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(54) COMPOSITIONS AND METHODS FOR ANTIBODIES TARGETING COMPLEMENT PROTEIN C5

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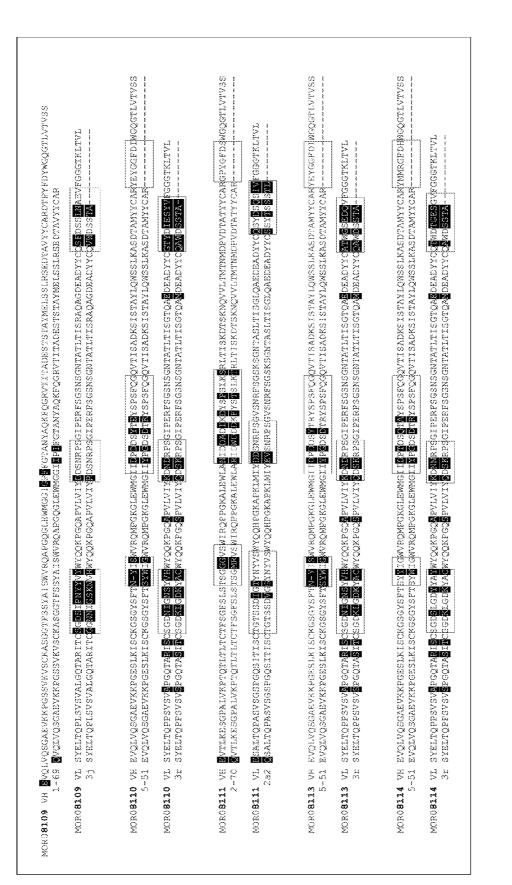
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(57) **ABSTRACT**

The present invention relates to antibodies targeting complement protein C5 and compositions and methods of use thereof.



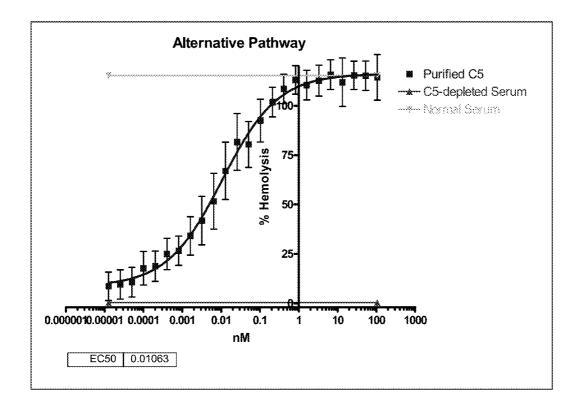


Fig. 2

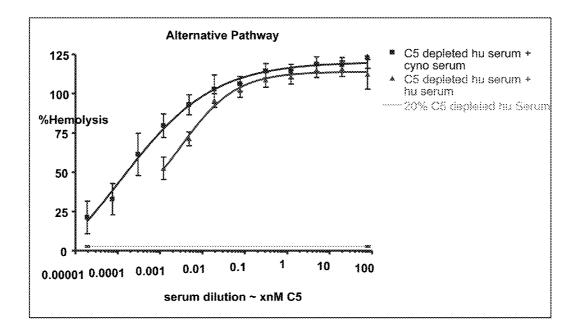


Fig. 3

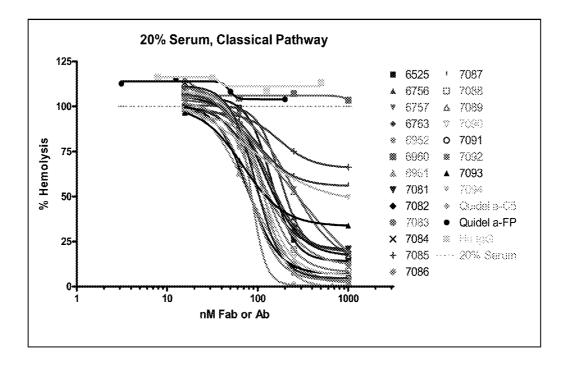


Fig. 4

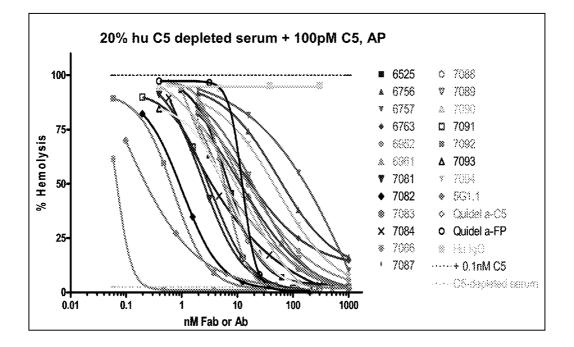


Fig. 5

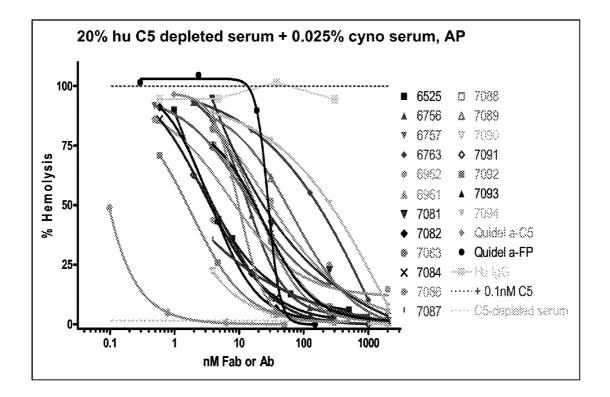


Fig. 6

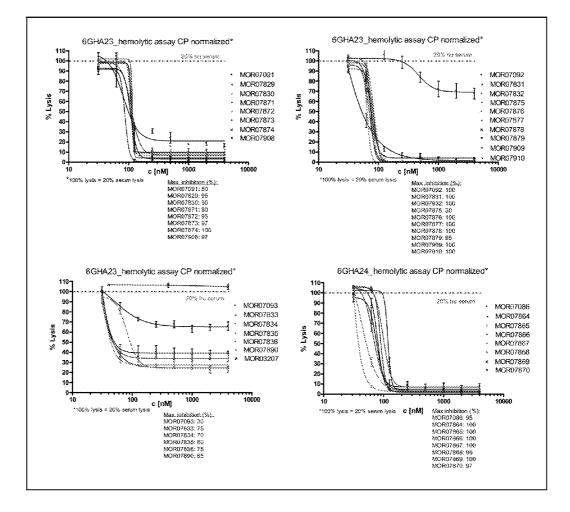


Fig. 7

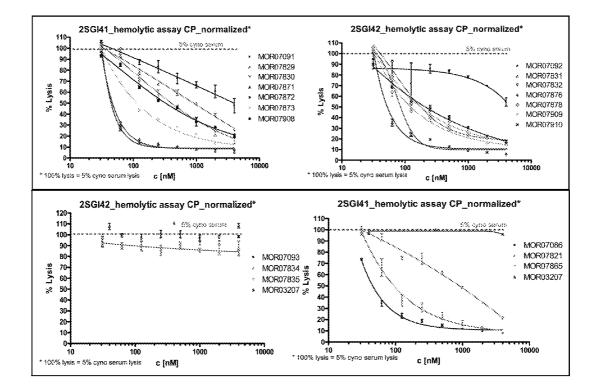


Fig. 8

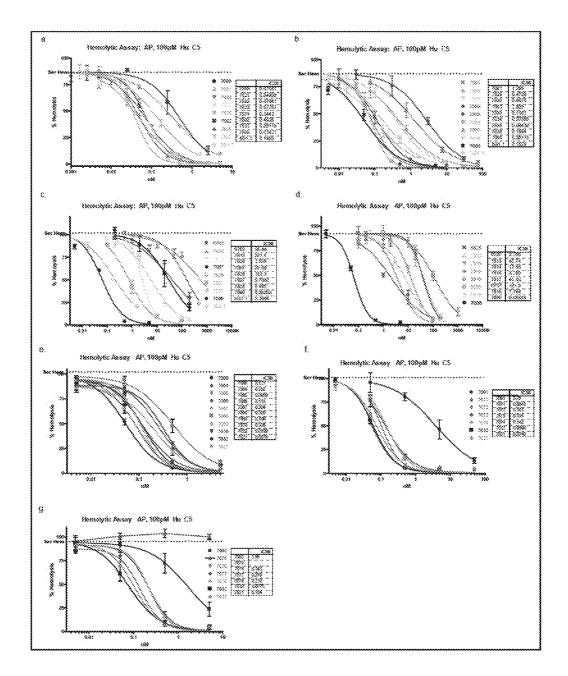


Fig. 9

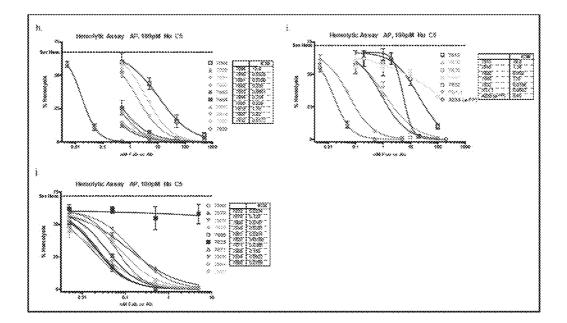


Fig. 9 (continued)

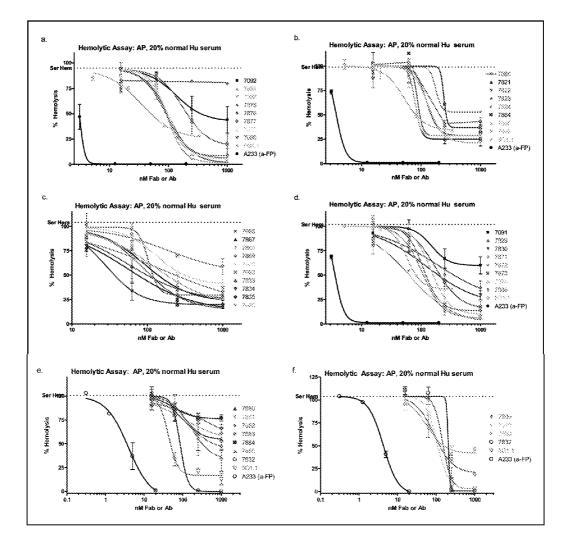


Fig. 10

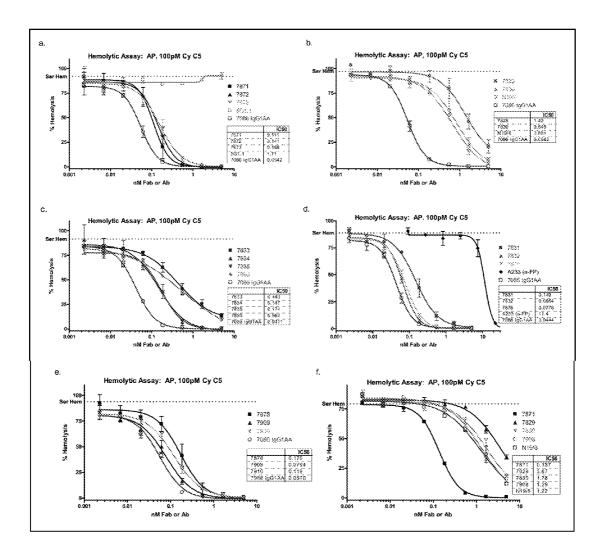


Fig. 11

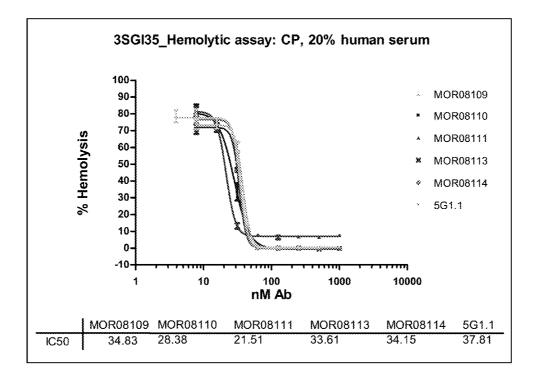


Fig. 12

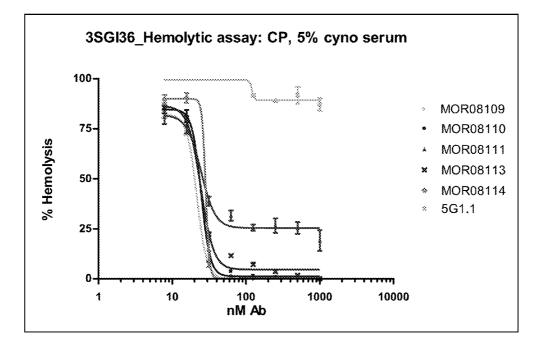
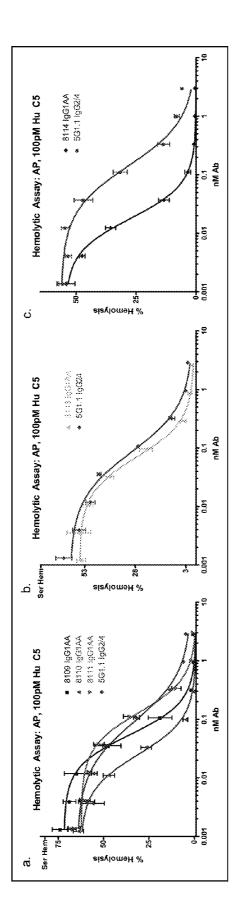
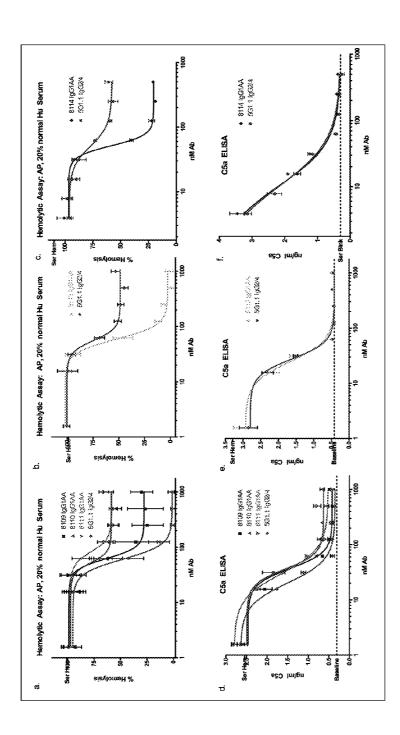


Fig. 13









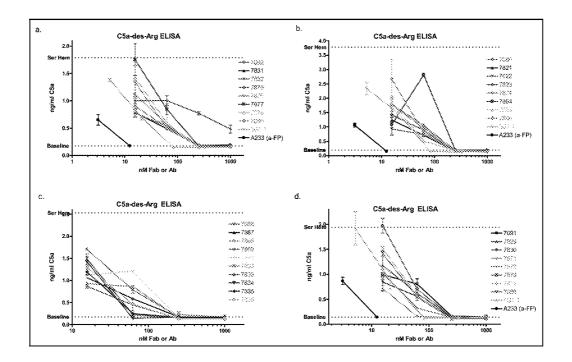


Fig. 16

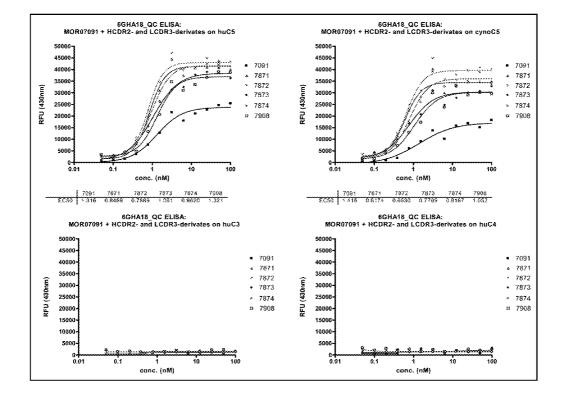


Fig. 17

	ЧO	4h	8h			
retained binding activity 88.02%	69.06% 66.95% 82.72% 78.55%	92.94% 74.84% 92.00% 90.70% 75.60%	89.57% 91.56% 86.05% 72.10% 70.34%			
MOR0 MOR07086	MOR07832 MOR07834 MOR07872 MOR07872	MOR07086 MOR07832 MOR07834 MOR07872 MOR07872	MOR07086 MOR07832 MOR07834 MOR07872 MOR07872			
10nM Fab in 50% hu serum and PBS (0h, 4h and 8h incubation at 37°C)	50000 0h 4h 8h 850% hu 8serum 35000 m 8h 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	ВFU ВFU				



		495	251	560	451	781	691	701	643	37405		gnal
lated Fat	0 X 0 X	1002	595	756	392	842	1188	621	1180	38078		= 100% SI
Columns: biotinylated Fab	02.02	694	499	455	1009	882	922	1394	891	33768	••••	npetition =
Columns	22.02	825	3601	609	619	944	1491	1366	2218	41651		biotinylated Fab without competition = 100% signal
	1202	1191	586	625	758	1486	1414	978	1228	43250		ed Fab W
00-fold excess)	1001	853	404	391	422	773	965	652	784	37340		biotinylat
		2692	1186	1727	1384	3199	3342	2535	2643	37112		- Fab
Rows: unlabelled Fab (1	0202	691	668	618	426	1553	800	892	850	36816		competition with identical Fab
: unlabe	01210	1315	1832	1834	1.137	1272		3743	3763			Billion will
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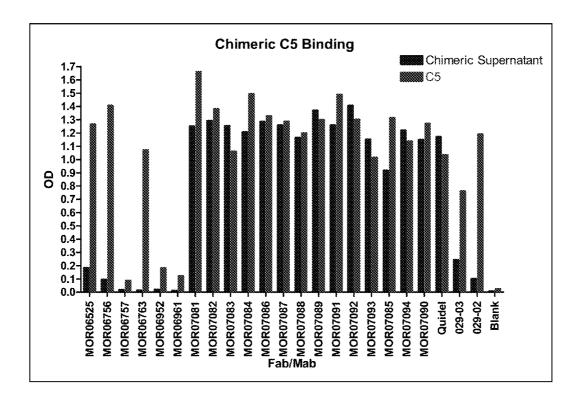


Fig. 20

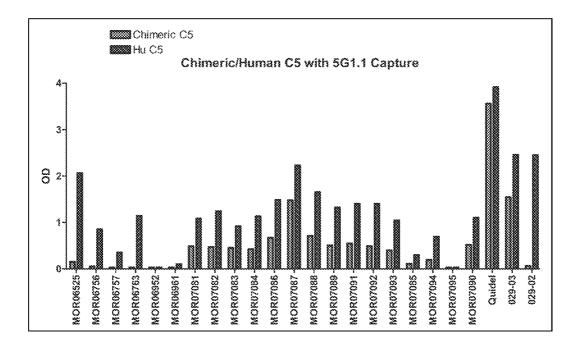


Fig. 21

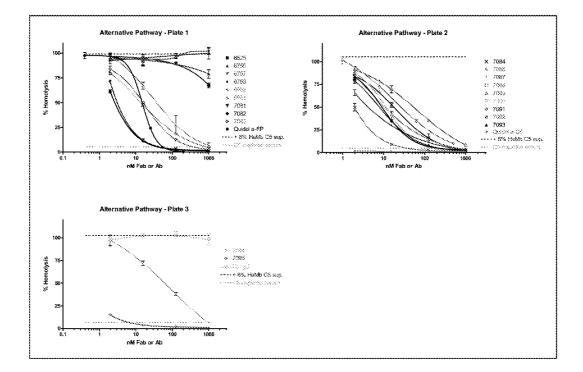


Fig. 22

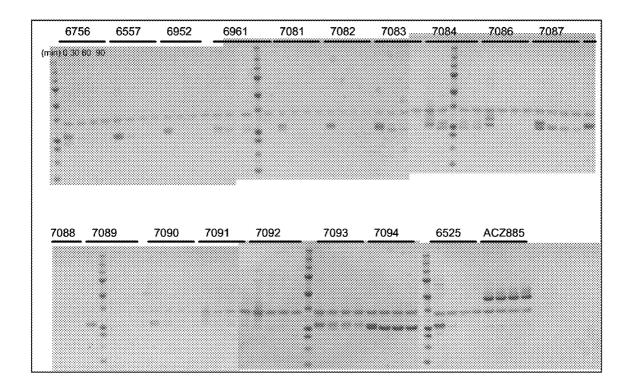


Fig. 23

7089	6952	7083	6525	6557	6961	7091	7093	ACZ885	7094	70
						******			~~~~~~~~~~~~	
7088	708	34 7086	3 7082	6756	7087	7081	7090	ACZ8	85	

Fig. 24

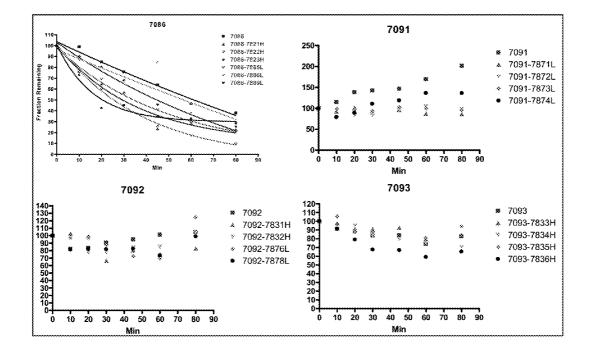


Fig. 25

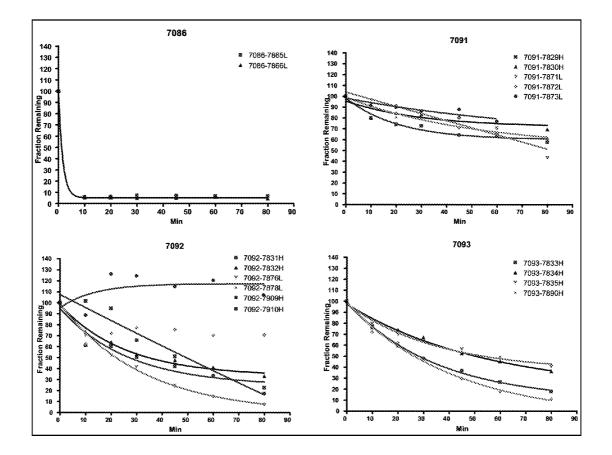
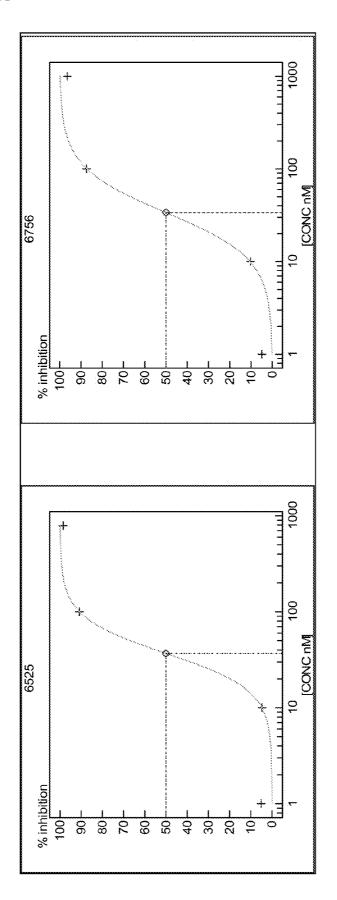


Fig. 26





COMPOSITIONS AND METHODS FOR ANTIBODIES TARGETING COMPLEMENT PROTEIN C5

1. INTRODUCTION

[0001] The present invention relates to antibodies targeting complement protein C5 and compositions and methods of use thereof.

2. BACKGROUND OF THE INVENTION

[0002] The normal role of complement, which is part of the innate immune system, is in host defense. Complement defends against bacterial infection, links adaptive and innate immunity, and disposes immune complexes and the products of inflammatory injury.

[0003] The defensive functions are accomplished by biologically active products generated in the course of complement activation, which opsonise infectious agents, promote inflammation or lyse susceptible targets (Marzari et al., Eur J Immunol 32:2773-2782 (2002)). The complement system consists of about 25-30 plasma proteins which play a role in the immune system. The complement cascade is activated by at least three major pathways. The classical pathway is typically activated by immune-complexes, the alternative pathway can be activated by unprotected cell surfaces, and the mannose binding lectin (MBL) pathway is initiated by binding of MBL to cell surface carbohydrates (Trendelenburg, Swiss Med Wkly 137:413-417 (2007)).

[0004] All three pathways lead to the cleavage of C5 by the C5 convertase. The result of this cleavage is release of C5a fragment, a potent inflammatory molecule, and C5b which initiates the membrane attack complex (MAC). The complement products, once released, do not differentiate between foreign and self targets and, if not tightly regulated, often cause extensive damage of bystander cells and tissues in clinical conditions associated with unrestricted complement activation (Marzari et al., 2002).

[0005] C5 is expressed intracellularly as a single pro-05 peptide of 1676 amino acids that consist of an 18 residue signal sequence and an Arg-rich linker sequence (RPRR) situated between the mature N-terminal β chain and the C-terminal α chain. The mature C5 has a molecular weight of about 190 kDa, and consists of two polypeptide chains (α , 115 kDa and β , 75 kDa) which are connected by disulfide bonds. The C5 convertase cleaves C5 between residues 74 and 75 of the alpha chain to release the 74 amino acid C5a peptide and the C5b fragment which is subsequently incorporated into the membrane-attack complex (MAC).

[0006] Macular degeneration is a medical condition predominantly found in the elderly in which the center of the inner lining of the eye, known as the macula area of the retina, suffers thinning, atrophy, and in some cases, bleeding. This can result in loss of central vision, which entails inability to see fine details, to read, or to recognize faces. Pathogenesis of new choroidal vessel formation is poorly understood, but factors such as inflammation, ischemia, and local production of angiogenic factors are thought to be important.

[0007] Despite current treatment options for treating diseases and disorders associated with the classical or alternative component pathways, particularly AMD, there remains a need for finding specific targets that lead to treatments which are effective and well-tolerated.

3. SUMMARY OF THE INVENTION

[0008] The present invention provides isolated complement C5-binding molecules (e.g., C5-binding antibodies or antigen binding fragments thereof), pharmaceutical compositions comprising such molecules, methods of making such molecules and compositions, and methods of use thereof.

[0009] In some embodiments, the present invention provides isolated antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibody has an affinity constant (K_A) of at least $1 \times 10^7 \text{ M}^{-1}$, 10^8 M^{-1} , 10^9 M^{-1} , 10^{10} M^{-1} , or 10^{11} M^{-1} .

[0010] In some embodiments, the present invention provides isolated antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, and inhibit the alternative complete pathway as measured by in vitro hemolytic assay with an IC_{50} range from about 20 pM to about 200 pM.

[0011] In some embodiments, the present invention provides isolated antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, and cross compete with an antibody described in Table 1 below. In some embodiments, the present invention provides isolated antibodies or antigen binding fragments thereof that bind to the same epitope of C5 protein as an antibody described in Table 1 below.

[0012] In some embodiments, the antibodies of the invention are isolated monoclonal antibodies that specifically bind to a C5 protein. In some embodiments, the antibodies of the invention are isolated human or humanized monoclonal antibodies that specifically bind to a C5 protein. In some embodiments, the antibodies of the invention are isolated chimeric antibodies that specifically bind to a C5 protein. In some embodiments, the antibodies of the invention are isolated chimeric antibodies that specifically bind to a C5 protein. In some embodiments, the antibodies of the invention comprise a human heavy chain constant region and a human light chain constant region.

[0013] In some embodiments, the present invention provides isolated antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies are single chain antibodies. In some embodiments, the antibodies of the invention are Fab fragments. In some embodiments, the antibodies of the invention are scFv.

[0014] In some embodiments, the present invention provides isolated antibodies or antigen-binding fragments thereof that specifically bind to both human C5 and cynomolgus C5. In some embodiments, the antibodies of the invention are an IgG isotype.

[0015] In some embodiments, the present invention provides isolated antibodies or antigen binding fragments thereof comprising a framework in which amino acids have been substituted into the antibody framework from the respective human VH or VL germline sequences.

[0016] In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise at least one complementarity determining (CDR) sequence having at least 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 1, 2, 3, 4, 5, 6, 17, 18, 19, 20, 21, 22, 33, 34, 35, 36, 37, 38, 49, 50, 61, 62, 63, 64, 65, 66, 77, 78, 89, 95, 101, 107, 113, 119, 120, 131, 132, 133, 134, 135, 136, 145, 146, 147, 148, 149, 150, 159, 160, 161, 162, 163, 164, 173, 174, 175, 176, 177, 178, 195, 196, 197, 198, 199, 200, 209, 226, 235, 236, 237, 238, 239, or 240.

[0017] In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise at least one heavy chain CDR sequence that is identical to SEQ ID NO: 1, 2, 3, 17, 18, 19, 33, 34, 35, 49, 61, 62, 63, 77, 77, 95, 107, 113, 119, 132, 131, 133, 145, 146, 147, 159, 160, 161, 173, 174, 175, 195, 196, 197, 226, 235, 236, or 237.

[0018] In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise at least one light chain CDR sequence that is identical to SEQ ID NO: 4, 5, 6, 20, 21, 22, 36, 37, 38, 50, 64, 65, 66, 78, 89, 101, 120, 134, 135, 136, 148, 149, 150, 162, 163, 164, 176, 177, 178, 198, 199, 200, 209, 238, 239, or 240.

[0019] In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise a heavy chain CDR 1 selected from the group consisting SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, and 235; a heavy chain CDR2 selected from the group consisting SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236; and a heavy chain CDR3 selected from the group consisting SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, and 237. In some embodiments, such antibodies or antigen binding fragments thereof further comprise a light chain CDR1 selected from the group consisting SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238; a light chain CDR2 selected from the group consisting SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239; and a light chain CDR3 selected from the group consisting SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240.

[0020] In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise a light chain CDR 1 selected from the group consisting SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238; a light chain CDR2 selected from the group consisting SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239; and a light chain CDR3 selected from the group consisting SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240.

[0021] In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise a heavy chain variable region having at least 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, or 281. In some embodiments, such antibodies or antigen binding fragments thereof further comprise a light chain variable region having at least 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, and 289.

[0022] In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise a light chain variable region having at least 90%, 95%, 97%, 98% or at least 99% sequence

identity to SEQ ID NO: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, and 289.

[0023] In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise a heavy chain having at least 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 9, 25, 41, 53, 69, 81, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, or 282. In some embodiments, such antibodies further comprise a light chain having at least 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, or 290.

[0024] In some embodiments, the present invention provides isolated monoclonal antibodies or antigen binding fragments thereof that specifically bind to a C5 protein, wherein said antibodies comprise a light chain having at least 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, or 290. **[0025]** The present invention also comprises pharmaceutical compositions comprising one or more C5-binding molecules of the invention (e.g., C5 binding antibodies or antigen binding fragments thereof) and a pharmaceutically acceptable carrier.

[0026] In some embodiments, the present invention provides nucleic acids comprising a nucleotide sequence encoding a polypeptide comprising a heavy chain variable region having at least 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, or 281.

[0027] In some embodiments, the present invention provides nucleic acids comprising a nucleotide sequence encoding a polypeptide comprising a light chain variable region having at least 90%, 95%, 97%, 98% or at least 99% sequence identity to SEQ ID NO: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, and 289.

[0028] The present invention also provides vectors and host cells comprising such nucleic acids. In one embodiment, the present invention provides isolated host cells comprising (1) a recombinant DNA segment encoding a heavy chain of the antibodies of the invention, and (2) a second recombinant DNA segment encoding a light chain of the antibodies of the invention; wherein said DNA segments are respectively operably linked to a first and a second promoter, and are capable of being expressed in said host cell. In another embodiment, the present invention provides isolated host cells comprising a recombinant DNA segment encoding a heavy chain, and a light chain of the antibodies of the invention, respectively, wherein said DNA segment is operably linked to a promoter, and is capable of being expressed in said host cells. In some embodiments, the host cells are non-human mammalian cell line. In some embodiments, the antibodies or antigen binding fragments thereof are a human monoclonal antibody, or an antigen binding fragment thereof.

[0029] The present invention further provides treatment of diagnostic methods using the C5 binding molecules (e.g., C5 binding antibodies or antigen binding fragments thereof) of the invention. In one embodiment, the present invention provides methods of treating age related macular degeneration

comprising administering to a subject in need thereof an effective amount of a composition comprising an antibody or an antigen binding fragment thereof of the invention.

[0030] In another embodiment, the present invention provides methods of treating a disease comprising administering to a subject in need thereof an effective amount of a composition comprising an antibody or an antigen binding fragment thereof of the invention, wherein said disease is asthma, arthritis, autoimmune heart disease, multiple sclerosis, inflammatory bowel disease, ischemia-reperfusion injuries, Barraquer-Simons Syndrome, hemodialysis, systemic lupus, lupus erythematosus, psoriasis, multiple sclerosis, transplantation, Alzheimer's disease, glomerulonephritis, or MPGN II. [0031] The present invention also provides methods of treating paroxysmal nocturnal hemoglobinuria (PNH) comprising administering to a subject in need thereof an effective amount of a composition comprising an antibody or antigen binding fragment thereof of the invention.

[0032] The present invention further provides methods of ameliorating a symptom associated with extracorporeal circulation comprising administering to a subject in need thereof an effective amount of a composition comprising an antibody or antigen binding fragment thereof of the invention.

3.1. Definitions

[0033] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by those of ordinary skill in the art to which this invention pertains.

[0034] The term "antibody" as used herein includes whole antibodies and any antigen binding fragment (i.e., "antigenbinding portion") or single chains thereof. A naturally occurring "antibody" is a glycoprotein comprising at least two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. 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 FRs arranged from aminoterminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, 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.

[0035] The term "antigen binding portion" of an antibody, as used herein, refers to one or more fragments of an intact antibody that retain the ability to specifically bind to a given antigen (e.g., C5). Antigen binding functions of an antibody can be performed by fragments of an intact antibody. Examples of binding fragments encompassed within the term "antigen binding portion" of an antibody include 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; an Fd fragment consisting of the VH and CH1 domains; an Fv fragment consisting of the VL and VH domains of a single arm of an antibody; a single domain antibody (dAb) fragment (Ward et al., 1989 Nature 341:544-546), which consists of a VH domain; and an isolated complementarity determining region (CDR).

[0036] 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 an artificial peptide 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 include one or more "antigen binding portions" of an antibody. 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.

[0037] Antigen binding portions can also be incorporated into single domain antibodies, maxibodies, minibodies, intrabodies, diabodies, triabodies, tetrabodies, v-NAR and bisscFv (see, e.g., Hollinger and Hudson, 2005, Nature Biotechnology, 23, 9, 1126-1136). Antigen binding portions of antibodies 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).

[0038] Antigen binding portions 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 regions (Zapata et al., 1995 Protein Eng. 8(10):1057-1062; and U.S. Pat. No. 5,641,870).

[0039] As used herein, the term "Affinity" refers to the strength of interaction between antibody and antigen at single antigenic sites. Within each antigenic site, the variable region of the antibody "arm" interacts through weak non-covalent forces with antigen at numerous sites; the more interactions, the stronger the affinity.

[0040] As used herein, the term "Avidity" refers to an informative measure of the overall stability or strength of the antibody-antigen complex. It is controlled by three major factors: antibody epitope affinity; the valency of both the antigen and antibody; and the structural arrangement of the interacting parts. Ultimately these factors define the specificity of the antibody, that is, the likelihood that the particular antibody is binding to a precise antigen epitope.

[0041] The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function in a manner similar to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, γ-carboxyglutamate, and O-phosphoserine. Amino acid analogs refer to compounds that have the same basic chemical structure as a naturally occurring amino acid, i.e., an alpha carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions in a manner similar to a naturally occurring amino acid.

[0042] The term "binding specificity" as used herein refers to the ability of an individual antibody combining site to react with only one antigenic determinant. The combining site of the antibody is located in the Fab portion of the molecule and is constructed from the hypervariable regions of the heavy and light chains. Binding affinity of an antibody is the strength of the reaction between a single antigenic determinant and a single combining site on the antibody. It is the sum of the attractive and repulsive forces operating between the antigenic determinant and the combining site of the antibody. [0043] Specific binding between two entities means a binding with an equilibrium constant (K_A) of at least 1×10⁷ M⁻¹, 10⁸ M⁻¹, 10⁹ M⁻¹, 10¹⁰ M⁻¹, or 10¹¹ M. The phrase "specifically (or selectively) binds" to an antibody (e.g., a C5-binding antibody) refers to a binding reaction that is determinative of the presence of a cognate antigen (e.g., a human C5 or cynomolgus C5) in a heterogeneous population of proteins and other biologics. In addition to the equilibrium constant (KA) noted above, an C5-binding antibody of the invention typically also has a dissociation rate constant (Kd) of about $1 \times 10^{-2} \text{ s}^{-1}$, $1 \times 10^{-3} \text{ s}^{-1}$, $1 \times 10^{-4} \text{ s}^{-1}$, $1 \times 10^{-4} \text{ s}^{-1}$, or lower, and binds to C5 with an affinity that is at least two-fold greater than its affinity for binding to a non-specific antigen (e.g., C3, C4, BSA). The phrases "an antibody recognizing an antigen" and "an antibody specific for an antigen" are used interchangeably herein with the term "an antibody which binds specifically to an antigen".

[0044] The term "chimeric antibody" is an antibody molecule in which (a) the constant region, or a portion thereof, is altered, replaced or exchanged so that the antigen binding site (variable region) is linked to a constant region of a different or altered class, effector function and/or species, or an entirely different molecule which confers new properties to the chimeric antibody, e.g., an enzyme, toxin, hormone, growth factor, drug, etc.; or (b) the variable region, or a portion thereof, is altered, replaced or exchanged with a variable region having a different or altered antigen specificity. For example, a mouse antibody can be modified by replacing its constant region with the constant region from a human immunoglobulin. Due to the replacement with a human constant region, the chimeric antibody can retain its specificity in recognizing the antigen while having reduced antigenicity in human as compared to the original mouse antibody.

[0045] The term "complement C5 protein" or "C5" are used interchangeably, and refers to the C5 protein in different species. For example, human C5 has the sequence as set in SEQ ID NO: 296, cynomolgus C5 has the sequence as set in SEQ ID NO: 297 (*Macacafascicularis*) (see Table 1). Human C5 can be obtained from Quidel (Cat. Number A403). Cynomolgus C5 can be produced as illustrated in the Example section below.

[0046] The term "conservatively modified variant" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid that encodes a polypeptide is implicit in each described sequence.

[0047] For polypeptide sequences, "conservatively modified variants" include individual substitutions, deletions or additions to a polypeptide sequence which result in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention. The following eight groups contain amino acids that are conservative substitutions for one another: 1) Alanine (A), Glycine (G); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W); 7) Serine (S), Threonine (T); and 8) Cysteine (C), Methionine (M) (see, e.g., Creighton, Proteins (1984)). In some embodiments, the term "conservative sequence modifications" are used to refer to amino acid modifications that do not significantly affect or alter the binding characteristics of the antibody containing the amino acid sequence.

[0048] The terms "cross-block", "cross-blocked" and "cross-blocking" are used interchangeably herein to mean the ability of an antibody or other binding agent to interfere with the binding of other antibodies or binding agents to C5 in a standard competitive binding assay.

[0049] The ability or extent to which an antibody or other binding agent is able to interfere with the binding of another antibody or binding molecule to C5, and therefore whether it can be said to cross-block according to the invention, can be determined using standard competition binding assays. One suitable assay involves the use of the Biacore technology (e.g. by using the BIAcore 3000 instrument (Biacore, Uppsala, Sweden)), which can measure the extent of interactions using surface plasmon resonance technology. Another assay for measuring cross-blocking uses an ELISA-based approach.

[0050] The term "epitope" means a protein determinant capable of specific binding to an antibody. Epitopes usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. Conformational and non-conformational epitopes are distinguished in that the binding to the former but not the latter is lost in the presence of denaturing solvents.

[0051] As used herein, the term "high affinity" for an IgG antibody refers to an antibody having a KD of 10^{-8} M or less, 10^{-9} M or less, or 10^{-10} M, or 10^{-11} M or less for a target antigen. However, "high affinity" binding can vary for other

antibody isotypes. For example, "high affinity" binding for an IgM isotype refers to an antibody having a KD of 10^{-7} M or less, or 10^{-8} M or less.

[0052] The term "human antibody", as used herein, is intended to include 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 human sequences, e.g., human germline sequences, or mutated versions of human germline sequences. The human antibodies of the invention may include amino acid residues not encoded by human sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo).

[0053] The term "human monoclonal antibody" refers to antibodies displaying a single binding specificity which have variable regions in which both the framework and CDR regions are derived from human sequences. In one embodiment, the human monoclonal antibodies are produced by a hybridoma which includes a B cell obtained from a transgenic nonhuman animal, e.g., a transgenic mouse, having a genome comprising a human heavy chain transgene and a light chain transgene fused to an immortalized cell.

[0054] A "humanized" antibody is an antibody that retains the reactivity of a non-human antibody while being less immunogenic in humans. This can be achieved, for instance, by retaining the non-human CDR regions and replacing the remaining parts of the antibody with their human counterparts (i.e., the constant region as well as the framework portions of the variable region). See, e.g., Morrison et al., Proc. Natl. Acad. Sci. USA, 81:6851-6855, 1984; Morrison and Oi, Adv. Immunol., 44:65-92, 1988; Verhoeyen et al., Science, 239:1534-1536, 1988; Padlan, Molec. Immun., 28:489-498, 1991; and Padlan, Molec. Immun., 31:169-217, 1994. Other examples of human engineering technology include, but is not limited to Xoma technology disclosed in U.S. Pat. No. 5,766,886.

[0055] The terms "identical" or percent "identity," in the context of two or more nucleic acids or polypeptide sequences, refer to two or more sequences or subsequences that are the same. Two sequences are "substantially identical" if two sequences have a specified percentage of amino acid residues or nucleotides that are the same (i.e., 60% identity, optionally 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identity over a specified region, or, when not specified, over the entire sequence), when compared and aligned for maximum correspondence over a comparison window, or designated region as measured using one of the following sequence comparison algorithms or by manual alignment and visual inspection. Optionally, the identity exists over a region that is at least about 50 nucleotides (or 10 amino acids) in length, or more preferably over a region that is 100 to 500 or 1000 or more nucleotides (or 20, 50, 200 or more amino acids) in length.

[0056] For sequence comparison, typically one sequence acts as a reference sequence, to which test sequences are compared. When using a sequence comparison algorithm, test and reference sequences are entered into a computer, subsequence coordinates are designated, if necessary, and sequence algorithm program parameters are designated. Default program parameters can be used, or alternative parameters can be designated. The sequence comparison

algorithm then calculates the percent sequence identities for the test sequences relative to the reference sequence, based on the program parameters.

[0057] A "comparison window", as used herein, includes reference to a segment of any one of the number of contiguous positions selected from the group consisting of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well known in the art. Optimal alignment of sequences for comparison can be conducted, e.g., by the local homology algorithm of Smith and Waterman (1970) Adv. Appl. Math. 2:482c, by the homology alignment algorithm of Needleman and Wunsch, J. Mol. Biol. 48:443, 1970, by the search for similarity method of Pearson and Lipman, Proc. Nat'l. Acad. Sci. USA 85:2444, 1988, by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, Wis.), or by manual alignment and visual inspection (see, e.g., Brent et al., Current Protocols in Molecular Biology, John Wiley & Sons, Inc. (ringbou ed., 2003)).

[0058] Two examples of algorithms that are suitable for determining percent sequence identity and sequence similarity are the BLAST and BLAST 2.0 algorithms, which are described in Altschul et al., Nuc. Acids Res. 25:3389-3402, 1977; and Altschul et al., J. Mol. Biol. 215:403-410, 1990, respectively. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information. This algorithm involves first identifying high scoring sequence pairs (HSPs) by identifying short words of length W in the query sequence, which either match or satisfy some positive-valued threshold score T when aligned with a word of the same length in a database sequence. T is referred to as the neighborhood word score threshold (Altschul et al., supra). These initial neighborhood word hits act as seeds for initiating searches to find longer HSPs containing them. The word hits are extended in both directions along each sequence for as far as the cumulative alignment score can be increased. Cumulative scores are calculated using, for nucleotide sequences, the parameters M (reward score for a pair of matching residues; always >0) and N (penalty score for mismatching residues; always <0). For amino acid sequences, a scoring matrix is used to calculate the cumulative score. Extension of the word hits in each direction are halted when: the cumulative alignment score falls off by the quantity X from its maximum achieved value; the cumulative score goes to zero or below, due to the accumulation of one or more negative-scoring residue alignments; or the end of either sequence is reached. The BLAST algorithm parameters W, T, and X determine the sensitivity and speed of the alignment. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) or 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff, Proc. Natl. Acad. Sci. USA 89:10915, 1989) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

[0059] The BLAST algorithm also performs a statistical analysis of the similarity between two sequences (see, e.g.,

Karlin and Altschul, Proc. Natl. Acad. Sci. USA 90:5873-5787, 1993). One measure of similarity provided by the BLAST algorithm is the smallest sum probability (P(N)), which provides an indication of the probability by which a match between two nucleotide or amino acid sequences would occur by chance. For example, a nucleic acid is considered similar to a reference sequence if the smallest sum probability in a comparison of the test nucleic acid to the reference nucleic acid is less than about 0.2, more preferably less than about 0.01, and most preferably less than about 0.001.

[0060] The percent identity between two amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller (Comput. Appl. Biosci., 4:11-17, 1988) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (J. Mol, Biol. 48:444-453, 1970) algorithm which has been incorporated into the GAP program in the GCG software package (available at www.gcg.com), using either a Blossom 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

[0061] Other than percentage of sequence identity noted above, another indication that two nucleic acid sequences or polypeptides are substantially identical is that the polypeptide encoded by the first nucleic acid is immunologically cross reactive with the antibodies raised against the polypeptide encoded by the second nucleic acid, as described below. Thus, a polypeptide is typically substantially identical to a second polypeptide, for example, where the two peptides differ only by conservative substitutions. Another indication that two nucleic acid sequences are substantially identical is that the two molecules or their complements hybridize to each other under stringent conditions, as described below. Yet another indication that two nucleic acid sequences are substantially identical is that the same primers can be used to amplify the sequence.

[0062] The term "isolated antibody" refers to an antibody that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds C5 is substantially free of antibodies that specifically bind antigens other than C5). An isolated antibody that specifically binds C5 may, however, have cross-reactivity to other antigens. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0063] The term "isotype" refers to the antibody class (e.g., IgM, IgE, IgG such as IgG1 or IgG4) that is provided by the heavy chain constant region genes. Isotype also includes modified versions of one of these classes, where modifications have been made to alter the Fc function, for example, to enhance or reduce effector functions or binding to Fc receptors.

[0064] The term "Kassoc" or "Ka", as used herein, is intended to refer to the association rate of a particular antibody-antigen interaction, whereas the term "Kdis" or "Kd," as used herein, is intended to refer to the dissociation rate of a particular antibody-antigen interaction. The term "K_D", as used herein, is intended to refer to the dissociation constant, which is obtained from the ratio of Kd to Ka (i.e. Kd/Ka) and is expressed as a molar concentration (M). K_D values for antibodies can be determined using methods well established in the art. A method for determining the K_D of an antibody is

by using surface plasmon resonance, or using a biosensor system such as a Biacore® system.

[0065] The terms "monoclonal antibody" or "monoclonal antibody composition" as used herein refer to a preparation of antibody molecules of single molecular composition. A monoclonal antibody composition displays a single binding specificity and affinity for a particular epitope.

[0066] The term "nucleic acid" is used herein interchangeably with the term "polynucleotide" and refers to deoxyribonucleotides or ribonucleotides and polymers thereof in either single- or double-stranded form. The term encompasses nucleic acids containing known nucleotide analogs or modified backbone residues or linkages, which are synthetic, naturally occurring, and non-naturally occurring, which have similar binding properties as the reference nucleic acid, and which are metabolized in a manner similar to the reference nucleotides. Examples of such analogs include, without limitation, phosphorothioates, phosphoramidates, methyl phosphonates, chiral-methyl phosphonates, 2-O-methyl ribonucleotides, peptide-nucleic acids (PNAs).

[0067] Unless otherwise indicated, a particular nucleic acid sequence also implicitly encompasses conservatively modified variants thereof (e.g., degenerate codon substitutions) and complementary sequences, as well as the sequence explicitly indicated. Specifically, as detailed below, degenerate codon substitutions may be achieved by generating sequences in which the third position of one or more selected (or all) codons is substituted with mixed-base and/or deoxyinosine residues (Batzer et al., Nucleic Acid Res. 19:5081, 1991; Ohtsuka et al., J. Biol. Chem. 260:2605-2608, 1985; and Rossolini et al., Mol. Cell. Probes 8:91-98, 1994).

[0068] The term "operably linked" refers to a functional relationship between two or more polynucleotide (e.g., DNA) segments. Typically, it refers to the functional relationship of a transcriptional regulatory sequence to a transcribed sequence. For example, a promoter or enhancer sequence is operably linked to a coding sequence if it stimulates or modulates the transcription of the coding sequence in an appropriate host cell or other expression system. Generally, promoter transcribed sequence, i.e., they are cis-acting. However, some transcriptional regulatory sequences, such as enhancers, need not be physically contiguous or located in close proximity to the coding sequences whose transcription they enhance.

[0069] As used herein, the term, "optimized" means that a nucleotide sequence has been altered to encode an amino acid sequence using codons that are preferred in the production cell or organism, generally a eukaryotic cell, for example, a cell of Pichia, a Chinese Hamster Ovary cell (CHO) or a human cell. The optimized nucleotide sequence is engineered to retain completely or as much as possible the amino acid sequence, which is also known as the "parental" sequence. The optimized sequences herein have been engineered to have codons that are preferred in mammalian cells. However, optimized expression of these sequences in other eukaryotic cells or prokaryotic cells is also envisioned herein. The amino acid sequences are also referred to as optimized.

[0070] The terms "polypeptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical

mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers and non-naturally occurring amino acid polymer. Unless otherwise indicated, a particular polypeptide sequence also implicitly encompasses conservatively modified variants thereof.

[0071] The term "recombinant human antibody", as used herein, includes all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies isolated from an animal (e.g., a mouse) that is transgenic or transchromosomal for human immunoglobulin genes or a hybridoma prepared therefrom, antibodies isolated from a host cell transformed to express the human antibody, e.g., from a transfectoma, antibodies 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. Such recombinant human 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.

[0072] The term "recombinant host cell" (or simply "host cell") refers to a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

[0073] The term "subject" includes human and non-human animals. Non-human animals include all vertebrates, e.g., mammals and non-mammals, such as non-human primates, sheep, dog, cow, chickens, amphibians, and reptiles. Except when noted, the terms "patient" or "subject" are used herein interchangeably.

[0074] The term "treating" includes the administration of compositions or antibodies to prevent or delay the onset of the symptoms, complications, or biochemical indicia of a disease (e.g., AMD), alleviating the symptoms or arresting or inhibiting further development of the disease, condition, or disorder. Treatment may be prophylactic (to prevent or delay the onset of the disease, or to prevent the manifestation of clinical or subclinical symptoms thereof) or therapeutic suppression or alleviation of symptoms after the manifestation of the disease.

[0075] The term "vector" is intended to refer to a polynucleotide molecule capable of transporting another polynucleotide to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors"). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

4. BRIEF DESCRIPTION OF THE FIGURES

[0076] FIG. **1** shows variable-region alignments of selected antibodies with their most closely related human germline sequences.

[0077] FIG. **2** shows a hemolytic assay in which human C5 is titrated into human C5-depleted serum to determine C5 activity.

[0078] FIG. **3** shows titration of cynomolgus serum into human C5-depleted serum to determine optimal cynomolgus C5 concentration for alternative pathway hemolytic assay.

[0079] FIG. **4** shows examples of classical pathway hemolytic assays with 20% human serum.

[0080] FIG. **5** shows example of alternative pathway hemolytic assays with 100 pM purified human C5 added to human C5-depleted serum.

[0081] FIG. **6** shows examples of alternative pathway hemolytic assays with 0.025% cynomolgus serum added to human C5-depleted serum.

[0082] FIG. **7** shows examples of classical pathway hemolytic assays (20% human serum) with matured Fabs in comparison to their respective parentals.

[0083] FIG. **8** shows examples of classical pathway hemolytic assays (5% cynomolgus serum) with matured Fabs.

[0084] FIG. **9** shows affinity matured Fab characterization in alternative pathway hemolytic assay using 100 pM human C5 added to 20% human C5-depleted serum.

[0085] FIG. **10** shows affinity matured Fab characterization in alternative pathway hemolytic assay using 20% human serum.

[0086] FIG. **11** shows affinity matured Fab characterization in alternative pathway hemolytic assay using 100 pM cynomolgus C5 added to 20% human C5-depleted serum.

[0087] FIG. **12** shows characterization of germlined IgGs in classical pathway hemolytic assay using 20% human serum.

[0088] FIG. **13** shows characterization of germlined IgGs in classical pathway hemolytic assay using 5% cynomolgus serum.

[0089] FIG. **14** shows characterization of germlined IgGs in alternative pathway hemolytic assay, 100 pM human C5.

[0090] FIG. 15 shows characterization of final germlined IgGs in alternative pathway hemolytic assay and C5a generation ELISA using 20% human serum.

[0091] FIG. **16** shows affinity matured Fab characterization in the C5a ELISA using supernatant from 20% human serum hemolytic assays.

[0092] FIG. **17** shows specificity solution ELISA on human C3, C4, C5 and cynomolgus C5 testing antibody 7091 and its derivatives.

[0093] FIG. **18** shows serum stability assays (binding to human C5 in the presence of 50% serum) with the Fabs.

[0094] FIG. **19** shows epitope binning of some affinity improved Fabs.

[0095] FIG. **20** shows an ELISA for antibody binding to mouse-human chimeric C5 or human C5 to determine alpha chain versus beta chain binders. C5 was presented by 5G1.1 to determine competition with 5G1.1.

[0096] FIG. **21** shows ELISA for testing alpha chain versus beta chain binders with 5G1.1 capture.

[0097] FIG. 22 shows results of hemolytic assay for testing alpha chain versus beta chain binders.

[0098] FIG. 23 show thermolysin proteolysis of parental Fabs at 37° C. (0, 30, 60 and 90 minutes).

[0099] FIG. 24 show thermolysin proteolysis of parental Fabs at 55° C. (0, 30, 60 and 90 minutes).

[0100] FIG. 25 shows thermolysin sensitivity of matured Fabs at 37° C.

[0101] FIG. 26 shows thermolysin sensitivity of matured Fabs at 55° C.

[0102] FIG. **27** shows examples of Fab inhibition of alternative pathway in MAC deposition assay.

5. DETAILED DESCRIPTION OF THE INVENTION

[0103] The present invention provides antibodies that specifically bind to complement C5 protein (e.g., human C5, cynomologus C5), pharmaceutical compositions, production methods, and methods of use of such antibodies and compositions.

5.1. C5 Antibodies

[0104] The present invention provides antibodies that specifically bind to C5 (e.g., human C5, cynomologus C5). In some embodiments, the present invention provides antibodies that specifically bind to both human and cynomologus C5. Antibodies of the invention include, but are not limited to, the human monoclonal antibodies, isolated as described, in the Examples (see Section 6 below).

[0105] The present invention provides antibodies that specifically bind a C5 protein (e.g., human and/or cynomologus C5), said antibodies comprising a VH domain having an amino acid sequence of SEQ ID NO: 7, 23, 39, 51, 67, 79, 96,

108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, or 281. The present invention also provides antibodies that specifically bind to a C5 protein (e.g., human and/or cynomologus C5), said antibodies comprising a VH CDR having an amino acid sequence of any one of the VH CDRs listed in Table 1, infra. In particular, the invention provides antibodies that specifically bind to a C5 protein (e.g., human and/or cynomologus C5), said antibodies comprising (or alternatively, consisting of) one, two, three, four, five or more VH CDRs having an amino acid sequence of any of the VH CDRs listed in Table 1, infra.

[0106] The present invention provides antibodies that specifically bind to a C5 protein (e.g., human and/or cynomologus C5), said antibodies comprising a VL domain having an amino acid sequence of SEQ ID NO: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, or 289. The present invention also provides antibodies that specifically bind to a C5 protein (e.g., human and/or cynomologus C5), said antibodies comprising a VL CDR having an amino acid sequence of any one of the VL CDRs listed in Table 1, infra. In particular, the invention provides antibodies that specifically bind to a C5 protein (e.g., human and/or cynomologus C5), said antibodies comprising (or alternatively, consisting of) one, two, three or more VL CDRs having an amino acid sequence of any of the VL CDRs listed in Table 1, infra.

[0107] Other antibodies of the invention include amino acids that have been mutated, yet have at least 60, 70, 80, 90 or 95 percent identity in the CDR regions with the CDR regions depicted in the sequences described in Table 1. In some embodiments, it includes mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the CDR regions when compared with the CDR regions depicted in the sequence described in Table 1.

[0108] The present invention also provides nucleic acid sequences that encode VH, VL, the full length heavy chain, and the full length light chain of the antibodies that specifically bind to a C5 protein (e.g., human and/or cynomologus C5). Such nucleic acid sequences can be optimized for expression in mammalian cells (for example, Table 1 shows the optimized nucleic acid sequences for the heavy chain and light chain of antibodies 8109, 8110, 8111, 8113, 8114, 8112, 8125, 8126, 8127, 8128, 8129, 8130, 8131, 8132, and 8091).

TABLE 1

	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
Antibody 8109	
CDRH1	1: SYAIS
CDRH2	2: GIGPFFGTANYAQKFQG
CDRH3	3: DTPYFDY
CDRL1	4: SGDSIPNYYVY
CDRL2	5: DDSNRPS
CDRL3	6: QSFDSSLNAEV
VH	7: EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIGPFFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTVSS

TABLE 1-continued	
Examples of C5 Antibodies of the Present Invention and C5 Proteins	
	Sequence Identifier (SEQ ID NO:) or comments/details
Ľ	8: SYELTQPLSVSVALGQTARITCSGDSIPNYYVYWYQQKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTISRA QAGDEADYYCQSFDSSLNAEVFGGGTKLTVL
leavy chain	9: EVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIGPFFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSNNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
ight chain	10: SYELTQPLSVSVALGQTARITCSGDSIPNYYVYWYQQKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTISR AQAGDEADYYCQSFDSSLNAEVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD SSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
N encoding EQ ID NO: 7	11: GAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGCAGCAGCGGGAAAGTGAGCTGCAAAG CCTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGGTGCGCCAAGCCCTGGGCAGGGTCTCGAGTGGAT GGGCGGTATCGGTCCGTTTTTTGGCACTGCGAATTACGCGCAGAAGTTTCAGGGCCGGGTGACCATTACCGCG GATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCGCGTGGTAGGCAGAGATACGGCCGTGTATTATTGCG CGCGTGATACTCCTTATTTTGATTATTGGGGCCAAGGCACCCTGGTGACCGTTAGCTCA
PN encoding EQ ID NO: 8	12: TCCTATGAACTCACACAGCCCTGAGCGTGAGCGTGGCCCTGGGCCAGACCGCCCGGATCACCTGCTCCG GCGACAGCATCCCCAACTACTACGTGTACTGGTACCAGCAGAAGCCCGGCCAGGCCCCGTGGTGGTGATCTA CGACGACAGCAACCGGCCCAGCGGCGATCCCCGAGCGGTTCAGCGGCAGCAACAGCGGCAACACCGCCACCC TGACCATTTCCAGAGCACGGCGAGGCGA
N encoding EQ ID NO: 9	13 : GAGGTGCAATTGGTTCAGTCTGGCCGCGGAAGTGAAAAAACCCGGGCAGCAGCGCGGAAAGTGAACTGCAAAG CCTCCGGAGGCACTTTTTTCTTCTTTTGCCATTTCTTGGGTGCGCCAAGCCCTGGGCAGGGTCCGAGTGGAT GGCCGTACGGTCCGTTTTTTGCACTGCGAATTACCGCCAAAGCTCAGGGCGGGGGACCATTACCGCG GATGAAAGCACCAGCACCGCGTATATGGAACTGGACACCGCGTAGCCAAGGACCGTGATATATTGCG CCCGTGATACTCCTTATTTTGATTATTGGGCCCAGGCCCGGGTGACCGTGACCATTACTGCG CCCATCGGTCTTCCCCCGGCACCCTCCCCAAGAGCACCCTCGGGGGCACAGCGGCCCTGGCCCACACGGC CCATCGGTCTTCCCCGAACCGGTGACGTGTGTGGAACTCAGCGCCTCCACCAGGGC CCCAGCGTCTCCCCCGAGCACCGTGTCCTCCCAGAGAGCCCCTGGGGGGCCCCGGCGCCCCGGC CCCGGCTGCCTACAGTCCCACGGGCGTCCCTCCCAGCAGCGGGGGGGCCCCCCCC
N encoding EQ ID NO: 10	14 : TCCTATGAACTCACACAGCCCCTGAGCGTGAGCGTGAGCCTGGGCCAGACCGCCCGGATCACCTGCTCCG OGGACAGCATCCCCAACTACTACGTGTACTGGTACCAGCAGAAGCCCGGCCAGGCCCCGGTGCTGGTGATCTA CGACGACAGCAACCGGCCCAGCGGCGACCCCGAGCGGCGACCACACAGCGGCAACACCGCCACCC TGACCATTTCCAGAGCACAGGCAGGCGACGAGGCGACCACTACTACTGCCAGAGCTTCGACAGCAGCCGAACACC CGAGGTGTTCGGCGGAGGGACCAAGTTAACCGTCCTAGGTCAGCCCAGGCCGCCCCCCGGTCACTCGTTC CCGCCCTCCTCTGAGGAGCTCAAGCCAACGCAACAGGCCACACCGGTGGTGTCTCATAAGTGACTTCTACCCGGGAG CCGTGACAGTGGCCTGGAAGGCAGCAACAGGCCACACCGGCGGAGTGGAGACCACCACACCCCCAAAC AAAGCAACAACAAGTACGCGGCCAGCAGCTATCTGAGCCTGAGCGGGGGGGAGGAGCACCACACCCCACAGCAC CAGCTGCCAGGTCACGCGACGAGCAACCGTGGAGAGACCGCCGAGAAGCACCACACCCCCCCAAAGTACCACCCGCGAAGCCACACCCGTGAAGCCCCGAGAAGCACGACGAGAGCACCACACCCCCACAGAAGCAA CAGCTGCCAGGTCACGCAGCAAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA
	15 : GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAGAAGCCCGGTAGCAGCGTCAAGGTGTCCTGCAAG GCCAGCGGCGGCACCTTCAGCAGCTACGCCGCCAACTACGCCGGGCAGGCCCCAGGGCCAGGGCCTGGAGTG GATGGGCGGCACCGGCCATTCTTCGGCACCGCCAACTACGCCCAGAAGTTCCAGGGCAGGGCACCGCCGTGTACTA CTGCGCCAGAGACACCCCCCTACTTCGACTACTGGGGCCAGGGCACCCTGGGGCGCGCGGGGCACCGCGCGTGACCACCCCGCGTGACCACCCCGCGTGACCACCCCGCGTGACCACCCCGCGTGACCACGCCCTGGCCCCGGGCCCCGGGCCCCGGGCCCCGGGCCCCGGGCCCC

	TABLE 1-continued
	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
	GGCCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCA AGCTGACCGTGGACAAGAGCAGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGGGTGATGCACGAGGCCCTGC ACAACCACTACACCCAGAAGAGCCTGAGCCTGTCACCCGGCAAG
-	16: AGCTACGAGCTGACCCAGCCCCTGAGCGTGAGCGTGGCCCTGGGCCAGACCGCCAGGATCACCTGCAGCG GCGACAGCATCCCCAACTACTACGTGTACTGGTATCAGCAGAAGCCCGGCCAGGCCCCGTGCTGGTGATCTA CGACGACAGCAACAGGCCCAGCGGCGACCACGGCGACGAGGGCCAGCACAGGCGCAACAGCGCCACCCT GACCATCAGCAGAGGCCCAGGCCGACGAGGCCGACTACTACTGCCAGAGCTTCGACAGCTCACTGAACGC CGAGGTGTTCGGCGGAGGGGCCAACGGGCCGACCAGCCTGGGCCGGCC
Antibody 8110	_
CDRH1	17: NYIS
CDRH2	18: IIDPDDSYTEYSPSFQG
CDRH3	19: YEYGGFDI
CDRL1	20: SGDNIGNSYVH
CDRL2	21: KDNDRPS
CDRL3	22: GTYDIESYV
VH	23: EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPDDSYTEYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSS
VL	$24: \ SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTISGTQAEDEADYYCGTYDIESYVFGGGTKLTVL$
Heavy chain	25: EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPDDSYTEYSPSFQQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKARGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
* 1 - 1 1 1	

Light chain 26: SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS ${\tt GTQAEDEADYYCGTYDIESYVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADS}$ SPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS

PN encoding 27: GAGGTGCAATTGGTTCAGAGCGGCGCGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG
SEQ ID NO: 23 TTCCGGATATTCCTTTACTAATTATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCA
TTATTGATCCTGATGATTCTTATACTGAGTATTCTCCCTTCTTTTCAGGGTCAGGTCACCATTAGCGCGGGATAAAAG
CATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG
AGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA

PN encoding 28: AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG SEQ ID NO: 24 CGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCCGGGCAGGCGCCAGTTCTTGTGATTTATAA GGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCGGTACTTATGATATTGAGTCTTATGTGTTTGG CGGCGGCACGAAGTTAACCGTCCTA

PN encoding 29: GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAAATTAGCTGCAAAGG SEO ID NO: 25 TTCCGGATATTCCTTTACTAATTATTTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCA TTATTGATCCTGATGATTCTTATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGTCACCATTAGCGCGGGATAAAAG AGTATGGTGGTTTTGATATTTGGGGCCCAAGGCACCCTGGTGACGGTTAGCTCAGCCTCCACCAAGGGTCCATC GGTCTTCCCCCTGGCACCCTCCCCAAGAGCACCTCTGGGGGGCACAGCGGCCCTGGGCTGCCTGGTCAAGGA CTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCCTGACCAGCGGCGTGCACACCTTCCCCGGC TGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGTGGTGGCCGTGCCCTCCAGCAGCTTGGGCACCCAG ACCTACATCTGCAACGTGAATCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTTGAGCCCAAATCTTGTGA CAAAACTCACACATGCCCACCGTGCCCAGCACCTGAAGCAGCGGGGGGGCCGTCAGTCTTCCCCCCCA ACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCATAATGCCAAGACAAAGCCGCGGGAGG ${\tt AGCAGTACAACAGCACGTACCGGGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGG}$ AGTACAAGTGCAAGGTCTCCCAACAAAGCCCTCCCAGCCCCCATCGAGAAAACCATCTCCAAAGCCAAAGGGCA GCCCCGAGAACCACAGGTGTACACCCTGCCCCATCCCGGGAGGAGATGACCAAGAACCAGGTCAGCCTGAC

	TABLE 1-continued
	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
	CTGCCTGGTCAAAGGCTTCTATCCCAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAA CTACAAGACCACGCCTCCCGTGGTGGACTCCGACGGCTCCTTCTTCCTCTACAGCAAGCTCACCGTGGACAAG AGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGA AGAGCCTCTCCCTGTCTCCGGGTAAA
PN encoding SEQ ID NO: 26	30: AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG GGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCAGTTCTTGTGATTTATAA GGATAATGATCGTCCCTCAGGCATCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCGGTACTTATGATATTGAGTCTTATGTGTTTGG CGGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTCCCGCCCTCCTCT GAGGAGCATCAAGCCAACAAGGCCACACGTGGTGTCTCATAAGTGACTTCTACCGGGAGCCGTGACAGTGG CCTGGAAGGCAAGATAGCAGCCCCATCAAGGCGGGAGGTGGAAGCCCCCCCC
	31: GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAGG GCAGCGGCTACAGCTACCCAACTACATCAGCCGGGTGGCGGCAGATGCCCGGCAAGGGCCTGGAGTGGATGG GCATCATCGACCCCGACAGCTACCTGCACGGGTGACAGCCCCAGCTTCCAGGGCCAGGTGACCATCAGCGCCG ACAAGACATCAGCACCCCCTGCAGCGCAGCGCGAGGCCCGGGCAGCCCGGCCAGGTGACCATCAGCCCA AGGCCCCAGCGTGTTCCCCCGGCAGCCGCGGCAGCCCTGGGCGCCCCGGCGCCCCAGCGCGCCCCAGCGCGCCCCGGCCCCCGGCGCGCCCCCGGCGCGCCCCCGGCGC
	32 : AGCTACGAGCTGACCCAGCCCCCAGCGTGAGCGTGGCCCCAGGCCAGACCGCCAGGATCAGCTGCAGC GCGACAACATCGGCAACAGCTACGTGCACTGGTATCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATC TACAAGGACAACGACAGGCCCAGCGGCATCCCCGAGAGGTTCAGCGGCAGCAACTCCGGCAACACCGCCACC CTGACCATCAGCGGCACCCAGGCCGAGGACGAGGCCGACTACTACTGCGGCACCTACGACATCGAGTCATAC GTGTTCGGCGGAGGACCAAGCTGGCCGGCCGGCCTACTACTACGCCGCAGCGTGACCCTGTTCCCC CCCAGCGAGGAGCGACCAAGCTGGGCCGACCGGCCTGGTGGCCGGCC
Antibody 8111	
CDRH1	- 33 : TSGGGV <i>S</i>
CDRH2	34: NIDDADIKDYSPSLKS
CDRH3	35: GPYGFDS
CDRL1	36: TGTSSDIGTYNYVS
CDRL2	37: DDSNRPS
CDRL3	38: QSYDSQSIV
VH	39: EVTLKESGPALVKPTQTLTLTCTFSGFSLSTSGGGVSWIRQPPGKALEWLANIDDADIKDYSPSLKSRLTISKDTSK NQVVLTMTNMDPVDTATYYCARGPYGFDSWGQGTLVTVSS
VL	40: ESALTQPASVSGSPGQSITISCTGTSSDIGTYNYVSWYQQHPGKAPKLMIYDDSNRPSGVSNRFSGSKSGNTASL TISGLQAEDEADYYCQSYDSQSIVFGGGTKLTVL
Heavy chain	41: EVTLKESGPALVKPTQTLTLTCTFSGFSLSTSGGGVSWIRQPPGKALEWLANIDDADIKDYSPSLKSRLTISKDTSK NQVVLTMTNMDPVDTATYYCARGPYGFDSWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEP VTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPCP APEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVL TVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWES NGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

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TABLE 1-continued		
	Examples of C5 Antibodies of the Present Invention and C5 Proteins	
	Sequence Identifier (SEQ ID NO:) or comments/details	
Light chain	42: ESALTQPASVSGSPGQSITISCTGTSSDIGTYNYVSWYQQHPGKAPKLMIYDDSNRPSGVSNRFSGSKSGNTASL TISGLQAEDEADYYCQSYDSQSIVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS	
PN encoding SEQ ID NO: 39	43: GAGGTGACATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCTGACCTGTACCTT TTCCGGATTTAGCCTGTCTACTTCTGGTGGTGGTGTGTCTTGGATTCGCCAGCCGCCTGGGAAAGCCCTCGAGT GGCTGGCTAATATTGATGATGATGATGATATTAAGGATTATTCTCCTTCTTAAGTCTCGTCTGACCATTAGCAAAGA TACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCGGTGGATACGGCCACCTATTATTGCGCGC GTGGTCCTTATGGTTTTGATTCTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA	
PN encoding SEQ ID NO: 40	44 : GAAAGCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACGGG TACTAGCAGCGATATTGGTACTTATAATTATGTGTCTTGGTACCAGCAGCATCCCGGGAAGGCGCCGAAACTTA TGATTTATGATGATTCTAATCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCAACACCGCG AGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTATGATTCTCAGTCTAT TGTGTTTGGCGGCGGCACGAAGTTAACCGTCCTA	
PN encoding SEQ ID NO: 41	45: GAGGTGACATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCTGACCTGTACTT TTCCGGATTTAGCCTGTCTACTTCTGGTGGTGGTGTGTCTTGGATTCGCCAGCCGCCGGGAAAGCCCTCGAGA GGCTGGCTAATATTGATGATGCTGATATTAAGGATTATTCTCCTTCTTAAGTCTCGTCTGACCATTAGCAAAGA TACTTCGAAAAATCAGGTGGTGCTGACATATGACCAACATGGACCCGGTGGATACGGCCACCTATTATTGCGCGC GTGGTCTTATGGTTTGATTCTGGGGCCAAGGCACCCTGGGGACAGCGCCCCACCTATTATTGCGCGC GTGGTCTTCCCCCTGGCACCCTCCCCAAGAGCACCTCTGGGGACAGCGGCCCTGGGCTGCACACCTTCC GGCTGTCCTACAGTCCTCAGGACCTCTGGGGACCCTGGGCCCCGGGGGGCCCCAAGGGCCCCG GGCTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGCGCGC	
PN encoding SEQ ID NO: 42	46 : GAAAGCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACGGG TACTAGCAGCGATATTGGTACTTATAATTATGTGTCTTGGTACCAGGCAGCAGCAGCAGCAGCGCGAAACTTA TGATTTATGATGATTCTAATCGTCCCTCAGGCGAGCAACCGTTTTAGCGGATCCCAAAAGCGGCAACACCGCG AGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCCAGTCTATGATTCTCAGTCTAT TGTGTTTGGCGGCGGCAGCAAGTTAACCGTCCTAGGTCAGCCCCAAGGCTGCCCCTCGGTCACTCTGTTCCCG CCCTCCTCTGAGGAGCTCCAAGCCAACAGGCCCCACCGGTGGTCTCTCATAAGTGACTCTCACCGGGAGCG CCCCCCCTCGGAAGGCAGATAACCAGCCCCACCTGGTGGTCTCCATAAGTGACTCTCACCCGGGGAGCGCG TGACAGTGGCCGGCAGCAGTAAGCAGCCCCGGCCGAGCGGGGGGGG	
+	47 : GAGGTGACCCTGAAGGAGAGCGGCCCAGCCTGGTGAAGCCCACCCA	
	48: GAGAGCGCCTGACCCAGCCCGCCAGCGTGAGCGGCAGCCCAGGCCAGGTCTATCACAATCAGCTGCACCG GCACCTCCAGCGATATCGGCACCTACAACTACGTGAGCTGGTATCAGCAGCACCCCGGCAAGAGCCGCCCAAGCT GATGATCTACGACGACAACAGGCCCAGCGGCGTGAGCAACAGGTTCCAGCGGCAGCAAGAGCGGCAACA CGCCAGCCTGACAATCAGCGGCCTGCAGGCCGAGGACGAGGCCGACGACTACTACTGCCAGAGCTACGACAGCCA GTCAATCGTGTCGGCGGAGGGGACCAAGCTGCTGGTGGCCCGCCTAAGGCTGCCCCCCAGCGTGCACCCT GTTCCCCCCCAGCAGCGAGGAGCTGCAGGCCAACAAGGCCACCCTGGTGGCCTGATCAGCGACTTCTACCC AGGCGCCGTGACCGGCGGCGGAGGAGCCGACGACGACCCCGTGAAGGCCGGCGTGGAGACCACCCCCA	

TABLE 1-continued

	TABLE 1-continued
	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
	GCAAGCAGAGCAACAACAAGTACGCCGCCAGCAGCTACCTGAGCCTGACCCCCGAGCAGTGGAAGAGCCACA GGTCCTACAGCTGCCAGGTGACCCACGAGGGCAGCACCGTGGAAAAGACCGTGGCCCCAACCGAGTGCAGC
Antibody 8113	_
CDRH1	SEQ ID NO: 17
CDRH2	49: IIDPDDSYTRYSPSFQG
CDRH3	SEQ ID NO: 19
CDRL1	SEQ ID NO: 20
CDRL2	SEQ ID NO: 21
CDRL3	50: ATWGSEDQV
VН	51: EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPDDSYTRYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSS
VL	52: SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCATWGSEDQVFGGGTKLTVL
Heavy chain	53: EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPDDSYTRYSPSFQGQVTISADKSI STAYLQWSSLKASDTAMYYCARYEYGGFDIWGGGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAMEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	54: SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCATWGSEDQVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD SSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
PN encoding SEQ ID NO: 51	55: GAGGTGCAATTGGTTCAGAGCGGCGGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGA
PN encoding SEQ ID NO: 52	56 : AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG 2 CGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCCCAGTTCTTGTGATTTATAA GGATAATGATCGTCCCTCAGGCATCCCGGAACGCCTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCCGATTATTATTGCGCTACTTGGGGTTCTGAGGATCAGGTGTTTG GCGGCGGCACGAAGTTAACCGTCCTA
PN encoding SEQ ID NO: 53	57: GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGGGAAAGTGAAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGCA TTATCGATCCGGATGATAGCTATACCGTTATTCTCCGAGCGTTCAGGGGACAGGTGACCATTAGCGCGGGATAAA AGCATTAGCACCGCGGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG
PN encoding SEQ ID NO: 54	58: AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAA GGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGCACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCGCTACTTGGGGTTCTGAGGATCAGGTGTTTG GCGGCGCACCAAGGTTAACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTTCCCGCCCCTCCTC

TABLE 1-continued

	TABLE 1-continued
	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
	GCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACCACCCTCCAAACAAA
	59: GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAGG GCAGCGGCTACAGCTTCACCAACTACATCAGCTGGGTGCGGCAGATGCCCGGCAAGGGCCTGGAGTGGAGGGCG GCATCATCGACCCCGACGCTACCTGCAGCGGGGCCAGGCTGAAGGCCACGGCCAGGGAGCCGCG ACAAGAGCATCAGCACCGCCTACCTGGCACGGGCAGGCCTGAAGGCCACCGGCCAGGCACCAGCCGCG CCAGATACGAGTACGGCGCCTCGGCACCCGGGGCACCCTGGGGCACCGCCGCGCGCG
-	60: AGCTACGAGCTGACCCAGCCCCCAGCGTGAGCGTGGCCCCAGGCCAGGACCGCCAGGATCAGCTGCAGC GGCGACAATATCGGCAACAGCTACGTGCACTGGTATCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATC TACAAGGACAACGACAGGCCCAGCGGCATCCCCCGAGAGGTTCAGCGGCAGCAACACCCGCCACC CTGACAATCAGCGGCACCCAGGCCGAGGACGAGGCCGACCTACTACTGCGCCACCTGGGGCTCAGAGGACCAG GTGTTCGGCGGAGGAGCCAAGCTGACCGTGGTGGGCCGACCTAGCGCTGTCCCC CCCAGCAGCGAGGGACCGAGCCAACAGGCCACCTGGGCCTGATCCCCGGCCCCAGCGGAGCCCCGGCCCC GTGACCGTGGCCTGGACGCCGACAACAAGGCCACCCTGGTGGCCGGCGTGGAGACCACCCCCAGCGGCC GTGACCGTGGCCTGGAAGGCCGACAGCAGCCCGTGAAGGCCGGCGGGGGGGG
Antibody 8114	_
CDRH1	61: SYYIG
CDRH2	62: IIDPTDSQTAYSPSFQG
CDRH3	63: YMMRGFDH
CDRL1	64: SGDSLGDYYAY
CDRL2	65: KDNNRPS
CDRL3	66: QTWDTGESGV
VH	67: EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWVRQMPGKGLEWMGIIDPTDSQTAYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSS
VL	68: SYELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTWDTGESGVFGGGTKLTVL
Heavy chain	69: EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWVRQMPGKGLEWMGIIDPTDSQTAYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYMMRGPDHWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTPPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	70: SYELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTWDTGESGVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
PN encoding SEQ ID NO: 67	71: GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG 7 TTCCGGATATTCCTTTATTTCTTATTATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGG GCATTATTGATCCTACTGATTCTCAGACTGCTTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGGATA AAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG

 ${\tt TATATGATGCGTGGTTTTGATCATTGGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA}$

	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
PN encoding SEQ ID NO: 68	72: AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCGAGTTCTTGTGATTTATA GGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACACGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTATTGCCAGACTTGGGATACTGGTGAGTCTGGTGTGTT TGGCGGCACGAAGTTAACCGTCCTA
PN encoding SEQ ID NO: 69	73 : GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAGG TTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCCGAGTGGATGG GCATTATTGATCCTACTGATTCTCAGACTGCTTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATA AAAGCATTAGCACGCGGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG
PN encoding SEQ ID NO: 70	74: AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG CGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCAGTTCTTGTGATTTATA GGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTGGGATACTGGTGAGTCTGGTGTGTT TGGCGGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCCTCC TCTGAGGAGGCTTCAAGCCAACAAGGCCACACTGGTGTCTCATAAGTGAACTTCTACCCGGGAGCCGTGACAG TGGCCTGGAAGGCAGATAGCAGCCGCTCAAGGCGGGGGGGG
-	75 : GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAGG GCAGCGGCTACAGCTTCACCAGCTACTACATCGGCTGGGGGGGG
Optimized PN encoding SEQ ID NO: 70	76: AGCTACGAGCTGACCCAGCCCCCAGCGTGAGCGTGGCCCCAGGCCAGGACCGCCAGGATCAGCTGCAGC GGCGACAGCCTGGGCGACTACTACGCCTACTGGTATCAGCAGAAGCCCGGCCAGGCCCCGTGGTGGTGATC TACAAGGACAACAACAGGCCCAGCGGCATCCCCGAGAGGTTCAGCGGCAGCAACAGCGGCAACACCGCCACC CTGACAATCAGCGGCACCCAGGCCGAGGACGAGGCCGACTACTACTGCCAGACCTGGGACACCGGCGAGTCA GGCGTGTTCGGCGGAGGGACCAAGCTGACCGTGGCTGAGCCTAGGGCTGCCCCCAGCGTGACCCTGTTC CCCCCCAGCAGCGAGGAGCTAAGCCGACCAACAAGGCCACCTGTGTGGCTGGACCACCGCGCGGCGGCGCGAGGCGACCAACAGGC GCCGTGACCGTGGCCTGGAAGGCCGACCACCGTGGAGGCCGGCGGGGGGGAGCCACCCAC
Antibody 8112	
CDDU1	-

CDRH1 SEQ ID NO: 61

CDRH2 77: IIDPSDSHTTYSPSFQG

	TABLE 1-continued Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
	Sequence Taenchiler (SEQ ID NO.) Of Comments/details
CDRH3	SEQ ID NO: 63
CDRL1	SEQ ID NO: 64
CDRL2	SEQ ID NO: 65
CDRL3	78: QTWDILPHGLV
VH	79: EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWVRQMPGKGLEWMGIIDPSDSHTTYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSS
VL	80: SYELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYC QTWDILPHGLVFGGGTKLTVL
Heavy chain	81: EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWVRQMPGKGLEWMGIIDPSDSHTTYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	82: SYELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTWDILPHGLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
PN encoding SEQ ID NO: 79	83: GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG TTCCGGATATTCCTTTACTTCTTATTATATGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGAGG GCATTATCGATCCGTCTGATAGCCATACCACTTATTCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGAT AAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG
PN encoding SEQ ID NO: 80	84 : AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG OCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATAA GGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTGGGATATTCTTCCTCATGGTCTTGT GTTTGGCGGCGGCACGAAGTTAACCGTCCTA
PN encoding SEQ ID NO: 81	85:GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG1TCCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGAGGGGGGGATACGCCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCCAGATACGCCAGTATATGGCGCGGAAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCCAGCATCCGCCAGTATATTATTGCGCGCGTTATATGGATCGCGGGTTTTGATCATTGGGGCCAAGGCCCTGGGGCACAGCGGCCTGGGCCCCGGCGTCATCGGTCTTCCCCTGGACCCCTCCCCAAGGCCCTGGGGCACAGCGGCCCTGGGCGCCCGGGTCAAGGACTACTTCCCCGAACCGGTGACGTGTGGTGGAACTCAGGCGCCTGGGCGCCCCGGCCCCGGCCCCGGCCCCGGCTGTCCTACAGTCCCCAGGACGTCTCCCCCCAGCAGCGTGGGGGCACAGCGGCGCCCCAGCAACCTTGTGACAAAACCCAACACGCGACGCCGCGCCCGCACCACAACA
<u> </u>	86: AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG 2 CGATTCTCTTGGTGATTATTATCCTTATTGGTACCAGCAGAAACCCGGGCAGGCCCAGTCTTTGTGATTTATAA GGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGAACCCAGCGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTGGGATATTCTTCCTCATGGGTGTTGT GTTTGGCGGCGCGGAAGGTAACCGGCCTAGGTCAGCCCAAGGCTGGGCCCCCCCC
-	87: GAGGTGCAGCTGGTGCAGAGGGGGGGGGGGGGGGGGGGG

	TABLE 1-continued
	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
	AAGGGCCCCAGCGTGTTCCCCCTGGCCCCAGCAGCAGCAGCACCTCCGGCGGCACAGCCGCCCTGGGCTG CCTGGTGAAGGACTACTTCCCCGAGCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCA CACCTTCCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGTCCAGCGGGGTGACAGTGCCAGCAGCAG CCTGGGCACCCAGACCTACATCTGCAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAGAGTGGAG CCCAAGAGCTGCGACAAGACCCACACCTGCCCCCCGCCAGCCA
	88: AGCTACGAGCTGACCCAGCCCCCAGCGTGAGCGTGGCCCCAGGCCAGACCGCCAGGATCAGCTGCAGC GGCGACAGCCTGGGCGACTACTACGCCTACTGGTATCAGCAGAAGCCCGGCCAGGCCCCCGTGCTGGTGATC TACAAGGACAACAACAGGCCCAGCGGCATCCCCGAGAGGTTCAGCGGCAGCAACAGCGGCAACACCGCCAC CTGACAATCAGCGGCACCCAGGCCGAGGACGAGGCGGCGACTACTACTGCCCAGACTTGGGATATTCTTCCTCATG GTCTTGTGTTCGCGGGAGGGACCAGCTGACCGTGGTCGGCCACCAGAGCTGGCCCCCGGCGGACGAGGGACGAGGCGACGACGGCCACCCTGGTGGCCCCCCAGCGACGGGCGACGAGCGACGGCGACGGCGGC
Antibody 3125	_
CDRH1	SEQ ID NO: 61
DRH2	SEQ ID NO: 77
DRH3	SEQ ID NO: 63
DRL1	SEQ ID NO: 64
DRL2	SEQ ID NO: 65
DRL3	89: QAWTDSPTGLV
ЛН	SEQ ID NO: 79
7L	90: SYELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQAWTDSPTGLVFGGGTKLTVL
Heavy chain	SEQ ID NO: 81
Light chain	91: SYELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQAWTDSPTGLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWK ADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
PN encoding SEQ ID NO: 79	SEQ ID NO: 83 9
5	92: AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG OCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCCCGGTTCTTGTGATTTATAA GGATAATAATCGTCCCTCAGGCATCCGGGACGCCTTTAGCGGATCCAACACGGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGGCTTGGACTGATTCTCCTACTGGTCTTGT GTTTGGCGGCGGCACGAAGTTAACCGTCCTA
PN encoding SEQ ID NO: 81	SEQ ID NO: 85 L
0	93: AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCGG L CGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGCAGAAACCCGGGCAGCGCCAGTCTTGTGATTTATAA GGATAATAATCGTCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGACC ATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGGCTTGGACTGATTCTCCTACTGGTCTTGT GTTTGGCGGCGGCACGAAGATTAACCGTCCTAGGTCAGCCCAAGGCTGCCCCCTCGGTCACTCTGTTCCCGCCC TCCTCTGAGGAGGCTCAAGCCAACAAGGCCACACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGA CAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCGAGCGGGGGGGG

CCAGGTCACGCATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAATGTTCA

CDRL3

SEQ ID NO: 89

TABLE	1-continued
IADLLE	I-CONCINUEU

	TABLE 1-continued	
	Examples of C5 Antibodies of the Present Invention and C5 Proteins	
	Sequence Identifier (SEQ ID NO:) or comments/details	
Optimized PN encoding SEQ ID NO: 81	SEQ ID NO: 87	
-	94 : AGCTACGAGCTGACCCAGCCCCCAGCGTGAGCGTGGCCCCAGGCCAGACCGCCAGGATCAGCTGCAGC GGCGACAGCCTGGGCGACTACTACGCCTACTGGTATCAGCAGAAGCCCGGGCAGGCCCCCGTGCTGGTGATC TACAAGGACAACAACAGGCCCAGCGCGACGACGAGGCCGACGA	
Antibody 8126	_	
CDRH1	SEQ ID NO: 61	
CDRH2	SEQ ID NO: 62	
CDRH3	SEQ ID NO: 63	
CDRL1	SEQ ID NO: 64	
CDRL2	SEQ ID NO: 65	
CDRL3	SEQ ID NO: 89	
VH	SEQ ID NO: 67	
VL	SEQ ID NO: 90	
Heavy chain	SEQ ID NO: 69	
Light chain	SEQ ID NO: 91	
PN encoding SEQ ID NO: 79	SEQ ID NO: 71	
PN encoding SEQ ID NO: 90	SEQ ID NO: 92	
PN encoding SEQ ID NO: 81	SEQ ID NO: 73	
PN encoding SEQ ID NO: 91	SEQ ID NO: 93	
Optimized PN encoding SEQ ID NO: 81	SEQ ID NO: 75	
Optimized PN encoding SEQ ID NO: 91	SEQ ID NO: 94	
Antibody 8127	_	
CDRH1	SEQ ID NO: 61	
CDRH2	95: IIDPTDSYTVYSPSFQG	
CDRH3	SEQ ID NO: 63	
CDRL1	SEQ ID NO: 64	
CDRL2	SEQ ID NO: 65	

	TABLE 1-continued
	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
VH	96: EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWVRQMPGKGLEWMGIIDPTDSYTVYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSS
VL	SEQ ID NO: 90
Heavy chain	97: EVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWVRQMPGKGLEWMGIIDPTDSYTVYSPSFQGQVTISADKS ISTAYLQMSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPP CPAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVS VLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKARGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	SEQ ID NO: 91
PN encoding SEQ ID NO: 9	98: GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAGG 6 TTCCGGATATTCCTTATTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGG GCATTATTGATCCTACTGATTCTTATACTGTTTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGGATAA AAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG
PN encoding SEQ ID NO: 9	SEQ ID NO: 92 0
PN encoding SEQ ID NO: 9	99: GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAGG 7 TTCCGGATATTCCTTATTGTTCTTATTATTGGTTGGGTGGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGG GCATTATTGATCCTACTGATTCTTATATTGGTTGGGTGGCCCAGATGCCTGGGAAGGGTCCGAGTGGATAA AAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG
PN encoding SEQ ID NO: 9	SEQ ID NO: 93 1
-	100: GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAG GGCAGCGGCTACAGCTTCACCAGCTACTACATCGGCTGGGTGCGGCAGATGCCCGGCAAGGGCCTGGAGTGG ATGGGCATTATTGATCCTACTGATTCTTATACTGTTTATTCTCCTTCTTTTCAGGGTCAGGTGACCATCAGGGC GACAAGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCGCCAGGCAACGCCAGCTACTACTGC GCCCGGTACATGATGAGGGGGCTTCGACCACTGGGGCCAGCCGGGCACCCTGGTGACCACCAGCTACGCCC ACCGCCCCCCCTTTCCCCCCCCCC

AAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCTCCGGCGGCACAGCCGCCCTGGGCTG CCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCA CCCAAGAGCTGCGACAAGACCCACACCTGCCCCCTGCCCAGCCCCCGAAGCTGCAGGCGGCCCTTCCGTG TTCCTGTTCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGTG GACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAG ACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGGTCCGTGCTGACCGTGCTGCACCAGGAC GCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCTTCTCGGGAGGAGATGACCAAGA ${\tt ACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACG}$ GCCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAA GCTGACCGTGGACAAGAGCAGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCA CAACCACTACACCCAGAAGAGCCTGAGCCTGTCACCCGGCAAG

	TABLE 1-continued
	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
Optimized PN encoding SEQ ID NO: 91	SEQ ID NO: 94
Antibody 8128	_
CDRH1	SEQ ID NO: 17
CDRH2	SEQ ID NO: 49
CDRH3	SEQ ID NO: 19
CDRL1	SEQ ID NO: 20
CDRL2	SEQ ID NO: 21
CDRL3	101: STWDIEPTYV
VH	SEQ ID NO: 51
VL	102: SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCSTWDIEPTYVFGGGTKLTVL
Heavy chain	SEQ ID NO: 53
light chain	103: SYELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCSTWDIEPTYVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD SSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
PN encoding SEQ ID NO: 51	SEQ ID NO: 55
PN encoding SEQ ID NO: 102	104: AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCCCCAGTTCTTGTGATTTATA AGGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCTCTACTTGGGATATTGAGCCTACTTATGTGT TTGGCGGCGCACGAAGTTAACCGTCCTA
PN encoding SEQ ID NO: 53	SEQ ID NO: 57
PN encoding SEQ ID NO: 103	105: AGTTACGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCCCCGGTTCTTGTGATTTATA AGGATAATGATCGTCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACGAAGATGACGCGGAGGAGCGGATTATTATTGCTCTACTTGGGATATTGAGCTACTTATGTGT TTGGCGCGGCACGAAGTTAACCGTCCTAGGTCAGCCCAAGAGGTGCCCCCCGGCCACCACGCGCCCTC CTCTGAGGAGCATCAAGCCCAACAAGGCCACCACTGGTGTGTCTCATAAGTGACTTCTACCCGGGAGCCGTGACA GTGGCCTGGAAGGCAGAATGACGCCCGTCAAGGCGGCGGGAGTGGAGACCACCACACCCCTCCAAACAAA
Optimized PN encoding SEQ ID NO: 53	SEQ ID NO: 59
	106: AGCTACGAGCTGACCCAGCCCCCAGGGTGAGCGTGGCCCAGGCCAGGACCGCCAGGATCAGCTGCAGC GGCGACAATATCGGCAACAGCTACGTGCACTGGTATCAGCAGAAGCCCGGCCAGGCCCCGTGGTGGTGATC TACAAGGACAACGACAGGCCCAGCGGCATCCCCGAGAGGTTCAGCGGCAGCAACTCCGGCAACACCGCCACC CTGACAATCAGCGCGCACCAGGCCGAGGACGAGGCCGACTACTACTGCTCTACTTGGGATATTGAGCCTACTT ATGTGTTCGGCGGAGGGACCAAGGCCGACGACGCCGACGCAGCGCCCCCGAGCGGGACCCAGCTGCCCCCCCC
Antibody 8129	_
CDRH1	SEQ ID NO: 17
CDRH2	107: IIDPQDSYTEYSPSFQG

TABLE	1-continued

	TABLE 1-continued
	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
CDRH3	SEQ ID NO: 19
CDRL1	SEQ ID NO: 20
CDRL2	SEQ ID NO: 21
CDRL3	SEQ ID NO: 22
VH	108: EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPQDSYTEYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSS
VL	SEQ ID NO: 24
Heavy chain	109: EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPQDSYTEYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	SEQ ID NO: 26
PN encoding SEQ ID NO: 108	110: GAGGTGCAATTGGTTCAGAGCGGCGGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTCAGGATTCTTATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGTCACCATTAGCGCGGGATAAAA GCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG
PN encoding SEQ ID NO: 24	SEQ ID NO: 28 4
PN encoding SEQ ID NO: 109	111: GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTCAGGATTCTTATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGCACCATTAGCGCGGATAAAA GCATTAGCACCGCGTATCTTCAATGGAGCAGCCGCAGAGCGGCACGGCATGTATTATTGCGCGCGTTAT GAGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGGGAGCGGCAGCCAGC
PN encoding SEQ ID NO: 20	SEQ ID NO: 30 5
-	112: GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAG GGCAGCGGCTACAGCTTCACCAACTACATCAGCTGGGTGGG

Examples of C5 Antibodies of the Present Invention and C5 Proteins

Sequence Identifier (SEQ ID NO:) or comments/details

 ${\tt GCCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAA}$ ${\tt GCTGACCGTGGACAAGAGCAGGTGGCAGCAGGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCA$ CAACCACTACACCCAGAAGAGCCTGAGCCTGTCACCCGGCAAG

Optimized PN SEQ ID NO: 32

encoding SEQ ID NO: 26	БЦĞ	10	110.	52
Antibody 8130	_			
CDRH1	SEQ	ID	NO :	17
CDRH2	SEQ	ID	NO :	107
CDRH3	SEQ	ID	NO :	19
CDRL1	SEQ	ID	NO :	20
CDRL2	SEQ	ID	NO :	21
CDRL3	SEQ	ID	NO :	101
VH	SEQ	ID	NO :	108
VL	SEQ	ID	NO :	102
Heavy chain	SEQ	ID	NO :	109
Light chain	SEQ	ID	NO :	103
PN encoding SEQ ID NO: 108	SEQ	ID	NO :	110
PN encoding SEQ ID NO: 102	SEQ	ID	NO :	104
PN encoding SEQ ID NO: 109	SEQ	ID	NO :	111
PN encoding SEQ ID NO: 103	SEQ	ID	NO :	105
Optimized PN encoding SEQ ID NO: 109	SEQ	ID	NO :	112
Optimized PN encoding SEQ ID NO: 103	SEQ	ID	NO :	106
Antibody 8131	_			
CDRH1	SEQ	ID	NO :	17
CDRH2	113	: I	IDPEI	OSHTEYSPSFQG
CDRH3	SEQ	ID	NO :	19
CDRL1	SEQ	ID	NO :	20

CDRL2

CDRL3

SEQ ID NO: 21

SEQ ID NO: 22

	TABLE 1-continued		
Examples of C5 Antibodies of the Present Invention and C5 Proteins			
	Sequence Identifier (SEQ ID NO:) or comments/details		
νн	114: EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPEDSHTEYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSS		
VL	SEQ ID NO: 24		
Heavy chain	115: EVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPEDSHTEYSPSFQGQVTISADKS ISTAYLQMSSLKASDTAMYYCARVEYGGPDIWGQGTLVTVSSASTKGPSVPPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKRVEPKSCDKTHTCPPC PAPEAAGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSV LTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWE SNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK		
Light chain	SEQ ID NO: 26		
PN encoding SEQ ID NO: 114	116: GAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATTTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTGAGGATTCTCATACTGAGTATTCTCCTTTTTCAGGGTCAGGTGACCATTAGCGCGGATAAA AGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG		
PN encoding SEQ ID NO: 2	SEQ ID NO: 28 4		
PN encoding SEQ ID NO: 115	117: GAGGTGCAATTGGTTCAGAGCGGCGGGAAGTGAAAAAACCGGGGGGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTTAAGGATTCTCATACTGAGTATTCCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATAAA AGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGACGGATACGGCCATGTATTATTGCGCGCGGTTA TGAGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCAGCCTCCACCAAGGGTCCA TCGGTCTTCCCCCTGGCACCCTCCCAAGAGCACCCTGGGGGCACAGCGGCCTGGCCAGCCTGGTCAAG GACTACTTCCCCGAACCGGTGACGGTGTCGTGGAACTCAGGCGCCTGACCAGCGGCGTGCCACCCCCC GGTGTCCTACAGTCCTCAGGACTCTACTCCCTCAGCAGCGGGGGGGACCAGCGGCGTGCACACCTTCCCG GCTGTCCTACAGTCCCACGGTGACCGTGCCCAGCACCCCAGCGACGTGGACCGTGCCCCAAGCCCC AGACCTACATCGCCACGTGACAGCCCAGCAACACCCAGGTGGACCGTGGAGGTGAGCCCAAATCTTGT GACAAAACCCAAGGACACCCCATGGTCCCGGCCCGG		
-	PN encoding SEQ ID NO: 30 SEQ ID NO: 26		
-	118: GAGGTGCAGCTGGTGCAGAGCGGAGCCGAGGTGAAAAAGCCCGGTGAGAGCCTGAAGATCAGCTGCAAG GGCAGCGGCTACAGCTTCACCAACTACATCAGCTGGGTGCGGCAGATGCCCGGCAAGGGCCTGGAGTGGATG GGCATCATCGACCCCGAGGACAGCCATACCGAGTACAGCCCCAGCTTCCAGGGCCAGGTGACCATCAGCGCC GACAAGAGCATCAGCACCGCCTACCTGCAGTGGAGCAGCCTGAAGGCCACGGACACCGCCATGTACTACTGC GCCAGATACGAGTACGGCGGCTTCGACATCTGGGGCCAGGCACCCTGGGTGACCGTCAGCTAGCACC AAGGGCCCCAGCGTGTTCCCCCTGGCCCCAGCAGCAAGAGCACCTCCGGCGGCACAGCGCCCTGGGCTG		

AAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGCAGCAAGAGCACCTCCGGCGGCACAGCCGCCCTGGGCTG CCTGGTGAAGGACTACTTCCCCGAGCCCGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCA CCCAAGAGCTGCGACAAGACCCACACCTGCCCCCTGCCCAGCCCCCGAAGCTGCAGGCGGCCCTTCCGTG TTCCTGTTCCCCCCCAAGCCCAAGGACACCCTGATGATCAGCAGGACCCCCGAGGTGACCTGCGTGGTGGTG GACGTGAGCCACGAGGACCCAGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCACAACGCCAAG ACCAAGCCCAGAGAGGAGCAGTACAACAGCACCTACAGGGTGGTGGTCCGTGCTGACCGTGCTGCACCAGGAC GCAAGGCCAAGGGCCAGCCACGGGAGCCCCAGGTGTACACCCTGCCCCCTTCTCGGGAGGAGATGACCAAGA ${\tt ACCAGGTGTCCCTGACCTGTCTGGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACG}$ GCCAGCCCGAGAACAACTACAAGACCACCCCCCCAGTGCTGGACAGCGACGGCAGCTTCTTCCTGTACAGCAA GCTGACCGTGGACAAGAGCAGGTGGCAGCAGGGCAACGTGTTCAGCTGCAGCGTGATGCACGAGGCCCTGCA CAACCACTACACCCAGAAGAGCCTGAGCCTGTCACCCGGCAAG

	TABLE 1-continued Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
Optimized PN encoding SEQ ID NO: 26	SEQ ID NO: 32
Antibody 8132	
CDRH1	- SEQ ID NO: 17
CDRH2	SEQ ID NO: 113
CDRH3	SEQ ID NO: 19
CDRL1	SEQ ID NO: 20
CDRL2	SEQ ID NO: 21
CDRL3	SEQ ID NO: 101
νн	SEQ ID NO: 114
VL	SEQ ID NO: 102
Heavy chain	SEQ ID NO: 115
Light chain	SEQ ID NO: 103
PN encoding SEQ ID NO: 114	SEQ ID NO: 116
PN encoding SEQ ID NO: 102	SEQ ID NO: 104
PN encoding SEQ ID NO: 115	SEQ ID NO: 117
PN encoding SEQ ID NO: 103	SEQ ID NO: 105
Optimized PN encoding SEQ ID NO: 115	SEQ ID NO: 118
Optimized PN encoding SEQ ID NO: 103	SEQ ID NO: 106
Antibody 8091	_
CDRH1	SEQ ID NO: 1
CDRH2	119: NIGPFFGIANYAQKFQG
CDRH3	SEQ ID NO: 3
CDRL1	SEQ ID NO: 4
CDRL2	SEQ ID NO: 5
CDRL3	120: QTYDDGSTAEV
VH	121: QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGNIGPFFGIANYAQKFQGRVTITAD ESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTVSS
VL	122: DIELTQPPSVSVAPGQTARISCSGDSIPNYYVYWYQQKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTYDDGSTAEVFGGGTKLTVL

	TABLE 1-continued
	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
Heavy chain	123: QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGNIGPFFGIANYAQKFQGRVTITAD ESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPCP APPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVVSVLTV VHQDWLNGKEYKCKVSNKGLPAPIEKTISKTKGQPREPQVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNG QPENNYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
Light chain	124: DIELTQPPSVSVAPGQTARISCSGDSIPNYYVYWYQQKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTYDDGSTAEVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTECS
PN encoding SEQ ID NO: 121	125: CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGCAGCAGCAGCGTGAAAGTGAGCTGCAAAG CCTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGGTGCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGAT GGGCAATATCGGTCCGTTTTTTGGCATTGCGAATTACGCGCAGAAGTTTCAGGGCCGGGTGACCATTACCGCG GATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGCGAAGATACGGCCGTGTATTATTGCG CGCGTGATACTCCTTATTTTGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO: 122	126: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGGGTATCTCGTGTAGCG GCGATTCTATTCCTAATTATTATGTTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATG ATGATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGAACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTATGATGATGGTGCTCTACTGCTGAGG TGTTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO: 123	127: CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAG CCTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGGTGCGCCAAGCCCTGGGCAGGGTCTCGAGTGGAT GGCAATATCGGTCCGTTTTTGGCATTGCGAATTACGCGCAGAGGTTCAGGGCGGGGGACCATTACCGCG GATGAAAGCACCAGCACCGCGTAATGGAACTGAGCAGCAGCGGCAGAGAGATACGGCCGGGTGACCATTACTGCG CCCGGCGTGTCCCCTGGCCCCCGCGAGAGACCAGCGGCGGGAGGCCCAGGCGCTGCGCCACAGGG CCCAGCGTGTCCCCCGGGCCCCTGCAGCAGAGCACCAGCGGGAGCCCTGGCCCAGCGGCGCCGGGG AAGGACTACTCCCTGGCCCCCGGAGCAGAGCCCGGGAGCCCGGGCCCGGGCGCCGGGCGCCGGG CCCAGCGTGCCGGAGCGCGGGACCGTGGACCAGCGGGGGGGG
PN encoding SEQ ID NO: 124	128: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGCTATCTCGTGTAGCG GCGATTCTATTCCTAATTATTATGTTTATTGGTACCAGCAGAAACCCGGGCAGGCCCAGTTCTTGTGATTTATG ATGATTCTAATCGTCCCTCAGGCATCCCGGAACGCCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTATGATGATGGTTCTACTGCTGAGG TGTTTGGCGGCGGCACGAAGATTAACCGTTCTTGGTCAGCCCAAGGCTGCCCCTCGGTCACTCTGTTCCCGCC CTCCTCTGAGGAGCTTCAAGCCAACAGGCCACACTGTGTGTCTCTAAGTGACTTCTACCCGGGAGCCGTG ACAGTGGCCTGGAAGGCAACAAGGCCCCCTCACGTGGAGGACCACCACCACCCCCCCAAGACCCTCCAAAAGC AACAACTAGCAGCAACAAGCCCCCTCAAGCCGGCGGAGTGGACCACCACCCCCCCAAGAAGCCAAAAGC AACAACAAGTACGCGGCCAGCAGCTATCTGAGCCCTGACCACGACGACGCACCACACGACGAAGCCACAAGC GCCAGGTCACGATGAAGGGAGCACCGTGGAGAAGACAGTGGCCCCTACAGAAGTCCA
-	129: CAGGTGCAGCTGGTGCAGTCCGGCGCGAGGTGAAGAAGCCCGGCTCCTCCGTGAAGGTGTCCTGCAAG GCCTCCGGCGGCACCTTCTCCTCCTCCGCGCCGGGTGGCGGGCG

GAAGTCCCTGTCCCTGTCCCCCGGCAAG

	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
-	130: GACATCGAGCTGACCCAGCCCCCTCCGTGTCCGTGGCCCGGCCAGACCGGCCGG
ntibody 525	_
DRH1	131: SYWIS
DRH2	132: IIDPDDSKTNYSPSFQG
DRH3	133: RSYYPMDY
DRL1	134: TGTSSDVVGVYNFVS
DRL2	135: YVDNRPS
DRL3	136: QSFDGFGIDMV
Ή	137: QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWISWVRQMPGKGLEWMGIIDPDDSKTNYSPSFQGQVTISAD KSISTAYLQWSSLKASDTAMYYCARRSYYPMDYWGQGTLVTVSS
Γ	138: DIALTQPASVSGSPGQSITISCTGTSSDVVGVYNFVSWYQQHPGKAPKLMIYYVDNRPSGVSNRFSGSKSGNTA SLTISGLQAEDEADYYCQSFDGFGIDMVFGGGTKLTVL
Heavy chain	139: QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWISWVRQMPGKGLEWMGIIDPDDSKTNYSPSFQGQVTISAD KSISTAYLQWSSLKASDTAMYYCARRSYYPMDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Jight chain	140: DIALTQPASVSGSPGQSITISCTGTSSDVVGVYNFVSWYQQHPGKAPKLMIYYVDNRPSGVSNRFSGSKSGNTA SLTISGLQAEDEADYYCQSFDGFGIDMVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTV AWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding EQ ID IO: 137	141: CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTATTGGATTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATG GCATTATCGATCCGGATGATAGCAAGACCAATTATTCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGA TAAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG
PN encoding SEQ ID NO: 138	142: GATATCGCACTGACCCAGCCTAGCTGCAGGGGGCGCCCACCAGGTCAGAGCATTACCATCTCGTGTACGG GTACTAGCAGCGATGTTGTTGGTGTTTATAATTTTGTGTCTTGGTACCAGCAGCATCCCGGGAAGGCGCCGAAA CTTATGATTATTATGTTGATAATCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCAACACC GCGAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTTTGATGGTTTTGG TATTGATATGGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO: 139	143: CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTTGGATTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATG GGCATTATCGATCGGATGATAGCAAGACCAATTATTCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGA TAAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG
PN encoding SEQ ID NO: 140	144: GATATCGCACTGACCCAGCCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACGG GTACTAGCAGCGATGTTGTTGGTGGTTTATAATTTTGTGTGTG

	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
	CGGGAGCCGTGACAGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCC TCCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCATCTGAGCCTGAGCGCTGAGCAGTGGAAGTCCCACA GAAGCTACAGCTGCCAGGTCACGCATGAGGGGAGGAGCACCGTGGAAAAAACCGTTGCGCCGACTGAGX (X can be TGCAGC or GCC)
Antibody 5756	_
CDRH1	145: SYWIA
CDRH2	146: IIYPGDSDTNYSPSFQG
CDRH3	147: SKYGSFDY
CDRL1	148: TGTSSDVGGYNYVS
CDRL2	149: NVNSRPS
CDRL3	150: QSYDDGQDNEV
VH	151: QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIAWVRQMPGKGLEWMGIIYPGDSDTNYSPSFQGQVTISAD KSISTAYLQWSSLKASDTAMYYCARSKYGSFDYWGQGTLVTVSS
VL	152: DIALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYNVNSRPSGVSNRFSGSKSGNTA: LTISGLQAEDEADYYCQSYDDGQDNEVFGGGTKLTVL
Heavy chain	153: QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYWIAWVRQMPGKGLEWMGIIYPGDSDTNYSPSFQGQVTISAD KSISTAYLQWSSLKASDTAMYYCARSKYGSFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	154: DIALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYNVNSRPSGVSNRFSGSKSGNTA: LTISGLQAEDEADYYCQSYDDGQDNEVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTV AWKADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding SEQ ID NO: 151	155: CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTATTGGATTGCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATG GGCATTATCTATCCGGGTGATAGCGATACCAATTATTCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGA TAAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG
PN encoding SEQ ID NO: 152	156: GATATCGCACTGACCCAGCCTAGCTGCAGGGGGCCCACCAGGTCAGAGCATTACCATCTCGTGTACGG GTACTAGCAGCGATGTTGGTGGTTATAATTATGTGTCTTGGTACCAGCAGCATCCCGGGAAGGCGCCGAAACTT ATGATTTATAATGTTAATTCTCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCAACACCGC GAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTATGATGATGGTCAG GATAATGAGGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO: 153	157: CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATCCTTTACTTCTTATTGGATTGCTTGGGTGCGCCAGATGCCTGGGAAGGTCTCGAGTGGATG GGCATTATCTATCCGGGTGATAGCGATACCAATTATTCTCCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGG TTAAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCCGAAAGCGAGCG
PN encoding SEQ ID NO: 154	158: GATATCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACGG GTACTAGCAGCGATGTTGGTGGTTATAATTATGTGTCTTGGTACCAGCAGCATCCCGGGAAGGCGCCGAAACTT ATGATTTATAATGTTAATTCTCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCAACACCGC GAGCCTGACCATTAGCGGCCGGCGGCAGAGCGAAGACGAAGCGGATTATTATTGCCAGTCTTATGATGATGGTCAG GATAATGAGGTGTTTGGCGGCGGCAGCAGAAGTTAACCGTTCTTGGCCAGCCGAAGCCGCACCGAGTGTGACGC TGTTTCCGCCGAGCGAGGAGAATTGCAGGCGAAGACAAAGCGACCTTGGCGCGGCGCGGCGCGGCGTGTATCC GGGAGCCGTGACAATGGCCTGGAAGGCGAAGACAAAGCGACCCGTGGCGGAGGTGGAGGCCCT CCAAACAAAGCAACAACAAGTACGCGGCCAGCAGCACCTTCTGAGCCTGACCGAGCGGGAGGTCCCACAG AAGCTACAGCGCCAGGTCACGCAGCGAGGGGGAGCACCGTGGAAAAAAACCGTTGCCGGACCGGACTGAGAG (X can be TGCAGC or GCC)

tinı

TABLE 1-continued		
	Examples of C5 Antibodies of the Present Invention and C5 Proteins	
	Sequence Identifier (SEQ ID NO:) or comments/details	
Antibody 6757	_	
CDRH1	159: SYAMH	
CDRH2	160: AISSSGSSTYYADSVKG	
CDRH3	161: ESWFLDL	
CDRL1	162: RASQSISNWLA	
CDRL2	163: LASSLQS	
CDRL3	164: QQYYDFSDT	
ЛН	165: QVQLVESGGGLVQPGGSLRLSCAASGFTFTSYAMHWVRQAPGKGLEWVSAISSSGSSTYYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCARESWFLDLWGQGTLVTVSS	
7L	166: DIQMTQSPSSLSASVGDRVTITCRASQSISNWLAWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTI SSLQPEDFAVYYCQQYYDFSDTFGQGTKVEIK	
Heavy chain	167: QVQLVESGGGLVQPGGSLRLSCAASGFTFTSYAMHWVRQAPGKGLENVSAISSSGSSTYYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCARESWFLDLWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)	
ight chain	168: DIQMTQSPSSLSASVGDRVTITCRASQSISNWLAWYQQKPGKAPKLLIYLASSLQSGVPSRFSGSGSGTDFTLTI SSLQPEDFAVYYCQQYYDFSDTFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEX (X can be C or A)	
PN encoding SEQ ID NO: 165	169: CAGGTGCAATTGGTGGAAAGCGGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGC GGCCTCCGGATTTACCTTTACTTCTTATGCTATGC	
PN encoding SEQ ID NO: 166	170: GATATCCAGATGACCCAGAGCCCGTCTAGCCTGAGCGCGAGCGTGGGTGATCGTGTGACCATTACCTGCA GAGCGAGCCAGTCTATTTCTAATTGGCTGGCTTGGTACCAGCAGAAACCAGGTAAAGCACCGAAACTATTAATT TATCTTGCTTCTTTGCAAAGCGGGGTCCCGTCCGGTTTAGCGGCTCTGGATCCGGCACTGATTTTACCCT GACCATTAGCAGCCTGCAACCTGAAGACTTTGCGGTTTATTATTGCCAGCAGTATTATGATTTTTCTGATACCTTT GGCCAGGGTACGAAAGTTGAAATTAAA	
PN encoding SEQ ID NO: 167	171: CAGGTGCAATTGGTGGAAAGCGGCGGCGGCGGCGGCGGCGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGC GGCCTCCGGATTTACCTTTTACTTCTTATGCTATGC	
PN encoding SEQ ID NO: 168	 A (X can be TGC, GAATTC or TGCGAATTC) 172: GATATCCAGATGACCCAGAGCCCGGTCTAGCCTGAGCGCGAGCGTGGGTGATCGTGTGACCATTACCTGCA GAGCGAGCCAGTCTATTTCTAATTGGCTGGCTTGGTACCAGCAGAAACCAGGTAAAGCACCGAAACTATTAATT TATCTTGCTTCTTTGCAAAGCGGGGGTCCCGTCCGGTTTAAGCGGCTCTGGATCCGGCACTGATTTACCCT GACCATTAGCAGCCTGCAACCTGAAGACTTTGCGGTTTATTATTGCCAGCAGCAGTATTATGATTTTTCCGACCAGCAGGATGA ACAACTGAAAAGCTGGAAAGTTGAAATTAAACGTACGGTGGCTGCTGCGAACAACTTTTATCCGCCGGGAGCGAAAGTTCAG TGGAAAAGCGGCACGGCCGCGCGCGCGCACAGCCCGGCAGGAAAGCCGGACCGAACAGGAAAGTTCAG TGGAAAGTAGACAACGCGCTGCAAAGCGGCAACAGCCAGGAAAGCCGGACCGAACAGGAAAGATAGCA 	
	ACAACTGAAAAGCGGCACGGCGAGCGTGGTGTGCCTGCTGAACAACTTTTATCCGCGTGAAGCGAAAGTTCAG	

CDRH2

SEQ ID NO: 2

TABLE 1-continued Examples of C5 Antibodies of the Present Invention and C5 Proteins		
Antibody 6763		
CDRH1	173: NYGMH	
CDRH2	174: VSYAGSFTNYADSVKG	
CDRH3	175: SWLFGYPDIFDY	
CDRL1	176: TGTSSDVGGYNYVS	
CDRL2	177: DVNNRPS	
CDRL3	178: SSYDKFQTV	
VH	179: QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVSVSYAGSFTNYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCARSWLFGYPDIFDYWGQGTLVTVSS	
VL	180: DIALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVNNRPSGVSNRFSGSKSGNTA SLTISGLQAEDEADYYCSSYDKFQTVFGGGTKLTVL	
Heavy chain	181: QVQLVESGGGLVQPGGSLRLSCAASGFTFSNYGMHWVRQAPGKGLEWVSVSYAGSFTNYADSVKGRFTISRD NSKNTLYLQMNSLRAEDTAVYYCARSWLFGYPDIFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCL VKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)	
Light chain	182: DIALTQPASVSGSPGQSITISCTGTSSDVGGYNYVSWYQQHPGKAPKLMIYDVNNRPSGVSNRFSGSKSGNTA SLTISGLQAEDEADYYCSSYDKFQTVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAW KADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)	
PN encoding SEQ ID NO: 179	183: CAGGTGCAATTGGTGGAAAGCGGCGGCGGCGGCCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGC GGCCTCCGGATTTACCTTTTCTAATTATGGTATGCATTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGG GTGAGCGTTTCTTATGCTGGTAGCTTTACCAATTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCACGTGAT AATTCGAAAAACACCCTGTATCTGCAAATGAACAGCCTGCGTGCG	
PN encoding SEQ ID NO: 180	184: GATATCGCACTGACCCAGCCTACCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACGG GTACTAGCAGCGATGTTGGTGGTTATAATTATGTGTCTTGGTACCAGCAGCATCCCGGGAAGGCGCCGAAACTT ATGATTTATGATGTTAATAATCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCAACACCGC GAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCTCTTCTTATGATAAGTTTCAGA CTGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTT	
PN encoding SEQ ID NO: 181	185: CAGGTGCAATTGGTGGAAAGCGGCGGCGGCGGCGGCTGGTGCAACCGGGCGGCAGCCTGCGTCTGAGCTGCGC GGCCTCCGGATTTACCTTTTCTAATTATGGTATGCATTGGGTGCGCCAAGCCCCTGGGAAGGGTCTCGAGTGG GTGAGCGTTTCTTATGCTGGTAGCTTTACCAATTATGCGGATAGCGTGAAAGGCCGTTTTACCATTTCACGTGAT AATTCGAAAAACACCCTGTATCTCGCAAATGAACAGCCTGCGGTCGGGAAGGACAGGTGACGGTTATTATTGCGCGCG TTCTTGGCTTTTTGGTTATCCTGATATTTTGATTATGGGGCCAAGGCCACGGTGGCGCGGCGCGCGC	
PN encoding SEQ ID NO: 182	186: GATATCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACGG GTACTAGCAGCGATGTTGGTGGTTATAATTATGTGTCTTGGTACCAGCAGCACCCGGGAAGCGCCGAAACTT ATGATTATGATGATGTTAATAATCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCACACCGC GAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTATGCTCTTCTTATGATAAGTTTCAGA CTGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCCGCACCGAGTGTGACGCTGTTTCC GCCGAGCAGCGAAGAATTGCAGGCGGAACAAAGCGACCCTGGTGTCCTGATTAGCGACTTTTATCCGGGAGCC GTGACAGTGGCCGGAAGAATAGCAGCCCCGTCAAGGCGGGAGTGGAGCCACACCCTCCCAAACAA AGCAACAACAAGTACGCGGCCAGCAGAAGCCCTGGAGCTGGAGGCGGAGGGGAGCCACCCCCCCC	
Antibody 7086	_	
CDRH1	SEQ ID NO: 1	

	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
CDRH3	SEQ ID NO: 3
CDRL1	SEQ ID NO: 4
CDRL2	SEQ ID NO: 5
CDRL3	SEQ ID NO: 6
ЛН	187: QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIGPFFGTANYAQKFQGRVTITA DESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTVSS
νL	188: DIELTQPPSVSVAPGQTARISCSGDSIPNYYVYWYQQKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQSFDSSLNAEVFGGGTKLTVL
Heavy chain	189: QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIGPFFGTANYAQKFQGRVTITA DESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDY FPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	190: DIELTQPPSVSVAPGQTARISCSGDSIPNYYVYWYQQKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQSFDSSLNAEVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding SEQ ID NO: 187	191: CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAG CCTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGGTGCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGAT GGCCGGTATCGGTCCGTTTTTTGGCACTGCGAATTACGCGCAGAAGTTTCAGGGCCGGGTGACCATTACCGCG GATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGCGAAGATACGGCCGTGTATTATTGCG CGCGTGATACTCCTTATTTTGATTATTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA
PN encoding SEQ ID NO: 188	192: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATTCTATTCCTAATTATTATGTTTATTGGTACCAGCAGAAACCCCGGGCAGGCCCAGTTCTTGTGATTTATG ATGATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTTTGATTCTTCTCTTTAATGCTGAGGT GTTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO: 189	193: CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAG CCTCCGGAGGCACTTTTTCTTCTTATGCCATTTCTTGGGTGCGCCAAGCCCCTGGGCAGGGTCTCCAAGTGGAT GGGCGGTATCGGTCCGTTTTTGGCACTGCGAATTACGCGCAGAAGTTCCAGGGCCGGGTGACCATTACCGCG GATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGCGAAGATACGGCCGTGTATTATTGCG CCGGTGATACTCCTTATTTGATTATTGGGGCCAAGGCACCCTGGTGACGGTAGCTCAGCGTCGACCAAAGGT CCAAGCGTGTTTCCGGTGGCAGCGACAACAAAGCACCAGCGGCGGCGCGCGC
PN encoding SEQ ID NO: 190	 (X can be TGC, GAATTC or TGCGAATTC) 194: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATTCTATTCCTAATTATTATTATTATTGTTATTGGTACCAGCAGAAACCCGGGCAGGCGCAGTCCTTGTGATTTATG ATGATTCTAATCGTCCCTCAGGCATCCCGGAACGCCTTTAGCGGATCCAACAGCGGCAACACCGCGGAACCCTGAC CATTAGCGGCACCTAGGCGGAAGACGAACGGATTATTATTGCCAGTCTTTGATTCTTCTCTTAATGCTGAGGT GTTTGGCGGCGGCACGAAGACGAACGGACCTGGTGGCCGGAAGACCGGAGTGTGACGCTGTTCCGCC GAGCAGCGAAGAATTGCAGGCGAACAAAGCGGACCCTGGTGGCCGGAAGACCGACC
Antibody 7087	_
CDRH1	195: SYYIS
DRH2	196: GIIPIFGTANYAQKFQG
CDRH3	197: GEIWHVHQPYKSGVYGAAY
CDRL1	198: RASQGISNWLN
CDRL2	199: GTSSLQS

TABLE 1-continued

	TABLE 1-Continued	
Examples of C5 Antibodies of the Present Invention and C5 Proteins		
	Sequence Identifier (SEQ ID NO:) or comments/details	
CDRL3	200: QQLDSFPAT	
VH	201: QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYYISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARGEIWHVHQPYKSGVYGAAYWGQGTLVTVSS	
VL	202: DIQMTQSPSSLSASVGDRVTITCRASQGISNWLNWYQQKPGKAPKLLIYGTSSLQSGVPSRFSGSGSGTDFTLTI SSLQPEDFATYYCQQLDSFPATFGQGTKVEIK	
Heavy chain	203: QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYYISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRVTITADE STSTAYMELSSLRSEDTAVYYCARGEIWHVHQPYKSGVYGAAYWGQGTLVTVSSASTKGPSVPPLAPSSKSTSGGT AALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVE PKSX (X can be C, EF or CEF)	
Light chain	204: DIQMTQSPSSLSASVGDRVTITCRASQGISNWLNWYQQKPGKAPKLLIYGTSSLQSGVPSRFSGSGSGTDFTLTI SSLQPEDFATYYCQQLDSFPATFGQGTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDN ALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEX (X can be C or A)	
PN encoding SEQ ID NO: 201	205: CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAG CCTCCGGAGGCACTTTTTCTTCTTATTATATTTCTTGGGTGCGCCAAGCCCCTGGGCAGGGTCTCGAGTGGATG GGCGGTATCATTCCGATTTTTGGCACTGCGAATTACGCGCAGAAGTTTCAGGGCCGGGTGACCATTACCGCGG ATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGCGAAGATACGGCCGTGTATTATTGCGC GCGTGGTGAGATTTGGCATGTTCATCAGCCCTTATAAGTCTGGTGTTTATGGTGCTGCTTATTGGGGCCAAGGCA CCCTGGTGACGGTTAGCTCA	
PN encoding SEQ ID NO: 202	206: GATATCCAGATGACCCAGAGCCCGTCTAGCCTGAGCGCGAGCGTGGGTGATCGTGTGACCATTACCTGCA GAGCGAGCCAGGGTATTTCTAATTGGCTGATTGGTACCAGCAGAAACCAGGTAAAGCACCGAAACTATTAATT TATGGTACTTCTTCTTTGCAAAGCGGGGTCCCGTCCC	
PN encoding SEQ ID NO: 203	207: CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGCAGCAGCGTGAAAGTGAGCTGCAAAG CCTCCGGAGGCACTTTTTCTTCTTATTATATTTCTTGGGTGCGCCAAGCCCTGGGCAGGGTCTCGAGTGGATG GGCGGTATCATTCCGATTTTTGGCACTGCGAATTACGCGCAGAAGTTCAGGGCCGGGTGACCATTACCGCG ATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCTGCGTAGCGAAGATACGGCCGTGATTATTGCGC GCGTGGTGAGAATTTGGCATGTTCATCAGCCTTATAAGTCTGGTGTTTTATGGTCTGCTTATTGGGGCCAAGGCA CCCTGGTGACGGTTAGCTCAGCGTCGCTAGCAAAGGTCCAAGCGTGTTTCCGGCGGCCGGGCAGCAAAGCAC CAGCGGCGGCGCGGC	
PN encoding SEQ ID NO: 204	208: GATATCCAGATGACCCAGAGCCCGTCTAGCCTGAGCGCGAGCGTGGGTGATCGTGTGACCATTACCTGCA GAGCGAGCCAGGGTATTTCTAATTGGCTGAATTGGTACCAGCAGAAACCAGGTAAAGCACCGGAACTATTAATT TATGGTACTTCTTTGCTAAGCGGGGGCCCGTCCGGTCCG	
Antibody 7091	_	
CDRH1	SEQ ID NO: 61	
CDRH2	SEQ ID NO: 77	
CDRH3	SEQ ID NO: 63	
CDRL1	SEQ ID NO: 64	
CDRL2	SEQ ID NO: 65	
CDRL3	209: QSWTDSPNTLV	
1711		

TABLE 1-continued

VH 210: QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWVRQMPGKGLEWMGIIDPSDSHTTYSPSFQGQVTISADK SISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSS

	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
νL	211: DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQSWTDSPNTLVFGGGTKLTVL
Heavy chain	212: QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWVRQMPGKGLEWMGIIDPSDSHTTYSPSFQGQVTISADK SISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	213: DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQSWTDSPNTLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding SEQ ID NO: 210	214: CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTATTATATGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATG GGCATTATCGATCCGTCTGATAGCCATACCACTTATTCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGA TAAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG
PN encoding SEQ ID NO: 211	215: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTGGACTGATTCTCCTAATACTCTTG TGTTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO: 212	216: CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGAAAGGTCTCGAGTGGATG GGCATTATCGATCCGTCTGATAGCCATACCACTTATTCTCCGAGCTTTCAGGGCCAGGTGACCATTAGCGCGGA TAAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG
PN encoding SEQ ID NO: 213	217: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATTCTCTTGGTGATTATTAGCTTATTGGTACCAGCAGAAACCCGGGCAGGCCCAGTTCTGTGATTATA AGGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAACGGAGCGTATTATTATTGCCAGTCTTGGACTGATTCTCCTAATACTCTTG TGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAGCCGCCGAGTGTGACGCTGTTTCCGCC GAGCAGCGAAGAATTGCAGGCGAACAAAGCGACCGTGGTGGCCGAATAGCGACCTTCGACTGATTACCGGGGGCCGGACGAAGACGAACAAAGCGACCGTGGCGGGGGGGG
Antibody	
7092	
CDRH1 CDRH2	SEQ ID NO: 17 SEQ ID NO: 49
CDRH2	SEQ ID NO: 49 SEQ ID NO: 19
CDRL1	SEQ ID NO: 20
CDRL2	SEQ ID NO: 21
CDRL3	SEQ ID NO: 22
ЛН	- 218: QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPDDSYTRYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSS
νL	219: DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCGTYDIESYVFGGGTKLTVL
Heavy chain	220: QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPDDSYTRYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)

	Examples of C5 Antibodies of the Present Invention and C5 Proteins	
Sequence Identifier (SEQ ID NO:) or comments/details		
Light chain	221: DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCGTYDIESYVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKADS SPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)	
PN encoding SEQ ID NO: 218	222: CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATCGATCCGGATGATAGCTATACCCGTTATTCTCCGAGCTTTCAGGGACAGGTGACCATTAGCGCGGATAA AAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG	
PN encoding SEQ ID NO: 219	223: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCCCCAGTTCTTGTGATTTATA AGGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCGGTACTTATGATATTGAGTCTTATGTGTTTG GCGGCGGCACGAAGTTAACCGTTCTT	
PN encoding SEQ ID NO: 220	224: CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGCC ATTATCGATCCGGATGATAGCTATACCCGTTATTCTCCGAGCGCCAGGTGACCATTAGCGCGGGATAA AAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG	
PN encoding SEQ ID NO: 221	225: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGCGCCAGTCCTTGTGGATTTATA AGGATAATGATCGTCCTCAGGCAACCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGCACCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGAGTATTATTATGCGGTACTTATGAGTCTTATGTGTTTG GCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCCGCACCGAAGTGTGACGCTGTTTCCGCCGAGCA GCGAAGAATTGCAGGCGGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCCGTGACAGT GCCCTGGAAGGCAGATCAACGCCCCGTCAAGGCGGGGAGTGGAGACCACCACACCCTCCAAACAAGCAACAA CAAGTACGCGCCGGCCAGCAGCCTGGCCTG	
Antibody		
7093	-	
CDRH1	SEQ ID NO: 33	
DRH2	226: HIFSDDDKYYSTSLKT	
DRH3	SEQ ID NO: 35	
CDRL1	SEQ ID NO: 36	
DRL2	SEQ ID NO: 37	
CDRL3	SEQ ID NO: 38	
7H	- 227: QVQLKESGPALVKPTQTLTLTCTFSGFSLSTSGGGVSWIRQPPGKALEWLAHIFSDDDKYYSTSLKTRLTISKDT SKNQVVLTMTNMDPVDTATYYCARGPYGFDSWGQGTLVTVSS	
7L	228: DIALTQPASVSGSPGQSITISCTGTSSDIGTYNYVSWYQQHPGKAPKLMIYDDSNRPSGVSNRFSGSKSGNTAS LTISGLQAEDEADYYCQSYDSQSIVFGGGTKLTVL	
Heavy chain	229: QVQLKESGPALVKPTQTLTLTCTFSGFSLSTSGGGVSWIRQPPGKALEWLAHIFSDDDKYYSTSLKTRLTISKDT SKNQVVLTMTNMDPVDTATYYCARGPYGFDSWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)	
jight chain	230: DIALTQPASVSGSPGQSITISCTGTSSDIGTYNYVSWYQQHPGKAPKLMIYDDSNRPSGVSNRFSGSKSGNTAS LTISGLQAEDEADYYCQSYDSQSIVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWK ADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)	
PN encoding SEQ ID	231: CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGTACCT TTTCCGGATTTAGCCTGTCTACTTCTGGTGGTGGTGTGTCTTGGATTCGCCAGCCGCCTGGGAAAGCCCTCGAG	

TABLE 1-continued		
	Examples of C5 Antibodies of the Present Invention and C5 Proteins	
	Sequence Identifier (SEQ ID NO:) or comments/details	
NO: 227	TGGCTGGCTCATATCTTTTCTGATGATGATAAGTATTATAGCACCAGCCTGAAAACGCGTCTGACCATTAGCAAA GATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCGGTGGATACGGCCACCTATTATTGCGC GCGTGGTCCTTATGGTTTTGATTCTTGGGGCCAAGGCACCCTGGTGACGGTTAGCTCA	
PN encoding SEQ ID NO: 228	232: GATATCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACGG GTACTAGCAGCGATATTGGTACTTATAATTATGTGTCTTGGTACCAGCAGCATCCCGGGAAGGCGCCGAAACTT ATGATTTATGATGATTCTAATCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCAACACCGC GAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCCAGTCTTATGATTCTCAGTCTA TTGTGTTTGGCGGCGCGCACGAAGTTAACCGTTCTT	
PN encoding SEQ ID NO: 229	233: CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGTACCT TTTCCGGATTTAGCCTGTCTACTTCTGGTGGTGGTGTGTCTTGGATTCGCCAGCCCTGGGAAAGCCCTCGAG TGGCTGGCTCATATCTTTTCTGATGATGATAAGTATTATAGCACCCAGCCTGAAAACGCGTCTGACCATTAGCAAA GATACTTCGAAAAATCAGGTGGTGCTGACTATGGGCCAACATGGACCCAGGTGGATACGGCCACCTATTATTGCGC GCGTGGTCCTTATGGTTTTGATTCTTGGGCCAAGGCAACATGGACCGGTGGACCGGCGGCGGCGGCGGCGACCGAAAGGT CCAAGCGTGTTTCCGCTGGCCCCGGGCAAAGCACCAGCGGCGGCGGCGGCGGCGGCG	
PN encoding SEQ ID NO: 230	234: GATATCGCACTGACCCAGCCAGCTTCAGTGAGCGGCTCACCAGGTCAGAGCATTACCATCTCGTGTACGG GTACTAGCAGCGATATTGGTACTTATAATTATGTGTCTTGGTACCAGCAGCATCCCGGGAAGGCGCCGAAACTT ATGATTTATGATGATTCTAATCGTCCCTCAGGCGTGAGCAACCGTTTTAGCGGATCCAAAAGCGGCGAACACCGC GAGCCTGACCATTAGCGGCCTGCAAGCGGAAGACGAAGCGGATTATTATTGCCAGTCTATGATTCTCAGTCTA TTGTGTTTTGGCGCCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAGCCGCACCGAGTGTGACGCTGTTTCC GCCGAGCAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCCGATTAGCGACTTTATCCGGGAGC GTGACAGTGGCCTGGAAGGCGAACAAAGCGCCCTGAGCGGGAGTGGAGCACCACCACCCCCCCAACAA AGCAACAACAAGTACGCGGCAGAATAGCAGCCCGTCAAGGCGGGAGTGGAAGTCCCACAGAAGCTACA GCTGCCAGGTCACGCACGAGGGAGCACCGTGGAAAAAAACCGTTGCGCCGACTGAGX (X can be TGCAGC or GCC)	
Antibody 7094		
CDRH1	235: TSGMSVG	
CDRH2	236: LIDWDEDKSYSTSLKT	
CDRH3	237: YNWYNPPGFDN	
CDRL1	238: SGSSSNIGSNYVS	
CDRL2	239: RNDKRPS	
CDRL3	240: QSADSSSMV	
VH	241: QVQLKESGPALVKPTQTLTLTCTFSGFSLSTSGMSVGWIRQPPGKALEWLALIDWDEDKSYSTSLKTRLTISKDT SKNQVVLTMTNMDPVDTATYYCARYNWYNPPGFDNWGQGTLVTVSS	
VL	242: DIVLTQPPSVSGAPGQRVTISCSGSSSNIGSNYVSWYQQLPGTAPKLLIYRNDKRPSGVPDRFSGSKSGTSASL AITGLQSEDEADYYCQSADSSSMVFGGGTKLTVL	
Heavy chain	243: QVQLKESGPALVKPTQTLTLTCTFSGFSLSTSGMSVGWIRQPPGKALEWLALIDWDEDKSYSTSLKTRLTISKDT SKNQVVLTMTNMDPVDTATYYCARYNWYNPPGFDNWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLV KDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)	
Light chain	244: DIVLTQPPSVSGAPGQRVTISCSGSSSNIGSNYVSWYQQLPGTAPKLLIYRNDKRPSGVPDRFSGSKSGTSASL AITGLQSEDEADYYCQSADSSSMVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWK ADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)	
PN encoding SEQ ID NO: 241	245: CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCCTGACCTGTACCT TTTCCGGATTTAGCCTGCTACTTCTGGTATGTCTGTGGGTTGGATTCGCCAGCGCCTGGGAAAGCCCTCGAG TGGCTGGCTCTTATCGATTGGGATGAGGATAAGTCTTATAGCACCAGCCTGGAAAACGCGTCTGACCATTAGCAA AGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCGGTGGATACGGCCACCTATTATTGCG CGCGTTATAATTGGTATAATCCTCCTGGTTTTGATAATTGGGGCCCAGGCCACCTGGTGACGGTTAGCCA	
PN encoding SEQ ID NO: 242	246: GATATCGTGCTGACCCAGCCGCCTTCAGTGAGTGGCGCACCAGGTCAGCGTGTGACCATCTCGTGTAGCG GCAGCAGCAACATTGGTTCTAATTATGTGTCTTGGTACCAGCAGTTGCCCGGGACGGCGCCGAAACTTCT GATTTATCGTAATGATAAGCGTCCCTCAGGCGTGCCGGATCGTTTTAGCGGATCCAAAAGCGGCACCAGCGCG	

	TABLE 1-continued		
	Examples of C5 Antibodies of the Present Invention and C5 Proteins		
	Sequence Identifier (SEQ ID NO:) or comments/details		
	AGCCTTGCGATTACGGGCCTGCAAAGCGAAGACGAAGCGGATTATTATTGCCAGTCTGCTGATTCTTCTTCTAT GGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTT		
PN encoding SEQ ID NO: 243	247: CAGGTGCAATTGAAAGAAAGCGGCCCGGCCCTGGTGAAACCGACCCAAACCCTGACCTGACCTGTACCT TTTCCGGATTTAGCCTGTCTACTTCTGGTATGTCTGTGGGTTGGATTCGCCAGCCGCCTGGAAAACCCCTGAAG TGGCTGGCTCTTATCGATTGGGATGAGGATAAGTCTTATAGCACCAGCCTGAAAACGCGTCTGACCATTAGCAA AGATACTTCGAAAAATCAGGTGGTGCTGACTATGACCAACATGGACCCGGTGGATACGGCCACCTATTATTGCG CGCGTTATAATTGGTATAATCCTCCTGGTTTGGATAATTGGGGCCAGGCACCCTGGTGACCGGTGACCAGCGG TCGACCAAAGGTCCAAGCGTGTTTCCGCGGCCCCGAGCAGCAGCAGCCGGCGGCGGCGCGCCCTG GGCTGCCTGGTTAAAATTTTTCCCGGAACCAGTCACCGTGGACCAGCGGCGGCGGCGCGCCGCCGG GGCCGCTGGTTAAAGATTATTTCCCGGAACCAGTCGACCGTGGACGGCGGGGCGCGCGC		
PN encoding SEQ ID NO: 244	248: GATATCGTGCTGACCCAGCCGCCTTCAGTGAGTGGCGCACCAGGTCAGCGTGTGACCATCTCGTGTAGCG GCAGCAGCAGCAACATTGGTTCTAATTATGTGTCTTGGTACCAGCAGTTGCCCGGGACGGCGCCGAAACTTCT GATTTATCGTAATGATAAGCGTCCCTCAGGCGTGCCGGATCGTTTAGCGGATCCAAAAGCGGCACCAGCGG AGCCTTGCGATTACGGGCCTGCAAAGCGAAGACGAAGCGGATTATTATTGCCAGTCTGCTGATTCTTCTTCTAT GGTGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCCGACCGA		
Antibody 7821	_		
CDRH1	SEQ ID NO: 1		
CDRH2	SEQ ID NO: 119		
CDRH3	SEQ ID NO: 3		
CDRL1	SEQ ID NO: 4		
CDRL2	SEQ ID NO: 5		
CDRL3	SEQ ID NO: 6		
VH	SEQ ID NO: 121		
VL	SEQ ID NO: 188		
Heavy chain	249: QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGNIGPFGIANYAQKFQGRVTITAD ESTSTAYMELSSLRSEDTAVYYCARDTPYFDYWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFP EPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)		
Light chain	SEQ ID NO: 190		
PN encoding SEQ ID NO: 121	SEQ ID NO: 125		
PN encoding SEQ ID NO: 188	SEQ ID NO: 192		
PN encoding SEQ ID NO: 249	250: CAGGTGCAATTGGTTCAGTCTGGCGCGGAAGTGAAAAAACCGGGCAGCAGCGTGAAAGTGAACTGCAAAG CCTCCGGAAGCACTTTTTCTTTTTTGCCATTGCGATTTCTGGGTGCGCAAAGCCCTGGGCAGGGTCTCGAAGGGAT GGGCAATATCGGTCCGTTTTTTGGCATTGCGAATTACGCGCAGAAGTTCAGGGCCGGGTGACCATTACCGCG GATGAAAGCACCAGCACCGCGTATATGGAACTGAGCAGCCGCGGCAGCGAAGATACGGCCGTGTATTATTGCG CGCGTGATACTCCTTATTTTGATTATTGGGGCCAAGGCACCCTGGTGACCGATGACCACGGCGGCGCCAAGGGT CCAAGCGTGTTTCCGCGGGCTCCAGGCAGCAAAAGCACCAGCGGCGGCGCGCGC		
PN encoding	SEQ ID NO: 194		

35

PN encoding SEQ ID NO: 19 SEQ ID NO: 190

	Examples of C5 Antibodies of the Present Invention and C5 Proteins		
	Sequence Identifier (SEQ ID NO:) or comments/details		
Antibody 7865			
CDRH1	SEQ ID NO: 1		
CDRH2	SEQ ID NO: 2		
CDRH3	SEQ ID NO: 3		
CDRL1	SEQ ID NO: 4		
CDRL2	SEQ ID NO: 5		
CDRL3	SEQ ID NO: 120		
VH	SEQ ID NO: 187		
VL	SEQ ID NO: 122		
Heavy chain	SEQ ID NO: 189		
Light chain	251: DIELTQPPSVSVAPGQTARISCSGDSIPNYYVYWYQQKPGQAPVLVIYDDSNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTYDDGSTAEVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)		
PN encoding SEQ ID NO: 187	SEQ ID NO: 191		
PN encoding SEQ ID NO: 122	SEQ ID NO: 126		
PN encoding SEQ ID NO: 189	SEQ ID NO: 193		
PN encoding SEQ ID NO: 251	252: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATTCTATTCCTAATTATTATGTTTATTGGTACCAGCAGAAACCCGGGCAGGCCCAGTCTTGTGATTTATG ATGATTCTAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGGCCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTATGCCAGACTATGGAGGGTCTAACTGCTGAGG TGTTTGGCGGCGGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCCGCAGCGGAGCGTGTTCCGCC GAGCAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGGCCGTGATTAGCGACTTTTATCCGGGAGCCGTG ACAGTGGCCTGGAAGGCAGATAACCAGCCCTGGTGGCGCGGAGGCACCCACC		
Antibody 7829	_		
CDRH1	SEQ ID NO: 61		
CDRH2	SEQ ID NO: 62		
CDRH3	SEQ ID NO: 63		
CDRL1	SEQ ID NO: 64		
CDRL2	SEQ ID NO: 65		
CDRL3	SEQ ID NO: 209		
VH	253: QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWVRQMPGKGLEWMGIIDPTDSQTAYSPSFQGQVTISADK		

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TABLE 1-continued			
	Examples of C5 Antibodies of the Present Invention and C5 Proteins		
	Sequence Identifier (SEQ ID NO:) or comments/details		
VL	SEQ ID NO: 211		
Heavy chain	254: QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWVRQMPGKGLEWMGIIDPTDSQTAYSPSFQGQVTISADK SISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)		
Light chain	SEQ ID NO: 213		
PN encoding SEQ ID NO: 253	255: CAGGTGCAATTGGTTCAGAGCGGCGGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGAATG GGCATTATTGATCCTACTGATTCTCAGACTGCTTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGAT AAAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG		
PN encoding SEQ ID NO: 211	SEQ ID NO: 215		
PN encoding SEQ ID NO: 254	256: CAGGTGCAATTGGTTCAGAGCGGCGGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGGG		
PN encoding SEQ ID NO: 213	SEQ ID NO: 217		
Antibody 7830			
CDRH1	SEQ ID NO: 61		
CDRH2	SEQ ID NO: 95		
CDRH3	SEQ ID NO: 63		
CDRL1	SEQ ID NO: 64		
CDRL2	SEQ ID NO: 65		
CDRL3	SEQ ID NO: 209		
VH	257: QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWVRQMPGKGLEWMGIIDPTDSYTVYSPSFQGQVTISADK SISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSS		
VL	SEQ ID NO: 211		
Heavy chain	258: QVQLVQSGAEVKKPGESLKISCKGSGYSFTSYYIGWVRQMPGKGLEWMGIIDPTDSYTVYSPSFQGQVTISADK SISTAYLQWSSLKASDTAMYYCARYMMRGFDHWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYF PEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)		
Light chain	SEQ ID NO: 213		
PN encoding SEQ ID	259: CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTCTTATTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATG		

TABLE 1-continued			
	Examples of C5 Antibodies of the Present Invention and C5 Proteins		
	Sequence Identifier (SEQ ID NO:) or comments/details		
PN encoding SEQ ID NO: 211	SEQ ID NO: 215		
PN encoding SEQ ID NO: 258	260: CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTTGTTATATTGGTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATG GGCATTATTGATCCTACTGATTCTTATACTGTTTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGGATA AAAGCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG		
PN encoding SEQ ID NO: 213	SEQ ID NO: 217		
Antibody 7871			
CDRH1	- SEQ ID NO: 61		
CDRH2	SEQ ID NO: 77		
CDRH3	SEQ ID NO: 63		
CDRL1	SEQ ID NO: 64		
CDRL2	SEQ ID NO: 65		
CDRL3	SEQ ID NO: 66		
VH	SEQ ID NO: 210		
VL	261: DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTWDTGESGVFGGGTKLTVL		
Heavy chain	SEQ ID NO: 212		
Light chain	262: DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTWDTGESGVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)		
PN encoding SEQ ID NO: 210	SEQ ID NO: 214		
PN encoding SEQ ID NO: 261	263: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTGGGATACTGGTGAGTCTGGTGGT TTTGGCGGCGCCCCGAAGTTAACCGTTCTT		
PN encoding SEQ ID NO: 212	SEQ ID NO: 216		
PN encoding SEQ ID NO: 262	264: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCCCAGTTCTTGTGATTATA AGGATAATAATCGTCCCTCAGGCATCCCGGAACGCCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCGCCACGAAGACGAAGCGGATTATTATTGCCAGACTTGGGATACTGGTGAGTCTGGTGTG TTTGGCGCGCGCACGAAGTTACCGTTCTTGGCCAGCCGAAAGCCGCACCGAGTGTGACCTGTTTCCGCCGA GCAGCGAAGAATTGCAGGCGAACAAAGCGACCTGGTGTGCCTGATTAGCGACTTTTATCCGGGGAGCCGTGAC AGTGGCCTGGAAGGCAGAACAAAGCGACCTGGTGTGCCTGATTAGCGACCTTCTATCCGGGGAGCCGTGAC AGTGGCCTGGAAGGCAGATAGCAGCCCGGTCAAGGCGGGAGTGGAGACCACCACACACCCTCCAAACAAA		

TABLE 1-continued		
	Examples of C5 Antibodies of the Present Invention and C5 Proteins	
	Sequence Identifier (SEQ ID NO:) or comments/details	
Antibody 7872	_	
CDRH1	SEQ ID NO: 61	
CDRH2	SEQ ID NO: 77	
CDRH3	SEQ ID NO: 63	
CDRL1	SEQ ID NO: 64	
CDRL2	SEQ ID NO: 65	
CDRL3	SEQ ID NO: 78	
VH	SEQ ID NO: 210	
VL	265: DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTWDILPHGLVFGGGTKLTVL	
Heavy chain	SEQ ID NO: 212	
Light chain	266: DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQTWDILPHGLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKA DSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)	
PN encoding SEQ ID NO: 210	SEQ ID NO: 214	
PN encoding SEQ ID NO: 265	267: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCCCAGTTCTTGTGATTTATA AGGATAATAATCGTCCCTCAGGCATCCCGGGAACGCGTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTGGGATATTCTTCCTCATGGTCTTG TGTTTGGCGGCACGAAGTTAACCGTTCTT	
PN encoding SEQ ID NO: 212	SEQ ID NO: 216	
PN encoding SEQ ID NO: 266	268: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCCCAGTTCTTGTGATTTATA AGGATAATAATCGTCCCTCAGGCATCCCGGAACGCGTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGACTTGGGATATTCTTCCTCATGGTCTTG TGTTTGGCGGCGGCACGAAGATTAACCGTTCTTGGCCAGCCGAAAGCCGCACCGAGTGTGACGCTGTTTCCGCC GAGCAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTTTTATCCGGGAGCCGTG ACAGTGGCCTGGAAGGACAGATAGCAGCCCCGTCAAGGCGGAGGCGAGCCACCACACCCCCCACAACAAAGC AACAACAAGTAGCGGCCAGCAGCTTGCCTGAGCGCGGAGTGGAGACCCACCACAGCACCACAACAAAGC ACCAGCGACGATGAGGGGAGCACCGTGGAAAAACCGTTGCGCCGACTGAGX (X can be TGCAGC or GCC)	
Antibody 7873		

7873	
CDRH1	SEQ ID NO: 61
CDRH2	SEQ ID NO: 77
CDRH3	SEQ ID NO: 63
CDRL1	SEQ ID NO: 64
CDRL2	SEQ ID NO: 65
CDRL3	SEQ ID NO: 89
VH	SEQ ID NO: 210

	TABLE 1-continued
	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
VL	269: DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQAWTDSPTGLVFGGGTKLTVL
Heavy chain	SEQ ID NO: 212
Light chain	270: DIELTQPPSVSVAPGQTARISCSGDSLGDYYAYWYQQKPGQAPVLVIYKDNNRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCQAWTDSPTGLVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWK ADSSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)
PN encoding SEQ ID NO: 210	SEQ ID NO: 214
PN encoding SEQ ID NO: 269	271: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATAATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCCAGGCTTGGACTGATTCTCCTACTGGTCTTG TGTTTGGCGGCGGCACGAAGTTAACCGTTCTT
PN encoding SEQ ID NO: 212	SEQ ID NO: 216
PN encoding SEQ ID NO: 270	272: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATTCTCTTGGTGATTATTATGCTTATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATAATCGTCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGAATTATTATTGCCAGGCTTGGACTGATCTCCTACTGGTCTTG TGTTTGGCGGCGGCACGAAGATAACCGTTCTTGGCCAGCCGAAAGCCGCACCGAGTGTGACGCTGTTTCCGCC GAGCAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTGTTTACCGGGGGCGGC ACCAGCGAGGAAGACGAACGAAGCCGTCGACGGGGGGGGG
Antibody 7832	
CDRH1	SEQ ID NO: 17
CDRH2	SEQ ID NO: 18
CDRH3	SEQ ID NO: 19
CDRL1	SEQ ID NO: 20
CDRL2	SEQ ID NO: 21
CDRL3	SEQ ID NO: 22
VH	273: QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPDDSYTEYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSS
VL	SEQ ID NO: 219
Heavy chain	274: QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPDDSYTEYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	SEQ ID NO: 221
PN encoding SEQ ID NO: 273	275: CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTGATGATTCTTATACTGAGTATTCTCCTTTTTCAGGGTCAGGTCACCATTAGCGCGGGATAAAA GCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG

CDRH3

SEQ ID NO: 19

	TABLE 1-continued
	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
PN encoding SEQ ID NO: 219	SEQ ID NO: 223
PN encoding SEQ ID NO: 274	276: CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTGATGATTCTTATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGTCACCATTAGCGCGGGATAAAA GCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGACGATACGGCCATGTATTATTGCGCGCGGTTAT GAGTATGGTGGTTTTGATATTTGGGGCCAAGGCACCCAGGGCGGCCAGGCTGCCTGGCCAAAGGTCCAA GCGTGTTCCGCTGGCCCGGACCAAGGCCACCAGCGGCGGCCGGC
Antibody 7909	_
CDRH1	SEQ ID NO: 17
CDRH2	SEQ ID NO: 107
CDRH3	SEQ ID NO: 19
CDRL1	SEQ ID NO: 20
CDRL2	SEQ ID NO: 21
CDRL3	SEQ ID NO: 22
VН	277: QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPQDSYTEYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSS
VL	SEQ ID NO: 219
Heavy chain	278: QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPQDSYTEYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	SEQ ID NO: 221
PN encoding SEQ ID NO: 277	279: CAGGTGCAATTGGTTCAGAGCGGCGGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTCAGGATTCTTATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGTCACCATTAGCGCGGGATAAAA GCATTAGCACCGCGTATCTTCAATGGAGCAGCCTGAAAGCGAGCG
PN encoding SEQ ID NO: 219	SEQ ID NO: 223
PN encoding SEQ ID NO: 278	280: CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGAAGGGTCTCGAATGGATGG
Antibody 7910	_
CDRH1	SEQ ID NO: 17
CDRH2	SEQ ID NO: 113

TABLE 1-continued

	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
CDRL1	SEQ ID NO: 20
CDRL2	SEQ ID NO: 21
CDRL3	SEQ ID NO: 22
VН	281: QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPEDSHTEYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSS
VL	SEQ ID NO: 219
Heavy chain	282: QVQLVQSGAEVKKPGESLKISCKGSGYSFTNYISWVRQMPGKGLEWMGIIDPEDSHTEYSPSFQGQVTISADKS ISTAYLQWSSLKASDTAMYYCARYEYGGFDIWGQGTLVTVSSASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPE PVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSX (X can be C, EF or CEF)
Light chain	SEQ ID NO: 221
PN encoding SEQ ID NO: 281	283: CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGA
PN encoding SEQ ID NO: 219	SEQ ID NO: 223
PN encoding SEQ ID NO: 282	284: CAGGTGCAATTGGTTCAGAGCGGCGCGGAAGTGAAAAAACCGGGCGAAAGCCTGAAAATTAGCTGCAAAG GTTCCGGATATTCCTTTACTAATTATATTTCTTGGGTGCGCCAGATGCCTGGGAAGGGTCTCGAGTGGATGGGC ATTATTGATCCTGAGGATTCTCATACTGAGTATTCTCCTTCTTTTCAGGGTCAGGTGACCATTAGCGCGGATAAA AGCATTAGCACCGCGTATCTTCAATGGAGCAGCCGCGAACGGCGATACGGCCATGTATTATTGCGCGCGTTA TGAGTATGGTGGTTTTGATATTGGGGCCAAGGCCAGGCC
Antibody 7876	_
CDRH1	SEQ ID NO: 17
CDRH2	SEQ ID NO: 49
CDRH3	SEQ ID NO: 19
CDRL1	SEQ ID NO: 20
CDRL2	SEQ ID NO: 21
CDRL3	SEQ ID NO: 50
ЛН	SEQ ID NO: 218
ΓL	285: DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCATWGSEDQVFGGGTKLTVL
Heavy chain	SEQ ID NO: 220
Light chain	286: DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCATWGSEDQVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD SSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)

TABLE 1-continued		
	Examples of C5 Antibodies of the Present Invention and C5 Proteins	
	Sequence Identifier (SEQ ID NO:) or comments/details	
PN encoding SEQ ID NO: 218	SEQ ID NO: 222	
PN encoding SEQ ID NO: 285	287: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATAATATTGGTAATTCTTATGTTATTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCGCTACTTGGGGTTCTGAGGATCAGGTGTTT GGCGGCGCACGAAGTTAACCGTTCTT	
PN encoding SEQ ID NO: 220	SEQ ID NO: 224	
PN encoding SEQ ID NO: 286	288: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATAATATTGGTAATTCTTATGTTACTTCGTGACCAGCAGAAACCCGGGCAGCGCCAGTTCTTGTGATTTATA AGGATAATGATCGTCCTCAGGCAACCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGAACCACCGGCA CATTAGCGGCACTCAGGCGGAAGACGAAGCGGAACGCCGAACGCCGCACCAGGGTTCTGAGGATCAGGTGTTT GGCGGCGGCACCAGAGGTAAACCGTTCTTGGCCAGCCGAAAGCCGCACCAGAGTGTGACGCTGTTTCCGGCGAGC AGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGGATCTTTATCCGGGAGCCGTGACAG TGGCCTGGAAGGCAGATAGCAACCCTGGTGAGGCGGAAGCCACCACCACCACCACCAACAAAGCAACA ACAAGTACGCGGCCAGCAGAAGCGGCGTGAGCGCGGAGGTGGAAGCCCCACCAACAAAGCAACA GGTCACGCGGCCAGCCGTGGAAAAACCGTTGCGCCGGACTGGAGA (X can be TGCAGC or GCC)	
Antibody 7878		
CDRH1	SEQ ID NO: 17	
CDRH2	SEQ ID NO: 49	
CDRH3	SEQ ID NO: 19	
CDRL1	SEQ ID NO: 20	
CDRL2	SEQ ID NO: 21	
CDRL3	SEQ ID NO: 101	
VH	SEQ ID NO: 218	
VL	289: DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCSTWDIEPTYVFGGGTKLTVL	
Heavy chain	SEQ ID NO: 220	
Light chain	290: DIELTQPPSVSVAPGQTARISCSGDNIGNSYVHWYQQKPGQAPVLVIYKDNDRPSGIPERFSGSNSGNTATLTIS GTQAEDEADYYCSTWDIEPTYVFGGGTKLTVLGQPKAAPSVTLFPPSSEELQANKATLVCLISDFYPGAVTVAWKAD SSPVKAGVETTTPSKQSNNKYAASSYLSLTPEQWKSHRSYSCQVTHEGSTVEKTVAPTEX (X can be CS or A)	
PN encoding SEQ ID NO: 218	SEQ ID NO: 222	
PN encoding SEQ ID NO: 289	291: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATAATATTGGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATGATCGTCCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAAGACGAAGCGGATTATTATTGCTCTACTTGGGATATTGAGCCTACTTATGTGT TTGGCGGCGCACGAAGTTAACCGTTCT	
PN encoding SEQ ID NO: 220	SEQ ID NO: 224	
PN encoding SEQ ID NO: 290	292: GATATCGAACTGACCCAGCCGCCTTCAGTGAGCGTTGCACCAGGTCAGACCGCGCGTATCTCGTGTAGCG GCGATAATATTGTAATTCTTATGTTCATTGGTACCAGCAGAAACCCGGGCAGGCGCCAGTTCTTGTGATTTATA AGGATAATGATCGTCCTCAGGCATCCCGGAACGCTTTAGCGGATCCAACAGCGGCAACACCGCGACCCTGAC CATTAGCGGCACTCAGGCGGAGAGCGAAGCGGATTATTATGCTCTACTTGGGATATTGAGCCTACTTATGTGT TTGGCGGCGCACGAAGTTAACCGTTCTTGGCCAGCCGAAAGCCGCACCGAGTGTGACGCTGTTTCCGCCGA GCAGCGAAGAATTGCAGGCGAACAAAGCGACCCTGGTGTGCCTGATTAGCGACTTTTATCCGGCAGCCGTGAC	

TABLE 1. ntinued

	TABLE 1-continued
	Examples of C5 Antibodies of the Present Invention and C5 Proteins
	Sequence Identifier (SEQ ID NO:) or comments/details
	AGTGGCCTGGAAGGCAGATAGCAGCCCCGTCAAGGCGGGAGTGGAGACCACCACACCTCCAAACAAA
Human (<i>Homo</i> <i>sapiens</i>) C5	296: MGLLGILCFLIFLGKTWGQEQTYVISAPKIFRVGASENIVIQVYGYTEAPDATISIKSYPDKKFSYSSGHVHLSSENK FQNSAILTIQPKQLPGGQNPVSYVYLEVVSKHPSKSKRMPITYDNGFLFIHTDKPVYTPDQSVKVRVYSLNDDLKPAK RETVLTFIDPEGSEVDMVEEIDHIGIISFPDFKIPSNPYGMWTIKAKYKEDFSTTGTAYFEVKEYVLPHFSVSIEPEYNF IGYKNFKNFEITIKARYFYNKVVTEADVYITFGIREDLKDDQKEMMQTAMQNTMLINGIAQVTPDSETAVKELSYYSLED LNNKYLYIAVTVIESTGGFSEEAEIPGIKYVLSPYKLNLVATPLFLKPGIPYPIKVQVKDSLDQLVGGVPVTLNAQTIDVN QETSDLDPSKSVTRVDDGVASFVLNLPSGVTVLEFNVKTDAPDLPEENQAREGYRAIAYSSLSQSYLYIDWTDNHKA LLVGEHLNIIVTFKSPYIDKITHYNYLILSKGKIIHFGTREKFSDASYQSINIPVTQNMVPSSRLLVYYIVTGEQTAELVSD SVWLNIEEKCGNQLQVHLSPDADAYSPGQTVSLNMATGMDSWVALAAVDSAVYGVQRGAKKPLERVPQFLEKSDL GCGAGGGLNNANVFHLAGLTFLTNANADDSQENDEPCKEILRPRRTLQKKIEEIAAKYKHSVVKKCCYDGACVNNDE TCEQRAARISLGPRCIKAFTECCVVASQLRANISHKDMQLGRLHMKTLLPVSKPEIRSYFPESWLWEVHLVPRKQL GPALPDSLTTWEIQGVGISNTGICVADTVKAKVFKDVFLEMNIPSSVVRGEQIQLKGTVYNYRTSGMQFCVKMSAVE GICTSESPVIDHQGTKSSKCVRQKVEGSSSHLVTFTVLPLEIGLHNINFSLETWFGKEILVKTLRVVPEGVKRESYSGV TLDPRGIYGTISRRKEFPYRIPLDLVPRTEIKRILSVKGLLVGEILSAVLSQEGINILTHLPKGSAEAELMSVVPVPYVFHY LETGNHWNIFHSDPLIEKQKLKKKKEGMLSIMSYRNADYSYSVWKGGSASTWLTAFALRVLGVNKVEGVMQNSIC NSLLWLVENYQLDNGSFKENSQYQPIKLQGTLPVEARENSLYLTAFTVIGIRKAFDICPLVKIDTALIKADNFLLENTLPA QSTFTLAISAYALSLGDKTHPQFRSIVSALKREALVKGNPPIYFKWKDNLQHKDSSVPNTGTARMVETTAYALLTSLNL KDINYVNPVIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLVKQLRLSMDIDVSYKHKGALHNYKMTDKNFLGRPVE VLLNDDLIVSTGFGSGLATVHVTTVVHKTSTSEEVCSFYLKIDTQDIESASHRGSONSDYKRIVACASYKPSREESSSG SSHAVMDISLPTGISANEEDLKALVEGVDQLFTDYQIKDGHVILQLNSIPSDFLCVRFRIFELFEVGFLSPAFFVYEY HRPDKQCTMFYSTSNIKIQKVCGGAACKCVEADCGQMQEELDLTISAETKQTACKPEIAYAYKNSITSITVENVFVKY KATLLDIYKTGEAVAEKDSEITFIKKVTCTNAELVKGRQYLIMGKEALQIKYNFSFRYIYPLDSLTWIEYWFDTTCSSC QAFLANLDEFAEDIFLNGC
Cynomolgus Macaque (Macaca fascicularis) C5	297: MGLLGILCFLIFLGKTWGQEQTYVISAPKIFRVGASENIVIQVYGYTEAFDATISIKSYPDKKFSYSSGHVHLSSENK FQNSAVLTIQPKQLPGGQNQVSYVYLEVVSKHFSKSKKIPITYDNGFLFIHTDKPVYTPDQSVKVRVYSLNDDLKPAK RETVLTFIDPEGSEIDMVEEIDHIGIISFPDFKIPSNPRYGMWTIQAKYKEDFSTTGTAFFEVKEYVLPHFSVSVEPESNF IGYKNFKNFEITIKARYFYNKVVTEADVYITFGIREDLKDDQKEMMQTAMQNTMLINGIAQVTFDSETAVKELSYYSLED LNNKYLYIAVTVIESTGGFSEEAEIPGIKYVLSPYKLNLVATPLFLKPGIPYSIKVQVKDALDQLVGGVPVTLNAQTIDVN QETSDLEPRKSVTRVDDGVASFVVNLPSGVTVLEFNVKTDAPDLPDENQAREGYRAIAYSSLSQSYLYIDWTDNHKA LLVGEYLNIIVTPKSPYIDKITHYNYLILSKGKIIHFGTREKLSDASYQSINIPVTQNMVPSSRLLVYYIVTGEQTAELVSDS WLNIEKCGNQLQVHLSPDADTYSPGGTVSLNMVTGMDSWALTAVDSAVYGVQRAKKPLERVPQFLEKSDLG CGAGGGLNNANVFHLAGLTFLTNANADDSQENDEPCKEIIRPRRMLQEKIELEIAAKYKHLVVKKCCYDGVRINHDETC EQRAARISVGPRCVKAFTECCVASQLRANNSHKDLQLGRLHMKTLLPVSKPEIRSYFPESWLWEVHLVPRKQLQ FALPDSVTTWEIQGVGISNSGICVADTIKAKVFKDVFLEMNIPYSVRGEQVQLKGTVYNYRTSGMQFCVKMSAVEGI CTSESPVIDHQGTKSSKCVRQKVEGSSNHLVTFTVLPLEIGLQNINFSLETSFGKEILVKSLRVVPEGVKRESYSGITLD PRGIYGTISRRKEFPYRIPLDLVPKTEIKRILSVKGLLVGEILSAVLSKEGINILTHLPKGSAEAELMSVVPVFYVPHYLET GNHWNIFHSDPLIEKKLKEGMVSIMSYRNADYSYSVKKGSASTWLTAFALRVLGQVHKYVEQNQNSICNS LLWLVENYQLDNGSFKENSQVQIKLGGTLPVEARENSLYLTAFTVIGIRKAFDICPLVKINTALIKADTFLLENTLPAQS TFTLAISAYALSLGDKTHPQFRSIVSALKREALVKGNPPIYRFWKDSLQHKDSSVPNTGTARMVETTAYALLTSLNLKD INYVNPIIKWLSEEQRYGGGFYSTQDTINAIEGLTEYSLLVKQLRLNMDIDVAYKHKGPLHNYKMTDKNFLGRPVEVLL NDDLVVSTGFGSGLATVHVTTVHKTSSEEVCSFYLKIDTQDIEASHTKGTGCNSDYKRIVACASYKPSKESSSGS HAVMDISLPTGINANEEDLKALVEGAVCKEADQLFDDYQIKDGHVILQLNSIPSSDFLCVRFRIFELFEVGFLSPATFTVVEYHR PDKQCTMFYSTSNIKIGKVCEGATCKCIEADCQMQKELDLTISAETRKQTACNPEIAYAKVIITSITTENVFVKXKAT LLDIYKTGEAVAEKDSEITFIKKVTCTNAELVKGRQYLIMGKEALQIKYNFTFRYIYPLDSLTWIEYWPRDTTCSSCQAF LANLDEFAEDIFLNGC

[0109] Other antibodies of the invention include those where the amino acids or nucleic acids encoding the amino acids have been mutated, yet have at least 60, 70, 80, 90 or 95 percent identity to the sequences described in Table 1. In some embodiments, it include mutant amino acid sequences wherein no more than 1, 2, 3, 4 or 5 amino acids have been mutated in the variable regions when compared with the variable regions depicted in the sequence described in Table 1, while retaining substantially the same therapeutic activity. [0110] Since each of these antibodies can bind to C5, the VH, VL, full length light chain, and full length heavy chain sequences (amino acid sequences and the nucleotide sequences encoding the amino acid sequences) can be "mixed and matched" to create other C5-binding antibodies of the invention. Such "mixed and matched" C5-binding antibodies can be tested using the binding assays known in the art (e.g., ELISAs, and other assays described in the Example section).

When these chains are mixed and matched, a VH sequence from a particular VH/VL pairing should be replaced with a structurally similar VH sequence. Likewise a full length heavy chain sequence from a particular full length heavy chain/full length light chain pairing should be replaced with a structurally similar full length heavy chain sequence. Likewise, a VL sequence from a particular VH/VL pairing should be replaced with a structurally similar VL sequence. Likewise a full length light chain sequence from a particular full length heavy chain/full length light chain pairing should be replaced with a structurally similar full length light chain sequence. Accordingly, in one aspect, the invention provides an isolated monoclonal antibody or antigen binding region thereof having: a heavy chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, and 281; and

a light chain variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, and 289; wherein the antibody specifically binds to C5 (e.g., human and/or cynomologus C5).

[0111] In another aspect, the invention provides (i) an isolated monoclonal antibody having: a full length heavy chain comprising an amino acid sequence that has been optimized for expression in the cell of a mammalian selected from the group consisting of SEQ ID NOS: 9, 25, 41, 53, 69, 81, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, and 282; and a full length light chain comprising an amino acid sequence that has been optimized for expression in the cell of a mammalian selected from the group consisting of SEQ ID NOs: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, and 290; or (ii) a functional protein comprising an antigen binding portion thereof.

[0112] In another aspect, the present invention provides C5-binding antibodies that comprise the heavy chain and light chain CDR1s, CDR2s and CDR3s as described in Table 1, or combinations thereof. The amino acid sequences of the VH CDR1s of the antibodies are shown in SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, and 235. The amino acid sequences of the VH CDR2s of the antibodies and are shown in SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236. The amino acid sequences of the VH CDR3s of the antibodies are shown in SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, and 237. The amino acid sequences of the VL CDR1s of the antibodies are shown in SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238. The amino acid sequences of the VL CDR2s of the antibodies are shown in SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239. The amino acid sequences of the VL CDR3s of the antibodies are shown in SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240. The CDR regions are delineated using the Kabat system (Kabat, E. A., et al., 1991 Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242).

[0113] Given that each of these antibodies can bind to C5 and that antigen-binding specificity is provided primarily by the CDR1, 2 and 3 regions, the VH CDR1, 2 and 3 sequences and VL CDR1, 2 and 3 sequences can be "mixed and matched" (i.e., CDRs from different antibodies can be mixed and match, although each antibody must contain a VH CDR1, 2 and 3 and a VL CDR1, 2 and 3 to create other C5-binding binding molecules of the invention. Such "mixed and matched" C5-binding antibodies can be tested using the binding assays known in the art and those described in the Examples (e.g., ELISAs). When VH CDR sequences are mixed and matched, the CDR1, CDR2 and/or CDR3 sequence from a particular VH sequence should be replaced with a structurally similar CDR sequence(s). Likewise, when VL CDR sequences are mixed and matched, the CDR1, CDR2 and/or CDR3 sequence from a particular VL sequence should be replaced with a structurally similar CDR sequence (s). It will be readily apparent to the ordinarily skilled artisan that novel VH and VL sequences can be created by substituting one or more VH and/or VL CDR region sequences with structurally similar sequences from the CDR sequences shown herein for monoclonal antibodies of the present invention.

[0114] Accordingly, the present invention provides an isolated monoclonal antibody or antigen binding region thereof comprising a heavy chain variable region CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, and 235; a heavy chain variable region CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236; a heavy chain variable region CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, and 237; a light chain variable region CDR1 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238; a light chain variable region CDR2 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239; and a light chain variable region CDR3 comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240; wherein the antibody specifically binds C5.

[0115] In a specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 1; a heavy chain variable region CDR2 of SEQ ID NO: 2; a heavy chain variable region CDR3 of SEQ ID NO: 3; a light chain variable region CDR2 of SEQ ID NO: 4; a light chain variable region CDR3 of SEQ ID NO: 6. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR3 of SEQ ID NO: 6. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR2 of SEQ ID NO: 17; a heavy chain variable region CDR3 of SEQ ID NO: 18; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR1 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 22.

[0116] In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 33; a heavy chain variable region CDR2 of SEQ ID NO: 34; a heavy chain variable region CDR3 of SEQ ID NO: 35; a light chain variable region CDR1 of SEQ ID NO: 36; a light chain variable region CDR2 of SEQ ID NO: 36; a light chain variable region CDR3 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 38. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 17; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 50.

[0117] In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR3 of SEQ ID NO: 62; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 66. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR3 of SEQ ID NO: 61; a heavy chain variable region CDR3 of SEQ ID NO: 61; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light

CDR1 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 78.

[0118] In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 61; a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR3 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 64; a light chain variable region CDR3 of SEQ ID NO: 64; a light chain variable region CDR3 of SEQ ID NO: 64; a light chain variable region CDR3 of SEQ ID NO: 64; a light chain variable region CDR3 of SEQ ID NO: 64; a light chain variable region CDR3 of SEQ ID NO: 64; a light chain variable region CDR3 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 89.

[0119] In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR3 of SEQ ID NO: 95; a heavy chain variable region CDR1 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 17; a heavy chain variable region CDR2 of SEQ ID NO: 19; a light chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR1 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 101.

[0120] In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 17; a heavy chain variable region CDR3 of SEQ ID NO: 107; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR1 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 22. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 17; a heavy chain variable region CDR1 of SEQ ID NO: 107; a heavy chain variable region CDR3 of SEQ ID NO: 107; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR1 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 101.

[0121] In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 17; a heavy chain variable region CDR3 of SEQ ID NO: 113; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR1 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 22. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 17; a heavy chain variable region CDR2 of SEQ ID NO: 113; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR1 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 19; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 20; a light chain variable region CDR3 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 101.

[0122] In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 1; a heavy chain variable region CDR2 of SEQ ID NO: 119; a heavy chain variable region CDR3 of SEQ ID NO: 3; a light chain variable region CDR1 of SEQ ID NO: 4; a light chain variable region CDR2 of SEQ ID NO: 5; and a light chain variable region CDR3 of SEQ ID NO: 120. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 131; a heavy chain variable region CDR2 of SEQ ID NO: 132; a heavy chain variable region CDR3 of SEQ ID NO: 133; a light chain variable region CDR3 of SEQ ID NO: 133; a light chain variable region CDR3 of SEQ ID NO: 134; a light chain variable region CDR2 of SEQ ID NO: 135; and a light chain variable region CDR3 of SEQ ID NO: 135; and a light chain variable region CDR3 of SEQ ID NO: 136.

[0123] In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 145; a heavy chain variable region CDR2 of SEQ ID NO: 146; a heavy chain variable region CDR3 of SEQ ID NO: 147; a light chain variable region CDR1 of SEQ ID NO: 148; a light chain variable region CDR3 of SEQ ID NO: 149; and a light chain variable region CDR3 of SEQ ID NO: 150. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR2 of SEQ ID NO: 150. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR3 of SEQ ID NO: 159; a heavy chain variable region CDR3 of SEQ ID NO: 160; a heavy chain variable region CDR3 of SEQ ID NO: 161; a light chain variable region CDR1 of SEQ ID NO: 162; a light chain variable region CDR2 of SEQ ID NO: 163; and a light chain variable region CDR3 of SEQ ID NO: 164.

[0124] In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 173; a heavy chain variable region CDR3 of SEQ ID NO: 174; a heavy chain variable region CDR3 of SEQ ID NO: 175; a light chain variable region CDR2 of SEQ ID NO: 176; a light chain variable region CDR3 of SEQ ID NO: 177; and a light chain variable region CDR3 of SEQ ID NO: 178. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 178. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR3 of SEQ ID NO: 195; a heavy chain variable region CDR3 of SEQ ID NO: 196; a heavy chain variable region CDR3 of SEQ ID NO: 197; a light chain variable region CDR1 of SEQ ID NO: 197; a light chain variable region CDR2 of SEQ ID NO: 198; a light chain variable region CDR3 of SEQ ID NO: 199; and a light chain variable region CDR3 of SEQ ID NO: 200.

[0125] In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR2 of SEQ ID NO: 77; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 209. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 17; a heavy chain variable region CDR2 of SEQ ID NO: 17; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR3 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 22.

[0126] In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 33; a heavy chain variable region CDR2 of SEQ ID NO: 226; a heavy chain variable

region CDR3 of SEQ ID NO: 35; a light chain variable region CDR1 of SEQ ID NO: 36; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 38. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 235; a heavy chain variable region CDR2 of SEQ ID NO: 236; a heavy chain variable region CDR3 of SEQ ID NO: 237; a light chain variable region CDR1 of SEQ ID NO: 237; a light chain variable region CDR1 of SEQ ID NO: 238; a light chain variable region CDR1 of SEQ ID NO: 239; and a light chain variable region CDR3 of SEQ ID NO: 239; and a light chain variable region CDR3 of SEQ ID NO: 240.

[0127] In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 1; a heavy chain variable region CDR2 of SEQ ID NO: 119; a heavy chain variable region CDR3 of SEQ ID NO: 3; a light chain variable region CDR1 of SEQ ID NO: 4; a light chain variable region CDR2 of SEQ ID NO: 5; and a light chain variable region CDR3 of SEQ ID NO: 6. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 1; a heavy chain variable region CDR3 of SEQ ID NO: 2; a heavy chain variable region CDR3 of SEQ ID NO: 3; a light chain variable region CDR3 of SEQ ID NO: 2; a heavy chain variable region CDR3 of SEQ ID NO: 4; a light chain variable region CDR1 of SEQ ID NO: 5; and a light chain variable region CDR3 of SEQ ID NO: 4; a light chain variable region CDR3 of SEQ ID NO: 4; a light chain variable region CDR3 of SEQ ID NO: 4; a light chain variable region CDR3 of SEQ ID NO: 4; a light chain variable region CDR3 of SEQ ID NO: 4; a light chain variable region CDR3 of SEQ ID NO: 4; a light chain variable region CDR3 of SEQ ID NO: 4; a light chain variable region CDR3 of SEQ ID NO: 5; and a light chain variable region CDR3 of SEQ ID NO: 120.

[0128] In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR3 of SEQ ID NO: 62; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR3 of SEQ ID NO: 64; a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 60; a heavy chain variable region CDR3 of SEQ ID NO: 60; a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR3 of SEQ ID NO: 61; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR3 of SEQ ID NO: 64; a light chain variable region CDR3 of SEQ ID NO: 65; and a lig

[0129] In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 66. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR3 of SEQ ID NO: 66. In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 63; a light chain variable region CDR2 of SEQ ID NO: 63; a light chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR2 of SEQ ID NO: 63; a light chain variable region CDR2 of SEQ ID NO: 63; a light chain variable region CDR2 of SEQ ID NO: 64; a light chain variable region CDR2 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 78.

[0130] In another specific embodiment, an antibody that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 61; a heavy chain variable region CDR2 of SEQ ID NO: 77; a heavy chain variable region CDR3 of SEQ ID NO: 63; a light chain variable region CDR1 of SEQ ID NO: 64; a light chain variable region CDR3 of SEQ ID NO: 65; and a light chain variable region CDR3 of SEQ ID NO: 89. In another specific embodiment, an antibody

that specifically binds to C5 comprising a heavy chain variable region CDR1 of SEQ ID NO: 17; a heavy chain variable region CDR2 of SEQ ID NO: 107; a heavy chain variable region CDR3 of SEQ ID NO: 19; a light chain variable region CDR1 of SEQ ID NO: 20; a light chain variable region CDR2 of SEQ ID NO: 21; and a light chain variable region CDR3 of SEQ ID NO: 22.

[0131] In certain embodiments, an antibody that specifically binds to C5 is an antibody that is described in Table 1. [0132] As used herein, a human antibody comprises heavy or light chain variable regions or full length heavy or light chains that are "the product of" or "derived from" a particular germline sequence if the variable regions or full length chains of the antibody are obtained from a system that uses human germline immunoglobulin genes. Such systems include immunizing a transgenic mouse carrying human immunoglobulin genes with the antigen of interest or screening a human immunoglobulin gene library displayed on phage with the antigen of interest. A human antibody that is "the product of" or "derived from" a human germline immunoglobulin sequence can be identified as such by comparing the amino acid sequence of the human antibody to the amino acid sequences of human germline immunoglobulins and selecting the human germline immunoglobulin sequence that is closest in sequence (i.e., greatest % identity) to the sequence of the human antibody. A human antibody that is "the product of" or "derived from" a particular human germline immunoglobulin sequence may contain amino acid differences as compared to the germline sequence, due to, for example, naturally occurring somatic mutations or intentional introduction of site-directed mutations. However, in the VH or VL framework regions, a selected human antibody typically is at least 90% identical in amino acids sequence to an amino acid sequence encoded by a human germline immunoglobulin gene and contains amino acid residues that identify the human antibody as being human when compared to the germline immunoglobulin amino acid sequences of other species (e.g., murine germline sequences). In certain cases, a human antibody may be at least 60%, 70%, 80%, 90%, or at least 95%, or even at least 96%, 97%, 98%, or 99% identical in amino acid sequence to the amino acid sequence encoded by the germline immunoglobulin gene. Typically, a recombinant human antibody will display no more than 10 amino acid differences from the amino acid sequence encoded by the human germline immunoglobulin gene in the VH or VL framework regions. In certain cases, the human antibody may display no more than 5, or even no more than 4, 3, 2, or 1 amino acid difference from the amino acid sequence encoded by the germline immunoglobulin gene.

Homologous Antibodies

[0133] In yet another embodiment, the present invention provides an antibody or an antigen-binding fragment thereof comprising amino acid sequences that are homologous to the sequences described in Table 1, and said antibody binds to a C5 protein (e.g., human and/or cynomologus C5), and retains the desired functional properties of those antibodies described in Table 1.

[0134] For example, the invention provides an isolated monoclonal antibody (or a functional antigen binding fragment thereof) comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region comprises an amino acid sequence that is at least 80%, at least 90%, or at least 95% identical to an amino acid

sequence selected from the group consisting of SEQ ID NOs: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, or 281; the light chain variable region comprises an amino acid sequence that is at least 80%, at least 90%, or at least 95% identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, or 289; the antibody specifically binds to C5 (e.g., human and/or cynomologus C5), and the antibody can inhibit red blood cell lysis in a hemolytic assay. In a specific example, such antibodies have an IC₅₀ value in a hemolytic assay of 20-200 pM when using human C5-depleted serum that is reconstituted with 100 pM human C5.

[0135] In other embodiments, the VH and/or VL amino acid sequences may be 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to the sequences set forth in Table 1. In other embodiments, the VH and/or VL amino acid sequences may be identical except an amino acid substitution in no more than 1, 2, 3, 4 or 5 amino acid position. An antibody having VH and VL regions having high (i.e., 80% or greater) identity to the VH and VL regions of those described in Table 1 can be obtained by mutagenesis (e.g., site-directed or PCR-mediated mutagenesis) of nucleic acid molecules encoding SEQ ID NOs: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, or 281; and 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, or 289 respectively, followed by testing of the encoded altered antibody for retained function using the functional assays described herein.

[0136] In other embodiments, the full length heavy chain and/or full length light chain amino acid sequences may be 50% 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to the sequences set forth in Table 1. An antibody having a full length heavy chain and full length light chain having high (i.e., 80% or greater) identity to the full length heavy chains of any of SEQ ID NOs: 9, 25, 41, 53, 69, 81, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, and 282 and full length light chains of any of SEQ ID NOs 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, and 290 respectively, can be obtained by mutagenesis (e.g., site-directed or PCR-mediated mutagenesis) of nucleic acid molecules encoding such polypeptides respectively, followed by testing of the encoded altered antibody for retained function using the functional assays described herein.

[0137] In other embodiments, the full length heavy chain and/or full length light chain nucleotide sequences may be 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to the sequences set forth above.

[0138] In other embodiments, the variable regions of heavy chain and/or light chain nucleotide sequences may be 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98% or 99% identical to the sequences set forth above

[0139] As used herein, the percent identity between the two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity equals number of identical positions/total number of positions×100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination

of percent identity between two sequences can be accomplished using a mathematical algorithm, as described in the non-limiting examples below.

[0140] Additionally or alternatively, the protein sequences of the present invention can further be used as a "query sequence" to perform a search against public databases to, for example, identify related sequences. For example, such searches can be performed using the BLAST program (version 2.0) of Altschul, et al., 1990 J. Mol. Biol. 215:403-10. Antibodies with Conservative Modifications

[0141] In certain embodiments, an antibody of the invention has a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein one or more of these CDR sequences have specified amino acid sequences based on the antibodies described herein or conservative modifications thereof, and wherein the antibodies retain the desired functional properties of the C5-binding antibodies of the invention. Accordingly, the invention provides an isolated monoclonal antibody, or a functional antigen binding fragment thereof, consisting of a heavy chain variable region comprising CDR1, CDR2, and CDR3 sequences and a light chain variable region comprising CDR1, CDR2, and CDR3 sequences, wherein: the heavy chain variable region CDR1 amino acid sequences are selected from the group consisting of SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, and 235, and conservative modifications thereof; the heavy chain variable region CDR2 amino acid sequences are selected from the group consisting of SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236, and conservative modifications thereof; the heavy chain variable region CDR3 amino acid sequences are selected from the group consisting of SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, and 237, and conservative modifications thereof; the light chain variable regions CDR1 amino acid sequences are selected from the group consisting of SEO ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238, and conservative modifications thereof; the light chain variable regions CDR2 amino acid sequences are selected from the group consisting of SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239, and conservative modifications thereof; the light chain variable regions of CDR3 amino acid sequences are selected from the group consisting of SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240, and conservative modifications thereof; the antibody or the antigen-binding fragment thereof specifically binds to C5, and inhibits red blood cell lysis in a hemolytic assay as described herein.

[0142] In other embodiments, an antibody of the invention optimized for expression in a mammalian cell has a full length heavy chain sequence and a full length light chain sequence, wherein one or more of these sequences have specified amino acid sequences based on the antibodies described herein or conservative modifications thereof, and wherein the antibodies retain the desired functional properties of the C5-binding antibodies of the invention. Accordingly, the invention provides an isolated monoclonal antibody optimized for expression in a mammalian cell consisting of a full length heavy chain and a full length light chain wherein: the full length heavy chain has amino acid sequences selected from the group of SEQ ID NOs: 9, 25, 41, 53, 69, 81, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, and 282, and conservative modifications thereof; and the full length light chain has amino acid

sequences selected from the group of SEQ ID NOs: 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, and 290, and conservative modifications thereof; the antibody specifically binds to C5 (e.g., human and/or cynomologus C5); and the antibody inhibits red blood cell lysis in a hemolytic assay as described herein. In a specific embodiment, such antibodies have an IC_{50} value in a hemolytic assay of 20-200 pM when using human C5-depleted serum that is reconstituted with 100 pM human C5.

Antibodies that Bind to the Same Epitope

[0143] The present invention provides antibodies that bind to the same epitope as do the C5-binding antibodies described in Table 1. Additional antibodies can therefore be identified based on their ability to cross-compete (e.g., to competitively inhibit the binding of, in a statistically significant manner) with other antibodies of the invention in C5 binding assays. The ability of a test antibody to inhibit the binding of antibodies of the present invention to a C5 protein (e.g., human and/or cynomolgus C5) demonstrates that the test antibody can compete with that antibody for binding to C5; such an antibody may, according to non-limiting theory, bind to the same or a related (e.g., a structurally similar or spatially proximal) epitope on the C5 protein as the antibody with which it competes. In a certain embodiment, the antibody that binds to the same epitope on C5 as the antibodies of the present invention is a human monoclonal antibody. Such human monoclonal antibodies can be prepared and isolated as described herein.

Engineered and Modified Antibodies

[0144] An antibody of the invention further can be prepared using an antibody having one or more of the VH and/or VL sequences shown herein as starting material to engineer a modified antibody, which modified antibody may have altered properties from the starting antibody. An antibody can be engineered by modifying one or more residues within one or both variable regions (i.e., VH and/or VL), for example within one or more CDR regions and/or within one or more framework regions. Additionally or alternatively, an antibody can be engineered by modifying residues within the constant region(s), for example to alter the effector function(s) of the antibody.

[0145] One type of variable region engineering that can be performed is CDR grafting. Antibodies interact with target antigens predominantly through amino acid residues that are located in the six heavy and light chain complementarity determining regions (CDRs). For this reason, the amino acid sequences within CDRs are more diverse between individual antibodies than sequences outside of CDRs. Because CDR sequences are responsible for most antibody-antigen interactions, it is possible to express recombinant antibodies that mimic the properties of specific naturally occurring antibodies by constructing expression vectors that include CDR sequences from the specific naturally occurring antibody grafted onto framework sequences from a different antibody with different properties (see, e.g., Riechmann, L. et al., 1998 Nature 332:323-327; Jones, P. et al., 1986 Nature 321:522-525; Queen, C. et al., 1989 Proc. Natl. Acad., U.S.A. 86:10029-10033; U.S. Pat. No. 5,225,539 to Winter, and U.S. Pat. Nos. 5,530,101; 5,585,089; 5,693,762 and 6,180,370 to Queen et al.)

[0146] Accordingly, another embodiment of the invention pertains to an isolated monoclonal antibody, or an antigen

binding fragment thereof, comprising a heavy chain variable region comprising CDR1 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, and 235; CDR2 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236; CDR3 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, and 237, respectively; and a light chain variable region having CDR1 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238; CDR2 sequences having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239; and CDR3 sequences consisting of an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240, respectively. Thus, such antibodies contain the VH and VL CDR sequences of monoclonal antibodies, yet may contain different framework sequences from these antibodies.

[0147] Such framework sequences can be obtained from public DNA databases or published references that include germline antibody gene sequences. For example, germline DNA sequences for human heavy and light chain variable region genes can be found in the "VBase" human germline sequence database (available on the Internet at www.mrc-cpe. cam.ac.uk/vbase), as well as in Kabat, E. A., et al., 1991 Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Tomlinson, I. M., et al., 1992 J. fol. Biol. 227:776-798; and Cox, J. P. L. et al., 1994 Eur. J Immunol. 24:827-836; the contents of each of which are expressly incorporated herein by reference.

[0148] An example of framework sequences for use in the antibodies of the invention are those that are structurally similar to the framework sequences used by selected antibodies of the invention, e.g., consensus sequences and/or framework sequences used by monoclonal antibodies of the invention. The VH CDR1, 2 and 3 sequences, and the VL CDR1, 2 and 3 sequences, can be grafted onto framework regions that have the identical sequence as that found in the germline immunoglobulin gene from which the framework sequence derive, or the CDR sequences can be grafted onto framework regions that contain one or more mutations as compared to the germline sequences. For example, it has been found that in certain instances it is beneficial to mutate residues within the framework regions to maintain or enhance the antigen binding ability of the antibody (see e.g., U.S. Pat. Nos. 5,530,101; 5,585,089; 5,693,762 and 6,180,370 to Queen et al).

[0149] Another type of variable region modification is to mutate amino acid residues within the VH and/or VL CDR1, CDR2 and/or CDR3 regions to thereby improve one or more binding properties (e.g., affinity) of the antibody of interest, known as "affinity maturation." Site-directed mutagenesis or PCR-mediated mutagenesis can be performed to introduce the mutation(s) and the effect on antibody binding, or other functional property of interest, can be evaluated in in vitro or in vivo assays as described herein and provided in the Examples. Conservative modifications (as discussed above) can be introduced. The mutations may be amino acid substi-

tutions, additions or deletions. Moreover, typically no more than one, two, three, four or five residues within a CDR region are altered.

[0150] Accordingly, in another embodiment, the invention provides isolated C5-binding monoclonal antibodies, or an antigen binding fragment thereof, consisting of a heavy chain variable region having: a VH CDR1 region consisting of an amino acid sequence selected from the group having SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, and 235 or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, and 235; a VH CDR2 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236; a VH CDR3 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, and 237, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, and 237; a VL CDR1 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238; a VL CDR2 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239; and a VL CDR3 region having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240, or an amino acid sequence having one, two, three, four or five amino acid substitutions, deletions or additions as compared to SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240.

Grafting Antigen-Binding Domains into Alternative Frameworks or Scaffolds

[0151] A wide variety of antibody/immunoglobulin frameworks or scaffolds can be employed so long as the resulting polypeptide includes at least one binding region which specifically binds to C5. Such frameworks or scaffolds include the 5 main idiotypes of human immunoglobulins, or fragments thereof, and include immunoglobulins of other animal species, preferably having humanized aspects. Single heavychain antibodies such as those identified in camelids are of particular interest in this regard. Novel frameworks, scaffolds and fragments continue to be discovered and developed by those skilled in the art.

[0152] In one aspect, the invention pertains to generating non-immunoglobulin based antibodies using non-immunoglobulin scaffolds onto which CDRs of the invention can be grafted. Known or future non-immunoglobulin frameworks and scaffolds may be employed, as long as they comprise a binding region specific for the target C5 protein (e.g., human and/or cynomolgus C5). Known non-immunoglobulin frameworks or scaffolds include, but are not limited to, fibronectin

(Compound Therapeutics, Inc., Waltham, Mass.), ankyrin (Molecular Partners AG, Zurich, Switzerland), domain antibodies (Domantis, Ltd., Cambridge, Mass., and Ablynx nv, Zwijnaarde, Belgium), lipocalin (Pieris Proteolab AG, Freising, Germany), small modular immuno-pharmaceuticals (Trubion Pharmaceuticals Inc., Seattle, Wash.), maxybodies (Avidia, Inc., Mountain View, Calif.), Protein A (Affibody AG, Sweden), and affilin (gamma-crystallin or ubiquitin) (Scil Proteins GmbH, Halle, Germany).

[0153] The fibronectin scaffolds are based on fibronectin type III domain (e.g., the tenth module of the fibronectin type III (10 Fn3 domain)). The fibronectin type III domain has 7 or 8 beta strands which are distributed between two beta sheets, which themselves pack against each other to form the core of the protein, and further containing loops (analogous to CDRs) which connect the beta strands to each other and are solvent exposed. There are at least three such loops at each edge of the beta sheet sandwich, where the edge is the boundary of the protein perpendicular to the direction of the beta strands (see U.S. Pat. No. 6,818,418). These fibronectin-based scaffolds are not an immunoglobulin, although the overall fold is closely related to that of the smallest functional antibody fragment, the variable region of the heavy chain, which comprises the entire antigen recognition unit in camel and llama IgG. Because of this structure, the non-immunoglobulin antibody mimics antigen binding properties that are similar in nature and affinity to those of antibodies. These scaffolds can be used in a loop randomization and shuffling strategy in vitro that is similar to the process of affinity maturation of antibodies in vivo. These fibronectin-based molecules can be used as scaffolds where the loop regions of the molecule can be replaced with CDRs of the invention using standard cloning techniques.

[0154] The ankyrin technology is based on using proteins with ankyrin derived repeat modules as scaffolds for bearing variable regions which can be used for binding to different targets. The ankyrin repeat module is a 33 amino acid polypeptide consisting of two anti-parallel α -helices and a β -turn. Binding of the variable regions is mostly optimized by using ribosome display.

[0155] Avimers are derived from natural A-domain containing protein such as LRP-1. These domains are used by nature for protein-protein interactions and in human over 250 proteins are structurally based on A-domains. Avimers consist of a number of different "A-domain" monomers (2-10) linked via amino acid linkers. Avimers can be created that can bind to the target antigen using the methodology described in, for example, U.S. Patent Application Publication Nos. 20040175756; 20050053973; 20050048512; and 20060008844.

[0156] Affibody affinity ligands are small, simple proteins composed of a three-helix bundle based on the scaffold of one of the IgG-binding domains of Protein A. Protein A is a surface protein from the bacterium *Staphylococcus aureus*. This scaffold domain consists of 58 amino acids, 13 of which are randomized to generate affibody libraries with a large number of ligand variants (See e.g., U.S. Pat. No. 5,831,012). Affibody molecules mimic antibodies, they have a molecular weight of 6 kDa, compared to the molecular weight of antibodies, which is 150 kDa. In spite of its small size, the binding site of affibody molecules is similar to that of an antibody.

[0157] Anticalins are products developed by the company Pieris ProteoLab AG. They are derived from lipocalins, a widespread group of small and robust proteins that are usually involved in the physiological transport or storage of chemically sensitive or insoluble compounds. Several natural lipocalins occur in human tissues or body liquids. The protein architecture is reminiscent of immunoglobulins, with hypervariable loops on top of a rigid framework. However, in contrast with antibodies or their recombinant fragments, lipocalins are composed of a single polypeptide chain with 160 to 180 amino acid residues, being just marginally bigger than a single immunoglobulin domain. The set of four loops, which makes up the binding pocket, shows pronounced structural plasticity and tolerates a variety of side chains. The binding site can thus be reshaped in a proprietary process in order to recognize prescribed target molecules of different shape with high affinity and specificity. One protein of lipocalin family, the bilin-binding protein (BBP) of Pieris Brassicae has been used to develop anticalins by mutagenizing the set of four loops. One example of a patent application describing anticalins is in PCT Publication No. WO 199916873.

[0158] Affilin molecules are small non-immunoglobulin proteins which are designed for specific affinities towards proteins and small molecules. New affilin molecules can be very quickly selected from two libraries, each of which is based on a different human derived scaffold protein. Affilin molecules do not show any structural homology to immunoglobulin proteins. Currently, two affilin scaffolds are employed, one of which is gamma crystalline, a human structural eye lens protein and the other is "ubiquitin" superfamily proteins. Both human scaffolds are very small, show high temperature stability and are almost resistant to pH changes and denaturing agents. This high stability is mainly due to the expanded beta sheet structure of the proteins. Examples of gamma crystalline derived proteins are described in WO200104144 and examples of "ubiquitin-like" proteins are described in WO2004106368.

[0159] Protein epitope mimetics (PEM) are medium-sized, cyclic, peptide-like molecules (MW 1-2 kDa) mimicking beta-hairpin secondary structures of proteins, the major secondary structure involved in protein-protein interactions.

[0160] In some embodiments, the Fabs are converted to silent IgG1 format by changing the Fc region. For example, antibodies 6525-7910 in Table 1 can be converted to silent IgG1 formate by substituting the "X" in the amino acid sequences for the heavy chain with: CDKTHTCPPCPA-PEAAGGPSVFLFPPKPKDTLMISRTPE-

VTCWVDVSHEDPEVKFNWYVD GVEVHNAKTKPRE-EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSN

KALPAPIEKTISKAKG QPREPQVYTLPPSREEMTKN-QVSLTCLVKGFYPSDIAVEWESNGQPEN-

NYKTTPPVLDSD GSFFLYSKLTVDKSRWQQGNVF-SCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 293) and substituting the "X" in the amino acid sequence for the light chain with: CS if the light chain is lambda, or C if the light chain is kappa. As used herein, a "silent IgG1" is an IgG1 Fc sequence in which the amino acid sequence has been altered to reduce Fc-mediated effector functions (for example ADCC and/or CDC). Such an antibody will typically have reduced binding to Fc receptors and/or C1q.

[0161] In some other embodiments, the Fabs are converted to IgG2 format. For example, antibodies 6525-7910 in Table 1 can be converted to IgG2 format by substituting the constant sequence ASTKGPSVFPLAPSSKSTSGGTAALG-CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG

LYSLSSVVTVPSSSLGTQTYICNVNH-KPSNTKVDKKVEPKSX (SEQ ID NO: 294) with the constant sequence for the heavy chain of IgG2: ASTKGPSVFPLAPCSRSTSESTAALG-CLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSG LYSLSSVVTVPSSNFGTQTYTCNVDH-KPSNTKVDKTVERKCCVECPPCPAPPVAGPSVFLF PPKPKDTLMISRTPEVTCVVVDVSHED-PEVQFNWYVDGVEVHNAKTKPREEQFNSTFRVV SVLTVVHQDWLNGKEYKCKVSNKGLPA-PIEKTISKTKGQPREPQVYTLPPSREEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPEN-NYKTTPPMLDSDGSFFLYSKLTVDKSRWQQGNVFS CSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 295) and substituting the "X" in the amino acid sequence for the light chain with CS if the light chain is lambda, or C if the light chain is kappa.

Human or Humanized Antibodies

[0162] The present invention provides fully human antibodies that specifically bind to a C5 protein (e.g., human and/or cynomolgus C5). Compared to the chimeric or humanized antibodies, the human C5-binding antibodies of the invention have further reduced antigenicity when administered to human subjects.

[0163] The human C5-binding antibodies can be generated using methods that are known in the art. For example, the humaneering technology used to converting non-human antibodies into engineered human antibodies. U.S. Patent Publication No. 20050008625 describes an in vivo method for replacing a nonhuman antibody variable region with a human variable region in an antibody while maintaining the same or providing better binding characteristics relative to that of the nonhuman antibody. The method relies on epitope guided replacement of variable regions of a non-human reference antibody with a fully human antibody. The resulting human antibody is generally unrelated structurally to the reference nonhuman antibody, but binds to the same epitope on the same antigen as the reference antibody. Briefly, the serial epitope-guided complementarity replacement approach is enabled by setting up a competition in cells between a "competitor" and a library of diverse hybrids of the reference antibody ("test antibodies") for binding to limiting amounts of antigen in the presence of a reporter system which responds to the binding of test antibody to antigen. The competitor can be the reference antibody or derivative thereof such as a single-chain Fv fragment. The competitor can also be a natural or artificial ligand of the antigen which binds to the same epitope as the reference antibody. The only requirements of the competitor are that it binds to the same epitope as the reference antibody, and that it competes with the reference antibody for antigen binding. The test antibodies have one antigen-binding V-region in common from the nonhuman reference antibody, and the other V-region selected at random from a diverse source such as a repertoire library of human antibodies. The common V-region from the reference antibody serves as a guide, positioning the test antibodies on the same epitope on the antigen, and in the same orientation, so that selection is biased toward the highest antigen-binding fidelity to the reference antibody.

[0164] Many types of reporter system can be used to detect desired interactions between test antibodies and antigen. For example, complementing reporter fragments may be linked to antigen and test antibody, respectively, so that reporter activation by fragment complementation only occurs when the test antibody binds to the antigen. When the test antibody- and

antigen-reporter fragment fusions are co-expressed with a competitor, reporter activation becomes dependent on the ability of the test antibody to compete with the competitor, which is proportional to the affinity of the test antibody for the antigen. Other reporter systems that can be used include the reactivator of an auto-inhibited reporter reactivation system (RAIR) as disclosed in U.S. patent application Ser. No. 10/208,730 (Publication No. 20030198971), or competitive activation system disclosed in U.S. patent application Ser. No. 10/076,845 (Publication No. 20030157579).

[0165] With the serial epitope-guided complementarity replacement system, selection is made to identify cells expresses a single test antibody along with the competitor, antigen, and reporter components. In these cells, each test antibody competes one-on-one with the competitor for binding to a limiting amount of antigen. Activity of the reporter is proportional to the amount of antigen bound to the test antibody, which in turn is proportional to the affinity of the test antibody for the antigen and the stability of the test antibody. Test antibodies are initially selected on the basis of their activity relative to that of the reference antibody when expressed as the test antibody. The result of the first round of selection is a set of "hybrid" antibodies, each of which is comprised of the same non-human V-region from the reference antibody and a human V-region from the library, and each of which binds to the same epitope on the antigen as the reference antibody. One of more of the hybrid antibodies selected in the first round will have an affinity for the antigen comparable to or higher than that of the reference antibody.

[0166] In the second V-region replacement step, the human V-regions selected in the first step are used as guide for the selection of human replacements for the remaining non-human reference antibody V-region with a diverse library of cognate human V-regions. The hybrid antibodies selected in the first round may also be used as competitors for the second round of selection. The result of the second round of selection is a set of fully human antibodies which differ structurally from the reference antibody, but which compete with the reference antibody for binding to the same antigen. Some of the selected human antibodies bind to the same epitope on the same antigen as the reference antibody. Among these selected human antibodies, one or more binds to the same epitope with an affinity which is comparable to or higher than that of the reference antibody.

[0167] Using one of the mouse or chimeric C5-binding antibodies described above as the reference antibody, this method can be readily employed to generate human antibodies that bind to human C5 with the same binding specificity and the same or better binding affinity. In addition, such human C5-binding antibodies can also be commercially obtained from companies which customarily produce human antibodies, e.g., KaloBios, Inc. (Mountain View, Calif.).

Camelid Antibodies

[0168] Antibody proteins obtained from members of the camel and dromedary (*Camelus bactrianus* and *Calelus dromaderius*) family including new world members such as llama species (*Lama paccos, Lama glama* and *Lama vicugna*) have been characterized with respect to size, structural complexity and antigenicity for human subjects. Certain IgG antibodies from this family of mammals as found in nature lack light chains, and are thus structurally distinct from the typical four chain quaternary structure having two heavy and two

light chains, for antibodies from other animals. See PCT/ EP93/02214 (WO 94/04678 published 3 Mar. 1994).

[0169] A region of the camelid antibody which is the small single variable domain identified as VHH can be obtained by genetic engineering to yield a small protein having high affinity for a target, resulting in a low molecular weight antibodyderived protein known as a "camelid nanobody". See U.S. Pat. No. 5,759,808 issued Jun. 2, 1998; see also Stijlemans, B. et al., 2004 J Biol Chem 279: 1256-1261; Dumoulin, M. et al., 2003 Nature 424: 783-788; Pleschberger, M. et al. 2003 Bioconjugate Chem 14: 440-448; Cortez-Retamozo, V. et al. 2002 Int J Cancer 89: 456-62; and Lauwereys, M. et al. 1998 EMBO J 17: 3512-3520. Engineered libraries of camelid antibodies and antibody fragments are commercially available, for example, from Ablynx, Ghent, Belgium. As with other antibodies of non-human origin, an amino acid sequence of a camelid antibody can be altered recombinantly to obtain a sequence that more closely resembles a human sequence, i.e., the nanobody can be "humanized". Thus the natural low antigenicity of camelid antibodies to humans can be further reduced.

[0170] The camelid nanobody has a molecular weight approximately one-tenth that of a human IgG molecule, and the protein has a physical diameter of only a few nanometers. One consequence of the small size is the ability of camelid nanobodies to bind to antigenic sites that are functionally invisible to larger antibody proteins, i.e., camelid nanobodies are useful as reagents detect antigens that are otherwise cryptic using classical immunological techniques, and as possible therapeutic agents. Thus yet another consequence of small size is that a camelid nanobody can inhibit as a result of binding to a specific site in a groove or narrow cleft of a target protein, and hence can serve in a capacity that more closely resembles the function of a classical low molecular weight drug than that of a classical antibody.

[0171] The low molecular weight and compact size further result in camelid nanobodies being extremely thermostable, stable to extreme pH and to proteolytic digestion, and poorly antigenic. Another consequence is that camelid nanobodies readily move from the circulatory system into tissues, and even cross the blood-brain barrier and can treat disorders that affect nervous tissue. Nanobodies can further facilitated drug transport across the blood brain barrier. See U.S. patent application 20040161738 published Aug. 19, 2004. These features combined with the low antigenicity to humans indicate great therapeutic potential. Further, these molecules can be fully expressed in prokaryotic cells such as *E. coli* and are expressed as fusion proteins with bacteriophage and are functional.

[0172] Accordingly, a feature of the present invention is a camelid antibody or nanobody having high affinity for C5. In certain embodiments herein, the camelid antibody or nanobody is naturally produced in the camelid animal, i.e., is produced by the camelid following immunization with C5 or a peptide fragment thereof, using techniques described herein for other antibodies. Alternatively, the C5-binding camelid nanobody is engineered, i.e., produced by selection for example from a library of phage displaying appropriately mutagenized camelid nanobody proteins using panning procedures with C5 as a target as described in the examples herein. Engineered nanobodies can further be customized by genetic engineering to have a half life in a recipient subject of from 45 minutes to two weeks. In a specific embodiment, the camelid antibody or nanobody is obtained by grafting the

CDRs sequences of the heavy or light chain of the human antibodies of the invention into nanobody or single domain antibody framework sequences, as described for example in PCT/EP93/02214.

Bispecific Molecules and Multivalent Antibodies

[0173] In another aspect, the present invention features bispecific or multispecific molecules comprising an C5-binding antibody, or a fragment thereof, of the invention. An antibody of the invention, or antigen-binding regions thereof, can be derivatized or linked to another functional molecule, e.g., another peptide or protein (e.g., another antibody or ligand for a receptor) to generate a bispecific molecule that binds to at least two different binding sites or target molecules. The antibody of the invention may in fact be derivatized or linked to more than one other functional molecule to generate multi-specific molecules that bind to more than two different binding sites and/or target molecules; such multispecific molecules are also intended to be encompassed by the term "bispecific molecule" as used herein. To create a bispecific molecule of the invention, an antibody of the invention can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other binding molecules, such as another antibody, antibody fragment, peptide or binding mimetic, such that a bispecific molecule results.

[0174] Accordingly, the present invention includes bispecific molecules comprising at least one first binding specificity for C5 and a second binding specificity for a second target epitope. For example, the second target epitope is another epitope of C5 different from the first target epitope.

[0175] Additionally, for the invention in which the bispecific molecule is multi-specific, the molecule can further include a third binding specificity, in addition to the first and second target epitope.

[0176] In one embodiment, the bispecific molecules of the invention comprise as a binding specificity at least one antibody, or an antibody fragment thereof, including, e.g., an Fab, Fab', F(ab')2, Fv, or a single chain Fv. The antibody may also be a light chain or heavy chain dimer, or any minimal fragment thereof such as a Fv or a single chain construct as described in Ladner et al. U.S. Pat. No. 4,946,778.

[0177] Diabodies are bivalent, bispecific molecules in which VH and VL domains are expressed on a single polypeptide chain, connected by a linker that is too short to allow for pairing between the two domains on the same chain. The VH and VL domains pair with complementary domains of another chain, thereby creating two antigen binding sites (see e.g., Holliger et al., 1993 Proc. Natl. Acad. Sci. USA 90:6444-6448; Poljak et al., 1994 Structure 2:1121-1123). Diabodies can be produced by expressing two polypeptide chains with either the structure VHA-VLB and VHB-VLA (VH-VL configuration), or VLA-VHB and VLB-VHA (VL-VH configuration) within the same cell. Most of them can be expressed in soluble form in bacteria. Single chain diabodies (scDb) are produced by connecting the two diabody-forming polypeptide chains with linker of approximately 15 amino acid residues (see Holliger and Winter, 1997 Cancer Immunol. Immunother., 45(3-4):128-30; Wu et al., 1996 Immunotechnology, 2(1):21-36). scDb can be expressed in bacteria in soluble, active monomeric form (see Holliger and Winter, 1997 Cancer Immunol. Immunother., 45(34): 128-30; Wu et al., 1996 Immunotechnology, 2(1):21-36; Pluckthun and Pack, 1997 Immunotechnology, 3(2): 83-105; Ridgway et al., 1996 Protein Eng., 9(7):617-21). A diabody can be fused to Fc to generate a "di-diabody" (see Lu et al., 2004 J. Biol. Chem., 279(4):2856-65).

[0178] Other antibodies which can be employed in the bispecific molecules of the invention are murine, chimeric and humanized monoclonal antibodies.

[0179] The bispecific molecules of the present invention can be prepared by conjugating the constituent binding specificities, using methods known in the art. For example, each binding specificity of the bispecific molecule can be generated separately and then conjugated to one another. When the binding specificities are proteins or peptides, a variety of coupling or cross-linking agents can be used for covalent conjugation. Examples of cross-linking agents include protein A, carbodiimide, N-succinimidyl-S-acetyl-thioacetate (SATA), 5,5'-dithiobis(2-nitrobenzoic acid) (DTNB), o-phenylenedimaleimide (oPDM), N-succinimidyl-3-(2-pyridyldithio)propionate (SPDP), and sulfosuccinimidyl 4-(Nmaleimidomethyl) cyclohaxane-I-carboxylate (sulfo-SMCC) (see e.g., Karpovsky et al., 1984 J. Exp. Med. 160: 1686; Liu, M A et al., 1985 Proc. Natl. Acad. Sci. USA 82:8648). Other methods include those described in Paulus, 1985 Behring Ins. Mitt. No. 78, 118-132; Brennan et al., 1985 Science 229:81-83), and Glennie et al., 1987 J. Immunol. 139: 2367-2375). Conjugating agents are SATA and sulfo-SMCC, both available from Pierce Chemical Co. (Rockford, III.).

[0180] When the binding specificities are antibodies, they can be conjugated by sulfhydryl bonding of the C-terminus hinge regions of the two heavy chains. In a particularly embodiment, the hinge region is modified to contain an odd number of sulfhydryl residues, for example one, prior to conjugation.

[0181] Alternatively, both binding specificities can be encoded in the same vector and expressed and assembled in the same host cell. This method is particularly useful where the bispecific molecule is a mAb×mAb, mAb×Fab, Fab×F (ab')2 or ligand×Fab fusion protein. A bispecific molecule of the invention can be a single chain molecule comprising one single chain antibody and a binding determinant, or a single chain bispecific molecule comprising two binding determinants. Bispecific molecules may comprise at least two single chain molecules. Methods for preparing bispecific molecules are described for example in U.S. Pat. No. 5,260,203; U.S. Pat. No. 5,455,030; U.S. Pat. No. 4,881,175; U.S. Pat. No. 5,132,405; U.S. Pat. No. 5,091,513; U.S. Pat. No. 5,476,786; U.S. Pat. No. 5,013,653; U.S. Pat. No. 5,258,498; and U.S. Pat. No. 5,482,858.

[0182] Binding of the bispecific molecules to their specific targets can be confirmed by, for example, enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (REA), FACS analysis, bioassay (e.g., growth inhibition), or Western Blot assay. Each of these assays generally detects the presence of protein-antibody complexes of particular interest by employing a labeled reagent (e.g., an antibody) specific for the complex of interest.

[0183] In another aspect, the present invention provides multivalent compounds comprising at least two identical or different antigen-binding portions of the antibodies of the invention binding to C5. The antigen-binding portions can be linked together via protein fusion or covalent or non covalent linkage. Alternatively, methods of linkage has been described for the bispecfic molecules. Tetravalent compounds can be obtained for example by cross-linking antibodies of the anti-

bodies of the invention with an antibody that binds to the constant regions of the antibodies of the invention, for example the Fc or hinge region.

[0184] Trimerizing domain are described for example in Borean patent EP 1 012 280B1. Pentamerizing modules are described for example in PCT/EP97/05897.

Antibodies with Extended Half Life

[0185] The present invention provides for antibodies that specifically bind to C5 protein which have an extended half-life in vivo.

[0186] Many factors may affect a protein's half life in vivo. For examples, kidney filtration, metabolism in the liver, degradation by proteolytic enzymes (proteases), and immunogenic responses (e.g., protein neutralization by antibodies and uptake by macrophages and dentritic cells). A variety of strategies can be used to extend the half life of the antibodies of the present invention. For example, by chemical linkage to polyethyleneglycol (PEG), reCODE PEG, antibody scaffold, polysialic acid (PSA), hydroxyethyl starch (HES), albuminbinding ligands, and carbohydrate shields; by genetic fusion to proteins binding to serum proteins, such as albumin, IgG, FcRn, and transferring; by coupling (genetically or chemically) to other binding moieties that bind to serum proteins, such as nanobodies, Fabs, DARPins, avimers, affibodies, and anticalins; by genetic fusion to rPEG, albumin, domain of albumin, albumin-binding proteins, and Fc; or by incorporation into nancarriers, slow release formulations, or medical devices.

[0187] To prolong the serum circulation of antibodies in vivo, inert polymer molecules such as high molecular weight PEG can be attached to the antibodies or a fragment thereof with or without a multifunctional linker either through sitespecific conjugation of the PEG to the N- or C-terminus of the antibodies or via epsilon-amino groups present on lysine residues. To pegylate an antibody, the antibody, or fragment thereof, typically is reacted with polyethylene glycol (PEG), such as a reactive ester or aldehyde derivative of PEG, under conditions in which one or more PEG groups become attached to the antibody or antibody fragment. The pegylation can be carried out by an acylation reaction or an alkylation reaction with a reactive PEG molecule (or an analogous reactive water-soluble polymer). As used herein, the term "polyethylene glycol" is intended to encompass any of the forms of PEG that have been used to derivatize other proteins, such as mono (C1-C10) alkoxy- or aryloxy-polyethylene glycol or polyethylene glycol-maleimide. In certain embodiments, the antibody to be pegylated is an aglycosylated antibody. Linear or branched polymer derivatization that results in minimal loss of biological activity will be used. The degree of conjugation can be closely monitored by SDS-PAGE and mass spectrometry to ensure proper conjugation of PEG molecules to the antibodies. Unreacted PEG can be separated from antibody-PEG conjugates by size-exclusion or by ion-exchange chromatography. PEG-derivatized antibodies can be tested for binding activity as well as for in vivo efficacy using methods well-known to those of skill in the art, for example, by immunoassays described herein. Methods for pegylating proteins are known in the art and can be applied to the antibodies of the invention. See for example, EP 0 154 316 by Nishimura et al. and EP 0 401 384 by Ishikawa et al.

[0188] Other modified pegylation technologies include reconstituting chemically orthogonal directed engineering technology (ReCODE PEG), which incorporates chemically specified side chains into biosynthetic proteins via a recon-

stituted system that includes tRNA synthetase and tRNA. This technology enables incorporation of more than 30 new amino acids into biosynthetic proteins in *E. coli*, yeast, and mammalian cells. The tRNA incorporates a nonnative amino acid any place an amber codon is positioned, converting the amber from a stop codon to one that signals incorporation of the chemically specified amino acid.

[0189] Recombinant pegylation technology (rPEG) can also be used for serum halflife extension. This technology involves genetically fusing a 300-600 amino acid unstructured protein tail to an existing pharmaceutical protein. Because the apparent molecular weight of such an unstructured protein chain is about 15-fold larger than its actual molecular weight, the serum halflife of the protein is greatly increased. In contrast to traditional PEGylation, which requires chemical conjugation and repurification, the manufacturing process is greatly simplified and the product is homogeneous.

[0190] Polysialytion is another technology, which uses the natural polymer polysialic acid (PSA) to prolong the active life and improve the stability of therapeutic peptides and proteins. PSA is a polymer of sialic acid (a sugar). When used for protein and therapeutic peptide drug delivery, polysialic acid provides a protective microenvironment on conjugation. This increases the active life of the therapeutic protein in the circulation and prevents it from being recognized by the immune system. The PSA polymer is naturally found in the human body. It was adopted by certain bacteria which evolved over millions of years to coat their walls with it. These naturally polysialylated bacteria were then able, by virtue of molecular mimicry, to foil the body's defense system. PSA, nature's ultimate stealth technology, can be easily produced from such bacteria in large quantities and with predetermined physical characteristics. Bacterial PSA is completely non-immunogenic, even when coupled to proteins, as it is chemically identical to PSA in the human body.

[0191] Another technology include the use of hydroxyethyl starch ("HES") derivatives linked to antibodies. HES is a modified natural polymer derived from waxy maize starch and can be metabolized by the body's enzymes. HES solutions are usually administered to substitute deficient blood volume and to improve the rheological properties of the blood. Hesylation of an antibody enables the prolongation of the circulation half-life by increasing the stability of the molecule, as well as by reducing renal clearance, resulting in an increased biological activity. By varying different parameters, such as the molecular weight of HES, a wide range of HES antibody conjugates can be customized.

[0192] Antibodies having an increased half-life in vivo can also be generated introducing one or more amino acid modifications (i.e., substitutions, insertions or deletions) into an IgG constant domain, or FcRn binding fragment thereof (preferably a Fc or hinge Fc domain fragment). See, e.g., International Publication No. WO 98/23289; International Publication No. WO 97/34631; and U.S. Pat. No. 6,277,375.

[0193] Further, antibodies can be conjugated to albumin in order to make the antibody or antibody fragment more stable in vivo or have a longer half life in vivo. The techniques are well-known in the art, see, e.g., International Publication Nos. WO 93/15199, WO 93/15200, and WO 01/77137; and European Patent No. EP 413,622.

[0194] The strategies for increasing half life is especially useful in nanobodies, fibronectin-based binders, and other antibodies or proteins for which increased in vivo half life is desired.

Antibody Conjugates

[0195] The present invention provides antibodies or fragments thereof that specifically bind to a C5 protein recombinantly fused or chemically conjugated (including both covalent and non-covalent conjugations) to a heterologous protein or polypeptide (or fragment thereof, preferably to a polypeptide of at least 10, at least 20, at least 30, at least 40, at least 50, at least 60, at least 70, at least 80, at least 90 or at least 100 amino acids) to generate fusion proteins. In particular, the invention provides fusion proteins comprising an antigenbinding fragment of an antibody described herein (e.g., a Fab fragment, Fd fragment, Fv fragment, F(ab)2 fragment, a VH domain, a VH CDR, a VL domain or a VL CDR) and a heterologous protein, polypeptide, or peptide. Methods for fusing or conjugating proteins, polypeptides, or peptides to an antibody or an antibody fragment are known in the art. See, e.g., U.S. Pat. Nos. 5,336,603, 5,622,929, 5,359,046, 5,349, 053, 5,447,851, and 5,112,946; European Patent Nos. EP 307,434 and EP 367,166; International Publication Nos. WO 96/04388 and WO 91/06570; Ashkenazi et al., 1991, Proc. Natl. Acad. Sci. USA 88: 10535-10539; Zheng et al., 1995, J. Immunol. 154:5590-5600; and Vil et al., 1992, Proc. Natl. Acad. Sci. USA 89:11337-11341.

[0196] Additional fusion proteins may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to alter the activities of antibodies of the invention or fragments thereof (e.g., antibodies or fragments thereof with higher affinities and lower dissociation rates). See, generally, U.S. Pat. Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458; Patten et al., 1997, Curr. Opinion Biotechnol. 8:724-33; Harayama, 1998, Trends Biotechnol. 16(2):76-82; Hansson, et al., 1999, J. Mol. Biol. 287:265-76; and Lorenzo and Blasco, 1998, Biotechniques 24(2):308-313 (each of these patents and publications are hereby incorporated by reference in its entirety). Antibodies or fragments thereof, or the encoded antibodies or fragments thereof, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. A polynucleotide encoding an antibody or fragment thereof that specifically binds to a C5 protein may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

[0197] Moreover, the antibodies or fragments thereof can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, Calif., 91311), among others, many of which are commercially available. As described in Gentz et al., 1989, Proc. Natl. Acad. Sci. USA 86:821-824, for instance, hexahistidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the hemagglutinin ("HA") tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., 1984, Cell 37:767), and the "flag" tag.

[0198] In other embodiments, antibodies of the present invention or fragments thereof conjugated to a diagnostic or detectable agent. Such antibodies can be useful for monitoring or prognosing the onset, development, progression and/or severity of a disease or disorder as part of a clinical testing procedure, such as determining the efficacy of a particular therapy. Such diagnosis and detection can accomplished by coupling the antibody to detectable substances including, but not limited to, various enzymes, such as, but not limited to, horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; prosthetic groups, such as, but not limited to, streptavidinlbiotin and avidin/biotin; fluorescent materials, such as, but not limited to, umbelliferone, fluorescein, fluorescein isothiocynate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; luminescent materials, such as, but not limited to, luminol; bioluminescent materials, such as but not limited to, luciferase, luciferin, and aequorin; radioactive materials, such as, but not limited to, iodine (1311, 1251, 1231, and 121I,), carbon (14C), sulfur (35S), tritium (3H), indium (115In, 113In, 112In, and 111In,), technetium (99Tc), thallium (201Ti), gallium (68Ga, 67Ga), palladium (103Pd), molybdenum (99Mo), xenon (133Xe), fluorine (18F), 153Sm, 177Lu, 159Gd, 149Pm, 140La, 175Yb, 166Ho, 90Y, 47Sc, 186Re, 188Re, 142Pr, 105Rh, 97Ru, 68Ge, 57Co, 65Zn, 85Sr, 32P, 153Gd, 169Yb, 51Cr, 54Mn, 75Se, 113Sn, and 117Tin; and positron emitting metals using various positron emission tomographies, and no radioactive paramagnetic metal ions.

[0199] The present invention further encompasses uses of antibodies or fragments thereof conjugated to a therapeutic moiety. An antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells.

[0200] Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety or drug moiety that modifies a given biological response. Therapeutic moieties or drug moieties are not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein, peptide, or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, cholera toxin, or diphtheria toxin; a protein such as tumor necrosis factor, α -interferon, β -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, an anti-angiogenic agent; or, a biological response modifier such as, for example, a lymphokine.

[0201] Moreover, an antibody can be conjugated to therapeutic moieties such as a radioactive metal ion, such as alphemiters such as 213Bi or macrocyclic chelators useful for conjugating radiometal ions, including but not limited to, 131In, 131LU, 131Y, 131Ho, 131Sm, to polypeptides. In certain embodiments, the macrocyclic chelator is 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) which can be attached to the antibody via a linker molecule. Such linker molecules are commonly known in the art and described in Denardo et al., 1998, Clin Cancer Res. 4(10): 2483-90; Peterson et al., 1999, Bioconjug. Chem. 10(4):553-7; and Zimmerman et al., 1999, Nucl. Med. Biol. 26(8):943-50, each incorporated by reference in their entireties.

[0202] Techniques for conjugating therapeutic moieties to antibodies are well known, see, e.g., Arnon et al., "Mono-

clonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies 84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., 1982, Immunol. Rev. 62:119-58.

[0203] Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

5.2. Methods of Producing Antibodies of the Invention

5.2.1. Nucleic Acids Encoding the Antibodies

[0204] The invention provides substantially purified nucleic acid molecules which encode polypeptides comprising segments or domains of the C5-binding antibody chains described above. Some of the nucleic acids of the invention comprise the nucleotide sequence encoding the heavy chain variable region shown in SEQ ID NO: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, or 281, and/or the nucleotide sequence encoding the light chain variable region shown in SEQ ID NO: 8, 24, 40, 52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, or 289. In a specific embodiment, the nucleic acid molecules are those identified in Table 1. Some other nucleic acid molecules of the invention comprise nucleotide sequences that are substantially identical (e.g., at least 65, 80%, 95%, or 99%) to the nucleotide sequences of those identified in Table 1. When expressed from appropriate expression vectors, polypeptides encoded by these polynucleotides are capable of exhibiting C5 antigen binding capacity.

[0205] Also provided in the invention are polynucleotides which encode at least one CDR region and usually all three CDR regions from the heavy or light chain of the C5-binding antibody set forth above. Some other polynucleotides encode all or substantially all of the variable region sequence of the heavy chain and/or the light chain of the C5-binding antibody set forth above. Because of the degeneracy of the code, a variety of nucleic acid sequences will encode each of the immunoglobulin amino acid sequences.

[0206] The nucleic acid molecules of the invention can encode both a variable region and a constant region of the antibody. Some of nucleic acid sequences of the invention comprise nucleotides encoding a mature heavy chain variable region sequence that is substantially identical (e.g., at least 80%, 90%, or 99%) to the mature heavy chain variable region sequence set forth in SEQ ID NO: 7, 23, 39, 51, 67, 79, 96, 108, 114, 121, 137, 151, 165, 179, 187, 201, 210, 218, 227, 241, 253, 257, 273, 277, or 281. Some other nucleic acid sequences comprising nucleotide encoding a mature light chain variable region sequence that is substantially identical (e.g., at least 80%, 90%, or 99%) to the mature light chain variable region sequence set forth in SEQ ID NO: 8, 24, 40,

52, 68, 80, 90, 102, 122, 138, 152, 166, 180, 188, 202, 211, 219, 228, 242, 261, 265, 269, 285, or 289.

[0207] The polynucleotide sequences can be produced by de novo solid-phase DNA synthesis or by PCR mutagenesis of an existing sequence (e.g., sequences as described in the Examples below) encoding an C5-binding antibody or its binding fragment. Direct chemical synthesis of nucleic acids can be accomplished by methods known in the art, such as the phosphotriester method of Narang et al., 1979, Meth. Enzymol. 68:90; the phosphodiester method of Brown et al., Meth. Enzymol. 68:109, 1979; the diethylphosphoramidite method of Beaucage et al., Tetra. Lett., 22:1859, 1981; and the solid support method of U.S. Pat. No. 4,458,066. Introducing mutations to a polynucleotide sequence by PCR can be performed as described in, e.g., PCR Technology: Principles and Applications for DNA Amplification, H. A. Erlich (Ed.), Freeman Press, NY, NY, 1992; PCR Protocols: A Guide to Methods and Applications, Innis et al. (Ed.), Academic Press, San Diego, Calif., 1990; Mattila et al., Nucleic Acids Res. 19:967, 1991; and Eckert et al., PCR Methods and Applications 1:17, 1991.

[0208] Also provided in the invention are expression vectors and host cells for producing the C5-binding antibodies described above. Various expression vectors can be employed to express the polynucleotides encoding the C5-binding antibody chains or binding fragments. Both viral-based and nonviral expression vectors can be used to produce the antibodies in a mammalian host cell. Nonviral vectors and systems include plasmids, episomal vectors, typically with an expression cassette for expressing a protein or RNA, and human artificial chromosomes (see, e.g., Harrington et al., Nat Genet 15:345, 1997). For example, nonviral vectors useful for expression of the C5-binding polynucleotides and polypeptides in mammalian (e.g., human) cells include pThioHis A, B & C, pcDNA3.1/His, pEBVHis A, B & C, (Invitrogen, San Diego, Calif.), MPSV vectors, and numerous other vectors known in the art for expressing other proteins. Useful viral vectors include vectors based on retroviruses, adenoviruses, adenoassociated viruses, herpes viruses, vectors based on SV40, papilloma virus, HBP Epstein Barr virus, vaccinia virus vectors and Semliki Forest virus (SFV). See, Brent et al., supra; Smith, Annu. Rev. Microbiol. 49:807, 1995; and Rosenfeld et al., Cell 68:143, 1992.

[0209] The choice of expression vector depends on the intended host cells in which the vector is to be expressed. Typically, the expression vectors contain a promoter and other regulatory sequences (e.g., enhancers) that are operably linked to the polynucleotides encoding an C5-binding antibody chain or fragment. In some embodiments, an inducible promoter is employed to prevent expression of inserted sequences except under inducing conditions. Inducible promoters include, e.g., arabinose, lacZ, metallothionein promoter or a heat shock promoter. Cultures of transformed organisms can be expanded under noninducing conditions without biasing the population for coding sequences whose expression products are better tolerated by the host cells. In addition to promoters, other regulatory elements may also be required or desired for efficient expression of an C5-binding antibody chain or fragment. These elements typically include an ATG initiation codon and adjacent ribosome binding site or other sequences. In addition, the efficiency of expression may be enhanced by the inclusion of enhancers appropriate to the cell system in use (see, e.g., Scharf et al., Results Probl. Cell Differ. 20:125, 1994; and Bittner et al., Meth. Enzymol., 153:516, 1987). For example, the SV40 enhancer or CMV enhancer may be used to increase expression in mammalian host cells.

[0210] The expression vectors may also provide a secretion signal sequence position to form a fusion protein with polypeptides encoded by inserted C5-binding antibody sequences. More often, the inserted C5-binding antibody sequences are linked to a signal sequences before inclusion in the vector. Vectors to be used to receive sequences encoding C5-binding antibody light and heavy chain variable domains sometimes also encode constant regions or parts thereof. Such vectors allow expression of the variable regions as fusion proteins with the constant regions thereby leading to production of intact antibodies or fragments thereof. Typically, such constant regions are human.

[0211] The host cells for harboring and expressing the C5-binding antibody chains can be either prokaryotic or eukaryotic. E. coli is one prokaryotic host useful for cloning and expressing the polynucleotides of the present invention. Other microbial hosts suitable for use include bacilli, such as Bacillus subtilis, and other enterobacteriaceae, such as Salmonella, Serratia, and various Pseudomonas species. In these prokaryotic hosts, one can also make expression vectors, which typically contain expression control sequences compatible with the host cell (e.g., an origin of replication). In addition, any number of a variety of well-known promoters will be present, such as the lactose promoter system, a tryptophan (trp) promoter system, a beta-lactamase promoter system, or a promoter system from phage lambda. The promoters typically control expression, optionally with an operator sequence, and have ribosome binding site sequences and the like, for initiating and completing transcription and translation. Other microbes, such as yeast, can also be employed to express C5-binding polypeptides of the invention. Insect cells in combination with baculovirus vectors can also be used.

[0212] In some preferred embodiments, mammalian host cells are used to express and produce the C5-binding polypeptides of the present invention. For example, they can be either a hybridoma cell line expressing endogenous immunoglobulin genes (e.g., the 1D6.C9 myeloma hybridoma clone as described in the Examples) or a mammalian cell line harboring an exogenous expression vector (e.g., the SP2/0 myeloma cells exemplified below). These include any normal mortal or normal or abnormal immortal animal or human cell. For example, a number of suitable host cell lines capable of secreting intact immunoglobulins have been developed including the CHO cell lines, various Cos cell lines, HeLa cells, myeloma cell lines, transformed B-cells and hybridomas. The use of mammalian tissue cell culture to express polypeptides is discussed generally in, e.g., Winnacker, FROM GENES TO CLONES, VCH Publishers, N.Y., N.Y., 1987. Expression vectors for mammalian host cells can include expression control sequences, such as an origin of replication, a promoter, and an enhancer (see, e.g., Queen, et al., Immunol. Rev. 89:49-68, 1986), and necessary processing information sites, such as ribosome binding sites, RNA splice sites, polyadenylation sites, and transcriptional terminator sequences. These expression vectors usually contain promoters derived from mammalian genes or from mammalian viruses. Suitable promoters may be constitutive, cell type-specific, stage-specific, and/or modulatable or regulatable. Useful promoters include, but are not limited to, the metallothionein promoter, the constitutive adenovirus major late promoter, the dexamethasone-inducible MMTV promoter, the SV40 promoter, the MRP poIIII promoter, the constitutive MPSV promoter, the tetracycline-inducible CMV promoter (such as the human immediate-early CMV promoter), the constitutive CMV promoter, and promoter-enhancer combinations known in the art.

[0213] Methods for introducing expression vectors containing the polynucleotide sequences of interest vary depending on the type of cellular host. For example, calcium chloride transfection is commonly utilized for prokaryotic cells, whereas calcium phosphate treatment or electroporation may be used for other cellular hosts. (See generally Sambrook, et al., supra). Other methods include, e.g., electroporation, calcium phosphate treatment, liposome-mediated transformation, injection and microinjection, ballistic methods, virosomes, immunoliposomes, polycation:nucleic acid conjugates, naked DNA, artificial virions, fusion to the herpes virus structural protein VP22 (Elliot and O'Hare, Cell 88:223, 1997), agent-enhanced uptake of DNA, and ex vivo transduction. For long-term, high-yield production of recombinant proteins, stable expression will often be desired. For example, cell lines which stably express C5-binding antibody chains or binding fragments can be prepared using expression vectors of the invention which contain viral origins of replication or endogenous expression elements and a selectable marker gene. Following the introduction of the vector, cells may be allowed to grow for 1-2 days in an enriched media before they are switched to selective media. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth of cells which successfully express the introduced sequences in selective media. Resistant, stably transfected cells can be proliferated using tissue culture techniques appropriate to the cell type.

5.2.2. Generation of Monoclonal Antibodies of the Invention

[0214] Monoclonal antibodies (mAbs) can be produced by a variety of techniques, including conventional monoclonal antibody methodology e.g., the standard somatic cell hybridization technique of Kohler and Milstein, 1975 Nature 256: 495. Many techniques for producing monoclonal antibody can be employed e.g., viral or oncogenic transformation of B lymphocytes.

[0215] An animal system for preparing hybridomas is the murine system. Hybridoma production in the mouse is a well established procedure. Immunization protocols and techniques for isolation of immunized splenocytes for fusion are known in the art. Fusion partners (e.g., murine myeloma cells) and fusion procedures are also known.

[0216] Chimeric or humanized antibodies of the present invention can be prepared based on the sequence of a murine monoclonal antibody prepared as described above. DNA encoding the heavy and light chain immunoglobulins can be obtained from the murine hybridoma of interest and engineered to contain non-murine (e.g., human) immunoglobulin sequences using standard molecular biology techniques. For example, to create a chimeric antibody, the murine variable regions can be linked to human constant regions using methods known in the art (see e.g., U.S. Pat. No. 4,816,567 to Cabilly et al.). To create a humanized antibody, the murine CDR regions can be inserted into a human framework using methods known in the art. See e.g., U.S. Pat. No. 5,222,539 to Winter, and U.S. Pat. Nos. 5,530,101; 5,585,089; 5,693,762 and 6,180,370 to Queen et al.

[0217] In a certain embodiment, the antibodies of the invention are human monoclonal antibodies. Such human mono-

clonal antibodies directed against C5 can be generated using transgenic or transchromosomic mice carrying parts of the human immune system rather than the mouse system. These transgenic and transchromosomic mice include mice referred to herein as HuMAb mice and KM mice, respectively, and are collectively referred to herein as "human Ig mice."

[0218] The HuMAb Mouse® (Medarex, Inc.) contains human immunoglobulin gene miniloci that encode un-rearranged human heavy (μ and γ) and κ light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous µ and κ chain loci (see e.g., Lonberg, et al., 1994 Nature 368(6474): 856-859). Accordingly, the mice exhibit reduced expression of mouse IgM or κ , and in response to immunization, the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity human IgGk monoclonal (Lonberg, N. et al., 1994 supra; reviewed in Lonberg, N., 1994 Handbook of Experimental Pharmacology 113:49-101; Lonberg, N. and Huszar, D., 1995 Intern. Rev. Immunol. 13: 65-93, and Harding, F. and Lonberg, N., 1995 Ann. N. Y. Acad. Sci. 764:536-546). The preparation and use of HuMAb mice, and the genomic modifications carried by such mice, is further described in Taylor, L. et al., 1992 Nucleic Acids Research 20:6287-6295; Chen, J. et at., 1993 International Immunology 5: 647-656; Tuaillon et al., 1993 Proc. Natl. Acad. Sci. USA 94:3720-3724; Choi et al., 1993 Nature Genetics 4:117-123; Chen, J. et al., 1993 EMBO J. 12: 821-830; Tuaillon et al., 1994 J. Immunol. 152:2912-2920; Taylor, L. et al., 1994 International Immunology 579-591; and Fishwild, D. et al., 1996 Nature Biotechnology 14: 845-851, the contents of all of which are hereby specifically incorporated by reference in their entirety. See further, U.S. Pat. Nos. 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,789,650; 5,877,397; 5,661,016; 5,814,318; 5,874,299; and 5,770,429; all to Lonberg and Kay; U.S. Pat. No. 5,545,807 to Surani et al.; PCT Publication Nos. WO 92103918, WO 93/12227, WO 94/25585, WO 97113852, WO 98/24884 and WO 99/45962, all to Lonberg and Kay; and PCT Publication No. WO 01/14424 to Korman et al.

[0219] In another embodiment, human antibodies of the invention can be raised using a mouse that carries human immunoglobulin sequences on transgenes and transchomosomes such as a mouse that carries a human heavy chain transgene and a human light chain transchromosome. Such mice, referred to herein as "KM mice", are described in detail in PCT Publication WO 02/43478 to Ishida et al.

[0220] Still further, alternative transgenic animal systems expressing human immunoglobulin genes are available in the art and can be used to raise C5-binding antibodies of the invention. For example, an alternative transgenic system referred to as the Xenomouse (Abgenix, Inc.) can be used. Such mice are described in, e.g., U.S. Pat. Nos. 5,939,598; 6,075,181; 6,114,598; 6, 150,584 and 6,162,963 to Kucherlapati et al.

[0221] Moreover, alternative transchromosomic animal systems expressing human immunoglobulin genes are available in the art and can be used to raise C5-binding antibodies of the invention. For example, mice carrying both a human heavy chain transchromosome and a human light chain tranchromosome, referred to as "TC mice" can be used; such mice are described in Tomizuka et al., 2000 Proc. Natl. Acad. Sci. USA 97:722-727. Furthermore, cows carrying human heavy and light chain transchromosomes have been described

in the art (Kuroiwa et al., 2002 Nature Biotechnology 20:889-894) and can be used to raise C5-binding antibodies of the invention.

[0222] Human monoclonal antibodies of the invention can also be prepared using phage display methods for screening libraries of human immunoglobulin genes. Such phage display methods for isolating human antibodies are established in the art or described in the examples below. See for example: U.S. Pat. Nos. 5,223,409; 5,403,484; and 5,571,698 to Ladner et al.; U.S. Pat. Nos. 5,427,908 and 5,580,717 to Dower et al.; U.S. Pat. Nos. 5,969,108 and 6,172,197 to McCafferty et al.; and U.S. Pat. Nos. 5,885,793; 6,521,404; 6,544,731; 6,555, 313; 6,582,915 and 6,593,081 to Griffiths et al.

[0223] Human monoclonal antibodies of the invention can also be prepared using SCID mice into which human immune cells have been reconstituted such that a human antibody response can be generated upon immunization. Such mice are described in, for example, U.S. Pat. Nos. 5,476,996 and 5,698,767 to Wilson et al.

5.2.3. Framework or Fc Engineering

[0224] Engineered antibodies of the invention include those in which modifications have been made to framework residues within VH and/or VL, e.g. to improve the properties of the antibody. Typically such framework modifications are made to decrease the immunogenicity of the antibody. For example, one approach is to "backmutate" one or more framework residues to the corresponding germline sequence. More specifically, an antibody that has undergone somatic mutation may contain framework residues that differ from the germline sequence from which the antibody is derived. Such residues can be identified by comparing the antibody framework sequences to the germline sequences from which the antibody is derived. To return the framework region sequences to their germline configuration, the somatic mutations can be "backmutated" to the germline sequence by, for example, site-directed mutagenesis. Such "backmutated" antibodies are also intended to be encompassed by the invention.

[0225] Another type of framework modification involves mutating one or more residues within the framework region, or even within one or more CDR regions, to remove T cell-epitopes to thereby reduce the potential immunogenicity of the antibody. This approach is also referred to as "deimmunization" and is described in further detail in U.S. Patent Publication No. 20030153043 by Carr et al.

[0226] In addition or alternative to modifications made within the framework or CDR regions, antibodies of the invention may be engineered to include modifications within the Fc region, typically to alter one or more functional properties of the antibody, such as serum half-life, complement fixation, Fc receptor binding, and/or antigen-dependent cellular cytotoxicity. Furthermore, an antibody of the invention may be chemically modified (e.g., one or more chemical moieties can be attached to the antibody) or be modified to alter its glycosylation, again to alter one or more functional properties of the antibody. Each of these embodiments is described in further detail below. The numbering of residues in the Fc region is that of the EU index of Kabat.

[0227] In one embodiment, the hinge region of CH1 is modified such that the number of cysteine residues in the hinge region is altered, e.g., increased or decreased. This approach is described further in U.S. Pat. No. 5,677,425 by Bodmer et al. The number of cysteine residues in the hinge

region of CH1 is altered to, for example, facilitate assembly of the light and heavy chains or to increase or decrease the stability of the antibody.

[0228] In another embodiment, the Fc hinge region of an antibody is mutated to decrease the biological half-life of the antibody. More specifically, one or more amino acid mutations are introduced into the CH2-CH3 domain interface region of the Fc-hinge fragment such that the antibody has impaired Staphylococcyl protein A (SpA) binding relative to native Fc-hinge domain SpA binding. This approach is described in further detail in U.S. Pat. No. 6,165,745 by Ward et al.

[0229] In another embodiment, the antibody is modified to increase its biological half-life. Various approaches are possible. For example, one or more of the following mutations can be introduced: T252L, T254S, T256F, as described in U.S. Pat. No. 6,277,375 to Ward. Alternatively, to increase the biological half life, the antibody can be altered within the CH1 or CL region to contain a salvage receptor binding epitope taken from two loops of a CH2 domain of an Fc region of an IgG, as described in U.S. Pat. Nos. 5,869,046 and 6,121,022 by Presta et al.

[0230] In yet other embodiments, the Fc region is altered by replacing at least one amino acid residue with a different amino acid residue to alter the effector functions of the antibody. For example, one or more amino acids can be replaced with a different amino acid residue such that the antibody has an altered affinity for an effector ligand but retains the antigen-binding ability of the parent antibody. The effector ligand to which affinity is altered can be, for example, an Fc receptor or the C1 component of complement. This approach is described in further detail in U.S. Pat. Nos. 5,624,821 and 5,648,260, both by Winter et al.

[0231] In another embodiment, one or more amino acids selected from amino acid residues can be replaced with a different amino acid residue such that the antibody has altered C1q binding and/or reduced or abolished complement dependent cytotoxicity (CDC). This approach is described in further detail in U.S. Pat. No. 6,194,551 by Idusogie et al.

[0232] In another embodiment, one or more amino acid residues are altered to thereby alter the ability of the antibody to fix complement. This approach is described further in PCT Publication WO 94/29351 by Bodmer et al.

[0233] In yet another embodiment, the Fc region is modified to increase the ability of the antibody to mediate antibody dependent cellular cytotoxicity (ADCC) and/or to increase the affinity of the antibody for an Fc γ receptor by modifying one or more amino acids. This approach is described further in PCT Publication WO 00/42072 by Presta. Moreover, the binding sites on human IgG1 for Fc γ RI, Fc γ RII, Fc γ RII and FcRn have been mapped and variants with improved binding have been described (see Shields, R. L. et al., 2001 J. Biol. Chen. 276:6591-6604).

[0234] In still another embodiment, the glycosylation of an antibody is modified. For example, an aglycoslated antibody can be made (i.e., the antibody lacks glycosylation). Glycosylation can be altered to, for example, increase the affinity of the antibody for "antigen". Such carbohydrate modifications can be accomplished by, for example, altering one or more sites of glycosylation within the antibody sequence. For example, one or more amino acid substitutions can be made that result in elimination of one or more variable region framework glycosylation sites to thereby eliminate glycosylation at that site. Such aglycosylation may increase the affini-

ity of the antibody for antigen. Such an approach is described in further detail in U.S. Pat. Nos. 5,714,350 and 6,350,861 by Co et al.

[0235] Additionally or alternatively, an antibody can be made that has an altered type of glycosylation, such as a hypofucosylated antibody having reduced amounts of fucosyl residues or an antibody having increased bisecting GlcNac structures. Such altered glycosylation patterns have been demonstrated to increase the ADCC ability of antibodies. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. For example, EP 1,176,195 by Hang et al. describes a cell line with a functionally disrupted FUT8 gene, which encodes a fucosyl transferase, such that antibodies expressed in such a cell line exhibit hypofucosylation. PCT Publication WO 03/035835 by Presta describes a variant CHO cell line, Lecl3 cells, with reduced ability to attach fucose to Asn(297)-linked carbohydrates, also resulting in hypofucosylation of antibodies expressed in that host cell (see also Shields, R. L. et al., 2002 J. Biol. Chem. 277:26733-26740). PCT Publication WO 99/54342 by Umana et al. describes cell lines engineered to express glycoprotein-modifying glycosyl transferases (e.g., beta(1,4)-N acetylglucosaminyltransferase III (GnTIII)) such that antibodies expressed in the engineered cell lines exhibit increased bisecting GlcNac structures which results in increased ADCC activity of the antibodies (see also Umana et al., 1999 Nat. Biotech. 17:176-180).

5.2.4. Methods of Engineering Altered Antibodies

[0236] As discussed above, the C5-binding antibodies having VH and VL sequences or full length heavy and light chain sequences shown herein can be used to create new C5-binding antibodies by modifying full length heavy chain and/or light chain sequences, VH and/or VL sequences, or the constant region(s) attached thereto. Thus, in another aspect of the invention, the structural features of a C5-binding antibody of the invention are used to create structurally related C5-binding antibodies that retain at least one functional property of the antibodies of the invention, such as binding to human C5 and also inhibiting one or more functional properties of C5 (e.g., inhibit red blood cell lysis in a hemolytic assay).

[0237] For example, one or more CDR regions of the antibodies of the present invention, or mutations thereof, can be combined recombinantly with known framework regions and/or other CDRs to create additional, recombinantly-engineered, C5-binding antibodies of the invention, as discussed above. Other types of modifications include those described in the previous section. The starting material for the engineering method is one or more of the VH and/or VL sequences provided herein, or one or more CDR regions thereof. To create the engineered antibody, it is not necessary to actually prepare (i.e., express as a protein) an antibody having one or more of the VH and/or VL sequences provided herein, or one or more CDR regions thereof. Rather, the information contained in the sequence(s) is used as the starting material to create a "second generation" sequence(s) derived from the original sequence(s) and then the "second generation" sequence(s) is prepared and expressed as a protein.

[0238] Accordingly, in another embodiment, the invention provides a method for preparing an C5-binding antibody consisting of: a heavy chain variable region antibody sequence having a CDR1 sequence selected from the group consisting of SEQ ID NOs: 1, 17, 33, 61, 131, 145, 159, 173, 195, and 235, a CDR2 sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 49, 62, 77, 95, 107, 113, 119, 132, 146, 160, 174, 196, 226, and 236, and/or a CDR3 sequence selected from the group consisting of SEQ ID NOs: 3, 19, 35, 63, 133, 147, 161, 175, 197, and 237; and a light chain variable region antibody sequence having a CDR1 sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 64, 134, 148, 162, 176, 198, and 238, a CDR2 sequence selected from the group consisting of SEQ ID NOs: 5, 21, 37, 65, 135, 149, 163, 177, 199, and 239, and/or a CDR3 sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 50, 66, 78, 89, 101, 120, 136, 150, 164, 178, 200, 209, and 240; altering at least one amino acid residue within the heavy chain variable region antibody sequence and/or the light chain variable region antibody sequence to create at least one altered antibody sequence; and expressing the altered antibody sequence as a protein.

[0239] Accordingly, in another embodiment, the invention provides a method for preparing an C5-binding antibody optimized for expression in a mammalian cell consisting of: a full length heavy chain antibody sequence having a sequence selected from the group of SEQ ID NOs: 9, 25, 41, 53, 69, 81, 97, 109, 115, 123, 139, 153, 167, 181, 189, 203, 212, 220, 229, 243, 249, 254, 258, 274, 278, and 282; and a full length light chain antibody sequence having a sequence selected from the group of 10, 26, 42, 54, 70, 82, 91, 103, 124, 140, 154, 168, 182, 190, 204, 213, 221, 230, 244, 251, 262, 266, 270, 286, and 290; altering at least one amino acid residue within the full length heavy chain antibody sequence and/or the full length light chain antibody sequence; and expressing the altered antibody sequence as a protein.

[0240] The altered antibody sequence can also be prepared by screening antibody libraries having fixed CDR3 sequences or minimal essential binding determinants as described in US20050255552 and diversity on CDR1 and CDR2 sequences. The screening can be performed according to any screening technology appropriate for screening antibodies from antibody libraries, such as phage display technology.

[0241] Standard molecular biology techniques can be used to prepare and express the altered antibody sequence. The antibody encoded by the altered antibody sequence(s) is one that retains one, some or all of the functional properties of the C5-binding antibodies described herein, which functional properties include, but are not limited to, specifically binding to human and/or cynomolgus C5; and the antibody inhibit red blood cell lysis in a hemolytic assay.

[0242] The functional properties of the altered antibodies can be assessed using standard assays available in the art and/or described herein, such as those set forth in the Examples (e.g., ELISAs).

[0243] In certain embodiments of the methods of engineering antibodies of the invention, mutations can be introduced randomly or selectively along all or part of an C5-binding antibody coding sequence and the resulting modified C5-binding antibodies can be screened for binding activity and/or other functional properties as described herein. Mutational methods have been described in the art. For example, PCT Publication WO 02/092780 by Short describes methods for creating and screening antibody mutations using saturation mutagenesis, synthetic ligation assembly, or a combination thereof. Alternatively, PCT Publication WO 03/074679 by Lazar et al. describes methods of using computational screening methods to optimize physiochemical properties of antibodies.

5.3. Characterization of the Antibodies of the Invention

[0244] The antibodies of the invention can be characterized by various functional assays. For example, they can be characterized by their ability to inhibit red blood cell lysis in hemolytic assays, their affinity to a C5 protein (e.g., human and/or cynomolgus C5), the epitope binning, their resistance to proteolysis, and their ability to block the complement cascade, for example, their ability to inhibit MAC formation. [0245] Various methods can be used to measure presence of complement pathway molecules and activation of the complement system (see, e.g., U.S. Pat. No. 6,087,120; and Newell et al., J Lab Clin Med, 100:437-44, 1982). For example, the complement activity can be monitored by (i) measurement of inhibition of complement-mediated lysis of red blood cells (hemolysis); (ii) measurement of ability to inhibit cleavage of C3 or C5; and (iii) inhibition of alternative pathway mediated hemolysis.

[0246] The two most commonly used techniques are hemolytic assays (see, e.g., Baatrup et al., Ann Rheum Dis, 51:892-7, 1992) and immunological assays (see, e.g., Auda et al., Rheumatol Int, 10:185-9, 1990). The hemolytic techniques measure the functional capacity of the entire sequence-either the classical or alternative pathway. Immunological techniques measure the protein concentration of a specific complement component or split product. Other assays that can be employed to detect complement activation or measure activities of complement components in the methods of the present invention include, e.g., T cell proliferation assay (Chain et al., J Immunol Methods, 99:221-8, 1987), and delayed type hypersensitivity (DTH) assay (Forstrom et al., 1983, Nature 303:627-629; Halliday et al., 1982, in Assessment of Immune Status by the Leukocyte Adherence Inhibition Test, Academic, New York pp. 1-26; Koppi et al., 1982, Cell. Immunol. 66:394-406; and U.S. Pat. No. 5,843,449).

[0247] In hemolytic techniques, all of the complement components must be present and functional. Therefore hemolytic techniques can screen both functional integrity and deficiencies of the complement system (see, e.g., Dijk et al., J Immunol Methods 36: 29-39, 1980; Minh et al., Clin Lab Haematol. 5:23-34 1983; and Tanaka et al., J Immunol 86: 161-170, 1986). To measure the functional capacity of the classical pathway, sheep red blood cells coated with hemolysin (rabbit IgG to sheep red blood cells) or chicken red blood cells that are sensitized with rabbit anti-chicken antibodies are used as target cells (sensitized cells). These Ag-Ab complexes activate the classical pathway and result in lysis of the target cells when the components are functional and present in adequate concentration. To determine the functional capacity of the alternative pathway, rabbit red blood cells are used as the target cell (see, e.g., U.S. Pat. No. 6,087,120).

[0248] To test the ability of an antibody to inhibit MAC (membrance attack complex) formation, a MAC deposition assay can be performed. Briefly, zymosan can be used to activate the alternative pathway and IgM can be used to active the classic pathway. Fabs are pre-inclubated with human serum and added to plates coated with zymosan or IgM. Percentage inhibition of MAC deposition can be calculated

for each sample relative to baseline (EDTA treated human serum) and positive control (human serum).

[0249] The ability of an antibody to bind to C5 can be detected by labelling the antibody of interest directly, or the antibody may be unlabelled and binding detected indirectly using various sandwich assay formats known in the art.

[0250] In some embodiments, the C5-binding antibodies of the invention block or compete with binding of a reference C5-binding antibody to a C5 polypeptide. These can be fully human C5-binding antibodies described above. They can also be other mouse, chimeric or humanized C5-binding antibodies which bind to the same epitope as the reference antibody. The capacity to block or compete with the reference antibody binding indicates that a C5-binding antibody under test binds to the same or similar epitope as that defined by the reference antibody, or to an epitope which is sufficiently proximal to the epitope bound by the reference C5-binding antibody. Such antibodies are especially likely to share the advantageous properties identified for the reference antibody. The capacity to block or compete with the reference antibody may be determined by, e.g., a competition binding assay. With a competition binding assay, the antibody under test is examined for ability to inhibit specific binding of the reference antibody to a common antigen, such as a C5 polypeptide. A test antibody competes with the reference antibody for specific binding to the antigen if an excess of the test antibody substantially inhibits binding of the reference antibody. Substantial inhibition means that the test antibody reduces specific binding of the reference antibody usually by at least 10%, 25%, 50%, 75%, or 90%.

[0251] There are a number of known competition binding assays that can be used to assess competition of a C5-binding antibody with the reference C5-binding antibody for binding to a C5 protein. These include, e.g., solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see Stahli et al., Methods in Enzymology 9:242-253, 1983); solid phase direct biotin-avidin EIA (see Kirkland et al., J. Immunol. 137:3614-3619, 1986); solid phase direct labeled assay, solid phase direct labeled sandwich assay (see Harlow & Lane, supra); solid phase direct label RIA using 1-125 label (see Morel et al., Molec. Immunol. 25:7-15, 1988); solid phase direct biotin-avidin EIA (Cheung et al., Virology 176:546-552, 1990); and direct labeled RIA (Moldenhauer et al., Scand. J. Immunol. 32:77-82, 1990). Typically, such an assay involves the use of purified antigen bound to a solid surface or cells bearing either of these, an unlabelled test C5-binding antibody and a labelled reference antibody. Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test antibody. Usually the test antibody is present in excess. Antibodies identified by competition assay (competing antibodies) include antibodies binding to the same epitope as the reference antibody and antibodies binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antibody for steric hindrance to occur.

[0252] To determine if the selected C5-binding monoclonal antibodies bind to unique epitopes, each antibody can be biotinylated using commercially available reagents (e.g., reagents from Pierce, Rockford, Ill.). Competition studies using unlabeled monoclonal antibodies and biotinylated monoclonal antibodies can be performed using a C5 polypeptide coated-ELISA plates. Biotinylated MAb binding can be detected with a strep-avidin-alkaline phosphatase probe. To

determine the isotype of a purified C5-binding antibody, isotype ELISAs can be performed. For example, wells of microtiter plates can be coated with 1 μ g/ml of anti-human IgG overnight at 4° C. After blocking with 1% BSA, the plates are reacted with 1 μ g/ml or less of the monoclonal C5-binding antibody or purified isotype controls, at ambient temperature for one to two hours. The wells can then be reacted with either human IgGI or human IgM-specific alkaline phosphataseconjugated probes. Plates are then developed and analyzed so that the isotype of the purified antibody can be determined.

[0253] To demonstrate binding of monoclonal C5-binding antibodies to live cells expressing a C5 polypeptide, flow cytometry can be used. Briefly, cell lines expressing C5 (grown under standard growth conditions) can be mixed with various concentrations of a C5-binding antibody in PBS containing 0.1% BSA and 10% fetal calf serum, and incubated at 37° C. for 1 hour. After washing, the cells are reacted with Fluorescein-labeled anti-human IgG antibody under the same conditions as the primary antibody staining. The samples can be analyzed by FACScan instrument using light and side scatter properties to gate on single cells. An alternative assay using fluorescence microscopy may be used (in addition to or instead of) the flow cytometry assay. Cells can be stained exactly as described above and examined by fluorescence microscopy. This method allows visualization of individual cells, but may have diminished sensitivity depending on the density of the antigen.

[0254] C5-binding antibodies of the invention can be further tested for reactivity with a C5 polypeptide or antigenic fragment by Western blotting. Briefly, purified C5 polypeptides or fusion proteins, or cell extracts from cells expressing C5 can be prepared and subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis. After electrophoresis, the separated antigens are transferred to nitrocellulose membranes, blocked with 10% fetal calf serum, and probed with the monoclonal antibodies to be tested. Human IgG binding can be detected using anti-human IgG alkaline phosphatase and developed with BCIP/NBT substrate tablets (Sigma Chem. Co., St. Louis, Mo.).

[0255] Examples of functional assays are also described in the Example section below.

5.4. Prophylactic and Therapeutic Uses

[0256] The present invention provides methods of treating a disease or disorder associated with increased complement activity by administering to a subject in need thereof an effective amount of the antibodies of the invention. In a specific embodiment, the present invention provides a method of treating age-related macular degeneration (AMD) by administering to a subject in need thereof an effective amount of the antibodies of the invention.

[0257] The antibodies of the invention can be used, inter alia, to prevent progression of dry AMD to wet AMD, to slow and/or prevent progression of geographic atrophy, and to improve vision lost due to dry AMD progression. It can also be used in combination with anti-VEGF therapies for the treatment of wet AMD patients.

[0258] In some embodiments, the present invention provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the antibodies of the invention. Examples of known complement related diseases or disorders include: neurological disorders, multiple sclerosis, stroke, Guillain Barre Syndrome, traumatic brain injury, Parkinson's disease,

disorders of inappropriate or undesirable complement activation, hemodialysis complications, hyperacute allograft rejection, xenograft rejection, interleukin-2 induced toxicity during IL-2 therapy, inflammatory disorders, inflammation of autoimmune diseases, Crohn's disease, adult respiratory distress syndrome, thermal injury including burns or frostbite, post-ischemic reperfusion conditions, myocardial infarction, balloon angioplasty, post-pump syndrome in cardiopulmonary bypass or renal bypass, hemodialysis, renal ischemia, mesenteric artery reperfusion after acrotic reconstruction, infectious disease or sepsis, immune complex disorders and autoimmune diseases, rheumatoid arthritis, systemic lupus erythematosus (SLE), SLE nephritis, proliferative nephritis, hemolytic anemia, and myasthenia gravis. In addition, other known complement related disease are lung disease and disorders such as dyspnea, hemoptysis, ARDS, asthma, chronic obstructive pulmonary disease (COPD), emphysema, pulmonary embolisms and infarcts, pneumonia, fibrogenic dust diseases, inert dusts and minerals (e.g., silicon, coal dust, beryllium, and asbestos), pulmonary fibrosis, organic dust diseases, chemical injury (due to irritant gasses and chemicals, e.g., chlorine, phosgene, sulfur dioxide, hydrogen sulfide, nitrogen dioxide, ammonia, and hydrochloric acid), smoke injury, thermal injury (e.g., burn, freeze), asthma, allergy, bronchoconstriction, hypersensitivity pneumonitis, parasitic diseases, Goodpasture's Syndrome, pulmonary vasculitis, and immune complex-associated inflammation.

[0259] In a specific embodiment, the present invention provides methods of treating a complement related disease or disorder by administering to a subject in need thereof an effective amount of the antibodies of the invention, wherein said disease or disorder is asthma, arthritis (e.g., rheumatoid arthritis), autoimmune heart disease, multiple sclerosis, inflammatory bowel disease, ischemia-reperfusion injuries, Barraquer-Simons Syndrome, hemodialysis, systemic lupus, lupus erythematosus, psoriasis, multiple sclerosis, transplantation, diseases of the central nervous system such as Alzheimer's disease and other neurodegenerative conditions, aHUS, glomerulonephritis, bullous pemphigoid or MPGN II. [0260] In a specific embodiment, the present invention provides methods of treating glomerulonephritis by administering to a subject in need thereof an effective amount of a composition comprising an antibody of the present invention. Symptoms of glomerulonephritis include, but not limited to, proteinuria; reduced glomerular filtration rate (GFR); serum electrolyte changes including azotemia (uremia, excessive blood urea nitrogen-BUN) and salt retention, leading to water retention resulting in hypertension and edema; hematuria and abnormal urinary sediments including red cell casts; hypoalbuminemia; hyperlipidemia; and lipiduria. In a specific embodiment, the present invention provides methods of treating paroxysmal nocturnal hemoglobinuria (PNH) by administering to a subject in need thereof an effective amount of a composition comprising an antibody of the present invention

[0261] In a specific embodiment, the present invention provides methods of reducing the dysfunction of the immune and hemostatic systems associated with extracorporeal circulation by administering to a subject in need thereof an effective amount of a composition comprising an antibody of the present invention. The antibodies of the present invention can be used in any procedure which involves circulating the patient's blood from a blood vessel of the patient, through a conduit, and back to a blood vessel of the patient, the conduit

having a luminal surface comprising a material capable of causing at least one of complement activation, platelet activation, leukocyte activation, or platelet-leukocyte adhesion. Such procedures include, but are not limited to, all forms of ECC, as well as procedures involving the introduction of an artificial or foreign organ, tissue, or vessel into the blood circuit of a patient.

[0262] Subjects to be treated with therapeutic agents of the present invention can also be administered other therapeutic agents with know methods of treating conditions associated with macular degeneration, such as antibiotic treatments as described in U.S. Pat. No. 6,218,368. In other treatments, immunosuppressive agents such as cyclosporine, are agents capable of suppressing immune responses. These agents include cytotoxic drugs, corticosteriods, nonsteroidal antiinflammatory drugs (NSAIDs), specific T-lymphocyte immunosuppressants, and antibodies or fragments thereof (see Physicians' Desk Reference, 53rd edition, Medical Economics Company Inc., Montvale, N.J. (1999). Immunosuppressive treatment is typically continued at intervals for a period of a week, a month, three months, six months or a year. In some patients, treatment is administered for up to the rest of a patient's life.

[0263] When the therapeutic agents of the present invention are administered together with another agent, the two can be administered sequentially in either order or simultaneously. In some aspects, an antibody of the present invention is administered to a subject who is also receiving therapy with a second agent (e.g., verteporfin). In other aspects, the binding molecule is administered in conjunction with surgical treatments.

[0264] Suitable agents for combination treatment with C5-binding antibodies include agents known in the art that are able to modulate the activities of complement components (see, e.g., U.S. Pat. No. 5,808,109). Other agents have been reported to diminish complement-mediated activity. Such agents include: amino acids (Takada, Y. et al. Immunology 1978, 34, 509); phosphonate esters (Becker, L. Biochem. Biophy. Acta 1967, 147, 289); polyanionic substances (Conrow, R. B. et al. J. Med. Chem. 1980, 23, 242); sulfonyl fluorides (Hansch, C.; Yoshimoto, M. J. Med. Chem. 1974, 17, 1160, and references cited therein); polynucleotides (De-Clercq, P. F. et al. Biochem. Biophys. Res. Commun. 1975, 67, 255); pimaric acids (Glovsky, M. M. et al. J. Immunol. 1969, 102, 1); porphines (Lapidus, M. and Tomasco, J. Immunopharmacol. 1981, 3, 137); several antiinflammatories (Burge, J. J. et al. J. Immunol. 1978, 120, 1625); phenols (Muller-Eberhard, H. J. 1978, in Molecular Basis of Biological Degradative Processes, Berlin, R. D. et al., eds. Academic Press, New York, p. 65); and benzamidines (Vogt, W. et al Immunology 1979, 36, 138). Some of these agents function by general inhibition of proteases and esterases. Others are not specific to any particular intermediate step in the complement pathway, but, rather, inhibit more than one step of complement activation. Examples of the latter compounds include the benzamidines, which block C1, C4 and C5 utilization (see, e.g., Vogt et al. Immunol. 1979, 36, 138).

[0265] Additional agents known in the art that can inhibit activity of complement components include K-76, a fungal metabolite from Stachybotrys (Corey et al., J. Amer. Chem. Soc. 104: 5551, 1982). Both K-76 and K-76 COOH have been shown to inhibit complement mainly at the C5 step (Hong et al., J. Immunol. 122: 2418, 1979; Miyazaki et al., Microbiol. Immunol. 24: 1091, 1980), and to prevent the generation of a

chemotactic factor from normal human complement (Bumpers et al., Lab. Clinc. Med. 102: 421, 1983). At high concentrations of K-76 or K-76 COOH, some inhibition of the reactions of C2, C3, C6, C7, and C9 with their respective preceding intermediaries is exhibited. K-76 or K-76 COOH has also been reported to inhibit the C3b inactivator system of complement (Hong et al., J. Immunol. 127: 104-108, 1981). Other suitable agents for practicing methods of the present invention include griseofulvin (Weinberg, in Principles of Medicinal Chemistry, 2d Ed., Foye, W. O., ed., Lea & Febiger, Philadelphia, Pa., p. 813, 1981), isopannarin (Djura et al., Aust. J. Chem. 36: 1057, 1983), and metabolites of Siphonodictyon coralli-phagum (Sullivan et al., Tetrahedron 37: 979, 1981).

[0266] A combination therapy regimen may be additive, or it may produce synergistic results (e.g., reductions in complement pathway activity more than expected for the combined use of the two agents). In some embodiments, the present invention provide a combination therapy for preventing and/ or treating AMD or another complement related disease as described above with a C5-binding antibody of the invention and an anti-angiogenic, such as anti-VEGF agent.

5.5. Diagnostic Uses

[0267] In one aspect, the invention encompasses diagnostic assays for determining C5 protein and/or nucleic acid expression as well as C5 protein function, in the context of a biological sample (e.g., blood, serum, cells, tissue) or from individual is afflicted with a disease or disorder, or is at risk of developing a disorder associated with AMD.

[0268] Diagnostic assays, such as competitive assays rely on the ability of a labelled analogue (the "tracer") to compete with the test sample analyte for a limited number of binding sites on a common binding partner. The binding partner generally is insolubilized before or after the competition and then the tracer and analyte bound to the binding partner are separated from the unbound tracer and analyte. This separation is accomplished by decanting (where the binding partner was preinsolubilized) or by centrifuging (where the binding partner was precipitated after the competitive reaction). The amount of test sample analyte is inversely proportional to the amount of bound tracer as measured by the amount of marker substance. Dose-response curves with known amounts of analyte are prepared and compared with the test results in order to quantitatively determine the amount of analyte present in the test sample. These assays are called ELISA systems when enzymes are used as the detectable markers. In an assay of this form, competitive binding between antibodies and C5-binding antibodies results in the bound C5 protein, preferably the C5 epitopes of the invention, being a measure of antibodies in the serum sample, most particularly, neutralising antibodies in the serum sample.

[0269] A significant advantage of the assay is that measurement is made of neutralising antibodies directly (i.e., those which interfere with binding of C5 protein, specifically, epitopes). Such an assay, particularly in the form of an ELISA test has considerable applications in the clinical environment and in routine blood screening.

[0270] Immunologic techniques employ polyclonal or monoclonal antibodies against the different epitopes of the various complement components (e.g., C3, C4, C5) to detect, e.g., the split products of complement components (see, e.g., Hugli et al., Immunoassays Clinical Laboratory Techniques 443-460, 1980; Gorski et al., J Immunol Meth 47: 61-73, 1981; Linder et al., J Immunol Meth 47: 49-59, 1981; and Burger et al., J Immunol 141: 553-558, 1988). Binding of the antibody with the split product in competition with a known concentration of labeled split product could then be measured. Various assays such as radio-immunoassays, ELISA's, and radial diffusion assays are available to detect complement split products.

[0271] The immunologic techniques provide high sensitivity to detect complement activation, since they allow measurement of split-product formation in blood from a test subject and control subjects with or without macular degeneration-related disorders. Accordingly, in some methods of the present invention, diagnosis of a disorder associated with ocular disorders is obtained by measurement of abnormal complement activation through quantification of the soluble split products of complement components in blood plasma from a test subject. The measurements can be performed as described, e.g., in Chenoweth et al., N Engl J Med 304: 497-502, 1981; and Bhakdi et al., Biochim Biophys Acta 737: 343-372, 1983. Preferably, only the complement activation formed in vivo is measured. This can be accomplished by collecting a biological sample from the subject (e.g., serum) in medium containing inhibitors of the complement system, and subsequently measuring complement activation (e.g., quantification of the split products) in the sample.

[0272] In the clinical diagnosis or monitoring of patients with disorders associated with ocular diseases or disorders, the detection of complement proteins in comparison to the levels in a corresponding biological sample from a normal subject is indicative of a patient with disorders associated with macular degeneration.

[0273] In vivo diagnostic or imaging is described in US2006/0067935. Briefly, these methods generally comprise administering or introducing to a patient a diagnostically effective amount of a C5 binding molecule that is operatively attached to a marker or label that is detectable by non-invasive methods. The antibody-marker conjugate is allowed sufficient time to localize and bind to complement proteins within the eye. The patient is then exposed to a detection device to identify the detectable marker, thus forming an image of the location of the C5 binding molecules in the eye of a patient. The presence of C5 binding antibody or an antigen-binding fragment thereof is detected by determining whether an antibody-marker binds to a component of the eye. Detection of an increased level in selected complement proteins or a combination of protein in comparison to a normal individual without AMD disease is indicative of a predisposition for and/or on set of disorders associated with macular degeneration. These aspects of the invention are also preferred for use in eye imaging methods and combined angiogenic diagnostic and treatment methods.

[0274] The invention also pertains to the field of predictive medicine in which diagnostic assays, prognostic assays, pharmacogenomics, and monitoring clinical trials are used for prognostic (predictive) purposes to thereby treat an individual prophylactically.

[0275] The invention also provides for prognostic (or predictive) assays for determining whether an individual is at risk of developing a disorder associated with dysregulation of complement pathway activity. For example, mutations in a C5 gene can be assayed in a biological sample. Such assays can be used for prognostic or predictive purpose to thereby prophylactically treat an individual prior to the onset of a disorder characterized by or associated with C5 protein, nucleic acid expression or activity.

[0276] Another aspect of the invention provides methods for determining C5 nucleic acid expression or C5 protein activity in an individual to thereby select appropriate therapeutic or prophylactic agents for that individual (referred to herein as "pharmacogenomics"). Pharmacogenomics allows for the selection of agents (e.g., drugs) for therapeutic or prophylactic treatment of an individual based on the genotype of the individual (e.g., the genotype of the individual examined to determine the ability of the individual to respond to a particular agent.)

[0277] Yet another aspect of the invention pertains to monitoring the influence of agents (e.g., drugs) on the expression or activity of C5 protein in clinical trials.

5.6. Pharmaceutical Compositions

[0278] The invention provides pharmaceutical compositions comprising the C5-binding antibodies (intact or binding fragments) formulated together with a pharmaceutically acceptable carrier. The compositions can additionally contain one or more other therapeutica agents that are suitable for treating or preventing a complement-associated disease (e.g., AMD). Pharmaceutically carriers enhance or stabilize the composition, or to facilitate preparation of the composition. Pharmaceutically acceptable carriers include solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible.

[0279] A pharmaceutical composition of the present invention can be administered by a variety of methods known in the art. The route and/or mode of administration vary depending upon the desired results. It is preferred that administration be intravenous, intramuscular, intraperitoneal, or subcutaneous, or administered proximal to the site of the target. In a specific embodiment, the antibodies of the invention are formulated so that they can be administered intravitreally into the eye. The pharmaceutically acceptable carrier should be suitable for intravenous, intramuscular, subcutaneous, parenteral, spinal or epidermal administration (e.g., by injection or infusion). Depending on the route of administration, the active compound, i.e., antibody, bispecific and multispecific molecule, may be coated in a material to protect the compound from the action of acids and other natural conditions that may inactivate the compound.

[0280] The composition should be sterile and fluid. Proper fluidity can be maintained, for example, by use of coating such as lecithin, by maintenance of required particle size in the case of dispersion and by use of surfactants. In many cases, it is preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol or sorbitol, and sodium chloride in the composition. Long-term absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate or gelatin.

[0281] Pharmaceutical compositions of the invention can be prepared in accordance with methods well known and routinely practiced in the art. See, e.g., Remington: The Science and Practice of Pharmacy, Mack Publishing Co., 20th ed., 2000; and Sustained and Controlled Release Drug Delivery Systems, J. R. Robinson, ed., Marcel Dekker, Inc., New York, 1978. Pharmaceutical compositions are preferably manufactured under GMP conditions. Typically, a therapeutically effective dose or efficacious dose of the C5-binding antibody is employed in the pharmaceutical compositions of the invention. The C5-binding antibodies are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art. Dosage regimens are adjusted to provide the optimum desired response (e.g., a therapeutic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subjects to be treated; each unit contains a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

[0282] Actual dosage levels of the active ingredients in the pharmaceutical compositions of the present invention can be varied so as to obtain an amount of the active ingredient which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient. The selected dosage level depends upon a variety of pharmacokinetic factors including the activity of the particular compositions of the present invention employed, or the ester, salt or amide thereof, the route of administration, the time of administration, the rate of excretion of the particular compound being employed, the duration of the treatment, other drugs, compounds and/or materials used in combination with the particular compositions employed, the age, sex, weight, condition, general health and prior medical history of the patient being treated, and like factors.

[0283] A physician or veterinarian can start doses of the antibodies of the invention employed in the pharmaceutical composition at levels lower than that required to achieve the desired therapeutic effect and gradually increase the dosage until the desired effect is achieved. In general, effective doses of the compositions of the present invention, for the treatment of an allergic inflammatory disorder described herein vary depending upon many different factors, including means of administration, target site, physiological state of the patient, whether the patient is human or an animal, other medications administered, and whether treatment is prophylactic or therapeutic. Treatment dosages need to be titrated to optimize safety and efficacy. For systemic administration with an antibody, the dosage ranges from about 0.0001 to 100 mg/kg, and more usually 0.01 to 15 mg/kg, of the host body weight. An exemplary treatment regime entails systemic administration once per every two weeks or once a month or once every 3 to 6 months. For intravitreal administration with an antibody, the dosage ranges from about 0.0001 to about 10 mg. An exemplary treatment regime entails systemic administration once per every two weeks or once a month or once every 3 to 6 months.

[0284] Antibody is usually administered on multiple occasions. Intervals between single dosages can be weekly, monthly or yearly. Intervals can also be irregular as indicated by measuring blood levels of C5-binding antibody in the patient. In some methods of systemic administration, dosage is adjusted to achieve a plasma antibody concentration of 1-1000 μ g/ml and in some methods 25-500 μ g/ml. Alternatively, antibody can be administered as a sustained release formulation, in which case less frequent administration is

required. Dosage and frequency vary depending on the halflife of the antibody in the patient. In general, humanized antibodies show longer half life than that of chimeric antibodies and nonhuman antibodies. The dosage and frequency of administration can vary depending on whether the treatment is prophylactic or therapeutic. In prophylactic applications, a relatively low dosage is administered at relatively infrequent intervals over a long period of time. Some patients continue to receive treatment for the rest of their lives. In therapeutic applications, a relatively high dosage at relatively short intervals is sometimes required until progression of the disease is reduced or terminated, and preferably until the patient shows partial or complete amelioration of symptoms of disease. Thereafter, the patient can be administered a prophylactic regime.

6. EXAMPLES

[0285] The following examples are provided to further illustrate the invention but not to limit its scope. Other variants of the invention will be readily apparent to one of ordinary skill in the art and are encompassed by the appended claims.

Example 1

Generation of Cynomolgus C5 and Human C5

1. Generation of Cynomolgus C5

[0286] Cynomolgus C5 was purified successfully from cynomolgus serum by affinity chromatography using MOR07086 hu IgG1. Cynomolgus C5 was quality tested by SDS-PAGE, Western blot, mass spectrometry and hemolytic assays. Quality of purified cynomolgus C5 was shown to be high by SDS-PAGE and Western blot. Lack of C3 contamination was confirmed by SDS and Western blot. In addition, the identity of cynomolgus C5 sequence was determined by mass spectrometric analysis and the activity of purified cynomolgus C5 was tested in hemolytic assays. In hemolytic assays the new preparation was equipotent to human C5 (e.g., Sample 6, which was used in affinity maturation pannings, reconstituted complement activity of 20% human C5-depleted serum with similar activity to purified human C5).

2. Quality Control of Human and Cynomolgus Biotinylated and Non-Biotinylated C5 Proteins

[0287] Bioactivity of purified human C5 was characterized and confirmed by the alternative pathway hemolytic activity. C5 was spiked into C5-depleted human serum at varying concentrations to obtain an EC50. EC50 values ranging between 0.02-0.1 nM were considered acceptable.

[0288] Before using, the bioactivity of every purified human C5 protein lot was tested in the hemolytic assay. The same quality control was done for cynomolgus C5 after purification from cynomolgus serum. After biotinylation of human and cynomolgus C5, the bioactivity of the material was also tested in hemolytic assays, in order to analyze if there was a loss of activity caused by biotinylation.

Example 2

Generation of C5-Specific Antibodies from the HuCAL GOLD® Library

[0289] C5 antibodies were generated by selection of clones having high binding affinities, using as the source of antibody

variant proteins a commercially available phage display library, the MorphoSys HuCAL GOLD® library.

[0290] HuCAL GOLD® library is a Fab library (Knappik et al., 2000) in which all six CDRs are diversified by appropriate mutation, and which employs the CysDisplayTM technology for linking the Fab to the phage surface (WO01/ 05950, Löhning et al., 2001).

1. Selection by Panning of C5 Specific Antibodies from the Library

[0291] For the selection of antibodies against C5, two different panning strategies were applied. The six different pools were individually subjected to three rounds of: (a) a solid phase panning where the antigens (human and cynomolgus C5) were directly coated on Maxisorp 96 well microtiter plates (Nunc, Wiesbaden, Germany); or (b) a solution panning with biotinylated human and cyno C5 where the phageantigen complex was captured by Streptavidin magnetic beads (Dynabeads M-280; Dynal) for each panning pool.

[0292] The HuCAL GOLD® library was amplified in 2×YT medium containing 34 µg/ml chloramphenicol and 1% glucose (2×YT-CG). After infection with VCSM13 helper phage at an OD600 nm of 0.5 (30 min at 37° C. without shaking; 30 min at 37° C. shaking at 250 rpm), cells were spun down (4120 g; 5 min; 4° C.), resuspended in 2×YT/34 µg/ml chloramphenicol/50 µg/ml kanamycin/0.25 mM IPTG and grown overnight at 22° C. Phage were PEG-precipitated from the supernatant, resuspended in PBS/20% glycerol and stored at -80° C. Phage amplification between two panning rounds was conducted as follows: mid-log phase E. coli TG1 cells were infected with eluted phage and plated onto LB-agar supplemented with 1% of glucose and 34 µg/ml of chloramphenicol (LB-CG plates). After overnight incubation at 30° C., the TG1 colonies were scraped off the agar plates and used to inoculate 2×YT-CG until an OD600 nm of 0.5 was reached. VCSM13 helper phage were added for infection as described above.

[0293] Taken together 354 clones derived from all panning strategies were sequenced, resulting in 64 unique clones with the desired profile: binding to human and cynomolgus C5 and no binding to the counter targets C3 and C4.

[0294] 45 clones derived from solid phase pannings and 19 clones from solution pannings were selected for protein expression and purification. Four Fabs from solid phase pannings (MOR06525, MOR06756, MOR06757 and MOR06763) and 6 Fabs from solution pannings (MOR07086, MOR07087, MOR07091, MOR07092, MOR07093 and MOR07094) entered affinity maturation.

Solid Phase Panning Against C5 on Directly Coated Protein

[0295] The first panning variant was solid phase panning alternating human C5 (first and third round of selection) and cynomolgus C5 (second round of selection).

[0296] Three wells of a Maxisorp plate (F96 Nunc-Immunoplate) were coated with 200 μ l of 50 nM C5 each o/n at 4° C. The coated wells were washed 2× with 400 μ l PBS and blocked with 350 μ l 5% MPBS for 2 h at RT on a microtiter plate shaker. For each panning about 10¹³ HuCAL GOLD® phage-antibodies were blocked with equal volume of PBST/ 5% milk powder for 2 h at room temperature. The coated wells were washed 2× with 400 μ l PBS after the blocking procedure. 200 μ l of pre-blocked HuCAL GOLD® phage-antibodies were added to each coated well and incubated for 2 h at RT on a shaker. Washing was performed by adding five times 350 μ l PBS/0.05% Tween, followed by washing

another five times with PBS. For some panning conditions a more stringent wash procedure was applied.

[0297] Elution of phage from the plate was performed with 200 μ l 20 mM DTT in 10 mM Tris/HCl pH8 per well for 10 min. The DTT phage eluate was added to 15 ml of *E. coli* TG1, which were grown to an OD600 of 0.6-0.8 at 37° C. in 2YT medium and incubated in 50 ml plastic tubes for 45 min at 37° C. without shaking for phage infection. After centrifugation for 5 min at 4120×g, the bacterial pellets were each resuspended in 600 μ l 2×YT medium, plated on 3×YT-CG agar plates and incubated overnight at 37° C. Colonies were scraped off the plates and phages were rescued and amplified as described above.

[0298] The second and third rounds of solid phase panning were performed according to the protocol of the first round. In the second selection round for some panning conditions the output of the first round was used for selections on cynomolgus C5 in order to enrich for cynomolgus cross-reactive antibodies.

[0299] For some panning conditions washing stringency was increased and antigen concentration was decreased within the three round of selection in order to generate high affinity antibodies.

[0300] The HuCAL GOLD® phagemid library was used to select specific Fab antibody fragments against human C5. First strategy was a solid phase panning on directly coated human C5 protein (panning procedure described above).

[0301] After the 3rd panning round, the enriched phage pools were subcloned from the pMORPH®23 library vector (allowing efficient antibody display on the phage surface) into the pMORPH®×9_Fab_MH expression vector which mediates periplasmic expression of soluble Fabs. Single clones were picked and soluble Fabs were expressed from these single clones.

[0302] In total, 6624 clones were analyzed in primary screening which was performed by binding of the Fabs directly from the bacterial lysates to human C5 immobilized on Maxisorp microtiter plates. 1660 hits were obtained from the primary screening on human C5 with signals >5-fold over background. 384 hits were further analyzed in a secondary screening to confirm binding on human C5 and to screen for binding to the counter targets human C3 and C4.

[0303] Many primary hits could be confirmed on human C5 and showed no cross-reactivity to human C3 and C4, but only 6 Fabs had weak cross-reactivity to cynomolgus C5.

[0304] As a first consequence new solid phase pannings were performed alternating on human and cynomolgus C5. In parallel, quality controls of the purified cynomolgus C5 batch revealed a high amount of cynomolgus C3 within the cynomolgus C5 batch. Considering this results, a new method to screen for cynomolgus cross-reactive antibodies was applied. Cynomolgus C5 was captured from cynomolgus serum using an C5-binding polyclonal antibody (see Example 3, section 3). Using this method the initial primary hits were screened again on cynomolgus C5 and 56 clones were confirmed for binding to cynomolgus C5.

[0305] For the alternating solid phase pannings, the 1st round output of the most successful 12 human solid phase pannings was used for selections on cynomolgus C5 (protein batch contaminated with cynomolgus C3; not known during pannings). 376 clones were confirmed in a secondary screening for binding to human C5 and 361 clones for binding to cynomolgus C5 captured from cynomolgus serum.

Solution Panning on Biotinylated C5 Protein

[0306] The second panning variant was solution panning against biologically active (in hemolytic assays) biotinylated human C5 and biotinylated cynomolgus C5.

[0307] For this panning 200 μ l of Streptavidin magnetic beads (Dynabeads M-280; Dynal) were washed once with PBS and blocked with Chemiblocker for 2 h at RT. 300 μ l of the PBS diluted phage were blocked also with Chemiblocker for 1-2 h at RT on a rotator. The blocked phages were twice pre-adsorbed against 50 μ l blocked Streptavidin magnetic beads for 30 min. The phage supernatant was transferred to a new blocked 2 ml reaction tube and human biotinylated C5 was added and incubated for 1 h at RT on a rotator. The blocked to each panning pool an incubated for 10 min on a rotator. The beads were collected with a particle separator (Dynal MPC-E) for approx. 2.5 min and the solution was removed carefully.

[0308] Beads were then washed $7 \times$ in PBS/0.05% Tween using a rotator, followed by washing another three times with PBS. Elution of phage from the Dynabeads was performed by adding 200 µl 20 mM DTT in 10 mM Tris/HCl pH 8 to each tube and incubation for 10 min. Dynabeads were removed by the magnetic particle separator and the supernatant was added to 15 ml of an E. coli TG-1 culture grown to OD600 nm of 0.6-0.8. Beads were then washed once with 200 µl PBS and together with additionally removed phages the PBS was added to the 15 ml E. coli TG-1 culture. For phage infection, the culture was incubated in 50 ml plastic tubes for 45 min at 37° C. without shaking. After centrifugation for 5 min at 4120×g, the bacterial pellets were resuspended each in $600 \,\mu$ l 2×YT medium, plated on 3×YT-CG agar plates and incubated overnight at 37° C. Colonies were scraped off the plates and phages were rescued and amplified as described above. The second and third rounds of selection were performed in an identical way to the first round of selection.

[0309] A further panning strategy was solution panning using human C5 and alternating human and cynomolgus C5 (protein batch contaminated with cynomolgus C3, not known during pannings). Therefore the proteins were biotinylated and the retained bio-functionality after the biotinylation procedure was confirmed in hemolytic bioassays.

[0310] The phage-antigen complex was captured on Streptavidin magnetic beads via the biotin moiety of the antigen. After washing only specific bound phage were eluted (panning procedure described above).

[0311] First screening was done on directly coated proteins (see Example 3, section 1) and only 80 clones could be confirmed on human C5. Due to the fact that during the pannings the antigen was kept in solution, a new screening method was developed. In a solution ELISA the Fabs were incubated with biotinylated antigen on a NeutrAvidin plate. Using this solution screening procedure, a significantly higher amount of human and cynomolgus C5 specific clones could be selected. These results confirmed that many Fabs derived from solution pannings recognize C5 only in solution or when captured (e.g. via a polyclonal C5-binding antibody).

2. Subcloning and Expression of Selected Fab Fragments

[0312] To facilitate rapid expression of soluble Fabs, the Fab-encoding inserts of the selected HuCAL GOLD® phages were subcloned via XbaI and EcoRI into the *E. coli* expression vector pMORPH®x9_MH. Fab fragments carry a C-terminal Myc tag and as a second C-terminal tag the 6× His-tag

(Chen et al., Gene 139:73-75 (1994)). After transformation of the expression plasmids into E. coli TG1 F-cells chloramphenicol-resistant single clones were picked into the wells of a sterile 384-well microtiter plate pre-filled with 60 µl 2×YT-CG medium and grown o/n at 30° C. 5 µl of each E. coli TG-1 o/n culture were transferred to a fresh, sterile 96-well microtiter plate pre-filled with 40 µl 2×YT medium supplemented with 34 µg/ml chloramphenicol per well. The microtiter plates were incubated at 30° C. shaking at 400 rpm on a microplate shaker until the cultures were slightly turbid (~2-4 h) with an OD600 nm of ~0.5. To these expression plates, 10 µl 2×YT medium supplemented with 34µ/ml chloramphenicol and 3 mM IPTG (isopropyl- β -D-thiogalactopyranoside) was added per well (end concentration 0.5 mM IPTG). The microtiter plates were sealed with a gas-permeable tape, and incubated o/n at 30° C. shaking at 400 rpm. To each well of the expression plates, 15 µl BEL buffer was added containing 2.5 mg/ml lysozyme, 4 mM EDTA and 10 U/µl Benzonase and incubated for 1 h at 22° C. on a microtiter plate shaker (400 rpm) followed by an optional freezing step for at least 2 h at -80° C. The BEL extracts were used for binding analysis by ELISA or Fab SET screening after affinity maturation.

[0313] Expression of Fab fragments encoded by pMORPH® x9_Fab_MH in TG-1 cells was carried out in shaker flask cultures using 750 ml of 2×YT medium supplemented with 34 µg/ml chloramphenicol. Cultures were shaken at 30° C. until the OD600 nm reached 0.5. Expression was induced by addition of 0.75 mM IPTG for 20 h at 30° C. Cells were disrupted using lysozyme and Fab fragments isolated by Ni-NTA chromatography (Qiagen, Hilden, Germany). Buffer exchange to 1× Dulbecco's PBS (pH 7.2) was performed using PD10 columns. Samples were filtered sterile $(0.2 \ \mu m, Millipore)$. Purity of samples was determined in denatured, reduced state by SDS-PAGE (15% Criterion Gels, BioRad) and in native state by size exclusion chromatography (HP-SEC). Protein concentrations were determined by UVspectrophotometry (Krebs et al., J. Immunol. Methods 254: 67-84 (2001)).

[0314] On Fab level, the overall expression rates and the percentage of monomeric fraction in SEC (Size Exclusion Chromatography) ranged from acceptable to good for most of the identified antibody fragments. 64 parental Fabs were expressed and 61 Fabs could be purified. 60 affinity matured Fabs were purified in the mg scale. Most of the Fabs were good expressors and had no aggregation tendency.

Example 3

Identification of C5-Specific Antibodies from the HuCAL GOLD® Library

[0315] Below four different Enzyme Linked Immunosorbent Assay (ELISA) methods describe the screening of C5-binding antibodies (as bacterial BEL lysates or purified Fabs) on specific and counter antigens.

1. Screening on Directly Coated Protein

[0316] Maxisorp (Nunc, Rochester, N.Y., USA) 384 well plates were coated with 20 μ l per well of 2.5 μ g/ml antigen (human C5 and the counter proteins human C3 and C4) in PBS, pH 7.4 o/n at 4° C. In parallel, plates were coated with 20 μ l per well of 5 μ g/ml sheep anti-human IgG, Fd fragment specific (The Binding Site, Birmingham, UK), diluted in PBS, pH 7.4 to check for Fab expression level.

[0317] The plates were blocked with PBS/0.05% Tween 20 (PBST) containing 5% milk powder for 1-2 h at RT. After washing the wells with PBST, BEL-extracts, purified HuCAL GOLD® Fabs or control Fabs diluted in PBS were added and incubated for 1 h at RT. To detect Fab binding, anti-HIS6 antibody coupled to peroxidase was applied (Roche).

[0318] For detection of POD-conjugates fluorogenic substrate QuantaBlu (Pierce) was used according to manufacturer's instructions. Between all incubation steps, the wells of the microtiter plates were washed three times and five times with PBST after the final incubation with the secondary antibody. Fluorescence was measured in a Tecan GENios Pro plate reader.

2. Solution Screening with Biotinylated Proteins

[0319] The ELISA method described below was used for screening of HuCAL GOLD® Fabs after solution pannings using biotinylated complement proteins.

[0320] NeutrAvidin plates were blocked with 1× Chemiblocker (Chemicon) diluted in PBS o/n at 4° C. These plates were used to screen for binding to human C5 and to the counter targets C3 and C4. In parallel, Maxisorp 384 well plates (Nunc, Rochester, N.Y., USA) were coated with 20 μ l per well of 5 μ g/ml sheep anti-human IgG, Fd fragment specific (The Binding Site, Birmingham, UK), diluted in PBS, pH 7.4. These plates were used to check for Fab expression levels and for non-specific biotin binding. On the next day, coated Maxisorp plates were washed 2× with PBST and blocked with 3% BSA in TBS for 1-2 h at RT. Periplasmic BEL extracts containing Fabs or purified HuCAL GOLD® Fabs were added to both blocked NeutrAvidin and Maxisorp plates.

[0321] Subsequently, 20 μ l per well of biotinylated human C5 (to detect specific binding) and in parallel, biotinylated human C3 and C4 (to detect unwanted binding) were added to wells of the NeutrAvidin plates. The biotinylated antigens were incubated with the HuCAL GOLD® Fabs for 1-2 h at RT. Biotinylated unrelated antigen Transferrin was then added to the Maxisorp plates to check for biotin binding Fabs (in this case the HuCAL®-Fab fragments were previously captured via anti-Fd antibody).

[0322] Following secondary antibodies were applied for detection: Alkaline phosphatase (AP)-conjugated Streptavidin-AP AffiniPure F(ab')2 fragment, goat anti-human, was added to the Maxisorp expression plates; anti-HIS6 Peroxidase conjugated mouse antibody, Roche, was added to the NeutrAvidin plates and Streptavidin-Alkaline Phosphatase, ZYMED, was added to the Maxisorp plates with the biotinylated Transferrin.

[0323] For detection of AP-conjugates, fluorogenic substrate AttoPhos (Roche Diagnostics, Mannheim, Germany) and for detection of POD-conjugates, fluorogenic substrate QuantaBlu (Pierce) were used according to manufacturer's instructions. Fluorescence was measured in a Tecan GENios Pro plate reader.

[0324] Using this method it was possible to screen for antihuman C5 Fabs which recognize human C5 in solution and to exclude antibodies binding to the biotin moiety of the target antigens.

3. Determination of Cross-Reactivity to Cynomolgus C5

[0325] A polyclonal C5-binding antibody (US Biological Cat#C7850-24) was used to capture cynomolgus C5 from cynomolgus serum.

[0326] 384 well Maxisorp plates were coated with 20 μ /well of 5 μ g/ml polyclonal C5-binding in PBS and incubated o/n at 4° C. On the next day the plates were washed 3× with PBST and blocked with 100 μ /well of diluent (4% BSN

0.1% Tween20/0.1% Triton-X 100/PBS) for 2 hours at RT. Cynomolgus serum was diluted 1:20 in diluent (4% BSN 0.1% Tween20/0.1% Triton-X 100/PBS) (~approx. concentration of cynomolgus C5 4 µg/ml) and 20 µl/well was added to the 2×PBST washed Maxisorp plates. After 1 h incubation at RT the plates were washed 3×PBST and BEL lysates containing Fab fragments or purified Fabs were added and incubated for 1 h at RT. The plates were washed again and detection antibody anti-HIS6-POD (Roche #1965085), was added. POD substrate, BM Blue, soluble, (Roche Applied Science) was added and the reaction was stopped with 1M H2SO4. Absorbance was read at 450 nm using the BMG Reader device.

Example 4

Affinity Maturation

1. Construction of Affinity Maturation Libraries of Selected C5-Binding Fabs

[0327] To increase affinity and biological activity of selected antibody fragments, L-CDR3 and H-CDR2 regions were optimized in parallel by cassette mutagenesis using trinucleotide directed mutagenesis (see e.g., Virnekas et al., Nucleic Acids Res. 22:5600-5607 (1994)), while the framework regions were kept constant. Prior to cloning for affinity maturation, all parental Fab fragments were transferred from the corresponding expression vector (pMORPH®x9_MH) into the CysDisplayTM vector pMORPH®25 via Xbal/EcoRI. pMORPH®25 was created from the HuCAL GOLD® display vector pMORPH®23 by removal of one BssHII site interfering with library cloning for H-CDR2 optimization. For optimizing L-CDR3 of parental Fabs, the L-CDR3, framework 4 and the constant region of the light chains (405 bp) of the binders were removed by Bpil/Sphl and replaced by a repertoire of diversified L-CDR3s together with framework 4 and the constant domain.

[0328] 10 parental C5-binding Fabs were divided in 7 pools according to different selection criteria and only Fabs with same framework were put together: (1) MOR07086; (2) MOR06525+6756 (same framework); (3) MOR06757; (4) MOR06763; (5) MOR07087; (6) MOR07091+7092 (same framework); (7) MOR07093+7094 (same framework).

[0329] Approximately 1.5 μ g of the single Fab vector fragment and of the Fab pool were ligated with a 3 to 5-fold molar excess of the insert fragment carrying the diversified L-CDR3s. In a second library set, the H-CDR2 (Xhol/BssHII) was diversified while the connecting framework regions were kept constant. In order to monitor the cloning efficiency, the parental H-CDR2 was replaced by a dummy before the diversified H-CDR2 cassette was cloned in.

[0330] Ligation mixtures of the different libraries were electroporated into *E. coli* TOP10 F' cells (Invitrogen) yielding from 2×10^7 to 2×10^8 independent colonies. The libraries were amplified. For quality control, several single clones per library were randomly picked and sequenced using primers CFR84 (VL) and OCAL_Seq_Hp (VH).

[0331] As described above, seven maturation sub pools were generated and kept separate during the subsequent selection process.

[0332] 14 different affinity maturation libraries (one LCDR3 and one HCDR3 library for each lead or pool) were generated by standard cloning procedures and transformation of the diversified clones into electro-competent *E. coli*

TOP10F' cells (Invitrogen). Library sizes were good, being in the range of $2 \times 10^7 \cdot 5 \times 10^8$. Sequencing of randomly picked clones showed a diversity of 100%. No parental binders but derivatives of all respective parental input binders were found. Finally phages of all 14 libraries were prepared separately.

TABLE 2

	Overview of maturation libraries							
MOR0	Maturation	VH/VL Type	Library Size					
6757	HCDR2	VH3	3.70 × 10E7					
6763	HCDR2	VH3	4.95 × 10E7					
7086	HCDR2	VH1A	$1.58 \times 10E8$					
7087	HCDR2	VH1A	7.85 × 10E7					
6525 + 6756	HCDR2	VH5	5.22 × 10E7					
7091 + 7092	HCDR2	VH5	3.51 × 10E7					
7093 + 7094	HCDR2	VH2	2.01 × 10E7					
6757	LCDR3	Vkappa1	1.89 × 10E7					
6763	LCDR3	Vlambda2	7.35 × 10E7					
7086	LCDR3	Vlambda3	7.54 × 10E7					
7087	LCDR3	Vkappa1	5.46 × 10E7					
6525 + 6756	LCDR3	Vlambda2	8.50 × 10E7					
7091 + 7092	LCDR3	Vlambda3	4.93 × 10E8					
7093 + 7094	LCDR3	Vlambda2	$1.33 \times 10E8$					

2. Preparation of Antibody-Phages for Affinity Maturation

[0333] The HuCAL® maturation libraries were amplified in 2×YT medium containing 34 μ g/ml chloramphenicol and 1% glucose (2×YT-CG). After infection with VCSM13 helper phage at an OD600 nm of 0.5 (30 min at 37° C. without shaking; 30 min at 37° C. shaking at 250 rpm), cells were spun down (4120×g; 5 min; 4° C.), resuspended in 2×YT/34 μ g/ml chloramphenicol/50 μ g/ml kanamycin/0.25 mM IPTG and grown o/n at 22° C. Phages were PEG-precipitated twice from the supernatant, resuspended in PBS and used for the maturation pannings described below.

3. Standard Solution Maturation Panning on Biotinylated C5 Protein

[0334] About 10^{12} phages rescued from the generated affinity maturation libraries, as described above, were subjected to pannings performed under very stringent conditions to select for affinity improved C5 specific Fabs.

[0335] Solution pannings using the respective phage pools were either performed using biotinylated human C5 or alternating biotinylated human and cynomolgus C5 proteins. In order to increase panning stringency and to select for improved off-rates, antigen concentration was decreased and prolonged washing periods were applied (washing conditions are listed in Table 3).

TABLE 3

Increased washing conditions within the selection rounds of solution maturation pannings							
Selection Rd. Washing conditions (modified: stringent)							
1st round	4x PBS/0.05% Tween 5 min on rotator 3x PBS/0.05% Tween 15 min on rotator-> transfer magnetic beads with the captured antigen and phages to a fresh blocked tube 4x PBS quick 3x PBS 5 min on rotator-> transfer magnetic beads with the captured antigen and phages to a fresh blocked tube						

TABLE 3-continued

solution maturation pannings					
Selection Rd.	Washing conditions (modified: stringent)				
2nd round	3x PBS/0.05% Tween quick				
	7x PBS/0.05% Tween 15 min on rotator-> transfer				
	magnetic beads with the captured antigen and phages				
	to a fresh blocked tube				
	3x PBS quick				
7x PBS 15 min on rotator-> transfer magnetic					
	beads with the captured antigen and phages to a				
	fresh blocked tube				
3rd round	5x PBS/0.05% Tween quick				
	8x PBS/0.05% Tween 15 min on rotator				
	1x PBS/0.05% Tween o/n on rotator				
	3x PBS/0.05% Tween quick				
	6x PBS/0.05% Tween 15 min on rotator -> transfer				
	magnetic beads with the captured antigen and phages				
	to a fresh blocked tube				

[0336] Pre-blocked phage (1:2 mixture with $2\times$ Chemiblocker incubated for 1 h at RT) were incubated with low concentration of biotinylated C5 protein for 1-2 h at RT. The panning strategy is similar to a standard solution panning described above. The phage antigen complex was captured via the biotin moiety of C5 to pre-blocked Streptavidin magnetic beads 30 min at RT. Beads were then washed more stringently compared to a normal panning. Elution and amplification of phage was performed as described above.

[0337] The second and third rounds of selection were performed in an identical way to the first round, but at higher stringency washing conditions and lower antigen concentrations. For each antibody lead or pool several different pannings were performed. For each panning strategy different stringency conditions were applied. Panning strategies are summarized in Table 4.

TABLE 4

	Overview of solution maturation pannings 1783 and 1784 on biotinylated human C5 and biotinylated cynomolgus C5							
Panning #	Library	Panning mode	Antigen 1st round	Antigen 2nd round	Antigen 3rd round	Antigen Conc.	Washing	
1783.1 1783.2 1783.3 1783.4 1783.5 1783.6 1783.7 1783.8	MOR06525 + 6756 HCDR2 MOR07086 HCDR2 MOR06763 HCDR2 MOR07087 HCDR2 MOR06525 + 6756 LCDR3 MOR07086 LCDR3 MOR06763 LCDR3 MOR07087 LCDR3	solution Streptavidin beads	human C5	human C5	human C5	50 nM human/ 5 nM human/ 0.25 nM human	modified (more stringent)	
1783.9 1783.10 1783.11 1783.12 1783.13 1783.14	MOR06525 + 6756 HCDR2 MOR07086 HCDR2 MOR06763 HCDR2 MOR06525 + 6756 LCDR3 MOR07086 LCDR3 MOR07086 LCDR3	solution Streptavidin beads	human C5	cyno C5	human C5	25 nM human/ 5 nM cyno/ 0.25 nM human	modified (more stringent)	
1784.1 1784.2 1784.3 1784.4 1784.5 1784.6	MOR06757 HCDR2 MOR07091 + 7092 HCDR2 MOR07093 + 7094 HCDR2 MOR06757 LCDR3 MOR07091 + 7092 LCDR3 MOR07093 + 7094 LCDR3	solution Streptavidin beads	human C5	human C5	human C5	50 nM human/ 5 nM human/ 0.25 nM human	modified (more stringent)	
1784.7 1784.8 1784.9 1784.10 1784.11 1784.12 1784.13 1784.14	MOR06757 HCDR2 MOR07091 + 7092 HCDR2 MOR07093 + 7094 HCDR2 MOR07087 HCDR2 MOR06757 LCDR3 MOR07091 + 7092 LCDR3 MOR07093 + 7094 LCDR3 MOR07087 LCDR3	solution Streptavidin beads	human C5	cyno C5	human C5	25 nM human/ 5 nM cyno/ 0.25 nM human	modified (more stringent)	

TABLE 3-continued

Increased washing conditions within the selection rounds of solution maturation pannings

Selection Rd. Washing conditions (modified: stringent)

5x PBS quick 8x PBS 15 min on rotator -> transfer magnetic beads with the captured antigen and phages to a fresh blocked tube **[0338]** After maturation pannings, the enriched phagemid pools were sub-cloned into pMORPH®x9_MH expression vector.

4. Cross-Combination of Optimized VL (L-CDR3) with Optimized VH (H-CDR2)

[0339] For further improvement of affinity and potency, the independently optimized heavy and light chains from matured antibodies, derived from the same parental clone, were combined (see e.g., Rauchenberger et al., J. Biol. Chem. 278:38194-38205 (2003); Chen et al., J. Mol. Biol. 293:865-881 (1999); and Schier et al., J. Mol. Biol. 263:551-567 (1996)). This procedure, called cross-cloning, was applied for binders deriving from the same parental clones.

5. Affinity Screening and Maturation Panning Outcome

[0340] A total of 2640 clones derived from all pannings were screened as bacterial lysates for improved affinities on human C5. Preliminary affinities were estimated by solution equilibrium titration (SET). Based on their estimated affinities, clones derived from each parental Fab or Fab pools were sequenced. Table 5 shows number of sequenced clones and number of obtained unique sequences for each panning condition.

TABLE 5

Overview of affit Parental/Maturation	Antigen	Sequenced clones	Unique Sequences	Parental of unique
MOR06525 + 6756 HCDR2	hu/hu/hu	10	9	6525
MOR07086 HCDR2	hu/hu/hu	10	4	7086
MOR06763 HCDR2	hu/hu/hu	22	10	6763(8x), 7086(2x)
MOR07087 HCDR2	hu/hu/hu	10	4	7087
MOR06757 HCDR2	hu/hu/hu	10	0	
MOR07091 + 7092 HCDR2	hu/hu/hu	24	7	7092
MOR07093 + 7094 HCDR2	hu/hu/hu	10	10	7093
MOR06525 + 6756 LCDR3	hu/hu/hu	20	5	6756
MOR07086 LCDR3	hu/hu/hu	10	5	7086
MOR06763 LCDR3	hu/hu/hu	10	8	7086
MOR07087 LCDR3	hu/hu/hu	6	1	7086
MOR06757 LCDR3	hu/hu/hu	16	0	
MOR07091 + 7092 LCDR3	hu/hu/hu	6	6	7091(1x), 7092(5x)
MOR07093 + 7094 LCDR3	hu/hu/hu	10	9	7094
MOR06525 + 6756 HCDR2	hu/cyno/hu	10	8	6525
MOR07086 HCDR2	hu/cyno/hu	10	6	7086
MOR06763 HCDR2	hu/cyno/hu	22	5	6763
MOR06757 HCDR2	hu/cyno/hu	15	2	6757
MOR07091 + 7092 HCDR2	hu/cyno/hu	15	6	7091(3x), 7092(3x)
MOR07093 + 7094 HCDR2	hu/cyno/hu	10	10	7093
MOR07087 HCDR2	hu/cyno/hu	10	6	7087(5x), 7086(1x)
MOR06525 + 6756 LCDR3	hu/cyno/hu	12	0	
MOR07086 LCDR3	hu/cyno/hu	10	1	7086
MOR06763 LCDR3	hu/cyno/hu	10	0	
MOR06757 LCDR3	hu/cyno/hu	9	1	7094
MOR07091 + 7092 LCDR3	hu/cyno/hu	11	9	7091(6x), 7092(3x)
MOR07093 + 7094 LCDR3	hu/cyno/hu	10	7	7094
MOR07087 LCDR3	hu/cyno/hu	10	0	
Sum		338	139	

6. Sequence Analysis and Selection of Affinity Optimized Fabs for Protein Production

[0341] A very good diversity was maintained by recovering derivatives of all 10 parental Fabs. The nucleotide sequences of the heavy chain (VH) for 188 HCDR2 improved clones and the light chain (VL) variable regions for 150 improved LCDR3 clones were determined. 87 unique HCDR2 and 52 unique LCDR3 sequences were selected for a detailed analysis of sequence diversity within the matured CDRs. Fabs containing possible glycosylations sites in the CDRs were omitted from further characterizations.

[0342] The VH and VL sequence analysis and affinity data showed that all 10 parental Fabs yielded affinity-improved successors. Parental Fabs MOR06525, MOR06757, MOR06763, MOR07087 and MOR07094 yielded only HCDR2 improved clones and parentals MOR06756 and MOR07093 yielded only LCDR3 improved clones. MOR07086, MOR07091 and MOR07092 had matured clones for both VH and VL. This later allowed cross-cloning of VH and VL matured chains. From all data, 60 clones with best affinity and highest diversity in the matured CDRs were

(VL) were subcloned from the pMORPH®x9_MH Fab expression vectors into pMORPH®2_h_Ig vector series for human IgG2. Restriction enzymes Mfel, and Blpl were used for subcloning of the VH domain fragment into pMORPH®2_h_IgG2. Subcloning of the VL domain fragment into pMORPH®2_h_Igk was performed via the EcoRV and BsiWl sites, whereas subcloning into pMORPH®2_h_Ig λ 2 was done using EcoRV and Hpal.

[0345] All ten parental Fabs (MOR06525, 6756, 6757, 6763, 7086, 7087, MOR07091, 7092, 7093 and 7094) were converted into human IgG2. The IgGs were also expressed. 2. Conversion into Human IgG1AA Format

[0346] In order to express full length immunoglobulin, variable domain fragments of Fab heavy (VH) and light chains (VL) were subcloned from the Fab expression vectors into IgG1 expression vectors. Restriction enzymes Mfel, and Blpl were used for subcloning of the VH domain fragment into pMORPH $@2_h_IgG1AA$, in which leucines at positions 234 and 235 were mutated to alanines to abrogate FcR γ binding and attenuate effector functions. The restrictions enzymes EcoRV and Hpal were used to subclone of the VL domain fragment into pMORPH $@2_h_IgA2$.

selected for Fab expression. Selected VH and VL amino acid, as well as nucleotide sequences, are listed in Table 1.

Example 5

IgG Conversion

[0343] 1. Conversion into Human IgG2 Format[0344] In order to express full length immunoglobulin (Ig), variable domain fragments of heavy (VH) and light chains

[0347] Following matured Fabs with desired profile were subcloned into human IgG1AA format: MOR07832, 7834, 7872, 7876, 7829, 7871, 7865, 7873, 7830, 7878, 7910. Cross-cloning on IgG level was achieved by transfecting cells with combinations of light and heavy chain constructs. For example, MOR08114 was the product of the germlined heavy chain from MOR07829 and the germlined light chain from MOR07871. Table 6 summarizes the most relevant cross-cloned germlined IgGs.

TABLE 6

Overview of most relevant cross-cloned germlined IgGs									
MOR0	VH/VL	VH/VL		mature	matured CDRs				
Nr.	germlined	$\mathbf{V}\mathbf{H}$	$\mathbf{V}\mathbf{L}$	matured VH	matured VL	format			
8114	yes	7829	7871	7091/HCDR2	7091/LCDR3	hutg1AA			
8125	yes	7091	7873		7091/LCDR3	hutg1AA			
8126	yes	7829	7873	7091/HCDR2	7091/LCDR3	hutg1AA			
8127	yes	7830	7873	7091/HCDR2	7091/LCDR3	hutg1AA			
8128	yes	7092	7878		7092/LCDR3	hutg1AA			
8129	yes	7909	7092	7092/HCDR2		hutg1AA			
8130	yes	7909	7878	7092/HCDR2	7092/LCDR3	hutg1AA			
8131	yes	7910	7092	7092/HCDR2		hutg1AA			
8132	yes	791 0	7878	7092/HCDR2	7092/LCDR3	hutg1AA			

3. Transient Expression and Purification of Human IgG

[0348] Eukaryotic HKB11 and HEK293 cells were transfected with an equimolar ratio of IgG heavy and light chain expression vector DNA. Cell culture supernatant was harvested at 3 or 7 days post transfection and subjected to standard protein A affinity chromatography (rProteinA FF or MabSelect SURE, GE Healthcare). As not otherwise stated, buffer exchange was performed to 1× Dulbcecco's PBS (pH 7.2, Invitrogen) and samples were sterile filtered (0.2 μ m). Purity of IgG was analyzed under denaturing, reducing and non-reducing conditions in SDS-PAGE or by using Agilent BioAnalyzer and in native state by HP-SEC.

Example 6

Germlining

[0349] IgG constructs were germlined via site-directed mutagenesis using QuickChange® Site-Directed Mutagenesis Kit (Stratagene). The N-terminal DI of MOR08111 V λ 2 were changed to ES to match human germline sequence as well as to avoid a terminal Q (N-terminal Q can form pyroglutamine). N-terminal DI of MOR08110 V λ 3, MOR08113 V λ 3, and MOR08114 V λ 3 were germlined to SY, the most commonly found sequence in human λ 3 genes. N-terminal QVQ of MOR08111 VH2 was germlined to EVT to match a λ 2 gene and avoid terminal Q. N-terminal Q in MOR08109 VH5, MOR08110 VH5, MOR08113 VH5 and MOR08114 VH5 was also mutated to E.

[0350] Framework sequences for MOR08109 V λ 3 were synthesized to match the human λ 3j gene and cloned into the expression vector using Nhel and Hpal restriction sites. Sequence alignments of the antibodies variable domains with their respective closest related human germline sequences are shown in FIG. 1.

Example 7

Affinity Determination

1. Kon/Koff and K_D Determination of Anti-Human C5 Antibodies Using Surface Plasmon Resonance (Biacore)

[0351] It was determined that anti-Fab antibodies used to immobilize Fabs to the Biacore chip were influencing differently the binding affinity of each Fab for human C5, thus making the comparison of the Fabs to each other difficult. Biacore analysis was performed on IgG antibodies.

[0352] A CM4 chip was coated with 50 µg/ml goat antihuman Fc antibody (500-2000 RU) in 10 mM acetate buffer, pH 4.5, using standard EDC-NHS amine coupling chemistry. Each anti-human C5 IgG was captured on the chip in HBS-EP buffer at constant flow rate of 10 µl/min for a contact time leading to a ligand density around 20 RU. After capturing the anti-hu C5 IgG, different concentrations of human or cynomolgus C5, in the range between 0.156 nM to 2.5 nM, were injected. Each cycle was completed with two regeneration steps with phosphoric acid. All running conditions were carried out at 25° C. in 1×HBS-EP buffer. The resulting signals were adjusted by double referencing, substracting the refraction index values from the reference flow cell and the binding step with no analyte. Data were collected at 10 Hz and analyzed using the Biacore T100 Evaluation Software Version 1.1 (GE). This program uses a global fitting analysis method for the determination of rate and affinity constants for each interaction.

[0353] The specificity of the antibodies were measured. Preferably, the Kon and Koff values for binding to human and cynomolgus C5 are as follows: Kon $>1\times10^5$, Koff $<1\times10^4$). These measurements were performed in Biacore for the germlined IgGs and resulting data are listed in Table 7.

TABLE 7

K _D , Kon and Koff values of the germlined IgGs determined in Biacore							
antiC5 final IgG	C5 sample	ka [1/Ms]	kd [1/s]	KD [pM]			
MOR08109	huC5	2.13E+06	2.56E-05	12			
	cynoC5	1.23E+06	4.49E-05	37			
MOR08110	huC5	4.15E+06	4.69E-05	12			
	cynoC5	1.81E+06	9.24E-05	60			
MOR08111	huC5	1.00E+06	3.07E-05	31			
	cynoC5	8.91E+05	1.28E-04	144			
MOR08113	huC5	2.51E+06	6.77E-05	28			
	cynoC5	1.53E+06	1.27E-04	83			
MOR08114	huC5	2.09E+06	3.12E-05	15			
	cynoC5	1.06E+06	3.13E-05	31			
5G1.1	huC5	1.29E+06	7.22E-05	56			

2. Determination of Picomolar Affinities Using Solution Equilibrium Titration (SET) for Purified Fabs or Fabs Bacterial Lysates (Meso Scale Discovery (MSD))

[0354] For K_D determination by solution equilibrium titration (SET), monomer fractions (at least 90% monomer content, analyzed by analytical SEC; Superdex75, Amersham Pharmacia) of Fab protein were used. Affinity determination in solution was basically performed as described in the literature (Friguet et al., J. Immunol Methods 77:305-319 (1985)). In order to improve the sensitivity and accuracy of the SET method, it was transferred from classical ELISA to ECL based technology (Haenel et al., Anal Biochem 339:182-184 (2005).

1 mg/ml goat-anti-human (Fab)₂ fragment specific antibodies (Dianova) were labelled with ECL Sulfo-TAGTM NHS-Ester (Meso Scale Discovery, Gaithersburg, Md., USA) according to manufacturers instructions. Experiments were carried out in polypropylene microtiter plates and PBS pH 7.4 with 0.5% BSA and 0.02% Tween 20 as assay buffer. Unlabelled antigen was diluted in 2ⁿ series, starting with a concentration at least 10 times higher than the K_D. Wells without antigen were used to determine Bmax values; wells with neither antigen nor Fab were used to determine background. After addition of e.g. 10 pM Fab (final concentration in 60 µl final volume), the mixture was incubated over night at RT. The applied Fab concentration was similar to or below the expected K_D.

[0355] Streptavidin MSD plates were coated with $0.2 \mu g/ml$ biotinylated human C5 (30 μ l/well) and blocked with 5% BSA in PBS. Subsequently the equilibrated samples were transferred to those plates (30 μ l per well) and incubated for 20 min. After washing, 30 μ l/well of the ECL Sulfo-tag labeled detection antibody (goat anti-human (Fab)2) in a final dilution of 1:1500 was added to the MSD plate and incubated for 30 min on an Eppendorf shaker (700 rpm).

[0356] After washing and adding 30μ l/well MSD Read Buffer T with surfactant Electrochemiluminescence signals were detected using a Sector Imager 6000 (Meso Scale Discovery, Gaithersburg, Md., USA).

[0357] Data were evaluated with XLfit (IDBS) software applying customized fitting models. For data evaluation i.e. K_D determination of Fab molecules the following fit model was used (model of Abraham et al 16, modified according to et al., 200515): y=Bmax-(Bmax/(2*cFab)*(x+cFab+KD-sqrt((x+cFab+KD)*(x+cFab+KD)-4*x*cFab))); cFab: applied Fab concentration; x: applied total soluble antigen concentration (binding sites); sqrt: square root. Using the assay conditions described above (monomeric) affinities for the affinity-optimized C5-binding Fabs were determined in solution.

Parental Fabs

[0358] In order to further characterize the C5-binding antibodies, affinity of the parental Fabs to human C5 was determined. Because characterization focus was on efficacy in hemolytic assays, affinity measurements were done only for the most relevant Fabs. For a reliable determination of monovalent affinities only Fab batches were used for measurements which showed $\geq 90\%$ monomeric fraction in a qualitative size exclusion chromatography.

[0359] Affinities of the 10 parental Fabs which entered affinity maturation are summarized in Table 8. Affinities ranged from 72 pM to 3.7 nM.

TABLE 8

Affinities of the 10 parental F	Affinities of the 10 parental Fabs determined in SET					
MOR0 Number	SET KD [pM]					
6525	72					
6756	1521					
6757	1186					
6763	820					
7086	108					
7087	3793					
7091	324					
7092	229					
7093	576					
7094	1364					
3207	no binding					
(negative control)	-					

(n = 1)

Matured Fabs

[0360] Monovalent affinities of the purified Fabs to human C5 were measured in SET. Affinities were in the low pM range and best affinities were obtained for derivatives of MOR07086, 7091, 7092 and 7093. Subsequently affinity measurements of these derivatives to cynomolgus C5 showed affinities in the mid to low pM range.

[0361] The affinity maturation process was very successful resulting in a repertoire of binders with markedly improved affinity. Table 9 summarizes affinities to human and cynomolgus C5 of the best improved binders. Certain Fabs have K_D to human C5≤30 pM and to cynomolgus C5≤150 pM.

TABLE 9

	Overview of affinities to human and cynomolgus C5 for the best affinity improved Fabs								
MOR	Matured	Set hu C5 (n = 1-2) KD [pM]	Set cyno C5 (n = 1) KD [pM]	MOR	Matured	Set hu C5 (n = 1-2) KD [pM]	Set cyno C5 (n = 1) KD [pM]		
6525		273/29		7871	LCDR3	3	4		
7813	HCRD2	437		7872	LCDR3	2	3		
7814	HCRD2	137		7873	LCDR3	13/13	6		
7816	HCRD2	116		7874	LCDR3	35	8		
6757		3650/1245		7092		96	481		
7818	HCRD2	491	70	7831	HCRD2	10	36		
7907	HCRD2	179		7832	HCRD2	4	13		
6763		673/962		7909	HCRD2	7	18		
7820	HCRD2	62		7910	HCRD2	27	31		
7086		12/65	10	7876	LCDR3	78	60		
7821	HCRD2	7	39	7877	LCDR3	29	144		
7822	HCRD2	5	14	7878	LCDR3	33	70		

			the best affinity	mpro			
MOR	Matured	Set hu C5 (n = 1-2) KD [pM]	Set cyno C5 (n = 1) KD [pM]	MOR	Matured	Set hu C5 (n = 1-2) KD [pM]	Set cyno C5 (n = 1) KD [pM]
7823	HCRD2	5	15	7879	LCDR3	25	122
7824	HCRD2	55/130		7093		431/992	3146
7864	LCDR3	22	974	7833	HCRD2	47	107
7865	LCDR3	10	88	7834	HCRD2	4	15
7866	LCDR3	10	191	7835	HCRD2	29	28
7867	LCDR3	19	154	7836	HCRD2	11	
7868	LCDR3		384	7890	HCRD2	46	
7869	LCDR3	2	83	7094			
7870	LCDR3	12	500	7880	LCDR3	13	13
7087		120		7881	LCDR3	88	
7827	HCRD2	361		7882	LCDR3	70	
7828	HCRD2	2477/1730		7883	LCDR3	49	
7091		135/138	704	7884	LCDR3	83	
7829	HCRD2	429	116	7885	LCDR3	35	
7830	HCRD2	399	75		criter	ion: KD hu C5 <30 pN	f; cy C5 <150 pM
7908	HCRD2	15*	39*			*	

*scattering (no reliable measurement)

3. K_D Determination of IgG Molecules Using Solution Equilibrium Titration (SET)

[0362] Affinities of the germlined IgGs (human IgG1AA format) to human and cynomolgus C5 were determined in SET as described below. Similar data sets between two independent measurements showed higher affinities of the lead IgGs to human C5 than reference IgG 5G1.1 (see U.S. Pat. No. 6,355,245). Final IgGs had affinities for human C5 ranging from 1 to 14 pM and affinities to cynomolgus C5 ranging from 3 to 29 pM.

TABLE 10

K_D values determination for the final lead IgGs (human IgG1AA format) in SET									
		1 st meas	surement	2 nd measurement					
		human C5 KD [pM]	cyno C5 KD [pM]	human C5 KD [pM]	cyno C5 KD [pM]				
hu	MOR08109	4	13	2	6				
IgG1AA germlined	MOR08110	7	18	3	8				
	MOR08111	5	14	3	17				
	MOR08113	14	29	8	16				
	MOR08114	1	5	2	4				
hu IgG2/4 (reference IgG)	5G1.1	24	no binding	19	no binding				

[0363] For K_D determination by solution equilibrium titration (SET), monomer fractions of IgG protein were used (at least 90% monomer content, analyzed by analytical SEC MALS; Tosoh TSKgel G3000SWXL, Wyatt Treos miniDAWN). Affinity determination in solution was basically performed as described in the literature (Friguet et al., J. Immunol Methods 77:305-319 (1985)). In order to improve the sensitivity and accuracy of the SET method, it was transferred from classical ELISA to ECL based technology (Haenel et al., Anal Biochem 339:182-184 (2005)).

[0364] 1 mg/ml goat-anti-human $(Fab)_2$ fragment specific antibodies (Dianova) were labelled with ECL Sulfo-TAGTM NHS-Ester (Meso Scale Discovery, Gaithersburg, Md., USA) according to the manufacturers instructions. The experiments were carried out in polypropylene microtiter plates and PBS pH 7.4 with 0.5% BSA and 0.02% Tween 20 as assay buffer. Unlabeled antigen was diluted in 2n or 1.75n series, respectively, starting with a concentration at least 10 timer higher than the K_{D} . Wells without antigen were used to determine Bmax values; wells containing neither antigen nor IgG were used to determine background. After addition of e.g. 10 pM IgG (final concentration in 60 µl final volume), the mixture was incubated over night at RT. The applied IgG concentration was similar to or below the expected K_{D} .

[0365] Streptavidin MSD plates were coated with 0.2 µg/ml biotinylated human C5 (30 µl/well) and blocked with 5% BSA in PBS. Subsequently the equilibrated samples were transferred to those plates (30 µl per well) and incubated for 20 min. After washing, 30 µl/well of the ECL Sulfo-tag labeled detection antibody (goat anti-human (Fab)₂) in a final dilution of 1:1500 was added to the MSD plate and incubated for 30 min on an Eppendorf shaker (700 rpm).

[0366] Electrochemiluminescence signals were detected after washing and adding $30 \,\mu$ /well MSD Read Buffer T with surfactant using a Sector Imager 6000 (Meso Scale Discovery, Gaithersburg, Md., USA).

[0367] Data were evaluated with XLfit (IDBS) software applying customized fitting models. For data evaluation i.e. K_D determination of IgG molecules the following fit model for IgG was used (modified according to Piehler et al., 199717): y=Bmax/(clgG/2)*(clgG/2-((x+clgG+KD)/2-((x+clgG+KD)^2/4-x*clgG^0.5)^2/(2*IgG)); clgG=applied IgG concentration, complete molecule (not binding sites); x=applied total soluble antigen concentration (binding sites); sqrt: square root.

Example 8

Characterization by Hemolytic Assays

[0368] The hemolytic assay is a basic functional assay that tests for complement activation and has been used to evaluate the ability of anti-human C5 mAbs and Fab molecules to block lysis of red blood cells (RBCS) by complement pathways (see e.g., Evans et al., Mol. Immunol 32: 1183-1195 (1995); Thomas et al., Mol Immunol 33:1389-1401 (1996);

Rinder et al., J Clin Invest 96:1564-1572 (1995)). Briefly, for classical pathway assays, sensitized red blood cells are used as targets for lysis by complement proteins present in serum. This assay is of interest for the characterization and screening of high-affinity anti-human C5 mAbs.

1. Classical Pathway

[0369] The desired number of chicken red blood cells was washed four times with cold gelatin veronal buffer (GVB++) and resuspended to 5×10^7 cells/ml. To sensitize the cells rabbit anti-chRBC IgG was added to RBC cell suspension to a final concentration of 1 µg/ml IgG. After 15 minutes incubation on ice, the sensitized chRBCs were centrifuged, washed twice with GVB++ and diluted to 8.33×10^7 cells/ml.

[0370] Round-bottom 96 well plates were used for hemolytic assay. Antibodies were diluted in GVB++ buffer and added to the wells (when calculating the required concentration of C5-binding Abs, it was considered that the sample will be diluted two-fold when serum is added). 50 μ l of 40% human serum (diluted in GVB++) was added to 50 μ l antibody dilutions, resulting in a final serum assay concentration of 20%.

[0371] The control and blank wells were prepared as described here: control wells: i) 0% lysis control \rightarrow 100 µl GVB++, ii) 100% lysis control \rightarrow 100 µl 0.1% NP-40, iii) 20% serum control \rightarrow 100 µl of 20% serum (0% Ab control). blank wells: i) 20% serum blank \rightarrow 100 µl 20% serum, ii) GVB++ blank \rightarrow 100 µl GVB++, iii) NP-40 blank \rightarrow 100 µl 0.1% NP-40.

[0372] $2.5 \times 10^6 (30 \,\mu\text{l})$ sensitized chRBCs/well were added to all sample and control wells. To the blank wells PBS was added instead of cells. Assay plate was incubated 30 min at 37° C., centrifuged (2.000 rpm, 5 min) and 85 μ l supernatant was transferred to a new, flat-bottomed 96-well plate. The new plate was centrifuged (2.000 rpm, 3 min) to get rid of any bubbles. Hemoglobin release was measured by reading absorbance at 415 nm. Percentage of hemolysis was calculated with respect to the control and blank wells using the following calculation algorithms:

% Hemolysis = 100 × $\frac{ODsample - ODnegativecontrol}{ODpositivecontrol - ODnegativecontrol}$ where

 $ODsample = \lfloor AverageOD_{sample} \rfloor - [AverageOD_{20\%SerumBlank}]$

 $ODnegative control = \lfloor Average OD_{0\%Lysis} \rfloor - \lceil Average OD_{GVB++Blank} \rceil$

 $ODpositive control = \lfloor Average OD_{100\% Lysis} \rfloor - \lceil Average OD_{NP-40Blank} \rceil$

[0373] Using this procedure, anti human-05 antibodies which were able to inhibit red blood cell lysis could be identified. To screen for cross-reactivity to cynomolgus C5, the classical pathway was performed using 5% cynomolgus serum.

2. Alternative Pathway

[0374] Hemolytic assays undergoing the alternative pathway were done in a similar way to the classical pathway hemolytic assays. In the alternative pathway RBCs cells from rabbit were used and there was no need to sensitize the cells.

The rabbit RBCs are different from chicken RBCs in that they are sensitive to lysis caused by the complement alternative pathway.

[0375] The working buffer was GVB++ supplemented with 10 mM EGTA and 5 mM Mg++, since the C5 convertase of the alternative pathway is Mg++ dependent and the C5 convertase of the classical pathway is Ca++ dependent.

[0376] Hemolytic assays of the alternative pathway were run with: i) 20% human serum, ii) 100 pM human C5 added to 20% human C5-depleted serum, iii) 0.025% cynomolgus serum added to 20% human C5-depleted serum, iv) 100 pM cynomolgus C5 added to 20% human C5-depleted serum, v) 10% cynomolgus serum. These settings were used to screen for antibodies with high affinity to the human and cynomolgus C5 proteins which were able to inhibit very effectively the red blood cell lysis induced by the alternative complement pathway.

3. Hemolytic Assays with Parental Fabs

[0377] Hemolytic assays were used as a basic bio-functional assay to evaluate the ability of anti-human C5 mAbs to block complement mediated lysis of red blood cells. C5 convertase cleaves C5 into C5a peptide and C5b fragment, that is subsequently incorporated into the membrane-attack complex (MAC), which leads to cell lysis. C5 convertase of the classical pathway, formed by a C3bC4bC2a complex has a different structure than the C5 convertase of the alternative pathway which is formed by a C3bC3bBb complex. HuCAL GOLD® generated antibodies should be inhibitory in both classical and alternative pathway, but with focus on the alternative pathway because mainly the alternative pathway (factor H, factor B and factor H-related genes) is implicated in AMD.

[0378] The classical and alternative pathway assays were performed with 20% human serum (~80 nM C5). To increase sensitivity of alternative pathway assays, new assay formats were developed. 10-100 pM purified human C5 or 0.025% cynomolgus serum (~100 pM cynomolgus C5) were added to human C5-depleted serum (but containing all other serum and complement components).

[0379] FIG. 2 shows that considerable hemolysis could be observed between 10 and 100 pM purified human C5 added to human C5-depleted serum. Cynomolgus serum was added to human C5-depleted serum to test for cross-reactivity. FIG. 3 shows that 0.025% of cynomolgus serum (~100 pM C5) added to human C5 depleted serum restores hemolytic activity.

Classical Pathway

[0380] First Fab selection was done in the classical pathway (20% human serum). Approximately half of the 61 purified parental Fabs were weak to strong inhibitors of the classical pathway. IC50 values of the best inhibitory Fabs were between 35 and 900 nM.

[0381] Assays were done showing congruent results (as shown in FIG. **4**). % hemolysis was calculated with respect to the control and blank wells. Fab inhibition of cell lysis was compared to a maximum lysis caused by 20% human serum (=100%). An irrelevant human Fab (hen egg white lysozyme binder MOR03207) was used as negative control and antihuman C5 IgG monoclonal antibody (Quidel) as positive control. FIG. **4** show an example with the best inhibitory Fabs.

Alternative Pathway

[0382] Fabs which showed inhibitory activity in the classical pathway were further evaluated in the alternative pathway. Hemolytic assays were run with 100 pM purified human C5 or 0.025% cynomolgus serum added to human C5-depleted serum. IC₅₀ values for the human alternative assays were between 0.1 and 90 nM (examples of assays with the most relevant Fabs are shown in FIG. **5**.

[0383] The positive control of the classical pathway (antihuman C5 antibody, Quidel) was not inhibitory in the alternative pathway. Therefore an anti-complement factor P antibody (Quidel) was used as positive control. As shown in FIG.
5, MOR07086 had best inhibitory activity and NVS data

revealed a better potency than for the reference antibody 5G1.1.

[0384] To test for cynomolgus cross-reactivity, hemolytic assays of the alternative pathway were performed with 0.025% cynomolgus serum added to human C5-depleted serum. A comparison to 5G1.1 was not possible, since 5G1.1 does not recognize cynomolgus C5. The anti-Factor P antibody was used as positive control. Results of assays revealed IC₅₀ values between 0.1 and 400 nM for the best inhibitory Fabs. Again, MOR07086 showed best potency (shown in FIG. **6**).

[0385] A consistent inhibitory activity of the Fabs was noticed in both classical and alternative pathway. Table 11 below summarizes the results of hemolytic assays for the most relevant 22 Fabs. To have a reliable comparison between different experiments, lysis caused by 20% human serum was normalized to 100%.

4. Hemolytic Assays with Matured Fabs

Classical Pathway

(1) Classical Pathway Using 20% Human Serum

[0386] Matured Fabs were tested in the classical pathway with 20% human serum. Derivatives of MOR07086, 7091, 7092 and 7093 showed highest potency (IC50 values in the low nM range). Descendants of MOR07091, 7092 and 7093 showed strongly improved potency. FIG. **7** shows examples of hemolytic assays with derivatives of MOR07086, 7091, 7092 and 7093.

(2) Classical Pathway Using 5% Cynomolgus Serum

[0387] Assays of the complement pathway were also run in the presence of 5% cynomolgus serum in order to test for cross-reactivity. Derivatives of MOR07086, 7091, 7092 and 7093 could very effectively inhibit red blood cell lysis. The negative control, MOR03207 (anti-lysozyme Fab), had no impact on the complement pathway. Results of these assays are shown in FIG. **8**.

Alternative Pathway

(1) Alternative Pathway Using 100 pM Human C5

[0388] Matured Fabs were tested in the alternative pathway hemolytic assay with 100 pM human C5. Some derivatives of MOR06525, 6757, 6763, and 7087 showed potency improvement compared to their parentals. MOR07086-, 7091-, 7092-, 7093-, and 7094-derived Fabs showed highest potency (IC50 values in the low nM range). Descendants of MOR07091, 7092, 7093, and 7094 showed highly improved potency,

Summary of hemolytic assays with the most relevant Fabs									
MOR-Nr	MOR IC50 [nM]			NVS IC50 [nM]					
	CP [human] normalized	AP (0.1 nM C5) [human] normalized	AP (0.025% cyno serum) [cyno] normalized	CP [human] normalized	AP (0.1 nM C5) [human] normalized	AP (0.025% cyno serum) [cyno] normalized			
6525	190	15	11	185	7	5			
6756	320	80	400	225	70	2500			
6757	500	90	30	305	130	25			
6763	250	45	110	195	20	360			
6764	n.t.	50	n.t.	n.t	25	30% inh			
6776	>4000	40		n.t.	20*	50% inh			
6952	90	20	>1000	110	15	200			
6961	100	25	600	85	15	30			
7081	180	5	40% inh	170	3	10			
7082	70	2.5	1	90	1	1			
7083	100	30	300	140	10	5			
7084	120	10	1.2	160	5	1.5			
7086	35	0.2/0.2	0.2/0.4	85	0.1	0.1			
7087	>4000	50	100	775	10	1			
7088	110	15	230	130	5	15			
7089	150	75	900	250	20	50			
7090	105	20	10	120	10	1			
7091	82	7	40	110	3	4			
7092	100	1	1.5	90	0.5	1.5			
7093	>4000	7	190	230	5	15			
7094				770	40	190			
7095*	120*	0.5**	1.3**	n.t.					

*not pure as MH

**as pMx9_FS

TABLE 11

many of which are more potent than reference antibody 5G1. 1. FIG. **9** shows examples of hemolytic assay results for the affinity matured Fabs and 5G1.1.

(2) Alternative Pathway Using 20% Human Serum

[0389] Matured Fabs were tested in the alternative pathway hemolytic assay with 20% human serum. MOR07086-, 7091-, 7092- and 7093-derived Fabs showed best inhibitory activity. Many of these Fabs had better inhibitory activity than 5G1.1. FIG. **10** shows examples of hemolytic assay results for the affinity matured Fabs and reference antibody 5G1.1.

(3) Alternative Pathway Using 100 pM Cynomolgus C5

[0390] Matured Fabs were tested in the alternative pathway hemolytic assay using 100 pM cynomolgus C5 added to 20% human C5-depleted serum. MOR07091-, 7092- and 7093-derived Fabs showed best inhibitory activity; 5G1.1 does not crossreact with cynomolgus C5. FIG. **11** shows examples of hemolytic assay results for the affinity matured Fabs. 5. Hemolytic Assays with Germlined IgGs (Human IgG1AA

Format)

Classical Pathway

(1) Classical Pathway Using 20% Human Serum

[0391] Classical pathway assays using 20% human serum were run at MOR. IC50 values of the final germlined hu IgGAA—MOR08109, 8110, 8113, 8114—were better or similar to reference IgG 5G1.1 (see FIG. **12**).

(2) Classical Pathway Using 5% Cynomolgus Serum

[0392] A comparison to 5G1.1 in the classical pathway using 5% cynomolgus serum was not applicable, since this reference antibody does not recognize cynomolgus C5. The final germlined IgGs could completely inhibit lysis of the red blood cells induced by cynomolgus serum except MOR08111. Data are shown in FIG. **13**.

Alternative Pathway

(1) Alternative Pathway Using 100 pM Human C5

[0393] The germlined IgGs were tested in the alternative pathway hemolytic assay using 100 pM human C5. All antibodies showed potent inhibitory activity with IC50 values between 28 and 128 pM (with the exception of MOR08111, see FIG. 14), all were equal to or better than 5G1.1. FIG. 14 shows examples of hemolytic assay results for the IgGs.

(2) Alternative Pathway Using 20% Human Serum and C5a Generation ELISA

[0394] The germlined IgGs were also tested in the alternative pathway hemolytic assay with 20% human serum. The majority of the antibodies tested achieve complete inhibition with IC50 values lower than 80 nM. Reference antibody 5G1.1 does not fully inhibit hemolysis in this assay. FIG. **15** shows examples of hemolytic assay results for the IgGs. Inhibition of C5a generation by the final IgGs was similar to 5G1.1 (IC50 values in the low nM range).

(3) Alternative Pathway Using 100 pM Cynomolgus C5

[0395] Hemolytic assays of the alternative pathway in 20% human C5-depleted serum were reconstituted with 100 pM

cynomolgus C5. Potency of the germlined final candidates against cynomolgus C5 was within 5-fold of that for human C5 (IC50 values in the low pM range).

(4) Alternative Pathway Using 10% Cynomolgus Serum

[0396] In hemolytic assays of the alternative pathway using 10% cynomolgus serum ([C5]~40 nM) the potency of the germlined candidates was similar to the potency in human serum (success criterion was to have a potency not more than 5-fold weaker than for the functional assay using human C5).

Example 9

C5a Generation ELISA

[0397] C5a-des-Arg ELISA was developed to measure C5a generation during hemolysis to confirm that antibodies that were inhibitory in the hemolytic assay also inhibited cleavage of C5 into C5a and C5b.

[0398] A Maxisorp plate was coated with 100 µl/well mouse anti-human C5a-des-Arg (US Biologics) at 1 µg/ml in coating buffer (bicarbonate pH 9.5-9.8) and was incubated overnight at 4° C. After washing 3× with PBST, the plate was blocked with 300 µl/well diluent (Synblock, AbD Serotec) for 2 hours at room temperature. After aspirating the blocking solution, 100 µl samples or standards diluted with diluent were incubated for 1 hour at room temperature. Standards were prepared as follows: start was at 20 ng/ml standard (rC5a-des-Arg) and 1:4 serial dilutions were prepared for a 7-point curve. Samples of hemolytic assays were diluted 1:5 in diluent (hemolytic assay supernatants should be stored at -80° C. until used in C5a ELISA). In between the plate was washed 3× with PBST. 100 µl/well of 0.4 µg/ml detection antibody (biotin-goat anti-human c5a, R&D Systems) diluted in diluent was added and after 1 hour incubation at room temperature, 100 µl/well Strep-HRP (poly-HRP streptavidin) diluted 1:5000 in HRP diluent (poly-HRP diluent) was added for 30 minutes. After washing 4× with PBST, 100 µl/well TMB Substrate (Ultra TMB substrate solution) was added for 5-10 minutes. Reaction was stopped with 50 µl/well stop solution (2N H2SO4). Absorbance was read (A450-A570) and data were analyzed using SoftMax Pro.

[0399] Matured Fabs were tested for C5a generation during hemolysis to confirm that inhibitory activity was due to blocking C5 cleavage into C5a and C5b. The supernatants from hemolytic assays in 20% human serum were used for quantifying the C5a formation.

[0400] All Fabs tested brought C5a levels down to baseline. FIG. **16** shows examples of C5a ELISA results.

Example 10

Specificity ELISA on Human C3, C4, C5 and Cynomolgus C5

[0401] All purified Fabs were analyzed in a solution ELISA (method described above) for binding to human C3, C4 and C5. Fabs were incubated with biotinylated antigen on a Neutravidin plate and detected via the histidin tag.

[0402] Improved binding was seen for almost all matured Fabs compared to their respective parental. No binding to the counter targets human C4 and C3 was detected up to 100 nM Fab. These results hit the success criteria for specificity: binding to human and cynomolgus C5 and no binding to human

complement proteins C3 and C4. Examples for derivatives of parental Fab MOR07091 are shown in FIG. **17**.

Example 11

Serum Stability Assays

[0403] Retained binding activity to human C5 in a binding assay at 50% human serum of C5-binding antibodies was determined as described below.

[0404] Antibodies (Fab format) were incubated up to 8 h at 37° C. with 100% human C5-depleted serum or with PBST/ 0.5% BSA (positive control). Wells of a blocked polypropylene plate were used for incubation to ensure no binding of the antibodies to the surface over the long incubation time. Samples were collected at different time points and stored at -20° C.

[0405] Samples were tested in a solution ELISA on NeutrAvidin plates to check binding ability to human C5. To the NeutrAvidin plates, which were blocked o/n with $1\times$ ChemiBlocker-PBST. 20 µl of serial dilutions of the different collected samples were added. First dilution of the samples was 1:2 (final serum concentration 50%), followed by 1:3 dilutions steps. After 1 h incubation the plate was washed $3\times$ with PBST and 20 µl biotinylated human C5 was applied to a concentration of 2.5 µg/ml. After 1 h plate was washed again $5\times$ with PBST (0.05% Tween) and anti-HIS6-POD detection antibody for Fabs was added.

[0406] Fluorescence of the substrate (Quanta Blue or AttoPhos) was measured after 5-10 min and retained binding activity was calculated compared with the respective maximum signal (antibody incubated with PBST/0.5% BSA).

[0407] One of the "must" criteria for the C5-binding antibodies is to retain 75-80% of binding activity in human serum i) in a functional assay at 10% serum and ii) in a binding assay at 50% serum. Because hemolytic assays were run in the presence of 20% serum it was only necessary to show retained binding in a binding assay at 50% serum.

[0408] Therefore matured final Fabs were incubated with 100% human C5-depleted serum at 37° C. for 8 h. Samples were collected at different time points and tested for binding to human C5 in a solution ELISA. Fab+serum samples used for ELISA were diluted to a concentration of 50% serum+10 nM Fab.

[0409] FIG. **18** illustrates the results of the final C5-binding final antibodies in the Fab format. 70-93% of the binding activity was retained after an 8 hour incubation time at 37° C. in 50% serum compared to incubation in PBS.

Example 12

Characterization by Epitope Binning

[0410] This procedure was used to group anti-human C5 Fabs into different epitope bins binding to the same or an overlapping epitope of the C5 protein.

[0411] Competition of each biotinylated anti-human C5 antibody with each unlabelled anti-human C5 antibody in 100-fold excess was tested in an ELISA (capture mode). It was compared with the highest signal of each antibody (bioti-nylated Fab without competition).

[0412] Human C5 was captured via a polyclonal anti-human C5 IgG (US Biological), which was coated previously o/n at 4° C. on a 384 well black Maxisorp plates. Next day the plate was washed twice with PBST and blocked for 2 h with 3% BSA-PBST. After washing $3\times$ with PBST, 20 µl human

C5 was added and incubated 2 h ar RT. The plate was washed $3 \times$ with PBST before adding the Fabs.

[0413] 20 μ l unlabelled Fab (200 μ g/ml or 400 μ g/ml) (100fold excess) was added to the wells of a Maxisorp plate and subsequently 20 ng/ml or 40 ng/ml of biotinylated Fab. The biotinylated and unlabelled Fabs were incubated for 1 h at RT. The plate was washed 3× with PBST and Strep-AP Zymax Streptavidin-Alkaline Phosphatase, ZYMED, Code: 43-8322, Lot: 50799648 was added for detection of the biotinylated Fab binding via C5 to the plates. AttoPhos substrate (Roche) was added to the plates and Fluorescence was read after 5-10 min.

Parental Fabs

[0414] C5 was captured (via a polyclonal antibody) and unlabelled FabY was applied in excess to biotinylated FabX. Binding of biotinylated FabX to human C5 was detected. Six groups of Fabs could be defined: Group 1: MOR06952, 6961; Group 2: MOR06525, 6756, 6757, 6763; Group 3: MOR07087; Group 4: MOR06764, 6776, 7081; Group 5: MOR07089; Group 6: MOR07082, 7083, 7084, 7086, 7088, 7090, 7091, 7092, 7093, 7095.

[0415] The Fabs were also divided into different epitope binding groups using a different method: FabX was immobilized, then FabY pre-incubated with biotinylated C5 was added. Following groups of Fabs could be defined: Group 1: MOR06952, 6961; Group 2: MOR06525,6757, 7083; Group 3: MOR07087; Group 4: MOR06763; Group 5: MOR07081; Group 6: MOR07082, 7083, 7084, 7086, 7088, 7091, 7092, 7093 (7089 competes with 7084). The conclusion was drawn that using two different methods, similar results could be obtained.

Matured Fabs

[0416] In order to complete Fab characterization competition of biotinylated Fab with unlabelled Fab (applied in 100fold excess) was measured in solution ELISA. Results were compared with the highest signal (biotinylated Fab without competition).

[0417] As shown in FIG. **19**, biotinylated Fabs compete with identical unlabelled Fabs and all Fabs compete for binding to the same or overlapping epitope. These results correlate with epitope binning data for the parental Fabs.

Example 13

Screening of C5 Alpha Versus Beta Chain Binders and Competition Assays

[0418] Two ELISA experiments and hemolytic assays were performed to test if a Fab was an alpha or beta chain binder as described below.

[0419] In the first experiment, Fab was coated on a plate and purified C5 or supernatant from chimeric C5 preparation (human alpha, mouse beta chain) was added. As a next step 5G1.1 was applied and detection was done via an anti-human IgG.

[0420] In a second experiment, 5G1.1 was coated on a plate, purified C5 or supernatant from chimeric C5 preparation (human alpha, mouse beta chain) was added, then Fab, which was detected with an anti-Myc antibody.

[0421] Reference IgG 5G1.1 recognizes the alpha chain and was used to determine if the MorhpSys generated Fabs compete with 5G1.1 for binding. In the hemolytic assays supernatant from chimeric C5 preparation was added to human C5-depleted serum and Fabs were tested for inhibition of hemolysis.

Parental Fabs

[0422] FIG. **20** shows the results of an ELISA experiment where the Fabs were coated on a plate, C5 or supernatant of a chimeric C5 preparation (human alpha chain and mouse beta chain) was added, then 5G1.1. FIG. **21** shows the results of an ELISA experiment where purified C5 and supernatant from chimeric C5 were captured via 5G1.1.

[0423] MOR06525, 6756, 6763 were beta chain binders (bind to C5 but not chimeric C5). Most MOR070XX Fabs (derived from solution pannings) are alpha chain binders (bind to C5 and chimeric C5). MOR06952 and 6961 compete with 5G1.1 so they are negative for both C5 and chimeric C5 and, thus, are most likely alpha chain binders as 5G1.1. MOR06757 behaves like MOR06952 and 6961, i.e. it likely is an alpha chain binder. However, MOR06757 does not inhibit hemolysis of chimeric C5 supernatant spiked into C5-depleted serum, while all the other alpha chain binders do (see FIG. **22**).

[0424] In the hemolytic assay supernatant from chimeric C5 prep was added to human C5-depleted serum and Fabs were tested for inhibition of hemolysis. MOR06525, 6756, 6757 and 6763 did not inhibit hemolysis with chimeric C5 and thus, could be beta chain binders. MOR06952, 6961, 7081, 7082, 7083, 7084, 7086, 7087, 7088, 7089, 7090, 7091, 7092, 7093, 7094, 7095 inhibited hemolysis and thus could be alpha chain binders.

Example 14

Resistance to Proteolysis

[0425] To investigate the structural rigidity of Fabs, resistance of Fabs to proteolysis by thermolysin was performed (thermolysin bacterial protease, Calbiochem). Fab was incubated with thermolysin (Fab:thermolysin=3:1 (w/w), reaction volume of $8 \,\mu$ L) either at 37° C. or at 55° C. (thermolysin activity is optimal at 55° C.). The reaction was stopped by adding 4 μ L of 0.5 M EDTA and 4 μ L of 4×LDS sample buffer (Invitrogen) and the stopped samples were run on 4-12% SDS-PAGE at non-reducing condition. Proteolysis of Fabs was analyzed by monitoring the disappearance of Fab bands that were visualized by Coomassie staining.

Parental Fabs

[0426] Parental Fabs were tested for resistance to thermolysin proteolysis at 37° C. and 55° C. Fab from a humanized

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 307 <210> SEQ ID NO 1 <211> LENGTH: 5 <212> TYPE: PRT <213> ORGANISM: homo sapiens <400> SEQUENCE: 1 Ser Tyr Ala ILe Ser 1 5 IL-1 β antibody was used as control. Most tested Fabs were resistant to degradation by thermolysis at 37° C. up to 90 min. To further differentiate the structural rigidity of Fabs, proteolysis was performed at higher temperature of 55° C. Many of the Fabs tested were quickly degraded at 55° C. (>90% Fab was degraded within 30 min), while some Fabs were still resistant to proteolysis after 90 min (e.g., 7094). The resistant Fabs were suggested to have a more rigid structure such that they might show better in vivo pharmacokinetic properties. Results of these experiments are shown in the FIG. **23** and FIG. **24**.

Matured Fabs

[0427] Fabs with the highest potency in hemolytic assays were tested for sensitivity to thermolysin at 37° C. and 55° C. In FIG. **25** and FIG. **26**, experiments with derivatives of MOR07086, 7091, 7092 and 7093 are shown.

[0428] Results of these tests revealed that derivatives of parentals MOR07091, 7092 and 7093 were less sensitive to proteolysis, while MOR07086 derivatives were more sensitive to proteolysis.

Example 15

MAC Deposition Assay

[0429] As the terminal complement cascade ends up with formation of the MAC, inhibition of MAC formation was a further hint for the antibody ability to block the complement cascade. The rational was to have an additional set-up independent of cells and cell behaviour

[0430] Zymosan (Sigma), which is an insoluble carbohydrate from the cell wall of yeast, used especially in the immunoassay of the alternative pathway, was coated to activate the Alternative Pathway and IgM (Sigma) was coated to activate the Classical Pathway for determination of MAC (membrane attack complex) deposition. Fabs were pre-incubated with human serum (6% for AP, 2% for CP) and added to plate. Percentage (%) inhibition of MAC deposition was calculated for each sample relative to baseline (EDTA treated human serum) and positive control (human serum), and used to generate the IC₅₀ curve with XLFit.

Parental Fabs

[0431] Parental Fabs were used in different concentrations and the maximal inhibition (if applicable also IC50 values) were determined (example shown in FIG. **27**). Most Fabs completely inhibited MAC deposition indicating blocking of C5 cleavage. Potency and ranking of Fabs were similar to data from hemolytic assays. -continued

79

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Ile	Ile 50	Asp	Pro	Asp	Asp	Ser 55	Tyr	Thr	Glu	Tyr	Ser 60	Pro	Ser	Phe	Gln
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Ala	Leu	Thr	Ser	Gly 165	Val	His	Thr	Phe	Pro 170	Ala	Val	Leu	Gln	Ser 175	Ser
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Lys	Val 210	Asb	Lys	Arg	Val	Glu 215	Pro	Lys	Ser	Сув	Asp 220	Lys	Thr	His	Thr
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Gln 385	Pro	Glu	Asn	Asn	Tyr 390	Lys	Thr	Thr	Pro	Pro 395	Val	Leu	Asp	Ser	Asp 400
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n Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys

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97

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 Ile Ile Asp Pro Asp Asp Ser Tyr Thr Arg Tyr Ser Pro Ser Phe Gln

 50
 55
 60

 Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu 65 70 75 80 Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala 90 85 95 Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val 105 100 110 Thr Val Ser Ser 115 <210> SEQ ID NO 52 <211> LENGTH: 106 <212> TYPE: PRT <213> ORGANISM: homo sapiens <400> SEQUENCE: 52 Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln 5 10 15 1 Thr Ala Arg Ile Ser Cys Ser Gly Asp Asn Ile Gly Asn Ser Tyr Val 25 20 30 His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr 35 40 Lys Asp As
n Asp Arg Pro \mbox{Ser} Gly Ile Pro \mbox{Glu} Arg Phe \mbox{Ser} Gly Ser 50 55 60 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu 70 75 65 80 Asp Glu Ala Asp Tyr Tyr Cys Ala Thr Trp Gly Ser Glu Asp Gln Val 85 90 95 Phe Gly Gly Gly Thr Lys Leu Thr Val Leu 100 105 <210> SEQ ID NO 53 <211> LENGTH: 446 <212> TYPE: PRT <213> ORGANISM: homo sapiens <400> SEQUENCE: 53 Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu 5 10 1 15

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Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu 355 360 Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg 405 410 Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys <210> SEO ID NO 70 <211> LENGTH: 213 <212> TYPE: PRT <213> ORGANISM: homo sapiens <400> SEQUENCE: 70 Ser Tyr Glu Leu Thr Gln Pro Pro Ser Val Ser Val Ala Pro Gly Gln Thr Ala Arg Ile Ser Cys Ser Gly Asp Ser Leu Gly Asp Tyr Tyr Ala Tyr Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr Lys Asp As
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210

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COILC	TITO	cu.

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Tyr	Ile	Gly 35	Trp	Val	Arg	Gln	Met 40	Pro	Gly	Lys	Gly	Leu 45	Glu	Trp	Met
Gly	Ile 50	Ile	Asp	Pro	Ser	Asp 55	Ser	His	Thr	Thr	Tyr 60	Ser	Pro	Ser	Phe
Gln 65	Gly	Gln	Val	Thr	Ile 70	Ser	Ala	Asp	Lys	Ser 75	Ile	Ser	Thr	Ala	Tyr 80
Leu	Gln	Trp	Ser	Ser 85	Leu	Lys	Ala	Ser	Asp 90	Thr	Ala	Met	Tyr	Tyr 95	Сув
Ala	Arg	Tyr	Met 100	Met	Arg	Gly	Phe	Asp 105	His	Trp	Gly	Gln	Gly 110	Thr	Leu
Val	Thr	Val 115	Ser	Ser	Ala	Ser	Thr 120	Lys	Gly	Pro	Ser	Val 125	Phe	Pro	Leu
Ala	Pro 130	Ser	Ser	Lys	Ser	Thr 135	Ser	Gly	Gly	Thr	Ala 140	Ala	Leu	Gly	Суз
Leu 145	Val	Lys	Asp	Tyr	Phe 150	Pro	Glu	Pro	Val	Thr 155	Val	Ser	Trp	Asn	Ser 160
Gly	Ala	Leu	Thr	Ser 165	Gly	Val	His	Thr	Phe 170	Pro	Ala	Val	Leu	Gln 175	Ser
Ser	Gly	Leu	Tyr 180	Ser	Leu	Ser	Ser	Val 185	Val	Thr	Val	Pro	Ser 190	Ser	Ser
Leu	Gly	Thr 195	Gln	Thr	Tyr	Ile	Сув 200	Asn	Val	Asn	His	Lys 205	Pro	Ser	Asn
Thr	Lys 210	Val	Asp	Lys	Arg	Val 215	Glu	Pro	Lys	Ser	Cys 220	Asp	Lys	Thr	His
Thr 225	Суз	Pro	Pro	Cys	Pro 230	Ala	Pro	Glu	Ala	Ala 235	Gly	Gly	Pro	Ser	Val 240
Phe	Leu	Phe	Pro	Pro 245	Lys	Pro	Lys	Asp	Thr 250	Leu	Met	Ile	Ser	Arg 255	Thr
Pro	Glu	Val	Thr 260	Суз	Val	Val	Val	Asp 265	Val	Ser	His	Glu	Asp 270	Pro	Glu
Val	Lys	Phe 275		Trp	Tyr	Val	Asp 280	Gly	Val	Glu	Val	His 285	Asn	Ala	Lys
Thr	Lys 290		Arg	Glu	Glu	Gln 295		Asn	Ser	Thr	Tyr 300		Val	Val	Ser
Val 305	Leu	Thr	Val	Leu	His 310		Asp	Trp	Leu	Asn 315		Гла	Glu	Tyr	Lys 320
	Lys	Val	Ser	Asn 325	Lys	Ala	Leu	Pro	Ala 330		Ile	Glu	Lys	Thr 335	
Ser	Lys	Ala	Lys 340			Pro	Arg	Glu 345		Gln	Val	Tyr	Thr 350		Pro
Pro	Ser	-		Glu	Met	Thr	-		Gln	Val	Ser			Cys	Leu
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Gly	370 Gln	Pro	Glu	Asn	Asn	375 Tyr	Lys	Thr	Thr	Pro	380 Pro	Val	Leu	Asp	Ser
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120

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300 351

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123

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le Ile Asp Pro Gln Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln 50 55 60	
tly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu 5 70 75 80	
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arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val	

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p Met Gly Ile Ile Asp Pro Gln Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu 130 135 Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val - 265 Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro

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145					150					155					160					
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Gln	Gln	Gly	Asn 420	Val	Phe	Ser	Суз	Ser 425	Val	Met	His	Glu	Ala 430	Leu	His					
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CCCC																				
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Gly	Leu	Tyr	Ser 180	Leu	Ser	Ser	Val	Val 185	Thr	Val	Pro	Ser	Ser 190	Asn	Phe
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Lys	Pro	Lys	Asp	Thr 245	Leu	Met	Ile	Ser	Arg 250	Thr	Pro	Glu	Val	Thr 255	Суз
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	Gln 290		Asn	Ser	Thr	Phe 295		Val	Val	Ser	Val 300		Thr	Val	Val
His		Asp	Trp	Leu	Asn		Lys	Glu	Tyr	-		Lys	Val	Ser	
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Gln	Pro	Arg		325 Pro	Gln	Val	Tyr		330 Leu	Pro	Pro	Ser		335 Glu	Glu
Met	Thr	Lys	340 Asn	Gln	Val	Ser	Leu	345 Thr	Сув	Leu	Val	Lys	350 Gly	Phe	Tyr
Pro	Ser	355 Asp	Ile	Ala	Val	Glu	360 Trp	Glu	Ser	Asn	Gly	365 Gln	Pro	Glu	Asn
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Tyr	Trp	Tyr 35	Gln	Gln	Lys	Pro	Gly 40	Gln	Ala	Pro	Val	Leu 45	Val	Ile	Tyr
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Feb. 4, 2016

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US 2016/0031975 A1

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 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

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Ala	Pro 130	Ser	Ser	ГÀа	Ser	Thr 135	Ser	Gly	Gly	Thr	Ala 140	Ala	Leu	Gly	Суа
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Ser	Gly	Leu	Tyr 180	Ser	Leu	Ser	Ser	Val 185	Val	Thr	Val	Pro	Ser 190	Ser	Ser
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Lys Tyr Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys 180 185 190	
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n \mbox{Trp} Ser Ser Leu Lys Ala Ser Asp \mbox{Thr} Ala Met
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n Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met
 Tyr Tyr Cys 85 90 Ala Arg Ser Lys Tyr Gly Ser Phe Asp Tyr Tr
p Gly Gln Gly Thr Leu 100 105 110 Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu 120 125 115 Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys 140 130 135 Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser 150 155 145 160 Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser 165 170 175 Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser 185 180 190

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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		
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Pro	Ser	Val 115	Phe	Ile	Phe	Pro	Pro 120	Ser	Asp	Glu	Gln	Leu 125	Lys	Ser	Gly
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Lys 145	Val	Gln	Trp	ГЛа	Val 150	Asp	Asn	Ala	Leu	Gln 155	Ser	Gly	Asn	Ser	Gln 160
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n Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser $% \mathcal{S}_{\mathcal{S}}$ 50 55 60 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu 75 65 70 80 Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Trp Thr Asp Ser Pro Asn Thr 85 90 95 Leu Val Phe Gly Gly Gly Thr Lys Leu Thr Val Leu 100 105 <210> SEQ ID NO 212 <211> LENGTH: 220 <212> TYPE: PRT <213> ORGANISM: homo sapiens <220> FEATURE: <221> NAME/KEY: MISC_FEATURE <222> LOCATION: (220)..(220) <223> OTHER INFORMATION: X can be C, EF, or CEF <400> SEQUENCE: 212 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu 5 10 Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Ser Tyr 25 20 30 Tyr Ile Gly Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met 40 35 Gly Ile Ile Asp Pro Ser Asp Ser His Thr Thr Tyr Ser Pro Ser Phe 50 55 60 Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr 75 65 70 80 Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys 85 90 95 Ala Arg Tyr Met Met Arg Gly Phe Asp His Trp Gly Gln Gly Thr Leu 100 105 110 Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu

Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr

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Gly	Ala	Leu	Thr	Ser 165	-	Val	His	Thr	Phe 170	Pro	Ala	Val	Leu	Gln 175	Ser
Ser	Gly	Leu	Tyr 180	Ser	Leu	Ser	Ser	Val 185		Thr	Val	Pro	Ser 190	Ser	Ser
Leu	Gly	Thr 195	Gln	Thr	Tyr	Ile	Сув 200	Asn	Val	Asn	His	Lys 205	Pro	Ser	Asn
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Val	Glu	Thr	Thr	Thr 165		Ser	Lys	Gln	Ser 170		Asn	Lys	Tyr	Ala 175	Ala
Ser	Ser	Tyr	Leu 180	Ser	Leu	Thr	Pro	Glu 185		Trp	ГЛа	Ser	His 190	Arg	Ser
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Pro Ser	Val Thr 115	Leu	Phe	Pro	Pro 120	Ser	Ser	Glu	Glu	Leu 125	Gln	Ala	Asn		
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Ser Gly Ser Lys Ser Gly Asn Thr Ala Ser Leu Thr Ile Ser Gly Leu 65 70 Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Gln 85 90 95 Ser Ile 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 190 180 185 Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr 195 200 205 Val Ala Pro Thr Glu Xaa 210 <210> SEQ ID NO 231 <211> LENGTH: 351 <212> TYPE: DNA <213> ORGANISM: homo sapiens <400> SEQUENCE: 231 caggtgcaat tgaaagaaag cggcccggcc ctggtgaaac cgacccaaac cctgaccctg 60 acctgtacct tttccggatt tagcctgtct acttctggtg gtggtgtgtc ttggattcgc 120 cagccgcctg ggaaagccct cgagtggctg gctcatatct tttctgatga tgataagtat 180 tatagcacca gcctgaaaac gcgtctgacc attagcaaag atacttcgaa aaatcaggtg 240 gtgctgacta tgaccaacat ggacccggtg gatacggcca cctattattg cgcgcgtggt 300 ccttatggtt ttgattcttg gggccaaggc accctggtga cggttagctc a 351 <210> SEQ ID NO 232 <211> LENGTH: 327 <212> TYPE: DNA <213> ORGANISM: homo sapiens <400> SEQUENCE: 232 gatategeac tgacceagee agetteagtg ageggeteac eaggteagag cattaceate 60 tcqtqtacqq qtactaqcaq cqatattqqt acttataatt atqtqtcttq qtaccaqcaq 120 catcccggga aggcgccgaa acttatgatt tatgatgatt ctaatcgtcc ctcaggcgtg 180 agcaaccgtt ttagcggatc caaaagcggc aacaccgcga gcctgaccat tagcggcctg 240 caageggaag acgaagegga ttattattge cagtettatg atteteagte tattgtgttt 300 ggcggcggca cgaagttaac cgttctt 327 <210> SEQ ID NO 233

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Ile Ile Asp Pro Asp Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln 50 55 Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser <210> SEQ ID NO 274 <211> LENGTH: 219 <212> TYPE: PRT <213> ORGANISM: homo sapiens <220> FEATURE: <221> NAME/KEY: MISC_FEATURE <222> LOCATION: (219)..(219) $<\!223\!>$ OTHER INFORMATION: X can be C, EF, or CEF <400> SEQUENCE: 274 Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu Ser Leu Lys Ile Ser Cys Lys Gly Ser Gly Tyr Ser Phe Thr Asn Tyr Ile Ser Trp Val Arg Gln Met Pro Gly Lys Gly Leu Glu Trp Met Gly Ile Ile Asp Pro Asp Asp Ser Tyr Thr Glu Tyr Ser Pro Ser Phe Gln Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly 150 155 Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Xaa <210> SEQ ID NO 275

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Ile Ile Asp Pro Glu Asp Ser His Thr Glu Tyr Ser Pro Ser Phe Gln 50 55 60
Gly Gln Val Thr Ile Ser Ala Asp Lys Ser Ile Ser Thr Ala Tyr Leu 65 70 75 80
Gln Trp Ser Ser Leu Lys Ala Ser Asp Thr Ala Met Tyr Tyr Cys Ala 85 90 95
Arg Tyr Glu Tyr Gly Gly Phe Asp Ile Trp Gly Gln Gly Thr Leu Val 100 105 110
Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala 115 120 125
Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu 130 135 140
Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly 145 150 155 160
Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser 165 170 175
Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu 180 185 190
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caatggagca gcctgaaagc gagcgatacg gccatgtatt attgcgcgcg ttatgagtat	300
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Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser 50 55 60	
Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Glu 65 70 75 80	
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His Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Val Leu Val Ile Tyr 35 40 45	
Lys Asp Asn Asp Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser	

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Asp	Glu	Ala	Asp	Tyr 85	Tyr	Cys	Ala	Thr	Trp 90	Gly	Ser	Glu	Asp	Gln 95	Val			
Phe	Gly	Gly	Gly 100	Thr	Lys	Leu	Thr	Val 105	Leu	Gly	Gln	Pro	Lys 110	Ala	Ala			
Pro	Ser	Val 115	Thr	Leu	Phe	Pro	Pro 120	Ser	Ser	Glu	Glu	Leu 125	Gln	Ala	Asn			
Lys	Ala 130	Thr	Leu	Val	Суз	Leu 135	Ile	Ser	Asp	Phe	Tyr 140	Pro	Gly	Ala	Val			
Thr 145	Val	Ala	Trp	Lys	Ala 150	Asp	Ser	Ser	Pro	Val 155	Lys	Ala	Gly	Val	Glu 160			
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His Trp Tyr 35	Gln (3ln L	ys Pro	Gly	Gln	Ala	Pro	Val	Leu 45	Val	Ile	Tyr	
Lys Asp Asn 50	. Asp A	Arg P	ro Sei 55		Ile	Pro	Glu	Arg 60		Ser	Gly	Ser	
Asn Ser Gly	Asn 1	Thr A 7	la Thi	: Leu	Thr	Ile	Ser 75		Thr	Gln	Ala	Glu 80	
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His Trp Tyr 35	Gln (3ln L	ys Pro	Gly 40	Gln	Ala	Pro	Val	Leu 45	Val	Ile	Tyr	
Lys Asp Asn 50	Asp A	Arg P	ro Sei 55	: Gly	Ile	Pro	Glu	Arg 60	Phe	Ser	Gly	Ser	
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Asp Glu Ala		fyr T		s Ser	Thr			Ile	Glu	Pro			
Val Phe Gly		35 31y T	hr Ly:	s Leu	Thr	90 Val	Leu	Gly	Gln	Pro	95 Lys	Ala	
- Ala Pro Ser	100	-	-		105			-		110	-		
115				120					125				
Asn Lys Ala	Thr I	leu V	al Cys	: Leu	Ile	Ser	Asb	Phe	Tyr	Pro	Gly	Ala	

			ıe	

130 135 140 Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys Ala Gly Val 150 155 145 160 Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr Ala Ala Ser 165 170 175 Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His Arg Ser Tyr 180 185 190 Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys Thr Val Ala 195 200 205 Pro Thr Glu Xaa 210 <210> SEQ ID NO 291 <211> LENGTH: 321 <212> TYPE: DNA <213> ORGANISM: homo sapiens <400> SEOUENCE: 291 gatategaac tgacceagee geetteagtg agegttgeae eaggteagae egegegtate 60 tcgtgtagcg gcgataatat tggtaattct tatgttcatt ggtaccagca gaaacccggg 120 caggegeeag ttettgtgat ttataaggat aatgategte eetcaggeat eeeggaaege 180 tttagcggat ccaacagcgg caacaccgcg accctgacca ttagcggcac tcaggcggaa 240 gacgaagcgg attattattg ctctacttgg gatattgagc ctacttatgt gtttggcggc 300 ggcacgaagt taaccgttct t 321 <210> SEQ ID NO 292 <211> LENGTH: 634 <212> TYPE: DNA <213> ORGANISM: homo sapiens <220> FEATURE: <221> NAME/KEY: misc_feature <222> LOCATION: (634)..(634) <223> OTHER INFORMATION: n can be TGCAGC or GCC <400> SEQUENCE: 292 gatategaae tgaeceagee geetteagtg agegttgeae eaggteagae egegegtate 60 tcgtgtagcg gcgataatat tggtaattet tatgtteatt ggtaccagea gaaaceeggg 120 caggegeeag ttettgtgat ttataaggat aatgategte eetcaggeat eeeggaaege 180 tttageggat ccaacagegg caacaeegeg accetgacea ttageggeae teaggeggaa 240 gacgaagcgg attattattg ctctacttgg gatattgagc ctacttatgt gtttggcggc 300 ggcacgaagt taaccgttct tggccagccg aaagccgcac cgagtgtgac gctgtttccg 360 420 ccqaqcaqcq aaqaattqca qqcqaacaaa qcqaccctqq tqtqcctqat taqcqacttt tatccgggag ccgtgacagt ggcctggaag gcagatagca gccccgtcaa ggcgggagtg 480 gagaccacca caccetecaa acaaagcaac aacaagtaeg eggeeageag etatetgage 540 ctgacgcctg agcagtggaa gtcccacaga agctacagct gccaggtcac gcatgagggg 600 agcaccgtgg aaaaaaccgt tgcgccgact gagn 634

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n Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys <210> SEQ ID NO 294 <211> LENGTH: 103 <212> TYPE: PRT <213> ORGANISM: homo sapiens <220> FEATURE: <221> NAME/KEY: misc_feature <222> LOCATION: (103)..(103) <223> OTHER INFORMATION: Xaa can be any naturally occurring amino acid <400> SEQUENCE: 294 Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys

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											_	<u>con</u>	ιm	ued	
				85					90					95	
Lys	Val	Glu	Pro 100	Lys	Ser	Xaa									
<211 <212	L> LI 2> TY	EQ II ENGTI YPE : RGAN:	H: 3 PRT		o saj	pien	ទ								
<400)> SI	EQUEI	NCE :	295											
Ala 1	Ser	Thr	Lys	Gly 5	Pro	Ser	Val	Phe	Pro 10	Leu	Ala	Pro	Сүз	Ser 15	Arg
Ser	Thr	Ser	Glu 20	Ser	Thr	Ala	Ala	Leu 25	Gly	Суз	Leu	Val	Lуз 30	Asp	Tyr
Phe	Pro	Glu 35	Pro	Val	Thr	Val	Ser 40	Trp	Asn	Ser	Gly	Ala 45	Leu	Thr	Ser
Gly	Val 50	His	Thr	Phe	Pro	Ala 55	Val	Leu	Gln	Ser	Ser 60	Gly	Leu	Tyr	Ser
Leu 65	Ser	Ser	Val	Val	Thr 70	Val	Pro	Ser	Ser	Asn 75	Phe	Gly	Thr	Gln	Thr 80
Tyr	Thr	Сүз	Asn	Val 85	Asp	His	Lys	Pro	Ser 90	Asn	Thr	Lys	Val	Asp 95	Lys
Thr	Val	Glu	Arg 100	Lya	Суа	Суз	Val	Glu 105	Cys	Pro	Pro	Суз	Pro 110	Ala	Pro
Pro	Val	Ala 115	Gly	Pro	Ser	Val	Phe 120	Leu	Phe	Pro	Pro	Lys 125	Pro	Гла	Asp
Thr	Leu 130	Met	Ile	Ser	Arg	Thr 135	Pro	Glu	Val	Thr	Cys 140	Val	Val	Val	Asp
Val 145	Ser	His	Glu	Asp	Pro 150	Glu	Val	Gln	Phe	Asn 155	Trp	Tyr	Val	Asp	Gly 160
Val	Glu	Val	His	Asn 165	Ala	Lys	Thr	Lys	Pro 170	Arg	Glu	Glu	Gln	Phe 175	Asn
Ser	Thr	Phe	Arg 180	Val	Val	Ser	Val	Leu 185	Thr	Val	Val	His	Gln 190	Asp	Trp
Leu	Asn	Gly 195	Lys	Glu	Tyr	Lys	Суз 200	Lys	Val	Ser	Asn	Lys 205	Gly	Leu	Pro
Ala	Pro 210	Ile	Glu	Lys	Thr	Ile 215	Ser	Гла	Thr	Lys	Gly 220	Gln	Pro	Arg	Glu
Pro 225	Gln	Val	Tyr	Thr	Leu 230	Pro	Pro	Ser	Arg	Glu 235	Glu	Met	Thr	Гла	Asn 240
Gln	Val	Ser	Leu	Thr 245	Cys	Leu	Val	Lys	Gly 250	Phe	Tyr	Pro	Ser	Asp 255	Ile
Ala	Val	Glu	Trp 260	Glu	Ser	Asn	Gly	Gln 265	Pro	Glu	Asn	Asn	Tyr 270	Lys	Thr
Thr	Pro	Pro 275	Met	Leu	Asp	Ser	Asp 280	-	Ser	Phe	Phe	Leu 285	Tyr	Ser	Lys
Leu	Thr 290	Val	Asp	Lys	Ser	Arg 295		Gln	Gln	Gly	Asn 300	Val	Phe	Ser	Сув
Ser 305	Val	Met	His	Glu	Ala 310	Leu	His	Asn	His	Tyr 315	Thr	Gln	ГÀа	Ser	Leu 320
Ser	Leu	Ser	Pro	Gly 325	Гла										

<210> SEQ ID NO 296 <211> LENGTH: 1676 <212> TYPE: PRT <213> ORGANISM: homo sapiens <400> SEQUENCE: 296 Met Gly Leu Cuy Ile Leu Cys Phe Leu Ile Phe Leu Gly Lys Thr Trp Gly Gln Glu Gln Thr Tyr Val Ile Ser Ala Pro Lys Ile Phe Arg Val Gly Ala Ser Glu Asn Ile Val Ile Gln Val Tyr Gly Tyr Thr Glu Ala Phe Asp Ala Thr Ile Ser Ile Lys Ser Tyr Pro Asp Lys Lys Phe Ser Tyr Ser Ser Gly His Val His Leu Ser Ser Glu Asn Lys Phe Gln Asn Ser Ala Ile Leu Thr Ile Gln Pro Lys Gln Leu Pro Gly Gly Gln Asn Pro Val Ser Tyr Val Tyr Leu Glu Val Val Ser Lys His Phe Ser Lys Ser Lys Arg Met Pro Ile Thr Tyr Asp Asn Gly Phe Leu Phe Ile His Thr Asp Lys Pro Val Tyr Thr Pro Asp Gln Ser Val Lys Val Arg Val Tyr Ser Leu Asn Asp Asp Leu Lys Pro Ala Lys Arg Glu Thr Val Leu Thr Phe Ile Asp Pro Glu Gly Ser Glu Val Asp Met Val Glu Glu Ile Asp His Ile Gly Ile Ile Ser Phe Pro Asp Phe Lys Ile Pro Ser Asn Pro Arg Tyr Gly Met Trp Thr Ile Lys Ala Lys Tyr Lys Glu Asp 2.05 Phe Ser Thr Thr Gly Thr Ala Tyr Phe Glu Val Lys Glu Tyr Val Leu Pro His Phe Ser Val Ser Ile Glu Pro Glu Tyr Asn Phe Ile Gly Tyr Lys Asn Phe Lys Asn Phe Glu Ile Thr Ile Lys Ala Arg Tyr Phe Tyr Asn Lys Val Val Thr Glu Ala Asp Val Tyr Ile Thr Phe Gly Ile Arg Glu Asp Leu Lys Asp Asp Gln Lys Glu Met Met Gln Thr Ala Met Gln Asn Thr Met Leu Ile Asn Gly Ile Ala Gln Val Thr Phe Asp Ser Glu Thr Ala Val Lys Glu Leu Ser Tyr Tyr Ser Leu Glu Asp Leu Asn Asn Lys Tyr Leu Tyr Ile Ala Val Thr Val Ile Glu Ser Thr Gly Gly Phe Ser Glu Glu Ala Glu Ile Pro Gly Ile Lys Tyr Val Leu Ser Pro Tyr Lys Leu Asn Leu Val Ala Thr Pro Leu Phe Leu Lys Pro Gly Ile Pro

Tyr Pro Ile Lys Val Gln Val Lys Asp Ser Leu Asp Gln Leu Val Gly Gly Val Pro Val Thr Leu Asn Ala Gln Thr Ile Asp Val Asn Gln Glu Thr Ser Asp Leu Asp Pro Ser Lys Ser Val Thr Arg Val Asp Asp Gly Val Ala Ser Phe Val Leu Asn Leu Pro Ser Gly Val Thr Val Leu Glu Phe Asn Val Lys Thr Asp Ala Pro Asp Leu Pro Glu Glu Asn Gln Ala Arg Glu Gly Tyr Arg Ala Ile Ala Tyr Ser Ser Leu Ser Gln Ser Tyr Leu Tyr Ile Asp Trp Thr Asp Asn His Lys Ala Leu Leu Val Gly Glu His Leu Asn Ile Ile Val Thr Pro Lys Ser Pro Tyr Ile Asp Lys Ile Thr His Tyr Asn Tyr Leu Ile Leu Ser Lys Gly Lys Ile Ile His Phe Gly Thr Arg Glu Lys Phe Ser Asp Ala Ser Tyr Gln Ser Ile Asn Ile Pro Val Thr Gln Asn Met Val Pro Ser Ser Arg Leu Leu Val Tyr Tyr Ile Val Thr Gly Glu Gln Thr Ala Glu Leu Val Ser Asp Ser Val Trp Leu Asn Ile Glu Glu Lys Cys Gly Asn Gln Leu Gln Val His Leu Ser Pro Asp Ala Asp Ala Tyr Ser Pro Gly Gln Thr Val Ser Leu Asn Met Ala Thr Gly Met Asp Ser Trp Val Ala Leu Ala Ala Val Asp Ser Ala Val Tyr Gly Val Gln Arg Gly Ala Lys Lys Pro Leu Glu Arg Val Phe Gln Phe Leu Glu Lys Ser Asp Leu Gly Cys Gly Ala Gly Gly Gly Leu Asn Asn Ala Asn Val Phe His Leu Ala Gly Leu Thr Phe Leu Thr Asn Ala Asn Ala Asp Asp Ser Gln Glu Asn Asp Glu Pro Cys Lys Glu Ile Leu Arg Pro Arg Arg Thr Leu Gln Lys Lys Ile Glu Glu Ile Ala Ala Lys Tyr Lys His Ser Val Val Lys Lys Cys Cys Tyr Asp Gly Ala Cys Val Asn Asn Asp Glu Thr Cys Glu Gln Arg Ala Ala Arg Ile Ser Leu Gly Pro Arg Cys Ile Lys Ala Phe Thr Glu Cys Cys Val Val Ala Ser Gln Leu Arg Ala Asn Ile Ser His Lys Asp Met Gln Leu Gly Arg Leu His Met Lys Thr Leu Leu Pro Val Ser Lys Pro Glu Ile Arg Ser Tyr

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Pro 770	Glu	Ser	Trp		Trp 775	Glu	Val	His	Leu) Arg	Arg	Lys
Leu	Gln	Phe	Ala	Leu 790	Pro	Asp	Ser	Leu			r Trp	Glu	. Ile	Gln 800
Val	Gly	Ile	Ser 805	Asn	Thr	Gly	Ile	Cys 810	Val	A1.	a Asr) Thr		Lys
Lys	Val	Phe 820	Lys	Asp	Val	Phe	Leu 825	Glu	Met	Ası	n Ile		-	Ser
	Arg 835	Gly	Glu	Gln		Gln 840	Leu	Lys	Gly	Th		-	Asn	Tyr
	Ser	Gly	Met	Gln		Cys	Val	Lys	Met			ı Val	Glu	Gly
	Thr	Ser	Glu			Val	Ile	Asp		Gl		r Thr	Гуз	Ser 880
	Cys	Val	-		Lys	Val	Glu	-			r Sei	His		Val
Phe	Thr			Pro	Leu	Glu			Leu	Hi	s Asr		Asn	
Leu	Glu	900 Thr	Trp	Phe	Gly	Lys	905 Glu	Ile	Leu	Va	l Lys			Arg
	915		-		-	920					925	5		-
930			-		935				-	94	0			
	-	-		950	-				955					960
Arg	Ile	Pro	Leu 965	Asp	Leu	Val	Pro	Lys 970	Thr	Gl	u Ile	e Lys		
Ser	Val	Lys 980	Gly	Leu	Leu	Val	Gly 985	Glu	Ile	Le	u Sei			Leu
	Glu 995	Gly	Ile	Asn				: Hi:	s Le	u P:	-		ly s	er A
		ı Leı	ı Met	: Sei			al Pi	co Va	al P		-	Val	Phe	His
		ı Thi	r Gly	/ Asr			rp As	an I	le P			Ser	Asp	Pro
		ı Lyı	s Glr	n Lys			ys Ly	ys Ly	/s L			Glu	Gly	Met
		e Met	: Sei	с Туз			an Al	la A:	зр Т			Tyr	Ser	Val
-	-	/ Gl	y Sei	r Ala			nr Ti	cp Le	∋u T		Ala 1080	Phe	Ala	Leu
1070 Val) Leu	-			107 L Asn	75 1 L3		-		lu (1080 Gln			
1070 Val 1085 Ile	D Leu Cys	ı Gl <u>y</u>	∕ Glr	n Val	107 L Asn 109 1 Leu	75 11 L3 200 11 T3	ys Ty	- yr Va	al G	lu (1u)	1080 Gln 1095 Asn	Asn	Gln .	Asn
1070 Val 1085) Leu 5 Cys	ı Gly	Y Glr n Sei	n Val r Leu	107 L Asn 109 Leu 110	75 1 Ly 90 1 Ti 95	ya T <u>y</u> rp Le	yr Va	al G al G	lu (lu ;	1080 Gln 1095 Asn 1110	Asn Tyr	Gln . Gln	Asn Leu
1070 Val 1085 Ile 1100 Asn 1115	Cyr Cyr Gly	ı Gly 5 Ası 7 Sei	y Glr n Sei r Phe	n Val r Lei e Lys	107 L Asn 109 L Leu 110 G Glu 112	75 1 Ly 00 1 Ti 05 1 As 20	ya T <u>y</u> rp Le an Se	yr Va eu Va er Gl	al G al G In T	lu (lu ; yr (1080 31n 1095 Asn 1110 31n 1125	Asn Tyr Pro	Gln . Gln Ile	Asn Leu Lys
1070 Val 1085 Ile 1100 Asn	D Lev Cyr Gly Gly	ı Gly 5 Ası 7 Sei	y Glr n Sei r Phe	n Val r Lei e Lys	107 L Asn 109 L Leu 110 G Glu 112	75 1 Ly 1 Ti 05 1 As 20	ya T <u>y</u> rp Le an Se	yr Va eu Va er Gl	al G al G In T	lu (lu) yr (lu)	1080 31n 1095 Asn 1110 31n 1125	Asn Tyr Pro	Gln . Gln Ile	Asn Leu Lys
1070 Val 1085 Ile 1100 Asn 1115 Gln	Cyr Cyr Gly Gly Ala	ı Gly s Asr 7 Sej 7 Thi	y Glr n Sei r Phe r Lei	n Val c Leu e Lys 1 Pro	107 L Asn 109 L Leu 110 S Glu 112 > Val 113	75 1 Ly 1 Tr 1 As 20 35 GI ⇒ GI	ys Ty rp Le sn Se lu Ai	yr Va eu Va er Gl La An	al G al G In T rg G	lu (yr (lu ;	1080 Gln 1095 Asn 1110 Gln 1125 Asn 1140	Asn Tyr Pro Ser	Gln . Gln Ile Leu	Asn Leu Lys Tyr
	770 Leu Val Lys Val Thr 850 Cys Lys Phe Leu Val 930 Pro Arg Ser Gln Ala (025 Ileu 1040 Ser 505	770 Leu Gln Val Gly Lys Val Val Arg 835 Cys Thr Cys Thr Lys Cys Phe Thr Leu Glu 915 Val Pro 930 Pro Arg Arg Ile Ser Val Gln Glu 995 Ala Glu 1025 Glu	770 Leu Gln Phe Val Gly Ile Lys Val Phe Lys Val Phe Sag Gly Val Arg Gly Thr Ser Gly Cys Thr Ser Lys Cys Val Phe Thr Val 915 Val Pro Glu Par Ile Pro Ser Val Lys Gln Glu Gly Ala Glu Leu Lous Glu Thr Lous Cys Cys Gly	770 Leu Gln Phe Ala Val Gly Ile Ser 805 Lys Val Phe Lys 820 Val Arg Gly Glu Arg Gly Met 50 Cys Thr Ser Glu Lys Cys Val Arg 885 Phe Thr Val Leu 900 Leu Glu Thr Trp 915 Val Pro Glu Gly Pro Arg Gly Ile Arg Ile Pro Leu 930 Ser Val Lys Gly Gln Glu Gly Ile Ala Glu Leu Met 1025 Ser Ile Met Ser	770 Leu Gln Phe Ala Leu 790 Val Gly Ile Ser Asn 805 Lys Val Phe Lys Asp 820 Val Arg Gly Glu Gln 611 835 Val Arg Gly Glu Gln 611 String Ser Gly Met Gln 850 Cys Thr Ser Glu Ser 870 Lys Cys Val Arg Gln 885 Phe Thr Val Leu Pro 900 Leu Glu Thr Trp Phe 915 Val Pro Glu Gly Val 930 Pro Arg Gly Ile Tyr 950 Arg Ile Pro Leu Asp 965 Ser Val Lys Gly Leu 980 Gln Glu Gly Ile Asn 995 Ala Glu Leu Met Ser 1000 Leu Glu Thr Gly Asr Ala Glu Lys Gln Lys 104 Hoto Ser Ile Met Ser Tyr	770 775 Leu Gln Phe Ala Leu Pro Val Gly Ile Ser Asn Thr 820 Val Arg Gly Glu Gln Gln Ile 820 Val Arg Gly Glu Gln Ile Sass Gly Cly Arg Gly Glu Gln Phe 835 Cys Thr Ser Glu Ser Pro 835 Cys Thr Ser Glu Ser Pro Lys Cys Val Arg Gln Lys Phe Thr Val Leu Pro Leu 915 Val Pro Glu Gly Val Lys 930 Pro Arg Gly Ile Tyr Gly 930 Pro Arg Gly Ile Asp Leu 965 Ser Val Lys Gly Leu Leu 980 Arg Ile Pro Leu Arg Leu 980 Arg Ile Arg Gly Ile Asp Ile 980 Arg Ile Arg Gly Ile Asp Ile 980 Arg Ile Cly Cly Arg Met Ser Val Arg Glu Lys Gly Leu Leu 995 Arg Glu Lys Gly Ley Asp His 1010 1025 Ala Glu Lys Gln Lys Ley 104 Ser Ile Met Ser Tyr Arg	770 775 Leu Gln Phe Ala Leu Pro Asp 790Val Gly Ile Ser Asn Thr Gly 805Lys Val Phe Lys Asp Val Phe 820Val Arg Gly Glu Gln Ile Gln 835Val Arg Gly Met Gln Phe Cys 850Thr Ser Glu Ser Pro Val 885Cys Thr Ser Glu Ser Pro Val 900Lys Cys Val Arg Gln Lys Val 900Leu Glu Thr Trp Phe Gly Lys 915Pro Arg Gly Ile Tyr Gly Thr 950Arg Ile Pro Leu Asp Leu Val 965Ser Val Lys Gly Leu Leu Val 980Gln Glu Gly Ile Asn Ile Leu 1005Ala Glu Leu Met Ser Val Log 1015Lieu Glu Thr Gly Asn His 1030	770 775 Leu Gln Phe Ala Leu Pro Asp SerVal Gly Ile Ser Asn Thr Gly Ile 805 Lys Val Phe Lys Asp Val Phe Leu 820 Val Arg Gly Glu Gln Ile Gln Leu 835 Gly Met Gln Phe Cys Val 850 Cys Thr Ser Glu Ser Pro Val IleLys Cys Val Arg Gln Lys Val GluPhe Thr Val Leu Pro Leu Glu Ile 915 Leu Glu Thr Trp Phe Gly Lys Glu 915 Pro Arg Gly Ile Tyr Gly Thr Ile 930 Pro Arg Gly Leu Leu Val Gly 985 Gln Glu Gly Ile Asn Ile Leu Thr 995 Gln Glu Gly Ile Asn Ile Leu Thr 995 Ala Glu Lys Gln Lys Leu Lys Lys 1000 Ala Glu Lys Gln Lys Leu Lys Lys 1040 Ser Ile Met Ser Tyr Arg Asn At	770775Leu Gln Phe Ala Leu Pro Asp Ser Leu 790Val Gly Ile Ser Asn Thr Gly Ile Cys 805Val Phe Lys Asp Val Phe Leu Glu 820Val Arg Gly Glu Gln Ile Gln Leu Lys 835Val Arg Cly Met Gln Phe Cys Val Lys 850Cys Thr Ser Glu Ser Pro Val Ile Asp 870Lys Cys Val Arg Gln Lys Val Glu Gly 900Phe Thr Val Leu Pro Leu Glu Ile Gly 905Leu Glu Thr Trp Phe Gly Lys Glu Ile 915Val Pro Glu Gly Val Lys Arg Glu Ser 930Pro Arg Gly Ile Tyr Gly Thr Ile Ser 950Arg Ile Pro Leu Asp Leu Val Pro Lys 965Arg Ile Pro Leu Asp Leu Val Gly Glu 980Gln Glu Gly Ile Asn Ile Leu Thr His 1000Ala Glu Leu Met Ser Val Val Pro Val 1015Leu Glu Thr Gly Asn His Trp Asn I: 1025Lys Glu Lys Gln Lys Leu Lys Lys Lys Ly 1040	770775Leu Gln Phe Ala Leu 805 Pro Asp Ser Leu Thr 795Val Gly Ile Ser Asn Thr Gly Ile Cys Val 805 Sar Pal Phe Leu Glu Met 820 Lys Val Phe Lys Asp Val Phe Leu Glu Met 820 Gly Glu Gln Ile Gln Leu Lys Gly 840 Val Arg Gly Glu Gln Phe Cys Val Lys Met 835 Gly Met Gln Phe Cys Val Lys Met 840 Thr Ser Gly Met Gln Phe Cys Val Ile Asp His 875 Sar Pro Val Ile Asp His 890 Cys Thr Ser Glu Ser Pro Val Ile Gly Leu 900 Pro Leu Glu Ile Gly Leu 905 Phe Thr Val Leu Pro Leu Glu Ile Gly Leu 915 Pro Glu Gly Val Lys Arg Glu Ser Tyr 930 Val Pro Glu Gly Val Lys Arg Glu Ser Tyr 930 Pro Leu Asp Leu Val Pro Lys Thr 965 Arg Ile Pro Leu Asp Leu Val Gly Glu Ile 980 Gly Leu Leu Val Gly Glu Ile 985 Gln Glu Gly Ile Asn Ile Leu Thr His Le 995 Pro Val Pro Val Pro Val P 1000 Ala Glu Leu Met Ser Val Val Val Pro Val P 1002 Thr Gly Asn His Trp Asn Ile P 1045	Pro Glu Ser Trp Leu Trp Glu Val His Leu Var 770 Yar Var 775 Leu Gln Phe Ala Leu Pro Asp Ser Leu Thr 790 Thr 795 Val Gly Ile Ser Asn Thr Gly Ile Cys Val Al. 805 Ser Val Phe Leu Glu Met Ass 825 Val Arg Gly Glu Gln Ile Gln Leu Lys Gly Thr 835 Ser Val Phe Lys Asp Val Phe Leu Glu Met Ass 825 Val Arg Gly Glu Gln Ile Gln Leu Lys Gly Thr 835 Ser Gly Net Gln Phe Cys Val Lys Met Ser 855 Cys Thr Ser Glu Ser Pro Val Ile Asp His Glu 885 Ser Ser 890 Phe Thr Val Leu Pro Leu Glu Ile Gly Leu His 900 Ser Ser 935 Phe Thr Val Leu Pro Leu Glu Ile Gly Leu His 900 Ser Tyr Ser 935 Val Pro Glu Gly Val Lys Arg Glu Ser Tyr Ser 930 Ser Tyr Ser 935 Pro Arg Gly Ile Tyr Gly Thr Ile Ser Arg Arg 955 Arg Ile Pro Leu Asp Leu Val Pro Lys Thr Gly 965 Ser Val Lys Gly Leu Leu Val Gly Glu Ile Leu 980 Gln Glu Gly Ile Asp Ile Uval Pro Val Phe 985 Gln Glu Gly Ile Asp Ile Leu Thr His Leu P 995 Ala Glu Leu Met Ser Val Val Pro Val Phe 1000 Ala Glu Leu Met Ser Val Val Pro Val Phe 1030 Ile Glu Lys Gln Lys Leu Lys Lys Lys Lys Leu 1040	ProGluSerTrpLeuTrpGluValHisLeuValPro770GluPieAlaLeuProAspSerLeuThrThrThrValGlyIleSerAsnThrGlyIleCysValAlaAspValGlyIleSerAsnThrGlyIleCysValAlaAspLysValPheLysAspValPheLeuGluMetAsnIleSa5GlyGluGlnIleGlnLeuLysGlyThrVal835GlyGluGlnPheLeuLysGlyThrVal855SerGluSerProValNetSerAla855SerGluSerProValIleAspHisGlnCysThrSerGluSerProValIleAspHisGlyGlyLysCysValArgGlnLysValGluGlySerSerSerSerLysCysValArgGluLeuProLeuGluGlySerSerSerSerLysCysValArgGluLeuProLeuGluGluSerSerSerSerPheThrValLeuProLeuAsp </td <td>ProGluSerTrpLeuTrpGluValHisLeuValProArg770InPheAlaLeuProAspSerLeuThrThrThrGluValGlyIleSerAsnThrGlyIleCysValAlaAspThrValGlyIleSerAsnThrGlyIleCysValAlaAspThrLysValPheLysAspValPheLeuGluMetAsnIlePro820ValPheLysAspValPheLeuGluMetAsnIlePro835GlyGluGlnIleGlnLeuLysGlyThrValYal850serGluGlnPheCysValMetSerAlaVal850serGluGluGlnPheCysValMetSerAlaVal850serGluSerValLysGluGluSerAsnIleSer11SerGlyMetGlnSerValGluGlySerSerHisSerIle12SerValArgGlnLysValGluGlyLysSerSerSerHisSerSerSerSerSerSerSerSerSe</td> <td>Leu Gln Phe Ala Leu Pro Asp Ser Leu Thr Thr Trp Glu Ile 790 795 795 795 795 795 795 795 795</td>	ProGluSerTrpLeuTrpGluValHisLeuValProArg770InPheAlaLeuProAspSerLeuThrThrThrGluValGlyIleSerAsnThrGlyIleCysValAlaAspThrValGlyIleSerAsnThrGlyIleCysValAlaAspThrLysValPheLysAspValPheLeuGluMetAsnIlePro820ValPheLysAspValPheLeuGluMetAsnIlePro835GlyGluGlnIleGlnLeuLysGlyThrValYal850serGluGlnPheCysValMetSerAlaVal850serGluGluGlnPheCysValMetSerAlaVal850serGluSerValLysGluGluSerAsnIleSer11SerGlyMetGlnSerValGluGlySerSerHisSerIle12SerValArgGlnLysValGluGlyLysSerSerSerHisSerSerSerSerSerSerSerSerSe	Leu Gln Phe Ala Leu Pro Asp Ser Leu Thr Thr Trp Glu Ile 790 795 795 795 795 795 795 795 795

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	1160					1165					1170			
Phe	Leu 1175	Leu	Glu	Asn	Thr	Leu 1180	Pro	Ala	Gln	Ser	Thr 1185	Phe	Thr	Leu
Ala	Ile 1190	Ser	Ala	Tyr	Ala	Leu 1195	Ser	Leu	Gly	Asp	Lys 1200	Thr	His	Pro
Gln	Phe 1205	Arg	Ser	Ile	Val	Ser 1210	Ala	Leu	Lys	Arg	Glu 1215	Ala	Leu	Val
ГЛа	Gly 1220	Asn	Pro	Pro	Ile	Tyr 1225	Arg	Phe	Trp	Гла	Asp 1230	Asn	Leu	Gln
His	Lys 1235	Asp	Ser	Ser	Val	Pro 1240	Asn	Thr	Gly	Thr	Ala 1245	Arg	Met	Val
Glu	Thr 1250	Thr	Ala	Tyr	Ala	Leu 1255	Leu	Thr	Ser	Leu	Asn 1260	Leu	Lys	Asp
Ile	Asn 1265	Tyr	Val	Asn	Pro	Val 1270	Ile	Lys	Trp	Leu	Ser 1275	Glu	Glu	Gln
Arg	Tyr 1280	Gly	Gly	Gly	Phe	Tyr 1285	Ser	Thr	Gln	Asp	Thr 1290	Ile	Asn	Ala
Ile	Glu 1295	Gly	Leu	Thr	Glu	Tyr 1300	Ser	Leu	Leu	Val	Lys 1305	Gln	Leu	Arg
Leu	Ser 1310	Met	Asp	Ile	Asp	Val 1315	Ser	Tyr	Lys	His	Lys 1320	Gly	Ala	Leu
His	Asn 1325	Tyr	ГЛа	Met	Thr	Asp 1330	ГЛа	Asn	Phe	Leu	Gly 1335	Arg	Pro	Val
Glu	Val 1340	Leu	Leu	Asn	Asp	Asp 1345	Leu	Ile	Val	Ser	Thr 1350	Gly	Phe	Gly
Ser	Gly 1355	Leu	Ala	Thr	Val	His 1360	Val	Thr	Thr	Val	Val 1365	His	Lys	Thr
Ser	Thr 1370	Ser	Glu	Glu	Val	Cys 1375	Ser	Phe	Tyr	Leu	Lys 1380	Ile	Asp	Thr
Gln	Asp 1385	Ile	Glu	Ala	Ser	His 1390	Tyr	Arg	Gly	Tyr	Gly 1395	Asn	Ser	Asp
Tyr	Lys 1400	Arg	Ile	Val	Ala	Cys 1405	Ala	Ser	Tyr	Гла	Pro 1410	Ser	Arg	Glu
Glu	Ser 1415	Ser	Ser	Gly	Ser	Ser 1420	His	Ala	Val	Met	Asp 1425	Ile	Ser	Leu
Pro	Thr 1430	Gly	Ile	Ser	Ala	Asn 1435	Glu	Glu	Asp	Leu	Lys 1440	Ala	Leu	Val
Glu	Gly 1445	Val	Asp	Gln	Leu	Phe 1450	Thr	Asp	Tyr	Gln	Ile 1455	Lys	Asp	Gly
His	Val 1460	Ile	Leu	Gln	Leu	Asn 1465	Ser	Ile	Pro	Ser	Ser 1470	Asp	Phe	Leu
Сүз	Val 1475	Arg	Phe	Arg	Ile	Phe 1480	Glu	Leu	Phe	Glu	Val 1485	Gly	Phe	Leu
Ser	Pro 1490	Ala	Thr	Phe	Thr	Val 1495	-	Glu	Tyr	His	Arg 1500	Pro	Asp	Гла
Gln	Cys 1505		Met	Phe	Tyr	Ser 1510		Ser	Asn	Ile	Lys 1515	Ile	Gln	Lys
Val	Cys 1520	Glu	Gly	Ala	Ala	Cys 1525	Lys	Суз	Val	Glu	Ala 1530	Asp	Суз	Gly
Gln	Met 1535	Gln	Glu	Glu	Leu	Asp 1540	Leu	Thr	Ile	Ser	Ala 1545	Glu	Thr	Arg

Lys Gln Thr Ala Cys Lys Pro Glu Ile Ala Tyr Ala Tyr Lys Val Ser Ile Thr Ser Ile Thr Val Glu Asn Val Phe Val Lys Tyr Lys Ala Thr Leu Leu Asp Ile Tyr Lys Thr Gly Glu Ala Val Ala Glu Lys Asp Ser Glu Ile Thr Phe Ile Lys Lys Val Thr Cys Thr Asn Ala Glu Leu Val Lys Gly Arg Gln Tyr Leu Ile Met Gly Lys Glu Ala Leu Gln Ile Lys Tyr Asn Phe Ser Phe Arg Tyr Ile Tyr Pro Leu Asp Ser Leu Thr Trp Ile Glu Tyr Trp Pro Arg Asp Thr Thr Cys Ser Ser Cys Gln Ala Phe Leu Ala Asn Leu Asp Glu Phe Ala Glu Asp Ile Phe Leu Asn Gly Cys <210> SEO ID NO 297 <211> LENGTH: 1676 <212> TYPE: PRT <213> ORGANISM: homo sapiens <400> SEQUENCE: 297 Met Gly Leu Cuy Ile Leu Cys Phe Leu Ile Phe Leu Gly Lys Thr Trp Gly Gln Glu Gln Thr Tyr Val Ile Ser Ala Pro Lys Ile Phe Arg Val Gly Ala Ser Glu Asn Ile Val Ile Gln Val Tyr Gly Tyr Thr Glu Ala Phe Asp Ala Thr Ile Ser Ile Lys Ser Tyr Pro Asp Lys Lys Phe Ser Tyr Ser Ser Gly His Val His Leu Ser Ser Glu Asn Lys Phe Gln Asn Ser Ala Val Leu Thr Ile Gln Pro Lys Gln Leu Pro Gly Gly Gln Asn Gln Val Ser Tyr Val Tyr Leu Glu Val Val Ser Lys His Phe Ser Lys Ser Lys Lys Ile Pro Ile Thr Tyr Asp Asn Gly Phe Leu Phe Ile His Thr Asp Lys Pro Val Tyr Thr Pro Asp Gln Ser Val Lys Val Arg Val Tyr Ser Leu Asn Asp Asp Leu Lys Pro Ala Lys Arg Glu Thr Val Leu Thr Phe Ile Asp Pro Glu Gly Ser Glu Ile Asp Met Val Glu Glu Ile Asp His Ile Gly Ile Ile Ser Phe Pro Asp Phe Lys Ile Pro Ser Asn Pro Arg Tyr Gly Met Trp Thr Ile Gln Ala Lys Tyr Lys Glu Asp Phe Ser Thr Thr Gly Thr Ala Phe Phe Glu Val Lys Glu Tyr Val Leu

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	210					215					220				
Pro 225	His	Phe	Ser	Val	Ser 230	Val	Glu	Pro	Glu	Ser 235	Asn	Phe	Ile	Gly	Tyr 240
Lys	Asn	Phe	Гуз	Asn 245	Phe	Glu	Ile	Thr	Ile 250	Lys	Ala	Arg	Tyr	Phe 255	Tyr
Asn	Lys	Val	Val 260	Thr	Glu	Ala	Asp	Val 265	Tyr	Ile	Thr	Phe	Gly 270	Ile	Arg
Glu	Asp	Leu 275	Lys	Asp	Asp	Gln	Lys 280	Glu	Met	Met	Gln	Thr 285	Ala	Met	Gln
Asn	Thr 290	Met	Leu	Ile	Asn	Gly 295	Ile	Ala	Gln	Val	Thr 300	Phe	Asp	Ser	Glu
Thr 305	Ala	Val	Lys	Glu	Leu 310	Ser	Tyr	Tyr	Ser	Leu 315	Glu	Asp	Leu	Asn	Asn 320
ГЛа	Tyr	Leu	Tyr	Ile 325	Ala	Val	Thr	Val	Ile 330	Glu	Ser	Thr	Gly	Gly 335	Phe
Ser	Glu	Glu	Ala 340	Glu	Ile	Pro	Gly	Ile 345	Lys	Tyr	Val	Leu	Ser 350	Pro	Tyr
-		355					360	Leu			-	365	-		
-	370		-			375	-	Asb			380				-
385					390			Gln		395	-				400
		-		405		-	-	Ser	410		-		_	415	-
			420					Pro 425		-			430		
		435	-		-		440	Asp			-	445			
	450					455		Tyr			460				
465	-		_	-	470	_		His	-	475				-	480
				485				Lys	490					495	
		-	500	-				Ser 505	-	_	-		510		
_		515		-			520	Ala Ser		-		525			
	530					535				-	540			-	-
545			-		550			Glu		555		-			560
Leu	Asn	Ile	Glu	Glu 565	ГЛа	СЛа	Gly	Asn	Gln 570	Leu	Gln	Val	His	Leu 575	Ser
Pro	Asp	Ala	Asp 580	Thr	Tyr	Ser	Pro	Gly 585	Gln	Thr	Val	Ser	Leu 590	Asn	Met
Val	Thr	Gly 595	Met	Asp	Ser	Trp	Val 600	Ala	Leu	Thr	Ala	Val 605	Asp	Ser	Ala
Val	Tyr 610	Gly	Val	Gln	Arg	Arg 615	Ala	Lys	Lys	Pro	Leu 620	Glu	Arg	Val	Phe

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Gln Phe Leu Glu Lys Ser Asp Leu Gly Cys Gly Ala Gly Gly Gly Leu Asn Asn Ala Asn Val Phe His Leu Ala Gly Leu Thr Phe Leu Thr Asn Ala Asn Ala Asp Asp Ser Gln Glu Asn Asp Glu Pro Cys Lys Glu Ile Ile Arg Pro Arg Arg Met Leu Gln Glu Lys Ile Glu Glu Ile Ala Ala Lys Tyr Lys His Leu Val Val Lys Lys Cys Cys Tyr Asp Gly Val Arg Ile Asn His Asp Glu Thr Cys Glu Gln Arg Ala Ala Arg Ile Ser Val Gly Pro Arg Cys Val Lys Ala Phe Thr Glu Cys Cys Val Val Ala Ser Gln Leu Arg Ala Asn Asn Ser His Lys Asp Leu Gln Leu Gly Arg Leu His Met Lys Thr Leu Leu Pro Val Ser Lys Pro Glu Ile Arg Ser Tyr 755 760 765 Phe Pro Glu Ser Trp Leu Trp Glu Val His Leu Val Pro Arg Arg Lys Gln Leu Gln Phe Ala Leu Pro Asp Ser Val Thr Thr Trp Glu Ile Gln Gly Val Gly Ile Ser Asn Ser Gly Ile Cys Val Ala Asp Thr Ile Lys Ala Lys Val Phe Lys Asp Val Phe Leu Glu Met Asn Ile Pro Tyr Ser Val Val Arg Gly Glu Gln Val Gln Leu Lys Gly Thr Val Tyr Asn Tyr Arg Thr Ser Gly Met Gln Phe Cys Val Lys Met Ser Ala Val Glu Gly Ile Cys Thr Ser Glu Ser Pro Val Ile Asp His Gln Gly Thr Lys Ser Ser Lys Cys Val Arg Gln Lys Val Glu Gly Ser Ser Asn His Leu Val Thr Phe Thr Val Leu Pro Leu Glu Ile Gly Leu Gln Asn Ile Asn Phe Ser Leu Glu Thr Ser Phe Gly Lys Glu Ile Leu Val Lys Ser Leu Arg Val Val Pro Glu Gly Val Lys Arg Glu Ser Tyr Ser Gly Ile Thr Leu Asp Pro Arg Gly Ile Tyr Gly Thr Ile Ser Arg Arg Lys Glu Phe Pro Tyr Arg Ile Pro Leu Asp Leu Val Pro Lys Thr Glu Ile Lys Arg Ile Leu Ser Val Lys Gly Leu Leu Val Gly Glu Ile Leu Ser Ala Val Leu Ser Arg Glu Gly Ile Asn Ile Leu Thr His Leu Pro Lys Gly Ser Ala Glu Ala Glu Leu Met Ser Val Val Pro Val Phe Tyr Val Phe His

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00110	

											-001		<u></u>	
Tyr	Leu 1025		Thr	Gly	Asn	His 1030	-	Asn	Ile	Phe	His 1035		Asp	Pro
Leu	Ile 1040		Lys	Arg	Asn	Leu 1045		Lys	Lys		Lys 1050	Glu	Gly	Met
Val	Ser 1055		Met	Ser	Tyr	Arg 1060		Ala	Asp	_	Ser 1065	Tyr	Ser	Val
Trp	Lys 1070	-	Gly	Ser	Ala	Ser 1075		Trp	Leu		Ala 1080	Phe	Ala	Leu
Arg	Val 1085		Gly	Gln	Val	His 1090					Gln 1095	Asn	Gln	Asn
Ser	Ile 1100		Asn	Ser	Leu	Leu 1105		Leu	Val		Asn 1110	Tyr	Gln	Leu
Asp	Asn 1115		Ser	Phe	Гла	Glu 1120					Gln 1125	Pro	Ile	Lys
Leu	Gln 1130			Leu	Pro	Val 1135				Glu		Ser	Leu	Tyr
Leu		Ala		Thr	Val	Ile 1150	Gly			Lys		Phe	Asp	Ile
Суа		Leu	Val	Lys	Ile	Asn 1165	Thr			Ile		Ala	Asp	Thr
Phe		Leu	Glu	Asn	Thr	Leu 1180		Ala	Gln	Ser		Phe	Thr	Leu
Ala		Ser	Ala	Tyr	Ala	Leu 1195	Ser	Leu	Gly	Asp		Thr	His	Pro
Gln		Arg	Ser	Ile	Val	Ser 1210		Leu	Lys	Arg		Ala	Leu	Val
		Asn	Pro	Pro	Ile	Tyr	Arg			Lys		Ser	Leu	Gln
His		Asp			Val	Pro 1240				Thr		Arg	Met	Val
		Thr			Ala	Leu 1255	Leu	Thr	Ser			Leu	Lys	Asp
	Asn	Tyr			Pro	Ile		-	_		Ser	Glu	Glu	Gln
	-	Gly			Phe	1270 Tyr		Thr				Ile	Asn	Ala
Ile		Gly	Leu	Thr	Glu	1285 Tyr	Ser	Leu	Leu	Val		Gln	Leu	Arg
		Met	Asp	Ile	Asp	1300 Val	Ala	Tyr	Lys	His	-	-	Pro	Leu
	1310 Asn		Lys	Met	Thr	1315 Asp	Lys	Asn	Phe	Leu	1320 Gly		Pro	Val
	1325 Val		Leu	Asn	Asp	1330 Asp		Val	Val	Ser	1335 Thr		Phe	Glv
	1340				-	1345					1350	-		-
	1355					His 1360					1365		-	
Ser	Thr 1370		Glu	Glu	Val	Cys 1375	Ser	Phe	Tyr	Leu	Lүз 1380	Ile	Asp	Thr
Gln	Asp 1385		Glu	Ala	Ser	His 1390	-	Arg	Gly	Tyr	Gly 1395	Asn	Ser	Asp
Tyr	Lys	Arg	Ile	Val	Ala	Суз	Ala	Ser	Tyr	Гла	Pro	Ser	Lys	Glu

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Glu	Ser 1415		Ser	Gly	Ser	Ser 1420		Ala	Val	Met	Asp 1425	Ile	Ser	Leu
Prc	Thr 1430		Ile	Asn	Ala	Asn 1435		Glu	Asp	Leu	Lys 1440	Ala	Leu	Val
Glu	Gly 1445		Asp	Gln	Leu	. Phe 1450		Asp	Tyr	Gln	Ile 1455	-	Asp	Gly
His	Val 1460		Leu	Gln	Leu	. Asn 1465		Ile	Pro	Ser	Ser 1470	-	Phe	Leu
Суз	Val 1475		Phe	Arg	Ile	Phe 1480		Leu	Phe	Glu	Val 1485	-	Phe	Leu
Ser	Pro 1490		Thr	Phe	Thr	Val 1495	-	Glu	Tyr	His	Arg 1500	Pro	Asp	ГЛа
Glr	Суя 1505		Met	Phe	Tyr	Ser 1510		Ser	Asn	Ile	Lys 1515		Gln	Lys
Val	Суз 1520		Gly	Ala	Thr	Cys 1525		Суз	Ile	Glu	Ala 1530	Asp	Сүз	Gly
Glr	Met 1535		Lys	Glu	Leu	. Asp 1540		Thr	Ile	Ser	Ala 1545		Thr	Arg
Lys	Gln 1550		Ala	Суз	Asn	Pro 1555		Ile	Ala	Tyr	Ala 1560	-	Lys	Val
Ile	Ile 1565		Ser	Ile	Thr	Thr 1570		Asn	Val	Phe	Val 1575	-	Tyr	Lys
Ala	Thr 1580		Leu	Asp	Ile	Tyr 1585		Thr	Gly	Glu	Ala 1590	Val	Ala	Glu
Lys	Asp 1595		Glu	Ile	Thr	Phe 1600		Lys	Lys	Val	Thr 1605	-	Thr	Asn
Ala	Glu 1610		Val	Lys	Gly	Arg 1615		Tyr	Leu	Ile	Met 1620	-	Lys	Glu
Ala	Leu 1625		Ile	Lys	Tyr	Asn 1630		Thr	Phe	Arg	Tyr 1635		Tyr	Pro
Leu	. Asp 1640		Leu	Thr	Trp	Ile 1645		Tyr	Trp	Pro	Arg 1650	-	Thr	Thr
Суз	Ser 1655		Суз	Gln	Ala	Phe 1660		Ala	Asn	Leu	Asp 1665	Glu	Phe	Ala
Glu	. Asp 1670		Phe	Leu	Asn	Gly 1675	-							
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Glr 1	Val	Gln 1		Val - 5	Gln	Ser G	ly A	la G 1		al L	ya Ly:	s Pro	Gly 15	/ Ser
Ser	Vali		Val : 20	Ser	Сүз	Lys A	la So 2!		ly G	ly T	hr Phe	e Sei 30	s Sei	r Tyr
Ala	Ile	Ser ' 35	Irp '	Val.	Arg	Gln A 4		ro G	ly G	ln G	ly Leu 45	ı Glı	ı Trş) Met
Gly	Gly 50	Ile :	Ilel	Pro		Phe G 55	ly Ti	hr A	la A	sn T 6	-	a Glr	n Lys	9 Phe

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Cys Trp Tyr Gln Gln Lys Pro Gly Gln Ser Pro Val Leu Val Ile Tyr 35 40 45 Gln Asp Ser Lys Arg Pro Ser Gly Ile Pro Glu Arg Phe Ser Gly Ser 55 50 60 Asn Ser Gly Asn Thr Ala Thr Leu Thr Ile Ser Gly Thr Gln Ala Met 65 70 75 80 Asp Glu Ala Asp Tyr Tyr Cys Gln Ala Trp Asp Ser Ser Thr Ala 85 90 95 <210> SEQ ID NO 302 <211> LENGTH: 99 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <400> SEQUENCE: 302 Gln Val Thr Leu Lys Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln 1 10 15 5 Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser 25 20 30 Gly Met Arg Val Ser Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu 35 40 Trp Leu Ala Arg Ile Asp Trp Asp Asp Asp Lys Phe Tyr Ser Thr Ser 50 55 60 Leu Lys Thr Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val 65 70 75 80 70 Val Leu Thr Met Thr Asn Met Asp Pro Val Asp Thr Ala Thr Tyr Tyr 85 90 95 Cys Ala Arg <210> SEQ ID NO 303 <211> LENGTH: 99 <212> TYPE: PRT <213> ORGANISM: Homo sapiens <400> SEQUENCE: 303 Gln Ser Ala Leu Thr Gln Pro Ala Ser Val Ser Gly Ser Pro Gly Gln 10 1 5 15 Ser Ile Thr Ile Ser Cys Thr Gly Thr Ser Ser Asp Val Gly Gly Tyr 20 25 30 Asn Tyr Val Ser Trp Tyr Gln Gln His Pro Gly Lys Ala Pro Lys Leu 35 40 Met Ile Tyr Glu Val Ser Asn Arg Pro Ser Gly Val Ser Asn Arg Phe 55 50 60 Ser Gly Ser Lys Ser Gly As
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Ser L	eu	Lys	Ile 20	Ser	Суз	Гла	Gly	Ser 25	Gly	Tyr	Ser	Phe	Thr 30	Ser	Tyr			
Trp I		Gly 35	Trp	Val	Arg	Gln	Met 40	Pro	Gly	ГЛа	Gly	Leu 45	Glu	Trp	Met			
Gly I 5		Ile	Tyr	Pro	Gly	Asp 55	Ser	Asp	Thr	Arg	Tyr 60	Ser	Pro	Ser	Phe			
Gln G 65	ly	Gln	Val	Thr	Ile 70	Ser	Ala	Asp	Lys	Ser 75	Ile	Ser	Thr	Ala	Tyr 80			
Leu G	ln	Trp	Ser	Ser 85	Leu	Гла	Ala	Ser	Asp 90	Thr	Ala	Met	Tyr	Tyr 95	Суз			
Ala A:	rg																	
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Ser T 1	yr	Glu	Leu	Thr 5	Gln	Pro	Pro	Ser	Val 10	Ser	Val	Ser	Pro	Gly 15	Gln			
Thr A	la	Ser	Ile 20	Thr	Суа	Ser	Gly	Asp 25	Lys	Leu	Gly	Asp	Lуз 30	Tyr	Ala			
Cys T:		Tyr 35	Gln	Gln	ГЛЗ	Pro	Gly 40	Gln	Ser	Pro	Val	Leu 45	Val	Ile	Tyr			
Gln A 5		Ser	Lys	Arg	Pro	Ser 55	Gly	Ile	Pro	Glu	Arg 60	Phe	Ser	Gly	Ser			
Asn Se 65	er	Gly	Asn	Thr	Ala 70	Thr	Leu	Thr	Ile	Ser 75	Gly	Thr	Gln	Ala	Met 80			
Asp G	lu	Ala	Asp	Tyr 85	Tyr	Сув	Gln	Ala	Trp 90	Asp	Ser	Ser	Thr	Ala 95				
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1 Ser L	eu	Lys	Ile	5 Ser	Сув	Lys	Gly	Ser	10 Gly	Tyr	Ser	Phe	Thr	15 Ser	Tyr			
m	1.	G]	20		а.	G 7		25 D:::-	a 7	T -	G 7	Ţ	30	m .				
Trp I		G1y 35	Trp	val	Arg	GIN	Met 40	Pro	стλ	гЛа	GIÀ	Leu 45	GIU	Trp	Met			
Gly I 5		Ile	Tyr	Pro	Gly	Asp 55	Ser	Asp	Thr	Arg	Tyr 60	Ser	Pro	Ser	Phe			
Gln G 65	ly	Gln	Val	Thr	Ile 70	Ser	Ala	Asp	Lys	Ser 75	Ile	Ser	Thr	Ala	Tyr 80			
Leu G	ln	Trp	Ser	Ser 85	Leu	Lys	Ala	Ser	Asp 90	Thr	Ala	Met	Tyr	Tyr 95	Cys			
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Thr Ala	. Ser	Ile 20	Thr	Суз	Ser	Gly	Asp 25	Lys	Leu	Gly	Asp	Lys 30	Tyr	Ala
Cys Trp	Tyr 35	Gln	Gln	Lys	Pro	Gly 40	Gln	Ser	Pro	Val	Leu 45	Val	Ile	Tyr
Gln Asp 50) Ser	Lys	Arg	Pro	Ser 55	Gly	Ile	Pro	Glu	Arg 60	Phe	Ser	Gly	Ser
Asn Ser 65	Gly	Asn	Thr	Ala 70	Thr	Leu	Thr	Ile	Ser 75	Gly	Thr	Gln	Ala	Met 80
Asp Glu	ı Ala	Asp	Tyr 85	Tyr	Сүз	Gln	Ala	Trp 90	Asp	Ser	Ser	Thr	Ala 95	

1-16. (canceled)

17. An isolated antibody, or an antigen binding fragment thereof, comprising a heavy chain variable region having the sequence of SEQ ID NO: 7 and a light chain variable region having the sequence of SEQ ID NO: 8.

. The antibody, or an antigen binding fragment thereof, of claim **17**, wherein said antibody is a monoclonal antibody.

. The antibody, or an antigen binding fragment thereof, of claim **18**, wherein said antibody is a human or humanized antibody.

. The antibody, or an antigen binding fragment thereof, of claim **18**, wherein said antibody is a chimeric antibody.

. The antibody, or an antigen binding fragment thereof, of claim **18**, wherein said antibody comprises a human heavy chain constant region and a human light chain constant region.

22. The antibody, or an antigen binding fragment thereof, of claim 18, wherein said antibody is a single chain antibody.

. The antibody, or an antigen binding fragment thereof, of claim **18**, wherein said antibody is a Fab fragment.

. The antibody, or an antigen binding fragment thereof, of claim **18**, wherein said antibody is a scFv.

. The antibody, or an antigen binding fragment thereof, of claim **18** binds to both human complement C5 and cynomolgus complement C5.

. The antibody of claim **18**, or an antigen binding fragment thereof, is an IgG isotype.

. The antibody, or an antigen binding fragment thereof, of claim **17**, wherein said antibody comprises a heavy chain having the sequence of SEQ ID NO: 9 and a light chain having the sequence of SEQ ID NO: 10.

* * * * *