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(54) **GLYCATED PEPTIDES AND METHODS OF USE**

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(58) **Field of Classification Search** ..... None
See application file for complete search history.

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(57) **ABSTRACT**

The invention provides glycated peptides and glycated fragments and glycated variants thereof, antibodies and aptamers which bind thereto, compositions and kits comprising the same, related conjugates, and a database comprising data indicating the concentration of glycated peptides present in diabetic and non-diabetic persons. The invention also provides a method of monitoring glycemic control, a method of treating or preventing diabetes, a method of preventing a complication of diabetes, a method of monitoring the status of diabetes, a method of determining the efficacy of a diabetes treatment, as well as methods of detecting diabetes or a predisposition thereto.

14 Claims, No Drawings

GLYCATED PEPTIDES AND METHODS OF USE

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a national phase patent application under 35 U.S.C. §371 of International Application No. PCT/US/2007/063385, which claims the benefit of U.S. Provisional Patent Application No. 60/779,710, filed Mar. 6, 2006, which are specifically incorporated by reference herein in their entirety.

SEQUENCE LISTING

Incorporated by reference in its entirety herein is a computer-readable nucleotide/amino acid sequence listing submitted concurrently herewith and identified as follows: One 110,954 byte ASCII (Text) file named "703368 ST25.txt," created on Sep. 5, 2008.

BACKGROUND OF THE INVENTION

Improved glycemic control can delay and possibly prevent the development of some of the long-term microvascular and, perhaps, macrovascular complications of both type 1 and type 2 diabetes (The Diabetes Control and Complications Trial Research Group, *N Engl J Med* 329: 977-986 (1993) and UK Prospective Diabetes Study Group, *Lancet* 352: 837-853 (1998); Nathan et al., *N Engl J Med* 353: 2643-2653 (2005)). Thus, improving day-to-day glycemic control in diabetes is one of the main goals of current therapy.

The current accepted method of monitoring glycemic control is by measuring the relative concentration of glycated red-cell hemoglobin, also known as hemoglobin A1C (HbA1C), wherein high levels of HbA1C typically indicate poor glycemic control. Glycation of hemoglobin involves the non-enzymatic covalent attachment of multiple glucose molecules to the amino terminal and internal lysine residues in the hemoglobin A molecule (Bunn, *Schweiz Med Wochenschr* 111: 1503-1507 (1981); Bunn et al., *Prog Clin Biol Res* 60: 83-94 (1981); Gabbay et al., *J Clin Endocrinol Metab* 44: 859-864 (1977); and Shapiro et al., *Metabolism* 28: 427-430 (1979)). Glycation results in electrophoretic and other changes in the behavior of the hemoglobin molecule such that its concentration as a fraction of the total hemoglobin can be readily measured.

It has been shown that the relative concentration of HbA1C as compared to total hemoglobin concentration reflects the glycemic control of a patient over a period of several months, presumably based on the lifetime of the erythrocyte in the circulation of approximately 120 days. However, measurement of HbA1C provides an imperfect index of glycemic control. Due to the relatively long period of time reflected in a single HbA1C measurement, acute modifications in glycemic control do not result in rapid changes in HbA1C levels. Also, HbA1C levels can be affected by artifacts caused by conditions such as thalassemia, uremia, and hypertriglyceridemia, as well as by drugs or other ingested substances, such as aspirin, penicillin, and ethanol.

Furthermore, HbA1C measurements are relatively insensitive to minor changes in glucose tolerance, which are now viewed as predictors of diabetes development (Rohlfing et al., *Diabetes Care* 23: 187-191 (2000)). Moreover, the incidence of cardiovascular disease appears to be linked to concentrations of HbA1C within the conventional "normal" range, even in the absence of known diabetes (de Vegt et al., *Diabetologia* 42: 926-931 (1999)).

Due to the limitations of the HbA1C assay, attempts have been made to develop new biomarkers of glycemic control. For instance, fructosamine, 1,5-anhydroglucitol (1,5AG), and albumin have been tested as a glycemic control markers (Armbruster, *Clin Chem* 33: 2153-2163 (1987); Nowatzke et al., *Clin Chim Acta* 350: 201-209 (2004); (Kouzuma et al., *Clin Chim Acta* 324: 61-71 (2002)). However, none of these biomarkers have gained widespread use.

Accordingly, there is a need for new methods and compositions that can be used to monitor glycemic control or detect abnormal glycemic control associated with the onset or progression of diabetes. The invention provides such methods and compositions.

BRIEF SUMMARY OF THE INVENTION

The invention provides an isolated or purified glycated peptide comprising (i) at least one of Peptides AA-DJ or (ii) an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-36, or a glycated fragment or glycated variant thereof.

The invention also provides an isolated or purified antibody, an antigen binding portion thereof, or an aptamer, any of which specifically binds to the glycated peptide described herein, or a glycated fragment or glycated variant thereof.

The invention further provides a conjugate comprising (i) a glucose-binding moiety, (ii) an antibody, antigen binding portion thereof, or aptamer which specifically binds to a peptide, or a fragment or variant thereof, comprising (a) at least one of Peptides AA-DJ or (b) an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-36, and (iii) a detectable label.

Compositions and kits comprising any of the glycated peptides, or a glycated fragment or glycated variant thereof, antibodies or antigen binding portions thereof, aptamers, or conjugates described herein are further provided by the invention.

Also provided is a database comprising data indicating the concentration of one or more of the glycated peptides described herein, or a glycated fragment or glycated variant thereof, present in diabetic persons, non-diabetic persons, or both diabetic and non-diabetic persons.

The invention further provides a method of monitoring glycemic control of a host. The method comprises measuring the concentration of a glycated peptide, or a glycated fragment or glycated variant thereof, in a host, wherein the glycated peptide comprises (i) at least one of Peptides AA-DJ or (ii) an amino acid sequence of the group consisting of SEQ ID NOs: 24-36.

Furthermore, the invention provides a method of treating or preventing diabetes or a complication of diabetes, a method of detecting the onset, progression, or regression of diabetes, a method of detecting diabetes or a predisposition to diabetes, and a method of determining the efficacy of a diabetes treatment. The methods comprise monitoring the glycemic control of a host in accordance with the invention, or other method steps described herein.

DETAILED DESCRIPTION OF THE INVENTION

The invention provides isolated or purified glycated peptides, as well as glycated fragments and glycated variants thereof. The glycated peptides comprise (i) at least one of Peptides AA-DJ or (ii) an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-36.

Glycated Peptides AA-DJ were found to be significantly increased in concentration in diabetic patients as compared to

non-diabetic patients, as discussed further herein. Peptides AA-DJ can be isolated upon carrying out the procedures described in Example 1. Specifically, all of Peptides AA-DJ are glycated tryptic peptides of plasma proteins that can be enriched in a plasma sample using affinity chromatography with m-aminophenylboronic acid. Such a procedure is explained in greater detail in Example 1. Further, Peptides AA-DJ have the specific properties set forth in Table 1, wherein m/z is the mass in Daltons per unit of charge (z) as determined by a mass spectrometer, R.T. (min) is the retention time on an HPLC column in minutes, z is the net charge of the peptide, and M+H is the calculated mass of the protonated peptide. The fold-change in the concentration of each of the peptides in diabetic patients as compared to diabetic patients also is provided in Table 1, as further discussed in the examples.

TABLE 1

Peptide	m/z	R.T. (min.)	z	m + H	Amino Acid Sequence	SEQ ID NO	P-value	Fold-change*
AA	440.24	38.11	3	1318.70	SKEQLTPLIK	1	7.54E-12	5.97
AB	529.27	37.78	3	1585.80			7.87E-11	7.77
AC	397.20	37.80	4	1585.78			2.47E-10	7.35
AD	482.93	31.70	3	1446.78			5.07E-10	6.73
AE	362.45	31.69	4	1446.78			1.OOE-09	7.06
AF	400.22	41.66	3	1198.65			3.78E-09	8.20
AG	659.86	38.10	2	1318.72	SKEQLTPLIK	1	7.20E-09	7.46
AH	312.17	28.79	3	934.50			1.69E-08	7.99
AI	428.22	27.51	3	1282.63	SIYKPGQTVK	2	3.62E-08	8.36
AJ	318.17	28.79	3	952.50			5.22E-08	8.05
AK	342.52	31.49	3	1025.55			6.58E-08	8.73
AL	454.56	28.69	3	1361.66	VKSPELQAEAK	3	7.21E-08	6.18
AM	336.52	31.49	3	1007.54			9.94E-08	8.57
AN	476.76	28.78	2	952.52			1.89E-07	9.02
AO	599.84	41.65	2	1198.67			2.43E-07	9.51
AP	466.91	37.05	3	1398.72	LVDGKGVPIPNK	4	7.37E-07	8.16
AQ	366.85	24.00	3	1098.53			9.61E-07	8.99
AR	394.55	28.14	3	1181.64			1.69E-06	10.10
AS	544.93	38.65	3	1632.77	SKAIGYLNTGYQR	5	1.73E-06	9.61
AT	414.88	35.20	3	1242.61			2.74E-06	7.06
AU	374.93	46.61	4	1496.71			3.52E-06	12.42
AV	507.76	29.87	2	1014.51			4.08E-06	5.29
AW	433.21	28.41	3	1297.60	QKLHELQEK	6	4.12E-06	3.88
AX	412.96	35.46	4	1648.82			4.16E-06	8.14
AY	365.18	24.30	3	1093.52			4.39E-06	5.25
AZ	344.52	41.31	3	1031.56			9.79E-06	5.55
BA	440.88	27.49	3	1320.61			1.30E-05	5.51
BB	525.30	41.31	2	1049.58	GKITDLIK	7	1.34E-05	5.78
BC	392.20	33.7S	3	1174.58			1 .43E-05	5.43
BD	451.55	29.96	3	1352.63			1.83E-05	8.90
BE	649.32	28.40	2	1297.63	QKLHELQEK	6	1.97E-05	6.22
BF	580.29	30.80	2	1159.57			2.08E-05	5.42
BG	381.18	32.68	4	1521.70			2.43E-05	5.45

TABLE 1-continued

Peptide	m/z	R.T. (min.)	z	m + H	Amino Acid Sequence	SEQ ID NO	P-value	Fold-change*
BH	440.55	26.45	3	1319.63	LEALKENGGAR	8	2.61E-05	4.65
BI	499.73	26.68	2	998.45			2.64E-05	5.35
BJ	327.48	26.70	3	980.43			2.70E-05	4.78
BK	461.57	47.69	3	1382.70			3.02E-05	10.90
BL	350.53	41.28	3	1049.57	GKITDLIK	7	3.03E-05	5.66
BM	516.23	34.59	3	1546.68			3.28E-05	6.53
BN	514.91	41.89	3	1542.71	VQPYLDDFQKK	9	3.44E-05	5.41
BO	402.70	35.33	4	1607.76	GDJVWVYPPEKK	10	3.48E-05	6.20
BP	336.50	28.74	3	1007.47			3.49E-05	6.08
BQ	581.29	40.20	3	1741.85			3.73E-05	5.87
BR	335.85	22.85	3	1005.54			3.95E-05	6.00
BS	309.18	27.36	3	925.51			4.02E-05	2.24
BT	399.51	25.34	3	1196.53			4.04E-05	6.66
BU	481.98	35.08	4	1924.88	VKAHYGGFTVQNEANK	11	4.25E-05	7.15
BV	403.21	31.31	3	1207.63			4.52E-05	6.22
BW	587.81	33.74	2	1174.61			4.59E-05	6.39
BX	436.21	40.21	4	1741.83			4.66E-05	5.88
BY	536.60	35.34	3	1607.78	GDJVVVVYPPEKK	10	4.81E-05	6.10
BZ	493.90	40.03	3	1479.68	GDJVWVYPPEK	12	5.42E-05	6.21
CA	333.48	26.69	3	998.43			5.65E-05	4.80
CB	507.59	39.15	3	1520.75			5.74E-05	9.28
CC	467.26	40.46	4	1866.03			7.48E-05	12.89
CD	374.20	27.40	3	1120.60			7.76E-05	3.21
CE	642.30	35.08	3	1924.90	VKAHYGGFTVQNEANK	11	8.40E-05	7.47
CF	350.82	20.59	3	1050.45	SYFEKSK	13	1.00E-04	4.73
CG	436.55	36.19	3	1307.64	VVVVYPPEKK	14	1.01E-04	6.35
CH	427.21	28.43	3	1279.61			1.02E-04	5.34
CI	477.90	40.65	3	1431.69			1.14E-04	6.81
CJ	374.86	22.34	3	1122.56			1.62E-04	5.49
CK	575.27	21.39	3	1723.78	AGVETTTPSKQSNNK	15	1.93E-04	5.42
CL	410.22	36.53	4	1637.86			2.07E-04	7.69
CM	374.85	29.12	3	1122.54			2.48E-04	9.25
CN	548.26	37.01	4	2190.00			3.28E-04	6.79
CO	349.20	32.63	3	1045.58			3.42E-04	9.62
CP	438.89	20.05	3	1314.64			5.38E-04	5.75
CQ	467.58	36.49	3	1400.72			7.42E-04	6.53
CR	637.54	50.20	4	2547.14			8.39E-04	15.86
CS	386.22	38.35	3	1156.65			8.63E-04	2.70

TABLE 1-continued

Peptide	m/z	R.T. (min.)	z	m + H	Amino Acid Sequence	SEQ ID NO	P-value	Fold-change*
CT	434.54	38.50	3	1301.61			1.30E-03	1.63
CU	427.22	46.06	3	1279.66	GFSPKDVLVR	16	1.45E-03	7.26
CV	402.23	51.18	3	1204.68	LKFIIPSPK	17	1.89E-03	4.95
CW	347.50	21.62	3	1040.47			2.07E-03	2.50
CX	430.19	40.37	3	1288.57	KASYLDCIR	18	3.10E-03	5.60
CY	379.20	28.27	3	1135.57			3.95E-03	4.32
CZ	511.99	33.71	4	2044.94	GDVAFVKHQTVPQNTGGK	19	3.99E-03	4.16
DA	466.27	37.30	1	466.27			4.23E-03	1.96
DB	476.92	33.84	3	1428.74	VSNKALPAPIEK	20	5.58E-03	6.34
DC	383.54	30.74	3	1148.60	KQLVEIEK	21	7.53E-03	5.83
DD	443.85	27.02	3	1329.52			7.55E-03	3.99
DE	443.72	31.80	2	886.43			1.03E-02	1.69
DF	538.59	44.23	3	1613.75	AKVQPYLDDFQK	22	1.23E-02	5.47
DG	337.16	24.45	2	673.30			1.30E-02	1.48
DH	461.52	27.70	3	1382.55			2.80E-02	-2.45
DI	403.23	42.18	2	805.46			3.65E-02	1.44
DJ	538.26	45.44	3	1612.77			4.59E-02	4.13

*Fold.increase in diabetic vs. non-diabetic patients is indicated by a positive number, and fold-decreases are indicated by a negative number

Without wishing to be bound by any particular theory, it is believed that some of Peptides AA-DJ are glycated fragments of a protein comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-36. For instance, it is contemplated that Peptide AA is a glycated fragment of SEQ ID NO: 24 (the amino acid sequence of Apolipoprotein A-II protein), Peptide AI is a glycated fragment of the SEQ ID NO: 25 (the amino acid sequence of α-2 macroglobulin protein), and Peptide BL is a glycated fragment of SEQ ID NO: 27 (the amino acid sequence of α-1 antichymotrypsin protein). Other such associations are set forth in Table 2. In this regard, the glycated peptide of the invention can comprise an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-36, which correspond to the mature proteins identified in Table 2.

The invention also provides glycated fragments of the glycated peptides described herein. The term "glycated fragment" when used in reference to a glycated peptide refers to any contiguous portion of 2, 3, 4, 5 or more amino acid residues of the glycated peptide of the invention, which portion comprises at least one of the glycated amino acid residues of the glycated peptide from which it originates (e.g., the "parent" glycated peptide) and a sufficient number of amino acid residues of the parent glycated peptide that flank the at least one glycated amino acid residue such that the glycated fragment can be detected for purposes of measuring its concentration. The concentration of the glycated fragment reflects the concentration of the parent glycated peptide. In reference to the parent glycated peptide, the glycated fragment can comprise, for instance, about 10%, 25%, 30%, 50%, 68%, 80%, 90%, 95%, or more contiguous amino acids of the parent peptide. In a preferred embodiment, the glycated fragment comprises 5 or more amino acids, such that a binding molecule or other agent used to detect the fragment, e.g., an antibody, aptamer, or conjugate comprising a glucose binding moiety, can bind to the glycated fragment.

The glycated fragment can comprise additional amino acids at the amino or carboxy terminus of the fragment, or at both termini, which additional amino acids are not found in the amino acid sequence of the parent glycated peptide. Desirably, the additional amino acids do not interfere with the ability of the glycated fragment to be detected.

Non-limiting examples of glycated fragments of peptides comprising SEQ ID NOs: 24-36 include, for example, peptides comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-23.

TABLE 2

Peptide	Protein Description	Accession No.[1]	SEQ ID NO:
AA	Apolipoprotein A-II (Apo-AII)	NP_001634.1	24
AG	Apolipoprotein A-II (Apo-AII)	NP_001634.1	24
AI	Alpha-2-macroglobulin (Alpha-2-M)	NP_000005.2	25
AL	Apolipoprotein A-II (Apo-AII)	NP_001634.1	24
AP	Alpha-2 macroglobulin (Alpha 2M)	NP_000005.2	25
AS	Alpha-2 macroglobulin (Alpha 2M)	NP_000005.2	25
AW	Apolipoprotein A-I (Apo-AI)	NP_000030.1	26
BB	Alpha-1-antichymotrypsin (ACT)	NP_001076.2	27
BE	Apolipoprotein A-I (Apo-AI)	NP_000030.1	26
BH	Apolipoprotein A-I (Apo-AI)	NP_000030.1	26
BL	Alpha-1-antichymotrypsin (ACT)	NP_001076.2	27
BN	Apolipoprotein A-I (Apo-AI)	NP_000030.1	26
BO	Hemopexin (Beta-1B-glycoprotein)	NP_000604.1	28
BU	Fibrinogen, beta chain	NP_005132.2	29
BY	Hemopexin (Beta-1B-glycoprotein)	NP_000604.1	28

TABLE 2-continued

Peptide	Protein Description	Accession No.[1]	SEQ ID NO:
BZ	Hemopexin (Beta-1B-glycoprotein)	NP_000604.1	28
CE	Fibrinogen, beta chain	NP_005132.2	29
CF	Apolipoprotein A-II (Apo-AII)	NP_001634.1	24
CG	Hemopexin (Beta-1B-glycoprotein)	NP_000604.1	28
CK	Ig lambda light chain	AAA59109	30
CU	Ig heavy chain, constant region	CAA09968	31
CV	Apolipoprotein B-100 (Apo B-100)	NP_000375.1	32
CV	Apolipoprotein B-48 (Apo B-48)	NP_000375.1	33
CX	Transferrin	NP_001054.1	34
CZ	Transferrin	NP_001054.1	34
DB	IhHG1	AAH19046	35
DC	Haptoglobin	NP_005134.1	36
DF	Apolipoprotein A-I (Apo-AI)	NP_000030.1	26

[1]Accession number of the GenBank database of the National Center for Biotechnology Information. In some instances, the accession number corresponds directly to a precursor protein sequence, with reference to the sequence of the mature protein. The precursor protein sequences, where applicable, are hereby incorporated by reference to the accession number.

The invention also provides glycated variants of the glycated peptides described herein. The term "glycated variant" when used in reference to a glycated peptide refers to a to a glycated peptide having substantial or significant sequence identity or similarity to a "parent" glycated peptide otherwise described herein (e.g., Peptides AA-DJ). The glycated variant preferably retains any activity that the parent glycated peptide may have. Glycated variants encompass, for example, those variants of a glycated peptide described herein (i.e., the parent glycated peptide) that retain the at least one glycated amino acid residue of the parent glycated peptide and retain sufficient sequence identity of the parent glycated peptide, such that the glycated variant can be detected for the purposes of measuring its concentration. In reference to the parent glycated peptide, the glycated variant can, for instance, have a sequence identity to the parent glycated peptide (e.g., comprising glycated Peptides AA-DJ or SEQ ID NOs: 24-36) of 30%, 50%, 75%, 80%, 90%, 95%, 98% or more. Sequence identity can be determined, for instance, using the Basic Local Alignment Search Tool (BLAST), made publicly available through the National Center for Biotechnology Information (NCBI), Bethesda, Md.

The glycated variant can, for example, comprise a variation of the amino acid sequence of the parent glycated peptide, or a glycated fragment thereof, wherein one or more amino acid residues of the parent amino acid sequence has been conservatively substituted. Conservative amino acid substitutions are known in the art, and include amino acid substitutions in which one amino acid having certain physical and/or chemical properties is exchanged for another amino acid that has the same or similar chemical or physical properties. For instance, the conservative amino acid substitution can be an acidic amino acid substituted for another acidic amino acid (e.g., Asp or Glu), an amino acid with a nonpolar side chain substituted for another amino acid with a nonpolar side chain (e.g., Ala, Gly, Val, Ile, Leu, Met, Phe, Pro, Tip, Val, etc.), a basic amino acid substituted for another basic amino acid (Lys, Arg, etc.), an amino acid with a polar side chain substituted for another amino acid with a polar side chain (Asn, Cys, Gln, Ser, Thr, Tyr, etc.), etc. Thus, glycated variants include glycated peptides comprising a variant of the amino acid sequence of Peptides AA-DJ or SEQ ID NOs: 24-36 comprising one or more conservative amino acid substitutions.

Alternatively or additionally, the glycated variants can comprise a variation of the amino acid sequence of the parent glycated peptide (e.g., comprising glycated Peptides AA-DJ or SEQ ID NOs: 24-36), or a glycated fragment thereof, comprising one or more non-conservative amino acid substitution. In this case, it is preferable that the non-conservative amino acid substitution does not interfere with or inhibit the ability of the glycated variant to be detected such that the concentration of the glycated variant represents the concentration of the parent glycated peptide.

Non-limiting examples of glycated variants of the invention include, for instance, a glycated peptide comprising a variant of SEQ ID NO: 6, wherein one or both of the Gln residues at positions 1 and 7 of SEQ ID NO: 6 are replaced with Glu. In this regard, the glycated variant can comprise the amino acid sequence of any of SEQ ID NOs: 37-39. Additionally or alternatively, the glycated variant can comprise a variant of SEQ ID NO: 6, wherein the Glu at position 5 of SEQ ID NO: 6 is replaced with pyroglutamate. In this respect, the glycated variant can comprise the amino acid sequence of any of SEQ ID NOs: 40-43. Similarly, glycated variants of the invention include, for instance, a glycated peptide comprising a variant of SEQ ID NO: 8, wherein the Asn at position 7 of SEQ ID NO: 8 is replaced with Asp. In this regard, the glycated variant can comprise the amino acid sequence of SEQ ID NO: 44. Gycated variants of the invention also include, for instance, a glycated peptide comprising a variant of SEQ ID NO: 9, wherein one or both of the Gln residues at positions 2 and 9 of SEQ ID NO: 9 are replaced with Glu. In this regard, the glycated variant can comprise an amino acid sequence of any of SEQ ID NOs: 45-47. Preferably, the glycated variant comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 37-47.

The glycated peptides of the invention, as well as glycated fragments and glycated variants thereof, can be of any length, i.e., can comprise any number of amino acids, provided that the peptides (including glycated fragments and glycated variants) are detectable, such that the concentration of the peptides can be ascertained. The glycated peptide, glycated fragment, or glycated variant can, for example, be 5 to 5000 amino acids long, such as 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 17, 19, 20, 25, 50, 75, 100, 200, 350, 500, 600, 700, 850, 990, 1000, 2225, 3550, 4550, 5000 or more amino acids in length. In this regard, the glycated peptides of the invention, as well as glycated fragments and glycated variants, include glycated polypeptides, glycated oligopeptides, and glycated proteins. In a preferred embodiment, the peptide, fragment, or variant comprises at least 5 amino acids, such that an agent which binds to the glycated peptide, fragment, or variant e.g., an antibody, aptamer, or glucose binding moiety, can bind to the glycated peptide, fragment, or variant in a glycated peptide-specific manner.

The glycated peptides of the invention, as well as glycated fragments and glycated variants thereof, can comprise synthetic amino acids in place of one or more naturally-occurring occurring amino acids. Such synthetic amino acids are known in the art, and include, for example, aminocyclohexane carboxylic acid, norleucine, α-amino n-decanoic acid, homoserine, S-acetylaminomethyl-cysteine, trans-3- and trans-4-hydroxyproline, 4-aminophenylalanine, 4-nitrophenylalanine, 4-chlorophenylalanine, 4-carboxyphenylalanine, β-phenylserine β-hydroxyphenylalanine, phenylglycine, α-naphthylalanine, cyclohexylalanine, cyclohexylglycine, indoline-2-carboxylic acid, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid, aminomalonic acid, aminomalonic acid monoamide, N'-benzyl-N'-methyl-lysine, N',N'-dibenzyl-lysine, 6-hydroxylysine, ornithine, α-aminocyclopentane carboxylic acid, α-aminocyclohexane carboxylic acid, α-aminocycloheptane carboxylic acid, α-(2-amino-2-nor-

bornane)-carboxylic acid, α,γ-diaminobutyric acid, α,β-diaminopropionic acid, homophenylalanine, and α-tert-butylglycine.

It is understood that the glycated peptides, and glycated fragments and glycated variants thereof, are glycated, meaning that at least one of the amino acids which make up the peptide contains one or more glucose groups attached thereto. The term "glycated" as used herein refers to the attachment of a sugar molecule (e.g., glucose) to a protein, typically by a non-enzymatic process. Glycation does not encompass N- or O-glycosylation. Typically, the amino acid which is glycated is a lysyl residue, although any other amino acid can be glycated, e.g., Trp, Ala, Arg, Asp, Glu, Gln, Asn, Cys, Phe, Gly, His, Ile, Leu, Met, Pro, Ser, Thr, Val, and Tyr. The glycated amino acid can be found within any region of, i.e., at any position within, the glycated peptide, glycated fragment, or glycated variant. For example, the glycated amino acid can be an amino acid within the amino terminal region of the peptide (e.g., within 50, 40, 30, 25, 10, 5, or 3 amino acids from the N-terminal amino acid). Alternatively, the glycated amino acid can be an amino acid within the carboxy terminal region of the peptide (e.g., within 50, 40, 30, 25, 10, 5, or 3 amino acids from the C-terminal amino acid). The glycated amino acid is, in some cases, preferably the N-terminal amino acid.

The inventive glycated peptides, glycated fragments, and glycated variants can additionally be O-glycosylated, N-glycosylated, amidated, deamidated, carboxylated, phosphorylated, esterified, N-acylated, cyclized via, e.g., a disulfide bridge, or converted into an acid addition salt and/or optionally dimerized or polymerized, or conjugated.

The glycated peptides, glycated fragments, and glycated variants can be in the form of a salt, preferably, a pharmaceutically acceptable salt. Suitable pharmaceutically acceptable acid addition salts include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, and sulphuric acids, and organic acids, such as tartaric, acetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic, and arylsulphonic acids, for example, p-toluenesulphonic acid.

The inventive glycated peptides, glycated fragments, and glycated variants can be charged or neutral. If charged, the peptide, fragment, or variant can be of any charge state, e.g., −4, −3, −2, −1, +1, +2, +3, +4, etc.

The glycated peptides of the invention, as well as glycated fragments and glycated variants thereof, can be obtained by methods known in the art, including a two-step method which comprises first obtaining or making the peptide in an unglycated form followed by glycation of the peptide.

Suitable methods of de novo synthesizing peptides (including fragments and variants thereof) are known in the art and are described in references, such as Chan et al., *Fmoc Solid Phase Peptide Synthesis*, Oxford University Press, Oxford, United Kingdom, 2005; *Peptide and Protein Drug Analysis*, ed. Reid, R., Marcel Dekker, Inc., 2000; *Epitope Mapping*, ed. Westwood et al., Oxford University Press, Oxford, United Kingdom, 2000; and U.S. Pat. No. 5,449,752. Also, peptides (including fragments and variants thereof) can be recombinantly produced using nucleic acids which encode the peptides in standard recombinant methods. See, for instance, Sambrook et al., *Molecular Cloning: A Laboratory Manual,* 3rd ed., Cold Spring Harbor Press, Cold Spring Harbor, N.Y. 2001; and Ausubel et al., *Current Protocols in Molecular Biology*, Greene Publishing Associates and John Wiley & Sons, NY, 1994. Further, the glycated peptides, glycated fragments, and glycated variants can be isolated and/or purified from a source, such as a plant, a bacterium, a mammal, e.g., a rat, a human, etc. Methods of isolation and purification are well-known in the art, and include the method described in Example 1. In this respect, the peptides, fragments, and variants of the invention can be synthetic, recombinant, isolated, and/or purified.

Glycation of the synthetic, recombinant, isolated, and/or purified peptides (including fragments and variants thereof) can be carried out by methods known in the art (see, for instance, Heinrikson, *J Biol Chem* 241: 1393-1405 (1966); and Gruber and Hofmann, *J Pept Res* 66: 111-124 (2005)).

The present invention further provides an antibody, or an antigen binding portion thereof, that binds to any of the glycated peptides, or glycated fragments or glycated variants thereof, described herein. The antibody can be any type of immunoglobulin that is known in the art. For instance, the antibody can be of any isotype, e.g., IgA, IgD, IgE, IgG, IgM, etc. The antibody can be monoclonal or polyclonal. The antibody can be a naturally-occurring antibody, e.g., an antibody isolated and/or purified from a mammal, e.g., mouse, rabbit, goat, horse, chicken, hamster, human, etc. Alternatively, the antibody can be a genetically-engineered antibody, e.g., a humanized antibody or a chimeric antibody. The antibody can be in monomeric or polymeric form. Also, the antibody can have any level of affinity or avidity for the glycated peptide, glycated fragment or glycated variant thereof, of the invention. Desirably, the antibody is specific for the glycated peptide, glycated fragment or glycated variant thereof, such that there is minimal cross-reaction with other peptides or proteins. The antibody can be specific for the glycated amino acid residue, e.g., glycated lysine, and the flanking amino acids of the glycated amino acid residue of a glycated peptide. An antibody of this type is ensured to bind to only glycated peptides, as opposed to unglycated peptides having the same amino acid sequence.

Also, the antibody, or antigen binding portion thereof, can be modified to comprise a detectable label, such as, for instance, a radioisotope, a fluorophore (e.g., fluorescein isothiocyanate (FITC), phycoerythrin (PE)), an enzyme (e.g., alkaline phosphatase, horseradish peroxidase), and element particles (e.g., gold particles).

Suitable methods of making antibodies are known in the art. For instance, standard hybridoma methods are described in, e.g., Köhler and Milstein, *Eur. J. Immunol.,* 5, 511-519 (1976), Harlow and Lane (eds.), *Antibodies: A Laboratory Manual*, CSH Press (1988), and C. A. Janeway et al. (eds.), *Immunobiology,* 5th Ed., Garland Publishing, New York, N.Y. (2001)). Alternatively, other methods, such as EBV-hybridoma methods (Haskard and Archer, *J. Immunol. Methods,* 74(2), 361-67 (1984), and Roder et al., *Methods Enzymol.,* 121, 140-67 (1986)), and bacteriophage vector expression systems (see, e.g., Huse et al., *Science,* 246, 1275-81 (1989)) are known in the art. Further, methods of producing antibodies in non-human animals are described in, e.g., U.S. Pat. Nos. 5,545,806, 5,569,825, and 5,714,352, and U.S. Patent Application Publication No. 2002/0197266 A1).

Phage display furthermore can be used to generate the antibody of the invention. In this regard, phage libraries encoding antigen-binding variable (V) domains of antibodies can be generated using standard molecular biology and recombinant DNA techniques (see, e.g., Sambrook et al. (eds.), *Molecular Cloning, A Laboratory Manual,* 3rd Edition, Cold Spring Harbor Laboratory Press, New York (2001)). Phage encoding a variable region with the desired specificity are selected for specific binding to the desired antigen, and a complete or partial antibody is reconstituted comprising the selected variable domain. Nucleic acid sequences encoding the reconstituted antibody are introduced into a suitable cell

line, such as a myeloma cell used for hybridoma production or a bacterial cell line, such that antibodies having the characteristics of monoclonal antibodies are secreted by the cell (see, e.g., Janeway et al., supra, Huse et al., supra, U.S. Pat. No. 6,265,150, and Knappik et al., *J. Mol. Biol.* 296: 57-86 (2000).

Antibodies can be produced by transgenic mice that are transgenic for specific heavy and light chain immunoglobulin genes. Such methods are known in the art and described in, for example U.S. Pat. Nos. 5,545,806 and 5,569,825, and Janeway et al., supra.

Methods for generating humanized antibodies are well known in the art and are described in detail in, for example, Janeway et al., supra, U.S. Pat. Nos. 5,225,539, 5,585,089 and 5,693,761, European Patent No. 0239400 B1, and United Kingdom Patent No. 2188638. Humanized antibodies can also be generated using the antibody resurfacing technology described in U.S. Pat. No. 5,639,641 and Pedersen et al., *J. Mol. Biol.,* 235, 959-973 (1994).

Methods of testing antibodies for the ability to bind to any of the glycated peptides, fragments, or variants are known in the art and include any antibody-antigen binding assay, such as, for example, radioimmunoassay (RIA), ELISA, Western blot, immunoprecipitation, and competitive inhibition assays (see, e.g., Janeway et al., supra, and U.S. Patent Application Publication No. 2002/0197266 A1).

The invention also provides antigen binding portions of any of the antibodies described herein. The antigen binding portion can be any portion that has at least one antigen binding site, such as Fab, $F(ab')_2$, dsFv, sFv, diabodies, and triabodies.

A single-chain variable region fragment (sFv) antibody fragment, which consists of a truncated Fab fragment comprising the variable (V) domain of an antibody heavy chain linked to a V domain of a light antibody chain via a synthetic peptide, can be generated using routine recombinant DNA technology techniques (see, e.g., Janeway et al., supra). Similarly, disulfide-stabilized variable region fragments (dsFv) can be prepared by recombinant DNA technology (see, e.g., Reiter et al., *Protein Engineering,* 7, 697-704 (1994)). Antibody fragments of the present invention, however, are not limited to these exemplary types of antibody fragments.

The invention further provides an aptamer that binds to any of the glycated peptides described herein, or glycated fragments or glycated variants thereof. The term "aptamer" as used herein refers to a nucleic acid (e.g., double stranded DNA or single stranded RNA molecule) that binds to a specific molecular target, such as a protein, peptide, or metabolite. Aptamers, as well as methods of making aptamers, are known in the art. See, for example, U.S. Pat. Nos. 5,475,096; 5,270,163; 6,974,706, and 5,656,739, as well as International Patent Application No. WO 91/19813.

The aptamer can be chemically synthesized using naturally occurring nucleotides or modified nucleotides designed to increase the biological stability of the molecule or to increase the physical stability of the duplex formed upon hybridization (e.g., phosphorothioate derivatives and acridine substituted nucleotides). Examples of modified nucleotides that can be used to generate the aptamers include, but are not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl)uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N^6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N^6-substituted adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N^6-isopentenyladenine, uracil-5-oxyacetic acid (v), butoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3) w, and 2,6-diaminopurine. Also, the aptamer can contain a natural, non-natural or altered internucleotide linkage, such as a phosphoroamidate linkage or a phosphorothioate linkage, instead of the phosphodiester found between the nucleotides of an unmodified oligonucleotide.

Furthermore, the aptamers described herein can be modified to comprise a detectable label, such as any of those described herein.

Also provided by the invention is a conjugate comprising (i) an antibody, antigen binding portion thereof, or aptamer which specifically binds to a peptide, or fragment or variant thereof, comprising (a) at least one of Peptides AA-DJ or (b) an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-36, and (ii) a detectable label. The conjugate can further comprise a glucose binding moiety. The glucose-binding moiety can be any moiety that will bind specifically to a glucose molecule, such as an antibody, a lectin, or a borate. The antibody, antigen-binding portion thereof, or aptamer can be any antibody, antigen binding portion thereof or aptamer that specifically binds to a peptide, or a fragment or variant thereof, comprising (a) at least one of Peptides AA-DJ or (b) an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-36. The peptide to which the antibody, antigen-binding portion thereof, or aptamer binds can be glycated or unglycated. In the instance that the peptide to which the antibody, antigen-binding portion thereof, or aptamer binds is unglycated, it is preferable for the detectable label to be detected only when the antibody, antigen-binding portion thereof, or aptamer binds to the peptide and the glucose-binding moiety binds to a glucose molecule(s) attached to the peptide. A conjugate of this type is ensured to be detectable only when bound to glycated peptides, as opposed to unglycated peptides having the same amino acid sequence. The detectable label can be any detectable label, such as any of those described herein. Conjugates, as well as methods of synthesizing conjugates, are known in the art (See, for instance, Hudecz, F., *Methods Mol Biol* 298: 209-223 (2005) and Kirin et al., *Inorg Chem* 44(15): 5405-5415 (2005)).

The inventive glycated peptides, glycated fragments, and glycated variants thereof, antibodies, antigen binding portions, aptamers, and conjugates can be isolated and/or purified. The term "isolated" as used herein means having been removed from its natural environment. The term "purified" as used herein means having been increased in purity, wherein "purity" is a relative term, and not to be necessarily construed as absolute purity. For example, the purity can be at least 50%, can be greater than 60%, 70% or 80%, or can be 100%.

The glycated peptides (including glycated fragments and glycated variants thereof), antibodies (including antigen binding portions thereof), aptamers, and conjugates described herein can be formulated into a composition, such as a pharmaceutical composition. In this regard, the invention provides a composition comprising any of the glycated peptides (including glycated fragments and glycated variants thereof), antibodies (including antigen binding portions thereof), aptamers, and conjugates, and a carrier, especially a pharmaceutically acceptable carrier. The inventive composition can further comprise more than one of any of the glycated peptides (including glycated fragments and glycated variants thereof), antibodies (including antigen binding portions

thereof), aptamers, and conjugates of the invention (e.g., a glycated peptide and an antibody that specifically binds to a glycated peptide, or two or more different glycated peptides, such as Peptides AA and AB). Alternatively or in addition, the composition can comprise a pharmaceutically active agent or drug (e.g., an anti-diabetic drug) or another agent that can be used to monitor glycemic control (e.g., an antibody specific for HbA1C).

The inventive glycated peptides (including glycated fragments and glycated variants thereof), antibodies (including antigen binding portions thereof), aptamers, conjugates, and compositions described herein can be used for any purpose. As the glycated peptides (including glycated fragments and glycated variants thereof) of the invention have been associated with glycemic control and diabetes, the foregoing compounds and compositions described herein are especially useful in connection with methods to research, monitor, detect, treat, or prevent diabetes. Such methods may comprise in vivo or in vitro use of such compounds or compositions. Certain methods involving the use of these compounds and compositions are described in greater detail herein; however, the described methods do not limit the utility of the foregoing compounds and compositions.

As previously mentioned, the glycated peptides, and glycated fragments and glycated variants, described herein have been associated with glycemic control and diabetes. More specifically, the concentration of the glycated peptides, and glycated fragments and variants thereof, can be increased in diabetic patients as compared to non-diabetic patients, thereby suggesting that these glycated peptides, and glycated fragments and glycated variants thereof, can be used as markers or indices of glycemic control. In this regard, the invention provides a method of monitoring glycemic control of a host comprising measuring the concentration of a glycated peptide, or a glycated fragment or glycated variant thereof, in a host, wherein the glycated peptide comprises (i) at least one of Peptides AA-DJ or (ii) an amino acid sequence of the group consisting of SEQ ID NOs: 24-36.

The term "concentration" as used herein encompasses absolute concentration as well as relative concentration. Typically, the methods described herein will be performed using relative concentrations. Relative concentration, in this regard, is the concentration of a molecule, compound, or substance (e.g., a glycated peptide) as compared to the concentration of a total population of molecules, compounds, or substances of which the molecule, compound, or substance of interest is a part (e.g., the total population of a given peptide in both glycated and non-glycated forms), or as compared to the concentration of a different molecule, compound, or substance (e.g., the non-glycated form of the same peptide). Thus, the relative concentration of a glycated peptide, fragment or variant can indicate a percentage of the total population of the given peptide, fragment, or variant in a sample that is in its glycated form. Alternatively, the relative concentration of a glycated peptide, fragment, or variant can indicate a ratio of glycated to non-glycated forms of the give peptide, fragment, or variant.

The term "glycemic control" as used herein does not refer to the level of blood glucose in a host taken at a particular point in time, as blood glucose levels vary throughout the day and fluctuate as a function of, for example, food intake by the host. Rather, "glycemic control" refers to the blood glucose level in a host over a period of time, e.g., a day, a week, a month, etc. Glycemic control also can be described as the area under a curve formed by plotting the minute-to-minute changes in blood glucose levels in a host over a given time period. The glycemic control of a host is considered "normal" or "good" when the blood glucose levels of a host (as represented, e.g., by the area under a glycemic control curve) are the same or nearly the same as the blood glucose levels of a "normal" or non-diabetic host (or a population of such normal or non-diabetic hosts) over a given time frame. In contrast, the glycemic control of a host can be described as "abnormal" or "poor" when the blood glucose levels of that host (as represented, e.g., by the area under a glycemic control curve) are different from the blood glucose levels of a "normal" or non-diabetic host (or a population of such normal or non-diabetic hosts) over a given time frame. Abnormal or poor glycemic control is typically indicated by abnormally elevated blood glucose levels in the case of diabetes, but also can be indicated by abnormally depressed blood glucose levels when certain conditions exist (e.g., an insulin-secreting tumor).

Although glycemic control reflects blood glucose levels over a period of time, the term "monitoring glycemic control of a host" does not necessarily involve making multiple measurements of blood glucose levels at different points in time. As previously mentioned with respect to HbA1C, a measurement of the concentration of a glycated peptide reflects a history of blood glucose levels over time. Thus, even a single measurement of a glycated peptide concentration can be informative of the history of glycemic control. Accordingly, monitoring glycemic control can comprise, for instance, taking a single measurement of a concentration of a glycated peptide in a host. Of course, monitoring glycemic control can comprise taking two or more measurements (e.g., three, five, eight, or more measurements) at different time points.

As used herein, the term "diabetes" refers to any type or stage of diabetes, including, but not limited to, Type 1 diabetes, Type 2 diabetes, diabetes mellitus, juvenile-onset diabetes, adult-onset diabetes, non-insulin-dependent diabetes, insulin-dependent diabetes, sugar diabetes, gestational diabetes, prediabetes, and other conditions associated with elevated glucose levels or impaired glycemic control including, without limitation, impaired glucose tolerance; impaired fasting glucose; pancreatic diabetes (e.g., from pancreatectomy), chronic pancreatitis, and hemochromatosis.

Improved glycemic control, i.e., maintenance of blood glucose levels at normal or non-diabetic levels, is a major goal of current diabetes therapy, and improved glycemic control has been shown to prevent or delay the onset of long-term diabetic complications in both Type 1 and Type 2 diabetic patients. In this regard, the invention further provides a method of preventing or treating diabetes, including any complication or symptom of diabetes, which method comprises monitoring the glycemic control of a host as described herein.

The terms "treat" and "prevent" as well as words stemming therefrom, as used herein, do not necessarily imply 100% or complete treatment or prevention. Rather, there are varying degrees of treatment or prevention. In this respect, the inventive method of treating or preventing diabetes can provide any level of treatment of diabetes in a host, including without limitation the reduction to any degree of any one or more symptoms or complications of diabetes. Similarly, the inventive method of treating or preventing diabetes can provide any level of prevention, including without limitation delaying the onset of any one or more symptoms or complications of diabetes.

As used herein, "symptom of diabetes" or "complication of diabetes" refers to a secondary condition that often occurs in diabetic patients due to the hyperglycemia of diabetes, and includes, for instance, microvascular complications (diseases of small blood vessels, e.g., retinopathy, neuropathy, nephropathy), macrovascular complications (diseases of large

blood vessels, e.g., coronary heart disease, atherosclerosis of other blood vessels, intermittent claudication, peripheral vascular disease, etc.), blindness (which is caused by diabetic retinopathy and other retinal disorders), kidney failure (which is caused by diabetic nephropathy), foot wounds, ulcers, foot and leg amputations (which are caused by diabetic peripheral vascular disease and/or diabetic neuropathy), paralysis of the stomach (also known as gastroparesis), chronic diarrhea, inability to control heart rate and blood pressure with posture changes, heart attack, stroke, peripheral vascular disease, and a predisposition to high blood pressure and high cholesterol and triglyceride levels.

The method of monitoring glycemic control by measuring the concentration of the inventive glycated peptides, or glycated fragments or glycated variants thereof, can be used to detect abnormal glycemic control and, thus, monitor or detect the onset, progression, or regression of diabetes. In this respect, the invention further provides a method of monitoring or detecting the onset, progression, or regression of diabetes in a host. The method comprises monitoring the glycemic control of a host as described herein, or, more particularly, detecting a change in glycemic control of a host. A change in the glycemic control of the host can be detected on the basis of a change in the concentration of a glycated peptide, or glycated fragment or glycated variant thereof, wherein a decrease in the concentration of a glycated peptide, or glycated fragment or glycated variant thereof, is indicative of a regression of diabetes in the host and an increase in such concentration is indicative of the onset or progression of diabetes in the host.

The change in concentration of a glycated peptide, or glycated fragment or glycated variant thereof, is typically a change in concentration relative to an earlier measured concentration of the same glycated peptide, or glycated fragment or glycated variant thereof, in the same host at a different point in time. However, a change in the concentration of the glycated peptide, or glycated fragment or glycated variant thereof, also can be detected by comparison to a control, such as the concentration of the same glycated peptide, or glycated fragment or variant thereof, in a known non-diabetic or diabetic patient. The control also can be provided by a standard profile or index of the concentrations of the glycated peptide, or glycated fragment or glycated variant thereof. Such a profile or index can reflect the relevant concentrations the glycated peptide, or glycated fragment or glycated variant thereof, in a population of known non-diabetic or diabetic patients.

The methods described herein also can be used to evaluate the effectiveness of a course of treatment in a host. For instance, the concentration of one or more of the glycated peptides, or glycated fragments or glycated variants thereof, can be measured before and after the administration of a treatment for diabetes and the concentration levels compared. If the concentration of one or more of the glycated peptides, or glycated fragments or glycated variants thereof, measured after treatment is lower than the concentration of the same glycated peptides, or glycated fragments or glycated variants thereof, before treatment, then the treatment would be deemed relatively effective. If the concentration of one or more of the glycated peptides, or glycated fragments or glycated variants thereof, measured after treatment is higher than or the same as the concentration of the glycated peptides, or glycated fragments or glycated variants thereof, measured before treatment, then the treatment would be deemed relatively ineffective. In this regard, the invention also provides a method of determining the efficacy of a diabetes treatment. The method comprises monitoring glycemic control in a host, as described herein, before, during, and/or, after the administration of a diabetes treatment.

The diabetes treatment can be any treatment, therapy, or regimen which is designed to counter diabetes or a symptom or condition thereof. The diabetes treatment can be, for example, a medication designed to treat diabetes, e.g., a sulfonylurea, a biguanide, an α-glucosidase inhibitor, a thiazolidinedione, a meglitinide, a D-phenylalanine derivative, an amylin synthetic derivative (e.g., pramlintide), an incretin mimetic (e.g., exenatide), and an insulin (e.g., a rapid-acting insulin (e.g., HUMULIN R, NOVOLIN R, HUMALOG, NOVOLOG, APIDRA, SEMILENTE), an intermediate-acting insulin (e.g., HUMULIN R, NOVOLIN R), a long-acting insulin (e.g., ULTRALENTE, LANTUS, LEVEMIR), and the like. The diabetes treatment can be a specific regimen of a drug, e.g., a once, twice, or thrice daily regimen of insulin injections.

The invention also provides a method of detecting diabetes or a predisposition to diabetes in a host. The method can comprise monitoring the glycemic control of the host as described herein. More particularly, the method can comprise detecting in the host an elevated concentration of a glycated peptide, or a glycated fragment or glycated variant thereof, as compared to a control, wherein the glycated peptide comprises (i) at least one of Peptides AA-DJ or (ii) an amino acid sequence of the group consisting of SEQ ID NOs: 24-36. Detection of an elevation in the concentration of the glycated peptide, or a glycated fragment or glycated variant thereof, is indicative of diabetes or a predisposition to diabetes in the host. While any elevation in the concentration of the glycated peptide, or glycated fragment or glycated variant thereof, can be indicative of diabetes or a predisposition to diabetes, the elevation is preferably a statistically significant elevation as compared to a control. Suitable controls are as described elsewhere herein. A preferred control can be an profile or index based on concentrations of the relevant glycated peptides, or fragments or variants thereof, from a population of known diabetic or non-diabetic hosts. Statistical significance can be represented by a low P value, such as a P value of 0.05 or less, 0.01 or less, 0.005, or less, or 0.001 or less. In a preferred embodiment, the P value is 0.001 or less. Of course, in practice, the statistical significance of any given elevation in concentration can be incorporated into the control or index that is chosen as appropriate for the particular application.

Any of the methods described herein can comprise any number of additional steps. The methods can, for instance, further comprise comparing the concentration of the glycated peptide, or glycated fragment or glycated variant thereof, to a control. Comparison to a control allows, for example, the detection of an elevated level of a glycated polypeptide, or glycated fragment or glycated variant thereof, which can indicate abnormal glycemic control or diabetes. Suitable controls are as described herein with respect to other aspects of the invention. Furthermore, the methods described herein can comprise comparing two or more measurements of the concentration of a glycated peptide, or glycated fragment or glycated variant thereof, taken from the same host at different points in time. Such a comparison allows, for instance, the detection of a change in the concentration of a glycated peptide, or glycated fragment or glycated variant thereof, which change can indicate a change in the glycemic control of the host, the onset, progression, or regression of diabetes in a host, or the effectiveness of a diabetes treatment in a host.

The inventive methods can further comprise measuring a concentration of HbA1C protein and/or the blood glucose level of the host. Methods of measuring the concentration of HbA1C and/or blood glucose levels are known in the art.

The concentration of one or more glycated peptides, or glycated fragments or glycated variants thereof, in a host can be measured in a sample of the host, i.e., a sample obtained directly from the host, optionally subject to further processing, or a sample derived from the host. The sample can be any sample from the host, including, but not limited to whole blood, blood plasma, or blood serum. Alternatively, the measurement can be taken directly within the host, such as by using a radio-labeled antibody which specifically binds to a glycated peptide or fragment or variant thereof, as described herein.

Suitable methods of measuring the concentration of a peptide (e.g., a glycated peptide, or glycated fragment or glycated variant thereof) in a sample or host are known in the art. For instance, the concentration of a glycated peptide, or glycated fragment or glycated variant thereof, can be measured by mass spectrometry (MS), high performance liquid chromatography (HPLC), or both MS and HPLC. Alternatively or in addition, the concentration of a glycated peptide, or glycated fragment or glycated variant thereof, can be measured indirectly, for example, by contacting the sample with an antibody, antigen binding portion thereof, aptamer, conjugate, or other detectable binding agent that specifically binds to the glycated peptide or glycated fragment or glycated variant thereof, and thereafter measuring the concentration of bound (e.g., complexed) antibody, antigen binding portion thereof, aptamer, conjugate, or other detectable binding agent. Methods of quantifying the concentration of a bound antibody, antigen binding portion, aptamer, or conjugate are known in the art and include, for instance, quantitative western blotting (e.g. western blotting followed by phosphorimaging or scintillation counting), solution-based immunoassays (e.g., ELISA, immunoprecipitation, radioimmunoassay), mass spectrometry, and HPLC.

The concentration of the glycated peptide, or glycated fragment or glycated variant thereof, also can be measured on the basis of the specific activity or biological activity of the protein of which the glycated peptide, fragment, or variant is a part. Such proteins are described herein. Without wishing to be bound to any particular theory, it is believed that glycation alters the mass and, in some instances, the biological activity of the protein. Accordingly, the specific activity and, perhaps, the enzyme activity of a sample of the protein will be changed if a high relative concentration of the glycated form of the protein is present. This change in the specific activity or biological activity of the protein, thus, can serve as an indirect measure of the concentration of the glycated peptide, or glycated fragment or variant thereof. Alternatively, a change in the specific activity or biological activity of the protein can, itself, serve as a basis for monitoring glycemic control. In this regard, the inventive method of monitoring glycemic control can comprise measuring or detecting a change in the biological activity or specific activity of a glycated protein, wherein the glycated protein comprises (i) at least one of Peptides AA-DJ or (ii) an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-36.

In this regard, the term "specific activity" refers to the biological activity (e.g., enzyme activity) of a protein divided by its mass. The term "biological activity" refers to any natural function of a protein, including, for example, enzyme activity, binding affinity, activating activity, inhibitory activity, etc. A change in the specific activity or biological activity of the protein can be detected by comparing the specific activity or biological activity of the protein in a sample to a suitable control, such as the specific activity or biological activity of the same protein in a known "normal" or "abnormal" sample, or a standardized or otherwise accepted value of the specific activity or biological activity known in the art.

In order to determine a relative concentration of a glycated peptide, or glycated fragment or glycated variant thereof, as previously described herein, it is necessary to determine the concentration of the non-glycated peptide, fragment, or variant, or the concentration of the total population of both glycated and non-glycated forms of the relevant peptide, fragment, or variant. The concentration of the non-glycated peptide, fragment, or variant, or the concentration of the total population of glycated and non-glycated forms of the relevant peptide, fragment, or variant, can be determined by any method of measuring a concentration of a peptide or protein known in the art. The method of measuring the total concentration can be the same or a different method used to determine the concentration of the corresponding glycated peptide, fragment, or variant, including methods previously described herein with obvious modifications (e.g., without enriching the sample for glycated peptides, or without removing non-glycated peptides). For example, MS or HPLC can be used to determine the concentration of both the non-glycated and glycated forms of the peptide, fragment, or variant. Alternatively, MS can be used to determine the total concentration, while HPLC is used to determine the concentration of the glycated peptide. Also, an antibody- or aptamer-based method can be used to measure or determine the concentration of the non-glycated and glycated forms of a given peptide, fragment, or variant. The antibody or aptamer used to detect the non-glycated forms of the peptide can be a different antibody or aptamer than the antibody or aptamer used to detect the glycated peptide. For instance, the antibody or aptamer used to determined the concentration of the glycated peptide can be specific for the glycated form of that peptide, such that it would not detect the unglycated form of the peptide, and a different antibody or aptamer that detects only the non-glycated form of the peptide, or that detects both non-glycated and glycated forms of the peptide, can be used to determine the concentration of the non-glycated peptide or total population of the peptide in both non-glycated and glycated forms.

With respect to the inventive methods, the glycated peptide, or glycated fragment or glycated variant thereof, can be any of those described herein. In a preferred embodiment, the glycated fragment comprises an amino acid sequence of any of peptides AA-DJ, e.g., an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-23. In another preferred embodiment, the methods comprise detecting or measuring the concentration of a glycated variant comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 37-47.

Further, with respect to the inventive methods, the methods can comprise measuring the concentration of two or more different glycated peptides, glycated fragments, and/or glycated variants, as described herein. For instance, the method can comprise measuring the concentration of 3, 4, 5 or more different glycated peptides or glycated fragments thereof, or even measuring the concentration of 6, 7, 8, 9, 10, 20, 35, 45, 50, 75 or more different glycated peptides or glycated fragments thereof, as described herein. The method can comprise measuring the concentration of each of Peptides AA-DJ, and of SEQ ID NOs: 37-47.

The term "host" as used herein refers to any eukaryotic host in which glycemic control can be monitored. The host can be, for instance, a bird, a reptile, or a mammal. As used herein, the term "mammal" refers to any mammal, including, but not limited to, mammals of the order Rodentia, such as mice and hamsters, and mammals of the order Logomorpha, such as

rabbits. It is preferred that the mammals are from the order Camivora, including Felines (cats) and Canines (dogs). It is more preferred that the mammals are from the order Artiodactyla, including Bovines (cows) and Swines (pigs) or of the order Perssodactyla, including Equines (horses). It is most preferred that the mammals are of the order Primates, Ceboids, or Simoids (monkeys) or of the order Anthropoids (humans and apes). An especially preferred mammal is the human. Any of the foregoing methods described herein can be performed in conjunction with any of the above-described hosts.

The invention further provides a database comprising data which indicates the concentration, preferably the relative concentration, of one or more of the glycated peptides described herein, or glycated fragments or glycated variants thereof, that is present in diabetic patients, non-diabetic patients, or both diabetic and non-diabetic patients. The data additionally can be indicative of a stage or level of severity of diabetes. The term "database" as used herein means a collection of data, and does not imply any particular format for the data. Thus, the database can be an electronic database, e.g., a computerized database, wherein data can be easily stored, queried, added, edited, deleted, updated, and/or organized. Alternatively, the data can be compiled in a non-electronic form (e.g., on paper or other suitable substrate). Regardless of whether the database is an electronic database or a non-electronic database, the data can be formatted as an index, chart, graph, or text. The database can be used for any purpose, but is particularly useful in conjunction with methods of researching, monitoring, screening, detecting, and diagnosing glycemic control, diabetes, and any symptom or complication thereof. Such methods include, but are not limited to, the methods described herein. In this regard, the database can be used, for example, as the control referred to in the methods described herein.

The database can be created by any suitable method, such as by measuring the relative concentration of one or more of the glycated peptides, or glycated fragments or variants thereof, as described herein, in a population of known diabetic or non-diabetic persons and compiling the data. Optionally, known statistical techniques can be employed, for example, to establish the significance of any variation in measurements between individuals in the population. Of course, the population can be further refined to include categories of diabetic or non-diabetic persons, for example, based on the type or level of severity of diabetes present. Suitable methods for determining the appropriate population size and type needed to establish a database of statistical significance are within the skill of the ordinary artisan.

The invention further provides a kit comprising one or more of the antibodies, or antigen binding fragments, aptamers, and/or conjugates described herein, or one or more glycated peptides, or glycated fragments or glycated variants thereof, as described herein. The kit can further comprise additional agents or materials, such as an agent used to measure other indices of glycemic control, for example, an agent which measures blood glucose level and/or an agent which measures the level of a glycated HbA1C protein. Additionally or alternatively, the kit can comprise (a) a reagent for the detection of a glycated peptide, antibody, antigen binding fragment, aptamer, or conjugate included in the lit, (b) a standard for determining the molecular weight or specific activity of a glycated peptide, or glycated fragment or glycated variant thereof (or the protein such peptide is derived from), (c) a database as described herein, or (d) a set of user instructions as to how to use the kit or any part thereof, especially for purposes consistent with the methods disclosed herein.

EXAMPLES

The following examples further illustrate the invention but, of course, should not be construed as in any way limiting its scope.

Example 1

This example demonstrates that elevated concentrations of Peptides AA-DJ, as well as the proteins of which some of the peptides are a part, are indicative of poor glycemic control and can be used to detect a diabetic condition.

All chemicals and biochemicals were purchased from Sigma-Aldrich, St. Louis, Mo., if not specified otherwise.

Plasma samples were obtained from nine diabetic patients with a hemoglobin A1C (HbA1C) concentration of greater than 14%, and from nine non-diabetic patients with an HbA1C concentration of less than 6%. The samples were thawed at 4° ° C. for 4 hours. 175 μl aliquots from each sample were subjected to an antibody affinity column (Agilent, Palo Alto, Calif.) to remove the six most abundant serum proteins: albumin, IgG, IgA, haptoglobin, transferrin, and antitrypsin proteins. Affinity column processing was carried out with 35 μl of plasma per run. The volume of each processed aliquot was then adjusted to about 100 μl using ultracentrifugation spin columns with 5 kDa molecular-weight cutoff (Millipore, Billerica, Mass.).

Each 100 μl aliquot was diluted with 1.0 mL of 6M guanidium hydrochloride, 100 mM Tris (pH 8.0). Dithiothreitol (DTT, Cleland's reagent) was then added to a final concentration of 10 mM. The aliquots were subsequently incubated at 37° ° C. for 4 hours. After allowing the aliquots to cool to room temperature, 25 μl of 1.0 M iodoacetic acid in 1.0 M sodium hydroxide was added and the mixture was incubated at room temperature for 30 minutes. The buffer condition of the mixture was then changed to 50 mM NH_4HCO_2 (pH 8.3) via centrifugation with ultracentrifugation spin columns, as described above.

After changing the buffer condition, modified trypsin (Promega, Madison, Wis.) was added to each aliquot at a weight ratio of 1:50 and digestion was carried out at 37° C. for 16 hours. The resulting tryptic peptides were desalted on a RapidTrace™ workstation (Caliper, Mountain View, Calif.) using C18 reversed phase cartridges (200 mg capacity, Waters, Milford, Mass.). The tryptic peptides were vacuum dried and then dissolved in buffer provided with a glycanase kit (Glyco® kit from Prozyme, San Leandro, Calif.) for deglycosylation. The tryptic peptide solution was treated at 37° C. overnight with a mixture of five glycanases: N-Glycanase, non-specific neuraminidase, O-glycosidase, beta-galactosidase, and beta-N-acetylhexosaminidase (Prozyme, San Leandro, Calif.). Free glycans were removed from the tryptic peptide mixture by C18 purification followed by lyophilization. The lyophilized mixture was dissolved in ammonium acetate (200 μl of 0.2 M solution at pH 8.8).

In order to enrich the tryptic peptide mixture for glycated peptides, the tryptic peptide mixture was incubated with 100 μl m-aminophenylboronic acid beads (Pierce, Rockford, Ill.) at room temperature for 15 minutes and the supernatant containing the non-glycated tryptic peptides was removed. The m-aminophenylboronic acid beads were then washed twice with 40% acetonitrile, 60% 0.2 M ammonium acetate (pH

8.2), and the glycated peptides were eluted from the beads with 0.4% formic acid in water. The supernatant was subsequently lyophilized.

The lyophilized glycated peptide mixture was dissolved in 20 μl 0.1% formic acid and analyzed by liquid chromatography-mass spectrometry (LC-MS). Those ions with significant quantitative differences at the $p<0.001$ level, or that were found only in the diabetic samples and not in the control samples, provided the m/z values used for targeted identification.

Of the 627 glycated tryptic peptides analyzed, the mean concentrations of 88 peptides (Peptides AA-DJ) were significantly greater in the samples from the diabetic patients than from controls ($P<0.05$). 71 of the 88 peptides had increased mean concentrations in the diabetic samples as compared to the controls with a statistical significance of P-value<0.001, and 79 of the 88 peptides peptides had increased mean concentrations in the diabetic samples as compared to the controls with a statistical significance of P-value<0.005, and 82 of the 88 peptides exhibited increased mean concentrations in the diabetic samples as compared to the controls with a statistical significance of P-value<0.01. The fold-change of each of glycated peptides AA-DJ in diabetic as compared to non-diabetic patients, along with the corresponding P-value, is provided in Table 1.

Only ten peptides of the 7929 total peptides (glycated and non-glycated peptides) found in the un-enriched fractions of the samples exhibited a significantly greater concentration in diabetic samples as compared to control samples ($P<0.001$). This suggests the importance of enriching the glycated peptides by treatment of m-amino phenylboronic acid.

Table 3 shows the fold increase in mean concentration of nine of Peptides AA-DJ having most significant fold-increase in the diabetic samples as compared to the control samples, as well as the fold increase in HbA1C in diabetic as compared to the control samples. As shown in Table 3, the elevation in these peptides was greater than the elevation in mean concentration of HbA1C. These results suggest that the glycated peptides identified herein might provide more sensitive indices of glycemic control than HbA1C.

TABLE 3

Peptide	Fold increase in diabetic samples vs. control samples	P value
HbA1C	2.8	10^{-8}
AA	6.0	10^{-12}
AB	7.8	10^{-11}
AC	7.4	10^{-10}
AD	6.7	10^{-10}
AE	7.1	10^{-9}
AF	8.2	10^{-9}
AG	7.5	10^{-9}
AH	8.0	10^{-8}
AI	8.4	10^{-8}

For some of Peptides AA-DJ, the amino acid sequences were determined by conducting ion-trap mass spectrometry on a Thermo Electron Corp, LTQ spectrometer (San Jose, Calif.) (Table 1). Initial attempts to identify the peptides involved performing MS^3 analysis on the $[M-3H_2O]''+$ neutral-loss ion that was frequently the most intense ion present in the MS^2 scan. This was only partially effective and it was found that, in many cases, the MS^3 spectrum produced only a fourth loss of a water molecule without clear peptide backbone fragmentation. Further identification attempts used a different neutral-loss ion to perform the MS^3 analysis. The neutral loss ion $[M-84]^+$, corresponding to the loss of three water molecules plus formaldehyde, was found to be much more likely to undergo observable peptide backbone fragmentation and therefore was used as the precursor for MS^3 scans in targeted identification analyses. Database searches using the Mascot software (Matrix Sciences, London, UK) were performed on resulting MS^3 spectra using a variable modification on lysine of +78 Daltons. As shown in Table 2, the sequences of these peptides were found to be part of larger plasma proteins.

This example demonstrates that peptides comprising glycated Peptides AA-DJ are markers of abnormal glycemic control and a diabetic condition.

Example 2

This prophetic example demonstrates a method of making antibodies to some of glycated Peptides AA-DJ.

Five or more of glycated Peptides AA-DJ are synthesized as described in Gruber and Hofmann, *J Pept Res* 66: 111-124 (2005). Non-glycated forms of the glycated peptides also are made using conventional peptide synthesis methods (see, for example, Chan et al., *Fmoc Solid Phase Peptide Synthesis*, Oxford University Press, Oxford, United Kingdom, 2005). Antibodies specific for the synthesized glycated and non-glycated peptides are made using conventional immunization techniques and/or display selection techniques (Blaydes et al, *Methods Mol Biol* 99: 177-189 (2000)).

Antibodies to the glycated peptides are tested for selectivity for the glycated peptides over the corresponding non-glycated peptides. The relative sensitivity and specificity for the glycated peptide-specific antibodies are evaluated by conventional western blotting techniques using stored plasma samples from anonymous subjects with varying degrees of glycemic control. The glycated peptide-specific antibodies also are tested against commercially available antibodies which bind to the plasma proteins of which the glycated peptides are a part. Antibodies having high selectivity for the glycated peptides are isolated.

This example demonstrates a method of making antibodies to the inventive glycated peptides described herein.

Example 3

This prophetic example demonstrates a method of creating a database in the form of an index showing the normal and abnormal levels of glycation for one or more glycated peptides present in both diabetic and non-diabetic persons. The example further demonstrates a method of detecting diabetes in a host, a method of determining the efficacy of a diabetes treatment, a method of monitoring the progression or regression of diabetes in a host, and a method of monitoring glycemic control in a host.

Plasma samples are obtained from a population of diabetic patients known to have "poor" or abnormal glycemic control, and from a population of non-diabetic patients known to have "good" or normal glycemic control. The population of diabetic patients is further subdivided into patients known having moderately poor glycemic control and those having severely poor glycemic control.

The concentrations of glycated peptides of Peptides AA-DJ are determined using the antibodies produced by the method of Example 2 in quantitative western blotting using chemiluminescence imaging. The total concentrations of the same peptides, including glycated and non-glycated forms of the peptides, are determined in parallel using commercially available antibodies that identify the peptides regardless of glycation. The relative concentration of the glycated peptides is calculated by dividing the concentration of a given glycated peptide by the total concentration of the same peptide in both glycated and non-glycated forms. The results are averaged within each population, and the average relative concentration for each glycated peptide is recorded into a computerized

database and classified as "normal," "moderately poor," and "severely poor." The computerized database is formatted as an index showing ranges of the relative concentrations of the assayed glycated peptides that fall within the above classifications.

Patient Smith, who has a family history of diabetes, does not know if he is currently diabetic and visits his doctor to determine whether or not he is diabetic. A blood sample from Patient Smith is assayed to determine the relative concentrations of certain glycated peptides of Peptides AA-DJ. The assay is performed using an immunoassay kit comprising antibodies and aptamers that bind to certain glycated peptides of Peptides AA-DJ, and a reagent for detecting the bound aptamers and antibodies.

The results show the percentage of the population of an assayed peptide or collection of peptides that are glycated. The percentage is compared to the above-described index to obtain a result of "normal," "moderately poor," or "poor." Patient Smith's test is rated as "poor."

Based on the above results and, perhaps, the results of other tests, Patient Smith's doctor prescribes a regimen of insulin injections. Patient Smith adheres to the prescribed regimen for 3 months and returns to the doctor for a follow-up visit. A blood sample from Patient Smith is again assayed for the relative concentrations of certain glycated peptides of Peptides AA-DJ and the result scored using the index as described above. Based on the comparison, Patient Smith's test is scored as "moderate," indicating an improvement in his glycemic control and the efficacy of the prescribed treatment.

Example 4

This prophetic example demonstrates a method of monitoring the efficacy of treatment of diabetic patients.

The fraction of glycated HbA1C (as compared to the concentration of total hemoglobin A) in a patient who was newly diagnosed with diabetes was monitored during a course of 16 weeks of intensive diabetes treatment. The fraction of glycated HbA1C (as compared to the concentration of total hemoglobin A) was found to decrease two-fold, suggesting that the treatment was effective in treating the diabetes in the patient.

The relative concentration of one or more of the glycated Peptides AA-DJ (as compared to the concentration of both glycated and non-glycated form of the corresponding peptide) in a patient undergoing treatment for diabetes is measured before, during, and after administration of the diabetes treatment. It is expected that the concentration of a glycated peptide decreases upon effective treatment of diabetes in the patient.

This example demonstrates monitoring the efficacy of treatment of diabetic patients based on the relative concentration of Peptides AA-DJ.

Example 5

This prophetic example demonstrates that the method of monitoring glycemic control according to the invention is more sensitive that methods based on HbA1C levels.

Plasma is obtained from subjects with HbA1C levels within or near the normal range, but who nonetheless have mild abnormalities of either glucose tolerance, as determined by either a two hour oral glucose tolerance test, or a slightly elevated fasting plasma glucose. The concentration of glycated Peptides AA-DJ (as compared to the concentration of the unglycated peptides) in these subjects is compared to HbA1C levels. It is expected that the concentrations of some of glycated Peptides AA-DJ will differ from control values more dramatically among these subjects than the concentrations of HbA1C.

This example demonstrated that certain glycated peptides will fluctuate in concentration more dramatically and possibly more rapidly than HbA1C, thereby providing better glycemic control indices.

All references, including publications, patent applications, and patents, cited herein are hereby incorporated by reference to the same extent as if each reference were individually and specifically indicated to be incorporated by reference and were set forth in its entirety herein.

The use of the terms "a" and "an" and "the" and similar referents in the context of describing the invention (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. The terms "comprising," "having," "including," and "containing" are to be construed as open-ended terms (i.e., meaning "including, but not limited to,") unless otherwise noted. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range, unless otherwise indicated herein, and each separate value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g., "such as") provided herein, is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention unless otherwise claimed. No language in the specification should be construed as indicating any non-claimed element as essential to the practice of the invention.

Preferred embodiments of this invention are described herein, including the best mode known to the inventors for carrying out the invention. Variations of those preferred embodiments may become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventors expect skilled artisans to employ such variations as appropriate, and the inventors intend for the invention to be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described elements in all possible variations thereof is encompassed by the invention unless otherwise indicated herein or otherwise clearly contradicted by context.

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Gly Phe Ser Pro Lys Asp Val Leu Val Arg
1 5 10

<210> SEQ ID NO 17
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 17

Leu Lys Phe Ile Ile Pro Ser Pro Lys
1 5

<210> SEQ ID NO 18
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 18

Lys Ala Ser Tyr Leu Asp Cys Ile Arg
1 5

<210> SEQ ID NO 19
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 19

-continued

Gly Asp Val Ala Phe Val Lys His Gln Thr Val Pro Gln Asn Thr Gly
1 5 10 15

Gly Lys

<210> SEQ ID NO 20
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 20

Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
1 5 10

<210> SEQ ID NO 21
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 21

Lys Gln Leu Val Glu Ile Glu Lys
1 5

<210> SEQ ID NO 22
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 22

Ala Lys Val Gln Pro Tyr Leu Asp Asp Phe Gln Lys
1 5 10

<210> SEQ ID NO 23
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 23

Val Lys Ala His Tyr Gly Gly Phe Thr Val Gln Asn Glu Ala Asn Gln
1 5 10 15

Lys

<210> SEQ ID NO 24
<211> LENGTH: 77
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: APO-A11 Region 24-100 of preprotein Acc. No.
NP_001634.1

<400> SEQUENCE: 24

Gln Ala Lys Glu Pro Cys Val Glu Ser Leu Val Ser Gln Tyr Phe Gln
1 5 10 15

Thr Val Thr Asp Tyr Gly Lys Asp Leu Met Glu Lys Val Lys Ser Pro
20 25 30

Glu Leu Gln Ala Glu Ala Lys Ser Tyr Phe Glu Lys Ser Lys Glu Gln
35 40 45

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Leu Thr Pro Leu Ile Lys Lys Ala Gly Thr Glu Leu Val Asn Phe Leu
    50                  55                  60

Ser Tyr Phe Val Glu Leu Gly Thr Gln Pro Ala Thr Gln
65                  70                  75


<210> SEQ ID NO 25
<211> LENGTH: 1451
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: Alpha-2M Region 24-1474 of preprotein Acc. No.
      NP_000005.2

<400> SEQUENCE: 25

Ser Val Ser Gly Lys Pro Gln Tyr Met Val Leu Val Pro Ser Leu Leu
1               5                   10                  15

His Thr Glu Thr Thr Glu Lys Gly Cys Val Leu Leu Ser Tyr Leu Asn
            20                  25                  30

Glu Thr Val Thr Val Ser Ala Ser Leu Glu Ser Val Arg Gly Asn Arg
        35                  40                  45

Ser Leu Phe Thr Asp Leu Glu Ala Glu Asn Asp Val Leu His Cys Val
    50                  55                  60

Ala Phe Ala Val Pro Lys Ser Ser Ser Asn Glu Glu Val Met Phe Leu
65                  70                  75                  80

Thr Val Gln Val Lys Gly Pro Thr Gln Glu Phe Lys Lys Arg Thr Thr
                85                  90                  95

Val Met Val Lys Asn Glu Asp Ser Leu Val Phe Val Gln Thr Asp Lys
            100                 105                 110

Ser Ile Tyr Lys Pro Gly Gln Thr Val Lys Phe Arg Val Val Ser Met
        115                 120                 125

Asp Glu Asn Phe His Pro Leu Asn Glu Leu Ile Pro Leu Val Tyr Ile
    130                 135                 140

Gln Asp Pro Lys Gly Asn Arg Ile Ala Gln Trp Gln Ser Phe Gln Leu
145                 150                 155                 160

Glu Gly Gly Leu Lys Gln Phe Ser Phe Pro Leu Ser Ser Glu Pro Phe
                165                 170                 175

Gln Gly Ser Tyr Lys Val Val Val Gln Lys Lys Ser Gly Gly Arg Thr
            180                 185                 190

Glu His Pro Phe Thr Val Glu Glu Phe Val Leu Pro Lys Phe Glu Val
        195                 200                 205

Gln Val Thr Val Pro Lys Ile Ile Thr Ile Leu Glu Glu Glu Met Asn
    210                 215                 220

Val Ser Val Cys Gly Leu Tyr Thr Tyr Gly Lys Pro Val Pro Gly His
225                 230                 235                 240

Val Thr Val Ser Ile Cys Arg Lys Tyr Ser Asp Ala Ser Asp Cys His
                245                 250                 255

Gly Glu Asp Ser Gln Ala Phe Cys Glu Lys Phe Ser Gly Gln Leu Asn
            260                 265                 270

Ser His Gly Cys Phe Tyr Gln Gln Val Lys Thr Lys Val Phe Gln Leu
        275                 280                 285

Lys Arg Lys Glu Tyr Glu Met Lys Leu His Thr Glu Ala Gln Ile Gln
    290                 295                 300

Glu Glu Gly Thr Val Val Glu Leu Thr Gly Arg Gln Ser Ser Glu Ile
305                 310                 315                 320

Thr Arg Thr Ile Thr Lys Leu Ser Phe Val Lys Val Asp Ser His Phe
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                325                 330                 335

Arg Gln Gly Ile Pro Phe Phe Gly Gln Val Arg Leu Val Asp Gly Lys
            340                 345                 350

Gly Val Pro Ile Pro Asn Lys Val Ile Phe Ile Arg Gly Asn Glu Ala
        355                 360                 365

Asn Tyr Tyr Ser Asn Ala Thr Thr Asp Glu His Gly Leu Val Gln Phe
    370                 375                 380

Ser Ile Asn Thr Thr Asn Val Met Gly Thr Ser Leu Thr Val Arg Val
385                 390                 395                 400

Asn Tyr Lys Asp Arg Ser Pro Cys Tyr Gly Tyr Gln Trp Val Ser Glu
                405                 410                 415

Glu His Glu Glu Ala His His Thr Ala Tyr Leu Val Phe Ser Pro Ser
            420                 425                 430

Lys Ser Phe Val His Leu Glu Pro Met Ser His Glu Leu Pro Cys Gly
        435                 440                 445

His Thr Gln Thr Val Gln Ala His Tyr Ile Leu Asn Gly Gly Thr Leu
    450                 455                 460

Leu Gly Leu Lys Lys Leu Ser Phe Tyr Tyr Leu Ile Met Ala Lys Gly
465                 470                 475                 480

Gly Ile Val Arg Thr Gly Thr His Gly Leu Leu Val Lys Gln Glu Asp
                485                 490                 495

Met Lys Gly His Phe Ser Ile Ser Ile Pro Val Lys Ser Asp Ile Ala
            500                 505                 510

Pro Val Ala Arg Leu Leu Ile Tyr Ala Val Leu Pro Thr Gly Asp Val
        515                 520                 525

Ile Gly Asp Ser Ala Lys Tyr Asp Val Glu Asn Cys Leu Ala Asn Lys
    530                 535                 540

Val Asp Leu Ser Phe Ser Pro Ser Gln Ser Leu Pro Ala Ser His Ala
545                 550                 555                 560

His Leu Arg Val Thr Ala Ala Pro Gln Ser Val Cys Ala Leu Arg Ala
                565                 570                 575

Val Asp Gln Ser Val Leu Leu Met Lys Pro Asp Ala Glu Leu Ser Ala
            580                 585                 590

Ser Ser Val Tyr Asn Leu Leu Pro Glu Lys Asp Leu Thr Gly Phe Pro
        595                 600                 605

Gly Pro Leu Asn Asp Gln Asp Asp Glu Asp Cys Ile Asn Arg His Asn
    610                 615                 620

Val Tyr Ile Asn Gly Ile Thr Tyr Thr Pro Val Ser Ser Thr Asn Glu
625                 630                 635                 640

Lys Asp Met Tyr Ser Phe Leu Glu Asp Met Gly Leu Lys Ala Phe Thr
                645                 650                 655

Asn Ser Lys Ile Arg Lys Pro Lys Met Cys Pro Gln Leu Gln Gln Tyr
            660                 665                 670

Glu Met His Gly Pro Glu Gly Leu Arg Val Gly Phe Tyr Glu Ser Asp
        675                 680                 685

Val Met Gly Arg Gly His Ala Arg Leu Val His Val Glu Glu Pro His
    690                 695                 700

Thr Glu Thr Val Arg Lys Tyr Phe Pro Glu Thr Trp Ile Trp Asp Leu
705                 710                 715                 720

Val Val Val Asn Ser Ala Gly Val Ala Glu Val Gly Val Thr Val Pro
                725                 730                 735

Asp Thr Ile Thr Glu Trp Lys Ala Gly Ala Phe Cys Leu Ser Glu Asp
            740                 745                 750
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Ala Gly Leu Gly Ile Ser Ser Thr Ala Ser Leu Arg Ala Phe Gln Pro
        755                 760                 765

Phe Phe Val Glu Leu Thr Met Pro Tyr Ser Val Ile Arg Gly Glu Ala
    770                 775                 780

Phe Thr Leu Lys Ala Thr Val Leu Asn Tyr Leu Pro Lys Cys Ile Arg
785                 790                 795                 800

Val Ser Val Gln Leu Glu Ala Ser Pro Ala Phe Leu Ala Val Pro Val
                805                 810                 815

Glu Lys Glu Gln Ala Pro His Cys Ile Cys Ala Asn Gly Arg Gln Thr
            820                 825                 830

Val Ser Trp Ala Val Thr Pro Lys Ser Leu Gly Asn Val Asn Phe Thr
        835                 840                 845

Val Ser Ala Glu Ala Leu Glu Ser Gln Glu Leu Cys Gly Thr Glu Val
    850                 855                 860

Pro Ser Val Pro Glu His Gly Arg Lys Asp Thr Val Ile Lys Pro Leu
865                 870                 875                 880

Leu Val Glu Pro Glu Gly Leu Glu Lys Glu Thr Thr Phe Asn Ser Leu
                885                 890                 895

Leu Cys Pro Ser Gly Gly Glu Val Ser Glu Glu Leu Ser Leu Lys Leu
            900                 905                 910

Pro Pro Asn Val Val Glu Glu Ser Ala Arg Ala Ser Val Ser Val Leu
        915                 920                 925

Gly Asp Ile Leu Gly Ser Ala Met Gln Asn Thr Gln Asn Leu Leu Gln
    930                 935                 940

Met Pro Tyr Gly Cys Gly Glu Gln Asn Met Val Leu Phe Ala Pro Asn
945                 950                 955                 960

Ile Tyr Val Leu Asp Tyr Leu Asn Glu Thr Gln Gln Leu Thr Pro Glu
                965                 970                 975

Ile Lys Ser Lys Ala Ile Gly Tyr Leu Asn Thr Gly Tyr Gln Arg Gln
            980                 985                 990

Leu Asn Tyr Lys His Tyr Asp Gly  Ser Tyr Ser Thr Phe  Gly Glu Arg
        995                 1000                1005

Tyr Gly  Arg Asn Gln Gly Asn  Thr Trp Leu Thr Ala  Phe Val Leu
    1010                1015                1020

Lys Thr  Phe Ala Gln Ala Arg  Ala Tyr Ile Phe Ile  Asp Glu Ala
    1025                1030                1035

His Ile  Thr Gln Ala Leu Ile  Trp Leu Ser Gln Arg  Gln Lys Asp
    1040                1045                1050

Asn Gly  Cys Phe Arg Ser Ser  Gly Ser Leu Leu Asn  Asn Ala Ile
    1055                1060                1065

Lys Gly  Gly Val Glu Asp Glu  Val Thr Leu Ser Ala  Tyr Ile Thr
    1070                1075                1080

Ile Ala  Leu Leu Glu Ile Pro  Leu Thr Val Thr His  Pro Val Val
    1085                1090                1095

Arg Asn  Ala Leu Phe Cys Leu  Glu Ser Ala Trp Lys  Thr Ala Gln
    1100                1105                1110

Glu Gly  Asp His Gly Ser His  Val Tyr Thr Lys Ala  Leu Leu Ala
    1115                1120                1125

Tyr Ala  Phe Ala Leu Ala Gly  Asn Gln Asp Lys Arg  Lys Glu Val
    1130                1135                1140

Leu Lys  Ser Leu Asn Glu Glu  Ala Val Lys Lys Asp  Asn Ser Val
    1145                1150                1155

His Trp  Glu Arg Pro Gln Lys  Pro Lys Ala Pro Val  Gly His Phe
    1160                1165                1170
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Tyr Glu  Pro Gln Ala Pro Ser  Ala Glu Val Glu Met  Thr Ser Tyr
    1175                1180                1185

Val Leu  Leu Ala Tyr Leu Thr  Ala Gln Pro Ala Pro  Thr Ser Glu
    1190                1195                1200

Asp Leu  Thr Ser Ala Thr Asn  Ile Val Lys Trp Ile  Thr Lys Gln
    1205                1210                1215

Gln Asn  Ala Gln Gly Gly Phe  Ser Ser Thr Gln Asp  Thr Val Val
    1220                1225                1230

Ala Leu  His Ala Leu Ser Lys  Tyr Gly Ala Ala Thr  Phe Thr Arg
    1235                1240                1245

Thr Gly  Lys Ala Ala Gln Val  Thr Ile Gln Ser Ser  Gly Thr Phe
    1250                1255                1260

Ser Ser  Lys Phe Gln Val Asp  Asn Asn Asn Arg Leu  Leu Leu Gln
    1265                1270                1275

Gln Val  Ser Leu Pro Glu Leu  Pro Gly Glu Tyr Ser  Met Lys Val
    1280                1285                1290

Thr Gly  Glu Gly Cys Val Tyr  Leu Gln Thr Ser Leu  Lys Tyr Asn
    1295                1300                1305

Ile Leu  Pro Glu Lys Glu Glu  Phe Pro Phe Ala Leu  Gly Val Gln
    1310                1315                1320

Thr Leu  Pro Gln Thr Cys Asp  Glu Pro Lys Ala His  Thr Ser Phe
    1325                1330                1335

Gln Ile  Ser Leu Ser Val Ser  Tyr Thr Gly Ser Arg  Ser Ala Ser
    1340                1345                1350

Asn Met  Ala Ile Val Asp Val  Lys Met Val Ser Gly  Phe Ile Pro
    1355                1360                1365

Leu Lys  Pro Thr Val Lys Met  Leu Glu Arg Ser Asn  His Val Ser
    1370                1375                1380

Arg Thr  Glu Val Ser Ser Asn  His Val Leu Ile Tyr  Leu Asp Lys
    1385                1390                1395

Val Ser  Asn Gln Thr Leu Ser  Leu Phe Phe Thr Val  Leu Gln Asp
    1400                1405                1410

Val Pro  Val Arg Asp Leu Lys  Pro Ala Ile Val Lys  Val Tyr Asp
    1415                1420                1425

Tyr Tyr  Glu Thr Asp Glu Phe  Ala Ile Ala Glu Tyr  Asn Ala Pro
    1430                1435                1440

Cys Ser  Lys Asp Leu Gly Asn  Ala
    1445                1450


<210> SEQ ID NO 26
<211> LENGTH: 243
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: APO-A1 Region 25-267 of preprotein NP_000030.1

<400> SEQUENCE: 26

Asp Glu Pro Pro Gln Ser Pro Trp Asp Arg Val Lys Asp Leu Ala Thr
1               5                  10                  15

Val Tyr Val Asp Val Leu Lys Asp Ser Gly Arg Asp Tyr Val Ser Gln
            20                  25                  30

Phe Glu Gly Ser Ala Leu Gly Lys Gln Leu Asn Leu Lys Leu Leu Asp
        35                  40                  45

Asn Trp Asp Ser Val Thr Ser Thr Phe Ser Lys Leu Arg Glu Gln Leu
    50                  55                  60
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Gly Pro Val Thr Gln Glu Phe Trp Asp Asn Leu Glu Lys Glu Thr Glu
65                  70                  75                  80

Gly Leu Arg Gln Glu Met Ser Lys Asp Leu Glu Glu Val Lys Ala Lys
                85                  90                  95

Val Gln Pro Tyr Leu Asp Asp Phe Gln Lys Lys Trp Gln Glu Glu Met
            100                 105                 110

Glu Leu Tyr Arg Gln Lys Val Glu Pro Leu Arg Ala Glu Leu Gln Glu
        115                 120                 125

Gly Ala Arg Gln Lys Leu His Glu Leu Gln Glu Lys Leu Ser Pro Leu
    130                 135                 140

Gly Glu Glu Met Arg Asp Arg Ala Arg Ala His Val Asp Ala Leu Arg
145                 150                 155                 160

Thr His Leu Ala Pro Tyr Ser Asp Glu Leu Arg Gln Arg Leu Ala Ala
                165                 170                 175

Arg Leu Glu Ala Leu Lys Glu Asn Gly Gly Ala Arg Leu Ala Glu Tyr
            180                 185                 190

His Ala Lys Ala Thr Glu His Leu Ser Thr Leu Ser Glu Lys Ala Lys
        195                 200                 205

Pro Ala Leu Glu Asp Leu Arg Gln Gly Leu Leu Pro Val Leu Glu Ser
    210                 215                 220

Phe Lys Val Ser Phe Leu Ser Ala Leu Glu Glu Tyr Thr Lys Lys Leu
225                 230                 235                 240

Asn Thr Gln


<210> SEQ ID NO 27
<211> LENGTH: 398
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: Serpin Peptidase Inhibitor Region 26-423 of
      preprotein Acc. No. NP_001076.2

<400> SEQUENCE: 27

Asn Ser Pro Leu Asp Glu Glu Asn Leu Thr Gln Glu Asn Gln Asp Arg
1               5                   10                  15

Gly Thr His Val Asp Leu Gly Leu Ala Ser Ala Asn Val Asp Phe Ala
            20                  25                  30

Phe Ser Leu Tyr Lys Gln Leu Val Leu Lys Ala Pro Asp Lys Asn Val
        35                  40                  45

Ile Phe Ser Pro Leu Ser Ile Ser Thr Ala Leu Ala Phe Leu Ser Leu
    50                  55                  60

Gly Ala His Asn Thr Thr Leu Thr Glu Ile Leu Lys Gly Leu Lys Phe
65                  70                  75                  80

Asn Leu Thr Glu Thr Ser Glu Ala Glu Ile His Gln Ser Phe Gln His
                85                  90                  95

Leu Leu Arg Thr Leu Asn Gln Ser Ser Asp Glu Leu Gln Leu Ser Met
            100                 105                 110

Gly Asn Ala Met Phe Val Lys Glu Gln Leu Ser Leu Leu Asp Arg Phe
        115                 120                 125

Thr Glu Asp Ala Lys Arg Leu Tyr Gly Ser Glu Ala Phe Ala Thr Asp
    130                 135                 140

Phe Gln Asp Ser Ala Ala Ala Lys Lys Leu Ile Asn Asp Tyr Val Lys
145                 150                 155                 160

Asn Gly Thr Arg Gly Lys Ile Thr Asp Leu Ile Lys Asp Leu Asp Ser
                165                 170                 175
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Gln Thr Met Met Val Leu Val Asn Tyr Ile Phe Phe Lys Ala Lys Trp
            180                 185                 190

Glu Met Pro Phe Asp Pro Gln Asp Thr His Gln Ser Arg Phe Tyr Leu
        195                 200                 205

Ser Lys Lys Lys Trp Val Met Val Pro Met Met Ser Leu His His Leu
    210                 215                 220

Thr Ile Pro Tyr Phe Arg Asp Glu Glu Leu Ser Cys Thr Val Val Glu
225                 230                 235                 240

Leu Lys Tyr Thr Gly Asn Ala Ser Ala Leu Phe Ile Leu Pro Asp Gln
                245                 250                 255

Asp Lys Met Glu Glu Val Glu Ala Met Leu Leu Pro Glu Thr Leu Lys
            260                 265                 270

Arg Trp Arg Asp Ser Leu Glu Phe Arg Glu Ile Gly Glu Leu Tyr Leu
        275                 280                 285

Pro Lys Phe Ser Ile Ser Arg Asp Tyr Asn Leu Asn Asp Ile Leu Leu
    290                 295                 300

Gln Leu Gly Ile Glu Glu Ala Phe Thr Ser Lys Ala Asp Leu Ser Gly
305                 310                 315                 320

Ile Thr Gly Ala Arg Asn Leu Ala Val Ser Gln Val Val His Lys Ala
                325                 330                 335

Val Leu Asp Val Phe Glu Glu Gly Thr Glu Ala Ser Ala Ala Thr Ala
            340                 345                 350

Val Lys Ile Thr Leu Leu Ser Ala Leu Val Glu Thr Arg Thr Ile Val
        355                 360                 365

Arg Phe Asn Arg Pro Phe Leu Met Ile Ile Val Pro Thr Asp Thr Gln
    370                 375                 380

Asn Ile Phe Phe Met Ser Lys Val Thr Asn Pro Lys Gln Ala
385                 390                 395


<210> SEQ ID NO 28
<211> LENGTH: 439
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: Hemopexin Region 24-462 of preprotein Acc. no.
      NP_000604.1

<400> SEQUENCE: 28

Thr Pro Leu Pro Pro Thr Ser Ala His Gly Asn Val Ala Glu Gly Glu
1               5                   10                  15

Thr Lys Pro Asp Pro Asp Val Thr Glu Arg Cys Ser Asp Gly Trp Ser
            20                  25                  30

Phe Asp Ala Thr Thr Leu Asp Asp Asn Gly Thr Met Leu Phe Phe Lys
        35                  40                  45

Gly Glu Phe Val Trp Lys Ser His Lys Trp Asp Arg Glu Leu Ile Ser
    50                  55                  60

Glu Arg Trp Lys Asn Phe Pro Ser Pro Val Asp Ala Ala Phe Arg Gln
65                  70                  75                  80

Gly His Asn Ser Val Phe Leu Ile Lys Gly Asp Lys Val Trp Val Tyr
                85                  90                  95

Pro Pro Glu Lys Lys Glu Lys Gly Tyr Pro Lys Leu Leu Gln Asp Glu
            100                 105                 110

Phe Pro Gly Ile Pro Ser Pro Leu Asp Ala Ala Val Glu Cys His Arg
        115                 120                 125

Gly Glu Cys Gln Ala Glu Gly Val Leu Phe Phe Gln Gly Asp Arg Glu
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    130                 135                 140

Trp Phe Trp Asp Leu Ala Thr Gly Thr Met Lys Glu Arg Ser Trp Pro
145                 150                 155                 160

Ala Val Gly Asn Cys Ser Ser Ala Leu Arg Trp Leu Gly Arg Tyr Tyr
                165                 170                 175

Cys Phe Gln Gly Asn Gln Phe Leu Arg Phe Asp Pro Val Arg Gly Glu
            180                 185                 190

Val Pro Pro Arg Tyr Pro Arg Asp Val Arg Asp Tyr Phe Met Pro Cys
        195                 200                 205

Pro Gly Arg Gly His Gly His Arg Asn Gly Thr Gly His Gly Asn Ser
    210                 215                 220

Thr His His Gly Pro Glu Tyr Met Arg Cys Ser Pro His Leu Val Leu
225                 230                 235                 240

Ser Ala Leu Thr Ser Asp Asn His Gly Ala Thr Tyr Ala Phe Ser Gly
                245                 250                 255

Thr His Tyr Trp Arg Leu Asp Thr Ser Arg Asp Gly Trp His Ser Trp
            260                 265                 270

Pro Ile Ala His Gln Trp Pro Gln Gly Pro Ser Ala Val Asp Ala Ala
        275                 280                 285

Phe Ser Trp Glu Glu Lys Leu Tyr Leu Val Gln Gly Thr Gln Val Tyr
    290                 295                 300

Val Phe Leu Thr Lys Gly Gly Tyr Thr Leu Val Ser Gly Tyr Pro Lys
305                 310                 315                 320

Arg Leu Glu Lys Glu Val Gly Thr Pro His Gly Ile Ile Leu Asp Ser
                325                 330                 335

Val Asp Ala Ala Phe Ile Cys Pro Gly Ser Ser Arg Leu His Ile Met
            340                 345                 350

Ala Gly Arg Arg Leu Trp Trp Leu Asp Leu Lys Ser Gly Ala Gln Ala
        355                 360                 365

Thr Trp Thr Glu Leu Pro Trp Pro His Glu Lys Val Asp Gly Ala Leu
    370                 375                 380

Cys Met Glu Lys Ser Leu Gly Pro Asn Ser Cys Ser Ala Asn Gly Pro
385                 390                 395                 400

Gly Leu Tyr Leu Ile His Gly Pro Asn Leu Tyr Cys Tyr Ser Asp Val
                405                 410                 415

Glu Lys Leu Asn Ala Ala Lys Ala Leu Pro Gln Pro Gln Asn Val Thr
            420                 425                 430

Ser Leu Leu Gly Cys Thr His
        435


<210> SEQ ID NO 29
<211> LENGTH: 491
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: Fibrinogen Beta Chain Region 45-491 of
      preprotein Acc. No. NP_005132.2

<400> SEQUENCE: 29

Met Lys Arg Met Val Ser Trp Ser Phe His Lys Leu Lys Thr Met Lys
1               5                   10                  15

His Leu Leu Leu Leu Leu Leu Cys Val Phe Leu Val Lys Ser Gln Gly
            20                  25                  30

Val Asn Asp Asn Glu Glu Gly Phe Phe Ser Ala Arg Gly His Arg Pro
        35                  40                  45
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Leu Asp Lys Lys Arg Glu Glu Ala Pro Ser Leu Arg Pro Ala Pro Pro
    50                  55                  60

Pro Ile Ser Gly Gly Gly Tyr Arg Ala Arg Pro Ala Lys Ala Ala Ala
65                  70                  75                  80

Thr Gln Lys Lys Val Glu Arg Lys Ala Pro Asp Ala Gly Gly Cys Leu
                85                  90                  95

His Ala Asp Pro Asp Leu Gly Val Leu Cys Pro Thr Gly Cys Gln Leu
            100                 105                 110

Gln Glu Ala Leu Leu Gln Gln Glu Arg Pro Ile Arg Asn Ser Val Asp
        115                 120                 125

Glu Leu Asn Asn Asn Val Glu Ala Val Ser Gln Thr Ser Ser Ser Ser
    130                 135                 140

Phe Gln Tyr Met Tyr Leu Leu Lys Asp Leu Trp Gln Lys Arg Gln Lys
145                 150                 155                 160

Gln Val Lys Asp Asn Glu Asn Val Val Asn Glu Tyr Ser Ser Glu Leu
                165                 170                 175

Glu Lys His Gln Leu Tyr Ile Asp Glu Thr Val Asn Ser Asn Ile Pro
            180                 185                 190

Thr Asn Leu Arg Val Leu Arg Ser Ile Leu Glu Asn Leu Arg Ser Lys
        195                 200                 205

Ile Gln Lys Leu Glu Ser Asp Val Ser Ala Gln Met Glu Tyr Cys Arg
    210                 215                 220

Thr Pro Cys Thr Val Ser Cys Asn Ile Pro Val Val Ser Gly Lys Glu
225                 230                 235                 240

Cys Glu Glu Ile Ile Arg Lys Gly Gly Glu Thr Ser Glu Met Tyr Leu
                245                 250                 255

Ile Gln Pro Asp Ser Ser Val Lys Pro Tyr Arg Val Tyr Cys Asp Met
            260                 265                 270

Asn Thr Glu Asn Gly Gly Trp Thr Val Ile Gln Asn Arg Gln Asp Gly
        275                 280                 285

Ser Val Asp Phe Gly Arg Lys Trp Asp Pro Tyr Lys Gln Gly Phe Gly
    290                 295                 300

Asn Val Ala Thr Asn Thr Asp Gly Lys Asn Tyr Cys Gly Leu Pro Gly
305                 310                 315                 320

Glu Tyr Trp Leu Gly Asn Asp Lys Ile Ser Gln Leu Thr Arg Met Gly
                325                 330                 335

Pro Thr Glu Leu Leu Ile Glu Met Glu Asp Trp Lys Gly Asp Lys Val
            340                 345                 350

Lys Ala His Tyr Gly Gly Phe Thr Val Gln Asn Glu Ala Asn Lys Tyr
        355                 360                 365

Gln Ile Ser Val Asn Lys Tyr Arg Gly Thr Ala Gly Asn Ala Leu Met
    370                 375                 380

Asp Gly Ala Ser Gln Leu Met Gly Glu Asn Arg Thr Met Thr Ile His
385                 390                 395                 400

Asn Gly Met Phe Phe Ser Thr Tyr Asp Arg Asp Asn Asp Gly Trp Leu
                405                 410                 415

Thr Ser Asp Pro Arg Lys Gln Cys Ser Lys Glu Asp Gly Gly Gly Trp
            420                 425                 430

Trp Tyr Asn Arg Cys His Ala Ala Asn Pro Asn Gly Arg Tyr Tyr Trp
        435                 440                 445

Gly Gly Gln Tyr Thr Trp Asp Met Ala Lys His Gly Thr Asp Asp Gly
    450                 455                 460

Val Val Trp Met Asn Trp Lys Gly Ser Trp Tyr Ser Met Arg Lys Met
465                 470                 475                 480
```

Ser Met Lys Ile Arg Pro Phe Phe Pro Gln Gln
485 490

<210> SEQ ID NO 30
<211> LENGTH: 104
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: Ig lambda light chain Acc. No. AAA59109

<400> SEQUENCE: 30

Pro Lys Ala Ala Pro Ser Val Thr Leu Phe Pro Pro Ser Ser Glu Glu
1 5 10 15

Leu Gln Ala Asn Lys Ala Thr Leu Val Cys Leu Ile Ser Asp Phe Tyr
20 25 30

Pro Gly Ala Val Thr Val Ala Trp Lys Ala Asp Ser Ser Pro Val Lys
35 40 45

Ala Gly Val Glu Thr Thr Thr Pro Ser Lys Gln Ser Asn Asn Lys Tyr
50 55 60

Ala Ala Ser Ser Tyr Leu Ser Leu Thr Pro Glu Gln Trp Lys Ser His
65 70 75 80

Lys Ser Tyr Ser Cys Gln Val Thr His Glu Gly Ser Thr Val Glu Lys
85 90 95

Thr Val Ala Pro Thr Glu Cys Ser
100

<210> SEQ ID NO 31
<211> LENGTH: 220
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: Ig heavy chain constant region Acc. No. CAA09968

<400> SEQUENCE: 31

Leu Glu Asp Leu Leu Leu Gly Ser Glu Ala Asn Leu Thr Cys Thr Leu
1 5 10 15

Thr Gly Leu Arg Asp Ala Ser Gly Ala Thr Phe Thr Trp Thr Pro Ser
20 25 30

Ser Gly Lys Ser Ala Val Gln Gly Pro Pro Glu Arg Asp Leu Cys Gly
35 40 45

Cys Tyr Ser Val Ser Ser Val Leu Pro Gly Cys Ala Gln Pro Trp Asn
50 55 60

His Gly Glu Thr Phe Thr Cys Thr Ala Ala His Pro Glu Leu Lys Thr
65 70 75 80

Pro Leu Thr Ala Asn Ile Thr Lys Ser Gly Asn Thr Phe Arg Pro Glu
85 90 95

Val His Leu Leu Pro Pro Pro Ser Glu Glu Leu Ala Leu Asn Glu Leu
100 105 110

Val Thr Leu Thr Cys Leu Ala Arg Gly Phe Ser Pro Lys Asp Val Leu
115 120 125

Val Arg Trp Leu Gln Gly Ser Gln Glu Leu Pro Arg Glu Lys Tyr Leu
130 135 140

Thr Trp Ala Ser Arg Gln Glu Pro Ser Gln Gly Thr Thr Thr Tyr Ala
145 150 155 160

Val Thr Ser Ile Leu Arg Val Ala Ala Glu Asp Trp Lys Lys Gly Glu
165 170 175

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Thr Phe Ser Cys Met Val Gly His Glu Ala Leu Pro Leu Ala Phe Thr
            180                 185                 190

Gln Lys Thr Ile Asp Arg Met Ala Gly Lys Pro Thr His Ile Asn Val
        195                 200                 205

Ser Val Val Met Ala Glu Ala Asp Gly Thr Cys Tyr
    210                 215                 220


<210> SEQ ID NO 32
<211> LENGTH: 4536
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: APO B100 Region 28-4563 of preprotein Acc. No.
      NP_000375.1

<400> SEQUENCE: 32

Glu Glu Glu Met Leu Glu Asn Val Ser Leu Val Cys Pro Lys Asp Ala
1               5                   10                  15

Thr Arg Phe Lys His Leu Arg Lys Tyr Thr Tyr Asn Tyr Glu Ala Glu
            20                  25                  30

Ser Ser Ser Gly Val Pro Gly Thr Ala Asp Ser Arg Ser Ala Thr Arg
        35                  40                  45

Ile Asn Cys Lys Val Glu Leu Glu Val Pro Gln Leu Cys Ser Phe Ile
    50                  55                  60

Leu Lys Thr Ser Gln Cys Thr Leu Lys Glu Val Tyr Gly Phe Asn Pro
65                  70                  75                  80

Glu Gly Lys Ala Leu Leu Lys Lys Thr Lys Asn Ser Glu Glu Phe Ala
                85                  90                  95

Ala Ala Met Ser Arg Tyr Glu Leu Lys Leu Ala Ile Pro Glu Gly Lys
            100                 105                 110

Gln Val Phe Leu Tyr Pro Glu Lys Asp Glu Pro Thr Tyr Ile Leu Asn
        115                 120                 125

Ile Lys Arg Gly Ile Ile Ser Ala Leu Leu Val Pro Pro Glu Thr Glu
    130                 135                 140

Glu Ala Lys Gln Val Leu Phe Leu Asp Thr Val Tyr Gly Asn Cys Ser
145                 150                 155                 160

Thr His Phe Thr Val Lys Thr Arg Lys Gly Asn Val Ala Thr Glu Ile
                165                 170                 175

Ser Thr Glu Arg Asp Leu Gly Gln Cys Asp Arg Phe Lys Pro Ile Arg
            180                 185                 190

Thr Gly Ile Ser Pro Leu Ala Leu Ile Lys Gly Met Thr Arg Pro Leu
        195                 200                 205

Ser Thr Leu Ile Ser Ser Ser Gln Ser Cys Gln Tyr Thr Leu Asp Ala
    210                 215                 220

Lys Arg Lys His Val Ala Glu Ala Ile Cys Lys Glu Gln His Leu Phe
225                 230                 235                 240

Leu Pro Phe Ser Tyr Asn Asn Lys Tyr Gly Met Val Ala Gln Val Thr
                245                 250                 255

Gln Thr Leu Lys Leu Glu Asp Thr Pro Lys Ile Asn Ser Arg Phe Phe
            260                 265                 270

Gly Glu Gly Thr Lys Lys Met Gly Leu Ala Phe Glu Ser Thr Lys Ser
        275                 280                 285

Thr Ser Pro Pro Lys Gln Ala Glu Ala Val Leu Lys Thr Leu Gln Glu
    290                 295                 300

Leu Lys Lys Leu Thr Ile Ser Glu Gln Asn Ile Gln Arg Ala Asn Leu
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305                 310                 315                 320

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

Thr Ser Leu Leu Pro Gln Leu Ile Glu Val Ser Ser Pro Ile Thr Leu
            340                 345                 350

Gln Ala Leu Val Gln Cys Gly Gln Pro Gln Cys Ser Thr His Ile Leu
        355                 360                 365

Gln Trp Leu Lys Arg Val His Ala Asn Pro Leu Leu Ile Asp Val Val
    370                 375                 380

Thr Tyr Leu Val Ala Leu Ile Pro Glu Pro Ser Ala Gln Gln Leu Arg
385                 390                 395                 400

Glu Ile Phe Asn Met Ala Arg Asp Gln Arg Ser Arg Ala Thr Leu Tyr
                405                 410                 415

Ala Leu Ser His Ala Val Asn Asn Tyr His Lys Thr Asn Pro Thr Gly
            420                 425                 430

Thr Gln Glu Leu Leu Asp Ile Ala Asn Tyr Leu Met Glu Gln Ile Gln
        435                 440                 445

Asp Asp Cys Thr Gly Asp Glu Asp Tyr Thr Tyr Leu Ile Leu Arg Val
    450                 455                 460

Ile Gly Asn Met Gly Gln Thr Met Glu Gln Leu Thr Pro Glu Leu Lys
465                 470                 475                 480

Ser Ser Ile Leu Lys Cys Val Gln Ser Thr Lys Pro Ser Leu Met Ile
                485                 490                 495

Gln Lys Ala Ala Ile Gln Ala Leu Arg Lys Met Glu Pro Lys Asp Lys
            500                 505                 510

Asp Gln Glu Val Leu Leu Gln Thr Phe Leu Asp Asp Ala Ser Pro Gly
        515                 520                 525

Asp Lys Arg Leu Ala Ala Tyr Leu Met Leu Met Arg Ser Pro Ser Gln
    530                 535                 540

Ala Asp Ile Asn Lys Ile Val Gln Ile Leu Pro Trp Glu Gln Asn Glu
545                 550                 555                 560

Gln Val Lys Asn Phe Val Ala Ser His Ile Ala Asn Ile Leu Asn Ser
                565                 570                 575

Glu Glu Leu Asp Ile Gln Asp Leu Lys Lys Leu Val Lys Glu Ala Leu
            580                 585                 590

Lys Glu Ser Gln Leu Pro Thr Val Met Asp Phe Arg Lys Phe Ser Arg
        595                 600                 605

Asn Tyr Gln Leu Tyr Lys Ser Val Ser Leu Pro Ser Leu Asp Pro Ala
    610                 615                 620

Ser Ala Lys Ile Glu Gly Asn Leu Ile Phe Asp Pro Asn Asn Tyr Leu
625                 630                 635                 640

Pro Lys Glu Ser Met Leu Lys Thr Thr Leu Thr Ala Phe Gly Phe Ala
                645                 650                 655

Ser Ala Asp Leu Ile Glu Ile Gly Leu Glu Gly Lys Gly Phe Glu Pro
            660                 665                 670

Thr Leu Glu Ala Leu Phe Gly Lys Gln Gly Phe Phe Pro Asp Ser Val
        675                 680                 685

Asn Lys Ala Leu Tyr Trp Val Asn Gly Gln Val Pro Asp Gly Val Ser
    690                 695                 700

Lys Val Leu Val Asp His Phe Gly Tyr Thr Lys Asp Asp Lys His Glu
705                 710                 715                 720

Gln Asp Met Val Asn Gly Ile Met Leu Ser Val Glu Lys Leu Ile Lys
                725                 730                 735
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Asp Leu Lys Ser Lys Glu Val Pro Glu Ala Arg Ala Tyr Leu Arg Ile
            740                 745                 750

Leu Gly Glu Glu Leu Gly Phe Ala Ser Leu His Asp Leu Gln Leu Leu
        755                 760                 765

Gly Lys Leu Leu Leu Met Gly Ala Arg Thr Leu Gln Gly Ile Pro Gln
    770                 775                 780

Met Ile Gly Glu Val Ile Arg Lys Gly Ser Lys Asn Asp Phe Phe Leu
785                 790                 795                 800

His Tyr Ile Phe Met Glu Asn Ala Phe Glu Leu Pro Thr Gly Ala Gly
                805                 810                 815

Leu Gln Leu Gln Ile Ser Ser Ser Gly Val Ile Ala Pro Gly Ala Lys
            820                 825                 830

Ala Gly Val Lys Leu Glu Val Ala Asn Met Gln Ala Glu Leu Val Ala
        835                 840                 845

Lys Pro Ser Val Ser Val Glu Phe Val Thr Asn Met Gly Ile Ile Ile
    850                 855                 860

Pro Asp Phe Ala Arg Ser Gly Val Gln Met Asn Thr Asn Phe Phe His
865                 870                 875                 880

Glu Ser Gly Leu Glu Ala His Val Ala Leu Lys Ala Gly Lys Leu Lys
                885                 890                 895

Phe Ile Ile Pro Ser Pro Lys Arg Pro Val Lys Leu Leu Ser Gly Gly
            900                 905                 910

Asn Thr Leu His Leu Val Ser Thr Thr Lys Thr Glu Val Ile Pro Pro
        915                 920                 925

Leu Ile Glu Asn Arg Gln Ser Trp Ser Val Cys Lys Gln Val Phe Pro
    930                 935                 940

Gly Leu Asn Tyr Cys Thr Ser Gly Ala Tyr Ser Asn Ala Ser Ser Thr
945                 950                 955                 960

Asp Ser Ala Ser Tyr Tyr Pro Leu Thr Gly Asp Thr Arg Leu Glu Leu
                965                 970                 975

Glu Leu Arg Pro Thr Gly Glu Ile Glu Gln Tyr Ser Val Ser Ala Thr
            980                 985                 990

Tyr Glu Leu Gln Arg Glu Asp Arg  Ala Leu Val Asp Thr  Leu Lys Phe
        995                 1000                1005

Val Thr  Gln Ala Glu Gly Ala  Lys Gln Thr Glu Ala  Thr Met Thr
    1010                1015                1020

Phe Lys  Tyr Asn Arg Gln Ser  Met Thr Leu Ser Ser  Glu Val Gln
    1025                1030                1035

Ile Pro  Asp Phe Asp Val Asp  Leu Gly Thr Ile Leu  Arg Val Asn
    1040                1045                1050

Asp Glu  Ser Thr Glu Gly Lys  Thr Ser Tyr Arg Leu  Thr Leu Asp
    1055                1060                1065

Ile Gln  Asn Lys Lys Ile Thr  Glu Val Ala Leu Met  Gly His Leu
    1070                1075                1080

Ser Cys  Asp Thr Lys Glu Glu  Arg Lys Ile Lys Gly  Val Ile Ser
    1085                1090                1095

Ile Pro  Arg Leu Gln Ala Glu  Ala Arg Ser Glu Ile  Leu Ala His
    1100                1105                1110

Trp Ser  Pro Ala Lys Leu Leu  Leu Gln Met Asp Ser  Ser Ala Thr
    1115                1120                1125

Ala Tyr  Gly Ser Thr Val Ser  Lys Arg Val Ala Trp  His Tyr Asp
    1130                1135                1140

Glu Glu  Lys Ile Glu Phe Glu  Trp Asn Thr Gly Thr  Asn Val Asp
    1145                1150                1155
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Thr Lys  Lys Met Thr Ser Asn  Phe Pro Val Asp Leu  Ser Asp Tyr
    1160                1165                1170

Pro Lys  Ser Leu His Met Tyr  Ala Asn Arg Leu Leu  Asp His Arg
    1175                1180                1185

Val Pro  Glu Thr Asp Met Thr  Phe Arg His Val Gly  Ser Lys Leu
    1190                1195                1200

Ile Val  Ala Met Ser Ser Trp  Leu Gln Lys Ala Ser  Gly Ser Leu
    1205                1210                1215

Pro Tyr  Thr Gln Thr Leu Gln  Asp His Leu Asn Ser  Leu Lys Glu
    1220                1225                1230

Phe Asn  Leu Gln Asn Met Gly  Leu Pro Asp Phe His  Ile Pro Glu
    1235                1240                1245

Asn Leu  Phe Leu Lys Ser Asp  Gly Arg Val Lys Tyr  Thr Leu Asn
    1250                1255                1260

Lys Asn  Ser Leu Lys Ile Glu  Ile Pro Leu Pro Phe  Gly Gly Lys
    1265                1270                1275

Ser Ser  Arg Asp Leu Lys Met  Leu Glu Thr Val Arg  Thr Pro Ala
    1280                1285                1290

Leu His  Phe Lys Ser Val Gly  Phe His Leu Pro Ser  Arg Glu Phe
    1295                1300                1305

Gln Val  Pro Thr Phe Thr Ile  Pro Lys Leu Tyr Gln  Leu Gln Val
    1310                1315                1320

Pro Leu  Leu Gly Val Leu Asp  Leu Ser Thr Asn Val  Tyr Ser Asn
    1325                1330                1335

Leu Tyr  Asn Trp Ser Ala Ser  Tyr Ser Gly Gly Asn  Thr Ser Thr
    1340                1345                1350

Asp His  Phe Ser Leu Arg Ala  Arg Tyr His Met Lys  Ala Asp Ser
    1355                1360                1365

Val Val  Asp Leu Leu Ser Tyr  Asn Val Gln Gly Ser  Gly Glu Thr
    1370                1375                1380

Thr Tyr  Asp His Lys Asn Thr  Phe Thr Leu Ser Cys  Asp Gly Ser
    1385                1390                1395

Leu Arg  His Lys Phe Leu Asp  Ser Asn Ile Lys Phe  Ser His Val
    1400                1405                1410

Glu Lys  Leu Gly Asn Asn Pro  Val Ser Lys Gly Leu  Leu Ile Phe
    1415                1420                1425

Asp Ala  Ser Ser Ser Trp Gly  Pro Gln Met Ser Ala  Ser Val His
    1430                1435                1440

Leu Asp  Ser Lys Lys Lys Gln  His Leu Phe Val Lys  Glu Val Lys
    1445                1450                1455

Ile Asp  Gly Gln Phe Arg Val  Ser Ser Phe Tyr Ala  Lys Gly Thr
    1460                1465                1470

Tyr Gly  Leu Ser Cys Gln Arg  Asp Pro Asn Thr Gly  Arg Leu Asn
    1475                1480                1485

Gly Glu  Ser Asn Leu Arg Phe  Asn Ser Ser Tyr Leu  Gln Gly Thr
    1490                1495                1500

Asn Gln  Ile Thr Gly Arg Tyr  Glu Asp Gly Thr Leu  Ser Leu Thr
    1505                1510                1515

Ser Thr  Ser Asp Leu Gln Ser  Gly Ile Ile Lys Asn  Thr Ala Ser
    1520                1525                1530

Leu Lys  Tyr Glu Asn Tyr Glu  Leu Thr Leu Lys Ser  Asp Thr Asn
    1535                1540                1545

Gly Lys  Tyr Lys Asn Phe Ala  Thr Ser Asn Lys Met  Asp Met Thr
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    1550                1555                1560

Phe Ser  Lys Gln Asn Ala Leu  Leu Arg Ser Glu Tyr  Gln Ala Asp
    1565                1570                1575

Tyr Glu  Ser Leu Arg Phe Phe  Ser Leu Leu Ser Gly  Ser Leu Asn
    1580                1585                1590

Ser His  Gly Leu Glu Leu Asn  Ala Asp Ile Leu Gly  Thr Asp Lys
    1595                1600                1605

Ile Asn  Ser Gly Ala His Lys  Ala Thr Leu Arg Ile  Gly Gln Asp
    1610                1615                1620

Gly Ile  Ser Thr Ser Ala Thr  Thr Asn Leu Lys Cys  Ser Leu Leu
    1625                1630                1635

Val Leu  Glu Asn Glu Leu Asn  Ala Glu Leu Gly Leu  Ser Gly Ala
    1640                1645                1650

Ser Met  Lys Leu Thr Thr Asn  Gly Arg Phe Arg Glu  His Asn Ala
    1655                1660                1665

Lys Phe  Ser Leu Asp Gly Lys  Ala Ala Leu Thr Glu  Leu Ser Leu
    1670                1675                1680

Gly Ser  Ala Tyr Gln Ala Met  Ile Leu Gly Val Asp  Ser Lys Asn
    1685                1690                1695

Ile Phe  Asn Phe Lys Val Ser  Gln Glu Gly Leu Lys  Leu Ser Asn
    1700                1705                1710

Asp Met  Met Gly Ser Tyr Ala  Glu Met Lys Phe Asp  His Thr Asn
    1715                1720                1725

Ser Leu  Asn Ile Ala Gly Leu  Ser Leu Asp Phe Ser  Ser Lys Leu
    1730                1735                1740

Asp Asn  Ile Tyr Ser Ser Asp  Lys Phe Tyr Lys Gln  Thr Val Asn
    1745                1750                1755

Leu Gln  Leu Gln Pro Tyr Ser  Leu Val Thr Thr Leu  Asn Ser Asp
    1760                1765                1770

Leu Lys  Tyr Asn Ala Leu Asp  Leu Thr Asn Asn Gly  Lys Leu Arg
    1775                1780                1785

Leu Glu  Pro Leu Lys Leu His  Val Ala Gly Asn Leu  Lys Gly Ala
    1790                1795                1800

Tyr Gln  Asn Asn Glu Ile Lys  His Ile Tyr Ala Ile  Ser Ser Ala
    1805                1810                1815

Ala Leu  Ser Ala Ser Tyr Lys  Ala Asp Thr Val Ala  Lys Val Gln
    1820                1825                1830

Gly Val  Glu Phe Ser His Arg  Leu Asn Thr Asp Ile  Ala Gly Leu
    1835                1840                1845

Ala Ser  Ala Ile Asp Met Ser  Thr Asn Tyr Asn Ser  Asp Ser Leu
    1850                1855                1860

His Phe  Ser Asn Val Phe Arg  Ser Val Met Ala Pro  Phe Thr Met
    1865                1870                1875

Thr Ile  Asp Ala His Thr Asn  Gly Asn Gly Lys Leu  Ala Leu Trp
    1880                1885                1890

Gly Glu  His Thr Gly Gln Leu  Tyr Ser Lys Phe Leu  Leu Lys Ala
    1895                1900                1905

Glu Pro  Leu Ala Phe Thr Phe  Ser His Asp Tyr Lys  Gly Ser Thr
    1910                1915                1920

Ser His  His Leu Val Ser Arg  Lys Ser Ile Ser Ala  Ala Leu Glu
    1925                1930                1935

His Lys  Val Ser Ala Leu Leu  Thr Pro Ala Glu Gln  Thr Gly Thr
    1940                1945                1950
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Trp Lys  Leu Lys Thr Gln Phe  Asn Asn Asn Glu Tyr  Ser Gln Asp
    1955                1960                1965

Leu Asp  Ala Tyr Asn Thr Lys  Asp Lys Ile Gly Val  Glu Leu Thr
    1970                1975                1980

Gly Arg  Thr Leu Ala Asp Leu  Thr Leu Leu Asp Ser  Pro Ile Lys
    1985                1990                1995

Val Pro  Leu Leu Leu Ser Glu  Pro Ile Asn Ile Ile  Asp Ala Leu
    2000                2005                2010

Glu Met  Arg Asp Ala Val Glu  Lys Pro Gln Glu Phe  Thr Ile Val
    2015                2020                2025

Ala Phe  Val Lys Tyr Asp Lys  Asn Gln Asp Val His  Ser Ile Asn
    2030                2035                2040

Leu Pro  Phe Phe Glu Thr Leu  Gln Glu Tyr Phe Glu  Arg Asn Arg
    2045                2050                2055

Gln Thr  Ile Ile Val Val Val  Glu Asn Val Gln Arg  Asn Leu Lys
    2060                2065                2070

His Ile  Asn Ile Asp Gln Phe  Val Arg Lys Tyr Arg  Ala Ala Leu
    2075                2080                2085

Gly Lys  Leu Pro Gln Gln Ala  Asn Asp Tyr Leu Asn  Ser Phe Asn
    2090                2095                2100

Trp Glu  Arg Gln Val Ser His  Ala Lys Glu Lys Leu  Thr Ala Leu
    2105                2110                2115

Thr Lys  Lys Tyr Arg Ile Thr  Glu Asn Asp Ile Gln  Ile Ala Leu
    2120                2125                2130

Asp Asp  Ala Lys Ile Asn Phe  Asn Glu Lys Leu Ser  Gln Leu Gln
    2135                2140                2145

Thr Tyr  Met Ile Gln Phe Asp  Gln Tyr Ile Lys Asp  Ser Tyr Asp
    2150                2155                2160

Leu His  Asp Leu Lys Ile Ala  Ile Ala Asn Ile Ile  Asp Glu Ile
    2165                2170                2175

Ile Glu  Lys Leu Lys Ser Leu  Asp Glu His Tyr His  Ile Arg Val
    2180                2185                2190

Asn Leu  Val Lys Thr Ile His  Asp Leu His Leu Phe  Ile Glu Asn
    2195                2200                2205

Ile Asp  Phe Asn Lys Ser Gly  Ser Ser Thr Ala Ser  Trp Ile Gln
    2210                2215                2220

Asn Val  Asp Thr Lys Tyr Gln  Ile Arg Ile Gln Ile  Gln Glu Lys
    2225                2230                2235

Leu Gln  Gln Leu Lys Arg His  Ile Gln Asn Ile Asp  Ile Gln His
    2240                2245                2250

Leu Ala  Gly Lys Leu Lys Gln  His Ile Glu Ala Ile  Asp Val Arg
    2255                2260                2265

Val Leu  Leu Asp Gln Leu Gly  Thr Thr Ile Ser Phe  Glu Arg Ile
    2270                2275                2280

Asn Asp  Val Leu Glu His Val  Lys His Phe Val Ile  Asn Leu Ile
    2285                2290                2295

Gly Asp  Phe Glu Val Ala Glu  Lys Ile Asn Ala Phe  Arg Ala Lys
    2300                2305                2310

Val His  Glu Leu Ile Glu Arg  Tyr Glu Val Asp Gln  Gln Ile Gln
    2315                2320                2325

Val Leu  Met Asp Lys Leu Val  Glu Leu Thr His Gln  Tyr Lys Leu
    2330                2335                2340

Lys Glu  Thr Ile Gln Lys Leu  Ser Asn Val Leu Gln  Gln Val Lys
    2345                2350                2355
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Ile Lys  Asp Tyr Phe Glu Lys  Leu Val Gly Phe Ile  Asp Asp Ala
    2360                2365                2370

Val Lys  Lys Leu Asn Glu Leu  Ser Phe Lys Thr Phe  Ile Glu Asp
    2375                2380                2385

Val Asn  Lys Phe Leu Asp Met  Leu Ile Lys Lys Leu  Lys Ser Phe
    2390                2395                2400

Asp Tyr  His Gln Phe Val Asp  Glu Thr Asn Asp Lys  Ile Arg Glu
    2405                2410                2415

Val Thr  Gln Arg Leu Asn Gly  Glu Ile Gln Ala Leu  Glu Leu Pro
    2420                2425                2430

Gln Lys  Ala Glu Ala Leu Lys  Leu Phe Leu Glu Glu  Thr Lys Ala
    2435                2440                2445

Thr Val  Ala Val Tyr Leu Glu  Ser Leu Gln Asp Thr  Lys Ile Thr
    2450                2455                2460

Leu Ile  Ile Asn Trp Leu Gln  Glu Ala Leu Ser Ser  Ala Ser Leu
    2465                2470                2475

Ala His  Met Lys Ala Lys Phe  Arg Glu Thr Leu Glu  Asp Thr Arg
    2480                2485                2490

Asp Arg  Met Tyr Gln Met Asp  Ile Gln Gln Glu Leu  Gln Arg Tyr
    2495                2500                2505

Leu Ser  Leu Val Gly Gln Val  Tyr Ser Thr Leu Val  Thr Tyr Ile
    2510                2515                2520

Ser Asp  Trp Trp Thr Leu Ala  Ala Lys Asn Leu Thr  Asp Phe Ala
    2525                2530                2535

Glu Gln  Tyr Ser Ile Gln Asp  Trp Ala Lys Arg Met  Lys Ala Leu
    2540                2545                2550

Val Glu  Gln Gly Phe Thr Val  Pro Glu Ile Lys Thr  Ile Leu Gly
    2555                2560                2565

Thr Met  Pro Ala Phe Glu Val  Ser Leu Gln Ala Leu  Gln Lys Ala
    2570                2575                2580

Thr Phe  Gln Thr Pro Asp Phe  Ile Val Pro Leu Thr  Asp Leu Arg
    2585                2590                2595

Ile Pro  Ser Val Gln Ile Asn  Phe Lys Asp Leu Lys  Asn Ile Lys
    2600                2605                2610

Ile Pro  Ser Arg Phe Ser Thr  Pro Glu Phe Thr Ile  Leu Asn Thr
    2615                2620                2625

Phe His  Ile Pro Ser Phe Thr  Ile Asp Phe Val Glu  Met Lys Val
    2630                2635                2640

Lys Ile  Ile Arg Thr Ile Asp  Gln Met Gln Asn Ser  Glu Leu Gln
    2645                2650                2655

Trp Pro  Val Pro Asp Ile Tyr  Leu Arg Asp Leu Lys  Val Glu Asp
    2660                2665                2670

Ile Pro  Leu Ala Arg Ile Thr  Leu Pro Asp Phe Arg  Leu Pro Glu
    2675                2680                2685

Ile Ala  Ile Pro Glu Phe Ile  Ile Pro Thr Leu Asn  Leu Asn Asp
    2690                2695                2700

Phe Gln  Val Pro Asp Leu His  Ile Pro Glu Phe Gln  Leu Pro His
    2705                2710                2715

Ile Ser  His Thr Ile Glu Val  Pro Thr Phe Gly Lys  Leu Tyr Ser
    2720                2725                2730

Ile Leu  Lys Ile Gln Ser Pro  Leu Phe Thr Leu Asp  Ala Asn Ala
    2735                2740                2745

Asp Ile  Gly Asn Gly Thr Thr  Ser Ala Asn Glu Ala  Gly Ile Ala
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    2750                2755                2760

Ala Ser  Ile Thr Ala Lys Gly  Glu Ser Lys Leu Glu  Val Leu Asn
    2765                2770                2775

Phe Asp  Phe Gln Ala Asn Ala  Gln Leu Ser Asn Pro  Lys Ile Asn
    2780                2785                2790

Pro Leu  Ala Leu Lys Glu Ser  Val Lys Phe Ser Ser  Lys Tyr Leu
    2795                2800                2805

Arg Thr  Glu His Gly Ser Glu  Met Leu Phe Phe Gly  Asn Ala Ile
    2810                2815                2820

Glu Gly  Lys Ser Asn Thr Val  Ala Ser Leu His Thr  Glu Lys Asn
    2825                2830                2835

Thr Leu  Glu Leu Ser Asn Gly  Val Ile Val Lys Ile  Asn Asn Gln
    2840                2845                2850

Leu Thr  Leu Asp Ser Asn Thr  Lys Tyr Phe His Lys  Leu Asn Ile
    2855                2860                2865

Pro Lys  Leu Asp Phe Ser Ser  Gln Ala Asp Leu Arg  Asn Glu Ile
    2870                2875                2880

Lys Thr  Leu Leu Lys Ala Gly  His Ile Ala Trp Thr  Ser Ser Gly
    2885                2890                2895

Lys Gly  Ser Trp Lys Trp Ala  Cys Pro Arg Phe Ser  Asp Glu Gly
    2900                2905                2910

Thr His  Glu Ser Gln Ile Ser  Phe Thr Ile Glu Gly  Pro Leu Thr
    2915                2920                2925

Ser Phe  Gly Leu Ser Asn Lys  Ile Asn Ser Lys His  Leu Arg Val
    2930                2935                2940

Asn Gln  Asn Leu Val Tyr Glu  Ser Gly Ser Leu Asn  Phe Ser Lys
    2945                2950                2955

Leu Glu  Ile Gln Ser Gln Val  Asp Ser Gln His Val  Gly His Ser
    2960                2965                2970

Val Leu  Thr Ala Lys Gly Met  Ala Leu Phe Gly Glu  Gly Lys Ala
    2975                2980                2985

Glu Phe  Thr Gly Arg His Asp  Ala His Leu Asn Gly  Lys Val Ile
    2990                2995                3000

Gly Thr  Leu Lys Asn Ser Leu  Phe Phe Ser Ala Gln  Pro Phe Glu
    3005                3010                3015

Ile Thr  Ala Ser Thr Asn Asn  Glu Gly Asn Leu Lys  Val Arg Phe
    3020                3025                3030

Pro Leu  Arg Leu Thr Gly Lys  Ile Asp Phe Leu Asn  Asn Tyr Ala
    3035                3040                3045

Leu Phe  Leu Ser Pro Ser Ala  Gln Gln Ala Ser Trp  Gln Val Ser
    3050                3055                3060

Ala Arg  Phe Asn Gln Tyr Lys  Tyr Asn Gln Asn Phe  Ser Ala Gly
    3065                3070                3075

Asn Asn  Glu Asn Ile Met Glu  Ala His Val Gly Ile  Asn Gly Glu
    3080                3085                3090

Ala Asn  Leu Asp Phe Leu Asn  Ile Pro Leu Thr Ile  Pro Glu Met
    3095                3100                3105

Arg Leu  Pro Tyr Thr Ile Ile  Thr Thr Pro Pro Leu  Lys Asp Phe
    3110                3115                3120

Ser Leu  Trp Glu Lys Thr Gly  Leu Lys Glu Phe Leu  Lys Thr Thr
    3125                3130                3135

Lys Gln  Ser Phe Asp Leu Ser  Val Lys Ala Gln Tyr  Lys Lys Asn
    3140                3145                3150
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Lys His  Arg His Ser Ile Thr  Asn Pro Leu Ala Val  Leu Cys Glu
    3155                3160                3165

Phe Ile  Ser Gln Ser Ile Lys  Ser Phe Asp Arg His  Phe Glu Lys
    3170                3175                3180

Asn Arg  Asn Asn Ala Leu Asp  Phe Val Thr Lys Ser  Tyr Asn Glu
    3185                3190                3195

Thr Lys  Ile Lys Phe Asp Lys  Tyr Lys Ala Glu Lys  Ser His Asp
    3200                3205                3210

Glu Leu  Pro Arg Thr Phe Gln  Ile Pro Gly Tyr Thr  Val Pro Val
    3215                3220                3225

Val Asn  Val Glu Val Ser Pro  Phe Thr Ile Glu Met  Ser Ala Phe
    3230                3235                3240

Gly Tyr  Val Phe Pro Lys Ala  Val Ser Met Pro Ser  Phe Ser Ile
    3245                3250                3255

Leu Gly  Ser Asp Val Arg Val  Pro Ser Tyr Thr Leu  Ile Leu Pro
    3260                3265                3270

Ser Leu  Glu Leu Pro Val Leu  His Val Pro Arg Asn  Leu Lys Leu
    3275                3280                3285

Ser Leu  Pro His Phe Lys Glu  Leu Cys Thr Ile Ser  His Ile Phe
    3290                3295                3300

Ile Pro  Ala Met Gly Asn Ile  Thr Tyr Asp Phe Ser  Phe Lys Ser
    3305                3310                3315

Ser Val  Ile Thr Leu Asn Thr  Asn Ala Glu Leu Phe  Asn Gln Ser
    3320                3325                3330

Asp Ile  Val Ala His Leu Leu  Ser Ser Ser Ser Ser  Val Ile Asp
    3335                3340                3345

Ala Leu  Gln Tyr Lys Leu Glu  Gly Thr Thr Arg Leu  Thr Arg Lys
    3350                3355                3360

Arg Gly  Leu Lys Leu Ala Thr  Ala Leu Ser Leu Ser  Asn Lys Phe
    3365                3370                3375

Val Glu  Gly Ser His Asn Ser  Thr Val Ser Leu Thr  Thr Lys Asn
    3380                3385                3390

Met Glu  Val Ser Val Ala Lys  Thr Thr Lys Ala Glu  Ile Pro Ile
    3395                3400                3405

Leu Arg  Met Asn Phe Lys Gln  Glu Leu Asn Gly Asn  Thr Lys Ser
    3410                3415                3420

Lys Pro  Thr Val Ser Ser Ser  Met Glu Phe Lys Tyr  Asp Phe Asn
    3425                3430                3435

Ser Ser  Met Leu Tyr Ser Thr  Ala Lys Gly Ala Val  Asp His Lys
    3440                3445                3450

Leu Ser  Leu Glu Ser Leu Thr  Ser Tyr Phe Ser Ile  Glu Ser Ser
    3455                3460                3465

Thr Lys  Gly Asp Val Lys Gly  Ser Val Leu Ser Arg  Glu Tyr Ser
    3470                3475                3480

Gly Thr  Ile Ala Ser Glu Ala  Asn Thr Tyr Leu Asn  Ser Lys Ser
    3485                3490                3495

Thr Arg  Ser Ser Val Lys Leu  Gln Gly Thr Ser Lys  Ile Asp Asp
    3500                3505                3510

Ile Trp  Asn Leu Glu Val Lys  Glu Asn Phe Ala Gly  Glu Ala Thr
    3515                3520                3525

Leu Gln  Arg Ile Tyr Ser Leu  Trp Glu His Ser Thr  Lys Asn His
    3530                3535                3540

Leu Gln  Leu Glu Gly Leu Phe  Phe Thr Asn Gly Glu  His Thr Ser
    3545                3550                3555
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Lys Ala  Thr Leu Glu Leu Ser  Pro Trp Gln Met Ser  Ala Leu Val
    3560                 3565                 3570

Gln Val  His Ala Ser Gln Pro  Ser Ser Phe His Asp  Phe Pro Asp
    3575                 3580                 3585

Leu Gly  Gln Glu Val Ala Leu  Asn Ala Asn Thr Lys  Asn Gln Lys
    3590                 3595                 3600

Ile Arg  Trp Lys Asn Glu Val  Arg Ile His Ser Gly  Ser Phe Gln
    3605                 3610                 3615

Ser Gln  Val Glu Leu Ser Asn  Asp Gln Glu Lys Ala  His Leu Asp
    3620                 3625                 3630

Ile Ala  Gly Ser Leu Glu Gly  His Leu Arg Phe Leu  Lys Asn Ile
    3635                 3640                 3645

Ile Leu  Pro Val Tyr Asp Lys  Ser Leu Trp Asp Phe  Leu Lys Leu
    3650                 3655                 3660

Asp Val  Thr Thr Ser Ile Gly  Arg Arg Gln His Leu  Arg Val Ser
    3665                 3670                 3675

Thr Ala  Phe Val Tyr Thr Lys  Asn Pro Asn Gly Tyr  Ser Phe Ser
    3680                 3685                 3690

Ile Pro  Val Lys Val Leu Ala  Asp Lys Phe Ile Thr  Pro Gly Leu
    3695                 3700                 3705

Lys Leu  Asn Asp Leu Asn Ser  Val Leu Val Met Pro  Thr Phe His
    3710                 3715                 3720

Val Pro  Phe Thr Asp Leu Gln  Val Pro Ser Cys Lys  Leu Asp Phe
    3725                 3730                 3735

Arg Glu  Ile Gln Ile Tyr Lys  Lys Leu Arg Thr Ser  Ser Phe Ala
    3740                 3745                 3750

Leu Asn  Leu Pro Thr Leu Pro  Glu Val Lys Phe Pro  Glu Val Asp
    3755                 3760                 3765

Val Leu  Thr Lys Tyr Ser Gln  Pro Glu Asp Ser Leu  Ile Pro Phe
    3770                 3775                 3780

Phe Glu  Ile Thr Val Pro Glu  Ser Gln Leu Thr Val  Ser Gln Phe
    3785                 3790                 3795

Thr Leu  Pro Lys Ser Val Ser  Asp Gly Ile Ala Ala  Leu Asp Leu
    3800                 3805                 3810

Asn Ala  Val Ala Asn Lys Ile  Ala Asp Phe Glu Leu  Pro Thr Ile
    3815                 3820                 3825

Ile Val  Pro Glu Gln Thr Ile  Glu Ile Pro Ser Ile  Lys Phe Ser
    3830                 3835                 3840

Val Pro  Ala Gly Ile Val Ile  Pro Ser Phe Gln Ala  Leu Thr Ala
    3845                 3850                 3855

Arg Phe  Glu Val Asp Ser Pro  Val Tyr Asn Ala Thr  Trp Ser Ala
    3860                 3865                 3870

Ser Leu  Lys Asn Lys Ala Asp  Tyr Val Glu Thr Val  Leu Asp Ser
    3875                 3880                 3885

Thr Cys  Ser Ser Thr Val Gln  Phe Leu Glu Tyr Glu  Leu Asn Val
    3890                 3895                 3900

Leu Gly  Thr His Lys Ile Glu  Asp Gly Thr Leu Ala  Ser Lys Thr
    3905                 3910                 3915

Lys Gly  Thr Leu Ala His Arg  Asp Phe Ser Ala Glu  Tyr Glu Glu
    3920                 3925                 3930

Asp Gly  Lys Phe Glu Gly Leu  Gln Glu Trp Glu Gly  Lys Ala His
    3935                 3940                 3945

Leu Asn  Ile Lys Ser Pro Ala  Phe Thr Asp Leu His  Leu Arg Tyr
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    3950                3955                3960

Gln Lys  Asp Lys Lys Gly Ile  Ser Thr Ser Ala Ala  Ser Pro Ala
    3965                3970                3975

Val Gly  Thr Val Gly Met Asp  Met Asp Glu Asp Asp  Asp Phe Ser
    3980                3985                3990

Lys Trp  Asn Phe Tyr Tyr Ser  Pro Gln Ser Ser Pro  Asp Lys Lys
    3995                4000                4005

Leu Thr  Ile Phe Lys Thr Glu  Leu Arg Val Arg Glu  Ser Asp Glu
    4010                4015                4020

Glu Thr  Gln Ile Lys Val Asn  Trp Glu Glu Glu Ala  Ala Ser Gly
    4025                4030                4035

Leu Leu  Thr Ser Leu Lys Asp  Asn Val Pro Lys Ala  Thr Gly Val
    4040                4045                4050

Leu Tyr  Asp Tyr Val Asn Lys  Tyr His Trp Glu His  Thr Gly Leu
    4055                4060                4065

Thr Leu  Arg Glu Val Ser Ser  Lys Leu Arg Arg Asn  Leu Gln Asn
    4070                4075                4080

Asn Ala  Glu Trp Val Tyr Gln  Gly Ala Ile Arg Gln  Ile Asp Asp
    4085                4090                4095

Ile Asp  Val Arg Phe Gln Lys  Ala Ala Ser Gly Thr  Thr Gly Thr
    4100                4105                4110

Tyr Gln  Glu Trp Lys Asp Lys  Ala Gln Asn Leu Tyr  Gln Glu Leu
    4115                4120                4125

Leu Thr  Gln Glu Gly Gln Ala  Ser Phe Gln Gly Leu  Lys Asp Asn
    4130                4135                4140

Val Phe  Asp Gly Leu Val Arg  Val Thr Gln Lys Phe  His Met Lys
    4145                4150                4155

Val Lys  His Leu Ile Asp Ser  Leu Ile Asp Phe Leu  Asn Phe Pro
    4160                4165                4170

Arg Phe  Gln Phe Pro Gly Lys  Pro Gly Ile Tyr Thr  Arg Glu Glu
    4175                4180                4185

Leu Cys  Thr Met Phe Ile Arg  Glu Val Gly Thr Val  Leu Ser Gln
    4190                4195                4200

Val Tyr  Ser Lys Val His Asn  Gly Ser Glu Ile Leu  Phe Ser Tyr
    4205                4210                4215

Phe Gln  Asp Leu Val Ile Thr  Leu Pro Phe Glu Leu  Arg Lys His
    4220                4225                4230

Lys Leu  Ile Asp Val Ile Ser  Met Tyr Arg Glu Leu  Leu Lys Asp
    4235                4240                4245

Leu Ser  Lys Glu Ala Gln Glu  Val Phe Lys Ala Ile  Gln Ser Leu
    4250                4255                4260

Lys Thr  Thr Glu Val Leu Arg  Asn Leu Gln Asp Leu  Leu Gln Phe
    4265                4270                4275

Ile Phe  Gln Leu Ile Glu Asp  Asn Ile Lys Gln Leu  Lys Glu Met
    4280                4285                4290

Lys Phe  Thr Tyr Leu Ile Asn  Tyr Ile Gln Asp Glu  Ile Asn Thr
    4295                4300                4305

Ile Phe  Asn Asp Tyr Ile Pro  Tyr Val Phe Lys Leu  Leu Lys Glu
    4310                4315                4320

Asn Leu  Cys Leu Asn Leu His  Lys Phe Asn Glu Phe  Ile Gln Asn
    4325                4330                4335

Glu Leu  Gln Glu Ala Ser Gln  Glu Leu Gln Gln Ile  His Gln Tyr
    4340                4345                4350
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Ile Met  Ala Leu Arg Glu Glu  Tyr Phe Asp Pro Ser  Ile Val Gly
    4355                 4360                 4365

Trp Thr  Val Lys Tyr Tyr Glu  Leu Glu Glu Lys Ile  Val Ser Leu
    4370                 4375                 4380

Ile Lys  Asn Leu Leu Val Ala  Leu Lys Asp Phe His  Ser Glu Tyr
    4385                 4390                 4395

Ile Val  Ser Ala Ser Asn Phe  Thr Ser Gln Leu Ser  Ser Gln Val
    4400                 4405                 4410

Glu Gln  Phe Leu His Arg Asn  Ile Gln Glu Tyr Leu  Ser Ile Leu
    4415                 4420                 4425

Thr Asp  Pro Asp Gly Lys Gly  Lys Glu Lys Ile Ala  Glu Leu Ser
    4430                 4435                 4440

Ala Thr  Ala Gln Glu Ile Ile  Lys Ser Gln Ala Ile  Ala Thr Lys
    4445                 4450                 4455

Lys Ile  Ile Ser Asp Tyr His  Gln Gln Phe Arg Tyr  Lys Leu Gln
    4460                 4465                 4470

Asp Phe  Ser Asp Gln Leu Ser  Asp Tyr Tyr Glu Lys  Phe Ile Ala
    4475                 4480                 4485

Glu Ser  Lys Arg Leu Ile Asp  Leu Ser Ile Gln Asn  Tyr His Thr
    4490                 4495                 4500

Phe Leu  Ile Tyr Ile Thr Glu  Leu Leu Lys Lys Leu  Gln Ser Thr
    4505                 4510                 4515

Thr Val  Met Asn Pro Tyr Met  Lys Leu Ala Pro Gly  Glu Leu Thr
    4520                 4525                 4530

Ile Ile  Leu
    4535


<210> SEQ ID NO 33
<211> LENGTH: 2152
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: APO B48 Region 28-2179 of preprotein Acc. No.
      NP_000375.1

<400> SEQUENCE: 33

Glu Glu Glu Met Leu Glu Asn Val Ser Leu Val Cys Pro Lys Asp Ala
1               5                  10                  15

Thr Arg Phe Lys His Leu Arg Lys Tyr Thr Tyr Asn Tyr Glu Ala Glu
            20                  25                  30

Ser Ser Ser Gly Val Pro Gly Thr Ala Asp Ser Arg Ser Ala Thr Arg
        35                  40                  45

Ile Asn Cys Lys Val Glu Leu Glu Val Pro Gln Leu Cys Ser Phe Ile
    50                  55                  60

Leu Lys Thr Ser Gln Cys Thr Leu Lys Glu Val Tyr Gly Phe Asn Pro
65                  70                  75                  80

Glu Gly Lys Ala Leu Leu Lys Lys Thr Lys Asn Ser Glu Glu Phe Ala
                85                  90                  95

Ala Ala Met Ser Arg Tyr Glu Leu Lys Leu Ala Ile Pro Glu Gly Lys
            100                 105                 110

Gln Val Phe Leu Tyr Pro Glu Lys Asp Glu Pro Thr Tyr Ile Leu Asn
        115                 120                 125

Ile Lys Arg Gly Ile Ile Ser Ala Leu Leu Val Pro Pro Glu Thr Glu
    130                 135                 140

Glu Ala Lys Gln Val Leu Phe Leu Asp Thr Val Tyr Gly Asn Cys Ser
145                 150                 155                 160
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Thr His Phe Thr Val Lys Thr Arg Lys Gly Asn Val Ala Thr Glu Ile
                165                 170                 175

Ser Thr Glu Arg Asp Leu Gly Gln Cys Asp Arg Phe Lys Pro Ile Arg
            180                 185                 190

Thr Gly Ile Ser Pro Leu Ala Leu Ile Lys Gly Met Thr Arg Pro Leu
        195                 200                 205

Ser Thr Leu Ile Ser Ser Ser Gln Ser Cys Gln Tyr Thr Leu Asp Ala
    210                 215                 220

Lys Arg Lys His Val Ala Glu Ala Ile Cys Lys Glu Gln His Leu Phe
225                 230                 235                 240

Leu Pro Phe Ser Tyr Asn Asn Lys Tyr Gly Met Val Ala Gln Val Thr
                245                 250                 255

Gln Thr Leu Lys Leu Glu Asp Thr Pro Lys Ile Asn Ser Arg Phe Phe
            260                 265                 270

Gly Glu Gly Thr Lys Lys Met Gly Leu Ala Phe Glu Ser Thr Lys Ser
        275                 280                 285

Thr Ser Pro Pro Lys Gln Ala Glu Ala Val Leu Lys Thr Leu Gln Glu
    290                 295                 300

Leu Lys Lys Leu Thr Ile Ser Glu Gln Asn Ile Gln Arg Ala Asn Leu
305                 310                 315                 320

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

Thr Ser Leu Leu Pro Gln Leu Ile Glu Val Ser Ser Pro Ile Thr Leu
            340                 345                 350

Gln Ala Leu Val Gln Cys Gly Gln Pro Gln Cys Ser Thr His Ile Leu
        355                 360                 365

Gln Trp Leu Lys Arg Val His Ala Asn Pro Leu Leu Ile Asp Val Val
    370                 375                 380

Thr Tyr Leu Val Ala Leu Ile Pro Glu Pro Ser Ala Gln Gln Leu Arg
385                 390                 395                 400

Glu Ile Phe Asn Met Ala Arg Asp Gln Arg Ser Arg Ala Thr Leu Tyr
                405                 410                 415

Ala Leu Ser His Ala Val Asn Asn Tyr His Lys Thr Asn Pro Thr Gly
            420                 425                 430

Thr Gln Glu Leu Leu Asp Ile Ala Asn Tyr Leu Met Glu Gln Ile Gln
        435                 440                 445

Asp Asp Cys Thr Gly Asp Glu Asp Tyr Thr Tyr Leu Ile Leu Arg Val
    450                 455                 460

Ile Gly Asn Met Gly Gln Thr Met Glu Gln Leu Thr Pro Glu Leu Lys
465                 470                 475                 480

Ser Ser Ile Leu Lys Cys Val Gln Ser Thr Lys Pro Ser Leu Met Ile
                485                 490                 495

Gln Lys Ala Ala Ile Gln Ala Leu Arg Lys Met Glu Pro Lys Asp Lys
            500                 505                 510

Asp Gln Glu Val Leu Leu Gln Thr Phe Leu Asp Asp Ala Ser Pro Gly
        515                 520                 525

Asp Lys Arg Leu Ala Ala Tyr Leu Met Leu Met Arg Ser Pro Ser Gln
    530                 535                 540

Ala Asp Ile Asn Lys Ile Val Gln Ile Leu Pro Trp Glu Gln Asn Glu
545                 550                 555                 560

Gln Val Lys Asn Phe Val Ala Ser His Ile Ala Asn Ile Leu Asn Ser
                565                 570                 575

Glu Glu Leu Asp Ile Gln Asp Leu Lys Lys Leu Val Lys Glu Ala Leu
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            580                 585                 590

Lys Glu Ser Gln Leu Pro Thr Val Met Asp Phe Arg Lys Phe Ser Arg
        595                 600                 605

Asn Tyr Gln Leu Tyr Lys Ser Val Ser Leu Pro Ser Leu Asp Pro Ala
    610                 615                 620

Ser Ala Lys Ile Glu Gly Asn Leu Ile Phe Asp Pro Asn Asn Tyr Leu
625                 630                 635                 640

Pro Lys Glu Ser Met Leu Lys Thr Thr Leu Thr Ala Phe Gly Phe Ala
                645                 650                 655

Ser Ala Asp Leu Ile Glu Ile Gly Leu Glu Gly Lys Gly Phe Glu Pro
            660                 665                 670

Thr Leu Glu Ala Leu Phe Gly Lys Gln Gly Phe Phe Pro Asp Ser Val
        675                 680                 685

Asn Lys Ala Leu Tyr Trp Val Asn Gly Gln Val Pro Asp Gly Val Ser
    690                 695                 700

Lys Val Leu Val Asp His Phe Gly Tyr Thr Lys Asp Asp Lys His Glu
705                 710                 715                 720

Gln Asp Met Val Asn Gly Ile Met Leu Ser Val Glu Lys Leu Ile Lys
                725                 730                 735

Asp Leu Lys Ser Lys Glu Val Pro Glu Ala Arg Ala Tyr Leu Arg Ile
            740                 745                 750

Leu Gly Glu Glu Leu Gly Phe Ala Ser Leu His Asp Leu Gln Leu Leu
        755                 760                 765

Gly Lys Leu Leu Leu Met Gly Ala Arg Thr Leu Gln Gly Ile Pro Gln
    770                 775                 780

Met Ile Gly Glu Val Ile Arg Lys Gly Ser Lys Asn Asp Phe Phe Leu
785                 790                 795                 800

His Tyr Ile Phe Met Glu Asn Ala Phe Glu Leu Pro Thr Gly Ala Gly
                805                 810                 815

Leu Gln Leu Gln Ile Ser Ser Ser Gly Val Ile Ala Pro Gly Ala Lys
            820                 825                 830

Ala Gly Val Lys Leu Glu Val Ala Asn Met Gln Ala Glu Leu Val Ala
        835                 840                 845

Lys Pro Ser Val Ser Val Glu Phe Val Thr Asn Met Gly Ile Ile Ile
    850                 855                 860

Pro Asp Phe Ala Arg Ser Gly Val Gln Met Asn Thr Asn Phe Phe His
865                 870                 875                 880

Glu Ser Gly Leu Glu Ala His Val Ala Leu Lys Ala Gly Lys Leu Lys
                885                 890                 895

Phe Ile Ile Pro Ser Pro Lys Arg Pro Val Lys Leu Leu Ser Gly Gly
            900                 905                 910

Asn Thr Leu His Leu Val Ser Thr Thr Lys Thr Glu Val Ile Pro Pro
        915                 920                 925

Leu Ile Glu Asn Arg Gln Ser Trp Ser Val Cys Lys Gln Val Phe Pro
    930                 935                 940

Gly Leu Asn Tyr Cys Thr Ser Gly Ala Tyr Ser Asn Ala Ser Ser Thr
945                 950                 955                 960

Asp Ser Ala Ser Tyr Tyr Pro Leu Thr Gly Asp Thr Arg Leu Glu Leu
                965                 970                 975

Glu Leu Arg Pro Thr Gly Glu Ile Glu Gln Tyr Ser Val Ser Ala Thr
            980                 985                 990

Tyr Glu Leu Gln Arg Glu Asp Arg  Ala Leu Val Asp Thr  Leu Lys Phe
        995                 1000                1005
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Val Thr  Gln Ala Glu Gly Ala  Lys Gln Thr Glu Ala  Thr Met Thr
    1010                1015                1020

Phe Lys  Tyr Asn Arg Gln Ser  Met Thr Leu Ser Ser  Glu Val Gln
    1025                1030                1035

Ile Pro  Asp Phe Asp Val Asp  Leu Gly Thr Ile Leu  Arg Val Asn
    1040                1045                1050

Asp Glu  Ser Thr Glu Gly Lys  Thr Ser Tyr Arg Leu  Thr Leu Asp
    1055                1060                1065

Ile Gln  Asn Lys Lys Ile Thr  Glu Val Ala Leu Met  Gly His Leu
    1070                1075                1080

Ser Cys  Asp Thr Lys Glu Glu  Arg Lys Ile Lys Gly  Val Ile Ser
    1085                1090                1095

Ile Pro  Arg Leu Gln Ala Glu  Ala Arg Ser Glu Ile  Leu Ala His
    1100                1105                1110

Trp Ser  Pro Ala Lys Leu Leu  Leu Gln Met Asp Ser  Ser Ala Thr
    1115                1120                1125

Ala Tyr  Gly Ser Thr Val Ser  Lys Arg Val Ala Trp  His Tyr Asp
    1130                1135                1140

Glu Glu  Lys Ile Glu Phe Glu  Trp Asn Thr Gly Thr  Asn Val Asp
    1145                1150                1155

Thr Lys  Lys Met Thr Ser Asn  Phe Pro Val Asp Leu  Ser Asp Tyr
    1160                1165                1170

Pro Lys  Ser Leu His Met Tyr  Ala Asn Arg Leu Leu  Asp His Arg
    1175                1180                1185

Val Pro  Glu Thr Asp Met Thr  Phe Arg His Val Gly  Ser Lys Leu
    1190                1195                1200

Ile Val  Ala Met Ser Ser Trp  Leu Gln Lys Ala Ser  Gly Ser Leu
    1205                1210                1215

Pro Tyr  Thr Gln Thr Leu Gln  Asp His Leu Asn Ser  Leu Lys Glu
    1220                1225                1230

Phe Asn  Leu Gln Asn Met Gly  Leu Pro Asp Phe His  Ile Pro Glu
    1235                1240                1245

Asn Leu  Phe Leu Lys Ser Asp  Gly Arg Val Lys Tyr  Thr Leu Asn
    1250                1255                1260

Lys Asn  Ser Leu Lys Ile Glu  Ile Pro Leu Pro Phe  Gly Gly Lys
    1265                1270                1275

Ser Ser  Arg Asp Leu Lys Met  Leu Glu Thr Val Arg  Thr Pro Ala
    1280                1285                1290

Leu His  Phe Lys Ser Val Gly  Phe His Leu Pro Ser  Arg Glu Phe
    1295                1300                1305

Gln Val  Pro Thr Phe Thr Ile  Pro Lys Leu Tyr Gln  Leu Gln Val
    1310                1315                1320

Pro Leu  Leu Gly Val Leu Asp  Leu Ser Thr Asn Val  Tyr Ser Asn
    1325                1330                1335

Leu Tyr  Asn Trp Ser Ala Ser  Tyr Ser Gly Gly Asn  Thr Ser Thr
    1340                1345                1350

Asp His  Phe Ser Leu Arg Ala  Arg Tyr His Met Lys  Ala Asp Ser
    1355                1360                1365

Val Val  Asp Leu Leu Ser Tyr  Asn Val Gln Gly Ser  Gly Glu Thr
    1370                1375                1380

Thr Tyr  Asp His Lys Asn Thr  Phe Thr Leu Ser Cys  Asp Gly Ser
    1385                1390                1395

Leu Arg  His Lys Phe Leu Asp  Ser Asn Ile Lys Phe  Ser His Val
    1400                1405                1410
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Glu Lys  Leu Gly Asn Asn Pro  Val Ser Lys Gly Leu  Leu Ile Phe
    1415                1420                1425

Asp Ala  Ser Ser Ser Trp Gly  Pro Gln Met Ser Ala  Ser Val His
    1430                1435                1440

Leu Asp  Ser Lys Lys Lys Gln  His Leu Phe Val Lys  Glu Val Lys
    1445                1450                1455

Ile Asp  Gly Gln Phe Arg Val  Ser Ser Phe Tyr Ala  Lys Gly Thr
    1460                1465                1470

Tyr Gly  Leu Ser Cys Gln Arg  Asp Pro Asn Thr Gly  Arg Leu Asn
    1475                1480                1485

Gly Glu  Ser Asn Leu Arg Phe  Asn Ser Ser Tyr Leu  Gln Gly Thr
    1490                1495                1500

Asn Gln  Ile Thr Gly Arg Tyr  Glu Asp Gly Thr Leu  Ser Leu Thr
    1505                1510                1515

Ser Thr  Ser Asp Leu Gln Ser  Gly Ile Ile Lys Asn  Thr Ala Ser
    1520                1525                1530

Leu Lys  Tyr Glu Asn Tyr Glu  Leu Thr Leu Lys Ser  Asp Thr Asn
    1535                1540                1545

Gly Lys  Tyr Lys Asn Phe Ala  Thr Ser Asn Lys Met  Asp Met Thr
    1550                1555                1560

Phe Ser  Lys Gln Asn Ala Leu  Leu Arg Ser Glu Tyr  Gln Ala Asp
    1565                1570                1575

Tyr Glu  Ser Leu Arg Phe Phe  Ser Leu Leu Ser Gly  Ser Leu Asn
    1580                1585                1590

Ser His  Gly Leu Glu Leu Asn  Ala Asp Ile Leu Gly  Thr Asp Lys
    1595                1600                1605

Ile Asn  Ser Gly Ala His Lys  Ala Thr Leu Arg Ile  Gly Gln Asp
    1610                1615                1620

Gly Ile  Ser Thr Ser Ala Thr  Thr Asn Leu Lys Cys  Ser Leu Leu
    1625                1630                1635

Val Leu  Glu Asn Glu Leu Asn  Ala Glu Leu Gly Leu  Ser Gly Ala
    1640                1645                1650

Ser Met  Lys Leu Thr Thr Asn  Gly Arg Phe Arg Glu  His Asn Ala
    1655                1660                1665

Lys Phe  Ser Leu Asp Gly Lys  Ala Ala Leu Thr Glu  Leu Ser Leu
    1670                1675                1680

Gly Ser  Ala Tyr Gln Ala Met  Ile Leu Gly Val Asp  Ser Lys Asn
    1685                1690                1695

Ile Phe  Asn Phe Lys Val Ser  Gln Glu Gly Leu Lys  Leu Ser Asn
    1700                1705                1710

Asp Met  Met Gly Ser Tyr Ala  Glu Met Lys Phe Asp  His Thr Asn
    1715                1720                1725

Ser Leu  Asn Ile Ala Gly Leu  Ser Leu Asp Phe Ser  Ser Lys Leu
    1730                1735                1740

Asp Asn  Ile Tyr Ser Ser Asp  Lys Phe Tyr Lys Gln  Thr Val Asn
    1745                1750                1755

Leu Gln  Leu Gln Pro Tyr Ser  Leu Val Thr Thr Leu  Asn Ser Asp
    1760                1765                1770

Leu Lys  Tyr Asn Ala Leu Asp  Leu Thr Asn Asn Gly  Lys Leu Arg
    1775                1780                1785

Leu Glu  Pro Leu Lys Leu His  Val Ala Gly Asn Leu  Lys Gly Ala
    1790                1795                1800

Tyr Gln  Asn Asn Glu Ile Lys  His Ile Tyr Ala Ile  Ser Ser Ala
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    1805                1810                1815

Ala Leu  Ser Ala Ser Tyr Lys  Ala Asp Thr Val Ala  Lys Val Gln
    1820                1825                1830

Gly Val  Glu Phe Ser His Arg  Leu Asn Thr Asp Ile  Ala Gly Leu
    1835                1840                1845

Ala Ser  Ala Ile Asp Met Ser  Thr Asn Tyr Asn Ser  Asp Ser Leu
    1850                1855                1860

His Phe  Ser Asn Val Phe Arg  Ser Val Met Ala Pro  Phe Thr Met
    1865                1870                1875

Thr Ile  Asp Ala His Thr Asn  Gly Asn Gly Lys Leu  Ala Leu Trp
    1880                1885                1890

Gly Glu  His Thr Gly Gln Leu  Tyr Ser Lys Phe Leu  Leu Lys Ala
    1895                1900                1905

Glu Pro  Leu Ala Phe Thr Phe  Ser His Asp Tyr Lys  Gly Ser Thr
    1910                1915                1920

Ser His  His Leu Val Ser Arg  Lys Ser Ile Ser Ala  Ala Leu Glu
    1925                1930                1935

His Lys  Val Ser Ala Leu Leu  Thr Pro Ala Glu Gln  Thr Gly Thr
    1940                1945                1950

Trp Lys  Leu Lys Thr Gln Phe  Asn Asn Asn Glu Tyr  Ser Gln Asp
    1955                1960                1965

Leu Asp  Ala Tyr Asn Thr Lys  Asp Lys Ile Gly Val  Glu Leu Thr
    1970                1975                1980

Gly Arg  Thr Leu Ala Asp Leu  Thr Leu Leu Asp Ser  Pro Ile Lys
    1985                1990                1995

Val Pro  Leu Leu Leu Ser Glu  Pro Ile Asn Ile Ile  Asp Ala Leu
    2000                2005                2010

Glu Met  Arg Asp Ala Val Glu  Lys Pro Gln Glu Phe  Thr Ile Val
    2015                2020                2025

Ala Phe  Val Lys Tyr Asp Lys  Asn Gln Asp Val His  Ser Ile Asn
    2030                2035                2040

Leu Pro  Phe Phe Glu Thr Leu  Gln Glu Tyr Phe Glu  Arg Asn Arg
    2045                2050                2055

Gln Thr  Ile Ile Val Val Val  Glu Asn Val Gln Arg  Asn Leu Lys
    2060                2065                2070

His Ile  Asn Ile Asp Gln Phe  Val Arg Lys Tyr Arg  Ala Ala Leu
    2075                2080                2085

Gly Lys  Leu Pro Gln Gln Ala  Asn Asp Tyr Leu Asn  Ser Phe Asn
    2090                2095                2100

Trp Glu  Arg Gln Val Ser His  Ala Lys Glu Lys Leu  Thr Ala Leu
    2105                2110                2115

Thr Lys  Lys Tyr Arg Ile Thr  Glu Asn Asp Ile Gln  Ile Ala Leu
    2120                2125                2130

Asp Asp  Ala Lys Ile Asn Phe  Asn Glu Lys Leu Ser  Gln Leu Gln
    2135                2140                2145

Thr Tyr  Met Ile
    2150


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<211> LENGTH: 679
<212> TYPE: PRT
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<220> FEATURE:
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      No. NP_001054.1
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Val Pro Asp Lys Thr Val Arg Trp Cys Ala Val Ser Glu His Glu Ala
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Thr Lys Cys Gln Ser Phe Arg Asp His Met Lys Ser Val Ile Pro Ser
            20                  25                  30

Asp Gly Pro Ser Val Ala Cys Val Lys Lys Ala Ser Tyr Leu Asp Cys
        35                  40                  45

Ile Arg Ala Ile Ala Ala Asn Glu Ala Asp Ala Val Thr Leu Asp Ala
    50                  55                  60

Gly Leu Val Tyr Asp Ala Tyr Leu Ala Pro Asn Asn Leu Lys Pro Val
65                  70                  75                  80

Val Ala Glu Phe Tyr Gly Ser Lys Glu Asp Pro Gln Thr Phe Tyr Tyr
                85                  90                  95

Ala Val Ala Val Val Lys Lys Asp Ser Gly Phe Gln Met Asn Gln Leu
            100                 105                 110

Arg Gly Lys Lys Ser Cys His Thr Gly Leu Gly Arg Ser Ala Gly Trp
        115                 120                 125

Asn Ile Pro Ile Gly Leu Leu Tyr Cys Asp Leu Pro Glu Pro Arg Lys
    130                 135                 140

Pro Leu Glu Lys Ala Val Ala Asn Phe Phe Ser Gly Ser Cys Ala Pro
145                 150                 155                 160

Cys Ala Asp Gly Thr Asp Phe Pro Gln Leu Cys Gln Leu Cys Pro Gly
                165                 170                 175

Cys Gly Cys Ser Thr Leu Asn Gln Tyr Phe Gly Tyr Ser Gly Ala Phe
            180                 185                 190

Lys Cys Leu Lys Asp Gly Ala Gly Asp Val Ala Phe Val Lys His Ser
        195                 200                 205

Thr Ile Phe Glu Asn Leu Ala Asn Lys Ala Asp Arg Asp Gln Tyr Glu
    210                 215                 220

Leu Leu Cys Leu Asp Asn Thr Arg Lys Pro Val Asp Glu Tyr Lys Asp
225                 230                 235                 240

Cys His Leu Ala Gln Val Pro Ser His Thr Val Val Ala Arg Ser Met
                245                 250                 255

Gly Gly Lys Glu Asp Leu Ile Trp Glu Leu Leu Asn Gln Ala Gln Glu
            260                 265                 270

His Phe Gly Lys Asp Lys Ser Lys Glu Phe Gln Leu Phe Ser Ser Pro
        275                 280                 285

His Gly Lys Asp Leu Leu Phe Lys Asp Ser Ala His Gly Phe Leu Lys
    290                 295                 300

Val Pro Pro Arg Met Asp Ala Lys Met Tyr Leu Gly Tyr Glu Tyr Val
305                 310                 315                 320

Thr Ala Ile Arg Asn Leu Arg Glu Gly Thr Cys Pro Glu Ala Pro Thr
                325                 330                 335

Asp Glu Cys Lys Pro Val Lys Trp Cys Ala Leu Ser His His Glu Arg
            340                 345                 350

Leu Lys Cys Asp Glu Trp Ser Val Asn Ser Val Gly Lys Ile Glu Cys
        355                 360                 365

Val Ser Ala Glu Thr Thr Glu Asp Cys Ile Ala Lys Ile Met Asn Gly
    370                 375                 380

Glu Ala Asp Ala Met Ser Leu Asp Gly Gly Phe Val Tyr Ile Ala Gly
385                 390                 395                 400

Lys Cys Gly Leu Val Pro Val Leu Ala Glu Asn Tyr Asn Lys Ser Asp
                405                 410                 415
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Asn Cys Glu Asp Thr Pro Glu Ala Gly Tyr Phe Ala Val Ala Val Val
            420                 425                 430

Lys Lys Ser Ala Ser Asp Leu Thr Trp Asp Asn Leu Lys Gly Lys Lys
        435                 440                 445

Ser Cys His Thr Ala Val Gly Arg Thr Ala Gly Trp Asn Ile Pro Met
    450                 455                 460

Gly Leu Leu Tyr Asn Lys Ile Asn His Cys Arg Phe Asp Glu Phe Phe
465                 470                 475                 480

Ser Glu Gly Cys Ala Pro Gly Ser Lys Lys Asp Ser Ser Leu Cys Lys
                485                 490                 495

Leu Cys Met Gly Ser Gly Leu Asn Leu Cys Glu Pro Asn Asn Lys Glu
            500                 505                 510

Gly Tyr Tyr Gly Tyr Thr Gly Ala Phe Arg Cys Leu Val Glu Lys Gly
        515                 520                 525

Asp Val Ala Phe Val Lys His Gln Thr Val Pro Gln Asn Thr Gly Gly
    530                 535                 540

Lys Asn Pro Asp Pro Trp Ala Lys Asn Leu Asn Glu Lys Asp Tyr Glu
545                 550                 555                 560

Leu Leu Cys Leu Asp Gly Thr Arg Lys Pro Val Glu Glu Tyr Ala Asn
                565                 570                 575

Cys His Leu Ala Arg Ala Pro Asn His Ala Val Val Thr Arg Lys Asp
            580                 585                 590

Lys Glu Ala Cys Val His Lys Ile Leu Arg Gln Gln Gln His Leu Phe
        595                 600                 605

Gly Ser Asn Val Thr Asp Cys Ser Gly Asn Phe Cys Leu Phe Arg Ser
    610                 615                 620

Glu Thr Lys Asp Leu Leu Phe Arg Asp Asp Thr Val Cys Leu Ala Lys
625                 630                 635                 640

Leu His Asp Arg Asn Thr Tyr Glu Lys Tyr Leu Gly Glu Glu Tyr Val
                645                 650                 655

Lys Ala Val Gly Asn Leu Arg Lys Cys Ser Thr Ser Ser Leu Leu Glu
            660                 665                 670

Ala Cys Thr Phe Arg Arg Pro
        675


<210> SEQ ID NO 35
<211> LENGTH: 544
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: IhHG1 Acc. No. AAH19046

<400> SEQUENCE: 35

Met Glu Phe Gly Leu Ser Trp Val Phe Leu Val Ala Leu Leu Arg Gly
1               5                   10                  15

Val Gln Cys Gln Ala Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln
            20                  25                  30

Pro Gly Ser Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Arg Phe
        35                  40                  45

Ser Asn Tyr Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu
    50                  55                  60

Glu Trp Val Ala Val Phe Ser Tyr Asp Glu Ser Asp Lys Tyr Tyr Ala
65                  70                  75                  80

Ala Ser Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn
                85                  90                  95
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Thr Leu Ser Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Val
            100                 105                 110

Tyr Tyr Cys Ala Lys Asp Gln Lys Pro Trp Tyr Ser Asn Ser Trp Phe
        115                 120                 125

Leu Thr Asn Phe Asp Ser Trp Gly Arg Gly Thr Leu Val Thr Val Ser
    130                 135                 140

Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser
145                 150                 155                 160

Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp
                165                 170                 175

Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr
            180                 185                 190

Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr
        195                 200                 205

Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln
    210                 215                 220

Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp
225                 230                 235                 240

Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro
                245                 250                 255

Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro
            260                 265                 270

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
        275                 280                 285

Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn
    290                 295                 300

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
305                 310                 315                 320

Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
                325                 330                 335

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
            340                 345                 350

Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys
        355                 360                 365

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp
    370                 375                 380

Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
385                 390                 395                 400

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
                405                 410                 415

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
            420                 425                 430

Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly
        435                 440                 445

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
    450                 455                 460

Thr Gln Lys Ser Leu Ser Leu Ser Pro Glu Leu Gln Leu Glu Glu Ser
465                 470                 475                 480

Cys Ala Glu Ala Gln Asp Gly Glu Leu Asp Gly Leu Trp Thr Thr Ile
                485                 490                 495

Thr Ile Phe Ile Thr Leu Phe Leu Leu Ser Val Cys Tyr Ser Ala Thr
            500                 505                 510

Val Thr Phe Phe Lys Val Lys Trp Ile Phe Ser Ser Val Val Asp Leu
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        515                 520                 525

Lys Gln Thr Ile Ile Pro Asp Tyr Arg Asn Met Ile Gly Gln Gly Ala
    530                 535                 540


<210> SEQ ID NO 36
<211> LENGTH: 406
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<223> OTHER INFORMATION: Haptoglobin Acc. No. NP_005134.1

<400> SEQUENCE: 36

Met Ser Ala Leu Gly Ala Val Ile Ala Leu Leu Leu Trp Gly Gln Leu
1               5                   10                  15

Phe Ala Val Asp Ser Gly Asn Asp Val Thr Asp Ile Ala Asp Asp Gly
            20                  25                  30

Cys Pro Lys Pro Pro Glu Ile Ala His Gly Tyr Val Glu His Ser Val
        35                  40                  45

Arg Tyr Gln Cys Lys Asn Tyr Tyr Lys Leu Arg Thr Glu Gly Asp Gly
    50                  55                  60

Val Tyr Thr Leu Asn Asp Lys Lys Gln Trp Ile Asn Lys Ala Val Gly
65                  70                  75                  80

Asp Lys Leu Pro Glu Cys Glu Ala Asp Asp Gly Cys Pro Lys Pro Pro
                85                  90                  95

Glu Ile Ala His Gly Tyr Val Glu His Ser Val Arg Tyr Gln Cys Lys
            100                 105                 110

Asn Tyr Tyr Lys Leu Arg Thr Glu Gly Asp Gly Val Tyr Thr Leu Asn
        115                 120                 125

Asn Glu Lys Gln Trp Ile Asn Lys Ala Val Gly Asp Lys Leu Pro Glu
    130                 135                 140

Cys Glu Ala Val Cys Gly Lys Pro Lys Asn Pro Ala Asn Pro Val Gln
145                 150                 155                 160

Arg Ile Leu Gly Gly His Leu Asp Ala Lys Gly Ser Phe Pro Trp Gln
                165                 170                 175

Ala Lys Met Val Ser His His Asn Leu Thr Thr Gly Ala Thr Leu Ile
            180                 185                 190

Asn Glu Gln Trp Leu Leu Thr Thr Ala Lys Asn Leu Phe Leu Asn His
        195                 200                 205

Ser Glu Asn Ala Thr Ala Lys Asp Ile Ala Pro Thr Leu Thr Leu Tyr
    210                 215                 220

Val Gly Lys Lys Gln Leu Val Glu Ile Glu Lys Val Val Leu His Pro
225                 230                 235                 240

Asn Tyr Ser Gln Val Asp Ile Gly Leu Ile Lys Leu Lys Gln Lys Val
                245                 250                 255

Ser Val Asn Glu Arg Val Met Pro Ile Cys Leu Pro Ser Lys Asp Tyr
            260                 265                 270

Ala Glu Val Gly Arg Val Gly Tyr Val Ser Gly Trp Gly Arg Asn Ala
        275                 280                 285

Asn Phe Lys Phe Thr Asp His Leu Lys Tyr Val Met Leu Pro Val Ala
    290                 295                 300

Asp Gln Asp Gln Cys Ile Arg His Tyr Glu Gly Ser Thr Val Pro Glu
305                 310                 315                 320

Lys Lys Thr Pro Lys Ser Pro Val Gly Val Gln Pro Ile Leu Asn Glu
                325                 330                 335

His Thr Phe Cys Ala Gly Met Ser Lys Tyr Gln Glu Asp Thr Cys Tyr
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-continued

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            340                 345                 350

Gly Asp Ala Gly Ser Ala Phe Ala Val His Asp Leu Glu Glu Asp Thr
        355                 360                 365

Trp Tyr Ala Thr Gly Ile Leu Ser Phe Asp Lys Ser Cys Ala Val Ala
    370                 375                 380

Glu Tyr Gly Val Tyr Val Lys Val Thr Ser Ile Gln Asp Trp Val Gln
385                 390                 395                 400

Lys Thr Ile Ala Glu Asn
                405


<210> SEQ ID NO 37
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

Glu Lys Leu His Glu Leu Gln Glu Lys
1               5


<210> SEQ ID NO 38
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

Gln Lys Leu His Glu Leu Glu Glu Lys
1               5


<210> SEQ ID NO 39
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

Glu Lys Leu His Glu Leu Glu Glu Lys
1               5


<210> SEQ ID NO 40
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa is pyroglutamate

<400> SEQUENCE: 40

Gln Lys Leu His Xaa Leu Gln Glu Lys
1               5


<210> SEQ ID NO 41
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa is pyroglutamate

<400> SEQUENCE: 41

Glu Lys Leu His Xaa Leu Gln Glu Lys
1               5


<210> SEQ ID NO 42
<211> LENGTH: 9
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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa is pyroglutamate

<400> SEQUENCE: 42

Gln Lys Leu His Xaa Leu Glu Glu Lys
1 5

<210> SEQ ID NO 43
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa is pyroglutamate

<400> SEQUENCE: 43

Glu Lys Leu His Xaa Leu Glu Glu Lys
1 5

<210> SEQ ID NO 44
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

Leu Glu Ala Leu Lys Glu Asp Gly Gly Ala Arg
1 5 10

<210> SEQ ID NO 45
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

Val Glu Pro Tyr Leu Asp Asp Phe Gln Lys Lys
1 5 10

<210> SEQ ID NO 46
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

Val Gln Pro Tyr Leu Asp Asp Phe Glu Lys Lys
1 5 10

<210> SEQ ID NO 47
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

Val Glu Pro Tyr Leu Asp Asp Phe Glu Lys Lys
1 5 10

The invention claimed is:

1. A method of monitoring the glycemic control of a host, comprising

(a) measuring the concentration of a glycated peptide in the host or in a sample from the host, wherein the glycated peptide comprises (i) at least one of Peptides AA-DJ of Table 1 or (ii) an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-36, and

(b) comparing the measured concentration to a control to determine whether the measured concentration in the host or sample from the host differs from the control.

2. The method of claim 1, further comprising detecting a change in the concentration of the glycated peptide, or glycated fragment or glycated variant thereof.

3. The method of claim 1, further comprising comparing the concentration of the glycated peptide, or glycated fragment or glycated variant thereof, to a control.

4. The method of claim 1, wherein the concentration of the glycated peptide, or glycated fragment or glycated variant thereof, is the relative concentration of the glycated peptide, or glycated fragment or glycated variant thereof, as compared to the total concentration of both the glycated and non-glycated forms of the corresponding peptide; fragment, or variant.

5. The method of claim 1, wherein the glycated fragment comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1-23.

6. The method of claim 1, wherein the glycated variant comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 37-47.

7. The method of claim 1, comprising measuring the concentration of five or more different glycated peptides, or glycated fragments or glycated variants thereof, each of which comprises (i) at least one of Peptides AA-DJ of Table 1 or (ii) an amino acid sequence selected from the group consisting of SEQ ID NOs: 24-36.

8. The method of claim 1, wherein measuring the concentration, of the glycated peptide, or glycated fragment or glycated variant thereof, comprises contacting a sample from the host with an antibody, or conjugate comprising an antibody, that specifically binds to the glycated peptide or the glycated fragment or glycated variant thereof.

9. The method of claim 1, wherein measuring the concentration of the glycated peptide, or glycated fragment or glycated-variant thereof, comprises contacting a sample from the host with an aptamer, or conjugate comprising an aptamer, that specifically binds to the glycated peptide, or the glycated fragment or glycated variant thereof.

10. The method of claim 1, wherein the concentration of the glycated peptide, or glycated fragment or variant thereof, is measured in a sample of blood, blood plasma, or blood serum from the host.

11. The method of claim 1, further comprising measuring glycated hemoglobin A1C in the host.

12. The method of claim 1, further comprising measuring a blood glucose level of the host.

13. The method of claim 1, wherein the method is used to prevent a complication of diabetes, detect the onset, progression, or regression of diabetes, or determine the efficacy of a diabetes treatment.

14. The method of claim 1, wherein the method is used to detect diabetes or a predisposition to diabetes in the host, the method further comprising detecting an elevated concentration of the glycated peptide, or glycated fragment or glycated variant thereof, as compared to a control, wherein an elevation in the concentration of the glycated peptide, fragment, or variant as compared to a control is indicative of diabetes or a predisposition of diabetes in the host.

* * * * *

专利名称(译)	糖化肽和使用方法		
公开(公告)号	US8309313	公开(公告)日	2012-11-13
申请号	US12/281909	申请日	2007-03-06
[标]申请(专利权)人(译)	美国卫生及公共服务部 与人类服务部		
申请(专利权)人(译)	美利坚合众国为代表局局长，卫生署 与人类服务部		
当前申请(专利权)人(译)	美利坚合众国为代表局局长，卫生署及人性化的服务		
[标]发明人	BLACKSHEAR PERRY J		
发明人	BLACKSHEAR, PERRY J.		
IPC分类号	G01N33/53 G01N31/00		
CPC分类号	C07K9/001 C07K14/47 C07K14/75 C07K14/775 C07K14/79 C07K14/8107 C07K14/8121 G01N33/6893 G01N2400/00 G01N2800/042 G01N2800/52		
审查员(译)	COOK，LISA		
优先权	60/779710 2006-03-06 US		
其他公开文献	US20090093066A1		
外部链接	Espacenet USPTO		

摘要(译)

本发明提供糖化肽和糖化片段及其糖化变体，与其结合的抗体和适体，包含相同缀合物的组合物和试剂盒，以及包含指示糖尿病和非糖尿病人中存在的糖化肽浓度的数据的数据库。本发明还提供监测血糖控制的方法，治疗或预防糖尿病的方法，预防糖尿病并发症的方法，监测糖尿病状态的方法，以及确定糖尿病治疗功效的方法，以及作为检测糖尿病或其易感性的方法。

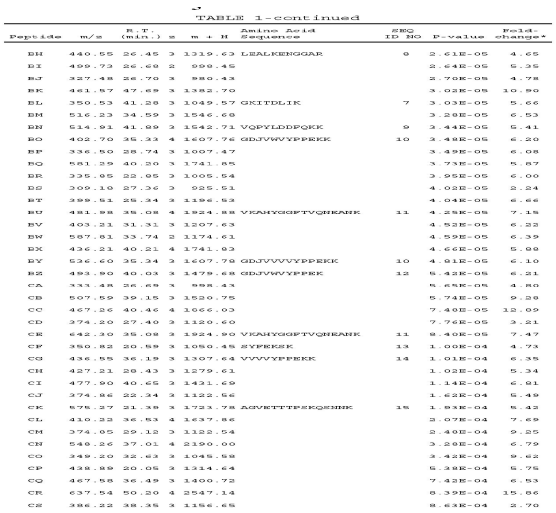

TABLE 1-continued

Peptide	m/z	R.T. (min.)	s	m + H	Amino Acid Sequence	SEQ ID NO	P-value	Fold-change*
BH	440.55	26.45	3	1319.63	LEALKENGGAR	9	2.61E-05	4.65
BI	499.73	26.69	2	999.45			2.64E-05	5.35
BJ	327.48	26.70	3	980.43			2.70E-05	4.78
BK	461.57	47.69	3	1382.70			3.02E-05	10.80
BL	350.53	41.28	3	1049.57	GKITDLIK	7	3.03E-05	5.66
BM	516.23	34.59	3	1546.68			3.20E-05	6.53
BN	514.91	41.99	3	1542.71	VQPYLDDPQKK	9	3.44E-05	5.41
BO	402.70	35.33	4	1607.78	GDJVWVYPPEKK	10	3.49E-05	6.20
BP	336.50	28.74	3	1007.47			3.49E-05	6.08
BQ	581.39	40.30	3	1741.85			3.73E-05	5.87
BR	335.95	22.05	3	1005.54			3.95E-05	6.00
BS	309.10	27.26	3	925.51			4.02E-05	2.24
BT	399.51	25.34	3	1196.53			4.04E-05	6.46
BU	481.98	38.08	4	1924.88	VKAHYGGPTVQNKANK	11	4.29E-05	7.15
BV	403.31	31.31	3	1207.63			4.52E-05	6.23
BW	587.61	33.74	2	1174.61			4.59E-05	6.39
BX	436.23	40.21	4	1741.93			4.62E-05	5.06
BY	536.60	35.34	3	1607.79	GDJVVVYPPEKK	10	4.81E-05	6.10
BZ	493.90	40.03	3	1479.68	GDJVWVYPPEK	12	5.42E-05	6.21
CA	333.48	26.69	3	998.43			5.65E-05	4.80
CB	507.59	39.15	3	1520.75			5.74E-05	9.20
CC	467.26	40.46	4	1866.03			7.40E-05	12.09
CD	374.20	27.40	3	1120.60			7.76E-05	3.21
CE	642.30	38.08	3	1924.90	VKAHYGGPTVQNKANK	11	8.40E-05	7.47
CF	350.82	20.59	3	1050.45	EVPKKEK	13	1.00E-04	4.73
CG	436.55	36.19	3	1307.64	VVVVYPPEKK	14	1.01E-04	6.35
CH	427.21	28.43	3	1279.61			1.02E-04	5.34
CI	477.90	40.65	3	1431.69			1.14E-04	6.91
CJ	374.86	22.34	3	1122.56			1.62E-04	5.49
CK	575.27	31.38	3	1723.78	AGVETTTPSEQSHNK	15	1.93E-04	5.42
CL	410.33	36.53	4	1637.86			3.07E-04	7.69
CM	374.05	29.12	3	1122.54			2.40E-04	9.25
CN	540.26	37.01	4	2190.00			3.20E-04	6.79
CO	349.20	32.63	3	1045.58			3.42E-04	9.62
CP	438.89	20.05	3	1314.64			5.38E-04	5.75
CQ	467.58	36.49	3	1400.73			7.42E-04	6.53
CR	637.54	50.30	4	2547.14			8.39E-04	15.86
CS	386.22	38.35	3	1156.65			8.63E-04	2.70