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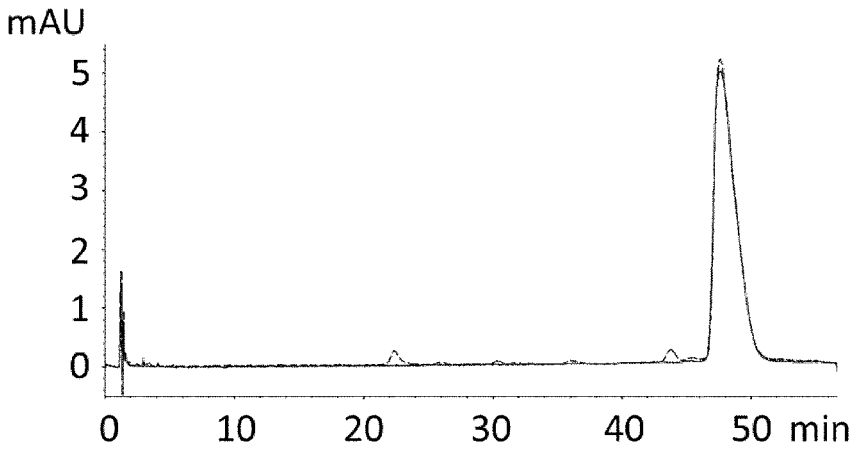

Figure 5

(57) Abstract: The invention relates to a polypeptide capable of binding human complement component 5 (C5), said polypeptide comprising the amino acid sequence [*BM*]-[L2]-QS$X_{42}X_{43}$LLX_{46}EAKKL$X_{52}X_{53}X_{54}$Q wherein [*BM*] is a C5 bindingmotif; [L2] is an interconnecting loop; X_{42} is selected from A and S; X_{43} is selected from N and E; X_{46} is selected from A, S and C; X_{52} is selected from E, N and S; X_{53} is selected from D, E and S, provided that X_{53} is not D when X_{52} is N; and X_{54} is selected from A and S.

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STABLE POLYPEPTIDES BINDING TO HUMAN COMPLEMENT C5

TECHNICAL FIELD

The present invention relates to polypeptides that bind to human complement component 5 (C5) and to the use of such polypeptides in therapy.

BACKGROUND ART

The complement protein C5 is a central component of the complement system; a key part of the innate immune system. The complement system is an intricate immune surveillance system with numerous tasks in tightly controlled, diverse processes. It functions as a first line host defense system against infection by other organisms, and also in discriminating healthy host tissues from cellular debris and apoptotic and necrotic cells. Furthermore, it is involved in clearance of immune complexes, regulation of the adaptive immune response, promotion of tissue regeneration, angiogenesis, mobilization of stem cells and development of the central nervous system (Woodruff *et al.* Mol Immunol 2011, 48 (14):1631-1642); Ricklin *et al.* Nat Immunol 2010, 11(9):785-795). Any trigger, for example erroneous or unrestricted activation or insufficient regulation, that disturbs the fine balance of complement activation and regulation may lead to pathologic conditions including self-attack of the host's cells leading to extensive tissue damage.

The complement system consists of about 30 proteins. There are three pathways to initiate complement; the classical pathway that employs C1q to recognize immune complexes on the surface of cells; the lectin pathway that is initiated when mannose-binding lectin (MBL) recognizes certain sugars; and the alternative pathway that is initiated spontaneously by hydrolysis of complement factor 3 (C3), a process suppressed by certain mammalian cell surface molecules not present on invading pathogens. The alternative pathway also acts as an amplification loop for the complement system. All three pathways converge at the level of C3. Cleavage of C3 into C3a and C3b leads to the formation of a convertase that in turn cleaves complement factor 5 (C5) into C5a and C5b. C5a is a very potent attractant of various immune cells while C5b oligomerizes with C6-9 to form a pore known as the membrane attack

complex (MAC) or sometimes the terminal complement complex (TCC). Activation of the complement system leads to a number of mechanisms with the purpose of neutralizing the pathogen; formation of MAC on the surface of a cell such as an invading bacteria leads to lysis, deposition of C3 and C4 cleavage products C3b and C4b aids opsonization leading to phagocytosis of the pathogen by macrophages and anaphylatoxins such as C3a and C5a attracts monocytes and neutrophils to the site of activation, up-regulates surface markers leading to increased immunologic susceptibility and to the release of cytokines.

C5 is a 190-kDa glycoprotein comprised of 2 disulfide-linked polypeptide chains, alpha and beta, with a molecular mass of 115 and 75 kDa, respectively (Tack *et al.* Biochem 1979, 18:1490-1497). Haviland *et al.* (J Immun 1991, 146: 362-368) constructed the complete cDNA sequence of human complement pro-C5, which is predicted to encode a 1,676-amino acid pro-molecule that contains an 18-amino acid leader peptide and a 4-amino acid linker separating the beta and alpha chains (SEQ ID NO: 251). Since C5 is common to all pathways of complement activation, blocking C5 will stop the progression of the cascade regardless of the stimuli and thereby prevent the deleterious properties of terminal complement activation while leaving the immunoprotective and immunoregulatory functions of the proximal complement cascade intact.

The complement system's key role in the defense against pathogens in general makes it an interesting target for pharmaceutical intervention. This is emphasized by the fact that many mutations or impaired regulation of complement is involved in various diseases and conditions. These include increased susceptibility to auto-immune diseases such as systemic lupus erythematosis (SLE) where deposition of immune complexes triggers the classical pathway (Manderson *et al.* Annu Rev Immunol 2004, 22:431-456). In addition, mutations of the complement proteins C1-C5 often result in SLE or SLE like symptoms. Other autoimmune diseases with a strong involvement of the complement system are rheumatoid arthritis (RA) where immune complexes may activate complement in the RA joint, Sjögren's syndrome, dermatomyositis and other autoantibody driven diseases such as Guillain-Barré syndrome (GBS), Fisher syndrome (Kaida *et al.* J. Neuroimmun 2010, 223:5-12), different types of vasculitis, systemic sclerosis, anti-glomerular basement membrane (anti-GBM) and anti-phospholipid syndrome (APS) (Chen *et al.* J Autoimmun 2010, 34:J276-J286). Furthermore,

complement inhibition have been proven effective in animal models of such different conditions as periodontitis (Abe *et al.* J Immunol 2012, 189:5442-5448), wound healing (Cazender *et al.* Clin Dev Immunol 2012, on-line publication), tumor growth (Markiewski *et al.* Nat Immunol 2008, 9:1225-1235) and diseases of the eye such as uveitis and age-related macular degeneration (AMD) (Copland *et al.* Clin Exp Immunol 2009, 159:303-314).

Antibodies targeted to human complement C5 are known from, e.g., WO 95/29697; WO 02/30985; and WO 2004/007553. Eculizumab (Soliris™) is a humanized monoclonal antibody directed against protein C5 and prevents cleavage of C5 into C5a and C5b. Eculizumab has been shown to be effective in treating paroxysmal nocturnal hemoglobinuria (PNH), a rare and sometimes life threatening disease of the blood characterized by intravascular hemolytic anemia, thrombophilia and bone marrow failure, and is approved for this indication. Eculizumab was also recently approved by the FDA for treatment of atypical hemolytic syndrome (aHUS), a rare but life threatening disease caused by loss of control of the alternative complement pathway leading to over-activation manifested as thrombotic microangiopathy (TMA) leading to constant risk of damage to vital organs such as kidney, heart and the brain. In aHUS, transplantation of the damaged organ only temporarily helps the patient as the liver continues to produce the mutated form of controlling protein (most often complement factor H or other proteins of the alternative pathway). A related disease with a transient acute pathophysiology is HUS caused by infection of Shiga toxin positive *E. coli* (STEC-HUS) and there are promising clinical data suggesting efficacy also for this condition (Lapeyraque *et al*, N Engl J Med 2011, 364:2561-2563). Finally, the C5 blocking antibody Eculizumab has proven efficacious in preventing antibody mediated rejection (AMR) in recipients of highly mismatched kidneys (Stegall, M. D. *et al.* Am J Transplant 2011, 11:2405-2413), and in treating autoimmune neuropathies such as neuromyelitis optica and myasthenia gravis (Pittock *et al.* Lancet Neurol 2013, 12:554-562; Howard *et al.* Muscle Nerve 2013, 48:76-84).

Apart from full length antibodies, single-chain variable fragments (scFV), minibodies and aptamers targeting C5 are described in literature. These C5 inhibitors may bind to different sites (epitopes) on the C5 molecule and may have different modes of action. For example, whereas Eculizumab interacts with C5 at some distance of the convertase

cleavage site, the minibody Mubodina® interacts with the cleavage site of C5. The C5 inhibitory protein *Ornithodoros moubata* Complement Inhibitor (OmCI, Nunn, M. A. *et al*. J Immunol 2005, 174:2084-2091) from soft tick *Ornithodoros moubata* has been hypothesized to bind to the distal end of the CUB-C5d-MG8 superdomain, which is close to the convertase cleavage site (Fredslund *et al*. Nat Immunol 2008, 9 (7):753-760). In contrast to the three proteins mentioned above inhibiting cleavage of C5, the monoclonal antibody TNX-558 binds to a C5a epitope present both on intact C5 and released C5a without inhibiting the cleavage of C5. (Fung *et al*. Clin Exp Immunol 2003, 133 (2):160-169).

C5 binding polypeptides, comprising a C5 binding motif, are disclosed in the International Patent Application No. PCT/SE2013/050139, published as WO 2013/126006. In particular, WO 2013/126006 discloses a C5 binding motif, *BM*, consisting of the amino acid sequence

$EX_2X_3X_4A\ X_6X_7EID\ X_{11}LPNL\ X_{16}X_{17}X_{18}QW\ X_{21}AFIX_{25}\ X_{26}LX_{28}D$,

wherein, independently of each other,

X_2 is selected from H, Q, S, T and V;

X_3 is selected from I, L, M and V;

X_4 is selected from A, D, E, H, K, L, N, Q, R, S, T and Y;

X_6 is selected from N and W;

X_7 is selected from A, D, E, H, N, Q, R, S and T;

X_{11} is selected from A, E, G, H, K, L, Q, R, S, T and Y;

X_{16} is selected from N and T;

X_{17} is selected from I, L and V;

X_{18} is selected from A, D, E, H, K, N, Q, R, S and T;

X_{21} is selected from I, L and V;

X_{25} is selected from D, E, G, H, N, S and T;

X_{26} is selected from K and S; and

X_{28} is selected from A, D, E, H, N, Q, S, T and Y.

Examples of specific C5 binding motifs, as previously disclosed in WO 2013/126006, are shown as SEQ ID NO: 1-248 in the present patent application.

It is known from WO 2013/126006 that additional peptides or polypeptides may improve stabilization of C5 binding polypeptides. One example of such a polypeptide is the albumin binding domain (ABD) shown as SEQ ID NO: 250 in the present description. Other examples of suitable albumin binding domains are disclosed in WO 2009/016043 and WO 2012/004384. An ABD-extended polypeptide binds to serum albumin *in vivo*, and benefits from its longer half-life, which increases the net half-life of the polypeptide itself (see e.g. WO 91/01743).

The continued provision of agents with comparable C5 blocking activity remains a matter of substantial interest within the field. In particular, there is a continued need for molecules that prevent the terminal complement cascade as well as the formation of the pro-inflammatory molecule C5a. Of great interest is also a provision of uses of such molecules in the treatment of disease.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates an SDS-PAGE gel wherein the bands represent the C5 binding compound PSI0242 (SEQ ID NO: 249) (0) prior to stability test; and (2w) after 2 weeks stability test.

Figure 2 is a chromatogram from reversed phase HPLC of PSI0242 (SEQ ID NO: 249) prior to stability test (solid line) and after 2 weeks stability test (dotted line).

Figure 3 illustrates an SDS-PAGE gel wherein the first lane contains SeeBlue 2P size marker and the bands represent (0) the initial samples; and (2w) the samples after 2 weeks stability test. Fig. 3A: SEQ ID NO: 249; Fig. 3B: SEQ ID NO: 261; Fig. 3C: SEQ ID NO: 262; Fig. 3D: SEQ ID NO: 264.

Figure 4 is a chromatogram from reversed phase HPLC of a C5 binding compound (SEQ ID NO: 253) prior to stability test (solid line) and after 2 weeks stability test (dotted line).

Figure 5 is a chromatogram from reversed phase HPLC of a C5 binding compound (SEQ ID NO: 264) prior to stability test (solid line) and after 2 weeks stability test (dotted line).

Figure 6A-D show images of SDS-PAGE gels comparing original and modified polypeptide variants (0) before and (2w) after 2 weeks stability test. The molecular size marker (Mw) was Novex® Sharp Pre-stained Protein Standard (216, 160, 110, 80, 60, 50, 40, 30, 20, 15, 10, 3.5 kDa). Fig. 6A shows a gel of HER2 binding polypeptides wherein the lanes show lane 1: Mw, lane 2: (0) Z02891 (SEQ ID NO: 272) , lane 3: (2w) Z02891 (SEQ ID NO: 272), lane 4: Mw, lane 5: (0) Z17341 (SEQ ID NO: 273), lane 6: (2w) Z17341 (SEQ ID NO: 273), lane 7: (0) Z17342 (SEQ ID NO: 274), lane 8: (2w) Z17342 (SEQ ID NO: 274). Fig. 6B is a gel of PDGF-Rβ binding polypeptides wherein the lanes show: lane 1: Mw, lane 2: (0) Z15805 (SEQ ID NO: 275), lane 3: (2w) Z15805 (SEQ ID NO: 275), lane 4: Mw, lane 5: (0) Z17343 (SEQ ID NO: 276), lane 6: (2w) Z17343 (SEQ ID NO: 276), lane 7: (0) Z17344 (SEQ ID NO: 277), lane 8: (2w) Z17344 (SEQ ID NO: 277). Fig. 6C shows a gel of FcRn binding polypeptides wherein the lanes show: lane 1: (0) Z10103 (SEQ ID NO: 278), lane 2: (2w) Z10103 (SEQ ID NO: 278), lane 3: Mw, lane 4: (0) Z17347 (SEQ ID NO: 279), lane 5: (2w) Z17347 (SEQ ID NO: 279), lane 6: (0) Z17348 (SEQ ID NO: 280), lane 7: (2w) Z17348 (SEQ ID NO: 280). The diagonal bands seen in Figure 6C is an artefact resulting from an imprint from a second gel stained in the same container. Fig. 6D is a gel of CAIX binding polypeptides wherein the lanes show lane 1:Mw, lane 2: (0) Z09782 (SEQ ID NO: 281), lane 3: (2w) Z09782 (SEQ ID NO: 281), lane 4: Mw, lane 5: (0) Z17351 (SEQ ID NO: 282), lane 6: (2w) Z17351 (SEQ ID NO: 282), lane 7: (0) Z17352 (SEQ ID NO: 283), lane 8: (2w) Z17352 (SEQ ID NO: 283); lane 9: (0) Z17355 (SEQ ID NO: 284), lane 10: (2w) Z17355 (SEQ ID NO: 284), lane 11: (0) Z17357 (SEQ ID NO: 285), lane 12: (2w) Z17357 (SEQ ID NO: 285), lane 13: (0) Z17359 (SEQ ID NO: 286), lane 14: (2w) Z17359 (SEQ ID NO: 286), lane 15: (0) Z17360 (SEQ ID NO: 287), lane 16: (2w) Z17360 (SEQ ID NO: 287).

Figure 7 is a table showing the amino acid sequences of:

- examples of C5 binding motifs (SEQ ID NO: 1-248);
- the C5 binding compound designated PSI0242 (SEQ NO: 249);
- an albumin binding domain (SEQ ID NO: 250);

- the Swiss-Prot entry P01031 of human C5 (SEQ ID NO:251) wherein the α-chain corresponds to amino acid residues 678-1676 and the β-chain corresponds to amino acid residues 19-673;
- examples of modified C5 binding polypeptides (SEQ ID NO: 260, 265-267).
- examples of modified C5 binding compounds (SEQ ID NO: 252-259, 261-264, 268-270).
- examples of polypeptide variants with binding affinity for other target molecules (SEQ ID NO: 272, 275, 278, 281)
- examples of stability improved polypeptide variants with binding affinity for other targets with (SEQ ID NO: 273-274, 276-277, 279-280, 282-287).

DISCLOSURE OF THE INVENTION

It has surprisingly been found that C5 binding polypeptides and compounds, wherein the amino acid sequences have been modified in specific positions, have improved stability when compared to previously known C5 binding polypeptides and compounds.

Consequently, this invention provides a polypeptide capable of binding human complement component 5 (C5), said polypeptide being selected from:

(a) a polypeptide comprising the amino acid sequence
[*BM*]-[L2]-QS$X_{42}X_{43}$LLX_{46}EAKKL$X_{52}X_{53}X_{54}$Q
wherein, independently of each other,
[*BM*] is a C5 binding motif;
[L2] is selected from DDPS and RQPE;
X_{42} is selected from A and S;
X_{43} is selected from N and E;
X_{46} is selected from A, S and C;
X_{52} is selected from E, N and S;
X_{53} is selected from D, E and S, provided that X_{53} is not D when X_{52} is N; and
X_{54} is selected from A and S; and

(b) a polypeptide which has at least 89 % amino acid sequence identity with the polypeptide of (a), provided that X_{53} is not D when X_{52} is N.

The inventors have surprisingly found that modification or substitution of amino acid residue(s) in certain position(s) of the amino acid sequence of the C5 binding polypeptides as described in WO 2013/126006 improves stability of the C5 binding polypeptides while biological activity, such as binding affinity for human complement component 5 (C5) and inhibition of complement pathway function, is essentially retained. Thus, the biological activity of the modified C5 binding polypeptides is comparable to the biological activity of the known C5 binding polypeptides. Stability testing of the C5 binding polypeptides of the present invention demonstrates that substitution in either X_{52}, from N to E or S, or X_{53}, from D to E or S, improves stability. It has moreover been found that specific amino acid substitution in [L2] independently may promote stability.

The terms “C5 binding” and ”binding affinity for C5” as used in this specification refers to a property of a polypeptide which may be tested for example by the use of surface plasmon resonance technology, such as in a Biacore instrument (GE Healthcare). C5 binding affinity may e.g. be tested in an experiment in which C5 is immobilized on a sensor chip of a Biacore instrument, and the sample containing the polypeptide to be tested is passed over the chip. Alternatively, the polypeptide to be tested is immobilized on a sensor chip of the instrument, and a sample containing C5, or fragment thereof, is passed over the chip. The skilled person may then interpret the results obtained by such experiments to establish at least a qualitative measure of the binding of the polypeptide to C5. If a quantitative measure is desired, for example to determine the apparent equilibrium dissociation constant K_D for the interaction, surface plasmon resonance methods may also be used. Binding values may for example be defined in a Biacore 2000 instrument (GE Healthcare). C5 is immobilized on a sensor chip of the measurement, and samples of the polypeptide whose affinity is to be determined are prepared by serial dilution and injected over the chip. K_D values may then be calculated from the results using for example the 1:1 Langmuir binding model of the BIAevaluation software provided by the instrument manufacturer. The C5 or fragment thereof used in the K_D determination may for example comprise the amino acid sequence represented by SEQ ID NO: 251. Examples of how C5 binding affinity may be tested are given herein, see Example 3 and 5.

In a preferred form of the invention, said polypeptide is selected from:

(a) a polypeptide comprising the amino acid sequence
AEAKYAK-[*BM*]-[L2]-QS$X_{42}X_{43}$LLX_{46}EAKKL$X_{52}X_{53}X_{54}$QAP
wherein, independently of each other,
[*BM*], [L2], X_{42}, X_{43}, X_{46}, X_{52}, X_{53} and X_{54} are as defined above; and

(b) a polypeptide which has at least 90 % amino acid sequence identity with the polypeptide of (a), provided that X_{53} is not D when X_{52} is N.

As previously disclosed in WO 2013/126006, the C5 binding polypeptide according to the invention may form part of a three-helix bundle protein domain. Said C5 binding motif [*BM*] essentially may form part of two alpha helices, with an interconnecting loop, within said three-helix bundle. A second interconnecting loop, referred to herein as [L2], connects the C5 binding motif to the third alpha helix, referred to as the "Backbone".

In one embodiment, the C5 binding motif [*BM*] is essentially as disclosed in WO 2013/126006. However, according to the present invention the C5 binding motif preferably consists of 28, rather than 29, amino acids, and may in addition carry further amino acid substitutions.

Thus in one embodiment, said [*BM*] carries at least one further amino acid substitution, e.g. in position 17, when compared to the [*BM*] as disclosed in WO 2013/126006. Thus, said [*BM*] is a polypeptide selected from:

(a) a polypeptide comprising the amino acid sequence
E$X_9X_{10}X_{11}$A $X_{13}X_{14}$EID$X_{17}X_{18}$LPNL$X_{23}X_{24}X_{25}$QWX_{28}AFI$X_{32}X_{33}$LX_{35};
wherein, independently of each other,
X_9 is selected from H, Q, S, T and V;
X_{10} is selected from I, L, M and V;
X_{11} is selected from A, D, E, H, K, L, N, Q, R, S, T and Y;
X_{13} is selected from N and W;
X_{14} is selected from A, D, E, H, N, Q, R, S and T;
X_{17} is selected from D and E;
X_{18} is selected from A, E, G, H, K, L, Q, R, S, T and Y;
X_{23} is selected from N and T;
X_{24} is selected from I, L and V;

X_{25} is selected from A, D, E, H, K, N, Q, R, S and T;
X_{28} is selected from I, L and V;
X_{32} is selected from A, D, E, G, H, N, S and T;
X_{33} is selected from K and S;
X_{35} is selected from A, D, E, H, N, Q, S, T and Y; and

(b) a polypeptide which has at least 85% amino acid sequence identity with the polypeptide of (a).

In a preferred embodiment, the C5 binding motif [*BM*] is essentially as disclosed in WO 2013/126006. Said [*BM*] is accordingly a polypeptide selected from:

(a) a polypeptide comprising the amino acid sequence
$EX_9X_{10}X_{11}A\ X_{13}X_{14}EIDX_{18}LPNLX_{23}X_{24}X_{25}QWX_{28}AFIX_{32}X_{33}LX_{35}$;
wherein, independently of each other,
X_9 is selected from H, Q, S, T and V;
X_{10} is selected from I, L, M and V;
X_{11} is selected from A, D, E, H, K, L, N, Q, R, S, T and Y;
X_{13} is selected from N and W;
X_{14} is selected from A, D, E, H, N, Q, R, S and T;
X_{18} is selected from A, E, G, H, K, L, Q, R, S, T and Y;
X_{23} is selected from N and T;
X_{24} is selected from I, L and V;
X_{25} is selected from A, D, E, H, K, N, Q, R, S and T;
X_{28} is selected from I, L and V;
X_{32} is selected from D, E, G, H, N, S and T;
X_{33} is selected from K and S;
X_{35} is selected from A, D, E, H, N, Q, S, T and Y; and

(b) a polypeptide which has at least 85 % amino acid sequence identity with the polypeptide of (a).

In a further preferred aspect, [*BM*] comprises or consists of an amino acid sequence selected from the group consisting of positions 1-28 in SEQ ID NOS: 1-248. More preferably, [*BM*] comprises or consists of the amino acid sequence shown as positions 1-28 in SEQ ID NO: 1.

In a further aspect, the C5 binding polypeptide according to the invention is selected from:

(a) a polypeptide comprising the amino acid sequence
AEAKYAKEX$_9$X$_{10}$X$_{11}$AX$_{13}$X$_{14}$EIX$_{17}$X$_{18}$LPNLX$_{23}$X$_{24}$X$_{25}$QWX$_{28}$AFIX$_{32}$
X$_{33}$LX$_{35}$-[L2]-QSX$_{42}$X$_{43}$LLX$_{46}$EAKKLX$_{52}$X$_{53}$X$_{54}$QAP;
wherein, independently of each other,
X$_9$ is selected from H, Q, S, T and V;
X$_{10}$ is selected from I, L, M and V;
X$_{11}$ is selected from A, D, E, H, K, L, N, Q, R, S, T and Y;
X$_{13}$ is selected from N and W;
X$_{14}$ is selected from A, D, E, H, N, Q, R, S and T;
X$_{17}$ is selected from D and E;
X$_{18}$ is selected from A, E, G, H, K, L, Q, R, S, T and Y;
X$_{23}$ is selected from N and T;
X$_{24}$ is selected from I, L and V;
X$_{25}$ is selected from A, D, E, H, K, N, Q, R, S and T;
X$_{28}$ is selected from I, L and V;
X$_{32}$ is selected from A, D, E, G, H, N, S and T;
X$_{33}$ is selected from K and S;
X$_{35}$ is selected from A, D, E, H, N, Q, S, T and Y;
[L2] is selected from DDPS and RQPE;
X$_{42}$ is selected from A and S;
X$_{43}$ is selected from N and E;
X$_{46}$ is selected from A, S and C;
X$_{52}$ is selected from E, N and S;
X$_{53}$ is selected from D, E and S, provided that X$_{53}$ is not D when X$_{52}$ is N; and
X$_{54}$ is selected from A and S; and

(b) a polypeptide which has at least 90 % amino acid sequence identity with the polypeptide of (a), provided that X$_{53}$ is not D when X$_{52}$ is N.

In a preferred embodiment, the C5 binding polypeptide according to the invention is selected from:

(a) a polypeptide comprising the amino acid sequence

$AEAKYAKEX_9X_{10}X_{11}AX_{13}X_{14}EIDX_{18}LPNLX_{23}X_{24}X_{25}QWX_{28}AFIX_{32}X_{33}L$
X_{35}-[L2]-$QSX_{42}X_{43}LLX_{46}EAKKLX_{52}X_{53}X_{54}QAP$;

wherein, independently of each other,

X_9 is selected from H, Q, S, T and V;

X_{10} is selected from I, L, M and V;

X_{11} is selected from A, D, E, H, K, L, N, Q, R, S, T and Y;

X_{13} is selected from N and W;

X_{14} is selected from A, D, E, H, N, Q, R, S and T;

X_{18} is selected from A, E, G, H, K, L, Q, R, S, T and Y;

X_{23} is selected from N and T;

X_{24} is selected from I, L and V;

X_{25} is selected from A, D, E, H, K, N, Q, R, S and T;

X_{28} is selected from I, L and V;

X_{32} is selected from D, E, G, H, N, S and T;

X_{33} is selected from K and S;

X_{35} is selected from A, D, E, H, N, Q, S, T and Y;

[L2] is selected from DDPS and RQPE;

X_{42} is selected from A and S;

X_{43} is selected from N and E;

X_{46} is selected from A, S and C;

X_{52} is selected from E, N and S;

X_{53} is selected from D, E and S, provided that X_{53} is not D when X_{52} is N; and

X_{54} is selected from A and S; and

(b) a polypeptide which has at least 90 % amino acid sequence identity with the polypeptide of (a), provided that X_{53} is not D when X_{52} is N.

In preferred forms of the invention, at least one of the following eighteen, optionally nineteen, conditions is fulfilled:

X_9 is V,

X_{10} is L,

X_{11} is E,

X_{13} is W,

X_{14} is D,

optionally X_{17} is D,
X_{18} is R,
X_{23} is T,
X_{24} is I,
X_{25} is E,
X_{28} is L,
X_{32} is N,
X_{33} is K,
X_{35} is D,
[L2] is DDPS,
X_{42} is S,
X_{43} is E,
X_{46} is S,
X_{54} is S.

More preferably, at least two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen, seventeen, eighteen or nineteen of the above conditions are fulfilled.

In an embodiment, X_{52} and X_{53} are independently selected from E and S. Preferably, (a) X_{52} is S and X_{53} is E, or (b) X_{52} is E and X_{53} is S.

In an embodiment, X_{52} is S and X_{53} is D.

In another embodiment, X_{52} is N and X_{53} is E.

In a further aspect, the polypeptide according to the invention comprises the amino sequence shown as SEQ ID NO: 260, SEQ ID NO: 265, SEQ ID NO: 266, or SEQ ID NO: 267.

In a further aspect, there is provided a compound capable of binding C5, said compound comprising:

a. at least one C5 binding polypeptide as defined above;

b. at least one albumin binding domain of streptococcal protein G, or a derivative thereof; and

c. optionally, at least one linking moiety for linking said at least one albumin binding domain or derivative thereof to the C or N terminal of said at least one C5 binding polypeptide.

Preferably, said albumin binding domain comprises the amino acid sequence shown as SEQ ID NO: 250.

Preferably, said linking moiety is a peptide comprising the amino acid sequence $KVX_{60}GS$, wherein X_{60} is selected from D, E and A. When X_{60} is D, a preferred compound comprises or consists of the amino sequence shown as SEQ ID NO: 253. When X_{60} is E, preferred compounds comprise or consist of the amino sequence shown as SEQ ID NO: 261, SEQ ID NO: 263, SEQ ID NO: 264, SEQ ID NO: 269 or SEQ ID NO: 270. When X_{60} is A, a preferred compound comprises or consists of the amino acid sequence shown as SEQ ID NO: 262. In the above listed amino acid sequences of the C5 binding compounds, amino acid residues 1-57 represent the amino acid sequence of a C5 binding polypeptide, residues 58-62 represent the amino acid sequence of a linker, and residues 63-108 represent the amino acid sequence of an albumin binding domain.

In an embodiment, the linking moiety is absent.

As discussed above, preferred C5 binding polypeptides according to the invention include those wherein X_{52} and X_{53} are independently selected from E and S. Specifically, compounds according to the invention can be derived from PSI0242 (SEQ ID NO: 249) but have modifications in at least one of positions 52, 53 and 60. For instance, as shown in Fig. 7 and the sequence listing, the preferred compound designated PSI0378 (SEQ ID NO: 261) carries the amino acid substitutions N52S, D53E and D60E; the preferred compound designated PSI0379 (SEQ ID NO: 262) carries the amino acid substitutions N52S, D53E and D60A; the preferred compound designated PSI0381 (SEQ ID NO: 263) carries the amino acid substitutions N52E, D53S and D60E; and the preferred compound designated PSI0383 (SEQ ID NO: 264) carries the amino acid substitutions N52S, D53E and D60E. Further, SEQ ID NO: 264 also carries substitutions in the loop [L2], namely D36R, D37Q and S39E. Moreover,

the preferred compound designated PSI0403 (SEQ ID NO: 269) carries the amino acid substitutions D53E and D60E, and the preferred compound designated PSI0404 (SEQ ID NO: 270) carries the amino acid substitutions N52S and D60E.

As accounted for above, the inventors have surprisingly found that amino acid substitutions in certain positions of the amino acid sequence of the C5 binding polypeptides as described in WO 2013/126006 may improve stability. Such substitutions improve stability of the C5 binding compounds while biological activity, such as C5 binding capability and inhibition of hemolysis *in vitro*, is retained. Stability testing of the C5 binding compounds of the present invention demonstrate that for instance each of N52S (X_{52}) and D53E (X_{53}) (SEQ ID NO: 253) individually, as well as removal of D60 (X_{60}) (SEQ ID NO: 259 lacking linking moiety) improves stability. The combination of the substitutions N52S, D53E and D60E or D60A further improves the stability (SEQ ID NO: 261 and SEQ ID NO: 262). Each of the combined substitutions of N52S and D60E (SEQ ID NO: 270) and D53E and D60E (SEQ ID NO: 269) has similarly been found to improve stability. This indicates that each of the listed amino acid substitutions is involved in improving the stability of the polypeptide, and thus that each of these substitutions will provide further stabilized C5 binding polypeptides and compounds compared to previously known C5 binding polypeptides and compounds.

However, the skilled person will be able to identify polypeptides and/or compounds which have modifications in at least one of positions 52, 53 and 60, and/or in the loop [L2], but which also carry additional modifications like substitutions, small deletions, insertions or inversions, and nevertheless have substantially the disclosed biological activities and improved stability. Further, a C5 binding polypeptide and/or compound according to the invention could comprise further C terminal and/or N terminal amino acids that improve production, purification, stabilization *in vivo* or *in vitro*, coupling, or detection of the polypeptide.

In a further aspect of the invention, there is provided a compound capable of binding C5, said compound comprising:

a. at least one C5 binding polypeptide, said polypeptide being selected from:

a-1. a polypeptide comprising the amino acid sequence

[*BM*]-[L2]-QS$X_{42}X_{43}$LLX_{46}EAKKL$X_{52}X_{53}X_{54}$Q

wherein, independently of each other,

[*BM*] is a C5 binding motif;

[L2] is selected from DDPS and RQPE;

X_{42} is selected from A and S;

X_{43} is selected from N and E;

X_{46} is selected from A, S and C;

X_{52} is selected from E, N and S;

X_{53} is selected from D, E and S;

X_{54} is selected from A and S; and

a-2. a polypeptide which has at least 89 % amino acid sequence identity with the polypeptide of a-1.;

b. at least one albumin binding domain of streptococcal protein G, or a derivative thereof; and

c. at least one linking moiety for linking said at least one albumin binding domain or derivative thereof to the C or N terminal of said at least one C5 binding polypeptide; wherein the linking moiety comprises or consists of KVEGS or KVAGS; or wherein said linking moiety is absent.

It has been found that removal of D60 or an amino acid substitution in position 60 of SEQ ID NO: 249 alone improves stability of the C5 binding compounds of the invention compared to previously known C5 binding compounds. Preferably, the linking moiety is KVEGS (X_{60}=E) while $X_{52}X_{53}$ may be ND, and an example of a preferred compound carrying such a linking moiety is PSI0410 (SEQ ID NO: 268). In another preferred embodiment, D60 and the entire linking moiety is absent and an example of such a compound is the preferred compound designated PSI0369 (SEQ ID NO: 259).

In embodiments of the above aspect, [*BM*] and the albumin binding domain are as defined above in related aspects. Preferably, [L2] is DDPS.

In a further aspect, there is provided a compound capable of binding C5, said compound comprising:

a. at least one C5 binding polypeptide, said polypeptide being selected from:

a-1. a polypeptide comprising the amino acid sequence
[*BM*]-[L2]-QS$X_{42}X_{43}$LLX_{46}EAKKL$X_{52}X_{53}X_{54}$Q
wherein, independently of each other,
[*BM*] is a C5 binding motif;
[L2] is RQPE;
X_{42} is selected from A and S;
X_{43} is selected from N and E;
X_{46} is selected from A, S and C;
X_{52} is selected from E, N and S;
X_{53} is selected from D, E and S;
X_{54} is selected from A and S; and

a-2. a polypeptide which has at least 89 % amino acid sequence identity with the polypeptide of a-1.;

b. at least one albumin binding domain of streptococcal protein G, or a derivative thereof; and

c. optionally, at least one linking moiety for linking said at least one albumin binding domain or derivative thereof to the C or N terminal of said at least one C5 binding polypeptide.

Specific amino acid substitutions in the loop [L2] have been found to improve stability of the C5 binding compounds (e.g. SEQ ID NO: 252) of the invention compared to previously known C5 binding compounds. In embodiments of the above aspect, said [*BM*] and albumin binding domain are individually as defined above in related aspects. Preferably, said linking moiety is a peptide comprising the amino acid sequence KVX_{60}GS, wherein X_{60} is selected from D, E and A.

The invention includes polynucleotides which encode polypeptides according to the invention. Further included in the invention are vectors, such as expression vectors, comprising polynucleotides which encode polypeptides according to the invention. Included are also host cells which comprise such vectors.

Included in the invention are C5 binding polypeptides and compounds as described above, for use in therapy. In particular, the C5 binding polypeptides and compounds according to the invention are useful in methods for the treatment and/or prophylaxis of C5-related conditions, such as inflammatory diseases; autoimmune diseases; infectious diseases; cardiovascular diseases; neurodegenerative disorders; graft injury; eye diseases; kidney diseases; pulmonary diseases; haematological diseases such as paroxysmal nocturnal hemoglobinuria (PNH); allergic diseases and dermatological diseases.

In methods for treatment and/or prophylaxis, the said C5 binding polypeptide or compound can preferably be administered intravenously, subcutaneously, by inhalation, nasally, orally, intravitreally, or topically.

EXAMPLES

EXAMPLE 1: Stability test of known C5 inhibitor

The C5 binding compound designated PSI0242 (SEQ ID NO: 249) was formulated in 25 mM NaP /125 mM NaCl pH 7.0 and subjected to an accelerated stability study for 2 weeks at 37 °C. The stability was measured by the appearance of new variants after the stability testing by SDS-PAGE and Reversed Phase HPLC (RPC). In both analyses the initial sample and the one subjected to the stability study were run in parallel. For the SDS-PAGE, 7.5 µg protein was loaded into each well. The RPC was run on an Agilent 1100 HPLC using a Mobile Phase A consisting of 0.1 % trifluoroacetic acid (TFA) in water, and using a Mobile Phase B consisting of 0.1 % TFA / 45 % MeOH / 45 % isopropylamine (IPA) / 10 % water.

The results show that new forms of the protein are formed during incubation, these new forms visualized as bands in SDS-PAGE (Fig.1) and as new peaks in Reversed Phase HPLC (RPC) chromatograms (Fig. 2). In Fig. 2, the main peak after 2 weeks incubation corresponds to 57 % of the original protein sample.

Positions 1-60 in SEQ ID NO: 249 correspond to the polypeptide Z06175a, previously disclosed in WO 2013/126006 as SEQ ID NO: 753. PSI0242 (SEQ ID NO: 249) was produced essentially as disclosed in WO 2013/126006.

EXAMPLE 2: Stability of modified C5 binding polypeptides and compounds

Modified C5 binding polypeptides and compounds were synthesized and purified essentially as described in WO 2013/126006.

Briefly, DNA encoding C5 binding Z variants was *E. coli* codon optimized and synthesized by GeneArt, GmbH. The synthetic genes representing the C5 binding Z variants were subcloned and expressed in *E. coli*.

Intracellularly expressed Z variants were purified using conventional chromatography methods. Homogenization and clarification was performed by sonication followed by centrifugation and filtration. Anion exchange chromatography was used as capture step. Further purification was obtained by hydrophobic interaction chromatography. The purifications were executed at acidic conditions (pH 5.5). Polishing and buffer exchange was performed by size exclusion chromatography.

The purified proteins were formulated in 25 mM NaP /125 mM NaCl pH 7.0 and subjected to an accelerated stability study for 2 weeks at 37 °C. The stability was measured by the appearance of new variants after the stability testing by SDS-PAGE and Reversed Phase HPLC (RPC). In both analyses the initial sample and the one subjected to the stability study were run in parallel. For the SDS-PAGE, 7.5 µg protein was loaded into each well. An example of a resulting gel is shown in Fig. 3.

The RPC was run on an Agilent 1100 HPLC using a Mobile Phase A consisting of 0.1 % trifluoroacetic acid (TFA) in water, and a Mobile Phase B consisting of 0.1 % TFA / 45 % MeOH / 45 % isopropylamine (IPA) / 10 % water. An example of a resulting chromatogram is shown in Fig. 4 for SEQ ID NO: 253.

The results of the stability testing are summarized in Table I, below.

TABLE I

SEQ ID NO:	Name	SDS-PAGE bands	RPC prepeaks	Main peak (% of total protein)	RPC post peaks
249	PSI0242	2	2	57	1
252	PSI0332	2	1	57	1
253	PSI0334	1	1	73	0
254	PSI0335	2	2	57	1
255	PSI0336	2	2	57	1
256	PSI0337	2	2	57	1
257	PSI0339	2	2	57	1
258	PSI0340	2	2	67	1
259	PSI0369	2	1	90	1
260	PSI0377	1	0	77	0
261	PSI0378	1	0	89	0
262	PSI0379	1	0	88	0
263	PSI0381	1	0	87	0
264	PSI0383	1	0	91	0
267	PSI0400	1	0	91	0
268	PSI0410	1	1	72	1
269	PSI0403	1	1	77	1
270	PSI0404	1	1	88	0

It can be concluded from Table I that certain modified C5 binding polypeptides or compounds have improved properties, such as increased stability, when compared with PSI0242. Such improved C5 binding polypeptides or compounds include PSI0334 (SEQ ID NO: 253), PSI0340 (SEQ ID NO: 258), PSI0369 (SEQ ID NO: 259), PSI0377 (SEQ ID NO: 260), PSI0378 (SEQ ID NO: 261), PSI0379 (SEQ ID NO: 262), PSI0381 (SEQ ID NO: 263), PSI0383 (SEQ ID NO: 264), PSI0400 (SEQ ID NO: 267), PSI0410 (SEQ ID NO: 268), PSI0403 (SEQ ID NO: 269) and PSI0404 (SEQ ID NO: 270). In six of the mentioned variants (SEQ ID NO: 253, 260, 261, 262, 264 and 267), the amino acid residues in positions 52-53 have been substituted from ND (cf PSI0242) to SE. In SEQ ID NO: 263, the corresponding substitution is from ND to ES. In SEQ ID NO: 269 only the amino acid residue in position 53 has been substituted from D to E, while in SEQ ID NO: 270 the amino acid residue in position 52 has been substituted from N to S.

Further, PSI0378 (SEQ ID NO: 261), PSI0381 (SEQ ID NO: 263), PSI0383 (SEQ ID NO: 264), PSI0410 (SEQ ID NO: 268), PSI0403 (SEQ ID NO: 269) and PSI0404 (SEQ ID NO: 270) have in common an amino acid residue substitution from D to E in position 60.

The combined benefit of stability enhancing substitutions in position 52 or 53 and position 60 can be seen in Fig. 5, showing the chromatogram of PSI0383 (SEQ ID NO: 264). In PSI0379 (SEQ ID NO: 262) the substitution in position 60 is from D to A.

In PSI0369 (SEQ ID NO: 259) the linker moeity (including D60) is altogether removed, yielding a more stable C5 binding compound and indicating the influence of position 60 upon stability of the C5 binding compounds.

EXAMPLE 3: Binding of modified compounds to human C5

Human serum albumin was immobilized to Amine Reactive 2nd generation (AR2G) Dip and Read Biosensors (Pall Life sciences (ForteBio) Cat # 18-5092) by amine coupling. PSI0242 (SEQ ID NO: 249; 1 μM) and C5 binding compounds (1 μM) in read buffer (HBS-EP Buffer ready-to-use 200 ml, GE Healthcare #BR100188) were loaded, each onto a separate sensor with HSA, for 120 seconds followed by a base line recording for 60 seconds in read buffer before being subjected to human C5 (Quidel Cat # 403) in concentrations ranging from 0.79 nM to 25 nM in read buffer with a regeneration cycle and a base line recording between each concentration. Regeneration conditions for the sensors were 10 mM Glycine, pH 2 (three pulses with 30 seconds and running buffer for 60 seconds). Each spectrogram was reference subtracted against an analogous construct containing an albumin binding domain (SEQ ID NO: 250) but without the C5 binding capacity. The data were analyzed according to Langmuir 1:1 model using ForteBio Analysis 7.1 (Pall Life sciences (ForteBio) kinetics software).

The K_D of the interaction with C5 relative to PSI0242 (SEQ ID NO: 249) is shown in Table II. The K_D of PSI0242 varied from 1-3 nM in different runs.

The results in Table II indicate that C5 binding compounds according to the invention have a binding capacity to human C5 which is similar to that of the polypeptide PSI0242 (SEQ ID NO: 249) disclosed in WO 2013/126006.

TABLE II

SEQ ID NO:	Name	Rel. K_D
249	PSI0242	1.0
253	PSI0334	1.1
261	PSI0378	1.3
263	PSI0381	23
264	PSI0383	2.1

EXAMPLE 4: Stability of chemically synthesized C5 binding polypeptide

A chemically synthesized PSI0400 (SEQ ID NO: 267) was ordered from BACHEM AG. The stability of the polypeptide was tested according to the same methodology as in Example 2. The results of the stability testing are shown in Table III.

TABLE III

SEQ ID NO:	Name	SDS-PAGE bands	RPC prepeaks	Main peak (% of total protein)	RPC post peaks
267	PSI0400	1	0	91	0

The stability of the PSI0400 was comparable to the polypeptides that were produced in *E.coli* in Example 2.

The integrity of the fold of PSI0400 (SEQ ID NO: 267) was compared to a recombinant C5 binding polypeptide (PSI0257, SEQ ID NO: 271), produced in accordance with the methods of Example 2, using far UV circular dichroism (CD) spectra.

The CD spectra were recorded by a J-720 CD spectropolarimeter (Jasco, Japan). The samples were diluted to 0.17 mg/ml protein concentration using Pi buffer (5 mM Na-K-PO_4, pH 7.0). A CD spectrum of Pi buffer was firstly recorded, then spectra were

recorded for each of the samples and lastly for the Pi buffer again. As the two buffer spectra coincide, the firstly recorded spectrum was used as the buffer spectrum. The buffer spectrum was smoothened using the Savitzky-Golay procedure with convolution width of 25. The other spectra were smoothened according to the same procedure with a convolution width of 15. The smoothened buffer spectrum was then subtracted from each of the other smoothened spectra. The CDNN program was used to estimate the secondary content of the proteins and the resulting estimations are presented in Table IV. The results showed that neither the two amino acid substitutions at position 52 and 53 nor the polypeptide production by chemical synthesis influence the secondary structure content of the chemically synthesized polypeptide. The integrity of the secondary structure content was compared to the recombinantly produced PSI0257 (SEQ ID NO: 271).

TABLE IV

	SEQ ID NO: 271	SEQ ID NO: 267
Helix	63 %	69 %
Antiparallel	3 %	2 %
Parallel	3 %	3 %
Beta-Turn	13 %	12 %
Rndm. Coil	13 %	11 %

EXAMPLE 5: Binding of modified compounds and polypeptides to human C5

The binding affinity of the C5 binding compounds PSI0242 (SEQ ID NO: 249), PSI0340 (SEQ ID NO: 258), PSI0378 (SEQ ID NO: 261), and PSI0410 (SEQ ID NO: 268) and the C5 binding polypeptide PSI0400 (SEQ ID NO: 267) for human C5 was analyzed using a Biacore T200 instrument (GE Healthcare). Human C5 (A403, Quidel Corporation) was coupled to a CM5 sensor chip (900 RU) using amine coupling chemistry according to the manufacturer's protocol. The coupling was performed by injecting hC5 at a concentration of 7.5 µg/mL in 10 mM Na-acetate buffer pH=5 (GE Healthcare). The reference cell was treated with the same reagents but without injecting human C5. Binding of the C5 binders to immobilized hC5 was studied with the single

cycle kinetics method, in which five concentrations of sample, typically 25, 12.5, 6.25, 3.12 and 1.56 nM in HBS-EP buffer (10 mM HEPES pH 7.4, 150 mM NaCl, 3 mM EDTA, 0.005% Surfactant P20, GE Healthcare) were injected one after the other at a flow rate of 30 μL/min at 25°C in the same cycle without regeneration between injections. Data from the reference cell were subtracted to compensate for bulk refractive index changes. In most cases, an injection of HBS-EP was also included as control so that the sensorgrams were double blanked. The surfaces were regenerated in HBS-EP buffer. Kinetic constants were calculated from the sensorgrams using the Langmuir 1:1 analyte model of the Biacore T200 Evaluation Software version 1.0.The resulting K_D values of the interactions are tabulated in the Table V.

TABLE V

SEQ ID NO:	Name	K_D (nM)
249	PSI0242	1.3
258	PSI0340	2.5
261	PSI0378	2.1
267	PSI0400	0.53
268	PSI0410	1.3

The stability enhancing amino acid substitutions are not detrimental for the ability of the molecules to bind to C5 and thus do not influence their biological activities.

EXAMPLE 6: Inhibition of hemolysis

For studies of classical complement pathway function and inhibition thereof by the C5 binding compounds PSI0378 (SEQ ID NO: 261) and PSI0410 (SEQ ID NO: 268), and C5 binding polypeptide PSI0400 (SEQ ID NO: 267), sheep erythrocytes were prepared from fresh sheep whole blood in Alsever's solution (Swedish National Veterinary Institute) and thereafter treated with rabbit anti-sheep erythrocyte antiserum (Sigma) to become antibody sensitized sheep erythrocyte (EA). The whole process was conducted under aseptic conditions. All other reagents were from commercial sources.

The *in vitro* assay was run in 96-well U-form microtiter plate by consecutive additions of a test protein, a complement serum and EA suspension. The final concentrations of

all reagents, in a total reaction volume of 50 µL per well and at pH 7.3-7.4, were: 0.15 mM CaCl 2; 0.5 mM MgCl 2; 3 mM NaN 3; 138 mM NaCl; 0.1 % gelatin; 1.8 mM sodium barbital; 3.1 mM barbituric acid; 5 million EA; complement protein C5 serum at suitable dilution, and C5 binding compound or polypeptide at desired concentrations.

The C5 binding compounds and polypeptide were pre-incubated with the above described complement serum for 20 min on ice prior to starting the reaction by the addition of EA suspension. The hemolytic reaction was allowed to proceed at 37 °C during agitation for 45 min and was then optionally ended by addition of 100 µL ice-cold saline containing 0.02 % Tween 20. The cells were centrifuged to the bottom and the upper portion, corresponding to 100 µL supernatant, was transferred to a transparent microplate having half-area and flat-bottom wells. The reaction results were analyzed as optical density using a microtiter plate reader at a wavelength of 415 nm.

On all test occasions, a control sample (PSI0242, SEQ ID NO: 249) and vehicle were included in each plate to define values for uninhibited and fully inhibited reactions, respectively. These values were used to calculate the % inhibition of the complement hemolysis at any given sample concentration. The inhibitory potencies (IC 50-values) of tested C5 binding compounds and polypeptide were defined by applying the same assay in the presence of a controlled concentration of human C5 added to C5 depleted serum. For highly potent inhibitors (low nanomolar to sub-nanomolar), a final C5 concentration of the reaction mixture was controlled at 0.1 nM, which was optionally established by using C5 depleted or deficient sera. The results are presented below in Table VI.

TABLE VI

SEQ ID NO:	Name	Potency (%)	IC 50 (nM)
249	PSI0242	100	0.47
261	PSI0378	83	0.58
267	PSI0400	-	4
268	PSI0410	107	0.49

The results from the hemolysis assay show that the improved C5 binding compounds SEQ ID NO: 261 and 268 are comparable to the reference compound. The C5 binding polypeptide SEQ ID NO: 267 was functional in the assay but since it does not contain

an albumin binding domain the results cannot be directly compared to the reference compound.

EXAMPLE 7: Binding to human albumin

For assessment of C5 binding compounds binding affinity for albumin, a human albumin ELISA utilizing recombinant human albumin (coating) and commercially available antibodies (primary and detecting) purchased from Novozymes, Affibody AB and DakoCytomation, respectively, was used. A method standard prepared from PSI0242 (SEQ ID NO:249), comprising a C5 binding polypeptide and an albumin binding domain of streptococcal protein G, was used for quantification of samples. A 96-well microplate was coated with recombinant human albumin. The plate was then washed with phosphate buffered saline containing 0.05 % Tween 20 (PBST) and blocked for 1-2 hours with 1 % casein in PBS. After a plate wash, the standard, method controls, control sample and test samples are added to the plate. After incubation for 2 hours, unbound material was removed by a wash. A goat Anti-Affibody® IgG (Affibody AB, cat no. 20.1000.01.0005) was added to the wells and the plate was incubated for 1.5 hours to allow binding to the bound C5 binding compounds. After a wash, rabbit anti-goat IgG HRP was allowed to bind to the goat antibodies for 1 h. After a final wash, the amount of bound HRP was detected by addition of TMB substrate, which was converted to a blue product by the enzyme. Addition of 1 M hydrochloric acid after 30 minutes stopped the reaction and the color of the well contents changed from blue to yellow. The absorbance at 450 nm was measured photometrically, using the absorbance at 650 nm as a reference wavelength. The color intensity was proportional to the amount of PSI0242 (SEQ ID NO:249) and the sample concentrations were determined from the standard curve.

The C5 binding compounds comprising an albumin binding domain of streptococcal protein G proved capable of binding to human albumin and the data is presented in Table VII below.

TABLE VII

SEQ ID NO:	Name	% of total protein content
249	PSI0242	103
261	PSI0378	85
268	PSI0410	150

The results from the assay showed that both of the investigated stability improved C5 binding compounds maintain their ability to bind human albumin.

EXAMPLE 8: 3 month stability test of C5 binding polypeptides/compounds

The C5 binding polypeptides/compounds that showed an improved stability compared toPSI0242 in the 2 weeks stability test at 37 °C (Example 2) were subjected to a longer 3 month stability test at 37 °C. The setup of the stability test was as described in Example 2 and the evaluation of the stability was made by measuring the main peak of the chromatogram percentage of the total protein content by Reversed Phase HPLC (RPC), the RPC method was performed as described in example 2. The 2 weeks data from example 2 is included in Table VIII below to make the interpretation easier.

TABLE VIII

SEQ ID NO:	Name	2 weeks, 37 °C Main peak (% of total protein)	3 months, 37 °C Main peak (% of total protein)
253	PSI0334	73	16
261	PSI0378	89	59
262	PSI0379	88	58
263	PSI0381	87	46
264	PSI0383	91	59
268	PSI0410	72	16
269	PSI0403	77	35
270	PSI0404	88	46

C5 binding compounds with amino acid substitutions in position 52, 53 from ND to SE and a replacement in position 60 from D to E or A (SEQ ID NO: 261, 264, and 262) compared to PSI0242 have a higher proportion of protein in the original form after 3

months at 37 °C than PSI0242 (SEQ ID NO: 249) has after 2 weeks at the same conditions. The other compounds also displayed an increased stability.

EXAMPLE 9: Stability of similarly modified polypeptides

Previously known polypeptide variants derived from protein Z (Grönwall *et al.* J Biotechnol 2007, 128:162-183) with binding affinity for other target molecules than C5 were similarly modified in specific positions of the amino acid sequence in order improve stability. Selection and production of the original polypeptide variants with binding affinity for the human epidermal growth factor receptor 2 (HER2), the platelet-derived growth factor receptor beta (PDGF-Rβ), the neonatal Fc receptor (FcRn), and the carbonic anhydrase IX (CAIX) is disclosed in e.g. WO 2009/080810, WO 2009/077175, PCT/EP2014/055299, and WO 2014/096163. The stability improved polypeptide variants were produced by site-directed mutagenesis at selected positions of the amino acid sequence. The stability improving amino acid substitutions in the polypeptide variants Z02891 (SEQ ID NO: 272), targeting HER2; Z15805 (SEQ ID NO: 275), targeting PDGF-Rβ; Z10103 (SEQ ID NO: 278), targeting FcRn; and Z09782 (SEQ ID NO: 281), targeting CAIX, are specified below in Table IX. These stability improved polypeptide variants differ from the C5 binding polypeptides of the present invention for example in that they have a binding motif [*BM*] with binding affinity for HER2, PDGF-Rβ, FcRn, and CAIX.

All variants were cloned with an N-terminal 6 x Histidine-tag (His6) and the achieved constructs encoded polypeptides in the format MGSSHHHHHHLQ-[Z#####]. Mutations were introduced in the plasmids of the polypeptide variants using overlapping oligonucleotide primer pairs encoding the desired amino acid substitutions and by applying established molecular biology techniques. The correct plasmid sequences were verified by DNA sequencing.

E coli (strain T7E2) cells (GeneBridge) were transformed with plasmids containing the gene fragments encoding the original and the modified polypeptides. The cells were cultivated at 37 °C in TSB-YE medium supplemented with 50 µg/ml kanamycin and protein expression was subsequently induced by addition of IPTG. Pelleted cells were

disrupted using a FastPrep®-24 homogenizer (Nordic Biolabs) and cell debris was removed by centrifugation. Each supernatant containing the polypeptide variant as a His6-tagged protein was purified by immobilized metal ion affinity chromatography (IMAC) using His GraviTrapTM columns (GE Healthcare) according to the manufacturers instructions. Purified polypeptide variants were buffer exchanged to phosphate-buffered saline (PBS; 1.47 mM KH2PO4, 8.1 mM Na2HPO4, 137 mM NaCl, 2.68 mM KCl, pH 7.4) using PD-10 desalting columns (GE Healthcare). The correct identity of each polypeptide was verified by SDS-PAGE and HPLC-MS.

TABLE IX.

SEQ ID NO:	Name	Target	Amino acid substitutions	Original vs modified
272	Z02891	HER2	-	Original
273	Z17341	HER2	N52S, D53E	Modified
274	Z17342	HER2	D36R, D37Q, S39E, N52S, D53E	Modified
275	Z15805	PDGF-Rβ	-	Original
276	Z17343	PDGF-Rβ	N52S, D53E	Modified
277	Z17344	PDGF-Rβ	D36R, D37Q, S39E, N52S, D53E	Modified
278	Z10103	FcRn	-	Original
279	Z17347	FcRn	N52S, D53E	Modified
280	Z17348	FcRn	D36R, D37Q, S39E, N52S, D53E	Modified
281	Z09782	CAIX	-	Original
282	Z17351	CAIX	N52S, D53E	Modified
283	Z17352	CAIX	D36R, D37Q, S39E, N52S, D53E	Modified
284	Z17355	CAIX	D53E	Modified
285	Z17357	CAIX	D36R, D37Q, S39E, D53E	Modified
286	Z17359	CAIX	N52S	Modified
287	Z17360	CAIX	D36R, D37Q, S39E, N52S	Modified

Apart from the substitutions of one of (SEQ ID NO: 284-287) or both of (SEQ ID NO: 273-274, 276-277, 279-280, 282-283) N52 and D53, substitutions were also performed in the positions corresponding to the loop [L2]. Thus, in the polypeptide variants of SEQ ID NO: 274, 277, 280, 283, 285, and 287, [L2] is RQPE.

For carrying out the stability testing, the polypeptide variants, formulated in PBS pH 7.4, were diluted to 1 mg/ml and 200 µl aliquotes were incubated at 37 °C for 2 weeks. Samples collected prior to and after the stability test were analyzed by SDS-PAGE using 10% Bis-Tris NuPAGE gels (Invitrogen) and loading 5 µg protein into each well. Resulting Coomassie blue stained gels are shown in Fig. 6. The stabilty was assessed by the appearance of new variants after incubation at the elevated temperature and mutated variants were compared to respective original polypeptide.

All polypeptide variants with the modifications as outlined in Table IX showed improved stability compared to the respective original polypeptide in the sense that a second band just above the main band observed for samples of the original polypeptide was not visible in samples of the modified polypeptides with the substitution D53E and/or N52S, see Fig. 6. Polypeptides with the substitutions D53E and/or N52S combined with the substitutions D36R, D37Q and S39E showed similar profiles on the SDS-PAGE gel. The substition D53E alone or in combination with the substitutions D36R, D37Q and S39E seemed to reduce the amount of the specie with an alternative confirmation observed as a second band on the SDS-PAGE gel, but could not completely prevent the formation of this species.

In addition, the binding capability of the modified polypeptide variants was tested. All polypeptide variants retained their binding affinity for their target after being modified (results not shown).

The results presented above for the polypeptide variants having binding affinity for other target molecules than C5 correspond well with the results presented for the C5 binding polypeptides and compounds of the present invention (see e.g. Example 2 and 4). Thus, the specific amino acid modifications as described herein appear to have a stabilizing effect irrespective of the amino acid sequence of the [*BM*]. The amino acid modifications or substitutions as described herein are thus considered to improve stability of all the C5 binding polypeptides and compounds as described herein and in WO 2013/126006.

CLAIMS

1. A polypeptide capable of binding human complement component 5 (C5), said polypeptide being selected from:

(a) a polypeptide comprising the amino acid sequence
[*BM*]-[L2]-QS$X_{42}X_{43}$LLX_{46}EAKKL$X_{52}X_{53}X_{54}$Q
wherein, independently of each other,
[*BM*] is a C5 binding motif;
[L2] is selected from DDPS and RQPE;
X_{42} is selected from A and S;
X_{43} is selected from N and E;
X_{46} is selected from A, S and C;
X_{52} is selected from E, N and S;
X_{53} is selected from D, E and S, provided that X_{53} is not D when X_{52} is N; and
X_{54} is selected from A and S; and

(b) a polypeptide which has at least 89 % amino acid sequence identity with the polypeptide of (a), provided that X_{53} is not D when X_{52} is N.

2. The polypeptide according to claim 1, said polypeptide being selected from:

(a) a polypeptide comprising the amino acid sequence
AEAKYAK-[*BM*]-[L2]-QS$X_{42}X_{43}$LLX_{46}EAKKL$X_{52}X_{53}X_{54}$QAP
wherein, independently of each other,
[*BM*], [L2], X_{42}, X_{43}, X_{46}, X_{52}, X_{53} and X_{54} are as defined in claim 1; and

(b) a polypeptide which has at least 90 % amino acid sequence identity with the polypeptide of (a), provided that X_{53} is not D when X_{52} is N.

3. The polypeptide according to claim 1 or 2, wherein X_{52} and X_{53} are independently selected from E and S.

4. The polypeptide according to claim 3, wherein (a) X_{52} is S and X_{53} is E, or (b) X_{52} is E and X_{53} is S.

5. The polypeptide according to claim 1 or 2, wherein X_{52} is S and X_{53} is D.

6. The polypeptide according to claim 1 or 2, wherein X_{52} is N and X_{53} is E.

7. The polypeptide according to any one of claims 1 to 6, wherein [*BM*] is a polypeptide selected from:

(a) a polypeptide comprising the amino acid sequence
$EX_9X_{10}X_{11}A\ X_{13}X_{14}EIDX_{18}LPNLX_{23}X_{24}X_{25}QWX_{28}AFIX_{32}X_{33}LX_{35}$;
wherein, independently of each other,
X_9 is selected from H, Q, S, T and V;
X_{10} is selected from I, L, M and V;
X_{11} is selected from A, D, E, H, K, L, N, Q, R, S, T and Y;
X_{13} is selected from N and W;
X_{14} is selected from A, D, E, H, N, Q, R, S and T;
X_{18} is selected from A, E, G, H, K, L, Q, R, S, T and Y;
X_{23} is selected from N and T;
X_{24} is selected from I, L and V;
X_{25} is selected from A, D, E, H, K, N, Q, R, S and T;
X_{28} is selected from I, L and V;
X_{32} is selected from D, E, G, H, N, S and T;
X_{33} is selected from K and S;
X_{35} is selected from A, D, E, H, N, Q, S, T and Y; and

(b) a polypeptide which has at least 85 % amino acid sequence identity with the polypeptide of (a).

8. The polypeptide according to any one of claims 1 to 7 being selected from:

(a) a polypeptide comprising the amino acid sequence

AEAKYAKE$X_9X_{10}X_{11}AX_{13}X_{14}EIDX_{18}LPNLX_{23}X_{24}X_{25}QWX_{28}AFIX_{32}X_{33}L$
X_{35}-[L2]-$QSX_{42}X_{43}LLX_{46}EAKKLX_{52}X_{53}X_{54}QAP$;
wherein, independently of each other,
X_9 is selected from H, Q, S, T and V;
X_{10} is selected from I, L, M and V;
X_{11} is selected from A, D, E, H, K, L, N, Q, R, S, T and Y;
X_{13} is selected from N and W;
X_{14} is selected from A, D, E, H, N, Q, R, S and T;
X_{18} is selected from A, E, G, H, K, L, Q, R, S, T and Y;
X_{23} is selected from N and T;
X_{24} is selected from I, L and V;
X_{25} is selected from A, D, E, H, K, N, Q, R, S and T;
X_{28} is selected from I, L and V;
X_{32} is selected from D, E, G, H, N, S and T;
X_{33} is selected from K and S;
X_{35} is selected from A, D, E, H, N, Q, S, T and Y;
[L2] is selected from DDPS and RQPE;
X_{42} is selected from A and S;
X_{43} is selected from N and E;
X_{46} is selected from A, S and C;
X_{52} is selected from E, N and S;
X_{53} is selected from D, E and S, provided that X_{53} is not D when X_{52} is N; and
X_{54} is selected from A and S; and

(b) a polypeptide which has at least 90 % amino acid sequence identity with the polypeptide of (a), provided that X_{53} is not D when X_{52} is N.

9. The polypeptide according to claim 7 or 8, wherein at least one of the following conditions is fulfilled:
X_9 is V,
X_{10} is L,
X_{11} is E,
X_{13} is W,

X_{14} is D,
X_{18} is R,
X_{23} is T,
X_{24} is I,
X_{25} is E,
X_{28} is L,
X_{32} is N,
X_{33} is K,
X_{35} is D,
[L2] is DDPS,
X_{42} is S,
X_{43} is E,
X_{46} is S,
X_{54} is S.

10. The polypeptide according to any one of claims 1 to 9, wherein [*BM*] comprises an amino acid sequence selected from the group consisting of positions 1-28 in SEQ ID NOS: 1-248.

11. The polypeptide according to claim 10, wherein [*BM*] comprises the amino acid sequence shown as positions 1-28 in SEQ ID NO: 1.

12. The polypeptide according to any one of claims 1 to 11, selected from a polypeptide comprising the amino sequence shown as SEQ ID NO: 260, SEQ ID NO: 265, SEQ ID NO: 266, or SEQ ID NO: 267.

13. A compound capable of binding C5, said compound comprising:
    a. at least one C5 binding polypeptide according to any one of the preceding claims;
    b. at least one albumin binding domain of streptococcal protein G, or a derivative thereof; and
    c. optionally, at least one linking moiety for linking said at least one albumin binding domain or derivative thereof to the C or N terminal of said at least one C5 binding polypeptide.

14. The compound according to claim 13, wherein the albumin binding domain comprises the amino acid sequence shown as SEQ ID NO: 250.

15. The compound according to claim 13 or 14, wherein the linking moiety is a peptide comprising the amino acid sequence $KVX_{60}GS$, wherein X_{60} is selected from D, E and A.

16. The compound according to claim 15, wherein X_{60} is D.

17. The compound according to claim 16, wherein the compound is a polypeptide comprising the amino sequence shown as SEQ ID NO: 253.

18. The compound according to claim 15, wherein X_{60} is E.

19. The compound according to claim 18, wherein the compound is a polypeptide comprising the amino sequence shown as SEQ ID NO: 261, SEQ ID NO: 263, SEQ ID NO: 264, SEQ ID NO: 269 or SEQ ID NO: 270.

20. The compound according to claim 15, wherein X_{60} is A.

21. The compound according to claim 20, wherein the compound is a polypeptide comprising the amino sequence shown as SEQ ID NO: 262.

22. The compound according to claim 15, wherein the linking moiety is absent.

23. A compound capable of binding C5, said compound comprising:

a. at least one C5 binding polypeptide, said polypeptide being selected from:

a-1. a polypeptide comprising the amino acid sequence
[*BM*]-[L2]-$QSX_{42}X_{43}LLX_{46}EAKKLX_{52}X_{53}X_{54}Q$
wherein, independently of each other,
[*BM*] is a C5 binding motif;
[L2] is selected from DDPS and RQPE;
X_{42} is selected from A and S;
X_{43} is selected from N and E;

X_{46} is selected from A, S and C;
X_{52} is selected from E, N and S;
X_{53} is selected from D, E and S;
X_{54} is selected from A and S; and

a-2. a polypeptide which has at least 89 % amino acid sequence identity with the polypeptide of a-1;

b. at least one albumin binding domain of streptococcal protein G, or a derivative thereof; and

c. at least one linking moiety for linking said at least one albumin binding domain or derivative thereof to the C or N terminal of said at least one C5 binding polypeptide; wherein the linking moiety comprises KVEGS or KVAGS; or wherein said linking moiety is absent.

24. A compound capable of binding C5, said compound comprising:

a. at least one C5 binding polypeptide, said polypeptide being selected from:

a-1. a polypeptide comprising the amino acid sequence
[*BM*]-[L2]-QS$X_{42}X_{43}$LLX_{46}EAKKL$X_{52}X_{53}X_{54}$Q
wherein, independently of each other,
[*BM*] is a C5 binding motif;
[L2] is RQPE;
X_{42} is selected from A and S;
X_{43} is selected from N and E;
X_{46} is selected from A, S and C;
X_{52} is selected from E, N and S;
X_{53} is selected from D, E and S;
X_{54} is selected from A and S; and

a-2. a polypeptide which has at least 89 % amino acid sequence identity with the polypeptide of a-1;

b. at least one albumin binding domain of streptococcal protein G, or a derivative thereof; and

c. optionally, at least one linking moiety for linking said at least one albumin binding domain or derivative thereof to the C or N terminal of said at least one C5 binding polypeptide.

25. The C5 binding polypeptide according to any one of claims 1-12 or the C5 binding compound according to any one of claims 13-24 for use in therapy.

26. The C5 binding polypeptide according to any one of claims 1-12 or the C5 binding compound according to any one of claims 13-24 for use in a method for treatment and/or prophylaxis of a C5-related condition.

27. The C5 binding polypeptide for use or the C5 binding compound for use according to claim 26, wherein said C5-related condition is a condition selected from inflammatory diseases; autoimmune diseases; infectious diseases; cardiovascular diseases; neurodegenerative disorders; graft injury; eye diseases; kidney diseases; pulmonary diseases; haematological diseases such as paroxysmal nocturnal hemoglobinuria (PNH); allergic diseases and dermatological diseases.

28. The C5 binding polypeptide for use or the C5 binding compound for use according to any one of claims 25-27, wherein said C5 binding polypeptide or compound is administered intravenously, subcutaneously, by inhalation, nasally, orally, intravitreally, or topically.

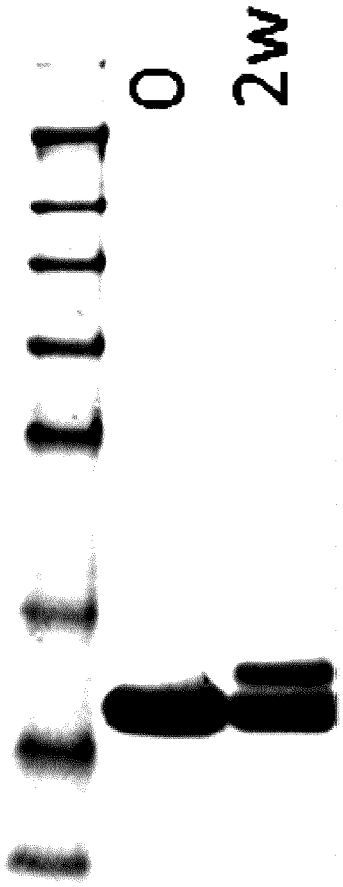

Figure 1

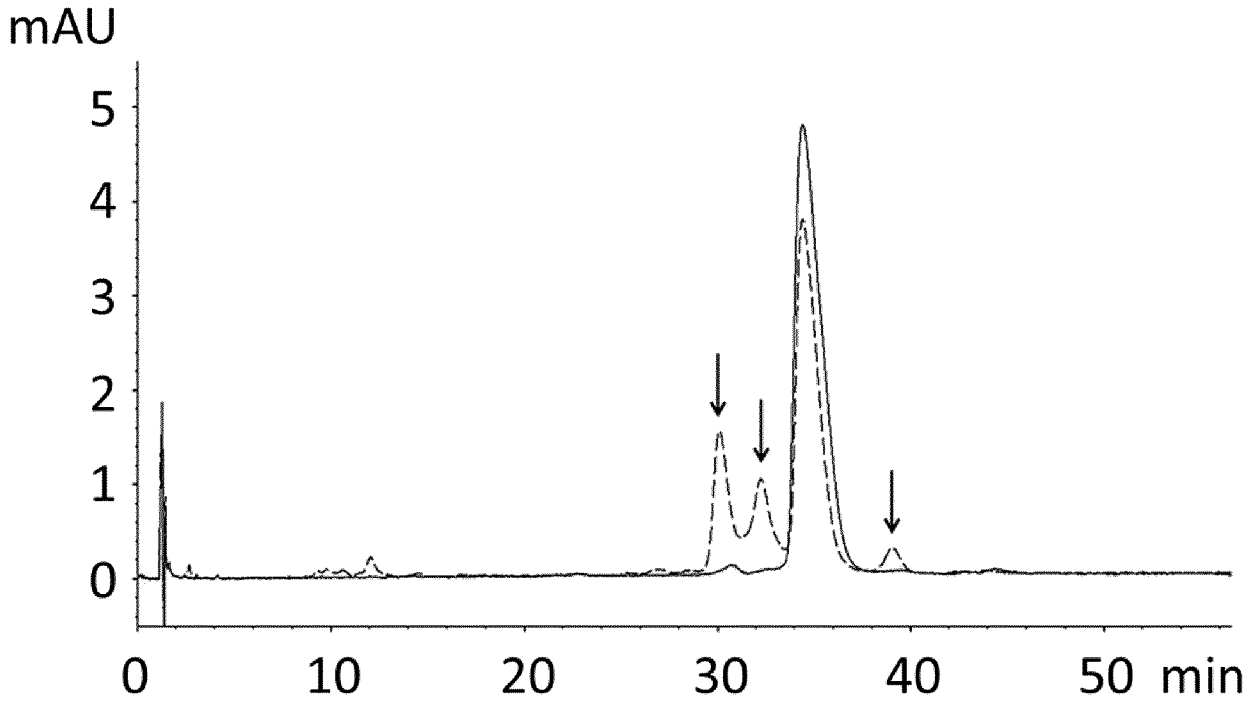

Figure 2

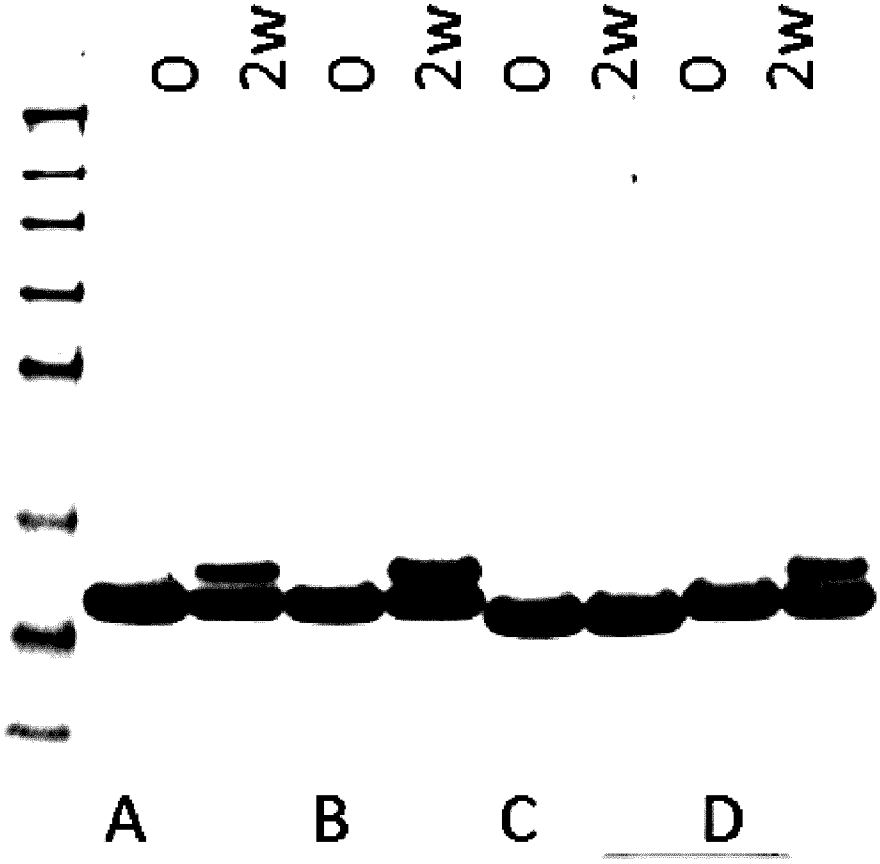

Figure 3

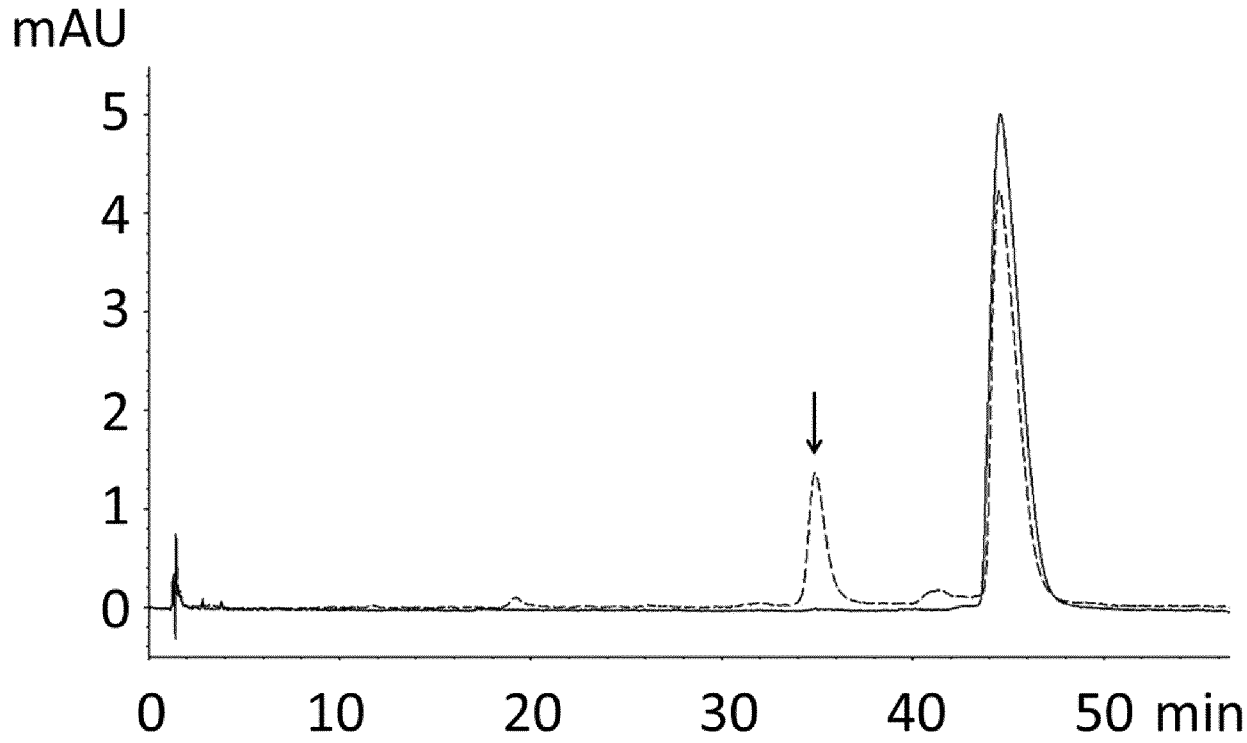

Figure 4

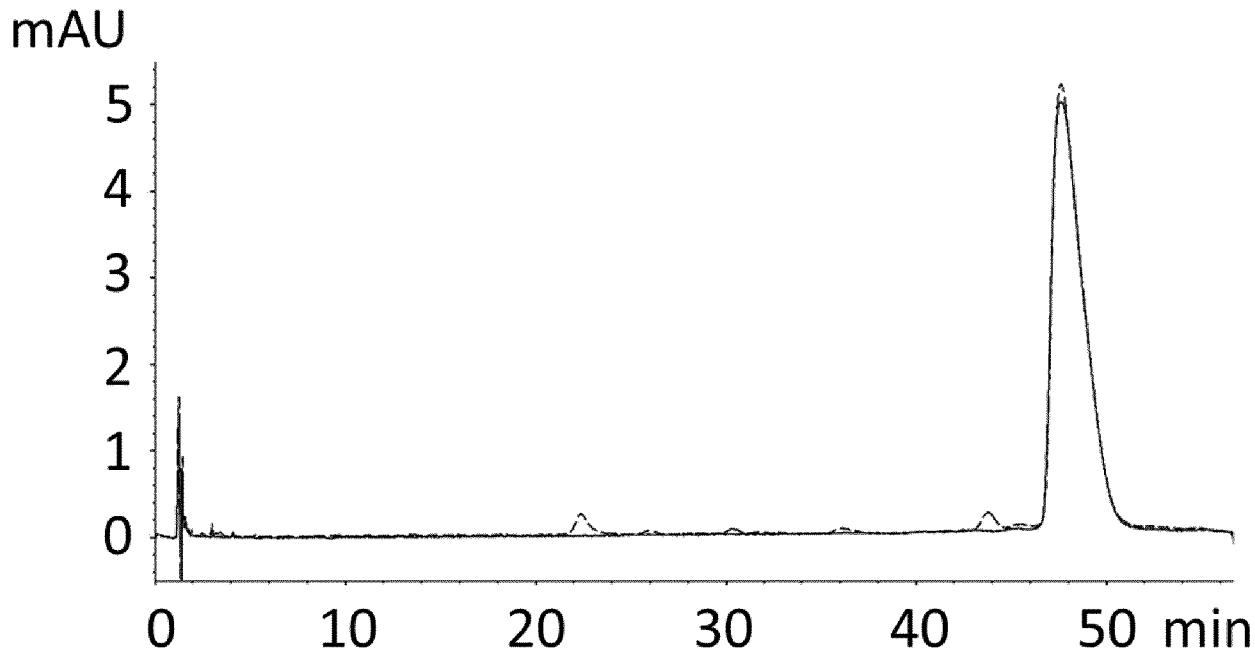

Figure 5

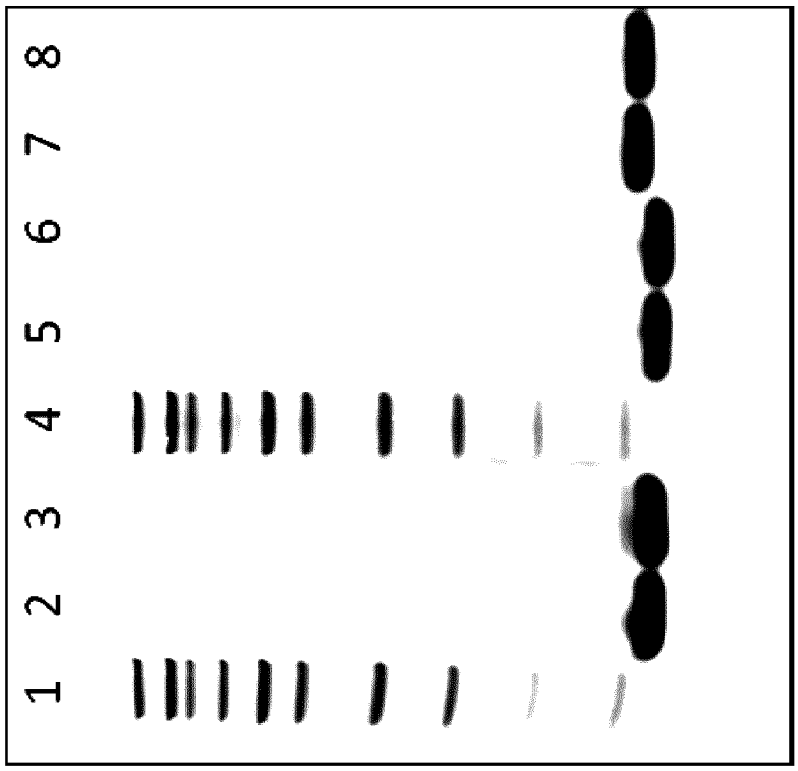

Figure 6B

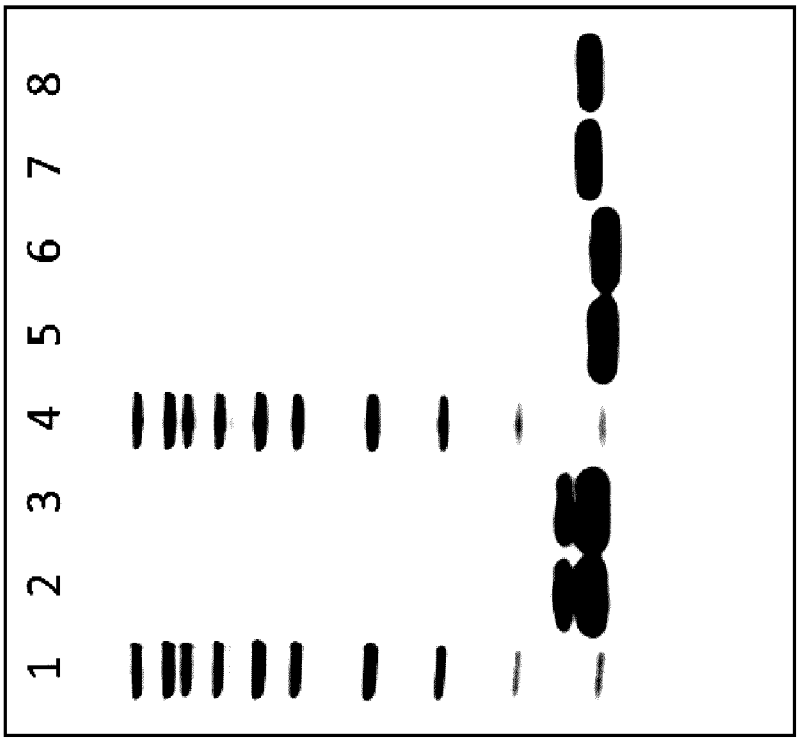

Figure 6A

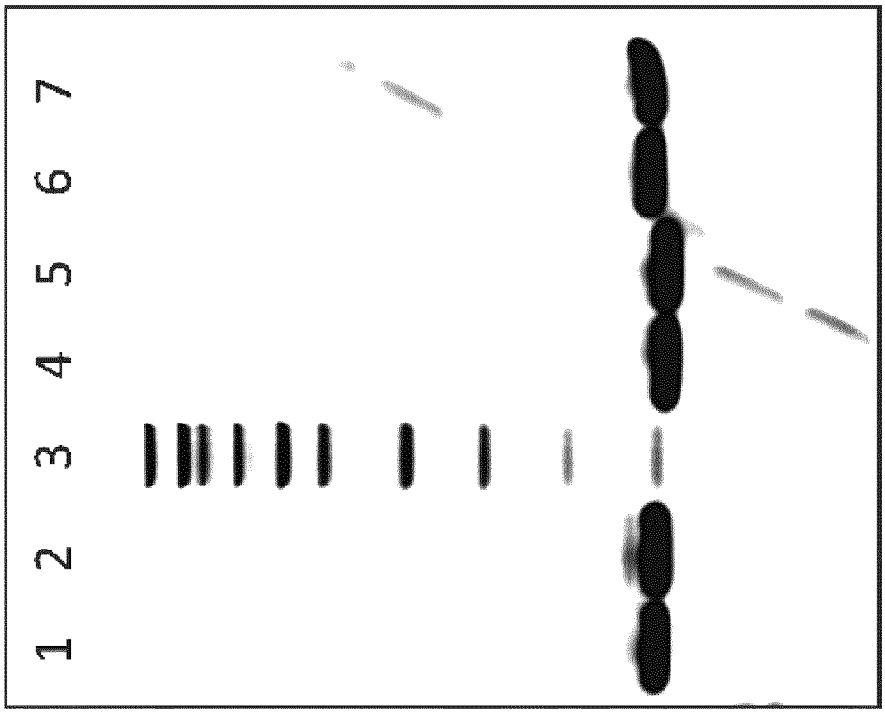

Figure 6C

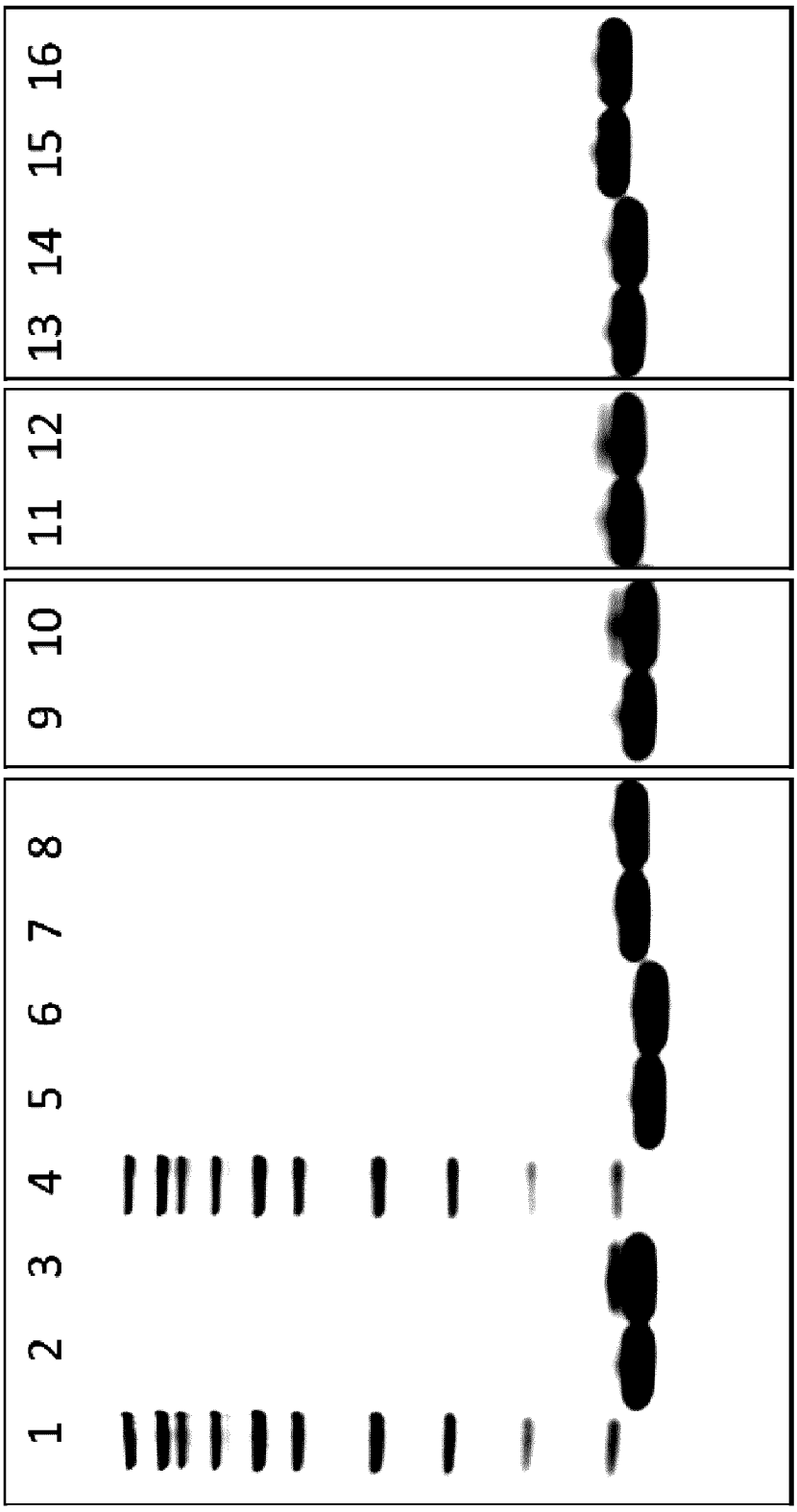

Figure 6D

Polypeptide	Amino Acid Sequence	SEQ ID NO:
CBM06175	EVLEAWDEIDRLPNLTIEQWLAFINKLDD	1
CBM08044	EVLEAWNEIDRLPNLTIEQWLAFINKLDD	2
CBM05998	EVIEAWNEIDRLPNLTIEQWLAFINKLDD	3
CBM06009	EVLEAWDEIDRLPNLTLDQWLAFINKLDD	4
CBM06079	EVLDAWDEIDALPNLTLEQWLAFINKLDD	5
CBM06126	EVIDAWDEIDRLPNLTLDQWLAFINKLDD	6
CBM06140	ETLEAWDEIDRLPNLTIEQWLAFINKLDD	7
CBM06189	EVIDAWNEIDALPNLTLDQWLAFINKLDD	8
CBM06214	EVLDAWDEIDKLPNLTIDQWLAFINKLDD	9
CBM06215	EVLEAWDEIDHLPNLTLDQWLAFINKLDD	10
CBM06226	EVLEAWDEIDALPNLTIEQWLAFINKLDD	11
CBM06018	EVLDAWDEIDKLPNLTLEQWLAFINKLDD	12
CBM05477	ETITAWDEIDKLPNLTIEQWLAFIGKLED	13
CBM05363	ESMKAWDEIDRLPNLNINQWVAFIDSLYD	14
CBM05483	ESIEAWTEIDHLPNLTIEQWLAFINKLTD	15
CBM05538	EVLDAWHEIDTLPNLTVRQWLAFISKLED	16
CBM05692	EHIQANEEIDRLPNLTIKQWLAFINKLHD	17
CBM05994	EVLHAWAEIDALPNLTIEQWLAFINKLDD	18
CBM05995	EVLAAWDEIDSLPNLTLQQWLAFINKLDD	19
CBM05996	EVIDAWNEIDALPNLTLEQWLAFINKLDD	20
CBM05997	EVLDAWNEIDALPNLTIDQWLAFINKLSD	21
CBM05999	EVIEAWDEIDGLPNLTIEQWLAFINKLDD	22
CBM06000	EVLEAWDEIDHLPNLTLQQWLAFINKLDD	23
CBM06001	EVIEAWNEIDALPNLTIEQWLAFINKLDD	24

Figure 7

CBM06002	EVIAAWNEIDRLPNLTLTQWLAFINKLDD	25
CBM06003	EVIEAWDEIDALPNLTLQQWLAFINKLDD	26
CBM06004	EVIAAWDEIDKLPNLTIEQWLAFINKLDD	27
CBM06005	EVIAAWDEIDKLPNLTLQQWLAFINKLDD	28
CBM06006	ETIAAWDEIDKLPNLTIEQWLAFINKLDD	29
CBM06007	ETIEAWNEIDRLPNLTIEQWLAFINKLDD	30
CBM06008	EVLEAWREIDALPNLTIQQWLAFINKLDD	31
CBM06010	EVIEAWDEIDQLPNLTIEQWLAFINKLDD	32
CBM06011	EVLRAWDEIDHLPNLTLEQWLAFINKLDD	33
CBM06012	EVLEAWDEIDRLPNLTLNQWLAFINKLDD	34
CBM06013	EVLDAWNEIDHLPNLTIEQWLAFINKLDD	35
CBM06014	EVIDAWNEIDKLPNLTIEQWLAFINKLDD	36
CBM06015	ETLEAWDEIDQLPNLTLQQWLAFINKLDD	37
CBM06016	EVIEAWNEIDALPNLTLDQWLAFINKLDD	38
CBM06017	EVIDAWNEIDRLPNLTLQQWLAFINKLDD	39
CBM06019	EVIDAWNEIDQLPNLTLEQWLAFINKLDD	40
CBM06020	ETIAAWDEIDHLPNLTLEQWLAFINKLDD	41
CBM06024	EVLQAWDEIDHLPNLTIQQWLAFINKLSD	42
CBM06025	ETLHAWAEIDRLPNLTIEQWLAFINKLDD	43
CBM06026	EVLEAWNEIDHLPNLTLAQWLAFINKLDD	44
CBM06027	EVIEAWDEIDKLPNLTIAQWLAFINKLDD	45
CBM06028	EVLDAWDEIDHLPNLTLQQWLAFINKLDD	46
CBM06029	ETIEAWNEIDKLPNLTLTQWLAFINKLDD	47
CBM06030	EVLEAWNEIDLLPNLTIEQWLAFINKLDD	48
CBM06031	EVIEAWDEIDHLPNLTIDQWLAFINKLDD	49
CBM06032	EVISAWNEIDALPNLTLQQWLAFINKLDD	50

Figure 7

CBM06033	EVIAAWNEIDKLPNLTLEQWLAFINKLDD	51
CBM06034	ETIEAWNEIDSLPNLTLDQWLAFINKLDD	52
CBM06035	EVLDAWNEIDQLPNLTLQQWLAFINKLDD	53
CBM06037	EVLAAWNEIDHLPNLTIEQWLAFINKLDD	54
CBM06038	EVLEAWDEIDHLPNLTITQWLAFINKLDD	55
CBM06039	ETIDAWNEIDHLPNLTIEQWLAFINKLDD	56
CBM06040	EVIEAWNEIDHLPNLTIQQWLAFINKLDD	57
CBM06041	EVIQAWNEIDALPNLTISQWLAFINKLDD	58
CBM06043	EVIAAWDEIDSLPNLTIEQWLAFINKLDD	59
CBM06044	EHIEAWNEIDALPNLTIEQWLAFINKLQD	60
CBM06045	EVLEAWNEIDKLPNLTLDQWLAFINKLDD	61
CBM06047	EVIDAWNEIDHLPNLTIEQWLAFINKLAD	62
CBM06048	ETIDAWDEIDKLPNLTIEQWLAFINKLDD	63
CBM06049	EVIAAWDEIDLLPNLTLQQWLAFINKLAD	64
CBM06050	EVIHAWDEIDKLPNLTIEQWLAFINKLDD	65
CBM06051	EVIAAWNEIDHLPNLTLEQWLAFINKLDD	66
CBM06052	ETLDAWNEIDKLPNLTLSQWLAFINKLDD	67
CBM06053	EVLEAWNEIDALPNLTLEQWLAFINKLDD	68
CBM06054	EVIQAWDEIDHLPNLTISQWLAFINKLDD	69
CBM06055	EVLQAWDEIDSLPNLTIEQWLAFINKLDD	70
CBM06056	ETLEAWDEIDHLPNLTIAQWLAFINKLDD	71
CBM06057	ETIDAWNEIDRLPNLTISQWLAFINKLDD	72
CBM06058	EVLDAWHEIDHLPNLTIQQWLAFINKLDD	73
CBM06059	EQIRAWDEIDKLPNLTIEQWLAFINKLAD	74
CBM06060	ETLYAWNEIDKLPNLTIEQWLAFIEKLQD	75
CBM06061	EVIEAWNEIDALPNLTIDQWLAFINKLDD	76

Figure 7

CBM06062	EVLEAWNEIDHLPNLTIQQWLAFINKLDD	77
CBM06063	ETIEAWDEIDALPNLTIEQWLAFINKLDD	78
CBM06065	EVIEAWNEIDHLPNLTLQQWLAFINKLDD	79
CBM06066	EVIEAWNEIDKLPNLTIQQWLAFINKLDD	80
CBM06068	ETLDAWAEIDHLPNLTLDQWLAFINKLDD	81
CBM06069	EHIDAWNEIDALPNLTLSQWLAFINKLDD	82
CBM06070	EVLDAWNEIDKLPNLTIAQWLAFINKLDD	83
CBM06071	EVIEAWTEIDYLPNLTLQQWLAFINKLDD	84
CBM06072	ETIEAWNEIDHLPNLTIAQWLAFINKLDD	85
CBM06073	EVIQAWNEIDKLPNLTLEQWLAFINKLDD	86
CBM06074	EVIEAWDEIDHLPNLTIEQWLAFINKLDD	87
CBM06075	ETIDAWNEIDLLPNLTIEQWLAFINKLDD	88
CBM06076	EHIDAWNEIDKLPNLTLDQWLAFINKLDD	89
CBM06077	EVVAAWNEIDALPNLTIEQWLAFINKLND	90
CBM06080	EVIEAWNEIDALPNLTLAQWLAFINKLDD	91
CBM06081	EVLQAWDEIDRLPNLTLDQWLAFINKLDD	92
CBM06082	EVIDAWDEIDHLPNLTIEQWLAFINKLSD	93
CBM06083	EVVEAWNEIDQLPNLTIEQWLAFINKLDD	94
CBM06084	EVIQAWNEIDALPNLTIEQWLAFINKLDD	95
CBM06085	EVIQAWDEIDKLPNLTIDQWLAFINKLAD	96
CBM06086	EVVAAWDEIDALPNLTLTQWLAFINKLDD	97
CBM06087	EVIQAWNEIDGLPNLTLSQWLAFINKLDD	98
CBM06088	ETIEAWDEIDALPNLTITQWLAFINKLDD	99
CBM06089	EVIDAWNEIDHLPNLTIQQWLAFINKLAD	100
CBM06090	ETIEAWNEIDALPNLTLDQWLAFINKLED	101
CBM06091	EHIHAWNEIDELPNLTIEQWLAFINKLAD	102

Figure 7

CBM06092	EVIDAWDEIDHLPNLTIDQWLAFINKLSD	103
CBM06093	EVIDANDEIDALPNLTIAQWLAFINKLHD	104
CBM06095	ETIEAWDEIDKLPNLTIEQWLAFINKLDD	105
CBM06097	EVLLAWDEIDHLPNLTLEQWLAFINKLDD	106
CBM06098	EHIDAWNEIDGLPNLTLEQWLAFINKLDD	107
CBM06099	EVIEAWSEIDALPNLTIDQWLAFINKLAD	108
CBM06100	EQLNAWAEIDALPNLTIEQWLAFINKLDD	109
CBM06101	EVIDAWNEIDALPNLTIAQWLAFINKLDD	110
CBM06103	ETIDAWNEIDQLPNLTIEQWLAFINKLDD	111
CBM06104	EVIEAWDEIDKLPNLTLAQWLAFINKLDD	112
CBM06105	EVLYAWAEIDHLPNLTIEQWLAFINKLDD	113
CBM06107	EQIDAWNEIDRLPNLTIQQWLAFINKLDD	114
CBM06108	EVLAAWDEIDRLPNLTIEQWLAFINKLDD	115
CBM06109	EVIEAWDEIDHLPNLTLHQWLAFINKLDD	116
CBM06110	EVIEAWNEIDKLPNLTLQQWLAFINKLDD	117
CBM06111	EVIDANDEIDALPNLTIEQWLAFINKLHD	118
CBM06112	EVIAAWDEIDALPNLTIEQWLAFINKLDD	119
CBM06113	EVIEAWTEIDQLPNLTLDQWLAFINKLDD	120
CBM06114	EVINAWNEIDALPNLTLQQWLAFINKLDD	121
CBM06115	EHIEAWDEIDHLPNLTIDQWLAFINKLAD	122
CBM06116	EHLEAWREIDALPNLTIEQWLAFINKLDD	123
CBM06117	EVLDAWNEIDKLPNLTLQQWLAFINKLDD	124
CBM06118	EVIAAWDEIDHLPNLTIQQWLAFINKLDD	125
CBM06119	EVIQAWNEIDALPNLTLEQWLAFINKLDD	126
CBM06121	EVIDAWNEIDHLPNLTIAQWLAFINKLDD	127
CBM06122	EQLDAWDEIDHLPNLTIDQWLAFINKLSD	128

Figure 7

CBM06123	EVLNAWDEIDKLPNLTIEQWLAFINKLDD	129
CBM06124	EVLEAWNEIDHLPNLTIDQWLAFINKLDD	130
CBM06125	EVLLAWDEIDRLPNLTIDQWLAFINKLAD	131
CBM06127	EVIAAWNEIDQLPNLTLDQWLAFINKLDD	132
CBM06128	ETLLAWDEIDALPNLTIEQWLAFINKLDD	133
CBM06129	EVIDAWNEIDTLPNLTLEQWLAFINKLDD	134
CBM06131	EVLHAWNEIDHLPNLTLNQWLAFINKLQD	135
CBM06132	EVIQAWNEIDALPNLTIAQWLAFINKLDD	136
CBM06133	ETVDAWNEIDALPNLTIEQWLAFINKLDD	137
CBM06134	EVIQAWDEIDHLPNLTIDQWLAFINKLDD	138
CBM06135	EVLDAWNEIDQLPNLTIQQWLAFINKLDD	139
CBM06136	ETIEAWNEIDALPNLTLDQWLAFINKLDD	140
CBM06137	EVIEAWDEIDALPNLTIDQWLAFINKLDD	141
CBM06138	EVIEAWNEIDQLPNLTIQQWLAFINKLDD	142
CBM06139	EVIEAWTEIDHLPNLTIEQWLAFINKLDD	143
CBM06141	EVIQAWNEIDHLPNLTLQQWLAFINKLED	144
CBM06142	EVIQANNEIDQLPNLTIEQWLAFINKLHD	145
CBM06143	EVLHAWSEIDKLPNLTIEQWLAFINKLDD	146
CBM06144	ETIQAWDEIDKLPNLTLDQWLAFINKLSD	147
CBM06145	ETLRAWDEIDKLPNLTIQQWLAFINKLAD	148
CBM06146	EVIDAWNEIDHLPNLTIEQWLAFINKLED	149
CBM06147	EVIDAWNEIDHLPNLTLQQWLAFINKLAD	150
CBM06148	ETIDAWNEIDALPNLTLDQWLAFINKLDD	151
CBM06149	EVIEAWNEIDQLPNLTIEQWLAFINKLDD	152
CBM06150	EVIRAWDEIDQLPNLTLSQWLAFINKLDD	153
CBM06151	EVIEAWNEIDRLPNLTIHQWLAFINKLDD	154

Figure 7

CBM06152	ETIEAWNEIDQLPNLTIEQWLAFINKLDD	155
CBM06153	EVLTAWAEIDALPNLTLSQWLAFINKLDD	156
CBM06154	EVIEAWDEIDKLPNLTVDQWLAFINKLDD	157
CBM06155	EVIDAWNEIDHLPNLTLTQWLAFINKLDD	158
CBM06156	EVIEAWNEIDQLPNLTLDQWLAFINKLDD	159
CBM06157	ETLQAWDEIDHLPNLTLNQWLAFINKLDD	160
CBM06158	EVIDAWNEIDHLPNLTIEQWLAFINKLDD	161
CBM06159	EVIEAWNEIDLLPNLTLSQWLAFINKLDD	162
CBM06160	EVIDAWDEIDRLPNLTLKQWLAFINKLDD	163
CBM06161	ETLHAWDEIDKLPNLTIEQWLAFINKLDD	164
CBM06162	EVIKAWDEIDHLPNLTLNQWLAFINKLDD	165
CBM06163	EVIEAWNEIDHLPNLTLAQWLAFINKLDD	166
CBM06164	EVIQAWNEIDHLPNLTIDQWLAFITKLED	167
CBM06165	EVIEAWNEIDRLPNLTIKQWLAFINKLDD	168
CBM06167	EVIEAWNEIDSLPNLTLQQWLAFINKLDD	169
CBM06168	ETIDAWNEIDKLPNLTIEQWLAFINKLDD	170
CBM06169	EVLEAWAEIDALPNLTIAQWLAFINKLDD	171
CBM06170	ETIDAWNEIDRLPNLTIEQWLAFINKLDD	172
CBM06171	ETLKAWDEIDRLPNLTLEQWLAFINKLDD	173
CBM06172	ETIAAWNEIDALPNLTLQQWLAFINKLDD	174
CBM06173	EVLQAWNEIDHLPNLTIQQWLAFINKLDD	175
CBM06174	EVIEAWSEIDHLPNLTLQQWLAFINKLDD	176
CBM06176	EVIDAWNEIDGLPNLTIEQWLAFINKLDD	177
CBM06178	EVIHAWNEIDHLPNLTLNQWLAFINKLED	178
CBM06179	EVLDAWNEIDSLPNLTLDQWLAFINKLDD	179
CBM06180	EQIEAWNEIDRLPNLTLEQWLAFINKLDD	180

Figure 7

CBM06181	EVVDAWNEIDALPNLTLQQWLAFINKLDD	181
CBM06182	EVIEAWNEIDKLPNLTIEQWLAFINKLDD	182
CBM06183	EVIEANDEIDRLPNLTIEQWLAFINKLHD	183
CBM06184	ETLQAWDEIDKLPNLTIEQWLAFINKLDD	184
CBM06185	EVIEAWDEIDHLPNLTIDQWLAFINKLAD	185
CBM06186	ETIDAWNEIDHLPNLTLQQWLAFINKLAD	186
CBM06187	EVIDAWDEIDKLPNLTIEQWLAFINKLDD	187
CBM06188	EVIEAWNEIDKLPNLTLAQWLAFINKLDD	188
CBM06190	EVLQAWDEIDKLPNLTIQQWLAFINKLDD	189
CBM06191	EVIAAWNEIDGLPNLTLQQWLAFINKLDD	190
CBM06192	ETLNAWNEIDALPNLTLQQWLAFINKLDD	191
CBM06193	EVLSAWNEIDQLPNLTLEQWLAFINKLDD	192
CBM06194	ETLEAWDEIDHLPNLTLHQWLAFINKLDD	193
CBM06195	EQIEAWNEIDHLPNLTLQQWLAFINKLAD	194
CBM06196	EVVEAWDEIDKLPNLTIEQWLAFINKLDD	195
CBM06197	EVLEAWNEIDELPNLTIEQWLAFINKLDD	196
CBM06198	EVIDAWNEIDQLPNLTLQQWLAFINKLDD	197
CBM06199	ETIDAWDEIDKLPNLTLSQWLAFINKLDD	198
CBM06200	ETIDAWNEIDQLPNLTLQQWLAFINKLDD	199
CBM06201	EVIQAWDEIDALPNLTLNQWLAFINKLDD	200
CBM06202	EVLDAWAEIDQLPNLTLQQWLAFINKLDD	201
CBM06203	EHIAAWDEIDALPNLTIEQWLAFINKLDD	202
CBM06206	EVIRAWDEIDALPNLTIEQWLAFINKLDD	203
CBM06207	EVIDAWDEIDALPNLTIDQWLAFINKLAD	204
CBM06208	EVIDAWNEIDRLPNLTIQQWLAFINKLDD	205
CBM06209	EVITAWNEIDHLPNLTLSQWLAFINKLDD	206

Figure 7

CBM06210	EVIDAWNEIDALPNLTIHQWLAFINKLDD	207
CBM06211	EQLKAWDEIDKLPNLTIEQWLAFIEKLQD	208
CBM06212	EHIDAWTEIDHLPNLTIEQWLAFINKLDD	209
CBM06213	EQLRAWDEIDKLPNLTIEQWLAFINKLQD	210
CBM06216	EVLEAWREIDSLPNLTIAQWLAFINKLDD	211
CBM06217	EVIQAWNEIDKLPNLTIEQWLAFINKLDD	212
CBM06218	EHVEAWNEIDQLPNLTIEQWLAFINKLAD	213
CBM06219	EVIDAWDEIDALPNLTIDQWLAFINKLSD	214
CBM06220	EVIEAWNEIDHLPNLTIEQWLAFINKLDD	215
CBM06221	EVLQAWDEIDKLPNLTIEQWLAFINKLSD	216
CBM06222	EVIKAWNEIDSLPNLTIEQWLAFINKLDD	217
CBM06223	EVLEAWHEIDLLPNLTIQQWLAFINKLDD	218
CBM06224	EVLEAWTEIDRLPNLTLDQWLAFINKLDD	219
CBM06225	EQLYAWNEIDHLPNLTIEQWLAFIEKLQD	220
CBM06227	EVLNAWDEIDKLPNLTIKQWLAFINKLDD	221
CBM06228	EVIRAWDEIDKLPNLTVEQWLAFINKLDD	222
CBM06230	EVVQAWDEIDQLPNLTLEQWLAFINKLDD	223
CBM06231	EVIRAWDEIDQLPNLTLEQWLAFINKLDD	224
CBM06232	ETIDAWNEIDHLPNLTLDQWLAFINKLDD	225
CBM06233	EVVAAWTEIDLLPNLTLDQWLAFINKLED	226
CBM06234	EVVAAWDEIDALPNLTIEQWLAFINKLSD	227
CBM06235	ETLEAWREIDSLPNLTLEQWLAFINKLDD	228
CBM06236	EVIKAWNEIDHLPNLTLDQWLAFINKLDD	229
CBM06237	EVLEAWTEIDKLPNLTIDQWLAFINKLDD	230
CBM06238	ETLEAWDEIDKLPNLTIDQWLAFINKLDD	231
CBM06239	EVIEAWNEIDKLPNLTIDQWLAFINKLDD	232

Figure 7

CBM06240	ETIDAWNEIDKLPNLTLEQWLAFINKLDD	233
CBM06241	ETLDAWDEIDALPNLTIDQWLAFINKLED	234
CBM06242	EVLSAWNEIDHLPNLTIQQWLAFINKLDD	235
CBM06244	EVIQANDEIDKLPNLTIEQWLAFIHKLHD	236
CBM06245	EHLDAWDEIDHLPNLTIQQWLAFINKLAD	237
CBM06246	EVIQAWNEIDQLPNLTIEQWLAFINKLDD	238
CBM06247	EVIEAWNEIDYLPNLTIAQWIAFINKLDD	239
CBM06248	ETIQAWDEIDRLPNLTLQQWLAFINKLDD	240
CBM06249	ETIQAWDEIDKLPNLTIEQWLAFINKLDD	241
CBM06250	ETLDAWAEIDHLPNLTIEQWLAFINKLDD	242
CBM06251	EVIEAWDEIDKLPNLTLNQWLAFINKLDD	243
CBM06252	EVLDAWNEIDQLPNLTIEQWLAFINKLDD	244
CBM06253	EVLHAWNEIDHLPNLTIEQWLAFIEKLED	245
CBM06254	EVIEAWQEIDKLPNLTIDQWLAFINKLDD	246
CBM06257	EVVDAWNEIDQLPNLTIEQWLAFINKLDD	247
CBM06258	EQIEAWNEIDALPNLTIEQWLAFINKLAD	248
PSI0242	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDDDPSQSSELLSEAKKLNDSQAPKVDGSLAEAKEAANAELDSYGVSDFYKRLIDKAKTV EGVEALKDAILAALP	249
ABD	LAEAKEAANAELDSYGVSDFYKRLIDKAKTVEGVEALKDAILAALP	250
Human C5	MGLLGILCFLIFLGKTWGQEQTYVISAPKIFRVGASENIVIQVYGYTEAFDATISIKSYPDKKFSYSSGHVHLSSENKFQ NSAILTIQPKQLPGGQNPVSYVYLEVVSKHFSKSKRMPITYDNGFLFIHTDKPVYTPDQSVKVRVYSLNDDLKPAKRETV LTFIDPEGSEVDMVEEIDHIGIISFPDFKIPSNPRYGMWTIKAKYKEDFSTTGTAYFEVKEYVLPHFSVSIEPEYNFIGY KNFKNFEITIKARYFYNKVVTEADVYITFGIREDLKDDQKEMMQTAMQNTMLINGIAQVTFDSETAVKELSYYSLEDLNN KYLYIAVTVIESTGGFSEEAEIPGIKYVLSPYKLNLVATPLFLKPGIPYPIKVQVKDSLDQLVGGVPVTLNAQTIDVNQE TSDLDPSKSVTRVDDGVASFVLNLPSGVTVLEFNVKTDAPDLPEENQAREGYRAIAYSSLSQSYLYIDWTDNHKALLVGE HLNIIVTPKSPYIDKITHYNYLILSKGKIIHFGTREKFSDASYQSINIPVTQNMVPSSRLLVYYIVTGEQTAELVSDSVW LNIEEKCGNQLQVHLSPDADAYSPGQTVSLNMATGMDSWVALAAVDSAVYGVQRGAKKPLERVFQFLEKSDLGCGAGGGL NNANVFHLAGLTFLTNANADDSQENDEPCKEILRPRRTLQKKIEEIAAKYKHSVVKKCCYDGACVNNDETCEQRAARISL	251

Figure 7

	GPRCIKAFTECCVVASQLRANISHKDMQLGRLHMKTLLPVSKPEIRSYFPESWLWEVHLVPRRKQLQFALPDSLTTWEIQ GVGISNTGICVADTVKAKVFKDVFLEMNIPYSVVRGEQIQLKGTVYNYRTSGMQFCVKMSAVEGICTSESPVIDHQGTKS SKCVRQKVEGSSSHLVTFTVLPLEIGLHNINFSLETWFGKEILVKTLRVVPEGVKRESYSGVTLDPRGIYGTISRRKEFP YRIPLDLVPKTEIKRILSVKGLLVGEILSAVLSQEGINILTHLPKGSAEAELMSVVPVFYVFHYLETGNHWNIFHSDPLI EKQKLKKKLKEGMLSIMSYRNADYSYSVWKGGSASTWLTAFALRVLGQVNKYVEQNQNSICNSLLWLVENYQLDNGSFKE NSQYQPIKLQGTLPVEARENSLYLTAFTVIGIRKAFDICPLVKIDTALIKADNFLLENTLPAQSTFTLAISAYALSLGDK THPQFRSIVSALKREALVKGNPPIYRFWKDNLQHKDSSVPNTGTARMVETTAYALLTSLNLKDINYVNPVIKWLSEEQRY GGGFYSTQDTINAIEGLTEYSLLVKQLRLSMDIDVSYKHKGALHNYKMTDKNFLGRPVEVLLNDDLIVSTGFGSGLATVH VTTVVHKTSTSEEVCSFYLKIDTQDIEASHYRGYGNSDYKRIVACASYKPSREESSSGSSHAVMDISLPTGISANEEDLK ALVEGVDQLFTDYQIKDGHVILQLNSIPSSDFLCVRFRIFELFEVGFLSPATFTVYEYHRPDKQCTMFYSTSNIKIQKVC EGAACKCVEADCGQMQEELDLTISAETRKQTACKPEIAYAYKVSITSITVENVFVKYKATLLDIYKTGEAVAEKDSEITF IKKVTCTNAELVKGRQYLIMGKEALQIKYNFSFRYIYPLDSLTWIEYWPRDTTCSSCQAFLANLDEFAEDIFLNGC	
PSI0332	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDRQPEQSSELLSEAKKLNDSQAPKVDGSLAEAKEAANAELDSYGVSDFYKRLIDKAKTV EGVEALKDAILAALP	252
PSI0334	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDDDPSQSSELLSEAKKLSESQAPKVDGSLAEAKEAANAELDSYGVSDFYKRLIDKAKTV EGVEALKDAILAALP	253
PSI0335	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDDDPSQSSELLSEAKKLNDSQAPKVDGSLAEAKVLANRELDKYGVSDFYKRLINKAKTV EGVEALKLHILAALP	254
PSI0336	AEAKYAKEVLEAWSEIDRLPNLTIEQWLAFINKLDDDPSQSSELLSEAKKLNDSQAPKVDGSLAEAKEAANAELDSYGVSDFYKRLIDKAKTV EGVEALKDAILAALP	255
PSI0337	AEAKYAKEVLEAWDEIERLPNLTIEQWLAFINKLDDDPSQSSELLSEAKKLNDSQAPKVDGSLAEAKEAANAELDSYGVSDFYKRLIDKAKTV EGVEALKDAILAALP	256
PSI0339	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFIAKLDDDPSQSSELLSEAKKLNDSQAPKVDGSLAEAKEAANAELDSYGVSDFYKRLIDKAKTV EGVEALKDAILAALP	257
PSI0340	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLEDDPSQSSELLSEAKKLNDSQAPKVDGSLAEAKEAANAELDSYGVSDFYKRLIDKAKTV EGVEALKDAILAALP	258
PSI0369	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDDDPSQSSELLSEAKKLNDSQAPLAEAKEAANAELDSYGVSDFYKRLIDKAKTVEGVEA LKDAILAALP	259
PSI0377	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDDDPSQSSELLSEAKKLSESQAP	260
PSI0378	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDDDPSQSSELLSEAKKLSESQAPKVEGSLAEAKEAANAELDSYGVSDFYKRLIDKAKTV EGVEALKDAILAALP	261
PSI0379	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDDDPSQSSELLSEAKKLSESQAPKVAGSLAEAKEAANAELDSYGVSDFYKRLIDKAKTV EGVEALKDAILAALP	262

Figure 7

PSI0381	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDDDPSQSSELLSEAKKLESSQAPKVEGSLAEAKEAANAELDSYGVSDFYKRLIDKAKTV EGVEALKDAILAALP	263
PSI0383	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDRQPEQSSELLSEAKKLSESQAPKVEGSLAEAKEAANAELDSYGVSDFYKRLIDKAKTV EGVEALKDAILAALP	264
PSI0389	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDDDPSQSSELLSEAKKLESSQAP	265
PSI0390	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDRQPEQSSELLSEAKKLSESQAP	266
PSI0400	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDDDPSQSSELLSEAKKLSESQAPK	267
PSI0410	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDDDPSQSSELLSEAKKLNDSQAPKVEGSLAEAKEAANAELDSYGVSDFYKRLIDKAKTV EGVEALKDAILAALP	268
PSI0403	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDDDPSQSSELLSEAKKLNESQAPKVEGSLAEAKEAANAELDSYGVSDFYKRLIDKAKTV EGVEALKDAILAALP	269
PSI0404	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDDDPSQSSELLSEAKKLSDSQAPKVEGSLAEAKEAANAELDSYGVSDFYKRLIDKAKTV EGVEALKDAILAALP	270
PSI0257	AEAKYAKEVLEAWDEIDRLPNLTIEQWLAFINKLDDDPSQSSELLSEAKKLNDSQAPKVDGS	271
Z02891	AEAKYAKEMRNAYWEIALLPNLTNQQKRAFIRKLYDDPSQSSELLSEAKKLNDSQAPK	272
Z17341	AEAKYAKEMRNAYWEIALLPNLTNQQKRAFIRKLYDDPSQSSELLSEAKKLSESQAPK	273
Z17342	AEAKYAKEMRNAYWEIALLPNLTNQQKRAFIRKLYRQPEQSSELLSEAKKLSESQAPK	274
Z15805	AEAKYAKELIEAAAEIDALPNLTRRQWNAFIKKLVDDPSQSSELLSEAKKLNDSQAPK	275
Z17343	AEAKYAKELIEAAAEIDALPNLTRRQWNAFIKKLVDDPSQSSELLSEAKKLSESQAPK	276
Z17344	AEAKYAKELIEAAAEIDALPNLTRRQWNAFIKKLVRQPEQSSELLSEAKKLSESQAPK	277
Z10103	AEAKYAKEQDAAAHEIRWLPNLTFDQRVAFIHKLADDPSQSSELLSEAKKLNDSQAPK	278
Z17347	AEAKYAKEQDAAAHEIRWLPNLTFDQRVAFIHKLADDPSQSSELLSEAKKLSESQAPK	279
Z17348	AEAKYAKEQDAAAHEIRWLPNLTFDQRVAFIHKLARQPEQSSELLSEAKKLSESQAPK	280
Z09782	AEAKYAKENLFAGWEISDLPNLTDYQRNAFIYKLWDDPSQSSELLSEAKKLNDSQAPK	281
Z17351	AEAKYAKENLFAGWEISDLPNLTDYQRNAFIYKLWDDPSQSSELLSEAKKLSESQAPK	282
Z17352	AEAKYAKENLFAGWEISDLPNLTDYQRNAFIYKLWRQPEQSSELLSEAKKLSESQAPK	283
Z17355	AEAKYAKENLFAGWEISDLPNLTDYQRNAFIYKLWDDPSQSSELLSEAKKLNESQAPK	284

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Z17357	AEAKYAKENLFAGWEISDLPNLTDYQRNAFIYKLWRQPEQSSELLSEAKKLNESQAPK	285
Z17359	AEAKYAKENLFAGWEISDLPNLTDYQRNAFIYKLWDDPSQSSELLSEAKKLSDSQAPK	286
Z17360	AEAKYAKENLFAGWEISDLPNLTDYQRNAFIYKLWRQPEQSSELLSEAKKLSDSQAPK	287

Figure 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2014/068282

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

   a. (means)

   [ ] on paper

   [X] in electronic form

   b. (time)

   [X] in the international application as filed

   [ ] together with the international application in electronic form

   [ ] subsequently to this Authority for the purpose of search

2. [ ] In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/068282

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/00 C07K14/47
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS, Sequence Search, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 2012/004384 A2 (AFFIBODY AB [SE]; EKBLAD CAROLINE [SE]; ABRAHMSEN LARS [SE]) 12 January 2012 (2012-01-12) claims 37, 42, 44; sequence 163	13,14,22
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Y	WO 2009/077175 A1 (AFFIBODY AB [SE]; LINDBORG MALIN [SE]; GUNNERIUSSON ELIN [SE]; LENDEL) 25 June 2009 (2009-06-25) sequence 537	1-28

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 2014	07/01/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Lanzrein, Markus

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2014/068282

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X,P	WO 2013/126006 A1 (SWEDISH ORPHAN BIOVITRUM AB PUBL [SE]) 29 August 2013 (2013-08-29) cited in the application the whole document -----	1-28

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2014/068282

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