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[Continued on next page]

(54) Title: HUMAN M2E PEPTIDE IMMUNOGENS

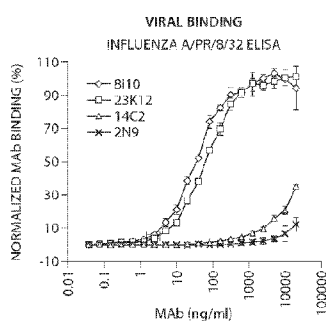


Fig. 2A

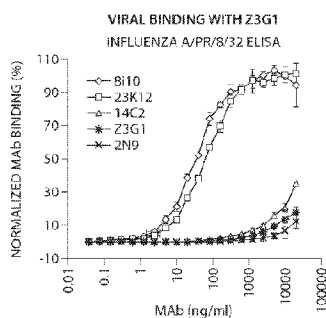


Fig. 2B

(57) Abstract: The present invention provides novel peptide immunogens comprising influenza virus matrix 2 protein epitopes and related compositions and methods. The present invention relates to a composition comprising a peptide immunogen useful for the prevention and treatment of an influenza virus-mediated disease. The invention also relates to vaccines, immunogenic products and immunogenic compositions containing the peptide immunogens.



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HUMAN M2e PEPTIDE IMMUNOGENS**RELATED APPLICATIONS**

[0001] This application is related to provisional application USSN 61/113,880, filed November 12, 2008, the contents of which are herein incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention relates generally to vaccines and therapeutics for influenza virus infection. The invention specifically relates to peptide immunogens suitable for generating influenza matrix 2 protein-specific antibodies and their manufacture and use.

BACKGROUND OF THE INVENTION

[0003] Influenza virus infects 5-20% of the population and results in 30,000-50,000 deaths each year in the U.S. Although the influenza vaccine is the primary method of infection prevention, four antiviral drugs are also available in the U.S.: amantadine, rimantadine, oseltamivir and zanamivir. As of December 2005, only oseltamivir (TAMIFLU™) is recommended for treatment of influenza A due to the increasing resistance of the virus to amantadine and rimantidine resulting from an amino acid substitution in the M2 protein of the virus. Recently, a drug resistant avian virus was found in a 14-year-girl in Viet Nam. Resistance to Tamiflu has also been found in human influenza as well (Mai Le et al., Nature 437:1108 (2005)).

[0004] Influenza vaccines have been demonstrated to have a protective effect against influenza infection. However, yearly emerging antigenic variants of influenza viruses necessitate surveillance to contemporary of circulating virus strains. In some cases, difficulty in the prediction of new variant strains has prevented the timely production of the vaccine (Frace et al., Vaccine 17:2237 (1999)). Recently, pandemic avian influenza has become a serious threat due to the emergence of avian influenza viruses such as H5N1 in southern Asia. The currently available vaccines would be ineffective against avian viruses (Lipatov et al., J. Virology 78:8951 (2004); Osterholm et al., N Engl. Med. 352:1839 (2005)). A third problem with the current vaccine is the ineffectiveness in certain populations with compromised immune systems, for instance premature infants, the elderly, AIDS and transplant patients.

[0005] Disease caused by influenza A viral infections is typified by its cyclical nature. Antigenic drift and shift allow for different A strains to emerge every year. Added to that, the

threat of highly pathogenic strains entering into the general population has stressed the need for novel therapies for flu infections.

SUMMARY OF THE INVENTION

[0006] The present invention relates to a synthetic peptide immunogen capable of inducing antibodies against a M2e target peptide of influenza A virus. In particular, the peptide immunogen of this invention comprises one or more epitopes. Optionally, the peptide immunogen further comprises a general immune stimulator. These peptide immunogens of the present invention are effective, capable of inducing antibodies against influenza A virus to prevent infection by the virus.

[0007] The peptide immunogen of this invention is represented by the following formula:

$[Xaa_0]_m-Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-[Xaa_6]_p-[Xaa_7]_q-[Xaa_8-[Xaa_0]_m-Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-[Xaa_6]_p-[Xaa_7]_q]_n$; wherein, m, p and q are independently 0 or 1, n is any number between 0 and 4, Xaa₀ is any amino acid, preferably C; Xaa₆ is any amino acid, preferably V or C; Xaa₇ is any amino acid, preferably E; Xaa₈ is any amino acid not including proline, preferably G or A; Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅- is S-L-L-T-E or, a peptide having a single substitution to the sequence S-L-L-T-E (SEQ ID NO: 47), the substitution selected from the group consisting of: Xaa₁ is C or T; Xaa₂ is A, C, F or K, Xaa₃ is A, C, E, F, I, K, M, Q, S, T or V, and Xaa₅ is D or C.

[0008] In another aspect the peptide immunogen of this invention is represented by the

following formula: $[Xaa_0]_m-Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-[Xaa_6]_p-[Xaa_7]_q-[Xaa_8-[Xaa_0]_m-Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-[Xaa_6]_p-[Xaa_7]_q]_n$; wherein, m, p and q are independently 0 or 1, n is any number between 0 and 4, Xaa₀ is any amino acid, preferably C; Xaa₆ is any amino acid, preferably V or C; Xaa₇ is any amino acid, preferably E; Xaa₈ is any amino acid not including proline, preferably G or A; Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅- is S-L-L-T-E or, a peptide having a single substitution to the sequence S-L-L-T-E (SEQ ID NO: 47), the substitution selected from the group consisting of: Xaa₁ is A, C, D, L, T or V, Xaa₂ is A, C, F, H, I, K, M, N, Q, R, T, W, or Y, Xaa₃ is any amino acid, Xaa₄ is M, N, Q, S, or W, and Xaa₅ is A, D, F, H, I, K, M, N, Q, S, W, Y, or C.

[0009] In some aspects of the inventions, one or more amino acids are D- amino acids.

[0010] In some aspects of the inventions, the peptide immunogens are cyclic. Cyclization of peptide immunogens can be performed by cross-linking cysteine residues present in the peptide or by chemical means.

[0011] In some aspects of the inventions, the peptide immunogens are conjugated to carrier proteins such as KLH through intermolecular crosslinking.

[0012] The invention relates to compositions comprising the peptide immunogen and a pharmaceutically acceptable adjuvant and/or carrier selected from the group consisting of alum, liposyn, saponin, squalene, L121, emulsion monophosphoryl lipid A (MPL), polysorbate 80, QS21, Montanide ISA51, ISA35, ISA206 and ISA 720.

[0013] The invention relates to preventing or treating a disease associated with influenza virus infection by administering compositions comprising the peptide immunogens of the invention.

[0014] The invention relates to methods for generating antibodies reactive to influenza matrix 2 (M2) protein by administering compositions comprising the peptide immunogens of the invention. It is an object of the invention to develop an immunogen that will enable the generation of high levels of high affinity antibodies against M2 protein.

[0015] One aspect of this invention provides a vaccine comprising an immunologically effective amount of a peptide immunogen composition in accordance with this invention and one or more pharmaceutically acceptable carriers. The vaccine when administered at an appropriate dosage will generate immunotherapeutic antibodies directed against influenza A virus.

[0016] The present invention provides a vaccine delivery vehicle that is suitable for human or veterinary use for the prophylaxis and treatment of influenza.

[0016a] Definitions of specific embodiments of the invention as claimed herein follow.

[0016b] According to a first embodiment of the invention, there is provided an isolated peptide immunogen comprising a sequence of:

$$[Xaa_0]_m-Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-[Xaa_6]_p-[Xaa_7]_q-[Xaa_8-[Xaa_0]_m-Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-[Xaa_6]_p-[Xaa_7]_q]_n$$

wherein:

m, p and q are independently 0 or 1;

n is any number between 1 and 4;

Xaa₀, Xaa₆, Xaa₇ and Xaa₈ are independently any amino acid; and

Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅ is S-L-L-T-E.

[0016c] According to a second embodiment of the invention, there is provided a vaccine composition comprising the isolated peptide immunogen of the first embodiment.

[0016d] According to a third embodiment of the invention, there is provided an immunogenic composition comprising the isolated peptide immunogen of the first embodiment and one or more pharmaceutically acceptable excipients, diluents and/or adjuvants.

[0016e] According to a fourth embodiment of the invention, there is provided a method of preventing or treating an influenza virus mediated disease by administering to a mammal the isolated peptide immunogen according to the first embodiment.

[0016f] According to a fifth embodiment of the invention, there is provided a method of preventing or treating an influenza virus mediated disease by administering to a mammal the vaccine composition according to the second embodiment.

[0016g] According to a sixth embodiment of the invention, there is provided a method of preventing or treating an influenza virus mediated disease by administering to a mammal the immunogenic composition according to the third embodiment.

[0016h] According to a seventh embodiment of the invention, there is provided a kit comprising the isolated peptide immunogen according to the first embodiment.

[0016i] The term “comprise” and variants of the term such as “comprises” or “comprising” are used herein to denote the inclusion of a stated integer or stated integers but not to exclude any other integer or any other integers, unless in the context or usage an exclusive interpretation of the term is required.

[0016j] Any reference to publications cited in this specification is not an admission that the disclosures constitute common general knowledge in Australia.

[0017] The present invention and other objects, features, and advantages of the present invention will become further apparent in the following Detailed Description of the invention and the accompanying figures and embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

[0018] Figure 1 shows the binding of three anti-M2 antibodies and control hul4C2 antibody to 293-HEK cells transfected with an M2 expression construct or control vector, in the presence or absence of free M2 peptide.

[0019] Figures 2A and 2B are graphs showing human monoclonal antibody binding to influenza A/PR/32.

[0020] Figure 3A is a chart showing amino acid sequences of extracellular domains of M2 variants.

[0021] Figures 3B and 3C are bar charts showing binding of human monoclonal anti-influenza antibody binding to M2 variants shown in Figure 3A.

[Text continues on page 4]

[0022] Figure 4 is a series of bar charts showing binding of MAbs 8I10 and 23K12 to M2 protein representing influenza strain A/HK/483/1997 sequence that was stably expressed in the CHO cell line DG44.

[0023] Figure 5 is an illustration showing the anti-M2 antibodies bind a highly conserved region in the N-Terminus of M2e.

[0024] Figures 6A and 6B are schematic diagrams that depict a core peptide immunogen and amino acid variants that are effective in binding anti-M2e huMAbs 8I10 and 23K12 under high (6A) and low (6B) stringency conditions.

[0025] Figure 6C is a schematic diagram that depicts variants of the core sequence.

[0026] Figures 6D, 6E and 6F are schematic diagrams that depict specific linear and cyclized peptide immunogens containing the core sequences of the invention.

DETAILED DESCRIPTION

[0027] The present invention relates to an immunogenic composition comprising synthetic peptide immunogens capable of inducing antibodies against the extracellular domain of the matrix 2 (M2) polypeptide of influenza A virus. The present invention provides peptides that bind human monoclonal antibodies specific against the extracellular domain of the matrix 2 (M2) polypeptide of influenza A virus.

[0028] The predominant fraction of neutralizing antibodies is directed to the polymorphic regions of the hemagglutinin and neuraminidase proteins. A third transmembrane protein of type A influenza virus, matrix protein 2 (M2), is abundantly expressed by virus-infected cells, where it is believed to provide an obligatory transmembrane proton flux for viral replication (Ciampor et al., *Virus Research* 22:247 (1992); Grambas and Hay, *Virology* 190:11 (1992); Sugrue et al., *EMBO J.* 9:3469 (1990)). Unlike HA and NA, M2 is conserved and may represent a target for the development of antibody-based passive immunotherapies for influenza patients (Ito et al., *J. Virology* 65:5491 (1991); Slepishkin et al., *Vaccine* 13:1399 (1995); Neirynck et al., *Nature Med.* 5:1157 (1999)). Thus, such a neutralizing MAb would presumably target only one or a few strains. A recent focus has been on the relatively invariant matrix 2 (M2) protein. Potentially, a neutralizing MAb to M2 would be an adequate therapy for all influenza A strains.

[0029] The M2 protein is found in a homotetramer that forms an ion channel and is thought to aid in the uncoating of the virus upon entering the cell. After infection, M2 can be found in abundance at the cell surface. It is subsequently incorporated into the virion coat, where it

only comprises about 2% of total coat protein. The M2 extracellular domain (M2e) is short, with the amino terminal 2-24 amino acids displayed outside of the cell.

[0030] Anti-M2 monoclonal antibodies to date have been directed towards this linear sequence. Thus, they may not exhibit desired binding properties to cellularly expressed M2, including conformational determinants on native M2.

[0031] Recent vaccine development has used immunogenic peptides conjugated to carrier proteins. However, carrier proteins are too complex for use in driving antibody responses to site-specific targets. The mass of the carrier molecule is much greater than that of the functionally important target peptide site. Consequently, the major immune response is directed to the carrier protein rather than to the target site of the peptide immunogen. Moreover, immunization with hapten-carrier conjugates frequently leads to carrier-induced immune suppression (Schutze et al., J Immunol, 1985, 135:2319). A disadvantage with the peptide-carrier protein conjugates is that these molecules are highly complex and are difficult to characterize and it is difficult to develop effective quality control procedures for the manufacturing process.

[0032] To be effective, a peptide immunogen must do more than merely evoke an anti-peptide response. An effective peptide immunogen must also evoke a functional immune response, i.e., the antibody produced must have immunological cross-reactivity to the authentic target. It is known that peptide immunogens generally do not retain a preferred structure. Therefore, it is important in designing a peptide target site to introduce structural constraints. However, the imposed structural constraint must be able to mimic the conformation of the targeted epitope so that antibodies evoked will be cross-reactivities to that site on the authentic molecule (Moore, Chapter 2 in Synthetic Peptides A User's guide, ed Grant, WH Freeman and Company: New York, 1992, pp 63-67). Peptide immunogens have been designed employing promiscuous Th epitopes, the invasin domain, and with imposed structural constraint for a peptide-based vaccine for HIV (U.S. Pat. No. 6,090,388).

[0033] A long-felt need exists in the art for new antibodies that bind to the cell-expressed M2 and conformational determinants on the native M2. Accordingly, a suitable peptide-based immunogen that mimic M2 is needed for generating vaccines and therapeutics against influenza virus. It would be desirable to provide a synthetic peptide immunogen that generates a site-specific immune response without epitopic suppression by undesirable T cell responses. The peptide-based anti-M2e immunogen should provoke an early and strong immune response in humans for protective immunity without the adverse carrier-induced immune suppression. The peptide immunogen should also be stable and well defined

chemically with no need of elaborate downstream processing for ease of manufacture and quality control to avoid the need of an elaborate production plant.

[0034] M2 is a 96 amino acid transmembrane protein present as a homotetramer on the surface of influenza virus and virally infected cells. M2 contains a 23 amino acid ectodomain (M2e) that is highly conserved across influenza A strains. Few amino acid changes have occurred since the 1918 pandemic strain thus M2e is an attractive target for influenza therapies. Peptides that incorporate immunogenic epitopes of M2e form a preferred aspect of the present invention.

[0035] Mimotopes which have the same characteristics as these epitopes, and immunogens comprising such mimotopes which generate an immune response which cross-react with the IgE epitope in the context of the IgE molecule, also form part of the present invention.

[0036] The present invention, therefore, includes isolated peptides encompassing these IgE epitopes themselves, and any mimotope thereof. The meaning of mimotope is defined as an entity which is sufficiently similar to the native M2e epitope so as to be capable of being recognized by antibodies which recognize the native M2e epitope; (Gheysen, H. M., et al., 1986, Synthetic peptides as antigens. Wiley, Chichester, Ciba foundation symposium 119, p130-149; Gheysen, H. M., 1986, Molecular Immunology, 23, 7, 709-715); or are capable of raising antibodies, when coupled to a suitable carrier, which antibodies cross-react with the native M2e epitope.

Monoclonal antibodies for screening M2e peptide immunogens

[0037] The antibodies used for screening the peptide immunogens are referred to herein as huM2e antibodies. Monoclonal antibodies used are specific to the M2 ectodomain (M2e) and derived from full-length M2 is expressed in cell lines. The huM2e antibodies bind conformational determinants on the M2-transfected cells, as well as native M2, either on influenza infected cells, or on the virus itself. The huM2e antibodies do not bind the linear M2e peptide, but they do bind several natural M2 variants expressed upon cDNA transfection into cell lines. The human monoclonal antibodies exhibit specificity for a very broad range of influenza A virus strains.

[0038] The huM2e antibodies have one or more of the following characteristics: the huM2e antibody binds a) to an epitope in the extracellular domain of the matrix 2 (M2) polypeptide of an influenza virus; b) binds to influenza A infected cells; and/or c) binds to influenza A virus (i.e., virions). The huM2e antibodies of the invention eliminate influenza infected cells through immune effector mechanisms such as ADCC and promotes direct viral clearance by binding to influenza virions. The huM2e antibodies of the invention bind to the amino-

terminal region of the M2e polypeptide. Preferably, the huM2e antibodies of the invention bind to the amino-terminal region of the M2e polypeptide wherein the N-terminal methionine residue is absent. Exemplary M2e sequences include those sequences listed on Table 1 below.

[0039] Table 1: Exemplary M2e sequences

Type	Name	Subtype	M2E Sequence	SEQ ID NO:
A	BREVI G MISSION.1.1918	H1N1	MSLLTEVETPTRNEWGCRCNDSSD	48
A	FORT MONMOUTH.1.1947	H1N1	MSLLTEVETPTKNEWGCRCNDSSD	49
A	.SINGAPORE.02.2005	H3N2	MSLLTEVETPIRNEWGCRCNDSSD	50
A	WISCONSIN.10.98	H1N1	MSLLTEVETPIRNGWECKCNDSSD	51
A	WISCONSIN.301.1976	H1N1	MSLLTEVETPIRSEWGCRCNDSSD	52
A	PANAMA.1.66	H2N2	MSFLPEVETPIRNEWGCRCNDSSD	53
A	NEW YORK.321.1999	H3N2	MSLLTEVETPIRNEWGCRCNDSSN	54
A	CARACAS.1.71	H3N2	MSLLTEVETPIRKEWGCRCNDSSD	55
A	TAIWAN.3.71	H3N2	MSFLTEVETPIRNEWGCRCNDSSD	56
A	WUHAN.359.95	H3N2	MSLPTEVETPIRSEWGCRCNDSSD	57
A	HONG KONG.1144.99	H3N2	MSLLPEVETPIRNEWGCRCNDSSD	58
A	HONG KONG.1180.99	H3N2	MSLLPEVETPIRNGWGCRCNDSSD	59
A	HONG KONG.1774.99	H3N2	MSLLTEVETPTRNGWECRCSSD	60
A	NEW YORK.217.02	H1N2	MSLLTEVETPIRNEWYRCNDSSD	61
A	NEW YORK.300.2003	H1N2	MSLLTEVETPIRNEWYRCSDSSD	62
A	SWINE.SPAIN.54008.2004	H3N2	MSLLTEVETPTRNGWECRYSDSSD	63
A	GUANGZHOU.333.99	H9N2	MSFLTEVETLTRNGWECRCSDSSD	64
A	HONG KONG.1073.99	H9N2	MSLLTEVETLTRNGWECKCRDSSD	65
A	HONG KONG.1.68	H3N2	MSLLTEVETPIRNEWGCRCNDSSD	66
A	SWINE.HONG KONG.126.1982	H3N2	MSLLTEVETPIRSEWGCRCNDSSD	67
A	NEW YORK.703.1995	H3N2	MSLLTEVETPIRNEWGCRCNGSSD	68
A	SWINE.QUEBEC.192.81	H1N1	MSLPTEVETPIRNEWGCRCNDSSD	69
A	PUERTO RICO.8.34	H1N1	MSLLTEVETPIRNEWGCRCNGSSD	70
A	HONG KONG.485.97	H5N1	MSLLTEVDTLTRNGWGCRCSDSSD	71
A	HONG KONG.542.97	H5N1	MSLLTEVETLTKNGWGCRCSDSSD	72
A	SILKY CHICKEN.SHANTOU.1826.2004	H9N2	MSLLTEVETPTRNGWECKCSDSSD	73
A	CHICKEN.TAIWAN.0305.04	H6N1	MSLLTEVETHTRNGWECKCSDSSD	74
A	QUAIL.ARKANSAS.16309-7.94	H7N3NSA	MSLLTEVKTPTRNGWECKCSDSSD	75
A	HONG KONG.486.97	H5N1	MSLLTEVETLTRNGWGCRCSDSSD	76
A	CHICKEN.PENNSYLVANIA.13552-1.98	H7N2NSB	MSLLTEVETPTRDGWECKCSDSSD	77
A	CHICKEN.HEILONGJIANG.48.01	H9N2	MSLLTEVETPTRNGWGCRCSDSSD	78
A	SWINE.KOREA.S5.2005	H1N2	MSLLTEVETPTRNGWECKCNDSSD	79

A	HONG KONG.1073.99	H9N2	MSLLTEVETLTRNGWECKCSDSSD	80
A	WISCONSIN.3523.88	H1N1	MSLLTEVETPIRNEWGCKCNDSSD	81
A	X-31 VACCINE STRAIN	H3N2	MSFLTEVETPIRNEWGCRCNGSSD	82
A	CHICKEN.ROSTOCK.8.1934	H7N1	MSLLTEVETPTRNGWECRCNDSSD	83
A	ENVIRONMENT.NEW YORK.16326-1.2005	H7N2	MSLLTEVETPIRKGWECNCSDSSD	84
A	INDONESIA.560H.2006	H5N1	MSLLTEVETPTRNEWECRCSDSSD	85
A	CHICKEN.HONG KONG.SF1.03	H9N2	MSLLTGVEVTHTRNGWGCKCSDSSD	86
A	CHICKEN.HONGKONG.YU427.03	H9N2	MSLLPEVETHTRNGWGCRCSDDSSD	87

[0040] In one embodiment, the peptide immunogens of the invention comprise a M2e peptide that wholly or partially includes the amino acid residues from position 2 to position 7 of M2e (SLLTEV). The huM2e antibodies bind wholly or partially to the amino acid sequence SLLTE (SEQ ID NO: 47) comprising the peptide immunogens of the invention.

[0041] Exemplary huM2e monoclonal antibodies that bind to the peptide immunogens are the 8I10, 21B15 and 23K12 antibodies described herein.

[0042] The 8I10 antibody includes a heavy chain variable region (SEQ ID NO: 88) encoded by the nucleic acid sequence shown below in SEQ ID NO: 89, and a light chain variable region (SEQ ID NO: 90) encoded by the nucleic acid sequence shown in SEQ ID NO: 91.

[0043] The amino acids encompassing the CDRs as defined by Chothia, C. et al. (1989, Nature, 342: 877-883) are underlined and those defined by Kabat E.A. et al. (1991, Sequences of Proteins of Immunological Interest, 5th edit., NIH Publication no. 91-3242 U.S. Department of Health and Human Services.) are highlighted in bold in the sequences below.

[0044] The heavy chain CDRs of the 8I10 antibody have the following sequences per Kabat definition: NYYWS (SEQ ID NO: 92), FIYYGGNTKYNPSLKS (SEQ ID NO: 93) and ASCSGGYCILD (SEQ ID NO: 94). The light chain CDRs of the 8I10 antibody have the following sequences per Kabat definition: RASQNIYKYLN (SEQ ID NO: 95), AA SGLQS (SEQ ID NO: 96) and QQSYSPPLT (SEQ ID NO: 97).

[0045] The heavy chain CDRs of the 8I10 antibody have the following sequences per Chothia definition: GSSISN (SEQ ID NO: 98), FIYYGGNTK (SEQ ID NO: 99) and ASCSGGYCILD (SEQ ID NO: 94). The light chain CDRs of the 8I10 antibody have the following sequences per Chothia definition: RASQNIYKYLN (SEQ ID NO: 95), AASGLQS (SEQ ID NO: 96) and QQSYSPPLT (SEQ ID NO: 97).

>8I10 VH nucleotide sequence: (SEQ ID NO: 89)

CAGGTGCAATTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCACCTGCACTGTCTCT
 GGTTCGTCCATCAGTAATTACTACTGGAGCTGGATCCGGCAGTCCCCAGGGAAGGGACTGGAGTGGATTGGGTTT
 ATCTATTACGGTGGAAACACCAAGTACAATCCCTCCCTCAAGAGCCGCGTCACCATATCACAAGACACTTCCAAG
 AGTCAGGTCTCCCTGACGATGAGCTCTGTGACCGCTGCGGAATCGGCCGTCTATTTCTGTGCGAGAGCGTCTTGT
 AGTGGTGGTTACTGTATCCTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCG

>8I10 VH amino acid sequence: (SEQ ID NO: 88)

Kabat Bold, Chothia underlined

Q	V	Q	L	Q	E	S	G	P	G	L	V	K	P	S	E	T	L	S	L	T	C	T	V	S
G	S	S	I	S	N	Y	Y	W	S	W	I	R	Q	S	P	G	K	G	L	E	W	I	G	F
I	Y	Y	G	G	N	T	K	Y	N	P	S	L	K	S	R	V	T	I	S	Q	D	T	S	K
S	Q	V	S	L	T	M	S	S	V	T	A	A	E	S	A	V	Y	F	C	A	R	A	S	C
S	G	G	Y	C	I	L	D	Y	W	G	Q	G	T	L	V	T	V	S						

>8I10 VL nucleotide sequence: (SEQ ID NO: 91)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGGGCG
 AGTCAGAACATTTACAAGTATTTAAATTGGTATCAGCAGAGACCAGGGAAAGCCCTAAGGGCCTGATCTCTGCT
 GCATCCGGGTTGCAAAGTGGGGTCCCATCAAGGTTCACTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATC
 ACCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACAGAGTTACAGTCCCCCTCTCACTTTTCGGCGGA
 GGGACCAGGGTGGAGATCAAAC

>8I10 VL amino acid sequence: (SEQ ID NO: 90)

Kabat Bold, Chothia underlined

D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A
S	Q	N	I	Y	K	Y	L	N	W	Y	Q	Q	R	P	G	K	A	P	K	G	L	I	S	A
A	S	G	L	Q	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I
T	S	L	Q	P	E	D	F	A	T	Y	Y	C	Q	Q	S	Y	S	P	P	L	T	F	G	G
G	T	R	V	E	I	K																		

[0046] The 21B15 antibody includes antibody includes a heavy chain variable region (SEQ ID NO: 100) encoded by the nucleic acid sequence shown below in SEQ ID NO: 101, and a light chain variable region (SEQ ID NO: 102) encoded by the nucleic acid sequence shown in SEQ ID NO: 103.

[0047] The amino acids encompassing the CDRs as defined by Chothia et al. 1989, are underlined and those defined by Kabat et al., 1991 are highlighted in bold in the sequences below.

[0048] The heavy chain CDRs of the 21B15 antibody have the following sequences per Kabat definition: NYYWS (SEQ ID NO: 92), FIYYGGNTKYNPSLKS (SEQ ID NO: 93) and ASCSGGYCILD (SEQ ID NO: 94). The light chain CDRs of the 21B15 antibody have the following sequences per Kabat definition: RASQNIYKYLN (SEQ ID NO: 95), AASGLQS (SEQ ID NO: 96) and QQSYSPPLT (SEQ ID NO: 97).

[0049] The heavy chain CDRs of the 21B15 antibody have the following sequences per Chothia definition: GSSISN (SEQ ID NO: 98), FIYYGGNTK (SEQ ID NO: 93) and ASCSGGYCILD (SEQ ID NO: 94). The light chain CDRs of the 21B15 antibody have the following sequences per Chothia definition: RASQNIYKYLN (SEQ ID NO: 95), AASGLQS (SEQ ID NO: 96) and QQSYSPPLT (SEQ ID NO: 97).

>21B15 VH nucleotide sequence: (SEQ ID NO: 101)

CAGGTGCAATTGCAGGAGTCGGGCCCAGGACTGGTGAAGCCTTCGGAGACCCTGTCCCTCACCTGCACTGTCTCT
GGTTCGTCCATCAGTAATTACTACTGGAGCTGGATCCGGCAGTCCCCAGGGAAGGGACTGGAGTGGATTGGGTTT
ATCTATTACGGTGGAAACACCAAGTACAATCCCTCCCTCAAGAGCCGCGTCACCATATCACAAGACACTTCCAAG
AGTCAGGTCTCCCTGACGATGAGCTCTGTGACCGCTGCGGAATCGGCCGTCTATTTCTGTGCGAGAGCGTCTTGT
AGTGGTGGTTACTGTATCCTTGACTACTGGGGCCAGGGAACCCTGGTCACCGTCTCG

>21B15 VH amino acid sequence: (SEQ ID NO: 100)

Kabat Bold, Chothia underlined

Q	V	Q	L	Q	E	S	G	P	G	L	V	K	P	S	E	T	L	S	L	T	C	T	V	S
G	S	S	I	S	N	Y	Y	W	S	W	I	R	Q	S	P	G	K	G	L	E	W	I	G	F
I	Y	Y	G	G	N	T	K	Y	N	P	S	L	K	S	R	V	T	I	S	Q	D	T	S	K
S	Q	V	S	L	T	M	S	S	V	T	A	A	E	S	A	V	Y	F	C	A	R	A	S	C
S	G	G	Y	C	I	L	D	Y	W	G	Q	G	T	L	V	T	V	S						

>21B15 VL nucleotide sequence: (SEQ ID NO: 103)

GACATCCAGGTGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGCGCG
AGTCAGAACATTTACAAGTATTTAAATTGGTATCAGCAGAGACCAGGGAAAGCCCCTAAGGGCCTGATCTCTGCT
GCATCCGGGTTGCAAAGTGGGGTCCCATCAAGTTTCACTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATC
ACCAGTCTGCAACCTGAAGATTTGCAACTTACTACTGTCAACAGAGTTACAGTCCCCCTCTCACTTTTCGGCGGA
GGGACCAGGTGGATATCAAAC

>21B15 VL amino acid sequence: (SEQ ID NO: 102)

Kabat Bold, Chothia underlined

D	I	Q	V	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	A
S	Q	N	I	Y	K	Y	L	N	W	Y	Q	Q	R	P	G	K	A	P	K	G	L	I	S	A
A	S	G	L	Q	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I
T	S	L	Q	P	E	D	F	A	T	Y	Y	C	Q	Q	S	Y	S	P	P	L	T	F	G	G
G	T	R	V	D	I	K																		

[0050] The 23K12 antibody includes antibody includes a heavy chain variable region (SEQ ID NO: 104) encoded by the nucleic acid sequence shown below in SEQ ID NO: 105, and a light chain variable region (SEQ ID NO: 106) encoded by the nucleic acid sequence shown in SEQ ID NO: 107.

[0051] The amino acids encompassing the CDRs as defined by Chothia et al., 1989 are underlined and those defined by Kabat et al., 1991 are highlighted in bold in the sequences below.

[0052] The heavy chain CDRs of the 23K12 antibody have the following sequences per Kabat definition: SNYMS (SEQ ID NO: 108), VIYSGGSTYYADSVK (SEQ ID NO: 109) and CLSRMRGYGLDV (SEQ ID NO: 110). The light chain CDRs of the 23K12 antibody have the following sequences per Kabat definition: RTSQSISSYLN (SEQ ID NO: 111), AASSLQSGVPSRF (SEQ ID NO: 112) and QQSYSMMPA (SEQ ID NO: 113).

[0053] The heavy chain CDRs of the 23K12 antibody have the following sequences per Chothia definition: GFTVSSN (SEQ ID NO: 114), VIYSGGSTY (SEQ ID NO: 115) and CLSRMRGYGLDV (SEQ ID NO: 110). The light chain CDRs of the 23K12 antibody have the following sequences per Chothia definition: RTSQSISSYLN (SEQ ID NO: 111), AASSLQSGVPSRF (SEQ ID NO: 112) and QQSYSMMPA (SEQ ID NO: 113).

>23K12 VH nucleotide sequence: (SEQ ID NO: 105)

GAGGTGCAGCTGGTGGAGTCTGGGGGAGGCTTGGTCCAGCCTGGGGGGTCCCTGAGAATCTCCTGTGCAGCCTCT
GGATTCACCGTCAGTAGCAACTACATGAGTTGGGTCCGCCAGGCTCCAGGGAAGGGGCTGGAGTGGGTCTCAGTT
ATTTATAGTGGTGGTAGCACATACTACGCAGACTCCGTGAAGGGCAGATTCTCCTTCTCCAGAGACAACTCCAAG
AACACAGTGTCTTCAAATGAACAGCCTGAGAGCCGAGGACACGGCTGTGTATTACTGTGCGAGATGTCTGAGC
AGGATGCGGGTTACGGTTTAGACGTCTGGGGCCAAGGGACACGGTCACCGTCTCG

>23K12 VH amino acid sequence: (SEQ ID NO: 104)

Kabat Bold, Chothia underlined

E	V	Q	L	V	E	S	G	G	G	L	V	Q	P	G	G	S	L	R	I	S	C	A	A	S
G	F	T	V	S	S	N	Y	M	S	W	V	R	Q	A	P	G	K	G	L	E	W	V	S	V
I	Y	S	G	G	S	T	Y	Y	A	D	S	V	K	G	R	F	S	F	S	R	D	N	S	K
N	T	V	F	L	Q	M	N	S	L	R	A	E	D	T	A	V	Y	Y	C	A	R	C	L	S
R	M	R	G	Y	G	L	D	V	W	G	Q	G	T	T	V	T	V	S						

>23K12 VL nucleotide sequence: (SEQ ID NO: 107)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTGCCGGACA
AGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCTAAACTCCTGATCTATGCT
GCATCCAGTTTGCAAAGTGGGGTCCCATCAAGTTTCACTGGCAGTGGATCTGGGACAGATTTCACTCTCACCATC
AGCGGTCTGCAACCTGAAGATTTTGCAACCTACTACTGTCAACAGAGTTACAGTATGCCTGCCTTTGGCCAGGG
ACCAAGCTGGAGATCAAA

>23K12 VL amino acid sequence: (SEQ ID NO: 106)

Kabat Bold, Chothia underlined

D	I	Q	M	T	Q	S	P	S	S	L	S	A	S	V	G	D	R	V	T	I	T	C	R	T
S	Q	S	I	S	S	Y	L	N	W	Y	Q	Q	K	P	G	K	A	P	K	L	L	I	Y	A
A	S	S	L	Q	S	G	V	P	S	R	F	S	G	S	G	S	G	T	D	F	T	L	T	I
S	G	L	Q	P	E	D	F	A	T	Y	Y	C	Q	Q	S	Y	S	M	P	A	F	G	Q	G
T	K	L	E	I	K																			

[0054] Unless otherwise defined, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary

skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures utilized in connection with, and techniques of, cell and tissue culture, molecular biology, and protein and oligo- or polynucleotide chemistry and hybridization described herein are those well known and commonly used in the art. Standard techniques are used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (*e.g.*, electroporation, lipofection). Enzymatic reactions and purification techniques are performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The practice of the present invention will employ, unless indicated specifically to the contrary, conventional methods of virology, immunology, microbiology, molecular biology and recombinant DNA techniques within the skill of the art, many of which are described below for the purpose of illustration. Such techniques are explained fully in the literature. See, *e.g.*, Sambrook, *et al.* Molecular Cloning: A Laboratory Manual (2nd Edition, 1989); Maniatis *et al.* Molecular Cloning: A Laboratory Manual (1982); DNA Cloning: A Practical Approach, vol. I & II (D. Glover, ed.); Oligonucleotide Synthesis (N. Gait, ed., 1984); Nucleic Acid Hybridization (B. Hames & S. Higgins, eds., 1985); Transcription and Translation (B. Hames & S. Higgins, eds., 1984); Animal Cell Culture (R. Freshney, ed., 1986); Perbal, A Practical Guide to Molecular Cloning (1984).

[0055] The nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

Definitions

[0056] The following definitions are useful in understanding the present invention:

[0057] The term “antibody” (Ab) as used herein includes monoclonal antibodies, polyclonal antibodies, multispecific antibodies (*e.g.*, bispecific antibodies), and antibody fragments, so long as they exhibit the desired biological activity. The term “immunoglobulin” (Ig) is used interchangeably with “antibody” herein.

[0058] An “isolated antibody” is one that has been separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody is purified: (1) to greater than 95% by weight of

antibody as determined by the Lowry method, and most preferably more than 99% by weight; (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator; or (3) to homogeneity by SDS-PAGE under reducing or non-reducing conditions using Coomassie blue or, preferably, silver stain.

Isolated antibody includes the antibody *in situ* within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

[0059] The basic four-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains. An IgM antibody consists of 5 of the basic heterotetramer unit along with an additional polypeptide called J chain, and therefore contain 10 antigen binding sites, while secreted IgA antibodies can polymerize to form polyvalent assemblages comprising 2-5 of the basic 4-chain units along with J chain. In the case of IgGs, the 4-chain unit is generally about 150,000 daltons. Each L chain is linked to an H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges. Each H chain has at the N-terminus, a variable domain (V_H) followed by three constant domains (C_H) for each of the α and γ chains and four C_H domains for μ and ϵ isotypes. Each L chain has at the N-terminus, a variable domain (V_L) followed by a constant domain (C_L) at its other end. The V_L is aligned with the V_H and the C_L is aligned with the first constant domain of the heavy chain (C_{H1}). Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The pairing of a V_H and V_L together forms a single antigen-binding site. For the structure and properties of the different classes of antibodies, see, *e.g.*, Basic and Clinical Immunology, 8th edition, Daniel P. Stites, Abba I. Terr and Tristram G. Parslow (eds.), Appleton & Lange, Norwalk, Conn., 1994, page 71, and Chapter 6.

[0060] The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino acid sequences of their constant domains (C_L). Depending on the amino acid sequence of the constant domain of their heavy chains (C_H), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated alpha (α), delta (δ), epsilon (ϵ), gamma (γ) and mu (μ), respectively. The γ and α classes are further divided into subclasses on the basis of relatively minor differences in C_H sequence and function, *e.g.*, humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.

[0061] The term “variable” refers to the fact that certain segments of the V domains differ extensively in sequence among antibodies. The V domain mediates antigen binding and defines specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the 110-amino acid span of the variable domains. Instead, the V regions consist of relatively invariant stretches called framework regions (FRs) of 15-30 amino acids separated by shorter regions of extreme variability called “hypervariable regions” that are each 9-12 amino acids long. The variable domains of native heavy and light chains each comprise four FRs, largely adopting a β -sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β -sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC).

[0062] The term “hypervariable region” when used herein refers to the amino acid residues of an antibody that are responsible for antigen binding. The hypervariable region generally comprises amino acid residues from a “complementarity determining region” or “CDR” (*e.g.*, around about residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the V_L , and around about 1-35 (H1), 50-65 (H2) and 95-102 (H3) in the V_H ; Kabat *et al.*, Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, Md. (1991)) and/or those residues from a “hypervariable loop” (*e.g.*, residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the V_L , and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the V_H ; Chothia and Lesk, J. Mol. Biol. 196:901-917 (1987)).

[0063] The term “monoclonal antibody” as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, *i.e.*, the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to polyclonal antibody preparations that include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they may be synthesized uncontaminated by other antibodies. The modifier “monoclonal” is not to be construed as

requiring production of the antibody by any particular method. For example, the monoclonal antibodies useful in the present invention may be prepared by the hybridoma methodology first described by Kohler *et al.*, *Nature*, 256:495 (1975), or may be made using recombinant DNA methods in bacterial, eukaryotic animal or plant cells (see, *e.g.*, U.S. Pat. No. 4,816,567). The “monoclonal antibodies” may also be isolated from phage antibody libraries using the techniques described in Clackson *et al.*, *Nature*, 352:624-628 (1991) and Marks *et al.*, *J. Mol. Biol.*, 222:581-597 (1991), for example.

[0064] The monoclonal antibodies herein include “chimeric” antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired biological activity (see U.S. Pat. No. 4,816,567; and Morrison *et al.*, *Proc. Natl. Acad. Sci. USA*, 81:6851-6855 (1984)). The present invention provides variable domainantigen-binding dequences derived from human antibodies. Accordingly, chimeric antibodies of primary interest hjerain include antibodies having one or more human antigen binding sequences (*e.g.*, CDRs) and containing one or more sequences derived from a non-human antibody, *e.g.*, an FR or C region sequence. In addition, chimeric antibodies of primary interest herein include those comprising a human variable domain antigen binding sequence of one antibody class or subclass and another sequence, *e.g.*, FR or C region sequence, derived from another antibody class or subclass. Chimeric antibodies of interest herein also include those containing variable domain antigen-binding sequences related to those described herein or derived from a different species, such as a non-human primate (*e.g.*, Old World Monkey, Ape, etc). Chimeric antibodies also include primatized and humanized antibodies.

[0065] Furthermore, chimeric antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. For further details, see Jones *et al.*, *Nature* 321:522-525 (1986); Riechmann *et al.*, *Nature* 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.* 2:593-596 (1992).

[0066] A “humanized antibody” is generally considered to be a human antibody that has one or more amino acid residues introduced into it from a source that is non-human. These non-human amino acid residues are often referred to as “import” residues, which are typically

taken from an “import” variable domain. Humanization is traditionally performed following the method of Winter and co-workers (Jones *et al.*, Nature, 321:522-525 (1986); Reichmann *et al.*, Nature, 332:323-327 (1988); Verhoeven *et al.*, Science, 239:1534-1536 (1988)), by substituting import hypervariable region sequences for the corresponding sequences of a human antibody. Accordingly, such “humanized” antibodies are chimeric antibodies (U.S. Pat. No. 4,816,567) wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species.

[0067] A “human antibody” is an antibody containing only sequences present in an antibody naturally produced by a human. However, as used herein, human antibodies may comprise residues or modifications not found in a naturally occurring human antibody, including those modifications and variant sequences described herein. These are typically made to further refine or enhance antibody performance.

[0068] An “intact” antibody is one that comprises an antigen-binding site as well as a C_L and at least heavy chain constant domains, C_H 1, C_H 2 and C_H 3. The constant domains may be native sequence constant domains (*e.g.*, human native sequence constant domains) or amino acid sequence variant thereof. Preferably, the intact antibody has one or more effector functions.

[0069] An “antibody fragment” comprises a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies (see U.S. Pat. No. 5,641,870; Zapata *et al.*, Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

[0070] The phrase “functional fragment or analog” of an antibody is a compound having qualitative biological activity in common with a full-length antibody. For example, a functional fragment or analog of an anti-IgE antibody is one that can bind to an IgE immunoglobulin in such a manner so as to prevent or substantially reduce the ability of such molecule from having the ability to bind to the high affinity receptor, Fc_εRI.

[0071] Papain digestion of antibodies produces two identical antigen-binding fragments, called “Fab” fragments, and a residual “Fc” fragment, a designation reflecting the ability to crystallize readily. The Fab fragment consists of an entire L chain along with the variable region domain of the H chain (V_H), and the first constant domain of one heavy chain (C_H 1). Each Fab fragment is monovalent with respect to antigen binding, *i.e.*, it has a single antigen-binding site. Pepsin treatment of an antibody yields a single large F(ab')₂ fragment that roughly corresponds to two disulfide linked Fab fragments having divalent antigen-binding

activity and is still capable of cross-linking antigen. Fab' fragments differ from Fab fragments by having additional few residues at the carboxy terminus of the C_H1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')₂ antibody fragments originally were produced as pairs of Fab' fragments that have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

[0072] The “Fc” fragment comprises the carboxy-terminal portions of both H chains held together by disulfides. The effector functions of antibodies are determined by sequences in the Fc region, which region is also the part recognized by Fc receptors (FcR) found on certain types of cells.

[0073] “Fv” is the minimum antibody fragment that contains a complete antigen-recognition and -binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable loops (three loops each from the H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

[0074] “Single-chain Fv” also abbreviated as “sFv” or “scFv” are antibody fragments that comprise the V_H and V_L antibody domains connected into a single polypeptide chain. Preferably, the sFv polypeptide further comprises a polypeptide linker between the V_H and V_L domains that enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in *The Pharmacology of Monoclonal Antibodies*, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994); Borrebaeck 1995, *infra*.

[0075] The term “diabodies” refers to small antibody fragments prepared by constructing sFv fragments (see preceding paragraph) with short linkers (about 5-10 residues) between the V_H and V_L domains such that inter-chain but not intra-chain pairing of the V domains is achieved, resulting in a bivalent fragment, *i.e.*, fragment having two antigen-binding sites. Bispecific diabodies are heterodimers of two “crossover” sFv fragments in which the V_H and V_L domains of the two antibodies are present on different polypeptide chains. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger *et al.*, *Proc. Natl. Acad. Sci. USA*, 90:6444-6448 (1993).

[0076] As used herein, an antibody that “internalizes” is one that is taken up by (*i.e.*, enters) the cell upon binding to an antigen on a mammalian cell (*e.g.*, a cell surface polypeptide or receptor). The internalizing antibody will of course include antibody fragments, human or chimeric antibody, and antibody conjugates. For certain therapeutic applications, internalization *in vivo* is contemplated. The number of antibody molecules internalized will be sufficient or adequate to kill a cell or inhibit its growth, especially an infected cell. Depending on the potency of the antibody or antibody conjugate, in some instances, the uptake of a single antibody molecule into the cell is sufficient to kill the target cell to which the antibody binds. For example, certain toxins are highly potent in killing such that internalization of one molecule of the toxin conjugated to the antibody is sufficient to kill the infected cell.

[0077] As used herein, an antibody is said to be “immunospecific,” “specific for” or to “specifically bind” an antigen if it reacts at a detectable level with the antigen, preferably with an affinity constant, K_a , of greater than or equal to about 10^4 M^{-1} , or greater than or equal to about 10^5 M^{-1} , greater than or equal to about 10^6 M^{-1} , greater than or equal to about 10^7 M^{-1} , or greater than or equal to 10^8 M^{-1} . Affinity of an antibody for its cognate antigen is also commonly expressed as a dissociation constant K_D , and in certain embodiments, HuM2e antibody specifically binds to M2e if it binds with a K_D of less than or equal to 10^{-4} M , less than or equal to about 10^{-5} M , less than or equal to about 10^{-6} M , less than or equal to 10^{-7} M , or less than or equal to 10^{-8} M . Affinities of antibodies can be readily determined using conventional techniques, for example, those described by Scatchard *et al.* (*Ann. N.Y. Acad. Sci. USA* 51:660 (1949)).

[0078] Binding properties of an antibody to antigens, cells or tissues thereof may generally be determined and assessed using immunodetection methods including, for example, immunofluorescence-based assays, such as immuno-histochemistry (IHC) and/or fluorescence-activated cell sorting (FACS).

[0079] An antibody having a “biological characteristic” of a designated antibody is one that possesses one or more of the biological characteristics of that antibody which distinguish it from other antibodies. For example, in certain embodiments, an antibody with a biological characteristic of a designated antibody will bind the same epitope as that bound by the designated antibody and/or have a common effector function as the designated antibody.

[0080] The term “antagonist” antibody is used in the broadest sense, and includes an antibody that partially or fully blocks, inhibits, or neutralizes a biological activity of an epitope, polypeptide, or cell that it specifically binds. Methods for identifying antagonist

antibodies may comprise contacting a polypeptide or cell specifically bound by a candidate antagonist antibody with the candidate antagonist antibody and measuring a detectable change in one or more biological activities normally associated with the polypeptide or cell.

[0081] An “antibody that inhibits the growth of infected cells” or a “growth inhibitory” antibody is one that binds to and results in measurable growth inhibition of infected cells expressing or capable of expressing an M2e epitope bound by an antibody. Preferred growth inhibitory antibodies inhibit growth of infected cells by greater than 20%, preferably from about 20% to about 50%, and even more preferably, by greater than 50% (*e.g.*, from about 50% to about 100%) as compared to the appropriate control, the control typically being infected cells not treated with the antibody being tested. Growth inhibition can be measured at an antibody concentration of about 0.1 to 30 µg/ml or about 0.5 nM to 200 nM in cell culture, where the growth inhibition is determined 1-10 days after exposure of the infected cells to the antibody. Growth inhibition of infected cells *in vivo* can be determined in various ways known in the art. The antibody is growth inhibitory *in vivo* if administration of the antibody at about 1 µg/kg to about 100 mg/kg body weight results in reduction the percent of infected cells or total number of infected cells within about 5 days to 3 months from the first administration of the antibody, preferably within about 5 to 30 days.

[0082] An antibody that “induces apoptosis” is one which induces programmed cell death as determined by binding of annexin V, fragmentation of DNA, cell shrinkage, dilation of endoplasmic reticulum, cell fragmentation, and/or formation of membrane vesicles (called apoptotic bodies). Preferably the cell is an infected cell. Various methods are available for evaluating the cellular events associated with apoptosis. For example, phosphatidyl serine (PS) translocation can be measured by annexin binding; DNA fragmentation can be evaluated through DNA laddering; and nuclear/chromatin condensation along with DNA fragmentation can be evaluated by any increase in hypodiploid cells. Preferably, the antibody that induces apoptosis is one that results in about 2 to 50 fold, preferably about 5 to 50 fold, and most preferably about 10 to 50 fold, induction of annexin binding relative to untreated cell in an annexin binding assay.

[0083] Antibody “effector functions” refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody, and vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (*e.g.*, B cell receptor); and B cell activation.

[0084] “Antibody-dependent cell-mediated cytotoxicity” or “ADCC” refers to a form of cytotoxicity in which secreted Ig bound to Fc receptors (FcRs) present on certain cytotoxic cells (*e.g.*, Natural Killer (NK) cells, neutrophils, and macrophages) enable these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. The antibodies “arm” the cytotoxic cells and are required for such killing. The primary cells for mediating ADCC, NK cells, express Fc γ RIII only, whereas monocytes express Fc γ RI, Fc γ RII and Fc γ RIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol* 9:457-92 (1991). To assess ADCC activity of a molecule of interest, an *in vitro* ADCC assay, such as that described in U.S. Pat. No. 5,500,362 or U.S. Pat. No. 5,821,337 may be performed. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, *e.g.*, in a animal model such as that disclosed in Clynes *et al.*, *PNAS (USA)* 95:652-656 (1998).

[0085] “Fc receptor” or “FcR” describes a receptor that binds to the Fc region of an antibody. In certain embodiments, the FcR is a native sequence human FcR. Moreover, a preferred FcR is one that binds an IgG antibody (a gamma receptor) and includes receptors of the Fc γ RI, Fc γ RII, and Fc γ RIII subclasses, including allelic variants and alternatively spliced forms of these receptors. Fc γ RII receptors include Fc γ RIIA (an “activating receptor”) and Fc γ RIIB (an “inhibiting receptor”), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor Fc γ RIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor Fc γ RIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain. (*see* review M. in Daeron, *Annu. Rev. Immunol.* 15:203-234 (1997)). FcRs are reviewed in Ravetch and Kinet, *Annu. Rev. Immunol* 9:457-92 (1991); Capel *et al.*, *Immunomethods* 4:25-34 (1994); and de Haas *et al.*, *J. Lab. Clin. Med.* 126:330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term “FcR” herein. The term also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer *et al.*, *J. Immunol.* 117:587 (1976) and Kim *et al.*, *J. Immunol.* 24:249 (1994)).

[0086] “Human effector cells” are leukocytes that express one or more FcRs and perform effector functions. Preferably, the cells express at least Fc γ RIII and perform ADCC effector function. Examples of human leukocytes that mediate ADCC include PBMC, NK cells,

monocytes, cytotoxic T cells and neutrophils; with PBMCs and NK cells being preferred. The effector cells may be isolated from a native source, *e.g.*, from blood.

[0087] “Complement dependent cytotoxicity” or “CDC” refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies (of the appropriate subclass) that are bound to their cognate antigen. To assess complement activation, a CDC assay, *e.g.*, as described in Gazzano-Santoro *et al.*, J. Immunol. Methods 202:163 (1996), may be performed.

[0088] The terms “influenza A” and “Influenzavirus A” refer to a genus of the Orthomyxoviridae family of viruses. Influenzavirus A includes only one species: influenza A virus which cause influenza in birds, humans, pigs, and horses. Strains of all subtypes of influenza A virus have been isolated from wild birds, although disease is uncommon. Some isolates of influenza A virus cause severe disease both in domestic poultry and, rarely, in humans.

[0089] A “mammal” for purposes of treating an infection, refers to any mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the mammal is human.

[0090] “Treating” or “treatment” or “alleviation” refers to both therapeutic treatment and prophylactic or preventative measures; wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented. A subject or mammal is successfully “treated” for an infection if, after receiving a therapeutic amount of an antibody according to the methods of the present invention, the patient shows observable and/or measurable reduction in or absence of one or more of the following: reduction in the number of infected cells or absence of the infected cells; reduction in the percent of total cells that are infected; and/or relief to some extent, one or more of the symptoms associated with the specific infection; reduced morbidity and mortality, and improvement in quality of life issues. The above parameters for assessing successful treatment and improvement in the disease are readily measurable by routine procedures familiar to a physician.

[0091] The term “therapeutically effective amount” refers to an amount of an antibody or a drug effective to “treat” a disease or disorder in a subject or mammal. See preceding definition of “treating.”

[0092] “Chronic” administration refers to administration of the agent(s) in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. “Intermittent” administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

[0093] Administration “in combination with” one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

[0094] “Carriers” as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers that are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN™ polycethylenc glycol (PEG), and PLURONICS™.

[0095] “Label” as used herein refers to a detectable compound or composition that is conjugated directly or indirectly to the antibody so as to generate a “labeled” antibody. The label may be detectable by itself (*e.g.*, radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition that is detectable.

[0096] The term “epitope tagged” as used herein refers to a chimeric polypeptide comprising a polypeptide fused to a “tag polypeptide.” The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide is also preferably fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

[0097] A “small molecule” is defined herein to have a molecular weight below about 500 Daltons.

[0098] The terms “nucleic acid” and “polynucleotide” are used interchangeably herein to refer to single- or double-stranded RNA, DNA, or mixed polymers. Polynucleotides may include genomic sequences, extra-genomic and plasmid sequences, and smaller engineered gene segments that express, or may be adapted to express polypeptides.

[0099] An “isolated nucleic acid” is a nucleic acid that is substantially separated from other genome DNA sequences as well as proteins or complexes such as ribosomes and polymerases, which naturally accompany a native sequence. The term embraces a nucleic acid sequence that has been removed from its naturally occurring environment, and includes recombinant or cloned DNA isolates and chemically synthesized analogues or analogues biologically synthesized by heterologous systems. A substantially pure nucleic acid includes isolated forms of the nucleic acid. Of course, this refers to the nucleic acid as originally isolated and does not exclude genes or sequences later added to the isolated nucleic acid by the hand of man.

[00100] The term “polypeptide” is used in its conventional meaning, *i.e.*, as a sequence of amino acids. The polypeptides are not limited to a specific length of the product. Peptides, oligopeptides, and proteins are included within the definition of polypeptide, and such terms may be used interchangeably herein unless specifically indicated otherwise. This term also does not refer to or exclude post-expression modifications of the polypeptide, for example, glycosylations, acetylations, phosphorylations and the like, as well as other modifications known in the art, both naturally occurring and non-naturally occurring. A polypeptide may be an entire protein, or a subsequence thereof. Particular polypeptides of interest in the context of this invention are amino acid subsequences comprising CDRs and being capable of binding an antigen or Influenza A-infected cell.

[00101] An “isolated polypeptide” is one that has been identified and separated and/or recovered from a component of its natural environment. In preferred embodiments, the isolated polypeptide will be purified (1) to greater than 95% by weight of polypeptide as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or non-reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes the polypeptide *in situ* within recombinant cells since at least one component of the polypeptide's natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

[00102] A “native sequence” polynucleotide is one that has the same nucleotide sequence as a polynucleotide derived from nature. A “native sequence” polypeptide is one that has the same amino acid sequence as a polypeptide (*e.g.*, antibody) derived from nature (*e.g.*, from any species). Such native sequence polynucleotides and polypeptides can be isolated from nature or can be produced by recombinant or synthetic means.

[00103] A polynucleotide “variant,” as the term is used herein, is a polynucleotide that typically differs from a polynucleotide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of the polynucleotide sequences of the invention and evaluating one or more biological activities of the encoded polypeptide as described herein and/or using any of a number of techniques well known in the art.

[00104] A polypeptide “variant,” as the term is used herein, is a polypeptide that typically differs from a polypeptide specifically disclosed herein in one or more substitutions, deletions, additions and/or insertions. Such variants may be naturally occurring or may be synthetically generated, for example, by modifying one or more of the above polypeptide sequences of the invention and evaluating one or more biological activities of the polypeptide as described herein and/or using any of a number of techniques well known in the art.

[00105] Modifications may be made in the structure of the polynucleotides and polypeptides of the present invention and still obtain a functional molecule that encodes a variant or derivative polypeptide with desirable characteristics. When it is desired to alter the amino acid sequence of a polypeptide to create an equivalent, or even an improved, variant or portion of a polypeptide of the invention, one skilled in the art will typically change one or more of the codons of the encoding DNA sequence.

[00106] For example, certain amino acids may be substituted for other amino acids in a protein structure without appreciable loss of its ability to bind other polypeptides (*e.g.*, antigens) or cells. Since it is the binding capacity and nature of a protein that defines that protein's biological functional activity, certain amino acid sequence substitutions can be made in a protein sequence, and, of course, its underlying DNA coding sequence, and nevertheless obtain a protein with like properties. It is thus contemplated that various changes may be made in the peptide sequences of the disclosed compositions, or corresponding DNA sequences that encode said peptides without appreciable loss of their biological utility or activity.

[00107] In many instances, a polypeptide variant will contain one or more conservative substitutions. A “conservative substitution” is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydrophobic nature of the polypeptide to be substantially unchanged.

[00108] In making such changes, the hydrophobic index of amino acids may be considered. The importance of the hydrophobic amino acid index in conferring interactive biologic function on a protein is generally understood in the art (Kyte and Doolittle, 1982). It is accepted that the relative hydrophobic character of the amino acid contributes to the secondary structure of the resultant protein, which in turn defines the interaction of the protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens, and the like. Each amino acid has been assigned a hydrophobic index on the basis of its hydrophobicity and charge characteristics (Kyte and Doolittle, 1982). These values are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (−0.4); threonine (−0.7); serine (−0.8); tryptophan (−0.9); tyrosine (−1.3); proline (−1.6); histidine (−3.2); glutamate (−3.5); glutamine (−3.5); aspartate (−3.5); asparagine (−3.5); lysine (−3.9); and arginine (−4.5).

[00109] It is known in the art that certain amino acids may be substituted by other amino acids having a similar hydrophobic index or score and still result in a protein with similar biological activity, *i.e.* still obtain a biological functionally equivalent protein. In making such changes, the substitution of amino acids whose hydrophobic indices are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred. It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity. U. S. Patent 4,554,101 states that the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with a biological property of the protein.

[00110] As detailed in U. S. Patent 4,554,101, the following hydrophilicity values have been assigned to amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 $\pm$ 1); glutamate (+3.0 $\pm$ 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (−0.4); proline (−0.5 $\pm$ 1); alanine (−0.5); histidine (−0.5); cysteine (−1.0); methionine (−1.3); valine (−1.5); leucine (−1.8); isoleucine (−1.8); tyrosine (−2.3); phenylalanine (−2.5); tryptophan (−3.4). It is understood that an amino acid can be substituted for another having a similar hydrophilicity value and still obtain a biologically

equivalent, and in particular, an immunologically equivalent protein. In such changes, the substitution of amino acids whose hydrophilicity values are within ± 2 is preferred, those within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

[00111] As outlined above, amino acid substitutions are generally therefore based on the relative similarity of the amino acid side-chain substituents, for example, their hydrophobicity, hydrophilicity, charge, size, and the like. Exemplary substitutions that take various of the foregoing characteristics into consideration are well known to those of skill in the art and include: arginine and lysine; glutamate and aspartate; serine and threonine; glutamine and asparagine; and valine, leucine and isoleucine.

[00112] Amino acid substitutions may further be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydrophobic nature of the polypeptide.

[00113] Polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein, which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (*e.g.*, poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

[00114] When comparing polynucleotide and polypeptide sequences, two sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence, as described below. Comparisons

between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A “comparison window” as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, 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.

[00115] Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) *Atlas of Protein Sequence and Structure*, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenies pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor* 11:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA* 80:726-730.

[00116] Alternatively, optimal alignment of sequences for comparison may be conducted by the local identity algorithm of Smith and Waterman (1981) *Add. APL. Math* 2:482, by the identity alignment algorithm of Needleman and Wunsch (1970) *J. Mol. Biol.* 48:443, by the search for similarity methods of Pearson and Lipman (1988) *Proc. Natl. Acad. Sci. USA* 85: 2444, by computerized implementations of these algorithms (GAP, BESTFIT, BLAST, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group (GCG), 575 Science Dr., Madison, WI), or by inspection.

[00117] One preferred example 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. (1977) *Nucl. Acids Res.* 25:3389-3402 and Altschul et al. (1990) *J. Mol. Biol.* 215:403-410, respectively. BLAST and BLAST 2.0 can be used, for example with the parameters described herein, to determine percent sequence identity for the

polynucleotides and polypeptides of the invention. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information.

[00118] In one illustrative example, cumulative scores can be 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). 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, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff and Henikoff (1989) *Proc. Natl. Acad. Sci. USA* 89:10915) alignments, (B) of 50, expectation (E) of 10, M=5, N=-4 and a comparison of both strands.

[00119] For amino acid sequences, a scoring matrix can be 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.

[00120] In one approach, the “percentage of sequence identity” is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residues occur in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

[00121] “Homology” refers to the percentage of residues in the polynucleotide or polypeptide sequence variant that are identical to the non-variant sequence after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent homology. In

particular embodiments, polynucleotide and polypeptide variants have at least 70%, at least 75%, at least 80%, at least 90%, at least 95%, at least 98%, or at least 99% polynucleotide or polypeptide homology with a polynucleotide or polypeptide described herein.

[00122] “Vector” includes shuttle and expression vectors. Typically, the plasmid construct will also include an origin of replication (e.g., the ColE1 origin of replication) and a selectable marker (e.g., ampicillin or tetracycline resistance), for replication and selection, respectively, of the plasmids in bacteria. An “expression vector” refers to a vector that contains the necessary control sequences or regulatory elements for expression of the antibodies including antibody fragment of the invention, in bacterial or eukaryotic cells. Suitable vectors are disclosed below.

[00123] As used in this specification and the appended claims, the singular forms “a,” “an” and “the” include plural references unless the content clearly dictates otherwise.

[00124] Preferred methods for determining mAb specificity and affinity by competitive inhibition can be found in Harlow, et al., *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1988), Colligan et al., eds., *Current Protocols in Immunology*, Greene Publishing Assoc. and Wiley Interscience, N.Y., (1992, 1993), and Muller, *Meth. Enzymol.* 92:589-601 (1983), which references are entirely incorporated herein by reference.

[00125] The techniques to raise antibodies of the present invention to small peptide sequences that recognize and bind to those sequences in the free or conjugated form or when presented as a native sequence in the context of a large protein are well known in the art. Such antibodies include murine, murine-human and human-human antibodies produced by hybridoma or recombinant techniques known in the art.

Screening peptide immunogens for specific binding to 8i10, or 23K12.

[00126] The present invention relates to peptide immunogens that bind HuM2c antibodies. In one embodiment, the antibody is an antibody designated herein as 8i10, 21B15, or 23K12. These antibodies are known to display preferential or specific binding to influenza A infected cells as compared to uninfected control cells of the same cell type.

[00127] In particular embodiments, the HuM2c antibodies bind to epitopes within M2e that are only present in the native conformation, i.e., as expressed in cells. In particular embodiments, these antibodies fail to specifically bind to an isolated M2e polypeptide, e.g., the 23 amino acid residue M2e fragment. It is understood that these antibodies recognize

non-linear (i.e. conformational) epitope(s) of the M2 peptide. M2 ectodomain (M2e) includes or consists of the amino acid sequence SLLTEVETPIRNEWGCRCNDSSD (SEQ ID NO: 326) and variants thereof (The Center for Disease Control (CDC) influenza A database at www.flu.lanl.gov/).

[00128] The specific conformational epitopes within the M2 protein, and particularly within M2e, were identified as peptide immunogens which can be used as vaccines to prevent the development of influenza infection within a subject.

[00129] The peptide immunogen sequences were identified by discontinuous epitope mapping using CLIPSTM (Chemically Linked Immunogenic Peptides on Scaffolds; PepScan) technology, which has been developed to improve the biological function of synthetic peptides. CLIPS uses small, chemical “scaffolds” onto which one or more peptides can be attached. In vaccine development, these are ideal for mapping conformational (or ‘discontinuous’) epitopes because they closely resemble the native structure of proteins.

[00130] Binding activity of anti-M2 antibodies to mutant M2 peptides was analyzed with an ELISA assay using different M2 peptides. Human anti-M2 antibody nos. Z3G1, 8I10 and 23K12 were used in the study. Peptides comprising M2e sequences were screened for the ability to specifically bind HuM2e antibodies 8I10 and 23K12 and distinguished from the ability to bind the anti-M2 human monoclonal antibody Z3G1 (ATCC Deposit No. PTA-5967) which has a broad M2 binding spectrum. 8I10 and 23K12 have been characterized for the ability to bind M2 and M2e under conditions resembling native conformation. The assays were performed at both 0.01 µg/mL and 0.001 µg/mL concentrations of peptides. At 0.01 µg/mL, signal levels of 1000 or greater were selected and at 0.001 µg/mL, signal levels of 300 or greater were selected as significant. Most peptides that bind strongly to 8I10 and 23K12 also bind Z3G1.

[00131] **Table 2:** Peptides that specifically bind for 23K21 and 8I10 (A numeral “1” in the peptide sequence indicates a differentially protected cystein allowing for selective CLIP attachment at certain residues)

SEQ ID NO:	Peptides that bind to 23K21 and 8I10	Signal
116	CLTEVETPIRNEWGSRCSLLTEVETPIRNEWGC	1922
117	CLLTEVETPIRNEWGSCSLLTEVETPIRC	1865
118	CSLLTEVETPIRNECSLLTEVETC	1829
119	CLTEVETPIRNEWGSRCSLLTEVETPIRNC	1825
120	CSLLTEVETPIRNCSSLLTEVETPIRC	1781
121	CSLLTEVETPIRCSLLTEVETPIRC	1767

122	CSLLTEVETPIRNEWCSLLTEVETC	1752
123	CSLLTEVETPIRNECLTEVETPIRNEWGSR	1702
124	CSLLTEVETPCSLLTEVETPIRC	1693
125	CTEVETPIRNEWGSRSCSLLTEVETPIRNEWGC	1659
126	CETPIRNEWGSRSDSCSLLTEVETPIRNC	1650
127	CSLLTEVETCSLLTEVETC	1647
128	CSLLTEVETCSLLTEVETPIC	1638
129	CSLLTEVETPIRNCSSLLTEVETPIRNC	1602
130	CSLLTEVETPIRNECSLLTEVETPIRC	1588
131	CSLLTEVETPIRCSLLTEVETPIRNC	1549
132	CVETPIRNEWGSRSDSCSLLTEVETPIC	1548
133	CSLLTEVETPIRNECSLLTEVETPIRNC	1534
134	CSLLTEVETCSLLTEVETPIRNC	1480
135	CSLLTEVETPIRNCSSLLTEVETPIRNEWC	1476
136	CLTEVETPIRNEWGSRSCSLLTEVETC	1470
137	CSLLTEVETPCSLLTEVETPIC	1458
138	CSLLTEVETPIRNEWGCCLLTEVETPIRNEWGSC	1456
139	CSLLTEVETPIRNCSSLLTEVETPIC	1449
140	CSLLTEVETPIRNEWGCSSLLTEVETPIRNEWGC	1434
141	CSLLTEVETPIRNEWCSLLTEVETPIRNEWGC	1427
142	CSLLTEVETCSLLTEVETPC	1424
143	CSLLTEVETPIRNEWGCSSLLTEVETPIRNC	1418
144	CSLLTEVETPIRNCSSLLTEVETPC	1405
145	CSLLTEVETPIRNECSLLTEVETPIC	1395
146	CSLLTEVETPIRNECSLLTEVETPIRNEWC	1394
147	CSLLTEVETPIRCSLLTEVETC	1388
148	CSLLTEVETPIRNCSSLLTEVETPIRNEWGC	1356
149	CTEVETPIRNEWGSRSCSLTEVETPIRNEWGSR	1348
150	CSLLTEVETCSLLTEVETPIRNEWC	1345
151	CSLLTEVETPIRCSLLTEVETPIC	1340
152	CSLLTEVETPIRNECSLLTEVETPIRNEWGC	1331
153	CSLLTEVETPCSLLTEVETPIRNC	1320
154	CETPIRNEWGSRSDSCSLLTEVETPIRNEC	1313
155	CSLLTEVETPIRNEWCSLLTEVETPIRC	1293
156	CSLLTEVETPCSLLTEVETPC	1286
157	CSLLTEVETPIRNEWGCSSLLTEVETPIRC	1278

158	CSLLTEVETPCSLLTEVETPIRNEWC	1269
159	CSLLTEVETPIRNEWGCVETPIRNEWGSRSDC	1241
160	CSLLTEVETPIRCLLTEVETPIRNEWGSC	1211
161	CPIRNEWGSRSDSSDCSLLTEVETC	1206
162	CLTEVETPIRNEWGSRCSLLTEVETPIRC	1203
163	CSLLTEVETCSLLTEVETPIRC	1200
164	CSLLTEVETPIRNECSLLTEVETPC	1194
165	CSLLTEVETPIRCSLLTEVETPIRNEC	1194
166	CSLLTEVETPIRNCSLLTEVETC	1192
167	CSLLTEVETPIRCSLLTEVETPIRNEWGC	1188
168	CVETPIRNEWGSRSDCSLLTEVETPIRC	1186
169	CTPIRNEWGSRSDSSCSLLTEVETPIRC	1180
170	CSLLTEVETPIRCLTEVETPIRNEWGSR	1175
171	CSLLTEVETCSLLTEVETPIRNEC	1172
172	CEVETPIRNEWGSRSDCSLLTEVETPIRC	1168
173	CSLLTEVETPIRCSLLTEVETPIRNEWC	1167
174	CSLLTEVETPIRNEWCSLLTEVETPIRNEWC	1165
175	CSLLTEVETPIRNEWGCLTEVETPIRNEWGSR	1148
176	CPIRNEWGSRSDSSDCSLLTEVETPIRC	1146
177	CSLLTEVETPIRNEWCSLLTEVETPIC	1144
178	CLLTEVETPIRNEWGSCSLLTEVETPIRNC	1141
179	CSLLTEVETCLLTEVETPIRNEWGSC	1141
180	CSLLTEVETPIRNEWCSLLTEVETPIRNC	1138
181	CSLLTEVETPIRCSLLTEVETPC	1115
182	CSLLTEVETPCLLTEVETPIRNEWGSC	1111
183	CSLLTEVETPIRNCSSLLTEVETPIRNEC	1110
184	CTEVETPIRNEWGSRSCSLLTEVETPIRC	1104
185	CTPIRNEWGSRSDSSCSLLTEVETPIRNC	1103
186	CSLLTEVETPCSLLTEVETPIRNEWGC	1103
187	CSLLTEVETPICSLLTEVETC	1089
188	CLTEVETPIRNEWGSRCSLLTEVETPIRNEWC	1079
189	CSLLTEVETPIRNEWCSLLTEVETPC	1074
190	CETPIRNEWGSRSDSCSLLTEVETPIRC	1069
191	CLTEVETPIRNEWGSRCSLLTEVETPIC	1040
192	CSLLTEVETPIRNCCLLTEVETPIRNEWGSC	1036
193	CSLLTEVETPCSLLTEVETPIRNEC	1032

194	CVETPIRNEWGSRSDCSLLTEVETPIRNC	1028
195	CSLLTEVETPIRNCCLTEVETPIRNEWGSRNC	1027
196	CEVETPIRNEWGSRSDCSLLTEVETPIRNC	1026
197	CSLLTEVETPIRNEWGCSLLTEVETPIC	1023
198	CSLLTEVETPCSLLTEVETC	1018
199	CSLLTEVETPIRNCCLTEVETPIRNEWGSRNC	1017
200	CSLLTEVETPIRNEWGCSLLTEVETC	1014
201	CEVETPIRNEWGSRSDCSLLTEVETC	1007
202	CPIRNEWGSRSDSDCSLLTEVETPIRNC	1004
203	CSLLTEVETPICSLLTEVETPIRNC	1001
204	CTEVETPIRNEWGSRSDCSLLTEVETPIRNC	1000
205	CLLTEVETPIRNEWGSCSLLTEVETPIRNEWGC	1000
206	CSLLTEVETPIRNEWGCSLLTEVETPIRNEC	994
207	CSLLTEVETPICSLLTEVETPC	986
208	CSLLTEVETPICSLLTEVETPIRNC	981
209	CSLLTEVETPIRNCCLTEVETPIRNEWGSRSD	980
210	CSLLTEVETPIRNCCLTEVETPIRNEWGSRNC	977
211	CSLLTEVETPICSLLTEVETPIRNEWC	975
212	CSLLTEVETPIRNEWGCSLLTEVETPIRNEWC	972
213	CETPIRNEWGSRSDCSLLTEVETC	971
214	CSLLTEVETPIRNEWCLLTEVETPIRNEWGSC	961
215	CSLLTEVETCLTEVETPIRNEWGSRNC	958
216	CTEVETPIRNEWGSRSDCSLLTEVETPIC	957
217	CSLLTEVETPIRNEWGCSLLTEVETPC	955
218	CLLTEVETPIRNEWGSCSLLTEVETPIRNEWC	922
219	CEVETPIRNEWGSRSDCSLLTEVETPIC	912
220	CSLLTEVETPIRNECCLLTEVETPIRNEC	910
221	CSLLTEVETPCCLTEVETPIRNEWGSRNC	907
222	CSLLTEVETPCCLTEVETPIRNEWGSRNC	907
223	CVETPIRNEWGSRSDCSLLTEVETC	905
224	CSLLTEVETPICLLTEVETPIRNEWGSC	901
225	CTEVETPIRNEWGSRSDCSLLTEVETPIRNEWC	900
226	CTEVETPIRNEWGSRSDCSLLTEVETC	891
227	CSLLTEVETPIRNECLLTEVETPIRNEWGSC	870
228	CLTEVETPIRNEWGSRSDCSLLTEVETPC	867
229	CEVETPIRNEWGSRSDCSLLTEVETPC	862

230	CTPIRNEWGSRSDSSCSLLTEVETC	861
231	CTPIRNEWGSRSDSSCSLLTEVETPIC	854
232	CETPIRNEWGSRSDSCSLLTEVETPC	842
233	CEVETPIRNEWGSRSNCSLLTEVETPIRNEWGC	838
234	CVETPIRNEWGSRSDCSLLTEVETPIRNEWC	837
235	CSLLTEVETPICL TEVETPIRNEWGSR	835
236	CSLLTEVETPICSLLTEVETPIRNEWGC	826
237	CETPIRNEWGSRSDSCSLLTEVETPIC	825
238	CEVETPIRNEWGSRSNCSLLTEVETPIRNEWC	825
239	CSLLTEVETCEVETPIRNEWGSRNC	821
240	CLTEVETPIRNEWGSRCSLLTEVETPIRNEC	817
241	CSLLTEVETPIRNEWCSLLTEVETPIRNEC	815
242	CVETPIRNEWGSRSDCSLLTEVETPC	814
243	CTPIRNEWGSRSDSSCSLLTEVETPIRNEWGC	812
244	CLLTEVETPIRNEWGSCSLLTEVETPIRNEC	808
245	CSLLTEVETPICSLLTEVETPIC	797
246	CTEVETPIRNEWGSRSCSLLTEVETPC	796
247	CTPIRNEWGSRSDSSCSLLTEVETPC	794
248	CPIRNEWGSRSDSSDCSLLTEVETPIRNEC	787
249	CPIRNEWGSRSDSSDCSLLTEVETPIRNEWC	786
250	CSLLTEVETCTEVETPIRNEWGSRSC	786
251	CETPIRNEWGSRSDSCSLLTEVETPIRNEWC	784
252	CLLTEVETPIRNEWGSCSLLTEVETPIC	762
253	CSLLTEVETPIRNC EVETPIRNEWGSRNC	761
254	CLLTEVETPIRNEWGSCSLLTEVETC	752
255	CETPIRNEWGSRSDSCSLLTEVETPIRNEWGC	749
256	CPIRNEWGSRSDSSDCSLLTEVETPIRNEWGC	742
257	CVETPIRNEWGSRSDCSLLTEVETPIRNEWGC	737
258	CSLLTEVETPIRNECTEVETPIRNEWGSRSC	736
259	CPIRNEWGSRSDSSDCSLLTEVETPC	733
260	CSLLTEVETPICEVETPIRNEWGSRNC	731
261	CTEVETPIRNEWGSRSCSLLTEVETPIRNEC	721
262	CSLLTEVETPIRNCVETPIRNEWGSRSDC	721
263	CSLLTEVETPIRNEWGCTEVETPIRNEWGSRSC	715
264	CSLLTEVETCVETPIRNEWGSRSDC	707
265	CSLLTEVETPCVETPIRNEWGSRSDC	704

266	CTPIRNEWGSRSDSSCSLLTEVETPIRNEC	699
267	CPIRNEWGSRSDSSDCSLLTEVETPIC	691
268	SLLTEVETPIRNECGCRCNDSSD	682
269	CVETPIRNEWGSRSDCSLLTEVETPIRNEC	679
270	CLLTEVETPIRNEWGSCSLLTEVETPC	678
271	CSLLTEVETPIRCVETPIRNEWGSRSDC	678
272	CTPIRNEWGSRSDSSCSLLTEVETPIRNEWC	677
273	CEVETPIRNEWGSRSDCSLLTEVETPIRNEC	669
274	CSLLTEVETPCEVETPIRNEWGSRSDC	650
275	CSLLTEVETPIRNEWGCEVETPIRNEWGSRSDC	607
276	CSLLTEVETPIRNECEVETPIRNEWGSRSDC	591
277	CSLLTEVETPIRNEWCTEVETPIRNEWGSRSC	575
278	CSLLTEVETPIRNEWCLTEVETPIRNEWGSRSC	561
279	CSLLTEVETPIRNECVETPIRNEWGSRSDC	538
280	CSLLTEVETPICTEVETPIRNEWGSRSC	526
281	CSLLTEVETCSLLTEVETPIRNEWGC	328
282	CSCLEVGMSCLCEC	2705
283	CSLLTEVGSLLTEV	2494
284	ASLLTEVGSLLTCTV	2443
285	MSLLTEVGMSLLTCTV	2389
286	CSLLTEVGMSLLTCTV	2311
287	MSLLTEVGMSLLTEV	2267
288	CSCLEVGMSLLTEV	2154
289	MSLCTEVGMSLCTEV	2153
290	CSLLTEVGSLLTCTV	2142
291	MSLLTEVGMCLCTCV	2110
292	CSLLTEVGSLLTEC	2094
293	CSLLTEVGMSLLTEV	2039
294	MSCLCEGMSLLTEV	2039
295	MSLCTEVGMSCLTEV	2026
296	MSLLTEVGMCLLTEV	2023
297	CSLLTEVGMCLCTCV	1972
298	SLCTEVGMSCLCEC	1967
299	SLLTEVGCLCTCV	1963
300	SLLTEVETKIRNEWGCRCDSSD	1960
301	SLLCEVGCSLLTEC	1959

302	ASLLTEVGSCLTEV	1944
303	CSLLTEVGMCLLTEV	1941
304	MSLCTEVGMSLLCEV	1935
305	CSCLCEVGMSSLLTEC	1925
306	CSLLTECGMSLLTCV	1918
307	SLCTEVGCLCTCV	1907
308	MSLCTEVGMCLCTCV	1902
309	CSLLTEVGMSSLLCEV	1891
310	MSCLCECGMSLLTEC	1887
311	SLLTEVGCLLTEV	1859
312	TLLTEVETPIRNEWGCRCNDSSD	1855
313	SLLTEVETPIRNEWGCRCNDSGD	1852
314	SLLTEVGSLLCEV	1834
315	MCLCTCVGCSLLTEC	1823
316	MSLLTEVGCSSLLTEV	1809
317	MSLLTEVGMSSLCTEV	1804
318	SLLTEVETPIRNEWGCRCNDSSD	1802
319	SLLTECGSLLTCV	1800
320	SLLTEVGSLLTEV	1794
321	ALLTEVETPIRNEWGCRCNDSSD	1794
322	SKLTEVETPIRNEWGCRCNDSSD	1784
323	SLCTEVGSLLTCV	1781
324	SLCTEVGSLLTEV	1772
325	SLLTECGSLLTEV	1770
326	SLLTEVETPIRNEWGCRCNDSSD	1749
327	SLMTEVETPIRNEWGCRCNDSSD	1729
328	SLETEVETPIRNEWGCRCNDSSD	1720
329	SLLTEVGSCLCEC	1708
330	SLLTEVETPIRNEWGCRCNDYSD	1694
331	MSLLTECGMSLLTCV	1690
332	SALTEVETPIRNEWGCRCNDSSD	1689
333	SLLTCVGSLLTEC	1683
334	CSLLTEVGMSSLCTEV	1682
335	CSCLCEVGCSSLLTEC	1677
336	SLLCEVGSLLTEV	1674
337	SLLTEVETPIRNEWGCRCNYSSD	1666

338	SLLTEVETPIRNEWGCRCNDGSD	1666
339	MSLLTECGMSLLTEV	1658
340	MSCLCECGCSLLTEC	1652
341	CSLLTEVCSLLTEC	1644
342	SLLTEVETPIRNEWGCRCNSSSD	1637
343	MSLLTEVGMSLLTEC	1630
344	SMLTEVETPIRNEWGCRCNDSSD	1622
345	CSLLTEVGSCLTEV	1616
346	SLLMEVETPIRNEWGCRCNDSSD	1616
347	SLLTEVETPIRNEWICRCNDSSD	1599
348	SLLTECGCSLLTEV	1597
349	SLATEVETPIRNEWGCRCNDSSD	1583
350	SLLTEVETPIRNEWGCRCNDSND	1577
351	SLLCEVGCSLLTEC	1564
352	SLQTEVETPIRNEWGCRCNDSSD	1561
353	SLLTEVGCSLLTEC	1556
354	SLLTEVGCSLLTEV	1555
355	SCLCECGCSLLTEV	1555
356	SLLTEVETPIRNEWGCRCNDSDD	1553
357	SLLTEVETPIRNEWGCRCNDSSD	1548
358	SFLTEVETPIRNEWGCRCNDSSD	1546
359	MSLLTEVGMSCLTEV	1535
360	CSLLTECGCSLLTEV	1534
361	SCLCECGCSLLTEC	1520
362	CSLLTECGMCLLTEV	1517
363	MSLLTECGCSLLTEV	1500
364	CSLLTEVGCSLLTEV	1499
365	CSLLTEVCMSSLLTEC	1498
366	SLLTEVETPIRNEWWCRCNDSSD	1498
367	SLCTEVGSLLTEC	1495
368	SLLTEVETPIRNEWG	1486
369	SLLTEAETPIRNEWGCRCNDSSD	1481
370	SLLTEVETPIRNEWGERCNDSSD	1474
371	MSLCTEVGMSLLTEV	1468
372	CSLLTEVGMSCLTEV	1466
373	CSLLTECGMSLLTEV	1458

374	SLLTECGCSLLTEC	1451
375	SLLTEVETPIRNEWGCRVNDSSD	1446
376	CSLLTECGMSLLTEC	1445
377	SLKTEVETPIRNEWGCRCNDSSD	1434
378	SLLTECGSLLTEC	1426
379	SLCTEVGCSCLEEV	1421
380	SLLTEVETPIRNTWGCRCNDSSD	1409
381	SLLQEVETPIRNEWGCRCNDSSD	1399
382	CSLLTECGSLLTEV	1393
383	CSLLTEVGCSSLLTEC	1380
384	SLLTEVETPIRNEYGCRCNDSSD	1377
385	CSLLTEVGCLCTCV	1375
386	SLLTEVETPIRNEVGCRCNDSSD	1371
387	SLLTEVETPIRTEWGCRCNDSSD	1365
388	CSLLTEVGCLLTEV	1351
389	SLLTEVETPYRNEWGCRCNDSSD	1350
390	CLLTEVGSLLTEV	1349
391	SNLTEVETPIRNEWGCRCNDSSD	1345
392	SLLTEVETPKRNEWGCRCNDSSD	1342
393	SLLTEVETPIRNEWGCRCNLSSD	1334
449	SLNTEVETPIRNEWGCRCNDSSD	1333
450	SLLTEVEHPIRNEWGCRCNDSSD	1331
451	CSLLTEVGMSLLTEC	1326
452	SLLTEVGSLLTEC	1326
453	SLLTEVETPIRNEAGCRCNDSSD	1311
454	SLLTEVETPIMNEWGCRCNDSSD	1308
455	CLCTCVGSLLTEC	1303
456	CSLLTECGMSLLCEV	1294
457	SLLTEVETPMRNEWGCRCNDSSD	1281
458	CSLLTECGSCLTEV	1278
459	SLITEVETPIRNEWGCRCNDSSD	1277
460	MSLLTECGMSLLCEV	1268
461	SLLTEVETPLRNEWGCRCNDSSD	1268
462	SLLTECGCLLTEV	1259
463	CSLLTECGSLLTCV	1258
464	SLLTEVGSCLTEV	1256

465	SLLTEVETPIRNEWGCRCNKSSD	1254
466	SCLTEVGCSLLTEV	1250
467	SLLTEVENPIRNEWGCRCNDSSD	1245
468	SCLCEGCSLLTEC	1244
469	MSLLTECGMSLLTEC	1236
470	MSLLTEVGCSLLTEC	1227
471	SLLTEEETPIRNEWGCRCNDSSD	1220
472	SLLTECGSLCTEV	1218
473	SLSTEVEVETPIRNEWGCRCNDSSD	1217
474	SLLTECETPIRNEWGCRCNDSSD	1214
475	MSLLTECGMSLCTEV	1212
476	CSLLTEVGCSCLCEV	1206
477	SLLTECGSLLCEV	1206
478	SLTTEVETPIRNEWGCRCNDSSD	1205
407	SLLTEVETPIRNEWGCRCNDHSD	1200
479	SLLTEDETPIRNEWGCRCNDSSD	1196
480	SLLTECGCLCTCV	1193
481	CSLLTECGMSLCTEV	1187
482	CLCTCVGSLLTEV	1178
483	CSLLTECGCSLLTEC	1177
484	SLVTEVETPIRNEWGCRCNDSSD	1175
485	CSLLTECGMCLCTCV	1168
486	SLFTEVETPIRNEWGCRCNDSSD	1156
487	SLLTNVETPIRNEWGCRCNDSSD	1142
394	SLLTEVETPIRNEWGCRCNMSSD	1133
488	SLLTEVETPIHNEWGCRCNDSSD	1112
489	MSLLTECGMCLLLEV	1111
490	SVLTEVETPIRNEWGCRCNDSSD	1109
491	SLLTEVETLIRNEWGCRCNDSSD	1109
492	MSLLTECGMCLCTCV	1107
493	SLLTEVETMIRNEWGCRCNDSSD	1104
494	SLLTEQETPIRNEWGCRCNDSSD	1102
495	SLLTEVETPGRNEWGCRCNDSSD	1097
496	SCLTEVGCSLLCEV	1095
436	SLLTEVETPI	1084
497	SLLTECGSCLCEC	1077

498	SLLTEMETPIRNEWGCRCNDSSD	1076
499	CSLLTEVGMSCCLCEC	1066
500	SCLTEVGSLLTEV	1066
501	SLLTEVETPIRNEWGCCNDSSD	1065
502	CSCCLCEVGSLLTEC	1064
503	SLLTEVETPIRNEWGCWCNDSSD	1061
504	SLLTEVETPIRNEWGFRNDSSD	1057
505	SLLTEKETPIRNEWGCRCNDSSD	1055
506	SLCTEVGSLLCEV	1050
507	SLCTEVETPIRNEWGCRCNDSSD	1050
508	MSLCTEVGCSLLTEV	1049
509	SLLTEVETPIYNEWGCRCNDSSD	1049
510	SLRTEVETPIRNEWGCRCNDSSD	1047
511	SLLCEVGCSSLLTEV	1044
512	SLLTEVETPIRNQWGCRCNDSSD	1039
513	MCLLTEVGMSSLLTEV	1032
514	SLLTEGETPIRNEWGCRCNDSSD	1029
515	SLLTEWETPIRNEWGCRCNDSSD	1025
516	SLLTEVETPIRNEWGCRCNDSSD	1024
517	SLLTEVETPIRNEMGCRCNDSSD	1020
518	SYLTEVETPIRNEWGCRCNDSSD	1019
519	SLLTEVETPIRNEWGCRSNDSSD	1016
520	VLLTEVETPIRNEWGCRCNDSSD	1014
437	SLLTEVETPIR	1012
521	SLLTAVETPIRNEWGCRCNDSSD	1012
522	SLLTMVETPIRNEWGCRCNDSSD	1011
523	SLLTEFETPIRNEWGCRCNDSSD	1009
524	SLLTEVETPIDNEWGCRCNDSSD	1001
401	SLLTEVETPIRNEWGCRCNWSSD	999
525	SLLTEVGCSCCLCEV	996
526	MSLLTECGMSCCLCEC	992
527	SLLTEVEQPIRNEWGCRCNDSSD	986
528	MSLLTCVGCSSLLTEV	978
529	SLLTEVETNIRNEWGCRCNDSSD	978
445	SLLTEVETPIRNEWGCRN	977
530	SLLTESETPIRNEWGCRCNDSSD	974

433	SLLTEVETPIRNEWGCRCNDSWD	971
531	MSLCTEVGMSLLTEC	970
532	MSCLTEVGMSLLTEV	968
533	CSLLTEVGSCLECEC	963
534	SLLTEVEKPIRNEWGCRCNDSSD	963
535	SLLTEVETPIRNEWGCRCNFSSD	963
408	SLLTEVETPIRNEWGCRCNDISD	962
536	MCLCTCVGCSLLTEV	954
537	SLLTEVEPPIRNEWGCRCNDSSD	953
538	LLLTEVETPIRNEWGCRCNDSSD	950
539	SLLTEYETPIRNEWGCRCNDSSD	950
422	SLLTEVETPIRNEWGCRCNDSFD	947
421	SLLTEVETPIRNEWGCRCNDSFD	944
540	SLLTEHETPIRNEWGCRCNDSSD	942
541	SLLTEVETPIRNEWKCRCNDSSD	932
418	SLLTEVETPIRNEWGCRCNDWSD	929
542	MSLCTEVGMSLLTCV	927
395	SLLTEVETPIRNEWGCRCNNSD	926
543	MSLLTCVGMSLLTEV	925
544	SLLTEVETPIRNEWGCRCRDSSD	924
545	SLLTEVSTPIRNEWGCRCNDSSD	923
546	SLLTEVETPIRNRWGCRCNDSSD	921
547	SLLTETETPIRNEWGCRCNDSSD	919
548	CSLLTECGSLCTEV	917
549	SLLTEVETFIRNEWGCRCNDSSD	916
550	SLLTENETPIRNEWGCRCNDSSD	914
551	SLLTEVATPIRNEWGCRCNDSSD	914
552	SLLTEVETPIRNEWGCYCNDSSD	913
553	SLLTEVTTPIRNEWGCRCNDSSD	909
554	CLLTEVGSLTTCV	902
555	SLLTEVETPIRNEWGCRCWDSSD	901
556	SLLTELETPIRNEWGCRCNDSSD	900
557	MSCLTEVGCSLLTEV	899
435	SLLTEVETP	899
409	SLLTEVETPIRNEWGCRCNDKSD	898
444	SLLTEVETPIRNEWGCRC	898

558	CSLLTECGMSCLCEC	897
559	SLLTEVETAIRNEWGCRCNDSSD	895
560	SLLTEVETPIRNEWGCRCFDSSD	894
561	SCLTEVETPIRNEWGCRCNDSSD	892
562	SLLTEVETPIRNEWGCRCNDSSD	890
398	SLLTEVETPIRNEWGCRCNRSSD	890
563	SLLTEVETPIRNEWGGRCNDSSD	887
564	SLLTEVELPIRNEWGCRCNDSSD	886
565	SLLTEVETPIRVEWGCRCNDSSD	884
566	SLLTEVCTPIRNEWGCRCNDSSD	881
567	SLLTECGCSCLCEV	879
568	SLLTEVETPIRNEWGCRCQDSSD	877
569	SLLTEVETPIRNEWLCRCNDSSD	876
570	MCLLTEVGCSSLTEV	875
571	SLLTEVETPIRNLWGCRCNDSSD	870
572	SLLTEVETPIRNEKGCRCNDSSD	868
573	SLLTEVETPIRNEWGCRTNDSSD	867
574	CLLTEVGSSLTEC	866
575	SLLTEVRTPIRNEWGCRCNDSSD	866
400	SLLTEVETPIRNEWGCRCNVSSD	865
443	SLLTEVETPIRNEWGCR	864
576	SLLTEVETPIFNEWGCRCNDSSD	862
577	SLLTEVETPIRNIWGCRCNDSSD	862
434	SLLTEVETPIRNEWGCRCNDSYD	862
415	SLLTEVETPIRNEWGCRCNDRSD	860
578	SLLTERETPIRNEWGCRCNDSSD	859
579	SLLTEVETPIRNEWGCRWNDSSD	859
580	SLCTEVGCSSLTEV	858
581	SLLTEVETYIRNEWGCRCNDSSD	857
582	SLLTEVETPIRAEWGCRCNDSSD	856
583	SLLTEVWTPIRNEWGCRCNDSSD	855
584	SLLTEVETPIRNEWGCRRNDSSD	855
585	SLLTEVETPIRLEWGCRCNDSSD	853
586	SLLTEVETPIRNEWGCRCNISSD	851
587	SLLTEVETPIRCEWGCRCNDSSD	850
396	SLLTEVETPIRNEWGCRCNPSSD	849

588	SLLTEVETPIRNEWGCRCNCSSD	848
589	CSLLTECGMSCLTEV	846
590	SLLTEVEMPIRNEWGCRCNDSSD	845
591	SLLTEVETPIRNEWGCRCNDSSD	844
397	SLLTEVETPIRNEWGCRCNQSSD	842
592	MSLCTEVGCSLLTEC	840
593	SLLTEVEIPIRNEWGCRCNDSSD	839
594	SLLTEVQTPIRNEWGCRCNDSSD	838
595	SLLTEVETPIRNEWGWRCNDSSD	838
596	SLLTEVETPIRNEWFCRCNDSSD	837
597	SLLTEVETGIRNEWGCRCNDSSD	835
598	SLLTEVETPIRNEWGCRKNDSSD	835
599	SLLTEVERPIRNEWGCRCNDSSD	834
430	SLLTEVETPIRNEWGCRCNDSRD	833
448	SLLTEVETPIRNEWGCRCNDSS	833
600	SLLTEVETPIRNEWGLRCNDSSD	831
601	SLLTECGSCLTEV	830
602	SLLTEVETEIRNEWGCRCNDSSD	828
603	SLLTEVETPIRNEWGCRCNGSSD	828
604	SLCTEVGCSCLTEV	824
605	SLLTEVETPIRNMWGCRCNDSSD	820
606	SLLTEVETQIRNEWGCRCNDSSD	819
607	SLLTEVESPIRNEWGCRCNDSSD	817
447	SLLTEVETPIRNEWGCRCNDS	817
608	SLLTEIETPIRNEWGCRCNDSSD	816
609	SLLTEVETHIRNEWGCRCNDSSD	816
610	SLLTEVETDIRNEWGCRCNDSSD	813
611	SLLTEVETRIRNEWGCRCNDSSD	813
612	SLLTEVETPIRNEWGCRCIDSSD	812
613	SLLTEVETPIRNEWGCRCNHSSD	812
614	SLLTEVETVIRNEWGCRCNDSSD	810
615	SLLTEVETPIRNEWGCDNDSSD	810
616	SLLTEVETPIRNPWGCRCNDSSD	808
617	SLLTEVETPIRNSWGCRCNDSSD	807
618	SLLTEVETPIRNEWGCRCLDSSD	807
619	SLLTEVETPIRNEWGCRCNASSD	807

620	SLLTEVETPIRFEWGCRCNDSSD	806
621	SLLTEVEFPIRNEWGCRCNDSSD	805
622	SLLTEVETPIRMEWGCRCNDSSD	805
623	SLLTEVETCIRNEWGCRCNDSSD	800
624	SLLTEVETPIRNEWVCRCNDSSD	799
413	SLLTEVETPIRNEWGCRCNDPSD	797
399	SLLTEVETPIRNEWGCRCNTSSD	795
625	SLLTEVETPIRNEWYCRCNDSSD	794
416	SLLTEVETPIRNEWGCRCNDTSD	794
626	SLLTEVETPIRNEWGCRCYDSSD	791
627	SLLTEVETPIRIEWGCRCNDSSD	789
406	SLLTEVETPIRNEWGCRCNDFSD	788
628	SLLTEVETPIRNEWGCRCMDSSD	786
629	SLLTEVMTPIRNEWGCRCNDSSD	783
630	SLLTEVETPERNEWGCRCNDSSD	783
631	SLLTEVETPIRKEWGCRCNDSSD	782
423	SLLTEVETPIRNEWGCRCNDSHD	782
426	SLLTEVETPIRNEWGCRCNDSLD	779
632	SLLTEVETPIRNEWGCRCVDSSD	775
633	SLLTEVETPIRNEWHCRCNDSSD	772
403	SLLTEVETPIRNEWGCRCNDCSD	772
417	SLLTEVETPIRNEWGCRCNDVSD	772
428	SLLTEVETPIRNEWGCRCNDSPD	772
634	SLLTEVETPIRNEWGCRANDSSD	770
425	SLLTEVETPIRNEWGCRCNDSKD	770
635	SLLTEVEAPIRNEWGCRCNDSSD	769
410	SLLTEVETPIRNEWGCRCNDLSD	769
636	SLLTEVETPIRNEIGCRCNDSSD	768
637	SLLTEVETPIRNENGRCRCNDSSD	768
638	SLLTEVETPIRNEWGTRCNDSSD	767
639	SLLTEVETPIRNEWGCFCNDSSD	767
640	SLLTEVETPIRNKWGCRCNDSSD	765
641	SLLTEVETPIRNELGCRCNDSSD	765
642	SLLTEVETPIRNEWMCRCNDSSD	765
643	SLLTEVETPIRNGWGCRCNDSSD	764
644	SLLTEVETPIRNEWGVRCNDSSD	764

645	SLLTEVVTPIRNEWGCRCNDSSD	763
646	SLLTEVEGPIRNEWGCRCNDSSD	763
647	SLLTEVETPIRNEWGHRCNDSSD	763
648	SLLTEVETPIRNEWGKRCNDSSD	762
649	SLLTEVETPIRNEWGCRCNDSSD	760
650	SLLTEVETPVRNEWGCRCNDSSD	758
651	SLLTEVETPIRNEWGCRCHDSSD	758
652	SLLTEVEEPIRNEWGCRCNDSSD	757
653	SLLTEVETIIRNEWGCRCNDSSD	756
654	SLLTEVETPIRYEWGCRCNDSSD	755
655	SLYTEVETPIRNEWGCRCNDSSD	753
656	SLLTEVETPIWNEWGCRCNDSSD	753
657	SLLTEVDTPIRNEWGCRCNDSSD	751
658	SLLTEVYTPIRNEWGCRCNDSSD	751
438	SLLTEVETPIRN	751
659	SLLTEVETPIRNEWGARCNDSSD	750
440	SLLTEVETPIRNEW	750
660	SLLTEVETPDRNEWGCRCNDSSD	749
661	SLLTEVETPIRQEWGCRCNDSSD	748
662	SLLTEVETPIRNFWGCRCNDSSD	747
663	MCLCTCVGMSLLTEV	746
664	SLLTEVETPIRNEWGNRCNDSSD	746
665	SLLTEVETPFRNEWGCRCNDSSD	745
411	SLLTEVETPIRNEWGCRCNDMSD	744
666	SLLTEVETPIRNAWGCRCNDSSD	743
667	SLLTEVETPIRNEWGIRCNDSSD	739
668	SLLTEVETPIRNEWGYRCNDSSD	739
414	SLLTEVETPIRNEWGCRCNDQSD	739
669	SLLTEVETPIRNEWTIRCNDSSD	738
446	SLLTEVETPIRNEWGCRCND	738
670	SLLTEVETWIRNEWGCRCNDSSD	736
671	SLLTEVETPIRNEPGCRCNDSSD	735
672	SLLTEVETPIRNEWGRRCDSSD	735
673	SLLTEVETPSRNEWGCRCNDSSD	733
674	SLLTEVETPIRNEWGCRCNDSSD	733
675	SLLTEVNTPIRNEWGCRCNDSSD	732

676	SLLTEVETPIENEWGCRCNDSSD	731
677	SLLTEVETPIQNEWGCRCNDSSD	731
678	SLLTEVETPIRSEWGCRCNDSSD	730
679	SLLTEVETPIRNEWGCECNDSSD	730
680	SLLTEVETPIVNEWGCRCNDSSD	729
681	SLLTEVETPIRNEWACRCNDSSD	729
682	SLLTEVETPIRNEWGSRCDSSD	729
683	SLLTEVETPIRNEWGCACNDSSD	729
684	SLLTEVETPIRNHWGCRCNDSSD	728
685	SLLTEVETPIRNVWGCRCNDSSD	728
686	SLLTEVETPIRNEWGCRLNDSSD	728
432	SLLTEVETPIRNEWGCRCNDSVD	728
420	SLLTEVETPIRNEWGCRCNDSCD	725
687	SLLTEVETPCRNEWGCRCNDSSD	724
688	SLLTEVETPIRNETGCRCNDSSD	724
689	SLLTEVETPIRNEWGCRCGDSSD	724
690	SLLTEVHTPIRNEWGCRCNDSSD	722
691	SLLTEVETPIRNEWGCRMNDSSD	722
692	SLLTEVETPILNEWGCRCNDSSD	721
693	SLLTEVETPWRNEWGCRCNDSSD	720
694	SLLTEVETPIRNEWGCRCNESSD	720
695	SLLTEVEVPIRNEWGCRCNDSSD	719
696	SLLTEVETPIRNEHGCRCNDSSD	719
697	SLLTEVETPIRNEWGCRINDSSD	718
698	SLLTEVETPIRDEWGCRCNDSSD	716
699	SLLTEVETPIRNEWGCRYNDSSD	716
700	SLLTEVETSIRNEWGCRCNDSSD	715
701	SLLTEVETPIRNEWGCKCNDSSD	715
702	SLLTEVETPIRNYWGCRCNDSSD	714
703	SLLTEVETPIRNWWGCRCNDSSD	713
704	SLLTEVETPIRNEWRCRCNDSSD	713
705	SLLTEVKTPIRNEWGCRCNDSSD	712
706	SLLTEVETPIRNEWGCRCADSSD	712
707	SLLTEVETPIANEWGCRCNDSSD	708
708	SLLTEVETPIRNEGGCRCNDSSD	708
412	SLLTEVETPIRNEWGCRCNDNSD	708

709	SLLTEVLTPIRNEWGCRCNDSSD	707
710	SLLTEVETPIRREWGRCRCNDSSD	707
711	CSLLTEVGSLCTEV	707
712	SLLTEVETPIRNDWGCRCNDSSD	706
713	SLLTEVETPIRNEWQRCNDSSD	705
714	SLLTEVETPIRNEWCCRCNDSSD	704
715	SLLTEVETPARNEWGCRCNDSSD	702
716	SLLTEVETPIRNEFGCRCNDSSD	702
717	SLLTEVETPIRNEWDCRCNDSSD	701
431	SLLTEVETPIRNEWGCRCNDSTD	701
718	SLLTEVECPIRNEWGCRCNDSSD	700
719	SLLTEVETPIRNEWGCTCNDSSD	700
720	SLLTEVETPIINEWGRCRCNDSSD	699
721	SLLTEVETPIRHEWGRCRCNDSSD	699
722	SLLTEVETPIRNEWGCICNDSSD	699
723	SLLTEVETPIRNEWGCRFNDSSD	698
724	MCLLTEVGMSLLTEC	697
725	SLLTEVETPICNEWGCRCNDSSD	697
726	SLLTEVETPIRNEWECRCNDSSD	697
727	SLLTEVETPIRNEWGPCNDSSD	696
728	SLLTEVETPIRNEWGCRCCDSSD	696
729	SLLTEVETPIRNEWGCRCSDSSD	696
730	SLLTEVETPIRNEWGCMCNDSSD	695
429	SLLTEVETPIRNEWGCRCNDSQD	695
731	SLLTEVFTPIRNEWGCRCNDSSD	694
732	SLLTEVETPIRNEWGMRCNDSSD	693
733	SLLTEVETPIRNCWGCRCNDSSD	692
734	SLLTEVETPIRNEWGCRHNDSSD	692
424	SLLTEVETPIRNEWGCRCNDSID	692
735	SLLTEVETPIRNEWSRCRCNDSSD	691
736	SLLTEVETPIRNEWGCSCNDSSD	691
737	SLLTEVETPIRNERGCRCNDSSD	690
738	SLLTEVETPPRNEWGCRCNDSSD	689
739	SLLTEVETPIRNEWGCRCECDSSD	687
740	SHLTEVETPIRNEWGCRCNDSSD	686
741	SLLTEVETPIRNNWGCRCNDSSD	686

742	SLLTEVETPIRNEWGVCNDSSD	684
404	SLLTEVETPIRNEWGCRCNDSSD	684
743	SLLTEVETPIRNEWGCNCNDSSD	683
402	SLLTEVETPIRNEWGCRCNDASD	683
744	SLLTEVETPIRNEWGCRCNDSSD	681
745	SLLTEVETPIRNEWGCRCNDSSD	681
746	SLLTEVETPIRNEWGCRCNDSSD	681
747	SLCTEVGCSLLTEC	680
748	SLLTEVETPIRNEWGCLCNDSSD	680
442	SLLTEVETPIRNEWGC	680
749	MSLLCEVGMSLLTEV	677
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405	SLLTEVETPIRNEWGCRCNDESD	676
751	SLLTEVETPIRNEWGCRCNDSSD	675
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755	SLLTQVETPIRNEWGCRCNDSSD	671
756	SLLTEVETPIRNEWGCRCNDSSD	671
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427	SLLTEVETPIRNEWGCRCNDSSD	668
759	SLHTEVETPIRNEWGCRCNDSSD	667
760	SLLTEVETPIRNEWGCRCNDSSD	667
761	MSLLTEVGCSCLEEV	663
762	SLLTEVETPIRNEWGCRCNDSSD	662
763	SLLTEVETPIRNEWGCRCNDSSD	660
764	SLLTEVETPIRNEWGCRCNDSSD	659
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767	SLLTEVETPIRNEWGCRCNDSSD	653
768	MSCLTEVGMSLLTEC	650
769	MCLLTEVGCSLLTEC	650
770	SLLTEVETPIRNEWGCRCNDSSD	649
771	SLLTEVETPIRNEWGCRCNDSSD	648
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773	SLLTEVETPIRGEWGCRCNDSSD	644
774	SLLTEVETPIRNEWPCRCNDSSD	644
775	SLLTEVETPIRNEWGCGCNDSSD	644
776	SLLTEVETPIRNEWGCHCNDSSD	640
777	SLLTEVPTPIRNEWGCRCNDSSD	639
419	SLLTEVETPIRNEWGCRCNDSAD	639
778	SLLTEVETPIKNEWGCRCNDSSD	638
779	SLLTEVEDPIRNEWGCRCNDSSD	635
780	SLLTEVETPINNEWGCRCNDSSD	632
781	MSLLCEVGCSSLTEV	631
782	SLLTEVETPQRNEWGCRCNDSSD	630
783	SLLTEVEYPIRNEWGCRCNDSSD	628
784	SLLTEVGTPIRNEWGCRCNDSSD	627
785	SLLTEVETPIRNEWNCRCNDSSD	618
786	SWLTEVETPIRNEWGCRCNDSSD	615
787	SLLTEVETPIRNEEGCRCNDSSD	613
788	SQLTEVETPIRNEWGCRCNDSSD	609
789	SLCTEVGSLCTEV	607
790	SLLTEVETPIRNEWGDRNDSSD	603
791	MSLCTEVGMCLLTEV	597
792	CSLLTEVGSSLCEV	593
793	MSLLTEVGMSLLCEV	591
794	SLLTEVETPIRNEWGCRDNDSSD	589
795	SLLTEVITPIRNEWGCRCNDSSD	587
796	SLLTEVETPIRNEWGCRENDSSD	579
797	SCLTEVGSLLTVCV	573
798	CLCTCVGCSLLTEV	567
799	MSCLTEVGCSLLTEC	557
800	MSLLTECGCSCLCEV	556
801	MSLLTECGMSCLTEV	554
802	SLGTEVETPIRNEWGCRCNDSSD	542
803	SLLSEVETPIRNEWGCRCNDSSD	532
804	SLWTEVETPIRNEWGCRCNDSSD	525
805	MSLLTCVGMSLLTEC	524
806	SLCTEVGCLLTEV	522
807	CLLTEVGCSLLTEV	520

808	SCLTEVGCSSLTEC	514
809	CSLLTECGCLLTEV	507
810	SLLTCVGCSSLTEV	504
811	CSLLTECGCLCTCV	458
812	SLLTCVGCSSLTEC	447
813	CSLLTECGSSLTEC	441
814	CSLLTECGSLLCEV	430
815	CSLLTECGSCLCEC	419
816	CLLTEVGCSSLTEC	409
817	CSLLTECGCSCLCEV	404
818	MSLLTECGCSLLTEC	386
819	CLCTCVGCSSLTEC	340
820	MSLLTCVGCSSLTEC	330
821	CSCLCEVGCSSLTEV	325
822	SLLTDVETPIRNEWGCRCNDSSD	324
823	SCLTEVGSLLTEC	321
824	SLLTCVGSLLTEV	320
825	MSLLCEVGMSLLTEC	314
826	MSLLCEVGCSSLTEC	312
827	MSCLCECGCSLLTEV	306
828	MCLCTCVGMSLLTEC	306
829	MSLLTEVGMSCLCEC	304
830	1CSLLTEVETP1SLLTEVETPCLLTEVETP1	2303
831	1CSLLTEVETP1SLLTEVETPCSSLTEVETP1	2147
832	1CLTEVETPIR1SLLTEVETPCLLTEVETP1	2145
833	SLLTEVETCSLLTEVETATPIRNEWGCRC	2133
834	SLLTEVET1CSLLTEVET1SLLTEVETCEWG1R	2107
835	SLLTEVET1CSLLTEVET1SLLTEVETAWGCR1	2103
836	1CLTEVETPIR1SLLTEVETPCSSLTEVETP1	1936
837	1CETPIRNEWG1SLLTEVETPCLLTEVETP1	1912
838	1CTEVETPIRN1SLLTEVETPCLLTEVETP1	1887
839	1CTEVETPIRN1SLLTEVETPCSSLTEVETP1	1796
840	SLLTEVET1CSLLTEVET1SLLTEVETCEWGS1	1765
841	1CSLLTEVETP1LTEVETPIRCSLLTEVETP1	1732
842	1CSLLTEVETP1TEVETPIRNCSSLTEVETP1	1717
843	1CVETPIRNEW1SLLTEVETPCLTEVETPIR1	1715

844	SLLTEVET1CSLLTEVET1SLLTEVETAGCR1N	1712
845	1CSLLTEVETP1SLLTEVETPCETPIRNEWG1	1704
846	SLLTEVETCSLLTEVETCNEWGSRSDSSC	1697
847	1CLLTEVETPI1SLLTEVETPCLLTEVETPI1	1665
848	1CEVETPIRNE1SLLTEVETPCSLLETEVETP1	1655
849	1CLLTEVETPI1LLETEVETPIRCSLLTEVETP1	1651
850	1CSLLTEVETP1SLLTEVETPCVETPIRNEW1	1649
851	1CSLLTEVETP1VETPIRNEWCSLLTEVETP1	1634
852	SLLTEVET1CSLLTEVET1SLLTEVETCIRNEW1	1598
853	SLLTEVET1CSLLTEVET1SLLTEVETCLLLEV1	1592
854	1CTEVETPIRN1LLETEVETPIRCSLLTEVETP1	1590
855	1CEVETPIRNE1SLLTEVETPCLLTEVETPI1	1584
856	SLLTEVETCSLLTEVETCVETPIRNEWGC	1584
857	1CLTEVETPIR1SLLTEVETPCLTEVETPIR1	1576
858	1CETPIRNEWG1SLLTEVETPCSLLETEVETP1	1559
859	1CSLLTEVETP1SLLTEVETPCLTEVETPIR1	1552
860	1CVETPIRNEW1SLLTEVETPCSLLETEVETP1	1531
861	SLLTEVET1CSLLTEVET1SLLTEVETCSLLTE1	1490
862	SLLTEVET1CSLLTEVET1SLLTEVETCTPIRN1	1481
863	1CLTEVETPIR1LLETEVETPIRCSLLTEVETP1	1458
864	1CTEVETPIRN1SLLTEVETPCLTEVETPIR1	1452
865	SLLTEVETCSLLTEVETAEWGCRCDSSD	1451
866	1CVETPIRNEW1SLLTEVETPCETPIRNEWG1	1446
867	1CLLTEVETPI1SLLTEVETPCSLLETEVETP1	1438
868	1CEVETPIRNE1SLLTEVETPCETPIRNEWG1	1425
869	1CSLLTEVETP1EVETPIRNECSLLTEVETP1	1405
870	1CEVETPIRNE1EVETPIRNECSLLTEVETP1	1400
871	1CVETPIRNEW1SLLTEVETPCLLTEVETPI1	1396
872	1CEVETPIRNE1LLETEVETPIRCSLLTEVETP1	1382
873	1CSLLTEVETP1VETPIRNEWCLLTEVETPI1	1382
874	SLLTEVETCSLLTEVETCEWGSRSDSSDC	1375
875	SLLTEVETCSLLTEVETCSLLTEVETPIRC	1369
876	1CVETPIRNEW1LLETEVETPIRCSLLTEVETP1	1327
877	1CVETPIRNEW1ETPIRNEWGCSLLTEVETP1	1317
878	1CSLLTEVETP1TEVETPIRNCLLTEVETPI1	1313
879	SLLTEVETCSLLTEVETCETPIRNEWGCR	1306

880	1CLTEVETPIR1TEVETPIRNCSSLTEVETP1	1290
881	CSLLTEVETPIRNEWGCETPIRNEWGSRSDSC	1289
882	1CETPIRNEWG1LTEVETPIRCSLLTEVETP1	1286
883	1CLLTEVETPI1TEVETPIRNCSSLTEVETP1	1270
884	SLLTEVETCSLLTEVETCRNEWGSRSDSC	1255
885	1CSLLTEVETP1ETPIRNEWGCSLLTEVETP1	1250
886	1CSLLTEVETP1LTEVETPIRCLTEVETPIR1	1241
887	1CTEVETPIRN1TEVETPIRNCSSLTEVETP1	1229
888	CSLLTEVETCPIRNEWGSRSDSSDC	1224
889	1CSLLTEVETP1EVETPIRNECLLTEVETPI1	1221
890	SLLTEVET1CSLLTEVET1SLLTEVETCETPIR1	1208
891	CSLLTEVETPIRNCETPIRNEWGSRSDSC	1204
892	1CSLLTEVETP1LLTEVETPICLTEVETPIR1	1203
893	SLLTEVET1CSLLTEVET1SLLTEVETCVETPI1	1200
894	CSLLTEVETCTPIRNEWGSRSDSSC	1196
895	SLLTEVET1CSLLTEVET1SLLTEVETCRNEWG1	1195
896	1CETPIRNEWG1ETPIRNEWGCSLLTEVETP1	1180
897	1CEVETPIRNE1SLLTEVETPCLTEVETPIR1	1169
898	SLLTEVET1CSLLTEVET1SLLTEVETACR1ND	1169
899	SLLTEVETCSLLTEVETAPIRNEWGCRCN	1165
900	1CSLLTEVETP1LLTEVETPICSSLTEVETP1	1157
901	SLLTEVET1CSLLTEVET1SLLTEVETCLTEVE1	1144
902	1CLTEVETPIR1ETPIRNEWGCSLLTEVETP1	1125
903	1CEVETPIRNE1ETPIRNEWGCSLLTEVETP1	1124
904	SLLTEVETCSLLTEVETAIRNEWGCRCND	1120
905	CSLLTEVETPICETPIRNEWGSRSDSC	1120
906	CSLLTEVETPIRNEWGCP1RNEWGSRSDSSDC	1118
907	SLLTEVET1CSLLTEVET1SLLTEVETCPIRNE1	1104
908	SLLTEVET1CSLLTEVET1SLLTEVETCNEWG1	1103
909	SLLTEVETCSLLTEVETCLLTEVETPIRNC	1101
910	1CETPIRNEWG1SLLTEVETPCLTEVETPIR1	1099
911	CSLLTEVETPIRCETPIRNEWGSRSDSC	1087
912	SLLTEVETCSLLTEVETCTPIRNEWGSRSC	1081
913	1CTEVETPIRN1SLLTEVETPCEVETPIRNE1	1079
914	SLLTEVET1CSLLTEVET1SLLTEVETCEVETP1	1062
915	SLLTEVET1CSLLTEVET1SLLTEVETCTEVET1	1053

916	1CSLLTEVETP1LLETEVETPIRCLLLETEVETPI1	1048
917	CSLLTEVETPIRNECETPIRNEWGSRSDSC	1037
918	1CSLLTEVETP1SLLTEVETPCTEVETPIRN1	1022
919	1CETPIRNEWG1TEVETPIRNCSSLLTEVETP1	1021
920	CSLLTEVETPIRNECTPIRNEWGSRSDSSC	1019
921	1CEVETPIRNE1TEVETPIRNCSSLLTEVETP1	1014
922	CSLLTEVETPCETPIRNEWGSRSDSC	1010
923	1CSLLTEVETP1LLLETEVETPICLLLETEVETPI1	1009
924	CSLLTEVETPIRCTPIRNEWGSRSDSSC	1000
925	SLLTEVETCSLLTEVETCVETPIRNEWGSC	979
926	SLLTEVETCSLLTEVETARNEWGCRCNDS	963
927	SLLTEVETCSLLTEVETCETPIRNEWGSR	935
928	SLLTEVETCSLLTEVETANNEWGCRCNDSS	897
929	1CETPIRNEWG1VETPIRNEWCSLLTEVETP1	890
930	SLLTEVETCSLLTEVETCEVETPIRNEWGC	867
931	CSLLTEVETPCPIRNEWGSRSDSSDC	853
932	1CLTEVETPIR1VETPIRNEWCSLLTEVETP1	852
933	SLLTEVETCSLLTEVETCPIRNEWGSRNC	840
934	1CEVETPIRNE1VETPIRNEWCSLLTEVETP1	834
935	1CVETPIRNEW1SLLTEVETPCVETPIRNEW1	815
936	1CETPIRNEWG1EVETPIRNECSLLTEVETP1	809
937	1CSLLTEVETP1ETPIRNEWGCLLLETEVETPI1	805
938	CSLLTEVETCETPIRNEWGSRSDSC	796
939	1CSLLTEVETP1LLLETEVETPICETPIRNEWG1	777
940	SLLTEVETCSLLTEVETCTEVETPIRNEWC	775
941	1CEVETPIRNE1SLLTEVETPCTEVETPIRN1	772
942	1CETPIRNEWG1SLLTEVETPCTEVETPIRN1	749
943	1CLLLETEVETPI1VETPIRNEWCSLLTEVETP1	743
944	1CSLLTEVETP1TEVETPIRNCLLETEVETPIR1	740
945	1CLTEVETPIR1SLLTEVETPCVETPIRNEW1	733
946	1CLTEVETPIR1SLLTEVETPCTEVETPIRN1	729
947	1CVETPIRNEW1SLLTEVETPCTEVETPIRN1	724
948	SLLTEVETCSLLTEVETCIRNEWGSRSDC	721
949	1CLLLETEVETPI1SLLTEVETPCLLETEVETPIR1	717
950	1CETPIRNEWG1SLLTEVETPCVETPIRNEW1	715
951	1CTEVETPIRN1SLLTEVETPCVETPIRNEW1	711

952	1CTEVETPIRN1VETPIRNEWCSLLTEVETP1	710
953	1CVETPIRNEW1TEVETPIRNCSSLLTEVETP1	708
954	CSLLTEVETPICPIRNEWGSRSDSSDC	700
955	1CVETPIRNEW1VETPIRNEWCSLLTEVETP1	699
956	1CTEVETPIRN1SLLTEVETPCETPIRNEWG1	691
957	1CTEVETPIRN1SLLTEVETPCTEVETPIRN1	684
958	1CSLLTEVETP1SLLTEVETPCVETPIRNE1	684
959	1CEVETPIRNE1SLLTEVETPCVETPIRNEW1	674
960	SLLTEVETCSLLTEVETCLTEVETPIRNEC	666
961	1CLTEVETPIR1EVETPIRNECSLLTEVETP1	665
962	1CLTEVETPIR1SLLTEVETPCETPIRNEWG1	657
963	1CVETPIRNEW1EVETPIRNECSLLTEVETP1	652
964	1CETPIRNEWG1SLLTEVETPCETPIRNEWG1	645
965	CSLLTEVETPCTPIRNEWGSRSDSSC	645
966	CSLLTEVETPICTPIRNEWGSRSDSSC	622
967	1CLLTEVETPI1EVETPIRNECSLLTEVETP1	617
968	1CLLTEVETPI1ETPIRNEWGCSLLTEVETP1	608
969	CSLLTEVETPIRCPIRNEWGSRSDSSDC	606
970	CSLLTEVETPIRNCPIRNEWGSRSDSSDC	589
971	1CSLLTEVETP1LTEVETPIRCTEVETPIRN1	571
972	1CSLLTEVETP1LTEVETPIRCETPIRNEWG1	564
973	CSLLTEVETPIRNECPIRNEWGSRSDSSDC	553
974	1CSLLTEVETP1LLTEVETPICVETPIRNEW1	551
975	1CLLTEVETPI1SLLTEVETPCVETPIRNEW1	539
976	1CLTEVETPIR1SLLTEVETPCVETPIRNE1	538
977	1CVETPIRNEW1LLTEVETPICSSLLTEVETP1	537
978	1CTEVETPIRN1EVETPIRNECSLLTEVETP1	535
979	CSLLTEVETPIRNCTPIRNEWGSRSDSSC	532
980	CSLLTEVETPIRNEWGCTPIRNEWGSRSDSSC	508
981	1CSLLTEVETP1TEVETPIRNCTEVETPIRN1	505
982	1CTEVETPIRN1ETPIRNEWGCSLLTEVETP1	504
983	SLLTEVET1CSLLTEVET1SLLTEVETCNEWGS1	346
984	CSLLTEVETPIRNC	2154
985	SLLTEVCTCIRNEWG	2047
986	SLLTEVETCSLLTEVETPIRNEWGSR	1883
987	SLLTEVCTPICNEWG	1857

988	SLLTEVCTPIRCEWG	1853
989	SLLTEVECPIRCEWG	1849
990	CSLLTEVCTPIRNE	1721
991	SLLTEVETCIRNEWGC	1707
992	SLLTEVETCIRNCWG	1691
993	SLLTEVETCCRNEWG	1675
994	SLLTEVETPIRCCWG	1674
995	SLLTEVETSLLTEVETPIRNEWGCRCND	1663
996	SLLTEVCTPCRNEWG	1551
997	CSLLTEVETPIRCE	1512
998	SLLTEVETCIRCEWG	1495
999	SLLTEVETCSLLTEVETPIRNEWGSRSC	1488
1000	SLLTEVCTPIRNCWG	1440
1001	SLLTEVECPIRNCWG	1438
1002	SLCTEVETCIRNEWG	1385
1003	SLLTECETCIRNEWG	1384
1004	SLLTEVECCIRNEWG	1377
1005	SLLTEVETPCRNCWG	1377
1006	SLLTEVETCICNEWG	1360
1007	SLLTEVECPIRNC	1341
1008	SLLTECETPIRNCWG	1298
1009	SLLTEVETCIRNEWG	1286
1010	SLLTEVETPICNCWG	1255
1011	SLLTEVETCSLLTEVETPIRNEWGSR SNC	1239
1012	CSLLTEVETPICNE	1232
1013	CSLLTEVETCIRNE	1220
1014	SLLTEVCCPIRNEWG	1195
1015	SLLTEVETPIRNCWGC	1177
1016	SLLTEVCTPIRNC	1163
1017	SLLTEVECPIRNEWC	1161
1018	CSLLTEVETPIRNE	1159
1019	SLLTEVCTPIRNEWG	1156
1020	CSLLTEVETPCRNE	1148
1021	SLLTEVETPIRCEWGC	1135
1022	SLLTEVETCIRNC	1134
1023	SLLTEVETPIRCECG	1121

1024	CSLLTEVECPIRNE	1116
1025	SLLTEVECPICRNEWG	1110
1026	SCLTEVETPCRNEWG	1083
1027	CSLLTECETPIRNE	1082
1028	SLLTEVECPICNEWG	1079
1029	SLLTECETPIRCEWG	1052
1030	SLLTEVETCIRNEWG	1049
1031	SLCTEVETPIRNC	1035
1032	SLLTEVETCSLLTEVETPIRNEWGCR	1032
1033	SLLTECECPICRNEWG	1031
1034	SLLTEVETPICCEWG	1029
1035	SLLTEVECPIRCE	1027
1036	SLLTEVETPIRNCWG	1021
1037	SCLTEVCTPIRNE	1019
1038	SCLTEVETCIRNEWG	1015
1039	SLLTEVETPIRNCWC	1002
1040	SLLTEVETCSLLTEVETPIRC	995
1041	SLLTEVECPICRNEWG	980
1042	SLLTEVETSLLTEVETPIRNEWGCRC	979
1043	SLLTEVETSLLTEVETPIRNEWGCRCN	970
1044	SLLTEVCTCIRNE	949
1045	SLCTEVETPIRCE	945
1046	SLLTEVETCIRNECG	941
1047	SCLTEVETPIRNC	940
1048	SLLTEVETCSLLTEVETPIRNEWGC	938
1049	SLLTEVCTPIRNEWG	937
1050	SLLTEVECPIRNE	927
1051	SLLTEVETPICNEWGC	923
1052	SLLTEVETCSLLTEVETPIRNEWGSRSDSSC	916
1053	SLLTEVETPIRCEWG	902
1054	SLCTEVETPIRNCWG	899
1055	SLLTEVETCIRCE	898
1056	SLLTECETPCRNEWG	897
1057	SLLTEVETPICNEWG	890
1058	SLLTEVETCSLLTEVETPIRNC	890
1059	SLLTECETPICNEWG	885

1060	SLLTECETPIRNEWG	880
1061	SLLTEVETPCRCEWG	875
1062	SLLTEVETCSLLTEVETPIRNEWGSRSDC	874
1063	SLLTECCTPIRNEWG	866
1064	SLLTEVETCSLLTEVETPIRNEWGSRSDSC	861
1065	SLLTEVCTPCRNE	853
1066	SCLTECETPIRNEWG	847
1067	SLLTEVETCSLLTEVETPC	844
995	SLLTEVETSLLTEVETPIRNEWGCRCNDS	836
1068	SLLTEVETCSLLTEVETPIRNEWGSRSDSSDC	831
1069	SLLTEVETCSLLTEVETPIC	830
1070	SLLTEVETCSLLTEVETC	820
1071	SLLTEVETPCRNEWG	813
1072	CSLLTEVETPIRNEWGC	798
1073	SLLTEVCTPIRCE	789
1074	SLLTECETCIRNE	785
1075	SCLTECETPIRNE	780
1076	SLLTEVETCSLLTEVETPIRNEWC	768
1077	SLLTEVETPCCNEWG	766
1078	SLCTEVECPIRNEWG	750
1079	SLCTEVETPIRCEWG	750
1080	SLLTECETPIRNEWC	741
1081	SLLTEVCTPIRNEWGC	739
1082	SLLTEVETPIRCEWC	732
1083	SCLTEVETCIRNE	727
1084	SLLTEVETCICNE	727
1085	SLLTEVETPICNEWC	724
1086	SLLTEVECPIRNEWGC	715
1087	SLCTEVETCIRNE	712
1088	SLLTEVETCSLLTEVETPIRNEWGSC	712
1089	SLLTEVETSLLTEVETPIRNEWGCRCNDSS	711
1090	SCLTEVECPIRNE	705
1091	SLLTEVCTPICNE	699
1092	SLLTEVETPCRNEWGC	696
1093	SLLTEVETCIRNE	675
1094	SLLTEVCTPIRNECG	674

1095	SLLTEVETSLLTEVETPIRNEWGCRCNDSSD	669
1096	SLLTEVETPICNC	665
1097	SCLTEVETPIRNCWG	662
1098	SLLTEVETPICNECG	660
1099	SLLTEVECPIRNECG	656
1100	SLCTEVCTPIRNE	653
1101	SLLTECETPIRCE	648
1102	SLCTECETPIRNEWG	648
1103	SLCTEVECPIRNE	645
1104	SLLTECETPIRNC	643
1105	SLCTEVCTPIRNEWG	641
1106	SLLTEVETPIRNCCG	638
1107	SLLTEVETCSLLTEVETPIRNEC	629
1108	SLLTECETPIRNEWGC	607
1109	SLCTEVETPCRNEWG	607
1110	SLLTEVETPCRNEWC	589
1111	SLLTEVETPCRNECG	587
1112	SLLTEVECPICNE	582
1113	SLLTECETPIRNE	578
1114	SLCTEVETPICNEWG	578
1115	SLLTEVETPCRNC	571
1116	SLLTEVCTPIRNE	568
1117	SLLTEVETPIRNEWC	558
1118	SCLTEVECPIRNEWG	542
1119	SLLTEVECPCRNE	538
1120	SLCTEVETPCRNE	535
1121	SLCTEVETPIRNEWC	535
1122	SLLTECETPICNE	531
1123	SLLTECETPIRNECG	528
1124	SLCTEVETPIRNEWG	510
1125	SLLTECECPIRNE	507
1126	CMSLLTEVETPIRNC	1864
1127	MSLLTEVEKPIRNEWGCRCN	1854
1128	MSLLTEVETPCRNC	1834
1129	MSLLTEVECPIRNC	1752
1130	MSLLTEVCTPIRNC	1738

1131	DSLLTEVETPIRNEWGCRCN	1713
1132	MSLLTEVETPIRNEAGCRCN	1700
1133	MSLLTEVETPCRCE	1651
1134	MSLLTEVETPCRNE	1638
1135	MSLLTEVEMPIRNEWGCRCN	1580
1136	MSLLTEVEAPIRNEWGCRCN	1544
1137	MSLLTEVELPIRNEWGCRCN	1521
1138	MSLLTELETPIRNEWGCRCN	1497
1139	MSLLTEVETPIRNAWGRCN	1480
1140	MSLTTEVETPIRNEWGCRCN	1474
1141	MTLLTEVETPIRNEWGCRCN	1470
1142	MSLLTEVETPICNC	1451
1143	MSLLTEVCTPIRCE	1428
1144	MSLLTEVETAIRNEWGCRCN	1398
1145	MSLCTEVETPIRNC	1395
1146	MSLLTEVETCIRNE	1387
1147	MSLLTEVETCICNE	1378
1148	MSLLTEVEEPIRNEWGCRCN	1361
1149	MSLLTEVETPIRNEWGCRCN	1360
1150	MSLLTEVEQPIRNEWGCRCN	1345
1151	MSLLTEVECPIRCE	1336
1152	MSLLTEKETPIRNEWGCRCN	1324
1153	ESLLTEVETPIRNEWGCRCN	1310
1154	MSLCTEVETCIRNE	1305
1155	MSLLTETETPIRNEWGCRCN	1279
1156	MSLLTEIETPIRNEWGCRCN	1255
1157	MSLLTEVETPIRNEWGCRAN	1252
1158	MSLLTEVCTPCRNE	1244
1159	TSLLTEVETPIRNEWGCRCN	1243
1160	MSLCTEVCTPIRNE	1243
1161	MSLLTEVETPIRNEWGCRCA	1233
1162	MSLVTEVETPIRNEWGCRCN	1202
1163	MSCLTEVETPIRCE	1192
1164	MSLATEVETPIRNEWGCRCN	1188
1165	MSLLTEVVTPIRNEWGCRCN	1183
1166	MSLLTEVQTPIRNEWGCRCN	1172

1167	MSLLTEVETPIRNEWGCRCN	1167
1168	MSLLTEVECPIRNE	1158
1169	MSLLTEVCTPICNE	1157
1170	MSLLTEPETPIRNEWGCRCN	1153
1171	MSLLTEVEFPIRNEWGCRCN	1149
1172	MSLLTEVETPARNEWGCRCN	1149
1173	MSLLTEVETPIRNEWGARCN	1149
1174	MSLLTEVMTPIRNEWGCRCN	1133
1175	MSLLTECETPIRCE	1131
1176	CMSLLTEVECPIRNE	1122
1177	ASLLTEVETPIRNEWGCRCN	1111
1178	MSLLTEVETCIRCE	1105
1179	MSCLTEVETPIRNC	1102
1180	MSLLTEVEGPIRNEWGCRCN	1099
1181	MSLLTEVETPIRNEWACRCN	1087
1182	MSLLTEMETPIRNEWGCRCN	1075
1183	KSLLTEVETPIRNEWGCRCN	1068
1184	MSLLTEVEVPIRNEWGCRCN	1064
1185	MSLCTEVETPCRNE	1064
1186	MSCLTEVCTPIRNE	1055
1187	CMSLLTEVCTPIRNE	1054
1188	VSLLTEVETPIRNEWGCRCN	1054
1189	MSLLTEVESPIRNEWGCRCN	1051
1190	MSLLTEVSTPIRNEWGCRCN	1045
1191	MSLLTEFETPIRNEWGCRCN	1044
1192	CMSLLTEVETPIRCE	1034
1193	MSLCTEVECPIRNE	1023
1194	MSLLTECETPICNE	1016
1195	MSLLTEVTTPIRNEWGCRCN	1013
1196	RSLLTEVETPIRNEWGCRCN	1012
1197	MSLLTEVEDPIRNEWGCRCN	1004
1198	MSLLTEAETPIRNEWGCRCN	1003
1199	CMSLLTEVETPCRNE	992
1200	MSLLTEVETPIRAEWGCRCN	978
1201	MSLLTEVCTCIRNE	959
1202	MSLLTECECPIRNE	958

1203	HSLLTEVETPIRNEWGCRCN	956
1204	CMSLLTECETPIRNE	937
1205	MSLLTEVENPIRNEWGCRCN	936
1206	MSLLTECETPCRNE	932
1207	MSLLTEVERPIRNEWGCRCN	926
1208	MSLLTEQETPIRNEWGCRCN	913
1209	MSLLTEVETCIRNC	908
1210	MSFLTEVETPIRNEWGCRCN	907
1211	CMSLLTEVETCIRNE	896
1212	PSLLTEVETPIRNEWGCRCN	841
1213	MSLETEVETPIRNEWGCRCN	838
1214	MSLLTEVEHPIRNEWGCRCN	838
1215	YSLLTEVETPIRNEWGCRCN	835
1216	MSLLTEVCTPIRNE	824
1217	MSLLTEVECPICNE	821
1218	MSLLTEVETPIANNEWGCRCN	814
1219	LSLLTEVETPIRNEWGCRCN	801
1220	WSLLTEVETPIRNEWGCRCN	742
1221	MSLLTEVETPIRNEWGCACN	739
1222	MSLLTEVECPCRNE	736
1223	MSCLTEVECPIRNE	730
1224	FSLLTEVETPIRNEWGCRCN	707
1225	NSLLTEVETPIRNEWGCRCN	706
1226	MSLLTEVEYPIRNEWGCRCN	685
1227	MSLLTDVETPIRNEWGCRCN	679
1228	MSKLTEVETPIRNEWGCRCN	672
1229	MSCLTEVETCIRNE	649
1230	MSLSTEVEVETPIRNEWGCRCN	648
1231	MSLLTECETPIRNE	630
1232	ISLLTEVETPIRNEWGCRCN	629
1233	MSCLTEVETPCRNE	625
1234	MSLCTEVETPIRNE	618
1235	CMSLLTEVETPICNE	615
1236	MSLLTEVEPPIRNEWGCRCN	610
1237	MSCLTEVETPIRNE	602
1238	GSLLTEVETPIRNEWGCRCN	584

1239	MSLCTEVETPIRCE	568
1240	MSLKTEVETPIRNEWGCRCN	567
1241	MSLLTEETPIRNEWGCRCN	545
1242	CSLCTEVETPIRNE	518
1243	QSLLTEVETPIRNEWGCRCN	440
1244	MSLLTEVEIPRNEWGCRCN	409
1245	MSLLTESETPIRNEWGCRCN	369
1246	MSLLTEGETPIRNEWGCRCN	357
1247	MSLLTECETPIRNC	344
1248	MSLLTECETCIRNE	312
1249	SLLLTEVETPIRNEWGCRCN	303

[00132] Table 3: Peptides that show specific binding to Z3G1 (A numeral "1" in the peptide sequence indicates a differentially protected cystein allowing for selective CLIP attachment at certain residues)

SEQ ID NO:	Peptides that bind to Z3G1	Signal
1177	ASLLTEVETPIRNEWGCRCN	2816
1131	DSLLTEVETPIRNEWGCRCN	2814
1153	ESLLTEVETPIRNEWGCRCN	2816
1224	FSLLTEVETPIRNEWGCRCN	2665
1238	GSLLTEVETPIRNEWGCRCN	2635
1203	HSLLTEVETPIRNEWGCRCN	2490
1232	ISLLTEVETPIRNEWGCRCN	2438
1183	KSLLTEVETPIRNEWGCRCN	2618
1219	LSLLTEVETPIRNEWGCRCN	2506
1149	MSLLTEVETPIRNEWGCRCN	2711
1225	NSLLTEVETPIRNEWGCRCN	2485
1212	PSLLTEVETPIRNEWGCRCN	2694
1243	QSLLTEVETPIRNEWGCRCN	2619
1196	RSLLTEVETPIRNEWGCRCN	2550
1249	SLLLTEVETPIRNEWGCRCN	2404
1159	TSLLTEVETPIRNEWGCRCN	2834
1188	VSLLTEVETPIRNEWGCRCN	2816
1220	WSLLTEVETPIRNEWGCRCN	2693
1215	YSLLTEVETPIRNEWGCRCN	2650
1250	MALLTEVETPIRNEWGCRCN	2604
1251	MDLLTEVETPIRNEWGCRCN	2726

1252	MELLTEVETPIRNEWGCRCN	2679
1253	MFLLTEVETPIRNEWGCRCN	1707
1254	MGLLTEVETPIRNEWGCRCN	2635
1255	MHLLTEVETPIRNEWGCRCN	2449
1256	MILLTEVETPIRNEWGCRCN	1634
1257	MKLLTEVETPIRNEWGCRCN	2629
1258	MLLLTEVETPIRNEWGCRCN	2091
1259	MMLLTEVETPIRNEWGCRCN	2666
1260	MNLLTEVETPIRNEWGCRCN	2733
1261	MPLLTEVETPIRNEWGCRCN	2521
1262	MQLLTEVETPIRNEWGCRCN	2526
1263	MRLLTEVETPIRNEWGCRCN	2519
1141	MTLLTEVETPIRNEWGCRCN	2809
1264	MVLLTEVETPIRNEWGCRCN	2465
1265	MWLLTEVETPIRNEWGCRCN	2615
1266	MYLLTEVETPIRNEWGCRCN	1960
1210	MSFLTEVETPIRNEWGCRCN	1087
1267	MSILTEVETPIRNEWGCRCN	2582
1268	MSMLTEVETPIRNEWGCRCN	1329
1269	MSVLTEVETPIRNEWGCRCN	2111
1164	MSLATEVETPIRNEWGCRCN	2747
1270	MSLDTEVETPIRNEWGCRCN	2594
1213	MSLETEVETPIRNEWGCRCN	2768
1271	MSLFTEVETPIRNEWGCRCN	2115
1272	MSLHTEVETPIRNEWGCRCN	2058
1167	MSLITEVETPIRNEWGCRCN	2684
1240	MSLKTEVETPIRNEWGCRCN	2691
1273	MSLMTEVETPIRNEWGCRCN	2804
1274	MSLNTEVETPIRNEWGCRCN	2787
1275	MSLPTEVETPIRNEWGCRCN	2007
1276	MSLQTEVETPIRNEWGCRCN	2792
1277	MSLRTEVETPIRNEWGCRCN	2554
1230	MSLSTEVETPIRNEWGCRCN	2768
1140	MSLTTEVETPIRNEWGCRCN	2742
1162	MSLVTEVETPIRNEWGCRCN	2776
1278	MSLYTEVETPIRNEWGCRCN	1313

1279	MSLLAEVETPIRNEWGCRCN	2807
1280	MSLLDEVETPIRNEWGCRCN	2763
1281	MSLLEEvetPIRNEWGCRCN	2805
1282	MSLLFEVETPIRNEWGCRCN	2581
1283	MSLLGEVETPIRNEWGCRCN	2717
1284	MSLLHEVETPIRNEWGCRCN	2691
1285	MSLLIEVETPIRNEWGCRCN	2371
1286	MSLLKEVETPIRNEWGCRCN	2825
1287	MSLLLEVETPIRNEWGCRCN	2804
1288	MSLLMEVETPIRNEWGCRCN	2847
1289	MSLLNEVETPIRNEWGCRCN	2824
1290	MSLLPEVETPIRNEWGCRCN	2728
1291	MSLLQEVETPIRNEWGCRCN	2792
1292	MSLLREVETPIRNEWGCRCN	2699
1293	MSLLSEVETPIRNEWGCRCN	2790
1294	MSLLVEVETPIRNEWGCRCN	2732
1295	MSLLWEVETPIRNEWGCRCN	2531
1296	MSLLYEvetPIRNEWGCRCN	2464
1227	MSLLTDVETPIRNEWGCRCN	2476
1297	MSLLTQVETPIRNEWGCRCN	1697
1298	MSLLTTVETPIRNEWGCRCN	2699
1156	MSLLTEIETPIRNEWGCRCN	2799
1138	MSLLTELETPIRNEWGCRCN	2589
1155	MSLLTETETPIRNEWGCRCN	2641
1299	MSLLTEVATPIRNEWGCRCN	2633
1300	MSLLTEVDTPIRNEWGCRCN	2856
1301	MSLLTEVFTPIRNEWGCRCN	1858
1302	MSLLTEVGTPIRNEWGCRCN	2789
1303	MSLLTEVHTPIRNEWGCRCN	2751
1304	MSLLTEVITPIRNEWGCRCN	2668
1305	MSLLTEVKTPIRNEWGCRCN	2708
1306	MSLLTEVLTPIRNEWGCRCN	2714
1174	MSLLTEVMTPIRNEWGCRCN	2813
1307	MSLLTEVNTPIRNEWGCRCN	2807
1308	MSLLTEVPTPIRNEWGCRCN	2380
1166	MSLLTEVQTPIRNEWGCRCN	2813

1309	MSLLTEVRTPIRNEWGCRCN	2668
1190	MSLLTEVSTPIRNEWGCRCN	2783
1195	MSLLTEVTTPIRNEWGCRCN	2791
1165	MSLLTEVVTPIRNEWGCRCN	2732
1310	MSLLTEVWTPIRNEWGCRCN	2546
1311	MSLLTEVYTPIRNEWGCRCN	2181
1136	MSLLTEVEAPIRNEWGCRCN	2833
1197	MSLLTEVEDPIRNEWGCRCN	2826
1148	MSLLTEVEEPIRNEWGCRCN	2835
1171	MSLLTEVEFPIRNEWGCRCN	2728
1180	MSLLTEVEGPIRNEWGCRCN	2802
1214	MSLLTEVEHPIRNEWGCRCN	2753
1244	MSLLTEVEIPIRNEWGCRCN	2742
1127	MSLLTEVEKPIRNEWGCRCN	2837
1137	MSLLTEVELPIRNEWGCRCN	2797
1135	MSLLTEVEMPIRNEWGCRCN	2839
1205	MSLLTEVENPIRNEWGCRCN	2805
1236	MSLLTEVEPPIRNEWGCRCN	2797
1150	MSLLTEVEQPIRNEWGCRCN	2826
1207	MSLLTEVERPIRNEWGCRCN	2753
1189	MSLLTEVESPIRNEWGCRCN	2712
1184	MSLLTEVEVPIRNEWGCRCN	2768
1312	MSLLTEVEWPIRNEWGCRCN	2541
1226	MSLLTEVEYPIRNEWGCRCN	2571
1144	MSLLTEVETAIRNEWGCRCN	2722
1172	MSLLTEVETPARNEWGCRCN	2774
1218	MSLLTEVETPIANNEWGCRCN	2683
1200	MSLLTEVETPIRAEWGCRCN	2742
1139	MSLLTEVETPIRNAWGCRCN	2803
1132	MSLLTEVETPIRNEAGCRCN	2831
1181	MSLLTEVETPIRNEWACRCN	2732
1173	MSLLTEVETPIRNEWGARCN	2760
1221	MSLLTEVETPIRNEWGCACN	2662
1157	MSLLTEVETPIRNEWGCRAN	2769
1161	MSLLTEVETPIRNEWGCRCN	2770
1126	CMSLLTEVETPIRNC	2767

1192	CMSLLTEVETPIRCE	2453
1235	CMSLLTEVETPICNE	2331
1199	CMSLLTEVETPCRNE	2789
1211	CMSLLTEVETCIRNE	2713
1176	CMSLLTEVECPİRNE	2730
1187	CMSLLTEVCTPIRNE	2633
1313	CMSLLCEVETPIRNE	2582
1314	CMSLCTEVETPIRNE	1705
1315	CMCLLTEVETPIRNE	2347
984	CSLLTEVETPIRNC	2782
997	CSLLTEVETPIRCE	2516
1012	CSLLTEVETPICNE	2444
1020	CSLLTEVETPCRNE	2470
1013	CSLLTEVETCIRNE	2301
1024	CSLLTEVECPİRNE	2226
990	CSLLTEVCTPIRNE	1942
1316	CSLLCEVETPIRNE	2527
1242	CSLCTEVETPIRNE	1832
1317	MCLLTEVETPIRNC	2743
1318	MCLLTEVETPIRCE	2307
1319	MCLLTEVETPICNE	2379
1320	MCLLTEVETPCRNE	2404
1321	MCLLTEVETCIRNE	1948
1322	MCLLTEVECPİRNE	2421
1323	MCLLTEVCTPIRNE	1407
1324	MCLLCEVETPIRNE	2038
1145	MSLCTEVETPIRNC	2601
1239	MSLCTEVETPIRCE	1555
1185	MSLCTEVETPCRNE	1673
1193	MSLCTEVECPİRNE	1538
1160	MSLCTEVCTPIRNE	1906
1325	MSLLCEVETPIRNC	2823
1326	MSLLCEVETPIRCE	2772
1327	MSLLCEVETPICNE	2704
1328	MSLLCEVETPCRNE	2652
1329	MSLLCEVETCIRNE	2589

1330	MSLLCEVECPIRNE	2606
1331	MSLLCEVCTPIRNE	2601
1130	MSLLTEVCTPIRNC	2787
1143	MSLLTEVCTPIRCE	2667
1169	MSLLTEVCTPICNE	2526
1158	MSLLTEVCTPCRNE	2572
1201	MSLLTEVCTCIRNE	2143
1168	MSLLTEVECPIRNE	2613
1129	MSLLTEVECPIRNC	2755
1151	MSLLTEVECPIRCE	2675
1217	MSLLTEVECPICNE	2440
1222	MSLLTEVECPCRNE	2361
1146	MSLLTEVETCIRNE	2129
1209	MSLLTEVETCIRNC	2309
1178	MSLLTEVETCIRCE	2739
1147	MSLLTEVETCICNE	2721
1134	MSLLTEVETPCRNE	2695
1128	MSLLTEVETPCRNC	2810
1133	MSLLTEVETPCRCE	2597
1142	MSLLTEVETPICNC	2758
1018	CSLLTEVETPIRNE	2211
1332	MCLLTEVETPIRNE	2364
1234	MSLCTEVETPIRNE	2054
1333	MSLLCEVETPIRNE	2454
1216	MSLLTEVCTPIRNE	2529
287	MSLLTEVGMSLLTEV	2878
293	CSLLTEVGMSLLTEV	2827
513	MCLLTEVGMSLLTEV	2697
532	MSCLTEVGMSLLTEV	2336
371	MSLCTEVGMSLLTEV	2691
749	MSLLCEVGMSLLTEV	2786
543	MSLLTCVGMSLLTEV	2627
339	MSLLTECGMSLLTEV	2170
288	CSCLCEVGMSLLTEV	1812
663	MCLCTCVGMSLLTEV	2509
294	MSCLCECGMSLLTEV	1006

373	CSLLTECGMSLLTEV	1235
316	MSLLTEVGCSSLTEV	2650
364	CSLLTEVGCSSLTEV	2503
570	MCLLTEVGCSSLTEV	2717
557	MSCLTEVGCSSLTEV	2506
508	MSLCTEVGCSSLTEV	2832
781	MSLLCEVGCSSLTEV	2761
528	MSLLTCVGCSSLTEV	2467
363	MSLLTECGCSSLTEV	1235
536	MCLCTCVGCSSLTEV	2241
360	CSLLTECGCSSLTEV	1427
296	MSLLTEVGMCLLTEV	2809
303	CSLLTEVGMCLLTEV	2618
1334	MSLLCEVGMCLLTEV	2676
359	MSLLTEVGMSCLTEV	2793
372	CSLLTEVGMSCLTEV	2554
1335	MCLLTEVGMSCLTEV	1869
1336	MSLLCEVGMSCLTEV	2846
317	MSLLTEVGMSCLTEV	2895
334	CSLLTEVGMSCLTEV	2857
1337	MCLLTEVGMSCLTEV	2513
289	MSLCTEVGMSCLTEV	1093
1338	MSLLCEVGMSCLTEV	2595
793	MSLLTEVGMSSLCEV	2819
309	CSLLTEVGMSSLCEV	2734
1339	MCLLTEVGMSSLCEV	2234
1340	MSCLTEVGMSSLCEV	2341
304	MSLCTEVGMSSLCEV	2616
1341	MSLLCEVGMSSLCEV	2851
1342	MSLLTCVGMSSLCEV	2712
460	MSLLTECGMSLLCEV	2373
1343	CSCLCEVGMSSLCEV	1945
1344	MCLCTCVGMSSLCEV	2431
1345	MSCLCECGMSLLCEV	1307
456	CSLLTECGMSLLCEV	1640
285	MSLLTEVGMSSLTCV	2872

286	CSLLTEVGMSSLTTCV	2768
1346	MCLLTEVGMSSLTTCV	1098
542	MSLCTEVGMSSLTTCV	2722
1347	MSLLCEVGMSSLTTCV	2784
343	MSLLTEVGMSSLTEC	2831
451	CSLLTEVGMSSLTEC	2613
825	MSLLCEVGMSSLTEC	2617
761	MSLLTEVGCSCSCEV	2053
476	CSLLTEVGCSCSCEV	1680
1348	MSLCTEVGCSCSCEV	2001
1349	MSLLCEVGCSCSCEV	2586
291	MSLLTEVGMCLCTCV	2842
297	CSLLTEVGMCLCTCV	2649
1350	MSLLCEVGMCLCTCV	2664
829	MSLLTEVGMSCSCEC	2444
499	CSLLTEVGMSCSCEC	2101
1351	MSLLCEVGMSCSCEC	2492
470	MSLLTEVGCSSLTEC	2349
383	CSLLTEVGCSSLTEC	2486
592	MSLCTEVGCSSLTEC	1971
826	MSLLCEVGCSSLTEC	2573
365	CSLLTEVCMSSLTEC	1891
1352	CCLLTEVETPIRNE	2155
1353	CLLTEVETPIRNC	1996
1354	CLLTEVETPIRCE	1813
1355	CLLTEVETPICNE	1647
1356	CLLTEVETPCRNE	1991
1357	CLLTEVETCIRNE	1661
1358	CLLTEVECPIRNE	2326
1359	CLLTEVCTPIRNE	1585
1360	CLLCEVETPIRNE	2314
1100	SLCTEVCTPIRNE	1674
1361	SLLCEVETPIRNC	2460
1362	SLLCEVETPIRCE	2307
1363	SLLCEVETPICNE	1921
1364	SLLCEVETPCRNE	2035

1365	SLLCEVETCIRNE	2305
1366	SLLCEVECPIRNE	2377
1367	SLLCEVCTPIRNE	2283
1016	SLLTEVCTPIRNC	2308
1073	SLLTEVCTPIRCE	1873
1091	SLLTEVCTPICNE	1659
1065	SLLTEVCTPCRNE	2016
1044	SLLTEVCTCIRNE	1695
1050	SLLTEVECPIRNE	2469
1007	SLLTEVECPIRNC	2635
1035	SLLTEVECPIRCE	2426
1112	SLLTEVECPICNE	2022
1119	SLLTEVECPCRNE	1840
1093	SLLTEVETCIRNE	1792
1022	SLLTEVETCIRNC	2289
1055	SLLTEVETCIRCE	2161
1084	SLLTEVETCICNE	1953
1368	SLLTEVETPCRNE	1665
1115	SLLTEVETPCRNC	1816
1369	SLLTEVETPCRCE	1546
1096	SLLTEVETPICNC	2075
1370	CLLTEVETPIRNE	1524
1371	SLLCEVETPIRNE	2511
1116	SLLTEVCTPIRNE	1854
1072	CSLLTEVETPIRNEWGC	2232
1372	CLLTEVETPIRNEWGC	1866
1373	SLLCEVETPIRNEWGC	2281
1081	SLLTEVCTPIRNEWGC	1866
1086	SLLTEVECPIRNEWGC	2142
991	SLLTEVETCIRNEWGC	2284
1092	SLLTEVETPCRNEWGC	1873
1051	SLLTEVETPICNEWGC	2101
1021	SLLTEVETPIRCEWGC	2435
1015	SLLTEVETPIRNCWGC	2513
1374	SLLTEVETPIRNECGC	1660
1375	SLLTEVETPIRNEWCC	1813

1376	CLLTEVETPIRNEWC	1743
1377	CLLTEVETPIRNECG	1501
1378	CLLTEVETPIRNCWG	2388
1379	CLLTEVETPIRCEWG	2169
1380	CLLTEVETPICNEWG	2120
1381	CLLTEVETPCRNEWG	2074
1382	CLLTEVETCIRNEWG	2296
1383	CLLTEVECPİRNEWG	2157
1384	CLLCEVETPIRNEWG	2388
1385	CLLTEVETPIRNEWG	2142
1105	SLCTEVCTPIRNEWG	1477
1386	SLCCEVETPIRNEWG	1603
1387	SLLCEVETPIRNEWC	2406
1388	SLLCEVETPIRNECG	2107
1389	SLLCEVETPIRNCWG	2789
1390	SLLCEVETPIRCEWG	2601
1391	SLLCEVETPICNEWG	2536
1392	SLLCEVETPCRNEWG	2465
1393	SLLCEVETCIRNEWG	2531
1394	SLLCEVECPİRNEWG	2529
1395	SLLCEVCTPIRNEWG	2384
1396	SLLCEVETPIRNEWG	2384
1049	SLLTEVCTPIRNEWC	1883
1094	SLLTEVCTPIRNECG	1782
1000	SLLTEVCTPIRNCWG	2420
988	SLLTEVCTPIRCEWG	2090
987	SLLTEVCTPICNEWG	1883
996	SLLTEVCTPCRNEWG	1841
985	SLLTEVCTCIRNEWG	1546
1014	SLLTEVCCPIRNEWG	2253
1019	SLLTEVCTPIRNEWG	2692
1397	CLLTEVCTPIRNEWG	1634
1017	SLLTEVECPİRNEWC	2141
1099	SLLTEVECPİRNECG	2001
1001	SLLTEVECPİRNCWG	2589
989	SLLTEVECPİRCEWG	2509

1028	SLLTEVECPICNEWG	2449
1025	SLLTEVECPICRNEWG	2303
1004	SLLTEVECCIRNEWG	2507
1041	SLLTEVECPICRNEWG	2267
1030	SLLTEVETCIRNEWG	2337
1046	SLLTEVETCIRNECG	2018
992	SLLTEVETCIRNCWG	2616
998	SLLTEVETCIRCEWG	2566
1006	SLLTEVETCICNEWG	2498
993	SLLTEVETCCRNEWG	2389
1009	SLLTEVETCIRNEWG	2462
1110	SLLTEVETPCRNEWG	1867
1111	SLLTEVETPCRNECG	1470
1005	SLLTEVETPCRNCWG	2602
1061	SLLTEVETPCRCEWG	2155
1077	SLLTEVETPCCNEWG	2208
1071	SLLTEVETPCRNEWG	2167
1085	SLLTEVETPICNEWG	2488
1098	SLLTEVETPICNECG	2041
1010	SLLTEVETPICNCWG	2624
1034	SLLTEVETPICCEWG	2525
1057	SLLTEVETPICNEWG	2395
1082	SLLTEVETPIRCEWG	2255
1023	SLLTEVETPIRCECG	2464
994	SLLTEVETPIRCCWG	2755
1053	SLLTEVETPIRCEWG	2365
1039	SLLTEVETPIRNCWG	2321
1106	SLLTEVETPIRNCCG	1923
1036	SLLTEVETPIRNCWG	2350
1398	SLLTEVETPIRNECC	1493
1399	SLLTEVETPIRNECG	1545
1117	SLLTEVETPIRNEWG	1856
1070	SLLTEVETCSLLTEVETC	2104
1067	SLLTEVETCSLLTEVETPC	2082
1069	SLLTEVETCSLLTEVETPIC	2169
1040	SLLTEVETCSLLTEVETPIRC	2402

1058	SLLTEVETCSLLTEVETPIRNC	2295
1107	SLLTEVETCSLLTEVETPIRNEC	2025
1076	SLLTEVETCSLLTEVETPIRNEWC	2169
1048	SLLTEVETCSLLTEVETPIRNEWGC	2010
1088	SLLTEVETCSLLTEVETPIRNEWGSC	2180
986	SLLTEVETCSLLTEVETPIRNEWGSR	2757
999	SLLTEVETCSLLTEVETPIRNEWGSRSC	2792
1011	SLLTEVETCSLLTEVETPIRNEWGSR SNC	2673
1062	SLLTEVETCSLLTEVETPIRNEWGSR SDC	2483
1064	SLLTEVETCSLLTEVETPIRNEWGSR SDC	2335
1052	SLLTEVETCSLLTEVETPIRNEWGSR SDC	2404
1068	SLLTEVETCSLLTEVETPIRNEWGSR SDC	2294
1032	SLLTEVETCSLLTEVETPIRNEWGCR	2395
1042	SLLTEVETCSLLTEVETPIRNEWGCR	2324
1043	SLLTEVETCSLLTEVETPIRNEWGCR CN	2390
995	SLLTEVETCSLLTEVETPIRNEWGCR CN	2393
995	SLLTEVETCSLLTEVETPIRNEWGCR CN	2260
1089	SLLTEVETCSLLTEVETPIRNEWGCR CN	2212
1095	SLLTEVETCSLLTEVETPIRNEWGCR CN	1980
831	1CSLLTEVETP1SLLTEVETPCSLLTEVETP1	2714
867	1CLLTEVETP1SLLTEVETPCSLLTEVETP1	2593
836	1CLTEVETPIR1SLLTEVETPCSLLTEVETP1	2645
839	1CTEVETPIRN1SLLTEVETPCSLLTEVETP1	2420
848	1CEVETPIRNE1SLLTEVETPCSLLTEVETP1	2460
860	1CVETPIRNEW1SLLTEVETPCSLLTEVETP1	2474
858	1CETPIRNEWG1SLLTEVETPCSLLTEVETP1	2566
900	1CSLLTEVETP1LLTEVETPICSLLETEVETP1	2437
1400	1CLLTEVETP1LLTEVETPICSLLETEVETP1	2220
1401	1CLTEVETPIR1LLTEVETPICSLLETEVETP1	2316
1402	1CTEVETPIRN1LLTEVETPICSLLETEVETP1	2258
1403	1CEVETPIRNE1LLTEVETPICSLLETEVETP1	2133
977	1CVETPIRNEW1LLTEVETPICSLLETEVETP1	1946
1404	1CETPIRNEWG1LLTEVETPICSLLETEVETP1	2288
841	1CSLLTEVETP1LLETEVETPIRCSLLTEVETP1	2521
849	1CLLTEVETP1LLETEVETPIRCSLLTEVETP1	2601
863	1CLTEVETPIR1LLETEVETPIRCSLLTEVETP1	2476

854	1CTEVETPIRN1L1TEVETPIRCSLLTEVETP1	2469
872	1CEVETPIRNE1L1TEVETPIRCSLLTEVETP1	2304
876	1CVETPIRNEW1L1TEVETPIRCSLLTEVETP1	2350
882	1CETPIRNEWG1L1TEVETPIRCSLLTEVETP1	2282
842	1CSLLTEVETP11TEVETPIRNCSSLLTEVETP1	2591
883	1CLL1TEVETPI11TEVETPIRNCSSLLTEVETP1	2492
880	1CLTEVETPIR11TEVETPIRNCSSLLTEVETP1	2396
887	1CTEVETPIRN11TEVETPIRNCSSLLTEVETP1	2405
921	1CEVETPIRNE11TEVETPIRNCSSLLTEVETP1	2272
953	1CVETPIRNEW11TEVETPIRNCSSLLTEVETP1	2118
919	1CETPIRNEWG11TEVETPIRNCSSLLTEVETP1	2223
869	1CSLLTEVETP11EVETPIRNECSSLLTEVETP1	2582
967	1CLL1TEVETPI11EVETPIRNECSSLLTEVETP1	2220
961	1CLTEVETPIR11EVETPIRNECSSLLTEVETP1	2331
978	1CTEVETPIRN11EVETPIRNECSSLLTEVETP1	2295
870	1CEVETPIRNE11EVETPIRNECSSLLTEVETP1	2618
963	1CVETPIRNEW11EVETPIRNECSSLLTEVETP1	2365
936	1CETPIRNEWG11EVETPIRNECSSLLTEVETP1	2368
851	1CSLLTEVETP11VETPIRNEWCSLLTEVETP1	2708
943	1CLL1TEVETPI11VETPIRNEWCSLLTEVETP1	2422
932	1CLTEVETPIR11VETPIRNEWCSLLTEVETP1	2344
952	1CTEVETPIRN11VETPIRNEWCSLLTEVETP1	2380
934	1CEVETPIRNE11VETPIRNEWCSLLTEVETP1	2448
955	1CVETPIRNEW11VETPIRNEWCSLLTEVETP1	2307
929	1CETPIRNEWG11VETPIRNEWCSLLTEVETP1	2419
885	1CSLLTEVETP11ETPIRNEWGCSLLTEVETP1	2591
968	1CLL1TEVETPI11ETPIRNEWGCSLLTEVETP1	2377
902	1CLTEVETPIR11ETPIRNEWGCSLLTEVETP1	2296
1405	1CTEVETPIRN11ETPIRNEWGCSLLTEVETP1	2268
903	1CEVETPIRNE11ETPIRNEWGCSLLTEVETP1	2140
877	1CVETPIRNEW11ETPIRNEWGCSLLTEVETP1	2349
896	1CETPIRNEWG11ETPIRNEWGCSLLTEVETP1	2425
830	1CSLLTEVETP1SLL1TEVETPCLL1TEVETPI1	2786
847	1CLL1TEVETPI1SLL1TEVETPCLL1TEVETPI1	2722
832	1CLTEVETPIR1SLL1TEVETPCLL1TEVETPI1	2711
838	1CTEVETPIRN1SLL1TEVETPCLL1TEVETPI1	2616

855	1CEVETPIRNE1SLLTEVETPCLLTEVETPI1	2576
871	1CVETPIRNEW1SLLTEVETPCLLTEVETPI1	2544
837	1CETPIRNEWG1SLLTEVETPCLLTEVETPI1	2653
923	1CSLLTEVETP1LLTEVETPICLLTEVETPI1	2534
1406	1CLLTEVETPI1LLTEVETPICLLTEVETPI1	2350
1407	1CLTEVETPIR1LLTEVETPICLLTEVETPI1	2316
1408	1CTEVETPIRN1LLTEVETPICLLTEVETPI1	2446
1409	1CEVETPIRNE1LLTEVETPICLLTEVETPI1	2194
1410	1CVETPIRNEW1LLTEVETPICLLTEVETPI1	2331
1411	1CETPIRNEWG1LLTEVETPICLLTEVETPI1	2405
916	1CSLLTEVETP1LTEVETPIRCLLTEVETPI1	2722
1412	1CLLTEVETPI1LTEVETPIRCLLTEVETPI1	2436
1413	1CLTEVETPIR1LTEVETPIRCLLTEVETPI1	1445
1414	1CTEVETPIRN1LTEVETPIRCLLTEVETPI1	1793
1415	1CEVETPIRNE1LTEVETPIRCLLTEVETPI1	1407
1416	1CVETPIRNEW1LTEVETPIRCLLTEVETPI1	1369
1417	1CETPIRNEWG1LTEVETPIRCLLTEVETPI1	1474
878	1CSLLTEVETP1TEVETPIRNCLLTEVETPI1	2664
1418	1CLLTEVETPI1TEVETPIRNCLLTEVETPI1	2371
1419	1CLTEVETPIR1TEVETPIRNCLLTEVETPI1	1907
1420	1CTEVETPIRN1TEVETPIRNCLLTEVETPI1	1905
1421	1CEVETPIRNE1TEVETPIRNCLLTEVETPI1	1469
1422	1CVETPIRNEW1TEVETPIRNCLLTEVETPI1	1452
1423	1CETPIRNEWG1TEVETPIRNCLLTEVETPI1	1735
889	1CSLLTEVETP1EVETPIRNECLLTEVETPI1	2595
1424	1CLLTEVETPI1EVETPIRNECLLTEVETPI1	2331
1425	1CLTEVETPIR1EVETPIRNECLLTEVETPI1	1049
1426	1CTEVETPIRN1EVETPIRNECLLTEVETPI1	1107
873	1CSLLTEVETP1VETPIRNEWCLLTEVETPI1	2767
1427	1CLLTEVETPI1VETPIRNEWCLLTEVETPI1	2410
1428	1CLTEVETPIR1VETPIRNEWCLLTEVETPI1	1465
1429	1CTEVETPIRN1VETPIRNEWCLLTEVETPI1	1559
1430	1CEVETPIRNE1VETPIRNEWCLLTEVETPI1	1477
1431	1CVETPIRNEW1VETPIRNEWCLLTEVETPI1	1588
1432	1CETPIRNEWG1VETPIRNEWCLLTEVETPI1	1453
937	1CSLLTEVETP1ETPIRNEWGCLLTEVETPI1	2646

1433	1CLLTEVETPI1ETPIRNEWGCLLTEVETPI1	2361
1434	1CLTEVETPIR1ETPIRNEWGCLLTEVETPI1	1699
1435	1CTEVETPIRN1ETPIRNEWGCLLTEVETPI1	1573
1436	1CEVETPIRNE1ETPIRNEWGCLLTEVETPI1	1434
1437	1CVETPIRNEW1ETPIRNEWGCLLTEVETPI1	1582
1438	1CETPIRNEWG1ETPIRNEWGCLLTEVETPI1	1968
1439	1CSLLTEVETPI1SLLTEVETPCLTEVETPIR1	2738
949	1CLLTEVETPI1SLLTEVETPCLTEVETPIR1	2403
857	1CLTEVETPIR1SLLTEVETPCLTEVETPIR1	2755
1440	1CTEVETPIRN1SLLTEVETPCLTEVETPIR1	2705
897	1CEVETPIRNE1SLLTEVETPCLTEVETPIR1	2565
843	1CVETPIRNEW1SLLTEVETPCLTEVETPIR1	2498
910	1CETPIRNEWG1SLLTEVETPCLTEVETPIR1	2473
892	1CSLLTEVETPI1LLTEVETPICLTEVETPIR1	2546
1441	1CLLTEVETPI1LLTEVETPICLTEVETPIR1	2288
1442	1CLTEVETPIR1LLTEVETPICLTEVETPIR1	2057
1443	1CTEVETPIRN1LLTEVETPICLTEVETPIR1	2213
1444	1CEVETPIRNE1LLTEVETPICLTEVETPIR1	2000
1445	1CVETPIRNEW1LLTEVETPICLTEVETPIR1	2280
1446	1CETPIRNEWG1LLTEVETPICLTEVETPIR1	2367
886	1CSLLTEVETPI1LTEVETPIRCLTEVETPIR1	2623
1447	1CLLTEVETPI1LTEVETPIRCLTEVETPIR1	2283
944	1CSLLTEVETPI1TEVETPIRNCLTEVETPIR1	2646
1448	1CLLTEVETPI1TEVETPIRNCLTEVETPIR1	2440
1449	1CSLLTEVETPI1EVETPIRNECLTEVETPIR1	2404
1450	1CLLTEVETPI1EVETPIRNECLTEVETPIR1	2188
1451	1CSLLTEVETPI1VETPIRNEWCLTEVETPIR1	2549
1452	1CLLTEVETPI1VETPIRNEWCLTEVETPIR1	2607
1453	1CSLLTEVETPI1ETPIRNEWGCLTEVETPIR1	2465
1454	1CLLTEVETPI1ETPIRNEWGCLTEVETPIR1	2218
918	1CSLLTEVETPI1SLLTEVETPCTEVETPIRN1	2618
1455	1CLLTEVETPI1SLLTEVETPCTEVETPIRN1	2283
946	1CLTEVETPIR1SLLTEVETPCTEVETPIRN1	2434
957	1CTEVETPIRN1SLLTEVETPCTEVETPIRN1	2402
941	1CEVETPIRNE1SLLTEVETPCTEVETPIRN1	2692
947	1CVETPIRNEW1SLLTEVETPCTEVETPIRN1	2733

942	1CETPIRNEWG1SLLTEVETPCTEVETPIRN1	2601
1456	1CSLLTEVETP1LLTEVETPICTEVETPIRN1	2103
1457	1CLLTEVETPI1LLTEVETPICTEVETPIRN1	1884
1458	1CLTEVETPIR1LLTEVETPICTEVETPIRN1	1756
1459	1CTEVETPIRN1LLTEVETPICTEVETPIRN1	1749
1460	1CEVETPIRNE1LLTEVETPICTEVETPIRN1	1620
1461	1CVETPIRNEW1LLTEVETPICTEVETPIRN1	1835
1462	1CETPIRNEWG1LLTEVETPICTEVETPIRN1	1710
971	1CSLLTEVETP1LTEVETPIRCEVETPIRN1	2360
1463	1CLLTEVETPI1LTEVETPIRCEVETPIRN1	2188
1464	1CSLLTEVETP1TEVETPIRNCEVETPIRN1	2755
1465	1CLLTEVETPI1TEVETPIRNCEVETPIRN1	2488
1466	1CSLLTEVETP1EVETPIRNECEVETPIRN1	2134
1467	1CLLTEVETPI1EVETPIRNECEVETPIRN1	1851
1468	1CSLLTEVETP1VETPIRNEWCEVETPIRN1	2301
1469	1CLLTEVETPI1VETPIRNEWCEVETPIRN1	1713
1470	1CSLLTEVETP1ETPIRNEWGCEVETPIRN1	2331
1471	1CLLTEVETPI1ETPIRNEWGCEVETPIRN1	1983
958	1CSLLTEVETP1SLLTEVETPCCEVETPIRNE1	2203
1472	1CLLTEVETPI1SLLTEVETPCCEVETPIRNE1	2057
976	1CLTEVETPIR1SLLTEVETPCCEVETPIRNE1	2216
913	1CTEVETPIRN1SLLTEVETPCCEVETPIRNE1	2139
1473	1CEVETPIRNE1SLLTEVETPCCEVETPIRNE1	2006
1474	1CVETPIRNEW1SLLTEVETPCCEVETPIRNE1	1986
1475	1CETPIRNEWG1SLLTEVETPCCEVETPIRNE1	2642
1476	1CSLLTEVETP1LLTEVETPICEVETPIRNE1	2472
1477	1CLLTEVETPI1LLTEVETPICEVETPIRNE1	2022
1478	1CLTEVETPIR1LLTEVETPICEVETPIRNE1	1681
1479	1CTEVETPIRN1LLTEVETPICEVETPIRNE1	1627
1480	1CEVETPIRNE1LLTEVETPICEVETPIRNE1	1394
1481	1CVETPIRNEW1LLTEVETPICEVETPIRNE1	1592
1482	1CETPIRNEWG1LLTEVETPICEVETPIRNE1	1648
1483	1CSLLTEVETP1LTEVETPIRCEVETPIRNE1	2040
1484	1CLLTEVETPI1LTEVETPIRCEVETPIRNE1	1777
1485	1CSLLTEVETP1TEVETPIRNCEVETPIRNE1	2036
1486	1CLLTEVETPI1TEVETPIRNCEVETPIRNE1	1798

1487	1CSLLTEVETP1EVETPIRNECEVETPIRNE1	1917
1488	1CLLTEVETPI1EVETPIRNECEVETPIRNE1	1631
1489	1CSLLTEVETP1VETPIRNEWCEVETPIRNE1	2359
1490	1CLLTEVETPI1VETPIRNEWCEVETPIRNE1	1730
1491	1CSLLTEVETP1ETPIRNEWGCEVETPIRNE1	2338
1492	1CLLTEVETPI1ETPIRNEWGCEVETPIRNE1	1781
850	1CSLLTEVETP1SLLTEVETPCVETPIRNEW1	2491
975	1CLLTEVETPI1SLLTEVETPCVETPIRNEW1	2316
945	1CLTEVETPIR1SLLTEVETPCVETPIRNEW1	2366
951	1CTEVETPIRN1SLLTEVETPCVETPIRNEW1	2460
959	1CEVETPIRNE1SLLTEVETPCVETPIRNEW1	2441
935	1CVETPIRNEW1SLLTEVETPCVETPIRNEW1	2470
950	1CETPIRNEWG1SLLTEVETPCVETPIRNEW1	2465
974	1CSLLTEVETP1LLTEVETPICVETPIRNEW1	2285
1493	1CLLTEVETPI1LLTEVETPICVETPIRNEW1	2661
1494	1CLTEVETPIR1LLTEVETPICVETPIRNEW1	2443
1495	1CTEVETPIRN1LLTEVETPICVETPIRNEW1	2088
1496	1CEVETPIRNE1LLTEVETPICVETPIRNEW1	1625
1497	1CVETPIRNEW1LLTEVETPICVETPIRNEW1	1817
1498	1CETPIRNEWG1LLTEVETPICVETPIRNEW1	1817
1499	1CSLLTEVETP1LTEVETPIRCVETPIRNEW1	2319
1500	1CLLTEVETPI1LTEVETPIRCVETPIRNEW1	2171
1501	1CSLLTEVETP1TEVETPIRNCVETPIRNEW1	2497
1502	1CLLTEVETPI1TEVETPIRNCVETPIRNEW1	2229
1503	1CSLLTEVETP1EVETPIRNECVETPIRNEW1	2469
1504	1CLLTEVETPI1EVETPIRNECVETPIRNEW1	2081
1505	1CSLLTEVETP1VETPIRNEWCVETPIRNEW1	2398
1506	1CLLTEVETPI1VETPIRNEWCVETPIRNEW1	2074
1507	1CSLLTEVETP1ETPIRNEWGCVETPIRNEW1	2778
1508	1CLLTEVETPI1ETPIRNEWGCVETPIRNEW1	2495
845	1CSLLTEVETP1SLLTEVETPCETPIRNEWG1	2417
1509	1CLLTEVETPI1SLLTEVETPCETPIRNEWG1	2057
962	1CLTEVETPIR1SLLTEVETPCETPIRNEWG1	2230
956	1CTEVETPIRN1SLLTEVETPCETPIRNEWG1	2352
868	1CEVETPIRNE1SLLTEVETPCETPIRNEWG1	2326
866	1CVETPIRNEW1SLLTEVETPCETPIRNEWG1	2328

964	1CETPIRNEWG1SLLTEVETPCETPIRNEWG1	2357
939	1CSLLTEVETP1LLTEVETPICETPIRNEWG1	2446
1510	1CLLTEVETPI1LLTEVETPICETPIRNEWG1	1999
1511	1CLTEVETPIR1LLTEVETPICETPIRNEWG1	2175
1512	1CTEVETPIRN1LLTEVETPICETPIRNEWG1	2645
1513	1CEVETPIRNE1LLTEVETPICETPIRNEWG1	2466
1514	1CVETPIRNEW1LLTEVETPICETPIRNEWG1	2575
1515	1CETPIRNEWG1LLTEVETPICETPIRNEWG1	2427
972	1CSLLTEVETP1LTEVETPIRCETPIRNEWG1	2583
1516	1CLLTEVETPI1LTEVETPIRCETPIRNEWG1	2320
1517	1CSLLTEVETP1TEVETPIRNCETPIRNEWG1	2299
1518	1CLLTEVETPI1TEVETPIRNCETPIRNEWG1	1972
1519	1CSLLTEVETP1EVETPIRNECETPIRNEWG1	2692
1520	1CLLTEVETPI1EVETPIRNECETPIRNEWG1	2433
1521	1CSLLTEVETP1VETPIRNEWCETPIRNEWG1	2569
1522	1CLLTEVETPI1VETPIRNEWCETPIRNEWG1	1931
1523	1CSLLTEVETP1ETPIRNEWGCETPIRNEWG1	2340
1524	1CLLTEVETPI1ETPIRNEWGCETPIRNEWG1	2007
861	SLLTEVET1CSLLTEVET1SLLTEVETCSLLTE1	2691
853	SLLTEVET1CSLLTEVET1SLLTEVETCLLTEV1	2690
901	SLLTEVET1CSLLTEVET1SLLTEVETCLTEVE1	2396
915	SLLTEVET1CSLLTEVET1SLLTEVETCTEVET1	2218
914	SLLTEVET1CSLLTEVET1SLLTEVETCEVETP1	2268
893	SLLTEVET1CSLLTEVET1SLLTEVETCVETPI1	2422
890	SLLTEVET1CSLLTEVET1SLLTEVETCETPIR1	2507
862	SLLTEVET1CSLLTEVET1SLLTEVETCTPIRN1	2690
907	SLLTEVET1CSLLTEVET1SLLTEVETCPIRNE1	2435
852	SLLTEVET1CSLLTEVET1SLLTEVETCIRNEW1	2663
895	SLLTEVET1CSLLTEVET1SLLTEVETCRNEWG1	2476
908	SLLTEVET1CSLLTEVET1SLLTEVETCNEWG1	2461
834	SLLTEVET1CSLLTEVET1SLLTEVETCEWG1R	2855
835	SLLTEVET1CSLLTEVET1SLLTEVETAWGCR1	2870
844	SLLTEVET1CSLLTEVET1SLLTEVETAGCR1N	2814
898	SLLTEVET1CSLLTEVET1SLLTEVETACR1ND	2686
908	SLLTEVET1CSLLTEVET1SLLTEVETCNEWGS1	2726
840	SLLTEVET1CSLLTEVET1SLLTEVETCEWGSR1	2730

1525	CLLTEVETPIRNEWGSCVETPIRNEWGSRSDNC	2278
938	CSLLTEVETCETPIRNEWGSRSDSC	1916
922	CSLLTEVETPCETPIRNEWGSRSDSC	2170
905	CSLLTEVETPICETPIRNEWGSRSDSC	2041
911	CSLLTEVETPIRCETPIRNEWGSRSDSC	2024
891	CSLLTEVETPIRNCETPIRNEWGSRSDSC	1931
917	CSLLTEVETPIRNECETPIRNEWGSRSDSC	1808
1526	CSLLTEVETPIRNEWCETPIRNEWGSRSDSC	2012
881	CSLLTEVETPIRNEWGCETPIRNEWGSRSDSC	2501
1527	CLLTEVETPIRNEWGSCETPIRNEWGSRSDSC	2414
894	CSLLTEVETCTPIRNEWGSRSDSSC	2068
965	CSLLTEVETPCTPIRNEWGSRSDSSC	2351
966	CSLLTEVETPICTPIRNEWGSRSDSSC	2125
924	CSLLTEVETPIRCTPIRNEWGSRSDSSC	2162
979	CSLLTEVETPIRNCTPIRNEWGSRSDSSC	1927
920	CSLLTEVETPIRNECTPIRNEWGSRSDSSC	1988
1528	CSLLTEVETPIRNEWCTPIRNEWGSRSDSSC	1959
980	CSLLTEVETPIRNEWGCTPIRNEWGSRSDSSC	2116
1529	CLLTEVETPIRNEWGCTPIRNEWGSRSDSSC	2268
888	CSLLTEVETCPIRNEWGSRSDSSDC	2246
931	CSLLTEVETPCPIRNEWGSRSDSSDC	2377
954	CSLLTEVETPICPIRNEWGSRSDSSDC	2267
969	CSLLTEVETPIRCPIRNEWGSRSDSSDC	2228
970	CSLLTEVETPIRNCPIRNEWGSRSDSSDC	2089
973	CSLLTEVETPIRNECPIRNEWGSRSDSSDC	1955
1530	CSLLTEVETPIRNEWCPPIRNEWGSRSDSSDC	1983
906	CSLLTEVETPIRNEWGCPPIRNEWGSRSDSSDC	1954
1531	CLLTEVETPIRNEWGSCPIRNEWGSRSDSSDC	1420
875	SLLTEVETCSLLTEVETCSLLTEVETPIRC	2643
909	SLLTEVETCSLLTEVETCLLTEVETPIRNC	2618
960	SLLTEVETCSLLTEVETCLTEVETPIRNEC	2157
940	SLLTEVETCSLLTEVETCTEVETPIRNEWC	2302
930	SLLTEVETCSLLTEVETCEVETPIRNEWGC	2300
925	SLLTEVETCSLLTEVETCVETPIRNEWGSC	2347
927	SLLTEVETCSLLTEVETCETPIRNEWGSRSC	2311
912	SLLTEVETCSLLTEVETCTPIRNEWGSRSC	2434

933	SLLTEVETCSLLTEVETCPIRNEWGSR SNC	2192
948	SLLTEVETCSLLTEVETCIRNEWGSR SDC	1961
884	SLLTEVETCSLLTEVETCRNEWGSR SDC	2620
846	SLLTEVETCSLLTEVETCNEWGSR SDC	2640
874	SLLTEVETCSLLTEVETCEWGSR SDC	2509
856	SLLTEVETCSLLTEVETCVETPIRNEWGC	2671
879	SLLTEVETCSLLTEVETCETPIRNEWGCR	2631
833	SLLTEVETCSLLTEVETATPIRNEWGCRC	2640
899	SLLTEVETCSLLTEVETAPIRNEWGCRCN	2576
904	SLLTEVETCSLLTEVETAIRNEWGCRCND	2538
926	SLLTEVETCSLLTEVETARNEWGCRCNDS	2463
928	SLLTEVETCSLLTEVETANNEWGCRCNDSS	2358
865	SLLTEVETCSLLTEVETAEWGCRCNDSSD	2254
1532	CSLLTEVETPIRNEWGCRCNDSSD	2284
1533	CLLTEVETPIRNEWGCRCNDSSD	1979
1534	SLLCEVETPIRNEWGCRCNDSSD	2161
566	SLLTEVCTPIRNEWGCRCNDSSD	1210
718	SLLTEVECPIRNEWGCRCNDSSD	1974
623	SLLTEVETCIRNEWGCRCNDSSD	1992
687	SLLTEVETPCRNEWGCRCNDSSD	2050
725	SLLTEVETPICNEWGCRCNDSSD	2005
587	SLLTEVETPIRCEWGCRNDSSD	1956
733	SLLTEVETPIRNCWGCRNDSSD	2006
268	SLLTEVETPIRNECGCRNDSSD	2554
714	SLLTEVETPIRNEWCCRCNDSSD	2388
127	CSLLTEVETCSLLTEVETC	2555
198	CSLLTEVETPCSLLTEVETC	2341
187	CSLLTEVETPICSLLTEVETC	2554
147	CSLLTEVETPIRCSLLTEVETC	2662
166	CSLLTEVETPIRNCSSLLTEVETC	2538
118	CSLLTEVETPIRNECSSLLTEVETC	2489
122	CSLLTEVETPIRNEWCSLLTEVETC	2454
200	CSLLTEVETPIRNEWGCSLLTEVETC	2371
254	CLLTEVETPIRNEWGSCSLLTEVETC	2177
136	CLTEVETPIRNEWGSRCSLLTEVETC	2026
226	CTEVETPIRNEWGSRCSLLTEVETC	2140

201	CEVETPIRNEWGSRSNCSLLTEVETC	2288
223	CVETPIRNEWGSRSDCSLLTEVETC	2233
213	CETPIRNEWGSRSDSCSLLTEVETC	1997
230	CTPIRNEWGSRSDSSCSLLTEVETC	2168
161	CPIRNEWGSRSDSSDCSLLTEVETC	2759
142	CSLLTEVETCSLLTEVETPC	2716
156	CSLLTEVETPCSLLTEVETPC	2673
207	CSLLTEVETPICSLLTEVETPC	2440
181	CSLLTEVETPIRCSLLTEVETPC	2448
144	CSLLTEVETPIRNCSSLLTEVETPC	2673
164	CSLLTEVETPIRNECSLLTEVETPC	2582
189	CSLLTEVETPIRNEWCSLLTEVETPC	2505
217	CSLLTEVETPIRNEWGCSLLTEVETPC	2445
270	CLLTEVETPIRNEWGSCSLLTEVETPC	2307
228	CLTEVETPIRNEWGSRCSLLTEVETPC	2237
246	CTEVETPIRNEWGSRSCSLLTEVETPC	2182
229	CEVETPIRNEWGSRSNCSLLTEVETPC	2290
242	CVETPIRNEWGSRSDCSLLTEVETPC	2379
232	CETPIRNEWGSRSDSCSLLTEVETPC	2425
247	CTPIRNEWGSRSDSSCSLLTEVETPC	2249
259	CPIRNEWGSRSDSSDCSLLTEVETPC	2441
128	CSLLTEVETCSLLTEVETPIC	2876
137	CSLLTEVETPCSLLTEVETPIC	2815
245	CSLLTEVETPICSLLTEVETPIC	2492
151	CSLLTEVETPIRCSLLTEVETPIC	2561
139	CSLLTEVETPIRNCSSLLTEVETPIC	2666
145	CSLLTEVETPIRNECSLLTEVETPIC	2684
177	CSLLTEVETPIRNEWCSLLTEVETPIC	2548
197	CSLLTEVETPIRNEWGCSLLTEVETPIC	2481
252	CLLTEVETPIRNEWGSCSLLTEVETPIC	2333
191	CLTEVETPIRNEWGSRCSLLTEVETPIC	2405
216	CTEVETPIRNEWGSRSCSLLTEVETPIC	2308
219	CEVETPIRNEWGSRSNCSLLTEVETPIC	2363
132	CVETPIRNEWGSRSDCSLLTEVETPIC	2372
237	CETPIRNEWGSRSDSCSLLTEVETPIC	2436
231	CTPIRNEWGSRSDSSCSLLTEVETPIC	2460

267	CPIRNEWGSRSDSSDCSLLTEVETPIC	2227
163	CSLLTEVETCSLLTEVETPIRC	2531
124	CSLLTEVETPCSLLETEVETPIRC	2839
203	CSLLTEVETPICSLLETEVETPIRC	2628
121	CSLLTEVETPIRCSLLTEVETPIRC	2767
120	CSLLTEVETPIRNCSSLLTEVETPIRC	2751
130	CSLLTEVETPIRNECSLLTEVETPIRC	2751
155	CSLLTEVETPIRNEWCSLLTEVETPIRC	2646
157	CSLLTEVETPIRNEWGCSLLTEVETPIRC	2619
117	CLLETEVETPIRNEWGSCSLLTEVETPIRC	2622
162	CLTEVETPIRNEWGSRCSLLTEVETPIRC	2476
184	CTEVETPIRNEWGSRSCSLLTEVETPIRC	2419
172	CEVETPIRNEWGSRSNCSLLTEVETPIRC	2467
168	CVETPIRNEWGSRSDCSLLTEVETPIRC	2484
190	CETPIRNEWGSRSDSCSLLTEVETPIRC	2514
169	CTPIRNEWGSRSDSSCSLLTEVETPIRC	2518
176	CPIRNEWGSRSDSSDCSLLTEVETPIRC	2586
134	CSLLTEVETCSLLTEVETPIRNC	2633
153	CSLLTEVETPCSLLETEVETPIRNC	2691
208	CSLLTEVETPICSLLETEVETPIRNC	2548
131	CSLLTEVETPIRCSLLTEVETPIRNC	2753
129	CSLLTEVETPIRNCSSLLTEVETPIRNC	2748
133	CSLLTEVETPIRNECSLLTEVETPIRNC	2724
180	CSLLTEVETPIRNEWCSLLTEVETPIRNC	2538
143	CSLLTEVETPIRNEWGCSLLTEVETPIRNC	2657
178	CLLETEVETPIRNEWGSCSLLTEVETPIRNC	2574
119	CLTEVETPIRNEWGSRCSLLTEVETPIRNC	2459
204	CTEVETPIRNEWGSRSCSLLTEVETPIRNC	2358
196	CEVETPIRNEWGSRSNCSLLTEVETPIRNC	2429
194	CVETPIRNEWGSRSDCSLLTEVETPIRNC	2440
126	CETPIRNEWGSRSDSCSLLTEVETPIRNC	2440
185	CTPIRNEWGSRSDSSCSLLTEVETPIRNC	2492
202	CPIRNEWGSRSDSSDCSLLTEVETPIRNC	2500
171	CSLLTEVETCSLLTEVETPIRNEC	2424
193	CSLLTEVETPCSLLETEVETPIRNEC	2387
1535	CSLLTEVETPICSLLETEVETPIRNEC	1851

165	CSLLTEVETPIRCSLLTEVETPIRNEC	2648
183	CSLLTEVETPIRNCSSLLTEVETPIRNEC	2580
220	CSLLTEVETPIRNECSSLLTEVETPIRNEC	2522
241	CSLLTEVETPIRNEWCSLLTEVETPIRNEC	2349
206	CSLLTEVETPIRNEWGCSLLTEVETPIRNEC	2419
244	CLLTEVETPIRNEWGSCSSLLTEVETPIRNEC	2327
240	CLTEVETPIRNEWGSRCSLLTEVETPIRNEC	2221
261	CTEVETPIRNEWGSRSCSSLLTEVETPIRNEC	2074
273	CEVETPIRNEWGSRSNCSLLTEVETPIRNEC	2008
269	CVETPIRNEWGSRSDCSLLTEVETPIRNEC	2140
154	CETPIRNEWGSRSDSCSSLLTEVETPIRNEC	2122
266	CTPIRNEWGSRSDSSCSLLTEVETPIRNEC	2080
248	CPIRNEWGSRSDSSDCSSLLTEVETPIRNEC	2249
150	CSLLTEVETCSLLTEVETPIRNEWC	2577
158	CSLLTEVETPCSSLLTEVETPIRNEWC	2567
211	CSLLTEVETPICSSLLTEVETPIRNEWC	2423
173	CSLLTEVETPIRCSLLTEVETPIRNEWC	2566
135	CSLLTEVETPIRNCSSLLTEVETPIRNEWC	2820
146	CSLLTEVETPIRNECSSLLTEVETPIRNEWC	2720
174	CSLLTEVETPIRNEWCSLLTEVETPIRNEWC	2647
212	CSLLTEVETPIRNEWGCSLLTEVETPIRNEWC	2545
218	CLLTEVETPIRNEWGSCSSLLTEVETPIRNEWC	2541
188	CLTEVETPIRNEWGSRCSLLTEVETPIRNEWC	2522
225	CTEVETPIRNEWGSRSCSSLLTEVETPIRNEWC	2482
238	CEVETPIRNEWGSRSNCSLLTEVETPIRNEWC	2391
234	CVETPIRNEWGSRSDCSLLTEVETPIRNEWC	2412
251	CETPIRNEWGSRSDSCSSLLTEVETPIRNEWC	2374
272	CTPIRNEWGSRSDSSCSLLTEVETPIRNEWC	2313
249	CPIRNEWGSRSDSSDCSSLLTEVETPIRNEWC	2397
281	CSLLTEVETCSLLTEVETPIRNEWGC	2479
186	CSLLTEVETPCSSLLTEVETPIRNEWGC	2523
236	CSLLTEVETPICSSLLTEVETPIRNEWGC	2345
167	CSLLTEVETPIRCSLLTEVETPIRNEWGC	2600
148	CSLLTEVETPIRNCSSLLTEVETPIRNEWGC	2553
152	CSLLTEVETPIRNECSSLLTEVETPIRNEWGC	2732
141	CSLLTEVETPIRNEWCSLLTEVETPIRNEWGC	2669

140	CSLLTEVETPIRNEWGCSLLTEVETPIRNEWGC	2678
205	CLLTEVETPIRNEWGSCSLLTEVETPIRNEWGC	2593
116	CLTEVETPIRNEWGSRCSLLTEVETPIRNEWGC	2492
125	CTEVETPIRNEWGSRSCSLLTEVETPIRNEWGC	2449
233	CEVETPIRNEWGSRSNCSLLTEVETPIRNEWGC	2442
257	CVETPIRNEWGSRSDCSLLTEVETPIRNEWGC	2400
255	CETPIRNEWGSRSDSCSLLTEVETPIRNEWGC	2414
243	CTPIRNEWGSRSDSSCSLLTEVETPIRNEWGC	2466
256	CPIRNEWGSRSDSSDCSLLTEVETPIRNEWGC	2460
179	CSLLTEVETCLLTEVETPIRNEWGSC	2416
182	CSLLTEVETPCLLTEVETPIRNEWGSC	2540
224	CSLLTEVETPICLLTEVETPIRNEWGSC	2388
160	CSLLTEVETPIRCLLTEVETPIRNEWGSC	2520
192	CSLLTEVETPIRNCLLTEVETPIRNEWGSC	2519
227	CSLLTEVETPIRNECLLTEVETPIRNEWGSC	2484
214	CSLLTEVETPIRNEWCLLTEVETPIRNEWGSC	2661
138	CSLLTEVETPIRNEWGCLLTEVETPIRNEWGSC	2624
1536	CLLTEVETPIRNEWGSCCLLTEVETPIRNEWGSC	2616
1537	CLTEVETPIRNEWGSRCLLTEVETPIRNEWGSC	2667
1538	CTEVETPIRNEWGSRSCCLLTEVETPIRNEWGSC	2425
1539	CEVETPIRNEWGSRSNCLLTEVETPIRNEWGSC	2461
1540	CVETPIRNEWGSRSDCLLTEVETPIRNEWGSC	2218
1541	CETPIRNEWGSRSDSCCLLTEVETPIRNEWGSC	2255
1542	CTPIRNEWGSRSDSSCLLTEVETPIRNEWGSC	2363
1543	CPIRNEWGSRSDSSDCCLLTEVETPIRNEWGSC	2260
215	CSLLTEVETCLTEVETPIRNEWGSR	2328
221	CSLLTEVETPCLTEVETPIRNEWGSR	2513
235	CSLLTEVETPICLTEVETPIRNEWGSR	2351
170	CSLLTEVETPIRCLTEVETPIRNEWGSR	2587
195	CSLLTEVETPIRNCLTEVETPIRNEWGSR	2585
123	CSLLTEVETPIRNECLTEVETPIRNEWGSR	2496
278	CSLLTEVETPIRNEWCLTEVETPIRNEWGSR	2429
175	CSLLTEVETPIRNEWGCLTEVETPIRNEWGSR	2641
1544	CLLTEVETPIRNEWGSCCLTEVETPIRNEWGSR	2500
250	CSLLTEVETCTEVETPIRNEWGSR	2474
222	CSLLTEVETPCTEVETPIRNEWGSR	2703

280	CSLLTEVETPICTEVETPIRNEWGSRSC	2241
199	CSLLTEVETPIRCTEVETPIRNEWGSRSC	2623
210	CSLLTEVETPIRNCTEVETPIRNEWGSRSC	2643
258	CSLLTEVETPIRNECTEVETPIRNEWGSRSC	2553
277	CSLLTEVETPIRNEWCTEVETPIRNEWGSRSC	2388
263	CSLLTEVETPIRNEWGCTEVETPIRNEWGSRSC	2496
1545	CLLTEVETPIRNEWGSCTEVETPIRNEWGSRSC	2592
239	CSLLTEVETCEVETPIRNEWGSRSC	2549
274	CSLLTEVETPCEVETPIRNEWGSRSC	2701
260	CSLLTEVETPICEVETPIRNEWGSRSC	2680
209	CSLLTEVETPIRCEVETPIRNEWGSRSC	2699
253	CSLLTEVETPIRNCEVETPIRNEWGSRSC	2699
276	CSLLTEVETPIRNECEVETPIRNEWGSRSC	2620
1546	CSLLTEVETPIRNEWCEVETPIRNEWGSRSC	2519
275	CSLLTEVETPIRNEWGCEVETPIRNEWGSRSC	2397
1547	CLLTEVETPIRNEWGSCCEVETPIRNEWGSRSC	2074
264	CSLLTEVETCVETPIRNEWGSRSC	2374
265	CSLLTEVETPCVETPIRNEWGSRSC	2484
1548	CSLLTEVETPICVETPIRNEWGSRSC	2174
271	CSLLTEVETPIRCVETPIRNEWGSRSC	2480
262	CSLLTEVETPIRNCVETPIRNEWGSRSC	2566
279	CSLLTEVETPIRNECVETPIRNEWGSRSC	2465
1549	CSLLTEVETPIRNEWCVETPIRNEWGSRSC	2433
159	CSLLTEVETPIRNEWGCVETPIRNEWGSRSC	2415
320	SLLTEVGSLLTEV	2530
283	CSLLTEVGSLLTEV	2903
390	CLLTEVGSLLTEV	2494
500	SCLTEVGSLLTEV	1610
324	SLCTEVGSLLTEV	1780
336	SLLCEVGSLLTEV	2475
824	SLLTCVGSLLTEV	1772
482	CLCTCVGSLLTEV	1953
354	SLLTEVGCSLLTEV	2511
807	CLLTEVGCSLLTEV	1558
580	SLCTEVGCSLLTEV	2382
511	SLLCEVGCSLLTEV	2562

810	SLLTCVGCSSLTEV	1992
798	CLCTCVGCSSLTEV	1489
311	SLLTEVGCLLTEV	1924
388	CSLLTEVGCLLTEV	2427
1550	SLLCEVGCLLTEV	1997
302	ASLLTEVGSCLTEV	2770
345	CSLLTEVGSCLTEV	2703
1551	SLLCEVGSCLTEV	2499
464	SLLTEVGSLCTEV	2219
711	CSLLTEVGSLCTEV	2409
1552	SLLCEVGSLCTEV	2722
314	SLLTEVGSLLCEV	2392
792	CSLLTEVGSLLCEV	2594
1553	CLLTEVGSLLCEV	2168
496	SCLTEVGSLLCEV	1896
506	SLCTEVGSLLCEV	1863
1554	SLLCEVGSLLCEV	2399
1555	SLLTCVGSLLCEV	2264
477	SLLTECGSLLCEV	2403
1556	CSCLCEVGSLLCEV	1583
1557	CLCTCVGSLLCEV	2246
1558	SCLCECGSLLCEV	1747
814	CSLLTECGSLLCEV	2256
284	ASLLTEVGSLLTCV	2358
290	CSLLTEVGSLLTCV	2503
1559	SLLCEVGSLLTCV	1972
452	SLLTEVGSLLTEC	1862
292	CSLLTEVGSLLTEC	2213
351	SLLCEVGSLLTEC	2438
525	SLLTEVGCSCLECEV	1829
379	SLCTEVGCSCLECEV	1500
1560	SLLCEVGCSCLECEV	2112
299	SLLTEVGCLCTCV	2346
385	CSLLTEVGCLCTCV	2474
1561	SLLCEVGCLCTCV	2331
329	SLLTEVGSCLCEC	2558

533	CSLLTEVGSCCLCEC	2625
1562	SLLCEVGSCCLCEC	2614
353	SLLTEVGCSLLTEC	2380
747	SLCTEVGCSLLTEC	2050
301	SLLCEVGCSLLTEC	2637
341	CSLLTEVCSLLTEC	1122
321	ALLTEVETPIRNEWGCRCNDSSD	2225
1563	DLLTEVETPIRNEWGCRCNDSSD	2320
1564	ELLTEVETPIRNEWGCRCNDSSD	2201
1565	FLLTEVETPIRNEWGCRCNDSSD	1018
1566	GLLTEVETPIRNEWGCRCNDSSD	2321
1567	HLLTEVETPIRNEWGCRCNDSSD	1946
1568	ILLTEVETPIRNEWGCRCNDSSD	1044
1569	KLLTEVETPIRNEWGCRCNDSSD	1826
538	LLLTEVETPIRNEWGCRCNDSSD	1399
1570	MLLTEVETPIRNEWGCRCNDSSD	2126
1571	NLLTEVETPIRNEWGCRCNDSSD	2135
1572	PLLTEVETPIRNEWGCRCNDSSD	1641
1573	QLLTEVETPIRNEWGCRCNDSSD	1627
1574	RLLTEVETPIRNEWGCRCNDSSD	1338
326	SLLTEVETPIRNEWGCRCNDSSD	2476
312	TLLTEVETPIRNEWGCRCNDSSD	2510
520	VLLTEVETPIRNEWGCRCNDSSD	1758
1575	WLLTEVETPIRNEWGCRCNDSSD	2180
1576	YLLTEVETPIRNEWGCRCNDSSD	1882
349	SLATEVETPIRNEWGCRCNDSSD	2145
1577	SLDTEVETPIRNEWGCRCNDSSD	1505
328	SLETEVETPIRNEWGCRCNDSSD	1963
459	SLITEVETPIRNEWGCRCNDSSD	1996
377	SLKTEVETPIRNEWGCRCNDSSD	1453
327	SLMTEVETPIRNEWGCRCNDSSD	2149
449	SLNTEVETPIRNEWGCRCNDSSD	1908
352	SLQTEVETPIRNEWGCRCNDSSD	2025
510	SLRTEVETPIRNEWGCRCNDSSD	1034
473	SLSTEVETPIRNEWGCRCNDSSD	2052
478	SLTTEVETPIRNEWGCRCNDSSD	1804

484	SLVTEVETPIRNEWGCRCNDSSD	2029
1578	SLLAEVETPIRNEWGCRCNDSSD	2356
1579	SLLDEVETPIRNEWGCRCNDSSD	2276
1580	SLLEEVETPIRNEWGCRCNDSSD	2420
1581	SLLFEVETPIRNEWGCRCNDSSD	2137
1582	SLLGEVETPIRNEWGCRCNDSSD	2301
1583	SLLHEVETPIRNEWGCRCNDSSD	2462
1584	SLLIEVETPIRNEWGCRCNDSSD	1899
1585	SLLKEVETPIRNEWGCRCNDSSD	2611
1586	SLLLEVETPIRNEWGCRCNDSSD	2344
346	SLLMEVETPIRNEWGCRCNDSSD	2477
1587	SLLNEVETPIRNEWGCRCNDSSD	2425
381	SLLQEVETPIRNEWGCRCNDSSD	2432
1588	SLLREVETPIRNEWGCRCNDSSD	2286
803	SLLSEVETPIRNEWGCRCNDSSD	2305
1589	SLLVEVETPIRNEWGCRCNDSSD	1932
1590	SLLWEVETPIRNEWGCRCNDSSD	2221
1591	SLLYEVETPIRNEWGCRCNDSSD	2181
822	SLLTDVETPIRNEWGCRCNDSSD	1113
522	SLLTMVETPIRNEWGCRCNDSSD	1244
608	SLLTEIETPIRNEWGCRCNDSSD	2016
556	SLLTELETPIRNEWGCRCNDSSD	1380
547	SLLTETETPIRNEWGCRCNDSSD	1594
551	SLLTEVATPIRNEWGCRCNDSSD	2093
657	SLLTEVDTPIRNEWGCRCNDSSD	2095
731	SLLTEVFTPIRNEWGCRCNDSSD	1708
784	SLLTEVGTPIRNEWGCRCNDSSD	2005
690	SLLTEVHTPIRNEWGCRCNDSSD	2057
795	SLLTEVITPIRNEWGCRCNDSSD	1438
705	SLLTEVKTPIRNEWGCRCNDSSD	1905
709	SLLTEVLTPIRNEWGCRCNDSSD	1743
629	SLLTEVMTPIRNEWGCRCNDSSD	2331
675	SLLTEVNTPIRNEWGCRCNDSSD	2150
594	SLLTEVQTPIRNEWGCRCNDSSD	2289
575	SLLTEVRTPIRNEWGCRCNDSSD	1024
545	SLLTEVSTPIRNEWGCRCNDSSD	2288

553	SLLTEVTTPIRNEWGCRCNDSSD	2102
645	SLLTEVVTPIRNEWGCRCNDSSD	1492
583	SLLTEVWTPIRNEWGCRCNDSSD	1889
658	SLLTEVYTPIRNEWGCRCNDSSD	1092
635	SLLTEVEAPIRNEWGCRCNDSSD	2325
779	SLLTEVEDPIRNEWGCRCNDSSD	2216
652	SLLTEVEEPIRNEWGCRCNDSSD	2362
621	SLLTEVEFPIRNEWGCRCNDSSD	2297
646	SLLTEVEGPIRNEWGCRCNDSSD	2341
450	SLLTEVEHPIRNEWGCRCNDSSD	2241
593	SLLTEVEIPIRNEWGCRCNDSSD	2365
534	SLLTEVEKPIRNEWGCRCNDSSD	2505
564	SLLTEVELPIRNEWGCRCNDSSD	2407
590	SLLTEVEMPIRNEWGCRCNDSSD	2516
467	SLLTEVENPIRNEWGCRCNDSSD	2549
537	SLLTEVEPPIRNEWGCRCNDSSD	2522
527	SLLTEVEQPIRNEWGCRCNDSSD	2344
599	SLLTEVERPIRNEWGCRCNDSSD	2131
607	SLLTEVESPIRNEWGCRCNDSSD	2156
695	SLLTEVEVPIRNEWGCRCNDSSD	2286
763	SLLTEVEWPIRNEWGCRCNDSSD	2178
783	SLLTEVEYPIRNEWGCRCNDSSD	2113
559	SLLTEVETAIRNEWGCRCNDSSD	2415
610	SLLTEVETDIRNEWGCRCNDSSD	2392
602	SLLTEVETEIRNEWGCRCNDSSD	2368
549	SLLTEVETFIRNEWGCRCNDSSD	2301
597	SLLTEVETGIRNEWGCRCNDSSD	2366
609	SLLTEVETHIRNEWGCRCNDSSD	2288
653	SLLTEVETIIRNEWGCRCNDSSD	2096
300	SLLTEVETKIRNEWGCRCNDSSD	2485
491	SLLTEVETLIRNEWGCRCNDSSD	2225
493	SLLTEVETMIRNEWGCRCNDSSD	2320
529	SLLTEVETNIRNEWGCRCNDSSD	2253
606	SLLTEVETQIRNEWGCRCNDSSD	2189
611	SLLTEVETRIRNEWGCRCNDSSD	2159
700	SLLTEVETSIRNEWGCRCNDSSD	2151

649	SLLTEVETTIRNEWGCRCNDSSD	2295
614	SLLTEVETVIRNEWGCRCNDSSD	2264
670	SLLTEVETWIRNEWGCRCNDSSD	2146
581	SLLTEVETYIRNEWGCRCNDSSD	2290
715	SLLTEVETPARNEWGCRCNDSSD	2244
660	SLLTEVETPDRNEWGCRCNDSSD	2390
630	SLLTEVETPERNEWGCRCNDSSD	2480
665	SLLTEVETPFRNEWGCRCNDSSD	2229
495	SLLTEVETPGRNEWGCRCNDSSD	2676
591	SLLTEVETPHRNEWGCRCNDSSD	2425
392	SLLTEVETPKRNEWGCRCNDSSD	2300
461	SLLTEVETPLRNEWGCRCNDSSD	2239
457	SLLTEVETPMRNEWGCRCNDSSD	2297
770	SLLTEVETPNRNEWGCRCNDSSD	2299
738	SLLTEVETPPRNEWGCRCNDSSD	2302
782	SLLTEVETPQRNEWGCRCNDSSD	2341
750	SLLTEVETPRRNEWGCRCNDSSD	2376
673	SLLTEVETPSRNEWGCRCNDSSD	2396
758	SLLTEVETPTRNEWGCRCNDSSD	2417
650	SLLTEVETPVRNEWGCRCNDSSD	2331
693	SLLTEVETPWRNEWGCRCNDSSD	2190
389	SLLTEVETPYRNEWGCRCNDSSD	2303
707	SLLTEVETPIANNEWGCRCNDSSD	2302
524	SLLTEVETPIDNEWGCRCNDSSD	2337
676	SLLTEVETPIENNEWGCRCNDSSD	2252
576	SLLTEVETPIFNEWGCRCNDSSD	2176
744	SLLTEVETPIGNEWGCRCNDSSD	2073
488	SLLTEVETPIHNEWGCRCNDSSD	2121
720	SLLTEVETPIINNEWGCRCNDSSD	2262
778	SLLTEVETPIKNEWGCRCNDSSD	2322
692	SLLTEVETPILNEWGCRCNDSSD	2363
454	SLLTEVETPIMNEWGCRCNDSSD	2369
780	SLLTEVETPINNEWGCRCNDSSD	2277
357	SLLTEVETPIPNEWGCRCNDSSD	2515
677	SLLTEVETPIQNEWGCRCNDSSD	2372
754	SLLTEVETPISNEWGCRCNDSSD	2292

766	SLLTEVETPITNEWGCRCNDSSD	2358
680	SLLTEVETPIVNEWGCRCNDSSD	2366
656	SLLTEVETPIWNEWGCRCNDSSD	2250
509	SLLTEVETPIYNEWGCRCNDSSD	2296
582	SLLTEVETPIRAEWGCRCNDSSD	2306
698	SLLTEVETPIRDEWGCRCNDSSD	2187
771	SLLTEVETPIREEWGCRCNDSSD	2156
620	SLLTEVETPIRFEWGCRCNDSSD	2364
773	SLLTEVETPIRGEWGCRCNDSSD	2228
721	SLLTEVETPIRHEWGCRCNDSSD	2296
627	SLLTEVETPIRIEWGCRCNDSSD	2444
631	SLLTEVETPIRKEWGCRCNDSSD	2437
585	SLLTEVETPIRLEWGCRCNDSSD	2468
622	SLLTEVETPIRMEWGCRCNDSSD	2385
753	SLLTEVETPIRPEWGCRCNDSSD	2301
661	SLLTEVETPIRQEWGCRCNDSSD	2367
710	SLLTEVETPIRREWGCRCNDSSD	2278
678	SLLTEVETPIRSEWGCRCNDSSD	2322
387	SLLTEVETPIRTEWGCRCNDSSD	2360
565	SLLTEVETPIRVEWGCRCNDSSD	2300
562	SLLTEVETPIRWEWGCRCNDSSD	2302
654	SLLTEVETPIRYEWGCRCNDSSD	2202
666	SLLTEVETPIRNAWGCRCNDSSD	2334
712	SLLTEVETPIRNDWGCRCNDSSD	2324
662	SLLTEVETPIRNFWGCRCNDSSD	2417
643	SLLTEVETPIRNGWGCRCNDSSD	2408
684	SLLTEVETPIRNHWGCRCNDSSD	2377
577	SLLTEVETPIRNIWGCRCNDSSD	2490
640	SLLTEVETPIRNKWGCRCNDSSD	2402
571	SLLTEVETPIRNLWGCRCNDSSD	2415
605	SLLTEVETPIRNMWGCRCNDSSD	2455
741	SLLTEVETPIRNNWGCRCNDSSD	2319
616	SLLTEVETPIRNPWGCRCNDSSD	2288
512	SLLTEVETPIRNQWGCRCNDSSD	2402
546	SLLTEVETPIRNRWGCRCNDSSD	2257
617	SLLTEVETPIRNSWGCRCNDSSD	2300

380	SLLTEVETPIRNTWGCRCNDSSD	2314
685	SLLTEVETPIRNVWGCRCNDSSD	2281
703	SLLTEVETPIRNWWGCRCNDSSD	2293
702	SLLTEVETPIRNYWGCRCNDSSD	2311
453	SLLTEVETPIRNEAGCRCNDSSD	2383
751	SLLTEVETPIRNEDGCRCNDSSD	2359
787	SLLTEVETPIRNEEGCRCNDSSD	2330
716	SLLTEVETPIRNEFGCRCNDSSD	2444
708	SLLTEVETPIRNEGGCRCNDSSD	2486
696	SLLTEVETPIRNEHGCRCNDSSD	2398
636	SLLTEVETPIRNEIGCRCNDSSD	2402
572	SLLTEVETPIRNEKGCRCNDSSD	2580
641	SLLTEVETPIRNELGCRCNDSSD	2436
517	SLLTEVETPIRNEMGCRCNDSSD	2398
637	SLLTEVETPIRNENGRCRCNDSSD	2265
671	SLLTEVETPIRNEPGCRCNDSSD	2279
765	SLLTEVETPIRNEQGCRCNDSSD	2264
737	SLLTEVETPIRNERGCRCNDSSD	2328
745	SLLTEVETPIRNESGCRCNDSSD	2346
688	SLLTEVETPIRNETGCRCNDSSD	2401
386	SLLTEVETPIRNEVGCRCNDSSD	2411
384	SLLTEVETPIRNEYGCRCNDSSD	2426
681	SLLTEVETPIRNEWACRCNDSSD	2431
717	SLLTEVETPIRNEWDCRCNDSSD	2322
726	SLLTEVETPIRNEWECRCNDSSD	2364
596	SLLTEVETPIRNEWFCRCNDSSD	2493
633	SLLTEVETPIRNEWHCRCNDSSD	2327
347	SLLTEVETPIRNEWICRCNDSSD	2359
541	SLLTEVETPIRNEWKRCRCNDSSD	2328
569	SLLTEVETPIRNEWLCRCNDSSD	2379
642	SLLTEVETPIRNEWMCRCNDSSD	2378
785	SLLTEVETPIRNEWNCRCNDSSD	2236
774	SLLTEVETPIRNEWPCRCNDSSD	2328
760	SLLTEVETPIRNEWQCRCNDSSD	2338
704	SLLTEVETPIRNEWRCRCNDSSD	2371
735	SLLTEVETPIRNEWSCRCNDSSD	2374

669	SLLTEVETPIRNEWTCRCNDSSD	2401
624	SLLTEVETPIRNEWVCRCNDSSD	2418
366	SLLTEVETPIRNEWWCRCNDSSD	2406
625	SLLTEVETPIRNEWYCRCNDSSD	2362
659	SLLTEVETPIRNEWGARCNDSSD	2396
790	SLLTEVETPIRNEWGDRCNDSSD	2267
370	SLLTEVETPIRNEWGERCNDSSD	2286
504	SLLTEVETPIRNEWGFRCDSSD	2349
563	SLLTEVETPIRNEWGGRCNDSSD	2270
647	SLLTEVETPIRNEWGHRCDSSD	2113
667	SLLTEVETPIRNEWGIRCNDSSD	2211
648	SLLTEVETPIRNEWGKRCNDSSD	2295
600	SLLTEVETPIRNEWGLRCNDSSD	2389
732	SLLTEVETPIRNEWGMRCNDSSD	2269
664	SLLTEVETPIRNEWGNRCNDSSD	2328
727	SLLTEVETPIRNEWGPCNDSSD	2334
713	SLLTEVETPIRNEWGQRCNDSSD	2369
672	SLLTEVETPIRNEWGRRCDSSD	2372
682	SLLTEVETPIRNEWGSRCDSSD	2346
638	SLLTEVETPIRNEWGTRCDSSD	2404
644	SLLTEVETPIRNEWGVRCNDSSD	2444
595	SLLTEVETPIRNEWGWRCNDSSD	2439
668	SLLTEVETPIRNEWGYRCNDSSD	2410
683	SLLTEVETPIRNEWGCACNDSSD	2301
501	SLLTEVETPIRNEWGCCNDSSD	2515
615	SLLTEVETPIRNEWGCDNDSSD	2207
679	SLLTEVETPIRNEWGCECNDSSD	2148
639	SLLTEVETPIRNEWGCFCNDSSD	2312
775	SLLTEVETPIRNEWGCGCNDSSD	2186
776	SLLTEVETPIRNEWGCHCNDSSD	2134
722	SLLTEVETPIRNEWGCICNDSSD	2269
701	SLLTEVETPIRNEWGCKCNDSSD	2290
748	SLLTEVETPIRNEWGCLCNDSSD	2292
730	SLLTEVETPIRNEWGCMCNDSSD	2413
743	SLLTEVETPIRNEWGCNCNDSSD	2340
767	SLLTEVETPIRNEWGCPCNDSSD	2295

756	SLLTEVETPIRNEWGCQCNDSSD	2294
736	SLLTEVETPIRNEWGCSCNDSSD	2348
719	SLLTEVETPIRNEWGCTCNDSSD	2347
742	SLLTEVETPIRNEWGCVCNDSSD	2334
503	SLLTEVETPIRNEWGCWCNDSSD	2437
552	SLLTEVETPIRNEWGCYCNDSSD	2397
634	SLLTEVETPIRNEWGCRANDSSD	2265
794	SLLTEVETPIRNEWGCRDNDSSD	2033
796	SLLTEVETPIRNEWGCRENDSSD	2097
723	SLLTEVETPIRNEWGCRFNDSSD	2303
752	SLLTEVETPIRNEWGCRGNDSSD	2345
734	SLLTEVETPIRNEWGCRHNDSSD	2353
697	SLLTEVETPIRNEWGCRINDSSD	2409
598	SLLTEVETPIRNEWGCRKNDSSD	2435
686	SLLTEVETPIRNEWGCRLNDSSD	2363
691	SLLTEVETPIRNEWGCRMNDSSD	2356
746	SLLTEVETPIRNEWGCRNNDSSD	2384
757	SLLTEVETPIRNEWGCRPNDSSD	2326
772	SLLTEVETPIRNEWGCRQNDSSD	2327
584	SLLTEVETPIRNEWGCRRNDSSD	2383
519	SLLTEVETPIRNEWGCRSNDSSD	2344
573	SLLTEVETPIRNEWGCRTNDSSD	2374
375	SLLTEVETPIRNEWGCRVNDSSD	2316
579	SLLTEVETPIRNEWGCRWNDSSD	2364
699	SLLTEVETPIRNEWGCRYNDSSD	2169
706	SLLTEVETPIRNEWGCRCADSSD	2329
728	SLLTEVETPIRNEWGCRCDDSSD	2377
762	SLLTEVETPIRNEWGCRCDDSSD	2289
739	SLLTEVETPIRNEWGCRCEDSSD	2273
560	SLLTEVETPIRNEWGCRCFDSSD	2538
689	SLLTEVETPIRNEWGCRCGDSSD	2343
651	SLLTEVETPIRNEWGCRCHDSSD	2350
612	SLLTEVETPIRNEWGCRCIDSSD	2450
318	SLLTEVETPIRNEWGCRCKDSSD	2549
618	SLLTEVETPIRNEWGCRCLDSSD	2480
628	SLLTEVETPIRNEWGCRCMDSSD	2470

516	SLLTEVETPIRNEWGCRCPDSSD	2449
568	SLLTEVETPIRNEWGCRCQDSSD	2438
544	SLLTEVETPIRNEWGCRCRDSSD	2447
729	SLLTEVETPIRNEWGCRCSDSSD	2141
674	SLLTEVETPIRNEWGCRCSTDSSD	2253
632	SLLTEVETPIRNEWGCRCVDSSD	2366
555	SLLTEVETPIRNEWGCRCWDSSD	2462
626	SLLTEVETPIRNEWGCRCYDSSD	2385
619	SLLTEVETPIRNEWGCRCNASSD	2454
588	SLLTEVETPIRNEWGCRCNCSSD	2505
694	SLLTEVETPIRNEWGCRCNESSD	2282
535	SLLTEVETPIRNEWGCRCNFSSD	2509
603	SLLTEVETPIRNEWGCRCNGSSD	2418
613	SLLTEVETPIRNEWGCRCNHSSD	2439
586	SLLTEVETPIRNEWGCRCNISSD	2517
465	SLLTEVETPIRNEWGCRCNKSSD	2597
393	SLLTEVETPIRNEWGCRCNLSSD	2634
394	SLLTEVETPIRNEWGCRCNMSSD	2574
395	SLLTEVETPIRNEWGCRCNNSSD	2502
396	SLLTEVETPIRNEWGCRCNPSSD	2445
397	SLLTEVETPIRNEWGCRCNQSSD	2376
398	SLLTEVETPIRNEWGCRCNRSSD	2514
342	SLLTEVETPIRNEWGCRCNSSSD	2440
399	SLLTEVETPIRNEWGCRCNTSSD	2483
400	SLLTEVETPIRNEWGCRCNVSSD	2476
401	SLLTEVETPIRNEWGCRCNWSSD	2556
337	SLLTEVETPIRNEWGCRCNYSSD	2475
402	SLLTEVETPIRNEWGCRCNDASD	2267
403	SLLTEVETPIRNEWGCRCNDACSD	2318
404	SLLTEVETPIRNEWGCRCNDADSD	2237
405	SLLTEVETPIRNEWGCRCNDESD	2203
406	SLLTEVETPIRNEWGCRCNDFSD	2395
338	SLLTEVETPIRNEWGCRCNDGSD	2226
407	SLLTEVETPIRNEWGCRCNDHSD	2537
408	SLLTEVETPIRNEWGCRCNDISD	2527
409	SLLTEVETPIRNEWGCRCNDKSD	2484

410	SLLTEVETPIRNEWGCRCNDLSD	2494
411	SLLTEVETPIRNEWGCRCNDMSD	2405
412	SLLTEVETPIRNEWGCRCNDNSD	2389
413	SLLTEVETPIRNEWGCRCNDPSD	2450
414	SLLTEVETPIRNEWGCRCNDQSD	2349
415	SLLTEVETPIRNEWGCRCNDRSD	2502
416	SLLTEVETPIRNEWGCRCNDTSD	2394
417	SLLTEVETPIRNEWGCRCNDVSD	2389
418	SLLTEVETPIRNEWGCRCNDWSD	2491
330	SLLTEVETPIRNEWGCRCNDYSD	2445
419	SLLTEVETPIRNEWGCRCNDSAD	2219
420	SLLTEVETPIRNEWGCRCNDS CD	2269
356	SLLTEVETPIRNEWGCRCNDSDD	2181
421	SLLTEVETPIRNEWGCRCNDS ED	2527
422	SLLTEVETPIRNEWGCRCNDSFD	2492
313	SLLTEVETPIRNEWGCRCNDSGD	2485
423	SLLTEVETPIRNEWGCRCNDSHD	2353
424	SLLTEVETPIRNEWGCRCNDSID	2320
425	SLLTEVETPIRNEWGCRCNDSKD	2361
426	SLLTEVETPIRNEWGCRCNDSL D	2400
427	SLLTEVETPIRNEWGCRCNDSMD	2304
350	SLLTEVETPIRNEWGCRCNDSND	2299
428	SLLTEVETPIRNEWGCRCNDS PD	2344
429	SLLTEVETPIRNEWGCRCNDSQD	2175
430	SLLTEVETPIRNEWGCRCNDSRD	2373
431	SLLTEVETPIRNEWGCRCNDSTD	2205
432	SLLTEVETPIRNEWGCRCNDSVD	2232
433	SLLTEVETPIRNEWGCRCNDSWD	2477
434	SLLTEVETPIRNEWGCRCNDSYD	2479
435	SLLTEVETP	2380
436	SLLTEVETPI	2465
437	SLLTEVETPIR	2297
438	SLLTEVETPIRN	2130
439	SLLTEVETPIRNE	1819
440	SLLTEVETPIRNEW	2334
368	SLLTEVETPIRNEWG	2429

442	SLLTEVETPIRNEWGC	2369
443	SLLTEVETPIRNEWGCR	2444
444	SLLTEVETPIRNEWGCRC	2478
445	SLLTEVETPIRNEWGCRCN	2506
446	SLLTEVETPIRNEWGCRCND	2276
447	SLLTEVETPIRNEWGCRCNDS	2348
448	SLLTEVETPIRNEWGCRCNDSS	2325

[00133] Further, the peptides were screened for the ability to specifically bind 23K21 and 8I10 and NOT Z3G. In one set, peptides with high binding values for 23K21 and 8I10 that are NOT recognized by Z3G1 were identified. In a second set, peptides with high binding values for Z3G1 that are NOT recognized by 23K21 and 8I10 were identified.

[00134] Peptide sequences with high binding values for 23K12 and BI10 with no binding to Z3G1 were identified for low stringency (0.01 µg/mL) conditions (Table 4A) and high stringency (0.001 µg/mL) conditions (Table 4B).

[00135] Table 4A:

MCLCTCVGCSLLTEC	SEQ ID NO: 315
CLCTCVGCSLLTEC	SEQ ID NO: 819
SLLTECGCSCLCEV	SEQ ID NO: 567
MSCLCECGCSLLTEC	SEQ ID NO: 340
SLLTECGCSLLTEC	SEQ ID NO: 374
CSLLTECGCSLLTEC	SEQ ID NO: 483
SLLTECGSCLCEC	SEQ ID NO: 497
MSLLTECGCSLLTEC	SEQ ID NO: 818
CSCCLCEVGCSSLLTEC	SEQ ID NO: 335
SLLTECGSCLTEV	SEQ ID NO: 601
CLCTCVGSLLTEC	SEQ ID NO: 455
SCLTEVGSLLTEC	SEQ ID NO: 823
CSLLTECGSCLCEC	SEQ ID NO: 815
CSLLTECGMSCLCEC	SEQ ID NO: 558
MSLLTCVGCSSLLTEC	SEQ ID NO: 820
CSLLTECGSLLTEC	SEQ ID NO: 813
SCLTEVGCSSLLTEC	SEQ ID NO: 808
SCLCECGCSLLTEC	SEQ ID NO: 361
MSCLTEVGCSSLLTEC	SEQ ID NO: 799
CSLLTECGCSCLCEV	SEQ ID NO: 817
CSCCLCEVGMSSLLTEC	SEQ ID NO: 305
SLLTECGCLLTEV	SEQ ID NO: 462

[00136] Table 4B:

CSLLTECG-SLLTCV	SEQ ID NO: 1592
CSLLTECGMSLLTCV	SEQ ID NO: 306
SLLTECG-SLLTCV	SEQ ID NO: 1593
MSLLTECGMCLLTEV	SEQ ID NO: 489
MSLLTECGMSLLTCV	SEQ ID NO: 331
SLLTECGCSLLTEC	SEQ ID NO: 374

[00137] Properties of the peptides that bind specifically to HuM2e antibodies 23K12/BI10 at different stringency conditions were analyzed. Antibodies 8i10 and 23k12 bind a conformational epitope with SLLTE as its core sequence. The best 23k12 binder is SLLTEVGSLLTEV (SEQ ID NO: 320), which is also recognized by Z3G1. The best 8i10 binder is CSLLTEVGSLLTEV (SEQ ID NO: 283), which is also recognized by Z3G1. The

very best specific binder is CSLLTECGSLLTCV (SEQ ID NO: 463). The binding sequences contain a remarkably high number of cysteines.

[00138] Peptide sequences with high binding values for Z3G1 with no binding to 23K12 and BI10 were identified for low stringency (0.01 µg/mL) conditions (Table 5A) and high stringency (0.001 µg/mL) conditions (Table 5B).

[00139] Table 5A:

High binding values with Z3G1

NO binding 23k12 & 8i10, [REDACTED]

CSLLCEVETPIRNE

SEQ ID NO: 1316

CLLLEVECPIRNE

SEQ ID NO: 1358

SLLCEVETPIRNE

SEQ ID NO: 1371

CMSLLCEVETPIRNE

SEQ ID NO: 1313

SLLCEVETPIRNCWG

SEQ ID NO: 1389

SLLCEVETPICNEWG

SEQ ID NO: 1391

MSLLLEVETPIRNEWGCRCN

SEQ ID NO: 1287

CSLLCEVETPIRNE

SEQ ID NO: 1316

MRLLETVETPIRNEWGCRCN

SEQ ID NO: 1263

SLLCEVETPIRCEWG

SEQ ID NO: 1390

CLLTEVETPCRNEWG

SEQ ID NO: 1381

SLLCEVETPIRNEWC

SEQ ID NO: 1387

MSLLCEVGMSLLCEV

SEQ ID NO: 1341

[00140] Table 5B:

High binding values with Z3G1

NO binding 23k12 & 8i10, [REDACTED]

MSLLTEVDTPIRNEWGCRCN
 MSLLMEVETPIRNEWGCRCN
 MSLLLEVETPIRNEWGCRCN
 MSLLCEVETPIRNC
 MSLLSEVETPIRNEWGCRCN
 MSLLNEVETPIRNEWGCRCN
 MSLLKEVETPIRNEWGCRCN
 SLLCEVECPIRNEWG
 MSLLAEVETPIRNEWGCRCN
 MSLLDEVETPIRNEWGCRCN
 MDLLTEVETPIRNEWGCRCN
 MNLLTEVETPIRNEWGCRCN

SEQ ID NO: 1300
 SEQ ID NO: 1288
 SEQ ID NO: 1281
 SEQ ID NO: 1325
 SEQ ID NO: 1293
 SEQ ID NO: 1289
 SEQ ID NO: 1286
 SEQ ID NO: 1394
 SEQ ID NO: 1279
 SEQ ID NO: 1280
 SEQ ID NO: 1251
 SEQ ID NO: 1260

Now dominant Motif occurs!

[00141] There is a clear difference between binding specificity between antibodies 8i10/23k12 versus Z3G1. The very best specific binder is a longer sequence than with 23k12/8i10, has no dimer topology and also no CLIPS. Among the very best specific binder is mostly the whole native sequence, MSLLTEVETPIRNEWGCRCN (SEQ ID NO: 1149). The result with 0.01 µg/ml shows that LLXEVEXPIN (SEQ ID NO: 1594) is the core of the Z3G1 binding epitope.

[00142] Specific binding motifs can derived from 0.001 µg/ml screening. Thus, mAbs 23k12/8i10 recognize M2e peptides with SLLTE as the core of the epitope. The T residue in S-L-L-T-E differentiates binding between 23k12/8i10 and Z3G1. In contrast, mAb Z3G1 recognize M2e with LLXEVEXPIN (SEQ ID NO: 1594) as the core of the epitope. (Tables 6A and 6B).

[00143] Table 6A:

0,001 ug/ml
CSLLTECG--SLLTCV
CSLLTECGMSLLTCV
SLLTECG--SLLTCV
MSLLTECGMCLLLEV
MSLLTECGMSLLTCV
SLLTECGCSLLTEC

SEQ ID NO: 1595

SEQ ID NO: 306

SEQ ID NO: 1596

SEQ ID NO: 489

SEQ ID NO: 331

SEQ ID NO: 374

[00144] Table 6B:

0,001 ug/ml
MSLLTEVDTPIRNEWGCRN
MSLLMEVETPIRNEWGCRN
MSLLREVETPIRNEWGCRN
MSLLCEVETPIRNC
MSLLSEVETPIRNEWGCRN
MSLLNEVETPIRNEWGCRN
MSLLKEVETPIRNEWGCRN
SLLCEVECFIRNEWG
MSLLAEVETPIRNEWGCRN
MSLLDEVETPIRNEWGCRN
MDLLTEVETPIRNEWGCRN
MNLLTEVETPIRNEWGCRN

SEQ ID NO: 1300

SEQ ID NO: 1288

SEQ ID NO: 1281

SEQ ID NO: 1325

SEQ ID NO: 1293

SEQ ID NO: 1289

SEQ ID NO: 1286

SEQ ID NO: 1394

SEQ ID NO: 1279

SEQ ID NO: 1280

SEQ ID NO: 1251

SEQ ID NO: 1260

Peptide immunogens

[00145] In particular, a peptide immunogen of this invention that binds the HuM2e 23k12/8i10 comprises a core sequence of S-L-L-T-E as well as variants, modifications and multimers thereof. Core sequences for low stringency (0.01 $\mu\text{g/mL}$) conditions (Figure 6A) and high stringency (0.001 $\mu\text{g/mL}$) conditions (Figure 6B) and variants thereof derived from the binding data are shown in figures 6A and 6B.

[00146] In some embodiments, the core sequence comprises a first additional amino acid at the C terminal end of S-L-L-T-E-Xaa₆, wherein Xaa₆ is any amino acid, preferably V or C. (Figure 6C)

[00147] Further, in some embodiments, the core sequence comprises a first additional amino acid at the C terminal end of S-L-L-T-E-Xaa₆-Xaa₇, wherein Xaa₇ is any amino acid, but preferably E. (Figure 6C)

[00148] In some embodiments, the peptide immunogens comprise a plurality of core sequences linked by an amino acid, preferably a small amino acid such as G or A. However, amino acids such as proline, which can act as a structural disruptor in the middle of regular secondary structure elements such as alpha helices and beta sheets, are less desirable. The number of core sequences in peptide immunogens of the invention can be 1, 2, 3, 4, 5 or more. (Figure 6D).

[00149] In some embodiments, an N-terminal amino acid Xaa₀ is present in the peptide immunogens. Xaa₀ can be any amino acid, but preferably is a cysteine. In some embodiments a N-terminal cysteine is used to cyclize the peptide immunogen. (Figure 6E)

[00150] Peptide immunogens (linear or cyclized) with particularly strong affinity for 23K12/8I10 binding are shown in Figure 6F.

[00151] The peptide immunogens of this invention that bind the huM2e monoclonal antibodies under high stringency conditions are represented by the following formula:

$$[Xaa_0]_m-Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-[Xaa_6]_p-[Xaa_7]_q-[Xaa_8-[Xaa_0]_m-Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-[Xaa_6]_p-[Xaa_7]_q]_n$$

wherein, m, p and q are independently 0 or 1,

n is any number between 0 and 4,

Xaa₀ is any amino acid, preferably C;

Xaa₆ is any amino acid, preferably V or C;

Xaa₇ is any amino acid, preferably E;

Xaa₈ is any amino acid not including proline, preferably G or A;

Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅ is S-L-L-T-E,

or a peptide having a single substitution to the sequence S-L-L-T-E, the substitution selected from the group consisting of:

Xaa₁ is C or T;

Xaa₂ is A, C, F or K,

Xaa₃ is A, C, E, F, I, K, M, Q, S, T or V, and

Xaa₅ is D or C.

[00152] The peptide immunogens of this invention that bind the huM2e monoclonal antibodies under low stringency conditions are represented by the following formula:

$$[Xaa_0]_m-Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-[Xaa_6]_p-[Xaa_7]_q-[Xaa_8-[Xaa_0]_m-Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-[Xaa_6]_p-[Xaa_7]_q]_n$$

wherein, m, p and q are independently 0 or 1,

n is any number between 0 and 4,

Xaa₀ is any amino acid, preferably C;

Xaa₆ is any amino acid, preferably V or C;

Xaa₇ is any amino acid, preferably E;

Xaa₈ is any amino acid not including proline, preferably G or A;

Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅ is S-L-L-T-E or,

a peptide having a single substitution to the sequence S-L-L-T-E, the substitution selected from the group consisting of:

Xaa₁ is A, C, D, L, T or V,

Xaa₂ is A, C, F, H, I, K, M, N, Q, R, T, W, or Y,

Xaa₃ is any amino acid,

Xaa₄ is M, N, Q, S, or W, and

Xaa₅ is A, D, F, H, I, K, M, N, Q, S, W, Y, or C.

Preparation of Linear and Cyclic peptide immunogens

[00153] Linear peptide immunogens can be prepared synthetically and then screened for a particular characteristic in various biological assays. E.g., Scott, J. K. and G. P. Smith, Science 249:386, 1990; Devlin, J. J., et al., Science 24:404, 1990; Furka, A. et al., Int. J. Pept. Protein Res. 37:487, 1991; Lam, K. S., et al., Nature 354:82, 1991.

[00154] Cyclized peptides are often found to possess superior immunogenic activity compared to linear peptide immunogens. Linear peptide immunogens comprising three or more core sequences are found to bind with the terminal sequences only, while cyclization allows binding by all core sequences present in the peptide immunogens. Various methods for producing cyclic peptides have been described. One involves solution or liquid phase peptide synthesis, where amino acid residues in solution are linked by peptide bonds, with reactive groups not involved in the peptide bond formation, such as the amino group of the N-terminal residue, the carboxy group of the C-terminal residue, sulfhydryl groups on cysteine residues and similar or other reactive groups in the amino acid side chains, protected by suitable protecting groups.

[00155] In one embodiment cyclic peptide immunogens are formed using terminal cysteine residues by reduction of thiol groups to form disulfide bridges.

[00156] Another approach involves solid phase peptide synthesis, in which synthesis is carried out on an insoluble solid matrix. Protecting groups are employed for reactive side

chains. The general methodology of solid phase synthesis is well known in the art. Merrifield, R. B., Solid phase synthesis (Nobel lecture). *Angew Chem* 24:799-810 (1985) and Barany et al., *The Peptides, Analysis, Synthesis and Biology*, Vol. 2, Gross, E. and Meienhofer, J., Eds. Academic Press 1-284 (1980). For example, chemical reaction protocols, such as those described in U.S. Pat. Nos. 4,033,940 and 4,102,877, have been devised to produce circularized peptides. In other techniques, biological and chemical methods are combined to produce cyclic peptides. These latter methods involve first expressing linear precursors of cyclic peptides in cells (e.g., bacteria) to produce linear precursors of cyclic peptides and then adding of an exogenous agent such as a protease or a nucleophilic reagent to chemically convert these linear precursors into cyclic peptides. See, e.g., Camarero, J. A., and Muir, T. W., *J. Am. Chem. Society.* 121:5597 (1999); Wu, H. et al, *Proc. Natl. Acad. Sci. USA*, 95:9226 (1998).

[00157] Head-to-tail (backbone) peptide cyclization has been used to rigidify structure and improve in vivo stability of small bioactive peptides (see Camarero and Muir, *J. Am. Chem. Soc.*, 121:5597-5598 (1999)). An important consequence of peptide cyclization is retention of biological activity and/or the identification of new classes of pharmacological agents. A chemical cross-linking approach was used to prepare a backbone cyclized version of bovine pancreatic trypsin inhibitor (Goldenberg and Creighton, *J. Mol. Biol.*, 165:407-413 (1983)). Other approaches include chemical (Camarero et al., *Angew. Chem. Int. Ed.*, 37:347-349 (1998); Tam and Lu, *Prot. Sci.*, 7:1583-1592 (1998); Camarero and Muir, *Chem. Commun.*, 1997:1369-1370 (1997); and Zhang and Tam, *J. Am. Chem. Soc.* 119:2363-2370 (1997)) and enzymatic (Jackson et al., *J. Am. Chem. Soc.*, 117:819-820 (1995)) intramolecular ligation methods which allow linear synthetic peptides to be efficiently cyclized under aqueous conditions.

[00158] A native chemical ligation approach utilizes inteins (internal proteins) to catalyze head-to-tail peptide and protein ligation in vivo (see, for example, Evans et al., *J. Biol. Chem.* 274:18359-18363 (1999); Iwai and Pluckthun, *FEBS Lett.* 459:166-172 (1999); Wood et al., *Nature Biotechnology* 17:889-892 (1999); Camarero and Muir, *J. Am. Chem. Soc.* 121:5597-5598 (1999); and Scott et al., *Proc. Natl. Acad. Sci. USA* 96:13638-13643 (1999)).

[00159] The invention also encompasses isolated nucleic acid molecules comprising a sequences that encode M2e peptide immunogens of the invention. Also provided by the present invention are nucleic acid expression constructs, and host cells containing such

nucleic acids, which encode M2e peptides, and variants thereof, which have at least one epitope characteristic of M2e peptide immunogens. This aspect of the invention pertains to isolated nucleic sequences encoding an M2e sequence or M2e peptide immunogen sequence as described herein, as well as those sequences readily derived from isolated nucleic molecules such as, for example, complementary sequences, reverse sequences and complements of reverse of sequences.

[00160] A related embodiment includes a nucleic acid expression construct comprising a promoter operably linked to the isolated nucleic acid molecule such that a M2e peptide immunogen or fusion protein comprising a M2e peptide immunogen as described herein is expressed in a host cell. In another embodiment, the invention provides a host cell containing such a nucleic acid expression construct. In a related embodiment, the invention provides a method for producing a peptide immunogen, comprising growing the described host cells for a time sufficient to express the peptide immunogen encoded by the nucleic acid expression construct.

Conjugated peptide immunogens

[00161] The approach of increasing immunogenicity of small immunogenic molecules by conjugating these molecules to large "carrier" molecules has been utilized successfully for decades (see, e.g., Goebel et al. (1939) J. Exp. Med. 69: 53). For example, many immunogenic compositions have been described in which purified capsular polymers have been conjugated to carrier proteins to create more effective immunogenic compositions by exploiting this "carrier effect." Schneerson et al. (1984) Infect. Immun. 45: 582-591).

[00162] In one aspect of the invention, method for conjugating a M2e peptide immunogen via a reactive group of an amino acid residue of the peptide immunogen to a protein/polypeptide carrier having one or more functional groups is provided. The protein/polypeptide carrier may be human serum albumin, keyhole limpet hemocyanin (KLH), immunoglobulin molecules, thyroglobulin, ovalbumin, influenza hemagglutinin, PAN-DR binding peptide (PADRE polypeptide), malaria circumsporozoite (CS) protein, hepatitis B surface antigen (HBsAg₁₉₋₂₈, Heat Shock Protein (HSP) 65, Bacillus Calmette-Guerin (BCG), cholera toxin, cholera toxin mutants with reduced toxicity, diphtheria toxin, CRM₁₉₇ protein that is cross-reactive with diphtheria toxin, recombinant Streptococcal C5a peptidase, Streptococcus pyogenes ORF1224, Streptococcus pyogenes ORF1664, Streptococcus pyogenes ORF 2452, Chlamydia pneumoniae ORF T367, Chlamydia pneumoniae ORF T858, Tetanus toxoid, HIV gp120 T1, microbial surface components

recognizing adhesive matrix molecules (MSCRAMMS), growth factor/hormone, cytokines or chemokines.

[00163] Methods for protecting a subject from infection or decreasing susceptibility of a subject to infection by one or more influenza strains/isolates or subtypes, i.e., prophylactic methods, are additionally provided. In one embodiment, a method includes administering to the subject an amount of M2e peptide immunogens that specifically bind influenza M2 effective to protect the subject from infection, or effective to decrease susceptibility of the subject to infection, by one or more influenza strains/isolates or subtypes.

[00164] Symptoms or complications of influenza infection that can be reduced or decreased include, for example, chills, fever, cough, sore throat, nasal congestion, sinus congestion, nasal infection, sinus infection, body ache, head ache, fatigue, pneumonia, bronchitis, ear infection, ear ache or death.

Peptide immunogens as vaccines

[00165] The peptide immunogens can be used as vaccines to generate an anti-influenza M2-mediated immune response in order to prevent influenza infections. Synthetic peptides require both stabilization and adjuvantation for the induction of an effective immune response in vivo. Various methods have been employed to protect synthetic peptide immunogens against degradation in vitro and in vivo, mediated by various processes including chemical and physical pathways. (Manning M C, et al. *Pharmaceutical Research*, 1989, 6:903-918).

[00166] Numerous adjuvants and/or depot-based parenteral, mucosal or transdermal delivery systems destined for use with human or veterinary vaccines have been developed to enhance the immune response. These include the use of mineral salts, water-in-oil (w/o)-emulsions, liposomes, polymeric microparticles, nanoparticles and gels/hydrogels. (Cox J C, et al. *Vaccine*, 1997, 15:248-256). Freund's complete adjuvant (FCA), a suspension of heat-killed *M. tuberculosis* mycobacteria in mineral oil containing a surfactant, has been recognized as one of the most powerful adjuvants. Adjuvants are well known in the art (*Vaccine Design--The Subunit and Adjuvant Approach*, 1995, Pharmaceutical Biotechnology, Volume 6, Eds. Powell, M. F., and Newman, M. J., Plenum Press, New York and London, ISBN 0-306-44867-X). Preferred adjuvants for use with immunogens of the present invention include aluminium or calcium salts (hydroxide or phosphate). Adjuvants may be selected from GM-CSF, 529 SE, IL-12, aluminum phosphate, aluminum hydroxide, *Mycobacterium tuberculosis*, *Bordetella pertussis*, bacterial lipopolysaccharides, aminoalkyl glucosane phosphate compounds, MPLTM (3-O-deacylated monophosphoryl lipid A), a

polypeptide, Quil A, STIMULON™ QS-21, a pertussis toxin (PT), an E. coli heat-labile toxin (LT), IL-1 α , IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, interferon- α , interferon- β , interferon- γ , G-CSF, TNF- α and TNF- β .

[00167] Still other adjuvants include mineral oil and water emulsions, calcium salts such as calcium phosphate, aluminum salts (alum), such as aluminum hydroxide, aluminum phosphate, etc., Amphigen, Avridine, L121/squalene, D-lactide-poly(lactide)/glycoside, pluronic acids, polyols, muramyl dipeptide, killed Bordetella, saponins, such as Stimulon.TM. QS-21 (Antigenics, Framingham, Mass.), described in U.S. Pat. No. 5,057,540, which is hereby incorporated by reference³, and particles generated therefrom such as ISCOMS (immunostimulating complexes), Mycobacterium tuberculosis, bacterial lipopolysaccharides, synthetic polynucleotides such as oligonucleotides containing a CpG motif (U.S. Pat. No. 6,207,646, which is hereby incorporated by reference), a pertussis toxin (PT), or an E. coli heat-labile toxin (LT), particularly LT-K63, LT-R72, PT-K9/G129; see, e.g., International Patent Publication Nos. WO 93/13302 and WO 92/19265, which are/are incorporated herein by reference for all purposes.

[00168] Also useful as adjuvants are cholera toxins and mutants thereof, including those described in published International Patent Application No. WO 00/18434 (wherein the glutamic acid at amino acid position 29 is replaced by another amino acid (other than aspartic acid, preferably a histidine). Similar CT toxins or mutants are described in published International Patent Application number WO 02/098368 (wherein the isoleucine at amino acid position 16 is replaced by another amino acid, either alone or in combination with the replacement of the serine at amino acid position 68 by another amino acid; and/or wherein the valine at amino acid position 72 is replaced by another amino acid). Other CT toxins are described in published International Patent Application number WO 02/098369 (wherein the arginine at amino acid position 25 is replaced by another amino acid; and/or an amino acid is inserted at amino acid position 49; and/or two amino acids are inserted at amino acid position 35 and 36).

[00169] Various methods may be employed to adjuvant synthetic peptide-based immunogens, but normally a carrier or depot system is required for effective long-term immunogenic responses. Notable examples include adsorbing the immunogen onto a mineral salt or gel. For example, encapsulating a peptide immunogen within a polymeric matrix (monolithic matrix) or gel, or layering a polymeric material around a peptide immunogen

(core-shell) may be an effective strategy. Or, an immunogen may be incorporated in a liposome or vesicular type of formulation, with the immunogen either embedded in the lipid matrix or physically entrapped in the internal aqueous phase. Another strategy may employ a mineral-based, vegetable-based or animal-based oil, with an aqueous solution of the immunogen in various proportions, to prepare a water-in-oil (w/o)-emulsion or a water-in-oil-in-water (w/o/w)-double emulsion. Powell M F, et al., *Pharmaceutical Biotechnology*, Vol. 6, Plenum Press, New York, 1995.

Kits

[00170] It is particularly useful to use antibody binding sequences in the kit, which correspond to defined epitope sequences known to be specific for the immunogen under investigation. This kit will lead to a more specific answer than those kits used today, and hence to a better selection of immunogen vaccine therapy for the individual patient.

[00171] In an extension of this approach, one could also characterize the patient's serum by identifying the corresponding antibody binding peptides among a random display library using the aforementioned methods. This again may lead to optimisation of the epitope information, and thus to a better diagnosis.

[00172] Further, one could use the individual antibody binding sequences as (immunogen) vaccines leading to more specific (immunogen) vaccines. These antibody binding sequences could be administered in an isolated form or fused to a membrane protein of the phage display system, or to another carrier protein, which may have beneficial effect for the immunoprotective effect of the antibody binding peptide (Dalum et al., *Nature Biotechnology*, Vol. 17, pp. 666-669 (1999)).

[00173] The present invention relates to a kit for predicting binding of a specific antibody to at least one potential immunogen. The kit of the invention would also be useful for other screening purposes where it is desirable to test for antibody binding to peptide sequences, such as epitope variant.

[00174] In one embodiment the peptide immunogen may be immobilized on a solid support. Suitable solid support could be any chemical support, including micro titer plates, beads, capillary tubing or membranes. Each of these supports could be activated, supporting covalent, ionic or hydrophobic binding, chelation or affinity binding, or inactivated, promoting ionic or hydrophobic binding. Immobilisation could take place by attachment through covalent binding, ionic or hydrophobic binding, chelation, affinity binding, or through van der Waal bonds. A solid support could also be biological in nature, such as

phages, bacteria, red blood cells or any related system allowing display of heterologous proteins or peptides.

[00175] The kit also can be used for screening different antigenic peptide sequences corresponding to structural epitopes at the same time. The kit above also can be used in a high throughput screening method for screening many samples, obtained e.g. from humans or animals, at the same time and thereby predicting which humans or animals will display an immunogenic response towards particular immunogens. Any practical combination of the number of antigenic peptide sequences and the number of humans or animals would be possible.

[00176] The following examples illustrate embodiments of the invention. It will be appreciated by one of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventors to function well in the practice of the invention. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the invention.

EXAMPLES

Example 1: Identification of M2-Specific Antibodies

[00177] Mononuclear or B cells expressing three of the MAbs identified in human serum were diluted into clonal populations and induced to produce antibodies. Antibody containing supernatants were screened for binding to 293 FT cells stably transfected with the full length M2E protein from influenza strain Influenza subtype H3N2. Supernatants which showed positive staining/binding were re-screened again on 293 FT cells stably transfected with the full length M2E protein from influenza strain Influenza subtype H3N2 and on vector alone transfected cells as a control.

[00178] The variable regions of the antibodies were then rescue cloned from the B cell wells whose supernatants showed positive binding. Transient transfections were performed in 293 FT cells to reconstitute and produce these antibodies. Reconstituted antibody supernatants were screened for binding to 293 FT cells stably transfected with the full length M2E protein as detailed above to identify the rescued anti-M2E antibodies. Three different antibodies were identified: 8i10, 21B15 and 23K12.

[00179] Antibodies 21B15, 23K12, and 8I10 bound to the surface of 293-HEK cells stably expressing the M2 protein, but not to vector transfected cells (see Figure 1). In

addition, binding of these antibodies was not competed by the presence of 5 mg/ml 24-mer M2 peptide, whereas the binding of the control chimeric mouse V-region/human IgG1 kappa 14C2 antibody (hu14C2) generated against the linear M2 peptide was completely inhibited by the M2 peptide (see Figure 1). These data confirm that these antibodies bind to conformational epitopes present in M2e expressed on the cell or virus surface, as opposed to the linear M2e peptide.

Example 2: Viral Binding of human anti-influenza monoclonal antibodies

[00180] UV-inactivated influenza A virus (A/PR/8/34) (Applied Biotechnologies) was plated in 384-well MaxiSorp plates (Nunc) at 1.2 µg/ml in PBS, with 25 µl/well, and was incubated at 4°C overnight. The plates were then washed three times with PBS, and blocked with 1% Nonfat dry milk in PBS, 50 µl/well, and then were incubated at room temp for 1 hr. After a second wash with PBS, MAbs were added at the indicated concentrations in triplicate, and the plates were incubated at room temp for 1 hour. After another wash with PBS, to each well was added 25 µl of a 1/5000 dilution of horseradish peroxidase (HRP) conjugated goat anti-human IgG Fc (Pierce) in PBS/1% Milk, and the plates were left at room temp for 1 hr. After the final PBS wash, the HRP substrate 1-Step™ Ultra-TMB-ELISA (Pierce) was added at 25 µl/well, and the reaction proceeded in the dark at room temp. The assay was stopped with 25 µl/well 1N H₂SO₄, and light absorbance at 450 nm (A₄₅₀) was read on a SpectroMax Plus plate reader. Data are normalized to the absorbance of MAb 8I10 binding at 10 µg/ml. Results are shown in Figures 2A and 2B.

Example 3: Binding of Human Anti-Influenza Monoclonal Antibodies to Full-Length M2 Variants

[00181] M2 variants (including those with a high pathology phenotype in vivo) were selected for analysis. See Figure 3A for sequences.

[00182] M2 cDNA constructs were transiently transfected in HEK293 cells and analyzed as follows: To analyze the transient transfectants by FACS, cells on 10 cm tissue culture plates were treated with 0.5 ml Cell Dissociation Buffer (Invitrogen), and harvested. Cells were washed in PBS containing 1% FBS, 0.2% NaN₃ (FACS buffer), and resuspended in 0.6 ml FACS buffer supplemented with 100 µg/ml rabbit IgG. Each transfectant was mixed with the indicated MAbs at 1 µg/ml in 0.2 ml FACS buffer, with 5 x 10⁵ to 10⁶ cells per sample. Cells were washed three times with FACS buffer, and each sample was resuspended in 0.1 ml containing 1 µg/ml alexafluor (AF) 647-anti human IgG H&L (Invitrogen). Cells were again washed and flow cytometry was performed on a FACSCanto device (Becton-

Dickenson). The data is expressed as a percentage of the mean fluorescence of the M2-D20 transient transfectant. Data for variant binding are representative of 2 experiments. Data for alanine mutants are average readouts from 3 separate experiments with standard error. Results are shown in Figure 3B and 3C.

Example 4: Epitope Blocking

[00183] To determine whether the MAbs 8I10 and 23K12 bind to the same site, M2 protein representing influenza strain A/HK/483/1997 sequence was stably expressed in the CHO (Chinese Hamster Ovary) cell line DG44. Cells were treated with Cell Dissociation Buffer (Invitrogen), and harvested. Cells were washed in PBS containing 1% FBS, 0.2% NaN₃ (FACS buffer), and resuspended at 10⁷ cells/ml in FACS buffer supplemented with 100 µg/ml rabbit IgG. The cells were pre-bound by either MAb (or the 2N9 control) at 10 µg/ml for 1 hr at 4 °C, and were then washed with FACS buffer. Directly conjugated AF647-8I10 or -23K12 (labeled with the AlexaFluor® 647 Protein Labeling kit (Invitrogen) was then used to stain the three pre-blocked cell samples at 1 µg/ml for 10⁶ cells per sample. Flow cytometric analyses proceeded as before with the FACSCanto. Data are average readouts from 3 separate experiments with standard error. Results are shown in Figure 4.

Example 5: Binding of human anti-influenza monoclonal antibodies to M2 Variants and Truncated M2 Peptides

[00184] The cross reactivity of mAbs 8I10 and 23K12 to other M2 peptide variants was assessed by ELISA. Peptide sequences are shown in Tables 7A and 7B. Additionally, a similar ELISA assay was used to determine binding activity to M2 truncated peptides.

[00185] In brief, each peptide was coated at 2 µg/mL to a flat bottom 384 well plate (Nunc) in 25 µL/ well of PBS buffer overnight at 4°C. Plates were washed three times and blocked with 1% Milk/PBS for one hour at room temperature. After washing three times, MAb titers were added and incubated for one hour at room temperature. Diluted HRP conjugated goat anti-human immunoglobulin FC specific (Pierce) was added to each well after washing three times. Plates were incubated for one hour at room temperature and washed three times. 1-Step™ Ultra-TMB-ELISA (Pierce) was added at 25 µl/well, and the reaction proceeded in the dark at room temp. The assay was stopped with 25 µl/well 1N H₂SO₄, and light absorbance at 450 nm (A450) was read on a SpectroMax Plus plate reader. Results are shown in Tables 7A and 7B.

[00186] **Table 7A:** Cross reactivity binding of anti-M2 antibodies to variant M2 peptides.

SeqNo.	Name	Size	Description	ELISA (OD 450)			
				14C2	8110	73K17	2N9
1	M2	23 aa	SLLTEVETPIRNEWGCRCDSSD	+	-	-	-
2	M25G	23 aa	SLLTEVETPIRSEWGCRCDSSD	+	-	-	-
3	M2EG	23 aa	SLLTEVETPIRNEWGCRCDSSD	+	-	-	-
4	M2P	23 aa	SLLTEVETPIRNEWGCRCDSSD	+	-	-	-
5	M2G	23 aa	SLLTEVETPIRNEWGCRCDSSD	+	-	-	-
6	M2DLTGS	23 aa	SLLTEVDTLRNGWGCRCDSSD	-	-	+	-
7	M2KNS	23 aa	SLLTEVETPIRKEWGCRCDSSD	+	-	-	-
8	M2LGS	23 aa	SLLTEVETLRNGWGCRCDSSD	-	-	-	-
9	M2LTGKS	23 aa	SLLTEVETLRNGWGCRCDSSD	-	-	-	-
10	M2SY	23 aa	SLLTEVETPIRSEWGCRCDSSD	+	-	-	-
11	M2TGEKS	23 aa	SLLTEVETPIRNGWCKCDSSD	+	-	-	-
12	M2HTGEKS	23 aa	SLLTEVETHRNGWCKCDSSD	-	-	-	-
13	M2KTGEKS	23 aa	SLLTEVETPIRNGWCKCDSSD	-	-	-	-
14	M2LTGS	23 aa	SLLTEVETLRNGWGCRCDSSD	-	-	+	-
15	M2TDGEKS	23 aa	SLLTEVETPIRNGWCKCDSSD	+	-	-	-
16	M2TGS	23 aa	SLLTEVETPIRNGWGCRCDSSD	+	-	W	-
17	M2TGEK	23 aa	SLLTEVETPIRNGWCKCDSSD	+	-	-	-
18	M2LTGEKS	23 aa	SLLTEVETLRNGWCKCDSSD	-	-	W	-
19	M2K	23 aa	SLLTEVETPIRNEWGCRCDSSD	+	W	+	-
20	M2FG	23 aa	SLLTEVETPIRNEWGCRCDSSD	+	W	-	-
21	M2TGE	23 aa	SLLTEVETPIRNGWCRCDSSD	+	-	-	-
22	M2KGNS	23 aa	SLLTEVETPIRKGWCRCDSSD	+	-	-	-
23	M2TES	23 aa	SLLTEVETPIRNEWGCRCDSSD	+	-	-	-
24	M2GHTGKS	23 aa	SLLTGVEHTRNGWGCRCDSSD	-	-	-	-
25	M2PHTGS	23 aa	SLLPEVETHTRNGWGCRCDSSD	-	-	-	-

Percentage compared relative to binding to wild-type peptide (Seq 1)

Note: mAbs were tested at 5 µg/ml

> 25 % - no binding
 25 - 40 % W weak binding
 > 40 % + positive binding

[00187] **Table 7B:** Binding activity of M2 antibodies to truncated M2 peptides.

Seq ID	Name	Size	Description	1A2	8D10	2A127	2A9
1	M2	23 aa	SLLTEVETPIRNEWGCRNDSSD	3.85	0.11	0.22	0.06
26	M16	16 aa	LLTEVETPIRNEWGCR	3.94	0.09	0.21	0.09
27	M15	15 aa	LTEVETPIRNEWGCR	3.95	0.09	0.21	0.09
28	M12	12 aa	VETPIRNEWGCR	0.15	0.09	0.20	0.09
29	CM17	17 aa	ETPIRNEWGCRNDSSD	0.19	0.11	0.34	0.11
30	CM16	16 aa	TPIRNEWGCRNDSSD	0.23	0.13	0.35	0.12
31	CM15	15 aa	PIRNEWGCRNDSSD	0.19	0.12	0.34	0.11
32	CM14	14 aa	IRNEWGCRNDSSD	0.23	0.14	0.36	0.13
33	CM13	13 aa	RNEWGCRNDSSD	0.22	0.14	0.34	0.13
34	CM12	12 aa	NEWGCRNDSSD	0.27	0.14	0.39	0.14
35	NM17	17 aa	SLLTEVETPIRNEWGCR	3.99	0.26	0.58	0.10
36	NM16	16 aa	SLLTEVETPIRNEWGC	3.90	0.29	0.62	0.09
37	NM15	15 aa	SLLTEVETPIRNEWG	3.97	0.12	0.30	0.11
38	NM14	14 aa	SLLTEVETPIRNEW	3.97	0.11	0.24	0.09
39	NM13	13 aa	SLLTEVETPIRNE	0.18	0.11	0.25	0.10
40	NM12	12 aa	SLLTEVETPIRN	0.20	0.10	0.24	0.09
41	NM11	11 aa	SLLTEVETPIR	0.21	0.13	0.30	0.12
42	NM10	10 aa	SLLTEVETPI	0.17	0.10	0.24	0.10
43	NM8	8 aa	SLTEVET	0.15	0.10	0.20	0.09
44	NM7	7 aa	SLTEVE	0.14	0.10	0.20	0.08
45	NM9	9 aa	SLLTEVETP	0.21	0.12	0.30	0.19
46	M2e	24 aa	MSLLTEVETPIRNEWGCRNDSSD	3.98	0.13	0.43	0.10
CMV	HSVIR1			0.16	0.11	0.21	3.99

Note: mAbs were tested at 5 µg/ml.

OTHER EMBODIMENTS

[00188] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application is specifically and individually indicated to be incorporated by reference.

[00189] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

CLAIMS

1. An isolated peptide immunogen comprising a sequence of:
 $[Xaa_0]_m-Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-[Xaa_6]_p-[Xaa_7]_q-[Xaa_8-[Xaa_0]_m-Xaa_1-Xaa_2-Xaa_3-Xaa_4-Xaa_5-[Xaa_6]_p-[Xaa_7]_q]_n$
 wherein:
 m, p and q are independently 0 or 1;
 n is any number between 1 and 4;
 Xaa₀, Xaa₆, Xaa₇ and Xaa₈ are independently any amino acid; and
 Xaa₁-Xaa₂-Xaa₃-Xaa₄-Xaa₅ is S-L-L-T-E.
2. The isolated peptide immunogen of claim 1, wherein Xaa₀ is C.
3. The isolated peptide immunogen of claim 1 or claim 2, wherein Xaa₆ is V or C.
4. The isolated peptide immunogen of any one of claims 1 to 3, wherein Xaa₇ is E.
5. The isolated peptide immunogen of any one of claims 1 to 4, wherein Xaa₈ is G or A.
6. The isolated peptide immunogen of any one of claims 1 to 5, wherein said peptide is non-linear.
7. The isolated peptide immunogen of any one of claims 1 to 5, wherein said peptide is cyclic.
8. The isolated peptide immunogen of any one of claims 1 to 7, wherein said peptide binds specifically to HuMe2 antibodies 8110 or 23K12, and wherein:
 - (a) the 8110 antibody comprises: a V_H CDR1 region comprising an amino acid sequence of NYYWS (SEQ ID NO: 72); a V_H CDR2 region comprising an amino acid sequence of FIYYGGNTKYNPSLKS (SEQ ID NO: 74); a V_H CDR3 region comprising an amino acid sequence of ASCSGGYCILD (SEQ ID NO: 76); a V_L CDR1 region comprising an amino acid sequence of RASQNIYKYLN (SEQ ID NO: 59); a V_L CDR2 region comprising an amino acid sequence of AASGLQS (SEQ ID NO: 61); and a V_L CDR3 region comprising an amino acid sequence of and QQSYSPPLT (SEQ ID NO: 63); and
 - (b) the 23K12 antibody comprises: a V_H CDR1 region comprising an amino acid sequence of SNYMS (SEQ ID NO: 103); a V_H CDR2 region comprising an amino acid sequence of VIYSGGSTYYADSVK (SEQ ID NO: 105); a V_H CDR3 region comprising an

amino acid sequence of CLSRMRGYGLDV (SEQ ID NO: 107); a V_L CDR1 region comprising an amino acid sequence of RTSQSISSYLN (SEQ ID NO: 92); a V_L CDR2 region comprising an amino acid sequence of AASSLQSGVPSRF (SEQ ID NO: 94); and a V_L CDR3 region comprising an amino acid sequence of QQSYSMPA (SEQ ID NO: 96).

9. The isolated peptide immunogen of claim 1, wherein said peptide comprises D-amino acids.
10. The isolated peptide immunogen of claim 1, wherein said peptide is a linear or cyclized peptide having a sequence of SLLTEVGSLLTEV (SEQ ID NO: 320).
11. The isolated peptide immunogen of claim 1, wherein said peptide is a linear or cyclized peptide having a sequence of CSLLTEVGSLLTEV (SEQ ID NO: 283).
12. The isolated peptide immunogen of claim 1, wherein said peptide is a linear or cyclized peptide having a sequence of CSLLTECGSLLTCV (SEQ ID NO: 463).
13. The isolated peptide immunogen of any one of claims 1 to 12, wherein said peptide is conjugated to a carrier.
14. The isolated peptide immunogen of claim 13, wherein the carrier is human serum albumin, keyhole limpet hemocyanin (KLH), immunoglobulin molecules, thyroglobulin, ovalbumin, influenza hemagglutinin, PAN-DR binding peptide (PADRE polypeptide), malaria circumsporozoite (CS) protein, hepatitis B surface antigen (HBsAg₁₉₋₂₈), Heat Shock Protein (HSP) 65, Bacillus Calmette-Guerin (BCG), cholera toxin, cholera toxin mutants with reduced toxicity, diphtheria toxin, CRM_{i97} protein that is cross-reactive with diphtheria toxin, recombinant Streptococcal C5 a peptidase, *Streptococcus pyogenes* ORF 1224, *Streptococcus pyogenes* ORF 1664, *Streptococcus pyogenes* ORF 2452, *Chlamydia pneumoniae* ORF T367, *Chlamydia pneumoniae* ORF T858, Tetanus toxoid, HIV gp120 T1, microbial surface components recognizing adhesive matrix molecules (MSCRAMMS), growth factor/hormone, cytokine or chemokine.
15. A vaccine composition comprising the isolated peptide immunogen of any one of claims 1 to 14.
16. The composition of claim 15, further comprising an adjuvant selected from the group consisting of mineral salts, GM-CSF, 529 SE, IL-12, aluminum phosphate, aluminum

hydroxide, *Mycobacterium tuberculosis*, *Bordetella pertussis*, bacterial lipopolysaccharides, aminoalkyl glucosane phosphate compounds, 3-0-deacylated monophosphoryl lipid A, a polypeptide, Quil A, a pertussis toxin (PT), an *E. coli* heat-labile toxin (LT), IL-1 alpha, IL-1 β , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, interferon-alpha, interferon- β , interferon-gamma, G-CSF, TNF-alpha, TNF- β and Freund's complete adjuvant (FCA).

17. An immunogenic composition comprising the isolated peptide immunogen of any one of claims 1 to 14 and one or more pharmaceutically acceptable excipients, diluents and/or adjuvants.
18. The immunogenic composition of claim 17, wherein the pharmaceutically acceptable excipients, diluents and/or adjuvants are selected from the group consisting of alum, liposyn, saponin, squalene, L 121, emulsion monophosphoryl lipid A, polysorbate 80 and QS21.
19. A method of preventing or treating an influenza virus mediated disease by administering to a mammal the isolated peptide immunogen according to any one of claims 1 to 14.
20. A method of preventing or treating an influenza virus mediated disease by administering to a mammal the vaccine composition according to claim 15 or claim 16.
21. A method of preventing or treating an influenza virus mediated disease by administering to a mammal the immunogenic composition according to claim 17 or claim 18.
22. A kit comprising the isolated peptide immunogen according to any one of claims 1 to 14.

Date: 20 April 2015

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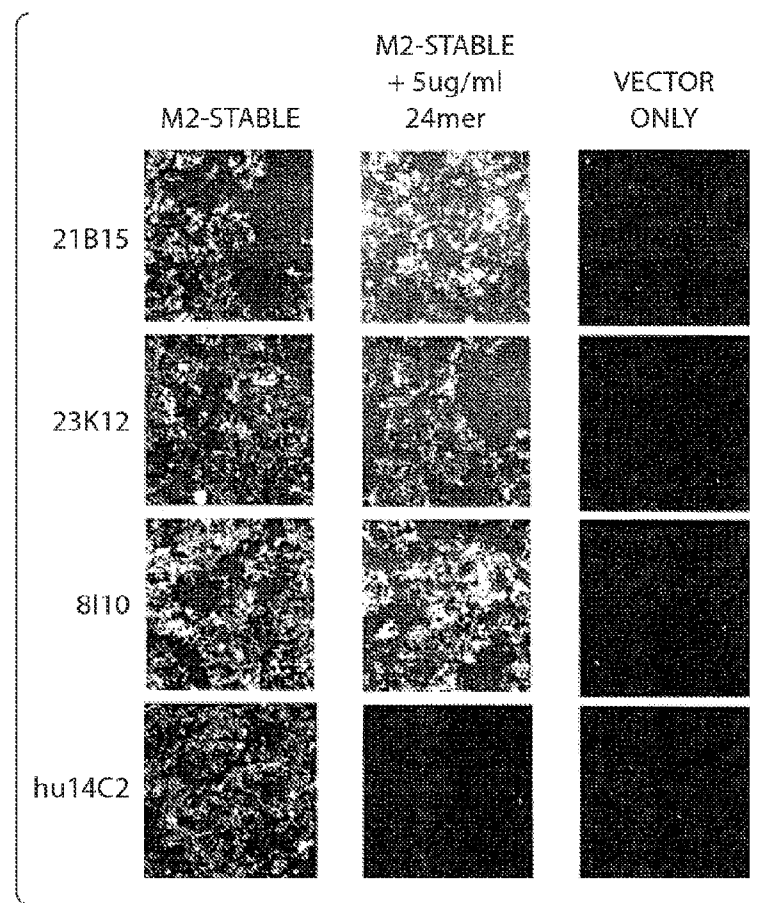


Fig. 1

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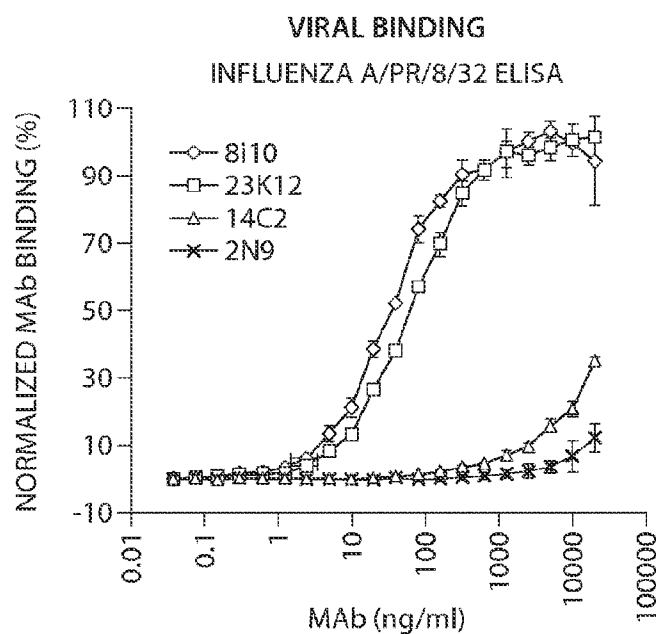


Fig. 2A

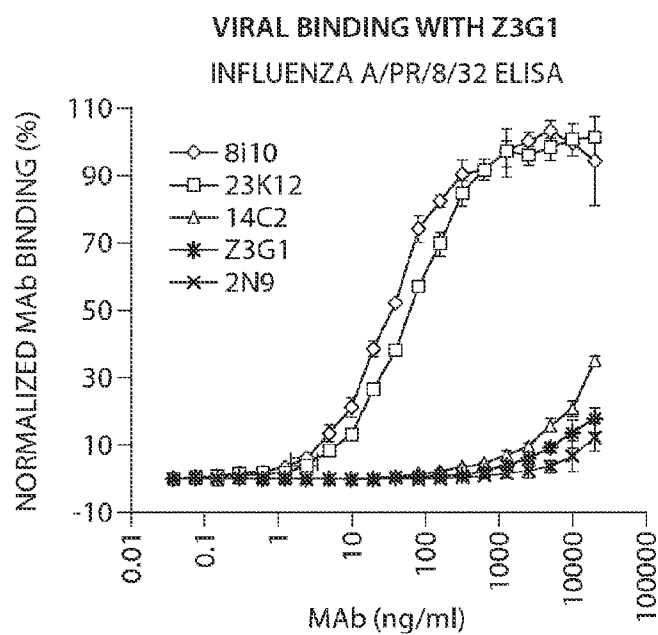


Fig. 2B

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FULL-LENGTH M2 VARIANT BINDING
AMINO ACID SEQUENCES OF EXTRACELLULAR DOMAINS OF M2 VARIANTS.

											10										20									
1	A.Brevig Mission.1.1918.H1N1	M	S	L	L	T	E	V	E		T	P	T	R	N	E	W	G		C	R	C	N	D	S	S	D			
2	A.Fort Monmouth.1.1947.H1N1	M	S	L	L	T	E	V	E		T	P	T	K	N	E	W	E		C	R	C	N	D	S	S	D			
3	A.Singapore.02.2005.H3N2	M	S	L	L	T	E	V	E		T	P	I	R	N	E	W	E		C	R	C	N	D	S	S	D			
4	A.Wisconsin.10.98.H1N1	M	S	L	L	T	E	V	E		T	P	I	K	N	G	W	E		C	K	C	N	D	S	S	D			
5	A.Wisconsin.301.1976.H1N1	M	S	L	L	T	E	V	E		T	P	I	R	S	E	W	G		C	R	C	N	D	S	S	D			
6	A.Panama.1.66.H2N2	M	S	F	L	P	E	V	E		T	P	I	R	N	E	W	G		C	R	C	N	D	S	S	D			
7	A.New York.321.1999.H3N2	M	S	L	L	T	E	V	E		T	P	I	R	N	E	W	G		C	R	C	N	D	S	S	N			
8	A.Caracas.1.71.H3N2	M	S	L	L	T	E	V	E		T	P	I	R	K	E	W	G		C	R	C	N	D	S	S	D			
9	A.Taiwan.3.71.H3N2	M	S	F	L	T	E	V	E		T	P	I	R	N	E	W	G		C	R	C	N	D	S	S	D			
10	A.Wuhan.359.95.H3N2	M	S	L	P	T	E	V	E		T	P	I	R	S	E	W	G		C	R	C	N	D	S	S	D			
11	A.Hong Kong.1144.99.H3N2	M	S	L	L	P	E	V	E		T	P	I	R	N	E	W	G		C	R	C	N	D	S	S	D			
12	A.Hong Kong.1180.99.H3N2	M	S	L	L	P	E	V	E		T	P	I	R	N	G	W	G		C	R	C	N	D	S	S	D			
13	A.Hong Kong.1774.99.H3N2	M	S	L	L	T	E	V	E		T	P	T	R	N	G	W	E		C	R	C	S	G	S	S	D			
14	A.New York.217.02.H1N2	M	S	L	L	T	E	V	E		T	P	I	R	N	E	W	E		Y	R	C	N	D	S	S	D			
15	A.New York.300.2003.H1N2	M	S	L	L	T	E	V	E		T	P	I	R	N	E	W	E		Y	R	C	S	D	S	S	D			
16	A.swine.Spain.54008.2004.H3N2	M	S	L	L	T	E	V	E		T	P	T	R	N	G	W	E		C	R	Y	S	D	S	S	D			
17	A.Guangzhou.333.99.H9N2	M	S	F	L	T	E	V	E		T	L	T	R	N	G	W	E		C	R	C	S	D	S	S	D			
18	A.Hong Kong.1073.99.H9N2	M	S	L	L	T	E	V	E		T	L	T	R	N	G	W	E		C	K	C	R	D	S	S	D			
19	A.Hong Kong.1.68.H3N2	M	S	L	L	T	E	V	E		T	P	I	R	N	E	W	G		C	R	C	N	D	S	S	D			
20	A.swine.Hong Kong.126.1982.H3N2	M	S	L	L	T	E	V	E		T	P	I	R	S	E	W	G		C	R	C	N	D	S	G	D			
21	A.New York.703.1995.H3N2	M	S	L	L	T	E	V	E		T	P	I	R	N	E	W	E		C	R	C	N	G	S	S	D			
22	A.swine.Quebec.192.81.H1N1	M	S	L	P	T	E	V	E		T	P	I	R	N	E	W	G		C	R	C	N	D	S	S	D			
23	A.Puerto Rico.8.34.H1N1	M	S	L	L	T	E	V	E		T	P	I	R	N	E	W	G		C	R	C	N	G	S	S	D			
24	A.Hong Kong.485.97.H5N1	M	S	L	L	T	E	V	D		T	L	T	R	N	G	W	G		C	R	C	S	D	S	S	D			
25	A.Hong Kong.542.97.H5N1	M	S	L	L	T	E	V	E		T	L	T	K	N	G	W	G		C	R	C	S	D	S	S	D			
26	A.silky chicken.Shantou.1826.2004.H	M	S	L	L	T	E	V	E		T	P	T	R	N	G	W	E		C	K	C	S	D	S	S	D			
27	A.chicken.Taiwan.0305.04.H6N1	M	S	L	L	T	E	V	E		T	H	T	R	N	G	W	E		C	K	C	S	D	S	S	D			
28	A.Quail.Arkansas.16309-7.94.H7N3	M	S	L	L	T	E	V	K		T	P	T	R	N	G	W	E		C	K	C	S	D	S	S	D			
29	A.Hong Kong.486.97.H5N1	M	S	L	L	T	E	V	E		T	L	T	R	N	G	W	G		C	R	C	S	D	S	S	D			
30	A.Chicken.Pennsylvania.13552-1.98	M	S	L	L	T	E	V	E		T	P	T	R	D	G	W	E		C	K	C	S	D	S	S	D			
31	A.chicken.Heilongjiang.48.01.H9N2	M	S	L	L	T	E	V	E		T	P	T	R	N	G	W	G		C	R	C	S	D	S	S	D			
32	A.swine.Korea.55.2005.H1N2	M	S	L	L	T	E	V	E		T	P	T	R	N	G	W	E		C	K	C	N	D	S	S	D			
33	A.Hong Kong.1073.99.H9N2	M	S	L	L	T	E	V	E		T	L	T	R	N	G	W	E		C	K	C	S	D	S	S	D			
34	A.Wisconsin.3523.88.H1N1	M	S	L	L	T	E	V	E		T	P	I	R	N	E	W	G		C	K	C	N	D	S	S	D			
35	A.X-31 Vaccine strain H3N2	M	S	F	L	T	E	V	E		T	P	I	R	N	E	W	G		C	R	C	N	G	S	S	D			
36	A.Chicken.Rostock.8.1934.H7N1	M	S	L	L	T	E	V	E		T	P	T	R	N	G	W	E		C	R	C	N	D	S	S	D			
37	A.environment.New York. 16326-1.2	M	S	L	L	T	E	V	E		T	P	I	R	K	G	W	E		C	N	C	S	D	S	S	D			
38	A.Indonesia.560H.2006.H5N1	M	S	L	L	T	E	V	E		T	P	T	R	N	E	W	E		C	R	C	S	D	S	S	D			
39	A.Chicken.Hong Kong.SF1.03.H9N2	M	S	L	L	T	G	V	E		T	H	T	R	N	G	W	G		C	K	C	S	D	S	S	D			
40	A.chicken.Hong Kong.YU427.03.H9N	M	S	L	L	P	E	V	E		T	H	T	R	N	G	W	G		C	R	C	S	D	S	S	D			

EXTRACELLULAR SEQUENCE OF D20 IS IDENTICAL
 TO #19, HK483 TO #29, AND VN1203 TO #38.

Fig. 3A

SUBSTITUTE SHEET (RULE 26)

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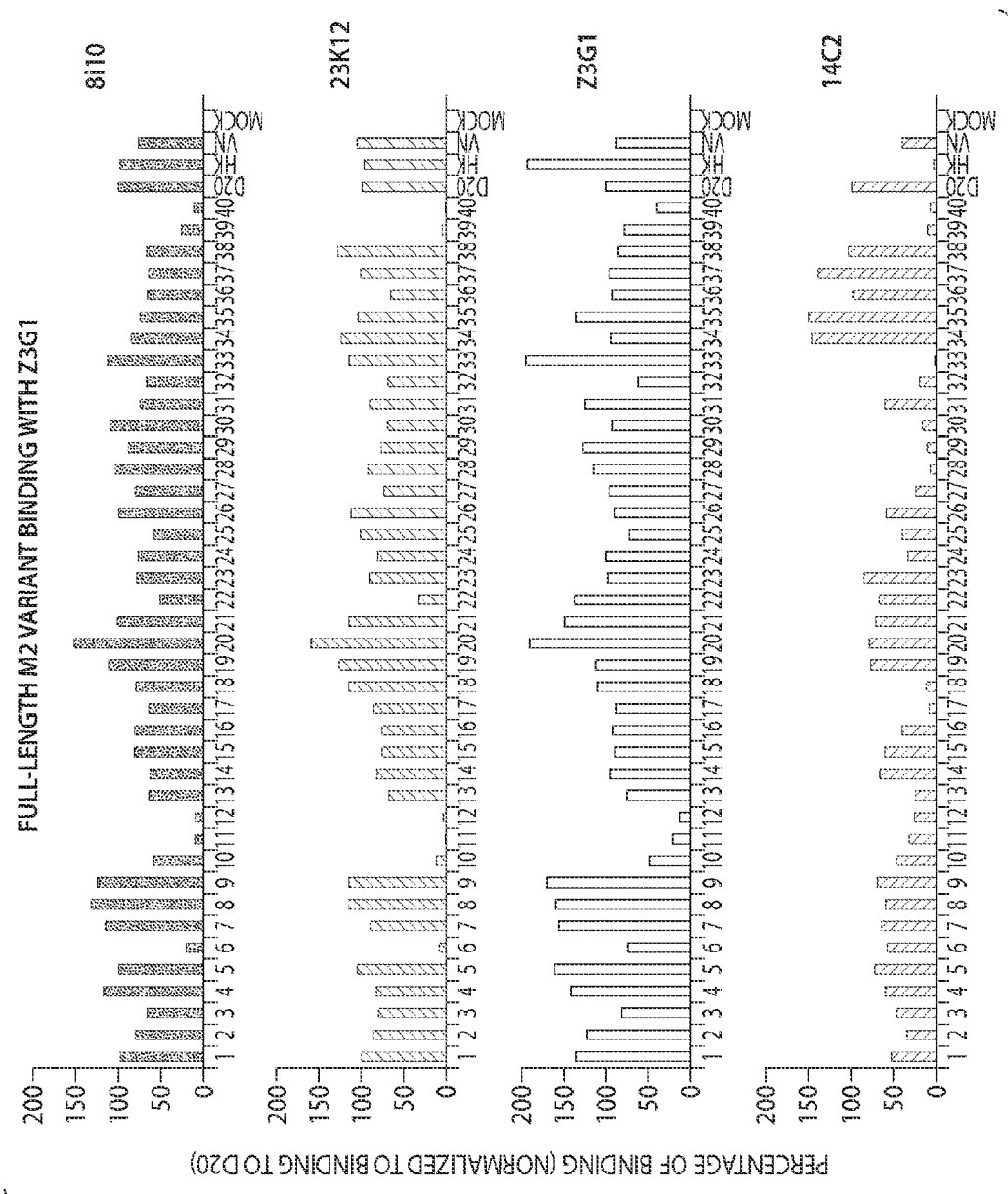


Fig. 3B

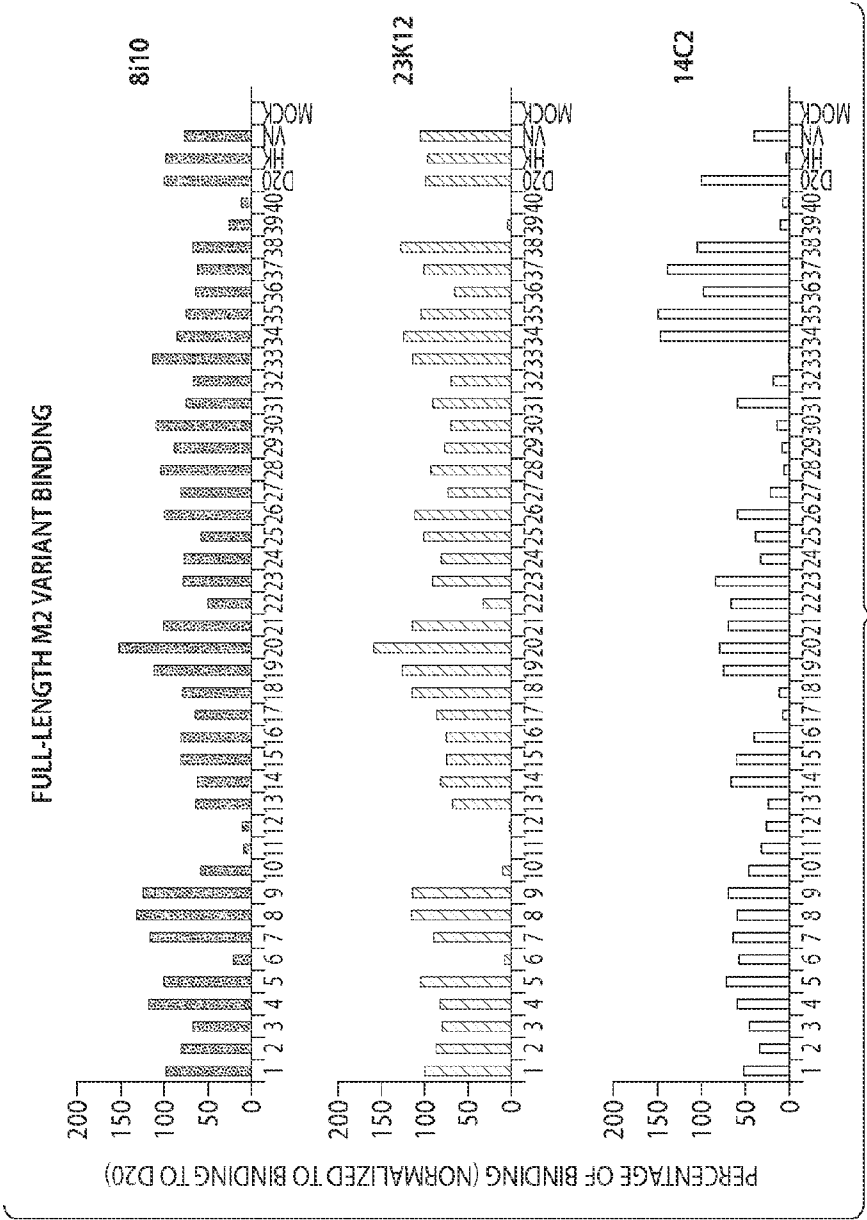


Fig. 3C

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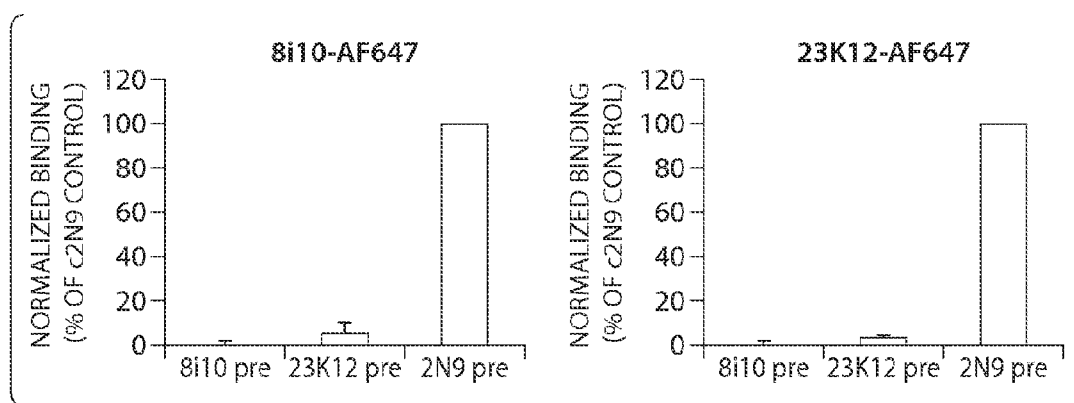


Fig. 4

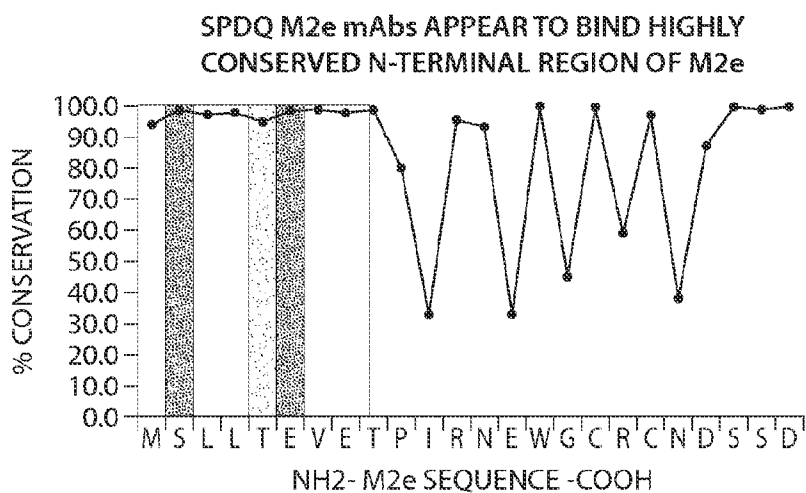


Fig. 5

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CORE SEQUENCES - 1:

S L L T E

C	A	A	-	D
T	C	C		C
	F	E		
	K	F		
		I		
		K		
		M		
		Q		
		S		
		T		
		V		

PREFERRED CORE SEQUENCE
SHOWN IN BOX; ALLOWABLE
VARIANT RESIDUES SHOWN
AT EACH POSITION

Fig. 6A

CORE SEQUENCES - 2:

S L L T E

A	A	B	M	A
C	C		N	D
D	F		Q	F
L	H		S	H
T	I		W	I
V	K			K
	M			M
	N			N
	Q			Q
	R			S
	T			W
	W			Y
	Y			C

PREFERRED CORE SEQUENCE
SHOWN IN BOX; ALLOWABLE
VARIANT RESIDUES SHOWN
AT EACH POSITION; B=ANY RESIDUE

Fig. 6B

CORE VARIANTS:

S	L	L	T	E	SEQ ID NO: 47		
S	L	L	T	E	X	SEQ ID NO: 1597	
S	L	L	T	E	X	Z	SEQ ID NO: 1598

WHERE X IS ANY AMINO ACID BUT PREFERABLY = V OR C
WHERE Z IS ANY AMINO ACID BUT PREFERABLY = E

Fig. 6C

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IMMUNOGENS (LINEAR & CYCLIZED PEPTIDES):

(CORE)
(CORE)G(CORE)
(CORE)G(CORE)G(CORE)
(CORE)G(CORE)G(CORE)G(CORE)
(CORE)G(CORE)G(CORE)G(CORE)G(CORE)

Fig. 6D

IMMUNOGENS (LINEAR & CYCLIZED PEPTIDES):

J(CORE)
J(CORE)G(CORE)
J(CORE)G(CORE)G(CORE)
J(CORE)G(CORE)G(CORE)G(CORE)
J(CORE)G(CORE)G(CORE)G(CORE)G(CORE)

WHERE J IS ANY AMINO ACID BUT PREFERABLY = C

Fig. 6E

SPECIFIC IMMUNOGENS (LINEAR & CYCLIZED PEPTIDES):

SLLTEVGSLLTEV	SEQ ID NO: 320
CSLLTEVGSLLTEV	SEQ ID NO: 283
CSLLTECGSLLTCV	SEQ ID NO: 463

Fig. 6F