POLYPEPTIDES

FIELD OF THE INVENTION

The present invention relates to polypeptides which bind to Lysophosphatidic Acid Receptor 1 ('LPAR1') as well as to constructs and compositions comprising these polypeptides. The present invention also relates to nucleic acids encoding such polypeptides, to methods for preparing such polypeptides, to vectors comprising nucleic acids encoding such polypeptides, to host cells expressing or capable of expressing such polypeptides and to uses of such polypeptides, compositions or constructs.

BACKGROUND OF THE INVENTION

LPAR1 is involved in several biological axes important in diseases such as inflammatory and/or fibrotic diseases. The previously leading small molecule drug to LPAR1 (BMS-986020) failed in Phase II clinical trials due to poor drug selectivity. There is therefore a need for new LPAR1 inhibitors.

SUMMARY OF THE INVENTION

According to a first aspect of the invention, there is provided a polypeptide which binds to Lysophosphatidic Acid Receptor 1 (LPAR1 or LPA1). Suitably, the polypeptide is an antibody or fragment thereof and more suitably the polypeptide binds to functionally active LPAR1 on the surface of a live cell.

This is a significant advancement to the field. To the author's knowledge, no polypeptide which binds to functionally active LPAR1 on the surface of a live cell, and in particular no inhibitor polypeptide which binds to functionally active LPAR1 on the surface of a live cell, has been disclosed in the art. Surprisingly, the present inventors have been able to produce such polypeptides.

Also provided is a polypeptide (such as an antibody or fragment thereof) which binds to LPAR1 wherein the polypeptide comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 wherein HCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 1, 7 or 107, HCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 2, 8 to 11, 100 or 108, HCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 3, 12 to 15, 101 or 109, LCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 4, 16 to 18, 103 or 110, LCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 5, 19, 98 or 111 and LCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 6, 20 to 22 or 112.

Also provided is a polypeptide (such as an antibody or fragment thereof) which binds to LPAR1 comprising a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 wherein HCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 1, HCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 2, HCDR3

comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 3, LCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 4, LCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 5 and LCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 6.

Also provided is a polypeptide (such as an antibody or fragment thereof) which binds to LPAR1 comprising a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 wherein HCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 1, HCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 2, HCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 15, LCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 4, LCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 5 and LCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 6.

Also provided is a polypeptide (such as an antibody or fragment thereof) which binds to LPAR1 comprising a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 wherein HCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 1, HCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 2, HCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 3, LCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 4, LCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 98 and LCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 6.

Also provided is a polypeptide (such as an antibody or fragment thereof) which binds to LPAR1 comprising a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 wherein HCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 1, HCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 100, HCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 101, LCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 4, LCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 98 and LCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 6.

Also provided is a polypeptide (such as an antibody or fragment thereof) which binds to LPAR1 comprising a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 wherein HCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 1, HCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 100, HCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 101, LCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 103, LCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 98 and LCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 6.

Also provided is a polypeptide (such as an antibody or fragment thereof) which binds to LPAR1 comprising a VH region comprising or consisting of a sequence having at least 80% identity

with SEQ ID NO: 36, 37 or SEQ ID NO: 102 and a VL region comprising or consisting of a sequence having at least 80% identity with SEQ ID NO: 38, 99 or 104.

Also provided is a polypeptide (such as an antibody) which binds to LPAR1 which comprises or consists of a heavy chain comprising or consisting of SEQ ID NO: 58, SEQ ID NO: 60 or SEQ ID NO: 1220, and a light chain comprising or consisting of SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 1219 or SEQ ID NO: 1221.

Also provided is a construct comprising the polypeptide of the invention.

Also provided is composition comprising the polypeptide or construct of the invention.

Also provided is a pharmaceutical composition comprising the polypeptide or construct of the invention, together with a pharmaceutically acceptable diluent or carrier.

Also provided is the polypeptide, construct or composition of the invention for use as a medicament.

Also provided is the polypeptide, construct or composition of the invention for use in the treatment of an inflammatory disease and/or fibrotic disease.

Also provided is the polypeptide, construct or composition of the invention for use in the treatment of a disease selected from the list consisting of chronic kidney disease, kidney fibrosis, peritoneal fibrosis, liver fibrosis, pulmonary fibrosis, dermal fibrosis, systemic sclerosis and osteoarthritis.

Also provided is a polynucleotide encoding the polypeptide or construct of the invention.

Also provided is an expression vector comprising the polynucleotide sequence of the invention.

Also provided is a cell comprising the polynucleotide sequence or expression vector of the invention.

In certain embodiments, the polypeptides of the invention may be expected to benefit from one or more of the following advantages over the prior art:

(a) binding of functional LPAR1 on the surface of live cells
(b) allosteric inhibition of LPAR1
(c) inverse agonism of LPAR1
(d) reduction of Gi/o and/or G13 and/or Gq signalling by the LPAR1
(e) reduction or prevention of LPA-induced or constitutive cAMP signalling
(f) reduction or prevention of LPA-induced calcium mobilisation
(g) binding to novel epitopes
(h) reduced toxicity
(i) increased potency

(j) increased binding affinity
(k) increased half-life
(l) reduced dosing
(m) binding to the extracellular region of LPAR1

DESCRIPTION OF THE FIGURES

Figure 1 – Antibody 12 expression level compared to an Adalimumab biosimilar, ability to bind to huLPAR1-HA cells, ability to increase cAMP signalling, ability to inhibit calcium signalling and ability to decrease cell proliferation
Figure 2 – Antibody 13 expression level compared to an Adalimumab biosimilar, ability to increase cAMP signalling, ability to inhibit calcium signalling and ability to decrease cell proliferation
Figure 3 – Epitope prediction for Antibody 7bFigure 4 – Paratope prediction for Antibody 7b
Figure 5 – *In vitro* epitope analysis
Figure 6 – Epitope depiction on LPAR1
Figure 7 – Antibody 15 expression level compared to a Palivizumab biosimilar, ability to increase cAMP signalling, ability to decrease cell proliferation and ability to bind to huLPAR1-HA cells
Figure 8 – Antibody 16 expression level compared to a Palivizumab biosimilar, ability to increase cAMP signalling and ability to decrease cell proliferation
Figure 9 – Antibody 17 expression level compared to a Palivizumab biosimilar, ability to increase cAMP signalling, ability to decrease cell proliferation and ability to bind to huLPAR1-HA cells
Figure 10 – Antibody 18 expression level compared to a Palivizumab biosimilar, ability to increase cAMP signalling, ability to decrease cell proliferation and ability to bind to huLPAR1-HA cells
Figure 11 – CIFAT assay microscopy imaging results for antibodies of the invention and the prior art (5 ug/ml concentration with live cells)
Figure 12 – CIFAT assay microscopy imaging results for antibodies of the invention and the prior art (20 ug/ml concentration with live cells)
Figure 13 – BRET investigation of Antibody 12 compared to small molecule inhibitor of the prior art
Figure 14 – Ability of Antibodies 12, 15, 17 and 18 to bind to human, guinea-pig, rabbit and mouse LPAR1
Figure 15 – Ability of Antibodies 12, 15, 17 and 18 to bind to human LPAR1, LPAR2 and LPAR3
Figure 16 – Pharmacokinetics of Antibodies 12, 15, 17 and 18 in rats
Figure 17 – SEC-MALS of Antibodies 12, 13, 15, 16, 17 and 18
Figure 18 – Unilateral ureteral obstruction efficacy analysis in guinea pigs using Antibody 13 and Antibody 17

DESCRIPTION OF THE SEQUENCES

SEQ ID NO:	Polypeptide Sequence of
1	12 HCDR1
2	12 HCDR2
3	12 HCDR3
4	12 LCDR1
5	12 LCDR2
6	12 LCDR3
7	02 HCDR1
8	01 HCDR2
9	02 HCDR2
10	04 HCDR2
11	07 HCDR2
12	01 HCDR3
13	02 HCDR3
14	04 HCDR3
15	11 HCDR3
16	01 LCDR1
17	02 LCDR1
18	04 LCDR1
19	01 LCDR2
20	01 LCDR3
21	02 LCDR3
22	05 LCDR3
23	1 VH
24	1 VL
25	2 VH
26	2 VL
27	3 VH
28	3 VL
29	4 VH
30	4 VL
31	5 VL
32	6 VL
33	7 VH
34	7 VL
35	9 VH
36	12 VH
37	11 VH
38	12 VL
39	11 VL
40	12 HFR1
41	12 HFR2
42	12 HFR3
43	12 HFR4
44	12 LFR1
45	12 LFR2
46	12 LFR3
47	12 LFR4
48	11 HFR1
49	11 HFR2
50	11 HFR3
51	11 HFR4
52	11 LFR1
53	11 LFR2
54	11 LFR3
55	11 LFR4
56	12 heavy chain constant region (LALA PS)
57	12 light chain constant region
58	12 heavy chain
59	12 light chain
60	11 heavy chain
61	11 light chain
62	full length LPAR1
63	an isoform of full length LPAR1
64	modified LPAR1
65	epitope region 1
66	epitope region 2
67	epitope region 3
68	epitope region 4
69	linker
70	VH formula 1
71	VL formula 1
72	HCDR1 formula 1
73	HCDR1 formula 2
74	HCDR1 formula 3
75	HCDR1 formula 4
76	HCDR2 formula 1
77	HCDR2 formula 2
78	HCDR2 formula 3
79	HCDR2 formula 4
80	HCDR3 formula 1
81	HCDR3 formula 2
82	HCDR3 formula 3
83	HCDR3 formula 4
84	LCDR1 formula 1
85	LCDR1 formula 2
86	LCDR1 formula 3
87	LCDR1 formula 4
88	LCDR2 formula 1
89	LCDR2 formula 2
90	LCDR2 formula 3
91	LCDR2 formula 4
92	LCDR3 formula 1
93	LCDR3 formula 2
94	LCDR3 formula 3
95	LCDR3 formula 4
96	14 VH
97	14 VL
98	15 LCDR2
99	15 VL
100	17 HCDR2

SEQ ID NO:	Polypeptide Sequence of
101	17 HCDR3
102	17 VH
103	18 LCDR1
104	18 VL
105	169A1 VH
106	169A1 VL
107	63D8 HCDR1
108	63D8 HCDR2
109	63D8 HCDR3
110	63D8 LCDR1
111	63D8 LCDR2
112	63D8 LCDR3
113	63D8 VH
114	63D8 VL
115	Tgex 207B7 Hu-VL3-germ-IGKV1-33*01
116	HuVL4_H90S93_Y87F
117	HuVL3_H90S93_S1D
118	HuVL4_H90S93_L54R
119	63D8_HuVL2_v2
120	63D8_HuVL1_v2
121	63D8_HuVL4_v2
122	63D8_HuVL3_v2
123	TGEX-LC Human Kappa 63D8
124	TGEX-HC Human IgG1 repurified 63D8
125	Tgex 63D8_HuVH3-sil
126	Tgex 63D8_HuVH1-sil
127	Tgex 63D8_HuVH2-sil
128	Hu-VL3_Q1G55H90S93
129	Tgex 63D8_HuVH4-sil (LALA_P331S)
130	TGEX-HC Human IgG1 207B7 (LPAR1)

SEQ ID NO:	Polypeptide Sequence of
131	TGEX-HC Human IgG1 207B7 germline 207B7169A1 CDRs
132	TGEX-HC Human IgG1 207B7 germline 207B7 CDRs
133	TGEX-HC Human IgG1 169A1
134	TGEX-HC Human IgG1 207B7 169A1 LCA
135	TGEX-HC Human IgG1 207B7 germline 169A1 CDRs
136	TGEX-HC Human IgG1 207B7 germline LCA CDRs
137	TGEX-HC Human IgG1 207B7 germline
138	huVH4_D30Q61K97G99 Fab
139	Tgex 207B7 huVH4_E30K31Q61K97G99 IgG1
140	Tgex 207B7 huVH4_E30Q61A97A99 IgG1
141	Tgex huVH4_E30Q61K97G98G99 sil (LALA_P331S)
142	huVH4_E30Q61K97G99 Fab
143	Tgex huVH4_E30Q61R97G98G99 sil (LALA_P331S)
144	Tgex huVH4_E30Q61-CDRH3-43 sil (LALA_P331S)
145	huVH4_G30Q61K97G99 Fab
146	huVH4_K30Q61K97G99 Fab
147	huVH4_N30Q61K97G99 Fab
148	huVH4_R30Q61K97G99 Fab
149	Tgex 207B7 huVH4_S30K60Q61A97A99 IgG1
150	Tgex 207B7 huVH4_S30K60Q61K97G99 IgG1

SEQ ID NO:	Polypeptide Sequence of
151	Tgex 207B7 huVH4_S30K60Q61K62E64A97A99 IgG1
152	Tgex 207B7 huVH4_S30K60Q61K62E64K97G99 IgG1
153	Tgex 207B7 huVH4_S30Q61A97A99 IgG1
154	huVH4_S30Q61K97G99 Fab
155	Tgex 207B7 huVH4_S30Q61K62E64A97A99 IgG1
156	Tgex 207B7 huVH4_S30Q61K62E64K97G99 IgG1
157	Tgex 207B7 huVH4_S30Q61K62A97A99 IgG1
158	Tgex 207B7 huVH4_S30Q61K62K97G99 IgG1
159	HuVH4-QRGG_A31
160	Tgex 207B7 huVH4_K31Q61A97A99 IgG1
161	Tgex 207B7 huVH4_K31Q61K97G99 IgG1
162	huVH4_R31D52Q61K97G99 IgG
163	huVH4_R31D53Q61K97G99 IgG
164	huVH4_R31D54Q61K97G99 IgG
165	huVH4_R31D56Q61K97G99 IgG
166	huVH4_R31E56Q61K97G99 IgG
167	huVH4_R31D58Q61K97G99 IgG
168	huVH4_R31E58Q61K97G99 IgG
169	huVH4_R31Q61A62K97G99 IgG
170	huVH4_R31Q61K97G99 IgG
171	huVH4_R31T32Q61K97G99 IgG

SEQ ID NO:	Polypeptide Sequence of
172	HuVH4-QRGG_A32
173	huVH4_H32Q35Q61A62K97G99 IgG
174	huVH4_H32Q35Q61K97G99 IgG
175	huVH4_H32Q61A62K97G99 IgG
176	huVH4_H32Q61K97G99 IgG
177	huVH4_R32Q61A62K97G99 IgG
178	huVH4_R32Q61K97G99 IgG
179	HuVH4-QRGG_A33N35
180	HuVH4-QRGG_A33
181	HuVH4-QRGG_A33M34N35
182	huVH4-QRGG_A35
183	huVH4_E35Q61K97G99 IgG
184	HuVH4-QRGG_N35
185	huVH4_Q35Q61K97G99 IgG
186	huVH3_E61G97G99G104
187	huVH3_E61R97G99G104
188	huVH3_E61R97S99G104
189	huVH4-QRGG_I48S75
190	huVH4-QRGG_I48F91
191	huVH4-QRGG_I48
192	huVH3_Q61G97G99G104
193	huVH3_Q61G97S99G104
194	huVH3_Q61R97G99G104
195	huVH3_Q61R97S99G104
196	huVH4-QRGG_I48L69
197	huVH4_D52Q61R97G99 Fab
198	huVH4_G52Q61R97G99 Fab
199	Tgex 207B7 huVH4_A52aQ61A97A99 IgG1
200	Tgex 207B7 huVH4_D52aQ61A97A99 IgG1
201	Tgex 207B7 huVH4_F52aQ61A97A99 IgG1

SEQ ID NO:	Polypeptide Sequence of
202	Tgex 207B7 huVH4_G52aQ61A97A99 IgG1
203	Tgex 207B7 huVH4_N52aQ61A97A99 IgG1
204	Tgex 207B7 huVH4_A53Q61A97A99 IgG1
205	Tgex 207B7 huVH4_D53Q61A97A99 IgG1
206	huVH4_D53Q61R97G99 Fab
207	Tgex 207B7 huVH4_E53Q61A97A99 IgG1
208	Tgex 207B7 huVH4_G53Q61A97A99 IgG1
209	Tgex 207B7 huVH4_H53Q61A97A99 IgG1
210	Tgex 207B7 huVH4_I53Q61A97A99 IgG1
211	Tgex 207B7 huVH4_K53Q61A97A99 IgG1
212	huVH4_K53Q61R97G99 Fab
213	Tgex 207B7 huVH4_L53Q61A97A99 IgG1
214	Tgex 207B7 huVH4_N53Q61A97A99 IgG1
215	Tgex 207B7 huVH4_Q53Q61A97A99 IgG1
216	huVH4_Q53Q61R97G99 Fab
217	huVH4_D54Q61R97G99 Fab
218	Tgex 207B7 huVH4_A55Q61A97A99 IgG1
219	Tgex 207B7 huVH4_D55Q61A97A99 IgG1
220	Tgex huVH4_D55Q61K97G98G99 sil (LALA_P331S)

SEQ ID NO:	Polypeptide Sequence of
221	Tgex huVH4_D55Q61R97G98G99 sil (LALA_P331S)
222	huVH4_D55Q61R97G99 Fab
223	Tgex huVH4_D55Q61_CDRH3-43 sil (LALA_P331S)
224	Tgex 207B7 huVH4_E55Q61A97A99 IgG1
225	Tgex huVH4_E55Q61_CDRH3-43 sil (LALA_P331S)
226	huVH4_D56Q61R97G99 Fab
227	huVH4_E56Q61R97G99 Fab
228	Tgex 207B7 huVH4_N56Q61A97A99 IgG1
229	Tgex 207B7 huVH4_P57Q61A97A99 IgG1
230	huVH4_D58Q61R97G99 Fab
231	huVH4_E58Q61R97G99 Fab
232	Tgex 207B7 huVH4_H58Q61-CDRH3-4-1- sil (LALA_P331S)
233	Tgex 207B7 huVH4_H58Q61-CDRH3-4-5- sil (LALA_P331S)
234	Tgex 207B7 huVH4_H58Q61Q99ins-sil (LALA_P331S)
235	Tgex 207B7 huVH4_H58Q61K97G98G99- sil (LALA_P331S)
236	Tgex 207B7 huVH4_H58Q61K97ins-sil (LALA_P331S)
237	Tgex 207B7 huVH4_H58Q61K97insQ98ins- sil (LALA_P331S)
238	Tgex 207B7 huVH4_H58Q61Q97ins-sil (LALA_P331S)

SEQ ID NO:	Polypeptide Sequence of
239	Tgex 207B7 huVH4_H58Q61Q97insK98ins- sil (LALA_P331S)
240	Tgex 207B7 huVH4_H58Q61R97ins- sil (LALA_P331S)
241	Tgex 207B7 huVH4_H58Q61-CDRH3-4-18- sil (LALA_P331S)
242	Tgex 207B7 huVH4_H58Q61-CDRH3-4-20- sil (LALA_P331S)
243	Tgex 207B7 huVH4_H58Q61-CDRH3-4-21- sil (LALA_P331S)
244	Tgex 207B7 huVH4_H58Q61-CDRH3-4-24- sil (LALA_P331S)
245	Tgex 207B7 huVH4_H58Q61-CDRH3-4-26- sil (LALA_P331S)
246	Tgex 207B7 huVH4_H58Q61CDRH3-7-30- sil (LALA_P331S)
247	Tgex 207B7 huVH4_H58Q61CDRH3-7-39- sil (LALA_P331S)
248	Tgex 207B7 huVH4_H58Q61-CDRH3-4-40- sil (LALA_P331S)
249	Tgex 207B7 huVH4_H58Q61CDRH3-7-41- sil (LALA_P331S)
250	Tgex 207B7 huVH4_H58Q61-CDRH3-4-46- sil (LALA_P331S)
251	Tgex 207B7 huVH4_H58Q61-CDRH3-4-60- sil (LALA_P331S)
252	Tgex 207B7 huVH4_H58Q61CDRH3-7-63- sil (LALA_P331S)
253	Tgex 207B7 huVH4_H58Q61CDRH3-7-64- sil (LALA_P331S)
254	Tgex 207B7 huVH4_H58Q61-CDRH3-4-76- sil (LALA_P331S)
255	Tgex 207B7 huVH4_H58Q61KPA99T- sil (LALA_P331S)
256	Tgex 207B7 huVH4_H58Q61-CDRH3-43- sil (LALA_P331S)
257	Tgex 207B7 huVH4_H58Q61-CDRH3-4-80- sil (LALA_P331S)
258	Tgex 207B7 huVH4_H58Q61CDRH3-7-82- sil (LALA_P331S)
259	Tgex 207B7 huVH4_H58Q61-CDRH3-4-84- sil (LALA_P331S)
260	Tgex 207B7 huVH4_H58Q61-CDRH3-4-90- sil (LALA_P331S)
261	Tgex 207B7 huVH4_H58Q61-CDRH3-4-92- sil (LALA_P331S)
262	Tgex 207B7 huVH4_H58Q61-CDRH3-4-96- sil (LALA_P331S)
263	Tgex 207B7 huVH4_K60Q61A97A99 IgG1
264	Tgex 207B7 huVH4_K60Q61K97G99 IgG1
265	Tgex 207B7 huVH4_K60Q61K62A97A99 IgG1
266	Tgex 207B7 huVH4_K60Q61K62K97G99 IgG1
267	huVH4_A61A97A99G104
268	huVH4_A61A97A99S104
269	huVH4_A61A97G99G104
270	huVH4_A61A97S99G104
271	huVH4_A61A97S99S104
272	huVH4_A61G97A99G104
273	huVH4_A61G97A99S104
274	huVH4_A61G97G99G104
275	huVH4_A61G97G99S104
276	huVH4_A61G97S99G104
277	huVH4_A61G97S99S104
278	huVH4_A61R97A99G104
279	huVH4_A61R97A99S104
280	huVH4_A61R97G99G104
281	huVH4_A61R97G99S104
282	207B7-HuVH4_D61
283	huVH4_E61A97A99G104
284	huVH4_E61A97A99S104
285	huVH4_E61A97S99G104
286	huVH4_E61A97S99S104
287	207B7-HuVH4_D97
288	207B7-HuVH4_E97
289	207B7-HuVH4_F97
290	huVH4_E61G97A99G104
291	huVH4_E61G97A99S104
292	207B7-HuVH4_D99
293	207B7-HuVH4_E99
294	207B7-HuVH4_F99
295	207B7-HuVH4_G99
296	207B7-HuVH4_H99
297	207B7-HuVH4_I99
298	207B7-HuVH4_K99
299	207B7-HuVH4_L99
300	207B7-HuVH4_M99
301	207B7-HuVH4_N99
302	207B7-HuVH4_P99
303	207B7-HuVH4_Q99
304	207B7-HuVH4_R99

SEQ ID NO:	Polypeptide Sequence of
305	huVH4_E61G97S99G104
306	huVH4_E61G97S99S104
307	207B7-HuVH4_T99
308	207B7-HuVH4_V99
309	207B7-HuVH4_W99
310	207B7-HuVH4_Y99
311	207B7-HuVH4_H97
312	207B7-HuVH4_I97
313	207B7-HuVH4_K97
314	207B7-HuVH4_L97
315	207B7-HuVH4_M97
316	207B7-HuVH4_N97
317	207B7-HuVH4_P97
318	207B7-HuVH4_Q97
319	huVH4_E61R97G99G104
320	207B7-HuVH4_R97
321	207B7-HuVH4_S97
322	207B7-HuVH4_T97
323	207B7-HuVH4_V97
324	207B7-HuVH4_W97
325	207B7-HuVH4_Y97
326	207B7-HuVH4_F61
327	huVH4_G61A97A99G104
328	huVH4_G61A97A99S104
329	huVH4_G61A97S99G104
330	huVH4_G61A97S99S104
331	huVH4_G61G97A99G104
332	huVH4_G61G97A99S104
333	huVH4_G61G97G99G104
334	huVH4_G61G97S99G104
335	huVH4_G61G97S99S104
336	huVH4_G61R97A99G104
337	huVH4_G61R97G99G104
338	207B7-HuVH4_H61

SEQ ID NO:	Polypeptide Sequence of
339	207B7-HuVH4_I61
340	207B7-HuVH4_K61
341	207B7-HuVH4_L61
342	207B7-HuVH4_M61
343	207B7-HuVH4_N61
344	207B7-HuVH4_P61
345	huVH4_Q61A62K97G99 IgG
346	huVH4_Q61E62K97G99 IgG
347	Tgex 207B7 huVH4_Q61E64A97A99 IgG1
348	Tgex huVH4_Q61E64K97G98G99 sil (LALA_P331S)
349	Tgex 207B7 huVH4_Q61E64K97G99 IgG1
350	Tgex huVH4_Q61E64R97G98G99 sil (LALA_P331S)
351	huVH4_Q61E64R97G99 Fab
352	Tgex huVH4_Q61E64_CDRH3-43 sil (LALA_P331S)
353	Tgex 207B7 huVH4_Q61K64A97A99 IgG1
354	Tgex 207B7 huVH4_Q61K64K97G99 IgG1
355	huVH4_Q61K64R97G99 Fab
356	huVH4_Q61M64R97G99 Fab
357	Tgex 207B7 huVH4_Q61Q64A97A99 IgG1
358	Tgex 207B7 huVH4_Q61Q64K97G99 IgG1
359	huVH4_Q61Q64R97G99 Fab
360	huVH4_Q61R64R97G99 Fab
361	huVH4-QRGG_S75F91
362	Tgex huVH4_Q61S75K97G98G99 sil (LALA_P331S)

SEQ ID NO:	Polypeptide Sequence of
363	Tgex huVH4_Q61S75R97G98G99 sil (LALA_P331S)
364	huVH4-QRGG_S75
365	Tgex huVH4_Q61S75_CDRH3-43_Fab
366	huVH4-QRGG_F91
367	Tgex 207B7 huVH4_Q61-CDRH3-4-1- sil (LALA_P331S)
368	Tgex 207B7 huVH4_Q61A97A99L100c IgG1
369	huVH4_Q61A97A99G104
370	Tgex 207B7 huVH4_Q61A99A97D100b IgG1
371	Tgex 207B7 huVH4_Q61A99A97E100b IgG1
372	Tgex 207B7 huVH4_Q61A97A99S100b IgG1
373	Tgex 207B7 huVH4_Q61A97A99T100b IgG1
374	huVH4_Q61A97G99G104
375	Tgex 207B7 huVH4_Q61-CDRH3-4-5- sil (LALA_P331S)
376	huVH4_Q61G97A99G104
377	huVH4_Q61G97A99S104
378	huVH4_Q61G97G99G104
379	huVH4_Q61G97G99S104
380	Tgex 207B7 huVH4_Q61Q99ins- sil (LALA_P331S)
381	207B7-HuVH4_Q61
382	Tgex 207B7 huVH4_Q61_CDRH3-10 IgG1
383	Tgex huVH4_Q61K97G98A99 sil (LALA_P331S)

SEQ ID NO:	Polypeptide Sequence of
384	Tgex 207B7 huVH4_Q61K97G98G99 IgG1
385	Tgex huVH4_Q61K97G98G99S100b sil (LALA_P331S)
386	Tgex 207B7 huVH4_Q61K97ins- sil (LALA_P331S)
387	Tgex 207B7 huVH4_Q61K97insQ98ins- sil (LALA_P331S)
388	Tgex 207B7 huVH4_Q61K97G99L100c IgG1
389	huVH4_Q61K97G99 Fab
390	Tgex 207B7 huVH4_Q61K97G99D100b IgG1
391	Tgex 207B7 huVH4_Q61K97G99E100b IgG1
392	Tgex 207B7 huVH4_Q61K97G99S100b IgG1
393	Tgex 207B7 huVH4_Q61K97G99T100b IgG1
394	huVH4_Q61P97 Fab
395	Tgex 207B7 huVH4_Q61Q97ins- sil (LALA_P331S)
396	Tgex 207B7 huVH4_Q61Q97insK98ins- sil (LALA_P331S)
397	huVH4_Q61Q97G99 Fab
398	huVH4_Q61Q97 Fab
399	207B7-HuVH4_A98
400	207B7-HuVH4_D98
401	207B7-HuVH4_E98
402	207B7-HuVH4_F98
403	Tgex huVH4_Q61R97G98A99 sil (LALA_P331S)

SEQ ID NO:	Polypeptide Sequence of
404	Tgex huVH4_Q61R97G98G99 sil (LALA_P331S)
405	Tgex huVH4_Q61R97G98G99S100b sil (LALA_P331S)
406	Tgex 207B7 huVH4_Q61R97ins- sil (LALA_P331S)
407	207B7-HuVH4_H98
408	207B7-HuVH4_I98
409	207B7-HuVH4_K98
410	207B7-HuVH4_L98
411	207B7-HuVH4_M98
412	207B7-HuVH4_N98
413	207B7-HuVH4_P98
414	207B7-HuVH4_Q98
415	207B7-HuVH4_QRGG-R98
416	huVH4_Q61R97A99G104
417	huVH4_Q61R97A99S104
418	huVH4_Q61R97G99G104
419	huVH4_Q61R97G99S104
420	huVH4_Q61R97S99G104
421	207B7-HuVH4_T98
422	207B7-HuVH4_V98
423	207B7-HuVH4_W98
424	207B7-HuVH4_Y98
425	Tgex 207B7 huVH4_Q61_CDRH3-22 IgG1
426	Tgex 207B7 huVH4_Q61-CDRH3-4-18- sil (LALA_P331S)
427	Tgex 207B7 huVH4_Q61-CDRH3-4-20- sil (LALA_P331S)
428	Tgex 207B7 huVH4_Q61-CDRH3-4-21- sil (LALA_P331S)
429	Tgex 207B7 huVH4_Q61-CDRH3-4-24- sil (LALA_P331S)

SEQ ID NO:	Polypeptide Sequence of
430	Tgex 207B7 huVH4_Q61-CDRH3-4-26- sil (LALA_P331S)
431	Tgex 207B7 huVH4_Q61CDRH3-7-30- sil (LALA_P331S)
432	Tgex 207B7 huVH4_Q61CDRH3-7-39- sil (LALA_P331S)
433	Tgex 207B7 huVH4_Q61-CDRH3-4-40- sil (LALA_P331S)
434	Tgex 207B7 huVH4_Q61CDRH3-7-41- sil (LALA_P331S)
435	Tgex 207B7 huVH4_Q61-CDRH3-4-46- sil (LALA_P331S)
436	Tgex 207B7 huVH4_Q61-CDRH3-4-60- sil (LALA_P331S)
437	Tgex 207B7 huVH4_Q61_CDRH3-38 IgG1
438	Tgex 207B7 huVH4_Q61_CDRH3-39 IgG1
439	Tgex 207B7 huVH4_Q61CDRH3-7-63- sil (LALA_P331S)
440	Tgex 207B7 huVH4_Q61CDRH3-7-64- sil (LALA_P331S)
441	Tgex 207B7 huVH4_Q61-CDRH3-4-76- sil (LALA_P331S)
442	Tgex huVH4_Q61K96A97P98T100b sil (LALA_P331S)
443	Tgex huVH4_Q61K96D97P98T100b sil (LALA_P331S)
444	Tgex huVH4_Q61K96G98T99 sil (LALA_P331S)
445	Tgex 207B7 huVH4_Q61_CDRH3-42 IgG1
446	Tgex huVH4_Q61K96P98A99T100b sil (LALA_P331S)

SEQ ID NO:	Polypeptide Sequence of
447	Tgex huVH4_Q61K96P98D99T100b sil (LALA_P331S)
448	Tgex huVH4_Q61K96P98G99T100b sil (LALA_P331S)
449	Tgex huVH4_Q61K96P98 sil (LALA_P331S)
450	Tgex huVH4_Q61K96P98D100b sil (LALA_P331S)
451	Tgex huVH4_Q61K96P98S100b sil (LALA_P331S)
452	Tgex 207B7 huVH4_Q61_CDRH3-43 lgG1
453	Tgex 207B7 huVH4_Q61-CDRH3-44 lgG1
454	Tgex 207B7 huVH4_Q61K96 lgG1
455	Tgex huVH4_Q61K96T100b sil (LALA_P331S)
456	Tgex huVH4_Q61_CDRH3-46 sil (LALA_P331S)
457	Tgex huVH4_Q61K96S97P98T100b sil (LALA_P331S)
458	Tgex 207B7 huVH4_Q61-CDRH3-4-80- sil (LALA_P331S)
459	Tgex 207B7 huVH4_Q61CDRH3-7-82- sil (LALA_P331S)
460	Tgex 207B7 huVH4_Q61-CDRH3-4-84- sil (LALA_P331S)
461	huVH4_Q61Q96 Fab
462	huVH4_Q61Q96P97A99 Fab
463	huVH4_Q61Q96P97G99 Fab
464	huVH4_Q61Q96P97 Fab
465	Tgex huVH4_Q61_CDRH3-58 sil (LALA_P331S)
466	Tgex HuVH4_Q61R96P98T100b sil (LALA_P331S)

SEQ ID NO:	Polypeptide Sequence of
467	Tgex huVH4_Q61R96L97 sil (LALA_P331S)
468	huVH4_Q61S96A97A99 Fab
469	huVH4_Q61S96G99 Fab
470	huVH4_Q61S96 Fab
471	Tgex 207B7 huVH4_Q61-CDRH3-4-90- sil (LALA_P331S)
472	Tgex 207B7 huVH4_Q61-CDRH3-4-92- sil (LALA_P331S)
473	Tgex 207B7 huVH4_Q61-CDRH3-4-96- sil (LALA_P331S)
474	Tgex huVH4_Q61T73K97G98G99 sil (LALA_P331S)
475	Tgex huVH4_Q61T73R97G98G99 sil (LALA_P331S)
476	Tgex huVH4_Q61T73_CDRH3-43 sil (LALA_P331S)
477	Tgex huVH4_Q61L71K97G98G99 sil (LALA_P331S)
478	Tgex huVH4_Q61L71R97G98G99 sil (LALA_P331S)
479	Tgex huVH4_Q61L71_CDRH3-43 sil (LALA_P331S)
480	huVH4-QRGG_L69S75
481	huVH4-QRGG_L69F91
482	huVH4-QRGG_L69
483	Tgex 207B7 huVH4_Q61K62E64A97A99 lgG1
484	Tgex 207B7 huVH4_Q61K62E64K97G99 lgG1
485	huVH4_Q61K62E64R97G99 Fab
486	Tgex 207B7 huVH4_Q61K62K64K97G99 lgG1
487	Tgex 207B7 huVH4_Q61K62Q64K97G99 lgG1

SEQ ID NO:	Polypeptide Sequence of
488	Tgex 207B7 huVH4_Q61K62A97A99 lgG1
489	huVH4_Q61K62K97G99 lgG
490	huVH4_Q61W62K97G99 lgG
491	207B7-HuVH4_R61
492	207B7-HuVH4_S61
493	207B7-HuVH4_T61
494	207B7-HuVH4_V61
495	207B7-HuVH4_W61
496	207B7-HuVH4_Y61
497	Tgex 207B7 huVH4_S58Q61-CDRH3-4-1- sil (LALA_P331S)
498	Tgex 207B7 huVH4_S58Q61-CDRH3-4-5- sil (LALA_P331S)
499	Tgex 207B7 huVH4_S58Q61Q99ins-sil (LALA_P331S)
500	Tgex 207B7 huVH4_S58Q61K97G98G99- sil (LALA_P331S)
501	Tgex 207B7 huVH4_S58Q61K97ins-sil (LALA_P331S)
502	Tgex 207B7 huVH4_S58Q61K97insQ98ins- sil (LALA_P331S)
503	Tgex 207B7 huVH4_S58Q61Q97ins-sil (LALA_P331S)
504	Tgex 207B7 huVH4_S58Q61Q97insK98ins- sil (LALA_P331S)
505	Tgex 207B7 huVH4_S58Q61R97ins-sil (LALA_P331S)
506	Tgex 207B7 huVH4_S58Q61-CDRH3-4-18- sil (LALA_P331S)
507	Tgex 207B7 huVH4_S58Q61-CDRH3-4-20- sil (LALA_P331S)

SEQ ID NO:	Polypeptide Sequence of
508	Tgex 207B7 huVH4_S58Q61-CDRH3-4-21- sil (LALA_P331S)
509	Tgex 207B7 huVH4_S58Q61-CDRH3-4-24- sil (LALA_P331S)
510	Tgex 207B7 huVH4_S58Q61-CDRH3-4-26- sil (LALA_P331S)
511	Tgex 207B7 huVH4_S58Q61CDRH3-7-30- sil (LALA_P331S)
512	Tgex 207B7 huVH4_S58Q61CDRH3-7-39- sil (LALA_P331S)
513	Tgex 207B7 huVH4_S58Q61-CDRH3-4-40- sil (LALA_P331S)
514	Tgex 207B7 huVH4_S58Q61CDRH3-7-41- sil (LALA_P331S)
515	Tgex 207B7 huVH4_S58Q61-CDRH3-4-46- sil (LALA_P331S)
516	Tgex 207B7 huVH4_S58Q61-CDRH3-4-60- sil (LALA_P331S)
517	Tgex 207B7 huVH4_S58Q61CDRH3-7-63- sil (LALA_P331S)
518	Tgex 207B7 huVH4_S58Q61CDRH3-7-64- sil (LALA_P331S)
519	Tgex 207B7 huVH4_S58Q61-CDRH3-4-76- sil (LALA_P331S)
520	Tgex 207B7 huVH4_S58Q61KPA99T- sil (LALA_P331S)
521	Tgex 207B7 huVH4_S58Q61-CDRH3-43- sil (LALA_P331S)

SEQ ID NO:	Polypeptide Sequence of
522	Tgex 207B7 huVH4_S58Q61-CDRH3-4-80- sil (LALA_P331S)
523	Tgex 207B7 huVH4_S58Q61CDRH3-7-82- sil (LALA_P331S)
524	Tgex 207B7 huVH4_S58Q61-CDRH3-4-84- sil (LALA_P331S)
525	Tgex 207B7 huVH4_S58Q61-CDRH3-4-90- sil (LALA_P331S)
526	Tgex 207B7 huVH4_S58Q61-CDRH3-4-92- sil (LALA_P331S)
527	Tgex 207B7 huVH4_S58Q61-CDRH3-4-96- sil (LALA_P331S)
528	Tgex 207B7 huVH4_T58Q61A97A99 lgG1
529	Tgex 207B7 huVH4_N55Q61A97A99 lgG1
530	Tgex 207B7 huVH4_R55Q61A97A99 lgG1
531	Tgex 207B7 huVH4_S55Q61A97A99 lgG1
532	Tgex huVH4_S55Q61K97G98G99 sil (LALA_P331S)
533	Tgex huVH4_S55Q61R97G98G99 sil (LALA_P331S)
534	Tgex huVH4_S55Q61_CDRH3-43 sil (LALA_P331S)
535	Tgex 207B7 huVH4_T55Q61A97A99 lgG1
536	Tgex huVH4_T55Q61_CDRH3-43 sil (LALA_P331S)
537	Tgex 207B7 huVH4_W55Q61A97A99 lgG1
538	Tgex 207B7 huVH4_Y55Q61A97A99 lgG1

SEQ ID NO:	Polypeptide Sequence of
539	Tgex 207B7 huVH4_T54Q61A97A99 lgG1
540	Tgex 207B7 huVH4_S53Q61A97A99 lgG1
541	Tgex 207B7 huVH4_T53Q61A97A99 lgG1
542	Tgex 207B7 huVH4_W53Q61A97A99 lgG1
543	huVH4_W53Q61R97G99 Fab
544	Tgex 207B7 huVH4_Y53Q61A97A99 lgG1
545	Tgex 207B7 huVH4_Q52aQ61A97A99 lgG1
546	Tgex 207B7 huVH4_S52aQ61A97A99 lgG1
547	Tgex 207B7 huVH4_T52aQ61A97A99 lgG1
548	Tgex 207B7 huVH4_W52aQ61A97A99 lgG1
549	Tgex 207B7 huVH4_Y52aQ61A97A99 lgG1
550	huVH4_N52Q61R97G99 Fab
551	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-4-1- sil (LALA_P331S)
552	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-4-5- sil (LALA_P331S)
553	Tgex 207B7 huVH4_Q52H58Q61Q99ins- sil (LALA_P331S)
554	Tgex 207B7 huVH4_Q52H58Q61K97G98G99- sil (LALA_P331S)
555	Tgex 207B7 huVH4_Q52H58Q61K97ins- sil (LALA_P331S)

SEQ ID NO:	Polypeptide Sequence of
556	Tgex 207B7 huVH4_Q52H58Q61K97insQ98ins-sil (LALA_P331S)
557	Tgex 207B7 huVH4_Q52H58Q61Q97ins- sil (LALA_P331S)
558	Tgex 207B7 huVH4_Q52H58Q61Q97insK98ins-sil (LALA_P331S)
559	Tgex 207B7 huVH4_Q52H58Q61R97ins- sil (LALA_P331S)
560	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-4-18- sil (LALA_P331S)
561	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-4-20- sil (LALA_P331S)
562	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-4-21- sil (LALA_P331S)
563	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-4-24- sil (LALA_P331S)
564	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-4-26- sil (LALA_P331S)
565	Tgex 207B7 huVH4_Q52H58Q61CDRH3-7-30- sil (LALA_P331S)
566	Tgex 207B7 huVH4_Q52H58Q61CDRH3-7-39- sil (LALA_P331S)
567	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-4-40- sil (LALA_P331S)
568	Tgex 207B7 huVH4_Q52H58Q61CDRH3-7-41- sil (LALA_P331S)
569	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-4-46- sil (LALA_P331S)
570	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-4-60- sil (LALA_P331S)
571	Tgex 207B7 huVH4_Q52H58Q61CDRH3-7-63- sil (LALA_P331S)
572	Tgex 207B7 huVH4_Q52H58Q61CDRH3-7-64- sil (LALA_P331S)
573	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-4-76- sil (LALA_P331S)
574	Tgex 207B7 huVH4_Q52H58Q61KPA99T- sil (LALA_P331S)
575	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-43- sil (LALA_P331S)
576	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-4-80- sil (LALA_P331S)
577	Tgex 207B7 huVH4_Q52H58Q61CDRH3-7-82- sil (LALA_P331S)
578	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-4-84- sil (LALA_P331S)
579	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-4-90- sil (LALA_P331S)
580	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-4-92- sil (LALA_P331S)
581	Tgex 207B7 huVH4_Q52H58Q61-CDRH3-4-96- sil (LALA_P331S)
582	Tgex 207B7 huVH4_Q52Q61-CDRH3-4-1- sil (LALA_P331S)
583	Tgex 207B7 huVH4_Q52Q61-CDRH3-4-5- sil (LALA_P331S)
584	Tgex 207B7 huVH4_Q52Q61Q99ins-sil (LALA_P331S)
585	Tgex 207B7 huVH4_Q52Q61K97G98G99- sil (LALA_P331S)
586	Tgex 207B7 huVH4_Q52Q61K97ins-sil (LALA_P331S)
587	Tgex 207B7 huVH4_Q52Q61K97insQ98ins- sil (LALA_P331S)
588	Tgex 207B7 huVH4_Q52Q61Q97ins-sil (LALA_P331S)
589	Tgex 207B7 huVH4_Q52Q61Q97insK98ins- sil (LALA_P331S)
590	Tgex 207B7 huVH4_Q52Q61R97ins-sil (LALA_P331S)
591	Tgex 207B7 huVH4_Q52Q61-CDRH3-4-18- sil (LALA_P331S)
592	Tgex 207B7 huVH4_Q52Q61-CDRH3-4-20- sil (LALA_P331S)
593	Tgex 207B7 huVH4_Q52Q61-CDRH3-4-21- sil (LALA_P331S)
594	Tgex 207B7 huVH4_Q52Q61-CDRH3-4-24- sil (LALA_P331S)
595	Tgex 207B7 huVH4_Q52Q61-CDRH3-4-26- sil (LALA_P331S)
596	Tgex 207B7 huVH4_Q52Q61CDRH3-7-30- sil (LALA_P331S)
597	Tgex 207B7 huVH4_Q52Q61CDRH3-7-39- sil (LALA_P331S)
598	Tgex 207B7 huVH4_Q52Q61-CDRH3-4-40- sil (LALA_P331S)

SEQ ID NO:	Polypeptide Sequence of
599	Tgex 207B7 huVH4_Q52Q61CDRH3-7-41- sil (LALA_P331S)
600	Tgex 207B7 huVH4_Q52Q61-CDRH3-4-46- sil (LALA_P331S)
601	Tgex 207B7 huVH4_Q52Q61-CDRH3-4-60- sil (LALA_P331S)
602	Tgex 207B7 huVH4_Q52Q61CDRH3-7-63- sil (LALA_P331S)
603	Tgex 207B7 huVH4_Q52Q61CDRH3-7-64- sil (LALA_P331S)
604	Tgex 207B7 huVH4_Q52Q61-CDRH3-4-76- sil (LALA_P331S)
605	Tgex 207B7 huVH4_Q52Q61KPA99T- sil (LALA_P331S)
606	Tgex 207B7 huVH4_Q52Q61-CDRH3-43- sil (LALA_P331S)
607	Tgex 207B7 huVH4_Q52Q61-CDRH3-4-80- sil (LALA_P331S)
608	Tgex 207B7 huVH4_Q52Q61CDRH3-7-82- sil (LALA_P331S)
609	Tgex 207B7 huVH4_Q52Q61-CDRH3-4-84- sil (LALA_P331S)
610	Tgex 207B7 huVH4_Q52Q61-CDRH3-4-90- sil (LALA_P331S)
611	Tgex 207B7 huVH4_Q52Q61-CDRH3-4-92- sil (LALA_P331S)
612	Tgex 207B7 huVH4_Q52Q61-CDRH3-4-96- sil (LALA_P331S)
613	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-4-1- sil (LALA_P331S)
614	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-4-5- sil (LALA_P331S)
615	Tgex 207B7 huVH4_Q52S58Q61Q99ins- sil (LALA_P331S)
616	Tgex 207B7 huVH4_Q52S58Q61K97G98G99- sil (LALA_P331S)
617	Tgex 207B7 huVH4_Q52S58Q61K97ins- sil (LALA_P331S)
618	Tgex 207B7 huVH4_Q52S58Q61K97insQ98ins-sil (LALA_P331S)
619	Tgex 207B7 huVH4_Q52S58Q61Q97ins- sil (LALA_P331S)
620	Tgex 207B7 huVH4_Q52S58Q61Q97insK98ins-sil (LALA_P331S)
621	Tgex 207B7 huVH4_Q52S58Q61R97ins- sil (LALA_P331S)
622	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-4-18- sil (LALA_P331S)
623	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-4-20- sil (LALA_P331S)
624	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-4-21- sil (LALA_P331S)
625	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-4-24- sil (LALA_P331S)
626	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-4-26- sil (LALA_P331S)
627	Tgex 207B7 huVH4_Q52S58Q61CDRH3-7-30- sil (LALA_P331S)
628	Tgex 207B7 huVH4_Q52S58Q61CDRH3-7-39- sil (LALA_P331S)
629	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-4-40- sil (LALA_P331S)
630	Tgex 207B7 huVH4_Q52S58Q61CDRH3-7-41- sil (LALA_P331S)
631	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-4-46- sil (LALA_P331S)
632	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-4-60- sil (LALA_P331S)
633	Tgex 207B7 huVH4_Q52S58Q61CDRH3-7-63- sil (LALA_P331S)
634	Tgex 207B7 huVH4_Q52S58Q61CDRH3-7-64- sil (LALA_P331S)
635	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-4-76- sil (LALA_P331S)
636	Tgex 207B7 huVH4_Q52S58Q61KPA99T- sil (LALA_P331S)
637	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-43- sil (LALA_P331S)
638	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-4-80- sil (LALA_P331S)
639	Tgex 207B7 huVH4_Q52S58Q61CDRH3-7-82- sil (LALA_P331S)
640	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-4-84- sil (LALA_P331S)

SEQ ID NO:	Polypeptide Sequence of
641	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-4-90- sil (LALA_P331S)
642	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-4-92- sil (LALA_P331S)
643	Tgex 207B7 huVH4_Q52S58Q61-CDRH3-4-96- sil (LALA_P331S)
644	Tgex 207B7 huVH4_W50Q61A97A99 IgG1
645	HuVH4-QRGG_M34
646	huVH4_T32Q35Q61K97G99 IgG
647	huVH4_T32Q61A62K97G99 IgG
648	huVH4_T32Q61K97G99 IgG
649	HuVH4-QRGG_Y32A33N35
650	HuVH4-QRGG_CDR1germ
651	Tgex VH-IGHV7-4-1*02 IgG1
652	HuVH4-QRGG_Y32N35
653	HuVH4-QRGG_Y32
654	huVH4_T31H32Q35Q61A62K97G99 IgG
655	huVH4_T31H32Q35Q61K97G99 IgG
656	huVH4_T31R32Q61K97G99 IgG
657	huVH4_T31Q35Q61K97G99 IgG
658	huVH4_T31Q61A62K97G99 IgG
659	huVH4_T31Q61K97G99 IgG
660	huVH4_T31T32Q35Q61K97G99 IgG
661	huVH4_T31T32Q61K97G99 IgG
662	Tgex 207B7 huVH4_Y30Q61A97A99 IgG1
663	huVH4_Y30Q61K97G99 Fab
664	Tgex 207B7 huVH4_Y30Q61K62E64K97G99 IgG1
665	Tgex 207B7 huVH4_Y30Q61K62K97G99 IgG1

SEQ ID NO:	Polypeptide Sequence of
666	Hu-VL3_G24H90S93
667	Hu-VL3_K24H90S93
668	Hu-VL3_D26H90S93
669	Hu-VL3_G26H90S93
670	Hu-VL3_N26H90S93
671	HuVL3_H90S93_S28D
672	Hu-VL3_G28H90S93
673	Hu-VL3_H28H90S93
674	Hu-VL3_I28H90S93
675	Hu-VL3_L28H90S93
676	Hu-VL3_N28H90S93
677	Hu-VL3_A29H90S93
678	Hu-VL3_D29H90S93
679	Hu-VL3_G29H90S93
680	Tgex 207B7huVL3_I29M33D56H90S93
681	Tgex 207B7huVL3_I29M33D56Y87H90S93
682	Tgex 207B7huVL3_I29M33E56H90S93
683	Tgex 207B7huVL3_I29M33E56Y87H90S93
684	Tgex 207B7huVL3_I29M33H90S93
685	Tgex 207B7huVL3_I29M33Y87H90S93
686	Tgex 207B7 huVL3_I29M33G34D56H90S93
687	Tgex 207B7 huVL3_I29M33G34D56Y87H90S93
688	Tgex 207B7huVL3_I29M33G34E56H90S93

SEQ ID NO:	Polypeptide Sequence of
689	Tgex 207B7huVL3_I29M33G34E56Y87H90S93
690	Tgex 207B7huVL3_I29M33G34H90S93
691	Tgex 207B7huVL3_I29M33G34Y87H90S93
692	Tgex 207B7huVL3_I29D56H90S93
693	Tgex 207B7huVL3_I29D56Y87H90S93
694	Tgex 207B7huVL3_I29E56H90S93
695	Tgex 207B7huVL3_I29E56Y87H90S93
696	HuVL3_H90S93_V29I
697	Tgex 207B7huVL3_I29Y87H90S93
698	Tgex 207B7huVL3_I29G34D56H90S93
699	Tgex 207B7huVL3_I29G34D56Y87H90S93
700	Tgex 207B7huVL3_I29G34E56H90S93
701	Tgex 207B7huVL3_I29G34E56Y87H90S93
702	Tgex 207B7huVL3_I29G34H90S93
703	Tgex 207B7huVL3_I29G34Y87H90S93
704	Hu-VL3_N29H90S93
705	Hu-VL3_P29H90S93
706	Hu-VL3_Q29H90S93
707	Hu-VL3_R29H90S93
708	Hu-VL3_S29H90S93
709	Hu-VL3_T29H90S93

SEQ ID NO:	Polypeptide Sequence of
710	Hu-VL3_A30H90S93
711	Hu-VL3_D30H90S93
712	Hu-VL3_G30H90S93
713	Hu-VL3_I30H90S93
714	Hu-VL3_K30H90S93
715	Hu-VL3_N30H90S93
716	HuVL3_H90S93_Y31N
717	Hu-VL3_A32H90S93
718	Hu-VL3_D32H90S93
719	Hu-VL3_F32H90S93
720	Hu-VL3_G32H90S93
721	Hu-VL3_H32H90S93
722	Hu-VL3_L32H90S93
723	Hu-VL3_A33H90S93
724	Hu-VL3_I33H90S93
725	Hu-VL3_K33H90S93
726	HuVL3_H90S93_V33L
727	Tgex 207B7huVL3_M33D56H90S93
728	Tgex 207B7huVL3_M33D56Y87H90S93
729	Tgex 207B7huVL3_M33E56H90S93
730	Tgex 207B7huVL3_M33E56Y87H90S93
731	Hu-VL3_M33H90S93
732	Tgex 207B7huVL3_M33Y87H90S93
733	Tgex 207B7huVL3_M33G34D56H90S93
734	Tgex 207B7huVL3_M33G34D56Y87H90S93
735	Tgex 207B7huVL3_M33G34E56H90S93
736	Tgex 207B7huVL3_M33G34E56Y87H90S93
737	Tgex 207B7huVL3_M33G34H90S93
738	Tgex 207B7huVL3_M33G34Y87H90S93
739	Hu-VL3_P33H90S93
740	HuVL3_H90S93_Y50A
741	HuVL3_H90S93_YRY-DLE
742	HuVL3_H90S93_Y50D
743	HuVL3_H90S93_S52A
744	HuVL3_H90S93_N53A
745	Hu-VL3_D53H90S93
746	Hu-VL3_E53H90S93
747	huVL3_K53D56H90D93
748	huVL3_K53D56H90S93
749	huVL3_K53K56H90D93
750	huVL3_K53K56H90S93
751	huVL3_K53H90D93
752	Hu-VL3_K53H90S93
753	HuVL3_H90S93_R54A
754	Hu-VL3_G54H90S93
755	Hu-VL3_K54H90S93
756	HuVL3_H90S93_RY-LE
757	HuVL3_H90S93_R54L
758	HuVL4_H90S93_D1S
759	HuVL3_H90S93_Y55A
760	HuVL3_H90S93_Y55E
761	HuVL3_H90S93_T56A
762	huVL3_D56H90D93
763	Tgex 207B7huVL3_D56Y87H90S93
764	Tgex 207B7huVL3_E56Y87H90S93
765	huVL3_K56H90D93
766	Hu-VL3_L89H90S93
767	Hu-VL3_L89
768	Hu-VL3_A90S93
769	Hu-VL3_G90S93
770	Hu-VL3_H90A91S93
771	Hu-VL3_H90D91S93
772	Hu-VL3_H90F91S93
773	Hu-VL3_H90G91S93
774	HuVL3_H90S93_Y92D
775	Hu-VL3_H90L92A93
776	Hu-VL3_H90L92S93
777	HuVL3_Q90H_A93
778	HuVL3_Q90H_D93
779	HuVL3_Q90H_E93
780	HuVL3_Q90H_F93
781	HuVL3_Q90H_G93
782	HuVL3_Q90H_H93
783	HuVL3_Q90H_I93
784	HuVL3_Q90H_K93
785	HuVL3_Q90H_L93
786	HuVL3_Q90H_M93
787	Hu-VL3_H90Y97
788	HuVL3_Q90H_P93
789	HuVL3_Q90H_Q93
790	HuVL3_Q90H_R93
791	Hu-VL3_H90S93A94
792	Hu-VL3_H90S93D94
793	Hu-VL3_H90S93F94
794	Hu-VL3_H90S93G94
795	Hu-VL3_H90S93I94
796	HuVL3_H90S93_S94L
797	Hu-VL3_H90S93N94
798	Hu-VL3_H90S93R94
799	Hu-VL3_H90S93E96
800	Hu-VL3_H90S93Y97

SEQ ID NO:	Polypeptide Sequence of
801	Hu-VL3_H90S93T94
802	Hu-VL3_H90S93V94
803	Hu-VL3_H90S93W94
804	Hu-VL3_H90S93Y94
805	HuVL3_Q90H_T93
806	HuVL3_Q90H_V93
807	HuVL3_Q90H_W93
808	HuVL3_Q90H_Y93
809	Hu-VL3_H90L91S93
810	Hu-VL3_H90R91S93
811	Hu-VL3_H90S91S93
812	Hu-VL3_H90T91S93
813	Hu-VL3_H90W91S93
814	HuVL3_H90S93_H91Y
815	Hu-VL3_L90S93
816	Hu-VL3_N90S93
817	Hu-VL3_L92A93
818	Hu-VL3_L92
819	Hu-VL3_E96
820	Hu-VL3_Y97
821	Hu-VL3_S90S93
822	Hu-VL3_T90S93
823	Hu-VL3_V90S93
824	Hu-VL3_S89H90S93
825	Hu-VL3_S89
826	HuVL3_H90S93_F87Y
827	Hu-VL3_S54H90S93
828	huVL3_Q53D56H90D93
829	huVL3_Q53D56H90S93
830	huVL3_Q53H90D93
831	Hu-VL3_Q53H90S93
832	Hu-VL3_R53H90S93
833	Hu-VL3_S53H90S93
834	Hu-VL3_T53H90S93

SEQ ID NO:	Polypeptide Sequence of
835	Hu-VL3_Y53H90S93
836	Hu-VL3_D34H90S93
837	Hu-VL3_E34H90S93
838	Tgex 207B7huVL3_G34D56H90S93
839	Tgex 207B7huVL3_G34D56Y87H90S93
840	Tgex 207B7huVL3_G34E56H90S93
841	Tgex 207B7huVL3_G34E56Y87H90S93
842	Hu-VL3_G34H90S93
843	Tgex 207B7huVL3_G34Y87H90S93
844	Hu-VL3_H34H90S93
845	HuVL3_H90S93_A34N
846	Hu-VL3_Q34H90S93
847	Hu-VL3_S34H90S93
848	Hu-VL3_T34H90S93
849	Hu-VL3_Y34H90S93
850	Hu-VL3_Y33H90S93
851	Hu-VL3_Q32H90S93
852	Hu-VL3_S32H90S93
853	Hu-VL3_T32H90S93
854	Hu-VL3_W32H90S93
855	HuVL3_H90S93_N32Y
856	HuVL3_H90S93_R30S
857	Hu-VL3_T30H90S93
858	Hu-VL3_V30H90S93
859	Hu-VL3_Y30H90S93
860	Hu-VL3_T28H90S93
861	Hu-VL3_V28H90S93
862	Hu-VL3_Y28H90S93
863	Hu-VL3_T26H90S93
864	Hu-VL3_G25H90S93
865	Hu-VL3_L25H90S93
866	Hu-VL3_R25H90S93

SEQ ID NO:	Polypeptide Sequence of
867	Hu-VL3_S25H90S93
868	Hu-VL3_T25H90S93
869	Hu-VL3_R24H90S93
870	Hu-VL3_S24H90S93
871	Hu-VL3_T24H90S93
872	TGEX-LC Human Kappa 207B7 germline
873	TGEX-LC Human Kappa 207B7 germline 169A1 CDRs
874	TGEX-LC Human Kappa 207B7 169A1 LCA
875	TGEX-LC Human Kappa 169A1
876	TGEX-LC Human Kappa 207B7mGF Q90H (was previously 207B7 germline 207B7 169A1 CDRs)
877	TGEX-LC Human Kappa 207B7 germline 207B7 CDRs
878	TGEX-LC Human Kappa 207B7 (LPAR1)
879	HuVL3_H90S93_S1A
880	huVL3_Q90H_S93_VL
881	HuVL3_H90S93_S1N
882	HuVL3_H90S93_S1E
883	HuVL3_H90S93_S1Q
884	AA_huVL3_Q90H_VL
885	AA_207B7_huVL3_VL
886	huVL3_S93_VL
887	HuVL3_H90S93_Q27E
888	HuVL3_H90S93_Q27K
889	HuVL3_H90S93_Q27L
890	HuVL3_H90S93_Q27M
891	HuVL3_H90S93_Q27V
892	HuVL3_H90S93_Q27W
893	HuVL3_H90S93_Q27A

SEQ ID NO:	Polypeptide Sequence of
894	HuVL3_H90S93_Q27D
895	HuVL3_H90S93_Q27F
896	HuVL3_H90S93_Q27G
897	HuVL3_H90S93_Q27H
898	HuVL3_H90S93_Q27I
899	HuVL3_H90S93_Q27N
900	HuVL3_H90S93_Q27P
901	HuVL3_H90S93_Q27R
902	HuVL3_H90S93_Q27S
903	HuVL3_H90S93_Q27T
904	HuVL3_H90S93_Q27Y
905	HuVL3_H90S93_Y31D
906	HuVL3_H90S93_Y31H
907	HuVL3_H90S93_Y31F
908	HuVL3_H90S93_Y31G
909	HuVL3_H90S93_Y31I
910	HuVL3_H90S93_Y31P
911	HuVL3_H90S93_Y31S
912	HuVL3_H90S93_Y31T
913	HuVL3_H90S93_Y31E
914	HuVL3_H90S93_Y31K
915	HuVL3_H90S93_Y31L
916	HuVL3_H90S93_Y31M
917	HuVL3_H90S93_Y31Q
918	HuVL3_H90S93_Y31R
919	HuVL3_H90S93_Y31V
920	HuVL3_H90S93_Y31W
921	HuVL3_H90S93_Y50E
922	HuVL3_H90S93_Y50F
923	HuVL3_H90S93_Y50G
924	HuVL3_H90S93_Y50H
925	HuVL3_H90S93_Y50I
926	HuVL3_H90S93_Y50K
927	HuVL3_H90S93_Y50L

SEQ ID NO:	Polypeptide Sequence of
928	HuVL3_H90S93_Y50M
929	HuVL3_H90S93_Y50N
930	HuVL3_H90S93_Y50P
931	HuVL3_H90S93_Y50Q
932	HuVL3_H90S93_Y50R
933	HuVL3_H90S93_Y50S
934	HuVL3_H90S93_Y50T
935	HuVL3_H90S93_Y50V
936	HuVL3_H90S93_Y50W
937	HuVL3_H90S93_S52G
938	HuVL3_H90S93_S52D
939	HuVL3_H90S93_S52F
940	HuVL3_H90S93_S52H
941	HuVL3_H90S93_S52I
942	HuVL3_H90S93_S52N
943	HuVL3_H90S93_S52P
944	HuVL3_H90S93_S52T
945	HuVL3_H90S93_S52Y
946	HuVL3_H90S93_T56I
947	HuVL3_H90S93_T56K
948	HuVL3_H90S93_T56M
949	HuVL3_H90S93_T56N
950	HuVL3_H90S93_T56R
951	HuVL3_H90S93_S52E
952	HuVL3_H90S93_S52K
953	HuVL3_H90S93_S52L
954	HuVL3_H90S93_S52M
955	HuVL3_H90S93_S52Q
956	HuVL3_H90S93_S52R
957	HuVL3_H90S93_S52V
958	HuVL3_H90S93_S52W
959	HuVL3_H90S93_Y55D
960	HuVL3_H90S93_Y55H
961	HuVL3_H90S93_Y55N

SEQ ID NO:	Polypeptide Sequence of
962	HuVL3_H90S93_Y55F
963	HuVL3_H90S93_Y55G
964	HuVL3_H90S93_Y55I
965	HuVL3_H90S93_Y55P
966	HuVL3_H90S93_Y55S
967	HuVL3_H90S93_Y55T
968	HuVL3_H90S93_Y55K
969	HuVL3_H90S93_Y55L
970	HuVL3_H90S93_Y55M
971	HuVL3_H90S93_Y55Q
972	HuVL3_H90S93_Y55R
973	HuVL3_H90S93_Y55V
974	HuVL3_H90S93_Y55W
975	HuVL3_H90S93_T56D
976	HuVL3_H90S93_T56E
977	HuVL3_H90S93_T56F
978	HuVL3_H90S93_T56G
979	HuVL3_H90S93_T56H
980	HuVL3_H90S93_T56L
981	HuVL3_H90S93_T56P
982	HuVL3_H90S93_T56Q
983	HuVL3_H90S93_T56S
984	HuVL3_H90S93_T56V
985	HuVL3_H90S93_T56W
986	HuVL3_H90S93_T56Y
987	TGEXLC_Human_Kappa_204B4_(LPAR1)
988	187D6_VL
989	Tgex_huVH4_Q61A75CDRH343__sil_(LALA_P331S)
990	Tgex_huVH4_Q61H96P97P98T99T100b__sil_(LALA_P331S)
991	Tgex_huVH4_Q61H96P98T100b__sil_(LALA_P331S)

SEQ ID NO:	Polypeptide Sequence of
992	Tgex_huVH4_Q61K96P97P98T99T100b__sil_(LALA_P331S)
993	Tgex_huVH4_Q61K96P97T99__sil_(LALA_P331S)
994	Tgex_huVH4_Q61S75CDRH343__sil_(LALA_P331S)
995	189E7_VL
996	186A3_VH
997	187D6_VH
998	189A11mGF_VH
999	189E7_VH
1000	207B7HuVH4_H97K98S99
1001	207B7HuVH4_Q61G97K98G99
1002	207B7HuVH4_Q61G97K98S99
1003	207B7HuVH4_Q61H97K98G99
1004	207B7HuVH4_Q61H97K98S99
1005	207B7HuVH4_Q61H97S98G99
1006	207B7HuVH4_Q61H97S98S99
1007	207B7_S100G_VH
1008	207B7_mGF_E61A_VH
1009	207B7_mGF_F96A_VH
1010	207B7_mGF_G55A_VH
1011	207B7_mGF_G97A_VH
1012	207B7_mGF_L52A_VH
1013	207B7_mGF_N58A_VH
1014	207B7_mGF_N60A_VH
1015	207B7_mGF_P52AA_VH
1016	207B7_mGF_R53A_VH
1017	207B7_mGF_S54A_VH
1018	207B7_mGF_S98A_VH
1019	207B7_mGF_S99A_VH
1020	207B7_mGF_T57A_VH
1021	207B7_mGF_Y100AA_VH
1022	207B7_mGF_Y56A_VH

SEQ ID NO:	Polypeptide Sequence of
1023	207B7mGF_D86E_VH
1024	207B7mGF_GLCDRH1_VH
1025	207B7mGF_GLCDRH3_VH
1026	207B7mGF_I34M_VH
1027	207B7mGF_L52Y_VH
1028	207B7mGF_N58Y_VH
1029	207B7mGF_YTNNTY_VH
1030	207mGF_189CDRmuts_VH
1031	207mGF_E61G_VH
1032	207mGF_G55A_E61G_VH
1033	207mGF_G55A_VH
1034	207mGF_G97D_S98N_VH
1035	207mGF_G97D_VH
1039	207mGF_M100L_E61G_VH
1037	207mGF_M100L_G55A_VH
1038	207mGF_M100L_G97D_VH
1039	207mGF_M100L_S98N_VH
1040	207mGF_M100L_VH
1041	207mGF_S98N_VH
1042	31D8_VH
1043	62A4_VH
1044	AA_207B7_huVH1_VH
1045	AA_207B7_huVH3_VH
1046	AA_207B7_huVH4_VH
1047	TGEXHC_Human_IgG1_189A11
1048	TGEXHC_Human_IgG1_189B8
1049	TGEXHC_Human_IgG1_192E9
1050	TGEXHC_Human_IgG1_92C5
1051	TGEXHC_silenced_Human_IgG1_140D6_(LPAR1)
1052	TGEXHC_silenced_Human_IgG1_204B4_(LPAR1)
1053	huVH4_Q61R97G99G104_Fab_F96A

SEQ ID NO:	Polypeptide Sequence of
1054	huVH4_Q61R97G99G104_Fab_F96D
1055	huVH4_Q61R97G99G104_Fab_F96E
1056	huVH4_Q61R97G99G104_Fab_F96G
1057	huVH4_Q61R97G99G104_Fab_F96H
1058	huVH4_Q61R97G99G104_Fab_F96I
1059	huVH4_Q61R97G99G104_Fab_F96K
1060	huVH4_Q61R97G99G104_Fab_F96L
1061	huVH4_Q61R97G99G104_Fab_F96M
1062	huVH4_Q61R97G99G104_Fab_F96N
1063	huVH4_Q61R97G99G104_Fab_F96P
1064	huVH4_Q61R97G99G104_Fab_F96Q
1065	huVH4_Q61R97G99G104_Fab_F96R
1066	huVH4_Q61R97G99G104_Fab_F96S
1067	huVH4_Q61R97G99G104_Fab_F96T
1068	huVH4_Q61R97G99G104_Fab_F96V
1069	huVH4_Q61R97G99G104_Fab_F96W
1070	huVH4_Q61R97G99G104_Fab_F96Y
1071	huVH4_Q61R97G99G104_Fab_G62A

SEQ ID NO:	Polypeptide Sequence of
1072	huVH4_Q61R97G99G104_Fab_G62D
1073	huVH4_Q61R97G99G104_Fab_G62E
1074	huVH4_Q61R97G99G104_Fab_G62F
1075	huVH4_Q61R97G99G104_Fab_G62H
1076	huVH4_Q61R97G99G104_Fab_G62I
1077	huVH4_Q61R97G99G104_Fab_G62K
1078	huVH4_Q61R97G99G104_Fab_G62L
1079	huVH4_Q61R97G99G104_Fab_G62M
1080	huVH4_Q61R97G99G104_Fab_G62N
1081	huVH4_Q61R97G99G104_Fab_G62P
1082	huVH4_Q61R97G99G104_Fab_G62Q
1083	huVH4_Q61R97G99G104_Fab_G62R
1084	huVH4_Q61R97G99G104_Fab_G62S
1085	huVH4_Q61R97G99G104_Fab_G62T
1086	huVH4_Q61R97G99G104_Fab_G62V
1087	huVH4_Q61R97G99G104_Fab_G62W
1088	huVH4_Q61R97G99G104_Fab_G62Y

SEQ ID NO:	Polypeptide Sequence of
1089	huVH4_Q61R97G99G104_Fab_N60D
1090	huVH4_Q61R97G99G104_Fab_N60E
1091	huVH4_Q61R97G99G104_Fab_N60F
1092	huVH4_Q61R97G99G104_Fab_N60G
1093	huVH4_Q61R97G99G104_Fab_N60H
1094	huVH4_Q61R97G99G104_Fab_N60I
1095	huVH4_Q61R97G99G104_Fab_N60K
1096	huVH4_Q61R97G99G104_Fab_N60L
1097	huVH4_Q61R97G99G104_Fab_N60M
1098	huVH4_Q61R97G99G104_Fab_N60P
1099	huVH4_Q61R97G99G104_Fab_N60Q
1100	huVH4_Q61R97G99G104_Fab_N60R
1101	huVH4_Q61R97G99G104_Fab_N60S
1102	huVH4_Q61R97G99G104_Fab_N60T
1103	huVH4_Q61R97G99G104_Fab_N60V
1104	huVH4_Q61R97G99G104_Fab_N60W
1105	huVH4_Q61R97G99G104_Fab_N60Y
1106	huVH4_Q61R97G99G104_Fab_R100A

SEQ ID NO:	Polypeptide Sequence of
1107	huVH4_Q61R97G99G104_Fab_R100D
1108	huVH4_Q61R97G99G104_Fab_R100E
1109	huVH4_Q61R97G99G104_Fab_R100F
1110	huVH4_Q61R97G99G104_Fab_R100G
1111	huVH4_Q61R97G99G104_Fab_R100H
1112	huVH4_Q61R97G99G104_Fab_R100I
1113	huVH4_Q61R97G99G104_Fab_R100K
1114	huVH4_Q61R97G99G104_Fab_R100L
1115	huVH4_Q61R97G99G104_Fab_R100M
1116	huVH4_Q61R97G99G104_Fab_R100N
1117	huVH4_Q61R97G99G104_Fab_R100P
1118	huVH4_Q61R97G99G104_Fab_R100Q
1119	huVH4_Q61R97G99G104_Fab_R100S
1120	huVH4_Q61R97G99G104_Fab_R100T
1121	huVH4_Q61R97G99G104_Fab_R100V
1122	huVH4_Q61R97G99G104_Fab_R100W
1123	huVH4_Q61R97G99G104_Fab_R100Y

SEQ ID NO:	Polypeptide Sequence of
1124	huVH4_Q61R97G99G104_Fab_S31D
1125	huVH4_Q61R97G99G104_Fab_S31E
1126	huVH4_Q61R97G99G104_Fab_S31F
1127	huVH4_Q61R97G99G104_Fab_S31G
1128	huVH4_Q61R97G99G104_Fab_S31H
1129	huVH4_Q61R97G99G104_Fab_S31I
1130	huVH4_Q61R97G99G104_Fab_S31K
1131	huVH4_Q61R97G99G104_Fab_S31L
1132	huVH4_Q61R97G99G104_Fab_S31M
1133	huVH4_Q61R97G99G104_Fab_S31N
1134	huVH4_Q61R97G99G104_Fab_S31P
1135	huVH4_Q61R97G99G104_Fab_S31Q
1136	huVH4_Q61R97G99G104_Fab_S31R
1137	huVH4_Q61R97G99G104_Fab_S31T
1138	huVH4_Q61R97G99G104_Fab_S31V
1139	huVH4_Q61R97G99G104_Fab_S31W
1140	huVH4_Q61R97G99G104_Fab_S31Y
1141	huVH4_Q61R97G99G104_Fab_S32D

SEQ ID NO:	Polypeptide Sequence of
1142	huVH4_Q61R97G99G104_Fab_S32E
1143	huVH4_Q61R97G99G104_Fab_S32F
1144	huVH4_Q61R97G99G104_Fab_S32G
1145	huVH4_Q61R97G99G104_Fab_S32H
1146	huVH4_Q61R97G99G104_Fab_S32I
1147	huVH4_Q61R97G99G104_Fab_S32K
1148	huVH4_Q61R97G99G104_Fab_S32L
1149	huVH4_Q61R97G99G104_Fab_S32M
1150	huVH4_Q61R97G99G104_Fab_S32N
1151	huVH4_Q61R97G99G104_Fab_S32P
1152	huVH4_Q61R97G99G104_Fab_S32Q
1153	huVH4_Q61R97G99G104_Fab_S32R
1154	huVH4_Q61R97G99G104_Fab_S32T
1155	huVH4_Q61R97G99G104_Fab_S32V
1156	huVH4_Q61R97G99G104_Fab_S32W
1157	huVH4_Q61R97G99G104_Fab_S35D
1158	huVH4_Q61R97G99G104_Fab_S35E
1159	huVH4_Q61R97G99G104_Fab_S35F

SEQ ID NO:	Polypeptide Sequence of
1160	huVH4_Q61R97G99G104_Fab_S35G
1161	huVH4_Q61R97G99G104_Fab_S35H
1162	huVH4_Q61R97G99G104_Fab_S35I
1163	huVH4_Q61R97G99G104_Fab_S35K
1164	huVH4_Q61R97G99G104_Fab_S35L
1165	huVH4_Q61R97G99G104_Fab_S35M
1166	huVH4_Q61R97G99G104_Fab_S35P
1167	huVH4_Q61R97G99G104_Fab_S35Q
1168	huVH4_Q61R97G99G104_Fab_S35R
1169	huVH4_Q61R97G99G104_Fab_S35T
1170	huVH4_Q61R97G99G104_Fab_S35V
1171	huVH4_Q61R97G99G104_Fab_S35W
1172	huVH4_Q61R97G99G104_Fab_S35Y
1173	huVH4_Q61R97G99G104_Fab_Y100aA
1174	huVH4_Q61R97G99G104_Fab_Y100aD
1175	huVH4_Q61R97G99G104_Fab_Y100aE
1176	huVH4_Q61R97G99G104_Fab_Y100aF
1177	huVH4_Q61R97G99G104_Fab_Y100aG

SEQ ID NO:	Polypeptide Sequence of
1178	huVH4_Q61R97G99G104_Fab_Y100aH
1179	huVH4_Q61R97G99G104_Fab_Y100aI
1180	huVH4_Q61R97G99G104_Fab_Y100aK
1181	huVH4_Q61R97G99G104_Fab_Y100aL
1182	huVH4_Q61R97G99G104_Fab_Y100aM
1183	huVH4_Q61R97G99G104_Fab_Y100aN
1184	huVH4_Q61R97G99G104_Fab_Y100aP
1185	huVH4_Q61R97G99G104_Fab_Y100aQ
1186	huVH4_Q61R97G99G104_Fab_Y100aR
1187	huVH4_Q61R97G99G104_Fab_Y100aS
1188	huVH4_Q61R97G99G104_Fab_Y100aT
1189	huVH4_Q61R97G99G104_Fab_Y100aV
1190	huVH4_Q61R97G99G104_Fab_Y100aW
1191	186A3_VL
1192	31D8_VL
1193	62A4_VL
1194	AA_207B7_huVL2_VL
1195	AA_207B7_huVL4_VL
1196	TGEXLC_Human_Kappa_140D6_(LPAR1)
1197	TGEXLC_Human_Kappa_192E9
1198	TGEXLC_Human_Kappa_92C5

SEQ ID NO:	Polypeptide Sequence of
1199	207B7mGF_H91A_VL
1200	207B7mGF_L96A_VL
1201	207B7mGF_N32A_VL
1202	207B7mGF_N93A_VL
1203	207B7mGF_P95A_VL
1204	207B7mGF_Q27A_VL
1205	207B7mGF_Q90A_VL
1206	207B7mGF_R30A_VL
1207	207B7mGF_S28A_VL
1208	207B7mGF_S94A_VL
1209	207B7mGF_T97A_VL
1210	207B7mGF_V29A_VL
1211	207B7mGF_V33A_VL
1212	207B7mGF_Y31A_VL
1213	AA_207B7_huVL1_VL
1214	LCA_G30R_Q90H_VL
1215	LCA_G30R_VL
1216	LCA_Q90H_S93N_VL
1217	TGEXLC_Human_Kappa_189A11
1218	TGEXLC_Human_Kappa_189B8
1219	15 light chain
1220	17 heavy chain
1221	18 light chain
1222	Mouse LPAR1
1223	Guinea-pig LPAR1
1224	Rabbit LPAR1
1225	Human LPAR2
1226	Human LPAR3
1227	Isotype antibody VH
1228	Isotype antibody VL
1235	16 heavy chain constant region (LALA)
1236	16 heavy chain

SEQ ID NO:	Polypeptide Sequence of
1237	Fc region with M252Y, S254T and T256E mutations
1238	Fc region with M252Y, S254T, T256E, LALA mutations
1239	Fc region with M252Y, S254T, T256E, LALA PS mutations
1240	Fc region with M252Y, S254T, T256E, LALA PG mutations
1241	Fc region with M252Y, S254T, T256E, LAGA mutations
1242	Fc region with H433K, N434F mutations
1243	Fc region with H433K, N434F, LALA mutations
1244	Fc region with H433K, N434F, LALA PS mutations
1245	Fc region with H433K, N434F, LALA PG mutations
1246	Fc region with H433K, N434F, LAGA mutations
1247	Fc region with H433K, N434F, Y436H mutations
1248	Fc region with H433K, N434F, Y436H, LALA mutations
1249	Fc region with H433K, N434F, Y436H, LALA PS mutations
1250	Fc region with H433K, N434F, Y436H, LALA PG mutations
1251	Fc region with H433K, N434F, Y436H, LAGA mutations
1252	Fc region with M252Y, S254T, T256E, H433K, N434F mutations
1253	Fc region with M252Y, S254T, T256E, H433K, N434F, LALA mutations

SEQ ID NO:	Polypeptide Sequence of
1254	Fc region with M252Y, S254T, T256E, H433K, N434F, LALA PS mutations
1255	Fc region with M252Y, S254T, T256E, H433K, N434F, LALA PG mutations
1256	Fc region with M252Y, S254T, T256E, H433K, N434F, LAGA mutations
1257	Fc region with M252Y, S254T, T256E, H433K, N434F, Y436H mutations
1258	Fc region with M252Y, S254T, T256E, H433K, N434F, Y436H, LALA mutations
1259	Fc region with M252Y, S254T, T256E, H433K, N434F, Y436H, LALA PS mutations
1260	Fc region with M252Y, S254T, T256E, H433K, N434F, Y436H, LALA PG mutations
1261	Fc region with M252Y, S254T, T256E, H433K, N434F, Y436H, LAGA mutations
1262	Fc region with M428L, N434S mutations
1263	Fc region with M428L, N434S, LALA mutations
1264	Fc region with M428L, N434S, LALA PS mutations
1265	Fc region with M428L, N434S, LALA PG mutations
1266	Fc region with M428L, N434S, LAGA mutations

SEQ ID NO:	Polypeptide Sequence of
1267	Fc region with T250Q, M428L mutations
1268	Fc region with T250Q, M428L, LALA mutations
1269	Fc region with T250Q, M428L, LALA PS mutations
1270	Fc region with T250Q, M428L, LALA PG mutations
1271	Fc region with T250Q, M428L, LAGA mutations
1272	Fc region with T307A, E380A, N434A mutations
1273	Fc region with T307A, E380A, N434A, LALA mutations
1274	Fc region with T307A, E380A, N434A, LALA PS mutations
1275	Fc region with T307A, E380A, N434A, LALA PG mutations
1276	Fc region with T307A, E380A, N434A, LAGA mutations
1277	Fc region with V308P mutations
1278	Fc region with V308P, LALA mutations
1279	Fc region with V308P, LALA PS mutations
1280	Fc region with V308P, LALA PG mutations
1281	Fc region with V308P, LAGA mutations
1282	Fc region with H285D, T307Q, A378V mutations
1283	Fc region with H285D, T307Q, A378V, LALA mutations

SEQ ID NO:	Polypeptide Sequence of
1284	Fc region with H285D, T307Q, A378V, LALA PS mutations
1285	Fc region with H285D, T307Q, A378V, LALA PG mutations
1286	Fc region with H285D, T307Q, A378V, LAGA mutations
1287	Fc region with L309D, Q311H, N434S mutations
1288	Fc region with L309D, Q311H, N434S, LALA mutations
1289	Fc region with L309D, Q311H, N434S, LALA PS mutations
1290	Fc region with L309D, Q311H, N434S, LALA PG mutations
1291	Fc region with L309D, Q311H, N434S, LAGA mutations
1292	Fc region with I253A, H310A, H435A mutations
1293	Fc region with I253A, H310A, H435A, LALA mutations
1294	Fc region with I253A, H310A, H435A, LALA PS mutations
1295	Fc region with I253A, H310A, H435A, LALA PG mutations
1296	Fc region with I253A, H310A, H435A, LAGA mutations
1297	Fc region with N434S, Q311I mutations
1298	Fc region with N434S, Q311I, LALA mutations
1299	Fc region with N434S, Q311I, LALA PS mutations
1300	Fc region with N434S, Q311I, LALA PG mutations

SEQ ID NO:	Polypeptide Sequence of
1301	Fc region with N434S, Q311I, LAGA mutations
1302	Fc region with N434S, Q311V mutations
1303	Fc region with N434S, Q311V, LALA mutations
1304	Fc region with N434S, Q311V, LALA PS mutations
1305	Fc region with N434S, Q311V, LALA PG mutations
1306	Fc region with N434S, Q311V, LAGA mutations
1307	Fc region with N434S, Y436I mutations
1308	Fc region with N434S, Y436I, LALA mutations
1309	Fc region with N434S, Y436I, LALA PS mutations
1310	Fc region with N434S, Y436I, LALA PG mutations
1311	Fc region with N434S, Y436I, LAGA mutations
1312	Fc region with N434S, Y436V mutations
1313	Fc region with N434S, Y436V, LALA mutations
1314	Fc region with N434S, Y436V, LALA PS mutations
1315	Fc region with N434S, Y436V, LALA PG mutations
1316	Fc region with N434S, Y436V, LAGA mutations
1317	Fc region with N434A mutations
1318	Fc region with N434A, LALA mutations
1319	Fc region with N434A, LALA PS mutations
1320	Fc region with N434A, LALA PG mutations
1321	Fc region with N434A, LAGA mutations
1322	Fc region with M252Y, V308P, N434Y mutations
1323	Fc region with M252Y, V308P, N434Y, LALA mutations
1324	Fc region with M252Y, V308P, N434Y, LALA PS mutations
1325	Fc region with M252Y, V308P, N434Y, LALA PG mutations
1326	Fc region with M252Y, V308P, N434Y, LAGA mutations
1327	Fc region with L234F, L235Q, K322Q, M252Y, S254T, T256E mutations
1328	Fc region with E294delta/T307P/N434Y mutations
1329	Fc region with E294delta/T307P/N434Y, LALA mutations
1330	Fc region with E294delta/T307P/N434Y, LALA PS mutations
1331	Fc region with E294delta/T307P/N434Y, LALA PG mutations
1332	Fc region with E294delta/T307P/N434Y, LAGA mutations
1333	Fc region with T256N/A378V/S383N/ N434Y mutations
1334	Fc region with T256N/A378V/S383N/ N434Y, LALA mutations
1335	Fc region with T256N/A378V/S383N/ N434Y, LALA PS mutations
1336	Fc region with T256N/A378V/S383N/ N434Y, LALA PG mutations
1337	Fc region with T256N/A378V/S383N/ N434Y, LAGA mutations
1338	Fc region with E294delta mutation
1339	Fc region with E294delta LALA mutations
1340	Fc region with E294delta LALA PS mutations
1341	FC region with E294delta LALA PG mutations
1342	Fc region with E294delta LAGA mutations
1343	Fc region with T256D/N286D/T307R/ Q311V/A378V mutations
1344	Fc region with T256D/N286D/T307R/ Q311V/A378V, LALA mutations
1345	Fc region with T256D/N286D/T307R/ Q311V/A378V, LALA PS mutations
1346	Fc region with T256D/N286D/T307R/ Q311V/A378V, LALA PG mutations
1347	Fc region with T256D/N286D/T307R/ Q311V/A378V, LAGA mutations
1348	Fc region with T256D/T307Q mutations
1349	Fc region with T256D/T307Q, LALA mutations

SEQ ID NO:	Polypeptide Sequence of
1350	Fc region with T256D/T307Q, LALA PS mutations
1351	Fc region with T256D/T307Q, LALA PG mutations
1352	Fc region with T256D/T307Q, LAGA mutations
1353	Fc region with T256D/T307W mutations
1354	Fc region with T256D/T307W LALA mutations
1355	Fc region with T256D/T307W LALA PS mutations
1356	Fc region with T256D/T307W LALA PG mutations
1357	Fc region with T256D/T307W LAGA mutations
1358	Fc region with M252Y/T256D mutations
1359	Fc region with M252Y/T256D, LALA mutations
1360	Fc region with M252Y/T256D, LALA PS mutations
1361	Fc region with M252Y/T256D, LALA PG mutations
1362	Fc region with M252Y/T256D, LAGA mutations
1363	Fc region with T307Q/Q311V/A378V mutations
1364	Fc region with T307Q/Q311V/A378V, LALA mutations
1365	Fc region with T307Q/Q311V/A378V, LALA PS mutations
1366	Fc region with T307Q/Q311V/A378V, LALA PG mutations
1367	Fc region with T307Q/Q311V/A378V, LAGA mutations
1375	Wildtype Fc region
1376	Fc region with LALA PG mutations
1377	Fc region with LAGA mutations

SEQ ID NO:	cDNA sequence of
1229	Human LPAR1
1230	Human LPAR2
1231	Human LPAR3
1232	Mouse LPAR1
1233	Guinea-pig LPAR1
1234	Rabbit LPAR1
1368	11 VH
1369	12 VH
1370	12 VL
1371	15 VL
1372	16 VH
1373	17 VH
1374	18 VL

DETAILED DESCRIPTION OF THE INVENTION

Definitions

Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this invention belongs. As used herein, the following terms have the meanings ascribed to them below.

Polypeptides are organic polymers consisting of a number of amino acid residues bonded together in a chain. As used herein, 'polypeptide' is used interchangeably with 'protein' and 'peptide'.

The term "antibody" includes any antibody protein construct comprising at least one antibody variable domain comprising at least one antigen binding site (ABS). Antibodies include, but are not limited to, immunoglobulins of types IgA, IgG, IgE, IgD, IgM (as well as subtypes thereof). The overall structure of Immunoglobulin G (IgG) antibodies assembled from two identical heavy (H)-chain and two identical light (L)-chain polypeptides is well established and highly conserved in mammals (Padlan 1994).

"Specificity" refers to the number of different types of antigens or antigenic determinants to which a particular antibody or fragment thereof can bind. The specificity of an antibody is the ability of the antibody to recognise a particular antigen as a unique molecular entity and distinguish it from another. An antibody that "specifically binds" to an antigen or an epitope is a term well understood in the art. A molecule is said to exhibit "specific binding" if it reacts more frequently, more rapidly, with greater duration and/or with greater affinity with a particular target antigen or epitope, than it does with alternative targets. An antibody "specifically binds" to a target antigen or epitope if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances. An antibody (or fragment thereof) may be considered to specifically bind to a target if the binding is statistically significant compared to a non-relevant binder. Specific binding of an antibody, or fragment thereof, to an antigen or antigenic determinant can be determined in any suitable known manner, including, for example, Scatchard analysis and/or competitive binding assays, such as radioimmunoassays (RIA), enzyme immunoassays (EIA) and sandwich competition assays, equilibrium dialysis, equilibrium binding, gel filtration, ELISA, or spectroscopy (e.g. using a fluorescence assay) and the different variants thereof known in the art.

"Affinity", represented by the equilibrium constant for the dissociation of an antigen with an antigen-binding polypeptide (K_D), is a measure of the binding strength between an antigenic determinant and an antigen-binding site on the antibody (or fragment thereof): the lesser the value of the K_D, the stronger the binding strength between an antigenic determinant and the antigen-binding polypeptide. Alternatively, the affinity can also be expressed as the affinity constant (KA), which is $1/K_D$. Affinity can be determined by known methods, depending on the specific antigen of interest. For example K_D may be determined by the method recited in the Examples section under method 1.14. Any K_D value less than 10^{-6} is considered to indicate binding. Suitably, polypeptides of the invention will bind with a dissociation constant of 10^{-6} M

or less, more suitably 10^{-7} M or less, more suitably 10^{-8} M or less and more suitably 10^{-9} M or less.

"Avidity" is the measure of the strength of binding between a polypeptide, an antibody or fragment thereof, and the pertinent antigen. Avidity is related to both the affinity between an antigenic determinant and its antigen binding site on the antibody and the number of pertinent binding sites present on the antibody.

Suitably, the polypeptide of the invention is isolated. An "isolated" polypeptide is one that is removed from its original environment. For example, a naturally-occurring polypeptide of the invention is isolated if it is separated from some or all of the coexisting materials in the natural system. The term "isolated" may also be used to refer to preparations where the isolated polypeptide is sufficiently pure to be administered therapeutically when formulated as an active ingredient of a pharmaceutical composition, or at least 70-80% (w/w) pure, more preferably, at least 80-90% (w/w) pure, even more preferably, 90-95% pure; and, most preferably, at least 95%, 96%, 97%, 98%, 99%, or 100% (w/w) pure.

Suitably, the polynucleotides used in the present invention are isolated. An "isolated" polynucleotide is one that is removed from its original environment. For example, a naturally-occurring polynucleotide is isolated if it is separated from some or all of the coexisting materials in the natural system. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of its natural environment or if it is comprised within cDNA.

For the purposes of comparing two closely-related polypeptide sequences, the "% sequence identity" between a first polypeptide sequence and a second polypeptide sequence may be calculated using NCBI BLAST v2.0, using standard settings for polypeptide sequences (BLASTP). For the purposes of comparing two closely-related polynucleotide sequences, the "% sequence identity" between a first nucleotide sequence and a second nucleotide sequence may be calculated using NCBI BLAST v2.0, using standard settings for nucleotide sequences (BLASTN).

Polypeptide or polynucleotide sequences are said to be the same as or "identical" to other polypeptide or polynucleotide sequences if they share 100% sequence identity over their entire length. Residues in sequences are numbered from left to right, *i.e.* from N- to C-terminus for polypeptides; from 5' to 3' terminus for polynucleotides.

A "difference" between polypeptide sequences refers to an insertion, deletion or substitution of a single amino acid residue in a position of the second sequence, compared to the first sequence. Two polypeptide sequences can contain one, two or more such amino acid differences. Insertions, deletions or substitutions in a second sequence which is otherwise identical (100% sequence identity) to a first sequence result in reduced % sequence identity. For example, if the identical sequences are 9 amino acid residues long, one substitution in the second sequence results in a sequence identity of 88.9%. If first and second polypeptide sequences are 9 amino acid residues long and share 6 identical residues, the first and second

polypeptide sequences share greater than 66% identity (the first and second polypeptide sequences share 66.7% identity).

Alternatively, for the purposes of comparing a first, reference polypeptide sequence to a second, comparison polypeptide sequence, the number of additions, substitutions and/or deletions made to the first sequence to produce the second sequence may be ascertained. An "addition" is the addition of one amino acid residue into the sequence of the first polypeptide (including addition at either terminus of the first polypeptide). A "substitution" is the substitution of one amino acid residue in the sequence of the first polypeptide with one different amino acid residue. Said substitution may be conservative or non-conservative. A "deletion" is the deletion of one amino acid residue from the sequence of the first polypeptide (including deletion at either terminus of the first polypeptide).

Using the three letter and one letter codes, the naturally occurring amino acids may be referred to as follows: glycine (G or Gly), alanine (A or Ala), valine (V or Val), leucine (L or Leu), isoleucine (I or Ile), proline (P or Pro), phenylalanine (F or Phe), tyrosine (Y or Tyr), tryptophan (W or Trp), lysine (K or Lys), arginine (R or Arg), histidine (H or His), aspartic acid (D or Asp), glutamic acid (E or Glu), asparagine (N or Asn), glutamine (Q or Gln), cysteine (C or Cys), methionine (M or Met), serine (S or Ser) and Threonine (T or Thr). Where a residue may be aspartic acid or asparagine, the symbols Asx or B may be used. Where a residue may be glutamic acid or glutamine, the symbols Glx or Z may be used. References to aspartic acid include aspartate, and glutamic acid include glutamate, unless the context specifies otherwise.

A "conservative" amino acid substitution is an amino acid substitution in which an amino acid residue is replaced with another amino acid residue of similar chemical structure and which is expected to have little influence on the function, activity or other biological properties of the polypeptide. Such conservative substitutions suitably are substitutions in which one amino acid within the following groups is substituted by another amino acid residue from within the same group, as shown in Table 1 below.

Table 1: Amino acids

Group	**Amino acid residue**
Non-polar aliphatic	Glycine
	Alanine
	Valine
	Methionine
	Leucine
	Isoleucine
Aromatic	Phenylalanine
	Tyrosine
	Tryptophan
Polar uncharged	Serine
	Threonine
	Cysteine
	Proline
	Asparagine
	Glutamine
Negatively charged	Aspartate
	Glutamate
Positively charged	Lysine
	Arginine
	Histidine

Suitably, a hydrophobic amino acid residue is a non-polar amino acid. More suitably, a hydrophobic amino acid residue is selected from V, I, L, M, F, W or C. In some embodiments, a hydrophobic amino acid residue is selected from glycine, alanine, valine, methionine, leucine, isoleucine, phenylalanine, tyrosine, or tryptophan. Suitably, any residues in a sequence which do not correspond to the residues provided in a reference sequence are conservative substitutions with respect to the residues of the reference sequence.

As used herein, numbering of polypeptide sequences and definitions of CDRs and FRs (i.e. HCDR1, HCDR2, HCDR3, HFR1, HFR2, HFR3, HFR4, LCDR1, LCDR2, LCDR3, LFR1, LFR2, LFR3 and LFR4) are as defined according to the Kabat system (Kabat *et al.*, 1991, herein incorporated by reference in its entirety), unless mentioned otherwise. In a limited number of specific embodiments disclosed herein (derived from the residue substitution work performed in Example 7), a non-Kabat numbering system is applied for CDR definition and this is specified when used. A "corresponding" amino acid residue between a first and second polypeptide sequence is an amino acid residue in a first sequence which shares the same position according to the Kabat system with an amino acid residue in a second sequence, whilst the amino acid residue in the second sequence may differ in identity from the first. Suitably corresponding residues will share the same number (and letter) if the framework and CDRs are the same length according to Kabat definition. Alignment can be achieved manually or by using, for example, a known computer algorithm for sequence alignment such as NCBI BLAST v2.0 (BLASTP or BLASTN) using standard settings.

References herein to an "epitope" refer to the portion of the target which is bound by the polypeptide, antibody or fragment thereof. Epitopes may also be referred to as "antigenic determinants". An antibody binds "essentially the same epitope" as another antibody when they both recognize identical or sterically overlapping epitopes. Commonly used methods to determine whether two antibodies bind to identical or overlapping epitopes are competition assays, which can be configured in a number of different formats (*e.g.* well plates using radioactive or enzyme labels, or flow cytometry on antigen-expressing cells) using either labelled antigen or labelled antibody. An antibody binds "the same epitope" as another antibody when they both recognize identical epitopes (i.e. all contact points between the antigen and the antibody are the same). For example, an antibody may bind the same epitope as another antibody when all contact points across a specified region of an antigen are identified as the same with the aid of a characterization method such as antibody/antigen cross-linking-coupled MS, HDX, X-ray crystallography, cryo-EM, or mutagenesis.

Further, with the aid of such characterization methods, it is also possible to characterize antibodies which bind essentially the same epitope by recognizing some but not all of the identical contact points. Specifically, such antibodies may share a sufficient number of identical contact points in a specified antigenic region to deliver a broadly equivalent technical effect and/or equivalent antigen interaction selectivity. Additionally, in some instances whereby antibodies recognize essentially the same epitope and confer a broadly equivalent technical effect and/or interaction selectivity, it can also be useful to define the epitope binding

footprint by the totality of antigen contacts inclusive of the most N-terminal antigen contact point through to the most C-terminal antigen contact point.

Epitopes found on protein targets may be defined as “linear epitopes” or “conformational epitopes”. Linear epitopes are formed by a continuous sequence of amino acids in a protein antigen. Conformational epitopes are formed of amino acids that are discontinuous in the protein sequence, but which are brought together upon folding of the protein into its three-dimensional structure.

The term “vector”, as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a “plasmid”, which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian and yeast vectors). Other vectors (*e.g.* non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as “recombinant expression vectors” (or simply, “expression vectors”). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, “plasmid” and “vector” may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include other forms of expression vectors, such as viral vectors (*e.g.* replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions, and also bacteriophage and phagemid systems. The term “recombinant host cell” (or simply “host cell”), as used herein, is intended to refer to a cell into which a recombinant expression vector has been introduced. Such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell, for example, when said progeny are employed to make a cell line or cell bank which is then optionally stored, provided, sold, transferred, or employed to manufacture a polypeptide, antibody or fragment thereof as described herein.

References to “subject”, “patient” or “individual” refer to a subject, in particular a mammalian subject, to be treated. Mammalian subjects include humans, non-human primates, farm animals (such as cows), sports animals, or pet animals, such as dogs, cats, guinea pigs, rabbits, rats or mice. In some embodiments, the subject is a human or a mouse. Most suitably the subject is a human.

The term "sufficient amount" means an amount sufficient to produce a desired effect. The term "therapeutically effective amount" is an amount that is effective to ameliorate a symptom of a disease or disorder. A therapeutically effective amount can be a "prophylactically effective amount" as prophylaxis can be considered therapy.

A disease or disorder is "ameliorated" if the severity of a sign or symptom of the disease or disorder, the frequency with which such a sign or symptom is experienced by a subject, or both, is reduced.

As used herein, "treating a disease or disorder" means reducing the frequency and/or severity of at least one sign or symptom of the disease or disorder experienced by a subject.

"Inflammation" refers to a chronic or acute triggering of the immune system resulting in an inflamed cell, cell type, tissue, or organ.

"Fibrosis" refers to pathological wound healing, wherein connective tissue replaces normal tissue, causing tissue remodelling and formation of scar tissue.

As used herein, the term "about" includes up to and including 10% greater and up to and including 10% lower than the value specified, suitably up to and including 5% greater and up to and including 5% lower than the value specified, especially the value specified. The term "between", includes the values of the specified boundaries.

"Potency" is a measure of the activity of a therapeutic agent expressed in terms of the amount required to produce an effect of given intensity. A highly potent agent evokes a greater response at low concentrations compared to an agent of lower potency that evokes a smaller response at low concentrations. Potency is a function of affinity and efficacy. Efficacy refers to the ability of therapeutic agent to produce a biological response upon binding to a target and the quantitative magnitude of this response. The term half maximal effective concentration (EC50) refers to the concentration of a therapeutic agent which causes a response halfway between the baseline and maximum after a specified exposure time. The therapeutic agent may cause inhibition or stimulation. It is commonly used, and is used herein, as a measure of potency.

Polypeptides which bind to LPAR1

Polypeptides are said to be binding polypeptides when they contain one or more stretches of amino acid residues which form an antigen-binding site, capable of binding to an epitope on a target antigen with an affinity (suitably expressed as a K_D value, a Ka value, a kon-rate and/or a koff-rate, as further described herein). 'Binding polypeptide' and 'antigen-binding polypeptide' are used synonymously herein, as are the terms 'binds to LPAR1' and 'anti-LPAR1'. A binding polypeptide is suitably capable of exerting a beneficial pharmacological effect upon administration to a subject. Suitably the polypeptide agonises, inversely agonises, antagonises or neutralises, LPAR1. In some embodiments the polypeptide may inversely agonise LPAR1. In some embodiments the polypeptide may bind the external surface of LPAR1, i.e. the extracellular region of LPAR1.

LPAR1 binding polypeptides may include antibodies (which are further described below), antibodies modified to comprise additional binding regions, antibody mimetics and antigen-binding antibody fragments (which are further described below). Further binding polypeptides

may include, for example, DARPins (Binz *et al.* 2003), Affimers™, Fynomers™, Centyrins, Nanofitins® and cyclic peptides.

Antibodies and fragments thereof

The polypeptide is preferably an antibody or fragment thereof.

A conventional antibody or immunoglobulin (Ig) is a protein comprising four polypeptide chains: two heavy (H, or HC) chains and two light (L, or LC) chains. Each chain is divided into a constant region and a variable region. The heavy (H) chain variable region is abbreviated herein as VH region, and the light (L) chain variable region is abbreviated herein as VL region. These domains, domains related thereto and domains derived therefrom, are referred to herein as variable domains. The VH and VL regions (or 'domains) can be further subdivided into regions of hypervariability, termed "complementarity determining regions" ("CDRs"), interspersed with regions that are more conserved, termed "framework regions" ("FRs"). The framework and complementarity determining regions have been precisely defined (Kabat *et al* 1991, herein incorporated by reference in its entirety). In a conventional antibody, each VH and VL region is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. The VH region CDRs and FRs are denoted HCDR1, HCDR2, HCDR3, HFR1, HFR2, HFR3 and HFR4. The VL region CDRs and FRs are denoted LCDR1, LCDR2, LCDR3, LFR1, LFR2, LFR3 and LFR4. The conventional antibody tetramer of two heavy immunoglobulin chains and two light immunoglobulin chains is formed with the heavy and the light immunoglobulin chains inter-connected by e.g. disulfide bonds, and the heavy chains similarly connected. The heavy chain constant region includes three domains, CH1, CH2 and CH3. The light chain constant region is comprised of one domain, CL. The variable domain of the heavy chains and the variable domain of the light chains are binding domains that interact with an antigen. The constant regions of the antibodies typically mediate the binding of the antibody to host tissues or factors, including various cells of the immune system (e.g. effector cells) and the first component (C1q) of the classical complement system.

A fragment of an antibody (which may also referred to as "antibody fragment", "immunoglobulin fragment", "antigen-binding fragment" or "antigen-binding polypeptide") as used herein refers to a portion of an antibody that specifically binds to the target (*e.g.* a molecule in which one or more immunoglobulin chains is not full length, but which specifically binds to the target). Examples of binding fragments encompassed within the term antibody fragment include:

(i) a Fab fragment (a monovalent fragment consisting of the VL, VH, CL and CH1 domains);

(ii) a F(ab')2 fragment (a bivalent fragment consisting of two Fab fragments linked by a disulphide bridge at the hinge region);

(iii) a Fd fragment (consisting of the VH and CH1 domains);

(iv) a Fv fragment (consisting of the VL and VH domains of a single arm of an antibody);

(v) a single chain variable fragment, scFv (consisting of VL and VH domains joined, using recombinant methods, by a synthetic linker that enables them to be made as a

single protein chain in which the VL and VH regions pair to form monovalent molecules);

(vi) a VH (a variable domain consisting of a VH domain);

(vii) a VL (a variable domain consisting of a VL domain);

(viii) a domain antibody (dAb, consisting of either the VH or VL domain);

(ix) a minibody (consisting of a pair of scFv fragments which are linked via CH3 domains); and

(x) a diabody (consisting of a noncovalent dimer of scFv fragments that consist of a VH domain from one antibody connected by a small peptide linker a VL domain from another antibody).

"Human antibody" refers to antibodies having variable and constant regions derived from human germline immunoglobulin sequences. Human subjects administered with said human antibodies do not generate cross-species antibody responses (for example termed HAMA responses - human-anti-mouse antibody) to the primary amino acids contained within said antibodies. Said human antibodies may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g. mutations introduced by random or site-specific mutagenesis or by somatic mutation), for example in the CDRs and in particular CDR3. However, the term is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences. Human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell, antibodies isolated from a recombinant, combinatorial human antibody library, antibodies isolated from an animal (e.g., a mouse) that is transgenic for human immunoglobulin genes or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences, may also be referred to as "recombinant human antibodies".

Substituting at least one amino acid residue in the framework region of a non-human immunoglobulin variable domain with the corresponding residue from a human variable domain is referred to as "humanisation". Humanisation of a variable domain may reduce immunogenicity in humans.

In one embodiment, the antibody or fragment thereof is an scFv, Fab, Fab', F(ab')2, Fv, variable domain (*e.g.* VH or VL), diabody, minibody or full length antibody. In a particular embodiment, the antibody or fragment thereof is an scFv or a full length antibody.

Antibodies of the invention can be of any class, *e.g.* IgG, IgA, IgM, IgE, IgD, or subclass thereof, and can comprise a kappa or lambda light chain. In one embodiment, the antibody is an IgG antibody, for example, at least one of subclasses, IgG1, IgG2, IgG3 or IgG4. In one embodiment, the antibody is an IgG1. In a further embodiment, the antibody may be in a format, such as an IgG format, that has been modified to confer desired properties, such as having the Fc mutated to reduce effector function, extend half-life, alter ADCC, or improve hinge stability. Such modifications are well known in the art and exemplary embodiments are described herein. For instance, an antibody or fragment thereof of the invention may comprise

an IgG1 heavy chain constant region comprising or consisting of an amino acid sequence according to SEQ ID NO: 56. Suitably, the heavy chain constant region comprises mutations to extend antibody half-life *in vivo* as described in Booth et al. 2018, Borrok et al. 2017, Dall'Acqua et al. 2006, Dall'Acqua et al. 2002, Datta-Mannan et al. 2012, Hinton et al. 2004, Igawa et al. 2013, Ko et al. 2021, Lee CH et al. 2019, Lie et al. 2020, Mackness et al. 2019, Petkova et al. 2006, Robbie et al. 2013, Saunders 2019, Shields et al. 2001, Vaccaro et al. 2006, Vaccaro et al. 2005, Zalevsky et al. 2010, US2014/056879A1, US8088376B2, WO2006053301, WO2009086320 and WO2018035107 (all incorporated by reference herein for the purpose of the Fc mutations disclosed therein). Suitably, the heavy chain constant region comprises Fc effector-enhancing mutations as described in WO2004029207, WO2004099249 and WO2006019447 (all incorporated by reference herein for the purpose of the Fc mutations disclosed therein).

Suitably, the heavy chain constant region comprises one or more of the following residues:

residue at position 250 is Q, residue at position 252 is Y, residue at position 252 is F, residue at position 252 is W, residue at position 252 is T, residue at position 253 is A, residue at position 254 is T, residue at position 256 is E, residue at position 256 is S, residue at position 256 is R, residue at position 256 is Q, residue at position 256 is D, residue at position 259 is I, residue at position 285 is D, residue at position 285 is N, residue at position 286 is D, residue at position 294 is deleted, residue at position 307 is A, residue at position 307 is Q, residue at position 307 is P, residue at position 307 is R, residue at position 307 is W, residue at position 308 is P, residue at position 308 is F, residue at position 309 is P, residue at position 309 is D, residue at position 309 is N, residue at position 310 is A, residue at position 311 is S, residue at position 311 is I, residue at position 311 is V, residue at position 311 is H, residue at position 315 is D, residue at position 378 is V, residue at position 380 is A, residue at position 385 is R, residue at position 385 is D, residue at position 385 is S, residue at position 385 is T, residue at position 385 is H, residue at position 385 is K, residue at position 385 is A, residue at position 385 is G, residue at position 386 is T, residue at position 386 is P, residue at position 386 is D, residue at position 386 is S, residue at position 386 is K, residue at position 386 is R, residue at position 386 is I, residue at position 386 is M, residue at position 387 is R, residue at position 387 is P, residue at position 387 is H, residue at position 387 is S, residue at position 387 is T, residue at position 387 is A, residue at position 389 is P, residue at position 389 is S, residue at position 389 is N, residue at position 428 is L, residue at position 433 is K, residue at position 433 is R, residue at position 433 is S, residue at position 433 is I, residue at position 433 is P, residue at position 433 is Q, residue at position 434 is F, residue at position 434 is H, residue at position 434 is Y, residue at position 434 is A, residue at position 434 is S, residue at position 435 is A, residue at position 436 is H, residue at position 436 is I or residue at position 436 is V.

More suitably, the heavy chain constant region comprises mutations at positions 252, 254 and 256; 428 and 434; 433, 434 and 436; 428, 434 and 436; 252, 254, 256 and 322; and 309, 311 and 434; or functional variants thereof. More suitably, the heavy chain constant region comprises mutations at positions 252, 254 and 256; 428 and 434; 433, 434 and 436; 428, 434

and 436; 252, 254, 256 and 322; and 309, 311 and 434. Most suitably, the heavy chain constant region comprises the mutations M252Y, S254T and T256E or mutations M428L and N434S. Alternatively the antibody could be PEGylated to increase half-life.

Alternatively, or in addition, the heavy chain constant region may comprise Fc silencing mutations. Suitably, the heavy chain constant region comprises the mutations L234A and L235A. More suitably, the heavy chain constant region comprises the mutations L234A, L235A and P331S (LALAPS). Alternatively, the heavy chain constant region comprises the mutations L234A, L235A and P239G (LALA PG). Alternatively, the heavy chain constant region comprises the mutations L235A and G237A (LAGA).

Accordingly, in certain embodiments the antibody may comprise the following combined heavy constant, heavy variable (VH), light constant and light variable (VL) polypeptide sequences in the antibody combinations 1 to 680 shown in Table 2. Suitably, the antibody comprises two heavy chains and two light chains, wherein each heavy chain comprises (e.g. consists of) the heavy constant and heavy variable (VH) sequences of one antibody combination of Table 2, and each light chain comprises (e.g. consists of) the light constant and light variable (VL) sequences of said antibody combination of Table 2.

Table 2: Antibody combinations 1 to 680 comprising heavy and light chain variable regions and constant regions

Mutations	**Combin-ation**	**Heavy constant SEQ ID NO:**	**Light constant SEQ ID NO:**	**VH SEQ ID NO:**	**VL SEQ ID NO:**
Wild type	1	1375	57	37	38
	2	1375	57	36	38
	3	1375	57	102	99
	4	1375	57	102	104
	5	1375	57	36	99
L234A and L235A (LALA)	6	1235	57	37	38
	7	1235	57	36	38
	8	1235	57	102	99
	9	1235	57	102	104
	10	1235	57	36	99
L234A, L235A and P331S (LALA PS)	11	56	57	37	38
	12	56	57	36	38
	13	56	57	102	99
	14	56	57	102	104
	15	56	57	36	99
L234A, L235A and P329G (LALA PG)	16	1376	57	37	38
	17	1376	57	36	38
	18	1376	57	102	99
	19	1376	57	102	104
	20	1376	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
L235A and G237A (LAGA)	21	1377	57	37	38
	22	1377	57	36	38
	23	1377	57	102	99
	24	1377	57	102	104
	25	1377	57	36	99
M252Y, S254T and T256E	26	1237	57	37	38
	27	1237	57	36	38
	28	1237	57	102	99
	29	1237	57	102	104
	30	1237	57	36	99
M252Y, S254T, T256E, LALA	31	1238	57	37	38
	32	1238	57	36	38
	33	1238	57	102	99
	34	1238	57	102	104
	35	1238	57	36	99
M252Y, S254T, T256E, LALA PS	36	1239	57	37	38
	37	1239	57	36	38
	38	1239	57	102	99
	39	1239	57	102	104
	40	1239	57	36	99
M252Y, S254T, T256E, LALA PG	41	1240	57	37	38
	42	1240	57	36	38
	43	1240	57	102	99
	44	1240	57	102	104
	45	1240	57	36	99
M252Y, S254T, T256E, LAGA	46	1241	57	37	38
	47	1241	57	36	38
	48	1241	57	102	99
	49	1241	57	102	104
	50	1241	57	36	99
H433K, N434F	51	1242	57	37	38
	52	1242	57	36	38
	53	1242	57	102	99
	54	1242	57	102	104
	55	1242	57	36	99
H433K, N434F, LALA	56	1243	57	37	38
	57	1243	57	36	38
	58	1243	57	102	99
	59	1243	57	102	104
	60	1243	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
H433K, N434F, LALA PS	61	1244	57	37	38
	62	1244	57	36	38
	63	1244	57	102	99
	64	1244	57	102	104
	65	1244	57	36	99
H433K, N434F, LALA PG	66	1245	57	37	38
	67	1245	57	36	38
	68	1245	57	102	99
	69	1245	57	102	104
	70	1245	57	36	99
H433K, N434F, LAGA	71	1246	57	37	38
	72	1246	57	36	38
	73	1246	57	102	99
	74	1246	57	102	104
	75	1246	57	36	99
H433K, N434F, Y436H	76	1247	57	37	38
	77	1247	57	36	38
	78	1247	57	102	99
	79	1247	57	102	104
	80	1247	57	36	99
H433K, N434F, Y436H, LALA	81	1248	57	37	38
	82	1248	57	36	38
	83	1248	57	102	99
	84	1248	57	102	104
	85	1248	57	36	99
H433K, N434F, Y436H, LALA PS	86	1249	57	37	38
	87	1249	57	36	38
	88	1249	57	102	99
	89	1249	57	102	104
	90	1249	57	36	99
H433K, N434F, Y436H, LALA PG	91	1250	57	37	38
	92	1250	57	36	38
	93	1250	57	102	99
	94	1250	57	102	104
	95	1250	57	36	99
H433K, N434F, Y436H, LAGA	96	1251	57	37	38
	97	1251	57	36	38
	98	1251	57	102	99
	99	1251	57	102	104
	100	1251	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
M252Y, S254T, T256E, H433K, N434F	101	1252	57	37	38
	102	1252	57	36	38
	103	1252	57	102	99
	104	1252	57	102	104
	105	1252	57	36	99
M252Y, S254T, T256E, H433K, N434F, LALA	106	1253	57	37	38
	107	1253	57	36	38
	108	1253	57	102	99
	109	1253	57	102	104
	110	1253	57	36	99
M252Y, S254T, T256E, H433K, N434F, LALA PS	111	1254	57	37	38
	112	1254	57	36	38
	113	1254	57	102	99
	114	1254	57	102	104
	115	1254	57	36	99
M252Y, S254T, T256E, H433K, N434F, LALA PG	116	1255	57	37	38
	117	1255	57	36	38
	118	1255	57	102	99
	119	1255	57	102	104
	120	1255	57	36	99
M252Y, S254T, T256E, H433K, N434F, LAGA	121	1256	57	37	38
	122	1256	57	36	38
	123	1256	57	102	99
	124	1256	57	102	104
	125	1256	57	36	99
M252Y, S254T, T256E, H433K, N434F, Y436H	126	1257	57	37	38
	127	1257	57	36	38
	128	1257	57	102	99
	129	1257	57	102	104
	130	1257	57	36	99
M252Y, S254T, T256E, H433K, N434F, Y436H, LALA	131	1258	57	37	38
	132	1258	57	36	38
	133	1258	57	102	99
	134	1258	57	102	104
	135	1258	57	36	99
M252Y, S254T, T256E, H433K, N434F, Y436H, LALA PS	136	1259	57	37	38
	137	1259	57	36	38
	138	1259	57	102	99
	139	1259	57	102	104
	140	1259	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
M252Y, S254T, T256E, H433K, N434F, Y436H, LALA PG	141	1260	57	37	38
	142	1260	57	36	38
	143	1260	57	102	99
	144	1260	57	102	104
	145	1260	57	36	99
M252Y, S254T, T256E, H433K, N434F, Y436H, LAGA	146	1261	57	37	38
	147	1261	57	36	38
	148	1261	57	102	99
	149	1261	57	102	104
	150	1261	57	36	99
M428L, N434S	151	1262	57	37	38
	152	1262	57	36	38
	153	1262	57	102	99
	154	1262	57	102	104
	155	1262	57	36	99
M428L, N434S, LALA	156	1263	57	37	38
	157	1263	57	36	38
	158	1263	57	102	99
	159	1263	57	102	104
	160	1263	57	36	99
M428L, N434S, LALA PS	161	1264	57	37	38
	162	1264	57	36	38
	163	1264	57	102	99
	164	1264	57	102	104
	165	1264	57	36	99
M428L, N434S, LALA PG	166	1265	57	37	38
	167	1265	57	36	38
	168	1265	57	102	99
	169	1265	57	102	104
	170	1265	57	36	99
M428L, N434S, LAGA	171	1266	57	37	38
	172	1266	57	36	38
	173	1266	57	102	99
	174	1266	57	102	104
	175	1266	57	36	99
T250Q, M428L	176	1267	57	37	38
	177	1267	57	36	38
	178	1267	57	102	99
	179	1267	57	102	104
	180	1267	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
T250Q, M428L, LALA	181	1268	57	37	38
	182	1268	57	36	38
	183	1268	57	102	99
	184	1268	57	102	104
	185	1268	57	36	99
T250Q, M428L, LALA PS	186	1269	57	37	38
	187	1269	57	36	38
	188	1269	57	102	99
	189	1269	57	102	104
	190	1269	57	36	99
T250Q, M428L, LALA PG	191	1270	57	37	38
	192	1270	57	36	38
	193	1270	57	102	99
	194	1270	57	102	104
	195	1270	57	36	99
T250Q, M428L, LAGA	196	1271	57	37	38
	197	1271	57	36	38
	198	1271	57	102	99
	199	1271	57	102	104
	200	1271	57	36	99
T307A, E380A, N434A	201	1272	57	37	38
	202	1272	57	36	38
	203	1272	57	102	99
	204	1272	57	102	104
	205	1272	57	36	99
T307A, E380A, N434A, LALA	206	1273	57	37	38
	207	1273	57	36	38
	208	1273	57	102	99
	209	1273	57	102	104
	210	1273	57	36	99
T307A, E380A, N434A, LALA PS	211	1274	57	37	38
	212	1274	57	36	38
	213	1274	57	102	99
	214	1274	57	102	104
	215	1274	57	36	99
T307A, E380A, N434A, LALA PG	216	1275	57	37	38
	217	1275	57	36	38
	218	1275	57	102	99
	219	1275	57	102	104
	220	1275	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
T307A, E380A, N434A, LAGA	221	1276	57	37	38
	222	1276	57	36	38
	223	1276	57	102	99
	224	1276	57	102	104
	225	1276	57	36	99
V308P	226	1277	57	37	38
	227	1277	57	36	38
	228	1277	57	102	99
	229	1277	57	102	104
	230	1277	57	36	99
V308P, LALA	231	1278	57	37	38
	232	1278	57	36	38
	233	1278	57	102	99
	234	1278	57	102	104
	235	1278	57	36	99
V308P, LALA PS	236	1279	57	37	38
	237	1279	57	36	38
	238	1279	57	102	99
	239	1279	57	102	104
	240	1279	57	36	99
V308P, LALA PG	241	1280	57	37	38
	242	1280	57	36	38
	243	1280	57	102	99
	244	1280	57	102	104
	245	1280	57	36	99
V308P, LAGA	246	1281	57	37	38
	247	1281	57	36	38
	248	1281	57	102	99
	249	1281	57	102	104
	250	1281	57	36	99
H285D, T307Q, A378V	251	1282	57	37	38
	252	1282	57	36	38
	253	1282	57	102	99
	254	1282	57	102	104
	255	1282	57	36	99
H285D, T307Q, A378V, LALA	256	1283	57	37	38
	257	1283	57	36	38
	258	1283	57	102	99
	259	1283	57	102	104
	260	1283	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
H285D, T307Q, A378V, LALA PS	261	1284	57	37	38
	262	1284	57	36	38
	263	1284	57	102	99
	264	1284	57	102	104
	265	1284	57	36	99
H285D, T307Q, A378V, LALA PG	266	1285	57	37	38
	267	1285	57	36	38
	268	1285	57	102	99
	269	1285	57	102	104
	270	1285	57	36	99
H285D, T307Q, A378V, LAGA	271	1286	57	37	38
	272	1286	57	36	38
	273	1286	57	102	99
	274	1286	57	102	104
	275	1286	57	36	99
L309D, Q311H, N434S	276	1287	57	37	38
	277	1287	57	36	38
	278	1287	57	102	99
	279	1287	57	102	104
	280	1287	57	36	99
L309D, Q311H, N434S, LALA	281	1288	57	37	38
	282	1288	57	36	38
	283	1288	57	102	99
	284	1288	57	102	104
	285	1288	57	36	99
L309D, Q311H, N434S, LALA PS	286	1289	57	37	38
	287	1289	57	36	38
	288	1289	57	102	99
	289	1289	57	102	104
	290	1289	57	36	99
L309D, Q311H, N434S, LALA PG	291	1290	57	37	38
	292	1290	57	36	38
	293	1290	57	102	99
	294	1290	57	102	104
	295	1290	57	36	99
L309D, Q311H, N434S, LAGA	296	1291	57	37	38
	297	1291	57	36	38
	298	1291	57	102	99
	299	1291	57	102	104
	300	1291	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
I253A, H310A, H435A	301	1292	57	37	38
	302	1292	57	36	38
	303	1292	57	102	99
	304	1292	57	102	104
	305	1292	57	36	99
I253A, H310A, H435A, LALA	306	1293	57	37	38
	307	1293	57	36	38
	308	1293	57	102	99
	309	1293	57	102	104
	310	1293	57	36	99
I253A, H310A, H435A, LALA PS	311	1294	57	37	38
	312	1294	57	36	38
	313	1294	57	102	99
	314	1294	57	102	104
	315	1294	57	36	99
I253A, H310A, H435A, LALA PG	316	1295	57	37	38
	317	1295	57	36	38
	318	1295	57	102	99
	319	1295	57	102	104
	320	1295	57	36	99
I253A, H310A, H435A, LAGA	321	1296	57	37	38
	322	1296	57	36	38
	323	1296	57	102	99
	324	1296	57	102	104
	325	1296	57	36	99
N434S, Q311I	326	1297	57	37	38
	327	1297	57	36	38
	328	1297	57	102	99
	329	1297	57	102	104
	330	1297	57	36	99
N434S, Q311I, LALA	331	1298	57	37	38
	332	1298	57	36	38
	333	1298	57	102	99
	334	1298	57	102	104
	335	1298	57	36	99
N434S, Q311I, LALA PS	336	1299	57	37	38
	337	1299	57	36	38
	338	1299	57	102	99
	339	1299	57	102	104
	340	1299	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
N434S, Q311I, LALA PG	341	1300	57	37	38
	342	1300	57	36	38
	343	1300	57	102	99
	344	1300	57	102	104
	345	1300	57	36	99
N434S, Q311I, LAGA	346	1301	57	37	38
	347	1301	57	36	38
	348	1301	57	102	99
	349	1301	57	102	104
	350	1301	57	36	99
N434S, Q311V	351	1302	57	37	38
	352	1302	57	36	38
	353	1302	57	102	99
	354	1302	57	102	104
	355	1302	57	36	99
N434S, Q311V, LALA	356	1303	57	37	38
	357	1303	57	36	38
	358	1303	57	102	99
	359	1303	57	102	104
	360	1303	57	36	99
N434S, Q311V, LALA PS	361	1304	57	37	38
	362	1304	57	36	38
	363	1304	57	102	99
	364	1304	57	102	104
	365	1304	57	36	99
N434S, Q311V, LALA PG	366	1305	57	37	38
	367	1305	57	36	38
	368	1305	57	102	99
	369	1305	57	102	104
	370	1305	57	36	99
N434S, Q311V, LAGA	371	1306	57	37	38
	372	1306	57	36	38
	373	1306	57	102	99
	374	1306	57	102	104
	375	1306	57	36	99
N434S, Y436I	376	1307	57	37	38
	377	1307	57	36	38
	378	1307	57	102	99
	379	1307	57	102	104
	380	1307	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
N434S, Y436I, LALA	381	1308	57	37	38
	382	1308	57	36	38
	383	1308	57	102	99
	384	1308	57	102	104
	385	1308	57	36	99
N434S, Y436I, LALA PS	386	1309	57	37	38
	387	1309	57	36	38
	388	1309	57	102	99
	389	1309	57	102	104
	390	1309	57	36	99
N434S, Y436I, LALA PG	391	1310	57	37	38
	392	1310	57	36	38
	393	1310	57	102	99
	394	1310	57	102	104
	395	1310	57	36	99
N434S, Y436I, LAGA	396	1311	57	37	38
	397	1311	57	36	38
	398	1311	57	102	99
	399	1311	57	102	104
	400	1311	57	36	99
N434S, Y436V	401	1312	57	37	38
	402	1312	57	36	38
	403	1312	57	102	99
	404	1312	57	102	104
	405	1312	57	36	99
N434S, Y436V, LALA	406	1313	57	37	38
	407	1313	57	36	38
	408	1313	57	102	99
	409	1313	57	102	104
	410	1313	57	36	99
N434S, Y436V, LALA PS	411	1314	57	37	38
	412	1314	57	36	38
	413	1314	57	102	99
	414	1314	57	102	104
	415	1314	57	36	99
N434S, Y436V, LALA PG	416	1315	57	37	38
	417	1315	57	36	38
	418	1315	57	102	99
	419	1315	57	102	104
	420	1315	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
N434S, Y436V, LAGA	421	1316	57	37	38
	422	1316	57	36	38
	423	1316	57	102	99
	424	1316	57	102	104
	425	1316	57	36	99
N434A	426	1317	57	37	38
	427	1317	57	36	38
	428	1317	57	102	99
	429	1317	57	102	104
	430	1317	57	36	99
N434A, LALA	431	1318	57	37	38
	432	1318	57	36	38
	433	1318	57	102	99
	434	1318	57	102	104
	435	1318	57	36	99
N434A, LALA PS	436	1319	57	37	38
	437	1319	57	36	38
	438	1319	57	102	99
	439	1319	57	102	104
	440	1319	57	36	99
N434A, LALA PG	441	1320	57	37	38
	442	1320	57	36	38
	443	1320	57	102	99
	444	1320	57	102	104
	445	1320	57	36	99
N434A, LAGA	446	1321	57	37	38
	447	1321	57	36	38
	448	1321	57	102	99
	449	1321	57	102	104
	450	1321	57	36	99
M252Y, V308P, N434Y	451	1322	57	37	38
	452	1322	57	36	38
	453	1322	57	102	99
	454	1322	57	102	104
	455	1322	57	36	99
M252Y, V308P, N434Y, LALA	456	1323	57	37	38
	457	1323	57	36	38
	458	1323	57	102	99
	459	1323	57	102	104
	460	1323	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
M252Y, V308P, N434Y, LALA PS	461	1324	57	37	38
	462	1324	57	36	38
	463	1324	57	102	99
	464	1324	57	102	104
	465	1324	57	36	99
M252Y, V308P, N434Y, LALA PG	466	1325	57	37	38
	467	1325	57	36	38
	468	1325	57	102	99
	469	1325	57	102	104
	470	1325	57	36	99
M252Y, V308P, N434Y, LAGA	471	1326	57	37	38
	472	1326	57	36	38
	473	1326	57	102	99
	474	1326	57	102	104
	475	1326	57	36	99
L234F, L235Q, K322Q, M252Y, S254T, T256E	476	1327	57	37	38
	477	1327	57	36	38
	478	1327	57	102	99
	479	1327	57	102	104
	480	1327	57	36	99
E294delta/T307 P/N434Y	481	1328	57	37	38
	482	1328	57	36	38
	483	1328	57	102	99
	484	1328	57	102	104
	485	1328	57	36	99
E294delta/T307 P/N434Y, LALA	486	1329	57	37	38
	487	1329	57	36	38
	488	1329	57	102	99
	489	1329	57	102	104
	490	1329	57	36	99
E294delta/T307 P/N434Y, LALA PS	491	1330	57	37	38
	492	1330	57	36	38
	493	1330	57	102	99
	494	1330	57	102	104
	495	1330	57	36	99
E294delta/T307 P/N434Y, LALA PG	496	1331	57	37	38
	497	1331	57	36	38
	498	1331	57	102	99
	499	1331	57	102	104
	500	1331	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
E294delta/T307P/N434Y, LAGA	501	1332	57	37	38
	502	1332	57	36	38
	503	1332	57	102	99
	504	1332	57	102	104
	505	1332	57	36	99
T256N/A378V/S383N/N434Y	506	1333	57	37	38
	507	1333	57	36	38
	508	1333	57	102	99
	509	1333	57	102	104
	510	1333	57	36	99
T256N/A378V/S383N/N434Y, LALA	511	1334	57	37	38
	512	1334	57	36	38
	513	1334	57	102	99
	514	1334	57	102	104
	515	1334	57	36	99
T256N/A378V/S383N/N434Y, LALA PS	516	1335	57	37	38
	517	1335	57	36	38
	518	1335	57	102	99
	519	1335	57	102	104
	520	1335	57	36	99
T256N/A378V/S383N/N434Y, LALA PG	521	1336	57	37	38
	522	1336	57	36	38
	523	1336	57	102	99
	524	1336	57	102	104
	525	1336	57	36	99
T256N/A378V/S383N/N434Y, LAGA	526	1337	57	37	38
	527	1337	57	36	38
	528	1337	57	102	99
	529	1337	57	102	104
	530	1337	57	36	99
E294delta	531	1338	57	37	38
	532	1338	57	36	38
	533	1338	57	102	99
	534	1338	57	102	104
	535	1338	57	36	99
E294delta LALA	536	1339	57	37	38
	537	1339	57	36	38
	538	1339	57	102	99
	539	1339	57	102	104
	540	1339	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
E294delta LALA PS	541	1340	57	37	38
	542	1340	57	36	38
	543	1340	57	102	99
	544	1340	57	102	104
	545	1340	57	36	99
E294delta LALA PG	546	1341	57	37	38
	547	1341	57	36	38
	548	1341	57	102	99
	549	1341	57	102	104
	550	1341	57	36	99
E294delta LAGA	551	1342	57	37	38
	552	1342	57	36	38
	553	1342	57	102	99
	554	1342	57	102	104
	555	1342	57	36	99
T256D/N286D/T307R/Q311V/A378V	556	1343	57	37	38
	557	1343	57	36	38
	558	1343	57	102	99
	559	1343	57	102	104
	560	1343	57	36	99
T256D/N286D/T307R/Q311V/A378V, LALA	561	1344	57	37	38
	562	1344	57	36	38
	563	1344	57	102	99
	564	1344	57	102	104
	565	1344	57	36	99
T256D/N286D/T307R/Q311V/A378V, LALA PS	566	1345	57	37	38
	567	1345	57	36	38
	568	1345	57	102	99
	569	1345	57	102	104
	570	1345	57	36	99
T256D/N286D/T307R/Q311V/A378V, LALA PG	571	1346	57	37	38
	572	1346	57	36	38
	573	1346	57	102	99
	574	1346	57	102	104
	575	1346	57	36	99
T256D/N286D/T307R/Q311V/A378V, LAGA	576	1347	57	37	38
	577	1347	57	36	38
	578	1347	57	102	99
	579	1347	57	102	104
	580	1347	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
T256D/T307Q	581	1348	57	37	38
	582	1348	57	36	38
	583	1348	57	102	99
	584	1348	57	102	104
	585	1348	57	36	99
T256D/T307Q, LALA	586	1349	57	37	38
	587	1349	57	36	38
	588	1349	57	102	99
	589	1349	57	102	104
	590	1349	57	36	99
T256D/T307Q, LALA PS	591	1350	57	37	38
	592	1350	57	36	38
	593	1350	57	102	99
	594	1350	57	102	104
	595	1350	57	36	99
T256D/T307Q, LALA PG	596	1351	57	37	38
	597	1351	57	36	38
	598	1351	57	102	99
	599	1351	57	102	104
	600	1351	57	36	99
T256D/T307Q, LAGA	601	1352	57	37	38
	602	1352	57	36	38
	603	1352	57	102	99
	604	1352	57	102	104
	605	1352	57	36	99
T256D/T307W	606	1353	57	37	38
	607	1353	57	36	38
	608	1353	57	102	99
	609	1353	57	102	104
	610	1353	57	36	99
T256D/T307W LALA	611	1354	57	37	38
	612	1354	57	36	38
	613	1354	57	102	99
	614	1354	57	102	104
	615	1354	57	36	99
T256D/T307W LALA PS	616	1355	57	37	38
	617	1355	57	36	38
	618	1355	57	102	99
	619	1355	57	102	104
	620	1355	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
T256D/T307W LALA PG	621	1356	57	37	38
	622	1356	57	36	38
	623	1356	57	102	99
	624	1356	57	102	104
	625	1356	57	36	99
T256D/T307W LAGA	626	1357	57	37	38
	627	1357	57	36	38
	628	1357	57	102	99
	629	1357	57	102	104
	630	1357	57	36	99
M252Y/T256D	631	1358	57	37	38
	632	1358	57	36	38
	633	1358	57	102	99
	634	1358	57	102	104
	635	1358	57	36	99
M252Y/T256D, LALA	636	1359	57	37	38
	637	1359	57	36	38
	638	1359	57	102	99
	639	1359	57	102	104
	640	1359	57	36	99
M252Y/T256D, LALA PS	641	1360	57	37	38
	642	1360	57	36	38
	643	1360	57	102	99
	644	1360	57	102	104
	645	1360	57	36	99
M252Y/T256D, LALA PG	646	1361	57	37	38
	647	1361	57	36	38
	648	1361	57	102	99
	649	1361	57	102	104
	650	1361	57	36	99
M252Y/T256D, LAGA	651	1362	57	37	38
	652	1362	57	36	38
	653	1362	57	102	99
	654	1362	57	102	104
	655	1362	57	36	99
T307Q/Q311V/A 378V	656	1363	57	37	38
	657	1363	57	36	38
	658	1363	57	102	99
	659	1363	57	102	104
	660	1363	57	36	99

Mutations	Combin-ation	Heavy constant SEQ ID NO:	Light constant SEQ ID NO:	VH SEQ ID NO:	VL SEQ ID NO:
T307Q/Q311V/A 378V, LALA	661	1364	57	37	38
	662	1364	57	36	38
	663	1364	57	102	99
	664	1364	57	102	104
	665	1364	57	36	99
T307Q/Q311V/A 378V, LALA PS	666	1365	57	37	38
	667	1365	57	36	38
	668	1365	57	102	99
	669	1365	57	102	104
	670	1365	57	36	99
T307Q/Q311V/A 378V, LALA PG	671	1366	57	37	38
	672	1366	57	36	38
	673	1366	57	102	99
	674	1366	57	102	104
	675	1366	57	36	99
T307Q/Q311V/A 378V, LAGA	676	1367	57	37	38
	677	1367	57	36	38
	678	1367	57	102	99
	679	1367	57	102	104
	680	1367	57	36	99

In further embodiments the antibody may comprise the combined heavy constant, heavy variable (VH), light constant and light variable (VL) polypeptide sequences in combinations 1 to 25 as shown above in Table 2, but wherein the heavy chain constant region comprises one or more of the following residues:

residue at position 250 is Q, residue at position 252 is Y, residue at position 252 is F, residue at position 252 is W, residue at position 252 is T, residue at position 253 is A, residue at position 254 is T, residue at position 256 is E, residue at position 256 is S, residue at position 256 is R, residue at position 256 is Q, residue at position 256 is D, residue at position 259 is I, residue at position 285 is D, residue at position 285 is N, residue at position 286 is D, residue at position 294 is deleted, residue at position 307 is A, residue at position 307 is Q, residue at position 307 is P, residue at position 307 is R, residue at position 307 is W, residue at position 308 is P, residue at position 308 is F, residue at position 309 is P, residue at position 309 is D, residue at position 309 is N, residue at position 310 is A, residue at position 311 is S, residue at position 311 is I, residue at position 311 is V, residue at position 311 is H, residue at position 315 is D, residue at position 378 is V, residue at position 380 is A, residue at position 385 is R, residue at position 385 is D, residue at position 385 is S, residue at position 385 is T, residue at position 385 is H, residue at position 385 is K, residue at position 385 is A, residue at position 385 is G, residue at position 386 is T, residue at position 386 is P, residue at position 386 is D, residue at position 386 is S, residue at position 386 is K, residue

at position 386 is R, residue at position 386 is I, residue at position 386 is M, residue at position 387 is R, residue at position 387 is P, residue at position 387 is H, residue at position 387 is S, residue at position 387 is T, residue at position 387 is A, residue at position 389 is P, residue at position 389 is S, residue at position 389 is N, residue at position 428 is L, residue at position 433 is K, residue at position 433 is R, residue at position 433 is S, residue at position 433 is I, residue at position 433 is P, residue at position 433 is Q, residue at position 434 is F, residue at position 434 is H, residue at position 434 is Y, residue at position 434 is A, residue at position 434 is S, residue at position 435 is A, residue at position 436 is H, residue at position 436 is I or residue at position 436 is V.

In one embodiment, the antibody or fragment thereof comprises a heavy chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 37 followed by SEQ ID NO: 1239 and a light chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 38 followed by SEQ ID NO: 57. In one embodiment, the antibody or fragment thereof comprises a heavy chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 36 followed by SEQ ID NO: 1239 and a light chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 38 followed by SEQ ID NO: 57. In one embodiment, the antibody or fragment thereof comprises a heavy chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 102 followed by SEQ ID NO: 1239 and a light chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 99 followed by SEQ ID NO: 57. In one embodiment, the antibody or fragment thereof comprises a heavy chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 102 followed by SEQ ID NO: 1239 and a light chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 104 followed by SEQ ID NO: 57. In one embodiment, the antibody or fragment thereof comprises a heavy chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 36 followed by SEQ ID NO: 1239 and a light chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 99 followed by SEQ ID NO: 57.

In one embodiment, the antibody or fragment thereof comprises a heavy chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 37 followed by SEQ ID NO: 1264 and a light chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 38 followed by SEQ ID NO: 57. In one embodiment, the antibody or fragment thereof comprises a heavy chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 36 followed by SEQ ID NO: 1264 and a light chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 38 followed by SEQ ID NO: 57. In one embodiment, the antibody or fragment thereof comprises a heavy chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 102 followed by SEQ ID NO: 1264 and a light chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 99 followed by SEQ ID NO: 57. In one embodiment, the antibody or fragment thereof comprises a heavy chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 102 followed by SEQ ID NO: 1264 and a light chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 104 followed by SEQ ID NO: 57. In one embodiment, the antibody or fragment thereof comprises a heavy chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 36

followed by SEQ ID NO: 1264 and a light chain polypeptide sequence from N-terminus to C-terminus of SEQ ID NO: 99 followed by SEQ ID NO: 57.

An anti-LPAR1 antibody described herein can, in some embodiments, comprise a variant human Fc constant region that binds to human neonatal Fc receptor (FcRn) with greater affinity than that of the native human Fc constant region from which the variant human Fc constant region was derived. For example, the Fc constant region can comprise one or more (e.g., two, three, four, five, six, seven, or eight or more) amino acid substitutions relative to the native human Fc constant region from which the variant human Fc constant region was derived. The substitutions can increase the binding affinity of an IgG antibody containing the variant Fc constant region to FcRn at pH 6.0, while maintaining the pH dependence of the interaction. See, e.g., Hinton et al. (2004) *J Biol Chem* 279:6213-6216 and Datta-Mannan et al. (2007) *Drug Metab Dispos* 35:1-9. Methods for testing whether one or more substitutions in the Fc constant region of an antibody increase the affinity of the Fc constant region for FcRn at pH 6.0 (while maintaining pH dependence of the interaction) are known in the art and exemplified in the working examples. See, e.g., Datta-Mannan et al. (2007) *J Biol Chem* 282(3):1709-1717; International Publication No. WO 98/23289; International Publication No. WO 97/34631; and U.S. Pat. No. 6,277,375, the disclosures of each of which are incorporated herein by reference in their entirety.

Substitutions that enhance the binding affinity of an antibody Fc constant region for FcRn are known in the art and include, e.g., (1) the M252Y/S254T/T256E triple substitution described by Dall'Acqua et al. (2006) *J Biol Chem* 281: 23514-23524; (2) the M428L or T250Q/M428L substitutions described in Hinton et al. (2004) *J Biol Chem* 279:6213-6216 and Hinton et al. (2006) *J Immunol* 176:346-356; and (3) the N434A or T307/E380A/N434A substitutions described in Petkova et al. (2006) *Int Immunol* 18(12):1759-69. The additional substitution pairings: P257I/Q311I, P257I/N434H, and D376V/N434H are described in, e.g., Datta-Mannan et al. (2007) *J Biol Chem* 282(3):1709-1717, the disclosure of which is incorporated herein by reference in its entirety.

In some embodiments, the variant constant region has a substitution at EU amino acid residue 255 for valine. In some embodiments, the variant constant region has a substitution at EU amino acid residue 309 for asparagine. In some embodiments, the variant constant region has a substitution at EU amino acid residue 312 for isoleucine. In some embodiments, the variant constant region has a substitution at EU amino acid residue 386.

In some embodiments, the variant Fc constant region comprises no more than 30 (e.g., no more than 29, 28, 27, 26, 25, 24, 23, 22, 21, 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, nine, eight, seven, six, five, four, three, or two) amino acid substitutions, insertions, or deletions relative to the native constant region from which it was derived. In some embodiments, the variant Fc constant region comprises one or more amino acid substitutions selected from the group consisting of: M252Y, S254T, T256E, N434S, M428L, V259I, T250I, and V308F. In some embodiments, the variant human Fc constant region comprises a methionine at position 428 and an asparagine at position 434, each in EU numbering. In some embodiments, the

variant Fc constant region comprises a 428L/434S double substitution as described in, e.g., U.S. Pat. No. 8,088,376.

In some embodiments, the variant constant region comprises a substitution at amino acid position 237, 238, 239, 248, 250, 252, 254, 255, 256, 257, 258, 265, 270, 286, 289, 297, 298, 303, 305, 307, 308, 309, 311, 312, 314, 315, 317, 325, 332, 334, 360, 376, 380, 382, 384, 385, 386, 387, 389, 424, 428, 433, 434, or 436 (EU numbering) relative to the native human Fc constant region. In some embodiments, the substitution is selected from the group consisting of: methionine for glycine at position 237; alanine for proline at position 238; lysine for serine at position 239; isoleucine for lysine at position 248; alanine, phenylalanine, isoleucine, methionine, glutamine, serine, valine, tryptophan, or tyrosine for threonine at position 250; phenylalanine, tryptophan, or tyrosine for methionine at position 252; threonine for serine at position 254; glutamic acid for arginine at position 255; aspartic acid, glutamic acid, or glutamine for threonine at position 256; alanine, glycine, isoleucine, leucine, methionine, asparagine, serine, threonine, or valine for proline at position 257; histidine for glutamic acid at position 258; alanine for aspartic acid at position 265; phenylalanine for aspartic acid at position 270; alanine, or glutamic acid for asparagine at position 286; histidine for threonine at position 289; alanine for asparagine at position 297; glycine for serine at position 298; alanine for valine at position 303; alanine for valine at position 305; alanine, aspartic acid, phenylalanine, glycine, histidine, isoleucine, lysine, leucine, methionine, asparagine, proline, glutamine, arginine, serine, valine, tryptophan, or tyrosine for threonine at position 307; alanine, phenylalanine, isoleucine, leucine, methionine, proline, glutamine, or threonine for valine at position 308; alanine, aspartic acid, glutamic acid, proline, or arginine for leucine or valine at position 309; alanine, histidine, or isoleucine for glutamine at position 311; alanine or histidine for aspartic acid at position 312; lysine or arginine for leucine at position 314; alanine or histidine for asparagine at position 315; alanine for lysine at position 317; glycine for asparagine at position 325; valine for isoleucine at position 332; leucine for lysine at position 334; histidine for lysine at position 360; alanine for aspartic acid at position 376; alanine for glutamic acid at position 380; alanine for glutamic acid at position 382; alanine for asparagine or serine at position 384; aspartic acid or histidine for glycine at position 385; proline for glutamine at position 386; glutamic acid for proline at position 387; alanine or serine for asparagine at position 389; alanine for serine at position 424; alanine, aspartic acid, phenylalanine, glycine, histidine, isoleucine, lysine, leucine, asparagine, proline, glutamine, serine, threonine, valine, tryptophan, or tyrosine for methionine at position 428; lysine for histidine at position 433; alanine, phenylalanine, histidine, serine, tryptophan, or tyrosine for asparagine at position 434; and histidine for tyrosine or phenylalanine at position 436, all in EU numbering.

In one embodiment, the antibody or fragment thereof is a human antibody or fragment thereof. Thus, the antibody or fragment thereof may be derived from a human immunoglobulin (Ig) sequence. The CDR, framework and/or constant region of the antibody (or fragment thereof) may be derived from a human Ig sequence, in particular a human IgG sequence. The CDR, framework and/or constant region may be substantially identical for a human Ig sequence, in

particular a human IgG sequence. An advantage of using human antibodies is that they have low or no immunogenicity in humans.

An antibody or fragment thereof can also be chimeric, for example a mouse-human antibody chimera.

Alternatively, the antibody or fragment thereof is derived from a non-human species, such as a mouse. Such non-human antibodies can be modified to increase their similarity to antibody variants produced naturally in humans, thus the antibody or fragment thereof can be partially or fully humanised. Therefore, in one embodiment, the antibody or fragment thereof is humanised. Suitably the antibody or fragment thereof is a human antibody or fragment thereof.

In one embodiment the antibody or fragment thereof may be a "functionally active variant" which also includes naturally occurring allelic variants, as well as mutants or any other non-naturally occurring variants. As is known in the art, an allelic variant is an alternate form of a (poly)peptide that is characterized as having a substitution, deletion, or addition of one or more amino acids that essentially does not alter the biological function of the polypeptide. By way of non-limiting example, said functionally active variants may still function when the frameworks containing the CDRs are modified, when the CDRs themselves are modified, when said CDRs are grafted to alternate frameworks, or when N- or C-terminal extensions are incorporated. Further, CDR-containing binding domains may be paired with differing partner chains such as those shared with another antibody. Upon sharing with so called 'common' light or 'common' heavy chains, said binding domains may still function. Further, said binding domains may function when multimerized.

Polypeptides targeted to epitopes

Provided herein are polypeptides which bind to an epitope of LPAR1. Binding of the epitope on LPAR1 in certain embodiments may have an effect on LPAR1 activity, such as preventing or reducing the rate of G proteins interacting with LPAR1, and thereby impacting inflammation, fibrosis, proliferation and migration of cells. The polypeptide may have a blocking effect by prevention of the binding or interaction of another antibody or molecule (e.g. LPA) or by stabilising a structure of LPAR1 that prevents downstream signalling (i.e. the blocking effect may not necessarily be by preventing the interaction of another molecule). Suitably the polypeptides of the invention are specific for LPAR1, and do not significantly bind to other antigens.

The present invention provides polypeptides which may bind to one or more of regions 30-44, 106-120, 190-204 and 280-294 of full length LPAR1 when using the numbering of UniProt Q92633 (SEQ ID NOs: 65-68, Example 6).

In one embodiment, the polypeptide may bind to one or more, such as two, three, four, five, six, seven, eight, nine, ten or more amino acid residues within the described regions.

The polypeptide does not need to bind to all amino acids within the defined range. For example, an antibody which binds to an epitope comprising amino acid residues within amino acid region 30-44 of SEQ ID NO: 62 (UniProt Q92633), may only bind with one or more of the amino acid residues in said range, *e.g.* the amino acid residues at each end of the range (*i.e.* amino acids 30 and 44), optionally including amino acids within the range (*i.e.* amino acids 32, 34, 36, 38 and 40).

Suitably the polypeptide binds to an epitope of LPAR1 comprising at least one of amino acids 30-44 of full length LPAR1 (SEQ ID NO: 62), such as comprising amino acids 35 and 36 of full length LPAR1 (SEQ ID NO: 62) and/or comprising amino acids 37 and 38 of full length LPAR1 (SEQ ID NO: 62) and/or comprising amino acids 32, 39, 40 and 41 of full length LPAR1 (SEQ ID NO: 62). Suitably the polypeptide binds to an epitope of LPAR1 comprising at least two, such as at least three, such as at least four, such as at least five, such as at least ten, such as all of amino acids 30-44 of full length LPAR1 (SEQ ID NO: 62).

Suitably the polypeptide binds to an epitope of LPAR1 comprising at least one of amino acids 106-120 of full length LPAR1 (SEQ ID NO: 62), such as comprising amino acid 114 of full length LPAR1 (SEQ ID NO: 62). Suitably the polypeptide binds to an epitope of LPAR1 comprising at least two, such as at least three, such as at least four, such as at least five, such as at least ten, such as all of amino acids 106-120 of full length LPAR1 (SEQ ID NO: 62).

Suitably the polypeptide binds to an epitope of LPAR1 comprising at least one of amino acids 190-204 of full length LPAR1 (SEQ ID NO: 62), such as comprising amino acid 193 of full length LPAR1 (SEQ ID NO: 62) and/or comprising amino acids 191, 192, 194 and 197 of full length LPAR1 (SEQ ID NO: 62) and/or comprising amino acid 190 of full length LPAR1 (SEQ ID NO: 62). Suitably the polypeptide binds to an epitope of LPAR1 comprising at least two, such as at least three, such as at least four, such as at least five, such as at least ten, such as all of amino acids 190-204 of full length LPAR1 (SEQ ID NO: 62).

Suitably the polypeptide binds to an epitope of LPAR1 comprising at least one of amino acids 280-294 of full length LPAR1 (SEQ ID NO: 62), such as comprising amino acid 286 of full length LPAR1 (SEQ ID NO: 62) and/or comprising amino acid 285 of full length LPAR1 (SEQ ID NO: 62). Suitably the polypeptide binds to an epitope of LPAR1 comprising at least two, such as at least three, such as at least four, such as at least five, such as at least ten, such as all of amino acids 280-294 of full length LPAR1 (SEQ ID NO: 62).

More suitably the polypeptide binds to an epitope of LPAR1 comprising or consisting of amino acids 30-44, 106-120, 190-204 and 280-294 of full length LPAR1 (SEQ ID NO: 62).

Suitably the polypeptide binds to an epitope of LPAR1 comprising residue 36 of full length LPAR1 (SEQ ID NO: 62). Suitably the polypeptide binds to an epitope of LPAR1 comprising residue 193 of full length LPAR1 (SEQ ID NO: 62). Suitably the polypeptide binds to an epitope of LPAR1 comprising residue 35 of full length LPAR1 (SEQ ID NO: 62). Suitably the polypeptide binds to an epitope of LPAR1 comprising residue 286 of LPAR1 (SEQ ID NO: 62).

Suitably the polypeptide binds to an epitope of LPAR1 comprising one or more of residues 36, 35, 193 or 286 of full length LPAR1 (SEQ ID NO: 62).

Suitably the polypeptide binds to a conformational epitope of human LPAR1 comprising one or more residues located within the N-terminal capping helix and one or more residues located within the extracellular domain 2. More suitably the polypeptide binds to an epitope of LPAR1 comprising residues 36 and 193 of full length LPAR1 (SEQ ID NO: 62).

In one embodiment there is provided a polypeptide wherein the polypeptide binds to the same, or essentially the same, epitope as, a polypeptide as defined herein.

In a further embodiment there is provided a polypeptide wherein the polypeptide competes with a polypeptide as defined herein for binding to LPAR1.

Polypeptide sequences

The polypeptides of the invention may be described by reference to their CDR sequences.

Specific polypeptides provided by the present invention and their CDRs include the following:

Table 3: Specific HCDRs

HCDR1	**HCDR2**	**HCDR3**
SSGIS (12 HCDR1) SEQ ID NO: 1	EILPRSGYTNYNQGFTG (12 HCDR2) SEQ ID NO: 2	DFKGGRYAMDY (12 HCDR3) SEQ ID NO: 3
SYGIS (02 HCDR1) SEQ ID NO: 7	EILPRSGYTNYNEKFKG (01 HCDR2) SEQ ID NO: 8	DFGSSRYAMDY (01 HCDR3) SEQ ID NO: 12
RYWMS (63D8 HCDR1) SEQ ID NO: 107	EIYPRSGNTYYNEKFKG (02 HCDR2) SEQ ID NO: 9	DYGSSRYAMDY (02 HCDR3) SEQ ID NO: 13
	EIYPRSGYTNYNEKFKG (04 HCDR2) SEQ ID NO: 10	DYDNSRYALDY (04 HCDR3) SEQ ID NO: 14
	EILPRSGYTNYNEGFTG (07 HCDR2) SEQ ID NO: 11	DKGPSRYTMDY (11 HCDR3) SEQ ID NO: 15
	EIQPRSGYTNYNQGFTG (17 HCDR2) SEQ ID NO: 100	DKGPARYTMDY (17 HCDR3) SEQ ID NO: 101
	EINPSRSAINYSPSLKD (63D8 HCDR2) SEQ ID NO: 108	QGQRLRYGMDY (63D8 HCDR3) SEQ ID NO: 109

Table 4: Specific LCDRs

LCDR1	**LCDR2**	**LCDR3**
QASQSVRYNVA (12 LCDR1) SEQ ID NO: 4	YASNRYD (12 LCDR2) SEQ ID NO: 5	QHHYSSPLTF (12 LCDR3) SEQ ID NO: 6
KASQSVRYNVA (01 LCDR1) SEQ ID NO: 16	YASNRYT (01 LCDR2) SEQ ID NO: 19	QQHYNSPLTF (01 LCDR3) SEQ ID NO: 20
KASQSVGNNVA (02 LCDR1) SEQ ID NO: 17	YASNRYE (15 LCDR2) SEQ ID NO: 98	QQHYSSPLTF (02 LCDR3) SEQ ID NO: 21
KASQSVGYNVA (04 LCDR1) SEQ ID NO: 18	WTSTRHT (63D8 LCDR2) SEQ ID NO: 111	QHHYNSPLTF (05 LCDR3) SEQ ID NO: 22
QASQSIRYNVA (18 LCDR1) SEQ ID NO: 103		QQHYGTPLT (63D8 LCDR3) SEQ ID NO: 112
RASQDVRTAVA (63D8 LCDR1) SEQ ID NO: 110		

Table 5: Specific combinations of CDRs

Antibody	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
Antibody 1	12 HCDR1 SEQ ID NO: 1	01 HCDR2 SEQ ID NO: 8	01 HCDR3 SEQ ID NO: 12	01 LCDR1 SEQ ID NO: 16	01 LCDR2 SEQ ID NO: 19	01 LCDR3 SEQ ID NO: 20
Antibody 2	02 HCDR1 SEQ ID NO: 7	02 HCDR2 SEQ ID NO: 9	02 HCDR3 SEQ ID NO: 13	02 LCDR1 SEQ ID NO: 17	01 LCDR2 SEQ ID NO: 19	02 LCDR3 SEQ ID NO: 21
Antibody 3 (same combination as Antibody 1)	12 HCDR1 SEQ ID NO: 1	01 HCDR2 SEQ ID NO: 8	01 HCDR3 SEQ ID NO: 12	01 LCDR1 SEQ ID NO: 16	01 LCDR2 SEQ ID NO: 19	01 LCDR3 SEQ ID NO: 20
Antibody 4	12 HCDR1 SEQ ID NO: 1	04 HCDR2 SEQ ID NO: 10	04 HCDR3 SEQ ID NO: 14	04 LCDR1 SEQ ID NO: 18	01 LCDR2 SEQ ID NO: 19	12 LCDR3 SEQ ID NO: 6
Antibody 5	12 HCDR1 SEQ ID NO: 1	01 HCDR2 SEQ ID NO: 8	01 HCDR3 SEQ ID NO: 12	01 LCDR1 SEQ ID NO: 16	01 LCDR2 SEQ ID NO: 19	05 LCDR3 SEQ ID NO: 22
Antibody 6	12 HCDR1 SEQ ID NO: 1	01 HCDR2 SEQ ID NO: 8	01 HCDR3 SEQ ID NO: 12	01 LCDR1 SEQ ID NO: 16	01 LCDR2 SEQ ID NO: 19	12 LCDR3 SEQ ID NO: 6
Antibody 7	12 HCDR1 SEQ ID NO: 1	07 HCDR2 SEQ ID NO: 11	01 HCDR3 SEQ ID NO: 12	12 LCDR1 SEQ ID NO: 4	01 LCDR2 SEQ ID NO: 19	01 LCDR3 SEQ ID NO: 20
Antibody 8	12 HCDR1 SEQ ID NO: 1	07 HCDR2 SEQ ID NO: 11	01 HCDR3 SEQ ID NO: 12	12 LCDR1 SEQ ID NO: 4	01 LCDR2 SEQ ID NO: 19	12 LCDR3 SEQ ID NO: 6
Antibody 9	12 HCDR1 SEQ ID NO: 1	12 HCDR2 SEQ ID NO: 2	01 HCDR3 SEQ ID NO: 12	12 LCDR1 SEQ ID NO: 4	01 LCDR2 SEQ ID NO: 19	12 LCDR3 SEQ ID NO: 6
Antibody 10	12 HCDR1 SEQ ID NO: 1	12 HCDR2 SEQ ID NO: 2	12 HCDR3 SEQ ID NO: 3	12 LCDR1 SEQ ID NO: 4	01 LCDR2 SEQ ID NO: 19	12 LCDR3 SEQ ID NO: 6
Antibody 11	12 HCDR1 SEQ ID NO: 1	12 HCDR2 SEQ ID NO: 2	11 HCDR3 SEQ ID NO: 15	12 LCDR1 SEQ ID NO: 4	01 LCDR2 SEQ ID NO: 19	12 LCDR3 SEQ ID NO: 6

Antibody	HCDR1	HCDR2	HCDR3	LCDR1	LCDR2	LCDR3
Antibody 12	12 HCDR1 SEQ ID NO: 1	12 HCDR2 SEQ ID NO: 2	12 HCDR3 SEQ ID NO: 3	12 LCDR1 SEQ ID NO: 4	12 LCDR2 SEQ ID NO: 5	12 LCDR3 SEQ ID NO: 6
Antibody 13	12 HCDR1 SEQ ID NO: 1	12 HCDR2 SEQ ID NO: 2	11 HCDR3 SEQ ID NO: 15	12 LCDR1 SEQ ID NO: 4	12 LCDR2 SEQ ID NO: 5	12 LCDR3 SEQ ID NO: 6
Antibody 14 (same combination as Antibody 7)	12 HCDR1 SEQ ID NO: 1	07 HCDR2 SEQ ID NO: 11	01 HCDR3 SEQ ID NO: 12	12 LCDR1 SEQ ID NO: 4	01 LCDR2 SEQ ID NO: 19	01 LCDR3 SEQ ID NO: 20
Antibody 15	12 HCDR1 SEQ ID NO: 1	12 HCDR2 SEQ ID NO: 2	12 HCDR3 SEQ ID NO: 3	12 LCDR1 SEQ ID NO: 4	15 LCDR2 SEQ ID NO: 98	12 LCDR3 SEQ ID NO: 6
Antibody 16 (same combination as Antibody 15)	12 HCDR1 SEQ ID NO: 1	12 HCDR2 SEQ ID NO: 2	12 HCDR3 SEQ ID NO: 3	12 LCDR1 SEQ ID NO: 4	15 LCDR2 SEQ ID NO: 98	12 LCDR3 SEQ ID NO: 6
Antibody 17	12 HCDR1 SEQ ID NO: 1	17 HCDR2 SEQ ID NO: 100	17 HCDR3 SEQ ID NO: 101	12 LCDR1 SEQ ID NO: 4	15 LCDR2 SEQ ID NO: 98	12 LCDR3 SEQ ID NO: 6
Antibody 18	12 HCDR1 SEQ ID NO: 1	17 HCDR2 SEQ ID NO: 100	17 HCDR3 SEQ ID NO: 101	18 LCDR1 SEQ ID NO: 103	15 LCDR2 SEQ ID NO: 98	12 LCDR3 SEQ ID NO: 6
63D8	63D8 HCDR1 SEQ ID NO: 107	63D8 HCDR2 SEQ ID NO: 108	63D8 HCDR3 SEQ ID NO: 109	63D8 LCDR1 SEQ ID NO: 110	63D8 LCDR2 SEQ ID NO: 111	63D8 LCDR3 SEQ ID NO: 112

The polypeptide may comprise three heavy chain CDRs (HCDR1-3). The polypeptide may comprise three light chain CDRs (LCDR1-3). Preferably, the polypeptide comprises three heavy chain CDRs (HCDR1-3) and three light chain CDRs (LCDR1-3).

The polypeptide may comprise a HCDR1 comprising a sequence having at least 40%, such as at least 60%, such as at least 80% identity with SEQ ID NO: 1 or SEQ ID NO: 7. The polypeptide may comprise a HCDR1 consisting of a sequence having at least 40%, such as at least 60%, such as at least 80% identity with SEQ ID NO: 1 or SEQ ID NO: 7. Suitably the polypeptide comprises a HCDR1 comprising SEQ ID NO: 1 or SEQ ID NO: 7. More suitably the polypeptide comprises a HCDR1 consisting of SEQ ID NO: 1 or SEQ ID NO: 7. More suitably the polypeptide comprises a HCDR1 comprising SEQ ID NO: 1, or more suitably consisting of SEQ ID NO: 1.

The polypeptide may comprise a HCDR2 comprising a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 85%, such as at least 90% identity with any one of SEQ ID NOs: 2, 8 to 11 or 100. The polypeptide may comprise a HCDR2 consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 85%, such as at least 90% identity with any one of SEQ ID NOs: 2, 8 to 11 or 100. Suitably the polypeptide comprises a HCDR2 comprising any one of SEQ ID NOs: 2, 8 to 11 or 100. More suitably, the polypeptide comprises a HCDR2 consisting of any one of SEQ ID NOs: 2, 8 to 11 or 100, such as a HCDR2 comprising SEQ ID NO: 2 or more suitably consisting of SEQ ID NO: 2.

The polypeptide may comprise a HCDR3 comprising a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with any one of SEQ ID NOs: 3, 12 to 15, or 101. The polypeptide may comprise a HCDR3 consisting of a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with any one of SEQ ID NOs: 3, 12 to 15, or 101. Suitably, the polypeptide comprises a HCDR3 comprising any one of SEQ ID NOs: 3, 12 to 15, or 101. More suitably the polypeptide comprises a HCDR3 consisting of any one of SEQ ID NOs: 3, 12 to 15, or 101. More suitably the polypeptide comprises a HCDR3 comprising SEQ ID NO: 3, such as a HCDR3 consisting of SEQ ID NO: 3. Alternatively, the polypeptide comprises a HCDR3 comprising SEQ ID NO: 15, such as consisting of SEQ ID NO: 15. Alternatively, the polypeptide comprises a HCDR3 comprising SEQ ID NO: 101, such as consisting of SEQ ID NO: 101.

The polypeptide may comprise a LCDR1 comprising a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with any one of SEQ ID NOs: 4, 16 to 18 or 103. The polypeptide may comprise a LCDR1 consisting of a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with any one of SEQ ID NOs: 4, 16 to 18 or 103. Suitably, the polypeptide comprises a LCDR1 comprising any one of SEQ ID NOs: 4, 16 to 18 or 103. More suitably, the polypeptide comprises a LCDR1 consisting of any one of SEQ ID NOs: 4, 16 to 18 or 103. More suitably the polypeptide comprises a LCDR1 comprising SEQ ID NO: 4, or more suitably consisting of SEQ ID NO: 4. More suitably the polypeptide comprises a LCDR1 comprising SEQ ID NO: 103, or more suitably consisting of SEQ ID NO: 103.

The polypeptide may comprise a LCDR2 comprising a sequence having at least 50% identity, such as at least 60%, such as at least 70%, such as at least 80% identity with SEQ ID NO: 5, 19 or 98. The polypeptide may comprise a LCDR2 consisting of a sequence having at least 50% identity, such as at least 60%, such as at least 70%, such as at least 80% identity with SEQ ID NO: 5, 19 or 98. Suitably the polypeptide comprises a LCDR2 comprising SEQ ID NO: 5, 19 or 98. More suitably the polypeptide comprises a LCDR2 consisting of SEQ ID NO: 5, 19 or 98. More suitably the polypeptide comprises a LCDR2 comprising SEQ ID NO: 5, more suitably consisting of SEQ ID NO: 5.

The polypeptide may comprise a LCDR3 comprising a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80% identity with any one of SEQ ID NOs: 6 or 20 to 22. The polypeptide may comprise a LCDR3 consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80% identity with any one of SEQ ID NOs: 6 or 20 to 22. More suitably the polypeptide comprises a LCDR3 comprising any one of SEQ ID NOs: 6 or 20 to 22. More suitably the polypeptide comprises a LCDR3 consisting of any one of SEQ ID NOs: 6 or 20 to 22, more suitably the polypeptide comprises a LCDR3 comprising SEQ ID NO: 6, more suitably consisting of SEQ ID NO: 6.

Alternatively, the polypeptide may comprise a HCDR1 comprising, such as consisting of, a sequence having at least 40%, such as at least 60%, such as at least 80%, such as 100% identity with SEQ ID NO: 107. Suitably the polypeptide comprises a HCDR2 comprising, such as consisting of, a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 85%, such as at least 90%, such as 100% identity with SEQ ID NO: 108. Suitably the polypeptide comprises a HCDR3 comprising, such as consisting of, a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as 100% identity with SEQ ID NO: 109. Suitably the polypeptide comprises a LCDR1 comprising, such as consisting of, a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90% such as 100% identity with SEQ ID NO: 110. Suitably the polypeptide comprises a LCDR2 comprising, such as consisting of, a sequence having at least 50% identity, such as at least 60%, such as at least 70%, such as at least 80% identity, such as 100% identity with SEQ ID NO: 111. Suitably the polypeptide comprises a LCDR3 comprising, such as consisting of, a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as 100% identity with SEQ ID NO: 112.

In one embodiment, the polypeptide comprises

(a) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 3, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 5 and a LCDR3 comprising SEQ ID NO: 6;

(b) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 8, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 16, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 20;

(c) a HCDR1 comprising SEQ ID NO: 7, a HCDR2 comprising SEQ ID NO: 9, a HCDR3 comprising SEQ ID NO: 13, a LCDR1 comprising SEQ ID NO: 17, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 21;

(d) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 10, a HCDR3 comprising SEQ ID NO: 14, a LCDR1 comprising SEQ ID NO: 18, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(e) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 8, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 16, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 22;

(f) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 8, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 16, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(g) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 11, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 20;

(h) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 11, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(i) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(j) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 3, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(k) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 15, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(l) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 15, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 5 and a LCDR3 comprising SEQ ID NO: 6;

(m) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 3, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 98 and a LCDR3 comprising SEQ ID NO: 6;

(n) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 100, a HCDR3 comprising SEQ ID NO: 101, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 98 and a LCDR3 comprising SEQ ID NO: 6 or

(o) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 100, a HCDR3 comprising SEQ ID NO: 101, a LCDR1 comprising SEQ ID NO: 103, a LCDR2 comprising SEQ ID NO: 98 and a LCDR3 comprising SEQ ID NO: 6.

More suitably, the polypeptide comprises

(a) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 3, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 5 and a LCDR3 consisting of SEQ ID NO: 6;

(b) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 8, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 16, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 20;

(c) a HCDR1 consisting of SEQ ID NO: 7, a HCDR2 consisting of SEQ ID NO: 9, a HCDR3 consisting of SEQ ID NO: 13, a LCDR1 consisting of SEQ ID NO: 17, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 21;

(d) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 10, a HCDR3 consisting of SEQ ID NO: 14, a LCDR1 consisting of SEQ ID NO: 18, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(e) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 8, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 16, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 22;

(f) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 8, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 16, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(g) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 11, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 20;

(h) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 11, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(i) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(j) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 3, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(k) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 15, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(l) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 15, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 5 and a LCDR3 consisting of SEQ ID NO: 6;

(m) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 3, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 98 and a LCDR3 consisting of SEQ ID NO: 6;

(n) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 100, a HCDR3 consisting of SEQ ID NO: 101, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 98 and a LCDR3 consisting of SEQ ID NO: 6 or

(o) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 100, a HCDR3 consisting of SEQ ID NO: 101, a LCDR1 consisting of SEQ ID NO: 103, a LCDR2 consisting of SEQ ID NO: 98 and a LCDR3 consisting of SEQ ID NO: 6.

The polypeptide may comprise four heavy chain framework regions (HFR1-HFR4).

The polypeptide may comprise a HFR1 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 40, a HFR2 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 41, a HFR3 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 42 and/or a HFR4 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 43. Suitably, the polypeptide comprises a HFR1 comprising SEQ ID NO: 40, a HFR2 comprising SEQ ID NO: 41, a HFR3 comprising SEQ ID NO: 42 and/or a HFR4 comprising SEQ ID NO: 43. More suitably, the polypeptide comprises a HFR1 consisting of SEQ ID NO: 40, a HFR2 consisting of SEQ ID NO: 41, a HFR3 consisting of SEQ ID NO: 42 and/or a HFR4 consisting of SEQ ID NO: 43.

Alternatively, the polypeptide may comprise a HFR1 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 48, a HFR2 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 49, a HFR3 comprising or consisting of a sequence

having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 50 and/or a HFR4 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 51. Suitably the polypeptide comprises a HFR1 comprising SEQ ID NO: 48, a HFR2 comprising SEQ ID NO: 49, a HFR3 comprising SEQ ID NO: 50 and/or a HFR4 comprising SEQ ID NO: 51. More suitably the polypeptide comprises a HFR1 consisting of SEQ ID NO: 48, a HFR2 consisting of SEQ ID NO: 49, a HFR3 consisting of SEQ ID NO: 50 and/or a HFR4 consisting of SEQ ID NO: 51.

The polypeptide may comprise four light chain framework regions (LFR1-LFR4).

The polypeptide may comprise a LFR1 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 44, a LFR2 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 45, a LFR3 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 46 and/or a LFR4 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 47. Suitably, the polypeptide comprises a LFR1 comprising SEQ ID NO: 44, a LFR2 comprising SEQ ID NO: 45, a LFR3 comprising SEQ ID NO: 46 and/or a LFR4 comprising SEQ ID NO: 47. More suitably, the polypeptide comprises a LFR1 consisting of SEQ ID NO: 44, a LFR2 consisting of SEQ ID NO: 45, a LFR3 consisting of SEQ ID NO: 46 and/or a LFR4 consisting of SEQ ID NO: 47.

Alternatively, the polypeptide may comprise a LFR1 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 52, a LFR2 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 53, a LFR3 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 54 and/or a LFR4 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 55. Suitably the polypeptide comprises a LFR1 comprising SEQ ID NO: 52, a LFR2 comprising SEQ ID NO: 53 a LFR3 comprising SEQ ID NO: 54 and/or a LFR4 comprising SEQ ID NO: 55. More suitably the polypeptide comprises a LFR1 consisting of SEQ ID NO: 52, a LFR2 consisting of SEQ ID NO: 53, a LFR3 consisting of SEQ ID NO: 54 and/or a LFR4 consisting of SEQ ID NO: 55.

The polypeptides of the invention may be described by reference to their VH and VL region sequences. The polypeptides may comprise a VH region and/or a VL region, most suitably a VH region and a VL region.

Specific polypeptides provided by the present invention and their VH and VL region sequences include the following:

Table 6: Specific combinations of VH and VL regions

	VH	**VL**
Antibody 1	1 VH SEQ ID NO: 23	1 VL SEQ ID NO: 24
Antibody 2	2 VH SEQ ID NO: 25	2 VL SEQ ID NO: 26
Antibody 3	3 VH SEQ ID NO: 27	3 VL SEQ ID NO: 28
Antibody 4	4 VH SEQ ID NO: 29	4 VL SEQ ID NO: 30
Antibody 5	3 VH SEQ ID NO: 27	5 VL SEQ ID NO: 31
Antibody 6	3 VH SEQ ID NO: 27	6 VL SEQ ID NO: 32
Antibody 7	7 VH SEQ ID NO: 33	7 VL SEQ ID NO: 34
Antibody 8	7 VH SEQ ID NO: 33	11 VL SEQ ID NO: 39
Antibody 9	9 VH SEQ ID NO: 35	11 VL SEQ ID NO: 39
Antibody 10	12 VH SEQ ID NO: 36	11 VL SEQ ID NO: 39
Antibody 11	11 VH SEQ ID NO: 37	11 VL SEQ ID NO: 39
Antibody 12	12 VH SEQ ID NO: 36	12 VL SEQ ID NO: 38
Antibody 13	11 VH SEQ ID NO: 37	12 VL SEQ ID NO: 38
Antibody 14	14 VH SEQ ID NO: 96	14 VL SEQ ID NO: 97
Antibody 15	12 VH SEQ ID NO: 36	15 VL SEQ ID NO: 99
Antibody 16	12 VH SEQ ID NO: 36	15 VL SEQ ID NO: 99
Antibody 17	17 VH SEQ ID NO: 102	15 VL SEQ ID NO: 99
Antibody 18	17 VH SEQ ID NO: 102	18 VL SEQ ID NO: 104
63D8	63D8 VH SEQ ID NO: 113	63D8 VL SEQ ID NO: 114

The VH region may comprise an amino acid sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 98%, such as at least 99% sequence identity with any one of SEQ ID NOs: 23, 25, 27, 29, 33, 35, 36, 37, 96 or 102. Suitably the VH region consists of an amino acid sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 98%, such as at least 99% sequence identity with any one of SEQ ID NOs: 23, 25, 27, 29, 33, 35, 36, 37, 96 or 102.

Suitably the VH region comprises an amino acid sequence of SEQ ID NOs: 23, 25, 27, 29, 33, 35, 36, 37, 96 or 102, more suitably the VH region comprises an amino acid sequence of SEQ ID NO: 36 or SEQ ID NO: 37. Alternatively, the VH region comprises the amino acid sequence of SEQ ID NO: 102. Suitably the VH region consists of an amino acid sequence of SEQ ID NOs: 23, 25, 27, 29, 33, 35, 36, 37, 96 or 102, more suitably the VH region consists of an amino acid sequence of SEQ ID NO: 36 or SEQ ID NO: 37. Alternatively, the VH region consists of the amino acid sequence of SEQ ID NO: 102.

The VL region may comprise an amino acid sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 98%, such as at least 99% sequence identity with any one of SEQ ID NOs: 24, 26, 28, 30, 31, 32, 34, 38, 39, 97, 99 or 104. Suitably the VL region consists of an amino acid sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 98%, such as at least 99% sequence identity with any one of SEQ ID NOs: 24, 26, 28, 30, 31, 32, 34, 38, 39, 97, 99 or 104.

Suitably the VL region comprises an amino acid sequence of SEQ ID NOs: 24, 26, 28, 30, 31, 32, 34, 38, 39, 97, 99 or 104. More suitably the VL region comprises an amino acid sequence of SEQ ID NO: 38 or SEQ ID NO: 39. Alternatively, the VL region comprises an amino acid sequence of SEQ ID NO: 99 or SEQ ID NO: 104.

Suitably the VL region consists of an amino acid sequence of SEQ ID NOs: 24, 26, 28, 30, 31, 32, 34, 38, 39, 97, 99 or 104. More suitably the VL region consists of an amino acid sequence of SEQ ID NO: 38 or SEQ ID NO: 39. Alternatively, the VL region consists of an amino acid sequence of SEQ ID NO: 99 or SEQ ID NO: 104.

In one embodiment the polypeptide comprises

(a) a VH region comprising SEQ ID NO: 23 and a VL region comprising SEQ ID NO: 24;

(b) a VH region comprising SEQ ID NO: 25 and a VL region comprising SEQ ID NO: 26;

(c) a VH region comprising SEQ ID NO: 27 and a VL region comprising SEQ ID NO: 28;

(d) a VH region comprising SEQ ID NO: 29 and a VL region comprising SEQ ID NO: 30;

(e) a VH region comprising SEQ ID NO: 27 and a VL region comprising SEQ ID NO: 31;

(f) a VH region comprising SEQ ID NO: 27 and a VL region comprising SEQ ID NO: 32;
(g) a VH region comprising SEQ ID NO: 33 and a VL region comprising SEQ ID NO: 34;
(h) a VH region comprising SEQ ID NO: 33 and a VL region comprising SEQ ID NO: 39;
(i) a VH region comprising SEQ ID NO: 35 and a VL region comprising SEQ ID NO: 39;
(j) a VH region comprising SEQ ID NO: 36 and a VL region comprising SEQ ID NO: 39;
(k) a VH region comprising SEQ ID NO: 37 and a VL region comprising SEQ ID NO: 39;
(l) a VH region comprising SEQ ID NO: 36 and a VL region comprising SEQ ID NO: 38;
(m) a VH region comprising SEQ ID NO: 37 and a VL region comprising SEQ ID NO: 38;
(n) a VH region comprising SEQ ID NO: 96 and a VL region comprising SEQ ID NO: 97;
(o) a VH region comprising SEQ ID NO: 36 and a VL region comprising SEQ ID NO: 99;
(p) a VH region comprising SEQ ID NO: 102 and a VL region comprising SEQ ID NO: 99 or
(q) a VH region comprising SEQ ID NO: 102 and a VL region comprising SEQ ID NO: 104.

More suitably, the polypeptide comprises
(a) a VH region consisting of SEQ ID NO: 23 and a VL region consisting of SEQ ID NO: 24;
(b) a VH region consisting of SEQ ID NO: 25 and a VL region consisting of SEQ ID NO: 26;
(c) a VH region consisting of SEQ ID NO: 27 and a VL region consisting of SEQ ID NO: 28;
(d) a VH region consisting of SEQ ID NO: 29 and a VL region consisting of SEQ ID NO: 30;
(e) a VH region consisting of SEQ ID NO: 27 and a VL region consisting of SEQ ID NO: 31;
(f) a VH region consisting of SEQ ID NO: 27 and a VL region consisting of SEQ ID NO: 32;
(g) a VH region consisting of SEQ ID NO: 33 and a VL region consisting of SEQ ID NO: 34;
(h) a VH region consisting of SEQ ID NO: 33 and a VL region consisting of SEQ ID NO: 39;
(i) a VH region consisting of SEQ ID NO: 35 and a VL region consisting of SEQ ID NO: 39;

(j) a VH region consisting of SEQ ID NO: 36 and a VL region consisting of SEQ ID NO: 39;
(k) a VH region consisting of SEQ ID NO: 37 and a VL region consisting of SEQ ID NO: 39;
(l) a VH region consisting of SEQ ID NO: 36 and a VL region consisting of SEQ ID NO: 38;
(m) a VH region consisting of SEQ ID NO: 37 and a VL region consisting of SEQ ID NO: 38;
(n) a VH region consisting of SEQ ID NO: 96 and a VL region consisting of SEQ ID NO: 97;
(o) a VH region consisting of SEQ ID NO: 36 and a VL region consisting of SEQ ID NO: 99;
(p) a VH region consisting of SEQ ID NO: 102 and a VL region consisting of SEQ ID NO: 99 or
(q) a VH region consisting of SEQ ID NO: 102 and a VL region consisting of SEQ ID NO: 104.

The inventors have identified multiple residues in the polypeptides of the invention which may be substituted without significant loss of function, without loss of function, or which provide enhancement of function (see, for example, Example 7 and Table 10).

Accordingly, in one embodiment the polypeptide comprises three heavy chain CDRs (HCDR1-HCDR3) and three light chain CDRs (LCDR1-LCDR3) (wherein the CDRs in this embodiment are defined by a non-Kabat numbering system) wherein HCDR1 comprises (e.g. consists of) $X_1X_2X_3X_4X_5X_6$ (SEQ ID NO: 72), HCDR2 comprises (e.g. consists of) $X_7IX_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}YX_{16}X_{17}X_{18}FX_{19}G$ (SEQ ID NO: 76), HCDR3 comprises (e.g. consists of) $DX_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}DY$ (SEQ ID NO: 80), LCDR1 comprises (e.g. consists of) $X_{30}X_{31}X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$ (SEQ ID NO: 84), LCDR2 comprises (e.g. consists of) $X_{41}AX_{42}X_{43}X_{44}X_{45}X_{46}$ (SEQ ID NO: 88) and LCDR3 comprises (e.g. consists of) $X_{47}X_{48}X_{49}X_{50}X_{51}X_{52}PLX_{53}$ (SEQ ID NO: 92), wherein:

the amino acid of X_1 is selected from the group consisting of S, Y, T, G, R, E, K, D and N;
the amino acid of X_2 is selected from the group consisting of K, R, L, T, G, V, A, S, F, W, Q, M, Y, I, E, H ,N, D and P;
the amino acid of X_3 is selected from the group consisting of R, K, H, T, S, F, G, V, A, L, N, Q, E, M, P, W and I;
the amino acid of X_4 is selected from the group consisting of A and G;
the amino acid of X_5 is selected from the group consisting of M and I;
the amino acid of X_6 is selected from the group consisting of S, E, G, D, L, T, N, Q, I, V, A, K, M, H and Y;
the amino acid of X_7 is selected from the group consisting of E;
the amino acid of X_8 is selected from the group consisting of L, Q and D;
the amino acid of X_9 is selected from the group consisting of P, A, G , F, S, T and W;
the amino acid of X_{10} is selected from the group consisting of R;

the amino acid of X_{11} is selected from the group consisting of S, T and D;
the amino acid of X_{12} is selected from the group consisting of G, R, S, Y, A, T, D, E and W;
the amino acid of X_{13} is selected from the group consisting of Y;
the amino acid of X_{14} is selected from the group consisting of T;
the amino acid of X_{15} is selected from the group consisting of N, H and S;
the amino acid of X_{16} is selected from the group consisting of R, N, F, K, Q, V, D, E, Y, G, M, P, W, H, L, I, S, T and A;
the amino acid of X_{17} is selected from the group consisting of Q, A, I, S, P, T, N, V, G, H, L, M, W, K, R, F, D, Y and E;
the amino acid of X_{18} is selected from the group consisting of G, D, E, H, L, V, Y, A, F, I, K, Q, W, R, M, P, S and N;
the amino acid of X_{19} is selected from the group consisting of T, K, Q, E, R and M;
the amino acid of X_{20} is selected from the group consisting of R, F, K, I, A, L, V, W, Y, M, P, Q, G and S;
the amino acid of X_{21} is not present or is selected from the group consisting of K and R
the amino acid of X_{22} is selected from the group consisting of K, R, A, H, S, Q, T, P, M, W, Y, G, L, F, V, E and N;
the amino acid of X_{23} is not present or is selected from the group consisting of K and R
the amino acid of X_{24} is selected from the group consisting of R, Y, A, H, P, L, K, G, Q, N, I, F, W, S, T, M, E, V and D;
the amino acid of X_{25} is selected from the group consisting of A, Q, T, S, G, V, R, I, H, K, P, L, M and F;
the amino acid of X_{26} is selected from the group consisting of R and S;
the amino acid of X_{27} is selected from the group consisting of Y, H, Q and A;
the amino acid of X_{28} is selected from the group consisting of A, T, S, D and E;
the amino acid of X_{29} is selected from the group consisting of M and L;
the amino acid of X_{30} is selected from the group consisting of Q, K, R, S and T;
the amino acid of X_{31} is selected from the group consisting of A, S and T;
the amino acid of X_{32} is selected from the group consisting of S, T and D;
the amino acid of X_{33} is selected from the group consisting of Q, G, R, K, L, M, P, Y, S, A, N, H, W, D, E, F, T and I;
the amino acid of X_{34} is selected from the group consisting of S, G, H, N, T, Y and D;
the amino acid of X_{35} is selected from the group consisting of V, A and I;
the amino acid of X_{36} is selected from the group consisting of R, K, S, G and A;
the amino acid of X_{37} is selected from the group consisting of Y, F, L, Q, S, H, T, G, I, M, V, W, K, N, R, D and P;
the amino acid of X_{38} is selected from the group consisting of N, A, G, H, Q, S, Y, F and W;
the amino acid of X_{39} is selected from the group consisting of V, I, M and L;
the amino acid of X_{40} is selected from the group consisting of A, G and D;

the amino acid of X_{41} is selected from the group consisting of Y, H, R, T, A, D, K, L, N, Q, M, W, E, F and S;
the amino acid of X_{42} is selected from the group consisting of S, K, M, Q, R, V, Y, G, E, D, T, A, F, I, N, W, H and L;
the amino acid of X_{43} is selected from the group consisting of N, K, R, Q, T, Y, A, S, D and E;
the amino acid of X_{44} is selected from the group consisting of R, L, K and A;
the amino acid of X_{45} is selected from the group consisting of Y, I, K, M, Q, R, V, A, N, S, W, H, L, T, P, D, F, G and E;
the amino acid of X_{46} is selected from the group consisting of T, A, D, E, Q, R, S, H, K, P, L, F, G, I, M, V, W, Y and N;
the amino acid of X_{47} is selected from the group consisting of Q, S and L;
the amino acid of X_{48} is selected from the group consisting of H, N, S, T, A, Q and V;
the amino acid of X_{49} is selected from the group consisting of H, A, D and F;
the amino acid of X_{50} is selected from the group consisting of Y and L;
the amino acid of X_{51} is selected from the group consisting of S, K, V, D, N, R, H, T, A, G, Q, I, M, F, W, Y and L;
the amino acid of X_{52} is selected from the group consisting of S, A, T, G, V, W and Y; and
the amino acid of X_{53} is selected from the group consisting of T and Y.

Accordingly, in a further embodiment the polypeptide comprises three heavy chain CDRs (HCDR1-HCDR3) and three light chain CDRs (LCDR1-LCDR3) (wherein the CDRs in this embodiment are defined by a non-Kabat numbering system) wherein HCDR1 comprises (e.g. consists of) $X_1X_2X_3X_4X_5X_6$ (SEQ ID NO: 73), HCDR2 comprises (e.g. consists of) $X_7IX_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}YX_{16}X_{17}X_{18}FX_{19}G$ (SEQ ID NO: 77), HCDR3 comprises (e.g. consists of) $DX_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}DY$ (SEQ ID NO: 81), LCDR1 comprises (e.g. consists of) $X_{30}X_{31}X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$ (SEQ ID NO: 85), LCDR2 comprises (e.g. consists of) $X_{41}AX_{42}X_{43}X_{44}X_{45}X_{46}$ (SEQ ID NO: 89) and LCDR3 comprises (e.g. consists of) $X_{47}X_{48}X_{49}X_{50}X_{51}X_{52}PLX_{53}$ (SEQ ID NO: 93), wherein:
the amino acid of X_1 is selected from the group consisting of S, Y, T, G, R, E and K;
the amino acid of X_2 is selected from the group consisting of K, R, L, T, G, V, A, S, F, W, Q, M, Y, I, E, H and N;
the amino acid of X_3 is selected from the group consisting of R, K, H, T, S, F, G, V, A, L, N, Q, E, M, P and W;
the amino acid of X_4 is selected from the group consisting of A and G;
the amino acid of X_5 is selected from the group consisting of M and I;
the amino acid of X_6 is selected from the group consisting of S, E, G, D, L, T, N, Q, I, V, A, K and M;
the amino acid of X_7 is selected from the group consisting of E;
the amino acid of X_8 is selected from the group consisting of L and Q;
the amino acid of X_9 is selected from the group consisting of P, A, G , F, S and T;
the amino acid of X_{10} is selected from the group consisting of R;
the amino acid of X_{11} is selected from the group consisting of S, T and D;

the amino acid of X_{12} is selected from the group consisting of G, R, S, Y, A, T, D, E and W;
the amino acid of X_{13} is selected from the group consisting of Y;
the amino acid of X_{14} is selected from the group consisting of T;
the amino acid of X_{15} is selected from the group consisting of N, H and S;
the amino acid of X_{16} is selected from the group consisting of R, N, F, K, Q, V, D, E, Y, G, M, P, W, H and L;
the amino acid of X_{17} is selected from the group consisting of Q, A, I, S, P, T, N, V, G, H, L, M, W, K, R, F, D, Y and E;
the amino acid of X_{18} is selected from the group consisting of G, D, E, H, L, V, Y, A, F, I, K, Q, W, R, M, P and S;
the amino acid of X_{19} is selected from the group consisting of T, K, Q, E, R and M;
the amino acid of X_{20} is selected from the group consisting of R, F, K, I, A, L, V, W, Y and M;
the amino acid of X_{21} is not present or is selected from the group consisting of K and R
the amino acid of X_{22} is selected from the group consisting of K, R, A, H, S, Q, T, P, M, W, Y, G, L, F and V;
the amino acid of X_{23} is not present or is selected from the group consisting of K and R
the amino acid of X_{24} is selected from the group consisting of R, Y, A, H, P, L, K, G, Q, N, I, F, W, S, T, M, E, V and D;
the amino acid of X_{25} is selected from the group consisting of A, Q, T, S, G, V, R and I;
the amino acid of X_{26} is selected from the group consisting of R and S;
the amino acid of X_{27} is selected from the group consisting of Y;
the amino acid of X_{28} is selected from the group consisting of A, T, S and D;
the amino acid of X_{29} is selected from the group consisting of M and L;
the amino acid of X_{30} is selected from the group consisting of Q, K, R, S and T;
the amino acid of X_{31} is selected from the group consisting of A, S and T;
the amino acid of X_{32} is selected from the group consisting of S, T and D;
the amino acid of X_{33} is selected from the group consisting of Q, G, R, K, L, M, P, Y, S, A, N, H, W, D and E;
the amino acid of X_{34} is selected from the group consisting of S, G, H, N, T and Y;
the amino acid of X_{35} is selected from the group consisting of V, A and I;
the amino acid of X_{36} is selected from the group consisting of R, K, S and G;
the amino acid of X_{37} is selected from the group consisting of Y, F, L, Q, S, H, T, G, I, M, V, W, K, N and R;
the amino acid of X_{38} is selected from the group consisting of N, A, G, H, Q and S;
the amino acid of X_{39} is selected from the group consisting of V, I, M and L;
the amino acid of X_{40} is selected from the group consisting of A, G and D;
the amino acid of X_{41} is selected from the group consisting of Y, H, R, T, A, D, K, L, N and Q;

the amino acid of X_{42} is selected from the group consisting of S, K, M, Q, R, V, Y, G, E, D, T, A, F, I, N, W and H;
the amino acid of X_{43} is selected from the group consisting of N, K, R, Q, T, Y, A, S, D and E;
the amino acid of X_{44} is selected from the group consisting of R, L and K;
the amino acid of X_{45} is selected from the group consisting of Y, I, K, M, Q, R, V, A, N, S, W, H, L, T, P, D, F and G;
the amino acid of X_{46} is selected from the group consisting of T, A, D, E, Q, R, S, H, K, P, L, F, G, I, M, V, W, Y and N;
the amino acid of X_{47} is selected from the group consisting of Q, S and L;
the amino acid of X_{48} is selected from the group consisting of H, N, S, T, A and Q;
the amino acid of X_{49} is selected from the group consisting of H;
the amino acid of X_{50} is selected from the group consisting of Y and L;
the amino acid of X_{51} is selected from the group consisting of S, K, V, D, N, R, H, T, A, G, Q, I, M, F, W and Y;
the amino acid of X_{52} is selected from the group consisting of S, A, T and G; and
the amino acid of X_{53} is selected from the group consisting of T and Y.

Accordingly, in a further embodiment the polypeptide comprises three heavy chain CDRs (HCDR1-HCDR3) and three light chain CDRs (LCDR1-LCDR3) (wherein the CDRs in this embodiment are defined by a non-Kabat numbering system) wherein HCDR1 comprises (e.g. consists of) $X_1X_2X_3X_4X_5X_6$ (SEQ ID NO: 74), HCDR2 comprises (e.g. consists of) $X_7IX_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}YX_{16}X_{17}X_{18}FX_{19}G$ (SEQ ID NO: 78), HCDR3 comprises (e.g. consists of) $DX_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}DY$ (SEQ ID NO: 82), LCDR1 comprises (e.g. consists of) $X_{30}X_{31}X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$ (SEQ ID NO: 86), LCDR2 comprises (e.g. consists of) $X_{41}AX_{42}X_{43}X_{44}X_{45}X_{46}$ (SEQ ID NO: 90) and LCDR3 comprises (e.g. consists of) $X_{47}X_{48}X_{49}X_{50}X_{51}X_{52}PLX_{53}$ (SEQ ID NO: 94), wherein:

the amino acid of X_1 is selected from the group consisting of S, Y, T, G and R;
the amino acid of X_2 is selected from the group consisting of K, R, L, T, G, V, A, S, F, W, Q, M, Y, I and E;
the amino acid of X_3 is selected from the group consisting of R, K, H, T, S, F, G, V, A, L, N and Q;
the amino acid of X_4 is selected from the group consisting of A and G;
the amino acid of X_5 is selected from the group consisting of M and I;
the amino acid of X_6 is selected from the group consisting of S, E, G, D, L, T, N, Q, I, V and A;
the amino acid of X_7 is selected from the group consisting of E;
the amino acid of X_8 is selected from the group consisting of L and Q;
the amino acid of X_9 is selected from the group consisting of P, A, G , F and S;
the amino acid of X_{10} is selected from the group consisting of R;
the amino acid of X_{11} is selected from the group consisting of S and T;
the amino acid of X_{12} is selected from the group consisting of G, R, S, Y, A and T;
the amino acid of X_{13} is selected from the group consisting of Y;
the amino acid of X_{14} is selected from the group consisting of T;

the amino acid of X_{15} is selected from the group consisting of N, H and S;
the amino acid of X_{16} is selected from the group consisting of R, N, F, K, Q, V, D, E, Y, G, M and P;
the amino acid of X_{17} is selected from the group consisting of Q, A, I, S, P, T, N, V, G, H, L, M, W, K, R and F;
the amino acid of X_{18} is selected from the group consisting of G, D, E, H, L, V, Y, A, F, I, K, Q, W, R, M, P and S;
the amino acid of X_{19} is selected from the group consisting of T, K, Q, E, R and M;
the amino acid of X_{20} is selected from the group consisting of R, F, K, I, A, L, V, W and Y;
the amino acid of X_{21} is not present or is selected from the group consisting of K and R
the amino acid of X_{22} is selected from the group consisting of K, R, A, H, S, Q, T, P, M, W, G and Y;
the amino acid of X_{23} is not present or is selected from the group consisting of K and R
the amino acid of X_{24} is selected from the group consisting of R, Y, A, H, P, L, K, G, Q, N, I, F, W, S, T, M, E and V;
the amino acid of X_{25} is selected from the group consisting of A, Q, T, S, G and V;
the amino acid of X_{26} is selected from the group consisting of R;
the amino acid of X_{27} is selected from the group consisting of Y;
the amino acid of X_{28} is selected from the group consisting of A, T, S and D;
the amino acid of X_{29} is selected from the group consisting of M;
the amino acid of X_{30} is selected from the group consisting of Q, K, R, S and T;
the amino acid of X_{31} is selected from the group consisting of A, S and T;
the amino acid of X_{32} is selected from the group consisting of S, T and D;
the amino acid of X_{33} is selected from the group consisting of Q, G, R, K, L, M, P, Y, S, A, N, H and W;
the amino acid of X_{34} is selected from the group consisting of S, G, H, N, T and Y;
the amino acid of X_{35} is selected from the group consisting of V, A and I;
the amino acid of X_{36} is selected from the group consisting of R, K and S;
the amino acid of X_{37} is selected from the group consisting of Y, F, L, Q, S, H, T, G, I, M, V, W, K, N and R;
the amino acid of X_{38} is selected from the group consisting of N, A, G, H, Q and S;
the amino acid of X_{39} is selected from the group consisting of V, I, M and L;
the amino acid of X_{40} is selected from the group consisting of A, G and D;
the amino acid of X_{41} is selected from the group consisting of Y, H, R, and T;
the amino acid of X_{42} is selected from the group consisting of S, K, M, Q, R, V, Y, G, E, D, T, A, F, I, N and W;
the amino acid of X_{43} is selected from the group consisting of N, K, R, Q, T, Y, A and S;
the amino acid of X_{44} is selected from the group consisting of R, L and K;
the amino acid of X_{45} is selected from the group consisting of Y, I, K, M, Q, R, V, A, N, S, W, H, L, T, P, D and F;

the amino acid of X_{46} is selected from the group consisting of T, A, D, E, Q, R, S, H, K, P, L, F, G, I, M, V, W, Y and N;
the amino acid of X_{47} is selected from the group consisting of Q and S;
the amino acid of X_{48} is selected from the group consisting of H, N, S, T, A and Q;
the amino acid of X_{49} is selected from the group consisting of H;
the amino acid of X_{50} is selected from the group consisting of Y;
the amino acid of X_{51} is selected from the group consisting of S, K, V, D, N, R, H, T, A and G;
the amino acid of X_{52} is selected from the group consisting of S and A; and
the amino acid of X_{53} is selected from the group consisting of T and Y.

Accordingly, in a further embodiment the polypeptide comprises three heavy chain CDRs (HCDR1-HCDR3) and three light chain CDRs (LCDR1-LCDR3) (wherein the CDRs in this embodiment are defined by a non-Kabat numbering system) wherein HCDR1 comprises (e.g. consists of) $X_1X_2X_3X_4X_5X_6$ (SEQ ID NO: 75), HCDR2 comprises (e.g. consists of) $X_7IX_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}YX_{16}X_{17}X_{18}FX_{19}G$ (SEQ ID NO: 79), HCDR3 comprises (e.g. consists of) $DX_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}DY$ (SEQ ID NO: 83), LCDR1 comprises (e.g. consists of) $X_{30}X_{31}X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$ (SEQ ID NO: 87), LCDR2 comprises (e.g. consists of) $X_{41}AX_{42}X_{43}X_{44}X_{45}X_{46}$ (SEQ ID NO: 91) and LCDR3 comprises (e.g. consists of) $X_{47}X_{48}X_{49}X_{50}X_{51}X_{52}PLX_{53}$ (SEQ ID NO: 95), wherein:
the amino acid of X_1 is selected from the group consisting of S, Y, T and G;
the amino acid of X_2 is selected from the group consisting of K, R, L, T, G, V, A, S, F, W, Q, M and Y;
the amino acid of X_3 is selected from the group consisting of R, K, H, T, S, F, G and V;
the amino acid of X_4 is selected from the group consisting of A and G;
the amino acid of X_5 is selected from the group consisting of M and I;
the amino acid of X_6 is selected from the group consisting of S, E, G, D, L and T;
the amino acid of X_7 is selected from the group consisting of E;
the amino acid of X_8 is selected from the group consisting of L and Q;
the amino acid of X_9 is selected from the group consisting of P, A and G;
the amino acid of X_{10} is selected from the group consisting of R;
the amino acid of X_{11} is selected from the group consisting of S and T;
the amino acid of X_{12} is selected from the group consisting of G and R;
the amino acid of X_{13} is selected from the group consisting of Y;
the amino acid of X_{14} is selected from the group consisting of T;
the amino acid of X_{15} is selected from the group consisting of N, H and S;
the amino acid of X_{16} is selected from the group consisting of R, N, F, K, Q, V, D and E;
the amino acid of X_{17} is selected from the group consisting of Q, A, I, S, P, T, N and V;
the amino acid of X_{18} is selected from the group consisting of G, D, E, H, L, V, Y, A, F, I, K, Q, W and R;
the amino acid of X_{19} is selected from the group consisting of T and K;
the amino acid of X_{20} is selected from the group consisting of R, F, K and I;

the amino acid of X_{21} is not present or is selected from the group consisting of K and R
the amino acid of X_{22} is selected from the group consisting of K, G and R;
the amino acid of X_{23} is not present or is selected from the group consisting of K and R
the amino acid of X_{24} is selected from the group consisting of R, Y, A, H, P, L, K, G, Q, N, I, F and W;
the amino acid of X_{25} is selected from the group consisting of A, Q, T, S and G;
the amino acid of X_{26} is selected from the group consisting of R;
the amino acid of X_{27} is selected from the group consisting of Y;
the amino acid of X_{28} is selected from the group consisting of A, T and S;
the amino acid of X_{29} is selected from the group consisting of M;
the amino acid of X_{30} is selected from the group consisting of Q, K, R, S and T;
the amino acid of X_{31} is selected from the group consisting of A and S;
the amino acid of X_{32} is selected from the group consisting of S and T;
the amino acid of X_{33} is selected from the group consisting of Q, G, R, K, L, M, P, Y and S;
the amino acid of X_{34} is selected from the group consisting of S, G, H and N;
the amino acid of X_{35} is selected from the group consisting of V, A and I;
the amino acid of X_{36} is selected from the group consisting of R;
the amino acid of X_{37} is selected from the group consisting of Y, F, L, Q, S, H, T, G, I, M, V and W;
the amino acid of X_{38} is selected from the group consisting of N, A, G, H, Q and S;
the amino acid of X_{39} is selected from the group consisting of V, I, M and L;
the amino acid of X_{40} is selected from the group consisting of A and G;
the amino acid of X_{41} is selected from the group consisting of Y and H
the amino acid of X_{42} is selected from the group consisting of S, K, M, Q, R, V, Y, G and E;
the amino acid of X_{43} is selected from the group consisting of N, K and R;
the amino acid of X_{44} is selected from the group consisting of R, L and K;
the amino acid of X_{45} is selected from the group consisting of Y, I, K, M, Q, R, V, A, N, S, W and H;
the amino acid of X_{46} is selected from the group consisting of T, A, D, E, Q, R, S, H, K, P, L, F, G, I, M and V;
the amino acid of X_{47} is selected from the group consisting of Q;
the amino acid of X_{48} is selected from the group consisting of H, N, S and T;
the amino acid of X_{49} is selected from the group consisting of H;
the amino acid of X_{50} is selected from the group consisting of Y;
the amino acid of X_{51} is selected from the group consisting of S, K and V;
the amino acid of X_{52} is selected from the group consisting of S and A; and
the amino acid of X_{53} is selected from the group consisting of T.

In one embodiment the polypeptide comprises three heavy chain CDRs (HCDR1-HCDR3) and three light chain CDRs (LCDR1-LCDR3) (wherein the CDRs in this embodiment are

defined by a non-Kabat numbering system) wherein HCDR1 comprises (e.g. consists of) $X_1X_2X_3X_4X_5X_6$ (SEQ ID NO: 72), HCDR2 comprises (e.g. consists of) $X_7IX_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}YX_{16}X_{17}X_{18}FX_{19}G$ (SEQ ID NO: 76), HCDR3 comprises (e.g. consists of) $DX_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}DY$ (SEQ ID NO: 80), LCDR1 comprises (e.g. consists of) $X_{30}X_{31}X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$ (SEQ ID NO: 84), LCDR2 comprises (e.g. consists of) $X_{41}AX_{42}X_{43}X_{44}X_{45}X_{46}$ (SEQ ID NO: 88) and LCDR3 comprises $X_{47}X_{48}X_{49}X_{50}X_{51}X_{52}PLX_{53}$ (SEQ ID NO: 92), wherein the amino acids X_1 to X_{53} correspond to X_1 to X_{53} as recited in the 'CDR numbering' column of Table 10 and are each selected from the amino acids recited in the corresponding rows in the 'Residues tested' column of Table 10. More suitably, amino acids X_1 to X_{53} are each selected from the amino acids recited in the corresponding rows in the '20-40% function of best residue', '40-60% function of best residue', '60-80% function of best residue' and 'Best Residue(s)' columns of Table 10. More suitably, amino acids X_1 to X_{53} are each selected from the amino acids recited in the corresponding rows in the '40-60% function of best residue', '60-80% function of best residue' and 'Best Residue(s)' columns of Table 10. More suitably, amino acids X_1 to X_{53} are each selected from the amino acids recited in the corresponding rows in the '60-80% function of best residue' and 'Best Residue(s)' columns of Table 10. Most suitably, amino acids X_1 to X_{53} are each selected from the amino acids recited in the corresponding rows in the 'Best Residue(s)' column of Table 10.

In one embodiment the polypeptide comprises a VH region and a VL region wherein the VH region comprises (e.g. consists of) the polypeptide sequence

QVQLVQSGSELKKPGASVKVSCKASGYTFX$_1$X$_2$X$_3$X$_4$X$_5$X$_6$WVRQAPGQGLEWX$_7$GX$_8$I
X$_9$X$_{10}$X$_{11}$X$_{12}$X$_{13}$X$_{14}$X$_{15}$X$_{16}$YX$_{17}$X$_{18}$X$_{19}$FX$_{20}$GRFX$_{21}$X$_{22}$SADKSX$_{23}$STAYLQISSLKAEDTAVYX$_{24}$C
ARDX$_{25}$X$_{26}$X$_{27}$X$_{28}$X$_{29}$X$_{30}$X$_{31}$X$_{32}$DYWX$_{33}$QGTTVTVSS (SEQ ID NO: 70)

and the VL region comprises (e.g. consists of) the polypeptide sequence

X$_{34}$IQMTQSPSSLSASVGDRVTITCX$_{35}$X$_{36}$X$_{37}$X$_{38}$X$_{39}$X$_{40}$X$_{41}$X$_{42}$X$_{43}$X$_{44}$X$_{45}$WYQQKPGKAPKLLIY
X$_{46}$AX$_{47}$X$_{48}$X$_{49}$X$_{50}$X$_{51}$GVPSRFSGSGSGTDFTFTISSLQPEDIATYX$_{52}$CX$_{53}$X$_{54}$X$_{55}$
X$_{56}$X$_{57}$X$_{58}$PLX$_{59}$FGGGTKLEIK (SEQ ID NO: 71)

wherein the amino acids X_1 to X_{59} correspond to X_1 to X_{59} as recited in the 'Full length numbering' column of Table 10 and are each selected from the amino acids recited in the corresponding rows in the 'Residues tested' column of Table 10 (wherein in this embodiment the CDRs are defined by a non-Kabat numbering system). More suitably, amino acids X_1 to X_{59} are each selected from the amino acids recited in the corresponding rows in the '20-40% function of best residue', '40-60% function of best residue', '60-80% function of best residue' and 'Best Residue(s)' columns of Table 10. More suitably, amino acids X_1 to X_{59} are each selected from the amino acids recited in the corresponding rows in the '40-60% function of best residue', '60-80% function of best residue' and 'Best Residue(s)' columns of Table 10. More suitably, amino acids X_1 to X_{59} are each selected from the amino acids recited in the corresponding rows in the '60-80% function of best residue' and 'Best Residue(s)' columns of

Table 10. Most suitably, amino acids X_1 to X_{59} are each selected from the amino acids recited in the corresponding rows in the 'Best Residue(s)' column of Table 10.

In certain embodiments the residue of HCDR2 corresponding to residue number 5 of SEQ ID NO: 2 is arginine and/or the residue of HCDR3 corresponding to residue number 6 of SEQ ID NO: 3 is arginine and/or the residue of HCDR3 corresponding to residue number 7 of SEQ ID NO: 3 is tyrosine and/or the residue of LCDR2 corresponding to residue number 1 of SEQ ID NO: 5 is tyrosine and/or the residue of LCDR3 corresponding to residue number 3 of SEQ ID NO: 6 is histidine.

In certain embodiments residue H53 is arginine and/or residue H100 is arginine and/or residue H100A is tyrosine and/or residue L50 is tyrosine and/or residue L91 is histidine, according to Kabat numbering.

In certain embodiments, the residue corresponding to position 74 of SEQ ID NO: 70 may be selected from lysine or threonine.

In certain embodiments the polypeptide comprises the paratope residues selected as very highly probable in Figure 4. Suitably, the residue corresponding to position 47 of SEQ ID NO: 418 is tryptophan, the residue corresponding to position 103 of SEQ ID NO: 418 is glycine, the residue corresponding to position 105 of SEQ ID NO: 418 is tyrosine, the residue corresponding to position 31 of SEQ ID NO: 39 is tyrosine, and the residue corresponding to position 92 of SEQ ID NO: 39 is tyrosine.

In further embodiments the polypeptide further comprises the paratope residues selected as highly probable in Figure 4. Suitably, the residue corresponding to position 52 of SEQ ID NO: 418 is leucine, the residue corresponding to position 54 of SEQ ID NO: 418 is arginine, the residue corresponding to position 104 of SEQ ID NO: 418 is arginine, the residue corresponding to position 26 of SEQ ID NO: 39 is serine, the residue corresponding to position 27 of SEQ ID NO: 39 is glutamine, the residue corresponding to position 49 of SEQ ID NO: 39 is tyrosine, and the residue corresponding to position 91 of SEQ ID NO: 39 is histidine.

In further embodiments the polypeptide further comprises the paratope residues selected as probable in Figure 4. Suitably, the residue corresponding to position 55 of SEQ ID NO: 418 is serine, the residue corresponding to position 58 of SEQ ID NO: 418 is threonine, the residue corresponding to position 59 of SEQ ID NO: 418 is asparagine, the residue corresponding to position 62 of SEQ ID NO: 418 is glutamine, the residue corresponding to position 100 of SEQ ID NO: 418 is phenylalanine, the residue corresponding to position 1 of SEQ ID NO: 39 is serine, the residue corresponding to position 29 of SEQ ID NO: 39 is valine, the residue corresponding to position 90 of SEQ ID NO: 39 is histidine, and the residue corresponding to position 93 of SEQ ID NO: 39 is serine.

In further embodiments the polypeptide further comprises the paratope residues selected as possible in Figure 4. Suitably, the residue corresponding to position 31 of SEQ ID NO: 418 is serine, the residue corresponding to position 60 of SEQ ID NO: 418 is tyrosine, the residue

corresponding to position 61 of SEQ ID NO: 418 is asparagine, the residue corresponding to position 65 of SEQ ID NO: 418 is threonine, the residue corresponding to position 99 of SEQ ID NO: 418 is aspartic acid, the residue corresponding to position 101 of SEQ ID NO: 418 is arginine, the residue corresponding to position 102 of SEQ ID NO: 418 is serine, the residue corresponding to position 25 of SEQ ID NO: 39 is alanine, the residue corresponding to position 30 of SEQ ID NO: 39 is arginine, the residue corresponding to position 67 of SEQ ID NO: 39 is serine, the residue corresponding to position 89 of SEQ ID NO: 39 is glutamine, and the residue corresponding to position 94 of SEQ ID NO: 39 is serine.

In one embodiment the VH region comprises, such as consists of, an amino acid sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 98%, such as at least 99%, such as 100% sequence identity with SEQ ID NO: 113. Suitably the VL region comprises, such as consists of, an amino acid sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 98%, such as at least 99%, such as 100% sequence identity with SEQ ID NO: 114.

The polypeptides of the invention may be described by reference to their heavy chain constant region sequences or light chain constant region sequences. The polypeptides of the invention may alternatively be described by reference to their heavy or light chain sequences. The polypeptides may comprise a heavy chain constant region and/or a light chain constant region, most suitably a heavy chain constant region and a light chain constant region.

Specific constant regions provided by the present invention include the following:

Table 7: Specific combinations of heavy chain, light chain and constant regions

	Heavy constant	**Light constant**	**Heavy chain**	**Light chain**
Antibody 11	12 heavy constant SEQ ID NO: 56	12 light constant SEQ ID NO: 57	11 HC SEQ ID NO: 60	11 LC SEQ ID NO: 61
Antibody 12	12 heavy constant SEQ ID NO: 56	12 light constant SEQ ID NO: 57	12 HC SEQ ID NO: 58	12 LC SEQ ID NO: 59
Antibody 13	12 heavy constant SEQ ID NO: 56	12 light constant SEQ ID NO: 57	11 HC SEQ ID NO: 60	12 LC SEQ ID NO: 59
Antibody 15	12 heavy constant SEQ ID NO: 56	12 light constant SEQ ID NO: 57	12 HC SEQ ID NO: 58	15 LC SEQ ID NO: 1219

Antibody 16	16 heavy constant SEQ ID NO: 1235	12 light constant SEQ ID NO: 57	16 HC SEQ ID NO: 1236	15 LC SEQ ID NO: 1219
Antibody 17	12 heavy constant SEQ ID NO: 56	12 light constant SEQ ID NO: 57	17 HC SEQ ID NO: 1220	15 LC SEQ ID NO: 1219
Antibody 18	12 heavy constant SEQ ID NO: 56	12 light constant SEQ ID NO: 57	17 HC SEQ ID NO: 1220	18 LC SEQ ID NO: 1221

Suitably the heavy chain comprises a polypeptide sequence having at least 50%, such as at least 70%, such as at least 90% identity with SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 1220 or SEQ ID NO: 1236. More suitably the heavy chain comprises SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 1220 or SEQ ID NO: 1236. More suitably the heavy chain consists of SEQ ID NO: 58, SEQ ID NO: 60, SEQ ID NO: 1220 or SEQ ID NO: 1236.

Suitably the heavy chain comprises a polypeptide sequence having at least 50%, such as at least 70%, such as at least 90% identity with SEQ ID NO: 58 or SEQ ID NO: 60. More suitably the heavy chain comprises SEQ ID NO: 58 or SEQ ID NO: 60. More suitably the heavy chain consists of SEQ ID NO: 58 or SEQ ID NO: 60.

Suitably the light chain comprises a polypeptide sequence having at least 50%, such as at least 70%, such as at least 90% identity with SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 1219 or SEQ ID NO: 1221. More suitably the light chain comprises SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 1219 or SEQ ID NO: 1221. More suitably the light chain consists of SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 1219 or SEQ ID NO: 1221.

Suitably the light chain comprises a polypeptide sequence having at least 50%, such as at least 70%, such as at least 90% identity with SEQ ID NO: 59 or SEQ ID NO: 61. More suitably the light chain comprises SEQ ID NO: 59 or SEQ ID NO: 61. More suitably the light chain consists of SEQ ID NO: 59 or SEQ ID NO: 61.

The polypeptides of the invention may be described by reference to multiple combined polypeptide sequences.

Suitably the polypeptide (such as an antibody or fragment thereof) comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 wherein HCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 1, HCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 2, HCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 3, LCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 4, LCDR2 comprises or consists of a

sequence having at least 80% identity with SEQ ID NO: 5 and LCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 6.

Suitably the polypeptide (such as an antibody or fragment thereof) comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 wherein HCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 1, HCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 2, HCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 15, LCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 4, LCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 5 and LCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 6.

Suitably the polypeptide (such as an antibody or fragment thereof) comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 wherein HCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 1, HCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 2, HCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 3, LCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 4, LCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 98 and LCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 6.

Suitably the polypeptide (such as an antibody or fragment thereof) comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 wherein HCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 1, HCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 100, HCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 101, LCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 4, LCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 98 and LCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 6.

Suitably the polypeptide (such as an antibody or fragment thereof) comprises a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2 and LCDR3 wherein HCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 1, HCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 100, HCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 101, LCDR1 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 103, LCDR2 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 98 and LCDR3 comprises or consists of a sequence having at least 80% identity with SEQ ID NO: 6.

Suitably the polypeptide (such as an antibody or fragment thereof) comprises a VH region comprising or consisting of a sequence having at least 80% identity with SEQ ID NO: 36 or SEQ ID NO: 102 and a VL region comprising or consisting of a sequence having at least 80% identity with SEQ ID NO: 99 or 104.

Suitably the polypeptide (such as an antibody or fragment thereof) further comprises heavy and light chain constant regions.

Suitably the polypeptide (such as an antibody) comprises or consists of a heavy chain comprising or consisting of SEQ ID NO: 58 or SEQ ID NO: 61 and a light chain comprising or consisting of SEQ ID NO: 59 or SEQ ID NO: 60.

In one embodiment, there is provided a polypeptide of any one of the sequences disclosed herein. In one embodiment, there is provided a polynucleotide encoding any one of the polypeptide sequences disclosed herein.

Embodiments which refer herein to "at least 80%" or "80% or greater", will be understood to include all values equal to or greater than 80%, such as 85%, 90%, 95%, 97%, 98%, 99% or 100% sequence identity.

Instead of percentage sequence identity, equivalent embodiments may also be defined with one or more amino acid changes, for examples one or more additions, substitutions and/or deletions. In one embodiment, the sequence may comprise up to five amino acid changes, such as up to three amino acid changes, in particular up to two amino acid changes. For example, the sequence may comprise up to five amino acid substitutions, such as up to three amino acid substitutions, in particular up to one or two amino acid substitutions. For example, CDR3 of the polypeptide of the present invention may comprise or more suitably consist of a sequence having no more than 2, more suitably no more than 1 substitution(s) compared to any one of SEQ ID NOs: 3.

For fragments comprising both the VH and VL regions, these may be associated either covalently (*e.g.* via disulphide bonds or a linker) or non-covalently. The antibody fragment described herein may comprise an scFv, *i.e.* a fragment comprising a VH region and a VL region joined by a linker. In one embodiment, the VH and VL region are joined by a (*e.g.* synthetic) polypeptide linker. The polypeptide linker may comprise a $(Gly_4Ser)_n$ linker, where n = from 1 to 8, *e.g.* 2, 3, 4, 5, 6 or 7. In a further embodiment, the linker comprises SEQ ID NO: 69. In a further embodiment, the linker consists of SEQ ID NO: 69.

In one embodiment, there is provided a polypeptide comprising one or more of a HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, VH or VL sequence provided in the accompanying sequence listing, or a polypeptide sharing at least 90%, such as at least 95%, such as at least 99% identity thereto. Most suitably, the polypeptide is an antibody or a fragment thereof.

Antibody sequence modifications

The antibodies and fragments thereof may be modified using known methods. Sequence modifications to antibody molecules described herein can be readily incorporate by those skilled in the art. The following examples are non-limiting.

During antibody discovery and sequence recovery from phage libraries, desired antibody variable domains may be re-formatted into full length IgG by sub-cloning. To accelerate the

process, variable domains are often transferred using restriction enzymes. These restriction sites may introduce additional/alternate amino acids and away from the canonical sequence (such canonical sequences may be found, for example, in the international ImMunoGeneTics [IMGT] information system, see http://www.imgt.org). These may be introduced as kappa or lambda light chain sequence modifications.

Binding

The polypeptide of the invention may bind to the LPAR1 with a binding affinity (K_D) of less than 3.0×10^{-7} M (*i.e.* 300 nM), less than 2.5×10^{-7} M (*i.e.* 250 nM), less than 2.0×10^{-7} M (*i.e.* 200 nM) or less than 1.5×10^{-7} M (*i.e.* 150 nM). In a further embodiment, the K_D is 1.3×10^{-7} M (*i.e.* 130 nM) or less, such as 1.0×10^{-7} M (*i.e.* 100 nM) or less. In a yet further embodiment, the K_D is less than 6.0×10^{-8} M (*i.e.* 60 nM), such as less than 5.0×10^{-8} M (*i.e.* 50 nM), less than 4.0×10^{-8} M (*i.e.* 40 nM), less than 3.0×10^{-8} M (*i.e.* 30 nM) or less than 2.0×10^{-8} M (*i.e.* 20 nM). In further embodiments, the K_D may be 1.5×10^{-8} M (*i.e.* 15 nM) or less, such as 1.0×10^{-8} M (*i.e.* 10 nM) or less, 9.0×10^{-9} M (*i.e.* 9 nM) or less, 8.0×10^{-9} M (*i.e.* 8 nM) or less, 7.0×10^{-9} M (*i.e.* 7 nM) or less, 6.0×10^{-9} M (*i.e.* 6 nM) or less, 5.0×10^{-9} M (*i.e.* 5 nM) or less, 4.0×10^{-9} M (*i.e.* 4 nM) or less, 3.0×10^{-9} M (*i.e.* 3 nM) or less, 2.0×10^{-9} M (*i.e.* 2 nM) or less, or 1.5×10^{-9} M (*i.e.* 1.5 nM) or less or 1.0×10^{-9} M (*i.e.* 1 nM) or less. For example, according to one aspect, there is provided an anti-LPAR1 antibody which binds to the LPAR1 with a binding affinity (K_D) of less than 1.5×10^{-7} M (*i.e.* 150 nM).

Suitably, the K_D of a polypeptide of the invention is determined using a kinetic exclusion assay (KinExA; a type of bioassay in which a solution containing receptor, ligand, and receptor-ligand complex is exposed to additional ligand immobilized on a solid phase). Suitably, the KinExA uses LPAR1 expressing cells as the titrated binding partner. Suitably the K_D is measured from a monovalent antibody, such as a Fab. In one embodiment, the K_D of a polypeptide of the invention may be established by method 1.14 detailed under the Examples section below.

Functional characterisation

Described herein are assays which may be used to characterise the function of the polypeptides of the invention. For example, the polypeptide described herein may be assessed by measuring calcium mobilisation or cAMP production. LPAR1 predominantly signals via Gi/o to inhibit cAMP production and Gq/11 to promote calcium mobilisation. LPAR1 also signals though G13 to promote Rho signalling.

The polypeptide described herein may also be assessed by measuring cell proliferation and migration. For example, DNA synthesis, a marker for cell proliferation, can be measured following application of the polypeptide to cells, e.g. by BrdU incorporation. Cell migration could be assessed by applying the polypeptide to cells before using a fluorescence microscope to count the proportion of cells which have migrated.

In functional assays, output may be measured by calculating the half maximal concentration, also referred to as “EC50” or “effective concentration at 50 percent”. The term "IC50" refers to the inhibitory concentration. Both EC50 and IC50 may be measured using methods known in

the art, such as flow cytometry methods. For the avoidance of doubt, the values of EC50 in the present application are provided using IgG1 formatted antibody. Such values can be easily converted based on the molecular weight of the antibody format for equivalent values as follows:

(µg/ml) / (MW in kDa) = µM

Millilitres may be denoted as "ml" or "mL" herein and used interchangeably.

The EC50 for downregulation upon polypeptide binding may be less than 0.5 µg/ml, such as less than 0.4 µg/ml, 0.3 µg/ml, 0.2 µg/ml, 0.15 µg/ml, 0.1 µg/ml or 0.05 µg/ml. In particular, said EC50 values are when the antibody is measured in an IgG1 format. For example, the EC50 value can be measured using flow cytometry.

In one embodiment the polypeptide of the invention modulates the function of LPAR1. More suitably the polypeptide on binding to LPAR1 is an inhibitor of LPAR1, such as an inverse agonist of LPAR1. In one embodiment the polypeptide of the invention is an allosteric inhibitor of LPAR1.

Suitably, binding to LPAR1 reduces Gi/o signalling by the LPAR1.

Suitably, binding to LPAR1 reduces or prevents LPA-induced or constitutive reduction in cAMP production (for example increases cAMP production in the assay detailed below (and utilised in Example 1.7)). In one embodiment, cAMP production is increased by at least 10%, such as at least 50%, such as at least 70%, such as at least 100%, such as at least 150%, such as at least 200%, such as at least 250%, such as at least 300%.

Suitably, binding to LPAR1 reduces or prevents LPA-induced calcium mobilisation (for example reduces calcium mobilisation in the assay detailed in Example 1.8).

In one embodiment the polypeptide on binding to LPAR1 reduces the activity of LPAR1 by at least 10%, such as at least 20%, such as at least 30%, such as at least 40%, such as at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 98%, such as at least 99%, such as at least 100%. More suitably the activity of LPAR1 is indicated by an assay detailed in Examples 1.1 to 1.16, such as the assay detailed in Example 1.7 or 1.11. Most suitably the activity of LPAR1 is indicated by the HTRF cAMP assay outlined below.

HTRF cAMP assay

CHO-K1 EDG2 Gi/Gq cells are seeded in multi well plates at 3000 cells per 25µL full growth medium and incubated for 24 hours at 37ºC. Cells are serum starved for 4 hours at 37ºC. Following serum starvation, medium is discarded and replaced with 5µL cell assay buffer (HBSS + 0.1% (w/v) BSA + 20mM HEPES). Cells are stimulated with human antibodies or human antibody-containing supernatants at various concentrations and incubated for 15 minutes at 37ºC. After pre-incubation, cells are stimulated with LPA (0.5µM) and forskolin

(5μM) and incubated for 1 hour at 37ºC. cAMP-cryptate and anti-cAMP-d2 working solutions are prepared in lysis and detection buffer and added to all wells of the plate. After incubation in the dark for 1 hour at room temperature, the plates are read on a plate reader. cAMP concentrations are determined by applying 620/665 nm fluorescence ratios to a standard curve of known cAMP concentrations.

Binding of an antibody of the invention to LPAR1 on the surface of a live cell is suitably indicated using the transient transfection CIFAT assay outlined below.

Transient-transfection CIFAT

CHO-K1 cells are seeded in multi well plates at 20,000 cells per 200μL full growth medium and incubated for 24 hours at 37ºC. In a sterile tube, 0.0309uL/well PEI is diluted into 10uL/well transfection medium (DMEM supplemented with 2mM L-glutamine and Penicillin-Streptomycin). The diluted PEI is added to 100 ng/well DNA, before mixing immediately and incubating the mixture for 10 minutes at room temperature. 200μL/well full growth medium is added to the PEI-DNA mixture, then medium in wells is taken off and 200ul full growth medium/PEI/DNA mixture is added in the wells of the adherent cell plate. The plate is incubated for 24 hours at 37ºC. The medium is discarded and replaced with 200μL full growth medium. The plate is incubated for 24 hours at 37ºC. Medium is removed from the wells and the cells incubated with primary antibody at varying concentrations for 75 minutes at 37ºC. After washing and cell fixation with 4% PFA, the binding of the antibodies is detected using a goat anti-human detection antibody, incubated for 1 hour at room temperature. Fluorescence at 488 nm is measured.

Multi-specific antibodies

The antibodies of the present invention may be mono-specific or they may bind additional targets and are therefore bi-specific or multi-specific. Multi-specific antibodies may be specific for different epitopes of one target polypeptide or may be specific for more than one target polypeptide. Therefore, in one embodiment, the polypeptide of the invention is comprised in a construct which comprises a first binding specificity to LPAR1 and a second binding specificity for a second target epitope.

The second binding specificity may target an antigen on the same cell as LPAR1 or on a different cell of the same tissue type or of a different tissue type. In certain embodiments, the target epitope may be on a different cell including a different T-cell, a B-cell, a tumour cell, an autoimmune tissue cell or a virally infected cell. Alternatively, the target epitope may be on the same cell.

In one embodiment, the construct comprises a polypeptide which binds to a target other than LPAR1.

Immunoconjugates

The polypeptides (such as antibodies or fragments thereof) of the present invention, may be conjugated to a therapeutic moiety, such as a cytotoxin or a chemotherapeutic agent. Most

preferably the polypeptide is conjugated to a therapeutic moiety which is an anti-fibrotic. Such conjugates may be referred to as immunoconjugates. As used herein, the term "immunoconjugate" refers to an antibody or fragment thereof which is chemically or biologically linked to another moiety, such as a cytotoxin, a radioactive agent, a cytokine, an interferon, a target or reporter moiety, an enzyme, a toxin, a peptide or protein or a therapeutic agent. Most preferably the therapeutic agent is an anti-fibrotic. The antibody or fragment thereof may be linked to the cytotoxin, radioactive agent, cytokine, interferon, target or reporter moiety, enzyme, toxin, peptide or therapeutic agent at any location along the molecule so long as it is able to bind its target. Examples of immunoconjugates include antibody-drug conjugates and antibody-toxin fusion proteins. In one embodiment, the agent may be a second different antibody to LPAR1. In certain embodiments, the antibody may be conjugated to an agent specific for a tumor cell or a virally infected cell. The type of therapeutic moiety that may be conjugated to the anti-LPAR1 antibody will take into account the condition to be treated and the desired therapeutic effect to be achieved.

Polynucleotides and expression vectors

In one aspect of the invention there is provided a polynucleotide encoding the polypeptide of the invention.

In one aspect of the invention there is provided a polynucleotide comprising or consisting of a sequence having at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 99% sequence identity with a polynucleotide encoding any one of the portions of SEQ ID NOs: 1 to 22, 40 to 55, 72 to 95, 98, 100, 101, 103, and 107 to 112 which encodes HCDR1, HCDR2, HCDR3, LCDR1, LCDR2, LCDR3, HFR1, HFR2, HFR3, HFR4, LFR1, LFR2, LFR3 or LFR4 of the encoded immunoglobulin chain variable domain.

In one aspect of the invention the polynucleotide comprises any one of SEQ ID NOs: 1368 to 1374.

To express the polypeptide, polynucleotides described herein may be inserted into expression vectors such that the genes are operatively linked to transcriptional and translational control sequences (which may be termed an 'expression cassette' as well understood in the art). Therefore, in one aspect of the invention there is provided an expression vector comprising a polynucleotide sequence of the invention as defined herein.

The present invention also provides polynucleotide sequences and expression vectors and plasmids encoding all of the polypeptide sequences disclosed herein, including any variant polypeptide sequences disclosed herein optionally comprising one or more amino acid substitutions.

Mutations can be made to the DNA or cDNA that encode polypeptides which are silent as to the amino acid sequence of the polypeptide, but which provide preferred codons for translation in a particular host. The preferred codons for translation of a nucleic acid in, *e.g.*, *E. coli* and *S. cerevisiae*, as well as mammalian, specifically human, are known.

Mutation of polypeptides can be achieved for example by substitutions, additions or deletions to a nucleic acid encoding the polypeptide. The substitutions, additions or deletions to a nucleic acid encoding the polypeptide can be introduced by many methods, including for example error-prone PCR, shuffling, oligonucleotide-directed mutagenesis, assembly PCR, PCR mutagenesis, *in vivo* mutagenesis, cassette mutagenesis, recursive ensemble mutagenesis, exponential ensemble mutagenesis, site-specific mutagenesis, gene reassembly, artificial gene synthesis, Gene Site Saturation Mutagenesis (GSSM), synthetic ligation reassembly (SLR) or a combination of these methods. The modifications, additions or deletions to a nucleic acid can also be introduced by a method comprising recombination, recursive sequence recombination, phosphothioate-modified DNA mutagenesis, uracil-containing template mutagenesis, gapped duplex mutagenesis, point mismatch repair mutagenesis, repair-deficient host strain mutagenesis, chemical mutagenesis, radiogenic mutagenesis, deletion mutagenesis, restriction-selection mutagenesis, restriction-purification mutagenesis, ensemble mutagenesis, chimeric nucleic acid multimer creation, or a combination thereof.

In particular, artificial gene synthesis may be used. A gene encoding a polypeptide of the invention can be synthetically produced by, for example, solid-phase DNA synthesis. Entire genes may be synthesized *de novo*, without the need for precursor template DNA. To obtain the desired oligonucleotide, the building blocks are sequentially coupled to the growing oligonucleotide chain in the order required by the sequence of the product. Upon the completion of the chain assembly, the product is released from the solid phase to solution, deprotected, and collected. Products can be isolated by high-performance liquid chromatography (HPLC) to obtain the desired oligonucleotides in high purity.

Expression vectors include, for example, plasmids, retroviruses, cosmids, yeast artificial chromosomes (YACs) and Epstein-Barr virus (EBV) derived episomes. The polynucleotide is ligated into a vector such that transcriptional and translational control sequences within the vector serve their intended function of regulating the transcription and translation of the polynucleotide. Expression and/or control sequences can include promoters, enhancers, transcription terminators, a start codon (i.e. ATG) 5′ to the coding sequence, splicing signals for introns and stop codons. The expression vector and expression control sequences are chosen to be compatible with the expression host cell used. Thus, the invention further provides a nucleotide sequence encoding polypeptides of the invention comprising a VH region and a VL region joined by a synthetic linker (encoding SEQ ID NO: 69). It will be understood that polynucleotides or expression vectors of the invention may comprise the VH region, the VL region or both (optionally including the linker). Therefore, polynucleotides encoding the VH and VL regions can be inserted into separate vectors, alternatively sequences encoding both regions are inserted into the same expression vector. The polynucleotide(s) are inserted into the expression vector by standard methods (*e.g.*, ligation of complementary restriction sites on the polynucleotide and vector, or blunt end ligation if no restriction sites are present).

A convenient vector is one that encodes a functionally complete CH and/or CL immunoglobulin sequence, with appropriate restriction sites engineered so that any VH or VL sequence can be easily inserted and expressed, as described herein. The expression vector can also encode a signal peptide that facilitates secretion of the polypeptide from a host cell. The polynucleotide may be cloned into the vector such that the signal peptide is linked in-frame to the amino terminus of the polypeptide. The signal peptide can be an immunoglobulin signal peptide or a heterologous signal peptide (*i.e.,* a signal peptide from a non-immunoglobulin protein).

In one aspect of the invention there is provided a cell (*e.g.* a host cell) comprising the polynucleotide or expression vector as defined herein. It will be understood that the cell may comprise a first vector encoding the light chain of the polypeptide, and a second vector encoding the heavy chain of the polypeptide. Alternatively, the heavy and light chains may both be encoded on the same expression vector introduced into the cell.

In one embodiment, the polynucleotide or expression vector encodes a membrane anchor or transmembrane domain fused to the polypeptide, wherein the polypeptide is presented on an extracellular surface of the cell.

Transformation can be by any known method for introducing polynucleotides into a host cell. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include dextran-mediated transfection, calcium phosphate precipitation, polybrene-mediated transfection, protoplast fusion, electroporation, transduction, encapsulation of the polynucleotide(s) in liposomes, biolistic injection and direct microinjection of the DNA into nuclei. In addition, nucleic acid molecules may be introduced into mammalian cells by viral vectors.

Mammalian cell lines available as hosts for expression are well known in the art and include many immortalized cell lines available from the American Type Culture Collection (ATCC). These include, inter alia, Chinese hamster ovary (CHO) cells, NSO, SP2 cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (*e.g.*, Hep G2), A549 cells, 3T3 cells, and a number of other cell lines. Mammalian host cells include human, mouse, rat, dog, monkey, pig, goat, bovine, horse and hamster cells. Cell lines of particular preference are selected through determining which cell lines have high expression levels. Other cell lines that may be used are insect cell lines, such as Sf9 cells, amphibian cells, bacterial cells, plant cells and fungal cells. Antigen-binding fragments of antibodies such as the scFv and Fv fragments can be isolated and expressed in *E. coli* using methods known in the art.

The polypeptides are produced by culturing the host cells for a period of time sufficient to allow for expression of the polypeptide in the host cells or, more preferably, secretion of the polypeptide into the culture medium in which the host cells are grown. Polypeptides can be recovered from the culture medium using standard protein purification methods.

Polypeptides of the invention can be obtained and manipulated using the techniques disclosed for example in Green and Sambrook, *Molecular Cloning: A Laboratory Manual* (2012) 4th Edition Cold Spring Harbour Laboratory Press.

Monoclonal antibodies can be produced using hybridoma technology, by fusing a specific antibody-producing B cell with a myeloma (B cell cancer) cell that is selected for its ability to grow in tissue culture and for an absence of antibody chain synthesis.

A monoclonal antibody directed against a determined antigen can, for example, be obtained by:

a) immortalizing lymphocytes obtained from the peripheral blood of an animal previously immunized with a determined antigen, with an immortal cell and preferably with myeloma cells, in order to form a hybridoma,

b) culturing the immortalized cells (hybridoma) formed and recovering the cells producing the antibodies having the desired specificity.

Alternatively, the use of a hybridoma cell is not required. Antibodies capable of binding to the target antigens as described herein may be isolated from a suitable antibody library via routine practice, for example, using the phage display, yeast display, ribosomal display, or mammalian display technology known in the art. Accordingly, monoclonal antibodies can be obtained, for example, by a process comprising the steps of:

a) cloning into vectors, especially into phages and more particularly filamentous bacteriophages, DNA or cDNA sequences obtained from lymphocytes especially peripheral blood lymphocytes of an animal (suitably previously immunized with determined antigens),

b) transforming prokaryotic cells with the above vectors in conditions allowing the production of the antibodies,

c) selecting the antibodies by subjecting them to antigen-affinity selection,

d) recovering the antibodies having the desired specificity.

Optionally, an isolated polynucleotide encoding a polypeptide as described herein and which binds to LPAR1 can also be readily manufactured to make sufficient quantities to be employed as a medicament to ameliorate the signs or symptoms of disease. When employed as a medicament in this manner, typically the polynucleotide of interest is first operatively linked to an expression vector or expression cassette designed to express said antibody or fragment thereof in a subject or patient. Such expression cassettes and methods of delivery of polynucleotides or what are sometime termed 'nucleic-based' medicaments and are well known in the art. For a recent review see Hollevoet and Declerck (2017).

Also provided is a method for the production of a polypeptide, anti-LPAR1 antibody or fragment or variant thereof, comprising culturing a host cell of the invention in a cell culture medium under conditions to express the encoding nucleic acid sequence of the plasmid or vector inside the cell. The method may further comprise obtaining the polypeptide, anti-LPAR1 antibody or fragment or variant thereof from the cell culture supernatant. The obtained antigen-binding molecule may then be formulated into a pharmaceutical composition. Further, there is provided a method of producing a cell that expresses a polypeptide, anti-LPAR1 antibody

or fragment or variant thereof, comprising transfecting said cell with a plasmid or vector of the invention. Said cells can then be cultured for the production of the polypeptide, anti-LPAR1 antibody or fragment or variant thereof.

Lysophosphatidic Acid Receptor 1 (LPAR1)

Lysophosphatidic acid (1-acyl-2-hydroxy-sn-glycero-3-phosphate; LPA) belongs to a family of endogenous lipid molecules that exert their effects through interactions with the LPA family of G protein-coupled receptors (GPCRs), of which there are currently 6 identified receptor subtypes. LPAR1-3 receptors belong to the endothelial differentiation gene (EDG) family GPCRs, and LPAR4-6 receptors are closely related to the purinergic family GPCRs. The LPAR1 receptor predominantly signals via Gi/o to inhibit cAMP production and Gq/11 to promote calcium mobilization, though also signals through G12/13 to activate the Rho GTPase nucleotide exchange factors (GEF).

LPAR1 may also be referred to as LPA-1, LPA receptor 1, Lysophosphatidic acid receptor 1 or Lysophosphatidic acid receptor Edg-2.

The crystal structure of LPAR1 was solved in 2015 (Chrencik *et al.* 2015). It exhibits many of the features typical of a family A GPCR, with 7 transmembrane helices, and 94 of the total of 364 amino acids facing the extracellular solvent. This includes an N terminal region 50 amino acids long. Unusually however the N-terminus forms a helical cap on the extracellular side, which folds over the 7-helix bundle to almost entirely occlude the ligand-binding site and bury the ligand. Human LPAR1 shares 99%, 99%, 97% and 97% amino acid identity with its orthologues in cynomolgus, rhesus, mouse and rat, respectively.

The extracellular region of LPAR1 comprises extracellular domains 0 to 3 (ECD0 to ECD3). In ECD0, the N-terminal region, residues 25-50 of SEQ ID NO: 62 form an unusual capping helix, held in place by a disulphide bridge between ECD0 and ECD2. By reference to SEQ ID NO: 62, the entire N-terminus is residues 1-50, the N-terminal capping helix is residues 25-50, the entire ECD1 is residues 106-121, the entire ECD2 is residues 185-204 and the entire ECD3 is residues 280-294.

In one embodiment the LPAR1 is human LPAR1. In one embodiment the LPAR1 is not human LPAR1. The LPAR1 may be native LPAR1 and/or full length LPAR1. Alternatively, the LPAR1 is a fragment of LPAR1, such as a fragment comprising one or more extracellular regions of LPAR1. In certain embodiments the fragment of LPAR1 is at least 50 amino acids long, such as at least 100 amino acids long, such as at least 150 amino acids long, such as at least 200 amino acids long, such as at least 250 amino acids long, such as at least 300 amino acids long, such as at least 350 amino acids long.

Suitably the LPAR1 comprises or consists of a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 99% identity with SEQ ID NO: 62, SEQ ID NO: 63 or SEQ ID NO: 64. More suitably the LPAR1 comprises or consists of SEQ ID NO: 62, SEQ ID NO: 63 or SEQ ID NO: 64.

In one embodiment the LPAR1 is functionally active LPAR1. By 'functionally active' it is meant that the LPAR1 is capable of signalling via downstream signalling pathways (e.g. cAMP, Ca mobilisation). The binding of LPA to functionally active LPAR1 results in the transduction of downstream signalling, and/or functionally active LPAR1 maintains a constitutive level of downstream signalling. Non-functionally active LPAR1 is not capable of initiating signalling.

In a further embodiment, the LPAR1 is localised on the extracellular surface. In a further embodiment, the LPAR1 is present on the surface of a live cell. In a further embodiment, the polypeptide is an antagonist of LPAR1. In a further embodiment, the polypeptide is an antagonist of LPA mediated signalling.

Compositions

According to a further aspect of the invention, there is provided a composition comprising the polypeptide or construct as defined herein. In such embodiments, the composition may comprise the polypeptide or construct, optionally in combination with other excipients. Also included are compositions comprising one or more additional active agents (e.g. active agents suitable for treating the diseases mentioned herein).

According to a further aspect of the invention, there is provided a pharmaceutical composition comprising the polypeptide or construct as defined herein, together with a pharmaceutically acceptable diluent or carrier. The polypeptide or construct of the invention can be incorporated into pharmaceutical compositions suitable for administration to a subject. Typically, the pharmaceutical composition comprises a polypeptide or construct of the invention and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include one or more of water, saline, salts, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Pharmaceutically acceptable substances such as wetting or minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the polypeptide may be included.

The compositions of this invention may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (*e.g.,* injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of injectable or infusible solutions.

The preferred mode of administration is parenteral (*e.g.*, intravenous, subcutaneous, intraperitoneal, intramuscular). In a preferred embodiment, administration is by intravenous infusion or injection. In another preferred embodiment, administration is by intramuscular or subcutaneous injection.

Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high drug concentration.

It is within the scope of the invention to use the pharmaceutical composition of the invention in therapeutic methods for the treatment of diseases as described herein as an adjunct to, or in conjunction with, other established therapies normally used in the treatment of such diseases.

In a further aspect of the invention, the polypeptide, composition or pharmaceutical composition is administered sequentially, simultaneously or separately with at least one active agent.

Treatment

Chronic kidney disease/diabetic kidney disease (CKD/DKD)

Chronic kidney disease (CKD) can be caused by many factors, including diabetes, with 25-55% of all dialysis patients worldwide having diabetic kidney disease. CKD is characterised by progressive loss of kidney function. Clinically this is initially diagnosed by an estimated glomerular filtration rate (eGRF) of <60 mL/minute (a healthy adult eGFR is >90 mL/minute). The presence of protein in the urine (proteinuria), is an indicator of kidney damage and prognostic of a deterioration of eGFR.

No LPAR1 inhibitor has yet been tested in human kidney disease. Three published studies examine the effect of LPAR1 (or LPAR1 and LPAR3) inhibition on kidney function, in three separate models (Zhang *et al.* (2017), Li *et al.* (2017) & Lee JH *et al.* (2019)). All three studies found reduction in albuminuria, as well as in kidney fibrosis and inflammation. Various components of the LPAR1 signalling pathway have been found to be upregulated in different forms of kidney disease.

When CKD is associated with and caused by diabetes, it is known as diabetic kidney disease (DKD).

LPAR1 inhibitors have not previously been trialled in the treatment of DKD though there is significant evidence to link LPAR1 biology with clinical disease. While LPAR1 plays a role in a range of biological pathways and diseases including neuropathic pain, bone growth and cancer, it has particular importance in three biological axes which are at the core of kidney disease; fibrosis, inflammation and metabolic syndrome. These three axes exert specific and measurable changes to the levels of a number of biochemicals found in blood and urine. These dovetail with molecules found to be modulated by LPAR1 inhibition in a Phase II study (Palmer *et al.* 2018) and various animal studies.

LPAR1 genetic knockout or pharmacological inhibition has been protective in a number of models of mouse kidney fibrosis (Zhang *et al.*, 2017; Pradère et al., 2007; Swaney *et al.* 2011). The Phase II efficacy trial for idiopathic lung fibrosis (Palmer *et al.* 2018) showed that the small

molecule inhibitor of LPAR1 was effective in maintaining forced vital capacity over the study period.

LPAR1 plays a role in the induction of inflammation. Addition of LPA to whole blood triggers histamine release through LPAR1 (Swaney *et al.* 2010). In a murine molecule of vasculitis, recruitment of neutrophils to vascular walls for inflammation was dependent on LPAR1 expression on the neutrophils (Miyabe *et al.* 2019).

Increased signalling has through the LPA/LPAR1 axis has been linked to metabolic syndrome and cardiovascular health. Li *et al.* 2017 found that LPAR1 was selectively upregulated on a mouse kidney mesenchymal cell line after exposure to high glucose concentration. Rancoule *et al.* 2013 found that mice treated for three weeks with an LPAR1/3 inhibitor had improved tolerance to an i.p. injection of glucose. Guo *et al.* (2013) found that administration of exogenous adiponectin to *db/db* mice significantly reduced albuminuria and histological evidence of kidney fibrosis.

Three studies that examine the effect of LPAR1 (or LPAR1 and LPAR3) inhibition on kidney function have been published (Zhang *et al.* 2017, Li *et al.* 2017, Lee JH *et al.* 2019), which are summarised in Table 8.

Table 8: Impact of LPAR1 inhibition on mouse models of diabetic nephropathy

Study author:	**Zhang *et al.* (2017)**	**Li *et al.* (2017)**	**Lee JH *et al.* (2019)**
Diabetes model	*db/db eNOS*$^{2/2}$ (aggressive model)	*db/db* (moderate model)	STZ-induced (early disease model)
Duration of drug treatment	12 weeks	8 weeks	8 weeks
LPAR1 Inhibitor	BMS-002 (LPAR1/3)	Ki16425 (LPAR1/3)	AM095 (LPAR1)
24h albuminuria vs untreated controls	~65% reduction	~30% reduction	~30% reduction

All three studies found reduction in albuminuria, kidney fibrosis and inflammation.

Conversely, upregulation of components of the LPAR1 signalling pathway has been found in different forms of kidney disease. Zhang *et al.* 2017 observed an increase in levels of autotaxin and LPAR1 in the kidneys of patients with diabetes. Sasagawa *et al.* 1998 observed a 2.6 fold increase in lysophosphatidic acid levels in the plasma of patients with renal failure compared to controls.

Peritoneal fibrosis

Sakai *et al.* 2013 showed that genetic deletion of pharmacological inhibition of LPAR1 protected mice from fibrosis in response to CG peritoneal injury.

Liver fibrosis

In a mouse model of NASH, treatment with an LPAR1 antagonist showed a strong decrease in the expression of fibrotic and inflammatory genes (Nishikawa *et al.* 2016). Correlation between the extent of liver fibrosis and plasma LPA level was shown in an *in vivo* mouse study in response to chronic liver injury (Watanabe *et al.* 2007)

Idiopathic lung fibrosis (IPF)

As described previously, the phase II clinical trial of IPF showed that a small molecule inhibitor of LPAR1 was effective in treating fibrosis of the lungs (Palmer *et al.* 2018). Furthermore, an *in vivo* mouse study using LPAR1 deficient mice found that LPAR1 deficiency protected the mice from fibrosis and mortality after a lung injury (Tager *et al.* 2007)

Dermal fibrosis

Using a mouse model of bleomycin-induced dermal fibrosis, LPAR1 knockout mouse were found to be resistant to bleomycin-induced increases in dermal thickness and collagen (Castelino *et al.* 2011).

Systemic sclerosis

Mass spectrometric analysis of the sera of systemic sclerosis patients found elevated levels of 2-arachidonoyl-LPA (Tokumura *et al.* 2009).

Osteoarthritis

Treatment with an LPAR1 antagonist caused decreased synovial inflammation, cartilage damage and bone erosion in mice (Orosa *et al.* 2014).

According to a further aspect of the invention, there is provided a polypeptide, construct or composition as defined herein for use as a medicament.

In one embodiment, the polypeptide, construct or composition is for use in therapy, particularly for use in the treatment of an inflammatory and/or fibrotic disease, or cancer. Suitably the polypeptide, construct or composition is for use in the treatment of an inflammatory and/or fibrotic disease. Suitably, the polypeptide, construct or composition is for use in the treatment of chronic kidney disease, kidney fibrosis, peritoneal fibrosis, liver fibrosis, pulmonary fibrosis (e.g. idiopathic pulmonary fibrosis), dermal fibrosis, systemic sclerosis or osteoarthritis. Suitably, the polypeptide is for use in the treatment of chronic kidney disease, such as diabetic kidney disease. Alternatively the polypeptide, construct or composition is for use in the treatment of chronic kidney disease, kidney fibrosis, peritoneal fibrosis, liver fibrosis, pulmonary fibrosis (e.g. idiopathic pulmonary fibrosis), dermal fibrosis, systemic sclerosis, osteoarthritis, NASH, rheumatoid arthritis, neuropathic pain or cancer.

In a further embodiment, there is provided a method for treating a disease in a subject in need thereof, comprising administering the polypeptide, construct or composition as defined herein. In a further embodiment, there is provided a method for treating an inflammatory disease and/or fibrotic disease in a subject in need thereof, comprising administering the polypeptide,

construct or composition as defined herein. In a further embodiment, there is provided a method for treating chronic kidney disease, kidney fibrosis, peritoneal fibrosis, liver fibrosis, pulmonary fibrosis (e.g. idiopathic pulmonary fibrosis), dermal fibrosis, systemic sclerosis or osteoarthritis comprising administering the polypeptide, construct or composition as defined herein. In a further embodiment, there is provided a method of treating chronic kidney disease, such as diabetic kidney disease comprising administering the polypeptide, construct or composition as defined herein. Alternatively there is provided a method of treating chronic kidney disease, kidney fibrosis, peritoneal fibrosis, liver fibrosis, pulmonary fibrosis (e.g. idiopathic pulmonary fibrosis), dermal fibrosis, systemic sclerosis, osteoarthritis, NASH, rheumatoid arthritis, neuropathic pain or cancer comprising administering the polypeptide, construct or composition as defined herein.

According to further aspects of the invention, there is provided the use of a polypeptide, construct or composition as defined herein for the manufacture of a medicament, for the treatment of disease. According to further aspects of the invention, there is provided the use of a polypeptide, construct or composition as defined herein for the manufacture of a medicament, for the treatment of an inflammatory disease and/or fibrotic disease. In a further embodiment, there is provided the use of a polypeptide, construct or composition as defined herein for the manufacture of a medicament for the treatment of chronic kidney disease, kidney fibrosis, peritoneal fibrosis, liver fibrosis, pulmonary fibrosis (e.g. idiopathic pulmonary fibrosis), dermal fibrosis, systemic sclerosis or osteoarthritis. In a further embodiment, there is provided the use of a polypeptide, construct or composition as defined herein for the manufacture of a medicament for the treatment of chronic kidney disease, such as diabetic kidney disease. Alternatively there is provided the use of a polypeptide, construct or composition as defined herein for the manufacture of a medicament for the treatment of chronic kidney disease, kidney fibrosis, peritoneal fibrosis, liver fibrosis, pulmonary fibrosis (e.g. idiopathic pulmonary fibrosis), dermal fibrosis, systemic sclerosis, osteoarthritis, NASH, rheumatoid arthritis, neuropathic pain or cancer.

In one embodiment, the polypeptide, construct or composition is administered in a therapeutically effective amount.

The present invention will now be further described by means of the following non-limiting examples.

EXAMPLES

Example 1: Methods

1.1 Immunisation protocol

Mice were immunized with LPAR1. After immunisation spleens were dissected into DMEM and homogenised as described in Forbes *et al.* (2011). After red cells were lysed and splenocytes pelleted, splenocytes were resuspended in 1.5mL FBS and refrigerated for 10 minutes before adding 1.5mL 20% DMSO in FBS. Suspended cells were then aliquoted into cryovials and frozen at a rate of -1°C per minute.

1.2 Hybridoma isolation

Cryo-frozen spleen cells from immunized mice were defrosted and fused with sp2/0 myeloma cells using polyethene glycol to produce hybridomas. Hybridomas were then plated into methylcellulose medium gel and productive hybridomas were selected using HAT (hypoxanthine-aminopterin-thymidine) reagent. After 5 days, hybridoma colonies producing IgG were identified using CloneDetect reagent (Molecular Devices), and then picked and seeded into monoclonal cultures. LPAR1-reactive hybridomas were identified by screening culture supernatants for differential binding to LPAR1-expressing cells in a FACS assay. Briefly, CHO cells were transiently transfected with a plasmid to express either LPAR1 or an irrelevant GPCR, and two days after CHO cell transfection, hybridoma supernatants were mixed with both populations of CHO cells. Binding of antibody to cells was detected with an anti-mouse IgG secondary antibody. Hybridoma supernatants that bound CHO-LPAR1 cells but not CHO-irrelevant GPCR cells were defined as LPAR1 binders.

1.3 Ig gene isolation from hybridoma

10^6 LPAR1-specific hybridoma cells were subjected to total RNA extraction and reverse transcription to generate a whole cDNA library. Next generation sequencing of the entire cDNA library was performed on an Illumina HiSeq sequencer. Contigs were assembled, and mined for DNA sequences encoding antibody VH or VL sequences.

1.4 Generation of recombinant vectors

DNA fragments for VH or VL regions were cloned into the human IgG1 heavy chain or human Kappa light chain expression vectors using an overhang cloning method. Variable region sequences were optimised for Homo Sapiens and cloned into vectors via 5' BspEI and 3' BsaI or via 5' BssHII and 3' ApaI. Mini-scale DNA samples were reconstituted to 100ng/µL in cell culture grade water. Plasmids were stored at -20°C until needed for transfection.

1.5 Antibody expression

For antibody expression, HEK293 cells were cultured at 37°C at 8% CO_2 and seeded at a density of 2 x 10^6 cells. Heavy and light chain plasmids were transiently co-transfected into HEK293 cells. Enhancers were added 18-22 hours after transfection. Supernatants were harvested 5 days after transfection. Cells were pelleted by centrifugation at 1000g for 10 minutes and supernatants were aliquoted into appropriate sterile plasticware.

1.6 Antibody purification

Recombinantly expressed human antibodies were purified from cell culture supernatants using Protein-A, 5mL gravity flow columns. Prior to sample loading, the column was equilibrated with Protein A IgG Binding Buffer, pH 8.0. Cell culture supernatants were clarified using 0.45µM filters and mixed with 1:1 Protein A IgG Binding Buffer, pH 8.0. Upon passing the sample through the column, the flow-through was collected and passed over the column a subsequent 5 times. The columns were washed with PBS and 0.5M L-arginine buffer, pH 7. The antibody was eluted from the column into 1M Tris-HCl, pH 8.0, using IgG elution buffer, pH 2.8. The eluted sample was buffer exchanged into PBS using centrifugal filter units and

sterile filtered using 0.2μM centrifuge tube filters. Purified antibodies were stored in PBS at 4°C.

1.7 HTRF cAMP assay

cAMP Hunter™ CHO-K1 EDG2 Gi/Gq cells (DiscoverX) were seeded in 384-well white plates at 3000 cells per 25μL full growth medium and incubated for 24 hours at 37ºC. The following day, cells were serum starved for 4 hours at 37ºC. Following serum starvation, medium was discarded and replaced with 5μL cell assay buffer (HBSS + 0.1% (w/v) BSA + 20mM HEPES). Cells were stimulated with human antibodies or human antibody-containing supernatants at various concentrations and incubated for 15 minutes at 37ºC. After pre-incubation, cells were stimulated with LPA (0.5μM) and forskolin (5μM) and incubated for 1 hour at 37ºC. Following the manufacturer protocol, cAMP-cryptate and anti-cAMP-d2 working solutions were prepared in lysis and detection buffer and added to all wells of the plate. After incubation in the dark for 1 hour at room temperature, the plates were read on a plate reader. cAMP concentrations were determined using Prism 5 (GraphPad Software, CA, USA) by applying the 620/665 nm fluorescence ratios to a standard curve of known cAMP concentrations.

1.8 Calcium mobilisation assay

Human pulmonary fibroblasts were seeded at 8000 cells per well in 50μL full growth medium into 384-well plates and incubated for 24 hours at 37ºC. The following day, the media was changed to serum-free and incubated for 24 hours at 37ºC. Following serum starvation, medium was replaced with Fluo-4 no wash dye (Molecular Devices) diluted in buffer (HBSS supplemented with 20mM HEPES, 2.5mM Probenecid, 0.1% (w/v) BSA, pH7.4) and equilibrated for 45 minutes at 37ºC. The plate was transferred to the FLIPR for the calcium mobilization assay. Human antibodies or human antibody-containing supernatants were dispensed onto the plate at various concentrations, whilst recording, over 120 seconds and incubated for 20 minutes at 37ºC. After pre-incubation, the EC80 concentration of ligand (100nM LPA) was dispensed on-line, whilst recording, over 120 seconds. Data were collected in ScreenWorks version 3.2 (Molecular Devices) and the relative fluorescent units (RFU) plotted against the log of compound concentration using nonlinear regression analysis in Prism 5 (GraphPad Software, CA, USA).

1.9 HPF BrdU incorporation assay

Human pulmonary fibroblasts were seeded at 1500 cells/well in 35μL assay medium (RPMI 1640 + 2mM L-glutamine + 0.1% (w/v) HSA + Penicillin-Streptomycin) into 384-well black view-plates. Cells were incubated for 24 hours at 37ºC. The following day, cells were stimulated with human antibodies at various concentrations and incubated for 30 minutes at 37ºC. After pre-incubation, cells were stimulated with LPA (10μM) and incubated for 8 hours at 37ºC. For the following steps, reagents from the Perkin Elmer DELFIA cell proliferation kit were used. Cells were treated with 10 μM BrdU labelling solution and incubated for 16 hours at 37ºC. After 16 hours of BrdU incorporation, medium was removed and cells were fixed. After washing, anti-BrdU-EU working solution was added to the plate and incubated for a further 2 hours at room temperature. After further washing, the DELFIA inducer solution was added to all wells of the plate followed by 20 minutes of shaking incubation at room

temperature. Time-resolved fluorescence was measured using a BMG LABTECH ClarioStar plate reader. Background levels of RFU were subtracted from the raw RFU values detected in each well and concentration-response curves fitted using a four-parameter logistic equation in Prism 5 (GraphPad Software, CA, USA).

1.10 HPF/HKF migration assay

Human pulmonary fibroblasts or human kidney fibroblasts were grown to 80% confluence in full growth medium in cell culture flasks. Prior to the experiment, the medium was replaced with serum free and the cells incubated for 24 hours at 37ºC. The underside membrane of a 96-well transwell chamber (5µM) was coated with 6.6µg/mL fibronectin (diluted in water supplemented with 20mM HEPES) and left to air dry in sterile conditions overnight. The next day, the other side of the chemotaxis membrane was coated with 6.6µg/mL fibronectin as above. Assay buffer containing chemoattractant (LPA) was added to the lower chamber of the plate, then once dry, the fibronectin-coated membrane with 5µM pore size was placed on top. Growth arrested fibroblasts were dissociated, washed and resuspended in RPMI 1640 + 0.1% (w/v) BSA, then 1 x 10^5 cells/well were loaded into the upper chamber. Human antibodies were diluted in assay buffer (RPMI 1640 + 0.1% (w/v) BSA) and added to the cell suspension in the upper chamber. After a 24 hour incubation at 37ºC, fibroblasts on the top side of the membrane were removed using tapered-ended cotton swabs so that only cells that had migrated through the membrane remained. The membrane was fixed with 100% methanol for 10 minutes, stained with DAPI for 10 minutes and rinsed with distilled water. The membrane chamber was mounted onto clear plasticware and the cells on the underside were counted using a fluorescence microscope at x10 magnification and images taken.

1.11 Transient-transfection CIFAT

CHO-K1 cells were seeded in clear 96-well plates at 20,000 cells per 200µL full growth medium and incubated for 24 hours at 37ºC. The following day, in a sterile tube, 0.0309uL/well PEI (Generon, MW 160,000) was diluted into 10uL/well transfection medium (DMEM supplemented with 2mM L-glutamine and Penicillin-Streptomycin). The diluted PEI was added to 100 ng/well DNA encoding the target protein (human LPAR1 (SEQ ID NO: 62) unless otherwise stated), before vortexing immediately and incubating the mixture for 10 minutes at room temperature. 200µL/well full growth medium was added to the PEI-DNA mixture, then medium in wells was taken off and 200ul full growth medium/PEI/DNA mixture was added in the wells of the adherent cell plate. The plate was incubated for 24 hours at 37ºC. The next day, the medium was discarded and replaced with 200µL full growth medium. The plate was incubated for 24 hours at 37ºC. The following day, medium was removed from the wells and the cells incubated with primary antibody at varying concentrations for 75 minutes at 37ºC. After washing and cell fixation with 4% PFA, the binding of the antibodies was detected using a goat anti-human Alexa Fluor 488 detection antibody (Invitrogen), incubated for 1 hour at room temperature. Fluorescence at 488 nm was measured using a BMG LABTECH ClarioStar plate reader and microscopy images were taken at 10x magnification.

1.12 Stable-cell CIFAT

CHO-LPAR1 and CHO-CXCR2 cells were seeded in black 96-well plates at a total of 50,000 cells/200µL full growth medium at a ratio of 2:23. Cells were incubated for 24 hours at 37ºC. The following day, the medium was removed from the wells and the cells incubated with primary antibody at varying concentrations for 75 minutes at 37ºC. After washing and cell fixation with 4% PFA, the binding of the antibodies was detected using a goat anti-human Alexa Fluor 488 detection antibody (Invitrogen), incubated for 1 hour at room temperature. Fluorescence at 488 nm was measured using a BMG LABTECH ClarioStar plate reader and microscopy images were taken at 10x magnification.

1.13 Competition CIFAT

CHO-LPAR1 (GenScript) cells were seeded in black 96-well plates at 50,000 cells/200µL full growth medium at and incubated for 24 hours at 37ºC. The following day, the medium was removed from the wells and the cells incubated with 100 µg/mL primary antibody for 20 minutes at 37ºC. After pre-incubation with the antibody, 10 µg/mL biotinylated competing antibody was added before incubation for 20 minutes at 37ºC. After washing and cell fixation with 4% PFA, the binding of the antibodies was detected using an Alexa Fluor 488 streptavidin detection antibody (Molecular Probes), incubated for 45 minutes at 4ºC. Fluorescence at 488 nm was measured using a BMG LABTECH ClarioStar plate reader and microscopy images were taken at 10x magnification.

1.14 K_D Measurement

The monomeric affinity constant K_D for the interaction of antibodies with LPAR1 was determined using monomeric Fabs derived from the antibodies, using the KinExA method. In this method, the concentration of unbound antibody is measured against a range of antigen concentrations. Because K_D = ([Free antigen][Free antibody])/[Antigen-antibody complex], the value of K_D can be deduced from these measurements. CHO-LPAR1 cells, the antigen source, are titrated in a background of constant binding partner (CBP, e.g. a Fab to be tested). Samples are gently rocked until equilibrium is reached. After incubation, cells are centrifuged and the free CBP is removed without disturbing the cell pellet. Beads coated with Anti-Species are used to capture a portion of free CBP. Captured CBP is detected with a fluorescently labelled Anti-CBP using the KinExA. The fluorescent signal is converted to a voltage signal that is directly proportional to the concentration of free CBP in the equilibrated sample.

Values of K_D in the present application are provided using Fab formatted antibodies.

1.15 BRET Assay

Using polyethylenimine (PEI) transfection agent at a 3:1 ratio, HEK293 cells were co-transfected in suspension with hLPAR1 and one of the following biosensors: G protein activation sensors (Gαi2, Gα13, and Gαq) and the βArrestin 2-PM recruitment biosensor (+ GRK2). Cells were directly seeded in 96-well plates immediately following transfection at a density of 35,000 cells/well. 48 hours post-transfection, BRET experiments were performed in both agonist and allosteric/antagonist mode. Using a plate washer, culture medium was aspirated and replaced with 30 µl of Hank's Balanced Salt Solution buffer (HBSS). Plates were

equilibrated at room temperature for 60 minutes. For agonist testing, serial dilutions of the antibodies were performed in PBS and then added to each well. Antibodies were assayed at 12 concentrations in technical duplicates. Small molecules were added to each relevant well. Small molecules were assayed at 22 concentrations with each biosensor. Cells were then incubated with the antibodies or small molecules at room temperature for 60 or 10 minutes, respectively. 10µl of 10µM e-Coelenterazine Prolume Purple (Nanolight) was then added to each well. Cells were incubated at room temperature for an additional 10 minutes. BRET readings were then collected with a 0.4sec integration time on a plate reader (filters: 400nm/70nm, 515nm/20nm). For allosteric testing (after agonist testing), an EC75 of the endogenous ligand (oleoyl-LPA) was added to each well already containing antibody or small molecule. Cells were incubated at room temperature for an additional 10 minutes. BRET readings were then collected with a 0.4sec integration time on a plate reader (filters: 400nm/70nm, 515nm/20nm). BRET signals were determined by calculating the ratio of light emitted by GFP-acceptor (515nm) over light emitted by luciferase-donor (400nm). All BRET ratios were standardized with pre-established BRET values for positive and negative controls. The standardized BRET ratio is referred to as universal BRET (uBRET). Resulting dose-response curves were fitted using the three- or four-parameter logistic non-linear regression model in GraphPad Prism 9.

1.16 Rat pharmacokinetics

The rat pharmacokinetics study was carried out in male Sprague Dawley rats (275-325 g). Rats received an IV slow bolus (3 mg/kg) of test antibody. Blood samples were taken at the following time-points: pre-dose, 2 min, 1 hour, 3 hours, 6 hours, 24 hours, 48 hours, 96 hours, 7 days, 14 days and 21 days after dosing. For each animal and for each blood sampling, 200 µL venous blood was obtained from the sublingual vein under isoflurane anaesthesia in K2EDTA vials. The blood samples were gently mixed, placed immediately on crushed ice and centrifuged within 30 min of sampling at approximately 1500 x g for approximately 10 min at approximately 4°C. For each blood sample, the resulting plasma was separated into 2 aliquots of 30 µL and transferred, using disposable plastic material, into polypropylene tubes with conical bottom and stored at -80°C until analysis by capture ELISA. Plates were coated overnight with 1 µg/mL capture IgG before washing and blocking with 3% (w/v) milk the next morning for 2 hours. Plasma dilutions were incubated on the plates for 2 hours at room temperature. Plates were washed with PBS + 0.05% tween 20 (PBST) before incubation with anti-human Fc HRP-conjugated secondary detection antibody (1:5000 in PBST) for 1 hour at room temperature. After washing, wells are incubated with TMB substrate for 15 minutes at room temperature before addition of 1M sulphuric acid. Absorbance was measured on a plate reader at 450nm. Antibody concentrations were calculated using interpolation off a standard curve constructed for each individual test IgG in Prism 5 (GraphPad Software, CA, USA). Interpolated data was analysed using Phoenix WinNonlin® version 8.1 (Certara USA, Inc., Princetn, NJ) to extract relevant PK parameters.

Example 2: Identification of anti-LPAR1 antibodies, determination of germline sequences and identification of clonally-related hybridomas

Mice were immunized as described in Example 1.1. A hybridoma producing an antibody specific to LPAR1 was isolated as described in Example 1.2. The antibody against LPAR1 produced by the hybridoma was sequenced using the method of Example 1.3 (Antibody 1). The variable domains of Antibody 1 were sequenced. The sequences are shown in in SEQ ID NO: 23 (VH) and 24 (VL).

The sequence of Antibody 1 was analysed to deduce the murine germline sequence the antibody was derived from (SEQ ID NO: 25 (VH) and 26 (VL), Antibody 2). Antibody 2 was produced and expressed, and then tested for LPAR1 binding affinity. Antibody 2 had extremely low binding affinity for LPAR1.

Antibody 3 was then designed, wherein the variable regions consist of the CDR regions of Antibody 1 and the framework regions of Antibody 2, shown in SEQ ID NOs: 27 (VH) and 28 (VL).

Hybridomas related to Antibody 1 were identified, which had also derived from the murine germline sequence of Antibody 2. One such hybridoma was Antibody 4 (SEQ ID NOs: 29 (VH) and 30 (VL)) which comprised a mutation in LCDR3 which was not present in Antibody 1 (Q90H).

The VL domain of Antibody 3 was then altered to include the Q90H mutation (Antibody 5, SEQ ID NOs: SEQ ID NO: 27 (VH) and 31 (VL)). This antibody had improved affinity and expression compared to the original Antibody 1 clone.

A further hybridoma producing antibodies specific to LPAR1 was also isolated. The further antibody (63D8) was sequenced using the method of Example 1.3. The VH and VL sequences of the antibody are shown in SEQ ID NOs: 113 (63D8 VH) and 114 (63D8 VL).

All antibodies referred to herein comprised the human kappa light chain constant region and the IgG1 heavy chain constant region (unless otherwise stated). For some antibodies, silencing mutations were introduced into the Fc region and/or IgG2 or IgG4 subtypes were produced.

Example 3: Humanisation and affinity maturation

Multiple humanised variants of Antibody 1 were produced, of which Antibody 7 (SEQ ID NOs: 33 (VH) and 34 (VL)) was the best in terms of expression, stability and function. The sequence of an alternate variant Antibody 14 (SEQ ID NOs: 96 (14 VH) and 97 (14 VL)) is also provided.

Mutated versions of Antibody 5 were produced, wherein each residue of the CDRs which has been deduced to be a product of somatic hypermutation was reverted to corresponding a murine germline residue. In most cases, reversion of these residues was found to be detrimental to the high-affinity binding properties of Antibody 5. The exception was a mutation

within LCDR3, wherein reversion to Serine (N93S) resulted in a large affinity gain (Antibody 6, SEQ ID NOs: 27 (VH) and 32 (VL)).

A version of Antibody 7 was produced which comprised the two light chain mutations Q90H and N93S (Antibody 8, SEQ ID NOs: 33 (VH) and 39 (VL)).

A residue E61 within HCDR2 of Antibody 8 was diversified to all amino-acids bar cysteine. It was found that the mutation E61Q significantly enhanced the function (Antibody 9, SEQ ID NOs: 35 (VH) and 39 (VL)).

In parallel, phage display of Antibody 3 was conducted to randomise HCDR3. Two HCDR3 sequences were discovered (Antibody 10, SEQ ID NOs: 36 (VH) and 39 (VL) and Antibody 11 SEQ ID NOs: 37 (VH) and 39 (VL)). It was noticed that the overall charge of the heavy chain in Antibodies 10 and 11 was increased by 2 compared to Antibody 3. To eliminate the risk of non-specific interactions driven by this high positive charge, a mutation in LCDR2 (T56D) was produced (Antibody 12 SEQ ID NOs: 36 (VH) and 38 (VL) and Antibody 13 SEQ ID NOs: 37 (VH) and 38 (VL)). Antibody 12 and 13 had reduced propensity for non-specific interactions with minimal effect on affinity.

Example 4: Investigation of Antibody 12

Further experiments were conducted on Antibody 12.

Antibody 12 was expressed by following method 1.5. The expression level was compared to an Adalimumab biosimilar (Figure 1A). The ability of Antibody 12 to bind to huLPAR1-HA cells was assessed using the transient transfection CIFAT assay (method 1.11). The results are shown in Figure 1B. The ability of Antibody 12 to increase cAMP signalling, inhibit calcium signalling and decrease cell proliferation was tested using methods 1.7, 1.8 and 1.9. The results are shown in Figures 1C-E. The K_D of Antibody 12 was measured using method 1.14. It was found that Antibody 12 had a K_D of 1.28 nM.

Example 5: Investigation of Antibody 13

The experiments described in Example 4 were also conducted on Antibody 13. The results are shown in Figures 2A (expression level compared to an Adalimumab biosimilar), 2B (ability to increase cAMP signalling), 2C (ability to inhibit calcium signalling) and 2D (ability to decrease cell proliferation). The K_D of Antibody 13 was measured. It was found that Antibody 13 had a K_D of 993 pM.

Example 6: Epitope analysis

In silico

The epitope of a variant of Antibody 7 (Antibody 7b, SEQ ID NOs: 418 (VH) and 39 (VL)) was elucidated *in silico* using SEQ ID NO: 64 as the sequence for LPAR1. SEQ ID NO: 64 is a modified, truncated version of LPAR1 (4Z35 LPAR1 crystal structure). Predicted epitope residues are shown in Figure 3A (on the sequence) and Figure 3B (on the 3D structure) using

numbering based on SEQ ID NO: 64 . Predicted epitope interaction regions 1 to 4 (SEQ ID NOs: 65 to 68) are shown in Figure 3A and Figure 3C.

The residues of the paratope of Antibody 7b were also predicted (Figure 4). CDRs are underlined using Chothia definitions in Figure 4.

It was also established by competition CIFAT (Example 1.13) that Antibody 1 and 63D8 compete for the same epitope (data not shown).

In vitro

Based on the epitope analysis presented in Figures 3 and 4, constructs were designed to test the important residues/interaction regions predicted *in silico*. Plasmids containing the human LPAR1 sequence (sourced from UniProt) with selected single or multiple residue substitutions to alanine were used. CHO-K1 cells were transiently transfected with these plasmids and the binding of an anti-LPAR1 mAb assessed to each of these receptor variants using protocol 1.11. The anti-LPAR1 mAb had the VH of SEQ ID NO: 369 and VL of SEQ ID NO: 39. Numbering of LPAR1 is based on UniProt Q92633 LPAR1 (SEQ ID NO: 62)

Figure 5 shows the epitope residue involved, *in silico* prediction and fluorescence images of cells stained with anti-HA (expression control), anti-LPAR1 mAb and negative control mAb. Table 9 shows a summary of the epitope residue, extracellular domain location and whether the residue was found to be important for epitope binding.

Table 9: Epitope analysis

Position tested	**Residue in human LPAR1**	**Location**	**Epitope residue**
35	N	N-terminus	Inconclusive
36	R	N-terminus	+
43	T	N-terminus	-
44	E	N-terminus	-
114	R	ECD1	-
115	R	ECD1	-
193	E	ECD2	+
194	N	ECD2	-
286	Q	ECD3	Inconclusive
289	V	ECD3	-

Figure 6 shows an updated version of Figure 3B which includes labels for the identified critical residues involved in epitope binding. This work showed that residues 36R and 193E are involved in the binding of the antibody to LPAR1, with potential involvement from residues 35N and 286Q.

Example 7: Residue Substitution

Key residues in Antibody 1 derived LPAR1 binding antibodies discussed above (produced either in cell supernatant or as purified IgG) were substituted individually or in combination before analysing the impact on LPAR1 function. The residues chosen to be substituted are depicted as X_n in the following sequences, wherein each CDR (wherein the CDRs in this example are defined by a non-Kabat numbering system) is underlined:

VH:
QVQLVQSGSELKKPGASVKVSCKASGYTF$\underline{X_1X_2X_3X_4X_5X_6}$WVRQAPGQGLEW$X_7G\underline{X_8}$
$\underline{I}$
$\underline{X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}X_{16}}YX_{17}\underline{X_{18}X_{19}}FX_{20}\underline{G}RFX_{21}X_{22}$SADKSX$_{23}$STAYLQISSLKAEDTA
VYX$_{24}$CAR$\underline{D}$X$_{25}\underline{X_{26}X_{27}X_{28}X_{29}X_{30}X_{31}X_{32}}$DYWX$_{33}$QGTTVTVSS (SEQ ID NO: 70)
VL:
X$_{34}$IQMTQSPSSLSASVGDRVTITC$\underline{X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}X_{41}X_{42}X_{43}X_{44}X_{45}}$WYQQKPGKA
PKLLIY$\underline{X_{46}}$A$\underline{X_{47}X_{48}X_{49}X_{50}X_{51}}$GVPSRFSGSGSGTDFTFTISSLQPEDIATYX$_{52}$C$\underline{X_{53}X_{54}X_{55}}$ $\underline{X_{56}X_{57}X_{58}}PL\underline{X_{59}}$FGGGTKLEIK (SEQ ID NO: 71)

The residues chosen to be substituted in the CDRs are depicted as X_n in the following sequences (wherein the CDRs in this example are defined by a non-Kabat numbering system), wherein residues X_{21} and X_{23} may or may not be present. If present, X_{21} and/or X_{23} are selected from K and R. These residues were not present in these experiments.

HCDR1: $X_1X_2X_3X_4X_5X_6$ (SEQ ID NO: 72)
HCDR2: $X_7IX_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}YX_{16}X_{17}X_{18}FX_{19}G$ (SEQ ID NO: 76)
HCDR3: $DX_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}DY$ (SEQ ID NO: 80)
LCDR1: $X_{30}X_{31}X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$ (SEQ ID NO: 84)
LCDR2: $X_{41}AX_{42}X_{43}X_{44}X_{45}X_{46}$ (SEQ ID NO: 88)
LCDR3: $X_{47}X_{48}X_{49}X_{50}X_{51}X_{52}PLX_{53}$ (SEQ ID NO: 92)

The result of each substitution is depicted in Table 10 below, wherein "full length numbering" X_n corresponds to the equivalent X_n of SEQ ID NO: 70 or 71. The "CDR numbering" X_n (if present) corresponds to the equivalent X_n of SEQ ID NOs: 72, 76, 80, 84, 88 and 92. Substitutions were tested using the cAMP assay (method 1.7), with the exception of residues indicated with *. * indicates that these substitutions were tested using the stable-cell CIFAT assay (method 1.12). During this work it was found that for maximum affinity, one out of residues X_{20}, X_{21} or X_{22} is preferably R or K.

In addition, it was found that the lysine residue at position 74 of SEQ ID NO: 70 could be substituted with threonine, while still maintaining function in the stable-cell CIFAT assay (method 1.12). Function was maintained to such an extent that both lysine and threonine at position 74 of SEQ ID NO: 70 were considered 'Best Residues' according to the function categories given in Table 10.

The VH and VL sequences of the further antibodies produced in this work are provided in the accompanying sequence listing.

Table 10: Substitutions tested

Full length numbering	CDR numbering	Residues tested	Best Residue(s)	60-80% function of best residue	40-60% function of best residue	20-40% function of best residue	0-20% function of best residue
X1	X1	E, S, Y, G, T, R, K, D, N	S,Y, T, G	R	E, K	D, N	
X2	X2	K, R, L, T, G, V, A, S, F, W, Q, M, Y, I, E, H, N, D, P	K, R, L, T, G, V, A, S, F, W, Q, M, Y	I, E	H ,N	D, P	
X3	X3	K, R, L, T, G, V, A, S, F, W, Q, M, Y, I, E, H, N, D, P	R, K, H, T, S, F, G, V	A, L, N, Q	E, M, P, W	I	Y, D
X4	X4	A, G	A, G				
X5	X5	M, I	M, I				
X6	X6	K, R, L, T, G, V, A, S, F, W, Q, M, Y, I, E, H, N, D, P	S, E, G, D, L, T	N, Q, I, V, A	K,M	H, Y	F, P, R, W
X7		I, M	I, M				
X8	X7	E, W	E				W
X9	X8	D, Q, L, G, N	L, Q			D	G, N, *A, *Y
X10	X9	P, A, G, F, S, T, W, D, N, Q, Y	P, A, G	F, S	T	W	D,N,Q,Y
X11	X10	R, D, Q, K, W, N, A, E, G, H, I, K, S, T, Y, L	R				D, Q, K, W, N, A, E, G, H, I, K, S, T, Y, L
X12	X11	S, T, D	S, T		D		*A
X13	X12	D, E, S, T, A, Y, R, G, N, W	G, R	S, Y, A, T	D, E, W		N
X14	X13	Y, N, D, E	Y				N, D, E, *A
X15	X14	T, P	T				P, *A
X16	X15	N, H, S, T, D, E	N, H, S				T, D, E, *A, *Y
X17	X16	R, N, F, K, Q, V, D, E, Y, G, M, P, W, H, L, I, S, T, A	R, N, F, K, Q, V, D, E	Y, G, M, P	W, H, L	I, S, T, *A	

Full length numbering	CDR numbering	Residues tested	Best Residue(s)	60-80% function of best residue	40-60% function of best residue	20-40% function of best residue	0-20% function of best residue
X18	X17	K, R, L, T, G, V, A, S, F, W, Q, M, Y, I, E, H, N, D, P	Q, A, I, S, P, T, N, V	G, H, L, M, W, K, R, F	D, Y, E		
X19	X18	K, R, L, T, G, V, A, S, F, W, Q, M, Y, I, E, H, N, D, P	G, D, E, H, L, V, Y, A, F, I, K, Q, W, R	M, P, S		N	T
X20	X19	T, K, Q, E, R, M	T, K	Q, E, R, M			
X21		V, S	V, *S				
X22		L, F	L, F				
X23		S, A, V	S, A, V				
X24		F, Y	F, Y				
X25	X20	K, R, L, T, G, V, A, S, F, W, Q, M, Y, I, E, H, N, D, P	R, F, K, I	A, L, V, W, Y	M	P, Q, G, S	H, N, T, D, E
X26	X22	K, R, L, T, G, V, A, S, F, W, Q, M, Y, I, E, H, N, D, P	K, R, G	A, H, S, Q, T, P, M, W, Y	L, F, V	E, N	D, I
X27	X24	K, R, L, T, G, V, A, S, F, W, Q, M, Y, I, E, H, N, D, P	R, Y, A, H, P, L, K, G, Q, N, I, F, W	S, T, M, E, V	D		
X28	X25	K, R, L, T, G, V, A, S, F, W, Q, M, Y, I, E, H, N, D, P	A, Q, T, S, G	V	R, I	H, K, P, L, M, F	D, N, W, Y, E
X29	X26	K, R, L, T, G, V, A, S, F, W, Q, M, Y, I, E, H, N, P	R		S		A, E, G, K, L, N, Q, T, V, W, Y, F, H, I, M, P
X30	X27	K, R, L, T, G, V, A, S, F, W, Q, M, Y, I, E, H, N, D, P	Y			H, Q, A	D, E, G, I, L, M, P, S, V, W, F, K, N, R, T
X31	X28	S, T, D, E, A	A, T, S	D		E	
X32	X29	L, M	M		L		

Full length numbering	CDR numbering	Residues tested	Best Residue(s)	60-80% function of best residue	40-60% function of best residue	20-40% function of best residue	0-20% function of best residue
X33		G, S	S		G		
X34		S, D, Q, E, N, A	S, D, Q, E, N, A				
X35	X30	Q,K,R,S,T,G	Q, K, R, S, T				G
X36	X31	A,S,T,G,L,R	A, S	T			G, L, R
X37	X32	S,D,T	S, T	D			G, N
X38	X33	Q, G, L, M, P, R, W, Y, A, D, E, F, S, T, V, N, H, I, K	Q, G, R, K, L, M, P, Y, S	A, N, H, W	D, E	F, T, I	V
X39	X34	S, D, G, H, I, L, N, T, V, Y	S, G, H, N	T, Y		D	I, L, V
X40	X35	V, I, A, D, G, N, P, Q, R, S, T	V, A, I				D, G, N, P, Q, R, S, T
X41	X36	R, S, A, D, G, I, K, N, S, T, V, Y	R	K, S	G	A	D, I, N, S, T, V, Y
X42	X37	Y, N, D, F, G, I, K, L, M, P, Q, S, E, H, T, R, V, W	Y, F, L, Q, S, H, T, G, I, M, V, W	K, N, R		D, P	E
X43	X38	N, Y, A, D, F, G, H, L, Q, S, T, W	N, A, G, H, Q, S			Y, F, W	D, L, T
X44	X39	V, L, A, I, K, M, P, Y	V, I, M, L				A, K, P, Y
X45	X40	A, N, D, E, G, H, Q, S, T, Y	A, G	D			N, E, H, Q, S, T, Y,
X46	X41	Y, A, D, G, I, K, L, M, N, P, Q, R, S, T, V, W, E, F, H	Y, H	R, T	A, D, K, L, N, Q	M, W, E, F, S	G, I, P, V
X47	X42	S, A, E, V, Y, D, F, G, H, I, K, L, M, N, P, Q, R, T, W	S, K, M, Q, R, V, Y, G, E	D, T, A, F, I, N, W	H	L	P
X48	X43	N, A, D, E, K, Q, R, S, T, Y	N, K, R	Q, T, Y, A, S	D, E		

Full length numbering	CDR numbering	Residues tested	Best Residue(s)	60-80% function of best residue	40-60% function of best residue	20-40% function of best residue	0-20% function of best residue
X49	X44	R, A, L, G, K, S	R, L, K			A	G, S
X50	X45	Y, A, E, N, P, Q, R, S, T, V, W, D, F, G, H, I, K, L, M	Y, I, K, M, Q, R, V, A, N, S, W, H	L, T, P, D, F	G	E	
X51	X46	T, A, Q, R ,V, W, Y, F, S, D, E, G, H, I, K, L, M, N, P	T, A, D, E, Q, R, S, H, K, P, L, F, G, I, M, V	W, Y, N			
X52		F, Y	F, Y				
X53	X47	Q, S, L	Q	S	L		
X54	X48	Q, H, A, G, L, N, S, T, V	H, N, S, T	A, Q		V	G, L
X55	X49	H, Y, A, D, F, G, L, R, S, T, W, Y	H			A, D, F	Y, G, L, R, S, T, W, Y
X56	X50	Y, L, D	Y		L		D
X57	X51	N, S, R, H, K, D, E, T, Q, P, I, L, M, F, W, Y, V, A, G	S, K, V	D, N, *R, *H, *T, *A, *G	*Q, *I, *M, *F, *W, *Y	*L	*E, *P
X58	X52	S, L, A, D, F, G, I, L, N, R, T, V, W, Y	S, A		T, G	V, W, Y	L, D, F, I, N, R
X59	X53	T, Y	T	Y			

Example 8: Antibody substitutions and investigation of Antibodies 15 to 18

Further optimised antibodies were created which include 'Best Residue' substitutions from Table 10. These include Antibody 15 (SEQ ID NOs: 36 (VH) and 99 (VL)), Antibody 16, Antibody 17 (SEQ ID NOs: 102 (VH) and 99 (VL)) and Antibody 18 (SEQ ID NOs: 102 (VH) and 104 (VL)).

To eliminate the risk of non-specific interactions driven by high positive charge, a mutation in LCDR2 (T56E) was introduced in Antibody 15. This mutation also eliminates the risk of isomerisation which occurred with the mutation T56D previously identified. Antibody 16 comprises the same VH and VL sequences as Antibody 15 (SEQ ID NOs: 36 and 99). The heavy chain constant region of Antibody 16 comprises different silencing mutations to that of Antibody 15.

Antibodies 15, 16, 17 and 18 were each expressed by following method 1.5. The expression levels were compared to a palivizumab biosimilar. The expression level of Antibody 15 is provided in Figure 7A, the expression level of Antibody 16 is provided in Figure 8A, the expression level of Antibody 17 is provided in Figure 9A and the expression level of Antibody 18 is provided in Figure 10A.

The ability of these antibodies to increase cAMP signalling was tested using method 1.7. The results for Antibody 15 are shown in Figure 7B. The results for Antibody 16 are shown in Figure 8B. The results for Antibody 17 are shown in Figure 9B. The results for Antibody 18 are shown in Figure 10B.

The ability of these antibodies to decrease cell proliferation was tested using method 1.9. The results for Antibody 15 are shown in Figure 7C. The results for Antibody 16 are shown in Figure 8C. The results for Antibody 17 are shown in Figure 9C. The results for Antibody 18 are shown in Figure 10C.

The ability of these antibodies to bind to huLPAR1-HA cells was assessed using the transient transfection CIFAT assay (method 1.11). The results for Antibody 15 are shown in Figure 7D. The results for Antibody 17 are shown in Figure 9D. The results for Antibody 18 are shown in Figure 10D.

The K_D of these antibodies was ascertained. The K_D of Antibody 15 was 824 pM. The K_D of Antibody 16 was also 824 pM. The K_D of Antibody 17 was 1 nM and the K_D of Antibody 18 was 1.39 nM.

Example 9: Comparison with commercially available anti-LPAR1 antibodies using the CIFAT assay

Anti-LPAR1 antibodies of the invention were tested alongside commercially available anti-LPAR1 antibodies in the transient-transfection CIFAT assay for live cells (method 1.11) and in the transient-transfection CIFAT assay for fixed cells (method 1.11). The tested antibodies are listed in Table 11.

Table 11: Antibodies tested:

Label	Source	Comments
Antibody 13	Antibody of the invention	LPAR1 – Significant fixed and live cell staining visible Irrelevant GPCR – No significant cell staining visible
Antibody 12	Antibody of the invention	LPAR1 – Significant fixed and live cell staining visible Irrelevant GPCR – No significant cell staining visible
EPR9710	Abcam, ab232400	LPAR1 – Significant fixed cell staining visible, no significant live cell staining visible Irrelevant GPCR – No significant cell staining visible
4C3	Thermo Fisher MA5-38395	LPAR1 – Significant fixed cell staining visible, no significant live cell staining visible Irrelevant GPCR – No significant cell staining visible
#999807	R&D Systems, MAB9963-100	LPAR1 – No significant cell staining visible Irrelevant GPCR – No significant cell staining visible
2E2	Abnova, H00001902-M08	LPAR1 – No significant cell staining visible Irrelevant GPCR – No significant cell staining visible
OTI1G6	Thermo Fisher CF503737	LPAR1 – Significant fixed cell staining visible, no significant live cell staining visible Irrelevant GPCR – No significant cell staining visible
2H7	Creative Diagnostics, DCABH-983	LPAR1 – Significant fixed cell staining visible, no significant live cell staining visible Irrelevant GPCR – No significant cell staining visible
63D8	Antibody of the invention	LPAR1 – Significant fixed and live cell staining visible Irrelevant GPCR – No significant cell staining visible
Antibody 4	Antibody of the invention	LPAR1 – Significant fixed and live cell staining visible Irrelevant GPCR – No significant cell staining visible

63D8 comprises SEQ ID NO: 113 (VH) and 114 (VL).

The results are shown in Figures 11 and 12, wherein the scale bar represents 100 µm. Figure 11 shows results of an experiment testing antibodies at 5 µg/mL against fixed/permeabilised cells, as well as at 5 µg/mL against live cells. Figure 12 shows results of an experiment testing antibodies at 5 µg/mL against fixed/permeabilised cells, and at 20 µg/mL against live cells. These data illustrate that antibodies of the prior art do not bind LPAR1 on the surface of live cells, whereas a panel of antibodies according to the invention have been produced which bind LPAR1 on the surface of live cells.

Example 10: Allosteric inhibition

The inhibition characteristics of Antibody 12 were investigated by Bioluminescence Resonance Energy Transfer (BRET, method 1.15) and compared to a small molecule LPAR1 inhibitor of the prior art (BMS-986020), see Figure 13. The upper lines are values recorded with LPA present and the lower lines are values recorded with LPA not present. In the presence of LPA (upper line, Figure 13A), the antibody does not deliver equivalent inhibition to the system where LPA is absent even at high concentrations (in this assay which measures the interaction of the G-protein G13 with the GPCR). This can only happen if the ligand (LPA) is also interacting with the receptor at the same time to enable some signalling. As the upper line flattens out at high concentrations, it can be assumed the system has reached maximal receptor occupancy and thus ligand is interacting with the receptor even when the antibody is at maximal occupancy. Thus, the antibody must be acting allosterically. A counter example is the prior art BMS-986020 molecule which is a competitive inhibitor and delivers 100% inhibition (in this assay), even in the presence of LPA (upper line, Figure 13B).

Example 11: Species cross-reactivity

The species cross-reactivity of Antibodies 12, 15, 17 and 18 was investigated using transient-transfection CIFAT (method 1.11). Cells were transfected with DNA encoding human LPAR1, mouse LPAR1, guinea-pig LPAR1 or rabbit LPAR1 according to Table 12. The results are shown in Figure 14A (Antibody 12), Figure 14B (Antibody 15), Figure 14C (Antibody 17) and Figure 14D (Antibody 18).

Table 12: LPAR1 molecules tested

Species	Polypeptide SEQ ID NO:	cDNA SEQ ID NO:	UniProt
Human	62	1229	Q92633-1
Mouse	1222	1232	P61793-1
Guinea-pig	1223	1233	A0A286XEY5
Rabbit	1224	1234	G1U0W0

Example 12: LPAR isoform specificity

The specificity of Antibodies 12, 15, 17 and 18 to human LPAR isoforms was investigated using transient-transfection CIFAT (method 1.11). Cells were transfected with DNA encoding human LPAR1, human LPAR2 or human LPAR3 according to Table 13. The results are shown in Figure 15A (Antibody 12), Figure 15B (Antibody 15), Figure 15C (Antibody 17) and Figure 15D (Antibody 18).

Table 13: LPAR isoforms tested

Isoform	Polypeptide SEQ ID NO:	cDNA SEQ ID NO:	UniProt
LPAR1	62	1229	Q92633-1
LPAR2	1225	1230	Q9HBW0-1
LPAR3	1226	1231	Q9UBY5

Example 13: Rat pharmacokinetics

The pharmacokinetics of Antibodies 12, 15, 17 and 18 in rats was investigated using method 1.16. A palivizumab biosimilar (SEQ ID NOs: 1227 (VH) and 1228 (VL)) was used as a control isotype antibody. The results are shown in Figure 16.

Upon visual inspection, all 5 antibodies have the same plasma concentration-time profiles after single intravenous administration at 3 mg/kg. For all antibodies, the median tmax was observed at 0.3 hours, i.e. the first blood sampling time after administration. The mean Cmax observed after intravenous administration were between 143.8 µg/mL and 217.5 µg/mL for Antibody 17 and Antibody 12, respectively. Plasma concentrations decrease in a similar way for all antibodies, i.e. a first fast phase and a second slower one with quantifiable plasma concentrations until 504 hours after administration for all antibodies and all animals.

Example 14: SEC-MALS

Size exclusion chromatography using multiangle light scattering was conducted on Antibodies 12, 13, 15, 16, 17 and 18. The results are shown in Figure 17A (Antibody 12), Figure 17B (Antibody 13), Figure 17C (Antibody 15), Figure 17D (Antibody 16), Figure 17E (Antibody 17) and Figure 17F (Antibody 18).

Example 15: Liver histopathology in cynomolgus monkeys

Small-molecule antagonist BMS-986020 showed efficacy in with patients with idiopathic pulmonary fibrosis (IPF) but showed off-target hepatobiliary toxicity. It was confirmed that the observed toxicity was compound-specific due to off-target binding to a number of hepatic bile acid efflux transporters (e.g., BSEP, MRP3 and MRP4) and not mediated via antagonism of LPAR1.

A dose range-finding study was carried out to determine the potential toxicity of Antibody 17 when given by the intravenous (infusion) route to cynomolgus monkeys. The test item, Antibody 17, was administered to 8 animals via intravenous infusion (30 minutes) on Day 1 (Group 1) or on Days 1, 8 and 15 (Groups 2 to 4). Animals were split by sex, allocated into 4 groups and dosed with Antibody 17 at 10, 33 or 100 mg/kg/day.

Table 14: Experimental Design

Group No.	Number of Animals		Dosage Level (mg/kg/day)
	Male	Female	
1	1	1	10

Group No.	Number of Animals		Dosage Level (mg/kg/day)
	Male	Female	
2	1	1	10
3	1	1	33
4	1	1	100

A complete gross pathological examination, organ weight recording and microscopic evaluation were performed on the six animals that were given 3 doses of Antibody 17 (Groups 2 to 4) two days after the third dose. There were no unscheduled deaths during the course of this study.

Antibody 17 administration was considered to be well tolerated at the injection sites. No adverse effects were observed throughout the study and no adverse findings were found on histopathology.

Example 16: Unilateral ureteral obstruction (UUO) efficacy model in guinea pigs

Unilateral ureteral obstruction (UUO) is a well-characterized disease model for renal fibrosis. The UUO model encompasses key pathophysiological features of chronic kidney disease; tubular necrosis and inflammatory cell infiltration within a relatively short period.

Method

Two unilateral ureteral obstruction (UUO) model efficacy studies were carried out in six-week old female Hartley guinea pigs. On Day 0, UUO surgery was performed. BMS-986020 was administered orally at a dose level of 30 mg/kg in a volume of 5 mL/kg twice daily at from Day -1 to 9. Isotype control and anti-LPAR1 antibody was intraperitoneally administered at a dose level of 6 mg/kg (low) or 20 mg/kg (high) in a volume of 10 mL/kg at Day -1, Day 0, Day 3 and Day 6. The viability, clinical signs, behaviour and individual body weight was monitored daily.

The animals were sacrificed at Day 10. The ligated left kidney and right kidney weight were measured at sacrifice.

Hydroxyproline is an amino acid, making up around 14% of collagen and acts as an important indicator of the severity of fibrosis. To quantify kidney hydroxyproline content, frozen posterior right section of left kidney samples were processed by an alkaline-acid hydrolysis method. AC buffer (2.2M acetic acid/0.48M citric acid) was added to the samples, followed by centrifugation to collect the supernatant. A standard curve of hydroxyproline was constructed with serial dilutions of trans-4-hydroxy-L-proline (Sigma-Aldrich, USA) starting at 16 µg/mL. The prepared samples and standards were mixed with chloramine T solution (Nacalai Tesque Inc., Japan) and incubated for 25 minutes at room temperature. The samples were then mixed with Ehrlich's solution and heated at 65°C for 20 minutes to develop the colour. After samples were cooled on ice and centrifuged to remove precipitates, the optical density of each supernatant was measured at 560 nm. The concentrations of hydroxyproline were calculated from the hydroxyproline standard curve. Protein concentrations of kidney samples were determined using a BCA protein assay kit (Thermo Fisher Scientific, USA) and used to

normalize the calculated hydroxyproline values. Kidney hydroxyproline contents were expressed as µg per mg protein.

The left kidney was fixed in Bouin's solution and embedded in paraffin. For PAS staining, sections were cut from paraffin blocks and stained with Schiff's reagent (FUJIFILM Wako pure chemical corporation, Japan) according to the manufacturer's instructions. To visualize collagen deposition, kidney sections were stained using picro-Sirius red solution (FUJIFILM Wako pure chemical corporation). For quantification of interstitial and medulla fibrosis area, bright field images in the corticomedullary region were captured using a digital camera (DFC295) at 200-fold magnification, and the positive areas in 5 fields/section were measured using ImageJ software (National Institute of Health, USA).

Results

Study 1 (Figure 18A) used Antibody 13 as the anti-LPAR1 antibody at 20 mg/kg dosage. Each group included 8 animals. Histological picrosirius staining showed an increase in fibrotic area in the cortex after UUO surgery (Vehicle in Fig 25A). Treatment with BMS-986020 reduced cortical fibrosis compared to vehicle. Treatment with anti-LPAR1 antibody produced a similar reduction in cortical fibrosis to the treatment with BMS-986020. No observable difference in hydroxyproline was found between groups.

Study 2 (Figure 18B) used Antibody 17 as the anti-LPAR1 antibody. Each batch included 20 animals. Treatment with BMS-986020 showed a trend towards reduced hydroxyproline compared to vehicle. Treatment with 20 mg/kg (high) of anti-LPAR1 showed a significant reduction in hydroxyproline compared to isotype antibody. No observable difference in histological picrosirius staining was shown between groups.

A reduction in fibrotic markers; histological picrosirius staining or hydroxyproline measurements, were observed in groups from both studies which received anti-LPAR1 mAb.

Clauses

A set of clauses defining the invention and its preferred aspects is as follows:

1. A polypeptide which binds to LPAR1.

2. The polypeptide of clause 1 wherein the polypeptide comprises three heavy chain CDRs (HCDR1-3).

3. The polypeptide of either clause 1 or 2 wherein the polypeptide comprises a HCDR1 comprising a sequence having at least 40%, such as at least 60%, such as at least 80% identity with SEQ ID NO: 1 or SEQ ID NO: 7.

4. The polypeptide of clause 3 wherein the polypeptide comprises a HCDR1 consisting of a sequence having at least 40%, such as at least 60%, such as at least 80% identity with SEQ ID NO: 1 or SEQ ID NO: 7.

5. The polypeptide of clause 3 wherein the polypeptide comprises a HCDR1 comprising SEQ ID NO: 1.

6. The polypeptide of clause 5 wherein the polypeptide comprises a HCDR1 consisting of SEQ ID NO: 1.

7. The polypeptide of clause 3 wherein the polypeptide comprises a HCDR1 comprising SEQ ID NO: 7.

8. The polypeptide of clause 7 wherein the polypeptide comprises a HCDR1 consisting of SEQ ID NO: 7.

9. The polypeptide of any one of clauses 1 to 8 wherein the polypeptide comprises a HCDR2 comprising a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 85%, such as at least 90% identity with any one of SEQ ID NOs: 2, 8 to 11 or 100.

10. The polypeptide of clause 9 wherein the polypeptide comprises a HCDR2 consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 85%, such as at least 90% identity with any one of SEQ ID NOs: 2, 8 to 11 or 100.

11. The polypeptide of clause 9 wherein the polypeptide comprises a HCDR2 comprising any one of SEQ ID NOs: 2, 8 to 11 or 100.

12. The polypeptide of clause 10 wherein the polypeptide comprises a HCDR2 consisting of any one of SEQ ID NOs: 2, 8 to 11 or 100.

13. The polypeptide of clause 11 wherein the polypeptide comprises a HCDR2 comprising SEQ ID NO: 2 or SEQ ID NO: 100.

14. The polypeptide of clause 12 wherein the polypeptide comprises a HCDR2 consisting of SEQ ID NO: 2 or SEQ ID NO: 100.

15. The polypeptide of any one of clauses 1 to 14 wherein the polypeptide comprises a HCDR3 comprising a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 85%, such as at least 90% identity with any one of SEQ ID NOs: 3, 12 to 15, or 101.

16. The polypeptide of clause 15 wherein the polypeptide comprises a HCDR3 consisting of a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 85%, such as at least 90% identity with any one of SEQ ID NOs: 3, 12 to 15, or 101.

17. The polypeptide of clause 15 wherein the polypeptide comprises a HCDR3 comprising any one of SEQ ID NOs: 3, 12 to 15, or 101.

18. The polypeptide of clause 16 wherein the polypeptide comprises a HCDR3 consisting of any one of SEQ ID NOs: 3, 12 to 15, or 101.

19. The polypeptide of clause 17 wherein the polypeptide comprises a HCDR3 comprising SEQ ID NO: 3 or SEQ ID NO: 101.

20. The polypeptide of clause 18 wherein the polypeptide comprises a HCDR3 consisting of SEQ ID NO: 3 or SEQ ID NO: 101.

21. The polypeptide of any one of clauses 1 to 20 wherein the polypeptide comprises three light chain CDRs (LCDR1-3).

22. The polypeptide of clause 21 wherein the polypeptide comprises a LCDR1 comprising a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with any one of SEQ ID NOs: 4, 16 to 18 or 103.

23. The polypeptide of clause 22 wherein the polypeptide comprises a LCDR1 consisting of a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with any one of SEQ ID NOs: 4, 16 to 18 or 103.

24. The polypeptide of clause 22 wherein the polypeptide comprises a LCDR1 comprising any one of SEQ ID NOs: 4, 16 to 18 or 103.

25. The polypeptide of clause 23 wherein the polypeptide comprises a LCDR1 consisting of any one of SEQ ID NOs: 4, 16 to 18 or 103.

26. The polypeptide of clause 24 wherein the polypeptide comprises a LCDR1 comprising SEQ ID NO: 4 or SEQ ID NO: 103.

27. The polypeptide of clause 25 wherein the polypeptide comprises a LCDR1 consisting of SEQ ID NO: 4 or SEQ ID NO: 103.

28. The polypeptide of any one of clauses 1 to 27 wherein the polypeptide comprises a LCDR2 comprising a sequence having at least 50% identity, such as at least 60%, such as at least 70%, such as at least 80% identity with SEQ ID NO: 5, 19 or 98.

29. The polypeptide of clause 28 wherein the polypeptide comprises a LCDR2 consisting of a sequence having at least 50% identity, such as at least 60%, such as at least 70%, such as at least 80% identity with SEQ ID NO: 5, 19 or 98.

30. The polypeptide of clause 28 wherein the polypeptide comprises a LCDR2 comprising SEQ ID NO: 5, 19 or 98.

31. The polypeptide of clause 29 wherein the polypeptide comprises a LCDR2 consisting of SEQ ID NO: 5, 19 or 98.

32. The polypeptide of clause 30 wherein the polypeptide comprises a LCDR2 comprising SEQ ID NO: 98.

33. The polypeptide of clause 31 wherein the polypeptide comprises a LCDR2 consisting of SEQ ID NO: 98.

34. The polypeptide of any one of clauses 1 to 33 wherein the polypeptide comprises a LCDR3 comprising a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80% identity with any one of SEQ ID NOs: 6 or 20 to 22.

35. The polypeptide of clause 34 wherein the polypeptide comprises a LCDR3 consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80% identity with any one of SEQ ID NOs: 6 or 20 to 22.

36. The polypeptide of clause 34 wherein the polypeptide comprises a LCDR3 comprising any one of SEQ ID NOs: 6 or 20 to 22.

37. The polypeptide of clause 35 wherein the polypeptide comprises a LCDR3 consisting of any one of SEQ ID NOs: 6 or 20 to 22.

38. The polypeptide of clause 36 wherein the polypeptide comprises a LCDR3 comprising SEQ ID NO: 6.

39. The polypeptide of clause 37 wherein the polypeptide comprises a LCDR3 consisting of SEQ ID NO: 6.

40. The polypeptide of any one of clauses 1 to 39 wherein the residue of HCDR2 corresponding to residue number 5 of SEQ ID NO: 2 is arginine.

41. The polypeptide of any one of clauses 1 to 40 wherein the residue of HCDR3 corresponding to residue number 6 of SEQ ID NO: 3 is arginine.

42. The polypeptide of any one of clauses 1 to 41 wherein the residue of HCDR3 corresponding to residue number 7 of SEQ ID NO: 3 is tyrosine.

43. The polypeptide of any one of clauses 1 to 42 wherein the residue of LCDR2 corresponding to residue number 1 of SEQ ID NO: 5 is tyrosine.

44. The polypeptide of any one of clauses 1 to 43 wherein the residue of LCDR3 corresponding to residue number 3 of SEQ ID NO: 6 is histidine.

45. The polypeptide of clause 1 wherein the polypeptide comprises

(a) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 3, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 5 and a LCDR3 comprising SEQ ID NO: 6;

(b) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 8, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 16, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 20;

(c) a HCDR1 comprising SEQ ID NO: 7, a HCDR2 comprising SEQ ID NO: 9, a HCDR3 comprising SEQ ID NO: 13, a LCDR1 comprising SEQ ID NO: 17, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 21;

(d) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 10, a HCDR3 comprising SEQ ID NO: 14, a LCDR1 comprising SEQ ID NO: 18, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(e) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 8, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 16, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 22;

(f) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 8, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 16, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(g) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 11, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 20;

(h) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 11, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(i) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(j) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 3, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(k) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 15, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(l) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 15, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 5 and a LCDR3 comprising SEQ ID NO: 6;

(m) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 3, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 98 and a LCDR3 comprising SEQ ID NO: 6;

(n) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 100, a HCDR3 comprising SEQ ID NO: 101, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 98 and a LCDR3 comprising SEQ ID NO: 6 or

(o) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 100, a HCDR3 comprising SEQ ID NO: 101, a LCDR1 comprising SEQ ID NO: 103, a LCDR2 comprising SEQ ID NO: 98 and a LCDR3 comprising SEQ ID NO: 6.

46. The polypeptide of clause 45 wherein the polypeptide comprises

(a) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 3, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 5 and a LCDR3 consisting of SEQ ID NO: 6;

(b) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 8, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 16, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 20;

(c) a HCDR1 consisting of SEQ ID NO: 7, a HCDR2 consisting of SEQ ID NO: 9, a HCDR3 consisting of SEQ ID NO: 13, a LCDR1 consisting of SEQ ID NO: 17, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 21;

(d) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 10, a HCDR3 consisting of SEQ ID NO: 14, a LCDR1 consisting of SEQ ID NO: 18, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(e) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 8, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 16, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 22;

(f) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 8, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 16, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(g) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 11, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 20;

(h) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 11, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(i) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(j) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 3, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(k) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 15, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(l) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 15, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 5 and a LCDR3 consisting of SEQ ID NO: 6;

(m) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 3, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 98 and a LCDR3 consisting of SEQ ID NO: 6;

(n) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 100, a HCDR3 consisting of SEQ ID NO: 101, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 98 and a LCDR3 consisting of SEQ ID NO: 6 or

(o) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 100, a HCDR3 consisting of SEQ ID NO: 101, a LCDR1 consisting of SEQ ID NO: 103, a LCDR2 consisting of SEQ ID NO: 98 and a LCDR3 consisting of SEQ ID NO: 6.

47. The polypeptide of any one of clauses 1 to 46 wherein the polypeptide comprises three heavy chain CDRs (HCDR1-HCDR3) and three light chain CDRs (LCDR1-LCDR3) (wherein the CDRs are defined by a non-Kabat numbering system in this clause) wherein HCDR1 comprises (e.g. consists of) $X_1X_2X_3X_4X_5X_6$ (SEQ ID NO: 72), HCDR2 comprises (e.g. consists of) $X_7IX_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}YX_{16}X_{17}X_{18}FX_{19}G$ (SEQ ID NO: 76), HCDR3 comprises (e.g. consists of) $DX_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}DY$ (SEQ ID NO: 80), LCDR1 comprises (e.g. consists of) $X_{30}X_{31}X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$ (SEQ ID NO: 84), LCDR2 comprises (e.g. consists of) $X_{41}AX_{42}X_{43}X_{44}X_{45}X_{46}$ (SEQ ID NO: 88) and LCDR3 comprises (e.g. consists of) $X_{47}X_{48}X_{49}X_{50}X_{51}X_{52}PLX_{53}$ (SEQ ID NO: 92), wherein:
the amino acid of X_1 is selected from the group consisting of S, Y, T, G, R, E, K, D and N;
the amino acid of X_2 is selected from the group consisting of K, R, L, T, G, V, A, S, F, W, Q, M, Y, I, E, H ,N, D and P;
the amino acid of X_3 is selected from the group consisting of R, K, H, T, S, F, G, V, A, L, N, Q, E, M, P, W and I;
the amino acid of X_4 is selected from the group consisting of A and G;

the amino acid of X_5 is selected from the group consisting of M and I;
the amino acid of X_6 is selected from the group consisting of S, E, G, D, L, T, N, Q, I, V, A, K, M, H and Y;
the amino acid of X_7 is selected from the group consisting of E;
the amino acid of X_8 is selected from the group consisting of L, Q and D;
the amino acid of X_9 is selected from the group consisting of P, A, G , F, S, T and W;
the amino acid of X_{10} is selected from the group consisting of R;
the amino acid of X_{11} is selected from the group consisting of S, T and D;
the amino acid of X_{12} is selected from the group consisting of G, R, S, Y, A, T, D, E and W;
the amino acid of X_{13} is selected from the group consisting of Y;
the amino acid of X_{14} is selected from the group consisting of T;
the amino acid of X_{15} is selected from the group consisting of N, H and S;
the amino acid of X_{16} is selected from the group consisting of R, N, F, K, Q, V, D, E, Y, G, M, P, W, H, L, I, S, T and A;
the amino acid of X_{17} is selected from the group consisting of Q, A, I, S, P, T, N, V, G, H, L, M, W, K, R, F, D, Y and E;
the amino acid of X_{18} is selected from the group consisting of G, D, E, H, L, V, Y, A, F, I, K, Q, W, R, M, P, S and N;
the amino acid of X_{19} is selected from the group consisting of T, K, Q, E, R and M;
the amino acid of X_{20} is selected from the group consisting of R, F, K, I, A, L, V, W, Y, M, P, Q, G and S;
the amino acid of X_{21} is not present or is selected from the group consisting of K and R;
the amino acid of X_{22} is selected from the group consisting of K, R, A, H, S, Q, T, P, M, W, Y, G, L, F, V, E and N;
the amino acid of X_{23} is not present or is selected from the group consisting of K and R;
the amino acid of X_{24} is selected from the group consisting of R, Y, A, H, P, L, K, G, Q, N, I, F, W, S, T, M, E, V and D;
the amino acid of X_{25} is selected from the group consisting of A, Q, T, S, G, V, R, I, H, K, P, L, M and F;
the amino acid of X_{26} is selected from the group consisting of R and S;
the amino acid of X_{27} is selected from the group consisting of Y, H, Q and A;
the amino acid of X_{28} is selected from the group consisting of A, T, S, D and E;
the amino acid of X_{29} is selected from the group consisting of M and L;
the amino acid of X_{30} is selected from the group consisting of Q, K, R, S and T;
the amino acid of X_{31} is selected from the group consisting of A, S and T;
the amino acid of X_{32} is selected from the group consisting of S, T and D;
the amino acid of X_{33} is selected from the group consisting of Q, G, R, K, L, M, P, Y, S, A, N, H, W, D, E, F, T and I;
the amino acid of X_{34} is selected from the group consisting of S, G, H, N, T, Y and D;
the amino acid of X_{35} is selected from the group consisting of V, A and I;
the amino acid of X_{36} is selected from the group consisting of R, K, S, G and A;
the amino acid of X_{37} is selected from the group consisting of Y, F, L, Q, S, H, T, G, I, M, V, W, K, N, R, D and P;

the amino acid of X_{38} is selected from the group consisting of N, A, G, H, Q, S, Y, F and W;
the amino acid of X_{39} is selected from the group consisting of V, I, M and L;
the amino acid of X_{40} is selected from the group consisting of A, G and D;
the amino acid of X_{41} is selected from the group consisting of Y, H, R, T, A, D, K, L, N, Q, M, W, E, F and S;
the amino acid of X_{42} is selected from the group consisting of S, K, M, Q, R, V, Y, G, E, D, T, A, F, I, N, W, H and L;
the amino acid of X_{43} is selected from the group consisting of N, K, R, Q, T, Y, A, S, D and E;
the amino acid of X_{44} is selected from the group consisting of R, L, K and A;
the amino acid of X_{45} is selected from the group consisting of Y, I, K, M, Q, R, V, A, N, S, W, H, L, T, P, D, F, G and E;
the amino acid of X_{46} is selected from the group consisting of T, A, D, E, Q, R, S, H, K, P, L, F, G, I, M, V, W, Y and N;
the amino acid of X_{47} is selected from the group consisting of Q, S and L;
the amino acid of X_{48} is selected from the group consisting of H, N, S, T, A, Q and V;
the amino acid of X_{49} is selected from the group consisting of H, A, D and F;
the amino acid of X_{50} is selected from the group consisting of Y and L;
the amino acid of X_{51} is selected from the group consisting of S, K, V, D, N, R, H, T, A, G, Q, I, M, F, W, Y and L;
the amino acid of X_{52} is selected from the group consisting of S, A, T, G, V, W and Y; and
the amino acid of X_{53} is selected from the group consisting of T and Y.

48. The polypeptide of clause 47 wherein HCDR1 comprises (e.g. consists of) $X_1X_2X_3X_4X_5X_6$ (SEQ ID NO: 73), HCDR2 comprises (e.g. consists of) $X_7IX_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}YX_{16}$-$X_{17}X_{18}FX_{19}G$ (SEQ ID NO: 77), HCDR3 comprises (e.g. consists of) $DX_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}DY$ (SEQ ID NO: 81), LCDR1 comprises (e.g. consists of) $X_{30}X_{31}X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$ (SEQ ID NO: 85), LCDR2 comprises (e.g. consists of) $X_{41}AX_{42}X_{43}X_{44}X_{45}X_{46}$ (SEQ ID NO: 89) and LCDR3 comprises (e.g. consists of) $X_{47}X_{48}X_{49}X_{50}X_{51}X_{52}PLX_{53}$ (SEQ ID NO: 93) (wherein the CDRs are defined by a non-Kabat numbering system in this clause), wherein:
the amino acid of X_1 is selected from the group consisting of S, Y, T, G, R, E and K;
the amino acid of X_2 is selected from the group consisting of K, R, L, T, G, V, A, S, F, W, Q, M, Y, I, E, H and N;
the amino acid of X_3 is selected from the group consisting of R, K, H, T, S, F, G, V, A, L, N, Q, E, M, P and W;
the amino acid of X_4 is selected from the group consisting of A and G;
the amino acid of X_5 is selected from the group consisting of M and I;
the amino acid of X_6 is selected from the group consisting of S, E, G, D, L, T, N, Q, I, V, A, K and M;
the amino acid of X_7 is selected from the group consisting of E;
the amino acid of X_8 is selected from the group consisting of L and Q;

the amino acid of X_9 is selected from the group consisting of P, A, G , F, S and T;
the amino acid of X_{10} is selected from the group consisting of R;
the amino acid of X_{11} is selected from the group consisting of S, T and D;
the amino acid of X_{12} is selected from the group consisting of G, R, S, Y, A, T, D, E and W;
the amino acid of X_{13} is selected from the group consisting of Y;
the amino acid of X_{14} is selected from the group consisting of T;
the amino acid of X_{15} is selected from the group consisting of N, H and S;
the amino acid of X_{16} is selected from the group consisting of R, N, F, K, Q, V, D, E, Y, G, M, P, W, H and L;
the amino acid of X_{17} is selected from the group consisting of Q, A, I, S, P, T, N, V, G, H, L, M, W, K, R, F, D, Y and E;
the amino acid of X_{18} is selected from the group consisting of G, D, E, H, L, V, Y, A, F, I, K, Q, W, R, M, P and S;
the amino acid of X_{19} is selected from the group consisting of T, K, Q, E, R and M;
the amino acid of X_{20} is selected from the group consisting of R, F, K, I, A, L, V, W, Y and M;
the amino acid of X_{21} is not present or is selected from the group consisting of K and R;
the amino acid of X_{22} is selected from the group consisting of K, R, A, H, S, Q, T, P, M, W, Y, G, L, F and V;
the amino acid of X_{23} is not present or is selected from the group consisting of K and R;
the amino acid of X_{24} is selected from the group consisting of R, Y, A, H, P, L, K, G, Q, N, I, F, W, S, T, M, E, V and D;
the amino acid of X_{25} is selected from the group consisting of A, Q, T, S, G, V, R and I;
the amino acid of X_{26} is selected from the group consisting of R and S;
the amino acid of X_{27} is selected from the group consisting of Y;
the amino acid of X_{28} is selected from the group consisting of A, T, S and D;
the amino acid of X_{29} is selected from the group consisting of M and L;
the amino acid of X_{30} is selected from the group consisting of Q, K, R, S and T;
the amino acid of X_{31} is selected from the group consisting of A, S and T;
the amino acid of X_{32} is selected from the group consisting of S, T and D;
the amino acid of X_{33} is selected from the group consisting of Q, G, R, K, L, M, P, Y, S, A, N, H, W, D and E;
the amino acid of X_{34} is selected from the group consisting of S, G, H, N, T and Y;
the amino acid of X_{35} is selected from the group consisting of V, A and I;
the amino acid of X_{36} is selected from the group consisting of R, K, S and G;
the amino acid of X_{37} is selected from the group consisting of Y, F, L, Q, S, H, T, G, I, M, V, W, K, N and R;
the amino acid of X_{38} is selected from the group consisting of N, A, G, H, Q and S;
the amino acid of X_{39} is selected from the group consisting of V, I, M and L;
the amino acid of X_{40} is selected from the group consisting of A, G and D;
the amino acid of X_{41} is selected from the group consisting of Y, H, R, T, A, D, K, L, N and Q;

the amino acid of X_{42} is selected from the group consisting of S, K, M, Q, R, V, Y, G, E, D, T, A, F, I, N, W and H;
the amino acid of X_{43} is selected from the group consisting of N, K, R, Q, T, Y, A, S, D and E;
the amino acid of X_{44} is selected from the group consisting of R, L and K;
the amino acid of X_{45} is selected from the group consisting of Y, I, K, M, Q, R, V, A, N, S, W, H, L, T, P, D, F and G;
the amino acid of X_{46} is selected from the group consisting of T, A, D, E, Q, R, S, H, K, P, L, F, G, I, M, V, W, Y and N;
the amino acid of X_{47} is selected from the group consisting of Q, S and L;
the amino acid of X_{48} is selected from the group consisting of H, N, S, T, A and Q;
the amino acid of X_{49} is selected from the group consisting of H;
the amino acid of X_{50} is selected from the group consisting of Y and L;
the amino acid of X_{51} is selected from the group consisting of S, K, V, D, N, R, H, T, A, G, Q, I, M, F, W and Y;
the amino acid of X_{52} is selected from the group consisting of S, A, T and G; and
the amino acid of X_{53} is selected from the group consisting of T and Y.

49. The polypeptide of clause 48 wherein HCDR1 comprises (e.g. consists of) $X_1X_2X_3X_4X_5X_6$ (SEQ ID NO: 74), HCDR2 comprises (e.g. consists of) $X_7IX_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}YX_{16}$-$X_{17}X_{18}FX_{19}G$ (SEQ ID NO: 78), HCDR3 comprises (e.g. consists of) $DX_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}DY$ (SEQ ID NO: 82), LCDR1 comprises (e.g. consists of) $X_{30}X_{31}X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$ (SEQ ID NO: 86), LCDR2 comprises (e.g. consists of) $X_{41}AX_{42}X_{43}X_{44}X_{45}X_{46}$ (SEQ ID NO: 90) and LCDR3 comprises (e.g. consists of) $X_{47}X_{48}X_{49}X_{50}X_{51}X_{52}PLX_{53}$ (SEQ ID NO: 94) (wherein the CDRs are defined by a non-Kabat numbering system in this clause), wherein:
the amino acid of X_1 is selected from the group consisting of S, Y, T, G and R;
the amino acid of X_2 is selected from the group consisting of K, R, L, T, G, V, A, S, F, W, Q, M, Y, I and E;
the amino acid of X_3 is selected from the group consisting of R, K, H, T, S, F, G, V, A, L, N and Q;
the amino acid of X_4 is selected from the group consisting of A and G;
the amino acid of X_5 is selected from the group consisting of M and I;
the amino acid of X_6 is selected from the group consisting of S, E, G, D, L, T, N, Q, I, V and A;
the amino acid of X_7 is selected from the group consisting of E;
the amino acid of X_8 is selected from the group consisting of L and Q;
the amino acid of X_9 is selected from the group consisting of P, A, G , F and S;
the amino acid of X_{10} is selected from the group consisting of R;
the amino acid of X_{11} is selected from the group consisting of S and T;
the amino acid of X_{12} is selected from the group consisting of G, R, S, Y, A and T;
the amino acid of X_{13} is selected from the group consisting of Y;
the amino acid of X_{14} is selected from the group consisting of T;
the amino acid of X_{15} is selected from the group consisting of N, H and S;

the amino acid of X_{16} is selected from the group consisting of R, N, F, K, Q, V, D, E, Y, G, M and P;
the amino acid of X_{17} is selected from the group consisting of Q, A, I, S, P, T, N, V, G, H, L, M, W, K, R and F;
the amino acid of X_{18} is selected from the group consisting of G, D, E, H, L, V, Y, A, F, I, K, Q, W, R, M, P and S;
the amino acid of X_{19} is selected from the group consisting of T, K, Q, E, R and M;
the amino acid of X_{20} is selected from the group consisting of R, F, K, I, A, L, V, W and Y;
the amino acid of X_{21} is not present or is selected from the group consisting of K and R
the amino acid of X_{22} is selected from the group consisting of K, R, A, H, S, Q, T, P, M, W, G and Y;
the amino acid of X_{23} is not present or is selected from the group consisting of K and R
the amino acid of X_{24} is selected from the group consisting of R, Y, A, H, P, L, K, G, Q, N, I, F, W, S, T, M, E and V;
the amino acid of X_{25} is selected from the group consisting of A, Q, T, S, G and V;
the amino acid of X_{26} is selected from the group consisting of R;
the amino acid of X_{27} is selected from the group consisting of Y;
the amino acid of X_{28} is selected from the group consisting of A, T, S and D;
the amino acid of X_{29} is selected from the group consisting of M;
the amino acid of X_{30} is selected from the group consisting of Q, K, R, S and T;
the amino acid of X_{31} is selected from the group consisting of A, S and T;
the amino acid of X_{32} is selected from the group consisting of S, T and D;
the amino acid of X_{33} is selected from the group consisting of Q, G, R, K, L, M, P, Y, S, A, N, H and W;
the amino acid of X_{34} is selected from the group consisting of S, G, H, N, T and Y;
the amino acid of X_{35} is selected from the group consisting of V, A and I;
the amino acid of X_{36} is selected from the group consisting of R, K and S;
the amino acid of X_{37} is selected from the group consisting of Y, F, L, Q, S, H, T, G, I, M, V, W, K, N and R;
the amino acid of X_{38} is selected from the group consisting of N, A, G, H, Q and S;
the amino acid of X_{39} is selected from the group consisting of V, I, M and L;
the amino acid of X_{40} is selected from the group consisting of A, G and D;
the amino acid of X_{41} is selected from the group consisting of Y, H, R, and T;
the amino acid of X_{42} is selected from the group consisting of S, K, M, Q, R, V, Y, G, E, D, T, A, F, I, N and W;
the amino acid of X_{43} is selected from the group consisting of N, K, R, Q, T, Y, A and S;
the amino acid of X_{44} is selected from the group consisting of R, L and K;
the amino acid of X_{45} is selected from the group consisting of Y, I, K, M, Q, R, V, A, N, S, W, H, L, T, P, D and F;
the amino acid of X_{46} is selected from the group consisting of T, A, D, E, Q, R, S, H, K, P, L, F, G, I, M, V, W, Y and N;
the amino acid of X_{47} is selected from the group consisting of Q and S;
the amino acid of X_{48} is selected from the group consisting of H, N, S, T, A and Q;

the amino acid of X_{49} is selected from the group consisting of H;
the amino acid of X_{50} is selected from the group consisting of Y;
the amino acid of X_{51} is selected from the group consisting of S, K, V, D, N, R, H, T, A and G;
the amino acid of X_{52} is selected from the group consisting of S and A; and
the amino acid of X_{53} is selected from the group consisting of T and Y.

50. The polypeptide of clause 49 wherein HCDR1 comprises (e.g. consists of) $X_1X_2X_3X_4X_5X_6$ (SEQ ID NO: 75), HCDR2 comprises (e.g. consists of) $X_7IX_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}YX_{16}$-$X_{17}X_{18}FX_{19}G$ (SEQ ID NO: 79), HCDR3 comprises (e.g. consists of) $DX_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}DY$ (SEQ ID NO: 83), LCDR1 comprises (e.g. consists of) $X_{30}X_{31}X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$ (SEQ ID NO: 87), LCDR2 comprises (e.g. consists of) $X_{41}AX_{42}X_{43}X_{44}X_{45}X_{46}$ (SEQ ID NO: 91) and LCDR3 comprises (e.g. consists of) $X_{47}X_{48}X_{49}X_{50}X_{51}X_{52}PLX_{53}$ (SEQ ID NO: 95) (wherein the CDRs are defined by a non-Kabat numbering system in this clause), wherein:
the amino acid of X_1 is selected from the group consisting of S, Y, T and G;
the amino acid of X_2 is selected from the group consisting of K, R, L, T, G, V, A, S, F, W, Q, M and Y;
the amino acid of X_3 is selected from the group consisting of R, K, H, T, S, F, G and V;
the amino acid of X_4 is selected from the group consisting of A and G;
the amino acid of X_5 is selected from the group consisting of M and I;
the amino acid of X_6 is selected from the group consisting of S, E, G, D, L and T;
the amino acid of X_7 is selected from the group consisting of E;
the amino acid of X_8 is selected from the group consisting of L and Q;
the amino acid of X_9 is selected from the group consisting of P, A and G;
the amino acid of X_{10} is selected from the group consisting of R;
the amino acid of X_{11} is selected from the group consisting of S and T;
the amino acid of X_{12} is selected from the group consisting of G and R;
the amino acid of X_{13} is selected from the group consisting of Y;
the amino acid of X_{14} is selected from the group consisting of T;
the amino acid of X_{15} is selected from the group consisting of N, H and S;
the amino acid of X_{16} is selected from the group consisting of R, N, F, K, Q, V, D and E;
the amino acid of X_{17} is selected from the group consisting of Q, A, I, S, P, T, N and V;
the amino acid of X_{18} is selected from the group consisting of G, D, E, H, L, V, Y, A, F, I, K, Q, W and R;
the amino acid of X_{19} is selected from the group consisting of T and K;
the amino acid of X_{20} is selected from the group consisting of R, F, K and I;
the amino acid of X_{21} is not present or is selected from the group consisting of K and R;
the amino acid of X_{22} is selected from the group consisting of K, G and R;
the amino acid of X_{23} is not present or is selected from the group consisting of K and R;
the amino acid of X_{24} is selected from the group consisting of R, Y, A, H, P, L, K, G, Q, N, I, F and W;
the amino acid of X_{25} is selected from the group consisting of A, Q, T, S and G;
the amino acid of X_{26} is selected from the group consisting of R;

the amino acid of X_{27} is selected from the group consisting of Y;
the amino acid of X_{28} is selected from the group consisting of A, T and S;
the amino acid of X_{29} is selected from the group consisting of M;
the amino acid of X_{30} is selected from the group consisting of Q, K, R, S and T;
the amino acid of X_{31} is selected from the group consisting of A and S;
the amino acid of X_{32} is selected from the group consisting of S and T;
the amino acid of X_{33} is selected from the group consisting of Q, G, R, K, L, M, P, Y and S;
the amino acid of X_{34} is selected from the group consisting of S, G, H and N;
the amino acid of X_{35} is selected from the group consisting of V, A and I;
the amino acid of X_{36} is selected from the group consisting of R;
the amino acid of X_{37} is selected from the group consisting of Y, F, L, Q, S, H, T, G, I, M, V and W;
the amino acid of X_{38} is selected from the group consisting of N, A, G, H, Q and S;
the amino acid of X_{39} is selected from the group consisting of V, I, M and L;
the amino acid of X_{40} is selected from the group consisting of A and G;
the amino acid of X_{41} is selected from the group consisting of Y and H
the amino acid of X_{42} is selected from the group consisting of S, K, M, Q, R, V, Y, G and E;
the amino acid of X_{43} is selected from the group consisting of N, K and R;
the amino acid of X_{44} is selected from the group consisting of R, L and K;
the amino acid of X_{45} is selected from the group consisting of Y, I, K, M, Q, R, V, A, N, S, W and H;
the amino acid of X_{46} is selected from the group consisting of T, A, D, E, Q, R, S, H, K, P, L, F, G, I, M and V;
the amino acid of X_{47} is selected from the group consisting of Q;
the amino acid of X_{48} is selected from the group consisting of H, N, S and T;
the amino acid of X_{49} is selected from the group consisting of H;
the amino acid of X_{50} is selected from the group consisting of Y;
the amino acid of X_{51} is selected from the group consisting of S, K and V;
the amino acid of X_{52} is selected from the group consisting of S and A; and
the amino acid of X_{53} is selected from the group consisting of T

51. The polypeptide of any one of clauses 47 to 50 wherein X_{21} and/or X_{23} are not present.

52. The polypeptide of any one of clauses 47 to 51 wherein at least one of X_{20}, X_{21}, X_{22}, X_{23}, X_{24} and X_{25} is Lysine or Arginine, such as at least one of X_{20}, X_{21} and X_{22}.

53. The polypeptide of clause 52 wherein no more than one of X_{20}, X_{21} and X_{22} are Lysine or Arginine, such as no more than one of X_{20}, X_{21}, X_{22}, X_{23}, X_{24} and X_{25}.

54. The polypeptide of any one of clauses 1 to 53 wherein the polypeptide comprises four heavy chain framework regions (HFR1-HFR4).

55. The polypeptide of clause 54 wherein the polypeptide comprises a HFR1 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 40, a HFR2 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 41, a HFR3 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 42 and/or a HFR4 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 43.

56. The polypeptide of clause 55 wherein the residue corresponding to residue 13 of SEQ ID NO: 41 is selected from I and M, the residue corresponding to residue 3 of SEQ ID NO: 42 is selected from V and S, the residue corresponding to residue 4 of SEQ ID NO: 42 is selected from L and F, the residue corresponding to residue 10 of SEQ ID NO: 42 is selected from S, A and V, the residue corresponding to residue 29 of SEQ ID NO: 42 is selected from F and Y, and/or the residue corresponding to residue 2 of SEQ ID NO: 43 is selected from G and S.

57. The polypeptide of either clause 55 or 56 wherein the polypeptide comprises a HFR1 comprising SEQ ID NO: 40, a HFR2 comprising SEQ ID NO: 41, a HFR3 comprising SEQ ID NO: 42 and/or a HFR4 comprising SEQ ID NO: 43.

58. The polypeptide of clause 57 wherein the polypeptide comprises a HFR1 consisting of SEQ ID NO: 40, a HFR2 consisting of SEQ ID NO: 41, a HFR3 consisting of SEQ ID NO: 42 and/or a HFR4 consisting of SEQ ID NO: 43.

59. The polypeptide of any one of clauses 1 to 58 wherein the polypeptide comprises four light chain framework regions (LFR1-LFR4).

60. The polypeptide of clause 59 wherein the polypeptide comprises a LFR1 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 44, a LFR2 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 45, a LFR3 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 46 and/or a LFR4 comprising or consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 47.

61. The polypeptide of clause 60 wherein the residue corresponding to residue 1 of SEQ ID NO: 44 is selected from S, D, Q, E, N and A and/or the residue corresponding to residue 31 of SEQ ID NO: 46 is selected from F and Y.

62. The polypeptide of either clause 60 or 61 wherein the polypeptide comprises a LFR1 comprising SEQ ID NO: 44, a LFR2 comprising SEQ ID NO: 45, a LFR3 comprising SEQ ID NO: 46 and/or a LFR4 comprising SEQ ID NO: 47.

63. The polypeptide of clause 62 wherein the polypeptide comprises a LFR1 consisting of SEQ ID NO: 44, a LFR2 consisting of SEQ ID NO: 45, a LFR3 consisting of SEQ ID NO: 46 and/or a LFR4 consisting of SEQ ID NO: 47.

64. The polypeptide of any one of clauses 1 to 63 wherein the polypeptide comprises a VH region.

65. The polypeptide of clause 64 wherein the VH region comprises an amino acid sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 98%, such as at least 99% sequence identity with any one of SEQ ID NOs: 23, 25, 27, 29, 33, 35, 36, 37, 96 or 102.

66. The polypeptide of clause 65 wherein the VH region consists of an amino acid sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 98%, such as at least 99% sequence identity with any one of SEQ ID NOs: 23, 25, 27, 29, 33, 35, 36, 37, 96 or 102.

67. The polypeptide of clause 65 wherein the VH region comprises an amino acid sequence of SEQ ID NOs: 23, 25, 27, 29, 33, 35, 36, 37, 96 or 102.

68. The polypeptide of clause 67 wherein the VH region comprises an amino acid sequence of SEQ ID NO: 36.

69. The polypeptide of clause 67 wherein the VH region comprises an amino acid sequence of SEQ ID NO: 37.

70. The polypeptide of clause 67 wherein the VH region comprises an amino acid sequence of SEQ ID NO: 102.

71. The polypeptide of clause 66 wherein the VH region consists of an amino acid sequence of SEQ ID NOs: 23, 25, 27, 29, 33, 35, 36, 37, 96 or 102.

72. The polypeptide of clause 71 wherein the VH region consists of an amino acid sequence of SEQ ID NO: 36.

73. The polypeptide of clause 71 wherein the VH region consists of an amino acid sequence of SEQ ID NO: 37.

74. The polypeptide of clause 71 wherein the VH region consists of an amino acid sequence of SEQ ID NO: 102.

75. The polypeptide of any one of clauses 1 to 74 wherein the polypeptide comprises a VL region.

76. The polypeptide of clause 75 wherein the VL region comprises an amino acid sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 98%, such as at least 99% sequence identity with any one of SEQ ID NOs: 24, 26, 28, 30, 31, 32, 34, 38, 39, 97, 99 or 104.

77. The polypeptide of any clause 76 wherein the VL region consists of an amino acid sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 98%, such as at least 99% sequence identity with any one of SEQ ID NOs: 24, 26, 28, 30, 31, 32, 34, 38, 39, 97, 99 or 104.

78. The polypeptide of clause 76 wherein the VL region comprises an amino acid sequence of SEQ ID NOs: 24, 26, 28, 30, 31, 32, 34, 38, 39, 97, 99 or 104.

79. The polypeptide of clause 78 wherein the VL region comprises an amino acid sequence of SEQ ID NO: 38.

80. The polypeptide of clause 78 wherein the VL region comprises an amino acid sequence of SEQ ID NO: 99.

81. The polypeptide of clause 78 wherein the VL region comprises an amino acid sequence of SEQ ID NO: 104.

82. The polypeptide of clause 77 wherein the VL region consists of an amino acid sequence of SEQ ID NOs: 24, 26, 28, 30, 31, 32, 34, 38, 39, 97, 99 or 104.

83. The polypeptide of clause 82 wherein the VL region consists of an amino acid sequence of SEQ ID NO: 38.

84. The polypeptide of clause 82 wherein the VL region consists of an amino acid sequence of SEQ ID NO: 99.

85. The polypeptide of clause 82 wherein the VL region consists of an amino acid sequence of SEQ ID NO: 104.

86. The polypeptide of any one of clauses 1 to 85 wherein the polypeptide comprises
(a) a VH region comprising SEQ ID NO: 23 and a VL region comprising SEQ ID NO: 24;
(b) a VH region comprising SEQ ID NO: 25 and a VL region comprising SEQ ID NO: 26;
(c) a VH region comprising SEQ ID NO: 27 and a VL region comprising SEQ ID NO: 28;
(d) a VH region comprising SEQ ID NO: 29 and a VL region comprising SEQ ID NO: 30;
(e) a VH region comprising SEQ ID NO: 27 and a VL region comprising SEQ ID NO: 31;
(f) a VH region comprising SEQ ID NO: 27 and a VL region comprising SEQ ID NO: 32;
(g) a VH region comprising SEQ ID NO: 33 and a VL region comprising SEQ ID NO: 34;
(h) a VH region comprising SEQ ID NO: 33 and a VL region comprising SEQ ID NO: 39;
(i) a VH region comprising SEQ ID NO: 35 and a VL region comprising SEQ ID NO: 39;
(j) a VH region comprising SEQ ID NO: 36 and a VL region comprising SEQ ID NO: 39;
(k) a VH region comprising SEQ ID NO: 37 and a VL region comprising SEQ ID NO: 39;

(l) a VH region comprising SEQ ID NO: 36 and a VL region comprising SEQ ID NO: 38;
(m) a VH region comprising SEQ ID NO: 37 and a VL region comprising SEQ ID NO: 38;
(n) a VH region comprising SEQ ID NO: 96 and a VL region comprising SEQ ID NO: 97;
(o) a VH region comprising SEQ ID NO: 36 and a VL region comprising SEQ ID NO: 99;
(p) a VH region comprising SEQ ID NO: 102 and a VL region comprising SEQ ID NO: 99 or
(q) a VH region comprising SEQ ID NO: 102 and a VL region comprising SEQ ID NO: 104.

87. The polypeptide of clause 86 wherein the polypeptide comprises
(a) a VH region consisting of SEQ ID NO: 23 and a VL region consisting of SEQ ID NO: 24;
(b) a VH region consisting of SEQ ID NO: 25 and a VL region consisting of SEQ ID NO: 26;
(c) a VH region consisting of SEQ ID NO: 27 and a VL region consisting of SEQ ID NO: 28;
(d) a VH region consisting of SEQ ID NO: 29 and a VL region consisting of SEQ ID NO: 30;
(e) a VH region consisting of SEQ ID NO: 27 and a VL region consisting of SEQ ID NO: 31;
(f) a VH region consisting of SEQ ID NO: 27 and a VL region consisting of SEQ ID NO: 32;
(g) a VH region consisting of SEQ ID NO: 33 and a VL region consisting of SEQ ID NO: 34;
(h) a VH region consisting of SEQ ID NO: 33 and a VL region consisting of SEQ ID NO: 39;
(i) a VH region consisting of SEQ ID NO: 35 and a VL region consisting of SEQ ID NO: 39;
(j) a VH region consisting of SEQ ID NO: 36 and a VL region consisting of SEQ ID NO: 39;
(k) a VH region consisting of SEQ ID NO: 37 and a VL region consisting of SEQ ID NO: 39;
(l) a VH region consisting of SEQ ID NO: 36 and a VL region consisting of SEQ ID NO: 38;
(m) a VH region consisting of SEQ ID NO: 37 and a VL region consisting of SEQ ID NO: 38;
(n) a VH region consisting of SEQ ID NO: 96 and a VL region consisting of SEQ ID NO: 97;
(o) a VH region consisting of SEQ ID NO: 36 and a VL region consisting of SEQ ID NO: 99;
(p) a VH region consisting of SEQ ID NO: 102 and a VL region consisting of SEQ ID NO: 99 or

(q) a VH region consisting of SEQ ID NO: 102 and a VL region consisting of SEQ ID NO: 104.

88. The polypeptide of any one of clauses 1 to 87 wherein residue H53 is arginine.

89. The polypeptide of any one of clauses 1 to 88 wherein residue H100 is arginine

90. The polypeptide of any one of clauses 1 to 89 wherein residue H100A is tyrosine.

91. The polypeptide of any one of clauses 1 to 90 wherein residue L50 is tyrosine.

92. The polypeptide of any one of clauses 1 to 91 wherein residue L91 is histidine.

93. The polypeptide of any one of clauses 1 to 92 wherein the residue corresponding to position 74 of SEQ ID NO: 70 is lysine or threonine.

94. The polypeptide of any one of clauses 1 to 93 wherein the residue corresponding to position 47 of SEQ ID NO: 418 is tryptophan, the residue corresponding to position 103 of SEQ ID NO: 418 is glycine, the residue corresponding to position 105 of SEQ ID NO: 418 is tyrosine, the residue corresponding to position 31 of SEQ ID NO: 39 is tyrosine, and the residue corresponding to position 92 of SEQ ID NO: 39 is tyrosine.

95. The polypeptide of clause 94 wherein the residue corresponding to position 52 of SEQ ID NO: 418 is leucine, the residue corresponding to position 54 of SEQ ID NO: 418 is arginine, the residue corresponding to position 104 of SEQ ID NO: 418 is arginine, the residue corresponding to position 26 of SEQ ID NO: 39 is serine, the residue corresponding to position 27 of SEQ ID NO: 39 is glutamine, the residue corresponding to position 49 of SEQ ID NO: 39 is tyrosine, and the residue corresponding to position 91 of SEQ ID NO: 39 is histidine.

96. The polypeptide of clause 95 wherein the residue corresponding to position 55 of SEQ ID NO: 418 is serine, the residue corresponding to position 58 of SEQ ID NO: 418 is threonine, the residue corresponding to position 59 of SEQ ID NO: 418 is asparagine, the residue corresponding to position 62 of SEQ ID NO: 418 is glutamine, the residue corresponding to position 100 of SEQ ID NO: 418 is phenylalanine, the residue corresponding to position 1 of SEQ ID NO: 39 is serine, the residue corresponding to position 29 of SEQ ID NO: 39 is valine, the residue corresponding to position 90 of SEQ ID NO: 39 is histidine, and the residue corresponding to position 93 of SEQ ID NO: 39 is serine.

97. The polypeptide of clause 96 wherein the residue corresponding to position 31 of SEQ ID NO: 418 is serine, the residue corresponding to position 60 of SEQ ID NO: 418 is tyrosine, the residue corresponding to position 61 of SEQ ID NO: 418 is asparagine, the residue corresponding to position 65 of SEQ ID NO: 418 is threonine, the residue corresponding to position 99 of SEQ ID NO: 418 is aspartic acid, the residue corresponding to position 101 of SEQ ID NO: 418 is arginine, the residue corresponding

to position 102 of SEQ ID NO: 418 is serine, the residue corresponding to position 25 of SEQ ID NO: 39 is alanine, the residue corresponding to position 30 of SEQ ID NO: 39 is arginine, the residue corresponding to position 67 of SEQ ID NO: 39 is serine, the residue corresponding to position 89 of SEQ ID NO: 39 is glutamine, and the residue corresponding to position 94 of SEQ ID NO: 39 is serine.

98. The polypeptide of clause 1 wherein the polypeptide comprises a HCDR1 comprising a sequence having at least 40%, such as at least 60%, such as at least 80% identity with SEQ ID NO: 107.

99. The polypeptide of clause 98 wherein the polypeptide comprises a HCDR1 consisting of a sequence having at least 40%, such as at least 60%, such as at least 80% identity with SEQ ID NO: 107.

100. The polypeptide of clause 99 wherein the polypeptide comprises a HCDR1 comprising SEQ ID NO: 107.

101. The polypeptide of any one of clause 100 wherein the polypeptide comprises a HCDR1 consisting of SEQ ID NO: 107.

102. The polypeptide of any one of clauses 1 or 98 to 101 wherein the polypeptide comprises a HCDR2 comprising a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 85%, such as at least 90% identity with SEQ ID NO: 108.

103. The polypeptide of clause 102 wherein the polypeptide comprises a HCDR2 consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 85%, such as at least 90% identity with SEQ ID NO: 108.

104. The polypeptide of clause 103 wherein the polypeptide comprises a HCDR2 comprising SEQ ID NO: 108.

105. The polypeptide of clause 104 wherein the polypeptide comprises a HCDR2 consisting of SEQ ID NO: 108.

106. The polypeptide of any one of clauses 1 or 98 to 105 wherein the polypeptide comprises a HCDR3 comprising a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 109.

107. The polypeptide of clause 106 wherein the polypeptide comprises a HCDR3 consisting of a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 109.

108. The polypeptide of clause 107 wherein the polypeptide comprises a HCDR3 comprising SEQ ID NO: 109.

109. The polypeptide of clause 108 wherein the polypeptide comprises a HCDR3 consisting of SEQ ID NO: 109.

110. The polypeptide of any one of clauses 1 or 98 to 109 wherein the polypeptide comprises a LCDR1 comprising a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 110.

111. The polypeptide of clause 110 wherein the polypeptide comprises a LCDR1 consisting of a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90% identity with SEQ ID NO: 110.

112. The polypeptide of clause 111 wherein the polypeptide comprises a LCDR1 comprising SEQ ID NO: 110.

113. The polypeptide of clause 112 wherein the polypeptide comprises a LCDR1 consisting of SEQ ID NO: 110.

114. The polypeptide of any one of clauses 1 or 98 to 113 wherein the polypeptide comprises a LCDR2 comprising a sequence having at least 50% identity, such as at least 60%, such as at least 70%, such as at least 80% identity with SEQ ID NO: 111.

115. The polypeptide of clause 114 wherein the polypeptide comprises a LCDR2 consisting of a sequence having at least 50% identity, such as at least 60%, such as at least 70%, such as at least 80% identity with SEQ ID NO: 111.

116. The polypeptide of clause 115 wherein the polypeptide comprises a LCDR2 comprising SEQ ID NO: 111.

117. The polypeptide of clause 116 wherein the polypeptide comprises a LCDR2 consisting of SEQ ID NO: 111.

118. The polypeptide of any one of clauses 1 or 98 to 117 wherein the polypeptide comprises a LCDR3 comprising a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80% identity with SEQ ID NO: 112.

119. The polypeptide of clause 118 wherein the polypeptide comprises a LCDR3 consisting of a sequence having at least 50%, such as at least 60%, such as at least 70%, such as at least 80% identity with SEQ ID NO: 112.

120. The polypeptide of clause 119 wherein the polypeptide comprises a LCDR3 comprising SEQ ID NO: 112.

121. The polypeptide of clause 120 wherein the polypeptide comprises a LCDR3 consisting of SEQ ID NO: 112.

122. The polypeptide of clause 1 wherein the polypeptide comprises a VH region comprising an amino acid sequence having at least 60%, such as at least 70%, such as at least

80%, such as at least 90%, such as at least 95%, such as at least 98%, such as at least 99% sequence identity with SEQ ID NO: 113.

123. The polypeptide of clause 122 wherein the VH region consists of an amino acid sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 98%, such as at least 99% sequence identity with SEQ ID NO: 113.

124. The polypeptide of clause 123 wherein the VH region comprises an amino acid sequence of SEQ ID NO: 113.

125. The polypeptide of clause 124 wherein the VH region consists of an amino acid sequence of SEQ ID NO: 113.

126. The polypeptide of any one of clauses 1 or 122 to 125 wherein the polypeptide comprises a VL region comprising an amino acid sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 98%, such as at least 99% sequence identity with SEQ ID NO: 114.

127. The polypeptide of any clause 126 wherein the VL region consists of an amino acid sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 98%, such as at least 99% sequence identity with SEQ ID NO: 114.

128. The polypeptide of clause 127 wherein the VL region comprises an amino acid sequence of SEQ ID NO: 114.

129. The polypeptide of clause 128 wherein the VL region consists of an amino acid sequence of SEQ ID NO: 114.

130. The polypeptide of any one of clauses 1 to 129 wherein the polypeptide comprises a heavy chain constant region.

131. The polypeptide of clause 130 wherein the heavy chain constant region comprises a polypeptide sequence having at least 50%, such as at least 70%, such as at least 90% identity with SEQ ID NO: 1375.

132. The polypeptide of clause 131 wherein the heavy chain constant region comprises SEQ ID NO: 1375.

133. The polypeptide of clause 132 wherein the heavy chain constant region consists of SEQ ID NO: 1375.

134. The polypeptide of any one of clauses 130 to 133 wherein the heavy chain region comprises a polypeptide sequence having at least 50%, such as at least 70%, such as at least 90% identity with SEQ ID NO: 58, SEQ ID NO: 60 or SEQ ID NO: 1220.

135. The polypeptide of clause 134 wherein the heavy chain region comprises SEQ ID NO: 58, SEQ ID NO: 60 or SEQ ID NO: 1220.

136. The polypeptide of clause 135 wherein the heavy chain region consists of SEQ ID NO: 58, SEQ ID NO: 60 or SEQ ID NO: 1220.

137. The polypeptide of any one of clauses 130 to 136 wherein the heavy chain constant region comprises or consists of IgG1 heavy chain constant region, such as human IgG1.

138. The polypeptide of any one of clauses 1 to 137 wherein the polypeptide comprises a light chain constant region.

139. The polypeptide of clause 138 wherein the light chain constant region comprises a polypeptide sequence having at least 50%, such as at least 70%, such as at least 90% identity with SEQ ID NO: 57.

140. The polypeptide of clause 139 wherein the light chain constant region comprises SEQ ID NO: 57.

141. The polypeptide of clause 140 wherein the light chain constant region consists of SEQ ID NO: 57.

142. The polypeptide of any one of clauses 138 to 141 wherein the light chain region comprises a polypeptide sequence having at least 50%, such as at least 70%, such as at least 90% identity with SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 1219 or SEQ ID NO: 1221.

143. The polypeptide of clause 142 wherein the light chain region comprises SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 1219 or SEQ ID NO: 1221.

144. The polypeptide of clause 143 wherein the light chain region consists of SEQ ID NO: 59, SEQ ID NO: 61, SEQ ID NO: 1219 or SEQ ID NO: 1221.

145. The polypeptide of any one of clauses 138 to 144 wherein the light chain constant region comprises or consists of kappa light chain constant region, such as human kappa light chain.

146. The polypeptide of any one of clauses 1 to 145, wherein the polypeptide comprises a VH and a VL region and the VH and VL region are joined by a linker, such as a polypeptide linker.

147. The polypeptide of clause 146, wherein the linker comprises a $(Gly_4Ser)_n$ format (SEQ ID NO: 69), wherein n = 1 to 8.

148. The polypeptide of any one of clauses 1 to 147 wherein the LPAR1 is human LPAR1.

149. The polypeptide of any one of clauses 1 to 148 wherein the LPAR1 is native LPAR1.

150. The polypeptide of any one of clauses 1 to 149 wherein the LPAR1 is full length LPAR1.

151. The polypeptide of any one of clauses 1 to 148 wherein the LPAR1 is a fragment of LPAR1.

152. The polypeptide of clause 151 wherein the fragment of LPAR1 comprises the extracellular region of LPAR1.

153. The polypeptide of either clause 151 or 152 wherein the fragment of LPAR1 is at least 50 amino acids long, such as at least 100 amino acids long, such as at least 150 amino acids long, such as at least 200 amino acids long, such as at least 250 amino acids long, such as at least 300 amino acids long, such as at least 350 amino acids long.

154. The polypeptide of any one of clauses 1 to 153 wherein the LPAR1 comprises a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 99% identity with SEQ ID NO: 62, SEQ ID NO: 63 or SEQ ID NO: 64.

155. The polypeptide of clause 154 wherein the LPAR1 consists of a sequence having at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 99% identity with SEQ ID NO: 62, SEQ ID NO: 63 or SEQ ID NO: 64.

156. The polypeptide of clause 155 wherein the LPAR1 comprises SEQ ID NO: 62, SEQ ID NO: 63 or SEQ ID NO: 64.

157. The polypeptide of clause 156 wherein the LPAR1 consists of SEQ ID NO: 62, SEQ ID NO: 63 or SEQ ID NO: 64.

158. The polypeptide of any one of clauses 1 to 157 wherein the polypeptide binds to functionally active LPAR1.

159. The polypeptide of any one of clauses 1 to 158 wherein the LPAR1 is on the surface of a cell.

160. The polypeptide of clause 159 wherein the cell is a living cell.

161. The polypeptide of any one of clauses 1 to 160 wherein the polypeptide modulates the function of LPAR1.

162. The polypeptide of clause 161 wherein the polypeptide is an inhibitor of LPAR1.

163. The polypeptide of clause 162 wherein the polypeptide is an allosteric inhibitor of LPAR1.

164. The polypeptide of any one of clauses 161 to 163 wherein the polypeptide is an inverse agonist of LPAR1.

165. The polypeptide of any one of clauses 1 to 164 wherein binding to LPAR1 reduces Gi/o signalling by the LPAR1.

166. The polypeptide of any one of clauses 1 to 165 wherein binding to LPAR1 reduces or prevents LPA-induced or constitutive reduction in cAMP production.

167. The polypeptide of clause 166 wherein binding to LPAR1 increases cAMP production in the HTRF cAMP assay.

168. The polypeptide of any one of clauses 1 to 167 wherein binding to LPAR1 reduces or prevents LPA-induced calcium mobilisation.

169. The polypeptide of clause 168 wherein binding to LPAR1 reduces calcium mobilisation in the assay detailed in Example 1.8.

170. The polypeptide of any one of clauses 1 to 169 wherein the polypeptide on binding to LPAR1 reduces the activity of LPAR1 by at least 10%, such as at least 20%, such as at least 30%, such as at least 40%, such as at least 50%, such as at least 60%, such as at least 70%, such as at least 80%, such as at least 90%, such as at least 95%, such as at least 98%, such as at least 99%, such as at least 100%.

171. The polypeptide of clause 170 wherein the activity of LPAR1 is indicated by the HTRF cAMP assay.

172. The polypeptide of any one of clauses 1 to 171 wherein the polypeptide binds to LPAR1 with a K_D of less than 150 nM, such as less than 30 nM, such as less than 15 nM, especially less than 1.5 nM.

173. The polypeptide of clause 172 wherein the K_D is measured using a kinetic exclusion assay.

174. The polypeptide of any one of clauses 1 to 173 wherein the polypeptide binds to an epitope of human LPAR1 comprising at least one of amino acids 30-44 of full length LPAR1 (SEQ ID NO: 62).

175. The polypeptide of clause 174 wherein the polypeptide binds to an epitope of human LPAR1 comprising amino acids 35 and 36 of full length LPAR1 (SEQ ID NO: 62).

176. The polypeptide of either clause 174 or 175 wherein the polypeptide binds to an epitope of human LPAR1 comprising amino acids 37 and 38 of full length LPAR1 (SEQ ID NO: 62).

177. The polypeptide of any one of clauses 174 to 176 wherein the polypeptide binds to an epitope of human LPAR1 comprising amino acids 32, 39, 40 and 41 of full length LPAR1 (SEQ ID NO: 62).

178. The polypeptide of any one of clauses 174 to 177 wherein the polypeptide binds to an epitope of human LPAR1 comprising at least five of amino acids 30-44 of full length LPAR1 (SEQ ID NO: 62).

179. The polypeptide of clause 178 wherein the polypeptide binds to an epitope of human LPAR1 comprising at least ten of amino acids 30-44 of full length LPAR1 (SEQ ID NO: 62).

180. The polypeptide of clause 179 wherein the polypeptide binds to an epitope of human LPAR1 comprising amino acids 30-44 of full length LPAR1 (SEQ ID NO: 62).

181. The polypeptide of any one of clauses 1 to 180 wherein the polypeptide binds to an epitope of human LPAR1 comprising at least one of amino acids 106-120 of full length LPAR1 (SEQ ID NO: 62).

182. The polypeptide of clause 181 wherein the polypeptide binds to an epitope of human LPAR1 comprising amino acid 114 of full length LPAR1 (SEQ ID NO: 62).

183. The polypeptide of either clause 181 or 182 wherein the polypeptide binds to an epitope of human LPAR1 comprising at least five of amino acids 106-120 of full length LPAR1 (SEQ ID NO: 62).

184. The polypeptide of clause 183 wherein the polypeptide binds to an epitope of human LPAR1 comprising at least ten of amino acids 106-120 of full length LPAR1 (SEQ ID NO: 62).

185. The polypeptide of clause 184 wherein the polypeptide binds to an epitope of human LPAR1 comprising amino acids 106-120 of full length LPAR1 (SEQ ID NO: 62).

186. The polypeptide of any one of clauses 1 to 185 wherein the polypeptide binds to an epitope of human LPAR1 comprising at least one of amino acids 190-204 of full length LPAR1 (SEQ ID NO: 62).

187. The polypeptide of clause 186 wherein the polypeptide binds to an epitope of human LPAR1 comprising amino acid 193 of full length LPAR1 (SEQ ID NO: 62).

188. The polypeptide of either clause 186 or 187 wherein the polypeptide binds to an epitope of human LPAR1 comprising amino acids 191, 192, 194 and 197 of full length LPAR1 (SEQ ID NO: 62).

189. The polypeptide of any one of clauses 186 to 188 wherein the polypeptide binds to an epitope of human LPAR1 comprising amino acid 190 of full length LPAR1 (SEQ ID NO: 62).

190. The polypeptide of any one of clauses 186 to 189 wherein the polypeptide binds to an epitope of human LPAR1 comprising at least five of amino acids 190-204 of full length LPAR1 (SEQ ID NO: 62).

191. The polypeptide of clause 190 wherein the polypeptide binds to an epitope of human LPAR1 comprising at least ten of amino acids 190-204 of full length LPAR1 (SEQ ID NO: 62).

192. The polypeptide of clause 191 wherein the polypeptide binds to an epitope of human LPAR1 comprising amino acids 190-204 of full length LPAR1 (SEQ ID NO: 62).

193. The polypeptide of any one of clauses 1 to 192 wherein the polypeptide binds to an epitope of human LPAR1 comprising at least one of amino acids 280-294 of full length LPAR1 (SEQ ID NO: 62).

194. The polypeptide of clause 193 wherein the polypeptide binds to an epitope of human LPAR1 comprising amino acid 286 of full length LPAR1 (SEQ ID NO: 62).

195. The polypeptide of either clause 193 or 194 wherein the polypeptide binds to an epitope of human LPAR1 comprising amino acids 285 of full length LPAR1 (SEQ ID NO: 62).

196. The polypeptide of any one of clauses 193 to 195 wherein the polypeptide binds to an epitope of human LPAR1 comprising at least five of amino acids 280-294 of full length LPAR1 (SEQ ID NO: 62).

197. The polypeptide of clause 196 wherein the polypeptide binds to an epitope of human LPAR1 comprising at least ten of amino acids 280-294 of full length LPAR1 (SEQ ID NO: 62).

198. The polypeptide of clause 197 wherein the polypeptide binds to an epitope of human LPAR1 comprising amino acids 280-294 of full length LPAR1 (SEQ ID NO: 62).

199. The polypeptide of any one of clauses 1 to 198 wherein the polypeptide binds to an epitope of human LPAR1 comprising amino acids 30-44, 106-120, 190-204 and 280-294 of full length LPAR1 (SEQ ID NO: 62).

200. The polypeptide of clause 199 wherein the polypeptide binds to an epitope of human LPAR1 consisting of amino acids 30-44, 106-120, 190-204 and 280-294 of full length LPAR1 (SEQ ID NO: 62).

201. The polypeptide of any one of clauses 1 to 173 wherein the polypeptide binds to an epitope of LPAR1 comprising one or more of residues 35, 36, 193 or 286 of full length LPAR1 (SEQ ID NO: 62).

202. The polypeptide of clause 201 wherein the polypeptide binds to an epitope of LPAR1 comprising residue 35 of full length LPAR1 (SEQ ID NO: 62).

203. The polypeptide of clause 201 wherein the polypeptide binds to an epitope of LPAR1 comprising residue 36 of full length LPAR1 (SEQ ID NO: 62).

204. The polypeptide of clause 201 wherein the polypeptide binds to an epitope of LPAR1 comprising residue 193 of full length LPAR1 (SEQ ID NO: 62).

205. The polypeptide of clause 201 wherein the polypeptide binds to an epitope of LPAR1 comprising residue 286 of full length LPAR1 (SEQ ID NO: 62).

206. The polypeptide of any one of clauses 1 to 205 wherein the polypeptide binds to a conformational epitope of human LPAR1 comprising one or more residues located within the N-terminal capping helix and one or more residues located within the extracellular domain 2.

207. The polypeptide of clause 206 wherein the polypeptide binds to an epitope of LPAR1 comprising residues 36 and 193 of full length LPAR1 (SEQ ID NO: 62).

208. A polypeptide wherein the polypeptide binds to the same, or essentially the same, epitope as, a polypeptide as defined in any one of clauses 1 to 207.

209. A polypeptide wherein the polypeptide competes with a polypeptide as defined in any one of clauses 1 to 208 for binding to LPAR1.

210. The polypeptide of any one of clauses 1 to 209 wherein the polypeptide is an antibody or fragment thereof.

211. The polypeptide of clause 210 wherein the antibody or fragment thereof is selected from the list consisting of an scFv, Fab, Fab', F(ab')2, Fv, variable domain (e.g. VH or VL), diabody, minibody or full length antibody.

212. The polypeptide of clause 211, wherein the antibody or fragment thereof is selected from the list consisting of an scFv, Fab or a full length antibody.

213. The polypeptide of clause 212, wherein the antibody or fragment thereof is a full length antibody or Fab.

214. The polypeptide of clause 213, wherein the full length antibody is an IgG1 antibody.

215. The polypeptide of any one of clauses 210 to 214 wherein the heavy chain constant region of the antibody comprises one or more mutations to reduce effector function, extend half-life, alter ADCC or improve hinge stability.

216. The polypeptide of clause 215 wherein the heavy chain constant region comprises any one of SEQ ID NOs: 56, 1235, 1376 and 1377.

217. The polypeptide of any one of clauses 210 to 214 or 216 wherein the heavy chain constant region of the antibody comprises one or more of the following residues:

residue at position 250 is Q, residue at position 252 is Y, residue at position 252 is F, residue at position 252 is W, residue at position 252 is T, residue at position 253 is A, residue at position 254 is T, residue at position 256 is E, residue at position 256 is S, residue at position 256 is R, residue at position 256 is Q, residue at position 256 is D, residue at position 259 is I, residue at position 285 is D, residue at position 285 is N, residue at position 286 is D, residue at position 294 is deleted, residue at position 307 is A, residue at position 307 is Q, residue at position 307 is P, residue at position 307 is R, residue at position 307 is W, residue at position 308 is P, residue at position 308 is F, residue at position 309 is P, residue at position 309 is D, residue at position 309 is N, residue at position 310 is A, residue at position 311 is S, residue at position 311 is I, residue at position 311 is V, residue at position 311 is H, residue at position 315 is D, residue at position 378 is V, residue at position 380 is A, residue at position 385 is R, residue at position 385 is D, residue at position 385 is S, residue at position 385 is T, residue at position 385 is H, residue at position 385 is K, residue at position 385 is A, residue at position 385 is G, residue at position 386 is T, residue at position 386 is P, residue at position 386 is D, residue at position 386 is S, residue at position 386 is K, residue at position 386 is R, residue at position 386 is I, residue at position 386 is M, residue at position 387 is R, residue at position 387 is P, residue at position 387 is H, residue at position 387 is S, residue at position 387 is T, residue at position 387 is A, residue at position 389 is P, residue at position 389 is S, residue at position 389 is N, residue at position 428 is L, residue at position 433 is K, residue at position 433 is R, residue at position 433 is S, residue at position 433 is I, residue at position 433 is P, residue at position 433 is Q, residue at position 434 is F, residue at position 434 is H, residue at position 434 is Y, residue at position 434 is A, residue at position 434 is S, residue at position 435 is A, residue at position 436 is H, residue at position 436 is I or residue at position 436 is V.

218. The polypeptide of clause 215 wherein the mutations are selected from the mutations listed in Table 2.

219. The polypeptide of clause 218 wherein the heavy chain constant region comprises the mutations M252Y, S254T and T256E or M428L and N434S.

220. The polypeptide of any one of clauses 217 to 219 wherein the heavy chain constant region comprises any one of SEQ ID NOs: 1237 to 1367.

221. The polypeptide of clause 220 wherein the heavy chain constant region consists of any one of SEQ ID NOs: 1237 to 1367.

222. The polypeptide of any one of clauses 210 to 221, wherein the antibody or fragment thereof is a human antibody or fragment thereof.

223. A construct comprising the polypeptide of any one of clauses 1 to 222.

224. The construct of clause 223 wherein the construct comprises a polypeptide which binds to a target other than LPAR1.

225. A composition comprising the polypeptide or construct of any one of clauses 1 to 224.

226. A pharmaceutical composition comprising the polypeptide or construct of any one of clauses 1 to 225, together with a pharmaceutically acceptable diluent or carrier.

227. The polypeptide, construct or composition of any one of clauses 1 to 226 for use as a medicament.

228. The polypeptide, construct or composition of any one of clauses 1 to 227 for use in the treatment of an inflammatory disease and/or fibrotic disease.

229. The polypeptide, construct or composition of clause 228 for use in the treatment of a disease selected from the list consisting of chronic kidney disease, kidney fibrosis, peritoneal fibrosis, liver fibrosis, pulmonary fibrosis, dermal fibrosis, systemic sclerosis and osteoarthritis.

230. The polypeptide, construct or composition of clause 227 for use in the treatment of a disease selected from the list consisting of chronic kidney disease, kidney fibrosis, peritoneal fibrosis, liver fibrosis, pulmonary fibrosis (e.g. idiopathic pulmonary fibrosis), dermal fibrosis, systemic sclerosis, osteoarthritis, NASH, rheumatoid arthritis, neuropathic pain or cancer.

231. A method of treating an inflammatory disease and/or fibrotic disease in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the polypeptide, construct or composition of any one of clauses 1 to 226.

232. A method of treating a disease selected from the list consisting of chronic kidney disease, kidney fibrosis, peritoneal fibrosis, liver fibrosis, pulmonary fibrosis, dermal fibrosis, systemic sclerosis and osteoarthritis in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the polypeptide, construct or composition of any one of clauses 1 to 226.

233. A method of treating a disease selected from the list consisting of chronic kidney disease, kidney fibrosis, peritoneal fibrosis, liver fibrosis, pulmonary fibrosis (e.g. idiopathic pulmonary fibrosis), dermal fibrosis, systemic sclerosis, osteoarthritis, NASH, rheumatoid arthritis, neuropathic pain or cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the polypeptide, construct or composition of any one of clauses 1 to 226.

234. Use of a polypeptide, construct or composition of any one of clauses 1 to 226 in the manufacture of a medicament for the treatment of an inflammatory disease and/or fibrotic disease.

235. Use of a polypeptide, construct or composition of any one of clauses 1 to 226 in the manufacture of a medicament for the treatment of a disease selected from the list consisting of chronic kidney disease, kidney fibrosis, peritoneal fibrosis, liver fibrosis, pulmonary fibrosis, dermal fibrosis, systemic sclerosis and osteoarthritis.

236. Use of a polypeptide, construct or composition of any one of clauses 1 to 226 in the manufacture of a medicament for the treatment of a disease selected from the list consisting of chronic kidney disease, kidney fibrosis, peritoneal fibrosis, liver fibrosis, pulmonary fibrosis (e.g. idiopathic pulmonary fibrosis), dermal fibrosis, systemic sclerosis, osteoarthritis, NASH, rheumatoid arthritis, neuropathic pain or cancer.

237. A polynucleotide sequence encoding the polypeptide or construct of any one of clauses 1 to 224.

238. The polynucleotide of clause 237 wherein the polynucleotide comprises any one of SEQ ID NOs: 1368 to 1374.

239. The polynucleotide of clause 238 wherein the polynucleotide consists of any one of SEQ ID NOs: 1368 to 1374.

240. An expression vector comprising the polynucleotide sequence of any one of clauses 237 to 239.

241. A cell comprising the polynucleotide sequence of any one of clauses 237 to 239 or the expression vector of clause 240.

Miscellaneous

All references referred to in this application, including patent and patent applications, are incorporated herein by reference to the fullest extent possible.

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer, step, group of integers or group of steps but not to the exclusion of any other integer, step, group of integers or group of steps.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims.

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CLAIMS

1. A polypeptide which binds to LPAR1, wherein the polypeptide is an inhibitor of LPAR1.

2 The polypeptide of claim 1 wherein the polypeptide binds to functionally active LPAR1.

3. The polypeptide of claim 1 or 2 wherein the LPAR1 is on the surface of a cell.

4. The polypeptide of claim 3 wherein the cell is a living cell.

5. The polypeptide of claim 1 to 4 wherein the polypeptide is an allosteric inhibitor of LPAR1.

6. The polypeptide of claim 1 to 5 wherein the polypeptide is an inverse agonist of LPAR1.

7. The polypeptide of any one of claims 1 to 6 wherein the polypeptide on binding to LPAR1 reduces the activity of LPAR1 by at least 50%.

8. The polypeptide of any one of claims 1 to 7 wherein the polypeptide binds to LPAR1 with a K_D of less than 150 nM.

9. The polypeptide of claim 8 wherein the polypeptide binds to LPAR1 with a K_D of less than 10 nM.

10. The polypeptide of claim 8 or claim 9 wherein the K_D is measured using a kinetic exclusion assay.

11. The polypeptide of any one of claims 1 to 10 wherein the polypeptide binds to a conformational epitope of human LPAR1 comprising one or more residues located within the N-terminal capping helix and one or more residues located within the extracellular domain 2.

12. The polypeptide of claim 11 wherein the polypeptide binds to an epitope of LPAR1 comprising residues 36 and 193 of full length LPAR1 (SEQ ID NO: 62).

13. The polypeptide of any one of claims 1 to 12 wherein the polypeptide comprises three heavy chain CDRs (HCDR1-3) and three light chain CDRs (LCDR1-3), wherein the polypeptide comprises:

(a) a HCDR1 comprising a sequence having at least 80% identity with SEQ ID NO: 1, SEQ ID NO: 7 or SEQ ID NO: 107,

(b) a HCDR2 comprising a sequence having at least 80% identity with any one of SEQ ID NOs: 2, 8 to 11, 100 or 108,

(c) a HCDR3 comprising a sequence having at least 80% identity with any one of SEQ ID NOs: 3, 12 to 15, 101 or 109,

(d) a LCDR1 comprising a sequence having at least 80% identity with any one of SEQ ID NOs: 4, 16 to 18, 103 or 110,

(e) a LCDR2 comprising a sequence having at least 80% identity with SEQ ID NO: 5, 19, 98 or 111, and

(f) a LCDR3 comprising a sequence having at least 80% identity with any one of SEQ ID NOs: 6, 20 to 22, or 112.

14. The polypeptide of claim 13 wherein the polypeptide comprises:

(a) a HCDR1 comprising any one of SEQ ID NO: 1, 7 or 107,

(b) a HCDR2 comprising any one of SEQ ID NOs: 2, 8 to 11, 100 or 108,

(c) a HCDR3 comprising any one of SEQ ID NOs: 3, 12 to 15, 101 or 109,

(d) a LCDR1 comprising any one of SEQ ID NOs: 4, 16 to 18, 103 or 110,

(e) a LCDR2 comprising any one of SEQ ID NO: 5, 19, 98 or 111, and

(f) a LCDR3 comprising any one of SEQ ID NOs: 6, 20 to 22, or 112.

15. The polypeptide of claim 14 wherein the polypeptide comprises:

(a) a HCDR1 comprising any one of SEQ ID NO: 1 or SEQ ID NO: 7,

(b) a HCDR2 comprising any one of SEQ ID NOs: 2, 8 to 11 or 100,

(c) a HCDR3 comprising any one of SEQ ID NOs: 3, 12 to 15 or 101,

(d) a LCDR1 comprising any one of SEQ ID NOs: 4, 16 to 18 or 103,

(e) a LCDR2 comprising any one of SEQ ID NO: 5, 19 or 98, and

(f) a LCDR3 comprising any one of SEQ ID NOs: 6, or 20 to 22.

16. The polypeptide of claim 13 or claim 14 wherein the polypeptide comprises:

(a) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 3, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 5 and a LCDR3 comprising SEQ ID NO: 6;

(b) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 8, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 16, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 20;

(c) a HCDR1 comprising SEQ ID NO: 7, a HCDR2 comprising SEQ ID NO: 9, a HCDR3 comprising SEQ ID NO: 13, a LCDR1 comprising SEQ ID NO: 17, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 21;

(d) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 10, a HCDR3 comprising SEQ ID NO: 14, a LCDR1 comprising SEQ ID NO: 18, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(e) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 8, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 16, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 22;

(f) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 8, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 16, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(g) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 11, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 20;

(h) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 11, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(i) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(j) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 3, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(k) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 15, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(l) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 15, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 5 and a LCDR3 comprising SEQ ID NO: 6;

(m) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 3, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 98 and a LCDR3 comprising SEQ ID NO: 6;

(n) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 100, a HCDR3 comprising SEQ ID NO: 101, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 98 and a LCDR3 comprising SEQ ID NO: 6;

(o) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 100, a HCDR3 comprising SEQ ID NO: 101, a LCDR1 comprising SEQ ID NO: 103, a LCDR2 comprising SEQ ID NO: 98 and a LCDR3 comprising SEQ ID NO: 6; or

(p) a HCDR1 comprising SEQ ID NO: 107, a HCDR2 comprising SEQ ID NO: 108, a HCDR3 comprising SEQ ID NO: 109, a LCDR1 comprising SEQ ID NO: 110, a LCDR2 comprising SEQ ID NO: 111 and a LCDR3 comprising SEQ ID NO: 112.

17. The polypeptide of claim 16 wherein the polypeptide comprises:

(a) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 3, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 5 and a LCDR3 comprising SEQ ID NO: 6;

(b) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 8, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 16, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 20;

(c) a HCDR1 comprising SEQ ID NO: 7, a HCDR2 comprising SEQ ID NO: 9, a HCDR3 comprising SEQ ID NO: 13, a LCDR1 comprising SEQ ID NO: 17, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 21;

(d) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 10, a HCDR3 comprising SEQ ID NO: 14, a LCDR1 comprising SEQ ID NO: 18, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(e) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 8, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 16, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 22;

(f) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 8, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 16, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(g) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 11, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 20;

(h) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 11, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(i) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 12, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(j) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 3, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(k) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 15, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 19 and a LCDR3 comprising SEQ ID NO: 6;

(l) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 15, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 5 and a LCDR3 comprising SEQ ID NO: 6;

(m) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 2, a HCDR3 comprising SEQ ID NO: 3, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 98 and a LCDR3 comprising SEQ ID NO: 6;

(n) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 100, a HCDR3 comprising SEQ ID NO: 101, a LCDR1 comprising SEQ ID NO: 4, a LCDR2 comprising SEQ ID NO: 98 and a LCDR3 comprising SEQ ID NO: 6; or

(o) a HCDR1 comprising SEQ ID NO: 1, a HCDR2 comprising SEQ ID NO: 100, a HCDR3 comprising SEQ ID NO: 101, a LCDR1 comprising SEQ ID NO: 103, a LCDR2 comprising SEQ ID NO: 98 and a LCDR3 comprising SEQ ID NO: 6.

18. The polypeptide of claim 16 wherein the polypeptide comprises:

(a) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 3, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 5 and a LCDR3 consisting of SEQ ID NO: 6;

(b) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 8, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 16, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 20;

(c) a HCDR1 consisting of SEQ ID NO: 7, a HCDR2 consisting of SEQ ID NO: 9, a HCDR3 consisting of SEQ ID NO: 13, a LCDR1 consisting of SEQ ID NO: 17, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 21;

(d) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 10, a HCDR3 consisting of SEQ ID NO: 14, a LCDR1 consisting of SEQ ID NO: 18, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(e) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 8, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 16, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 22;

(f) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 8, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 16, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(g) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 11, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 20;

(h) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 11, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(i) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 12, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(j) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 3, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(k) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 15, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 19 and a LCDR3 consisting of SEQ ID NO: 6;

(l) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 15, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 5 and a LCDR3 consisting of SEQ ID NO: 6;

(m) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 2, a HCDR3 consisting of SEQ ID NO: 3, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 98 and a LCDR3 consisting of SEQ ID NO: 6;

(n) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 100, a HCDR3 consisting of SEQ ID NO: 101, a LCDR1 consisting of SEQ ID NO: 4, a LCDR2 consisting of SEQ ID NO: 98 and a LCDR3 consisting of SEQ ID NO: 6;

(o) a HCDR1 consisting of SEQ ID NO: 1, a HCDR2 consisting of SEQ ID NO: 100, a HCDR3 consisting of SEQ ID NO: 101, a LCDR1 consisting of SEQ ID NO: 103, a LCDR2 consisting of SEQ ID NO: 98 and a LCDR3 consisting of SEQ ID NO: 6; or

(p) a HCDR1 consisting of SEQ ID NO: 107, a HCDR2 consisting of SEQ ID NO: 108, a HCDR3 consisting of SEQ ID NO: 109, a LCDR1 consisting of SEQ ID NO: 110, a LCDR2 consisting of SEQ ID NO: 111 and a LCDR3 consisting of SEQ ID NO: 112.

19. The polypeptide of any one of claims 1 to 12 wherein the polypeptide comprises three heavy chain CDRs (HCDR1-HCDR3) and three light chain CDRs (LCDR1-LCDR3) (wherein the CDRs are defined by a non-Kabat numbering system) wherein HCDR1 comprises (e.g. consists of) $X_1X_2X_3X_4X_5X_6$ (SEQ ID NO: 72), HCDR2 comprises (e.g. consists of) $X_7IX_8X_9X_{10}X_{11}X_{12}X_{13}X_{14}X_{15}YX_{16}X_{17}X_{18}FX_{19}G$ (SEQ ID NO: 76), HCDR3 comprises (e.g. consists of) $DX_{20}X_{21}X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}DY$ (SEQ ID NO: 80), LCDR1 comprises (e.g. consists of) $X_{30}X_{31}X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}X_{40}$ (SEQ ID NO: 84), LCDR2 comprises (e.g. consists of) $X_{41}AX_{42}X_{43}X_{44}X_{45}X_{46}$ (SEQ ID NO: 88) and LCDR3 comprises (e.g. consists of) $X_{47}X_{48}X_{49}X_{50}X_{51}X_{52}PLX_{53}$ (SEQ ID NO: 92), wherein:

the amino acid of X_1 is selected from the group consisting of S, Y, T, G, R, E, K, D and N;

the amino acid of X_2 is selected from the group consisting of K, R, L, T, G, V, A, S, F, W, Q, M, Y, I, E, H ,N, D and P;

the amino acid of X_3 is selected from the group consisting of R, K, H, T, S, F, G, V, A, L, N, Q, E, M, P, W and I;

the amino acid of X_4 is selected from the group consisting of A and G;

the amino acid of X_5 is selected from the group consisting of M and I;

the amino acid of X_6 is selected from the group consisting of S, E, G, D, L, T, N, Q, I, V, A, K, M, H and Y;

the amino acid of X_7 is selected from the group consisting of E;

the amino acid of X_8 is selected from the group consisting of L, Q and D;

the amino acid of X_9 is selected from the group consisting of P, A, G , F, S, T and W;

the amino acid of X_{10} is selected from the group consisting of R;

the amino acid of X_{11} is selected from the group consisting of S, T and D;

the amino acid of X_{12} is selected from the group consisting of G, R, S, Y, A, T, D, E and W;

the amino acid of X_{13} is selected from the group consisting of Y;

the amino acid of X_{14} is selected from the group consisting of T;

the amino acid of X_{15} is selected from the group consisting of N, H and S;

the amino acid of X_{16} is selected from the group consisting of R, N, F, K, Q, V, D, E, Y, G, M, P, W, H, L, I, S, T and A;

the amino acid of X_{17} is selected from the group consisting of Q, A, I, S, P, T, N, V, G, H, L, M, W, K, R, F, D, Y and E;

the amino acid of X_{18} is selected from the group consisting of G, D, E, H, L, V, Y, A, F, I, K, Q, W, R, M, P, S and N;

the amino acid of X_{19} is selected from the group consisting of T, K, Q, E, R and M;

the amino acid of X_{20} is selected from the group consisting of R, F, K, I, A, L, V, W, Y, M, P, Q, G and S;

the amino acid of X_{21} is not present or is selected from the group consisting of K and R

the amino acid of X_{22} is selected from the group consisting of K, R, A, H, S, Q, T, P, M, W, Y, G, L, F, V, E and N;

the amino acid of X_{23} is not present or is selected from the group consisting of K and R

the amino acid of X_{24} is selected from the group consisting of R, Y, A, H, P, L, K, G, Q, N, I, F, W, S, T, M, E, V and D;

the amino acid of X_{25} is selected from the group consisting of A, Q, T, S, G, V, R, I, H, K, P, L, M and F;

the amino acid of X_{26} is selected from the group consisting of R and S;

the amino acid of X_{27} is selected from the group consisting of Y, H, Q and A;

the amino acid of X_{28} is selected from the group consisting of A, T, S, D and E;

the amino acid of X_{29} is selected from the group consisting of M and L;

the amino acid of X_{30} is selected from the group consisting of Q, K, R, S and T;

the amino acid of X_{31} is selected from the group consisting of A, S and T;

the amino acid of X_{32} is selected from the group consisting of S, T and D;

the amino acid of X_{33} is selected from the group consisting of Q, G, R, K, L, M, P, Y, S, A, N, H, W, D, E, F, T and I;

the amino acid of X_{34} is selected from the group consisting of S, G, H, N, T, Y and D;

the amino acid of X_{35} is selected from the group consisting of V, A and I;

the amino acid of X_{36} is selected from the group consisting of R, K, S, G and A;

the amino acid of X_{37} is selected from the group consisting of Y, F, L, Q, S, H, T, G, I, M, V, W, K, N, R, D and P;

the amino acid of X_{38} is selected from the group consisting of N, A, G, H, Q, S, Y, F and W;

the amino acid of X_{39} is selected from the group consisting of V, I, M and L;

the amino acid of X_{40} is selected from the group consisting of A, G and D;

the amino acid of X_{41} is selected from the group consisting of Y, H, R, T, A, D, K, L, N, Q, M, W, E, F and S;

the amino acid of X_{42} is selected from the group consisting of S, K, M, Q, R, V, Y, G, E, D, T, A, F, I, N, W, H and L;

the amino acid of X_{43} is selected from the group consisting of N, K, R, Q, T, Y, A, S, D and E;

the amino acid of X_{44} is selected from the group consisting of R, L, K and A;

the amino acid of X_{45} is selected from the group consisting of Y, I, K, M, Q, R, V, A, N, S, W, H, L, T, P, D, F, G and E;

the amino acid of X_{46} is selected from the group consisting of T, A, D, E, Q, R, S, H, K, P, L, F, G, I, M, V, W, Y and N;

the amino acid of X_{47} is selected from the group consisting of Q, S and L;

the amino acid of X_{48} is selected from the group consisting of H, N, S, T, A, Q and V;

the amino acid of X_{49} is selected from the group consisting of H, A, D and F;

the amino acid of X_{50} is selected from the group consisting of Y and L;

the amino acid of X_{51} is selected from the group consisting of S, K, V, D, N, R, H, T, A, G, Q, I, M, F, W, Y and L;

the amino acid of X_{52} is selected from the group consisting of S, A, T, G, V, W and Y; and

the amino acid of X_{53} is selected from the group consisting of T and Y.

20. The polypeptide of claim 19 wherein X_{21} and/or X_{23} are not present.

21. The polypeptide of any one of claims 1 to 20 wherein the polypeptide comprises four heavy chain framework regions (HFR1-HFR4) and four light chain framework regions (LFR1-LFR4), wherein the polypeptide comprises:

(a) a HFR1 comprising or consisting of a sequence having at least 60% identity to SEQ ID NO: 40;

(b) a HFR2 comprising or consisting of a sequence having at least 60% identity to SEQ ID NO: 41;

(c) a HFR3 comprising or consisting of a sequence having at least 60% identity to SEQ ID NO: 42;

(d) a HFR4 comprising or consisting of a sequence having at least 60% identity to SEQ ID NO: 43;

(e) a LFR1 comprising or consisting of a sequence having at least 60% identity to SEQ ID NO: 44;

(f) a LFR2 comprising or consisting of a sequence having at least 60% identity to SEQ ID NO: 45;

(g) a LFR3 comprising or consisting of a sequence having at least 60% identity to SEQ ID NO: 46; and

(h) a LFR4 comprising or consisting of a sequence having at least 60% identity to SEQ ID NO: 47.

22. The polypeptide of claim 21 wherein the polypeptide comprises:

(a) a HFR1 comprising or consisting of a sequence having at least 80% identity to SEQ ID NO: 40;

(b) a HFR2 comprising or consisting of a sequence having at least 80% identity to SEQ ID NO: 41;

(c) a HFR3 comprising or consisting of a sequence having at least 80% identity to SEQ ID NO: 42;

(d) a HFR4 comprising or consisting of a sequence having at least 80% identity to SEQ ID NO: 43;

(e) a LFR1 comprising or consisting of a sequence having at least 80% identity to SEQ ID NO: 44;

(f) a LFR2 comprising or consisting of a sequence having at least 80% identity to SEQ ID NO: 45;

(g) a LFR3 comprising or consisting of a sequence having at least 80% identity to SEQ ID NO: 46; and

(h) a LFR4 comprising or consisting of a sequence having at least 80% identity to SEQ ID NO: 47.

23. The polypeptide of any one of claims 1 to 22 wherein the polypeptide comprises a VH region and a VL region, wherein the polypeptide comprises

(a) a VH region comprising or consisting of a sequence having at least 70% identity with any one of SEQ ID NOs: 23, 25, 27, 29, 33, 35, 36, 37, 96, 102 or 113; and

(b) an VL region comprising or consisting of a sequence having at least 70% identity with any one of SEQ ID NOs: 24, 26, 28, 30, 31, 32, 34, 38, 39, 97, 99. 104 or 114.

24. The polypeptide of claim 23 wherein the polypeptide comprises

(a) a VH region comprising SEQ ID NO: 23 and a VL region comprising SEQ ID NO: 24;

(b) a VH region comprising SEQ ID NO: 25 and a VL region comprising SEQ ID NO: 26;

(c) a VH region comprising SEQ ID NO: 27 and a VL region comprising SEQ ID NO: 28;

(d) a VH region comprising SEQ ID NO: 29 and a VL region comprising SEQ ID NO: 30;

(e) a VH region comprising SEQ ID NO: 27 and a VL region comprising SEQ ID NO: 31;

(f) a VH region comprising SEQ ID NO: 27 and a VL region comprising SEQ ID NO: 32;

(g) a VH region comprising SEQ ID NO: 33 and a VL region comprising SEQ ID NO: 34;

(h) a VH region comprising SEQ ID NO: 33 and a VL region comprising SEQ ID NO: 39;

(i) a VH region comprising SEQ ID NO: 35 and a VL region comprising SEQ ID NO: 39;

(j) a VH region comprising SEQ ID NO: 36 and a VL region comprising SEQ ID NO: 39;

(k) a VH region comprising SEQ ID NO: 37 and a VL region comprising SEQ ID NO: 39;

(l) a VH region comprising SEQ ID NO: 36 and a VL region comprising SEQ ID NO: 38;

(m) a VH region comprising SEQ ID NO: 37 and a VL region comprising SEQ ID NO: 38;

(n) a VH region comprising SEQ ID NO: 96 and a VL region comprising SEQ ID NO: 97;

(o) a VH region comprising SEQ ID NO: 36 and a VL region comprising SEQ ID NO: 99;

(p) a VH region comprising SEQ ID NO: 102 and a VL region comprising SEQ ID NO: 99;

(q) a VH region comprising SEQ ID NO: 102 and a VL region comprising SEQ ID NO: 104; or

(s) a VH region comprising SEQ ID NO: 113 and a VL region comprising SEQ ID NO: 114.

25. The polypeptide of any one of claims 1 to 24, wherein the polypeptide comprises a VH and a VL region and the VH and VL region are joined by a linker, such as a polypeptide linker.

26. The polypeptide of any one of claims 1 to 25 wherein the polypeptide is an antibody or fragment thereof.

27. The polypeptide of claim 26 wherein the antibody or fragment thereof is selected from the list consisting of an scFv, Fab, Fab', F(ab')2, Fv, variable domain (e.g. VH or VL), diabody, minibody or full length antibody.

28. The polypeptide of claim 26 or 27 wherein the Fc region of the antibody has been mutated to reduce effector function, extend half-life, alter ADCC or improve hinge stability.

29. A construct comprising the polypeptide of any one of claims 1 to 28.

30. A pharmaceutical composition comprising the polypeptide or construct of any one of claims 1 to 29, together with a pharmaceutically acceptable diluent or carrier.

31. The polypeptide, construct or composition of any one of claims 1 to 30 for use as a medicament.

32. The polypeptide, construct or composition of any one of claims 1 to 30 for use in the treatment of chronic kidney disease, kidney fibrosis, peritoneal fibrosis, liver fibrosis, pulmonary fibrosis (e.g. idiopathic pulmonary fibrosis), dermal fibrosis, systemic sclerosis, osteoarthritis, NASH, rheumatoid arthritis, neuropathic pain or cancer.

33. A polynucleotide sequence encoding the polypeptide or construct of any one of claims 1 to 29.

34. An expression vector comprising the polynucleotide sequence of claim 33.

35. A cell comprising the polynucleotide sequence of claim 33 or the expression vector of claim 34.

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