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(54) ANTIBODIES TARGETING C5AR

(71) Applicant: **MORPHOSYS AG**, Martinsried/Planegg (DE)

(72) Inventors: **Julia NEUGEBAUER**, Munich (DE); **Barbara BACHLER-KONETZKI**, Hamburg (DE); **Tanja HERRMANN**, Munich (DE); **Winfried ELLIS**, Wittnau (DE)

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(57) **ABSTRACT**

The present invention provides novel antibodies or antibody fragments specifically binding to human C5aR. In particular, it relates to antibodies or antibody fragments that have combined beneficial properties and are therefore useful for the treatment of inflammatory or autoimmune diseases or cancer.

Specification includes a Sequence Listing.

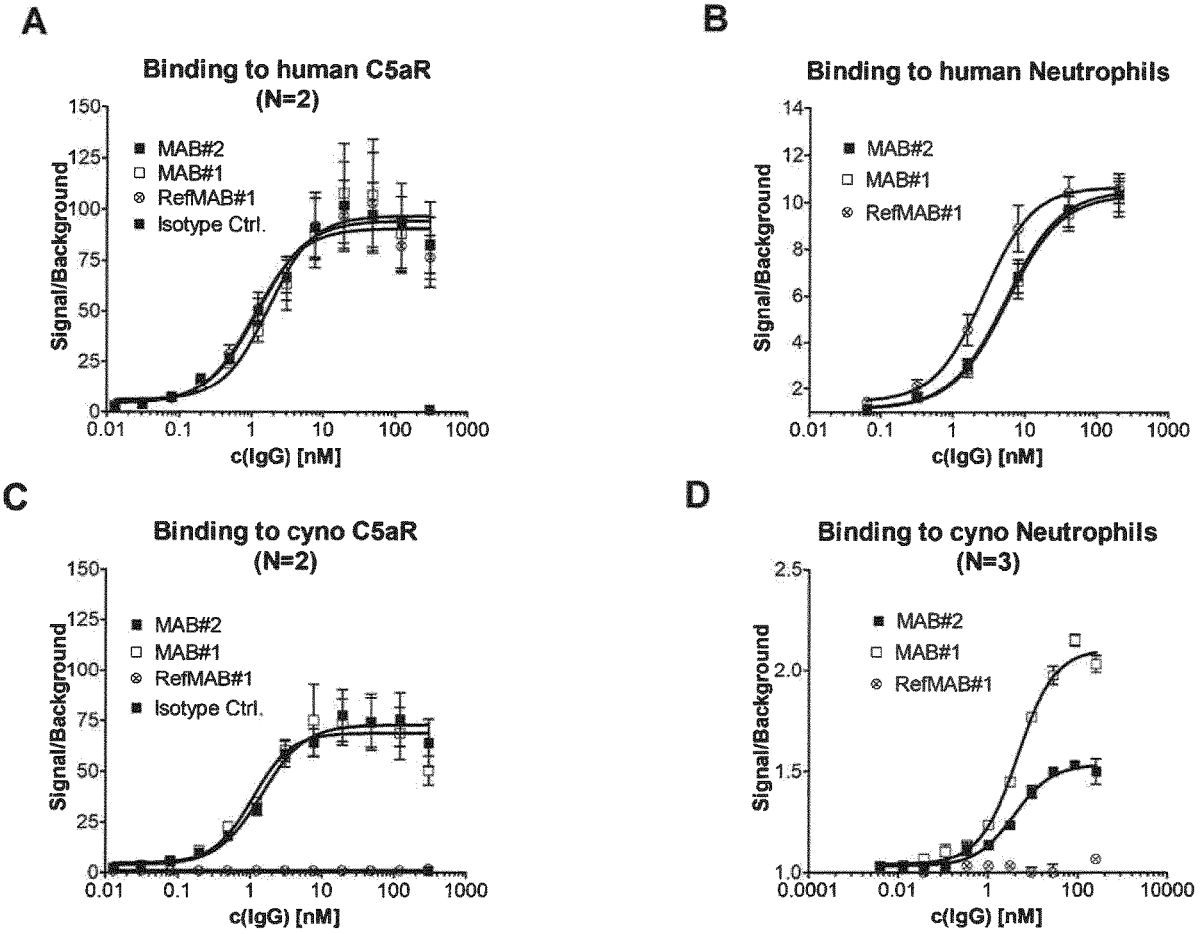


Figure 1

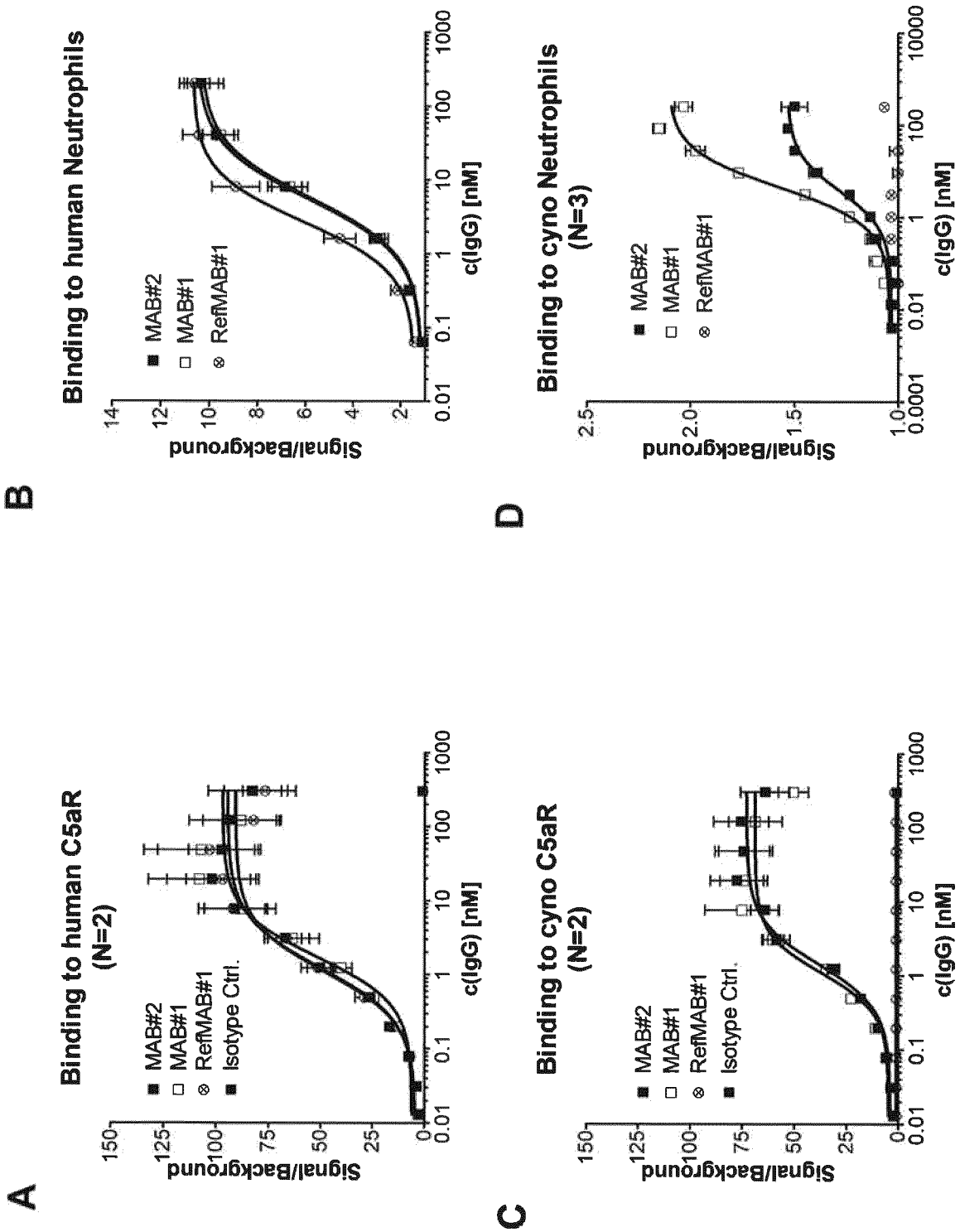

A
Binding to human C5aR
(N=2)
MAB#2
MAB#1
RefMAB#1
Isotype Ctrl.
Signal/Background
c(IgG) [nM]
B
Binding to human Neutrophils
MAB#2
MAB#1
RefMAB#1
Signal/Background
c(IgG) [nM]
C
Binding to cyno C5aR
(N=2)
MAB#2
MAB#1
RefMAB#1
Isotype Ctrl.
Signal/Background
c(IgG) [nM]
D
Binding to cyno Neutrophils
(N=3)
MAB#2
MAB#1
RefMAB#1
Signal/Background
c(IgG) [nM]

Figure 2

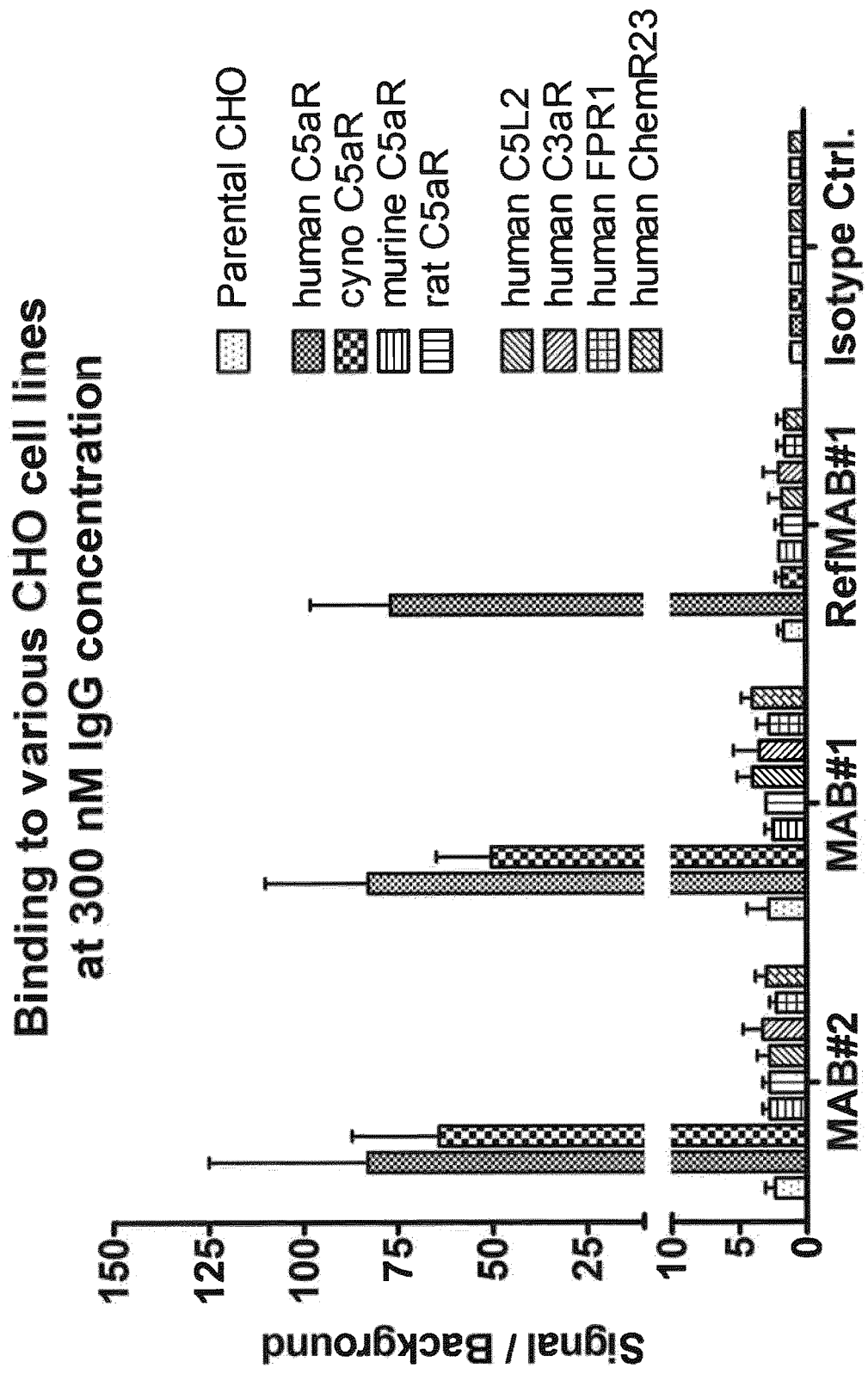

Binding to various CHO cell lines
at 300 nM IgG concentration
Parental CHO
human C5aR
cyno C5aR
murine C5aR
rat C5aR
human C5L2
human C3aR
human FPR1
human ChemR23
Signal / Background
150
125
100
75
50
25
10
5
0
MAB#2
MAB#1
RefMAB#1
Isotype Ctrl.

Figure 3

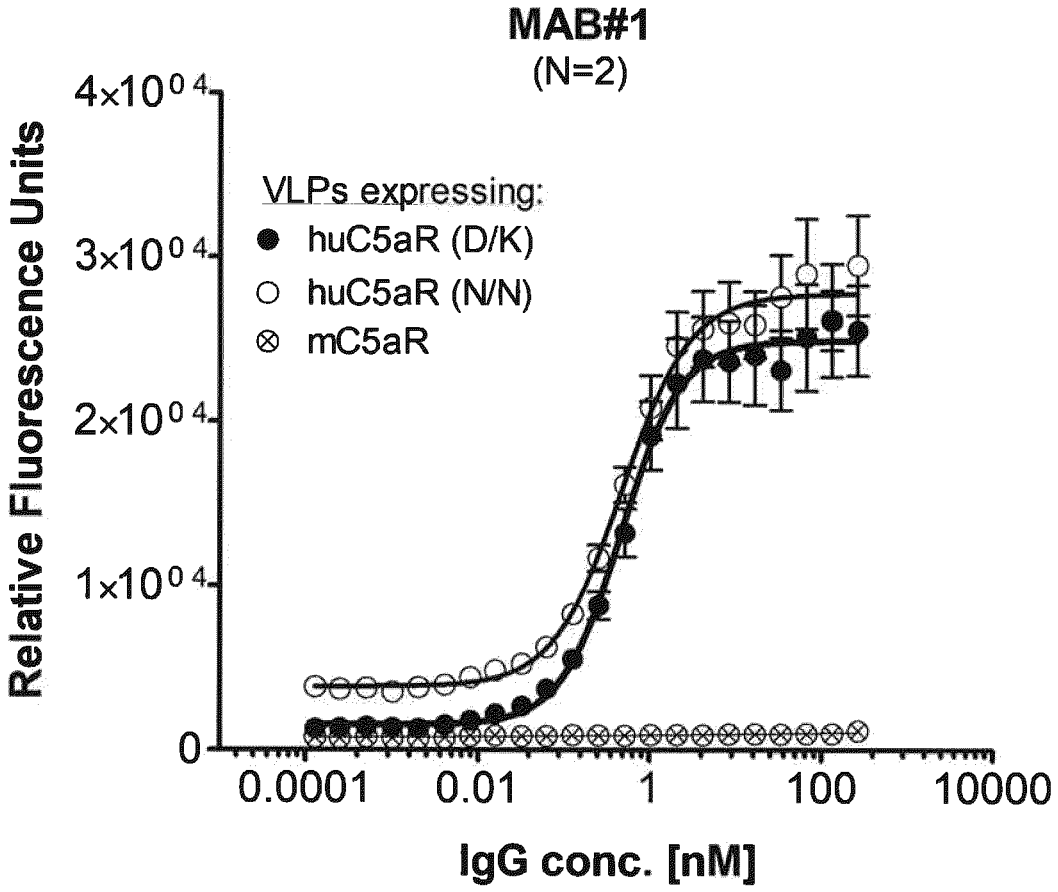
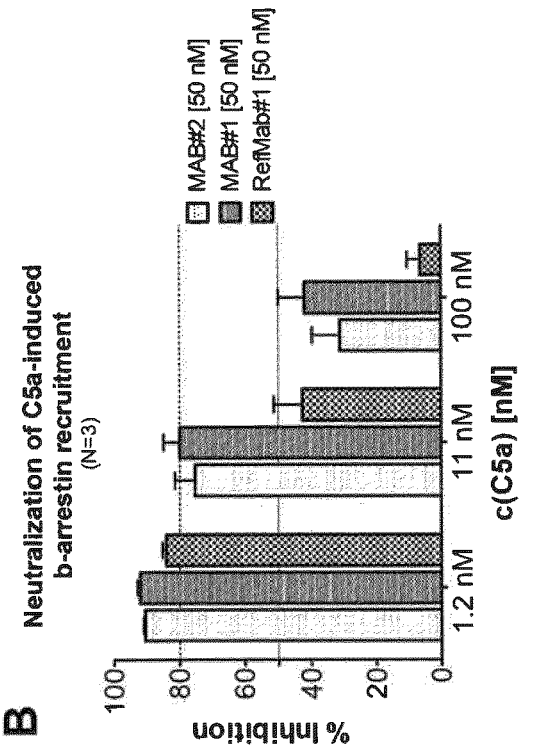

MAB#1
(N=2)
Relative Fluorescence Units
4x10^04
3x10^04
2x10^04
1x10^04
0
VLPs expressing:
huC5aR (D/K)
huC5aR (N/N)
mC5aR
0.0001
0.01
1
100
10000
IgG conc. [nM]

Figure 4


B
Neutralization of C5a-induced
b-arrestin recruitment
(N=3)
MAB#2 [50 nM]
MAB#1 [50 nM]
RefMab#1 [50 nM]
% Inhibition
0
20
40
60
80
100
1.2 nM
11 nM
100 nM
c(C5a) [nM]

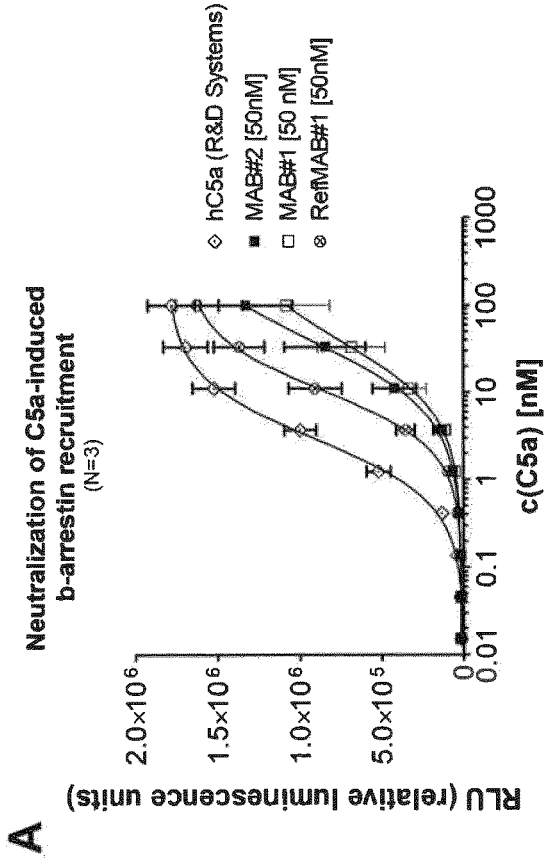

A
Neutralization of C5a-induced
b-arrestin recruitment
(N=3)
hC5a (R&D Systems)
MAB#2 [50nM]
MAB#1 [50 nM]
RefMAB#1 [50nM]
RLU (relative luminescence units)
0
5.0x10^5
1.0x10^6
1.5x10^6
2.0x10^6
0.01
0.1
1
10
100
1000
c(C5a) [nM]

Figure 5

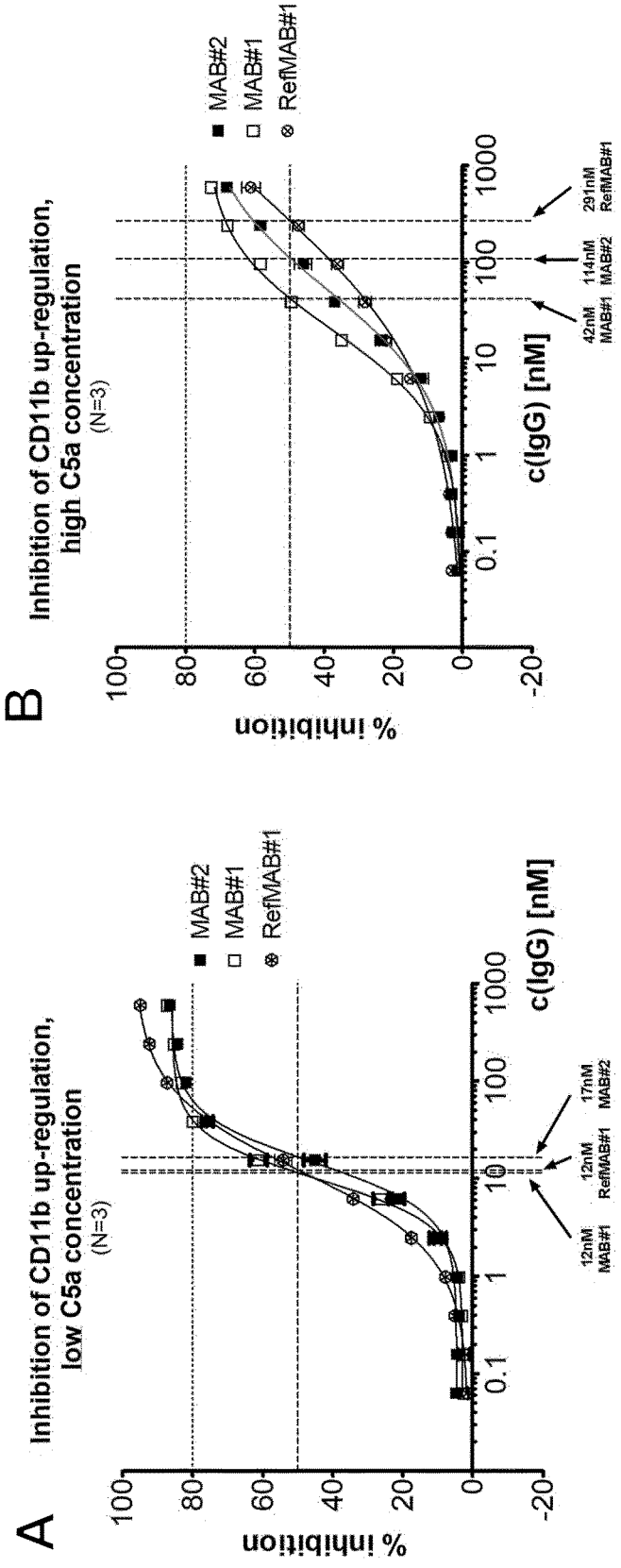

A
Inhibition of CD11b up-regulation,
low C5a concentration
(N=3)
MAB#2
MAB#1
RefMAB#1
% inhibition
c(IgG) [nM]
12nM MAB#1
12nM RefMAB#1
17nM MAB#2
B
Inhibition of CD11b up-regulation,
high C5a concentration
(N=3)
MAB#2
MAB#1
RefMAB#1
% inhibition
c(IgG) [nM]
42nM MAB#1
114nM MAB#2
291nM RefMAB#1

Figure 6

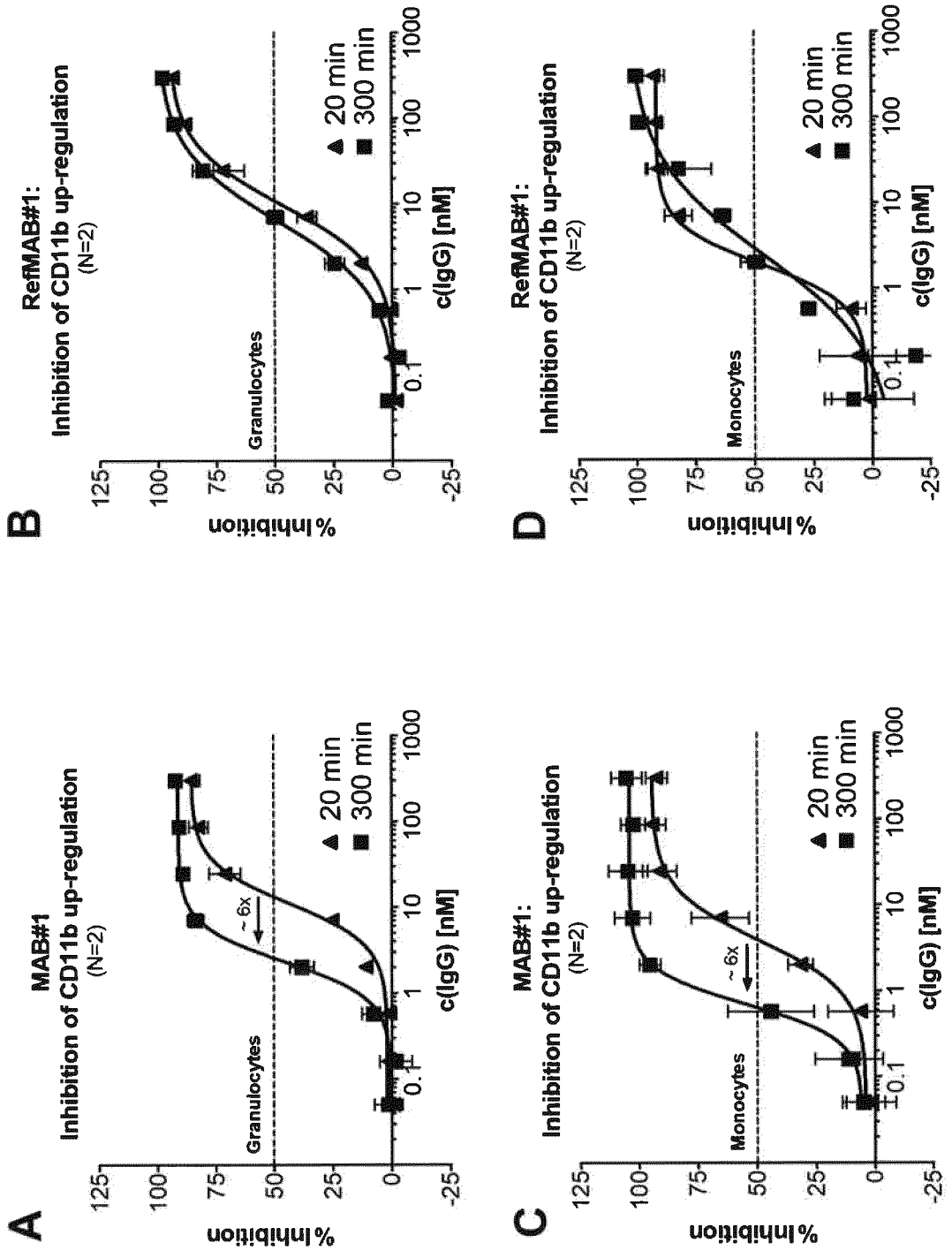

A
MAB#1
Inhibition of CD11b up-regulation
(N=2)
Granulocytes
~ 6x
20 min
300 min
% Inhibition
c(IgG) [nM]
B
RefMAB#1:
Inhibition of CD11b up-regulation
(N=2)
Granulocytes
20 min
300 min
% Inhibition
c(IgG) [nM]
C
MAB#1:
Inhibition of CD11b up-regulation
(N=2)
Monocytes
~ 6x
20 min
300 min
% Inhibition
c(IgG) [nM]
D
RefMAB#1:
Inhibition of CD11b up-regulation
(N=2)
Monocytes
20 min
300 min
% Inhibition
c(IgG) [nM]

Figure 7

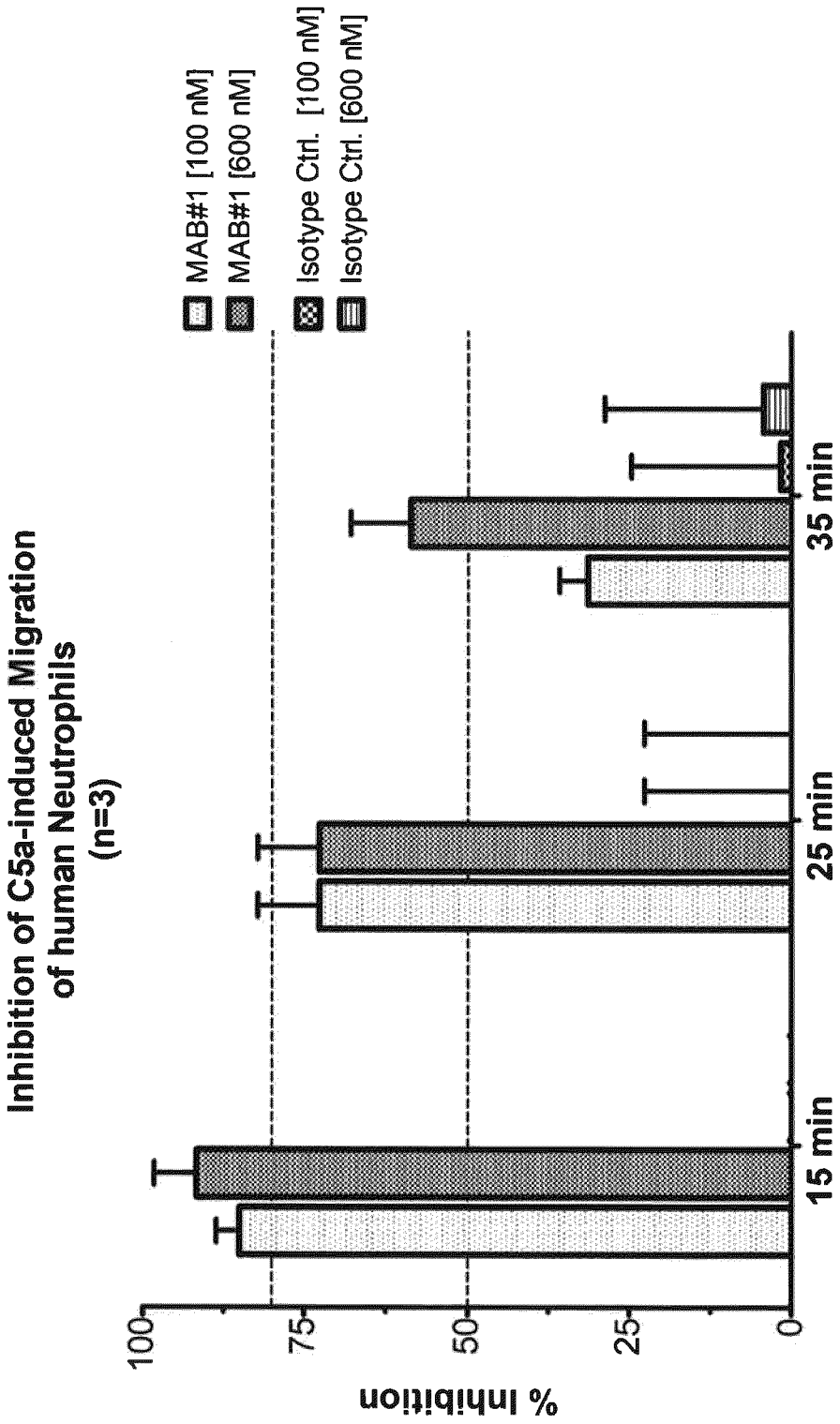

Inhibition of C5a-induced Migration
of human Neutrophils
(n=3)
MAB#1 [100 nM]
MAB#1 [600 nM]
Isotype Ctrl. [100 nM]
Isotype Ctrl. [600 nM]
% Inhibition
100
75
50
25
0
15 min
25 min
35 min

Figure 8

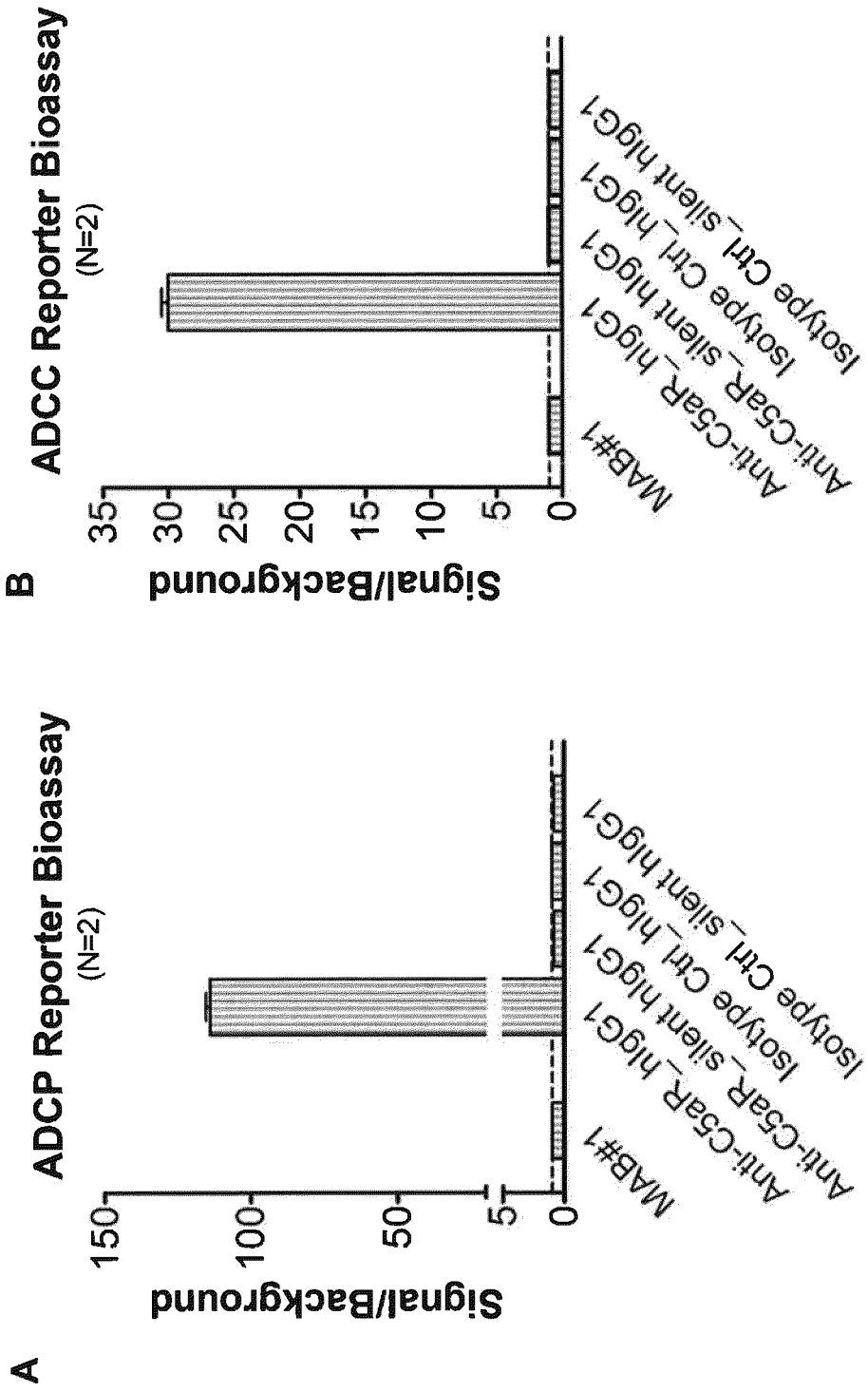

A
ADCP Reporter Bioassay
(N=2)
Signal/Background
150
100
50
5
0
MAB#1
Anti-C5aR_hIgG1
Anti-C5aR_silent hIgG1
Isotype Ctrl_hIgG1
Isotype Ctrl_silent hIgG1
B
ADCC Reporter Bioassay
(N=2)
Signal/Background
35
30
25
20
15
10
5
0
MAB#1
Anti-C5aR_hIgG1
Anti-C5aR_silent hIgG1
Isotype Ctrl_hIgG1
Isotype Ctrl_silent hIgG1

Figure 9

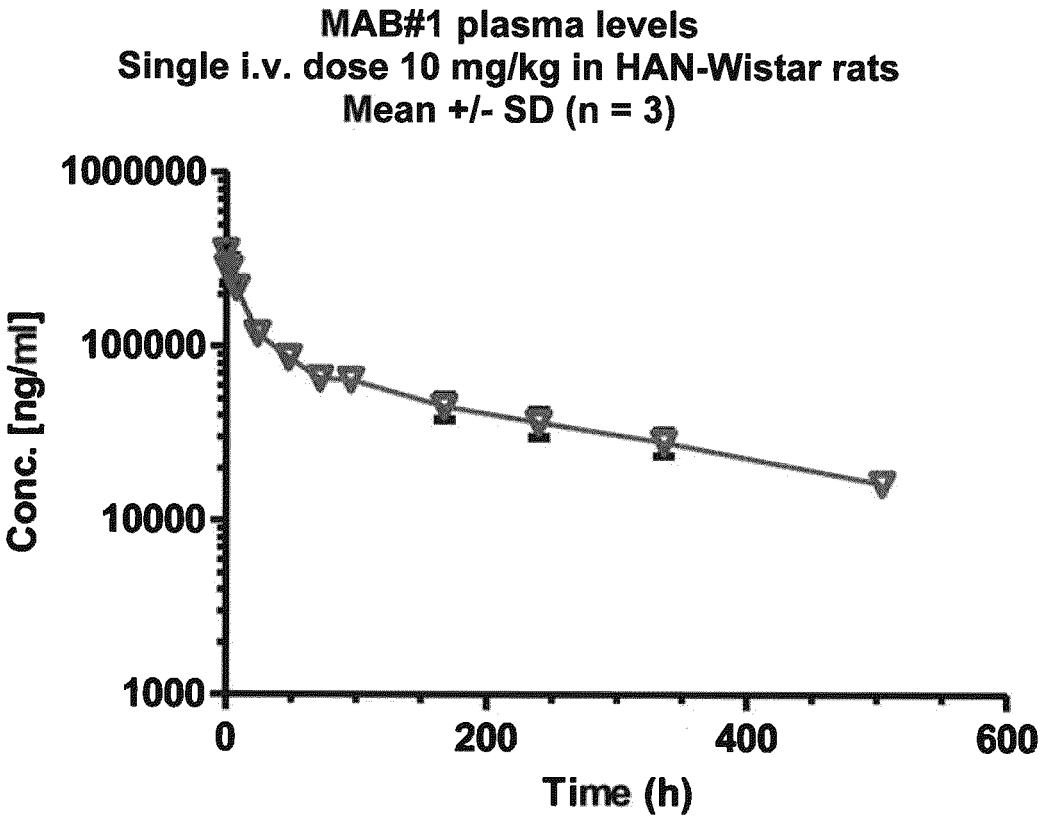
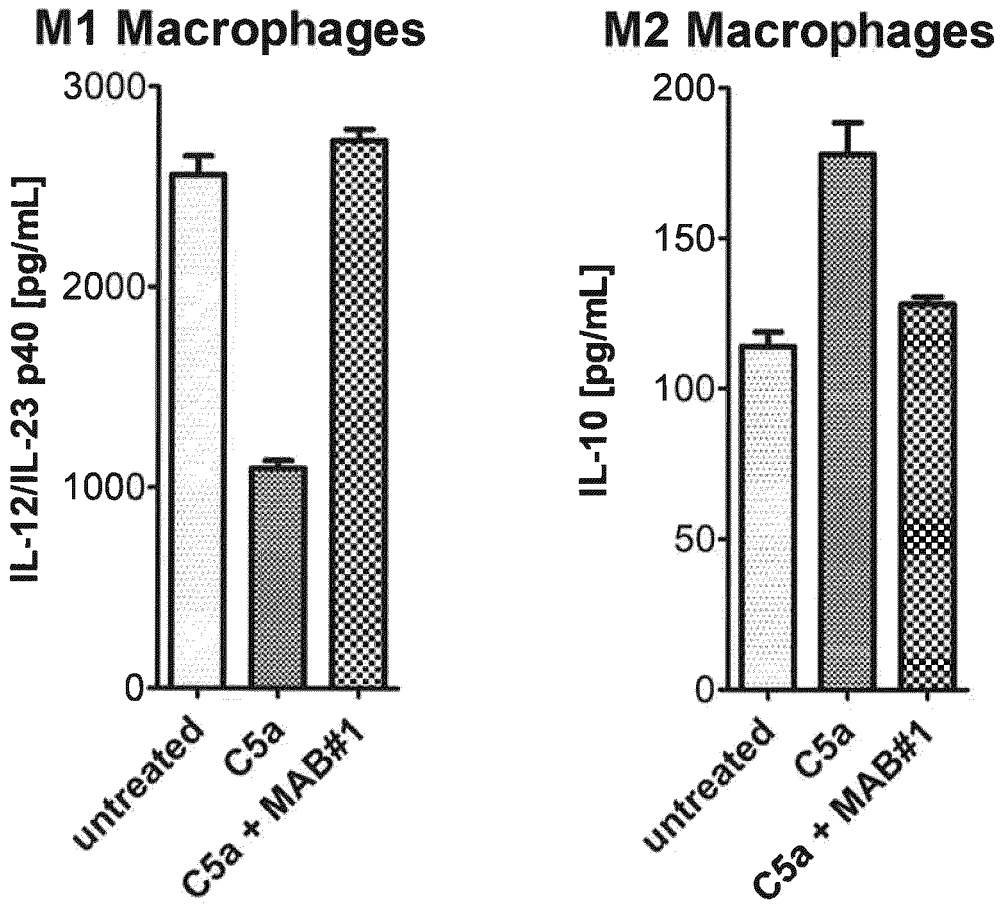

MAB#1 plasma levels
Single i.v. dose 10 mg/kg in HAN-Wistar rats
Mean +/- SD (n = 3)
1000000
100000
10000
1000
Conc. [ng/ml]
0
200
400
600
Time (h)

Figure 10

Antigen	MAB#2		MAB#1	
	100 nM	10 nM	100 nM	10 nM
Blank	2	1	2	1
huC5aR_NT_bio	49	46	84	82
Protein A	1	1	1	1
Serum albumin (h)	2	1	2	2
Fibrinogen (b)	2	1	2	1
Hemoglobin (h)	2	1	2	1
Transferrin (b)	9	4	19	8
Antitrypsin	2	2	2	1
Cell surface rec. 1_Lys (h)	2	1	2	1
Cell surface rec. 2_Fc (h)	2	1	2	1
Cell surface rec. 3_Fc (h)	2	2	2	2
GFP	2	1	2	1
Baculovirus particles	3	1	3	1
Fc (h)	3	1	2	1
HKB11 vesicle	3	1	3	1
Dextransulfate sodium salt	2	1	2	1
Pepsinogen	5	1	4	1
Amyloglycosidase	2	1	3	1
Trypsin inhibitor	7	3	5	2
Cytochrome C	2	1	2	1
Myoglobin	2	1	2	1
Lectin	2	1	2	1
Ovalbumin	4	1	2	1
Trypsinogen	2	1	2	1
Milk powder	2	1	2	1
RNase B	2	1	2	1
RNase A	6	2	4	2
Lysozyme	2	1	2	1
anti-human Fab (Dianova)	1	1	1	1
anti-human Fc	1	1	1	1
Blank	2	1	2	1
Blank	2	1	2	1

Figure 11


M1 Macrophages
IL-12/IL-23 p40 [pg/mL]
3000
2000
1000
0
untreated
C5a
C5a + MAB#1
M2 Macrophages
IL-10 [pg/mL]
200
150
100
50
0
untreated
C5a
C5a + MAB#1

ANTIBODIES TARGETING C5AR

FIELD OF THE INVENTION

[0001] The present disclosure relates to antibodies, which interact with C5aR, in particular with human C5aR. The present disclosure also relates to nucleic acid compositions, vector composition and host cells capable of expressing said antibodies, pharmaceutical compositions comprising said antibodies and uses of said antibodies for the treatment of specific diseases and/or for diagnostic purposes.

BACKGROUND

[0002] The C5a anaphylatoxin chemotactic receptor 1 (C5aR) (also known as CD88) is a G-protein-coupled receptor (GPCR) belonging to the rhodopsin family and is one of the two high-affinity receptors for the ligand, C5a, which is produced in serum as one of the core effector components of the complement response. Under physiological conditions, C5a acts as chemotactic agent for inflammatory cells, stimulates their respiratory burst as well as cytokine and chemokine release, and functions to increase vascular permeability.

[0003] C5aR appears widely expressed by various cell types. Highest C5aR expression levels are described for neutrophils. Low-to-moderate expression levels have been shown for macrophages/monocytes, dendritic cells, mast cells, eosinophils, lung vascular smooth muscle cells, astrocytes, microglia, osteoblasts, osteoclasts, epithelial and endothelial cells (Monk P N et al., Br J Pharmacol. 2007, 152: 429-448; Wetsel R A, Immunol Lett. 1995, 44: 183-187). For human T cells, low expression levels have been observed (Nataf S, J Immunol. 1999, 162: 4018-4023).

[0004] Cell responses to C5a are tightly controlled by ligand-induced receptor internalization. C5aR is described to rapidly and dose-dependently internalize upon C5a treatment and up to 90% of the receptor is recycled back to the cell surface. Thus, the high expression levels of C5aR in combination with its fast turn-over rate could be limiting in terms of efficacy due to target-mediated drug disposition (TMDD) effects.

[0005] The interaction of C5aR with C5a has been described in many different disease settings; most of them being involved in inflammatory and autoimmune diseases (Morgan B P et al., Nat Rev Drug Discov. 2015, 14: 857-877; Hawksworth O A et al., Mol Immunol. 2017, 89: 36-43). Some initial research has been performed to identify the underlying mechanisms by which C5a stimulates tumor growth (Markiewski M M et al., Nat Immunol. 2008, 9: 1225-1235; Corrales L. et al, J Immunol. 2012, 189: 4674-4683; Cho M S et al., Cell Rep. 2014, 6: 1085-1095). Most of the data implicates that C5a increases cancer cell proliferation, intra-tumor angiogenesis and enhances tumor invasiveness and metastasis. More recent data also implicate a role for C5a/C5aR in the generation of immunosuppressive environments in the context of solid tumors (Sayegh E T et al., Cancer Med. 2014, 3: 747-758; Darling V R et al., Expert Rev Clin Immunol. 2015, 11: 255-263; Markiewski M M et al., Cancer Res. 2009, 69: 6367-6370) resulting in enhanced primary tumor growth by inhibiting antitumor responses (e.g. increased recruitment of C5aR-expressing myeloid cells such as myeloid-derived suppressor cell (MDSC) or M2 macrophages). Based on these findings, combination strategies with already known anti-tumor agents, such as immune checkpoint protein inhibitors in order to boost a subject's immune response by reducing the immunosuppressive microenvironment are in focus of research and clinical development (Wang Y, et al.: Cancer Discov. 2016, 6: 1022-1035).

[0006] To date, only one specific complement therapeutic has been approved, which targets the upstream molecule of C5a, namely C5. The humanized anti-C5 mAb Eculizumab is capable of binding C5, preventing its cleavage and formation of C5a and C5b proteins, and subsequent MAC formation. Various other therapeutic monoclonal C5 specific antibodies, such as ALXN1210 or LFG316 are under clinical evaluation (Hawksworth O A et al., Mol Immunol. 2017, 89: 36-43). However, since increased infection risk is a major concern with chronic C5 treatment, specific targeting of downstream molecules whilst preventing the biological activities of other complement components is clearly advantageous. Accordingly, a number of antagonistic C5a specific monoclonal antibodies are under development.

[0007] Direct targeting of C5aR has a number of advantages over targeting C5 or C5a, respectively. First, the inhibition of the receptor alone would preserve MAC activity, thereby reducing the potential risk of infections. Second, C5aR blockade permits continued C5a interaction with its second receptor C5L2. Since C5L2 has been reported to have anti-inflammatory effects, maintaining an effective C5L2 signalling pathway may result in increased efficacy or reduced dosing requirements. Third, direct C5aR targeting may provide pharmacodynamic advantages over inhibition of soluble C5a, due to its small molecular weight and its high turnover rate. Overall, there is strong interest in developing C5aR inhibitors, such as aptamers, peptides, and non-peptide small molecules being tested in pre-clinical and clinical trials.

[0008] Neutralizing polyclonal antiserum or monoclonal antibodies directed against the N-terminal extracellular region of human C5aR and being able to interfere with C5aR-C5a interaction has been described in the art (see e.g. Morgan et al., The Journal of Immunology, Vol 151, 377-388. No. 1, Jul. 1, 1993; Oppermann et al., The Journal of Immunology, Vol 151, 3785-3794, No. 7, Oct. 1, 1993),

[0009] However, these C5aR specific antibodies are not suited for the clinical development and therapeutic use in human, especially due to their animal origin (which makes them immunogenic in human patients), clonality, and/or lack of cross-reactivity to relevant animal species.

[0010] Therapeutic antibodies targeting C5aR has been considered for clinical development. However, the clinical development of the antagonistic C5aR specific antibody Neutrazumab, a humanized IgG4 mAb was stopped in Phase II clinical trials due to issues with immune cell depletion and immunogenicity (Daniluk S et al., Annals of the Rheumatic Diseases. 2014, 73: 684-685). Since C5aR appears constitutively expressed on a variety of cell types, it is important that an antagonistic antibody does not induce any depletion of the target cells.

[0011] To overcome the limitations of Neutrazumab, a second generation of a C5aR specific antibody has been generated, namely NNC0215-0384 (US2013/0295116 (NOVO NORDISK); clone 32F3A6GL). This antibody is a human IgG1 antibody derived from transgenic mice and is currently under clinical development as IPH5401 in the field of cancer (Olivier Demaria et al., Innate Pharma 2017. Poster #B184. CRI-CIMT-EATI-AACR Mainz). IPH5401 bears a silenced human IgG1 Fc region to eliminate the

ability of the antibody to induce effector function. This antibody is herein referred to as RefMAB#1.

SUMMARY OF THE INVENTION

[0012] The present disclosure provides novel antibodies and antibody fragments.

[0013] The antibodies and antibody fragments disclosed herein can specifically bind to human C5aR and preferably cross-react with C5aR from cynomolgus monkey. Accordingly, in some embodiments, the disclosed antibodies are specific for human C5aR and cynomolgus C5aR. In some other embodiments, the disclosed antibodies or antibody fragments bind to the N-terminal extracellular region of human and cynomolgus C5aR.

[0014] This is in contrast to the above referenced prior art antibody IPH5401, which binds to the second extracellular loop of human C5aR resulting in the lack of binding to cynomolgus monkey C5aR, a commonly used relevant toxicology species.

[0015] In addition, the inventors of the present invention surprisingly found that the presently claimed C5aR specific antibodies are not only significantly more potent in neutralizing pathophysiological C5a concentrations when compared to IPH5401 but also revealed an increased potency over time in inhibiting C5 mediated activation of neutrophils in vitro.

[0016] Accordingly, in some embodiments, the disclosed antibodies can efficiently inhibit C5a induced C5aR activity in vitro, most notably at pathophysiological C5a concentration. The disclosed antibodies or antibody fragments may also inhibit C5a induced leucocyte activation in vitro as determined by their ability to inhibit C5a induced upregulation of CD11b in granulocytes and/or monocytes. In some embodiments, the disclosed antibodies or antibody fragments inhibit human C5a induced CD11b expression in human granulocytes with an IC_{50} concentration of 42 nM in the presence of 150 nM human C5a in vitro. In some other embodiments, the disclosed antibodies may exhibit an increased potency to inhibit C5a induced upregulation of CD11b in granulocytes and/or monocytes after a prolonged period of incubation time. The disclosed antibodies may be also efficient in inhibiting C5a induced neutrophil migration.

[0017] In sum, the present disclosure provides novel antibodies, which are superior to the C5aR specific antibodies known from the art. In particular, the antibodies of the present disclosure are human antibodies with high affinity binding to human C5aR, which preferably cross-react with cynomolgus monkey C5aR and have favourable functional and safety properties never have been observed before. These features makes the antibodies of the present disclosure highly desirable for therapeutic use such as for preventing and/or treating inflammatory and autoimmune diseases as well as cancer.

[0018] The present disclosure provides isolated antibodies or antibody fragments that specifically bind to human C5aR having CDR regions according to Table 1 or Table 2 of the present specification. The present disclosure also provides isolated antibodies or antibody fragments specific for human C5aR having a variable heavy chain region (VH) and a variable light chain region (VL) comprising the amino acid sequences according to Table 1 or Table 2 of the present specification. The present disclosure also provides isolated antibodies or antibody fragments specific for C5aR having a heavy chain (HC) and a light chain (LC) comprising the amino acid sequences according to Table 1 or Table 2 of the present specification.

[0019] The isolated antibodies of the present disclosure do not substantially induce effector function in vitro. Such effector function may comprise ADCP, ADCC or CDC. Furthermore, the isolated antibody or antibody fragments of the present disclosure comprise one or more amino acid substitution selected from the group of: L234A, L235E, G237A, A330S and P331S, with numbering according to EU index. In particular, the isolated antibodies or antibody fragments of the present disclosure comprise a variant human IgG1 Fc region, which comprises the following amino acid substitutions: L234A, L235E, G237A, A330S and P331S with numbering according EU index.

[0020] The present disclosure also provides the isolated antibodies or antibody fragments of the present disclosure for use in medicine.

[0021] The present disclosure also provides methods for treating a subject suffering from a disease, such as an inflammatory or autoimmune disease or cancer, by administering to said subject an effective amount of the antibodies or antibody fragments of the present disclosure. Preferably, said subject is a human.

[0022] The present disclosure also provides pharmaceutical compositions comprising the isolated antibodies or antibody fragments of the present disclosure, and a pharmaceutically acceptable carrier.

[0023] The present disclosure also provides nucleic acid compositions encoding the isolated antibodies or antibody fragments of the present disclosure. The present disclosure also provides vector compositions comprising the nucleic acid compositions encoding the isolated antibodies or antibody fragments of the present disclosure. The present disclosure also provides host cells comprising the vector compositions or nucleic acids compositions encoding the isolated antibodies or antibody fragments of the present disclosure.

[0024] The present disclosure also provides methods for treating a subject suffering from a disease, such as an inflammatory disease, autoimmune disease or cancer by administering to said subject an effective amount of the isolated antibodies or antibody fragments of the present disclosure. Preferably, said subject is a human.

[0025] The present disclosure also provides pharmaceutical compositions comprising the isolated antibodies or antibody fragments of the present disclosure, and a pharmaceutically acceptable carrier.

[0026] There is utility in the claimed antibodies or antibody fragments. Furthermore, there is utility in the claimed method to identify such antibodies or antibody fragments.

[0027] Utilization of the claimed antibodies or antibody fragments is to alter the biological activity of human C5aR. In particular, the claimed antibodies or antibody fragments are for therapeutic use, such as the treatment of inflammatory or autoimmune disease or cancer

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] FIG. **1**: Cell binding of MAB#1, MAB#2, RefMAB#1 and negative isotype control MOR03207 to human and cynomolgus monkey C5aR determined via FACS. A Dose response binding to human C5aR overexpressed on Flp-In CHO cells. B Dose response binding to cynomolgus monkey C5aR overexpressed on Flp-In CHO cells. C Aver-

age dose response binding to purified human neutrophils obtained from whole blood of three different donors. D Average dose response binding to purified cynomolgus monkey neutrophils obtained from whole blood from three different monkeys.

[0029] FIG. **2**: Cell binding of MAB#1, MAB#2, RefMAB#1 and negative isotype control MOR03207 to human, cynomolgus and rodent C5aR as well as to the C5aR related GPCRs human C5L2, human C3aR, human FPR1 and human ChemR23 determined via FACS at an IgG concentration of 600 nM.

[0030] FIG. **3**: ELISA binding of MAB#1 to two natural variants of human C5aR as well as to mouse C5aR expressed on virus-like-particles (VLPs).

[0031] FIG. **4**: PathHunter®—β-arrestin assay from DiscoveRx. Neutralization of human C5a induced β-arrestin recruitment. A Log dose-response curves for increasing concentrations of recombinant human C5a in absence or presence of MAB#1 (50 nM), MAB#2 (50 nM) and RefMAB#1 (50 nM). B Percentage inhibition was calculated for three increasing concentrations of human C5a (1.2 nM, 11 nM and 100 nM, respectively) at a final IgG concentration of 50 nM.

[0032] FIG. **5**: Inhibition of human C5a induced CD11b upregulation in human granulocytes at regular and pathophysiological C5a concentrations. A+B Comparison of MAB#1, MAB#2 and RefMAB#1 in a CD11b whole blood assay. Log dose-inhibition curves are shown. Human granulocytes were gated as target cells. As quantitative read-out, the IgG concentration needed to reach 50% inhibition of CD11b upregulation was calculated (IC_{50} concentration). IC_{50} concentrations for each IgG are depicted below the x-axis. A Log dose-response curves for increasing concentrations of IgG and 15 nM human C5a. B Log dose-response curves for increasing concentrations of IgG and 150 nM human C5a.

[0033] FIG. **6**: Inhibition of human C5a induced CD11b upregulation in human granulocytes and monocytes determined over a prolonged period of time of incubation. Comparison of MAB#1 and RefMAB#1 in a CD11b whole blood assay after incubation of IgGs with target cells for either 20 minutes or 300 minutes. IgGs were added in serial dilutions and incubated for either 20 minutes or 300 minutes with subsequent stimulation with 15 nM human C5a. Either granulocytes (FIGS. **6**A and B) or monocytes (FIGS. **6**C and D) were gated as target cells. CD11b levels were determined. Log dose-inhibition curves are shown. Data are expressed as % inhibition of CD11b upregulation at 15 nM human C5a. Results for MAB#1 are shown in FIGS. **6**A and C and results for RefMAB#1 are provided in FIGS. **6**B and D.

[0034] FIG. **7**: Inhibition of human C5a induced human neutrophil migration. MAB#1 and negative control MOR03207 were each tested at two IgG concentration (100 nM and 600 nM, respectively) in the presence of 10 nM human C5a. Average values from three independent assay runs at 3 different time points (15 min., 25 min., 35 min.) are shown. Neutrophils were obtained from 3 different human donors. Percentage inhibition was calculated on the basis of neutrophil migration in the absence of antibody.

[0035] FIG. **8**: Promega ADCC and ADCP reporter bioassay. Comparison of MAB#1 and a monoclonal anti-C5aR control IgG bearing either a wild-type (non-silent) human IgG1 Fc region or a variant (silent) Fc region identical to the Fc region of MAB#1. In addition, isotype control antibody MOR03207 was included with either the variant or wild-type human IgG1 Fc region. Assays were performed according to the supplier's instructions using engineered Jurkat cells either expressing FcγRIIa_H to mimic the ADCP pathway or Jurkat cells expressing the FcγRIIIa, V158 high affinity variant to mimic the ADCC pathway and C5aR expressing CHO cells. A Results from the ADCP reporter bioassay at an IgG concentration of 10 μg/ml. B Results from the ADCC reporter bioassay at an IgG concentration of 10 μg/ml. Data are provided as average fluorescence signal over background.

[0036] FIG. **9**: Group mean pharmacokinetic profile of MAB#1 in Han Wistar rats following a single intravenous administration of 10 mg/kg IgG. Data are provided as mean values (IgG concentration over time)±standard deviation (S) (n=3).

[0037] FIG. **10**: Protein Panel Profiling (3P) results for MAB#1 and MAB#2. The numbers for each antibody represents the obtained binding signal for each antibody and tested protein compared to the binding of isotype negative control antibody MOR03207. Antibodies were tested at a concentration of 10 nM and 100 nM, respectively.

[0038] FIG. **11**: Cytokine release by monocyte-derived in vitro-matured M1 and M2 macrophages. IL-10 and IL-12 levels were determined by ELISA after treatment with MAB#1 and incubation with C5a overnight.

DETAILED DESCRIPTION OF THE INVENTION

[0039] The disclosure pertains to a number of human antibodies, which recognize human C5aR.

Definitions

[0040] The term "C5aR" refers to a protein known as C5a anaphylatoxin chemotactic receptor 1 or CD88.

Human C5aR (Uniprot: P2173011-350) (referred to herein as the "D/K variant") has the amino acid sequence of:

(SEQ ID NO: 1)

MDSFNYTTPDYGHYDDKDTLDLNTPVDKTSNTLRVPDILALVIFAVVFLVG

VLGNALVVWVTAFEAKRTINAIWFLNLAVADFLSCLALPILFTSIVQHHHW

PFGGAACSILPSLILLNMYASILLLATISADRFLLVFKPIWCQNFRGAGLA

WIACAVAWGLALLLTIPSFLYRVVREEYFPPKVLCGVDYSHDKRRERAVAI

VRLVLGFLWPLLTLTICYTFILLRTWSRRATRSTKTLKVVVAVVASFFIFW

LPYQVTGIMMSFLEPSSPTFLLLKKLDSLCVSFAYINCCINPIIYVVAGQG

FQGRLRKSLPSLLRNVLTEESVVRESKSFTRSTVDTMAQKTQAV

[0041] Two natural missense mutations of human C5aR are described ((http://www.uniprot.org/uniprot/P21730): Reference SNP (refSNP) Cluster Report: rs4467185 (MAF: 0.03) and Cluster Report: rs11880097 (MAF: 0.03). One mutation is located within the N-terminal extracellular region of human C5aR (Position 2 of SEQ ID NO: 1) resulting in a D to N substitution.

[0042] A human C5aR protein which comprises both natural missense mutations in its sequence (also referred to herein as the "N/N variant") has the amino acid sequence of:

(SEQ ID NO: 2)

MNSFNYTTPDYGHYDDKDTLDLNTPVDKTSNTLRVPDILALVIFAVVFLVG

VLGNALVVWVTAFEAKRTINAIWFLNLAVADFLSCLALPILFTSIVQHHHW

PFGGAACSILPSLILLNMYASILLLATISADRFLLVFKPIWCQNFRGAGLA

WIACAVAWGLALLLTIPSFLYRVVREEYFPPKVLCGVDYSHDKRRERAVAI

VRLVLGFLWPLLTLTICYTFILLRTWSRRATRSTKTLKVVVAVVASFFIFW

LPYQVTGIMMSFLEPSSPTFLLLNKLDSLCVSFAYINCCINPIIYVVAGQG

FQGRLRKSLPSLLRNVLTEESVVRESKSFTRSTVDTMAQKTQAV

Cynomolgus monkey (*Macaca fascicularis*) C5aR has the amino acid sequence of:

(SEQ ID NO: 3)

MDPFSSTTLDYEHYDGKNVLDSDTPVDKTSNTLRVPDILALVVFAVVFLVG

VLGNALVVWVTAFEVKRTINAIWFLNLAVADFLSCLALPILFTSIVQHHHW

PFGGTACRILPSLILLNMYASILLLATISADRFLLVFNPIWCQNFRGAGLA

WIACAVAWGLALLLTIPSFLYRAVRQEEYSPKVLCGVDYNNDTRRERAVAI

VRLVLGFLWPLLTLMICYTFLLLRTWSRRATRSTKTLKVVVAVVASFFIFW

LPYQVTGTMMSFLRPSSPTYLQLKKLDSLSISFAYINCCINPVIYVVAGQG

FQGRLRKSLPSLLRNVLTEESVVRESKSFTRSTVDTMTEKTQAV

Mouse (*Mus musculus*) C5aR has the amino acid sequence of

(SEQ ID NO: 4)

MDPIDNSSFEINYDHYGTMAPNIPADGIHLPKRQPGDVAALIIYSVVFLVG

VPGNALVVWVTAFEARRAVNAIWFLNLAVADLLSCLALPVLFTTVLNHNYV

VYFDATACIVLPSLILLNMYASILLLATISADRFLLVFKPIWCQKVRGTGL

AWMACGVAWVLALLLTIPSFVYREAYKDFYSEHTVCGINYGGGSFPKEKAV

AILRLMVGFVLPLLTLNICYTFLLLRTWSRKATRSTKTLKVVMAVVICFFI

FWLPYQVTGVMIAWLPPSSPTLKRVEKLNSLCVSLAYINCCVNPIIYVMAG

QGFHGRLLRSLPSIIRNALSEDSVGRDSKTFTPSTTDTSTRKSQAV

Rat (*Rattus norvegicus*) C5aR has the amino acid sequence of

(SEQ ID NO: 5)

MDPISNDSSEITYDYSDGTPNPDMPADGVYIPKMEPGDIAALIIYLAVFLV

GVTGNALVVWVTAFEAKRTVNAIWFLNLAVADLLSCLALPILFTSIVKHNH

WPFGDQACIVLPSLILLNMYSSILLLATISADRFLLVFKPIWCQKFRRPGL

AWMACGVTWVLALLLTIPSFVFRRIHKDPYSDSILCNIDYSKGPFFIEKAI

AILRLMVGFVLPLLTLNICYTFLLIRTWSRKATRSTKTLKVVMAVVTCFFV

FWLPYQVTGVILAWLPRSSSTFQSVERLNSLCVSLAYINCCVNPIIYVMAG

QGFHGRLRRSLPSIIRNVLSEDSLGRDSKSFTRSTMDTSTQKSQAV

[0043] The term "C5a" refers to a protein known as Human Complement Component C5a Human C5a (Uniprot: P01031|678-751) has the amino acid sequence of:

(SEQ ID NO: 6)

TLQKKIEEIAAKYKHSVVKKCCYDGACVNNDETCEQRAARISLGPRCIKAF

TECCVVASQLRANISHKDMQLGR

[0044] The term "C5L2" refers to a protein known as C5a anaphylatoxin chemotactic receptor 2. Human C5L2 has the amino acid sequence of:

(SEQ ID NO: 7)

MGNDSVSYEYGDYSDLSDRPVDCLDGACLAIDPLRVAPLPLYAAIFLVGVP

GNAMVAWVAGKVARRRVGATWLLHLAVADLLCCLSLPILAVPIARGGHWPY

GAVGCRALPSIILLTMYASVLLLAALSADLCFLALGPAWWSTVQRACGVQV

ACGAAWTLALLLTVPSAIYRRLHQEHFPARLQCVVDYGGSSSTENAVTAIR

FLFGFLGPLVAVASCHSALLCWAARRCRPLGTAIVVGFFVCWAPYHLLGLV

LTVAAPNSALLARALRAEPLIVGLALAHSCLNPMLFLYFGRAQLRRSLPAA

CHWALRESQGQDESVDSKKSTSHDLVSEMEV.

[0045] The term "C3aR" refers to a protein known as C3a anaphylatoxin chemotactic receptor. Human C3aR has the amino acid sequence of:

(SEQ ID NO: 8)

MASFSAETNSTDLLSQPWNEPPVILSMVILSLTFLLGLPGNGLVLWVAGLK

MQRTVNTIWFLHLTLADLLCCLSLPFSLAHLALQGQWPYGRFLCKLIPSII

VLNMFASVFLLTAISLDRCLVVFKPIWCQNHRNVGMACSICGCIWVVACVM

CIPVFVYREIFTTDNHNRCGYKFGLSSSLDYPDFYGDPLENRSLENIVQPP

GEMNDRLDPSSFQTNDHPWTVPTVFQPQTFQRPSADSLPRGSARLTSQNLY

SNVFKPADVVSPKIPSGFPIEDHETSPLDNSDAFLSTHLKLFPSASSNSFY

ESELPQGFQDYYNLGQFTDDDQVPTPLVAITITRLVVGFLLPSVIMIACYS

FIVFRMQRGRFAKSQSKTFRVAVVVVAVFLVCWTPYHIFGVLSLLTDPETP

LGKTLMSWDHVCIALASANSCFNPFLYALLGKDFRKKARQSIQGILEAAFS

EELTRSTHCPSNNVISERNSTTV

[0046] The term "FPR1" refers to a protein known as fMet-Leu-Phe receptor Human FPR1 has the amino acid sequence of:

(SEQ ID NO: 9)

METNSSLPTNISGGTPAVSAGYLFLDIITYLVFAVTFVLGVLGNGLVIWVA

GFRMTHTVTTISYLNLAVADFCFTSTLPFFMVRKAMGGHWPFGWFLCKFLF

TIVDINLFGSVFLIALIALDRCVCVLHPVWTQNHRTVSLAKKVIIGPWVMA

LLLTLPVIIRVTTVPGKTGTVACTFNFSPWTNDPKERINVAVAMLTVRGII

RFIIGFSAPMSIVAVSYGLIATKIHKQGLIKSSPPLRVLSFVAAAFFLCWS

PYQVVALIATVRIRELLQGMYKEIGIAVDVTSALAFFNSCLNPMLYVFMGQ

DFRERLIHALPASLERALTEDSTQTSDTATNSTLPSAEVALQAK

[0047] The term "ChemR23" refers to a protein known as Chemokine-like receptor 1. Human ChemR23 has the amino acid sequence of:

(SEQ ID NO: 10)
MRMEDEDYNTSISYGDEYPDYLDSIVVLEDLSPLEARVTRIFLVVVYSIVC

FLGILGNGLVIIIATFKMKKTVNMVWFLNLAVADFLFNVFLPIHITYAAMD

YHWVFGTAMCKISNFLLIHNMFTSVFLLTIISSDRCISVLLPVWSQNHRSV

RLAYMACMVIWVLAFFLSSPSLVFRDTANLHGKISCFNNFSLSTPGSSSWP

THSQMDPVGYSRHMVVTVTRFLCGFLVPVLIITACYLTIVCKLHRNRLAKT

KKPFKIIVTIIITFFLCWCPYHTLNLLELHHTAMPGSVFSLGLPLATALAI

ANSCMNPILYVFMGQDFKKFKVALFSRLVNALSEDTGHSSYPSHRSFTKMS

SMNERTSMNERETGML

[0048] The term "antibody" as used herein refers to a protein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, which interacts with an antigen. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains, CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FR's arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The variable regions of the heavy and light chains contain a binding domain that interacts with an antigen. The constant regions of the antibodies may mediate the binding of the immunoglobulin to host tissues or factors, including various cells of the immune system (e.g., effector cells) and the first component (Clq) of the classical complement system. The term "antibody" includes for example, monoclonal antibodies, human antibodies, humanized antibodies, camelised antibodies and chimeric antibodies. The antibodies can be of any isotype (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass. Both the light and heavy chains are divided into regions of structural and functional homology.

[0049] The phrase "antibody fragment", as used herein, refers to one or more portions of an antibody that retain the ability to specifically interact with (e.g., by binding, steric hindrance, stabilizing spatial distribution) an antigen. Examples of binding fragments include, but are not limited to, a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; a F(ab)2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the VH and CH1 domains; a Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a dAb fragment (Ward et al., (1989) Nature 341:544-546), which consists of a VH domain; and an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be 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 (known as single chain Fv (scFv); see e.g., Bird et al., (1988) Science 242:423-426; and Huston et al., (1988) Proc. Natl. Acad. Sci. 85:5879-5883). Such single chain antibodies are also intended to be encompassed within the term "antibody fragment". These antibody fragments are obtained using conventional techniques known to those of skill in the art, and the fragments are screened for utility in the same manner as are intact antibodies. Antibody fragments can also be incorporated into single domain antibodies, maxibodies, minibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bis-scFv (see, e.g., Hollinger and Hudson, (2005) Nature Biotechnology 23:1126-1136). Antibody fragments can be grafted into scaffolds based on polypeptides such as Fibronectin type III (Fn3) (see U.S. Pat. No. 6,703,199, which describes fibronectin polypeptide monobodies). Antibody fragments can be incorporated into single chain molecules comprising a pair of tandem Fv segments (VH-CH1-VH-CH1) which, together with complementary light chain polypeptides, form a pair of antigen-binding sites (Zapata et al., (1995) Protein Eng. 8:1057-1062; and U.S. Pat. No. 5,641,870).

[0050] A "human antibody" or "human antibody fragment", as used herein, is an antibody and antibody fragment having variable regions in which both the framework and CDR regions are from sequences of human origin. Human antibodies can also be isolated from synthetic libraries or from transgenic mice (e.g. Xenomouse) provided the respective system yield in antibodies having variable regions in which both the framework and CDR regions are derived from sequences of human origin. Furthermore, if the antibody contains a constant region, the constant region also is derived from such sequences. Human origin includes, e.g., human germline sequences, or mutated versions of human germline sequences or antibody containing consensus framework sequences derived from human framework sequences analysis, for example, as described in Knappik et al., (2000) J Mol Biol 296:57-86).

[0051] The structures and locations of immunoglobulin variable domains, e.g., CDRs, may be defined using well known numbering schemes, e.g., the Kabat numbering scheme, the Chothia numbering scheme, or a combination of Kabat and Chothia (see, e.g. Sequences of Proteins of Immunological Interest, U.S. Department of Health and Human Services (1991), eds. Kabat et al.; Lazikani et al., (1997) J. Mol. Bio. 273:927-948); Kabat et al., (1991) Sequences of Proteins of Immunological Interest, 5th edit., NIH Publication no. 91-3242 U.S. Department of Health and Human Services; Chothia et al., (1987) J. Mol. Biol. 196: 901-917; Chothia et al., (1989) Nature 342:877-883; and Al-Lazikani et al., (1997) J. Mol. Biol. 273:927-948.

[0052] A "humanized antibody" or "humanized antibody fragment" is defined herein as an antibody molecule, which has constant antibody regions derived from sequences of human origin and the variable antibody regions or parts thereof or only the CDRs are derived from another species. For example, a humanized antibody can be CDR-grafted, wherein the CDRs of the variable domain are from a non-human origin, while one or more frameworks of the variable domain are of human origin and the constant domain (if any) is of human origin.

[0053] The term "chimeric antibody" or "chimeric antibody fragment" is defined herein as an antibody molecule, which has constant antibody regions derived from, or corresponding to, sequences found in one species and variable antibody regions derived from another species. Preferably,

the constant antibody regions are derived from, or corresponding to, sequences found in humans, and the variable antibody regions (e.g. VH, VL, CDR or FR regions) are derived from sequences found in a non-human animal, e.g. a mouse, rat, rabbit or hamster.

[0054] The term "isolated antibody" refers to an antibody or antibody fragment that is substantially free of other antibodies or antibody fragments having different antigenic specificities. Moreover, an isolated antibody or antibody fragment may be substantially free of other cellular material and/or chemicals. Thus, in some aspects, antibodies provided are isolated antibodies, which have been separated from antibodies with a different specificity. An isolated antibody may be a monoclonal antibody. An isolated antibody may be a recombinant monoclonal antibody. An isolated antibody that specifically binds to an epitope, isoform or variant of a target may, however, have cross-reactivity to other related antigens, e.g., from other species (e.g., species homologs).

[0055] The term "recombinant antibody", as used herein, includes all antibodies that are prepared, expressed, created or segregated by means not existing in nature. For example, antibodies isolated from a host cell transformed to express the antibody, antibodies selected and isolated from a recombinant, combinatorial human antibody library, and antibodies prepared, expressed, created or isolated by any other means that involve splicing of all or a portion of a human immunoglobulin gene, sequences to other DNA sequences or antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom. Preferably, such recombinant antibodies have variable regions in which the framework and CDR regions are derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies can be subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire in vivo. A recombinant antibody may be a monoclonal antibody. In an embodiment, the antibodies and antibody fragment disclosed herein are isolated from the HuCAL library (Rothe et al, J. Mol. Biol. (2008) 376, 1182-1200).

[0056] As used herein, an antibody "binds specifically to", "specifically binds to", is "specific to/for" or "specifically recognizes" an antigen, such as human C5aR, if such antibody is able to discriminate between such antigen and one or more reference antigen(s), since binding specificity is not an absolute, but a relative property. For example, a standard ELISA assay can be carried out. The scoring may be carried out by standard color development (e.g. secondary antibody with horseradish peroxide and tetramethyl benzidine with hydrogen peroxide). The reaction in certain wells is scored by the optical density, for example, at 450 nm. Typical background (=negative reaction) may be 0.1 OD; typical positive reaction may be 1 OD. This means the difference positive/negative can be more than 10-fold. Typically, determination of binding specificity is performed by using not a single reference antigen, but a set of about three to five unrelated antigens, such as milk powder, BSA, transferrin or the like.

[0057] As used herein, the term "affinity" refers to the strength of interaction between the polypeptide and its target at a single site. Within each site, the binding region of the polypeptide interacts through weak non-covalent forces with its target at numerous sites; the more interactions, the stronger the affinity.

[0058] The term "K_D", as used herein, refers to the dissociation constant, which is obtained from the ratio of k_{off} to K_{on} (i.e. k_{off}/k_{on}) and is expressed as a molar concentration (M). K_D values for antigen binding moieties like e.g. monoclonal antibodies can be determined using methods well established in the art. Methods for determining the K_D of an antigen binding moiety like e.g. a monoclonal antibody are SET (solution equilibrium titration) or surface plasmon resonance using a biosensor system such as a Biacore® system. In the present disclosure an antibody specific for C5aR typically has a dissociation rate constant (K_D) (k_{off}/k_{on}) of less than 5×10^{-2}M, less than 10^{-2}M, less than 5×10^{-3}M, less than 10^{-3}M, less than 5×10^{-4}M, less than 10^{-4}M, less than 5×10^{-5}M, less than 10^{-5}M, less than 5×10^{-6}M, less than 10^{-6}M, less than 5×10^{-7}M, less than 10^{-7}M, less than 5×10^{-6}M, less than 10^{-8}M, less than 5×10^{-9}M, less than 10^{-9}M, less than 5×10^{-10}M, less than 10^{-10}M, less than 5×10^{-11}M, less than 10^{-11}M, less than 5×10^{-12}M, less than 10^{-12}M, less than 5×10^{-13}M, less than 10^{-13}M, less than 5×10^{-14}M, less than 10^{-14}M, less than 5×10^{-15}M, or less than 10^{-15}M or lower.

[0059] The term "epitope" includes any proteinacious region which is specifically recognized by an antibody or antibody fragment thereof or otherwise interacts with a molecule. Generally, epitopes are of chemically active surface groupings of molecules such as amino acids or carbohydrate or sugar side chains and generally may have specific three-dimensional structural characteristics, as well as specific charge characteristics. As will be appreciated by one of skill in the art, practically anything to which an antibody can specifically bind could be an epitope.

[0060] "Compositions" of the present disclosure may be used for therapeutic or prophylactic applications. The present disclosure, therefore, includes a pharmaceutical composition containing an antibody or antibody fragment as disclosed herein and a pharmaceutically acceptable carrier or excipient therefor. In a related aspect, the present disclosure provides a method for treating cancer. Such method contains the steps of administering to a subject in need thereof an effective amount of the pharmaceutical composition that contains an antibody or antibody fragment as described herein.

[0061] The present disclosure provides therapeutic methods comprising the administration of a therapeutically effective amount of an antibody or antibody fragment as disclosed herein to a subject in need of such treatment. A "therapeutically effective amount" or "effective amount", as used herein, refers to the amount of a C5aR antibody necessary to elicit the desired biological response. In accordance with the subject disclosure, the therapeutic effective amount is the amount of a C5aR antibody necessary to treat and/or prevent a disease.

[0062] "Administered" or "administration" includes but is not limited to delivery of a drug by an injectable form, such as, for example, an intravenous, intramuscular, intradermal or subcutaneous route or mucosal route, for example, as a

nasal spray or aerosol for inhalation or as an ingestible solution, capsule or tablet. Preferably, the administration is by an injectable form.

[0063] As used herein, "treatment", "treat" or "treating" and the like refers to clinical intervention in an attempt to alter the natural course of a disease in the subject being treated, and can be performed either for prophylaxis or during the course of clinical pathology. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of disease, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease, preventing metastasis, decreasing the rate of disease progression, amelioration or palliation of the disease state, and remission or improved prognosis. In some embodiments, antibodies or antibody fragments according to the preset disclosure are used to delay development of a disease or to slow the progression of a disease.

[0064] The term "effector function" refers to those biological activities attributable to the Fc region of an antibody, which vary with the antibody isotype. Non-limiting examples of antibody effector functions include C1q binding and complement dependent cytotoxicity (CDC); Fc receptor binding and antibody-dependent cell-mediated cytotoxicity (ADCC) and/or antibody-dependent cellular phagocytosis (ADCP); down regulation of cell surface receptors (e.g. B cell receptor); and B cell activation.

[0065] "Antibody-dependent cell-mediated cytotoxicity" or "ADCC" refers to a form of cytotoxicity in which antibodies bound onto Fc receptors (FcRs) present on certain cytotoxic cells (e.g. NK cells, neutrophils, and macrophages) enable these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. The primary cells for mediating ADCC, NK cells, express FcγRIII only, whereas monocytes express FcγRI, FcγRII, and FcγRIII.

[0066] "Complement-dependent cytotoxicity" or "CDC" refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies (of the appropriate subclass) of the present disclosure, which are bound to their cognate antigen.

[0067] "Antibody-dependent cellular phagocytosis" or "ADCP" refers to a mechanism of elimination of antibody-coated target cells by internalization by phagocytic cells, such as macrophages or dendritic cells.

[0068] 'Preventing' or 'prevention' refers to a reduction in risk of acquiring or developing a disease (i.e. causing at least one of the clinical symptoms of the disease not to develop in a subject that may be exposed to a disease-causing agent, or predisposed to the disease in advance of disease onset). "Prevention" also refers to methods which aim to prevent the onset of a disease or its symptoms or which delay the onset of a disease or its symptoms.

[0069] "Subject" or "species" or as used in this context refers to any mammal, including rodents, such as mouse or rat, and primates, such as cynomolgus monkey (*Macaca fascicularis*), rhesus monkey (*Macaca mulatta*) or humans (*Homo sapiens*). Preferably, the subject is a primate, most preferably a human.

[0070] Throughout this specification, unless the context requires otherwise, the words "comprise", "have" and "include" and their respective variations such as "comprises", "comprising", "has", "having", "includes" and "including" will be understood to imply the inclusion of a stated element or integer or group of elements or integers but not the exclusion of any other element or integer or group of elements or integers.

[0071] The terms "engineered" or "modified" as used herein includes manipulation of nucleic acids or polypeptides by synthetic means (e.g. by recombinant techniques, in vitro peptide synthesis, by enzymatic or chemical coupling of peptides or some combination of these techniques). Preferably, the antibodies or antibody fragments according to the present disclosure are engineered or modified to improve one or more properties, such as antigen binding, stability, half-life, effector function, immunogenicity, safety and the like.

[0072] "Variant" as used herein refers to a polypeptide that differs from a reference polypeptide by one or more modifications for example amino acid substitutions, insertions or deletions.

[0073] The term "amino acid mutation" as used herein is meant to encompass amino acid substitutions, deletions, insertions, and modifications. Any combination of substitution, deletion, insertion, and modification can be made as long as the final construct possesses the desired characteristics, e.g., reduced binding to an Fc receptor. Amino acid sequence deletions and insertions include N- and/or C-terminal deletions and insertions of amino acid residues. Particular amino acid mutations are amino acid substitutions. Amino acid substitutions include replacement by non-naturally occurring amino acids or by naturally occurring amino acid derivatives of the twenty standard amino acids. Amino acid mutations can be generated using genetic or chemical methods well known in the art. Genetic methods may include site-directed mutagenesis, PCR, gene synthesis and the like. It is contemplated that methods of altering the side chain group of an amino acid residue by methods other than genetic engineering, such as chemical modification, may also be useful. Various designations may be used herein to indicate the same amino acid mutation. For example, a substitution from glyince at position 327 of the Fc region to alanine can be indicated as 237A, G337, G337A, or Gly329Ala.

[0074] The term "EC_{50}" as used herein, refers to the concentration of an antibody or antibody fragment or ligand, which induces a response in an assay half way between the baseline and maximum. It therefore represents the antibody or ligand concentration at which 50% of the maximal effect is observed

[0075] The term "IC_{50}" as used herein, refers to the concentration of an antibody or antibody fragment that inhibits a response in an assay half way between the maximal response and the baseline. It represents the antibody concentration that reduces a given response by 50%.

[0076] The terms "inhibition" or "inhibit" or "reduction" or "reduce" or "neutralization" or "neutralize" refer to a decrease or cessation of any phenotypic characteristic (such as binding or a biological activity or function) or to the decrease or cessation in the incidence, degree, or likelihood of that characteristic. The "inhibition", "reduction" or "neutralization" needs not to be complete as long as it is detectable using an appropriate assay. In some embodiments, by "reduce" or "inhibit" or "neutralize" is meant the ability to cause a decrease of 20% or greater. In another embodiment, by "reduce" or "inhibit" or "neutralize" is meant the ability to cause a decrease of 50% or greater. In

yet another embodiment, by "reduce" or "inhibit" or "neutralize" is meant the ability to cause an overall decrease of 75%, 85%, 90%, 95%, or greater.

[0077] The term "antagonistic" antibody as used herein refers to an antibody or antibody fragment that interacts with an antigen and partially or fully inhibits or neutralizes a biological activity or function or any other phenotypic characteristic of a target antigen.

[0078] A "wild-type" protein is a version or variant of the protein as it is found in nature. An amino acid sequence of a wildtype protein, e.g., a Fc region of an human IgG1 antibody, is the amino acid sequence of the protein as it occurs in nature. Due to allotypic differences, there can be more than one amino acid sequence for a wildtype protein. For example, there are several allotypes of naturally occurring human IGg1 heavy chain constant regions (see, e.g., Jeffries et al. (2009) mAbs 1:1).

[0079] The "Fc region" is used to define the C-terminal region of an immunoglobulin heavy chain. The Fc region of an immunoglobulin generally comprises two constant domains, a CH2 domain and a CH3 domain. Although the boundaries of the Fc region of an IgG heavy chain might vary slightly, the human IgG heavy chain Fc region is usually defined to extend from Cys226, or from Pro230, to the C-terminus of the heavy chain. However, the C-terminal lysine (Lys447) of the Fc region may or may not be present. Unless otherwise specified herein, numbering of amino acid residues in the Fc region is according to the EU numbering system, also called the EU index, as described in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md., 1991.

Embodiments

[0080] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises

[0081] a) the HCDR1 region comprising the amino acid sequence of SEQ ID NO: 27, the HCDR2 region comprising the amino acid sequence of SEQ ID NO: 28, the HCDR3 region comprising the amino acid sequence of SEQ ID NO: 29, the LCDR1 region comprising the amino acid sequence of SEQ ID NO: 32, the LCDR2 region comprising the amino acid sequence of SEQ ID NO: 33 and the LCDR3 region comprising the amino acid sequence of SEQ ID NO: 34, or

[0082] b) the HCDR1 region comprising the amino acid sequence of SEQ ID NO: 27, the HCDR2 region comprising the amino acid sequence of SEQ ID NO: 39, the HCDR3 region comprising the amino acid sequence of SEQ ID NO: 40, the LCDR1 region comprising the amino acid sequence of SEQ ID NO: 32, the LCDR2 region comprising the amino acid sequence of SEQ ID NO: 33 and the LCDR3 region comprising the amino acid sequence of SEQ ID NO: 34.

[0083] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises

[0084] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0085] b) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0086] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises

[0087] a) the HCDR1 region comprising the amino acid sequence of SEQ ID NO: 30, the HCDR2 region comprising the amino acid sequence of SEQ ID NO: 31, the HCDR3 region comprising the amino acid sequence of SEQ ID NO: 29, the LCDR1 region comprising the amino acid sequence of SEQ ID NO: 32, the LCDR2 region comprising the amino acid sequence of SEQ ID NO: 33 and the LCDR3 region comprising the amino acid sequence of SEQ ID NO: 34, or

[0088] b) the HCDR1 region comprising the amino acid sequence of SEQ ID NO: 30, the HCDR2 region comprising the amino acid sequence of SEQ ID NO: 41, the HCDR3 region comprising the amino acid sequence of SEQ ID NO: 40, the LCDR1 region comprising the amino acid sequence of SEQ ID NO: 32, the LCDR2 region comprising the amino acid sequence of SEQ ID NO: 33 and the LCDR3 region comprising the amino acid sequence of SEQ ID NO: 34.

[0089] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises

[0090] a) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0091] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0092] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises

[0093] a) the HCDR1 region comprising the amino acid sequence of SEQ ID NO: 27, the HCDR2 region comprising the amino acid sequence of SEQ ID NO: 28, the HCDR3 region comprising the amino acid sequence of SEQ ID NO: 29, the LCDR1 region comprising the amino acid sequence of SEQ ID NO: 32, the LCDR2 region comprising the amino acid sequence of SEQ ID NO: 33 and the LCDR3 region comprising the amino acid sequence of SEQ ID NO: 34, or

[0094] b) the HCDR1 region comprising the amino acid sequence of SEQ ID NO: 30, the HCDR2 region comprising the amino acid sequence of SEQ ID NO: 31, the HCDR3 region comprising the amino acid

sequence of SEQ ID NO: 29, the LCDR1 region comprising the amino acid sequence of SEQ ID NO: 32, the LCDR2 region comprising the amino acid sequence of SEQ ID NO: 33 and the LCDR3 region comprising the amino acid sequence of SEQ ID NO: 34, or

[0095] c) the HCDR1 region comprising the amino acid sequence of SEQ ID NO: 27, the HCDR2 region comprising the amino acid sequence of SEQ ID NO: 39, the HCDR3 region comprising the amino acid sequence of SEQ ID NO: 40, the LCDR1 region comprising the amino acid sequence of SEQ ID NO: 32, the LCDR2 region comprising the amino acid sequence of SEQ ID NO: 33 and the LCDR3 region comprising the amino acid sequence of SEQ ID NO: 34, or

[0096] d) the HCDR1 region comprising the amino acid sequence of SEQ ID NO: 30, the HCDR2 region comprising the amino acid sequence of SEQ ID NO: 41, the HCDR3 region comprising the amino acid sequence of SEQ ID NO: 40, the LCDR1 region comprising the amino acid sequence of SEQ ID NO: 32, the LCDR2 region comprising the amino acid sequence of SEQ ID NO: 33 and the LCDR3 region comprising the amino acid sequence of SEQ ID NO: 34.

[0097] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises

[0098] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0099] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0100] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0101] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0102] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0103] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0104] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0105] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0106] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR comprising 6 CDRs defined by Kabat of any one of the antibodies disclosed in Table 1 or Table 2.

[0107] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR comprising 6 CDRs defined by Chothia of any one of the antibodies disclosed in Table 1 or Table 2.

[0108] In an embodiment of the present disclosure, the isolated antibody or antibody fragment is a monoclonal antibody or antibody fragment. In an embodiment of the present disclosure, the isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment. In another embodiment of the present disclosure, the isolated antibody or antibody fragment is recombinant antibody or antibody fragment. In an embodiment of the present disclosure, the isolated antibody or antibody fragment is of the IgG isotype. In an embodiment of the present disclosure, the isolated antibody or antibody fragment is of the IgG1 class. In another embodiment of the present disclosure, the isolated antibody or antibody fragment does not substantially induce effector function in vitro.

[0109] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises

[0110] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34 and further comprises the VH of SEQ ID NO: 35 or the VL of SEQ ID NO: 36, or

[0111] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34 and further comprises the VH of SEQ ID NO: 35 or the VL of SEQ ID NO: 36, or

[0112] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the

LCDR3 region of SEQ ID NO: 34 and further comprises the VH of SEQ ID NO: 42 or the VL of SEQ ID NO: 43, or

[0113] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34 and further comprises the VH of SEQ ID NO: 42 or the VL of SEQ ID NO: 43.

[0114] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises

[0115] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0116] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43.

[0117] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36.

[0118] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43.

[0119] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38.

[0120] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45.

[0121] In an embodiment, the present disclosure refers to an isolated_antibody or antibody fragment specific for human C5aR comprising the variable heavy chain (VH) and the variable light chain (VL) of any one of the antibodies disclosed in Table 1 or Table 2.

[0122] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR comprising the heavy chain (HC) and the light chain (LC) of any one of the antibodies disclosed in Table 1 or Table 2.

[0123] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34 and further comprises the VH of SEQ ID NO: 35 or the VL of SEQ ID NO: 36

[0124] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34 and further comprises the VH of SEQ ID NO: 42 or the VL of SEQ ID NO: 43

[0125] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34 and further comprises the VH of SEQ ID NO: 35 or the VL of SEQ ID NO: 36

[0126] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34 and further comprises the VH of SEQ ID NO: 42 or the VL of SEQ ID NO: 43.

[0127] In an embodiment of the present disclosure, the isolated antibody or antibody fragment is a monoclonal antibody or antibody fragment. In an embodiment of the present disclosure, the isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment. In another embodiment of the present disclosure, the isolated antibody or antibody fragment is recombinant antibody or antibody fragment.

[0128] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises

[0129] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0130] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43 or

[0131] a VH and a VL that has at least at 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 or SEQ ID NO: 42 and to the VL of SEQ ID NO: 36 or SEQ ID NO: 43.

[0132] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36, or a VH and a VL that has at least at 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 and to the VL of SEQ ID NO: 36.

[0133] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43, or a VH and a VL that has at least at 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 42 and to the VL of SEQ ID NO: 43.

[0134] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises

[0135] a) the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or

[0136] b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or

[0137] a HC and a LC that has at least at 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 37 or SEQ ID NO: 44 and to the LC of SEQ ID NO:38 or SEQ ID NO: 45.

[0138] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or a HC and a LC that has at least at 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 37 and to the LC of SEQ ID NO: 38.

[0139] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or a HC and a LC that has at least at 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 44 and to the LC of SEQ ID NO: 45.

[0140] In an embodiment of the present disclosure, the isolated antibody or antibody fragment is a monoclonal antibody or antibody fragment. In an embodiment of the present disclosure, the isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment. In another embodiment of the present disclosure, the isolated antibody or antibody fragment is recombinant antibody or antibody fragment. In an embodiment, said isolated antibody or an antibody fragment is a human or humanized antibody or antibody fragment. In one embodiment, said isolated antibody or an antibody fragment is a human antibody or antibody fragment.

[0141] In an embodiment, the isolated antibody or antibody fragment specific for human C5aR of the present disclosure is a recombinant or synthetic antibody or antibody fragment. In a further embodiment, the isolated antibody or antibody fragment specific for C5aR according to the present disclosure is an isolated recombinant monoclonal antibody or antibody fragment. In a further embodiment, the isolated antibody or antibody fragment specific for C5aR according to the present disclosure is an isolated recombinant monoclonal human antibody or antibody fragment.

[0142] In an embodiment, the isolated antibody or antibody fragment specific for C5aR according to the present disclosure is of the IgG isotype. In another embodiment, said isolated antibody or antibody fragment is of the IgG1 class. In another embodiment, said isolated antibody or antibody fragment is of the human IgG1 class.

Nucleic Acids

[0143] In an embodiment, the present disclosure refers to a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or antibody fragment specific for human C5aR, wherein said isolated said antibody or antibody fragment comprise

[0144] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0145] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0146] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0147] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0148] In another embodiment, the present disclosure refers to a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding the heavy chain sequence and light chain sequence of an isolated antibody or antibody fragment specific for human C5aR, wherein the nucleic acid sequence or a plurality of nucleic acid sequences comprises

[0149] a) the HCDR1 region of SEQ ID NO: 46, the HCDR2 region of SEQ ID NO: 47, the HCDR3 region of SEQ ID NO: 48, the LCDR1 region of SEQ ID NO: 51, the LCDR2 region of SEQ ID NO: 52 and the LCDR3 region of SEQ ID NO: 53, or

[0150] b) the HCDR1 region of SEQ ID NO: 49, the HCDR2 region of SEQ ID NO: 50, the HCDR3 region of SEQ ID NO: 48, the LCDR1 region of SEQ ID NO: 51, the LCDR2 region of SEQ ID NO: 52 and the LCDR3 region of SEQ ID NO: 53, or

[0151] c) the HCDR1 region of SEQ ID NO: 58, the HCDR2 region of SEQ ID NO: 59, the HCDR3 region of SEQ ID NO: 60, the LCDR1 region of SEQ ID NO: 63, the LCDR2 region of SEQ ID NO: 64 and the LCDR3 region of SEQ ID NO: 65, or

[0152] d) the HCDR1 region of SEQ ID NO: 61, the HCDR2 region of SEQ ID NO: 62, the HCDR3 region of SEQ ID NO: 60, the LCDR1 region of SEQ ID NO: 63, the LCDR2 region of SEQ ID NO: 64 and the LCDR3 region of SEQ ID NO: 65.

[0153] In another embodiment, the present disclosure refers to a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding the heavy chain sequence and light chain sequence of an isolated antibody or antibody fragment specific for human C5aR, wherein the nucleic acid sequence or a plurality of nucleic acid sequences comprise

[0154] a) the HCDR1 region of SEQ ID NO: 70, the HCDR2 region of SEQ ID NO: 71, the HCDR3 region of SEQ ID NO: 72, the LCDR1 region of SEQ ID NO: 75, the LCDR2 region of SEQ ID NO: 76 and the LCDR3 region of SEQ ID NO: 77, or

[0155] b) the HCDR1 region of SEQ ID NO: 73, the HCDR2 region of SEQ ID NO: 74, the HCDR3 region of SEQ ID NO: 72, the LCDR1 region of SEQ ID NO: 75, the LCDR2 region of SEQ ID NO: 76 and the LCDR3 region of SEQ ID NO: 77, or

[0156] c) the HCDR1 region of SEQ ID NO: 82, the HCDR2 region of SEQ ID NO: 83, the HCDR3 region of SEQ ID NO: 84, the LCDR1 region of SEQ ID NO: 87, the LCDR2 region of SEQ ID NO: 88 and the LCDR3 region of SEQ ID NO: 89, or

[0157] d) the HCDR1 region of SEQ ID NO: 85, the HCDR2 region of SEQ ID NO: 86, the HCDR3 region of SEQ ID NO: 84, the LCDR1 region of SEQ ID NO: 87, the LCDR2 region of SEQ ID NO: 88 and the LCDR3 region of SEQ ID NO: 89.

[0158] In an embodiment, the present disclosure refers to a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or antibody fragment specific for human C5aR, wherein said nucleic acid sequence or plurality of nucleic acid sequences comprise the VH of SEQ ID NO: 54 and the VL of SEQ ID NO: 55, or a VH and a VL that has at least 60%, at least 70%, at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 54 and/or the VL of SEQ ID NO: 55.

[0159] In an embodiment, the present disclosure refers to a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or antibody fragment specific for human C5aR, wherein said nucleic acid sequence or plurality of nucleic acid sequences comprise the VH of SEQ ID NO: 66 and the VL of SEQ ID NO: 67, or a VH and a VL that has at least 60%, at least 70%, at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 66 and/or the VL of SEQ ID NO: 67.

[0160] In an embodiment, the present disclosure refers to a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or antibody fragment specific for human C5aR, wherein said nucleic acid sequence or plurality of nucleic acid sequences comprise the VH of SEQ ID NO: 78 and the VL of SEQ ID NO: 79, or a VH and a VL that has at least 60%, at least 70%, at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 78 and/or the VL of SEQ ID NO: 79.

[0161] In an embodiment, the present disclosure refers to a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or antibody fragment specific for human C5aR, wherein said nucleic acid sequence or plurality of nucleic acid sequences comprise the VH of SEQ ID NO: 90 and the VL of SEQ ID NO: 91, or a VH and a VL that has at least 60%, at least 70%, at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 90 and/or the VL of SEQ ID NO: 91.

[0162] In an embodiment, the present disclosure refers to a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or antibody fragment specific for human C5aR, wherein said nucleic acid sequence or plurality of nucleic acid sequences comprise the HC of SEQ ID NO: 56 and the LC of SEQ ID NO: 57, or a HC and a LC that has at least 60%, at least 70%, at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 56 and/or the LC of SEQ ID NO: 57.

[0163] In an embodiment, the present disclosure refers to an nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or antibody fragment specific for human C5aR, wherein said nucleic acid sequence or plurality of nucleic acid sequences comprise the HC of SEQ ID NO: 68 and the LC of SEQ ID NO: 69, or a HC and a LC that has at least 60%, at least 70%, at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 68 and/or the LC of SEQ ID NO: 69.

[0164] In an embodiment, the present disclosure refers to an nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or antibody fragment specific for human C5aR, wherein said nucleic acid sequence or plurality of nucleic acid sequences comprise the HC of SEQ ID NO: 80 and the LC of SEQ ID NO: 81, or a HC and a LC that has at least 60%, at least 70%, at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 80 and/or the LC of SEQ ID NO: 81.

[0165] In an embodiment, the present disclosure refers to an nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or antibody fragment specific for human C5aR, wherein said nucleic acid sequence or plurality of nucleic acid sequences comprise the HC of SEQ ID NO: 92 and the LC of SEQ ID NO: 93, or a HC and a LC that has at least 60%, at least 70%, at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 92 and/or the LC of SEQ ID NO: 93.

[0166] In an embodiment, the present disclosure refers to a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or antibody fragment specific for human C5aR, wherein said nucleic acid sequence or plurality of nucleic acid sequences comprise the HC of SEQ ID NO: 56 and the LC of SEQ ID NO: 57.

[0167] In an embodiment, the present disclosure refers to a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or antibody fragment specific for human C5aR, wherein said nucleic acid sequence or plurality of nucleic acid sequences comprise the HC of SEQ ID NO: 68 and the LC of SEQ ID NO: 69.

[0168] In an embodiment, the present disclosure refers to a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or antibody fragment specific for human C5aR, wherein said nucleic acid sequence or plurality of nucleic acid sequences comprise the HC of SEQ ID NO: 80 and the LC of SEQ ID NO: 81.

[0169] In an embodiment, the present disclosure refers to an nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an antibody or antibody fragment specific for human C5aR disclosed herein, wherein said nucleic acid sequence or plurality of nucleic acid sequences comprise the HC of SEQ ID NO: 92 and the LC of SEQ ID NO: 93.

[0170] In another embodiment, the present disclosure refers to a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or fragment specific for human C5aR, wherein the nucleic acid sequence or the plurality of nucleic acid sequences comprise the VH and VL of any one of the antibodies disclosed in Table 1 or Table 2.

[0171] In an embodiment, the present disclosure provides an isolated antibody or antibody fragment specific for human C5aR, encoded by any one of the nucleic acid sequences or plurality of nucleic acid sequences disclosed in Table 1 or Table 2.

[0172] In an embodiment, the present disclosure provides a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding any one of the isolated antibodies or antibody fragments disclosed in Table 1 or Table 2.

[0173] In an embodiment, the present disclosure provides a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding

any one of the isolated antibodies or antibody fragments specific for human C5aR according to the present disclosure.

[0174] In another embodiment, the present disclosure refers to a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or antibody fragment specific for human C5aR, wherein the nucleic acid sequence or the plurality of nucleic acid sequences comprises a HC and a LC of any one of the antibodies or antibody fragments disclosed in Table 1 or Table 2.

[0175] In an embodiment, said nucleic acid composition and/or said nucleic acid sequence and/or plurality of nucleic acid sequences are isolated.

Vectors

[0176] In an embodiment, the present disclosure provides a vector composition comprising a vector or a plurality of vectors comprising a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or antibody fragment specific for human C5aR according to the present disclosure.

[0177] In an embodiment, the present disclosure provides a vector composition comprising a vector or a plurality of vectors comprising a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding any one of the isolated antibodies or antibody fragments specific for human C5aR disclosed in Tables 1 or Table 2.

[0178] In an embodiment, the present disclosure provides a vector composition comprising a vector or a plurality of vectors comprising a nucleic acid sequence or a plurality of nucleic acid sequences disclosed in Table 1 or Table 2.

[0179] In an embodiment, said vector composition and/or vector and/or plurality of vectors are isolated.

Host Cells

[0180] In an embodiment, the present disclosure provides a host cell comprising a vector composition comprising a vector or a plurality of vectors comprising a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or antibody fragment specific for human C5aR according to the present disclosure.

[0181] In an embodiment, the present disclosure refers to a host cell comprising a vector composition comprising a vector or a plurality of vectors comprising a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an isolated antibody or antibody fragment specific for C5aR disclosed in Table 1 or Table 2.

[0182] In an embodiment, the host cell according to the present disclosure is able to express the isolated antibody or antibody fragment specific for human C5aR encoded by the vector composition or the nucleic acid composition.

[0183] In a further embodiment, the host cell is an isolated host cell. In a further embodiment, said host cell is a mammalian cell. In an embodiment, said mammalian cell is a human cell. In another embodiment, said mammalian cell is a CHO cell. In an embodiment, said cell is a HEK cell. In another embodiment, said cell is a PERC.6 cell. In an embodiment, said cell is a HKB11 cell.

[0184] The skilled man will realize that the nucleic acid sequence or the plurality of nucleic acid sequences encoding the heavy and/or light chain of an antibody or antibody fragment of the present disclosure can be cloned into different vectors or into the same vector.

[0185] The vectors can be introduced into the appropriate host cells such as prokaryotic (e.g., bacterial) or eukaryotic (e.g., yeast or mammalian) cells by methods well known in the art (see e.g., "Current Protocol in Molecular Biology", Ausubel et al. (eds.), Greene Publishing Assoc. and John Wiley Interscience, New York, 1989 and 1992). Numerous cloning vectors are known to those of skill in the art, and the selection of an appropriate cloning vector is a matter of choice. The gene can be placed under the control of a promoter, ribosome binding site (for bacterial expression) and, optionally, an operator (collectively referred to herein as "control" elements), so that the nucleic acid sequence encoding the desired protein is transcribed into RNA in the host cell transformed by a vector containing this expression construction. The coding sequence may or may not contain a signal peptide or leader sequence. Upon expression in host cells, the antibodies or antibody fragments of the present disclosure are obtained. These steps can be achieved in different ways, as will be known by the person skilled in the art. In general, such steps typically include transforming or transfecting a suitable host cell with a nucleic acid composition or vector composition or an infectious particle, which encodes the antibody, or antibody fragments. Further, such steps typically include culturing said host cells under conditions suitable for the proliferation (multiplication, growth) of said host cells and a culturing step under conditions suitable for the production (expression, synthesis) of the encoded antibody or antibody fragment. The culturing of host cells under conditions suitable for proliferation or expression is typically accomplished in the presence of media comprising components suitable for cell growth or induction of expression. In particular, embodiments, the methods for the production of the antibodies or antibody fragments of the present disclosure further comprise the step of isolating and purifying the produced antibody or antibody fragment from the host cells or medium. If the expression system secretes the protein into growth media, the protein can be purified directly from the media. If the protein is not secreted, it is isolated from cell lysates or recovered from the cell membrane fraction. The selection of the appropriate growth conditions and recovery methods are within the skill of the art. The antibody or antibody fragment of the present disclosure can then be purified by a number of techniques as known to the person skilled in the art.

[0186] In an embodiment, the present disclosure refers to a method of producing an isolated antibody or antibody fragment specific for human C5aR of any of the antibodies disclosed in Table 1 or Table 2. In an embodiment, a method of producing an isolated antibody or antibody fragment according to the present disclosure is provided, wherein the method comprises culturing a host cell comprising a vector composition comprising a vector or a plurality of vectors comprising a nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding an antibody or antibody fragment according to the present disclosure, under conditions suitable for expression of the antibody or antibody fragment, and isolating the antibody or antibody fragment from the host cell or host cell culture medium. An antibody or antibody fragment isolated

as described herein may be purified techniques know in the art, such as high performance liquid chromatography (HPLC), ion exchange chromatography, gel electrophoresis, affinity chromatography, size exclusion chromatography, and the like. The conditions used to purify a particular antibody or antibody fragment will depend, in part, on factors such as net charge, hydrophobicity, hydrophilicity etc., and will be apparent to those having skill in the art. For affinity chromatography purification an antibody, ligand, receptor or antigen can be used to which the antibody or antibody fragment binds. For example, for affinity chromatography purification of antibody or antibody fragment according to the present disclosure, a matrix with protein A or protein G may be used. The purity of an antibody or antibody fragment can be determined by any of a variety of well-known analytical methods including gel electrophoresis, high-pressure liquid chromatography, and the like.

Specificity

[0187] In an embodiment, the present disclosure pertains to an isolated antibody or antibody fragment specific for human C5aR disclosed in Table 1 or Table 2. In an embodiment, the isolated antibody or antibody fragment according to the present disclosure is specific for human C5aR.

[0188] In an embodiment, the isolated antibody or antibody fragment according to the present disclosure is specific for human C5aR encoded by the amino acid sequence of SEQ ID NO: 1 and/or SEQ ID NO: 2. In an embodiment, the isolated antibody or antibody fragment according to the present disclosure is specific for a polypeptide comprising the amino acid sequence of SEQ ID NO: 1 and/or SEQ ID NO: 2. In an embodiment, the isolated antibody or antibody fragment according to the present disclosure is specific for a polypeptide consisting of the amino acid sequence of SEQ ID NO: 1 and/or SEQ ID NO: 2.

[0189] In an embodiment, the isolated antibody or antibody fragment according to the present disclosure specifically binds to the extracellular region human C5aR. In an embodiment, the isolated antibody or antibody fragment according to the present disclosure specifically binds to the N-terminal extracellular region of human C5aR. In an embodiment, the isolated antibody or antibody fragment according to the present disclosure specifically binds to the N-terminal extracellular region of human C5aR, wherein the N-terminal extracellular region comprises the amino acid sequence of SEQ ID NO: 13. In an embodiment, the isolated antibody or antibody fragment according to the present disclosure specifically binds to the N-terminus of human C5aR comprising the amino acid sequence of SEQ ID NO: 13. In an embodiment, the isolated antibody or antibody fragment according to the present disclosure specifically binds to a peptide comprising the amino acid sequence of SEQ ID NO: 13. In an embodiment, the isolated antibody or antibody fragment according to the present disclosure specifically binds to a peptide consisting of the amino acid sequence of SEQ ID NO: 13.

[0190] In an embodiment, the said isolated antibody or antibody fragment specific for human C5aR, comprises

[0191] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0192] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0193] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0194] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0195] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0196] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0197] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43 or a VH and a VL that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 or 42 and to the VL of SEQ ID NO: 36 or 43.

[0198] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0199] a) the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or

[0200] b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or a HC and a LC that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 37 or 44 and to the LC of SEQ ID NO: 38 or 45.

[0201] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a monoclonal antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a human, humanized or chimeric antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a recombinant antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is an isolated recombinant human monoclonal antibody or antibody fragment.

Species Cross-Reactivity

[0202] In further embodiments, the isolated antibody or antibody fragment according to the present disclosure is cross-reactive to cynomolgus monkey (cynomolgus) C5aR. In another embodiment, the isolated antibody or antibody fragment according to the present disclosure is specific for human C5aR and cynomolgus C5aR.

[0203] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment cross-reactively binds to cynomolgus C5aR. In an embodiment, the isolated antibody or antibody fragment according to the present disclosure specifically binds to the extracellular region of human C5aR and cynomolgus C5aR. In an embodiment, the isolated antibody or antibody fragment according to the present disclosure binds to the N-terminal extracellular region of human C5aR and cynomolgus C5aR. In an embodiment, the isolated antibody or antibody fragment according to the present disclosure binds to the N-ter-

minal extracellular region of human C5aR and cynomolgus C5aR, wherein the N-terminal extracellular region of C5aR comprises the amino acid sequence of SEQ ID NO: 13 or SEQ ID NO: 14.

[0204] In yet another embodiment, the isolated antibody or antibody fragment according to the present disclosure does not bind to rodent C5aR, such as mouse or rat C5aR.

[0205] In an embodiment, the antibody or antibody fragment according to the present disclosure binds to a peptide comprising the amino acid sequence of SEQ ID NO: 13 and/or SEQ ID NO: 14.

[0206] In an embodiment, the antibody or antibody fragment according to the present disclosure binds to a peptide consisting of the amino acid sequence of SEQ ID NO: 13 and/or SEQ ID NO: 14.

[0207] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR and cynomolgus C5aR, comprises

[0208] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0209] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0210] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0211] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0212] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0213] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0214] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43 or a VH and a VL that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 or 42 and to the VL of SEQ ID NO: 36 or 43.

[0215] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0216] a) the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or

[0217] b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or a HC and a LC that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 37 or 44 and to the LC of SEQ ID NO: 38 or 45.

[0218] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a monoclonal antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a recombinant antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment.

Monovalent Affinity for C5aR Peptides

[0219] In further embodiments, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment has a monovalent affinity for a human C5aR peptide comprising SEQ ID NO: 13 with a K_D of 100 nM or less, such as 90 nM or less, 80 nM or less, 70 nM or less, 60 nM or less, 50 nM or less, 40 nM or less, 30 nM or less, 20 nM or less, 10 nM or less, 5 nM or 1 nM less.

[0220] In an embodiment, said monovalent affinity is determined in IgG format. In certain embodiments, said monovalent affinity is determined by surface plasmon resonance (SPR) as described herein in Example 4.

[0221] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR, comprises

[0222] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0223] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0224] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0225] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0226] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0227] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0228] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43 or a VH and a VL that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 or 42 and to the VL of SEQ ID NO: 36 or 43.

[0229] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0230] a) the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or

[0231] b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or

[0232] a HC and a LC that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 37 or 44 and to the LC of SEQ ID NO: 38 or 45.

[0233] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a monoclonal antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a recombinant antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment.

Apparent Affinity (Bivalent) for C5aR Peptides

[0234] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said isolated antibody has an apparent affinity for a human C5aR peptide comprising SEQ ID NO: 13 with a K_D of 1 nM or less, such as 0.5 nM or less, 0.4 nM or less, 0.3 nM or less, 0.2 nM or less, 0.1 nM or less, 90 pM or less, 80 pM or less, 70 pM or less, 60 pM or less, 50 pM or less, 40 pM or less, 30 pM or less, 20 pM or less, 10 pM or less, 5 pM or less or 1 pM or less.

[0235] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said isolated antibody has an apparent affinity for a cynomolgus C5aR peptide comprising SEQ ID NO: 14 with a K_D of 300 nM or less, such as 250 nM or less, 200 nM or less, 150 nM or less, 100 nM or less, 90 nM or less, 80 nM or less, 70 nM or less, 60 nM or less, 50 nM or less, 40 nM or less, 30 nM or less, 20 nM or less, 10 nM or 1 nM or less.

[0236] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said isolated antibody has an apparent affinity to a human C5aR peptide comprising SEQ ID NO: 13 with a K_D of 0.3 nM or less and to a cynomolgus C5aR peptide comprising SEQ ID NO: 14 with a K_D of 150 nM or less.

[0237] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said isolated antibody has an apparent affinity for a human C5aR peptide comprising SEQ ID NO: 13 with a K_D of 0.05 nM or less and for a cynomolgus C5aR peptide comprising SEQ ID NO: 14 with a K_D of 80 nM or less.

[0238] In certain embodiments, said apparent affinity is determined in IgG format. In an embodiment, said apparent affinity is determined by biolayer interferometry (BLI) as described herein in Example 5.

[0239] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR, comprises

[0240] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0241] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0242] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0243] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0244] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0245] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0246] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43 or

[0247] a VH and a VL that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 or 42 and to the VL of SEQ ID NO: 36 or 43.

[0248] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0249] a) the FIC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or

[0250] b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or

[0251] a HC and a LC that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 37 or 44 and to the LC of SEQ ID NO: 38 or 45.

[0252] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a monoclonal antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a recombinant antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment.

Apparent Affinity (Bivalent) for Full-Length C5aR

[0253] In further embodiments, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said isolated antibody has an apparent affinity for human C5aR with a K_D of 10 nM or less, such as 5 nM or less, 4 nM or less, 3 nM or less, 2 nM or less, 1 nM or less, 0.5 nM or less, 0.4 nM or less, 0.3 nM or less, 0.2 nM or less or 0.1 nM or less.

[0254] In embodiments, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said isolated antibody has an apparent affinity for cynomolgus C5aR with a K_D of 10 nM or less, such as 9 nM or less, 8 nM or less, 7 nM or less, 6 nM or less, 5 nM or less, 4 nM or less, 3 nM or less, or 1 nM or less.

[0255] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said isolated antibody has an apparent affinity to human C5aR with a K_D of 0.5 nM or less and to cynomolgus C5aR with a K_D of 5 nM or less.

[0256] In an embodiment, said human C5aR comprises the amino acid sequence of SEQ ID NO: 1. In an embodiment, said human C5aR comprises the amino acid sequence of SEQ ID NO: 2. In an embodiment, said cynomolgus C5aR comprises the amino acid sequence of SEQ ID NO: 3.

[0257] In certain embodiments, said apparent affinity is determined in IgG format. In embodiments, said human C5aR or cynomolgus C5aR is expressed on cells. In embodiments, said human C5aR or cynomolgus C5aR is expressed on engineered CHO cells expressing full-length human. In embodiments, said CHO cells are Flp-In CHO cells.

[0258] In certain embodiments, said apparent affinity is determined as described herein in Example 6.

[0259] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR, comprises

[0260] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region

of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0261] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region comprising the amino acid sequence of SEQ ID NO: 34, or

[0262] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region comprising the amino acid sequence of SEQ ID NO: 34, or

[0263] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region comprising the amino acid sequence of SEQ ID NO: 34.

[0264] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0265] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0266] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43 or

[0267] a VH and a VL that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 or 42 and to the VL of SEQ ID NO: 36 or 43.

[0268] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0269] a) the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or

[0270] b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or

[0271] a HC and a LC that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 37 or 44 and to the LC of SEQ ID NO: 38 or 45.

[0272] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a monoclonal antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a recombinant antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment.

Apparent EC_{50} for Full-Length C5aR

[0273] In further embodiments, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said isolated antibody binds to human C5aR with an EC_{50} concentration of 20 nM or less, 15 nM or less, 10 nM or less, 5 nM or less, 4 nM or less, 3 nM or less, 2 nM or less, 1 nM or less, 0.5 nM or less, 0.4 nM or less, 0.3 nM or less, 0.2 nM or less or 0.1 nM or less.

[0274] In embodiments, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said isolated antibody binds to cynomolgus C5aR with an EC_{50} concentration of 20 nM or less, 10 nM or less, 9 nM or less, 8 nM or less, 7 nM or less, 6 nM or less, 5 nM or less, 4 nM or less, 3 nM or less, or 1 nM or less.

[0275] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said isolated antibody binds to human C5aR and cynomolgus C5aR with an EC_{50} concentration of K_D of 10 nM or less.

[0276] In an embodiment, said human C5aR comprises the amino acid sequence of SEQ ID NO: 1. In an embodiment, said human C5aR comprises the amino acid sequence of SEQ ID NO: 2. In an embodiment, said cynomolgus C5aR comprises the amino acid sequence of SEQ ID NO: 3.

[0277] In certain embodiments, said EC_{50} concentration is determined in IgG format. In embodiments, said human C5aR or cynomolgus C5aR is expressed on cells. In embodiments, said human C5aR or cynomolgus C5aR is expressed on engineered CHO cells expressing full-length human. In embodiments, said CHO cells are Flp-In CHO cells. In certain embodiments, said human C5aR or cynomolgus C5aR is expressed on neutrophils. In embodiments, said human C5aR is expressed on human neutrophils. In embodiments, said cynomolgus C5aR is expressed on cynomolgus neutrophils. In certain embodiments, said neutrophils are derived from whole-blood. In certain embodiments, said EC_{50} concentration is determined as described herein in Example 7.

[0278] In further embodiments, said isolated antibody or antibody fragment specific for human C5aR does substantially not bind to a C5aR related antigen selected from the group consisting of human C5L2, human ChemR23, human FPR1 and C3aR. In certain embodiments, said isolated antibody or antibody fragment specific for human C5aR does not substantially bind to a C5aR related antigen selected from the group consisting of human C5L2, human ChemR23, human FPR1 and C3aR at an IgG concentration of 300 nM. In an embodiment, said binding is determined as described in Example 7.

[0279] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR, comprises

[0280] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0281] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region comprising the amino acid sequence of SEQ ID NO: 34, or

[0282] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region comprising the amino acid sequence of SEQ ID NO: 34, or

[0283] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region comprising the amino acid sequence of SEQ ID NO: 34.

[0284] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0285] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0286] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43 or

[0287] a VH and a VL that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 or 42 and to the VL of SEQ ID NO: 36 or 43.

[0288] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0289] a) the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or

[0290] b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or

[0291] a HC and a LC that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 37 or 44 and to the VL of SEQ ID NO: 38 or 45.

[0292] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a monoclonal antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a recombinant antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment.

[0293] In an embodiment, the present disclosure refers to an isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment binds to human C5aR comprising SEQ ID NO: 1 and/or SEQ ID NO: 2 with an EC_{50} concentration of 5 nM or less, such as 4 nM or less, 3 nM or less, 2 nM or less, 1 nM or less or 0.5 nM or less.

[0294] In certain embodiments, said human C5aR is presented on virus-like-particles. In certain embodiments, said human C5aR is expressed as a fusion protein. In certain embodiments, said human C5aR is fused to a GAG protein. In embodiments, said fusion protein comprises an amino acid sequence disclosed in Table 8. In certain embodiments, said binding is determined by ELISA as described in Example 8.

[0295] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR, comprises

[0296] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0297] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0298] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0299] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0300] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR

[0301] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0302] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43 or

[0303] a VH and a VL that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 or 42 and to the VL of SEQ ID NO: 36 or 43.

[0304] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR

[0305] a) the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or

[0306] b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or

[0307] a HC and a LC that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 37 or 44 and to the LC of SEQ ID NO: 38 or 45.

[0308] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a monoclonal antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a recombinant antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment.

Functionality—C5A-Induced Activation of C5aR

[0309] In general, the isolated antibody or antibody fragment specific for human C5aR according to the present disclosure can be used to prevent or to inhibit the interaction between human C5aR and human C5a, thereby preventing, inhibiting, neutralizing or reducing the signaling pathways that are mediated by C5aR and/or modulating the biological pathways and mechanisms in which C5aR is involved.

[0310] In an embodiment, the present disclosure pertains to an isolated antibody or antibody fragment specific for human C5aR, wherein said isolated antibody or antibody fragment specifically interferes with C5aR-mediated signal transduction.

[0311] In a further embodiment of the present disclosure, the isolated antibody or antibody fragment specific for human C5aR specifically interferes with the interaction of C5a with C5aR expressed on cells. In yet a further embodiment, said isolated antibody or antibody fragment is capable of specifically interfering with C5a induced signal transduction mediated by C5aR.

[0312] Methods for assaying for functional activity of a C5aR specific antibody may utilize binding assays, such as the enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), fluorescence activated cell sorting (FACS) and other methods that are well known in the art (see Hampton, R. et al. (1990; Serological Methods a Laboratory Manual, APS Press, St Paul, Minn.) and Maddox, D. E. et al. (1983; J. Exp. Med. 158:1211-1216)). Alternatively, assays may test the ability of the isolated antibody or antibody fragment of the present disclosure in eliciting a biological response as a result of binding to C5aR, either in vivo or in vitro. Such assays are described in the Examples disclosed herein. Other suitable assays will be known to those of skill in the art.

[0313] In certain embodiments, the isolated antibody or antibody fragment of the present disclosure antagonizes human C5aR activity. In an embodiment, the isolated antibody or antibody fragment neutralizes human C5aR activity. In an embodiment, the isolated antibody or antibody fragment of the present disclosure inhibits human C5aR activity.

In an embodiment, the isolated antibody or antibody fragment of the present disclosure inhibits human C5aR signaling. In an embodiment, said human C5aR activity or human C5aR signaling is induced by C5a. In an embodiment, said human C5aR activity or human C5aR signaling is induced by the interaction of human C5a with human C5aR. In an embodiment, said C5aR activity or C5aR signaling is induced by the binding of human C5a to human C5aR. In an embodiment, said C5aR is expressed on cells. In an embodiment, said human C5aR activity or human C5aR signaling is inhibited in vitro and/or ex vivo and/or in vivo.

C5A-Induced β-Arrestin Recruitment

[0314] The ability of the isolated antibody or antibody fragment specific for human C5aR according to the present disclosure to inhibit C5a induced C5aR activation was tested in a β-arrestin recruitment assay as described in Example 14 and revealed that both antibodies are even more potent antagonists of C5aR activity when compared to the prior art antibody RefMAB#1, in particular at high pathophysiological C5a concentrations.

[0315] Accordingly, in an embodiment of the present disclosure, the isolated antibody or antibody fragment specific for human C5aR inhibits the ability of C5a to induce C5aR activity. In an embodiment, said C5a induced C5aR activity is determined in a β-arrestin recruitment assay as described in Example 14. In an embodiment, said C5a induced C5aR activity is determined in vitro.

[0316] In one such embodiment, the present disclosure provides an isolated antibody or antibody fragment specific for human C5aR, wherein said isolated antibody or antibody fragment inhibits the ability of human C5a to induce human C5aR-mediated β-arrestin recruitment. In an embodiment, said isolated antibody or antibody fragment inhibits human C5a induced β-arrestin recruitment. In an embodiment, said isolated antibody or antibody fragment inhibits human C5aR mediated β-arrestin recruitment.

[0317] In a further embodiment of the present disclosure, the isolated antibody or antibody fragment specific for human C5aR inhibits human C5a induced human C5aR interaction with β-arrestin. In one such embodiment, said human C5a induced human C5aR interaction with β-arrestin and/or that human C5a induced beta-arrestin recruitment is measured using beta-galactosidase enzyme fragment complementation. In an embodiment, said human C5a induced human C5aR interaction with β-arrestin and/or that human C5a induced β-arrestin recruitment is determined as described in Example 14. In one such embodiment, said human C5a induced human C5aR interaction with β-arrestin and/or that human C5a induced β-arrestin recruitment is tested at an IgG concentration of 50 nM.

[0318] The ability of an isolated antibody or antibody fragment according to the present disclosure to inhibit human C5a induced human C5aR activity, such as to inhibit human C5a induced human C5aR interaction with β-arrestin and/or human C5a induced human C5aR mediated β-recruitment can be determined by generating dose-response curves for increasing concentrations of human C5a and a fixed concentration of IgG and by calculating respective EC50 concentrations.

[0319] In an embodiment, the present disclosure provides an isolated antibody or antibody fragment specific for human C5aR, wherein said isolated antibody or antibody fragment increases the EC_{50} concentration determined for human C5a in a β-arrestin recruitment assay by at least 5-fold or more, such as at least 6-fold, at least 7-fold, at least 8-fold, at least 9-fold, at least 10-fold, at least 11-fold, at least 12-fold or at least 13-fold at an IgG concentration of 50 nM when compared to the EC_{50} concentration determined in the absence of said isolated antibody or antibody fragment.

[0320] In an embodiment, the present disclosure provides an isolated antibody or antibody fragment specific for human C5aR, wherein said isolated antibody or antibody fragment increases the EC_{50} concentration determined for human C5a in a β-arrestin recruitment assay at an IgG concentration of 50 nM of about 5-fold, of about 6-fold, of about 7-fold, of about 8-fold, of about 9-fold, of about 10-fold, of about 11-fold, of about 12-fold or of about 13-fold when compared to the EC_{50} concentration determined in the absence of said isolated antibody or antibody fragment.

[0321] In an embodiment, the present disclosure provides an antibody or antibody fragment specific for human C5aR, wherein said human C5a needs to be present in an at least 5-fold or higher, such as at least 6-fold or higher, at least 7-fold or higher, at least 8-fold or higher, at least 9-fold or higher, at least 10-fold or higher, at least 11-fold or higher, at least 12-fold or higher, or at least 13-fold or higher concentration in order to induce the same human C5aR activity in a β-arrestin recruitment assay at an IgG concentration of 50 nM when compared to the concentration of human C5a in the absence of said antibody or antibody fragment.

[0322] In an embodiment, said β-arrestin recruitment assay is performed as described in Example 14. In an embodiment, said β-arrestin recruitment assay is performed in vitro.

[0323] Alternatively, the ability of the isolated antibody or antibody fragment specific for C5aR according to the present disclosure to inhibit C5a induced C5aR mediated β-arrestin recruitment can be determined by calculating the % inhibition for different human C5a concentrations.

[0324] In one such embodiment, the isolated antibody or antibody fragment specific for C5aR according to the present disclosure inhibits human C5a induced human C5aR mediated β-arrestin recruitment by at least 50%, by at least 55%, by at least 60%, by at least 70%, by at least 80% or by at least 90% at an IgG concentration of 50 nM and in the presence of 1.2 nM or 11 nM human C5a compared to the level of human C5a induced human C5aR mediated β-arrestin recruitment in the presence of 1.2 nM or 11 nM human C5a and absence of said antibody or antibody fragment.

[0325] In one such embodiment, the isolated antibody or antibody fragments specific for C5aR according to the present disclosure inhibits human C5a induced human C5aR mediated beta-arrestin recruitment by at least 25%, such as by at least 30%, by at least 35%, by at least 40%, by at least 45% or by at least 50% at an IgG concentration of 50 nM and in the presence of 1.2 nM or 11 nM human C5a compared to the level of human C5a induced human C5aR mediated β-arrestin recruitment in the presence of 100 nM human C5a and absence of said antibody or antibody fragment.

[0326] In an embodiment, said β-arrestin recruitment assay is performed as described in Example 14. In an embodiment, said β-arrestin recruitment assay is performed in vitro.

[0327] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0328] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0329] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0330] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0331] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region comprising the amino acid sequence of SEQ ID NO: 34.

[0332] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR for comprises

[0333] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0334] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43 or

[0335] a VH and a VL that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 or 42 and to the VL of SEQ ID NO: 36 or 43.

[0336] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR for comprises

[0337] a) the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or

[0338] b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or

[0339] a HC and a LC that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 37 or 44 and to the LC of SEQ ID NO: 38 or 45.

[0340] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a monoclonal antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a recombinant antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment.

C5A-Induced Upregulation of CD11b Expression

[0341] C5a, as a potent activator of human neutrophils and monocytes, induces up-regulation of the cell surface antigen CD11b in such cells. Thus, the ability of an isolated antibody or antibody fragment specific for human C5aR according to the present disclosure to inhibit C5a induced activation of granulocytes and/or monocytes can be assessed by determine CD11b expression levels in such cells.

[0342] The ability of the isolated antibody or antibody fragments according to the present disclosure to inhibit CD11b expression in granulocytes and/or monocytes can be determined by generating dose-response curves for increasing concentrations of IgG and fixed concentration of human C5a and calculating the respective IC_{50} concentrations. Alternatively, the ability of an isolated antibody or antibody fragments according to the present disclosure to inhibit CD11b expression in granulocytes and/or monocytes C5a can be determined by calculating the % inhibition of CD11b expression for different IgG concentrations.

[0343] In one such embodiment, the isolated antibody or antibody fragment specific for human C5aR according to the present disclosure inhibits human C5a induced CD11b expression in human granuloyctes and/or human monocytes with an IC_{50} concentration of 30 nM or less, 25 nM or less, 20 nM or less, 15 nM or less, 10 nM or less or 5 nM or less, in the presence of 15 nM human C5a.

[0344] In another embodiment, the isolated antibody or antibody fragment specific for human C5aR according to the present disclosure inhibits human C5a induced CD11b expression in human granuloyctes and/or human monocytes by at least 70%, by at least 75%, by at 80%, by at least 85% or by at least 90% in the presence of 15 nM human C5a and an IgG concentration of 600 nM compared to the level of CD11b expression in the presence of 15 nM human C5a and absence of said antibody or antibody fragment.

[0345] In a further embodiment, the isolated antibody or antibody fragment specific for human C5aR according to the present disclosure inhibits human C5a induced CD11b expression in human granuloyctes with an IC_{50} concentration of 150 nM or less, 125 nM or less, 100 nM or less, 90 nM or less, 80 nM or less, 70 nM or less, 60 nM or less, 50 nM or less, or 40 nM or less in the presence of 150 nM human C5a.

[0346] In an embodiment, the isolated antibody or antibody fragment specific for human C5aR according to the present disclosure inhibits human C5a induced CD11b expression in human granulocytes with an IC_{50} concentration of 42 nM in the presence of 150 nM human C5a.

[0347] In a further embodiment, the isolated antibody or antibody fragment specific for human C5aR according to the present disclosure inhibits human C5a induced CD11b expression in human granuloyctes by at least by at least 65%, at least 70%, at least 75%, at least 80% or at least 90% in the presence of 150 nM human C5a and an IgG concentration of 600 nM compared to the level of CD11b expression in the presence of 150 nM human C5a and absence of said antibody or antibody fragment.

[0348] In an embodiment, the isolated antibody or antibody fragments specific for human C5aR according to the present disclosure inhibits C5a induced CD11b expression in human granuloyctes by at least 45%, at least 50%, at least 55%, at least 60% or at least 65% in the presence of 150 nM human C5a and an IgG concentration of 100 nM compared to the level of CD11b expression in the presence of 150 nM human C5a and absence of said antibody or antibody fragment.

[0349] In an embodiment, said determination of CD11b expression is performed as described in Example 15. In an embodiment, said determination of CD11b expression in performed in vitro and/or ex vivo.

[0350] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0351] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0352] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0353] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0354] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0355] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR for comprises

[0356] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0357] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43 or

[0358] a VH and a VL that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 or 42 and to the VL of SEQ ID NO: 36 or 43.

[0359] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR for comprises

[0360] a) the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or

[0361] b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or

[0362] a HC and a LC that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 37 or 44 and to the LC of SEQ ID NO: 38 or 45.

[0363] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a monoclonal antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a recombinant antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment.

[0364] Furthermore, the inhibitory activity of the isolated antibody or antibody fragment according to the present disclosure on human C5a induced CD11b expression was further analyzed over a prolonged period of time meaning that the antibodies were pre-incubated with granulocytes and/or monocytes present in whole-blood over time of varying length (e.g. 300 minutes vs. 20 minutes) before human C5a was added. Surprisingly, the experiment revealed that the isolated antibodies according to the present disclosure are even more potent antagonists of C5aR activity over a longer period of time, e.g. a prolonged period of incubation time, in particular when compared to the prior art antibody RefMAB#1.

[0365] Accordingly, the ability of the isolated antibody or antibody fragment according to the present disclosure to inhibit human C5a induced CD11b expression in granulocytes and/or monocytes over a prolonged period of time can be determined by generating dose-response curves for increasing concentrations of IgG and a fixed concentration of human C5a and by calculating respective EC_{50} values after incubating said isolated antibodies with said granulocytes and/or monocytes for different incubation times.

[0366] As shown in FIGS. **6**A and C, the isolated antibodies or antibody fragments of the present disclosure exhibited a clear shift of the determined dose-response curve to lower IgG concentrations determined after 300 minutes of incubation when compared to the dose-response curve determined after 20 minutes of incubation. Interestingly, RefMAB#1 revealed no increased potency over time (see FIGS. **6**B and D).

[0367] Thus, in an embodiment, the isolated antibody or antibody fragment according to the present disclosure is more potent in inhibiting C5a induced CD11b expression in human granuloyctes and/or human monocytes after a prolonged period of incubation time with said cells.

[0368] In one such embodiment, the isolated antibody or antibody fragment according to the present disclosure inhibits human C5a induced CD11b expression in human granuloyctes and/or human monocytes with an at least 2-fold, at least 4-fold, at least 5-fold or at least 6-fold lower IC_{50} concentration determined after a prolonged period of incubation time of 50 minutes, of 100 minutes, of 150 minutes, of 200 minutes, of 250 minutes, or of 300 minutes when compared to the IC_{50} concentration determined after a period of incubation time of 20 minutes.

[0369] In an embodiment, the isolated antibody or antibody fragment according to the present disclosure inhibits human C5a induced CD11b expression in human granuloyctes and/or human monocytes with an about 5-fold lower IC_{50} concentration determined after a prolonged period of incubation time of 300 minutes when compared to the IC_{50} concentration determined after a period of incubation time of 20 minutes.

[0370] In an embodiment, the isolated antibody or antibody fragment according to the present disclosure inhibits human C5a induced CD11b expression in human granuloyctes and/or human monocytes with an at least 3-fold, at least 4-fold, at least 5-fold, at least 10-fold, at least 15-fold or at least 19-fold lower IC_{50} concentration determined after a prolonged period of incubation time of 300 minutes when compared to the corresponding IC_{50} concentration of RefMAB#1.

[0371] In an embodiment, the isolated antibody or antibody fragment according to the present disclosure inhibits human C5a induced CD11b expression in human granuloyctes and/or human monocytes with an IC_{50} concentration of 3 nM or less, 2.5 nM or less, 2 nM or less, 1.5 nM or less or 1 nM or less, after a prolonged period of incubation time of 300 minutes with said cells.

[0372] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0373] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0374] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0375] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0376] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0377] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0378] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0379] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43 or

[0380] a VH and a VL that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 or 42 and to the VL of SEQ ID NO: 36 or 43.

[0381] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0382] a) the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or

[0383] b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or

[0384] a HC and a LC that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 37 or 44 and to the LC of SEQ ID NO: 38 or 45.

[0385] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a monoclonal antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a recombinant antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment.

C5A-Induced Migration of Neutrophils

[0386] In further assays, the ability of the isolated antibody or antibody fragment specific for human C5aR according to the present disclosure to inhibit human C5a induced migration of human neutrophils was evaluated and revealed that MAB#1 efficiently inhibited C5 induced neutrophil migration in vitro.

[0387] Thus, in an embodiment of the present disclosure, said isolated antibody or antibody fragment specific for human C5aR of the present disclosure inhibits human C5a induced migration of human neutrophils in vitro.

[0388] In a further embodiment, said isolated antibody or antibody fragment inhibits human C5a induced migration of human neutrophils by at least 25%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75 or at least 80% compared to the level of migration in the presence of 10 nM human C5a and absence of said isolated antibody or antibody fragment in vitro.

[0389] In an embodiment, said migration of human neutrophils is determined after 15 minutes, after 25 minutes and/or after 35 minutes. In certain embodiments, said isolated antibody or antibody fragment according to the present disclosure is tested at an IgG concentration of 100 nM and/or 600 nM.

[0390] In an embodiment, said isolated antibody or antibody fragment of the present disclosure inhibits human C5a induced migration of human neutrophils by at least 25% after 35 minutes and at an IgG concentration of 100 nM compared to the level of migration after 35 minutes in the presence of 10 nM human C5a and absence of said antibody or antibody fragment.

[0391] In an embodiment, said isolated antibody or antibody fragment of the present disclosure inhibits human C5a induced migration of human neutrophils by at least 60% after 25 minutes and at an IgG concentration of 100 nM and/or 600 nM compared to the level of migration after 25 minutes in the presence of 10 nM human C5a and absence of said antibody or antibody fragment.

[0392] In an embodiment, said isolated antibody or antibody fragment of the present disclosure inhibits human C5a induced migration of human neutrophils by at least 40% after 35 minutes at an IgG concentration of 600 nM compared to the level of migration after 35 minutes in the presence of 10 nM human C5a and absence of said antibody.

[0393] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0394] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0395] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0396] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0397] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0398] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0399] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0400] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43 or

[0401] a VH and a VL that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 or 42 and to the VL of SEQ ID NO: 36 or 43.

[0402] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0403] a) the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or

[0404] b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or

[0405] a HC and a LC that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 37 or 44 and to the LC of SEQ ID NO: 38 or 45.

[0406] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a monoclonal antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a recombinant antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment.

Effector Function

[0407] The Fc region of an immunoglobulin generally confers to the favorable pharmacokinetic properties of antibodies, such as prolonged half-life in serum and to the ability to induce effector function via binding to Fc receptors expressed on cells. On the other hand, binding to Fc receptors might also results in an undesirable activation of certain cell surface receptors leading to unwanted cytokine release and severe side effects upon systemic administration.

[0408] Accordingly, for certain therapeutic situations, it is desirable to reduce or abolish the normal binding of the wild-type Fc region of an antibody, such as of an wild-type IgG Fc region to one or more or all of Fc receptors and/or binding to a complement component, such as C1q in order to reduce or abolish the ability of the antibody to induce effector function. For instance, it may be desirable to reduce or abolish the binding of the Fc region of an antibody to one or more or all of the Fcγ receptors, such as: FcγRI, FcγRIIa, FcγRIIb, FcγRIIIa.

[0409] Effector function can include, but is not limited to, one or more of the following: complement dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), cytokine secretion, immune complex-mediated antigen uptake by antigen-presenting cells, binding to NK cells, binding to macrophages, binding to monocytes, binding to polymorphonuclear cells, direct signaling inducing apoptosis, crosslinking of target-bound antibodies, dendritic cell maturation, or T cell priming.

[0410] A reduced or abolished binding of an Fc region to an Fc receptor and/or to C1q is typically achieved by mutating a wild-type Fc region, such as of an IgG1 Fc region, more particular a human IgG1 Fc region, resulting in a variant or engineered Fc region of said wild-type Fc region, e.g. a variant human IgG1 Fc region. Substitutions that result in reduced binding can be useful. For reducing or abolishing the binding properties of an Fc region to an Fc receptor, non-conservative amino acid substitutions, i.e. replacing one amino acid with another amino acid having different structural and/or chemical properties, are preferred.

[0411] Accordingly, in an embodiment, the isolated antibody or antibody fragment specific for human C5aR according to the present disclosure comprises a variant Fc region having a reduced or abolished binding to an Fc receptor and/or to C1q when compared to the wild-type Fc region. In one such embodiment, the isolated antibody or antibody fragment according to the present disclosure comprises a variant Fc region that reduces or abolishes the ability of the antibody to induce effector function. In a further embodiment, the isolated antibody or antibody fragment according to the present disclosure does not substantially induce effector function.

[0412] In certain embodiments, the effector function is one or more selected from the group consisting of CDC, ADCC and ADCP. In an embodiment, the effector function is ADCC. In an embodiment, the effector function is CDC. In an embodiment, the effector function is ADCP. In an embodiment, the isolated antibody or antibody fragment according to the present disclosure does not substantially induce ADCC and/or CDC and/or ADCP. In an embodiment, the isolated antibody or antibody fragment according to the present disclosure does not induce ADCC or ADCP in vitro.

[0413] In an embodiment, the variant Fc region of the isolated antibody or antibody fragment according to the present disclosure comprises one or more amino acid substitutions that reduce or abolish the binding of the variant Fc region to one or more Fc receptors and/or to C1q when compared to the wild-type Fc region. In an embodiment, the variant Fc region of the isolated antibody or antibody fragment according to the present disclosure comprises one or more amino acid substitutions that reduce or abolish the ability of the antibody to induce effector function when compared to the wild-type Fc region.

[0414] In a particular embodiment, the one or more amino acid substitutions may reduce the binding affinity of the variant Fc region for one or more Fc receptors and/or to C1q by at least 2-fold, at least 5-fold, at least 10-fold, at least 20-fold or even at least 50-fold when compared to the wild-type Fc region. In alternative embodiments, the one or more amino acid substitutions may reduce the ability of the isolated antibody or antibody fragment according to the present disclosure to induce effector function by at least 2-fold, at least 5-fold, at least 10-fold, at least 20-fold or even at least 50-fold when compared to the wild-type Fc region.

[0415] In an embodiment, the variant Fc region of the isolated antibody or antibody fragment according to the present disclosure does not substantially bind to one or more Fc receptors and/or C1q. In an embodiment, the variant Fc region of the antibody according to the present disclosure does substantially abolish the ability of said antibody to induce effector function. In an embodiment, the antibody or antibody fragment according to the present disclosure does not substantially induce effector function. In an embodiment, said effect function is ADCC and/or ADCP and/or CDC. In an embodiment, the antibody or antibody fragment according to the present disclosure does not substantially induce effector function meaning that the level of induced effector function is not significantly above the background as measured in the absence of said antibody.

[0416] In an embodiment, the Fc receptor is a human Fc receptor. In an embodiment, the Fc receptor is an Fcγ receptor. In an embodiment, the Fc receptor is a human FcγRIIIa, FcγRI, FcγRIIa and/or FcγRIIb.

[0417] In an embodiment, the effector function is one or more selected from the group of CDC, ADCC and ADCP. In a particular embodiment, the effector function is ADCC, CDC and ADCP. In a more particular embodiment, the effector function is ADCC and ADCP.

[0418] In an embodiment, the wild-type Fc region is an IgG1 Fc region. In an embodiment, the wild-type Fc region is a human IgG1 Fc region. In an embodiment, the wild-type Fc region is a human IgG1 Fc region. In an embodiment, the wild-type Fc region is a human IgG1 Fc region comprising the amino acid sequence of:

(SEQ ID NO: 11)
PELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGV

EVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIE

KTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESN

GQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNH

YTQKSLSLSPGK.

[0419] In an embodiment, the isolated antibody or antibody fragment according to the present disclosure comprises a variant human IgG1 Fc region, which comprises one or

more amino acid substitutions compared to the wild-type human IgG1 Fc region. In an embodiment, that one or more amino acid substitutions reduce or abolish the binding of the variant Fc region to an Fc receptor and/or to C1q and/or reduces the ability of said antibody to induce effector function when compared to the wild-type Fc region.

[0420] In an embodiment, the variant human IgG1 Fc region of the antibody or antibody fragment according to the present disclosure comprises an amino acid substitution at one or more positions selected from the group of 234, 235, 237, 330 and 331 with numbering according EU index compared to the wild type IgG1 Fc region comprising the amino acid sequence of SEQ ID NO: 11.

[0421] In an embodiment, said variant human IgG1 Fc region comprises an amino acid substitution at one or more positions selected from the group of L234, L235 and G237 with numbering according EU index compared to the wild-type IgG1 Fc region comprising the amino acid sequence of SEQ ID NO: 11.

[0422] In an embodiment, the variant human IgG1 Fc region comprises the amino acid substitutions at one or more positions selected from the group of L234A, L235E G237A with numbering according EU index compared to the wild-type IgG1 Fc region comprising the amino acid sequence of SEQ ID NO: 11.

[0423] In an embodiment, the variant human IgG1 Fc region comprises the amino acid substitutions L234A and L235E with numbering according EU index compared to the wild-type IgG1 Fc region comprising the amino acid sequence of SEQ ID NO: 11.

[0424] In an embodiment, the variant human IgG1 Fc region comprises the amino acid substitutions L234A, L235E and G237A with numbering according EU index compared to the wild-type IgG1 Fc region comprising the amino acid sequence of SEQ ID NO: 11.

[0425] In an embodiment, the variant human IgG1 Fc region comprises an amino acid substitution at one or more position selected from the group of A330 and P331 with numbering according EU index compared to the wild-type IgG1 Fc region comprising the amino acid sequence of SEQ ID NO: 11.

[0426] In an embodiment, the variant human IgG1 Fc region comprises the amino acid substitutions at one or more positions selected from the group of A330S and P331S with numbering according EU index compared to the wild-type IgG1 Fc region comprising the amino acid sequence of SEQ ID NO: 11.

[0427] In an embodiment, the variant human IgG1 Fc region comprises the amino acid substitutions A330S and P331S with numbering according EU index compared to the wild-type IgG1 Fc region comprising the amino acid sequence of SEQ ID NO: 11.

[0428] In an embodiment, the variant human IgG1 Fc region comprises the amino acid substitutions L234A, L235E, G237A, A330S and P331S with numbering according EU index compared to the wild type IgG1 Fc region comprising the amino acid sequence of SEQ ID NO: 11.

[0429] In an embodiment, the antibody or antibody fragment according to the present disclosure comprises a variant human IgG1 Fc region, which comprises one or more amino acid substitutions compared to the wild-type human IgG1 Fc region comprising the sequence of SEQ ID NO: 11, that reduce or abolish the binding affinity of the variant Fc region to one or more Fc receptors and/or to C1q and/or reduces the ability of said antibody to induce effector function, wherein the one or more amino acid substitutions are L234A, L235E, G237A, A330S and P331S with numbering according EU index.

[0430] In an embodiment, the isolated antibody or antibody fragment according to the present disclosure is of the human IgG1 class. In an embodiment, the isolated antibody or antibody fragment according to the present disclosure is of a variant human IgG1 class. In an embodiment, the isolated antibody or antibody fragment according to the present disclosure does not substantially induce effector function in vitro. In an embodiment, the variant human IgG1 Fc region does not substantially bind to one or more Fc receptors and/or C1q. In one such embodiment, the isolated antibody or antibody fragment according to the present disclosure comprises the amino acid substitution selected from the group of: L234A, L235E, G237A, A330S and P331S, with numbering according to EU index compared to the wild type IgG1 Fc region comprising the amino acid sequence of SEQ ID NO: 11.

[0431] In an embodiment, the isolated antibody or antibody fragment according to the present disclosure is of the human IgG1 class comprising the amino acid substitution L234A, L235E, G237A, A330S and P331S, with numbering according to EU index.

[0432] In an embodiment, the isolated antibody or antibody fragment according to the present disclosure comprises the amino acid substitution L234A, L235E, G237A, A330S and P331S, with numbering according to EU index.

[0433] In an embodiment, the isolated antibody or antibody fragment according to the present disclosure comprises the amino acid substitution L234A, L235E, G237A, A330S and P331S, with numbering according to EU index compared to the wild type IgG1 Fc region comprising the amino acid sequence of SEQ ID NO: 11.

[0434] In one such embodiment, the isolated antibody or antibody fragment according to the present disclosure comprises the amino acid substitution L234A, L235E, G237A, A330S and P331S, with numbering according to EU index and does not substantially induce effector function in vitro. In an embodiment, the effector function is one or more selected from the group of CDC, ADCC and ADCP.

[0435] In one such embodiment, the isolated antibody or antibody fragment according to the present disclosure comprises the amino acid substitution L234A, L235E, G237A, A330S and P331S, with numbering according to EU index compared to the wild-type human IgG1 Fc region comprising the amino acid sequence of SEQ ID NO: 11 and does not substantially bind to one or more Fc receptors and/or C1q in vitro.

[0436] In an embodiment, the isolated antibody or antibody fragment according to the preset disclosure is of the human IgG1 class. In an embodiment, the isolated antibody or antibody fragment to the preset disclosure does not substantially induce effector function in vitro. In an embodiment, the isolated antibody or antibody fragment according to the present disclosure comprises one or more amino acid substitution selected from the group of: L234A, L235E, G237A, A330S and P331S, with numbering according to EU index.

[0437] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0438] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region

of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0439] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0440] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0441] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0442] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR for comprises

[0443] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0444] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43 or

[0445] a VH and a VL that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 or 42 and to the VL of SEQ ID NO: 36 or 43.

[0446] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR for comprises

[0447] a) the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or

[0448] b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or

[0449] a HC and a LC that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 37 or 44 and to the LC of SEQ ID NO: 38 or 45.

[0450] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a monoclonal antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a recombinant antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment.

[0451] Binding of an antibody to Fc receptors via its Fc region can be easily determined e.g. by ELISA, or by Surface Plasmon Resonance (SPR) using standard instrumentation such as a Biacore® instrument (GE Healthcare), and Fc receptors may be obtained by recombinant expression. Alternatively, the binding affinity of Fc regions may be evaluated using cell lines known to express particular Fc receptors, such as NK cells expressing FcγIIIa receptor. Effector function of an antibody can be measured by methods known in the art. Suitable in vitro assays to assess ADCC activity of a molecule of interest are for instance described in WO2012130831. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed in vivo, e.g. in an animal model such as that disclosed in Clynes et al., Proc Natl Acad Sci USA 95, 652-656 (1998). To assess complement activation, a CDC assay may be performed (see, for example, Gazzano-Santoro et al., J Immunol Methods 202, 163 (1996); Cragg et al., Blood 101, 1045-1052 (2003); and Cragg and Glennie, Blood 103, 2738-2743 (2004)). C1q binding assays (such as ELISA) may be carried out to determine whether an antibody is able to bind C1q and hence has CDC activity (see, for example WO 2006/029879). In vitro methods to asses binding to Fc receptors or to asses immune effector function are described herein in Examples 10-13.

Fusion Proteins

[0452] The isolated antibody or antibody fragment according to the present disclosure may or may not be fused to one or more other amino acid residues, polypeptides or moieties. Such a fusion protein may be prepared in any suitable manner, including genetically or chemically approaches. Said linked moieties may contain secretory or leader sequences, sequences that aid detection, expression, separation or purification, or sequences that confer to increased protein stability, for example, during recombinant production. Non-limiting examples of potential moieties include beta-galactosidase, glutathione-S-transferase, luciferase, a T7 polymerase fragment, a secretion signal peptide, an antibody or antibody fragment, a toxin, a reporter enzyme, a moiety being capable of binding a metal ion like a poly-histidine tag, a tag suitable for detection and/or purification, a homo- or hetero-association domain, a moiety which increases solubility of a protein, or a moiety which comprises an enzymatic cleavage site.

[0453] Accordingly, the isolated antibody or antibody fragment according to the present disclosure may optionally contain one or more moieties for binding to other targets or target proteins of interest. It should be clear that such further moieties may or may not provide further functionality to the antibody and may or may not modify the properties of the isolated antibody or antibody fragment according to the present disclosure. Diagnostic use

[0454] In an embodiment, the present disclosure provides the use of an isolated antibody or antibody fragment specific for human C5aR according to the present disclosure for the diagnosis of a disease. In an embodiment, the present disclosure provides the use of an antibody or antibody fragment according to the present disclosure for the detection of C5aR, in particular human C5aR and/or cynomolgus C5aR. In an embodiment, the present disclosure provides a method for detecting C5aR in a subject or a sample, comprising the step of contacting said subject or sample with an isolated antibody or antibody fragment specific for human C5aR of the present disclosure. In an embodiment, the present disclosure provides a method for diagnosing a disease in a subject, comprising the step of contacting said subject or sample with an isolated antibody or antibody fragment according to the present disclosure.

[0455] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0456] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0457] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0458] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0459] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0460] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR for comprises

[0461] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0462] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43 or

[0463] a VH and a VL that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 or 42 and to the VL of SEQ ID NO: 36 or 43.

[0464] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR for comprises

[0465] a) the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or

[0466] b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or

[0467] a HC and a LC that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 37 or 44 and to the LC of SEQ ID NO: 38 or 45.

[0468] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a monoclonal antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a recombinant antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment.

Therapeutic Methods

[0469] The isolated antibody or antibody fragment according to the present disclosure may be used in therapeutic methods. The antibody or antibody fragment according to the present disclosure may be used for the treatment of a disease, such as cancer, an autoimmune disease or inflammatory disease.

[0470] In an embodiment, the present disclosure provides a method for the treatment of a disease.

[0471] In an embodiment, the present disclosure provides an isolated antibody or antibody fragment according to the present disclosure for the treatment of a disease. In an embodiment, the present disclosure provides an isolated antibody or antibody fragment according to the present disclosure for use in the treatment of a disease. In an embodiment, the present disclosure provides an isolated antibody or antibody fragment according to the present disclosure for use in the treatment of a disease in a subject in need thereof.

[0472] In an embodiment, the present disclosure provides the use of an isolated antibody or antibody fragment according to the present disclosure for the manufacture of a medicament. In an embodiment, the present disclosure provides an isolated antibody or antibody fragment according to the present disclosure for use as a medicament. In an embodiment, the present disclosure provides an isolated antibody or antibody fragment according to the present disclosure for use in medicine. In an embodiment, the present disclosure provides an isolated antibody or antibody fragment according to the present disclosure for use as a medicament for the treatment of a subject in need thereof.

[0473] In an embodiment, the disease is associated with the undesired presence of C5aR, in particular human C5aR. In an embodiment, the disease is associated with the undesired presence of C5a, in particular human C5a.

[0474] In an embodiment, the disease to be treated is a proliferative disease. In a particular embodiment, the disease is cancer. Non-limiting examples of cancers include bladder cancer, brain cancer, head and neck cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, uterine cancer, cervical cancer, endometrial cancer, esophageal cancer, colon cancer, colorectal cancer, rectal cancer, gastric cancer, prostate cancer, blood cancer, sarcoma, skin cancer, squamous cell carcinoma, bone cancer, melanoma, renal cell carcinoma, and kidney cancer.

[0475] In an embodiment, the disease to be treated is an autoimmune or inflammatory disease. Non-limiting examples an autoimmune or inflammatory disease include rheumatoid arthritis (RA), psoriasis, psoriatic arthritis, systemic lupus erythematosus (SLE), lupus nephritis, type I diabetes, Grave's disease, Inflammatory bowel disease (IBD), Crohn's disease (CD), ulcerative colitis (UC), irritable bowel syndrome, multiple sclerosis (MS), autoimmune myocarditis, Kawasaki disease, coronary artery disease, chronic obstructive pulmonary disease (COPD), interstitial lung disease, autoimmune thyroiditis, scleroderma, systemic sclerosis, osteoarthritis, atoptic dermatitis, vitiligo, graft vs. host disease, Sjogren's syndrome, autoimmune nephritis, Goodpasture's syndrome, chronic inflammatory demyelinating polyneuropathy, ANCA-associated vasculitis, uveitis, scleroderma, bullous pemphigoid, Alzheimer's Disease, amyotrophic lateral sclerosis, Huntington's Chorea, cystic fibrosis, gout, age-related macular degeneration, allergy, asthma, antiphospholipid syndrome (APS), atherosclerosis, C3 glomerulopathy and IgA nephropathy, ischemia/reperfusion injury, peritonitis, sepsis and other autoimmune diseases that are a result of either acute or chronic inflammation.

[0476] In an embodiment, the present disclosure provides an isolated antibody or antibody fragment specific for human C5aR according to the present disclosure for use in a method of treating a subject having a disease comprising administering to the subject a therapeutically effective amount of an antibody or antibody fragment according to the present disclosure.

[0477] In an embodiment, the method further comprises administering to the subject a therapeutically effective amount of at least one additional therapeutic agent. The subject in need of treatment is typically a mammal, more specifically a human. For use in therapeutic methods, an isolated antibody or antibody fragment according to the present disclosure would be formulated, dosed, and administered in a way consistent with good medical practice.

[0478] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0479] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0480] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO:

32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0481] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0482] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 of SEQ ID NO: 34.

[0483] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0484] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0485] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43 or

[0486] a VH and a VL that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 or 42 and to the VL of SEQ ID NO: 36 or 43.

[0487] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR comprises

[0488] a) the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or

[0489] b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or

[0490] a HC and a LC that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the HC of SEQ ID NO: 37 or 44 and to the LC of SEQ ID NO: 38 or 45.

[0491] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a monoclonal antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a recombinant antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment.

Pharmaceutical Compositions

[0492] In an embodiment, the present disclosure provides a pharmaceutical composition comprising an isolated antibody or antibody fragment according to the present disclosure and a pharmaceutically acceptable carrier or excipient.

[0493] The pharmaceutical compositions may further comprise at least one other pharmaceutically active compound. The pharmaceutical composition according to the present disclosure can be used in the diagnosis, prevention and/or treatment of diseases associated with the undesired presence of C5aR, in particular human C5aR. In particular, the present disclosure provides a pharmaceutical compositions comprising an antibody or antibody fragment according to the present disclosure that is suitable for prophylactic, therapeutic and/or diagnostic use in a mammal, more particular in a human.

[0494] In general, an antibody or antibody fragment according to the present disclosure may be formulated as a pharmaceutical composition comprising at least one antibody or antibody fragment according to the present disclosure and at least one pharmaceutically acceptable carrier or excipient, and optionally one or more further pharmaceutically active compounds. Such a formulation may be suitable for oral, parenteral, topical administration or for administration by inhalation. Accordingly, a pharmaceutical composition comprising at least one antibody or antibody fragment according to the present disclosure may be administered parenterally, such as intravenously, or intramuscularly, or subcutaneously. Alternatively, an antibody of the invention may be administered via a non-parenteral route, such as per-orally or topically. In a preferred embodiment, a pharmaceutical composition comprising an antibody or antibody fragment according to the present disclosure is administered intravenously or subcutaneously.

[0495] In particular, an antibody or antibody fragment according to the present disclosure may be used in combination with one or more pharmaceutically active compounds that are or can be used for the prevention and/or treatment of the diseases in which a target antigen of interest is involved, as a result of which a synergistic effect may or may not be obtained. Examples of such compounds, as well as routes, methods and pharmaceutical formulations or compositions for administering them will be clear to the clinician.

[0496] In an embodiment, the present disclosure provides a pharmaceutical composition comprising an antibody or antibody fragment according to the present disclosure for use in the prevention and/or treatment of a disease associated with the undesired presence of C5aR. In an embodiment, the present disclosure provides a pharmaceutical composition comprising an antibody or antibody fragment according to the present disclosure for the use as a medicament. In an embodiment, the present disclosure provides a pharmaceutical composition comprising an antibody or antibody fragment according to the present disclosure for use in the prevention and/or treatment of an autoimmune disease and/or inflammatory disease and/or cancer.

[0497] In an embodiment, the present disclosure provides a method for the treatment of an autoimmune disease and/or inflammatory disease and/or cancer in a subject in need thereof using a pharmaceutical composition comprising an antibody or antibody fragment according to the present disclosure.

[0498] Further provided is a method of producing an antibody or antibody fragment according to the present disclosure in a form suitable for administration in vivo, the method comprising (a) obtaining an antibody or antibody fragment by a method according to the present disclosure, and (b) formulating said antibody or antibody fragment with at least one pharmaceutically acceptable carrier or excipient, whereby a preparation of antibody or antibody fragment is formulated for administration in vivo. Pharmaceutical compositions according to the present disclosure comprise a therapeutically effective amount of one or more antibodies or antibody fragments according to the present disclosure dissolved in a pharmaceutically acceptable carrier or excipient.

[0499] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR according to the present disclosure comprises

[0500] a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0501] b) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 31, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO:

32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0502] c) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

[0503] d) the HCDR1 region of SEQ ID NO: 30, the HCDR2 region of SEQ ID NO: 41, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

[0504] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR for comprises

[0505] a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO: 36 or

[0506] b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO: 43 or

[0507] a VH and a VL that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 35 or 42 and to the VL of SEQ ID NO: 36 or 43.

[0508] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR for comprises

[0509] a) the HC of SEQ ID NO: 37 and the LC of SEQ ID NO: 38 or

[0510] b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO: 45 or

[0511] a HC and a LC that has at least at least 80%, at least 85%, at least 90% or at least 95% identity to the VH of SEQ ID NO: 37 or 44 and to the VL of SEQ ID NO: 38 or 45.

[0512] In an embodiment, said isolated antibody or antibody fragment specific for human C5aR is a monoclonal antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a recombinant antibody or antibody fragment. In an embodiment, said isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment.

Antibody Sequences

[0513]

TABLE 1

Antibody sequences of MAB#1

MAB#1	SEQ ID NO:	[aa] / DNA
MAB#1 Protein		
HCDR1 (Kabat)	SEQ ID NO: 27	SYAMH
HCDR2 (Kabat)	SEQ ID NO: 28	RIKSKAQGGTTDYAAHVKG
HCDR3 (Kabat)	SEQ ID NO: 29	VSFSTFDV
HCDR1 (Chothia)	SEQ ID NO: 30	GFTFSSY
HCDR2 (Chothia)	SEQ ID NO: 31	KSKAQGGT
HCDR3 (Chothia)	SEQ ID NO: 29	VSFSTFDV
LCDR1 (Kabat)	SEQ ID NO: 32	SGSSSNIGSYYVS
LCDR2 (Kabat)	SEQ ID NO: 33	RNNQRPS
LCDR3 (Kabat)	SEQ ID NO: 34	DSWDHSSMNV
LCDR1 (Chothia)	SEQ ID NO: 32	SGSSSNIGSYYVS
LCDR2 (Chothia)	SEQ ID NO: 33	RNNQRPS
LCDR3 (Chothia)	SEQ ID NO: 34	DSWDHSSMNV
VH	SEQ ID NO: 35	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSY AMHWVRQAPGKGLEWVGRIKSKAQGGTTDY AAHVKGRFTISRDDSKNTLYLQMNSLKTEDTA VYYCARVSFSTFDVWGQGTLVTVSS
VL	SEQ ID NO: 36	QSVLTQPPSVSGAPGQRVTISCSGSSSNIGSY YVSWYQQLPGTAPKVLIYRNNQRPSGVPDRF SGSKSGTSASLAITGLQAEDEADYYCDSWDH SSMNVFGGGTKLTVLGQ
Heavy chain IgG1_AEASS	SEQ ID NO: 37	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSY AMHWVRQAPGKGLEWVGRIKSKAQGGTTDY AAHVKGRFTISRDDSKNTLYLQMNSLKTEDTA VYYCARVSFSTFDVWGQGTLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGV

TABLE 1-continued

Antibody sequences of MAB#1

MAB#1	SEQ ID NO:	[aa] / DNA
		EVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPSSIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
Light chain	SEQ ID NO: 38	QSVLTQPPSVSGAPGQRVTISCSGSSSNIGSY YVSWYQQLPGTAPKVLIYRNNQRPSGVPDRF SGSKSGTSASLAITGLQAEDEADYYCDSWDH SSMNVFGGGTKLTVLGQPKAAPSVTLFPPSSE ELQANKATLVCLISDFYPGAVTVAWKADSSPV KAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS

MAB#1 DNA

HCDR1 (Kabat)	SEQ ID NO: 46	AGCTATGCGATGCAC
HCDR2 (Kabat)	SEQ ID NO: 47	CGTATCAAATCCAAAGCCCAGGGCGGTACG ACCGACTACGCGGCGCACGTGAAAGGC
HCDR3 (Kabat)	SEQ ID NO: 48	GTTTCTTTCTCCACTTTCGATGTT
HCDR1 (Chothia)	SEQ ID NO: 49	GGATTTACCTTCAGCAGCTAT
HCDR2 (Chothia)	SEQ ID NO: 50	AAATCCAAAGCCCAGGGCGGTACG
HCDR3 (Chothia)	SEQ ID NO: 48	GTTTCTTTCTCCACTTTCGATGTT
LCDR1 (Kabat)	SEQ ID NO: 51	AGCGGCAGCTCCTCCAATATTGGTAGCTATT ACGTGAGC
LCDR2 (Kabat)	SEQ ID NO: 52	CGTAATAATCAACGTCCTAGC
LCDR3 (Kabat)	SEQ ID NO: 53	GACAGCTGGGATCACAGCTCCATGAATGTT
LCDR1 (Chothia)	SEQ ID NO: 51	AGCGGCAGCTCCTCCAATATTGGTAGCTATT ACGTGAGC
LCDR2 (Chothia)	SEQ ID NO: 52	CGTAATAATCAACGTCCTAGC
LCDR3 (Chothia)	SEQ ID NO: 53	GACAGCTGGGATCACAGCTCCATGAATGTT
VH	SEQ ID NO: 54	GAGGTGCAATTGGTGGAAAGCGGCGGTGGC CTGGTGAAACCAGGCGGCAGCCTGCGCCTG AGCTGCGCCGCCTCCGGATTTACCTTCAGC AGCTATGCGATGCACTGGGTGCGCCAGGCC CCGGGCAAAGGTCTCGAATGGGTGGGTCGT ATCAAATCCAAAGCCCAGGGCGGTACGACC GACTACGCGGCGCACGTGAAAGGCCGCTTT ACCATTAGCCGCGATGATTCGAAAAACACCC TGTATCTGCAAATGAACAGCCTGAAAACCGA AGATACGGCCGTGTATTATTGCGCGCGTGTT TCTTTCTCCACTTTCGATGTTTGGGGCCAAG GCACCCTGGTGACTGTCTCGAGC
VL	SEQ ID NO: 55	CAGAGCGTGCTGACCCAGCCTCCTAGCGTG AGCGGTGCACCGGGCCAGCGCGTGACCATT AGCTGTAGCGGCAGCTCCTCCAATATTGGTA GCTATTACGTGAGCTGGTATCAGCAGCTGC CGGGCACGGCGCCGAAAGTTCTGATCTATC GTAATAATCAACGTCCTAGCGGCGTGCCGG ATCGCTTTAGCGGATCCAAAAGCGGCACCA GCGCCAGCCTGGCGATTACCGGCCTGCAAG CAGAAGATGAAGCGGATTATTACTGCGACAG CTGGGATCACAGCTCCATGAATGTTTTTGGC GGCGGTACCAAGCTGACCGTGCTGGGCCAG
Heavy chain (IgG1) IgG1 AEASS	SEQ ID NO: 56	GAGGTGCAATTGGTGGAAAGCGGCGGTGGC CTGGTGAAACCAGGCGGCAGCCTGCGCCTG AGCTGCGCCGCCTCCGGATTTACCTTCAGC AGCTATGCGATGCACTGGGTGCGCCAGGCC

TABLE 1-continued

Antibody sequences of MAB#1

MAB#1	SEQ ID NO:	[aa] / DNA
		CCGGGCAAAGGTCTCGAATGGGTGGGTCGT
		ATCAAATCCAAAGCCCAGGGCGGTACGACC
		GACTACGCGGCGCACGTGAAAGGCCGCTTT
		ACCATTAGCCGCGATGATTCGAAAAACACCC
		TGTATCTGCAAATGAACAGCCTGAAAACCGA
		AGATACGGCCGTGTATTATTGCGCGCGTGTT
		TCTTTCTCCACTTTCGATGTTTGGGGCCAAG
		GCACCCTGGTGACTGTCTCGAGCGCGTCGA
		CCAAAGGCCCCAGCGTGTTCCCTCTGGCCC
		CCAGCAGCAAGAGCACCTCTGGCGGAACAG
		CCGCCCTGGGCTGCCTGGTCAAGGACTACT
		TCCCCGAGCCCGTGACCGTGTCCTGGAACT
		CTGGCGCCCTGACCAGCGGCGTGCACACCT
		TTCCAGCCGTGCTCCAGAGCAGCGGCCTGT
		ACAGCCTGAGCAGCGTCGTGACCGTGCCCA
		GCAGCAGCCTGGGCACCCAGACCTACATCT
		GCAACGTGAACCACAAGCCCAGCAACACAA
		AGGTGGACAAGCGGGTGGAACCCAAGAGCT
		GCGACAAGACCCACACCTGTCCCCCCTGCC
		CTGCCCCTGAAGCGGAGGGAGCCCCCTCC
		GTGTTCCTGTTCCCCCCAAAGCCTAAGGACA
		CCCTGATGATCAGCCGGACCCCCGAAGTGA
		CCTGCGTGGTGGTGGACGTGTCCCACGAGG
		ACCCTGAAGTGAAGTTTAATTGGTACGTGGA
		CGGCGTGGAAGTGCACAACGCCAAGACCAA
		GCCCAGAGAGGAACAGTACAACAGCACCTA
		CCGGGTGGTGTCCGTGCTGACCGTGCTGCA
		CCAGGACTGGCTGAACGGCAAAGAGTACAA
		GTGCAAGGTGTCCAACAAGGCCCTGCCTTC
		CTCCATCGAGAAAACCATCAGCAAGGCCAAA
		GGCCAGCCCCGCGAGCCCCAGGTGTACACA
		CTGCCCCCTAGCCGGGAAGAGATGACCAAG
		AACCAGGTGTCCCTGACCTGCCTCGTGAAG
		GGCTTCTACCCCAGCGACATTGCCGTGGAA
		TGGGAGAGCAACGGCCAGCCCGAGAACAAC
		TACAAGACCACCCCCCCTGTGCTGGACAGC
		GACGGCTCATTCTTCCTGTACAGCAAGCTGA
		CCGTGGACAAGAGCCGGTGGCAGCAGGGC
		AACGTGTTCAGCTGCTCCGTGATGCACGAG
		GCCCTGCACAACCACTACACCCAGAAGTCC
		CTGAGCCTGAGCCCCGGCAAG
Light chain (DNA)	SEQ ID NO: 57	CAGAGCGTGCTGACCCAGCCTCCTAGCGTG
		AGCGGTGCACCGGGCCAGCGCGTGACCATT
		AGCTGTAGCGGCAGCTCCTCCAATATTGGTA
		GCTATTACGTGAGCTGGTATCAGCAGCTGC
		CGGGCACGGCGCCGAAAGTTCTGATCTATC
		GTAATAATCAACGTCCTAGCGGCGTGCCGG
		ATCGCTTTAGCGGATCCAAAAGCGGCACCA
		GCGCCAGCCTGGCGATTACCGGCCTGCAAG
		CAGAAGATGAAGCGGATTATTACTGCGACAG
		CTGGGATCACAGCTCCATGAATGTTTTTGGC
		GGCGGTACCAAGCTGACCGTGCTGGGCCAG
		CCCAAAGCCGCCCCTAGCGTGACCCTGTTC
		CCCCCCTCGAGTGAGGAACTCCAGGCCAAC
		AAGGCCACCCTCGTGTGCCTGATCAGCGAC
		TTCTACCCTGGCGCCGTGACCGTGGCCTGG
		AAGGCCGATAGCAGCCCTGTGAAGGCCGGC
		GTGGAAACCACCACCCCCAGCAAGCAGAGC
		AACAACAAATACGCCGCCAGCAGCTACCTG
		AGCCTGACCCCCGAGCAGTGGAAGTCCCAC
		AGATCCTACAGCTGCCAGGTCACACACGAG
		GGCAGCACCGTGGAAAAGACCGTGGCCCCC
		ACCGAGTGCAGC

MAB#1 DNA (optimized)

HCDR1 (Kabat)	SEQ ID NO: 70	AGCTACGCTATGCAC
HCDR2 (Kabat)	SEQ ID NO: 71	CGGATCAAGAGCAAGGCTCAAGGCGGCACC ACCGATTACGCCGCTCATGTGAAGGGC
HCDR3 (Kabat)	SEQ ID NO: 72	GTGTCCTTCTCCACCTTCGATGTG

TABLE 1-continued

Antibody sequences of MAB#1

MAB#1	SEQ ID NO:	[aa] / DNA
HCDR1 (Chothia)	SEQ ID NO: 73	GGCTTCACCTTCTCCAGCTAC
HCDR2 (Chothia)	SEQ ID NO: 74	AAGAGCAAGGCTCAAGGCGGCACC
HCDR3 (Chothia)	SEQ ID NO: 72	GTGTCCTTCTCCACCTTCGATGTG
LCDR1 (Kabat)	SEQ ID NO: 75	TCCGGCTCCTCCTCCAACATCGGCTCCTACT ACGTGTCC
LCDR2 (Kabat)	SEQ ID NO: 76	CGGAACAACCAGCGGCCTTCT
LCDR3 (Kabat)	SEQ ID NO: 77	GACTCTTGGGACCACTCCTCCATGAACGTG
LCDR1 (Chothia)	SEQ ID NO: 75	TCCGGCTCCTCCTCCAACATCGGCTCCTACT ACGTGTCC
LCDR2 (Chothia)	SEQ ID NO: 76	CGGAACAACCAGCGGCCTTCT
LCDR3 (Chothia)	SEQ ID NO: 77	GACTCTTGGGACCACTCCTCCATGAACGTG
VH	SEQ ID NO: 78	GAAGTGCAGCTGGTGGAATCTGGCGGCGGA CTTGTGAAACCTGGCGGCTCTCTGAGACTGT CTTGTGCCGCTTCCGGCTTCACCTTCTCCAG CTACGCTATGCACTGGGTCCGACAGGCCCC TGGCAAAGGATTGGAGTGGGTCGGACGGAT CAAGAGCAAGGCTCAAGGCGGCACCACCGA TTACGCCGCTCATGTGAAGGGCAGATTCAC CATCTCTCGGGACGACTCCAAGAACACCCT GTACCTGCAGATGAACTCCCTGAAAACCGA GGACACCGCCGTGTACTACTGCGCCAGAGT GTCCTTCTCCACCTTCGATGTGTGGGGCCA GGGCACACTGGTTACAGTCTCGAGC
VL	SEQ ID NO: 79	CAGTCCGTGCTGACCCAGCCTCCTTCTGTTT CTGGTGCTCCTGGCCAGAGAGTGACCATCT CTTGCTCCGGCTCCTCCTCCAACATCGGCTC CTACTACGTGTCCTGGTATCAGCAGCTGCCT GGCACCGCTCCTAAGGTGCTGATCTACCGG AACAACCAGCGGCCTTCTGGCGTGCCCGAT AGATTCTCCGGCTCTAAGTCTGGCACCTCTG CCAGCCTGGCTATCACTGGACTGCAGGCTG AGGACGAGGCCGACTACTACTGCGACTCTT GGGACCACTCCTCCATGAACGTGTTCGGCG GAGGTACCAAGCTGACCGTGCTGGGACAG
Heavy chain (IgG1) IgG1 AEASS	SEQ ID NO: 80	GAAGTGCAGCTGGTGGAATCTGGCGGCGGA CTTGTGAAACCTGGCGGCTCTCTGAGACTGT CTTGTGCCGCTTCCGGCTTCACCTTCTCCAG CTACGCTATGCACTGGGTCCGACAGGCCCC TGGCAAAGGATTGGAGTGGGTCGGACGGAT CAAGAGCAAGGCTCAAGGCGGCACCACCGA TTACGCCGCTCATGTGAAGGGCAGATTCAC CATCTCTCGGGACGACTCCAAGAACACCCT GTACCTGCAGATGAACTCCCTGAAAACCGA GGACACCGCCGTGTACTACTGCGCCAGAGT GTCCTTCTCCACCTTCGATGTGTGGGGCCA GGGCACACTGGTTACAGTCTCGAGCGCCTC CACCAAAGGACCCTCTGTGTTTCCTCTGGCT CCCTCCAGCAAGTCTACCTCTGGTGGAACA GCTGCCCTGGGCTGCCTGGTCAAGGATTAC TTTCCTGAGCCTGTGACCGTGTCCTGGAACT CTGGCGCTCTGACATCTGGCGTGCACACCT TTCCAGCTGTGCTGCAGTCCTCTGGCCTGTA CAGCCTGTCCTCTGTCGTGACCGTGCCTTCT AGCTCTCTGGGCACCCAGACCTACATCTGC AATGTGAACCACAAGCCTTCCAACACCAAGG TGGACAAGAGAGTGGAACCCAAGTCCTGCG ACAAGACCCACACCTGTCCTCCATGTCCTGC TCCAGAAGCTGAGGGCGCTCCTTCCGTGTT CCTGTTTCCTCCAAAGCCTAAGGACACCCTG ATGATCTCTCGGACCCCTGAAGTGACCTGC GTGGTGGTGGATGTGTCTCACGAGGACCCA

TABLE 1-continued

Antibody sequences of MAB#1		
MAB#1	SEQ ID NO:	[aa] / DNA
		GAAGTGAAGTTCAATTGGTACGTGGACGGC GTGGAAGTGCACAACGCCAAGACCAAGCCT AGAGAGGAACAGTACAACTCCACCTACAGA GTGGTGTCCGTGCTGACCGTGCTGCACCAG GATTGGCTGAACGGCAAAGAGTACAAGTGC AAGGTGTCCAACAAGGCCCTGCCTTCCAGC ATCGAAAAGACCATCTCCAAGGCCAAGGGC CAGCCTNGGGAACCCCAGGITTACACCCTG CCTCCAAGCCGGGAAGAGATGACCAAGAAC CAGGTGTCCCTGACCTGCCTCGTGAAGGGC TTCTACCCTTCCGATATCGCCGTGGAATGGG AGAGCAATGGCCAGCCTGAGAACAACTACA AGACAACCCCTCCTGTGCTGGACTCCGACG GCTCATTCTTCCTGTACTCCAAGCTGACAGT GGACAAGTCCAGATGGCAGCAGGGCAACGT GTTCTCCTGCTCCGTGATGCACGAGGCCCT GCACAATCACTACACACAGAAGTCCCTGTCT CTGTCCCCTGGCAAG
Light chain (DNA)	SEQ ID NO: 81	CAGTCCGTGCTGACCCAGCCTCCTTCTGTTT CTGGTGCTCCTGGCCAGAGAGTGACCATCT CTTGCTCCGGCTCCTCCTCCAACATCGGCTC CTACTACGTGTCCTGGTATCAGCAGCTGCCT GGCACCGCTCCTAAGGTGCTGATCTACCGG AACAACCAGCGGCCTTCTGGCGTGCCCGAT AGATTCTCCGGCTCTAAGTCTGGCACCTCTG CCAGCCTGGCTATCACTGGACTGCAGGCTG AGGACGAGGCCGACTACTACTGCGACTCTT GGGACCACTCCTCCATGAACGTGTTCGGCG GAGGTACCAAGCTGACCGTGCTGGGACAGC CTAAGGCTGCCCCTTCCGTGACACTGTTCCC TCCATCCTCTGAGGAACTGCAGGCCAACAA GGCTACCCTCGTGTGCCTGATCTCCGACTTT TACCCTGGCGCTGTGACCGTGGCCTGGAAG GCTGATAGTTCTCCTGTGAAGGCCGGCGTG GAAACCACCACACCTTCCAAGCAGTCCAACA ACAAATACGCCGCCTCCTCCTACCTGTCTCT GACCCCTGAACAGTGGAAGTCCCACCGGTC CTACAGCTGCCAAGTGACCCATGAGGGCTC CACCGTGGAAAAGACCGTGGCTCCTACCGA GTGCTCT

TABLE 2

Antibody sequences of MAB#2		
MAB#2	SEQ ID NO:	[aa] / DNA
MAB#2 Protein		
HCDR1 (Kabat)	SEQ ID NO: 27	SYAMH
HCDR2 (Kabat)	SEQ ID NO: 39	RIKSVAQGGTTDYAAHVKG
HCDR3 (Kabat)	SEQ ID NO: 40	VSHSTFDV
HCDR1 (Chothia)	SEQ ID NO: 30	GFTFSSY
HCDR2 (Chothia)	SEQ ID NO: 41	KSVAQGGT
HCDR3 (Chothia)	SEQ ID NO: 40	VSHSTFDV
LCDR1 (Kabat)	SEQ ID NO: 32	SGSSSNIGSYYVS
LCDR2 (Kabat)	SEQ ID NO: 33	RNNQRPS
LCDR3 (Kabat)	SEQ ID NO: 34	DSWDHSSMNV
LCDR1 (Chothia)	SEQ ID NO: 32	SGSSSNIGSYYVS

TABLE 2-continued

Antibody sequences of MAB#2

MAB#2	SEQ ID NO:	[aa] / DNA
LCDR2 (Chothia)	SEQ ID NO: 33	RNNQRPS
LCDR3 (Chothia)	SEQ ID NO: 34	DSWDHSSMNV
VH	SEQ ID NO: 42	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSY AMHWVRQAPGKGLEWVGRIKSVAQGGTTDY AAHVKGRFTISRDDSKNTLYLQMNSLKTEDTA VYYCARVSHSTFDVWGQGTLVTVSS
VL	SEQ ID NO: 43	QSVLTQPPSVSGAPGQRVTISCSGSSSNIGSY YVSWYQQLPGTAPKVLIYRNNQRPSGVPDRF SGSKSGTSASLAITGLQAEDEADYYCDSWDH SSMNVFGGGTKLTVLGQ
Heavy chain IgG1_AEASS	SEQ ID NO: 44	EVQLVESGGGLVKPGGSLRLSCAASGFTFSSY AMHWVRQAPGKGLEWVGRIKSVAQGGTTDY AAHVKGRFTISRDDSKNTLYLQMNSLKTEDTA VYYCARVSHSTFDVWGQGTLVTVSSASTKGP SVFPLAPSSKSTSGGTAALGCLVKDYFPEPVT VSWNSGALTSGVHTFPAVLQSSGLYSLSSVVT VPSSSLGTQTYICNVNHKPSNTKVDKRVEPKS CDKTHTCPPCPAPEAEGAPSVFLFPPPKPKDTL MISRTPEVTCVVVDVSHEDPEVKFNWYVDGV EVHNAKTKPREEQYNSTYRVVSVLTVLHQDW LNGKEYKCKVSNKALPSSIEKTISKAKGQPREP QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSK LTVDKSRWQQGNVFSCSVMHEALHNHYTQKS LSLSPGK
Light chain	SEQ ID NO: 45	QSVLTQPPSVSGAPGQRVTISCSGSSSNIGSY YVSWYQQLPGTAPKVLIYRNNQRPSGVPDRF SGSKSGTSASLAITGLQAEDEADYYCDSWDH SSMNVFGGGTKLTVLGQPKAAPSVTLFPPSSE ELQANKATLVCLISDFYPGAVTVAWKADSSPV KAGVETTTPSKQSNNKYAASSYLSLTPEQWKS HRSYSCQVTHEGSTVEKTVAPTECS

MAB#2 DNA

HCDR1 (Kabat)	SEQ ID NO: 58	AGCTATGCGATGCAC
HCDR2 (Kabat)	SEQ ID NO: 59	CGTATCAAATCCGTGGCCCAGGGCGGTACG ACCGACTACGCGGCGCACGTGAAAGGC
HCDR3 (Kabat)	SEQ ID NO: 60	GTTTCTCATTCCACTTTCGATGTT
HCDR1 (Chothia)	SEQ ID NO: 61	GGATTTACCTTCAGCAGCTAT
HCDR2 (Chothia)	SEQ ID NO: 62	AAATCCGTGGCCCAGGGCGGTACG
HCDR3 (Chothia)	SEQ ID NO: 60	GTTTCTCATTCCACTTTCGATGTT
LCDR1 (Kabat)	SEQ ID NO: 63	AGCGGCAGCTCCTCCAATATTGGTAGCTATT ACGTGAGC
LCDR2 (Kabat)	SEQ ID NO: 64	CGTAATAATCAACGTCCTAGC
LCDR3 (Kabat)	SEQ ID NO: 65	GACAGCTGGGATCACAGCTCCATGAATGTT
LCDR1 (Chothia)	SEQ ID NO: 63	AGCGGCAGCTCCTCCAATATTGGTAGCTATT ACGTGAGC
LCDR2 (Chothia)	SEQ ID NO: 64	CGTAATAATCAACGTCCTAGC
LCDR3 (Chothia)	SEQ ID NO: 65	GACAGCTGGGATCACAGCTCCATGAATGTT
VH	SEQ ID NO: 66	GAGGTGCAATTGGTGGAAAGCGGCGGTGGC CTGGTGAAACCAGGCGGCAGCCTGCGCCTG AGCTGCGCCGCCTCCGGATTTACCTTCAGC AGCTATGCGATGCACTGGGTGCGCCAGGCC CCGGGCAAAGGTCTCGAATGGGTGGGTCGT ATCAAATCCGTGGCCCAGGGCGGTACGACC

TABLE 2-continued

Antibody sequences of MAB#2

MAB#2	SEQ ID NO:	[aa] / DNA
		GACTACGCGGCGCACGTGAAAGGCCGCTTT
		ACCATTAGCCGCGATGATTCGAAAAACACCC
		TGTATCTGCAAATGAACAGCCTGAAAACCGA
		AGATACGGCCGTGTATTATTGCGCGCGTGTT
		TCTCATTCCACTTTCGATGTTTGGGGCCAAG
		GCACCCTGGTGACTGTCTCGAGC
VL	SEQ ID NO: 67	CAGAGCGTGCTGACCCAGCCTCCTAGCGTG
		AGCGGTGCACCGGGCCAGCGCGTGACCATT
		AGCTGTAGCGGCAGCTCCTCCAATATTGGTA
		GCTATTACGTGAGCTGGTATCAGCAGCTGC
		CGGGCACGGCGCCGAAAGTTCTGATCTATC
		GTAATAATCAACGTCCTAGCGGCGTGCCGG
		ATCGCTTTAGCGGATCCAAAAGCGGCACCA
		GCGCCAGCCTGGCGATTACCGGCCTGCAAG
		CAGAAGATGAAGCGGATTATTACTGCGACAG
		CTGGGATCACAGCTCCATGAATGTTTTTGGC
		GGCGGTACCAAGCTGACCGTGCTGGGCCAG
Heavy chain (IgG1) IgG1 AEASS	SEQ ID NO: 68	GAGGTGCAATTGGTGGAAAGCGGCGGTGGC
		CTGGTGAAACCAGGCGGCAGCCTGCGCCTG
		AGCTGCGCCGCCTCCGGATTTACCTTCAGC
		AGCTATGCGATGCACTGGGTGCGCCAGGCC
		CCGGGCAAAGGTCTCGAATGGGTGGGTCGT
		ATCAAATCCGTGGCCCAGGGCGGTACGACC
		GACTACGCGGCGCACGTGAAAGGCCGCTTT
		ACCATTAGCCGCGATGATTCGAAAAACACCC
		TGTATCTGCAAATGAACAGCCTGAAAACCGA
		AGATACGGCCGTGTATTATTGCGCGCGTGTT
		TCTCATTCCACTTTCGATGTTTGGGGCCAAG
		GCACCCTGGTGACTGTCTCGAGCGCGTCGA
		CCAAAGGCCCCAGCGTGTTCCCTCTGGCCC
		CCAGCAGCAAGAGCACCTCTGGCGGAACAG
		CCGCCCTGGGCTGCCTGGTCAAGGACTACT
		TCCCCGAGCCCGTGACCGTGTCCTGGAACT
		CTGGCGCCCTGACCAGCGGCGTGCACACCT
		TTCCAGCCGTGCTCCAGAGCAGCGGCCTGT
		ACAGCCTGAGCAGCGTCGTGACCGTGCCCA
		GCAGCAGCCTGGGCACCCAGACCTACATCT
		GCAACGTGAACCACAAGCCCAGCAACACAA
		AGGTGGACAAGCGGGTGGAACCCAAGAGCT
		GCGACAAGACCCACACCTGTCCCCCCTGCC
		CTGCCCCTGAAGCGGAGGGAGCCCCCTCC
		GTGTTCCTGTTCCCCCCAAAGCCTAAGGACA
		CCCTGATGATCAGCCGGACCCCCGAAGTGA
		CCTGCGTGGTGGTGGACGTGTCCCACGAGG
		ACCCTGAAGTGAAGTTTAATTGGTACGTGGA
		CGGCGTGGAAGTGCACAACGCCAAGACCAA
		GCCCAGAGAGGAACAGTACAACAGCACCTA
		CCGGGTGGTGTCCGTGCTGACCGTGCTGCA
		CCAGGACTGGCTGAACGGCAAAGAGTACAA
		GTGCAAGGTGTCCAACAAGGCCCTGCCTTC
		CTCCATCGAGAAAACCATCAGCAAGGCCAAA
		GGCCAGCCCCGCGAGCCCCAGGTGTACACA
		CTGCCCCCTAGCCGGGAAGAGATGACCAAG
		AACCAGGTGTCCCTGACCTGCCTCGTGAAG
		GGCTTCTACCCCAGCGACATTGCCGTGGAA
		TGGGAGAGCAACGGCCAGCCCGAGAACAAC
		TACAAGACCACCCCCCCTGTGCTGGACAGC
		GACGGCTCATTCTTCCTGTACAGCAAGCTGA
		CCGTGGACAAGAGCCGGTGGCAGCAGGGC
		AACGTGTTCAGCTGCTCCGTGATGCACGAG
		GCCCTGCACAACCACTACACCCAGAAGTCC
		CTGAGCCTGAGCCCCGGCAAG
Light chain (DNA)	SEQ ID NO: 69	CAGAGCGTGCTGACCCAGCCTCCTAGCGTG
		AGCGGTGCACCGGGCCAGCGCGTGACCATT
		AGCTGTAGCGGCAGCTCCTCCAATATTGGTA
		GCTATTACGTGAGCTGGTATCAGCAGCTGC
		CGGGCACGGCGCCGAAAGTTCTGATCTATC
		GTAATAATCAACGTCCTAGCGGCGTGCCGG
		ATCGCTTTAGCGGATCCAAAAGCGGCACCA
		GCGCCAGCCTGGCGATTACCGGCCTGCAAG

TABLE 2-continued

Antibody sequences of MAB#2

MAB#2	SEQ ID NO:	[aa] / DNA
		CAGAAGATGAAGCGGATTATTACTGCGACAG
		CTGGGATCACAGCTCCATGAATGTTTTTGGC
		GGCGGTACCAAGCTGACCGTGCTGGGCCAG
		CCCAAAGCCGCCCCTAGCGTGACCCTGTTC
		CCCCCCTCGAGTGAGGAACTCCAGGCCAAC
		AAGGCCACCCTCGTGTGCCTGATCAGCGAC
		TTCTACCCTGGCGCCGTGACCGTGGCCTGG
		AAGGCCGATAGCAGCCCTGTGAAGGCCGGC
		GTGGAAACCACCACCCCCAGCAAGCAGAGC
		AACAACAAATACGCCGCCAGCAGCTACCTG
		AGCCTGACCCCCGAGCAGTGGAAGTCCCAC
		AGATCCTACAGCTGCCAGGTCACACACGAG
		GGCAGCACCGTGGAAAAGACCGTGGCCCCC
		ACCGAGTGCAGC

MAB#2 DNA OPTIMIZED

HCDR1 (Kabat)	SEQ ID NO: 82	AGCTACGCTATGCAC
HCDR2 (Kabat)	SEQ ID NO: 83	CGGATCAAGAGCGTTGCCCAAGGCGGCACC ACCGATTACGCTGCTCATGTGAAGGGC
HCDR3 (Kabat)	SEQ ID NO: 84	GTGTCCCACTCTACCTTCGATGTG
HCDR1 (Chothia)	SEQ ID NO: 85	GGCTTCACCTTCTCCAGCTAC
HCDR2 (Chothia)	SEQ ID NO: 86	AAGAGCGTTGCCCAAGGCGGCACC
HCDR3 (Chothia)	SEQ ID NO: 84	GTGTCCCACTCTACCTTCGATGTG
LCDR1 (Kabat)	SEQ ID NO: 87	TCCGGCTCCTCCTCCAACATCGGCTCCTACT ACGTGTCC
LCDR2 (Kabat)	SEQ ID NO: 88	CGGAACAACCAGCGGCCTTCT
LCDR3 (Kabat)	SEQ ID NO: 89	GACTCTTGGGACCACTCCTCCATGAACGTG
LCDR1 (Chothia)	SEQ ID NO: 87	TCCGGCTCCTCCTCCAACATCGGCTCCTACT ACGTGTCC
LCDR2 (Chothia)	SEQ ID NO: 88	CGGAACAACCAGCGGCCTTCT
LCDR3 (Chothia)	SEQ ID NO: 89	GACTCTTGGGACCACTCCTCCATGAACGTG
VH	SEQ ID NO: 90	GAAGTGCAGCTGGTGGAATCTGGCGGCGGA CTTGTGAAACCTGGCGGCTCTCTGAGACTGT CTTGTGCCGCTTCCGGCTTCACCTTCTCCAG CTACGCTATGCACTGGGTCCGACAGGCCCC TGGCAAAGGATTGGAGTGGGTCGGACGGAT CAAGAGCGTTGCCCAAGGCGGCACCACCGA TTACGCTGCTCATGTGAAGGGCAGATTCACC ATCAGCCGGGACGACTCCAAGAACACCCTG TACCTGCAGATGAACTCCCTGAAAACCGAG GACACCGCCGTGTACTACTGCGCCAGAGTG TCCCACTCTACCTTCGATGTGTGGGGCCAG GGCACACTGGTTACAGTCTCGAGC
VL	SEQ ID NO: 91	CAGTCCGTGCTGACCCAGCCTCCTTCTGTTT CTGGTGCTCCTGGCCAGAGAGTGACCATCT CTTGCTCCGGCTCCTCCTCCAACATCGGCTC CTACTACGTGTCCTGGTATCAGCAGCTGCCT GGCACCGCTCCTAAGGTGCTGATCTACCGG AACAACCAGCGGCCTTCTGGCGTGCCCGAT AGATTCTCCGGCTCTAAGTCTGGCACCTCTG CCAGCCTGGCTATCACTGGACTGCAGGCTG AGGACGAGGCCGACTACTACTGCGACTCTT GGGACCACTCCTCCATGAACGTGTTCGGCG GAGGTACCAAGCTGACCGTGCTGGGACAG
Heavy chain (IgG1) IgG1 AEASS	SEQ ID NO: 92	GAAGTGCAGCTGGTGGAATCTGGCGGCGGA CTTGTGAAACCTGGCGGCTCTCTGAGACTGT CTTGTGCCGCTTCCGGCTTCACCTTCTCCAG CTACGCTATGCACTGGGTCCGACAGGCCCC

TABLE 2-continued

Antibody sequences of MAB#2

MAB#2	SEQ ID NO:	[aa] / DNA
		TGGCAAAGGATTGGAGTGGGTCGGACGGAT
		CAAGAGCGTTGCCCAAGGCGGCACCACCGA
		TTACGCTGCTCATGTGAAGGGCAGATTCACC
		ATCAGCCGGGACGACTCCAAGAACACCCTG
		TACCTGCAGATGAACTCCCTGAAAACCGAG
		GACACCGCCGTGTACTACTGCGCCAGAGTG
		TCCCACTCTACCTTCGATGTGTGGGGCCAG
		GGCACACTGGTTACAGTCTCGAGCGCCTCC
		ACCAAAGGACCCTCTGTGTTTCCTCTGGCTC
		CCTCCAGCAAGTCTACCTCTGGTGGAACAG
		CTGCCCTGGGCTGCCTGGTCAAGGATTACT
		TTCCTGAGCCTGTGACCGTGTCCTGGAACTC
		TGGCGCTCTGACATCTGGCGTGCACACCTTT
		CCAGCTGTGCTGCAGTCCTCTGGCCTGTAC
		AGCCTGTCCTCTGTCGTGACCGTGCCTTCTA
		GCTCTCTGGGCACCCAGACCTACATCTGCA
		ATGTGAACCACAAGCCTTCCAACACCAAGGT
		GGACAAGAGAGTGGAACCCAAGTCCTGCGA
		CAAGACCCACACCTGTCCTCCATGTCCTGCT
		CCAGAAGCTGAGGGCGCTCCTTCCGTGTTC
		CTGTTTCCTCCAAAGCCTAAGGACACCCTGA
		TGATCTCTCGGACCCCTGAAGTGACCTGCG
		TGGTGGTGGATGTGTCTCACGAGGACCCAG
		AAGTGAAGTTCAATTGGTACGTGGACGGCG
		TGGAAGTGCACAACGCCAAGACCAAGCCTA
		GAGAGGAACAGTACAACTCCACCTACAGAG
		TGGTGTCCGTGCTGACCGTGCTGCACCAGG
		ATTGGCTGAACGGCAAAGAGTACAAGTGCA
		AGGTGTCCAACAAGGCCCTGCCTTCCAGCA
		TCGAAAAGACCATCTCCAAGGCCAAGGGCC
		AGCCTAGGGAACCCCAGGTTTACACCCTGC
		CTCCAAGCCGGGAAGAGATGACCAAGAACC
		AGGTGTCCCTGACCTGCCTCGTGAAGGGCT
		TCTACCCTTCCGATATCGCCGTGGAATGGGA
		GAGCAATGGCCAGCCTGAGAACAACTACAA
		GACAACCCCTCCTGTGCTGGACTCCGACGG
		CTCATTCTTCCTGTACTCCAAGCTGACAGTG
		GACAAGTCCAGATGGCAGCAGGGCAACGTG
		TTCTCCTGCTCCGTGATGCACGAGGCCCTG
		CACAATCACTACACACAGAAGTCCCTGTCTC
		TGTCCCCTGGCAAG
Light chain (DNA)	SEQ ID NO: 93	CAGTCCGTGCTGACCCAGCCTCCTTCTGTTT
		CTGGTGCTCCTGGCCAGAGAGTGACCATCT
		CTTGCTCCGGCTCCTCCTCCAACATCGGCTC
		CTACTACGTGTCCTGGTATCAGCAGCTGCCT
		GGCACCGCTCCTAAGGTGCTGATCTACCGG
		AACAACCAGCGGCCTTCTGGCGTGCCCGAT
		AGATTCTCCGGCTCTAAGTCTGGCACCTCTG
		CCAGCCTGGCTATCACTGGACTGCAGGCTG
		AGGACGAGGCCGACTACTACTGCGACTCTT
		GGGACCACTCCTCCATGAACGTGTTCGGCG
		GAGGTACCAAGCTGACCGTGCTGGGACAGC
		CTAAGGCTGCCCCTTCCGTGACACTGTTCCC
		TCCATCCTCTGAGGAACTGCAGGCCAACAA
		GGCTACCCTCGTGTGCCTGATCTCCGACTTT
		TACCCTGGCGCTGTGACCGTGGCCTGGAAG
		GCTGATAGTTCTCCTGTGAAGGCCGGCGTG
		GAAACCACCACACCTTCCAAGCAGTCCAACA
		ACAAATACGCCGCCTCCTCCTACCTGTCTCT
		GACCCCTGAACAGTGGAAGTCCCACCGGTC
		CTACAGCTGCCAAGTGACCCATGAGGGCTC
		CACCGTGGAAAAGACCGTGGCTCCTACCGA
		GTGCTCT

TABLE 3

Antibody sequences of RefMAB#1

RefMAB#1	SEQ ID NO:	[aa]
RefMAB#1 Protein		
Heavy chain IgG1_AEASS	SEQ ID NO: 94	EVQLVESGGGLVQPGGSLRLSCAASGFTFSS YVMHVVVRQATGKGLEVVVSAIDTGGGTYYA DSVKGRFTISRENAKNSLYLQMNSLRAGDTA VYYCARDYYYYASGSYYKAFDIWGQGTMVT VSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQ SSGLYSLSSVVTVPSSSLGTQTYICNVNHKP SNTKVDKRVEPKSCDKTHTCPPCPAPEAEG APSVFLFPPKPKDTLMISRTPEVTCVVVDVS HEDPEVKFNWYVDGVEVHNAKTKPREEQYNS TYRVVSVLTVLHQDWLNGKEYKCKVSNKAL PSSIEKTISKAKGQPREPQVYTLPPSREEMT KNQVSLTCLVKGFYPSDIAVEWESNGQPENN YKTTPPVLDSDGSFFLYSKLTVDKSRWQQG NVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	SEQ ID NO: 95	EIVLTQSPGTLSLSPGERATLSCRASQSVSS RYLAVVYQQKPGQAPRLLIYGASSRATGIPD RFSGSGSGTDFTLTISRLEPEDFAVYYCQQY GSPLTFGQGTKLEIKRTVAAPSVFIFPPSDE QLKSGTASVVCLLNNFYPREAKVQWKVDNAL QSGNSQESVTEQDSKDSTYSLSSTLTLSKAD YEKHKVYACEVTHQGLSSPVTKSFNRGEC

WORKING EXAMPLES

Example 1: Antigen Generation and Quality Control

[0514] Amino acid sequences of C5aR and C5aR related GPCRs from various species were retrieved from publicly available sources (e.g. Uniprot), verified and produced in-house or by external service providers.

Synthetic Peptides

[0515] As antigens for the initial panning and screening, linear peptides covering the N-terminal extracellular region of human C5aR were used. The peptides were chemically synthesized with a biotin tag (JPT), RP-HPLC purified and delivered as lyophilized material. The lyophilized peptides were stored at −80° C. Alternatively, the peptides were conjugated to Transferrin or bovine serum albumin (BSA).

TABLE 4

Amino acid sequence of N-terminal human C5aR peptide used for initial panning and screening.

N-terminal C5aR peptides		
Human	SEQ ID NO: 12	MDSFNYTTPDYGHYDDKDTLDLNTPVDKTSN

[0516] As antigens for later binding studies, linear peptides comprising the N-terminal region of human and cynomolgus monkey C5aR were used. The peptides were chemically synthesized with a biotin tag (Genscript), RP-HPLC purified and delivered as lyophilized material. The lyophilized peptides were stored at −80° C. For reconstitution, peptides were dissolved in the desired volume of PBS and stored at −80° C.

TABLE 5

Amino acid sequences of N-terminal C5aR peptides used for binding studies.

N-terminal C5aR peptides (C5aR_NT peptide)		
Human	SEQ ID NO: 13	MDSFNYTTPDYGHYDDKDTLDLNTP VDKTSNTLRVPD
Cynomolgus	SEQ ID NO: 14	MDPFSSTTLDYEHYDGKNVLDSDTP VDKTSNTLRVPD

Recombinant Proteins

C1q Protein

[0517] C1q protein purified from pooled normal human plasma was purchased from Complement Technology, Inc. (Catalog #A099).

Human C5a Protein

[0518] Recombinant human C5a was either purchased from R&D Systems (CAT #: 2037-05) or was produced in house.

[0519] For in-house production, DNA encoding the amino acids of human C5a (Uniprot: P010311 Lys679-Arg751) was cloned into a pET21a expression vector (Novagen) in frame with an N-terminal ompA signal sequence followed by a sequence coding for maltose-binding protein (MBP), a FXa cleavage site and a GS linker.

[0520] Human C5a (hC5a) was expressed in *E. coli* BL21 (DE3) cells (Novagen) as a N-terminally tagged maltose-binding protein (MBP)-fusion protein. Protein expression was induced by the addition of IPTG and cultures were further cultivated for 20-23 h. Cells were harvested by centrifugation and the pellet was resuspended in lysis buffer (PBS buffer plus 2 mM $MgCl_2$, 20 U/ml Benzonase (Roche) and 1 tablet/50 ml complete, EDTA-free protease inhibitor cocktail tablets (Roche)). Cells were disrupted either by chemical lysis or high-pressure homogenization. The resulting suspension was centrifuged and the supernatant was sterile filtered for further purification steps.

[0521] The hC5a-MBP-fusion protein was purified by Dextrin-Sepharose affinity chromatography using a MBP-Trap column (GE-Healthcare) and optionally polished by cation exchange chromatography using a Hi-Trap SP FF column (GE LifeSciences). The purified MBP-fusions were buffer-exchanged by PD10 columns (GE Healthcare) into FXa-digest buffer (20 mM Tris/HCl pH 8.0; 100 mM NaCl; 2 mM $CaCl_2$)). The hC5a protein was released from the maltose-binding protein by addition of Factor Xa (1:100 (w/w)) and incubation 0/N in a rotary shaker at room temperature. The released hC5a was purified by cation exchange chromatography using a Hi-Trap SP FF column (GE LifeSciences). All affinity chromatography steps were performed using an ÄKTA Avant 25 preparative chromatography system.

[0522] Buffer exchange to PBS was performed using PD 10 columns (GE Healthcare). Samples were sterile filtered and hC5a concentration was determined by UV-spectrophotometry. The purity and integrity of the samples were analyzed in denaturing, reducing or non-reducing SDS-PAGE, SEC-HPLC and mass spectrometry.

Fc Gamma Receptors (FcγR) and FcRn Receptors

[0523] DNA encoding the extracellular region of human FcγRI, human FcγRIIa (131H), human FcγRIIa (131R), human FcγRIIb, human FcγRIIIa (158F) and human FcγRIIIa (158V) were cloned in frame with an N-terminal V_K leader sequence and a C-terminal 6×His-tag into a pMAX expression vector, which is a modified expression vector based on pcDNA3.1 (Thermo Fisher).

[0524] DNA encoding the extracellular region of human, cynomolgus, mouse or rat FcRn large subunit p51 was cloned in frame with an N-terminal V_K leader sequence and a C-terminal AVI-6×His-tag into a pMAX expression vector, which is a modified expression vector based on pcDNA3.1 (Thermo Fisher). In addition, DNA encoding human, cynomolgus monkey, mouse or rat FcRn small subunit p14 (=identical with beta-2 microglobulin) protein was cloned into a second open reading frame in frame with an N-terminal Vk leader sequence. The amino acid sequences of the produced receptors are summarized in Table 6 and 7.

[0525] The HEK293-6E cell line was developed by the National Research Council of Canada (NRC). Cells were maintained in Freestyle F17 medium (Thermo Scientific) in a humidified CO2-incubator at 37° C. and 6% CO_2. HKB11 (Parental clone: U.S. Pat. No. 6,136,599. J. Biomed. Sci. 2002; 9:631-638) is a human hybrid cell line resulting from a fusion of HEK293 human embryonic kidney and 2B8 Burkitt lymphoma cells. HKB11 #52 cells were maintained in MAC1.0 medium containing 1% FCS in a humidified CO_2 incubator at 37° C. and 6% CO_2.

[0526] HKB11#52 or HEK293-6E cells were transiently transfected one day post seeding with a commercially available transfection reagent according to the manufacturer's instructions. The cells were cultured for 3 days and the conditioned cell culture supernatant was harvested by centrifugation followed by sterile filtration (0.22 μm). Stably transfected HKB11#52 pools were generated by transfection of cells followed by selection with 800 μg/mL G418 (Thermo Scientific). Expression of antigens from stable pools was done for 4 days post seeding. The conditioned cell culture supernatants were harvested by centrifugation followed by sterile filtration (0.22 μm).

[0527] The respective proteins were purified by IMAC using Protino Ni-NTA columns (Macherey-Nagel). All chromatography steps were performed using ÄKTA chromatography systems (GE Healthcare). The samples were buffer-exchanged to D-PBS using PD10 columns (GE Healthcare). In some cases, a polishing preparative SEC step was performed in D-PBS using a Superdex 200 column (GE Healthcare).

[0528] Biotinylation of FcRn heterodimers was performed by in vitro biotinylation using the BirA Kit (Avidity) followed by a preparative SEC using a Superdex 200 column (GE Healthcare).

[0529] The quality of the samples was analyzed by denaturing, reducing or non-reducing SDS-PAGE, Streptavidin-Shift Assay, HP-SEC and DLS.

TABLE 6

Amino acid sequences of produced FcRn proteins.

FcRn Fusion Protein	UniProt IDs:	SEQ ID NO:	Protein sequence
Human FcRn p51 [1-297] / AviHis / p14 biotinylated	P55899 (p51) P61769 (p14)	SEQ ID NO: 15	AESHLSLLYHLTAVSSPAPGTPAFWVSGWLGPQ QYLSYNSLRGEAEPCGAWVWENQVSWYWEKE TTDLRIKEKLFLEAFKALGGKGPYTLQGLLGCEL GPDNTSVPTAKFALNGEEFMNFDLKQGTWGGD WPEALAISQRWQQQDKAANKELTFLLFSCPHRL REHLERGRGNLEWKEPPSMRLKARPSSPGFSV LTCSAFSFYPPELQLRFLRNGLAAGTGQGDFGP NSDGSFHASSSLTVKSGDEHHYCCIVQHAGLAQ PLRVELESPAKSSVNSRGLNDIFEAQKIEWHEHH HHHHIQRTPKIQVYSRHPAENGKSNFLNCYVSG FHPSDIEVDLLKNGERIEKVEHSDLSFSKDWSFY LLYYTEFTPTEKDEYACRVNHVTLSQPKIVKWDR DM
Cynomolgus FcRn p51 [1-297]_AviHis / p14 biotinylated	Q8SPV9 (p51) P61769 (p14)	SEQ ID NO: 16	AESHLSLLYHLTAVSSPAPGTPAFVVVSGWLGPQ QYLSYDSLRGQAEPCGAWVWENQVSWYWEKE TTDLRIKEKLFLEAFKALGGKGPYTLQGLLGCEL SPDNTSVPTAKFALNGEEFMNFDLKQGTWGGD WPEALAISQRWQQQDKAANKELTFLLFSCPHRL REHLERGRGNLEWKEPPSMRLKARPGNPGFSV LTCSAFSFYPPELQLRFLRNGMAAGTGQGDFGP NSDGSFHASSSLTVKSGDEHHYCCIVQHAGLAQ PLRVELETPAKSSVNSRGLNDIFEAQKIEWHEHH HHHHIQRTPKIQVYSRHPPENGKPNFLNCYVSG FHPSDIEVDLLKNGEKMGKVEHSDLSFSKDWSF YLLYYTEFTPNEKDEYACRVNHVTLSGPRTVKW DRDM
Mouse FcRn p51 [1-297] / AviHis / p14 biotinylated	Q61559 (p51) P61769 (p14)	SEQ ID NO: 17	SETRPPLMYHLTAVSNPSTGLPSFWATGWLGP QQYLTYNSLRQEADPCGAWMWENQVSWYWEK ETTDLKSKEQLFLEALKTLEKILNGTYTLQGLLGC ELASDNSSVPTAVFALNGEEFMKFNPRIGNWTG EWPETEIVANLWMKQPDAARKESEFLLNSCPER LLGHLERGRRNLEWKEPPSMRLKARPGNSGSS VLTCAAFSFYPPELKFRFLRNGLASGSGNCSTG

TABLE 6-continued

Amino acid sequences of produced FcRn proteins.

FcRn Fusion Protein	UniProt IDs:	SEQ ID NO:	Protein sequence
			PNGDGSFHAWSLLEVKRGDEHHYQCQVEHEGL AQPLTVDLDSSARSSVNSRGLNDIFEAQKIEWHE HHHHHHIQKTPQIQVYSRHPPENGKPNILNCYVT QFHPPHIEIQMLKNGKKIPKVEMSDMSFSKDWS FYILAHTEFTPTETDTYACRVKHDSMAEPKTVYW DRDM
Rat FcRn p51 [1-298] / AviHis / p14 biotinylated	P13599 (p51) P61769 (p14)	SEQ ID NO: 96	AEPRLPLMYHLAAVSDLSTGLPSFWATGWLGAQ QYLTYNNLRQEADPCGAWIWENQVSWYWEKET TDLKSKEQLFLEAIRTLENQINGTFTLQGLLGCEL APDNSSLPTAVFALNGEEFMRFNPRTGNWSGE WPETDIVGNLWMKQPEAARKESEFLLTSCPERL LGHLERGRQNLEWKEPPSMRLKARPGNSGSSV LTCAAFSFYPPELKFRFLRNGLASGSGNCSTGP NGDGSFHAWSLLEVKRGDEHHYQCQVEHEGLA QPLTVDLDSPARSSVNSRGLNDIFEAQKIEWHEH HHHHHIQKTPQIQVYSRHPPENGKPNFLNCYVS QFHPPQIEIELLKNGKKIPNIEMSDLSFSKDWSFY ILAHTEFTPTETDVYACRVKHVTLKEPKTVTWDR DM

TABLE 7

Amino acid sequences of produced human FcγR proteins.

FcγR Fusion Protein	UniProt IDs:	SEQ ID NO:	Protein sequence
Human FcγRI (1-279)_HIS$_6$	P12314	SEQ ID NO: 18	QVDTTKAVITLQPPWVSVFQEETVTLHCEVLHLP GSSSTQWFLNGTATQTSTPSYRITSASVNDSGE YRCQRGLSGRSDPIQLEIHRGWLLLQVSSRVFT EGEPLALRCHAWKDKLVYNVLYYRNGKAFKFFH WNSNLTILKTNISHNGTYHCSGMGKHRYTSAGIS VTVKELFPAPVLNASVTSPLLEGNLVTLSCETKLL LQRPGLQLYFSFYMGSKTLRGRNTSSEYQILTAR REDSGLYWCEAATEDGNVLKRSPELELQVNSR HHHHHH
Human FcγRIIa (1-209)-(131H)-HIS$_6$(133-2)	P12318	SEQ ID NO: 19	QAAAPPKAVLKLEPPWINVLQEDSVTLTCQGAR SPESDSIQWFHNGNLIPTHTQPSYRFKANNNDS GEYTCQTGQTSLSDPVHLTVLSEWLVLQTPHLE FQEGETIMLRCHSWKDKPLVKVTFFQNGKSQKF SHLDPTFSIPQANHSHSGDYHCTGNIGYTLFSSK PVTITVQVPSVNSRHHHHHH
Human FcγRIIa (1-209)-(131R)-HIS$_6$ (137-3)	P12318	SEQ ID NO: 20	QAAAPPKAVLKLEPPWINVLQEDSVTLICQGAR SPESDSIQWFHNGNLIPTHTQPSYRFKANNNDS GEYTCQTGQTSLSDPVHLTVLSEWLVLQTPHLE FQEGETIMLRCHSWKDKPLVKVTFFQNGKSQKF SRLDPTFSIPQANHSHSGDYHCTGNIGYTLFSSK PVTITVQVPSVNSRHHHHHH
Human FcγRIIIa (1-193)-(158F)-HIS$_6$ (141-2)	P08637	SEQ ID NO: 21	GMRTEDLPKAVVFLEPQWYRVLEKDSVTLKCQG AYSPEDNSTQWFHNESLISSQASSYFIDAATVDD SGEYRCQTNLSTLSDPVQLEVHIGWLLLQAPRW VFKEEDPIHLRCHSWKNTALHKVTYLQNGKGRK YFHHNSDFYIPKATLKDSGSYFCRGLFGSKNVSS ETVNITITQGVNSRHHHHHH
Human FcγRIIIa (1-193)-(158V)-HIS$_6$	P08637	SEQ ID NO: 22	GMRTEDLPKAVVFLEPQWYRVLEKDSVTLKCQG AYSPEDNSTQWFHNESLISSQASSYFIDAATVDD SGEYRCQTNLSTLSDPVQLEVHIGWLLLQAPRW VFKEEDPIHLRCHSWKNTALHKVTYLQNGKGRK YFHHNSDFYIPKATLKDSGSYFCRGLVGSKNVS SETVNITITQGVNSRHHHHHH
Human FcγRIIB (1-202)-HIS$_6$	P31994	SEQ ID NO: 23	TPAAPPKAVLKLEPQWINVLQEDSVTLTCRGTHS PESDSIQWFHNGNLIPTHTQPSYRFKANNNDSG EYTCQTGQTSLSDPVHLTVLSEWLVLQTPHLEF

TABLE 7-continued

Amino acid sequences of produced human FcγR proteins.

FcγR Fusion Protein	UniProt IDs:	SEQ ID NO:	Protein sequence
			QEGETIVLRCHSWKDKPLVKVTFFQNGKSKKFS RSDPNFSIPQANHSHSGDYHCTGNIGYTLYSSK PVTITVQAPSDNSRHHHHHH

Virus-Like-Particles (VLPs)

[0530] VLPs stably expressing either one of the two natural variants of human C5aR (D/K variant or N/N variant) as well as mouse C5aR were generated in house as described in WO 2015/193143. All cloning experiments were performed using standard technologies. Antigens of interest were cloned in a suited two vector system for the expression in mammalian cells. In this system, one vector expresses GAG and the other vector expresses the GPCR-GAG fusion protein. Expression in these vectors is under the control of the CMV promoter. Subsequently, host cells were transfected with the two vectors. The generated constructs were produced as fusion proteins, in which the antigen of interest is fused N-terminal to the GAG-protein (HV1B1 (Uni-Prot ID: P03347)). Expression of the proteins and production of the VLPs was done under standard conditions in suspension cultures. Host cells used in the present experiments were HKB11 cells (ATCC; CRL-12568) and HEK cells (Life Technologies). Three days post transfection the supernatants containing the VLPs were harvested and purified using standard procedures (including precipitation and ion exchange chromatography). The proteins isolated were subjected to SDS-PAGE chromatography. The supernatants were probed with a commercial anti-GAG antibody or a commercial anti-C5aR antibody and revealed that co-expression of GAG and a GPCR-GAG fusion protein resulted in a high expression level of GAG and GPCR-GAG in the VLPs. This confirmed that the C5aR antigens were efficiently integrated into the VLPs, and that the C5aR antigens were detectable with antibodies. The amino acid sequences of the produced fusion proteins are summarized in Table 8.

TABLE 8

Protein sequences of C5aR-GAG fusion protein expressed on virus-like-particles.

C5aR-HV1B1 fusion protein	SEQ ID NO:	Protein sequence
HIS_6-human C5aR (D/K variant)-HV1B1-GAG	SEQ ID NO: 24	DGSHHHHHHGTMDSFNYTTPDYGHYDDKDTLDLNTPVDKTSNT LRVPDILALVIFAVVFLVGVLGNALVVWVTAFEAKRTINAIWFLNLA VADFLSCLALPILFTSIVQHHHWPFGGAACSILPSLILLNMYASILL LATISADRFLLVFKPIWCQNFRGAGLAWIACAVAWGLALLLTIPSF LYRVVREEYFPPKVLCGVDYSHDKRRERAVAIVRLVLGFLWPLL TLTICYTFILLRTWSRRATRSTKTLKVVVAVVASFFIFWLPYQVTGI MMSFLEPSSPTFLLLKKLDSLCVSFAYINCCINPIIYVVAGQGFQG RLRKSLPSLLRNVLTEESVVRESKSFTRSTVDTMAQKTQAVDIDY KDDDDKIEGRMDGARASVLSGGELDRWEKIRLRPGGKKKYKLK HIVWASRELERFAVNPGLLETSEGCRQILGQLQPSLQTGSEELR SLYNTVATLYCVHQRIEIKDTKEALDKIEEEQNKSKKKAQQAAAD TGHSSQVSQNYPIVQNIQGQMVHQAISPRTLNAWVKVVEEKAFS PEVIPMFSALSEGATPQDLNTMLNTVGGHQAAMQMLKETINEEA AEWDRVHPVHAGPIAPGQMREPRGSDIAGTTSTLQEQIGWMTN NPPIPVGEIYKRWIILGLNKIVRMYSPTSILDIRQGPKEPFRDYVDR FYKTLRAEQASQEVKNWMTETLLVQNANPDCKTILKALGPAATL EEMMTACQGVGGPGHKARVLAEAMSQVTNTATIMMQRGNFRN QRKMVKCFNCGKEGHTARNCRAPRKKGCWKCGKEGHQMKDC TERQANFLGKIWPSYKGRPGNFLQSRPEPTAPPFLQSRPEPTAP PEESFRSGVETTTPPQKQEPIDKELYPLTSLRSLFGNDPSSQVN SRGLNDIFEAQKIEWHE
HIS_6-human C5aR (N/N variant)-HV1B1-GAG	SEQ ID NO: 25	DGSHHHHHHGTMNSFNYTTPDYGHYDDKDTLDLNTPVDKTSNT LRVPDILALVIFAVVFLVGVLGNALVVWVTAFEAKRTINAIWFLNLA VADFLSCLALPILFTSIVQHHHWPFGGAACSILPSLILLNMYASILL LATISADRFLLVFKPIWCQNFRGAGLAWIACAVAWGLALLLTIPSF LYRVVREEYFPPKVLCGVDYSHDKRRERAVAIVRLVLGFLWPLL TLTICYTFILLRTWSRRATRSTKTLKVVVAVVASFFIFWLPYQVTGI MMSFLEPSSPTFLLLNKLDSLCVSFAYINCCINPIIYVVAGQGFQG RLRKSLPSLLRNVLTEESVVRESKSFTRSTVDTMAQKTQAVDIGA RASVLSGGELDRWEKIRLRPGGKKKYKLKHIVWASRELERFAVN PGLLETSEGCRQILGQLQPSLQTGSEELRSLYNTVATLYCVHQRI EIKDTKEALDKIEEEQNKSKKKAQQAAADTGHSSQVSQNYPIVQ NIQGQMVHQAISPRTLNAWVKVVEEKAFSPEVIPMFSALSEGAT PQDLNTMLNTVGGHQAAMQMLKETINEEAAEWDRVHPVHAGPI APGQMREPRGSDIAGTTSTLQEQIGWMTNNPPIPVGEIYKRWIIL GLNKIVRMYSPTSILDIRQGPKEPFRDYVDRFYKTLRAEQASQEV

TABLE 8-continued

Protein sequences of C5aR-GAG fusion protein expressed on virus-like-particles.

C5aR-HV1B1 fusion protein	SEQ ID NO:	Protein sequence
		KNWMTETLLVQNANPDCKTILKALGPAATLEEMMTACQGVGGP GHKARVLAEAMSQVTNTATIMMQRGNFRNQRKMVKCFNCGKE GHTARNCRAPRKKGCWKCGKEGHQMKDCTERQANFLGKIWPS YKGRPGNFLQSRPEPTAPPFLQSRPEPTAPPEESFRSGVETTTP PQKQEPIDKELYPLTSLRSLFGNDPSSQ
HIS_6_mouse C5aR-HV1B1-GAG	SEQ ID NO: 26	DGSHHHHHHGTMDPIDNSSFEINYDHYGTMAPNIPADGIHLPKR QPGDVAALIIYSVVFLVGVPGNALWWVTAFEARRAVNAIWFLNL AVADLLSCLALPVLFTTVLNHNYWYFDATACIVLPSLILLNMYASIL LLATISADRFLLVFKPIWCQKVRGTGLAWMACGVAVVVLALLLTIP SFVYREAYKDFYSEHTVCGINYGGGSFPKEKAVAILRLMVGFVLP LLTLNICYTFLLLRTWSRKATRSTKTLKVVMAVVICFFIFWLPYQV TGVMIAWLPPSSPTLKRVEKLNSLCVSLAYINCCVNPIIYVMAGQ GFHGRLLRSLPSIIRNALSEDSVGRDSKTFTPSTTDTSTRKSQAV DIDYKDDDDKIEGRMDGARASVLSGGELDRWEKIRLRPGGKKKY KLKHIVWASRELERFAVNPGLLETSEGCRQILGQLQPSLQTGSE ELRSLYNTVATLYCVHQRIEIKDTKEALDKIEEEQNKSKKKAQQA AADTGHSSQVSQNYPIVQNIQGQMVHQAISPRTLNAWVKVVEEK AFSPEVIPMFSALSEGATPQDLNTMLNTVGGHQAAMQMLKETIN EEAAEWDRVHPVHAGPIAPGQMREPRGSDIAGTTSTLQEQIGW MTNNPPIPVGEIYKRWIILGLNKIVRMYSPTSILDIRQGPKEPFRDY VDRFYKTLRAEQASQEVKNWMTETLLVQNANPDCKTILKALGPA ATLEEMMTACQGVGGPGHKARVLAEAMSQVTNTATIMMQRGN FRNQRKMVKCFNCGKEGHTARNCRAPRKKGCWKCGKEGHQM KDCTERQANFLGKIWPSYKGRPGNFLQSRPEPTAPPFLQSRPE PTAPPEESFRSGVETTTPPQKQEPIDKELYPLTSLRSLFGNDPSS QVNSRGLNDIFEAQKIEWHE

Cell Lines

[0531] CHO Flp-In cells stably expressing full length human C5aR, cynomolgus C5aR, mouse C5aR, rat C5aR and the C5aR related GPCRs human C5L2, human C3aR, human FPR1 and human ChemR23 were generated. For the generation of Flp-In CHO cells, various vector constructs were gene synthesized in-house and transfection of cells was performed according to the instructor's manual (Thermofischer/Invitrogen). All constructs contained an N-terminal V5/His tag. Commercially available anti-His (e.g. Dianova CAT #DIA-910) or anti-V5 (e.g. AbD Serotec CAT #MCA2285GA) detection antibodies were used to confirm the expression of the respective GPCR on the surface of the cell line, even in the absence of a commercially available specific anti-GPCR tool antibody.

Example 2: Generation of Human C5aR Specific Antibodies from the HuCAL PLATINUM® Library

[0532] For antibody generation, the HuCAL Platinum® library was used to select for antibodies with specificity for human C5aR. The HuCAL PLATINUM® library is a phagemid library based on the HuCAL concept (Knappik et al., (2000) J Mol Biol 296:57-86) and employs the CysDisplay® technology for displaying the Fab on the phage surface (Lohning et al., WO2001/05950).

[0533] To identify human C5aR specific antibodies, panning strategies were performed using human and cynomolgus monkey C5aR antigen material to select species cross-reactive antibodies. Each conducted panning comprised of at least 3 individual rounds of selection against various C5aR antigens (either as soluble recombinant antigens or overexpressed on cells).

[0534] Although the overall homology between cynomolgus and human C5aR with 90% is rather high, the extracellular domains share only 75% identity of the protein sequences. Indeed, the identification of cynomolgus C5aR cross-reactive antibodies turned out to be challenging, with the ancestor antibody of MAB#1 and MAB#2 being one of a few candidates revealing specific cell binding to human C5aR expressed on cells, cross-reactivity to cynomolgus monkey C5aR and no binding to other related GPCRs.

[0535] Bead based solution pannings against peptides representing the N-terminus (NT) of human C5aR were conducted which resulted in the identification of the ancestor antibody of MAB#1 and MAB#2 with specificity for human and cynomolgus monkey C5aR and being able to bind to full-length human C5aR expressed on cells.

[0536] This clone was subjected to two consecutively conducted affinity maturation panning using CHO Flp-In cells engineered to overexpress either human or cynomolgus C5aR in order to further increase affinity and specificity for human and cynomolgus C5aR. In addition, antibody engineering was conducted to further increase specificity, to remove potential posttranslational modification sites (PTM motifs) and for germlining purposes.

[0537] With this last step of engineering process, MAB#1 and MAB#2 were identified as potential therapeutic candidates. Since both candidates, MAB#1 and MAB#2 are derived from the same ancestors, they share similar amino acid sequences and in vitro characteristics.

These two antibodies are further described in the examples as outlined below.

Example 3: Production of Human C5aR Specific Antibodies

[0538] Both, MAB#1 and MAB#2 are of the human IgG1f isotype but are engineered in the Fc region to abolish the

ability of the antibodies to mediate immune effector function. The Fc region comprises 5 amino acid substitutions compared to the wild-type human IgG1 Fc region, namely L234A, L235E, G237A, A330S and P331S (h_IgG1f_AEASS) with numbering according EU index.

[0539] The antibodies consist of the heavy chain framework VH3-15 and the antibody light chain framework lambda 1.

Transient Antibody Production—Advanced Micro Scale Production HKB11

[0540] Eukaryotic HKB11#52 cells were transiently transfected with mammalian expression vectors encoding heavy and light chains of MAB#1 or MAB#2 (human IgG1_AEASS), respectively. Cell culture supernatants were harvested 7 days post transfection and subjected to Protein A affinity chromatography (MabSelect SuRe|GE Healthcare) using a liquid handling station. The samples remained in neutralized elution buffer (NaPS: 137 mM NaPhosphate, 81 mM NaCl, pH 7). Samples were sterile filtered (0.2 μm pore size). Protein concentrations were determined by UV-spectrophotometry at 280 μm and purity of IgG was analysed under denaturing, reducing conditions using CE-SDS (LabChip GXII|Perkin Elmer). UHP-SEC was performed to analyse IgG preparations in native state.

Transient Antibody Production—Exploratory Scale Production in CHO

[0541] CHO3-E7 cells were transiently transfected with mammalian expression vector encoding heavy and light chains of MAB#1 or MAB#2 (human IgG1_AEASS), respectively. Cell culture supernatants were harvested on day 6 post transfection and subjected to standard Protein A affinity chromatography (MabSelect SuRe|GE Healthcare). If not stated otherwise, buffer exchange was performed to 1×Dulbecco's PBS (pH 7.2|Invitrogen) and samples were sterile filtered (0.2 μm pore size). Protein concentrations were determined by UV-spectrophotometry at 280 nm and purity of IgG was analysed under denaturing, reducing and non-reducing conditions using CE-SDS (LabChip GXII|Perkin Elmer). UHP-SEC was performed to analyse IgG preparations in native state.

Results Transient Production

[0542] Data on product quality (SEC monomer content) and productivity of MAB#1 and MAB#2 are summarized in Table 9. Overall, acceptable monomer contents (>95%) and yields (>55 mg/L in HKB11 cells) were achieved. Volumetric yields derived from CHO3E-7 transient Exploratory Scale productions were also in the expected range.

TABLE 9

Production data of MAB#1 and MAB#2 in transient expression

Antibody	Production Platform	SEC Monomer %	Volumetric yield [mg/L]
MAB#1	Advanced Micro HKB11	97.5	56.1
	Exploratory CHO	96.4	3.0
MAB#2	Advanced Micro HKB11	97.4	58.9
	Exploratory CHO	98.5	2.4

Generation of Stable HKB11 Pools

[0543] For the generation of HKB11#52 pools stably expressing MAB#1 or MAB#2, a two-vector system was used for co-transfection.

[0544] In order to facilitate pool selection these vectors contain Zeocin and Neomycin resistance cassettes. The two vectors were transiently co-transfected into actively dividing HKB11#52 cells in a 1:1 ratio. One day post transfection selection was started by the addition of 160 μg/mL Zeocin and 800 μg/mL Geneticin to the cell suspension. During the selection cell count and viability initially decreased. 20 days after transfection cells started to recover. Reaching a viability of ~80%, stable pools were scaled up to the desired volume depending on the amount needed. Cell culture supernatants of the batch productions were harvested on day 6 post seeding.

Large Scale Purification of MAB#1 and MAB#2

[0545] Purification of MAB#1 and MAB#2 from cell culture supernatants of HKB11#52 stable pools via Protein A affinity chromatography (MabSelect SURE|GE Healthcare) was performed using 100 mM Citrate, 150 mM NaCl pH 3.5 as elution buffer. After incubation at pH 3.5 for 60 minutes, the samples were neutralized. Buffer exchange was performed into 150 mM Histidine, pH 6.0 and samples were sterile filtered (0.2 μm pore size). Protein concentrations were determined by UV-spectrophotometry at 280 nm and purity of IgG was analysed under denaturing, reducing and non-reducing conditions using CE-SDS (LabChip GXII|Perkin Elmer). UHP-SEC was performed to analyse IgG preparations in native state.

Results Large Scale Production

[0546] As summarized in Table 10, production of MAB#1 and MAB#2 resulted in favorable yields, purity and integrity.

TABLE 10

Production data of MAB#1 and MAB#2 derived from stable cell pool expressions

		SEC			Volumetric
Antibody	Production Platform	Monomer [%]	HMW [%]	LMW [%]	yield [mg/L]
MAB#1	Large Scale HKB11	99.1	0.5	0.4	60.5
MAB#2	Large Scale HKB11	99.1	0.6	0.3	100.5

Control Antibodies

[0547] Various control antibodies were produced and included in experiments for comparative purposes:

RefMAB#1: Benchmark Antibody

[0548] Nucleotide sequences encoding the VH and VL region from the human C5aR specific antibody "IPH5401" were retrieved from US patent application US2013/0295116 (NOVO NORDISK-clone 32F3A6GL). Nucleotide sequences were gene synthesized as linear DNA fragments with appropriate flanking regions (e.g. suitable restriction enzyme recognition sites, linker sequences) either in-house or by an external provider. The DNA fragments were cloned

into suited mammalian IgG expression vectors encoding heavy and light chains of human IgG1_AEASS as described above by using standard molecular biology methods. RefMAB#1 was transiently produced as described above. The heavy and light chain amino acid sequences of RefMAB#1 are depicted in Table 3.

Additional Control Antibodies:

[0549] An in-house negative isotype control antibody with specificity for hen-egg lysozyme (MOR03207) as well as an in-house positive control antibody (anti-C5aR antibody) with specificity for the N-terminus of human C5aR were transiently produced as described above either in human IgG1 or human IgG1_AEASS format.

[0550] Characterization of the Binding Properties of MAB#1 and MAB#2

Example 4: Monovalent Affinity Determination for MAB#1 and MAB#2 for C5aR N-Terminal Peptides Using SPR

Method

[0551] K_D determination via IgG capture setup was performed at 25° C. with a Biacore T200 instrument (Biacore, GE Healthcare). Approx. 500 RU of IgG diluted in HBS-EP+, pH 7.4, were captured on a CM5 chip (Biacore, GE Healthcare) immobilised with anti-human-Fc antibody (GE Healthcare) using standard EDC-NHS amine coupling chemistry. The reference flow cell 1 was only activated and deactivated. Kinetic measurements were done using 6 different human or cynomolgus C5aR_NT-bio peptide concentrations (SEQ ID NO: 13 or SEQ ID NO: 14, respectively) (2n serial dilution, 2000 to 62.5 nM) with HBS-EP+(GE Healthcare) as running buffer (injection time 300 s; dissociation time 600 s; flow rate 30 μL/min). After each cycle the sensor chip was regenerated to remove bound peptide/antibody complex with 3×20 s injections of 3 mM $MgCl_2$. A blank injection of running buffer was used for double referencing. All sensorgrams were fitted using Biacore T200 Evaluation Software 3.1, (Biacore, GE Healthcare) to determine k_{on} and k_{off} rate constants, which were used to calculate K_D. The raw data was fitted with a 1:1 binding model, with parameters R_{max} set to local and RI set to 0.

Results

[0552] Results are summarized in Table 11. Both antibodies revealed similar binding to the human C5aR peptide with K_D values in the low double-digit nanomolar range and weaker binding to the cynomolgus C5aR peptide.

TABLE 11

Determination of association and dissociation rate constants for binding of MAB#1 and MAB#2 to human and cynomolgus C5aR N-terminal peptides.

Antibody	Antigen	k_{on} [1/Ms]	k_{off} [1/s]	K_D [nM]	Comment
MAB#2	Human	4.33E+04	1.27E−03	29	
MAB#1	C5aR_NT	5.01E+04	1.79E−03	36	
MAB#2	Cynomolgus C5aR_NT	*4.29E+03**	*1 45E−01**	*34000**	fast k_{on}, fast k_{off}
MAB#1		*1.36E+04**	*1.11E−01*	*8200**	fast k_{on}, fast k_{off}

*Values formatted in grey italics are intended for ranking purposes.

Example 5: Apparent Affinity (Bivalent) Determination of MAB#1 and MAB#2 for C5aR N-Terminal Peptides Using Octet

Method

[0553] Apparent K_D determination via C5aR_NT-bio peptide capture setup was performed at 27° C. with the Octet HTX instrument (FortéBIO, Pall Life Sciences). Approx. 0.03 nm of peptide diluted in PBS, pH 7.4, were loaded onto streptavidin (SA) sensors (FortéBIO, Pall Life Sciences). Kinetic measurements were done using 7 different IgG concentrations (3-fold serial dilution, 200 to 0.27 nM for human C5aR_NT-bio peptide (SEQ ID NO: 13) and 1000 to 1.4 nM for cynomolgus C5aR_NT-bio peptide (SEQ ID NO: 14) in Octet buffer (PBS, 0.05% (v/v) Tween-20, 0.1% (w/v) BSA) with 480 s association time and 900 s dissociation time. After each dissociation step the sensors were regenerated to remove bound antibody (3×30 s Gly/HCl, pH 1.5). All sensorgrams were fitted using Octet Data Analysis Software 10.0 (FortéBio) to determine apparent k_{om} and app. k_{off} rate constants, which were used to calculate apparent K_D (using a 1:1 binding model).

Results

[0554] Results are summarized in Table 12. Both antibodies revealed strong binding to the human C5aR peptide in bivalent format with apparent K_D values in the double to triple digit picomolar range. Binding to the cynomolgus C5aR peptide was approx. 1000-fold weaker. The observed weaker binding to cynomolgus monkey C5aR peptide appeared mainly due to fast Ice rates. In terms of apparent affinities to human C5aR_NT, MAB#2 exhibited an about 10-fold weaker binding affinity compared to MAB#1 (K_D: 290 pM vs. 20 pM).

TABLE 12

Determination of apparent association and dissociation rate constants for binding of MAB#1 and MAB#2 to human and cynomolgus C5aR N-terminal peptide.

Antibody	Antigen Name	Apparent k_{on} [1/Ms]	Apparent k_{off} [1/s]	Apparent K_D [nM]	Comment
MAB#2	Human	3.78E+05	1.11E−04	0.29	
MAB#1	C5aR_NT	4.76E+05	9.99E−06	0.02	
MAB#2	Cynomolgus	1.38E+05	1.89E−02	140	fast k_{off}
MAB#1	C5aR_NT	1.71E+05	1.08E−02	63	fast k_{off}

Example 6: Apparent Affinity (Bivalent) Determination for MAB#1 on Full-Length C5aR Expressed on Cells by Using KinExA

[0555] Since C5aR belongs to the family of GPCRs, it is very difficult to generate recombinant full-length antigen material that can be used for SPR measurements. Therefore, Flp-In CHO cells stably expressing human C5aR or cynomolgus C5aR and KinExA measurements were performed.

Method

[0556] Apparent K_D determination on C5aR-expressing cells was performed at RT with a KinExA 3200 instrument (Sapidyne Instruments). PBS (Gibco), supplemented with BSA (1 mg/mL) and 0.02% (v/v) NaN_3 was used as assay

buffer. MAB#1 (conc.: of 2 nM and 30 pM) was used as analyte and Flip-In CHO hC5aR_V5/His cells (final concentration 3 Mio cells/mL and 1 Mio cells/mL, 2n serial dilution) or Flip-In CHO cyC5aR_V5/His cells (final concentration 25 Mio cells/ml and 6 Mio cells/ml, 2n serial dilution) as titrant and equilibrated over night at RT in an overhead shaker. After equilibration, the samples were centrifuged and the supernatants were used for analysis. Free concentration of MAB#1 was determined using polymethylmethacrylate (PMMA) beads coated with MabSSL (GE Healthcare) and anti-human Fab2 Alexa Fluor 647 (500 ng/mL) was used for detection. The apparent K_D was obtained using KinExA software and by "n-curve analysis," which fits all of the given curves to a single K_D value simultaneously.

Results

[0557] Results are summarized in Table 13. MAB#1 revealed strong binding to full-length human C5aR with an apparent K_D value of 130 pM. Binding to full-length cynomolgus C5aR appeared about 20× weaker with an apparent K_D value of approx. 3 nM. Similar findings concerning binding to cynomolgus C5aR were observable before in Octet and Biacore measurements (see Example 4 and Example 5).

TABLE 13

Bivalent binding of MAB#1 to full-length human and cynomolgus C5aR expressed on Flp-In CHO cells

	Flp-In CHO	Apparent K_D [nM]
MAB#1	human_C5aR	0.130
	cyno_C5aR	2.98

Example 7: Binding of MAB#1 and MAB#2 to Full-Length C5aR Expressed on Flp-In CHO Cells and Whole-Blood Derived Neutrophils (FACS Analysis)

[0558] Cell binding to CHO Flp-In cell lines stably expressing various full-length C5aR antigens and related GPCRs as well as binding to purified human or cynomolgus neutrophils, expressing human or cynomolgus C5aR endogenously, was investigated via FACS. Cynomolgus neutrophils were obtained from whole-blood of cynomolgus monkey from three different animals (LPT Hamburg).

Methods

[0559] The C5aR-CHO Flp-In cell lines were blocked and IgGs were added either in serial dilutions or at a single (high) concentration of 300 nM. For detection of IgG binding, an R-phycoerythrin (R-PE) conjugated anti-human IgG (Fc-gamma fragment specific)2 antibody was added and fluorescence was measured using the FACS Array or Novocyte device.

[0560] Neutrophils were purified from EDTA-whole blood samples using a MACSexpress Neutrophil Isolation Cocktail from Miltenyi Biotec. Briefly, using this kit, cells are isolated using magnetic labeling and negative magnetic separation. After removal of erythrocytes, the cells were stained by adding the IgGs in a serial dilution, followed by a Alexa Fluor 647-conjugated anti-Human F(ab)2 fragment specific detection antibody. Measurements were done at the FACS Array device. FACS data were evaluated using FlowJo, entered into GraphPad Prism (v4.0) and fitted to the sigmoidal dose-response curve using non-linear regression to calculate the EC50.

Results

[0561] Results are summarized in Table 14 and FIGS. **1** and **2**. FIGS. **1**A and C depict binding of MAB#1, MAB#2 and RefMAB#1 to human and cynomolgus C5aR present on engineered CHO cells expressing the respective full-length receptor. Overall, very comparable binding curves on human C5aR with almost identical EC_{50} concentrations were determined for MAB#1, MAB#2 and RefMAB#1. Similar results were obtained on cynomolgus C5aR for MAB#1 and MAB#2. As expected, RefMAB#1 revealed no binding to cynomolgus C5aR expressed on CHO cells.

[0562] Binding to cynomolgus and human C5aR was also confirmed using purified neutrophils obtained from human or cynomolgus whole-blood (FIGS. **1**B and D). Again, very comparable binding curves with almost identical EC_{50} values on human and cynomolgus neutrophils were observable for MAB#1. Interestingly, MAB#2 revealed overall lower signal over background levels on cynomolgus neutrophils when compared to MAB#1. This finding was not observable when binding to cynomolgus C5aR expressed on CHO cells was analyzed. Lack of binding to cynomolgus monkey neutrophils was confirmed for RefMAB#1

[0563] For rodent C5aR, no cross-reactivity to rat and mouse C5aR was expected due to the low sequence homology (66% overall identity). Indeed, neither MAB#1 nor MAB#2 showed any significant binding to rat or mouse C5aR expressed on CHO-Flp cell when tested at an IgG concentration of 300 nM (FIG. **2**). In order to exclude cross-reactivity to any other member of the C5aR subfamily, binding to full-length human C5L2, ChemR23, FPR1 and C3aR expressed on CHO Flp-In cells was also determined via FACS (compared to non-transfected parental CHO Flp-In cells). As shown in FIG. **2**, even at an IgG concentration of 300 nM, no significant cell binding of MAB#1 and MAB#2 was detectable to any of the C5aR-related GPCRs or to the parental CHO cells.

[0564] Taken together, both, MAB#1 and MAB#2 revealed specific binding to human and cynomolgus monkey C5aR.

TABLE 14

Binding of MAB#1, MAB#2 and Ref MAB#1 to full-length human or cynomolgus C5aR expressed by engineered CHO cells or purified neutrophils. Each antibody was tested in at least in two independent assay runs.

Full-length protein expressed on cells	MAB#1	MAB#2	RefMAB#1
human C5aR expressed on CHO cells	EC_{50} = 1.7 nM	EC_{50} = 1.2 nM	EC_{50} = 1.1 nM
C5aR expressed on purified human neutrophils	EC_{50} = 6.0 nM	ECK = 5.4 nM	EC_{50} = 3.1 nM
cynomolgus C5aR expressed on CHO cells	EC_{50} = 1.1 nM	EC_{50} = 1.4 nM	No binding
C5aR expressed on purified cynomolgus neutrophils	EC_{50} = 4.5 nM	EC_{50} = 3.8 nM	No binding

Example 8: Binding of MAB#1 and MAB#2 to Full-Length Human C5aR Displayed on Virus-Like-Particles (VLPs)—Binding to Natural Variants of Human C5aR

[0565] Two natural variants of human C5aR (SEQ ID NO: 1; D/K variant and SEQ ID NO: 2; N/N variant) are reported.

[0566] To compare binding of MAB#1 and Mab#2 to the two natural variants, VLPs expressing either of the two C5aR variants were generated as described in Example 1. As negative control, VLPs expressing murine C5aR were included, since MAB#1 and Mab#2 are not cross-reactive to murine C5aR.

Method

[0567] For assessment of binding, produced VLPs were coated overnight and after a blocking step, IgG titrations were added on the next day. Binding of the IgGs to the coated antigen was detected using an Alkaline Phosphatase-conjugated anti-human IgG2 antibody and AttoPhos as substrate.

Results

[0568] Results are summarized in Table 15 and depicted in FIG. **3**. Both, MAB#1 and MAB#2 revealed comparable titration curves on both natural variants of human C5aR with equal EC_{50} concentrations. As expected, no binding to murine C5aR was detected. Based on these data, high affinity binding of MAB#1 and MAB#2 to human C5aR can be expected in vivo, independent of the natural variant present on the respective target cells.

TABLE 15

Binding of MAB#1 and MAB#2 to two natural variants of human C5aR expressed on VLPs.

C5aR variant	MAB#1	MAB#2
huC5aR (D/K)	EC_{50} = 0.5 nM (N = 2)	EC_{50} = 0.5 nM (N = 2)
huC5aR (N/N)	EC_{50} = 0.5 nM (N = 2)	EC_{50} = 0.5 nM (N = 2)

Example 9: Protein Panel Profiling (3P)

[0569] Potential unspecific off-target binding for MAB#1 was determined in the generic 3P assay.

Method:

[0570] Protein panel profiling was mainly performed as described by Frese et al. (mAbs 5:2, 279-287; March/April 2013). 32 different proteins and controls were coated on two 384-well MSD standard plates at a concentration of 1.0 μg/mL at 4° C. over night. The coating solution was discarded and plates were blocked with 50 μL 3% (w/v) BSA in PBS for one hour at RT on a microtiter plate shaker (~500 rpm) followed by three washing steps with 50 μL washing buffer (PBS with 0.05% (v/v) Tween 20). IgG samples were diluted to 100 nM and 10 nM in assay buffer (PBS with 0.5% (w/v) BSA, 0.05% (v/v) Tween 20). As controls, isotype control antibody MOR03207 (IgG1f_AEASS) and assay buffer were used. Samples and controls were added at 30 μL/well and incubated for three hours at RT on a microtiter plate shaker. The plates were washed three times and 30 μL detection antibody (ECL-labeled anti-human Fab) were added per well and incubated for one hour on a microtiter plate shaker (~500 rpm). After washing the MSD plate and adding 35 μL/well MSD Read Buffer T with surfactant, electro-chemiluminescence signals were detected using a SECTOR Imager S600 instrument (Meso Scale Diagnostics).

[0571] For evaluation, binding signals of the antibody sample to a certain protein were divided by the respective binding signals of the reference antibody MOR03207 resulting in a binding ratio (BR). The cumulative binding ratio (CBR) of all proteins except the controls (25 in total) was then calculated: CBR up to 150 indicates an IgG without detectable unspecific binding. Values above 150 indicates an IgG with increased unspecific binding compared to the reference antibody MOR03207.

Results

[0572] Results for MAB#1 and MAB#2 are summarized in FIG. **10**. In sum, no critical unspecific binding was detectable to any of the tested proteins. Very low (MAB#2) and low (MAB#1) binding to bovine transferrin was observed. Binding to bovine transferrin was confirmed in an Octet based binding assay, but no binding to rat and cynomolgus transferrin was detected (data not shown). Thus, the observed binding to bovine transferrin was regarded as non-critical.

Final Antibody Format and Safety

[0573] C5aR is expressed on various immune cells, such as leukocytes, neutrophils and lymphocytes and human IgG1 Fc-mediated depletion of such cells needs to be prevented to avoid unwanted side effects. Accordingly, the final IgG format of an anti-C5aR antibody needs to be silent in terms of its ability to induce any effector function during therapeutic intervention.

[0574] Both, MAB#1 and MAB#2 contain five amino acid substitutions in the Fc region of human IgG1f, namely L234A, L235E, G237A, A330S and P331S (hIgG1f_AEASS, numbering according EU index) to abolish antibody induced effector function. Clinical safety of this format in the context of C5aR antibody therapy has been described in the art (Wagner F et al. Annals of the Rheumatic Diseases. 2014; 73: 499. doi: 10.1136/annrheumdis-2014-eular.2156.)

[0575] The lack of ability of MAB#1 and MAB#2 to induce effector function was confirmed in various assays, such as binding studies to Fcγ receptors or C1q as well as in vitro ADCC and ADCP assays as outlined below.

Example 10: Binding of MAB#1 and MAB#2 to FcRn Receptor Using Octet

Method

[0576] Apparent K_D determination to immobilized neonatal Fc receptor (FcRn) from different species was performed at pH 6.0 and 7.2 at 27° C. using an Octet HTX instrument (FortéBIO, Pall Life Sciences). 0.5 nm of biotinylated human, cynomolgus, mouse and rat FcRn were captured on streptavidin (SA) sensors (FortéBIO, Pall Life Sciences). Kinetic measurements were performed using 8 different concentrations of IgGs (3n serial dilution, 1000 to 0.46 nM) in Octet buffer (PBS, 0.05% (w/v) Tween-20, 0.1% (w/v) BSA) with 240 s association time and 180 s dissociation time. After each cycle the sensor was regenerated to remove

bound ligand/antibody complex (2×30 s in HBS-EP+, pH 8.0). All sensorgrams were fitted using Data Analysis Software 10.0 (FortéBIO, Pall Life Sciences) to determine the apparent affinity and the data was fitted with a steady state model.

Results

[0577] Results are summarized in Table 16. MAB#1 and MAB#2 revealed apparent binding affinities to FcRn from different species in an expected affinity range (comparable to isotype control antibody MOR03207 IgG1f and the physiological binding behavior for binding to human FcRn could be confirmed for both IgG molecules, i.e. no binding at neutral pH (7.2) was detectable. Accordingly, the introduced 5 mutations into the Fc region of the antibodies did not adversely affected human FcRn binding.

TABLE 16

Binding of MAB#1 and MAB#2 to FcRn via the Fc region at pH 6.0 and 7.2.

Antibody	Antigen	K_D [nM] pH 6.0	K_D [nM] pH 7.2
MAB#2	Human FcRn	*36**	no binding
MAB#1		*9.0**	no binding
MAB#2	Cynomolgus	*30**	no binding
MAB#1	FcRn	*6.8**	*560***
MAB#2	Murine FcRn	7.3	130
MAB#1		4.3	39
MAB#2	Rat FcRn	10	300
MAB#1		5.7	110

*Deviation from fit model (pH 6.0)

**Slight binding at pH 7.2

*** Values formatted in italics are mainly intended for ranking purposes

Example 11: Binding of MAB#1 and MAB#2 to Human Fcγ Receptors Using Octet

Method

[0578] K_D determination via IgG capture setup was performed at 27° C. using Octet (FortéBIO, Pall Life Sciences). 2.0 nm of IgGs diluted in Octet assay buffer (PBS, 0.05% (v/v) Tween-20, 0.1% (w/v) BSA) were captured on Protein A sensors (FortéBIO, Pall Life Sciences). Kinetic measurements were performed using 7 concentrations of Fc gamma receptors (2n serial dilution) in assay buffer. After each cycle the sensors were regenerated to remove bound ligand/antibody complex (2×30 s in 10 mM Gly/HCl, pH 1.5). All sensorgrams were fitted using Data Analysis Software 10.0, (FortéBIO, Pall Life Sciences) to determine k_{on} and k_{off} rate constants, which were used to calculate K_D. The raw data was fitted with a 1:1 binding model, with parameter R_{max} set to local.

Results

[0579] Results are summarized in Table 17. No or only very weak binding of MAB#1 and MAB#2 to any of the tested Fcγ receptors could be detected and confirmed that the introduced mutations into the human IgG1 Fc region are effective in abolishing Fcγ receptor binding.

TABLE 17

Binding of MAB#1 and MAB#2 to human Fcγ receptors via Fc-region

FcγR	MAB#2	Mab#1
hu_FcγRI	no binding	no binding
hu_FcγRIIa (131H)	no binding	no binding
hu_FcγRIIa(131R)	very slight binding only at highest antibody concentration observed	very slight binding only at highest antibody concentration observed
hu_FcγRIIIa (158F)	no binding	no binding
hu_FcγRIIIa (158V)	no binding	no binding
hu_FcγRIIb	no binding	no binding

Example 12: Binding of MAB#1 and MAB#2 to C1q Using Octet

Method

[0580] Apparent (bivalent) K_D determination via IgG capture setup was performed at 27° C. using Octet (Fortébio Pall Life Sciences). 2.0 nm of IgGs diluted in Octet buffer were captured onto anti-hu Fab CH1 kappa/lambda (BAC) immobilised onto streptavidin (SA) sensors (FortéBIO, Pall Life Sciences). Kinetic measurements were done using 8 concentrations of C1q (3n serial dilution, 500 to 0.69 nM) in Octet assay buffer (see above) with 240 s association time and 240 s dissociation time. After each cycle the sensors were regenerated to remove bound ligand/antibody complex (2×50 mM NaOH, 1×10 mM Gly/HCl, pH 1.5, for 30 s each). All sensorgrams were fitted using Data Analysis Software 9 (FortéBIO, Pall Life Sciences) to determine the apparent affinity. The data was fitted with a steady state model.

Results

[0581] Results are summarized in Table 18. As expected, no binding of MAB#1 and MAB#2 to C1q (isolated from pooled human plasma) was observable and confirmed that the introduced mutations into the human IgG1 Fc region are effective in abolishing C1q binding.

TABLE 18

Binding of MAB#1 and MAB#2 to human C1q.

Antigen	MAB#2	MAB#1
Human C1q	no binding	no binding

Example 13: ADCC and ADCP In Vitro Activity of MAB#1

Methods

[0582] ADCC and ADCP activity for MAB#1 was tested using the Promega ADCC and ADCP Reporter Bioassays according to the manufacturer's instructions (Cat #G7017 and Cat #G988A, respectively). The kits employs engineered Jurkat cells as effector cells. The cells either stably express the FcγRIIIa receptor, V158 (high affinity) variant for ADCC and FcγRIIa_H receptors for ADCP and an NFAT response element driving expression of firefly luciferase. As target cells, CHO Flp-In cells expressing human C5aR were

used. Binding of the effector cells to the target through the antibody bridge (e.g. through MAB#1 or MAB#2) initiates a cascade of events in the NFAT pathway, resulting in the expression of the firefly luciferase protein. The enzymatic reaction produces luminescence, which is proportional to the luciferase concentration, directly correlating to ADCC or ADCP activity. ADCC or ADCP activity was analyzed for MAB#1 by plotting the average signal to background values.

[0583] Since for MAB#1, a wild-type human IgG1f version was not available, a wild-type IgG1f as well as a Fc-silent human IgG1f_AEASS version of an in-house human anti-C5aR control antibody was included as positive control. In addition, a Fc-silent (hIgG1_AEASS) and wild-type version (hIgG1f) version of the isotype control antibody MOR03207 was included as negative control.

Results

[0584] Results are summarized in Table 19 and depicted in FIGS. **8**A (ADCP) and B (ADCC) for an IgG concentration of 10 μg/ml. MAB#1 did not induce FcγRIIIa or FcγRIIa_H activation of the NFAT pathway in engineered effector cells in the presence of C5aR overexpressing CHO cells, similar to the Fc-silent version of the anti-C5aR control antibody and the Fc-silent version of MOR03207. The wild-type (non-silent) version of the C5aR specific control antibody clearly induced luciferase production in engineered Jurkat cells in the presence of C5aR expressing CHO cells.

[0585] In sum, the experiment clearly confirmed that the introduced mutations into the wild-type human IgG1 Fc region are efficient in preventing ADCC and ADCP activity.

TABLE 19

Overview of the conducted in vitro assays to confirm that MAB#1 (hIgG1f_AEASS) does not mediate effector function.

Criteria	Assay	Results for MAB#1
No ADCC	ADCC Reporter Bioassay	No FcγRIIIa_V activation of NFAT pathway in engineered effector cells detectable
No ADCP	ADCP Reporter Bioassay	No FcγRIIa_H activation of NFAT pathway in engineered effector cells detectable
No CDC	huC1q Binding (Octet)	No binding to human C1q detectable
No binding to Fcγ Receptors	FcγR Binding (Octet)	No binding to the FcγRs. Highest background (close to slight binding) on hFcγRIIa_R
Physiological FcRn binding	FcRn Binding (Octet)	Physiological binding with apparent K_D in the expected range

Functional Characterization of MAB#1 and MAB#2

[0586] The neutralizing activities of MAB#1 and MAB#2 were analyzed in different in vitro assays which monitor C5a induced activation of C5aR.

[0587] As elevated levels of C5a has been described under pathophysiological conditions, the capability of a C5aR antagonistic antibody to neutralize high concentrations of C5a, which may be present locally at the disease site, is expected to provide a beneficial therapeutic effect in vivo. Accordingly, the in vitro experiments were also set-up to reflect such in vivo pathological conditions.

Example 14: PathHunter® β-Arrestin Assay (DiscoveRx)

Methods:

[0588] The PathHunter® β-Arrestin assay from DiscoveRx was performed according to the manufacturer's instructions. In brief, human C5a induced human C5aR activity was measured by the detection of the interaction of β-arrestin with the activated C5aR using β-galactosidase enzyme fragment complementation.

[0589] β-arrestin recruitment was induced using recombinant human C5a and enzyme activity was measured using chemiluminescent detection reagents from DiscoverRx. Chinese hamster ovarian cells (CHO) cells, expressing the engineered version of human C5aR were seeded overnight and serial dilutions of human C5a (R&D Systems) were added and incubated at 37° C. and 5% CO2 for 1.5 h (generating the titration curves in absence of the antagonist). In parallel, titration curves of human C5a were determined in presence of the C5aR specific antibodies (fixed IgG conc. of 50 nM). For doing so, IgGs were added to the cells before stimulation with human C5a and incubated for 1 h at 37° C. and 5% CO_2. Results were expressed as relative luminescence units. Titration curves for human C5a in the presence and absence of the antagonistic IgGs were generated via GraphPad Prism.

[0590] For the β-arrestin assay, the shifts in the dose-response curves for human C5a to higher doses (i.e. horizontally to the right on the dose axis) were compared for MAB#1, MAB#2 and RefMAB#1 (FIG. **4**A). Additionally, the % inhibition at three increasing C5a concentrations (1.2 nM, 11 nM and 100 nM) was calculated and compared (FIG. **4**B).

Results

[0591] The results from the β-arrestin assays are depicted in FIGS. **4**A and **4**B and summarized in Table 20 and Table 21. In the absence of antibody, a dose-response curve for human C5a with an average EC_{50}, concentration of 2.9 nM was obtained (FIG. **4**A).

[0592] Adding MAB#1 or MAB#2 to human C5a at a final IgG concentration of 50 nM resulted in a significant shift in the dose-response curve of more than 12-fold to higher doses of human C5a. Being more precisely, in the presence of 50 nM MAB#1 or MAB#2, a dose-response curve for human C5a with an average EC_{50} concentration of 37 nM was obtained (FIG. **4**A, Table 20). In other word, the presence of MAB#1 or MAB#2 significantly reduces the ability of human C5 to induce C5aR activation or, alternatively, in the presence of MAB#1 or MAB#2, human C5a needs to be added in an at least 12-fold higher concentration in order to induce the same C5aR activity when compared to its activity in the absence of antibody.

[0593] This observation was also reflected when the % inhibition at three increasing C5a concentrations was calculated (FIG. **4**B). At 1.2 nM human C5a, all three tested antibodies, MAB#1, MAB#2 and RefMAB#1, revealed a comparable inhibition of C5a induced C5aR activity of more than 80% at an IgG concentration of 50 nM. If however, an about 10-fold higher concentration of human C5a (11 nM) was used for activation of C5aR, RefMAB#1 was only able to neutralize of about 50% of C5a induced C5aR activity.

This is in strong contrast to MAB#1 and MAB#2, which were still able to neutralize up to 80% of C5a induced C5aR activity.

[0594] This effect was even more pronounced when a 100-fold higher concentration of human C5a (100 nM) for activation of C5aR was used. Here, almost no neutralizing activity was detectable for RefMAB#1, whereas MAB#1 and MAB#2 were still able to neutralize of about 40% and 30%, respectively, of the human C5a induced C5aR activity.

[0595] Accordingly, both, MAB#1 and MAB#2 are efficient in neutralizing pathophysiological C5a concentrations in vitro and are significant more potent compared to RefMAB#1.

TABLE 20

In vitro β-arrestin assay (n = 3): Inhibitory activity of C5aR specific antibodies on C5a-induced C5aR activity measured by the detection of the interaction of β-arrestin with activated C5aR using β-galactosidase enzyme fragment complementation.

	Activity of human C5a EC_{50} (nM) in absence or presence of anti-C5aR antibody	x fold reduced activity of C5a in presence of anti C5aR antibody
hC5a	2.9	—
hC5a + MAB#1 (50 nM)	37	12.8
hC5a + MAB#2 (50 nM)	37	12.8
hC5a + RefMAB#1 (50 nM)	10	3.4

TABLE 21

In vitro β-arrestin assay (n = 3): Inhibitory activity of C5aR specific antibodies on C5a-induced C5aR activity calculated for 3 concentrations of C5a and a fixed IgG concentration of 50 nM and measured by the detection of the interaction of β-arrestin with activated C5aR using β-galactosidase enzyme fragment complementation.

	MAB#2	MAB#1	RefMab#1
[%] inhibition at 1.2 nM C5a and 50 nM IgG	90.5	91.9	84.2
[%] inhibition at 11 nM C5a and 50 nM IgG	75.2	79.9	38.9
[%] inhibition at 100 nM C5a and 50 nM IgG	31.2	41.8	6.4

Example 15: Inhibition of Neutrophil and Monocyte Activation by MAB#1 and MAB#2-CD11b Assay

[0596] The neutralization potency of MAB#1 and MAB#2 was furthermore determined in a functional CD11b whole blood assay representing a more physiological set up. CD11b combines with CD18 to form the integrin Mac-1 complex, which serves as a multi-ligand receptor. CD11b is constitutively expressed on the surface of >50% peripheral blood leukocytes; upon leukocyte activation, its expression is up regulated through the fusion of CD11b containing secretory granules into the cell membrane. CD11b expression is thus widely used as a marker of leukocyte activation both in vivo and in vitro.

[0597] C5a, as a potent activator of human neutrophils and monocytes, induces up-regulation of surface antigen CD11b. Thus, the ability of MAB#1 and MAB#2 to prevent C5a-induced activation of granulocytes and monocytes was investigated by assessing the CD11b levels in whole-blood derived granulocytes and monocytes. The experiments were basically performed as described in US patent application US2013/0295116 (NOVO NORDISK).

Method

[0598] In a first assays set-up, whole heparinized blood was mixed with IgG (in serial dilutions) and incubated for 20 min at 37° C., 5% CO_2. Human C5a was added at a standard concentration of 15 nM and incubated for 20 min at 37° C., 5% CO_2. Anti-CD11b-PE or isotype control antibody MOR03207 was added and the plate was incubated for 20 min. at 37° C., 5% CO_2. Finally, a red blood cell lysing buffer was added and incubated at room temperature for 15 min in the dark, the cells were washed and again re-suspended in lysing buffer.

[0599] In a second experimental set-up, human C5a was added at a more clinical relevant pathophysiological concentration of 150 nM without modifying the remaining assays set-up as described above.

[0600] To investigate the receptor residence time of MAB#1, the assay was further adapted by prolonging the incubating time of the heparinized whole blood with IgG from 20 min to 300 min.

[0601] Fluorescence was measured using the FACS Array or Novocyte device. Samples were gated to exclude dead cells and debris. Monocytes and granulocytes were identified according to their FSC and SSC profiles and gated. The median fluorescence intensity (MFI) of the gated granulocytes and/or monocytes in the CD11b-PE channel (Yellow-A) was calculated. Results were expressed as a percentage of inhibition (% Inhibition). Maximum CD11b expression (MFI_{max}) was the average MFI of the cells, incubated with C5a but without IgG. The minimum (background) CD11b expression (MFI_{Min}) was the average MFI of the cells incubated without C5a and without IgG. The formula used to calculate % inhibition for each samples was:

$$\% \text{ Inhibition} = 100 - (((MFI_{sample} - MFI_{Min}))/((MFI_{Max} - MFI_{Min})) \times 100)$$

[0602] Data was evaluated using FlowJo, entered into GraphPad Prism (v4.0) and fitted to the sigmoidal dose-response curve using non-linear regression to calculate the IC_{50}.

Results for MAB#1 Using 15 nM C5a Ligand

[0603] Results for MAB#1 from the CD11b whole blood assays are summarized in Table 22. For both gated cell populations (monocytes and granulocytes), IC_{50} values in the single-digit nM range were determined with maximum inhibition of almost 88% for granulocytes and 83% for monocytes.

TABLE 22

Ability of MAB#1 to prevent C5a-mediated activation of granulocytes and monocytes. Overview maximum inhibition and IC_{50} values was determined in the CD11b assay using 15 nM C5a (n = 3).

Cell type	MAB#1 – Inhibition of CD11b expression	
CD11b Granulocytes	max % inhibition (at 600 nM IgG)	87.2 ± 1.7 (N = 3)
	IC_{50} (nM)	9.8 ± 0.6 (N = 3)
CD11b Monocytes	max % inhibition (at 600 nM IgG)	83.3 ± 3.6 (N = 3)
	IC_{50} (nM)	4.2 ± 0.8 (N = 3)

Results for MAB#1, MAB#2 and RefMAB#1 Using 15 nM Vs. 150 nM C5a Ligand

[0604] Besides adding 15 nM of human C5a for stimulation of granulocytes (as described above), a ten-fold higher concentration (150 nM) of ligand was used to simulate a more pathophysiological ligand concentration.

[0605] Again, MAB#1, MAB#2 and RefMAB#1 were dose-titrated and inhibition curves were generated using GraphPad Prism via the nonlinear regression function. The results are quantitatively expressed as "concentration of antagonist needed in order to induce 50% of inhibition".

[0606] The results from this CD11b whole blood assay are shown in FIGS. **5**A and B.

[0607] FIG. **5**A depicts the neutralizing activity of MAB#1, MAB#2 and RefMAB#1 at 15 nM C5a and FIG. **5**B depicts the respective neutralizing activity at 150 nM C5a. As a quantitative read-out, the IgG concentration for reaching 50% inhibition of CD11b upregulation was calculated and the results are indicated below the x-axis in both Figures.

[0608] Overall, similar observations as for the β-arrestin assay (Example 14) were made when using increasing C5a concentrations in the CD11b whole blood assay gated on granulocytes as primary target cells. In order to block the effects of 15 nM human C5a to 50%, an IgG concentration of 12 nM for MAB#1 and RefMAB#1 was needed, whereas for MAB#2 an IgG concentration of 17 nM was sufficient. However, in order to block 50% of CD11b upregulation induced by a 10 fold higher C5a concentration (150 nM) significant different amounts of the antagonists were required. While for MAB#1, an IgG concentration of 42 nM were now sufficient to inhibit 50% of the C5a induced activation of C5aR, a 7-fold higher concentration of RefMAB#1 (291 nM) was required to reach the same blocking effect. For MAB#2 an IgG concentration of 114 nM was sufficient.

[0609] Accordingly, the same ranking of the 3 IgGs in terms of potency as already seen in the b-arrestin assay (MAB#1>MAB#2>RefMAB#1) could be done and both, MAB#1 and MAB#2 appeared very efficient in neutralizing pathophysiological C5a concentrations in vitro and were significant more potent compared to RefMAB#1.

Results for MAB#1—Influence on Receptor Residence Time

[0610] Seow and colleagues (Seow V et al., Sci Rep. 2016; 6: 24575) reported that the generation of C5a is localized at the cell membrane and can be profoundly high for brief but repeated periods. Therefore, it was suggested that an antagonist of C5aR with long residence time could be advantageous in systems with rapid and transient signaling. It was also concluded that an increased receptor residence time measured in vitro could also translate to the duration of action and degree of efficacy in vivo.

[0611] To compare the receptor residence time of the two antibodies in a similar set up as published by Seow and co-workers, log dose inhibition curves for 20 minutes and 300 minutes of IgG incubation with granulocytes and monocytes present in whole blood was evaluated as described above.

[0612] The results from this experimental set-up of the CD11b whole blood assay are shown in FIG. **6**A-D. Surprisingly, a significant increase in the neutralizing activity over a prolonged period of incubation time was observable of MAB#1. As shown in FIGS. **6**A and C, for both, granulocytes and monocytes populations, the calculated IC_{50} concentration for MAB#1 decreased over time of about 6-fold (IC_{50} values are summarized in Table 23). For RefMAB#1, no shift or decrease in the inhibition curves was observable after 300 minutes (FIGS. **6**B and D).

TABLE 23

CD11b assay after 20 minutes or 300 minutes of IgG incubation with whole-blood at 15 nM C5a. Provided are IC_{50} values and x-fold potency improvements (20 min. vs 300 min.) for granulocytes (upper panel) and monocytes (lower panel)

	MAB#1		RefMAB#1	
CD11b Granulocytes	IC50 (in nM)	x-fold improvement	IC50 (in nM)	x-fold improvement
20 minutes	11.0 ± 1.0 (N = 2)	4.8	10.2 ± 1.9 (N = 2)	1.6
300 minutes	2.3 ± 0.0 (N = 2)		6.5 ± 0.5 (N = 2)	

	MAB#1		RefMAB#1	
CD11b Monocytes	IC50 (in nM)	x-fold improvement	IC50 (in nM)	x-fold improvement
20 minutes	4.0 ± 1.0 (N = 2)	5.7	1.8 ± 0.5 (N = 2)	0.3
300 minutes	0.7 ± 0.2 (N = 2)		5.3 ± 1.0 (N = 2)	

[0613] In sum, the combination of both, efficient neutralization of pathophysiological C5a levels and an increased potency over time is expected to be beneficial in vivo.

Example 16: C5a Induced Migration of Neutrophils

[0614] C5a induced chemotaxis of purified neutrophils was analyzed. The experiment was basically performed as described in US patent application US2013/0295116.

Methods

[0615] Neutrophils were isolated and purified from whole blood of three different human donors using the MACSxpress Whole Blood Neutrophil Isolation Kit, human (Miltenyi Biotec Cat #130-104-434 and the MACSxpress Erythrocyte Depletion Kit, human (Miltenyi Biotec, CAT #130-098-196).

[0616] The potency of the IgGs to inhibit hC5a dependent neutrophil migration was analyzed by the Boyden chamber technique using Fluor® Blok® 3.0 μM pore size 96-well plates. The membrane of the Boyden chamber pore was coated with 1 mg/mL human fibrinogen for 2 hrs at 37° C. After washing, the membranes were blocked with a solution containing 2% bovine serum albumin (BSA) for 1 hr at 37° C. Purified neutrophils were then stained with calcein and 10^5 stained cells added to the upper compartment in the Boyden chamber with and without the antagonistic IgGs (100 and 600 nM). hC5a (R&D Systems, 10 nM) was applied to the lower compartment in the Boyden chamber. The plate was measured at 485/538 nm at 37° C. every 5 min for 60 min in a plate reader (Tecan M1000Pro). The ability of neutrophils to migrate to the lower chamber is determined measuring the calcein-stained neutrophils passing through

the fluoroblok membrane. The results are expressed as kinetic migration curves (5-60 min) as well as percentage inhibition calculated at selected time points (15, 25 and 35 min).

The formula used to calculate % inhibition was

$$\% \text{ Inhibition} = 100 - (((RFU_{sample} - RFU_{Min}))/((RFU_{Max} - RFU_{Min})) \times 100)$$

Results

[0617] The average percentage inhibition of neutrophil migration at selected time points at two tested IgG concentrations was calculated from 3 independent experiments using neutrophils from three different human donors.

[0618] As depicted in FIG. **7**, after 15 min of migration, almost complete inhibition of C5a-induced neutrophil migration was reached for MAB#1. After 35 min of migration and the highest IgG concentration tested (600 nM), MAB#1 still revealed >50% inhibition. The negative isotype control antibody MOR03207 showed no inhibitory effect on neutrophil migration.

Example 17: C5a Induced Release of Cytokines by Macrophages

[0619] Macrophages release pro- or anti-inflammatory cytokines upon activation depending on their polarization. Hence, it was evaluated whether blockade of the C5a/C5aR interaction with MAB#1 affects the C5a-induced release of cytokines by M1 and M2 macrophages. A cytokine ELISA was performed to detect the production of anti-inflammatory IL-10 by M2 macrophages and pro-inflammatory IL-12 by M1 macrophages.

Methods

[0620] Briefly, peripheral blood mononuclear cells (PBMCs) were prepared from whole blood of healthy human donors by density-gradient centrifugation with Biocoll separating solution and SepMate tubes (Stemcell). Monocytes were isolated from PBMCs using a CD14+ selection kit (Miltenyi Biotech) and cultured in RPMI supplemented with 10% FCS and 1×GlutaMax in 96 well plates. Overnight-plated monocytes were polarized for 24 hours at 37° C. to M1 macrophages using LPS (20 ng/ml) and IFNγ (50 ng/ml) and pre-incubated with MAB#1 (30 nM) for 30 minutes followed by addition of C5a (15 nM) for another 24 hours. M1 macrophages stimulated with C5a in absence of MAB#1 and untreated controls were included. After 24 hours, cell supernatants were analyzed by an IL-12/IL23 DuoSet ELISA (R&D Systems) according to manufacturer's instructions. For generation of M2 macrophages, monocytes were pre-differentiated into macrophages by culture for 5 days in RPMI/10% FCS supplemented with M-CSF and addition of M-CSF, IL-4, IL-13 and IL-6 (40 ng/ml each) at day 5. C5a (15 nM)+/−MAB#1 (30 nM) were added daily from day 5 until 9. On day 9, cell supernatants were analyzed by an IL-10 DuoSet ELISA (R&D Systems) according to manufacturer's instructions.

Results

[0621] While incubation with C5a lead to decreased IL-12 production of M1 macrophages, no reduction in IL-12 levels could be observed after pre-treatment with MAB#1 in comparison to the untreated control. On the other hand, treatment with MAB#1 inhibited C5a-induced IL-10 production in M2 macrophages (see FIG. **11**)

[0622] In conclusion, MAB#1 efficiently inhibited C5a-induced production of anti-inflammatory IL-10 by M2 macrophages and restored the production of pro-inflammatory IL-12 by M1 macrophages thereby demonstrating the mode of action of MAB#1 in vitro.

Pharmacokinetics

Example 18: Pharmacokinetics

[0623] The pharmacokinetic profile of MAB#1 was assessed in male Han-Wistar rats (n=3 animals) after a single intravenous (i.v.) administration of 10 mg/kg IgG.

Methods

[0624] Plasma samples were collected from each animal via retro-orbital sinus or mandibular vein puncture at the following time-points: Predose, 0.083, 1, 3, 8, 24, 48, 72, 96, 168, 240, 336 and 504 hours post administration.

[0625] Free, bioactive MAB#1 concentrations in rat plasma were determined using a MSD-based ligand-binding assay. Briefly, a biotinylated N-terminal human C5aR peptide was coated on the surface of a 96-well Streptavidin-MSD plate. The bound analyte was detected using a drug-specific anti-idiotypic ECL-labelled antibody. Pharmacokinetic properties of MAB#1 were evaluated using non-compartmental data analysis (NCA) based on free drug concentrations in plasma.

Results

[0626] The mean plasma concentrations over time is depicted in FIG. **9**. The mean maximum plasma concentrations of MAB#1 after a single i.v. administration were observed at 5 minutes (i.e. 0.083 hours) after administration (T_{max}) in all three animals (i.e. first sampling time point post administration). The mean volume of distribution (Vz) of 106 mL/kg was between plasma volume and extracellular volume (Davies et al., 1993). The mean terminal elimination half-life following i.v. administration was determined at 9.0 days, the mean total clearance was determined at 0.341 mL/h/kg.

[0627] Overall, MAB#1 demonstrated a typical pharmacokinetic profile of a human IgG1 antibody in rat plasma with no cross-reactivity to the rodent C5aR. No signs of anti-drug-antibody (ADA)-mediated clearance could be detected.

SEQUENCE LISTING

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Met Asp Ser Phe Asn Tyr Thr Thr Pro Asp Tyr Gly His Tyr Asp Asp
1 5 10 15

Lys Asp Thr Leu Asp Leu Asn Thr Pro Val Asp Lys Thr Ser Asn Thr
20 25 30

Leu Arg Val Pro Asp Ile Leu Ala Leu Val Ile Phe Ala Val Val Phe
35 40 45

Leu Val Gly Val Leu Gly Asn Ala Leu Val Val Trp Val Thr Ala Phe
50 55 60

Glu Ala Lys Arg Thr Ile Asn Ala Ile Trp Phe Leu Asn Leu Ala Val
65 70 75 80

Ala Asp Phe Leu Ser Cys Leu Ala Leu Pro Ile Leu Phe Thr Ser Ile
85 90 95

Val Gln His His His Trp Pro Phe Gly Gly Ala Ala Cys Ser Ile Leu
100 105 110

Pro Ser Leu Ile Leu Leu Asn Met Tyr Ala Ser Ile Leu Leu Leu Ala
115 120 125

Thr Ile Ser Ala Asp Arg Phe Leu Leu Val Phe Lys Pro Ile Trp Cys
130 135 140

Gln Asn Phe Arg Gly Ala Gly Leu Ala Trp Ile Ala Cys Ala Val Ala
145 150 155 160

Trp Gly Leu Ala Leu Leu Leu Thr Ile Pro Ser Phe Leu Tyr Arg Val
165 170 175

Val Arg Glu Glu Tyr Phe Pro Pro Lys Val Leu Cys Gly Val Asp Tyr
180 185 190

Ser His Asp Lys Arg Arg Glu Arg Ala Val Ala Ile Val Arg Leu Val
195 200 205

Leu Gly Phe Leu Trp Pro Leu Leu Thr Leu Thr Ile Cys Tyr Thr Phe
210 215 220

Ile Leu Leu Arg Thr Trp Ser Arg Arg Ala Thr Arg Ser Thr Lys Thr
225 230 235 240

Leu Lys Val Val Val Ala Val Val Ala Ser Phe Phe Ile Phe Trp Leu
245 250 255

Pro Tyr Gln Val Thr Gly Ile Met Met Ser Phe Leu Glu Pro Ser Ser
260 265 270

Pro Thr Phe Leu Leu Leu Lys Lys Leu Asp Ser Leu Cys Val Ser Phe
275 280 285

Ala Tyr Ile Asn Cys Cys Ile Asn Pro Ile Ile Tyr Val Val Ala Gly
290 295 300

Gln Gly Phe Gln Gly Arg Leu Arg Lys Ser Leu Pro Ser Leu Leu Arg
305 310 315 320

Asn Val Leu Thr Glu Glu Ser Val Val Arg Glu Ser Lys Ser Phe Thr
325 330 335

Arg Ser Thr Val Asp Thr Met Ala Gln Lys Thr Gln Ala Val
340 345 350

<210> SEQ ID NO 2
<211> LENGTH: 350
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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<400> SEQUENCE: 2

Met Asn Ser Phe Asn Tyr Thr Thr Pro Asp Tyr Gly His Tyr Asp Asp
1 5 10 15

Lys Asp Thr Leu Asp Leu Asn Thr Pro Val Asp Lys Thr Ser Asn Thr
20 25 30

Leu Arg Val Pro Asp Ile Leu Ala Leu Val Ile Phe Ala Val Val Phe
35 40 45

Leu Val Gly Val Leu Gly Asn Ala Leu Val Val Trp Val Thr Ala Phe
50 55 60

Glu Ala Lys Arg Thr Ile Asn Ala Ile Trp Phe Leu Asn Leu Ala Val
65 70 75 80

Ala Asp Phe Leu Ser Cys Leu Ala Leu Pro Ile Leu Phe Thr Ser Ile
85 90 95

Val Gln His His His Trp Pro Phe Gly Gly Ala Ala Cys Ser Ile Leu
100 105 110

Pro Ser Leu Ile Leu Leu Asn Met Tyr Ala Ser Ile Leu Leu Leu Ala
115 120 125

Thr Ile Ser Ala Asp Arg Phe Leu Leu Val Phe Lys Pro Ile Trp Cys
130 135 140

Gln Asn Phe Arg Gly Ala Gly Leu Ala Trp Ile Ala Cys Ala Val Ala
145 150 155 160

Trp Gly Leu Ala Leu Leu Leu Thr Ile Pro Ser Phe Leu Tyr Arg Val
165 170 175

Val Arg Glu Glu Tyr Phe Pro Pro Lys Val Leu Cys Gly Val Asp Tyr
180 185 190

Ser His Asp Lys Arg Arg Glu Arg Ala Val Ala Ile Val Arg Leu Val
195 200 205

Leu Gly Phe Leu Trp Pro Leu Leu Thr Leu Thr Ile Cys Tyr Thr Phe
210 215 220

Ile Leu Leu Arg Thr Trp Ser Arg Arg Ala Thr Arg Ser Thr Lys Thr
225 230 235 240

Leu Lys Val Val Val Ala Val Val Ala Ser Phe Phe Ile Phe Trp Leu
245 250 255

Pro Tyr Gln Val Thr Gly Ile Met Met Ser Phe Leu Glu Pro Ser Ser
260 265 270

Pro Thr Phe Leu Leu Leu Asn Lys Leu Asp Ser Leu Cys Val Ser Phe
275 280 285

Ala Tyr Ile Asn Cys Cys Ile Asn Pro Ile Ile Tyr Val Val Ala Gly
290 295 300

Gln Gly Phe Gln Gly Arg Leu Arg Lys Ser Leu Pro Ser Leu Leu Arg
305 310 315 320

Asn Val Leu Thr Glu Glu Ser Val Val Arg Glu Ser Lys Ser Phe Thr
325 330 335

Arg Ser Thr Val Asp Thr Met Ala Gln Lys Thr Gln Ala Val
340 345 350

<210> SEQ ID NO 3
<211> LENGTH: 350
<212> TYPE: PRT
<213> ORGANISM: Macaca fascicularis

<400> SEQUENCE: 3

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Met Asp Pro Phe Ser Ser Thr Thr Leu Asp Tyr Glu His Tyr Asp Gly
1               5                  10                  15

Lys Asn Val Leu Asp Ser Asp Thr Pro Val Asp Lys Thr Ser Asn Thr
            20                  25                  30

Leu Arg Val Pro Asp Ile Leu Ala Leu Val Val Phe Ala Val Val Phe
        35                  40                  45

Leu Val Gly Val Leu Gly Asn Ala Leu Val Val Trp Val Thr Ala Phe
    50                  55                  60

Glu Val Lys Arg Thr Ile Asn Ala Ile Trp Phe Leu Asn Leu Ala Val
65                  70                  75                  80

Ala Asp Phe Leu Ser Cys Leu Ala Leu Pro Ile Leu Phe Thr Ser Ile
                85                  90                  95

Val Gln His His His Trp Pro Phe Gly Gly Thr Ala Cys Arg Ile Leu
            100                 105                 110

Pro Ser Leu Ile Leu Leu Asn Met Tyr Ala Ser Ile Leu Leu Leu Ala
        115                 120                 125

Thr Ile Ser Ala Asp Arg Phe Leu Leu Val Phe Asn Pro Ile Trp Cys
    130                 135                 140

Gln Asn Phe Arg Gly Ala Gly Leu Ala Trp Ile Ala Cys Ala Val Ala
145                 150                 155                 160

Trp Gly Leu Ala Leu Leu Leu Thr Ile Pro Ser Phe Leu Tyr Arg Ala
                165                 170                 175

Val Arg Gln Glu Glu Tyr Ser Pro Lys Val Leu Cys Gly Val Asp Tyr
            180                 185                 190

Asn Asn Asp Thr Arg Arg Glu Arg Ala Val Ala Ile Val Arg Leu Val
        195                 200                 205

Leu Gly Phe Leu Trp Pro Leu Leu Thr Leu Met Ile Cys Tyr Thr Phe
    210                 215                 220

Leu Leu Leu Arg Thr Trp Ser Arg Arg Ala Thr Arg Ser Thr Lys Thr
225                 230                 235                 240

Leu Lys Val Val Val Ala Val Val Ala Ser Phe Phe Ile Phe Trp Leu
                245                 250                 255

Pro Tyr Gln Val Thr Gly Thr Met Met Ser Phe Leu Arg Pro Ser Ser
            260                 265                 270

Pro Thr Tyr Leu Gln Leu Lys Lys Leu Asp Ser Leu Ser Ile Ser Phe
        275                 280                 285

Ala Tyr Ile Asn Cys Cys Ile Asn Pro Val Ile Tyr Val Val Ala Gly
    290                 295                 300

Gln Gly Phe Gln Gly Arg Leu Arg Lys Ser Leu Pro Ser Leu Leu Arg
305                 310                 315                 320

Asn Val Leu Thr Glu Glu Ser Val Val Arg Glu Ser Lys Ser Phe Thr
                325                 330                 335

Arg Ser Thr Val Asp Thr Met Thr Glu Lys Thr Gln Ala Val
            340                 345                 350


<210> SEQ ID NO 4
<211> LENGTH: 351
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 4

Met Asp Pro Ile Asp Asn Ser Ser Phe Glu Ile Asn Tyr Asp His Tyr
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1               5                   10                  15

Gly Thr Met Ala Pro Asn Ile Pro Ala Asp Gly Ile His Leu Pro Lys
            20                  25                  30

Arg Gln Pro Gly Asp Val Ala Ala Leu Ile Ile Tyr Ser Val Val Phe
        35                  40                  45

Leu Val Gly Val Pro Gly Asn Ala Leu Val Val Trp Val Thr Ala Phe
    50                  55                  60

Glu Ala Arg Arg Ala Val Asn Ala Ile Trp Phe Leu Asn Leu Ala Val
65                  70                  75                  80

Ala Asp Leu Leu Ser Cys Leu Ala Leu Pro Val Leu Phe Thr Thr Val
                85                  90                  95

Leu Asn His Asn Tyr Trp Tyr Phe Asp Ala Thr Ala Cys Ile Val Leu
            100                 105                 110

Pro Ser Leu Ile Leu Leu Asn Met Tyr Ala Ser Ile Leu Leu Leu Ala
        115                 120                 125

Thr Ile Ser Ala Asp Arg Phe Leu Leu Val Phe Lys Pro Ile Trp Cys
    130                 135                 140

Gln Lys Val Arg Gly Thr Gly Leu Ala Trp Met Ala Cys Gly Val Ala
145                 150                 155                 160

Trp Val Leu Ala Leu Leu Leu Thr Ile Pro Ser Phe Val Tyr Arg Glu
                165                 170                 175

Ala Tyr Lys Asp Phe Tyr Ser Glu His Thr Val Cys Gly Ile Asn Tyr
            180                 185                 190

Gly Gly Gly Ser Phe Pro Lys Glu Lys Ala Val Ala Ile Leu Arg Leu
        195                 200                 205

Met Val Gly Phe Val Leu Pro Leu Leu Thr Leu Asn Ile Cys Tyr Thr
    210                 215                 220

Phe Leu Leu Leu Arg Thr Trp Ser Arg Lys Ala Thr Arg Ser Thr Lys
225                 230                 235                 240

Thr Leu Lys Val Val Met Ala Val Val Ile Cys Phe Phe Ile Phe Trp
                245                 250                 255

Leu Pro Tyr Gln Val Thr Gly Val Met Ile Ala Trp Leu Pro Pro Ser
            260                 265                 270

Ser Pro Thr Leu Lys Arg Val Glu Lys Leu Asn Ser Leu Cys Val Ser
        275                 280                 285

Leu Ala Tyr Ile Asn Cys Cys Val Asn Pro Ile Ile Tyr Val Met Ala
    290                 295                 300

Gly Gln Gly Phe His Gly Arg Leu Leu Arg Ser Leu Pro Ser Ile Ile
305                 310                 315                 320

Arg Asn Ala Leu Ser Glu Asp Ser Val Gly Arg Asp Ser Lys Thr Phe
                325                 330                 335

Thr Pro Ser Thr Thr Asp Thr Ser Thr Arg Lys Ser Gln Ala Val
            340                 345                 350


<210> SEQ ID NO 5
<211> LENGTH: 352
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus

<400> SEQUENCE: 5

Met Asp Pro Ile Ser Asn Asp Ser Ser Glu Ile Thr Tyr Asp Tyr Ser
1               5                   10                  15
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Asp Gly Thr Pro Asn Pro Asp Met Pro Ala Asp Gly Val Tyr Ile Pro
            20                  25                  30

Lys Met Glu Pro Gly Asp Ile Ala Ala Leu Ile Ile Tyr Leu Ala Val
        35                  40                  45

Phe Leu Val Gly Val Thr Gly Asn Ala Leu Val Val Trp Val Thr Ala
    50                  55                  60

Phe Glu Ala Lys Arg Thr Val Asn Ala Ile Trp Phe Leu Asn Leu Ala
65                  70                  75                  80

Val Ala Asp Leu Leu Ser Cys Leu Ala Leu Pro Ile Leu Phe Thr Ser
                85                  90                  95

Ile Val Lys His Asn His Trp Pro Phe Gly Asp Gln Ala Cys Ile Val
            100                 105                 110

Leu Pro Ser Leu Ile Leu Leu Asn Met Tyr Ser Ser Ile Leu Leu Leu
        115                 120                 125

Ala Thr Ile Ser Ala Asp Arg Phe Leu Leu Val Phe Lys Pro Ile Trp
    130                 135                 140

Cys Gln Lys Phe Arg Arg Pro Gly Leu Ala Trp Met Ala Cys Gly Val
145                 150                 155                 160

Thr Trp Val Leu Ala Leu Leu Leu Thr Ile Pro Ser Phe Val Phe Arg
                165                 170                 175

Arg Ile His Lys Asp Pro Tyr Ser Asp Ser Ile Leu Cys Asn Ile Asp
            180                 185                 190

Tyr Ser Lys Gly Pro Phe Phe Ile Glu Lys Ala Ile Ala Ile Leu Arg
        195                 200                 205

Leu Met Val Gly Phe Val Leu Pro Leu Leu Thr Leu Asn Ile Cys Tyr
    210                 215                 220

Thr Phe Leu Leu Ile Arg Thr Trp Ser Arg Lys Ala Thr Arg Ser Thr
225                 230                 235                 240

Lys Thr Leu Lys Val Val Met Ala Val Val Thr Cys Phe Phe Val Phe
                245                 250                 255

Trp Leu Pro Tyr Gln Val Thr Gly Val Ile Leu Ala Trp Leu Pro Arg
            260                 265                 270

Ser Ser Ser Thr Phe Gln Ser Val Glu Arg Leu Asn Ser Leu Cys Val
        275                 280                 285

Ser Leu Ala Tyr Ile Asn Cys Cys Val Asn Pro Ile Ile Tyr Val Met
    290                 295                 300

Ala Gly Gln Gly Phe His Gly Arg Leu Arg Arg Ser Leu Pro Ser Ile
305                 310                 315                 320

Ile Arg Asn Val Leu Ser Glu Asp Ser Leu Gly Arg Asp Ser Lys Ser
                325                 330                 335

Phe Thr Arg Ser Thr Met Asp Thr Ser Thr Gln Lys Ser Gln Ala Val
            340                 345                 350


<210> SEQ ID NO 6
<211> LENGTH: 74
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 6

Thr Leu Gln Lys Lys Ile Glu Glu Ile Ala Ala Lys Tyr Lys His Ser
1               5                   10                  15

Val Val Lys Lys Cys Cys Tyr Asp Gly Ala Cys Val Asn Asn Asp Glu
            20                  25                  30
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Thr Cys Glu Gln Arg Ala Ala Arg Ile Ser Leu Gly Pro Arg Cys Ile
        35                  40                  45

Lys Ala Phe Thr Glu Cys Cys Val Val Ala Ser Gln Leu Arg Ala Asn
    50                  55                  60

Ile Ser His Lys Asp Met Gln Leu Gly Arg
65                  70


<210> SEQ ID NO 7
<211> LENGTH: 337
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 7

Met Gly Asn Asp Ser Val Ser Tyr Glu Tyr Gly Asp Tyr Ser Asp Leu
1               5                   10                  15

Ser Asp Arg Pro Val Asp Cys Leu Asp Gly Ala Cys Leu Ala Ile Asp
            20                  25                  30

Pro Leu Arg Val Ala Pro Leu Pro Leu Tyr Ala Ala Ile Phe Leu Val
        35                  40                  45

Gly Val Pro Gly Asn Ala Met Val Ala Trp Val Ala Gly Lys Val Ala
    50                  55                  60

Arg Arg Arg Val Gly Ala Thr Trp Leu Leu His Leu Ala Val Ala Asp
65                  70                  75                  80

Leu Leu Cys Cys Leu Ser Leu Pro Ile Leu Ala Val Pro Ile Ala Arg
                85                  90                  95

Gly Gly His Trp Pro Tyr Gly Ala Val Gly Cys Arg Ala Leu Pro Ser
            100                 105                 110

Ile Ile Leu Leu Thr Met Tyr Ala Ser Val Leu Leu Leu Ala Ala Leu
        115                 120                 125

Ser Ala Asp Leu Cys Phe Leu Ala Leu Gly Pro Ala Trp Trp Ser Thr
    130                 135                 140

Val Gln Arg Ala Cys Gly Val Gln Val Ala Cys Gly Ala Ala Trp Thr
145                 150                 155                 160

Leu Ala Leu Leu Leu Thr Val Pro Ser Ala Ile Tyr Arg Arg Leu His
                165                 170                 175

Gln Glu His Phe Pro Ala Arg Leu Gln Cys Val Val Asp Tyr Gly Gly
            180                 185                 190

Ser Ser Ser Thr Glu Asn Ala Val Thr Ala Ile Arg Phe Leu Phe Gly
        195                 200                 205

Phe Leu Gly Pro Leu Val Ala Val Ala Ser Cys His Ser Ala Leu Leu
    210                 215                 220

Cys Trp Ala Ala Arg Arg Cys Arg Pro Leu Gly Thr Ala Ile Val Val
225                 230                 235                 240

Gly Phe Phe Val Cys Trp Ala Pro Tyr His Leu Leu Gly Leu Val Leu
                245                 250                 255

Thr Val Ala Ala Pro Asn Ser Ala Leu Leu Ala Arg Ala Leu Arg Ala
            260                 265                 270

Glu Pro Leu Ile Val Gly Leu Ala Leu Ala His Ser Cys Leu Asn Pro
        275                 280                 285

Met Leu Phe Leu Tyr Phe Gly Arg Ala Gln Leu Arg Arg Ser Leu Pro
    290                 295                 300

Ala Ala Cys His Trp Ala Leu Arg Glu Ser Gln Gly Gln Asp Glu Ser
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305                 310                 315                 320

Val Asp Ser Lys Lys Ser Thr Ser His Asp Leu Val Ser Glu Met Glu
                325                 330                 335

Val


<210> SEQ ID NO 8
<211> LENGTH: 482
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 8

Met Ala Ser Phe Ser Ala Glu Thr Asn Ser Thr Asp Leu Leu Ser Gln
1               5                   10                  15

Pro Trp Asn Glu Pro Pro Val Ile Leu Ser Met Val Ile Leu Ser Leu
            20                  25                  30

Thr Phe Leu Leu Gly Leu Pro Gly Asn Gly Leu Val Leu Trp Val Ala
        35                  40                  45

Gly Leu Lys Met Gln Arg Thr Val Asn Thr Ile Trp Phe Leu His Leu
    50                  55                  60

Thr Leu Ala Asp Leu Leu Cys Cys Leu Ser Leu Pro Phe Ser Leu Ala
65                  70                  75                  80

His Leu Ala Leu Gln Gly Gln Trp Pro Tyr Gly Arg Phe Leu Cys Lys
                85                  90                  95

Leu Ile Pro Ser Ile Ile Val Leu Asn Met Phe Ala Ser Val Phe Leu
            100                 105                 110

Leu Thr Ala Ile Ser Leu Asp Arg Cys Leu Val Val Phe Lys Pro Ile
        115                 120                 125

Trp Cys Gln Asn His Arg Asn Val Gly Met Ala Cys Ser Ile Cys Gly
    130                 135                 140

Cys Ile Trp Val Val Ala Cys Val Met Cys Ile Pro Val Phe Val Tyr
145                 150                 155                 160

Arg Glu Ile Phe Thr Thr Asp Asn His Asn Arg Cys Gly Tyr Lys Phe
                165                 170                 175

Gly Leu Ser Ser Ser Leu Asp Tyr Pro Asp Phe Tyr Gly Asp Pro Leu
            180                 185                 190

Glu Asn Arg Ser Leu Glu Asn Ile Val Gln Pro Pro Gly Glu Met Asn
        195                 200                 205

Asp Arg Leu Asp Pro Ser Ser Phe Gln Thr Asn Asp His Pro Trp Thr
    210                 215                 220

Val Pro Thr Val Phe Gln Pro Gln Thr Phe Gln Arg Pro Ser Ala Asp
225                 230                 235                 240

Ser Leu Pro Arg Gly Ser Ala Arg Leu Thr Ser Gln Asn Leu Tyr Ser
                245                 250                 255

Asn Val Phe Lys Pro Ala Asp Val Val Ser Pro Lys Ile Pro Ser Gly
            260                 265                 270

Phe Pro Ile Glu Asp His Glu Thr Ser Pro Leu Asp Asn Ser Asp Ala
        275                 280                 285

Phe Leu Ser Thr His Leu Lys Leu Phe Pro Ser Ala Ser Ser Asn Ser
    290                 295                 300

Phe Tyr Glu Ser Glu Leu Pro Gln Gly Phe Gln Asp Tyr Tyr Asn Leu
305                 310                 315                 320

Gly Gln Phe Thr Asp Asp Asp Gln Val Pro Thr Pro Leu Val Ala Ile
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                325                 330                 335

Thr Ile Thr Arg Leu Val Val Gly Phe Leu Leu Pro Ser Val Ile Met
            340                 345                 350

Ile Ala Cys Tyr Ser Phe Ile Val Phe Arg Met Gln Arg Gly Arg Phe
        355                 360                 365

Ala Lys Ser Gln Ser Lys Thr Phe Arg Val Ala Val Val Val Val Ala
    370                 375                 380

Val Phe Leu Val Cys Trp Thr Pro Tyr His Ile Phe Gly Val Leu Ser
385                 390                 395                 400

Leu Leu Thr Asp Pro Glu Thr Pro Leu Gly Lys Thr Leu Met Ser Trp
                405                 410                 415

Asp His Val Cys Ile Ala Leu Ala Ser Ala Asn Ser Cys Phe Asn Pro
            420                 425                 430

Phe Leu Tyr Ala Leu Leu Gly Lys Asp Phe Arg Lys Lys Ala Arg Gln
        435                 440                 445

Ser Ile Gln Gly Ile Leu Glu Ala Ala Phe Ser Glu Glu Leu Thr Arg
    450                 455                 460

Ser Thr His Cys Pro Ser Asn Asn Val Ile Ser Glu Arg Asn Ser Thr
465                 470                 475                 480

Thr Val


<210> SEQ ID NO 9
<211> LENGTH: 350
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 9

Met Glu Thr Asn Ser Ser Leu Pro Thr Asn Ile Ser Gly Gly Thr Pro
1               5                   10                  15

Ala Val Ser Ala Gly Tyr Leu Phe Leu Asp Ile Ile Thr Tyr Leu Val
            20                  25                  30

Phe Ala Val Thr Phe Val Leu Gly Val Leu Gly Asn Gly Leu Val Ile
        35                  40                  45

Trp Val Ala Gly Phe Arg Met Thr His Thr Val Thr Thr Ile Ser Tyr
    50                  55                  60

Leu Asn Leu Ala Val Ala Asp Phe Cys Phe Thr Ser Thr Leu Pro Phe
65                  70                  75                  80

Phe Met Val Arg Lys Ala Met Gly Gly His Trp Pro Phe Gly Trp Phe
                85                  90                  95

Leu Cys Lys Phe Leu Phe Thr Ile Val Asp Ile Asn Leu Phe Gly Ser
            100                 105                 110

Val Phe Leu Ile Ala Leu Ile Ala Leu Asp Arg Cys Val Cys Val Leu
        115                 120                 125

His Pro Val Trp Thr Gln Asn His Arg Thr Val Ser Leu Ala Lys Lys
    130                 135                 140

Val Ile Ile Gly Pro Trp Val Met Ala Leu Leu Leu Thr Leu Pro Val
145                 150                 155                 160

Ile Ile Arg Val Thr Thr Val Pro Gly Lys Thr Gly Thr Val Ala Cys
                165                 170                 175

Thr Phe Asn Phe Ser Pro Trp Thr Asn Asp Pro Lys Glu Arg Ile Asn
            180                 185                 190

Val Ala Val Ala Met Leu Thr Val Arg Gly Ile Ile Arg Phe Ile Ile
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        195                 200                 205

Gly Phe Ser Ala Pro Met Ser Ile Val Ala Val Ser Tyr Gly Leu Ile
    210                 215                 220

Ala Thr Lys Ile His Lys Gln Gly Leu Ile Lys Ser Ser Pro Pro Leu
225                 230                 235                 240

Arg Val Leu Ser Phe Val Ala Ala Ala Phe Phe Leu Cys Trp Ser Pro
                245                 250                 255

Tyr Gln Val Val Ala Leu Ile Ala Thr Val Arg Ile Arg Glu Leu Leu
            260                 265                 270

Gln Gly Met Tyr Lys Glu Ile Gly Ile Ala Val Asp Val Thr Ser Ala
        275                 280                 285

Leu Ala Phe Phe Asn Ser Cys Leu Asn Pro Met Leu Tyr Val Phe Met
    290                 295                 300

Gly Gln Asp Phe Arg Glu Arg Leu Ile His Ala Leu Pro Ala Ser Leu
305                 310                 315                 320

Glu Arg Ala Leu Thr Glu Asp Ser Thr Gln Thr Ser Asp Thr Ala Thr
                325                 330                 335

Asn Ser Thr Leu Pro Ser Ala Glu Val Ala Leu Gln Ala Lys
            340                 345                 350


<210> SEQ ID NO 10
<211> LENGTH: 373
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 10

Met Arg Met Glu Asp Glu Asp Tyr Asn Thr Ser Ile Ser Tyr Gly Asp
1               5                   10                  15

Glu Tyr Pro Asp Tyr Leu Asp Ser Ile Val Val Leu Glu Asp Leu Ser
            20                  25                  30

Pro Leu Glu Ala Arg Val Thr Arg Ile Phe Leu Val Val Val Tyr Ser
        35                  40                  45

Ile Val Cys Phe Leu Gly Ile Leu Gly Asn Gly Leu Val Ile Ile Ile
    50                  55                  60

Ala Thr Phe Lys Met Lys Lys Thr Val Asn Met Val Trp Phe Leu Asn
65                  70                  75                  80

Leu Ala Val Ala Asp Phe Leu Phe Asn Val Phe Leu Pro Ile His Ile
                85                  90                  95

Thr Tyr Ala Ala Met Asp Tyr His Trp Val Phe Gly Thr Ala Met Cys
            100                 105                 110

Lys Ile Ser Asn Phe Leu Leu Ile His Asn Met Phe Thr Ser Val Phe
        115                 120                 125

Leu Leu Thr Ile Ile Ser Ser Asp Arg Cys Ile Ser Val Leu Leu Pro
    130                 135                 140

Val Trp Ser Gln Asn His Arg Ser Val Arg Leu Ala Tyr Met Ala Cys
145                 150                 155                 160

Met Val Ile Trp Val Leu Ala Phe Phe Leu Ser Ser Pro Ser Leu Val
                165                 170                 175

Phe Arg Asp Thr Ala Asn Leu His Gly Lys Ile Ser Cys Phe Asn Asn
            180                 185                 190

Phe Ser Leu Ser Thr Pro Gly Ser Ser Ser Trp Pro Thr His Ser Gln
        195                 200                 205
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```
Met Asp Pro Val Gly Tyr Ser Arg His Met Val Val Thr Val Thr Arg
    210                 215                 220

Phe Leu Cys Gly Phe Leu Val Pro Val Leu Ile Ile Thr Ala Cys Tyr
225                 230                 235                 240

Leu Thr Ile Val Cys Lys Leu His Arg Asn Arg Leu Ala Lys Thr Lys
                245                 250                 255

Lys Pro Phe Lys Ile Ile Val Thr Ile Ile Ile Thr Phe Phe Leu Cys
            260                 265                 270

Trp Cys Pro Tyr His Thr Leu Asn Leu Leu Glu Leu His His Thr Ala
        275                 280                 285

Met Pro Gly Ser Val Phe Ser Leu Gly Leu Pro Leu Ala Thr Ala Leu
    290                 295                 300

Ala Ile Ala Asn Ser Cys Met Asn Pro Ile Leu Tyr Val Phe Met Gly
305                 310                 315                 320

Gln Asp Phe Lys Lys Phe Lys Val Ala Leu Phe Ser Arg Leu Val Asn
                325                 330                 335

Ala Leu Ser Glu Asp Thr Gly His Ser Ser Tyr Pro Ser His Arg Ser
            340                 345                 350

Phe Thr Lys Met Ser Ser Met Asn Glu Arg Thr Ser Met Asn Glu Arg
        355                 360                 365

Glu Thr Gly Met Leu
    370


<210> SEQ ID NO 11
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 11

Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro
1               5                   10                  15

Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val
            20                  25                  30

Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val
        35                  40                  45

Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln
    50                  55                  60

Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln
65                  70                  75                  80

Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala
                85                  90                  95

Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro
            100                 105                 110

Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr
        115                 120                 125

Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser
    130                 135                 140

Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr
145                 150                 155                 160

Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr
                165                 170                 175

Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe
            180                 185                 190
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```
Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys
        195                 200                 205

Ser Leu Ser Leu Ser Pro Gly Lys
    210                 215


<210> SEQ ID NO 12
<211> LENGTH: 31
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 12

Met Asp Ser Phe Asn Tyr Thr Thr Pro Asp Tyr Gly His Tyr Asp Asp
1               5                   10                  15

Lys Asp Thr Leu Asp Leu Asn Thr Pro Val Asp Lys Thr Ser Asn
            20                  25                  30


<210> SEQ ID NO 13
<211> LENGTH: 37
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 13

Met Asp Ser Phe Asn Tyr Thr Thr Pro Asp Tyr Gly His Tyr Asp Asp
1               5                   10                  15

Lys Asp Thr Leu Asp Leu Asn Thr Pro Val Asp Lys Thr Ser Asn Thr
            20                  25                  30

Leu Arg Val Pro Asp
        35


<210> SEQ ID NO 14
<211> LENGTH: 37
<212> TYPE: PRT
<213> ORGANISM: Macaca fascicularis

<400> SEQUENCE: 14

Met Asp Pro Phe Ser Ser Thr Thr Leu Asp Tyr Glu His Tyr Asp Gly
1               5                   10                  15

Lys Asn Val Leu Asp Ser Asp Thr Pro Val Asp Lys Thr Ser Asn Thr
            20                  25                  30

Leu Arg Val Pro Asp
        35


<210> SEQ ID NO 15
<211> LENGTH: 398
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 15

Ala Glu Ser His Leu Ser Leu Leu Tyr His Leu Thr Ala Val Ser Ser
1               5                   10                  15

Pro Ala Pro Gly Thr Pro Ala Phe Trp Val Ser Gly Trp Leu Gly Pro
            20                  25                  30

Gln Gln Tyr Leu Ser Tyr Asn Ser Leu Arg Gly Glu Ala Glu Pro Cys
        35                  40                  45
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Gly Ala Trp Val Trp Glu Asn Gln Val Ser Trp Tyr Trp Glu Lys Glu
    50                  55                  60

Thr Thr Asp Leu Arg Ile Lys Glu Lys Leu Phe Leu Glu Ala Phe Lys
65                  70                  75                  80

Ala Leu Gly Gly Lys Gly Pro Tyr Thr Leu Gln Gly Leu Leu Gly Cys
                85                  90                  95

Glu Leu Gly Pro Asp Asn Thr Ser Val Pro Thr Ala Lys Phe Ala Leu
            100                 105                 110

Asn Gly Glu Glu Phe Met Asn Phe Asp Leu Lys Gln Gly Thr Trp Gly
        115                 120                 125

Gly Asp Trp Pro Glu Ala Leu Ala Ile Ser Gln Arg Trp Gln Gln Gln
    130                 135                 140

Asp Lys Ala Ala Asn Lys Glu Leu Thr Phe Leu Leu Phe Ser Cys Pro
145                 150                 155                 160

His Arg Leu Arg Glu His Leu Glu Arg Gly Arg Gly Asn Leu Glu Trp
                165                 170                 175

Lys Glu Pro Pro Ser Met Arg Leu Lys Ala Arg Pro Ser Ser Pro Gly
            180                 185                 190

Phe Ser Val Leu Thr Cys Ser Ala Phe Ser Phe Tyr Pro Pro Glu Leu
        195                 200                 205

Gln Leu Arg Phe Leu Arg Asn Gly Leu Ala Ala Gly Thr Gly Gln Gly
    210                 215                 220

Asp Phe Gly Pro Asn Ser Asp Gly Ser Phe His Ala Ser Ser Ser Leu
225                 230                 235                 240

Thr Val Lys Ser Gly Asp Glu His His Tyr Cys Cys Ile Val Gln His
                245                 250                 255

Ala Gly Leu Ala Gln Pro Leu Arg Val Glu Leu Glu Ser Pro Ala Lys
            260                 265                 270

Ser Ser Val Asn Ser Arg Gly Leu Asn Asp Ile Phe Glu Ala Gln Lys
        275                 280                 285

Ile Glu Trp His Glu His His His His His His Ile Gln Arg Thr Pro
    290                 295                 300

Lys Ile Gln Val Tyr Ser Arg His Pro Ala Glu Asn Gly Lys Ser Asn
305                 310                 315                 320

Phe Leu Asn Cys Tyr Val Ser Gly Phe His Pro Ser Asp Ile Glu Val
                325                 330                 335

Asp Leu Leu Lys Asn Gly Glu Arg Ile Glu Lys Val Glu His Ser Asp
            340                 345                 350

Leu Ser Phe Ser Lys Asp Trp Ser Phe Tyr Leu Leu Tyr Tyr Thr Glu
        355                 360                 365

Phe Thr Pro Thr Glu Lys Asp Glu Tyr Ala Cys Arg Val Asn His Val
    370                 375                 380

Thr Leu Ser Gln Pro Lys Ile Val Lys Trp Asp Arg Asp Met
385                 390                 395


<210> SEQ ID NO 16
<211> LENGTH: 398
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"
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<400> SEQUENCE: 16

```
Ala Glu Ser His Leu Ser Leu Leu Tyr His Leu Thr Ala Val Ser Ser
1               5                  10                  15

Pro Ala Pro Gly Thr Pro Ala Phe Trp Val Ser Gly Trp Leu Gly Pro
            20                  25                  30

Gln Gln Tyr Leu Ser Tyr Asp Ser Leu Arg Gly Gln Ala Glu Pro Cys
        35                  40                  45

Gly Ala Trp Val Trp Glu Asn Gln Val Ser Trp Tyr Trp Glu Lys Glu
    50                  55                  60

Thr Thr Asp Leu Arg Ile Lys Glu Lys Leu Phe Leu Glu Ala Phe Lys
65                  70                  75                  80

Ala Leu Gly Gly Lys Gly Pro Tyr Thr Leu Gln Gly Leu Leu Gly Cys
                85                  90                  95

Glu Leu Ser Pro Asp Asn Thr Ser Val Pro Thr Ala Lys Phe Ala Leu
            100                 105                 110

Asn Gly Glu Glu Phe Met Asn Phe Asp Leu Lys Gln Gly Thr Trp Gly
        115                 120                 125

Gly Asp Trp Pro Glu Ala Leu Ala Ile Ser Gln Arg Trp Gln Gln Gln
    130                 135                 140

Asp Lys Ala Ala Asn Lys Glu Leu Thr Phe Leu Leu Phe Ser Cys Pro
145                 150                 155                 160

His Arg Leu Arg Glu His Leu Glu Arg Gly Arg Gly Asn Leu Glu Trp
                165                 170                 175

Lys Glu Pro Pro Ser Met Arg Leu Lys Ala Arg Pro Gly Asn Pro Gly
            180                 185                 190

Phe Ser Val Leu Thr Cys Ser Ala Phe Ser Phe Tyr Pro Pro Glu Leu
        195                 200                 205

Gln Leu Arg Phe Leu Arg Asn Gly Met Ala Ala Gly Thr Gly Gln Gly
    210                 215                 220

Asp Phe Gly Pro Asn Ser Asp Gly Ser Phe His Ala Ser Ser Ser Leu
225                 230                 235                 240

Thr Val Lys Ser Gly Asp Glu His His Tyr Cys Cys Ile Val Gln His
                245                 250                 255

Ala Gly Leu Ala Gln Pro Leu Arg Val Glu Leu Glu Thr Pro Ala Lys
            260                 265                 270

Ser Ser Val Asn Ser Arg Gly Leu Asn Asp Ile Phe Glu Ala Gln Lys
        275                 280                 285

Ile Glu Trp His Glu His His His His His His Ile Gln Arg Thr Pro
    290                 295                 300

Lys Ile Gln Val Tyr Ser Arg His Pro Pro Glu Asn Gly Lys Pro Asn
305                 310                 315                 320

Phe Leu Asn Cys Tyr Val Ser Gly Phe His Pro Ser Asp Ile Glu Val
                325                 330                 335

Asp Leu Leu Lys Asn Gly Glu Lys Met Gly Lys Val Glu His Ser Asp
            340                 345                 350

Leu Ser Phe Ser Lys Asp Trp Ser Phe Tyr Leu Leu Tyr Tyr Thr Glu
        355                 360                 365

Phe Thr Pro Asn Glu Lys Asp Glu Tyr Ala Cys Arg Val Asn His Val
    370                 375                 380

Thr Leu Ser Gly Pro Arg Thr Val Lys Trp Asp Arg Asp Met
385                 390                 395
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<210> SEQ ID NO 17
<211> LENGTH: 400
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 17

Ser Glu Thr Arg Pro Pro Leu Met Tyr His Leu Thr Ala Val Ser Asn
1 5 10 15

Pro Ser Thr Gly Leu Pro Ser Phe Trp Ala Thr Gly Trp Leu Gly Pro
20 25 30

Gln Gln Tyr Leu Thr Tyr Asn Ser Leu Arg Gln Glu Ala Asp Pro Cys
35 40 45

Gly Ala Trp Met Trp Glu Asn Gln Val Ser Trp Tyr Trp Glu Lys Glu
50 55 60

Thr Thr Asp Leu Lys Ser Lys Glu Gln Leu Phe Leu Glu Ala Leu Lys
65 70 75 80

Thr Leu Glu Lys Ile Leu Asn Gly Thr Tyr Thr Leu Gln Gly Leu Leu
85 90 95

Gly Cys Glu Leu Ala Ser Asp Asn Ser Ser Val Pro Thr Ala Val Phe
100 105 110

Ala Leu Asn Gly Glu Glu Phe Met Lys Phe Asn Pro Arg Ile Gly Asn
115 120 125

Trp Thr Gly Glu Trp Pro Glu Thr Glu Ile Val Ala Asn Leu Trp Met
130 135 140

Lys Gln Pro Asp Ala Ala Arg Lys Glu Ser Glu Phe Leu Leu Asn Ser
145 150 155 160

Cys Pro Glu Arg Leu Leu Gly His Leu Glu Arg Gly Arg Arg Asn Leu
165 170 175

Glu Trp Lys Glu Pro Pro Ser Met Arg Leu Lys Ala Arg Pro Gly Asn
180 185 190

Ser Gly Ser Ser Val Leu Thr Cys Ala Ala Phe Ser Phe Tyr Pro Pro
195 200 205

Glu Leu Lys Phe Arg Phe Leu Arg Asn Gly Leu Ala Ser Gly Ser Gly
210 215 220

Asn Cys Ser Thr Gly Pro Asn Gly Asp Gly Ser Phe His Ala Trp Ser
225 230 235 240

Leu Leu Glu Val Lys Arg Gly Asp Glu His His Tyr Gln Cys Gln Val
245 250 255

Glu His Glu Gly Leu Ala Gln Pro Leu Thr Val Asp Leu Asp Ser Ser
260 265 270

Ala Arg Ser Ser Val Asn Ser Arg Gly Leu Asn Asp Ile Phe Glu Ala
275 280 285

Gln Lys Ile Glu Trp His Glu His His His His His His Ile Gln Lys
290 295 300

Thr Pro Gln Ile Gln Val Tyr Ser Arg His Pro Pro Glu Asn Gly Lys
305 310 315 320

Pro Asn Ile Leu Asn Cys Tyr Val Thr Gln Phe His Pro Pro His Ile
325 330 335

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Glu Ile Gln Met Leu Lys Asn Gly Lys Lys Ile Pro Lys Val Glu Met
            340                 345                 350

Ser Asp Met Ser Phe Ser Lys Asp Trp Ser Phe Tyr Ile Leu Ala His
        355                 360                 365

Thr Glu Phe Thr Pro Thr Glu Thr Asp Thr Tyr Ala Cys Arg Val Lys
    370                 375                 380

His Asp Ser Met Ala Glu Pro Lys Thr Val Tyr Trp Asp Arg Asp Met
385                 390                 395                 400


<210> SEQ ID NO 18
<211> LENGTH: 274
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 18

Gln Val Asp Thr Thr Lys Ala Val Ile Thr Leu Gln Pro Pro Trp Val
1               5                   10                  15

Ser Val Phe Gln Glu Glu Thr Val Thr Leu His Cys Glu Val Leu His
            20                  25                  30

Leu Pro Gly Ser Ser Ser Thr Gln Trp Phe Leu Asn Gly Thr Ala Thr
        35                  40                  45

Gln Thr Ser Thr Pro Ser Tyr Arg Ile Thr Ser Ala Ser Val Asn Asp
    50                  55                  60

Ser Gly Glu Tyr Arg Cys Gln Arg Gly Leu Ser Gly Arg Ser Asp Pro
65                  70                  75                  80

Ile Gln Leu Glu Ile His Arg Gly Trp Leu Leu Leu Gln Val Ser Ser
                85                  90                  95

Arg Val Phe Thr Glu Gly Glu Pro Leu Ala Leu Arg Cys His Ala Trp
            100                 105                 110

Lys Asp Lys Leu Val Tyr Asn Val Leu Tyr Tyr Arg Asn Gly Lys Ala
        115                 120                 125

Phe Lys Phe Phe His Trp Asn Ser Asn Leu Thr Ile Leu Lys Thr Asn
    130                 135                 140

Ile Ser His Asn Gly Thr Tyr His Cys Ser Gly Met Gly Lys His Arg
145                 150                 155                 160

Tyr Thr Ser Ala Gly Ile Ser Val Thr Val Lys Glu Leu Phe Pro Ala
                165                 170                 175

Pro Val Leu Asn Ala Ser Val Thr Ser Pro Leu Leu Glu Gly Asn Leu
            180                 185                 190

Val Thr Leu Ser Cys Glu Thr Lys Leu Leu Leu Gln Arg Pro Gly Leu
        195                 200                 205

Gln Leu Tyr Phe Ser Phe Tyr Met Gly Ser Lys Thr Leu Arg Gly Arg
    210                 215                 220

Asn Thr Ser Ser Glu Tyr Gln Ile Leu Thr Ala Arg Arg Glu Asp Ser
225                 230                 235                 240

Gly Leu Tyr Trp Cys Glu Ala Ala Thr Glu Asp Gly Asn Val Leu Lys
                245                 250                 255

Arg Ser Pro Glu Leu Glu Leu Gln Val Asn Ser Arg His His His His
            260                 265                 270

His His
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<210> SEQ ID NO 19
<211> LENGTH: 186
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 19

Gln Ala Ala Ala Pro Pro Lys Ala Val Leu Lys Leu Glu Pro Pro Trp
1 5 10 15

Ile Asn Val Leu Gln Glu Asp Ser Val Thr Leu Thr Cys Gln Gly Ala
20 25 30

Arg Ser Pro Glu Ser Asp Ser Ile Gln Trp Phe His Asn Gly Asn Leu
35 40 45

Ile Pro Thr His Thr Gln Pro Ser Tyr Arg Phe Lys Ala Asn Asn Asn
50 55 60

Asp Ser Gly Glu Tyr Thr Cys Gln Thr Gly Gln Thr Ser Leu Ser Asp
65 70 75 80

Pro Val His Leu Thr Val Leu Ser Glu Trp Leu Val Leu Gln Thr Pro
85 90 95

His Leu Glu Phe Gln Glu Gly Glu Thr Ile Met Leu Arg Cys His Ser
100 105 110

Trp Lys Asp Lys Pro Leu Val Lys Val Thr Phe Phe Gln Asn Gly Lys
115 120 125

Ser Gln Lys Phe Ser His Leu Asp Pro Thr Phe Ser Ile Pro Gln Ala
130 135 140

Asn His Ser His Ser Gly Asp Tyr His Cys Thr Gly Asn Ile Gly Tyr
145 150 155 160

Thr Leu Phe Ser Ser Lys Pro Val Thr Ile Thr Val Gln Val Pro Ser
165 170 175

Val Asn Ser Arg His His His His His His
180 185

<210> SEQ ID NO 20
<211> LENGTH: 186
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 20

Gln Ala Ala Ala Pro Pro Lys Ala Val Leu Lys Leu Glu Pro Pro Trp
1 5 10 15

Ile Asn Val Leu Gln Glu Asp Ser Val Thr Leu Thr Cys Gln Gly Ala
20 25 30

Arg Ser Pro Glu Ser Asp Ser Ile Gln Trp Phe His Asn Gly Asn Leu
35 40 45

Ile Pro Thr His Thr Gln Pro Ser Tyr Arg Phe Lys Ala Asn Asn Asn
50 55 60

Asp Ser Gly Glu Tyr Thr Cys Gln Thr Gly Gln Thr Ser Leu Ser Asp
65 70 75 80

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Pro Val His Leu Thr Val Leu Ser Glu Trp Leu Val Leu Gln Thr Pro
                85                  90                  95

His Leu Glu Phe Gln Glu Gly Glu Thr Ile Met Leu Arg Cys His Ser
            100                 105                 110

Trp Lys Asp Lys Pro Leu Val Lys Val Thr Phe Phe Gln Asn Gly Lys
        115                 120                 125

Ser Gln Lys Phe Ser Arg Leu Asp Pro Thr Phe Ser Ile Pro Gln Ala
    130                 135                 140

Asn His Ser His Ser Gly Asp Tyr His Cys Thr Gly Asn Ile Gly Tyr
145                 150                 155                 160

Thr Leu Phe Ser Ser Lys Pro Val Thr Ile Thr Val Gln Val Pro Ser
                165                 170                 175

Val Asn Ser Arg His His His His His His
            180                 185


<210> SEQ ID NO 21
<211> LENGTH: 187
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 21

Gly Met Arg Thr Glu Asp Leu Pro Lys Ala Val Val Phe Leu Glu Pro
1               5                   10                  15

Gln Trp Tyr Arg Val Leu Glu Lys Asp Ser Val Thr Leu Lys Cys Gln
            20                  25                  30

Gly Ala Tyr Ser Pro Glu Asp Asn Ser Thr Gln Trp Phe His Asn Glu
        35                  40                  45

Ser Leu Ile Ser Ser Gln Ala Ser Ser Tyr Phe Ile Asp Ala Ala Thr
    50                  55                  60

Val Asp Asp Ser Gly Glu Tyr Arg Cys Gln Thr Asn Leu Ser Thr Leu
65                  70                  75                  80

Ser Asp Pro Val Gln Leu Glu Val His Ile Gly Trp Leu Leu Leu Gln
                85                  90                  95

Ala Pro Arg Trp Val Phe Lys Glu Glu Asp Pro Ile His Leu Arg Cys
            100                 105                 110

His Ser Trp Lys Asn Thr Ala Leu His Lys Val Thr Tyr Leu Gln Asn
        115                 120                 125

Gly Lys Gly Arg Lys Tyr Phe His His Asn Ser Asp Phe Tyr Ile Pro
    130                 135                 140

Lys Ala Thr Leu Lys Asp Ser Gly Ser Tyr Phe Cys Arg Gly Leu Phe
145                 150                 155                 160

Gly Ser Lys Asn Val Ser Ser Glu Thr Val Asn Ile Thr Ile Thr Gln
                165                 170                 175

Gly Val Asn Ser Arg His His His His His His
            180                 185


<210> SEQ ID NO 22
<211> LENGTH: 187
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 22

Gly Met Arg Thr Glu Asp Leu Pro Lys Ala Val Val Phe Leu Glu Pro
1 5 10 15

Gln Trp Tyr Arg Val Leu Glu Lys Asp Ser Val Thr Leu Lys Cys Gln
20 25 30

Gly Ala Tyr Ser Pro Glu Asp Asn Ser Thr Gln Trp Phe His Asn Glu
35 40 45

Ser Leu Ile Ser Ser Gln Ala Ser Ser Tyr Phe Ile Asp Ala Ala Thr
50 55 60

Val Asp Asp Ser Gly Glu Tyr Arg Cys Gln Thr Asn Leu Ser Thr Leu
65 70 75 80

Ser Asp Pro Val Gln Leu Glu Val His Ile Gly Trp Leu Leu Leu Gln
85 90 95

Ala Pro Arg Trp Val Phe Lys Glu Glu Asp Pro Ile His Leu Arg Cys
100 105 110

His Ser Trp Lys Asn Thr Ala Leu His Lys Val Thr Tyr Leu Gln Asn
115 120 125

Gly Lys Gly Arg Lys Tyr Phe His His Asn Ser Asp Phe Tyr Ile Pro
130 135 140

Lys Ala Thr Leu Lys Asp Ser Gly Ser Tyr Phe Cys Arg Gly Leu Val
145 150 155 160

Gly Ser Lys Asn Val Ser Ser Glu Thr Val Asn Ile Thr Ile Thr Gln
165 170 175

Gly Val Asn Ser Arg His His His His His His
180 185

<210> SEQ ID NO 23
<211> LENGTH: 186
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 23

Thr Pro Ala Ala Pro Pro Lys Ala Val Leu Lys Leu Glu Pro Gln Trp
1 5 10 15

Ile Asn Val Leu Gln Glu Asp Ser Val Thr Leu Thr Cys Arg Gly Thr
20 25 30

His Ser Pro Glu Ser Asp Ser Ile Gln Trp Phe His Asn Gly Asn Leu
35 40 45

Ile Pro Thr His Thr Gln Pro Ser Tyr Arg Phe Lys Ala Asn Asn Asn
50 55 60

Asp Ser Gly Glu Tyr Thr Cys Gln Thr Gly Gln Thr Ser Leu Ser Asp
65 70 75 80

Pro Val His Leu Thr Val Leu Ser Glu Trp Leu Val Leu Gln Thr Pro
85 90 95

His Leu Glu Phe Gln Glu Gly Glu Thr Ile Val Leu Arg Cys His Ser
100 105 110

Trp Lys Asp Lys Pro Leu Val Lys Val Thr Phe Phe Gln Asn Gly Lys
115 120 125

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Ser Lys Lys Phe Ser Arg Ser Asp Pro Asn Phe Ser Ile Pro Gln Ala
    130                 135                 140

Asn His Ser His Ser Gly Asp Tyr His Cys Thr Gly Asn Ile Gly Tyr
145                 150                 155                 160

Thr Leu Tyr Ser Ser Lys Pro Val Thr Ile Thr Val Gln Ala Pro Ser
                165                 170                 175

Asp Asn Ser Arg His His His His His His
            180                 185


<210> SEQ ID NO 24
<211> LENGTH: 907
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 24

Asp Gly Ser His His His His His His Gly Thr Met Asp Ser Phe Asn
1               5                   10                  15

Tyr Thr Thr Pro Asp Tyr Gly His Tyr Asp Asp Lys Asp Thr Leu Asp
            20                  25                  30

Leu Asn Thr Pro Val Asp Lys Thr Ser Asn Thr Leu Arg Val Pro Asp
        35                  40                  45

Ile Leu Ala Leu Val Ile Phe Ala Val Val Phe Leu Val Gly Val Leu
    50                  55                  60

Gly Asn Ala Leu Val Val Trp Val Thr Ala Phe Glu Ala Lys Arg Thr
65                  70                  75                  80

Ile Asn Ala Ile Trp Phe Leu Asn Leu Ala Val Ala Asp Phe Leu Ser
                85                  90                  95

Cys Leu Ala Leu Pro Ile Leu Phe Thr Ser Ile Val Gln His His His
            100                 105                 110

Trp Pro Phe Gly Gly Ala Ala Cys Ser Ile Leu Pro Ser Leu Ile Leu
        115                 120                 125

Leu Asn Met Tyr Ala Ser Ile Leu Leu Leu Ala Thr Ile Ser Ala Asp
    130                 135                 140

Arg Phe Leu Leu Val Phe Lys Pro Ile Trp Cys Gln Asn Phe Arg Gly
145                 150                 155                 160

Ala Gly Leu Ala Trp Ile Ala Cys Ala Val Ala Trp Gly Leu Ala Leu
                165                 170                 175

Leu Leu Thr Ile Pro Ser Phe Leu Tyr Arg Val Val Arg Glu Glu Tyr
            180                 185                 190

Phe Pro Pro Lys Val Leu Cys Gly Val Asp Tyr Ser His Asp Lys Arg
        195                 200                 205

Arg Glu Arg Ala Val Ala Ile Val Arg Leu Val Leu Gly Phe Leu Trp
    210                 215                 220

Pro Leu Leu Thr Leu Thr Ile Cys Tyr Thr Phe Ile Leu Leu Arg Thr
225                 230                 235                 240

Trp Ser Arg Arg Ala Thr Arg Ser Thr Lys Thr Leu Lys Val Val Val
                245                 250                 255

Ala Val Val Ala Ser Phe Phe Ile Phe Trp Leu Pro Tyr Gln Val Thr
            260                 265                 270
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Gly Ile Met Met Ser Phe Leu Glu Pro Ser Ser Pro Thr Phe Leu Leu
        275                 280                 285

Leu Lys Lys Leu Asp Ser Leu Cys Val Ser Phe Ala Tyr Ile Asn Cys
    290                 295                 300

Cys Ile Asn Pro Ile Ile Tyr Val Val Ala Gly Gln Gly Phe Gln Gly
305                 310                 315                 320

Arg Leu Arg Lys Ser Leu Pro Ser Leu Leu Arg Asn Val Leu Thr Glu
                325                 330                 335

Glu Ser Val Val Arg Glu Ser Lys Ser Phe Thr Arg Ser Thr Val Asp
            340                 345                 350

Thr Met Ala Gln Lys Thr Gln Ala Val Asp Ile Asp Tyr Lys Asp Asp
        355                 360                 365

Asp Asp Lys Ile Glu Gly Arg Met Asp Gly Ala Arg Ala Ser Val Leu
    370                 375                 380

Ser Gly Gly Glu Leu Asp Arg Trp Glu Lys Ile Arg Leu Arg Pro Gly
385                 390                 395                 400

Gly Lys Lys Lys Tyr Lys Leu Lys His Ile Val Trp Ala Ser Arg Glu
                405                 410                 415

Leu Glu Arg Phe Ala Val Asn Pro Gly Leu Leu Glu Thr Ser Glu Gly
            420                 425                 430

Cys Arg Gln Ile Leu Gly Gln Leu Gln Pro Ser Leu Gln Thr Gly Ser
        435                 440                 445

Glu Glu Leu Arg Ser Leu Tyr Asn Thr Val Ala Thr Leu Tyr Cys Val
    450                 455                 460

His Gln Arg Ile Glu Ile Lys Asp Thr Lys Glu Ala Leu Asp Lys Ile
465                 470                 475                 480

Glu Glu Glu Gln Asn Lys Ser Lys Lys Lys Ala Gln Gln Ala Ala Ala
                485                 490                 495

Asp Thr Gly His Ser Ser Gln Val Ser Gln Asn Tyr Pro Ile Val Gln
            500                 505                 510

Asn Ile Gln Gly Gln Met Val His Gln Ala Ile Ser Pro Arg Thr Leu
        515                 520                 525

Asn Ala Trp Val Lys Val Val Glu Glu Lys Ala Phe Ser Pro Glu Val
    530                 535                 540

Ile Pro Met Phe Ser Ala Leu Ser Glu Gly Ala Thr Pro Gln Asp Leu
545                 550                 555                 560

Asn Thr Met Leu Asn Thr Val Gly Gly His Gln Ala Ala Met Gln Met
                565                 570                 575

Leu Lys Glu Thr Ile Asn Glu Glu Ala Ala Glu Trp Asp Arg Val His
            580                 585                 590

Pro Val His Ala Gly Pro Ile Ala Pro Gly Gln Met Arg Glu Pro Arg
        595                 600                 605

Gly Ser Asp Ile Ala Gly Thr Thr Ser Thr Leu Gln Glu Gln Ile Gly
    610                 615                 620

Trp Met Thr Asn Asn Pro Pro Ile Pro Val Gly Glu Ile Tyr Lys Arg
625                 630                 635                 640

Trp Ile Ile Leu Gly Leu Asn Lys Ile Val Arg Met Tyr Ser Pro Thr
                645                 650                 655

Ser Ile Leu Asp Ile Arg Gln Gly Pro Lys Glu Pro Phe Arg Asp Tyr
            660                 665                 670

Val Asp Arg Phe Tyr Lys Thr Leu Arg Ala Glu Gln Ala Ser Gln Glu
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        675                 680                 685

Val Lys Asn Trp Met Thr Glu Thr Leu Leu Val Gln Asn Ala Asn Pro
    690                 695                 700

Asp Cys Lys Thr Ile Leu Lys Ala Leu Gly Pro Ala Ala Thr Leu Glu
705                 710                 715                 720

Glu Met Met Thr Ala Cys Gln Gly Val Gly Gly Pro Gly His Lys Ala
                725                 730                 735

Arg Val Leu Ala Glu Ala Met Ser Gln Val Thr Asn Thr Ala Thr Ile
            740                 745                 750

Met Met Gln Arg Gly Asn Phe Arg Asn Gln Arg Lys Met Val Lys Cys
        755                 760                 765

Phe Asn Cys Gly Lys Glu Gly His Thr Ala Arg Asn Cys Arg Ala Pro
    770                 775                 780

Arg Lys Lys Gly Cys Trp Lys Cys Gly Lys Glu Gly His Gln Met Lys
785                 790                 795                 800

Asp Cys Thr Glu Arg Gln Ala Asn Phe Leu Gly Lys Ile Trp Pro Ser
                805                 810                 815

Tyr Lys Gly Arg Pro Gly Asn Phe Leu Gln Ser Arg Pro Glu Pro Thr
            820                 825                 830

Ala Pro Pro Phe Leu Gln Ser Arg Pro Glu Pro Thr Ala Pro Pro Glu
        835                 840                 845

Glu Ser Phe Arg Ser Gly Val Glu Thr Thr Thr Pro Pro Gln Lys Gln
    850                 855                 860

Glu Pro Ile Asp Lys Glu Leu Tyr Pro Leu Thr Ser Leu Arg Ser Leu
865                 870                 875                 880

Phe Gly Asn Asp Pro Ser Ser Gln Val Asn Ser Arg Gly Leu Asn Asp
                885                 890                 895

Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu
            900                 905


<210> SEQ ID NO 25
<211> LENGTH: 874
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 25

Asp Gly Ser His His His His His His Gly Thr Met Asn Ser Phe Asn
1               5                   10                  15

Tyr Thr Thr Pro Asp Tyr Gly His Tyr Asp Asp Lys Asp Thr Leu Asp
            20                  25                  30

Leu Asn Thr Pro Val Asp Lys Thr Ser Asn Thr Leu Arg Val Pro Asp
        35                  40                  45

Ile Leu Ala Leu Val Ile Phe Ala Val Val Phe Leu Val Gly Val Leu
    50                  55                  60

Gly Asn Ala Leu Val Val Trp Val Thr Ala Phe Glu Ala Lys Arg Thr
65                  70                  75                  80

Ile Asn Ala Ile Trp Phe Leu Asn Leu Ala Val Ala Asp Phe Leu Ser
                85                  90                  95

Cys Leu Ala Leu Pro Ile Leu Phe Thr Ser Ile Val Gln His His His
            100                 105                 110
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Trp Pro Phe Gly Gly Ala Ala Cys Ser Ile Leu Pro Ser Leu Ile Leu
        115                 120                 125

Leu Asn Met Tyr Ala Ser Ile Leu Leu Leu Ala Thr Ile Ser Ala Asp
    130                 135                 140

Arg Phe Leu Leu Val Phe Lys Pro Ile Trp Cys Gln Asn Phe Arg Gly
145                 150                 155                 160

Ala Gly Leu Ala Trp Ile Ala Cys Ala Val Ala Trp Gly Leu Ala Leu
                165                 170                 175

Leu Leu Thr Ile Pro Ser Phe Leu Tyr Arg Val Val Arg Glu Glu Tyr
            180                 185                 190

Phe Pro Pro Lys Val Leu Cys Gly Val Asp Tyr Ser His Asp Lys Arg
        195                 200                 205

Arg Glu Arg Ala Val Ala Ile Val Arg Leu Val Leu Gly Phe Leu Trp
    210                 215                 220

Pro Leu Leu Thr Leu Thr Ile Cys Tyr Thr Phe Ile Leu Leu Arg Thr
225                 230                 235                 240

Trp Ser Arg Arg Ala Thr Arg Ser Thr Lys Thr Leu Lys Val Val Val
                245                 250                 255

Ala Val Val Ala Ser Phe Phe Ile Phe Trp Leu Pro Tyr Gln Val Thr
            260                 265                 270

Gly Ile Met Met Ser Phe Leu Glu Pro Ser Ser Pro Thr Phe Leu Leu
        275                 280                 285

Leu Asn Lys Leu Asp Ser Leu Cys Val Ser Phe Ala Tyr Ile Asn Cys
    290                 295                 300

Cys Ile Asn Pro Ile Ile Tyr Val Val Ala Gly Gln Gly Phe Gln Gly
305                 310                 315                 320

Arg Leu Arg Lys Ser Leu Pro Ser Leu Leu Arg Asn Val Leu Thr Glu
                325                 330                 335

Glu Ser Val Val Arg Glu Ser Lys Ser Phe Thr Arg Ser Thr Val Asp
            340                 345                 350

Thr Met Ala Gln Lys Thr Gln Ala Val Asp Ile Gly Ala Arg Ala Ser
        355                 360                 365

Val Leu Ser Gly Gly Glu Leu Asp Arg Trp Glu Lys Ile Arg Leu Arg
    370                 375                 380

Pro Gly Gly Lys Lys Lys Tyr Lys Leu Lys His Ile Val Trp Ala Ser
385                 390                 395                 400

Arg Glu Leu Glu Arg Phe Ala Val Asn Pro Gly Leu Leu Glu Thr Ser
                405                 410                 415

Glu Gly Cys Arg Gln Ile Leu Gly Gln Leu Gln Pro Ser Leu Gln Thr
            420                 425                 430

Gly Ser Glu Glu Leu Arg Ser Leu Tyr Asn Thr Val Ala Thr Leu Tyr
        435                 440                 445

Cys Val His Gln Arg Ile Glu Ile Lys Asp Thr Lys Glu Ala Leu Asp
    450                 455                 460

Lys Ile Glu Glu Glu Gln Asn Lys Ser Lys Lys Lys Ala Gln Gln Ala
465                 470                 475                 480

Ala Ala Asp Thr Gly His Ser Ser Gln Val Ser Gln Asn Tyr Pro Ile
                485                 490                 495

Val Gln Asn Ile Gln Gly Gln Met Val His Gln Ala Ile Ser Pro Arg
            500                 505                 510
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Thr Leu Asn Ala Trp Val Lys Val Val Glu Glu Lys Ala Phe Ser Pro
        515                 520                 525

Glu Val Ile Pro Met Phe Ser Ala Leu Ser Glu Gly Ala Thr Pro Gln
    530                 535                 540

Asp Leu Asn Thr Met Leu Asn Thr Val Gly Gly His Gln Ala Ala Met
545                 550                 555                 560

Gln Met Leu Lys Glu Thr Ile Asn Glu Glu Ala Ala Glu Trp Asp Arg
                565                 570                 575

Val His Pro Val His Ala Gly Pro Ile Ala Pro Gly Gln Met Arg Glu
            580                 585                 590

Pro Arg Gly Ser Asp Ile Ala Gly Thr Thr Ser Thr Leu Gln Glu Gln
        595                 600                 605

Ile Gly Trp Met Thr Asn Asn Pro Pro Ile Pro Val Gly Glu Ile Tyr
    610                 615                 620

Lys Arg Trp Ile Ile Leu Gly Leu Asn Lys Ile Val Arg Met Tyr Ser
625                 630                 635                 640

Pro Thr Ser Ile Leu Asp Ile Arg Gln Gly Pro Lys Glu Pro Phe Arg
                645                 650                 655

Asp Tyr Val Asp Arg Phe Tyr Lys Thr Leu Arg Ala Glu Gln Ala Ser
            660                 665                 670

Gln Glu Val Lys Asn Trp Met Thr Glu Thr Leu Leu Val Gln Asn Ala
        675                 680                 685

Asn Pro Asp Cys Lys Thr Ile Leu Lys Ala Leu Gly Pro Ala Ala Thr
    690                 695                 700

Leu Glu Glu Met Met Thr Ala Cys Gln Gly Val Gly Gly Pro Gly His
705                 710                 715                 720

Lys Ala Arg Val Leu Ala Glu Ala Met Ser Gln Val Thr Asn Thr Ala
                725                 730                 735

Thr Ile Met Met Gln Arg Gly Asn Phe Arg Asn Gln Arg Lys Met Val
            740                 745                 750

Lys Cys Phe Asn Cys Gly Lys Glu Gly His Thr Ala Arg Asn Cys Arg
        755                 760                 765

Ala Pro Arg Lys Lys Gly Cys Trp Lys Cys Gly Lys Glu Gly His Gln
    770                 775                 780

Met Lys Asp Cys Thr Glu Arg Gln Ala Asn Phe Leu Gly Lys Ile Trp
785                 790                 795                 800

Pro Ser Tyr Lys Gly Arg Pro Gly Asn Phe Leu Gln Ser Arg Pro Glu
                805                 810                 815

Pro Thr Ala Pro Pro Phe Leu Gln Ser Arg Pro Glu Pro Thr Ala Pro
            820                 825                 830

Pro Glu Glu Ser Phe Arg Ser Gly Val Glu Thr Thr Thr Pro Pro Gln
        835                 840                 845

Lys Gln Glu Pro Ile Asp Lys Glu Leu Tyr Pro Leu Thr Ser Leu Arg
    850                 855                 860

Ser Leu Phe Gly Asn Asp Pro Ser Ser Gln
865                 870


<210> SEQ ID NO 26
<211> LENGTH: 908
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 26

Asp Gly Ser His His His His His His Gly Thr Met Asp Pro Ile Asp
1 5 10 15

Asn Ser Ser Phe Glu Ile Asn Tyr Asp His Tyr Gly Thr Met Ala Pro
20 25 30

Asn Ile Pro Ala Asp Gly Ile His Leu Pro Lys Arg Gln Pro Gly Asp
35 40 45

Val Ala Ala Leu Ile Ile Tyr Ser Val Val Phe Leu Val Gly Val Pro
50 55 60

Gly Asn Ala Leu Val Val Trp Val Thr Ala Phe Glu Ala Arg Arg Ala
65 70 75 80

Val Asn Ala Ile Trp Phe Leu Asn Leu Ala Val Ala Asp Leu Leu Ser
85 90 95

Cys Leu Ala Leu Pro Val Leu Phe Thr Thr Val Leu Asn His Asn Tyr
100 105 110

Trp Tyr Phe Asp Ala Thr Ala Cys Ile Val Leu Pro Ser Leu Ile Leu
115 120 125

Leu Asn Met Tyr Ala Ser Ile Leu Leu Leu Ala Thr Ile Ser Ala Asp
130 135 140

Arg Phe Leu Leu Val Phe Lys Pro Ile Trp Cys Gln Lys Val Arg Gly
145 150 155 160

Thr Gly Leu Ala Trp Met Ala Cys Gly Val Ala Trp Val Leu Ala Leu
165 170 175

Leu Leu Thr Ile Pro Ser Phe Val Tyr Arg Glu Ala Tyr Lys Asp Phe
180 185 190

Tyr Ser Glu His Thr Val Cys Gly Ile Asn Tyr Gly Gly Gly Ser Phe
195 200 205

Pro Lys Glu Lys Ala Val Ala Ile Leu Arg Leu Met Val Gly Phe Val
210 215 220

Leu Pro Leu Leu Thr Leu Asn Ile Cys Tyr Thr Phe Leu Leu Leu Arg
225 230 235 240

Thr Trp Ser Arg Lys Ala Thr Arg Ser Thr Lys Thr Leu Lys Val Val
245 250 255

Met Ala Val Val Ile Cys Phe Phe Ile Phe Trp Leu Pro Tyr Gln Val
260 265 270

Thr Gly Val Met Ile Ala Trp Leu Pro Pro Ser Ser Pro Thr Leu Lys
275 280 285

Arg Val Glu Lys Leu Asn Ser Leu Cys Val Ser Leu Ala Tyr Ile Asn
290 295 300

Cys Cys Val Asn Pro Ile Ile Tyr Val Met Ala Gly Gln Gly Phe His
305 310 315 320

Gly Arg Leu Leu Arg Ser Leu Pro Ser Ile Ile Arg Asn Ala Leu Ser
325 330 335

Glu Asp Ser Val Gly Arg Asp Ser Lys Thr Phe Thr Pro Ser Thr Thr
340 345 350

Asp Thr Ser Thr Arg Lys Ser Gln Ala Val Asp Ile Asp Tyr Lys Asp
355 360 365

Asp Asp Asp Lys Ile Glu Gly Arg Met Asp Gly Ala Arg Ala Ser Val
370 375 380

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Leu Ser Gly Gly Glu Leu Asp Arg Trp Glu Lys Ile Arg Leu Arg Pro
385                 390                 395                 400

Gly Gly Lys Lys Lys Tyr Lys Leu Lys His Ile Val Trp Ala Ser Arg
                405                 410                 415

Glu Leu Glu Arg Phe Ala Val Asn Pro Gly Leu Leu Glu Thr Ser Glu
            420                 425                 430

Gly Cys Arg Gln Ile Leu Gly Gln Leu Gln Pro Ser Leu Gln Thr Gly
        435                 440                 445

Ser Glu Glu Leu Arg Ser Leu Tyr Asn Thr Val Ala Thr Leu Tyr Cys
    450                 455                 460

Val His Gln Arg Ile Glu Ile Lys Asp Thr Lys Glu Ala Leu Asp Lys
465                 470                 475                 480

Ile Glu Glu Glu Gln Asn Lys Ser Lys Lys Lys Ala Gln Gln Ala Ala
                485                 490                 495

Ala Asp Thr Gly His Ser Ser Gln Val Ser Gln Asn Tyr Pro Ile Val
            500                 505                 510

Gln Asn Ile Gln Gly Gln Met Val His Gln Ala Ile Ser Pro Arg Thr
        515                 520                 525

Leu Asn Ala Trp Val Lys Val Val Glu Glu Lys Ala Phe Ser Pro Glu
    530                 535                 540

Val Ile Pro Met Phe Ser Ala Leu Ser Glu Gly Ala Thr Pro Gln Asp
545                 550                 555                 560

Leu Asn Thr Met Leu Asn Thr Val Gly Gly His Gln Ala Ala Met Gln
                565                 570                 575

Met Leu Lys Glu Thr Ile Asn Glu Glu Ala Ala Glu Trp Asp Arg Val
            580                 585                 590

His Pro Val His Ala Gly Pro Ile Ala Pro Gly Gln Met Arg Glu Pro
        595                 600                 605

Arg Gly Ser Asp Ile Ala Gly Thr Thr Ser Thr Leu Gln Glu Gln Ile
    610                 615                 620

Gly Trp Met Thr Asn Asn Pro Pro Ile Pro Val Gly Glu Ile Tyr Lys
625                 630                 635                 640

Arg Trp Ile Ile Leu Gly Leu Asn Lys Ile Val Arg Met Tyr Ser Pro
                645                 650                 655

Thr Ser Ile Leu Asp Ile Arg Gln Gly Pro Lys Glu Pro Phe Arg Asp
            660                 665                 670

Tyr Val Asp Arg Phe Tyr Lys Thr Leu Arg Ala Glu Gln Ala Ser Gln
        675                 680                 685

Glu Val Lys Asn Trp Met Thr Glu Thr Leu Leu Val Gln Asn Ala Asn
    690                 695                 700

Pro Asp Cys Lys Thr Ile Leu Lys Ala Leu Gly Pro Ala Ala Thr Leu
705                 710                 715                 720

Glu Glu Met Met Thr Ala Cys Gln Gly Val Gly Gly Pro Gly His Lys
                725                 730                 735

Ala Arg Val Leu Ala Glu Ala Met Ser Gln Val Thr Asn Thr Ala Thr
            740                 745                 750

Ile Met Met Gln Arg Gly Asn Phe Arg Asn Gln Arg Lys Met Val Lys
        755                 760                 765

Cys Phe Asn Cys Gly Lys Glu Gly His Thr Ala Arg Asn Cys Arg Ala
    770                 775                 780
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Pro Arg Lys Lys Gly Cys Trp Lys Cys Gly Lys Glu Gly His Gln Met
785                 790                 795                 800

Lys Asp Cys Thr Glu Arg Gln Ala Asn Phe Leu Gly Lys Ile Trp Pro
                805                 810                 815

Ser Tyr Lys Gly Arg Pro Gly Asn Phe Leu Gln Ser Arg Pro Glu Pro
            820                 825                 830

Thr Ala Pro Pro Phe Leu Gln Ser Arg Pro Glu Pro Thr Ala Pro Pro
        835                 840                 845

Glu Glu Ser Phe Arg Ser Gly Val Glu Thr Thr Thr Pro Pro Gln Lys
    850                 855                 860

Gln Glu Pro Ile Asp Lys Glu Leu Tyr Pro Leu Thr Ser Leu Arg Ser
865                 870                 875                 880

Leu Phe Gly Asn Asp Pro Ser Ser Gln Val Asn Ser Arg Gly Leu Asn
                885                 890                 895

Asp Ile Phe Glu Ala Gln Lys Ile Glu Trp His Glu
            900                 905


<210> SEQ ID NO 27
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic peptide"

<400> SEQUENCE: 27

Ser Tyr Ala Met His
1               5


<210> SEQ ID NO 28
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic peptide"

<400> SEQUENCE: 28

Arg Ile Lys Ser Lys Ala Gln Gly Gly Thr Thr Asp Tyr Ala Ala His
1               5                   10                  15

Val Lys Gly


<210> SEQ ID NO 29
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic peptide"

<400> SEQUENCE: 29

Val Ser Phe Ser Thr Phe Asp Val
1               5


<210> SEQ ID NO 30
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
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-continued

<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic peptide"

<400> SEQUENCE: 30

Gly Phe Thr Phe Ser Ser Tyr
1 5

<210> SEQ ID NO 31
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic peptide"

<400> SEQUENCE: 31

Lys Ser Lys Ala Gln Gly Gly Thr
1 5

<210> SEQ ID NO 32
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic peptide"

<400> SEQUENCE: 32

Ser Gly Ser Ser Ser Asn Ile Gly Ser Tyr Tyr Val Ser
1 5 10

<210> SEQ ID NO 33
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic peptide"

<400> SEQUENCE: 33

Arg Asn Asn Gln Arg Pro Ser
1 5

<210> SEQ ID NO 34
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic peptide"

<400> SEQUENCE: 34

Asp Ser Trp Asp His Ser Ser Met Asn Val
1 5 10

<210> SEQ ID NO 35
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 35

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Arg Ile Lys Ser Lys Ala Gln Gly Gly Thr Thr Asp Tyr Ala Ala
50 55 60

His Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Val Ser Phe Ser Thr Phe Asp Val Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 36
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 36

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Tyr
20 25 30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Val Leu
35 40 45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asp Ser Trp Asp His Ser Ser
85 90 95

Met Asn Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

<210> SEQ ID NO 37
<211> LENGTH: 449
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 37

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly

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1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Arg Ile Lys Ser Lys Ala Gln Gly Gly Thr Thr Asp Tyr Ala Ala
    50                  55                  60

His Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Ala Arg Val Ser Phe Ser Thr Phe Asp Val Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
        115                 120                 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
    130                 135                 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145                 150                 155                 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
                165                 170                 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
            180                 185                 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Glu Gly Ala Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415
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Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445

Lys


<210> SEQ ID NO 38
<211> LENGTH: 215
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 38

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Tyr
            20                  25                  30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Val Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asp Ser Trp Asp His Ser Ser
                85                  90                  95

Met Asn Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
            100                 105                 110

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
        115                 120                 125

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
    130                 135                 140

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145                 150                 155                 160

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
                165                 170                 175

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
            180                 185                 190

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
        195                 200                 205

Val Ala Pro Thr Glu Cys Ser
    210                 215


<210> SEQ ID NO 39
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic peptide"

<400> SEQUENCE: 39

Arg Ile Lys Ser Val Ala Gln Gly Gly Thr Thr Asp Tyr Ala Ala His
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1               5                   10                  15

Val Lys Gly


<210> SEQ ID NO 40
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic peptide"

<400> SEQUENCE: 40

Val Ser His Ser Thr Phe Asp Val
1               5


<210> SEQ ID NO 41
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic peptide"

<400> SEQUENCE: 41

Lys Ser Val Ala Gln Gly Gly Thr
1               5


<210> SEQ ID NO 42
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 42

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
            20                  25                  30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Gly Arg Ile Lys Ser Val Ala Gln Gly Gly Thr Thr Asp Tyr Ala Ala
    50                  55                  60

His Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65                  70                  75                  80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Ala Arg Val Ser His Ser Thr Phe Asp Val Trp Gly Gln Gly
            100                 105                 110

Thr Leu Val Thr Val Ser Ser
        115


<210> SEQ ID NO 43
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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-continued

<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 43

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Tyr
20 25 30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Val Leu
35 40 45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
50 55 60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65 70 75 80

Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asp Ser Trp Asp His Ser Ser
85 90 95

Met Asn Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln
100 105 110

<210> SEQ ID NO 44
<211> LENGTH: 449
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 44

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Arg Ile Lys Ser Val Ala Gln Gly Gly Thr Thr Asp Tyr Ala Ala
50 55 60

His Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asp Ser Lys Asn Thr
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Lys Thr Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Ala Arg Val Ser His Ser Thr Phe Asp Val Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro

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        195                 200                 205

Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys
    210                 215                 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Glu Gly Ala Pro
225                 230                 235                 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
                245                 250                 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
            260                 265                 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
        275                 280                 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
    290                 295                 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
305                 310                 315                 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ser Ser Ile Glu Lys
                325                 330                 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
            340                 345                 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
        355                 360                 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
    370                 375                 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
385                 390                 395                 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
                405                 410                 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
            420                 425                 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445

Lys


<210> SEQ ID NO 45
<211> LENGTH: 215
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 45

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1               5                   10                  15

Arg Val Thr Ile Ser Cys Ser Gly Ser Ser Ser Asn Ile Gly Ser Tyr
            20                  25                  30

Tyr Val Ser Trp Tyr Gln Gln Leu Pro Gly Thr Ala Pro Lys Val Leu
        35                  40                  45

Ile Tyr Arg Asn Asn Gln Arg Pro Ser Gly Val Pro Asp Arg Phe Ser
    50                  55                  60

Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu Gln
65                  70                  75                  80
```

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Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Asp Ser Trp Asp His Ser Ser
85 90 95

Met Asn Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu Gly Gln Pro
100 105 110

Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu Leu
115 120 125

Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr Pro
130 135 140

Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala
145 150 155 160

Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala
165 170 175

Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg
180 185 190

Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr
195 200 205

Val Ala Pro Thr Glu Cys Ser
210 215

<210> SEQ ID NO 46
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 46

agctatgcga tgcac 15

<210> SEQ ID NO 47
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 47

cgtatcaaat ccaaagccca gggcggtacg accgactacg cggcgcacgt gaaaggc 57

<210> SEQ ID NO 48
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 48

gtttctttct ccactttcga tgtt 24

<210> SEQ ID NO 49
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source

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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 49

ggatttacct tcagcagcta t 21

<210> SEQ ID NO 50
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 50

aaatccaaag cccagggcgg tacg 24

<210> SEQ ID NO 51
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 51

agcggcagct cctccaatat tggtagctat tacgtgagc 39

<210> SEQ ID NO 52
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 52

cgtaataatc aacgtcctag c 21

<210> SEQ ID NO 53
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 53

gacagctggg atcacagctc catgaatgtt 30

<210> SEQ ID NO 54
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 54

gaggtgcaat tggtggaaag cggcggtggc ctggtgaaac caggcggcag cctgcgcctg 60

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agctgcgccg cctccggatt taccttcagc agctatgcga tgcactgggt gcgccaggcc 120

ccgggcaaag gtctcgaatg ggtgggtcgt atcaaatcca aagcccaggg cggtacgacc 180

gactacgcgg cgcacgtgaa aggccgcttt accattagcc gcgatgattc gaaaaacacc 240

ctgtatctgc aaatgaacag cctgaaaacc gaagatacgg ccgtgtatta ttgcgcgcgt 300

gtttctttct ccactttcga tgtttggggc caaggcaccc tggtgactgt ctcgagc 357

<210> SEQ ID NO 55
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 55

cagagcgtgc tgacccagcc tcctagcgtg agcggtgcac cgggccagcg cgtgaccatt 60

agctgtagcg gcagctcctc caatattggt agctattacg tgagctggta tcagcagctg 120

ccgggcacgg cgccgaaagt tctgatctat cgtaataatc aacgtcctag cggcgtgccg 180

gatcgcttta gcggatccaa aagcggcacc agcgccagcc tggcgattac cggcctgcaa 240

gcagaagatg aagcggatta ttactgcgac agctgggatc acagctccat gaatgttttt 300

ggcggcggta ccaagctgac cgtgctgggc cag 333

<210> SEQ ID NO 56
<211> LENGTH: 1347
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 56

gaggtgcaat tggtggaaag cggcggtggc ctggtgaaac caggcggcag cctgcgcctg 60

agctgcgccg cctccggatt taccttcagc agctatgcga tgcactgggt gcgccaggcc 120

ccgggcaaag gtctcgaatg ggtgggtcgt atcaaatcca aagcccaggg cggtacgacc 180

gactacgcgg cgcacgtgaa aggccgcttt accattagcc gcgatgattc gaaaaacacc 240

ctgtatctgc aaatgaacag cctgaaaacc gaagatacgg ccgtgtatta ttgcgcgcgt 300

gtttctttct ccactttcga tgtttggggc caaggcaccc tggtgactgt ctcgagcgcg 360

tcgaccaaag gccccagcgt gttccctctg gcccccagca gcaagagcac ctctggcgga 420

acagccgccc tgggctgcct ggtcaaggac tacttccccg agcccgtgac cgtgtcctgg 480

aactctggcg ccctgaccag cggcgtgcac acctttccag ccgtgctcca gagcagcggc 540

ctgtacagcc tgagcagcgt cgtgaccgtg cccagcagca gcctgggcac ccagacctac 600

atctgcaacg tgaaccacaa gcccagcaac acaaaggtgg acaagcgggt ggaacccaag 660

agctgcgaca agacccacac ctgtcccccc tgccctgccc ctgaagcgga gggagccccc 720

tccgtgttcc tgttcccccc aaagcctaag gacaccctga tgatcagccg gacccccgaa 780

gtgacctgcg tggtggtgga cgtgtcccac gaggaccctg aagtgaagtt taattggtac 840

gtggacggcg tggaagtgca caacgccaag accaagccca gagaggaaca gtacaacagc 900

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acctaccggg tggtgtccgt gctgaccgtg ctgcaccagg actggctgaa cggcaaagag 960

tacaagtgca aggtgtccaa caaggccctg ccttcctcca tcgagaaaac catcagcaag 1020

gccaaaggcc agccccgcga gccccaggtg tacacactgc cccctagccg ggaagagatg 1080

accaagaacc aggtgtccct gacctgcctc gtgaagggct tctaccccag cgacattgcc 1140

gtggaatggg agagcaacgg ccagcccgag aacaactaca agaccacccc ccctgtgctg 1200

gacagcgacg gctcattctt cctgtacagc aagctgaccg tggacaagag ccggtggcag 1260

cagggcaacg tgttcagctg ctccgtgatg cacgaggccc tgcacaacca ctacacccag 1320

aagtccctga gcctgagccc cggcaag 1347

<210> SEQ ID NO 57
<211> LENGTH: 645
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 57

cagagcgtgc tgacccagcc tcctagcgtg agcggtgcac cgggccagcg cgtgaccatt 60

agctgtagcg gcagctcctc caatattggt agctattacg tgagctggta tcagcagctg 120

ccgggcacgg cgccgaaagt tctgatctat cgtaataatc aacgtcctag cggcgtgccg 180

gatcgcttta gcggatccaa aagcggcacc agcgccagcc tggcgattac cggcctgcaa 240

gcagaagatg aagcggatta ttactgcgac agctgggatc acagctccat gaatgttttt 300

ggcggcggta ccaagctgac cgtgctgggc cagcccaaag ccgcccctag cgtgaccctg 360

ttcccccccct cgagtgagga actccaggcc aacaaggcca ccctcgtgtg cctgatcagc 420

gacttctacc ctggcgccgt gaccgtggcc tggaaggccg atagcagccc tgtgaaggcc 480

ggcgtggaaa ccaccacccc cagcaagcag agcaacaaca aatacgccgc cagcagctac 540

ctgagcctga cccccgagca gtggaagtcc cacagatcct acagctgcca ggtcacacac 600

gagggcagca ccgtggaaaa gaccgtggcc cccaccgagt gcagc 645

<210> SEQ ID NO 58
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 58

agctatgcga tgcac 15

<210> SEQ ID NO 59
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 59

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cgtatcaaat ccgtggccca gggcggtacg accgactacg cggcgcacgt gaaaggc 57

<210> SEQ ID NO 60
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 60

gtttctcatt ccactttcga tgtt 24

<210> SEQ ID NO 61
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 61

ggatttacct tcagcagcta t 21

<210> SEQ ID NO 62
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 62

aaatccgtgg cccagggcgg tacg 24

<210> SEQ ID NO 63
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 63

agcggcagct cctccaatat tggtagctat tacgtgagc 39

<210> SEQ ID NO 64
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 64

cgtaataatc aacgtcctag c 21

<210> SEQ ID NO 65
<211> LENGTH: 30

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 65

gacagctggg atcacagctc catgaatgtt 30

<210> SEQ ID NO 66
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 66

gaggtgcaat tggtggaaag cggcggtggc ctggtgaaac caggcggcag cctgcgcctg 60

agctgcgccg cctccggatt taccttcagc agctatgcga tgcactgggt gcgccaggcc 120

ccgggcaaag gtctcgaatg ggtgggtcgt atcaaatccg tggcccaggg cggtacgacc 180

gactacgcgg cgcacgtgaa aggccgcttt accattagcc gcgatgattc gaaaaacacc 240

ctgtatctgc aaatgaacag cctgaaaacc gaagatacgg ccgtgtatta ttgcgcgcgt 300

gtttctcatt ccactttcga tgtttggggc caaggcaccc tggtgactgt ctcgagc 357

<210> SEQ ID NO 67
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 67

cagagcgtgc tgacccagcc tcctagcgtg agcggtgcac cgggccagcg cgtgaccatt 60

agctgtagcg gcagctcctc caatattggt agctattacg tgagctggta tcagcagctg 120

ccgggcacgg cgccgaaagt tctgatctat cgtaataatc aacgtcctag cggcgtgccg 180

gatcgcttta gcggatccaa aagcggcacc agcgccagcc tggcgattac cggcctgcaa 240

gcagaagatg aagcggatta ttactgcgac agctgggatc acagctccat gaatgttttt 300

ggcggcggta ccaagctgac cgtgctgggc cag 333

<210> SEQ ID NO 68
<211> LENGTH: 1347
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 68

gaggtgcaat tggtggaaag cggcggtggc ctggtgaaac caggcggcag cctgcgcctg 60

agctgcgccg cctccggatt taccttcagc agctatgcga tgcactgggt gcgccaggcc 120

ccgggcaaag gtctcgaatg ggtgggtcgt atcaaatccg tggcccaggg cggtacgacc 180

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gactacgcgg cgcacgtgaa aggccgcttt accattagcc gcgatgattc gaaaaacacc 240

ctgtatctgc aaatgaacag cctgaaaacc gaagatacgg ccgtgtatta ttgcgcgcgt 300

gtttctcatt ccactttcga tgtttggggc caaggcaccc tggtgactgt ctcgagcgcg 360

tcgaccaaag gccccagcgt gttccctctg gcccccagca gcaagagcac ctctggcgga 420

acagccgccc tgggctgcct ggtcaaggac tacttccccg agcccgtgac cgtgtcctgg 480

aactctggcg ccctgaccag cggcgtgcac acctttccag ccgtgctcca gagcagcggc 540

ctgtacagcc tgagcagcgt cgtgaccgtg cccagcagca gcctgggcac ccagacctac 600

atctgcaacg tgaaccacaa gcccagcaac acaaaggtgg acaagcgggt ggaacccaag 660

agctgcgaca agacccacac ctgtcccccc tgccctgccc ctgaagcgga gggagccccc 720

tccgtgttcc tgttcccccc aaagcctaag gacaccctga tgatcagccg gacccccgaa 780

gtgacctgcg tggtggtgga cgtgtcccac gaggaccctg aagtgaagtt taattggtac 840

gtggacggcg tggaagtgca caacgccaag accaagccca gagaggaaca gtacaacagc 900

acctaccggg tggtgtccgt gctgaccgtg ctgcaccagg actggctgaa cggcaaagag 960

tacaagtgca aggtgtccaa caaggccctg ccttcctcca tcgagaaaac catcagcaag 1020

gccaaaggcc agccccgcga gccccaggtg tacacactgc cccctagccg ggaagagatg 1080

accaagaacc aggtgtccct gacctgcctc gtgaagggct tctaccccag cgacattgcc 1140

gtggaatggg agagcaacgg ccagcccgag aacaactaca agaccacccc ccctgtgctg 1200

gacagcgacg gctcattctt cctgtacagc aagctgaccg tggacaagag ccggtggcag 1260

cagggcaacg tgttcagctg ctccgtgatg cacgaggccc tgcacaacca ctacacccag 1320

aagtccctga gcctgagccc cggcaag 1347

<210> SEQ ID NO 69
<211> LENGTH: 645
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 69

cagagcgtgc tgacccagcc tcctagcgtg agcggtgcac cgggccagcg cgtgaccatt 60

agctgtagcg gcagctcctc caatattggt agctattacg tgagctggta tcagcagctg 120

ccgggcacgg cgccgaaagt tctgatctat cgtaataatc aacgtcctag cggcgtgccg 180

gatcgcttta gcggatccaa aagcggcacc agcgccagcc tggcgattac cggcctgcaa 240

gcagaagatg aagcggatta ttactgcgac agctgggatc acagctccat gaatgttttt 300

ggcggcggta ccaagctgac cgtgctgggc cagcccaaag ccgcccctag cgtgaccctg 360

ttccccccct cgagtgagga actccaggcc aacaaggcca ccctcgtgtg cctgatcagc 420

gacttctacc ctggcgccgt gaccgtggcc tggaaggccg atagcagccc tgtgaaggcc 480

ggcgtggaaa ccaccacccc cagcaagcag agcaacaaca aatacgccgc cagcagctac 540

ctgagcctga cccccgagca gtggaagtcc cacagatcct acagctgcca ggtcacacac 600

gagggcagca ccgtggaaaa gaccgtggcc cccaccgagt gcagc 645

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<210> SEQ ID NO 70
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 70

agctacgcta tgcac 15

<210> SEQ ID NO 71
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 71

cggatcaaga gcaaggctca aggcggcacc accgattacg ccgctcatgt gaagggc 57

<210> SEQ ID NO 72
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 72

gtgtccttct ccaccttcga tgtg 24

<210> SEQ ID NO 73
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 73

ggcttcacct tctccagcta c 21

<210> SEQ ID NO 74
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 74

aagagcaagg ctcaaggcgg cacc 24

<210> SEQ ID NO 75
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source

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<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 75

tccggctcct cctccaacat cggctcctac tacgtgtcc 39

<210> SEQ ID NO 76
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 76

cggaacaacc agcggccttc t 21

<210> SEQ ID NO 77
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 77

gactcttggg accactcctc catgaacgtg 30

<210> SEQ ID NO 78
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 78

gaagtgcagc tggtggaatc tggcggcgga cttgtgaaac ctggcggctc tctgagactg 60

tcttgtgccg cttccggctt caccttctcc agctacgcta tgcactgggt ccgacaggcc 120

cctggcaaag gattggagtg ggtcggacgg atcaagagca aggctcaagg cggcaccacc 180

gattacgccg ctcatgtgaa gggcagattc accatctctc gggacgactc caagaacacc 240

ctgtacctgc agatgaactc cctgaaaacc gaggacaccg ccgtgtacta ctgcgccaga 300

gtgtccttct ccaccttcga tgtgtggggc cagggcacac tggttacagt ctcgagc 357

<210> SEQ ID NO 79
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 79

cagtccgtgc tgacccagcc tccttctgtt tctggtgctc ctggccagag agtgaccatc 60

tcttgctccg gctcctcctc caacatcggc tcctactacg tgtcctggta tcagcagctg 120

cctggcaccg ctcctaaggt gctgatctac cggaacaacc agcggccttc tggcgtgccc 180

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gatagattct ccggctctaa gtctggcacc tctgccagcc tggctatcac tggactgcag 240

gctgaggacg aggccgacta ctactgcgac tcttgggacc actcctccat gaacgtgttc 300

ggcggaggta ccaagctgac cgtgctggga cag 333

<210> SEQ ID NO 80
<211> LENGTH: 1347
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 80

gaagtgcagc tggtggaatc tggcggcgga cttgtgaaac ctggcggctc tctgagactg 60

tcttgtgccg cttccggctt caccttctcc agctacgcta tgcactgggt ccgacaggcc 120

cctggcaaag gattggagtg ggtcggacgg atcaagagca aggctcaagg cggcaccacc 180

gattacgccg ctcatgtgaa gggcagattc accatctctc gggacgactc caagaacacc 240

ctgtacctgc agatgaactc cctgaaaacc gaggacaccg ccgtgtacta ctgcgccaga 300

gtgtccttct ccaccttcga tgtgtggggc cagggcacac tggttacagt ctcgagcgcc 360

tccaccaaag gaccctctgt gtttcctctg gctccctcca gcaagtctac ctctggtgga 420

acagctgccc tgggctgcct ggtcaaggat tactttcctg agcctgtgac cgtgtcctgg 480

aactctggcg ctctgacatc tggcgtgcac acctttccag ctgtgctgca gtcctctggc 540

ctgtacagcc tgtcctctgt cgtgaccgtg ccttctagct ctctgggcac ccagacctac 600

atctgcaatg tgaaccacaa gccttccaac accaaggtgg acaagagagt ggaacccaag 660

tcctgcgaca agacccacac ctgtcctcca tgtcctgctc cagaagctga gggcgctcct 720

tccgtgttcc tgtttcctcc aaagcctaag gacaccctga tgatctctcg gacccctgaa 780

gtgacctgcg tggtggtgga tgtgtctcac gaggacccag aagtgaagtt caattggtac 840

gtggacggcg tggaagtgca caacgccaag accaagccta gagaggaaca gtacaactcc 900

acctacagag tggtgtccgt gctgaccgtg ctgcaccagg attggctgaa cggcaaagag 960

tacaagtgca aggtgtccaa caaggccctg ccttccagca tcgaaaagac catctccaag 1020

gccaagggcc agcctaggga accccaggtt tacaccctgc ctccaagccg ggaagagatg 1080

accaagaacc aggtgtccct gacctgcctc gtgaagggct tctacccttc cgatatcgcc 1140

gtggaatggg agagcaatgg ccagcctgag aacaactaca agacaacccc tcctgtgctg 1200

gactccgacg gctcattctt cctgtactcc aagctgacag tggacaagtc cagatggcag 1260

cagggcaacg tgttctcctg ctccgtgatg cacgaggccc tgcacaatca ctacacacag 1320

aagtccctgt ctctgtcccc tggcaag 1347

<210> SEQ ID NO 81
<211> LENGTH: 645
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 81

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cagtccgtgc tgacccagcc tccttctgtt tctggtgctc ctggccagag agtgaccatc 60

tcttgctccg gctcctcctc caacatcggc tcctactacg tgtcctggta tcagcagctg 120

cctggcaccg ctcctaaggt gctgatctac cggaacaacc agcggccttc tggcgtgccc 180

gatagattct ccggctctaa gtctggcacc tctgccagcc tggctatcac tggactgcag 240

gctgaggacg aggccgacta ctactgcgac tcttgggacc actcctccat gaacgtgttc 300

ggcggaggta ccaagctgac cgtgctggga cagcctaagg ctgccccttc cgtgacactg 360

ttccctccat cctctgagga actgcaggcc aacaaggcta ccctcgtgtg cctgatctcc 420

gacttttacc ctggcgctgt gaccgtggcc tggaaggctg atagttctcc tgtgaaggcc 480

ggcgtggaaa ccaccacacc ttccaagcag tccaacaaca aatacgccgc ctcctcctac 540

ctgtctctga cccctgaaca gtggaagtcc caccggtcct acagctgcca agtgacccat 600

gagggctcca ccgtggaaaa gaccgtggct cctaccgagt gctct 645

<210> SEQ ID NO 82
<211> LENGTH: 15
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 82

agctacgcta tgcac 15

<210> SEQ ID NO 83
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 83

cggatcaaga gcgttgccca aggcggcacc accgattacg ctgctcatgt gaagggc 57

<210> SEQ ID NO 84
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 84

gtgtcccact ctaccttcga tgtg 24

<210> SEQ ID NO 85
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 85

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ggcttcacct tctccagcta c 21

<210> SEQ ID NO 86
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 86

aagagcgttg cccaaggcgg cacc 24

<210> SEQ ID NO 87
<211> LENGTH: 39
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 87

tccggctcct cctccaacat cggctcctac tacgtgtcc 39

<210> SEQ ID NO 88
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 88

cggaacaacc agcggccttc t 21

<210> SEQ ID NO 89
<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic oligonucleotide"

<400> SEQUENCE: 89

gactcttggg accactcctc catgaacgtg 30

<210> SEQ ID NO 90
<211> LENGTH: 357
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 90

gaagtgcagc tggtggaatc tggcggcgga cttgtgaaac ctggcggctc tctgagactg 60

tcttgtgccg cttccggctt caccttctcc agctacgcta tgcactgggt ccgacaggcc 120

cctggcaaag gattggagtg ggtcggacgg atcaagagcg ttgcccaagg cggcaccacc 180

-continued

gattacgctg ctcatgtgaa gggcagattc accatcagcc gggacgactc caagaacacc 240

ctgtacctgc agatgaactc cctgaaaacc gaggacaccg ccgtgtacta ctgcgccaga 300

gtgtcccact ctaccttcga tgtgtggggc cagggcacac tggttacagt ctcgagc 357

<210> SEQ ID NO 91
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 91

cagtccgtgc tgacccagcc tccttctgtt tctggtgctc ctggccagag agtgaccatc 60

tcttgctccg gctcctcctc caacatcggc tcctactacg tgtcctggta tcagcagctg 120

cctggcaccg ctcctaaggt gctgatctac cggaacaacc agcggccttc tggcgtgccc 180

gatagattct ccggctctaa gtctggcacc tctgccagcc tggctatcac tggactgcag 240

gctgaggacg aggccgacta ctactgcgac tcttgggacc actcctccat gaacgtgttc 300

ggcggaggta ccaagctgac cgtgctggga cag 333

<210> SEQ ID NO 92
<211> LENGTH: 1347
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 92

gaagtgcagc tggtggaatc tggcggcgga cttgtgaaac ctggcggctc tctgagactg 60

tcttgtgccg cttccggctt caccttctcc agctacgcta tgcactgggt ccgacaggcc 120

cctggcaaag gattggagtg ggtcggacgg atcaagagcg ttgcccaagg cggcaccacc 180

gattacgctg ctcatgtgaa gggcagattc accatcagcc gggacgactc caagaacacc 240

ctgtacctgc agatgaactc cctgaaaacc gaggacaccg ccgtgtacta ctgcgccaga 300

gtgtcccact ctaccttcga tgtgtggggc cagggcacac tggttacagt ctcgagcgcc 360

tccaccaaag gaccctctgt gtttcctctg gctccctcca gcaagtctac ctctggtgga 420

acagctgccc tgggctgcct ggtcaaggat tactttcctg agcctgtgac cgtgtcctgg 480

aactctggcg ctctgacatc tggcgtgcac acctttccag ctgtgctgca gtcctctggc 540

ctgtacagcc tgtcctctgt cgtgaccgtg ccttctagct ctctgggcac ccagacctac 600

atctgcaatg tgaaccacaa gccttccaac accaaggtgg acaagagagt ggaacccaag 660

tcctgcgaca agacccacac ctgtcctcca tgtcctgctc cagaagctga gggcgctcct 720

tccgtgttcc tgtttcctcc aaagcctaag gacaccctga tgatctctcg gacccctgaa 780

gtgacctgcg tggtggtgga tgtgtctcac gaggacccag aagtgaagtt caattggtac 840

gtggacggcg tggaagtgca caacgccaag accaagccta gagaggaaca gtacaactcc 900

acctacagag tggtgtccgt gctgaccgtg ctgcaccagg attggctgaa cggcaaagag 960

tacaagtgca aggtgtccaa caaggccctg ccttccagca tcgaaaagac catctccaag 1020

-continued

gccaagggcc agcctaggga accccaggtt tacaccctgc ctccaagccg ggaagagatg 1080

accaagaacc aggtgtccct gacctgcctc gtgaagggct tctacccttc cgatatcgcc 1140

gtggaatggg agagcaatgg ccagcctgag aacaactaca agacaacccc tcctgtgctg 1200

gactccgacg gctcattctt cctgtactcc aagctgacag tggacaagtc cagatggcag 1260

cagggcaacg tgttctcctg ctccgtgatg cacgaggccc tgcacaatca ctacacacag 1320

aagtccctgt ctctgtcccc tggcaag 1347

<210> SEQ ID NO 93
<211> LENGTH: 645
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polynucleotide"

<400> SEQUENCE: 93

cagtccgtgc tgacccagcc tccttctgtt tctggtgctc ctggccagag agtgaccatc 60

tcttgctccg gctcctcctc caacatcggc tcctactacg tgtcctggta tcagcagctg 120

cctggcaccg ctcctaaggt gctgatctac cggaacaacc agcggccttc tggcgtgccc 180

gatagattct ccggctctaa gtctggcacc tctgccagcc tggctatcac tggactgcag 240

gctgaggacg aggccgacta ctactgcgac tcttgggacc actcctccat gaacgtgttc 300

ggcggaggta ccaagctgac cgtgctggga cagcctaagg ctgcccccttc cgtgacactg 360

ttccctccat cctctgagga actgcaggcc aacaaggcta ccctcgtgtg cctgatctcc 420

gacttttacc ctggcgctgt gaccgtggcc tggaaggctg atagttctcc tgtgaaggcc 480

ggcgtggaaa ccaccacacc ttccaagcag tccaacaaca aatacgccgc ctcctcctac 540

ctgtctctga cccctgaaca gtggaagtcc caccggtcct acagctgcca agtgacccat 600

gagggctcca ccgtggaaaa gaccgtggct cctaccgagt gctct 645

<210> SEQ ID NO 94
<211> LENGTH: 454
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 94

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Val Met His Trp Val Arg Gln Ala Thr Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ala Ile Asp Thr Gly Gly Gly Thr Tyr Tyr Ala Asp Ser Val Lys
50 55 60

Gly Arg Phe Thr Ile Ser Arg Glu Asn Ala Lys Asn Ser Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Gly Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

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Arg Asp Tyr Tyr Tyr Tyr Ala Ser Gly Ser Tyr Tyr Lys Ala Phe Asp
            100                 105                 110

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys
        115                 120                 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
    130                 135                 140

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145                 150                 155                 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
                165                 170                 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
            180                 185                 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
        195                 200                 205

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro
    210                 215                 220

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
225                 230                 235                 240

Ala Glu Gly Ala Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
                245                 250                 255

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
            260                 265                 270

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
        275                 280                 285

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
    290                 295                 300

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
305                 310                 315                 320

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
                325                 330                 335

Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
            340                 345                 350

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn
        355                 360                 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
    370                 375                 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385                 390                 395                 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
                405                 410                 415

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
            420                 425                 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
        435                 440                 445

Ser Leu Ser Pro Gly Lys
    450


<210> SEQ ID NO 95
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 95

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Arg
20 25 30

Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
35 40 45

Ile Tyr Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
65 70 75 80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Gly Ser Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 96
<211> LENGTH: 400
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 96

Ala Glu Pro Arg Leu Pro Leu Met Tyr His Leu Ala Ala Val Ser Asp
1 5 10 15

Leu Ser Thr Gly Leu Pro Ser Phe Trp Ala Thr Gly Trp Leu Gly Ala
20 25 30

Gln Gln Tyr Leu Thr Tyr Asn Asn Leu Arg Gln Glu Ala Asp Pro Cys
35 40 45

Gly Ala Trp Ile Trp Glu Asn Gln Val Ser Trp Tyr Trp Glu Lys Glu
50 55 60

Thr Thr Asp Leu Lys Ser Lys Glu Gln Leu Phe Leu Glu Ala Ile Arg
65 70 75 80

Thr Leu Glu Asn Gln Ile Asn Gly Thr Phe Thr Leu Gln Gly Leu Leu

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                85                  90                  95

Gly Cys Glu Leu Ala Pro Asp Asn Ser Ser Leu Pro Thr Ala Val Phe
            100                 105                 110

Ala Leu Asn Gly Glu Glu Phe Met Arg Phe Asn Pro Arg Thr Gly Asn
        115                 120                 125

Trp Ser Gly Glu Trp Pro Glu Thr Asp Ile Val Gly Asn Leu Trp Met
    130                 135                 140

Lys Gln Pro Glu Ala Ala Arg Lys Glu Ser Glu Phe Leu Leu Thr Ser
145                 150                 155                 160

Cys Pro Glu Arg Leu Leu Gly His Leu Glu Arg Gly Arg Gln Asn Leu
                165                 170                 175

Glu Trp Lys Glu Pro Pro Ser Met Arg Leu Lys Ala Arg Pro Gly Asn
            180                 185                 190

Ser Gly Ser Ser Val Leu Thr Cys Ala Ala Phe Ser Phe Tyr Pro Pro
        195                 200                 205

Glu Leu Lys Phe Arg Phe Leu Arg Asn Gly Leu Ala Ser Gly Ser Gly
    210                 215                 220

Asn Cys Ser Thr Gly Pro Asn Gly Asp Gly Ser Phe His Ala Trp Ser
225                 230                 235                 240

Leu Leu Glu Val Lys Arg Gly Asp Glu His His Tyr Gln Cys Gln Val
                245                 250                 255

Glu His Glu Gly Leu Ala Gln Pro Leu Thr Val Asp Leu Asp Ser Pro
            260                 265                 270

Ala Arg Ser Ser Val Asn Ser Arg Gly Leu Asn Asp Ile Phe Glu Ala
        275                 280                 285

Gln Lys Ile Glu Trp His Glu His His His His His His Ile Gln Lys
    290                 295                 300

Thr Pro Gln Ile Gln Val Tyr Ser Arg His Pro Pro Glu Asn Gly Lys
305                 310                 315                 320

Pro Asn Phe Leu Asn Cys Tyr Val Ser Gln Phe His Pro Pro Gln Ile
                325                 330                 335

Glu Ile Glu Leu Leu Lys Asn Gly Lys Lys Ile Pro Asn Ile Glu Met
            340                 345                 350

Ser Asp Leu Ser Phe Ser Lys Asp Trp Ser Phe Tyr Ile Leu Ala His
        355                 360                 365

Thr Glu Phe Thr Pro Thr Glu Thr Asp Val Tyr Ala Cys Arg Val Lys
    370                 375                 380

His Val Thr Leu Lys Glu Pro Lys Thr Val Thr Trp Asp Arg Asp Met
385                 390                 395                 400
```

1: An isolated antibody or antibody fragment specific for human C5aR, wherein said antibody or antibody fragment comprises

a) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 28, the HCDR3 region of SEQ ID NO: 29, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34, or

b) the HCDR1 region of SEQ ID NO: 27, the HCDR2 region of SEQ ID NO: 39, the HCDR3 region of SEQ ID NO: 40, the LCDR1 region of SEQ ID NO: 32, the LCDR2 region of SEQ ID NO: 33 and the LCDR3 region of SEQ ID NO: 34.

2: The isolated antibody or antibody fragment according to claim **1**, wherein said antibody or antibody fragment comprises

a) the VH of SEQ ID NO: 35 and the VL of SEQ ID NO 36, or

b) the VH of SEQ ID NO: 42 and the VL of SEQ ID NO 43.

3: The isolated antibody or antibody fragment according to claim **1**, wherein said antibody or antibody fragment comprises

a) the HC of SEQ ID NO: 37 and the LC of SEQ ID NO 38, or

b) the HC of SEQ ID NO: 44 and the LC of SEQ ID NO 45.

4: The isolated antibody or antibody fragment according to claim **1**, wherein said antibody or antibody fragment is of the human IgG1 class.

5: The isolated antibody or antibody fragment according to claim **1**, wherein said antibody or antibody fragment does not substantially induce effector function in vitro.

6: The isolated antibody or antibody fragment according to claim **1**, wherein said antibody or antibody fragment comprises one or more amino acid substitution selected from the group of: L234A, L235E, G237A, A330S and P331S, with numbering according to EU index.

7: The isolated antibody or antibody fragment according to claim **1**, wherein said isolated antibody or antibody fragment is specific for human C5aR and cynomolgus C5aR.

8: The isolated antibody or antibody fragment according to claim **1**, wherein said isolated antibody or antibody fragment inhibits human C5a induced CD11b expression in human granulocytes with an IC_{50} concentration of 42 nM in the presence of 150 nM human C5a in vitro.

9: The isolated antibody or antibody fragment according to claim **1**, wherein said isolated antibody or antibody fragment is a monoclonal antibody or antibody fragment.

10: The isolated antibody or antibody fragment according to claim **1**, wherein said isolated antibody or antibody fragment is a human, humanized or chimeric antibody or antibody fragment.

11: The A method for altering biological activity of human C5aR comprising administering the isolated antibody or antibody fragment of claim **1**.

12: A nucleic acid composition comprising a nucleic acid sequence or a plurality of nucleic acid sequences encoding the isolated antibody or antibody fragment according to claim **1**.

13: A vector composition comprising a vector or a plurality of vectors comprising the nucleic acid composition of claim **12**.

14: A host cell comprising the vector composition of claim **13**.

15: A pharmaceutical composition comprising the isolated antibody or antibody fragment according to claim **1** and a pharmaceutically acceptable carrier or excipient.

16: A host cell comprising the nucleic acid composition of claim **12**.

17: A method for treating a disease in a subject comprising administering to the subject the antibody or antibody fragment of claim **1**.

18: A method for detecting C5aR in a subject or a sample, said method comprising the step of contacting said subject or sample with the antibody or antibody fragment of claim **1**.

* * * * *