprises the step of administering to the subject an antigen binding protein of the present ~~invention~~disclosure.

The ~~invention~~ disclosure also provides a method of treating a subject afflicted with a disease associated with upregulated expression of IL-17, which method comprises the step of administering to the subject an antigen binding protein of the present ~~invention~~disclosure.

In particular, the autoimmune or inflammatory disease, the disease in which pathogenic T_H17 cells are implicated, or the disease associated with up-regulated expression of IL17 may be multiple sclerosis (MS), SLE, rheumatoid arthritis, Behcet's disease or asthma. In an embodiment, the antigen binding protein of the ~~invention~~ disclosure will be useful in a method of treating multiple sclerosis. Other diseases which may be treated by the administration of the antigen binding proteins of the ~~invention~~ disclosure are described herein.

The ~~invention~~ disclosure also provides an antigen binding protein as described herein for use in the treatment of a subject afflicted with an autoimmune or inflammatory disease; a disease in which pathogenic T_H17 cells are implicated; or a disease associated with up-regulated expression of IL17.

The ~~invention~~ disclosure provides the use of an antigen binding protein as described herein in the manufacture of a medicament for use in the treatment of a subject afflicted with an autoimmune or inflammatory disease; a disease in which pathogenic T_H17 cells are implicated; or a disease associated with up-regulated expression of IL17.

According to one aspect, there is provided an isolated antigen-binding protein comprising a heavy chain variable region with a sequence selected from the group consisting of SEQ ID NO: 11, 12, 13, 14, 15, 16, 17, 121, 123, 125, 127, 129 and 131 and a light chain variable region comprising the following complementarity determining regions:

(i) CDRL1 as set out in SEQ ID NO:5,

(ii) CDRL2 as set out in SEQ ID NO:6, and

(iv) CDRL3 as set out in SEQ ID NO:7.

According to another aspect, there is provided an isolated antigen-binding protein comprising the following complementarity determining regions:

(i) CDRH1 as set out in SEQ ID NO:2,

(ii) CDRH2 as set out in SEQ ID NO:3,

(iii) CDRH3 as set out in SEQ ID NO:132-137,

(iv) CDRL1 as set out in SEQ ID NO:5,

(v) CDRL2 as set out in SEQ ID NO:6, and

(vi) CDRL3 as set out in SEQ ID NO:7.

According to another aspect, there is provided an isolated nucleic acid molecule encoding an isolated antigen-binding protein as discussed herein.

According to another aspect, there is provided an expression vector comprising a nucleic acid molecule as discussed herein.

According to another aspect, there is provided an isolated host cell comprising an expression vector as discussed herein.

According to another aspect, there is provided an isolated antigen-binding protein expressed by a host cell as discussed herein.

According to another aspect, there is provided a method for the production of an isolated antigen-binding protein, comprising the step of culturing a host cell as discussed herein in a

medium to produce the isolated antigen-binding protein, and isolating or purifying the isolated antigen-binding protein therefrom.

According to another aspect, there is provided a pharmaceutical composition comprising an isolated antigen-binding protein as discussed herein and a pharmaceutically acceptable carrier or excipient.

Other aspects and embodiments of the ~~invention~~ disclosure will be apparent from the detailed description that follows.

Brief description of the drawings

Figure 1 shows the complement dependent cytotoxicity of the anti-IL7R mAb 1A11 H3L4 on HEK293 cells expressing hIL-7R.
Figure 2 shows the antibody dependent cell-mediated cytotoxicity of the humanised anti-IL7R mAb 1A11 H3L4 and the Fc-disabled anti-IL7R mAb (1A11 H3L4Fc) on HEK293 cells expressing hIL-7R, in the presence of peripheral blood mononuclear cells.
Figures 3A and 3B show the inhibition of IL-7-induced STAT5 phosphorylation by 1A11 H3L4 in human PBMC provided by two separate donors.
Figures 4A to 4D show the inhibition of IL-7-induced IL-17 production in differentiated human Th17 cells by 1A11 H3L4 (in four different donors).
Figures 5A to 5E show that 1A11 H3L4 does not affect TSLP-induction of TARC (thymus and activation-regulated chemokine).

Detailed description

IL-7/IL-7R signalling is critically required for survival and expansion of committed T_H17 cells in both mouse and human systems, while its role in T_H17 differentiation is not essential compared to that of IL-6 (Liu *et al*, (2010) Nature Medicine 16:191-197). Surprisingly, the *in vivo* effect on the immune system by IL-7R antagonism is highly selective in EAE, an animal model for multiple sclerosis, affecting T_H17 cells and, to a lesser extent, T_H1 cells predominantly of the memory phenotype, and sparing T_{reg} cells. This selectivity appears to play an important role in rebalancing the ratio of pathogenic T_H17 cells and T_{reg} cells by IL-7R antagonism in EAE and is attributable to the treatment efficacy.