

**(12) STANDARD PATENT
(19) AUSTRALIAN PATENT OFFICE**

(11) Application No. AU 2009238550 B2

(54) Title
Neutralizing proprotein convertase subtilisin kexin type 9 (PCSK9) variants and uses thereof

(51) International Patent Classification(s)
A61K 38/48 (2006.01) **C12N 9/64** (2006.01)
A61P 3/06 (2006.01)

(21) Application No: 2009238550 (22) Date of Filing: 2009.02.20

(87) WIPO No: WO09/131740

(30) Priority Data

(31) Number (32) Date (33) Country
61/125,304 2008.04.23 US

(43) Publication Date: 2009.10.29
(44) Accepted Journal Date: 2014.11.27

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(56) Related Art
BENJANNET S. et al, The Proprotein Convertase (PC) PCSK9 Is Inactivated by Furin and/or PC5/6A, The Journal of Biological Chemistry, 2006, Vol. 281(41), pg. 30561-30572

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
29 October 2009 (29.10.2009)(10) International Publication Number
WO 2009/131740 A3(51) International Patent Classification:
A61K 38/48 (2006.01) A61P 3/06 (2006.01)
C12N 9/64 (2006.01)(21) International Application Number:
PCT/US2009/034775(22) International Filing Date:
20 February 2009 (20.02.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/125,304 23 April 2008 (23.04.2008) US

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN,

HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
- with sequence listing part of description (Rule 5.2(a))

(88) Date of publication of the international search report:
7 January 2010

(54) Title: NEUTRALIZING PROPROTEIN CONVERTASE SUBTILISIN KEXIN TYPE 9 (PCSK9) VARIANTS AND USES THEREOF

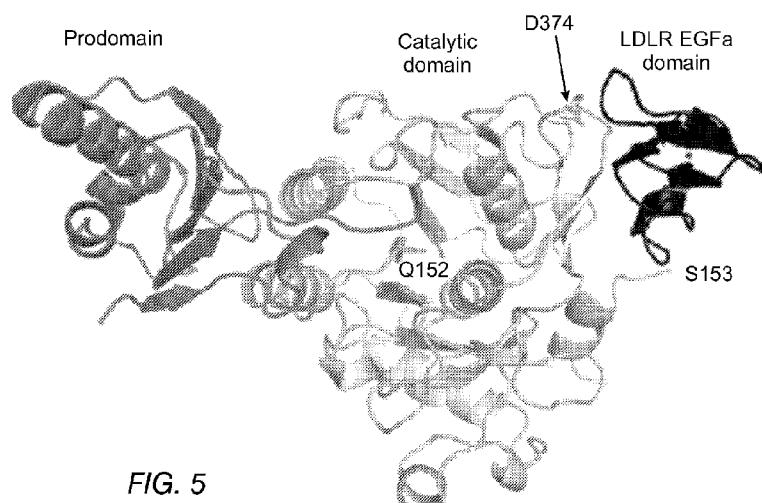


FIG. 5

(57) Abstract: Neutralizing PCSK9 variants that interact with low density lipoprotein receptor (LDLR) are described. Methods and compositions for treating disorders by administering a pharmaceutically effective amount of a neutralizing PCSK9 variant are described.

NEUTRALIZING PROPROTEIN CONVERTASE SUBTILISINKEXIN TYPE 9 (PCSK9) VARIANTS AND USES THEREOF

RELATED APPLICATIONS

[0001] The present application claims priority to U.S. Provisional Application 61/125,304, filed April 23, 2008, the entirety of which is hereby incorporated by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to variants of proprotein convertase subtilisin kexin type 9 (and molecules related thereto) and methods of using the variants (and molecules related thereto) for treating various disorders.

BACKGROUND OF VARIOUS EMBODIMENTS

[0002a] Any discussion of the prior art throughout the specification should in no way be considered as an admission that such prior art is widely known or forms part of common general knowledge in the field.

[0003] Proprotein convertase subtilisin kexin type 9 (PCSK9) is a serine protease involved in regulating the levels of the low density lipoprotein receptor (LDLR) protein (Horton *et al.*, 2007; Seidah and Prat, 2007). *In vitro* experiments have shown that adding PCSK9 to HepG2 cells lowers the levels of cell surface LDLR (Benjannet *et al.*, 2004; Lagace *et al.*, 2006; Maxwell *et al.*, 2005; Park *et al.*, 2004). Experiments with mice have shown that increasing PCSK9 protein levels decreases levels of LDLR protein in the liver (Benjannet *et al.*, 2004; Lagace *et al.*, 2006; Maxwell *et al.*, 2005; Park *et al.*, 2004), while PCSK9 knockout mice have increased levels of LDLR in the liver (Rashid *et al.*, 2005). Additionally, various human PCSK9 mutations that result in either increased or decreased levels of plasma LDL have been identified (Kotowski *et al.*, 2006; Zhao *et al.*, 2006). PCSK9 has been shown to directly interact with the LDLR protein, be endocytosed along with the LDLR, and co-immunofluoresce with the LDLR throughout the endosomal pathway (Lagace *et al.*, 2006). Degradation of the LDLR by PCSK9 has not been observed and the mechanism through which it lowers extracellular LDLR protein levels is uncertain.

[0004] PCSK9 is a prohormone-proprotein convertase in the subtilisin (S8) family of serine proteases (Seidah *et al.*, 2003). Humans have nine prohormone-proprotein convertases that can be divided between the S8A and S8B subfamilies (Rawlings *et al.*, 2006). Furin,

PC1/PC3, PC2, PACE4, PC4, PC5/PC6 and PC7/PC8/LPC/SPC7 are classified in subfamily S8B. Crystal and NMR structures of different domains from mouse furin and PC1 reveal subtilisin-like pro- and catalytic domains, and a P domain directly C-terminal to the catalytic domain (Henrich *et al.*, 2003; Tangrea *et al.*, 2002). Based on the amino acid sequence similarity within this subfamily, all seven members are predicted to have similar structures (Henrich *et al.*, 2005). SKI-1/S1P and PCSK9 are classified in subfamily S8A. Sequence comparisons with these proteins also suggest the presence of subtilisin-like pro- and catalytic domains (Sakai *et al.*, 1998; Seidah *et al.*, 2003; Seidah *et al.*, 1999). In these proteins the amino acid sequence C-terminal to the catalytic domain is more variable and does not suggest the presence of a P domain.

[0005] Prohormone-proprotein convertases are expressed as zymogens and they mature through a multi step process. The function of the pro-domain in this process is two-fold. The pro-domain first acts as a chaperone and is required for proper folding of the catalytic domain (Ikemura *et al.*, 1987). Once the catalytic domain is folded, autocatalysis occurs between the pro-domain and catalytic domain. Following this initial cleavage reaction, the pro-domain remains bound to the catalytic domain where it then acts as an inhibitor of catalytic activity (Fu *et al.*, 2000). When conditions are correct, maturation proceeds with a second autocatalytic event at a site within the pro-domain (Anderson *et al.*, 1997). After this second cleavage event occurs the pro-domain and catalytic domain dissociate, giving rise to an active protease.

[0006] Autocatalysis of the PCSK9 zymogen occurs between Gln152 and Ser153 (VFAQ|SIP) (Naureckiene *et al.*, 2003), and has been shown to be required for its secretion from cells (Seidah *et al.*, 2003). A second autocatalytic event at a site within PCSK9's pro-domain has not been observed. Purified PCSK9 is made up of two species that can be separated by non-reducing SDS-PAGE; the pro-domain at 17 Kd, and the catalytic plus C-terminal domains at 65 Kd. PCSK9 has not been isolated without its inhibitory pro-domain, and measurements of PCSK9's catalytic activity have been variable (Naureckiene *et al.*, 2003; Seidah *et al.*, 2003).

SUMMARY OF VARIOUS EMBODIMENTS

[0006a] According to a first aspect, the present invention relates to an isolated neutralizing PCSK9 variant comprising:

- (a) a Pro/Cat domain, or fragment thereof; and
- (b) an inactive V domain,

wherein the Pro/Cat domain or the fragment thereof

- i) lacks amino acids 1-60 of SEQ ID NO: 3; or
- ii) lacks amino acids 1-30 of SEQ ID NO: 3; and

wherein the neutralizing PCSK9 variant lacks at least 14 C-terminal amino acids of SEQ ID NO: 3, preferably the PCSK9 variant lacks the protein sequence defined from amino acids 453 to 692 of SEQ ID NO: 3.

[0006b] According to a second aspect, the present invention relates to an isolated nucleic acid molecule encoding the neutralizing PCSK9 variant according to the first aspect, preferably operably linked to a control sequence.

[0006c] According to a third aspect, the present invention relates to a vector comprising a nucleic acid molecule according to the second aspect.

[0006d] According to a fourth aspect, the present invention relates to a host cell comprising the nucleic acid molecule according to the second aspect or the vector according to the third aspect.

[0006e] According to a fifth aspect, the present invention relates to a pharmaceutical composition comprising at least one neutralizing PCSK9 variant according to the first aspect, and a pharmaceutically acceptable excipient, optionally further comprising an additional active agent, preferably selected from the group consisting of a radioisotope, radionuclide, a toxin, or a therapeutic and a chemotherapeutic group.

[0006f] According to a sixth aspect, the present invention relates to a method for treating or preventing a condition associated with elevated serum cholesterol in a patient, comprising administering to a patient in thereof an effective amount of at least one neutralizing PCSK9 variant according to the first aspect, wherein the condition preferably is hypercholesterolemia.

[0006g] According to a seventh aspect, the present invention relates to a method of inhibiting binding of PCSK9 to LDLR in a patient comprising administering an effective amount of a neutralizing PCSK9 variant according to the first aspect.

[0006d] According to an eighth aspect, the present invention relates to method for treating or preventing a condition associated with elevated serum cholesterol in a subject, said method comprising administering to a subject in need thereof an effective amount of at least one neutralizing PCSK9 variant according to the first aspect simultaneously or sequentially with an agent that elevates the availability of low density lipoprotein receptor (LDLR) protein,

wherein the agent that elevates the availability of LDLR protein optionally comprises a statin, preferably selected from the group consisting of atorvastatin, cerivastatin, fluvastatin,

lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, or a combination thereof.

[0006h] According to a ninth aspect, the present invention relates to a method of lowering serum cholesterol in a subject, said method comprising administering to a subject an effective amount of at least one isolated neutralizing PCSK9 variant according to the first aspect, preferably simultaneously or sequentially with an agent that elevates the availability of low density lipoprotein receptor (LDLR) protein.

[0006i] According to a tenth aspect, the present invention relates to use of a neutralizing PCSK9 variant of the first aspect in the manufacture of a medicament for the treatment of hypercholesterolemia.

[0006j] According to an eleventh aspect, the present invention relates to use of a neutralizing PCSK9 variant of the first aspect in the manufacture of a medicament for inhibiting binding of PCSK9 to LDLR.

[0006k] According to a twelfth aspect, the present invention relates to use of a neutralizing PCSK9 variant of the first aspect in the manufacture of a medicament for treating a condition associated with elevated serum cholesterol in a subject, wherein said medicament is adapted for simultaneous or sequential administration with an agent that elevates the availability of low density lipoprotein receptor (LDLR) protein,

wherein the agent that elevates the availability of LDLR protein optionally comprises a statin, preferably selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, or a combination thereof.

[0006l] According to a thirteenth aspect, the present invention relates to use of a neutralizing PCSK9 variant of the first aspect in the manufacture of a medicament for lowering serum cholesterol in a subject, wherein said medicament is adapted for simultaneous or sequential administration with an agent that elevates the availability of low density lipoprotein receptor (LDLR) protein.

[0006m] According to a fourteenth aspect, the present invention relates to a pharmaceutical composition comprising at least one neutralizing PCSK9 variant according to the first aspect, wherein the neutralizing PCSK9 variant is present in an amount effective for the treatment of a cholesterol related disorder.

[0006n] According to a fifteenth aspect, the present invention relates to a pharmaceutical composition comprising:

- (a) a Pro/Cat domain, or fragment thereof;
- (b) an inactive V domain; and
- (c) a pharmaceutically acceptable carrier or diluent,

wherein the Pro/Cat domain, or the fragment thereof

- (i) lacks amino acids 1-60 of SEQ ID NO: 3; or
- (ii) lacks amino acids 1-30 of SEQ ID NO: 3; and

wherein the neutralizing PCSK9 variant lacks at least 14 C-terminal amino acids of SEQ ID NO: 3, preferably the PCSK9 variant lacks the protein sequence defined from amino acids 453 to 692 of SEQ ID NO: 3.

[0006o] According to a sixteenth aspect, the present invention relates to a pharmaceutical composition comprising a Pro/Cat domain, or fragment thereof, and an inactive V domain, wherein the Pro/Cat domain is present in an amount sufficient for the treatment of a cholesterol related disorder,

wherein the Pro/Cat domain:

- (i) comprises the amino acid sequence of the Pro/Cat domain in SEQ ID NO: 9 or 30; or
- (ii) consists of the amino acid sequence of the Pro/Cat domain in SEQ ID NO: 9 or 30; or
- (iii) consists essentially of the amino acid sequence of the Pro/Cat domain in SEQ ID NO: 9 or 30; or
- (iv) comprises the Cat domain of at least one of the amino acids sequences of SEQ ID NOs: 9, 11, 13, 15 or 3.

[0006p] Unless the context clearly requires otherwise, throughout the description and the claims, the words "comprise", "comprising", and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

[0007] In some embodiments, the invention comprises a PCSK9 variant and/or a use thereof.

[0008] In some embodiments, the PCSK9 variant can be a neutralizing PCSK9 variant that can include a Pro/Cat domain, or fragment thereof, that binds to low density lipoprotein receptor (LDLR) and an inactive V domain to LDLR activity. The inactive V domain does not result in the degradation of LDLR.

[0009] In some embodiments, the invention comprises a nucleic acid molecule that encodes for a PCSK9 variant (or neutralizing variant).

[0010] In some embodiments, the invention comprises a host cell that comprises a herein disclosed nucleic acid molecule that encodes for a PCSK9 variant.

[0011] In some embodiments, the invention comprises a vector that comprises a herein disclosed nucleic acid molecule that encodes for a PCSK9 variant.

[0012] In some embodiments, the invention comprises a pharmaceutical composition comprising at least one neutralizing PCSK9 variant (or a nucleic acid sequence encoding for a neutralizing PCSK9 variant) and a pharmaceutically acceptable carrier and/or excipient.

[0013] In some embodiments, the invention comprises a method of treating or preventing a condition associated with elevated serum cholesterol in a patient. In some embodiments, the method can comprise administering to a patient in need thereof an effective amount of at least one of the herein disclosed compounds (including, for example, a neutralizing PCSK9 variant and/or a nucleic acid sequence encoding a neutralizing PCSK9 variant).

[0014] In some embodiments, the invention comprises a method of inhibiting the binding of endogenous PCSK9 to LDLR in a patient. In some embodiments, the method comprises administering an effective amount of at least one of the herein disclosed compounds (including, for example, a neutralizing PCSK9 variant and/or a nucleic acid sequence encoding a neutralizing PCSK9 variant) to a subject in need thereof.

[0015] In some embodiments, the invention comprises a method of treating or preventing a condition associated with elevated serum cholesterol in a subject. In some embodiments, the method can comprise administering to a subject in need thereof an effective amount at least one of the herein disclosed compounds (including, for example, a neutralizing PCSK9 variant and/or a nucleic acid sequence encoding a neutralizing PCSK9 variant) simultaneously or sequentially with an agent that elevates the availability of low density lipoprotein receptor (LDLR) protein.

[0016] In some embodiments, the invention comprises a method of lowering serum cholesterol in a subject. In some embodiments, the method can comprise administering to a subject an effective amount of at least one of the herein disclosed compounds (including, for example, a neutralizing PCSK9 variant and/or a nucleic acid sequence encoding a neutralizing PCSK9 variant).

[0017] In some embodiments, the invention comprises a method of lowering serum cholesterol in a subject. In some embodiments, the method can comprise administering to a subject an effective amount of at least one of the herein disclosed compounds (including, for example, a neutralizing PCSK9 variant and/or a nucleic acid sequence encoding a neutralizing PCSK9 variant) simultaneously or sequentially with an agent that elevates the availability of low density lipoprotein receptor (LDLR) protein.

[0018] In some embodiments, the invention comprises the use of at least one of the herein disclosed compounds (including, for example, a neutralizing PCSK9 variant and/or a nucleic acid sequence encoding a neutralizing PCSK9 variant) in the manufacture of a medicament for the treatment of hypercholesterolemia.

[0019] In some embodiments, the invention comprises at least one of the herein disclosed compounds (including, for example, a neutralizing PCSK9 variant and/or a nucleic acid sequence encoding a neutralizing PCSK9 variant) for use as a medicament.

[0020] In some embodiments, the invention comprises at least one of the herein disclosed compounds (including, for example, a neutralizing PCSK9 variant and/or a nucleic acid sequence encoding a neutralizing PCSK9 variant) for use in treating hypercholesterolemia.

[0021] In some embodiments, the invention comprises a pharmaceutical composition comprising a Pro/Cat domain, or fragment thereof, that binds to low density lipoprotein receptor (LDLR), and an inactive V domain to LDLR activity. The inactive V domain does not result in the degradation of LDLR. The pharmaceutical composition further comprises a pharmaceutically acceptable carrier or diluent.

[0022] In some embodiments, the invention comprises a pharmaceutical composition comprising a Pro/Cat domain, or fragment thereof, that binds to low density lipoprotein receptor (LDLR) and an inactive V domain to LDLR activity. The inactive V domain does not result in the degradation of LDLR. The pro/cat domain is present in an amount sufficient for the treatment of a cholesterol related disorder.

BRIEF DESCRIPTION OF THE FIGURES

[0023] FIG. 1A depicts an amino acid sequence of the mature form of the PCSK9 with the pro-domain underlined.

[0024] FIGs. 1B₁-1B₄ depict amino acid and nucleic acid sequences of PCSK9 with the pro-domain underlined and the signal sequence in bold.

[0025] FIG. 1C is a comparison on the sequences of PCSK9 from various organisms. (Any “O” in FIGs. 1C-1E are actually “Q”)

[0026] FIG. 1D is a continuation of FIG. 1C.

[0027] FIG. 1E is a continuation of FIG. 1D.

[0028] FIG. 1F is an alignment of the Cat domain of the PCSK9 protein of SEQ ID NO: 3 with another Cat domain of another PCSK9 protein.

[0029] FIG. 1G is an alignment of the Cat domain of the PCSK9 protein of SEQ ID NO: 3 with another Cat domain of another PCSK9 protein.

[0030] FIG. 1H is an alignment of the Cat domain of the PCSK9 protein of SEQ ID NO: 3 with another Cat domain of another PCSK9 protein.

[0031] FIG. 1I is an alignment and consensus sequence for the amino acid sequence of LDLR.

[0032] FIG. 1J is a continuation of the alignment and consensus sequence for the amino acid sequence of LDLR presented in FIG. 1I.

[0033] FIG. 1K is an alignment and consensus sequence for the amino acid sequence of LDLR.

[0034] FIG. 1L is a continuation of the alignment and consensus sequence for the amino acid sequence of LDLR presented in FIG. 1K.

[0035] FIGs. 1M₁ and 1M₂ depict an embodiment of a PCSK9 protein.

[0036] FIGs. 1N₁ and 1N₂ depict an embodiment of a PCSK9 protein.

[0037] FIGs. 1O₁ and 1O₂ depict an embodiment of a PCSK9 protein.

[0038] FIGs. 1P₁ and 1P₂ depict an embodiment of a PCSK9 protein.

[0039] FIGs. 1Q₁ and 1Q₂ depict an embodiment of a PCSK9 protein.

[0040] FIGs. 1R₁ and 1R₂ depict an embodiment of a consensus sequence for a PCSK9 protein.

[0041] FIGs. 1S₁ and 1S₂ depict an embodiment of a human PCSK9 protein.

[0042] FIG. 2 is a graph depicting the results of a binding assay between LDLR and biotin-labeled full length PCSK9, competed with either a) unlabeled full length PCSK9, b) unlabeled residues 31-447 of PCSK9, or c) the unlabeled V domain of PCSK9 (residues 450-692).

[0043] FIG. 3A is a graph depicting the results of the activity of residues 31-447 of PCSK9 on LDL uptake.

[0044] FIG. 3B is a graph depicting the results of the activity of residues 31-447 of PCSK9 on LDL uptake.

[0045] FIG. 4 is a depiction of a Western blot comparing the effect of full length PCSK9 vs. residues 31-447 of PCSK9 (a Pro/Cat fragment) on LDLR protein levels and PCSK9 uptake. As can be seen in the left-hand side of the gel, full length PCSK9 (FL PC9) results in a decrease in LDLR, while residues 31-447 of PCSK9 (a Pro/Cat fragment that functions as a neutralizing PCSK9 variant) does not result in a decrease in LDLR.

[0046] FIG. 5 is a depiction of the structure of PCSK9 and the EGFa section of LDLR.

[0047] FIG. 6 is a depiction of a structural model of PCSK9 and LDLR.

[0048] FIG. 7 is a depiction of the structural model of PCSK9 and LDLR from an alternative perspective.

[0049] FIG. 8 is a graph depicting the results of the activity of the D374Y variant of residues 31-447 of PCSK9 (an example of another variant of the Pro/Cat domain) on LDL uptake.

[0050] FIG. 9 is a graph depicting the results of a competition assay which included the D374Y variant of residues 31-447 of PCSK9.

DETAILED DESCRIPTION OF CERTAIN EXEMPLARY EMBODIMENTS

[0051] Proprotein convertase subtilisin kexin type 9 (PCSK9) is a serine protease involved in regulating the levels of the low density lipoprotein receptor (LDLR) protein. It is believed that native PCSK9 binds to LDLR *in vivo* and is involved in the degradation of LDLR. This can be problematic because the reduction in available LDLR results in less binding between

LDLR and LDL, which in turn results in more LDL in the serum of the subject, resulting in an increase in serum cholesterol.

[0052] The full length PCSK9 protein includes a signal sequence (generally amino acids 1-30), a N-terminal prodomain (“Pro” domain, generally amino acids 31-152), a subtilisin-like catalytic domain (“Cat” domain, generally amino acids 153-446), a loop region (generally amino acids 447-453) and a C-terminal domain (“V” domain, generally amino acids 454-692).

[0053] Some embodiments of the invention relate to the discovery that the ability of PCSK9 (or variants thereof) to bind to LDLR can be separated from the ability of PCSK9 to effectively degrade or reduce the amount of available LDLR. It has been discovered that while parts of the Pro and/or Cat domains are involved in binding to PCSK9, the V domain is important for the effective degradation of LDLR. Furthermore, variants of PCSK9 that include an active part of the Pro and/or Cat domain can be used to block native PCSK9 from binding to LDLR. Thus, in some embodiments, the invention relates to a neutralizing PCSK9 variant that can block native PCSK9 from binding to LDLR, while the neutralizing PCSK9 variant itself will not effectively degrade LDLR. In some embodiments, the invention comprises a variant of PCSK9 that still includes an active Pro/Cat domain and that lacks a functional V domain (and thus lacks the ability to effectively lower LDLR in a subject). This variant can be used to prevent or reduce native PCSK9 from binding to LDLR. In turn, this can effectively elevate the level of LDLR in a subject and result in lower levels of LDL in the serum.

[0054] Some embodiments of the invention relate to the discovery that using a neutralizing PCSK9 variant (*e.g.*, a variant that includes an active Pro/Cat domain and an inactive V domain) can result in the neutralizing PCSK9 variant competitively blocking and preventing native PCSK9 from binding to and degrading LDLR, while still allowing LDLR to perform its beneficial role of sequestering LDL. As such, neutralizing variants of PCSK9 can be used to lower serum LDL in a subject. Thus, in some embodiments, the invention comprises a neutralizing PCSK9 variant (or its use) that can bind to LDLR and prevent native PCSK9 from binding to LDLR, while still allowing LDLR to bind to and act on LDL.

[0055] Some embodiments of the invention relate to the discovery that using a neutralizing PCSK9 variant (*e.g.*, a variant that includes an active Pro/Cat domain and an inactive V domain) can result in the neutralizing PCSK9 variant competitively blocking and preventing native PCSK9 from binding to and degrading LDLR, while still allowing LDLR to

recycle (e.g., be endocytosed and then return back to the plasma membrane). Thus, in some embodiments, the invention comprises a neutralizing PCSK9 variant (or its use) that can bind to LDLR and prevent native PCSK9 from binding to LDLR, while still allowing LDLR to recycle.

[0056] In some embodiments, the neutralizing PCSK9 variant comprises, consists, or consists essentially of some or all of the Pro and/or Cat domains of PCSK9. In some embodiments, the neutralizing PCSK9 variant does not include some or all of the V domain. In some embodiments the neutralizing PCSK9 variant does not have a fully functional LDLR degrading V domain. In some embodiments the neutralizing PCSK9 variant has an inactive V domain. As will be appreciated by one of skill in the art, some of these embodiments can be beneficial in situations in which one wishes to lower the serum cholesterol in a subject, such as in hypercholesterolemia. Neutralizing PCSK9 variants can be used in various methods and compositions for treating subjects with elevated serum cholesterol levels, at risk of elevated serum cholesterol levels, or in those that could benefit from a reduction in their serum cholesterol levels. Thus, various methods and techniques for lowering, maintaining, or preventing an increase in serum cholesterol are also described herein.

[0057] Exemplary human PCSK9 amino acid sequences are presented as SEQ ID NOs: 1 and 3. An exemplary human PCSK9 coding sequence is presented as SEQ ID NO: 2, in FIG. 1A (depicting the “pro” domain of the protein as underlined) and FIG. 1B (depicting the signal sequence in bold and the pro domain underlined). Additional variants of PCSK9 (or the Cat domain of PCSK9) are shown in FIGs. 1C-1H. The structure of the PCSK9 protein has recently been solved by two groups (Cunningham et al., *Nature Structural & Molecular Biology*, 2007, and Piper et al., *Structure*, 15:1-8, 2007), the entireties of both of which are herein incorporated by reference.

[0058] For convenience, the following sections generally outline the various meanings of the terms used herein. Following this discussion, general aspects regarding neutralizing PCSK9 variants are discussed, followed by specific examples.

Definitions and Embodiments

[0059] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention as claimed. In this application, the use of the singular includes the plural unless

specifically stated otherwise. In this disclosure, the use of “or” means “and/or” unless stated otherwise. Furthermore, the use of the term “including”, as well as other forms, such as “includes” and “included”, is not limiting. Also, terms such as “element” or “component” encompass both elements and components comprising one unit and elements and components that comprise more than one subunit unless specifically stated otherwise. Also, the use of the term “portion” can include part of a moiety or the entire moiety.

[0060] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in this application, including but not limited to patents, patent applications, articles, books, and treatises, are hereby expressly incorporated by reference in their entirety for any purpose. As utilized in accordance with the present disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

[0061] The term “proprotein convertase subtilisin kexin type 9” or “PCSK9” refers to a polypeptide as set forth in SEQ ID NO: 1 and/or 3 or fragments thereof, as well as related polypeptides, which include, but are not limited to, allelic variants, splice variants, derivative variants, substitution variants, and/or insertion variants including the addition of an N-terminal methionine, fusion polypeptides, and interspecies homologs. Examples of related proteins are put forth in FIGs. 1C-1H. In some embodiments, a PCSK9 polypeptide includes terminal residues, such as, but not limited to, leader sequence residues, targeting residues, amino terminal methionine residues, lysine residues, tag residues and/or fusion protein residues. “PCSK9” has also been referred to as FH3, NARC1, HCHOLA3, proprotein convertase subtilisin/kexin type 9, and neural apoptosis regulated convertase 1. The PCSK9 gene encodes a proprotein convertase protein that belongs to the proteinase K subfamily of the secretory subtilase family. The term “PCSK9” denotes both the proprotein and the product generated following autocatalysis of the proprotein. When only the autocatalyzed product is being referred to, the protein can be referred to as the “cleaved” or “processed” PCSK9. When only the inert form is being referred to, the protein can be referred to as the “inert”, “pro-form”, or “unprocessed” form of PCSK9. The term PCSK9 as used herein also includes naturally occurring alleles, such as the mutations D374Y, D374H, S127R, F216L, R46L, R237W, L253F, A443T, H553R, and others (Kotowski IK et al, A spectrum of PCSK9 alleles contributes to plasma levels of low-density lipoprotein cholesterol, Am J. Hum. Genet. 2006; 78:410-422). The term PCSK9 also encompasses PCSK9 molecules

incorporating post-translational modifications of the PCSK9 amino acid sequence, such as PCSK9 sequences that have been glycosylated, PEGylated, PCSK9 sequences from which its signal sequence has been cleaved, PCSK9 sequence from which its pro domain has been cleaved from the catalytic domain but not separated from the catalytic domain (e.g., FIGs. 1A and 1B).

[0062] The term “PCSK9 activity” includes any biological effect of PCSK9. In some embodiments, PCSK9 activity includes the ability of PCSK9 to interact or bind to a substrate or receptor. In some embodiments, PCSK9 activity is represented by the ability of PCSK9 to bind to a LDL receptor (LDLR). In some embodiments, PCSK9 binds to and catalyzes a reaction involving LDLR. In some embodiments, PCSK9 activity includes the ability of PCSK9 to alter (e.g., reduce) the availability of LDLR. In some embodiments, PCSK9 activity includes the ability of PCSK9 to increase the amount of LDL in a subject. In some embodiments, PCSK9 activity includes the ability of PCSK9 to decrease the amount of LDLR that is available to bind to LDL. In some embodiments, “PCSK9 activity” includes any biological activity resulting from PCSK9 signaling. Exemplary activities include, but are not limited to, PCSK9 binding to LDLR, PCSK9 enzyme activity that cleaves LDLR or other proteins, PCSK9 binding to proteins other than LDLR that facilitate PCSK9 action, PCSK9 altering APOB secretion (Sun X-M et al, “Evidence for effect of mutant PCSK9 on apolipoprotein B secretion as the cause of unusually severe dominant hypercholesterolemia, Human Molecular Genetics 14: 1161-1169, 2005 and Ouguerram K et al, “Apolipoprotein B100 metabolism in autosomal-dominant hypercholesterolemia related to mutations in PCSK9, Arterioscler thromb Vasc Biol. 24: 1448-1453, 2004), PCSK9’s role in liver regeneration and neuronal cell differentiation (Seidah NG et al, “The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): Liver regeneration and neuronal differentiation” PNAS 100: 928-933, 2003), and PCSK9s role in hepatic glucose metabolism (Costet et al., “Hepatic PCSK9 expression is regulated by nutritional status via insulin and sterol regulatory element-binding protein 1c” J. Biol. Chem. 281(10):6211-18, 2006). PCSK9 activity can be distinct from the terms “active Pro/Cat domain” or “inactive V domain” as defined herein.

[0063] The term “hypercholesterolemia,” as used herein, refers to a condition in which cholesterol levels are elevated above a desired level. In some embodiments, this denotes that serum cholesterol levels are elevated. In some embodiments, the desired level takes into

account various “risk factors” that are known to one of skill in the art (and are described or referenced herein).

[0064] The term “polynucleotide” or “nucleic acid” includes both single-stranded and double-stranded nucleotide polymers. The nucleotides comprising the polynucleotide can be ribonucleotides or deoxyribonucleotides or a modified form of either type of nucleotide. Said modifications include base modifications such as bromouridine and inosine derivatives, ribose modifications such as 2',3'-dideoxyribose, and internucleotide linkage modifications such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phosphoranylilate and phosphoroamidate.

[0065] The term “oligonucleotide” means a polynucleotide comprising 200 or fewer nucleotides. In some embodiments, oligonucleotides are 10 to 60 bases in length. In other embodiments, oligonucleotides are 12, 13, 14, 15, 16, 17, 18, 19, or 20 to 40 nucleotides in length. Oligonucleotides can be single stranded or double stranded, e.g., for use in the construction of a mutant gene. Oligonucleotides can be sense or antisense oligonucleotides. An oligonucleotide can include a label, including a radiolabel, a fluorescent label, a hapten or an antigenic label, for detection assays. Oligonucleotides can be used, for example, as PCR primers, cloning primers or hybridization probes.

[0066] An “isolated nucleic acid molecule” means a DNA or RNA of genomic, mRNA, cDNA, or synthetic origin or some combination thereof which is not associated with all or a portion of a polynucleotide in which the isolated polynucleotide is found in nature, or is linked to a polynucleotide to which it is not linked in nature. For purposes of this disclosure, it should be understood that “a nucleic acid molecule comprising” a particular nucleotide sequence does not encompass intact chromosomes. Isolated nucleic acid molecules “comprising” specified nucleic acid sequences can include, in addition to the specified sequences, coding sequences for up to ten or even up to twenty other proteins or portions thereof, or can include operably linked regulatory sequences that control expression of the coding region of the recited nucleic acid sequences, and/or can include vector sequences.

[0067] Unless specified otherwise, the left-hand end of any single-stranded polynucleotide sequence discussed herein is the 5' end; the left-hand direction of double-stranded polynucleotide sequences is referred to as the 5' direction. The direction of 5' to 3' addition of nascent RNA transcripts is referred to as the transcription direction; sequence regions

on the DNA strand having the same sequence as the RNA transcript that are 5' to the 5' end of the RNA transcript are referred to as "upstream sequences;" sequence regions on the DNA strand having the same sequence as the RNA transcript that are 3' to the 3' end of the RNA transcript are referred to as "downstream sequences."

[0068] The term "control sequence" refers to a polynucleotide sequence that can affect the expression and processing of coding sequences to which it is ligated. The nature of such control sequences can depend upon the host organism. In particular embodiments, control sequences for prokaryotes can include a promoter, a ribosomal binding site, and a transcription termination sequence. For example, control sequences for eukaryotes can include promoters comprising one or a plurality of recognition sites for transcription factors, transcription enhancer sequences, and transcription termination sequence. "Control sequences" can include leader sequences and/or fusion partner sequences.

[0069] The term "vector" means any molecule or entity (*e.g.*, nucleic acid, plasmid, bacteriophage or virus) used to transfer protein coding information into a host cell.

[0070] The term "expression vector" or "expression construct" refers to a vector that is suitable for transformation of a host cell and contains nucleic acid sequences that direct and/or control (in conjunction with the host cell) expression of one or more heterologous coding regions operatively linked thereto. An expression construct can include, but is not limited to, sequences that affect or control transcription, translation, and, if introns are present, affect RNA splicing of a coding region operably linked thereto.

[0071] As used herein, "operably linked" means that the components to which the term is applied are in a relationship that allows them to carry out their inherent functions under suitable conditions. For example, a control sequence in a vector that is "operably linked" to a protein coding sequence is ligated thereto so that expression of the protein coding sequence is achieved under conditions compatible with the transcriptional activity of the control sequences.

[0072] The term "host cell" means a cell that has been transformed, or is capable of being transformed, with a nucleic acid sequence and thereby expresses a gene of interest. The term includes the progeny of the parent cell, whether or not the progeny is identical in morphology or in genetic make-up to the original parent cell, so long as the gene of interest is present.

[0073] The term “transfection” means the uptake of foreign or exogenous DNA by a cell, and a cell has been “transfected” when the exogenous DNA has been introduced inside the cell membrane. A number of transfection techniques are well known in the art and are disclosed herein. *See, e.g.*, Graham *et al.*, 1973, *Virology* 52:456; Sambrook *et al.*, 2001, *Molecular Cloning: A Laboratory Manual, supra*; Davis *et al.*, 1986, *Basic Methods in Molecular Biology*, Elsevier; Chu *et al.*, 1981, *Gene* 13:197. Such techniques can be used to introduce one or more exogenous DNA moieties into suitable host cells.

[0074] The term “transformation” refers to a change in a cell's genetic characteristics, and a cell has been transformed when it has been modified to contain new DNA or RNA. For example, a cell is transformed where it is genetically modified from its native state by introducing new genetic material *via* transfection, transduction, or other techniques. Following transfection or transduction, the transforming DNA can recombine with that of the cell by physically integrating into a chromosome of the cell, or can be maintained transiently as an episomal element without being replicated, or can replicate independently as a plasmid. A cell is considered to have been “stably transformed” when the transforming DNA is replicated with the division of the cell.

[0075] The terms “polypeptide” or “protein” means a macromolecule having the amino acid sequence of a native protein, that is, a protein produced by a naturally-occurring and non-recombinant cell; or it is produced by a genetically-engineered or recombinant cell, and comprise molecules having the amino acid sequence of the native protein, or molecules having deletions from, additions to, and/or substitutions of one or more amino acids of the native sequence. The term also includes amino acid polymers in which one or more amino acids are chemical analogs of a corresponding naturally-occurring amino acid and polymers. The terms “polypeptide” and “protein” specifically encompass neutralizing PCSK9 variants, or sequences that have deletions from, additions to, and/or substitutions of one or more amino acid of the PCSK9 protein or variant. The term “polypeptide fragment” refers to a polypeptide that has an amino-terminal deletion, a carboxyl-terminal deletion, and/or an internal deletion as compared with the full-length native protein. Such fragments can also contain modified amino acids as compared with the native protein. In some embodiments, fragments are about five to 500 amino acids long. For example, fragments can be at least 5, 6, 7, 8, 9, 10, 10-14, 14-20, 20-50, 50-70,

70-100, 100-110, 110-150, 150-200, 200-250, 250-300, 300-350, 350-400, or 400-450 amino acids long.

[0076] The term “isolated protein” means that a subject protein (1) is free of at least some other proteins with which it would normally be found, (2) is essentially free of other proteins from the same source, *e.g.*, from the same species, (3) is expressed by a cell from a different species, (4) has been separated from at least about 50 percent of polynucleotides, lipids, carbohydrates, or other materials with which it is associated in nature, (5) is operably associated (by covalent or noncovalent interaction) with a polypeptide with which it is not associated in nature, or (6) does not occur in nature. Typically, an “isolated protein” constitutes at least about 5%, at least about 10%, at least about 25%, or at least about 50% of a given sample. Genomic DNA, cDNA, mRNA or other RNA, of synthetic origin, or any combination thereof can encode such an isolated protein. Preferably, the isolated protein is substantially free from proteins or polypeptides or other contaminants that are found in its natural environment that would interfere with its therapeutic, diagnostic, prophylactic, research or other use.

[0077] The term “amino acid” includes its normal meaning in the art and includes both naturally and non-naturally occurring amino acids.

[0078] A “variant” of a polypeptide (*e.g.*, a neutralizing PCSK9 variant) comprises an amino acid sequence wherein one or more amino acid residues are inserted into, deleted from and/or substituted into the amino acid sequence relative to another polypeptide sequence. Variants include fusion proteins.

[0079] The term “identity” refers to a relationship between the sequences of two or more polypeptide molecules or two or more nucleic acid molecules, as determined by aligning and comparing the sequences. “Percent identity” means the percent of identical residues between the amino acids or nucleotides in the compared molecules and is calculated based on the size of the smallest of the molecules being compared. For these calculations, gaps in alignments (if any) are preferably addressed by a particular mathematical model or computer program (*i.e.*, an “algorithm”). Methods that can be used to calculate the identity of the aligned nucleic acids or polypeptides include those described in *Computational Molecular Biology*, (Lesk, A. M., ed.), 1988, New York: Oxford University Press; *Biocomputing Informatics and Genome Projects*, (Smith, D. W., ed.), 1993, New York: Academic Press; *Computer Analysis of Sequence Data*, Part I, (Griffin, A. M., and Griffin, H. G., eds.), 1994, New Jersey: Humana Press; von Heinje,

G., 1987, Sequence Analysis in Molecular Biology, New York: Academic Press; Sequence Analysis Primer, (Gribskov, M. and Devereux, J., eds.), 1991, New York: M. Stockton Press; and Carillo *et al.*, 1988, *SIAM J. Applied Math.* **48**:1073.

[0080] In calculating percent identity, the sequences being compared are typically aligned in a way that gives the largest match between the sequences. One example of a computer program that can be used to determine percent identity is the GCG program package, which includes GAP (Devereux *et al.*, 1984, *Nucl. Acid Res.* **12**:387; Genetics Computer Group, University of Wisconsin, Madison, WI). The computer algorithm GAP is used to align the two polypeptides or polynucleotides for which the percent sequence identity is to be determined. The sequences are aligned for optimal matching of their respective amino acid or nucleotide (the “matched span”, as determined by the algorithm). A gap opening penalty (which is calculated as 3x the average diagonal, wherein the “average diagonal” is the average of the diagonal of the comparison matrix being used; the “diagonal” is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are used in conjunction with the algorithm. In some embodiments, a standard comparison matrix (see, Dayhoff *et al.*, 1978, *Atlas of Protein Sequence and Structure* 5:345-352 for the PAM 250 comparison matrix; Henikoff *et al.*, 1992, *Proc. Natl. Acad. Sci. U.S.A.* **89**:10915-10919 for the BLOSUM 62 comparison matrix) is also used by the algorithm.

[0081] Examples of parameters that can be employed in determining percent identity for polypeptides or nucleotide sequences using the GAP program are the following:

- Algorithm: Needleman *et al.*, 1970, *J. Mol. Biol.* **48**:443-453
- Comparison matrix: BLOSUM 62 from Henikoff *et al.*, 1992, *supra*
- Gap Penalty: 12 (but with no penalty for end gaps)
- Gap Length Penalty: 4
- Threshold of Similarity: 0

[0082] Certain alignment schemes for aligning two amino acid sequences may result in matching of only a short region of the two sequences, and this small aligned region may have very high sequence identity even though there is no significant relationship between the two full-length sequences. Accordingly, the selected alignment method (GAP program) can be adjusted

if so desired to result in an alignment that spans at least 50 or other number of contiguous amino acids of the target polypeptide.

[0083] As used herein, the twenty conventional (e.g., naturally occurring) amino acids and their abbreviations follow conventional usage. See *Immunology--A Synthesis* (2nd Edition, E. S. Golub and D. R. Gren, Eds., Sinauer Associates, Sunderland, Mass. (1991)), which is incorporated herein by reference for any purpose. Stereoisomers (e.g., D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as α -, α -disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids can also be suitable components for polypeptides. Examples of unconventional amino acids include: 4-hydroxyproline, γ -carboxyglutamate, ϵ -N,N,N-trimethyllysine, ϵ -N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ -N-methylarginine, and other similar amino acids and imino acids (e.g., 4-hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

[0084] Similarly, unless specified otherwise, the left-hand end of single-stranded polynucleotide sequences is the 5' end; the left-hand direction of double-stranded polynucleotide sequences is referred to as the 5' direction. The direction of 5' to 3' addition of nascent RNA transcripts is referred to as the transcription direction; sequence regions on the DNA strand having the same sequence as the RNA and which are 5' to the 5' end of the RNA transcript are referred to as "upstream sequences"; sequence regions on the DNA strand having the same sequence as the RNA and which are 3' to the 3' end of the RNA transcript are referred to as "downstream sequences."

[0085] Conservative amino acid substitutions can encompass non-naturally occurring amino acid residues, which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. These include peptidomimetics and other reversed or inverted forms of amino acid moieties.

[0086] Naturally occurring residues can be divided into classes based on common side chain properties:

- 1) hydrophobic: norleucine, Met, Ala, Val, Leu, Ile;
- 2) neutral hydrophilic: Cys, Ser, Thr, Asn, Gln;

- 3) acidic: Asp, Glu;
- 4) basic: His, Lys, Arg;
- 5) residues that influence chain orientation: Gly, Pro; and
- 6) aromatic: Trp, Tyr, Phe.

For example, non-conservative substitutions can involve the exchange of a member of one of these classes for a member from another class. Such substituted residues can be introduced, for example, into regions of a PCSK9 protein that are homologous with non-human PCSK9 proteins, or into the non-homologous regions of the molecule.

[0087] In making changes to the PCSK9 protein or variant thereof, according to certain embodiments, the hydropathic index of amino acids can be considered. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics. They are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

[0088] The importance of the hydropathic amino acid index in conferring interactive biological function on a protein is understood in the art. Kyte *et al.*, *J. Mol. Biol.*, 157:105-131 (1982). It is known that certain amino acids can be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making changes based upon the hydropathic index, in some embodiments, the substitution of amino acids whose hydropathic indices are within ± 2 is included. In some embodiments, those which are within ± 1 are included, and in some embodiments, those within ± 0.5 are included.

[0089] It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity, particularly where the biologically functional protein or peptide thereby created is intended for use in immunological embodiments, as in the present case. In some embodiments, the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its immunogenicity and antigenicity, i.e., with a biological property of the protein.

[0090] The following hydrophilicity values have been assigned to these amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0 \pm 1); glutamate (+3.0 \pm 1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (-0.4); proline (-0.5 \pm 1); alanine (-

0.5); histidine (-0.5); cysteine (-1.0); methionine (-1.3); valine (-1.5); leucine (-1.8); isoleucine (-1.8); tyrosine (-2.3); phenylalanine (-2.5) and tryptophan (-3.4). In making changes based upon similar hydrophilicity values, in some embodiments, the substitution of amino acids whose hydrophilicity values are within ± 2 is included, in some embodiments, those which are within ± 1 are included, and in some embodiments, those within ± 0.5 are included. One can also identify epitopes from primary amino acid sequences on the basis of hydrophilicity. These regions are also referred to as "epitopic core regions."

[0091] Exemplary amino acid substitutions are set forth in Table 1.

TABLE 1
Amino Acid Substitutions

| Original Residues | Exemplary Substitutions | Preferred Substitutions |
|-------------------|---|-------------------------|
| Ala | Val, Leu, Ile | Val |
| Arg | Lys, Gln, Asn | Lys |
| Asn | Gln | Gln |
| Asp | Glu | Glu |
| Cys | Ser, Ala | Ser |
| Gln | Asn | Asn |
| Glu | Asp | Asp |
| Gly | Pro, Ala | Ala |
| His | Asn, Gln, Lys, Arg | Arg |
| Ile | Leu, Val, Met, Ala, Phe, Norleucine | Leu |
| Leu | Norleucine, Ile, Val, Met, Ala, Phe | Ile |
| Lys | Arg, 1,4 Diamino-butyric Acid, Gln, Asn | Arg |
| Met | Leu, Phe, Ile | Leu |
| Phe | Leu, Val, Ile, Ala, Tyr | Leu |
| Pro | Ala | Gly |

| Original Residues | Exemplary Substitutions | Preferred Substitutions |
|-------------------|--|-------------------------|
| Ser | Thr, Ala, Cys | Thr |
| Thr | Ser | Ser |
| Trp | Tyr, Phe | Tyr |
| Tyr | Trp, Phe, Thr, Ser | Phe |
| Val | Ile, Met, Leu, Phe, Ala, Norleucine | Leu |

[0092] The term “derivative” refers to a molecule that includes a chemical modification other than an insertion, deletion, or substitution of amino acids (or nucleic acids). In some embodiments, derivatives comprise covalent modifications, including, but not limited to, chemical bonding with polymers, lipids, or other organic or inorganic moieties. In some embodiments, a chemically modified neutralizing PCSK9 variant can have a greater circulating half-life than a neutralizing PCSK9 variant that is not chemically modified. In some embodiments, a chemically modified neutralizing PCSK9 variant can have improved targeting capacity for desired cells, tissues, and/or organs. In some embodiments, a derivative neutralizing PCSK9 variant is covalently modified to include one or more water soluble polymer attachments, including, but not limited to, polyethylene glycol, polyoxyethylene glycol, or polypropylene glycol. *See, e.g.*, U.S. Patent Nos: 4,640,835, 4,496,689, 4,301,144, 4,670,417, 4,791,192 and 4,179,337. In some embodiments, a derivative neutralizing PCSK9 variant comprises one or more polymer, including, but not limited to, monomethoxy-polyethylene glycol, dextran, cellulose, or other carbohydrate based polymers, poly-(N-vinyl pyrrolidone)-polyethylene glycol, propylene glycol homopolymers, a polypropylene oxide/ethylene oxide co-polymer, polyoxyethylated polyols (e.g., glycerol) and polyvinyl alcohol, as well as mixtures of such polymers.

[0093] In some embodiments, a derivative is covalently modified with polyethylene glycol (PEG) subunits. In some embodiments, one or more water-soluble polymer is bonded at one or more specific position, for example at the amino terminus, of a derivative. In some embodiments, one or more water-soluble polymer is randomly attached to one or more side chains of a derivative. In some embodiments, PEG is used to improve the therapeutic capacity

for a neutralizing PCSK9 variant. In some embodiments, PEG is used to improve the therapeutic capacity of a molecule. Certain such methods are discussed, for example, in U.S. Patent No. 6,133,426, which is hereby incorporated by reference for any purpose.

[0094] Peptide analogs are commonly used in the pharmaceutical industry as non-peptide drugs with properties analogous to those of the template peptide. These types of non-peptide compound are termed “peptide mimetics” or “peptidomimetics.” Fauchere, J., *Adv. Drug Res.*, 15:29 (1986); Veber & Freidinger, *TINS*, p.392 (1985); and Evans *et al.*, *J. Med. Chem.*, 30:1229 (1987), which are incorporated herein by reference for any purpose. Such compounds are often developed with the aid of computerized molecular modeling. Peptide mimetics that are structurally similar to therapeutically useful peptides can be used to produce a similar therapeutic or prophylactic effect. Generally, peptidomimetics are structurally similar to a paradigm polypeptide (*i.e.*, a polypeptide that has a biochemical property or pharmacological activity), such as human antibody, but have one or more peptide linkages optionally replaced by a linkage selected from: --CH₂ NH--, --CH₂ S--, --CH₂ -CH₂ --, --CH=CH-(*cis* and *trans*), --COCH₂ --, --CH(OH)CH₂ --, and --CH₂ SO--, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (*e.g.*, D-lysine in place of L-lysine) can be used in some embodiments to generate more stable peptides. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation can be generated by methods known in the art (Rizo and Giersch, *Ann. Rev. Biochem.*, 61:387 (1992), incorporated herein by reference for any purpose); for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

[0095] The term “naturally occurring” as used throughout the specification in connection with biological materials such as polypeptides, nucleic acids, host cells, and the like, refers to materials which are found in nature or a form of the materials that is found in nature.

[0096] A “recombinant neutralizing PCSK9 variant” is a protein made using recombinant techniques, *i.e.*, through the expression of a recombinant nucleic acid as described herein. Methods and techniques for the production of recombinant proteins are well known in the art.

[0097] The term “neutralizing PCSK9 variant” refers to a PCSK9 variant that associates and/or binds to LDLR competitively with a full length human PCSK9. The

neutralizing PCSK9 variant also has a reduced ability to degrade or remove LDLR from a system compared to wild-type PCSK9 (e.g., SEQ ID NO: 3). In some embodiments, the neutralizing PCSK9 variant lacks a fully functional LDLR degrading V domain (e.g., the PCSK9 protein has an inactive V domain). In some embodiments, the neutralizing PCSK9 variant has a reduced ability to degrade or take LDLR out of a system compared to a similar variant lacking a fully functional V domain. Stated another way, a neutralizing PCSK9 variant has the ability to directly or indirectly reduce the degradation of LDLR and thus maintain or increase LDLR levels in a system.

[0098] The term “pro” or “pro domain” is used to refer to at least a part of the prodomain of PCSK9. In some embodiments, the prodomain of PCSK9 is involved (either directly or indirectly (such as by allowing proper folding of the Cat domain)) in the binding of PCSK9 to LDLR. While the exact starting and ending residue of the pro domain can vary based on the specific embodiment, the pro domain will at least comprise residues 61-152 of SEQ ID NO: 3 and variants thereof. In some embodiments, the pro domain comprises amino acids 31-152 of SEQ ID NO: 3, or variants thereof. Variants of the Pro domain can be 50% or more (e.g., 50-60, 60-70, 70-80, 80-90, 90-95, 95-98, 98-99, or 99-100 percent identical to the corresponding Pro domain of SEQ ID NO: 3 and/or a consensus sequence (e.g., shown in FIG. 1C-1E).

[0099] The term “Cat” or “cat domain” is used to refer to at least a part of the catalytic domain of PCSK9. In some embodiments, the “cat domain” is involved in the binding of PCSK9 to LDLR. While the exact starting and ending residue of the Cat domain can vary based on the specific embodiment, the Cat domain will at least comprise residues 153-381 and in some embodiments will comprise at least residues 153-445 of SEQ ID NO: 3 and variants thereof. Variants of the Cat domain can be 50% or more (e.g., 50-60, 60-70, 70-80, 80-90, 90-95, 95-98, 98-99, or 99-100 percent) identical to the corresponding Cat domain of SEQ ID NO: 3. In some embodiments, the cat domain can starts at residue 153 of SEQ ID NO: 3 (and variants thereof) and ends at any one of residues 447, 448, 449, 450, 451, 452, or 453 of SEQ ID NO: 3 (and variants thereof). Thus, the Cat domain can include residues 153-447, 153-448, 153-449, 153-450, 153-451, 153-452, 153-453, or 153-454 of SEQ ID NO: 3 (and variants thereof) and/or a consensus sequences (e.g., shown in FIGs. 1C-1H and FIGs. 1R₁-1R₂, SEQ ID NOs: 9, 11, 13, 15, and 30 where FIGs. 1F-1H display examples of a Cat domain).

[0100] The term “Pro/Cat” or “Pro/Cat domain” is used to refer to the section of PCSK9 that is involved in binding to LDLR. The “Pro/Cat domain” need not include both the Pro and Cat domain. In particular, something referred to as the “Pro/Cat domain” can comprise the Pro domain without the Cat domain, or the Cat domain without the Pro domain. While the term also encompasses a PCSK9 protein that includes both the Pro and the Cat domain, when both of these domains are required to be present the phrase “Pro domain and Cat domain” or similar phrase is generally employed. In some embodiments, the pro/cat domain can start at residues 31 or 61 of SEQ ID NO: 3 (and variants thereof) and end at any one of residues 447, 448, 449, 450, 451, 452, or 453 of SEQ ID NO: 3 (and variants thereof). Thus, in some embodiments, the Pro/Cat domain can include residues 31-447, 31-448, 31-449, 31-450, 31-451, 31-452, 31-453, 61-447, 61-448, 61-449, 61-450, 61-451, 61-452, and 61-453 of SEQ ID NO: 3 (and variants thereof), and/or SEQ ID NOs: 4, 5, 6, 7, 8, 24-29 and/or 31 and/or a consensus sequence (e.g., shown in FIGs. 1C-1E and 1R₁-1R₂ SEQ ID NOs: 9 and 30 (and F-H for the Cat domain, SEQ ID Nos: 11, 13, and 15)). Of course, the “pro/cat” domain can also simply include the pro or cat regions noted above. In some embodiments, variants of the pro/cat domain can be 50% or more (e.g., 50-60, 60-70, 70-80, 80-90, 90-95, 95-98, 98-99, or 99-100 percent) identical to the corresponding pro/cat domain of SEQ ID NO: 3. In some embodiments, the pro/cat domain is at least 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 96, 97, 98, 99, or more percent identical for the conserved sections of the pro/cat domain. In some embodiments, while the sections of the pro/cat domain that are 100% conserved (shown in FIGs. 1C-1E) are conserved in the pro/cat variant, the remaining positions can be changed. In some embodiments, the changes in these remaining positions can result in a pro/cat variant that is 50-60, 60-70, 70-80, 80-90, 90-95, 95-98, 98-99, or 99-100 percent identical to the corresponding pro/cat domain of SEQ ID NO: 3. In some embodiments, the variable positions are those shown as spaces or gaps in the consensus sequence in FIGs. 1C-1E and FIG. 1R₁-1R₂ or non specific amino acids in FIGs. 1F-1H (and/or shown as “Xaa” in SEQ ID NOs: 9, 11, 13, 15, and 30).

[0101] As will be appreciated by one of skill in the art, the sequence alignment shown in the attached figures (1C-1H and 1I-1L) denote the residues that, in some embodiments (including various neutralizing PCSK9 variants), can be conserved in order to obtain a functional Pro, Cat, Pro/Cat, or LDLR domain or protein and those that can be changed (and how they can be changed). In some embodiments, the sections denoted by spaces in the consensus sequences

are amino acid(s) where conservation is not required and any or no amino acid can be used at these locations (e.g., variation is readily allowable at these locations). In some embodiments, the sections denoted by “+” can similarly be altered with any amino acid. In some embodiments, the sections denoted by “+” are conservative replacements, or the replacements noted for that position in the sequence listing (or in the various organisms for the sequence alignment). As noted herein, various consensus sequences are disclosed within FIGs. 1C-1L. Thus, consensus sequences in addition to the consensus sequence explicitly identified in the figures are also disclosed herein.

[0102] The term “V” or “V domain” is used to refer the section of the PCSK9 protein that is involved in the effective degradation of LDLR. While the exact starting and ending residues of the V domain can vary based on the specific embodiment, the V domain will at least comprise residues 455-682 of SEQ ID NO: 3 and variants thereof. In some embodiment the V domain will at least comprise residues 457-679, 454-692, 457-692, 457-682, 455-692, 455-679, 454-682, or 454-679. Variants of the V domain can be 55% or more (e.g., 55-60, 60-70, 70-80, 80-90, 90-95, 95-98, 98-99, or 99-100 percent identical to the corresponding V domain of SEQ ID NO: 3. Simply because there is an amino acid sequence on the c-terminal end of a pro/cat domain does not make that sequence a V domain or an active V domain. An active V domain will also have the above noted function in regard to LDLR. As will be appreciated by one of skill in the art, inactive V domains encompass a broader scope of possible domains, sequences, and structures than do active V domains. Any protein, or a lack of PCSK9 protein, that does not achieve the V domain’s function noted above can be characterized as an inactive V domain.

[0103] The term “loop” is used to refer to the section between the V domain and the Cat domain. This section need not be called out explicitly in every embodiment. While the exact starting and ending residues of the loop can vary based on the specific embodiment, the loop can comprise residues 447-453 of SEQ ID NO: 3 and variants thereof. Variants of the loop can be 0% or more (e.g., 0-10, 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, 90-95, 95-98, 98-99, 99 percent identical to the loop of SEQ ID NO: 3. In some embodiments, any structure or section connecting the V domain to the Cat domain can be considered as a loop section. In some embodiments, the loop domain is not explicitly denoted as such and is simply part of either the Cat domain or the V domain.

[0104] The phrase “LDLR degrading” refers to the ability of the V domain (or subpart thereof), when part of a whole PCSK9 protein, to promote the degradation of LDLR. As will be appreciated by one of skill in the art in light of the present disclosure, the LDLR degrading ability of the V domain need not be a direct role. In particular, it can be possible for LDLR to be degraded by PCSK9 variants that lack the V domain. Thus, the LDLR “degrading role” or “ability” of the V domain denotes that this section of the PCSK9 protein is involved in the effective degradation of LDLR. The removal of the V domain need not completely prevent all LDLR degradation under all possible variables and circumstances (and, as noted below in the examples, in some circumstances, does not).

[0105] The phrase “fully functional LDLR degrading” or “fully functional LDLR degradation” refers to the amount of LDLR degradation that occurs from a PCSK9 protein that has the wild-type V domain following amino acid 450 of SEQ ID NO: 3. Thus, a “fully functional LDLR degrading V domain” will degrade LDLR at a rate equal to and/or greater than wild type PCSK9 (for example, SEQ ID NO: 3). Proteins that are not fully functional for LDLR degradation, that have an inactive V domain, or that lack a fully functional LDLR degrading V domain will degrade LDLR less effectively than the wild type PCSK9. Thus, for example, a variant of PCSK9 that is only 90% as effective as wild-type PCSK9 can be characterized as lacking a fully functional LDLR degrading V domain or as having an inactive V domain. A PCSK9 variant that lacks a V domain can also be described as lacking a fully functional LDLR degrading V domain or as having an inactive V domain. A PCSK9 protein that lacks a fully functional LDLR degrading V domain, that has an inactive V domain, or that lacks a V domain is less than 100% as effective as the wild type PCSK9 (SEQ ID NO: 3), include, for example, PCSK9 proteins that are 99-90, 90-80, 80-70, 70-60, 60-50, 50-40, 40-30, 30-20, 20-10, 10-5, 5-1, 1-0.1, 0.1-0.01, 0.01-0.001, 0.001-0.0001, and 0.0001 to 0% as effective as the wild type PCSK9 protein. As will be appreciated by one of skill in the art, a neutralizing PCSK9 variant can contain some or all of the V domain, as long as the V domain is not fully functional for LDLR degradation. The functionality of the V domain can be adjusted by various approaches, including, for example, removal, point mutations, insertions, deletions, etc.

[0106] The phrase term “active” as used in “active Pro domain,” “active Pro/Cat domain,” or “active Cat domain” denotes that the protein can bind to LDLR.

[0107] The term “inactive” as used in “inactive V domain” denotes that the molecule in question does not have a PCSK9 V domain that functions in LDLR degradation as effectively as the V domain in wild-type PCSK9. An inactive V domain does not require that the sequence of the V domain be present. In some embodiments, a neutralizing PCSK9 variant will have an inactive V domain if it lacks a V domain protein sequence.

[0108] The phrase “has an inactive V domain” denotes that the section of the V domain, if any section is present, is not as effective at degrading LDLR as the V domain in the full length PCSK9 protein. This does not require that any part of the V domain actually be present. Thus, a PCSK9 protein that lacks the entire V domain can also be characterized as “having an inactive V domain.” As above, the definition does not require that the protein with the inactive V domain exhibit a complete absence of LDLR degrading ability. A PCSK9 protein that has an inactive V domain will be less than 100% as effective as the wild type PCSK9 (SEQ ID NO: 3). Examples of such lower levels of effectiveness include, for example, PCSK9 proteins having V domains that are 99-90, 90-80, 80-70, 70-60, 60-50, 50-40, 40-30, 30-20, 20-10, 10-5, 5-1, 1-0.1, 0.1-0.01, 0.01-0.001, 0.001-0.0001, and 0.0001 to 0% as effective as the wild type PCSK9 protein. Nonlimiting examples of inactive or inactivated V domains include, for example, proteins that lack V domains (*e.g.*, the entire V domain is absent from the PCSK9 protein), proteins that lack 14 or more amino acids from the end (c-terminal) of the PCSK9 protein (*e.g.*, SEQ ID NO: 3), proteins in which the V domain is improperly folded (in comparison to wild-type PCSK9; *e.g.*, the C679X mutation).

[0109] The phrase “lacks the entirety of amino acids #####” denotes that the entire and exact amino acid sequence defined therein is absent from the protein. Subparts of the amino acid sequence or range can be present. For example, if the protein “lacks the entirety of amino acids 10-100 of SEQ ID NO: X,” then amino acids 10-99 or 11-100 of SEQ ID NO: X can be present, although 10-100 are excluded from being present.

[0110] The phrase “attached adjacent to an amino acid #### of SEQ ID NO: X” denotes that whatever is (or is not) to be attached is (or is not) attached immediately adjacent to a specific amino acid (####). When the phrase is being used in a negative context (for example as an exclusion), then it denotes that, if amino acid #### is present, then the item in question is not attached adjacent to it. However, the use of this phrase does not imply or require that amino acid #### is actually present when used in its negative context. As an example, the phrase “lacks the

entirety of amino acids 10-100 of SEQ ID NO: X attached adjacent to an amino acid 9 of SEQ ID NO: X" denotes that all 91 amino acids of amino acids 10-100 of SEQ ID NO: X are missing from the position adjacent to amino acid 9 of SEQ ID NO: X (if amino acid 9 is present). Thus, amino acids 11-100 can be present and attached adjacent to amino acid 9, amino acids 10-99 can be present and attached adjacent to amino acid 9, or amino acids 10-100 can be present and attached to either amino acid 8 or 11 of SEQ ID NO: 3. It is noted that, for the above type of exclusion, amino acid 9 does not need to be present. Thus, amino acids 1-5 of SEQ ID NO: X would also meet the above description, (as there is no amino acid 9 and there can be no amino acid adjacent to it). In addition, unless explicitly noted, the position "adjacent to" a specific amino acid is only the position that is greater than the noted amino acid. Thus, if the relevant amino acid is 9, then the only position adjacent to 9 is 10 (and thus position 8 is not considered "adjacent" to position 9 for the purposes of this definition). In other words, adjacent to only applies to the amino acid in the carboxy direction, not in the amino direction.

[0111] The phrase "at the appropriate position" as used in the phrase "at the appropriate position in the variant," denotes that, the appropriate position is present in the variant. For example, the phrase, "the neutralizing PCSK9 variant has a cysteine at position 30" denotes that the variant has an amino acid at position 30 and that it is a cysteine. When the phrase is used in reference to another SEQ ID NO:, it denotes that the variant is (or is not) similar to that other SEQ ID NO: in the manner described. When the phrase is used as an exclusion, then, as noted in the above definition, the position itself need not be present in the variant, but if it is, then it will not be the item described.

[0112] The term "target" refers to a molecule or a portion of a molecule capable of being bound by a neutralizing PCSK9 variant.

[0113] The terms "compete" or "competitive," when used in reference to "neutralizing PCSK9 variant" refers to the competition between a) native PCSK9 and b) PCSK9 variants for LDLR. Numerous types of competitive binding assays can be used to determine if one neutralizing PCSK9 variant competes with native PCSK9, for example: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see, e.g., Stahli *et al.*, 1983, *Methods in Enzymology* 9:242-253); solid phase direct biotin-avidin EIA (see, e.g., Kirkland *et al.*, 1986, *J. Immunol.* 137:3614-3619) solid phase direct labeled assay, solid phase direct labeled sandwich assay (see, e.g., Harlow and

Lane, 1988, *Antibodies, A Laboratory Manual*, Cold Spring Harbor Press); solid phase direct label RIA using I-125 label (see, e.g., Morel *et al.*, 1988, *Molec. Immunol.* 25:7-15); solid phase direct biotin-avidin EIA (see, e.g., Cheung, *et al.*, 1990, *Virology* 176:546-552); and direct labeled RIA (Moldenhauer *et al.*, 1990, *Scand. J. Immunol.* 32:77-82).

[0114] As used herein, “substantially pure” means that the described species of molecule is the predominant species present, that is, on a molar basis it is more abundant than any other individual species in the same mixture. In some embodiments, a substantially pure molecule is a composition wherein the object species comprises at least 50% (on a molar basis) of all macromolecular species present. In other embodiments, a substantially pure composition will comprise at least 80%, 85%, 90%, 95%, or 99% of all macromolecular species present in the composition. In other embodiments, the object species is purified to essential homogeneity wherein contaminating species cannot be detected in the composition by conventional detection methods and thus the composition consists of a single detectable macromolecular species.

[0115] The term “agent” is used herein to denote a chemical compound, a mixture of chemical compounds, a biological macromolecule, or an extract made from biological materials.

[0116] As used herein, the terms “label” or “labeled” refers to incorporation of a detectable marker. Examples include incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotin moieties that can be detected by marked avidin (e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or colorimetric methods). In some embodiments, the label or marker can also be therapeutic. Various methods of labeling polypeptides and glycoproteins are known in the art and can be used. Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (e.g., ³H, ¹⁴C, ¹⁵N, ³⁵S, ⁹⁰Y, ⁹⁹Tc, ¹¹¹In, ¹²⁵I, ¹³¹I), fluorescent labels (e.g., FITC, rhodamine, lanthanide phosphors), enzymatic labels (e.g., horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase), chemiluminescent, biotinyl groups, predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance.

[0117] The term “biological sample”, as used herein, includes, but is not limited to, any quantity of a substance from a living thing or formerly living thing. Such living things

include, but are not limited to, humans, mice, monkeys, rats, rabbits, and other animals. Such substances include, but are not limited to, blood, serum, urine, cells, organs, tissues, bone, bone marrow, lymph nodes, and skin.

[0118] The term “pharmaceutical agent composition” (or agent or drug) as used herein refers to a chemical compound, composition, agent or drug capable of inducing a desired therapeutic effect when properly administered to a patient. It does not necessarily require more than one type of ingredient.

[0119] The term “therapeutically effective amount” refers to the amount of a neutralizing PCSK9 variant determined to produce a therapeutic response in a mammal. Such therapeutically effective amounts are readily ascertained by one of ordinary skill in the art.

[0120] The term “modulator,” as used herein, is a substance that changes or alters the activity or function of a molecule. For example, a modulator can cause an increase or decrease in the magnitude of a certain activity or function of a molecule compared to the magnitude of the activity or function observed in the absence of the modulator. In some embodiments, a modulator is an inhibitor, which decreases the magnitude of at least one activity or function of a molecule. Certain exemplary activities and functions of a molecule include, but are not limited to, binding affinity, enzymatic activity, and signal transduction. Certain exemplary inhibitors include, but are not limited to, proteins, peptides, antibodies, peptibodies, carbohydrates or small organic molecules. Peptibodies are described in, e.g., U.S. Patent No. 6,660,843 (corresponding to PCT Application No. WO 01/83525).

[0121] The terms “patient” and “subject” are used interchangeably and include human and non-human animal subjects as well as those with formally diagnosed disorders, those without formally recognized disorders, those receiving medical attention, those at risk of developing the disorders, etc.

[0122] The term “treat” and “treatment” includes therapeutic treatments, prophylactic treatments, and applications in which one reduces the risk that a subject will develop a disorder or other risk factor. Treatment does not require the complete curing of a disorder and encompasses embodiments in which one reduces symptoms and/or underlying risk factors.

[0123] The term “prevent” does not require the 100% elimination of the possibility of an event. Rather, it denotes that the likelihood of the occurrence of the event has been reduced in the presence of the compound or method.

[0124] The term "native Fc" refers to molecule or sequence comprising the sequence of a non-antigen-binding fragment resulting from digestion of whole antibody, whether in monomeric or multimeric form. The original immunoglobulin source of the native Fc is preferably of human origin and can be any of the immunoglobulins, although IgG1 and IgG2 are preferred. Native Fc's are made up of monomeric polypeptides that can be linked into dimeric or multimeric forms by covalent (i.e., disulfide bonds) and non-covalent association. The number of intermolecular disulfide bonds between monomeric subunits of native Fc molecules ranges from 1 to 4 depending on class (e.g., IgG, IgA, and IgE) or subclass (e.g., IgG1, IgG2, IgG3, IgA1, IgGA2). One example of a native Fc is a disulfide-bonded dimer resulting from papain digestion of an IgG (see Ellison et al. (1982), Nucleic Acids Res. 10: 4071-9). The term "native Fc" as used herein is generic to the monomeric, dimeric, and multimeric forms.

[0125] The term "Fc variant" refers to a molecule or sequence that is modified from a native Fc but still comprises a binding site for the salvage receptor, FcRn. International applications WO 97/34631 (published Sep. 25, 1997) and WO 96/32478 describe exemplary Fc variants, as well as interaction with the salvage receptor, and are hereby incorporated by reference. Thus, the term "Fc variant" comprises a molecule or sequence that is humanized from a non-human native Fc. Furthermore, a native Fc comprises sites that can be removed because they provide structural features or biological activity that are not required for the fusion molecules of PCSK9. Thus, the term "Fc variant" comprises a molecule or sequence that lacks one or more native Fc sites or residues that affect or are involved in (1) disulfide bond formation, (2) incompatibility with a selected host cell (3) N-terminal heterogeneity upon expression in a selected host cell, (4) glycosylation, (5) interaction with complement, (6) binding to an Fc receptor other than a salvage receptor, or (7) antibody-dependent cellular cytotoxicity (ADCC). Fc variants are described in further detail hereinafter.

[0126] The term "Fc domain" encompasses native Fc and Fc variant molecules and sequences as defined above. As with Fc variants and native Fc's, the term "Fc domain" includes molecules in monomeric or multimeric form, whether digested from whole antibody or produced by other means. In some embodiments, an Fc domain can be associated to a neutralizing PCSK9 variant (e.g., via a covalent bond between the Fc domain and the neutralizing PCSK9 variant).

[0127] The term "multimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two or more polypeptide chains associated covalently,

noncovalently, or by both covalent and non-covalent interactions. IgG molecules typically form dimers; IgM, pentamers; IgD, dimers; and IgA, monomers, dimers, trimers, or tetramers. Multimers can be formed by exploiting the sequence and resulting activity of the native Ig source of the Fc or by derivatizing (as defined below) such a native Fc.

[0128] The term "dimer" as applied to Fc domains or molecules comprising Fc domains refers to molecules having two polypeptide chains associated covalently or non-covalently.

[0129] Standard techniques can be used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Enzymatic reactions and purification techniques can be performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures can be generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. *See, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual* (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)), which is incorporated herein by reference for any purpose. Unless specific definitions are provided, the nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

Neutralizing PCSK9 Variants

[0130] In some embodiments, the neutralizing PCSK9 variant provided herein is capable of inhibiting native PCSK9 from binding to LDLR. In some embodiments, this blocking results in a decrease in the degradation of LDLR *in vivo*; thereby resulting in a lowering of serum LDL in a subject.

[0131] As noted above, the ability of PCSK9 to bind to LDLR and the ability of wild-type PCSK9 to effectively degrade LDLR appear to be due to two different sections of the PCSK9 protein. As noted in the examples below, the ability of PCSK9 to effectively degrade LDLR appears to be linked to the V domain of PCSK9. Thus, in some embodiments, variants of

PCSK9 that lack fully functional LDLR degrading V domains (or have an inactive V domain) can be introduced into a system or subject without adversely increasing the amount of LDLR degradation. Moreover, as described herein, the binding of PCSK9 to LDLR is mediated by sections of the Pro and/or Cat domains of PCSK9. Thus, neutralizing PCSK9 variants that contain sufficient sections of the Pro and/or Cat domain(s) can still bind to LDLR and compete with native PCSK9 for binding to LDLR. In some embodiments, when the variant also lacks a fully functional LDLR degrading V domain (or have an inactive V domain), then the PCSK9 variant will not only block native PCSK9, but will do so while lowering LDLR degradation, thereby increasing LDLR availability and in turn decreasing the amount of LDL in the serum. Thus, in some embodiments, a neutralizing PCSK9 variant is a PCSK9 protein that has an active Pro/Cat domain and an inactive V domain.

[0132] In some embodiments, the neutralizing PCSK9 variant includes, consists, or consists essentially of the Pro and/or Cat domain(s) of PCSK9. In some embodiments, the variant includes a signal sequence (for example, amino acids 1-30 of SEQ ID NO: 3). In some embodiments, the neutralizing PCSK9 variant comprises, consists, or consists essentially of amino acids 31-447 of SEQ ID NO: 3 (or a variant of amino acids 31-447). In some embodiments, the neutralizing PCSK9 variant comprises, consists, or consists essentially of amino acids 153-374 of SEQ ID NO: 3 (or a variant of amino acids 153-374). In some embodiments, the neutralizing PCSK9 variant comprises, consists, or consists essentially of amino acids 31-374 of SEQ ID NO: 3 (or a variant of amino acids 31-374). In some embodiments, the neutralizing PCSK9 variant comprises, consists, or consists essentially of amino acids 153-454 of SEQ ID NO: 3 (or a variant of amino acids 153-454). In some embodiments, the neutralizing PCSK9 variant comprises, consists, or consists essentially of amino acids 31-449 of SEQ ID NO: 3 (or a variant of amino acids 31-449). In some embodiments, the neutralizing PCSK9 variant comprises, consists, or consists essentially of amino acids 153-381 of SEQ ID NO: 3 (or a variant of amino acids 153-381). In some embodiments, the neutralizing PCSK9 variant comprises, consists, or consists essentially of amino acids 31-381 of SEQ ID NO: 3 (or a variant of amino acids 31-381). In some embodiments, the neutralizing PCSK9 variant comprises, consists, or consists essentially of amino acids 153-382 of SEQ ID NO: 3 (or a variant of amino acids 153-382). In some embodiments, the neutralizing PCSK9 variant comprises, consists, or consists essentially of

amino acids 31-382 of SEQ ID NO: 3 (or a variant of amino acids 31-382). In some embodiments, the neutralizing PCSK9 variant comprises, consists, or consists essentially of an amino acid starting at either position 31, 61, or 153 of SEQ ID NO: 3 and ending at position 374, 381, 382, 447, 448, 449, 450, 451, 452, 453, 454, or 455 of SEQ ID NO: 3 (or a variant thereof). In some embodiments, variants can be at least 50 percent identical, for example 50-60, 60-70, 70-80, 80-90, 90-95, 95-98, 98-99 or greater identity, to the relevant section (e.g., any of the above noted sections) of SEQ ID NO: 3. In some embodiments, variants can have at least 70% homology, for example 50-60, 60-70, 70-80, 80-90, 90-95, 95-98, 98-99 or greater homology, to the relevant section of SEQ ID NO: 3.

[0133] In some embodiments, the V domain can be entirely removed. In some embodiments, a section of the V domain can be removed or altered. The section can be sufficient to prevent the neutralizing PCSK9 variant from significantly degrading LDLR.

[0134] In some embodiments, the variant lacks some or all of the V domain. In some embodiments, the V domain will be inactive and will not allow for wild-type levels of degradation of LDLR. In some embodiments, the neutralizing PCSK9 variant lacks the V domain completely. In some embodiments, the variant lacks residues 447-692, 448-692, 449-692, 450-692, 451-692, 452-692, 453-692, or 454-692 of SEQ ID NO: 3. In some embodiments, any of the above missing sections, can be present in the variant, but will not be placed immediately adjacent to the amino acid positioned in front of it in SEQ ID NO: 3. Thus, for example, 453-692, 454-692, 450-692, or 447-692 of SEQ ID NO: 3 can be present in the variant, but will not be positioned following amino acid 452, 453, 449, or 446 respectively of SEQ ID NO: 3. In some embodiments, at least the last 14 amino acids from the C-terminus of SEQ ID NO: 3 are missing (or different from the amino acids in SEQ ID NO: 3), thereby creating an inactive V domain. For example, 14-16, 16-20, 20-25, 25-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, 90-100, 100-120, 120-140, 140-160, 160-200, 200-220, 220-225 amino acids can be deleted from the C terminal portion of the V domain to produce an inactive V domain.

[0135] In some embodiments, the neutralizing PCSK9 variant includes a point mutation. In some embodiments, the point mutation is the D374Y point mutation that has an increased binding affinity to LDLR. In some embodiments, one or more other point mutations are also included in the neutralizing PCSK9 variant. For example, mutations such as I474V, R273W, H87N, A103D, G308R, S376G, D480G, R499C, D374X, where X can be Y, A, H, R,

E, F, K, L,, Y142X, C679X, R46L, L253F, A443T, A53V, H553R, Q619P, E670G and those disclosed in Kotowski IK et al, Am. J. Hum. Genet. 2006;78:410-422, (incorporated herein by reference).

[0136] In some embodiments, any of the above variations (including mutations) and lengths of the V domain can be included or excluded from any of the above variations (including mutations) in the above noted pro and/or cat domains in order to produce a neutralizing PCSK9 variant. Thus, for example, the neutralizing variant can lack residues 453-692, 454-692, 450-692, or 447-692 of SEQ ID NO: 3 (or a variant thereof) positioned next to positions 452, 453, 449, or 446 respectively of SEQ ID NO: 3, while having any one of the above pro and/or cat regions (for example, 331-454, 31-447, 31-449, 153-374, 153-454, and 31-374 of SEQ ID NO: 3 (or a variant thereof)). In addition, any of the herein disclosed neutralizing PCSK9 variants can include a valine at 474 (instead of an isoleucine), a glycine at 670 (instead of a glutamate), and/or a glutamate at 620 (instead of a glycine). In some embodiments, the wild-type PCSK9 protein is that sequence defined in Genbank sequence NM_174936. Other SNP variants can be found in Kotowski IK et al, Am. J. Hum. Genet. 2006; 78:410-422 and include R46L, A53V, L253F, R237W, A443T, I474V, Q619P, E670G, and others.

[0137] In some embodiments, variants of neutralizing PCSK9 proteins are selected by comparing various PCSK9 sequences to one another in order to determine those positions that are conserved and those positions that vary between PCSK9 sequences. In some embodiments, amino acids in the pro and/or cat domains that are conserved between various organisms are conserved while amino acids that are not conserved across two or more species are allowed to vary. Such variants can still have pro and/or cat domain(s) that still compete with native PCSK9 for binding. An example of a sequence alignment between PCSK9 proteins of various organisms can be found in FIGs. 1C to 1E. As will be appreciated by one of skill in the art, the space(s) in the consensus sequence can be filled with any of the other amino acids in the comparison at the corresponding location, or, in some embodiments, any amino acid. FIGs. 1F-1H depict another series of alignments of just the cat domain (the top sequence in the figures are from SEQ ID NO: 3, where amino acid 1-153 (of SEQ ID NO: 3) and amino acid 321-454 (of SEQ ID NO: 3)). As will be appreciated by one of skill in the art, the space(s) in the consensus sequences can be filled with any of the other amino acids in the comparison at the corresponding location, or, in some embodiments, any amino acid. Given the similarity between the sequences in FIG. 1C-1H and

SEQ ID NO: 3, the present invention contemplates that any of the above pro and/or cat domains can function as desired in a neutralizing PCSK9 variant (including variants that contain any one of the identified consensus sequences). As such, in some embodiments, any position that varies between the different PCSK9 sequences can be a position that can be altered in a neutralizing PCSK9 variant. In some embodiments, the position is altered to the other amino acid noted in the alignment. In some embodiments, the position is altered to a different amino acid. It is noted that the human PCSK9 sequence in FIGs. 1C-1E, while similar to SEQ ID NO: 3, includes an extra series of amino acids on the end of the sequence, including a glycine, followed by a proline, followed by 8 histidines. While the glycine or proline can be present or can be absent in various embodiments, the histidines are just part of a histidine tag, and are not a necessary part of the alignment or any of the proteins in the alignment. Thus, the consensus sequence need not have any of the histidines in it (all 8 can be removed in some embodiments as these are not structural elements of the protein). In some embodiments, the rat sequence in FIGs. 1C-1E has a glycine, followed by a proline, followed by 8 histidines on its end, just like the other sequences shown in FIG. 1E. Additional embodiments of PCSK9 sequences can be found in FIGs. 1M₁-1S₂, SEQ ID Nos: 25-31.

[0138] As noted above, the consensus sequences shown in the attached figures (1C-1H) indicate the residues that, in some embodiments, can be conserved in order to obtain a functional Pro/Cat domain and those that can be changed (and how they can be changed). In some embodiments, the sections of the consensus sequence denoted by spaces are amino acid(s) where conservation is not required and any or no amino acid can be used at these locations (e.g., variation is readily allowable at these locations). In some embodiments, the sections denoted by “+” can similarly be altered with any amino acid. In some embodiments, the sections denoted by “+” are conservative replacements, or the replacements noted for that position in the sequence listing (or in the various organisms for the sequence alignment).

[0139] In FIGs. 1C-1E, as more than two amino acid sequences have been aligned, the consensus sequence does not display spaces at each amino acid position that can be varied without the Pro/Cat domain losing its functionality. Thus, in this alignment, for some embodiments, even amino acids designated as a specific amino acid in the explicitly noted consensus sequence can be varied and still result in a functioning Pro/Cat domain. For example, in some embodiments, an amino acid position that is assigned a specific amino acid in the

consensus sequence (in FIGs. 1C-1E), but varies between the various organisms, can be altered. Thus, in some embodiments, amino acid positions that are conserved between organisms (for example, as shown in FIGs. 1C-1E), are conserved in the neutralizing PCSK9 variant, but the other amino acid positions (those that are different between the various organisms) can be replaced with amino acids that are different from the amino acid denoted in their particular position of the consensus sequence. In some embodiments, the amino acid that replaces the amino acid in the consensus sequence is any amino acid (or none) and need not be limited to those amino acids appearing in the different sequences shown in FIGs. 1C-1E. In some embodiments, the amino acid change is to an amino acid that is the same as at least one of the amino acids shown in that position in the various amino acid sequences shown. In some embodiments, if the amino acids aligned for one position are different, but are conserved, then the amino acid position in the consensus sequence can be any amino acid having conserved properties (e.g., polar). In some embodiments, while amino acids that are identical between one or more of the species are present in the neutralizing PCK9 variant, one or more of the other amino acids at the other position(s) are varied. In some embodiments, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, or more amino acids that are not identical between the various organisms in FIGs. 1C-1E can be replaced by any other amino acid. In some embodiments, while the amino acids that are identical across all of the species noted in the figures are kept the same, the amino acids at the other positions are allowed to vary, with as much as 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100% of these amino acids being altered to another amino acid. In some embodiments, the conserved amino acids noted in the figures can be altered or replaced by another amino acid(s).

[0140] In some embodiments, in creating a neutralizing PCSK9 variant, amino acids in the V domain that are conserved between various PCSK9 proteins of various organisms are

altered while amino acids that are not conserved across one or more species are conserved, thereby producing a protein where the V domain is not active (or is inactive). An example of this comparison, between PCSK9 from various animals, can be found in FIGs. 1C to 1E. Thus, in some embodiments, any of the conserved amino acids in the V domain of PCSK9 can be altered while the conserved amino acids in the pro and/or cat domains can be maintained in order to produce a neutralizing PCSK9 variant. In some embodiments, the amino acid is altered to the other amino acid noted in the alignment. In some embodiments, the amino acid is altered to a different amino acid.

[0141] In some embodiments, residues that are important in the binding of PCSK9 to LDLR are maintained in the pro and/or cat domain(s). For example, those residues identified herein as part of the binding surface between LDLR and LDL or LDLR and PCSK9, or involved in the creation of the binding surface, as well as those residues discussed in “Molecular basis for LDL recognition by PCSK9” (PNAS, 105:1820-1825, 2008), such as Arg 194 and Phe 379 are maintained, if present within the fragment sequence. In some embodiments, the neutralizing PCSK9 variant includes at least residues 194-379.

[0142] In some embodiments, a neutralizing PCSK9 variant can inhibit, interfere with or modulate one or more biological activities of PCSK9. In one embodiment, the neutralizing PCSK9 variant competes with native PCSK9 for binding to LDLR. In some embodiments, the neutralizing PCSK9 variant reduces binding of native PCSK9 to LDLR by at least 1%, for example, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 percent reduction of native PCSK9 binding to LDLR.

[0143] In some embodiments, the neutralizing PCSK9 variant has an IC₅₀ for blocking the binding of native PCSK9 to LDLR of less than 1 microMolar, 1000 nM to 100 nM, 100nM to 10 nM, 10nM to 1 nM, 1000pM to 500pM, 500 pM to 200 pM, less than 200 pM, 200 pM to 150 pM, 200 pM to 100 pM, 100 pM to 10 pM, 10 pM to 1 pM. This IC₅₀ can be measured between native PCSK9 to LDLR and the neutralizing PCSK9 variant to LDLR.

[0144] In some embodiments, a neutralizing PCSK9 variant does not include a C679X and/or a Q554E point mutation. In some embodiments, the neutralizing PCSK9 variant

does not include a His tag. In some embodiments, the neutralizing PCSK9 variant does not include a GST tag. In some embodiments, the neutralizing PCSK9 variant includes residue 453 of SEQ ID NO: 3, at the corresponding position in the variant. In some embodiments, the PCSK9 variant does not have the entirety of residues 453-692 removed from the protein. For example, in some embodiments, the neutralizing PCSK9 variant includes residues 31-453. In some embodiments, the neutralizing PCSK9 variant lacks residues such as 447, 448, 449, 450, 451, and 452 (or some combination thereof) of SEQ ID NO: 3. In some embodiments, the neutralizing PCSK9 variant lacks any amino acid at these positions. In some embodiments, the neutralizing PCSK9 variant lacks the corresponding amino acid at the specific position identified above in regard to SEQ ID NO: 3. In some embodiments, when explicitly stated, the neutralizing PCSK9 variants can exclude the PCSK9 variants disclosed in U.S. application 12/197093, filed August 22, 2008, hereby incorporated by reference in its entirety and especially in regard to its disclosure regarding antigen binding proteins and PCSK9 proteins and variants thereof. For example, when explicitly stated, the neutralizing PCSK9 variants can exclude a PCSK9 proteins/variants such as PCSK9 ProCat 31-449 and/or PCSK9 ProCat 31-454, with or without a his tag. In some embodiments, when explicitly stated, the neutralizing PCSK9 variants can exclude the PCSK9 variants that consist of residues 1-452 (having a His tag or a GST tag, (sequence numbering as defined in Fan et al., *American Chemical Society*, “Self-Association of Human PCSK9 Correlates with its LDLR-Degrading Activity”); residues 1-454, and 1-681 219-692 (sequence numbering as defined in Benjannet et al., *Journal of Biological Chemistry*, “NARC-1/PCSK9 and Its Natural Mutants,” 279:48865-48875, 2004); residues 219-692 (sequence numbering as defined in Benhannet et al., *J. of Biol. Chemistry*, “The Proprotein Convertase (PC) PCSK9 is Inactivated by Furin and/or PC5/6A,” 281 (41):30561-30572 (2006); residues 1-452 and 423-692 (sequence numbering as defined in Fan et al., *Biochemistry*, “Self-Assoication of Human PCSK9 Correlates with its LDLR-Degrading Activity,” 47:1631-1639 2008); residues 1-455, 1-454, and/or residues 31-454 (sequence numbering as defined by Nassoury et al., *Traffic*, “The Cellular Trafficking of Secretory Proprotein Convertase PCSK9 and its Dependence on the LDLR,” 8:718-732, 2007); any C terminal deletions in WO 2007/128121; residues 1-454 (sequence numbering as defined by Zhang et al., *PNAS*, “Structural Requirements for PCSK9-mediated degradation of the low-density lipoprotein Receptor,” 105:13045-13050, 2008); residues 1-425, 1-453, 1-694, 31-453, and 1-507 (sequence

numbering as defined by Naureckiene S. et al, Archives of Biochemistry and Biophysics, "Functional Characterization of Narc1, a Novel Proteinase Related to Proteinase K", 420:55-67, 2003); residues 31-451 and/or residues 53-451 (including variants of either of these, such as the following: P155G, W156L, N157K, L158A, I161A, R194A, D238A, D374Y, S386A, with or without a his tag)(sequence numbering as defined in Bottomley et al., J. of Biological Chemistry, "Structural and Biochemical Characterization of the Wild Type PCSK9/EGF-AB Complex and Natural FH mutants," 284:1313-23, 2008); an in-frame deletion of the eighth exon of 58 amino acids, *e.g.*, deletion of residues 395-452 (keeping 1-394 and 453 to the end, as described in Schmidt et al., DNA and Cell Biology, "A Novel Splicing Variant of Proprotein Convertase Subtilisin/Kexin Type 9, 27:183-189, 2008); and/or residues 1-692 (human), 1-691 (rat), 1-316 (rat), 1-390 (rat), 1-390 (S385A, rat), 1-425 (rat), 1-453 (rat), 1-507 (rat), 31-691 (rat), 148-691 (rat), 1-691 (rat, including optional deletion of 31-147, optional deletion of 148-425, optional deletion of 219-395, histidine 225 to tryptophan, serine 385 to alanine, or histidine 225 to tryptophan and serine 385 to alanine), 1-142, and/or 1-679 (sequence numbering as defined in Bingham et al., Cytometry A, "Proapoptotic effects of NARC 1 (= PCSK9), the gene encoding a novel serine proteinase," 69(11):1123-31, 2006). The entirety of the disclosure of each of the above noted references is incorporated herein by reference, especially in regard to their disclosures of the various PCSK9 sequences and discussion thereof. In some embodiments, any one or more of the above variants are encompassed within the group of useful neutralizing PCSK9 variants. In some embodiments, any or all of the above can be combined with or in a pharmaceutically acceptable carrier or be used for the preparation of a medicament.

[0145] In some embodiments, the neutralizing PCSK9 variant has a pro/cat domain that is different from the pro/cat domain in the cDNA sequence of NM-174936 or gi31317306. In some embodiments, the neutralizing PCSK9 variant includes point mutations at least one of the following positions: 474, 620, or 670. In some embodiments, the point mutation is Val474Iso, Gly670Glu, and/or Glu620Gly.

Vehicles

[0146] The term "vehicle" refers to a molecule that prevents degradation and/or increases half-life, reduces toxicity, reduces immunogenicity, or increases biological activity of a therapeutic protein when covalently or non-covalently bound to the therapeutic protein.

Exemplary vehicles include an Fc domain (including, for example, native Fcs, Fc variants, Fc domains, multimers, and dimers) as well as a linear polymer (e.g., polyethylene glycol (PEG), polylysine, dextran, etc.); a branched-chain polymer (see, for example, U.S. Pat. No. 4,289,872 to Denkenwalters et al., issued Sep. 15, 1981; U.S. Pat. No. 5,229,490 to Tam, issued Jul. 20, 1993; WO 93/21259 by Fréchet et al., published Oct. 28, 1993); a lipid; a cholesterol group (such as a steroid); a carbohydrate or oligosaccharide; or any natural or synthetic protein, polypeptide or peptide that binds to a salvage receptor. Vehicles are further described in U.S. Pat. No. 6,660,843, herein incorporated by reference in its entirety. In some embodiments, multiple vehicles are used, for example, Fc's at each terminus or an Fc at a terminus and a PEG group at the other terminus or a sidechain. In some embodiments, the neutralizing PCSK9 variant is combined, associated, mixed, or bonded to any one or more of the above vehicles.

[0147] An alternative vehicle would be a protein, polypeptide, peptide, antibody, antibody fragment, or small molecule (e.g., a peptidomimetic compound) capable of binding to a salvage receptor. For example, one could use as a vehicle a polypeptide as described in U.S. Pat. No. 5,739,277, issued Apr. 14, 1998 to Presta et al. Peptides could also be selected by phage display for binding to the FcRn salvage receptor. Such salvage receptor-binding compounds are also included within the meaning of "vehicle" and are within the scope of this invention. Such vehicles should be selected for increased half-life (e.g., by avoiding sequences recognized by proteases) and decreased immunogenicity (e.g., by favoring non-immunogenic sequences, as discovered in antibody humanization).

[0148] As noted above, polymer vehicles can also be used. Various means for attaching chemical moieties useful as vehicles are currently available, see e.g., Patent Cooperation Treaty ("PCT") International Publication No. WO 96/11953, entitled "N-Terminally Chemically Modified Protein Compositions and Methods," herein incorporated by reference in its entirety. This PCT publication discloses, among other things, the selective attachment of water soluble polymers to the N-terminus of proteins.

[0149] In some embodiments, the polymer vehicle is polyethylene glycol (PEG). The PEG group can be of any convenient molecular weight and can be linear or branched. The average molecular weight of the PEG will preferably range from about 2 kiloDalton ("kD") to about 100 kDa and more preferably from about 5 kDa to about 50 kDa. The PEG groups will generally be attached to the neutralizing PCSK9 variant via acylation or reductive alkylation

through a reactive group on the PEG moiety (e.g., an aldehyde, amino, thiol, or ester group) to a reactive group on the inventive compound (e.g., an aldehyde, amino, or ester group).

[0150] In some embodiments, a useful strategy for the PEGylation of synthetic peptides involves combining, through forming a conjugate linkage in solution, a peptide and a PEG moiety, each bearing a special functionality that is mutually reactive toward the other. The peptides can be easily prepared with conventional solid phase synthesis. The peptides are "preactivated" with an appropriate functional group at a specific site. The precursors are purified and fully characterized prior to reacting with the PEG moiety. Ligation of the peptide with PEG usually takes place in aqueous phase and can be easily monitored by reverse phase analytical HPLC. The PEGylated peptides can be easily purified by preparative HPLC and characterized by analytical HPLC, amino acid analysis and laser desorption mass spectrometry.

[0151] Polysaccharide polymers are another type of water soluble polymer which can be used for protein modification. Dextrans are polysaccharide polymers comprised of individual subunits of glucose predominantly linked by alpha 1-6 linkages. The dextran itself is available in many molecular weight ranges, and is readily available in molecular weights from about 1 kD to about 70 kD. Dextran is a suitable water soluble polymer for use as a vehicle by itself or in combination with another vehicle (e.g., Fc). See, for example, WO 96/11953 and WO 96/05309. The use of dextran conjugated to therapeutic or diagnostic immunoglobulins has been reported; see, for example, European Patent Publication No. 0 315 456, which is hereby incorporated by reference. Dextran of about 1 kD to about 20 kD can be used.

[0152] In another embodiment a vehicle is a non-Fc peptide or polypeptide known or believed to prevent degradation and/or increases half-life, reduces toxicity, reduces immunogenicity, or increases biological activity of a therapeutic protein. Examples of such a protein vehicle include transthyretin or HSA protein fusions. These vehicles can be fused to a PCSK9 variant.

Linkers

[0153] Any "linker" group is optional. When present, its chemical structure is not critical, since it serves primarily as a spacer. The linker can be made up of amino acids linked together by peptide bonds. Thus, in some embodiments, the linker is made up of from 1 to 20 amino acids linked by peptide bonds, wherein the amino acids are selected from the 20 naturally

occurring amino acids. Some of these amino acids can be glycosylated, as is well understood by those in the art. In some embodiments, the 1 to 20 amino acids are selected from glycine, alanine, proline, asparagine, glutamine, and lysine. In some embodiments, a linker is made up of a majority of amino acids that are sterically unhindered, such as glycine and alanine. In some embodiments, linkers are polyglycines (particularly (Gly)₄, (Gly)₅), poly(Gly-Ala), and polyalanines. Other specific examples of linkers are: (Gly)₃ Lys(Gly)₄; (Gly)₃ AsnGlySer(Gly)₂; (Gly)₃ Cys(Gly)₄; and GlyProAsnGlyGly.

[0154] To explain the above nomenclature, for example, (Gly)₃ Lys(Gly)₄ means Gly-Gly-Gly-Lys-Gly-Gly-Gly-Gly. Combinations of Gly and Ala are also preferred. The linkers shown here are exemplary and can be much longer and can include other residues.

[0155] Non-peptide linkers are also possible. For example, alkyl linkers such as --NH--(CH₂)_s--C(O)--, wherein s=2-20 could be used. These alkyl linkers can further be substituted by any non-sterically hindering group such as lower alkyl (e.g., C₁--C₆) lower acyl, halogen (e.g., Cl, Br), CN, NH₂, phenyl, etc. An exemplary non-peptide linker is a PEG linker, wherein the linker has a molecular weight of 100 to 5000 kD, for example, 100 to 500 kD. The peptide linkers can be altered to form derivatives in the same manner as described above.

Derivatives

[0156] In some embodiments, the neutralizing PCSK9 variant (and/or the vehicle) is derivatized. Such derivatives can improve the solubility, absorption, biological half life, and the like of the compounds. The moieties can alternatively eliminate or attenuate any undesirable side-effect of the compounds and the like. In some embodiments, the moiety can add additional properties to the molecule as a whole. Exemplary derivatives are provided herein.

[0157] The neutralizing PCSK9 variant or some portion thereof is cyclic. For example, the peptide portion can be modified to contain two or more Cys residues (e.g., in the linker), which could cyclize by disulfide bond formation.

[0158] The neutralizing PCSK9 variant is cross-linked or is rendered capable of cross-linking between molecules. For example, the peptide portion can be modified to contain one Cys residue and thereby be able to form an intermolecular disulfide bond with a like molecule. The compound can also be cross-linked through its C-terminus.

[0159] One or more peptidyl [--C(O)NR--] linkages (bonds) is replaced by a non-peptidyl linkage. Exemplary non-peptidyl linkages are --CH₂ -carbamate [--CH₂ --OC(O)NR--], phosphonate, --CH₂ -sulfonamide [--CH₂ --S(O)₂ NR--], urea [--NHC(O)NH--], --CH₂ -secondary amine, and alkylated peptide [--C(O)NR₆ -- wherein R₆ is lower alkyl].

[0160] The N-terminus is derivatized. Typically, the N-terminus can be acylated or modified to a substituted amine. Exemplary N-terminal derivative groups include --NRR₁ (other than --NH₂), --NRC(O)R₄, --NRC(O)OR₁, --NRS(O)₂ R₁, --NHC(O)NHR₁, succinimide, or benzyloxycarbonyl-NH-- (CBZ--NH--), wherein R and R₁ are each independently hydrogen or lower alkyl and wherein the phenyl ring can be substituted with 1 to 3 substituents selected from the group consisting of C₁ -C₄ alkyl, C₁ -C₄ alkoxy, chloro, and bromo.

[0161] The free C-terminus is derivatized. Typically, the C-terminus is esterified or amidated. For example, one can use methods described in the art to add (NH--CH₂ --CH₂ --NH₂)₂ to neutralizing PCSK9 variants. Likewise, one can use methods described in the art to add --NH₂ to neutralizing PCSK9 variants. Exemplary C-terminal derivative groups include, for example, --C(O)R₂ wherein R₂ is lower alkoxy or --NR₃ R₄ wherein R₃ and R₄ are independently hydrogen or C₁ -C₈ alkyl (preferably C₁ -C₄ alkyl).

[0162] A disulfide bond is replaced with another, preferably more stable, cross-linking moiety (e.g., an alkylene). See, e.g., Bhatnagar et al. (1996), J. Med. Chem. 39: 3814-9; Alberts et al. (1993) Thirteenth Am. Pep. Symp., 357-9. 8. One or more individual amino acid residues are modified. Various derivatizing agents are known to react specifically with selected sidechains or terminal residues, as described in detail below.

[0163] Lysinyl residues and amino terminal residues can be reacted with succinic or other carboxylic acid anhydrides, which reverse the charge of the lysinyl residues. Other suitable reagents for derivatizing alpha-amino-containing residues include imidoesters such as methyl picolinimidate; pyridoxal phosphate; pyridoxal; chloroborohydride; trinitrobenzenesulfonic acid; O-methylisourea; 2,4 pentanedione; and transaminase-catalyzed reaction with glyoxylate. Arginyl residues can be modified by reaction with any one or combination of several conventional reagents, including phenylglyoxal, 2,3-butanedione, 1,2-cyclohexanedione, and ninhydrin. Derivatization of arginyl residues requires that the reaction be performed in alkaline conditions because of the high pKa of the guanidine functional group. Furthermore, these reagents can react with the groups of lysine as well as the arginine epsilon-amino group.

Specific modification of tyrosyl residues has been studied extensively, with particular interest in introducing spectral labels into tyrosyl residues by reaction with aromatic diazonium compounds or tetranitromethane. Most commonly, N-acetylimidazole and tetranitromethane are used to form O-acetyl tyrosyl species and 3-nitro derivatives, respectively. Carboxyl sidechain groups (aspartyl or glutamyl) can be selectively modified by reaction with carbodiimides ($R'-N=C=N-R'$) such as 1-cyclohexyl-3-(2-morpholinyl-(4-ethyl) carbodiimide or 1-ethyl-3-(4-azonia-4,4-dimethylpentyl) carbodiimide. Furthermore, aspartyl and glutamyl residues can be converted to asparaginyl and glutaminyl residues by reaction with ammonium ions. Glutaminyl and asparaginyl residues can be deamidated to the corresponding glutamyl and aspartyl residues. Alternatively, these residues are deamidated under mildly acidic conditions. Cysteinyl residues can be replaced by amino acid residues or other moieties either to eliminate disulfide bonding or, conversely, to stabilize cross-linking. See, e.g., Bhatnagar et al. (1996), *J. Med. Chem.* 39: 3814-9.

[0164] Derivatization with bifunctional agents can be useful for cross-linking the peptides or their functional derivatives to a water-insoluble support matrix or to other macromolecular vehicles. Commonly used cross-linking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), and bifunctional maleimides such as bis-N-maleimido-1,8-octane. Derivatizing agents such as methyl-3-[(*p*-azidophenyl)dithio]propioimidate yield photoactivatable intermediates that are capable of forming crosslinks in the presence of light. Alternatively, reactive water-insoluble matrices such as cyanogen bromide-activated carbohydrates and the reactive substrates described in U.S. Pat. Nos. 3,969,287; 3,691,016; 4,195,128; 4,247,642; 4,229,537; and 4,330,440 are employed for protein immobilization.

[0165] Carbohydrate (oligosaccharide) groups can be attached to sites that are known to be glycosylation sites in proteins. Generally, O-linked oligosaccharides are attached to serine (Ser) or threonine (Thr) residues while N-linked oligosaccharides are attached to asparagine (Asn) residues when they are part of the sequence Asn-X-Ser/Thr, where X can be any amino acid except proline. X is preferably one of the 19 naturally occurring amino acids other than proline. The structures of N-linked and O-linked oligosaccharides and the sugar residues found

in each type are different. One type of sugar that is commonly found on both is N-acetylneuraminic acid (referred to as sialic acid). Sialic acid is usually the terminal residue of both N-linked and O-linked oligosaccharides and, by virtue of its negative charge, can confer acidic properties to the glycosylated compound. Such site(s) can be incorporated in the linker of the neutralizing PCSK9 variant and can be glycosylated by a cell during recombinant production of the polypeptide compounds (e.g., in mammalian cells such as CHO, BHK, COS). However, such sites can further be glycosylated by synthetic or semi-synthetic procedures known in the art.

[0166] Other possible modifications include hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, oxidation of the sulfur atom in Cys, methylation of the alpha-amino groups of lysine, arginine, and histidine side chains. Creighton, Proteins: Structure and Molecule Properties (W. H. Freeman & Co., San Francisco), pp. 79-86 (1983).

[0167] In some embodiments, cysteine(s), arginine(s), and/or lysine(s) can be introduced into the neutralizing PCSK9 variant as a cite(s) of pegylation.

[0168] Neutralizing PCSK9 variants can be changed at the DNA level, as well. The DNA sequence of any portion of the compound can be changed to codons more compatible with the chosen host cell. Codons can be substituted to eliminate restriction sites or to include silent restriction sites, which can aid in processing of the DNA in the selected host cell. The vehicle, linker and peptide DNA sequences can be modified to include any of the foregoing sequence changes.

[0169] In some embodiments, neutralizing PCSK9 variants include glycosylation wherein the number and/or type of glycosylation site has been altered compared to the amino acid sequences of a parent polypeptide. In some embodiments, protein variants comprise a greater or a lesser number of N-linked glycosylation sites than the native protein. An N-linked glycosylation site is characterized by the sequence: Asn-X-Ser or Asn-X-Thr, wherein the amino acid residue designated as X can be any amino acid residue except proline. The substitution of amino acid residues to create this sequence provides a potential new site for the addition of an N-linked carbohydrate chain. Alternatively, substitutions which eliminate this sequence will remove an existing N-linked carbohydrate chain. Also provided is a rearrangement of N-linked carbohydrate chains wherein one or more N-linked glycosylation sites (typically those that are naturally occurring) are eliminated and one or more new N-linked sites are created. Additional

preferred variants include cysteine variants wherein one or more cysteine residues are deleted from or substituted for another amino acid (e.g., serine) as compared to the parent amino acid sequence. Cysteine variants generally have fewer cysteine residues than the native protein, and typically have an even number to minimize interactions resulting from unpaired cysteines.

[0170] In some embodiments, the neutralizing PCSK9 variant is associated with at least a part of an antibody. In some embodiments, the neutralizing PCSK9 variant is part of an antibody fusion protein. As will be appreciated by one of skill in the art, a fusion protein can include various antibody sequences. In some embodiments, the neutralizing PCSK9 variant is fused to a full length antibody. In some embodiments, the neutralizing PCSK9 variant is fused to an antibody that binds to LDLR, thereby further increasing the likelihood that the neutralizing PCSK9 variant will be directed to its target. Non-neutralizing antibody fusions also form an aspect of the present invention. In this embodiment the non-neutralizing antibody fused to a PCSK9 variant can perform the function of increasing the half life of the PCSK9 variant.

[0171] In some embodiments, as noted above, the neutralizing PCSK9 variant is fused to a fragment of an antibody, such as a Fc domain. In some embodiments, the fusion protein will comprise, consist, or consist essentially of a Fc domain. In some embodiments, the fusion protein will comprise, consist, or consist essentially of a native Fc region. In some embodiments, the antibody or binding fragment thereof that is attached or fused to the neutralizing PCSK9 variant will bind to LDLR.

[0172] In some embodiments, any of the herein disclosed neutralizing PCSK9 variants, including antibody fusions, can be made from nucleic acid sequences encoding such protein sequences. Thus, nucleic acid sequences, vectors, and cells comprising these compounds are also contemplated herein.

[0173] In some embodiments, the neutralizing PCSK9 variant binds to a LDLR variant. In some embodiments, the variants of LDLR are at least 50% identical to human LDLR. It is noted that variants of LDLR are known to those of skill in the art (e.g., Brown MS et al, "Calcium cages, acid baths and recycling receptors" *Nature* 388: 629-630, 1997). In some embodiments, the neutralizing PCSK9 variant can raise the level of effective LDLR in heterozygote familial hypercholesterolemia (where a loss-of function variant of LDLR is present). Three exemplary LDLR sequences are shown in FIGS. 1I-1L (mouse, cynomolgus monkey, and human amino acid sequences). In some embodiments, the neutralizing PCSK9

variant will bind to a protein comprising at least one of the sequences in FIG. 1I-1L. In some embodiments the native PCSK9 variant will bind to a LDLR variant that comprises, consists, or consists essentially of the consensus sequence in FIGS. 1I-1L. In some embodiments, the LDLR variant will comprise each of the conserved amino acids identified in the consensus sequence in FIGS. 1I-1L. As will be appreciated by one of skill in the art, the space(s) in the consensus sequence can be filled with any of the other amino acids in the comparison at the corresponding location, or, in some embodiments, any amino acid.

[0174] In some embodiments, the neutralizing PCSK9 variant binds to and blocks LDLR from binding to other variants of PCSK9. These variants of PCSK9 are at least 50%, 50-60, 60-70, 70-80, 80-90, 90-95, 95-99, or greater percent identity to the form of PCSK9 depicted in FIG. 1A. In some embodiments, the neutralizing PCSK9 variant is a human variant, such as variants at position 474. In some embodiments, the amino acid at position 474 is valine (as in other humans) or threonine (as in cyno and mouse).

[0175] In some embodiments, variants of PCSK9 are contemplated, wherein one freely mutates the amino acids on the exterior of PCSK9, while conservatively altering those inside of PCSK9. In some embodiments, variants of PCSK9 are contemplated where one does not or only conservatively alters those residues on the binding surface between PCSK9 and LDLR, while freely or conservatively altering the residues on the rest of the PCSK9 surface or the inside of the protein. Various neutralizing PCSK9 variants are discussed herein and in the above sections.

[0176] In some embodiments, the neutralizing PCSK9 variant comprises a protein that has a sequence that start at residues 31 or 61 of SEQ ID NO: 3 (and variants thereof) and ends at any one of residues 447, 448, 449, 450, 451, 452, or 453 of SEQ ID NO: 3 (and variants thereof). Thus, in some embodiments, the neutralizing PCSK9 variant can include residues 31-447, 31-448, 31-449, 31-450, 31-451, 31-452, 31-453, 61-447, 61-448, 61-449, 61-450, 61-451, 61-452, and 61-453 of SEQ ID NO: 3 (and variants thereof) and/or a consensus sequence (e.g., shown in FIGs. 1C-1E, FIG. 1R₁-1R₂ (SEQ ID NO: 30) and FIG. F-H (for the Cat domain). In some embodiments, variants can be 50% or more (e.g., 50-60, 60-70, 70-80, 80-90, 90-95, 95-98, 98-99, or 99-100 percent) identical to the pro/cat domain of SEQ ID NO: 3 over the specific sequence length. In some embodiments, the neutralizing PCSK9 variant is at least 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 96, 97, 98, 99%, or more identical for the conserved sections of the pro/cat

domain. In some embodiments, while the sections of the pro/cat domain in the neutralizing PCSK9 variant that are 100% conserved (e.g., as shown in FIGs. 1C-1E) are present, the remaining positions can be changed. In some embodiments, the changes in these remaining positions can result in a pro/cat section in the neutralizing PCSK9 variant that is 50-60, 60-70, 70-80, 80-90, 90-95, 95-98, 98-99, or 99-100 percent identical to the corresponding pro/cat domain of SEQ ID NO: 3.

[0177] Additionally, one skilled in the art can review structure-function studies identifying residues in similar polypeptides that are important for activity or structure. In view of such a comparison, one can predict the importance of amino acid residues in a protein that correspond to amino acid residues which are important for activity or structure in similar proteins. One skilled in the art can opt for chemically similar amino acid substitutions for such predicted important amino acid residues.

[0178] One skilled in the art can also analyze the three-dimensional structure and amino acid sequence in relation to that structure. In view of such information, one skilled in the art can predict the alignment of amino acid residues of a protein fragment with respect to its three dimensional structure. In some embodiments, one skilled in the art can choose not to make radical changes to amino acid residues predicted to be on the surface of the protein, since such residues can be involved in important interactions with other molecules. Moreover, one skilled in the art can generate and test variants containing a single amino acid substitution at each desired amino acid residue. The variants can then be screened using activity assays known to those skilled in the art, or as described in the Examples disclosed herein. Such variants can be used to gather information about suitable variants. For example, if one discovered that a change to a particular amino acid residue resulted in destroyed, undesirably reduced, or unsuitable activity, variants with such a change can be avoided. In other words, based on information gathered from such routine experiments, one skilled in the art can readily determine the amino acids where further substitutions should be avoided either alone or in combination with other mutations.

[0179] A number of scientific publications have been devoted to the prediction of secondary structure. See Moult J., Curr. Op. in Biotech., 7(4):422-427 (1996), Chou *et al.*, Biochemistry, 13(2):222-245 (1974); Chou *et al.*, Biochemistry, 113(2):211-222 (1974); Chou *et al.*, Adv. Enzymol. Relat. Areas Mol. Biol., 47:45-148 (1978); Chou *et al.*, Ann. Rev. Biochem.,

47:251-276 and Chou *et al.*, *Biophys. J.*, 26:367-384 (1979). Moreover, computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two polypeptides or proteins which have a sequence identity of greater than 30%, or similarity greater than 40% often have similar structural topologies. The recent growth of the protein structural database (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within a polypeptide's or protein's structure. *See* Holm *et al.*, *Nucl. Acid. Res.*, 27(1):244-247 (1999).

[0180] Additional methods of predicting secondary structure include “threading” (Jones, D., *Curr. Opin. Struct. Biol.*, 7(3):377-87 (1997); Sippl *et al.*, *Structure*, 4(1):15-19 (1996)), “profile analysis” (Bowie *et al.*, *Science*, 253:164-170 (1991); Gribskov *et al.*, *Meth. Enzym.*, 183:146-159 (1990); Gribskov *et al.*, *Proc. Nat. Acad. Sci. USA*, 84(13):4355-4358 (1987)), and “evolutionary linkage” (*See* Holm, *supra* (1999), and Brenner, *supra* (1997)).

[0181] According to certain embodiments, amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and/or (4) confer or modify other physicochemical or functional properties on such polypeptides. According to certain embodiments, single or multiple amino acid substitutions (in some embodiments, conservative amino acid substitutions) can be made in the naturally-occurring sequence (in some embodiments, in the portion of the polypeptide outside the domain(s) forming intermolecular contacts). In some embodiments, a conservative amino acid substitution typically may not substantially change the structural characteristics of the parent sequence (e.g., a replacement amino acid should not tend to break a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described in *Proteins, Structures and Molecular Principles* (Creighton, Ed., W. H. Freeman and Company, New York (1984)); *Introduction to Protein Structure* (C. Branden & J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton *et al.*, *Nature*, 354:105 (1991), which are each incorporated herein by reference.

[0182] In some embodiments, the neutralizing PCSK9 variant (or nucleic acid sequence encoding it) is a variant if the nucleic acid sequence that encodes the particular neutralizing PCSK9 variant can selectively hybridize to any of the nucleic acid sequences that

encode the protein in SEQ ID NO: 3 under moderately stringent or stringent conditions. In one embodiment, suitable moderately stringent conditions include prewashing in a solution of 5XSSC; 0.5% SDS, 1.0 mM EDTA (pH 8:0); hybridizing at 50° C, -65° C, 5xSSC, overnight or, in the event of cross-species homology, at 45° C with 0.5xSSC; followed by washing twice at 65° C for 20 minutes with each of 2x, 0.5x and 0.2xSSC containing 0.1% SDS. Such hybridizing DNA sequences are also within the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode a variant that is encoded by a hybridizing DNA sequence and the amino acid sequences that are encoded by these nucleic acid sequences. In some embodiments, suitable high stringency conditions are used and include hybridization at about 65° C in 0.1xSSC. In some embodiments, suitable high stringency conditions include washing in 0.1xSSPE and 0.2% SDS at 65° C for 15 minutes. In some embodiments, suitable high stringency conditions include 31% v/v to 50% v/v formamide and 0.01M to 0.15M salt at 42° C and washing conditions of 0.1×SCC, 0.5% w/v SDS at 60° C. Such hybridizing DNA sequences are also within the scope of this invention, as are nucleotide sequences that, due to code degeneracy, encode a variant that is encoded by a hybridizing DNA sequence and the amino acid sequences that are encoded by these nucleic acid sequences.

[0183] The phrase "selectively hybridize" referred to in this context means to detectably and selectively bind. Such, polynucleotides, oligonucleotides, and fragments thereof selectively hybridize to nucleic acid strands under hybridization and wash conditions that minimize appreciable amounts of detectable binding to nonspecific nucleic acids. High stringency conditions can be used to achieve selective hybridization conditions as known in the art and discussed herein. Generally, the nucleic acid sequence homology between the polynucleotides, oligonucleotides, and fragments and a nucleic acid sequence of interest will be at least 80%, and more typically with preferably increasing homologies of at least 85%, 90%, 95%, 99%, and 100%. Two amino acid sequences are homologous if there is a partial or complete identity between their sequences. For example, 85% homology means that 85% of the amino acids are identical when the two sequences are aligned for maximum matching. Gaps (in either of the two sequences being matched) are allowed in maximizing matching; gap lengths of 5 or less are preferred with 2 or less being more preferred. Alternatively and preferably, two protein sequences (or polypeptide sequences derived from them of at least 30 amino acids in length) are homologous, as this term is used herein, if they have an alignment score of at more

than 5 (in standard deviation units) using the program ALIGN with the mutation data matrix and a gap penalty of 6 or greater. See Dayhoff, M. O., in *Atlas of Protein Sequence and Structure*, pp. 101-110 (Volume 5, National Biomedical Research Foundation (1972)) and Supplement 2 to this volume, pp. 1-10. The two sequences or parts thereof are more preferably homologous if their amino acids are greater than or equal to 50% identical when optimally aligned using the ALIGN program. The term "corresponds to" is used herein to mean that a polynucleotide sequence is homologous (i.e., is identical, not strictly evolutionarily related) to all or a portion of a reference polynucleotide sequence, or that a polypeptide sequence is identical to a reference polypeptide sequence. In contradistinction, the term "complementary to" is used herein to mean that the complementary sequence is homologous to all or a portion of a reference polynucleotide sequence. For illustration, the nucleotide sequence "TATAC" corresponds to a reference sequence "TATAC" and is complementary to a reference sequence "GTATA".

[0184] For example, a "conservative amino acid substitution" can involve a substitution of a native amino acid residue with a nonnative residue such that there is little or no effect on the polarity or charge of the amino acid residue at that position. Furthermore, any native residue in the polypeptide can also be substituted with alanine and/or arginine, as has been previously described for "alanine scanning mutagenesis" and "arginine scanning mutagenesis."

[0185] Desired amino acid substitutions (whether conservative or non-conservative) can be determined by those skilled in the art at the time such substitutions are desired. In some embodiments, amino acid substitutions can be used to identify important residues of PCSK9, or to increase or decrease the affinity of the neutralizing PCSK9 variant as described herein.

Antibodies to Neutralizing PCSK9 Variants

[0186] In some embodiments, antibodies to any of the sequences or neutralizing PCSK9 variants described herein can be made and used. These antibodies are selective for the neutralizing PCSK9 variant over native PCSK9. In some embodiments, the antibody binds to a neutralizing PCSK9 variant that consists essentially of the Pro/Cat domain of PCSK9. In some embodiments, the antibody is selective for this neutralizing PCSK9 variant over wild-type PCSK9.

[0187] As will be appreciated by one of skill in the art, the antibodies can be created by raising antibodies to the neutralizing PCSK9 variant and then identifying those antibodies that

will not bind (or will not bind as effectively as antibodies to native PCSK9) to native PCSK9. In some embodiments, the antibodies will bind to the neutralizing PCSK9 variant with a K_D that is at least 1, 1-10, 10-50, or 50-100% better than the K_D of the antibody to human PCSK9. In some embodiments, the antibodies will bind to the neutralizing PCSK9 variant with a K_D that is at least 2-5, 5-10, 10-50, 50-100, 100-1000, 1000-10,000, 10,000-100,000, or 100,000- 10^6 better than the K_D of the antibody for the native PCSK9. As will be appreciated by one of skill in the art, as the neutralizing PCSK9 variant will have an inactive V domain that can be structurally different (and even absent) from the wild type PCSK9 protein, such selective antibodies will be readily attainable given the present disclosure. In some embodiments, an adjuvant is used with the neutralizing PCSK9 variant to create the above antibodies.

[0188] As will be appreciated by one of skill in the art, the antibodies can be used to selectively observe the amount of the neutralizing PCSK9 variant without inadvertently detecting native PCSK9 as well.

Cell Lines and Expression of Neutralizing PCSK9 Variants

[0189] In some embodiments, neutralizing PCSK9 variants can be expressed in cell lines. In some embodiments, sequences encoding particular neutralizing PCSK9 variants can be used for transformation of a suitable mammalian host cell. According to certain embodiments, transformation can be by any known method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus (or into a viral vector) and transducing a host cell with the virus (or vector) or by transfection procedures known in the art, as exemplified by U.S. Pat. Nos. 4,399,216, 4,912,040, 4,740,461, and 4,959,455 (which patents are hereby incorporated herein by reference for any purpose). In some embodiments, the transformation procedure used can depend upon the host to be transformed. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include, but are not limited to, dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, and direct microinjection of the DNA into nuclei.

[0190] Mammalian cell lines available as hosts for expression are well known in the art and include, but are not limited to, many immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO)

cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), and a number of other cell lines. In some embodiments, cell lines can be selected through determining which cell lines have high expression levels. Appropriate expression vectors for mammalian host cells are well known.

[0191] In some embodiments, any of a variety of expression vector/host systems can be utilized to express polynucleotide molecules encoding polypeptides comprising one or more protein segments. Such systems include, but are not limited to, microorganisms, such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with virus expression vectors (e.g., baculovirus); plant cell systems transfected with virus expression vectors (e.g., cauliflower mosaic virus, CaMV, tobacco mosaic virus, TMV) or transformed with bacterial expression vectors (e.g., Ti or pBR322 plasmid); or animal cell systems.

[0192] In some embodiments, a polypeptide comprising one or more neutralizing PCSK9 variant is recombinantly expressed in yeast. Certain such embodiments use commercially available expression systems, e.g., the *Pichia* Expression System (Invitrogen, San Diego, CA), following the manufacturer's instructions. In some embodiments, such a system relies on the pre-pro-alpha sequence to direct secretion. In some embodiments, transcription of the insert is driven by the alcohol oxidase (AOX1) promoter upon induction by methanol.

[0193] In some embodiments, a secreted polypeptide comprising one or more neutralizing PCSK9 variant is purified from yeast growth medium. In some embodiments, the methods used to purify a polypeptide from yeast growth medium is the same as those used to purify the polypeptide from bacterial and mammalian cell supernatants.

[0194] In some embodiments, a nucleic acid encoding a polypeptide comprising one or more neutralizing PCSK9 variant is cloned into a baculovirus expression vector, such as pVL1393 (PharMingen, San Diego, CA). In some embodiments, such a vector can be used according to the manufacturer's directions (PharMingen) to infect *Spodoptera frugiperda* cells in sF9 protein-free media and to produce recombinant polypeptide. In some embodiments, a polypeptide is purified and concentrated from such media using a heparin-Sepharose column (Pharmacia).

[0195] In some embodiments, a polypeptide comprising one or more neutralizing PCSK9 variant is expressed in an insect system. Certain insect systems for polypeptide

expression are well known to those of skill in the art. In one such system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. In some embodiments, a nucleic acid molecule encoding a polypeptide can be inserted into a nonessential gene of the virus, for example, within the polyhedrin gene, and placed under control of the promoter for that gene. In some embodiments, successful insertion of a nucleic acid molecule will render the nonessential gene inactive. In some embodiments, that inactivation results in a detectable characteristic. For example, inactivation of the polyhedrin gene results in the production of virus lacking coat protein.

[0196] In some embodiments, recombinant viruses can be used to infect *S. frugiperda* cells or *Trichoplusia* larvae. See, e.g., Smith *et al.*, J. Virol., 46: 584 (1983); Engelhard *et al.*, Proc. Nat. Acad. Sci. (USA), 91: 3224-7 (1994).

[0197] In some embodiments, polypeptides comprising one or more neutralizing PCSK9 variant made in bacterial cells are produced as insoluble inclusion bodies in the bacteria. In some embodiments, host cells comprising such inclusion bodies are collected by centrifugation; washed in 0.15 M NaCl, 10 mM Tris, pH 8, 1 mM EDTA; and treated with 0.1 mg/ml lysozyme (Sigma, St. Louis, MO) for 15 minutes at room temperature. In some embodiments, the lysate is cleared by sonication, and cell debris is pelleted by centrifugation for 10 minutes at 12,000 X g. In some embodiments, the polypeptide-containing pellet is resuspended in 50 mM Tris, pH 8, and 10 mM EDTA; layered over 50% glycerol; and centrifuged for 30 minutes at 6000 X g. In some embodiments, that pellet can be resuspended in standard phosphate buffered saline solution (PBS) free of Mg⁺⁺ and Ca⁺⁺. In some embodiments, the polypeptide is further purified by fractionating the resuspended pellet in a denaturing SDS polyacrylamide gel (See, e.g., Sambrook *et al.*, *supra*). In some embodiments, such a gel can be soaked in 0.4 M KCl to visualize the protein, which can be excised and electroeluted in gel-running buffer lacking SDS. According to certain embodiments, a Glutathione-S-Transferase (GST) fusion protein is produced in bacteria as a soluble protein. In some embodiments, such GST fusion protein is purified using a GST Purification Module (Pharmacia).

[0198] In some embodiments, it is desirable to “refold” certain polypeptides, e.g., polypeptides comprising one or more neutralizing PCSK9 variant. In some embodiments, such polypeptides are produced using certain recombinant systems discussed herein. In some

embodiments, polypeptides are “refolded” and/or oxidized to form desired tertiary structure and/or to generate disulfide linkages. In some embodiments, such structure and/or linkages are related to certain biological activity of a polypeptide. In some embodiments, refolding is accomplished using any of a number of procedures known in the art. Exemplary methods include, but are not limited to, exposing the solubilized polypeptide agent to a pH typically above 7 in the presence of a chaotropic agent. An exemplary chaotropic agent is guanidine. In some embodiments, the refolding/oxidation solution also contains a reducing agent and the oxidized form of that reducing agent. In some embodiments, the reducing agent and its oxidized form are present in a ratio that will generate a particular redox potential that allows disulfide shuffling to occur. In some embodiments, such shuffling allows the formation of cysteine bridges. Exemplary redox couples include, but are not limited to, cysteine/cystamine, glutathione/dithiobisGSH, cupric chloride, dithiothreitol DTT/dithiane DTT, and 2-mercaptoethanol (bME)/dithio-bME. In some embodiments, a co-solvent is used to increase the efficiency of refolding. Exemplary cosolvents include, but are not limited to, glycerol, polyethylene glycol of various molecular weights, and arginine.

[0199] In some embodiments, a polypeptide comprising one or more neutralizing PCSK9 variants is substantially purified. Certain protein purification techniques are known to those of skill in the art. In some embodiments, protein purification involves crude fractionation of polypeptide fractionations from non-polypeptide fractions. In some embodiments, polypeptides are purified using chromatographic and/or electrophoretic techniques. Exemplary purification methods include, but are not limited to, precipitation with ammonium sulphate; precipitation with PEG; immunoprecipitation; heat denaturation followed by centrifugation; chromatography, including, but not limited to, affinity chromatography (e.g., Protein-A-Sepharose), ion exchange chromatography, exclusion chromatography, and reverse phase chromatography; gel filtration; hydroxyapatite chromatography; isoelectric focusing; polyacrylamide gel electrophoresis; and combinations of such and other techniques. In some embodiments, a polypeptide is purified by fast protein liquid chromatography or by high pressure liquid chromatography (HPLC). In some embodiments, purification steps can be changed or certain steps can be omitted, and still result in a suitable method for the preparation of a substantially purified polypeptide.

[0200] In some embodiments, one quantitates the degree of purification of a polypeptide preparation. Certain methods for quantifying the degree of purification are known to those of skill in the art. Certain exemplary methods include, but are not limited to, determining the specific binding activity of the preparation and assessing the amount of a polypeptide within a preparation by SDS/PAGE analysis. Certain exemplary methods for assessing the amount of purification of a polypeptide preparation comprise calculating the binding activity of a preparation and comparing it to the binding activity of an initial extract. In some embodiments, the results of such a calculation are expressed as “fold purification.” The units used to represent the amount of binding activity depend upon the particular assay performed.

[0201] In some embodiments, a polypeptide comprising one or more neutralizing PCSK9 variants is partially purified. In some embodiments, partial purification can be accomplished by using fewer purification steps or by utilizing different forms of the same general purification scheme. For example, in some embodiments, cation-exchange column chromatography performed utilizing an HPLC apparatus will generally result in a greater “fold purification” than the same technique utilizing a low-pressure chromatography system. In some embodiments, methods resulting in a lower degree of purification can have advantages in total recovery of polypeptide, or in maintaining binding activity of a polypeptide.

[0202] In certain instances, the electrophoretic migration of a polypeptide can vary, sometimes significantly, with different conditions of SDS/PAGE. *See, e.g., Capaldi et al., Biochem. Biophys. Res. Comm., 76: 425 (1977).* It will be appreciated that under different electrophoresis conditions, the apparent molecular weights of purified or partially purified polypeptide can be different.

Examples of Therapeutic Uses and Pharmaceutical Compositions

[0203] In certain instances, PCSK9 activity correlates with a number of human disease states. For example, in certain instances, too much or too little PCSK9 activity correlates with certain conditions, such as hypercholesterolemia. Therefore, in certain instances, modulating PCSK9 activity can be therapeutically useful.

[0204] In some embodiments, a neutralizing PCSK9 variant is used to modulate at least one native PCSK9 activity (*e.g.,* binding of native PCSK9 to LDLR). Such methods can

treat and/or prevent and/or reduce the risk of disorders that relate to elevated serum cholesterol levels or in which elevated cholesterol levels are relevant.

[0205] As will be appreciated by one of skill in the art, in light of the present disclosure, disorders that relate to, involve, or can be influenced by varied cholesterol, LDL, or LDLR levels can be addressed by various embodiments of the neutralizing PCSK9 variants. The neutralizing PCSK9 variants can be used in a variety of therapeutic applications. For example, in some embodiments the neutralizing PCSK9 variants are useful for treating conditions associated with PCSK9, such as cholesterol related disorders (or “serum cholesterol related disorders”) such as hypercholesterolemia, as further described herein. Some of the neutralizing PCSK9 variants described herein are useful in treating consequences, symptoms, and/or the pathology associated with PCSK9 activity.

[0206] In some embodiments, a “cholesterol related disorder” (which includes “serum cholesterol related disorders”) includes any one or more of the following: hypercholesterolemia, heart disease, metabolic syndrome, diabetes, coronary heart disease, stroke, cardiovascular diseases, Alzheimers disease and generally dyslipidemias, which can be manifested, for example, by an elevated total serum cholesterol, elevated LDL, elevated triglycerides, elevated VLDL, and/or low HDL. Some non-limiting examples of primary and secondary dyslipidemias that can be treated using a neutralizing PCSK9 variant, either alone, or in combination with one or more other agents include the metabolic syndrome, diabetes mellitus, familial combined hyperlipidemia, familial hypertriglyceridemia, familial hypercholesterolemias, including heterozygous hypercholesterolemia, homozygous hypercholesterolemia, familial defective apolipoprotein B-100; polygenic hypercholesterolemia; remnant removal disease, hepatic lipase deficiency; dyslipidemia secondary to any of the following: dietary indiscretion, hypothyroidism, drugs including estrogen and progestin therapy, beta-blockers, and thiazide diuretics; nephrotic syndrome, chronic renal failure, Cushing's syndrome, primary biliary cirrhosis, glycogen storage diseases, hepatoma, cholestasis, acromegaly, insulinoma, isolated growth hormone deficiency, and alcohol-induced hypertriglyceridemia. Neutralizing PCSK9 variants can also be useful in preventing or treating atherosclerotic diseases, such as, for example, coronary heart disease, coronary artery disease, peripheral arterial disease, stroke (ischaemic and hemorrhagic), angina pectoris, or cerebrovascular disease and acute coronary syndrome, myocardial infarction. In some embodiments, the neutralizing PCSK9 variant is

useful in reducing the risk of: nonfatal heart attacks, fatal and non-fatal strokes, certain types of heart surgery, hospitalization for heart failure, chest pain in patients with heart disease, and/or cardiovascular events because of established heart disease such as prior heart attack, prior heart surgery, and/or chest pain with evidence of clogged arteries. In some embodiments, a neutralizing PCSK9 variant of PCSK9 and methods can be used to reduce the risk of recurrent cardiovascular events.

[0207] As will be appreciated by one of skill in the art, diseases or disorders that are generally addressable (either treatable or preventable) through the use of statins can also benefit from the application of the instant neutralizing PCSK9 variants. In addition, in some embodiments, disorders or diseases that can benefit from the prevention of cholesterol synthesis or increased LDLR expression can also be treated by various embodiments of the neutralizing PCSK9 variants. In addition, as will be appreciated by one of skill in the art, the use of the neutralizing PCSK9 variants can be especially useful in the treatment of Diabetes. Not only is Diabetes a risk factor for coronary heart disease, but insulin increases the expression of PCSK9. That is, people with Diabetes have elevated plasma lipid levels (which can be related to high PCSK9 levels) and can benefit from lowering those levels or modulating the activity of those levels. This is generally discussed in more detail in Costet et al. ("Hepatic PCSK9 Expression is Regulated by Nutritional Status via Insulin and Sterol Regulatory Element-binding Protein 1C", *J. Biol. Chem.*, 281: 6211-6218, 2006), the entirety of which is incorporated herein by reference.

[0208] In some embodiments, the neutralizing PCSK9 variant is administered to those who have diabetes mellitus, abdominal aortic aneurysm, atherosclerosis and/or peripheral vascular disease in order to decrease their serum cholesterol levels to a safer range. In some embodiments, the neutralizing PCSK9 variant is administered to patients at risk of developing any of the herein described disorders. In some embodiments, the neutralizing PCSK9 variants are administered to subjects that smoke, have hypertension or a familial history of early heart attacks.

[0209] In some embodiments, a subject is administered a neutralizing PCSK9 variant if they are at a moderate risk or higher on the 2004 NCEP treatment goals. In some embodiments, the neutralizing PCSK9 variant is administered to a subject if the subject's LDL cholesterol level is greater than 160 mg/dl. In some embodiments, the neutralizing PCSK9 variant is administered if the subject's LDL cholesterol level is greater than 130 (and they have a

moderate or moderately high risk according to the 2004 NCEP treatment goals). In some embodiments, the neutralizing PCSK9 variant is administered if the subjects LDL cholesterol level is greater than 100 (and they have a high or very high risk according to the 2004 NCEP treatment goals). In some embodiments, the neutralizing PCSK9 variant is administered if the subjects LDL cholesterol level does not reach a goal of less than 90, or less than 80, or less than 70 mg/dl. In some embodiments, the neutralizing PCSK9 variant is administered if the subject is intolerant or resistant to other lipid modifying regimens and medications.

[0210] A physician will be able to select an appropriate treatment based on the indications and target lipid levels depending on the individual profile of a particular patient. One well-accepted standard for guiding treatment of hyperlipidemia is the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of the High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report, National Institutes of Health, NIH Publication No. 02-5215 (2002), the printed publication of which is hereby incorporated by reference in its entirety.

[0211] In some embodiments, neutralizing PCSK9 variants to PCSK9 are used to decrease the amount of PCSK9 activity (degradation of PCSK9) from an abnormally high level or even a normal level. In some embodiments, neutralizing PCSK9 variants to PCSK9 are used to treat or prevent hypercholesterolemia and/or in the preparation of medicaments therefore and/or for other cholesterol related disorders (such as those noted herein). In some embodiments, a neutralizing PCSK9 variant is used to treat or prevent conditions such as hypercholesterolemia in which PCSK9 activity is normal. In such conditions, for example, reduction of PCSK9 activity to below normal can provide a therapeutic effect.

[0212] In some embodiments, more than one neutralizing PCSK9 variant is used to modulate native PCSK9 activity.

[0213] In some embodiments, methods are provided of treating a cholesterol related disorder, such as hypercholesterolemia comprising administering a therapeutically effective amount of one or more neutralizing PCSK9 variants and another therapeutic agent.

[0214] In some embodiments, a neutralizing PCSK9 variant is administered alone. In some embodiments, a neutralizing PCSK9 variant is administered prior to the administration of at least one other therapeutic agent. In some embodiments, a neutralizing PCSK9 variant is administered concurrent with the administration of at least one other therapeutic agent. In some

embodiments, a neutralizing PCSK9 variant is administered subsequent to the administration of at least one other therapeutic agent. In other embodiments, a neutralizing PCSK9 variant is administered prior to the administration of at least one other therapeutic agent. Therapeutic agents (apart from the neutralizing PCSK9 variant), include, but are not limited to, at least one other cholesterol-lowering (serum and/or total body cholesterol) agent or an agent. In some embodiments, the agent increases the expression of LDLR, have been observed to increase serum HDL levels, lower serum LDL levels or lower triglyceride levels. Exemplary agents include, but are not limited to, statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin), Nicotinic acid (Niacin) (NIACOR, NIASPAN (slow release niacin), SLO-NIACIN (slow release niacin)), Fibric acid (LOPID (Gemfibrozil), TRICOR (fenofibrate), Bile acid sequestrants (QUESTRAN (cholestyramine), colestevam (WELCHOL), COLESTID (colestipol)), Cholesterol absorption inhibitors (ZETIA (ezetimibe)), Combining nicotinic acid with statin (ADVICOR (LOVASTATIN and NIASPAN), Combining a statin with an absorption inhibitor (VYTORIN (ZOCOR and ZETIA) and/or lipid modifying agents. In some embodiments, the neutralizing PCSK9 variant is combined with PPAR gamma agonists, PPAR alpha/gamma agonists, squalene synthase inhibitors, CETP inhibitors, anti-hypertensives, anti-diabetic agents (such as sulphonyl ureas, insulin, GLP-1 analogs, DDPIV inhibitors), ApoB modulators, MTP inhibitors and /or arteriosclerosis obliterans treatments. In some embodiments, the neutralizing PCSK9 variant is combined with an agent that increases the level of LDLR protein in a subject, such as statins, certain cytokines like oncostatin M, estrogen, and/or certain herbal ingredients such as berberine. In some embodiments, the neutralizing PCSK9 variant is combined with an agent that increases serum cholesterol levels in a subject (such as certain anti-psycotic agents, certain HIV protease inhibitors, dietary factors such as high fructose, sucrose, cholesterol or certain fatty acids and certain nuclear receptor agonists and antagonists for RXR, RAR, LXR, FXR). In some embodiments, the neutralizing PCSK9 variant is combined with an agent that increases the level of PCSK9 in a subject, such as statins and/or insulin. The combination of the two can allow for the undesirable side-effects of other agents to be mitigated by the neutralizing PCSK9 variant. As will be appreciated by one of skill in the art, in some embodiments, the neutralizing PCSK9 variant is combined with the other agent/compound. In some embodiments, the neutralizing PCSK9 variant and other agent are administered concurrently. In some embodiments, the

neutralizing PCSK9 variant and other agent are not administered simultaneously, with the neutralizing PCSK9 variant being administered before or after the agent is administered. In some embodiments, the subject receives both the neutralizing PCSK9 variant and the other agent (that increases the level of LDLR) during a same period of prevention, occurrence of a disorder, and/or period of treatment.

[0215] Pharmaceutical compositions can be administered in combination therapy, *i.e.*, combined with other agents. In some embodiments, the combination therapy comprises a neutralizing PCSK9 variant, in combination with at least one anti-cholesterol agent. Agents include, but are not limited to, in vitro synthetically prepared chemical compositions, antibodies, antigen binding regions, and combinations and conjugates thereof. In some embodiments, an agent can act as an agonist, antagonist, allosteric modulator, or toxin. In some embodiments, an agent can act to inhibit or stimulate its target (e.g., receptor or enzyme activation or inhibition), and thereby promote increased expression of LDLR or decrease serum cholesterol levels.

[0216] In some embodiments, a neutralizing PCSK9 variant can be administered prior to, concurrent with, and subsequent to treatment with a cholesterol-lowering (serum and/or total cholesterol) agent. In some embodiments, a neutralizing PCSK9 variant can be administered prophylactically to prevent or mitigate the onset of hypercholesterolemia, heart disease, diabetes, and/or any of the cholesterol related disorder. In some embodiments, a neutralizing PCSK9 variant can be administered for the treatment of an existing hypercholesterolemia condition. In some embodiments, the neutralizing PCSK9 variant delays the onset of the disorder and/or symptoms associated with the disorder. In some embodiments, the neutralizing PCSK9 variant is provided to a subject lacking any symptoms of any one of the cholesterol related disorders or a subset thereof.

[0217] In some embodiments, a neutralizing PCSK9 variant is used with particular therapeutic agents to treat various cholesterol related disorders, such as hypercholesterolemia. In some embodiments, in view of the condition and the desired level of treatment, two, three, or more agents can be administered. In some embodiments, such agents can be provided together by inclusion in the same formulation. In some embodiments, such agent(s) and a neutralizing PCSK9 variant can be provided together by inclusion in the same formulation. In some embodiments, such agents can be formulated separately and provided together by inclusion in a treatment kit. In some embodiments, such agents and a neutralizing PCSK9 variant can be

formulated separately and provided together by inclusion in a treatment kit. In some embodiments, such agents can be provided separately. In some embodiments, when administered by gene therapy, the genes encoding protein agents and/or a neutralizing PCSK9 variant can be included in the same vector. In some embodiments, the genes encoding protein agents and/or a neutralizing PCSK9 variant can be under the control of the same promoter region. In some embodiments, the genes encoding protein agents and/or a neutralizing PCSK9 variant can be in separate vectors.

[0218] In some embodiments, a pharmaceutical composition comprising a neutralizing PCSK9 variant is combined with a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant.

[0219] In some embodiments, a pharmaceutical compositions comprising a neutralizing PCSK9 variant and a therapeutically effective amount of at least one additional therapeutic agent are combined together with a pharmaceutically acceptable diluent, carrier, solubilizer, emulsifier, preservative and/or adjuvant.

[0220] In some embodiments, a neutralizing PCSK9 variant can be used with at least one therapeutic agent for inflammation. In some embodiments, a neutralizing PCSK9 variant can be used with at least one therapeutic agent for an immune disorder. Exemplary therapeutic agents for inflammation and immune disorders include, but are not limited to cyclooxygenase type 1 (COX-1) and cyclooxygenase type 2 (COX-2) inhibitors small molecule modulators of 38 kDa mitogen-activated protein kinase (p38-MAPK); small molecule modulators of intracellular molecules involved in inflammation pathways, wherein such intracellular molecules include, but are not limited to, jnk, IKK, NF- κ B, ZAP70, and lck. Certain exemplary therapeutic agents for inflammation are described, e.g., in C.A. Dinarello & L.L. Moldawer *Proinflammatory and Anti-Inflammatory Cytokines in Rheumatoid Arthritis: A Primer for Clinicians* Third Edition (2001) Amgen Inc. Thousand Oaks, CA.

[0221] In some embodiments, pharmaceutical compositions will include more than one different neutralizing PCSK9 variant(s). In some embodiments, pharmaceutical compositions will include more than one neutralizing PCSK9 variant wherein the neutralizing PCSK9 variants bind more than one epitope. In some embodiments, the various neutralizing PCSK9 variants will not compete with one another for binding to PCSK9.

[0222] In some embodiments, acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed. In some embodiments, the formulation material(s) are for s.c. and/or I.V. administration. In some embodiments, the pharmaceutical composition can contain formulation materials for modifying, maintaining or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release, adsorption or penetration of the composition. In some embodiments, suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine or lysine); antimicrobials; antioxidants (such as ascorbic acid, sodium sulfite or sodium hydrogen-sulfite); buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates or other organic acids); bulking agents (such as mannitol or glycine); chelating agents (such as ethylenediamine tetraacetic acid (EDTA)); complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin or hydroxypropyl-beta-cyclodextrin); fillers; monosaccharides; disaccharides; and other carbohydrates (such as glucose, mannose or dextrans); proteins (such as serum albumin, gelatin or immunoglobulins); coloring, flavoring and diluting agents; emulsifying agents; hydrophilic polymers (such as polyvinylpyrrolidone); low molecular weight polypeptides; salt-forming counterions (such as sodium); preservatives (such as benzalkonium chloride, benzoic acid, salicylic acid, thimerosal, phenethyl alcohol, methylparaben, propylparaben, chlorhexidine, sorbic acid or hydrogen peroxide); solvents (such as glycerin, propylene glycol or polyethylene glycol); sugar alcohols (such as mannitol or sorbitol); suspending agents; surfactants or wetting agents (such as pluronic, PEG, sorbitan esters, polysorbates such as polysorbate 20, polysorbate 80, triton, tromethamine, lecithin, cholesterol, tyloxapal); stability enhancing agents (such as sucrose or sorbitol); tonicity enhancing agents (such as alkali metal halides, preferably sodium or potassium chloride, mannitol sorbitol); delivery vehicles; diluents; excipients and/or pharmaceutical adjuvants. (*Remington's Pharmaceutical Sciences*, 18th Edition, A.R. Gennaro, ed., Mack Publishing Company (1995).

[0223] As noted above, in some embodiments, a neutralizing PCSK9 variant and/or a therapeutic molecule is linked to a half-life extending vehicle known in the art. Such vehicles include, but are not limited to, polyethylene glycol, glycogen (e.g., glycosylation of the neutralizing PCSK9 variant), and dextran. Such vehicles are described, e.g., in U.S. Application

Serial No. 09/428,082, now US Patent No. 6,660,843 and published PCT Application No. WO 99/25044, which are hereby incorporated by reference for any purpose.

[0224] In some embodiments, the optimal pharmaceutical composition can be determined by one skilled in the art depending upon, for example, the intended route of administration, delivery format and desired dosage. See, for example, *Remington's Pharmaceutical Sciences*, *supra*. In some embodiments, such compositions may influence the physical state, stability, rate of *in vivo* release and rate of *in vivo* clearance of the variants of PCSK9.

[0225] In some embodiments, the primary vehicle or carrier in a pharmaceutical composition can be either aqueous or non-aqueous in nature. For example, in some embodiments, a suitable vehicle or carrier can be water for injection, physiological saline solution or artificial cerebrospinal fluid, possibly supplemented with other materials common in compositions for parenteral administration. In some embodiments, the saline comprises isotonic phosphate-buffered saline. In some embodiments, neutral buffered saline or saline mixed with serum albumin are further exemplary vehicles. In some embodiments, pharmaceutical compositions comprise Tris buffer of about pH 7.0-8.5, or acetate buffer of about pH 4.0-5.5, which can further include sorbitol or a suitable substitute therefore. In some embodiments, a composition comprising a neutralizing PCSK9 variant, with or without at least one additional therapeutic agents, can be prepared for storage by mixing the selected composition having the desired degree of purity with optional formulation agents (*Remington's Pharmaceutical Sciences*, *supra*) in the form of a lyophilized cake or an aqueous solution. Further, in some embodiments, a composition comprising a neutralizing PCSK9 variant, with or without at least one additional therapeutic agent, can be formulated as a lyophilizate using appropriate excipients such as sucrose.

[0226] In some embodiments, the pharmaceutical composition can be selected for parenteral delivery. In some embodiments, the compositions can be selected for inhalation or for delivery through the digestive tract, such as orally. The preparation of such pharmaceutically acceptable compositions is within the ability of one skilled in the art.

[0227] In some embodiments, the formulation components are present in concentrations that are acceptable to the site of administration. In some embodiments, buffers

are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

[0228] In some embodiments, when parenteral administration is contemplated, a therapeutic composition can be in the form of a pyrogen-free, parenterally acceptable aqueous solution comprising a desired neutralizing PCSK9 variant, with or without additional therapeutic agents, in a pharmaceutically acceptable vehicle. In some embodiments, a vehicle for parenteral injection is sterile distilled water in which a neutralizing PCSK9 variant, with or without at least one additional therapeutic agent, is formulated as a sterile, isotonic solution, properly preserved. In some embodiments, the preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads or liposomes, that can provide for the controlled or sustained release of the product which can then be delivered via a depot injection. In some embodiments, hyaluronic acid can also be used, and can have the effect of promoting sustained duration in the circulation. In some embodiments, implantable drug delivery devices can be used to introduce the desired molecule.

[0229] In some embodiments, a pharmaceutical composition can be formulated for inhalation. In some embodiments, a neutralizing PCSK9 variant, with or without at least one additional therapeutic agent, can be formulated as a dry powder for inhalation. In some embodiments, an inhalation solution comprising a neutralizing PCSK9 variant, with or without at least one additional therapeutic agent, can be formulated with a propellant for aerosol delivery. In some embodiments, solutions can be nebulized. Pulmonary administration is further described in PCT application no. PCT/US94/001875, which describes pulmonary delivery of chemically modified proteins.

[0230] In some embodiments, it is contemplated that formulations can be administered orally. In some embodiments, a neutralizing PCSK9 variant, with or without at least one additional therapeutic agents, that is administered in this fashion can be formulated with or without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. In some embodiments, a capsule can be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. In some embodiments, at least one additional agent can be included to facilitate absorption of a neutralizing PCSK9 variant and/or

any additional therapeutic agents. In some embodiments, diluents, flavorings, low melting point waxes, vegetable oils, lubricants, suspending agents, tablet disintegrating agents, and binders can also be employed.

[0231] In some embodiments, a pharmaceutical composition can involve an effective quantity of a neutralizing PCSK9 variant, with or without at least one additional therapeutic agent, in a mixture with non-toxic excipients which are suitable for the manufacture of tablets. In some embodiments, by dissolving the tablets in sterile water, or another appropriate vehicle, solutions can be prepared in unit-dose form. In some embodiments, suitable excipients include, but are not limited to, inert diluents, such as calcium carbonate, sodium carbonate or bicarbonate, lactose, or calcium phosphate; or binding agents, such as starch, gelatin, or acacia; or lubricating agents such as magnesium stearate, stearic acid, or talc.

[0232] Additional pharmaceutical compositions will be evident to those skilled in the art, including formulations involving neutralizing PCSK9 variants, with or without at least one additional therapeutic agent(s), in sustained- or controlled-delivery formulations. In some embodiments, techniques for formulating a variety of other sustained- or controlled-delivery means, such as liposome carriers, bio-erodible microparticles or porous beads and depot injections, are also known to those skilled in the art. See for example, PCT Application No. PCT/US93/00829 which describes the controlled release of porous polymeric microparticles for the delivery of pharmaceutical compositions. In some embodiments, sustained-release preparations can include semipermeable polymer matrices in the form of shaped articles, *e.g.* films, or microcapsules. Sustained release matrices can include polyesters, hydrogels, polylactides (U.S. 3,773,919 and EP 058,481), copolymers of L-glutamic acid and gamma ethyl-L-glutamate (Sidman *et al.*, *Biopolymers*, 22:547-556 (1983)), poly (2-hydroxyethyl-methacrylate) (Langer *et al.*, *J. Biomed. Mater. Res.*, 15:167-277 (1981) and Langer, *Chem. Tech.*, 12:98-105 (1982)), ethylene vinyl acetate (Langer *et al.*, *supra*) or poly-D(-)-3-hydroxybutyric acid (EP 133,988). In some embodiments, sustained release compositions can also include liposomes, which can be prepared by any of several methods known in the art. *See, e.g.*, Eppstein *et al.*, *Proc. Natl. Acad. Sci. USA*, 82:3688-3692 (1985); EP 036,676; EP 088,046 and EP 143,949.

[0233] The pharmaceutical composition to be used for *in vivo* administration typically is sterile. In some embodiments, this can be accomplished by filtration through sterile

filtration membranes. In some embodiments, where the composition is lyophilized, sterilization using this method can be conducted either prior to or following lyophilization and reconstitution. In some embodiments, the composition for parenteral administration can be stored in lyophilized form or in a solution. In some embodiments, parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle. In some embodiments, the pharmaceutical composition is sterile.

[0234] In some embodiments, the pharmaceutical composition will comprise at least a sufficient amount of the neutralizing PCSK9 variant to reduce an amount of native PCSK9 from binding in a human, *in vivo*. In some embodiments the pharmaceutical composition will comprise at least a sufficient amount of the neutralizing PCSK9 variant to reduce a symptom of a “cholesterol related disorder” (which includes “serum cholesterol related disorders”). In some embodiments the pharmaceutical composition will comprise at least a sufficient amount of the neutralizing PCSK9 variant to modulate at least one native PCSK9 activity (e.g., binding of native PCSK9 to LDLR).

[0235] In some embodiments, the pharmaceutical composition comprises at least an amount of a neutralizing PCSK9 variant sufficient for treating any one or more of the cholesterol related disorders disclosed herein.

[0236] In some embodiments, the pharmaceutical composition comprises at least an amount of a neutralizing PCSK9 variant sufficient to treat a symptom of a cholesterol related disorder of an adult male and/or female. In some embodiments the amount of the neutralizing PCSK9 variant is at least sufficient to treat (e.g., reduce a symptom of) an adult male weighing between 10 and 250 kg. In some embodiments, the amount is at least sufficient to treat a 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, or 200 kg subject so as to lessen a symptom of at least any one of the cholesterol related disorders, to raise the level of LDLR in the subject, or to lower the level of LDL in the subject. In some embodiments, the amount of a neutralizing PCSK9 variant present in the pharmaceutical composition is at least sufficient to raise the level of LDLR in a subject by some detectable amount. In some embodiments, the level of LDLR in a subject is raised by at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100 percent. In some embodiments the level of LDLR in a

subject is increased by at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100 fold over an untreated healthy subject and/or over an untreated subject that has a cholesterol related disorder. In yet other embodiments the neutralizing PCSK9 variant is sufficient to maintain the level of LDLR in a subject at a desired level. The appropriate level can be determined by the subject's health care provider and can take into account particular aspects of the subject's physical condition and health issues and concerns.

[0237] In some embodiments, the amount of neutralizing PCSK9 variant present in the pharmaceutical composition is at least sufficient to block a significant amount of the activity of the native PCSK9 *in vivo*. In some embodiments, the amount is sufficient to block at least 1% of the activity of native PCSK9, for example, at least 1, 1-10, 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, 90-95, 95-98, 98-99, 99-100 percent of the native PCSK9 is blocked by the amount of PCSK9 present in the pharmaceutical composition.

[0238] In some embodiments, the amount of neutralizing PCSK9 variant present in the pharmaceutical composition is at least sufficient to lower serum LDL in a subject. In some embodiments, the amount is sufficient to lower the amount of serum LDL in a subject by at least 1% of the native level of serum LDL, for example, at least 1, 1-10, 10-20, 20-30, 30-40, 40-50, 50-60, 60-70, 70-80, 80-90, 90-95, 95-98, 98-99, 99-100 percent of the level of serum LDL for the subject, for a subject having a cholesterol related disorder, or for a healthy subject.

[0239] In some embodiments, the amount of neutralizing PCSK9 variant present in the pharmaceutical composition is a significant amount. In some embodiments, the amount of neutralizing PCSK9 variant present in a pharmaceutical dose to be given to a subject is at least 1 ng, for example, the amount is at least 1, 10, 20, 50, 100, 500, 1000, 10,000, 10^5 , 10^6 , 10^7 , 10^8 , 10^9 , 10^{10} , or 10^{11} nanograms, including any amount defined between any two of the previous numbers and any amount above any of the previous numbers. In some embodiments the amount is in a single pill. In some embodiments, the amount is in multiple pills. In some embodiments, the amount of the neutralizing PCSK9 variant administered is from about 1 to 500 mg, 50 to 400 mg, or 100 to 300 mg.

[0240] In some embodiments, the neutralizing PCSK9 variant is included in a solid form, such as in a tablet or pill.

[0241] In some embodiments, the amount of the neutralizing PCSK9 variant is a dosage sufficient to achieve any of the herein described goals (or amounts) for at least 1 hour. In

some embodiments, the amount is sufficient to treat a cholesterol related disorder for at least one hour, for example, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, or 24 hours. In some embodiments, the amount of the neutralizing PCSK9 variant that is present is sufficient to achieve any of the herein described goals for at least one day. Thus, in some embodiments, the dosage is a once daily amount.

[0242] In some embodiments, the neutralizing PCSK9 variant is relatively pure. In some embodiments, apart from a pharmaceutical acceptable carrier or diluent and the neutralizing PCSK9 variant, nothing else is present in the composition. In some embodiments, a compound comprising the neutralizing PCSK9 variant is at least 0.01% neutralizing PCSK9 variant (by weight). In some embodiments, at least 1×10^{-8} , 1×10^{-7} , 1×10^{-6} , 1×10^{-5} , 0.0001, 0.001, 0.01, 0.1, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 98, 99, or 100 percent of the compound is a neutralizing PCSK9 variant. In some embodiments, the percent is a range defined between any two of the previous percents.

[0243] As will be appreciated by one of skill in the art, any of the above parameters describing the amount of the neutralizing PCSK9 variant present can be combined with any of the other parameters. For example, any of the parameters regarding the percent of native PCSK9 blocked *in vivo* can be combined for any of the specific weights supplied for the subjects.

[0244] In some embodiments, the pharmaceutical composition does not include ingredients that are harmful to a subject.

[0245] In some embodiments, the pharmaceutical composition does not include 50 mM sodium phosphate and/or 50 mM sodium chloride. In some embodiments, the pharmaceutical composition does not include sodium phosphate and/or sodium chloride. In some embodiments the pharmaceutical composition does not contain cell lysates. In some embodiments the pharmaceutical composition does not contain cell medium. In some embodiments, the pharmaceutical composition does not include BS3 (bis[sulfosuccinimidyl]suberate). In some embodiments, the pharmaceutical composition does not include potassium formate. In some embodiments, the pharmaceutical composition does not include PEG 3350. In some embodiments, the pharmaceutical composition does not include 0.2 M potassium formate. In some embodiments, the pharmaceutical composition does not include 20% PEG 3350. In some embodiments, the pharmaceutical composition does not include 50 mM Tris. In some embodiments, the pharmaceutical composition does not include 4 mM

EDTA. In some embodiments, the pharmaceutical composition does not include 0.01-2% Triton X-100. In some embodiments, the pharmaceutical composition does not include 0.5 sodium deoxycholate. In some embodiments, the pharmaceutical composition does not include 0.1-2% sodium dodecyl sulfate. In some embodiments, the pharmaceutical composition does not include 10-20% glycerol. In some embodiments, the pharmaceutical composition does not include 1M NDSB. In some embodiments, the pharmaceutical composition does not include 1-20 mM calcium chloride. In some embodiments, the pharmaceutical composition does not include KH₂PO₄/NaOH. In some embodiments, the pharmaceutical composition does not include citric acid and sodium phosphate. In some embodiments, the pharmaceutical composition does not include Na₂HPO₄ and NaOH. In some embodiments, the pharmaceutical composition does not include the combination of two or more of the above ingredients. In some embodiments, the pharmaceutical composition does not include the combination of three or more of the above ingredients. In some embodiments, the pharmaceutical composition does not include the combination of four or more of the above ingredients. In some embodiments, the pharmaceutical composition does include one or more of the above ingredients.

[0246] In some embodiments, the neutralizing PCSK9 variant is not created in *E. coli*. In some embodiments, any of the herein disclosed neutralizing PCSK9 variants is a self-processed or self-cleaved protein. In some embodiments, any of the herein disclosed neutralizing PCSK9 variants is a processed or cleaved protein.

[0247] In some embodiments, once the pharmaceutical composition has been formulated, it can be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or as a dehydrated or lyophilized powder. In some embodiments, such formulations can be stored either in a ready-to-use form or in a form (*e.g.*, lyophilized) that is reconstituted prior to administration.

[0248] In some embodiments, kits are provided for producing a single-dose administration unit. In some embodiments, the kit can contain both a first container having a dried protein and a second container having an aqueous formulation. In some embodiments, kits containing single and multi-chambered pre-filled syringes (*e.g.*, liquid syringes and lyosyringes) are included.

[0249] In some embodiments, the effective amount of a pharmaceutical composition comprising a neutralizing PCSK9 variant, with or without at least one additional therapeutic agent, to be employed therapeutically will depend, for example, upon the therapeutic context and

objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment, according to certain embodiments, will thus vary depending, in part, upon the molecule delivered, the indication for which a neutralizing PCSK9 variant, with or without at least one additional therapeutic agent, is being used, the route of administration, and the size (body weight, body surface or organ size) and/or condition (the age and general health) of the patient. In some embodiments, a clinician can titer the dosage and modify the route of administration to obtain the optimal therapeutic effect. In some embodiments, a typical dosage can range from about 0.1 μ g/kg to up to about 100 mg/kg or more, depending on the factors mentioned above. In some embodiments, the dosage can range from 0.1 μ g/kg up to about 100 mg/kg; or 1 μ g/kg up to about 100 mg/kg; or 5 μ g/kg up to about 100 mg/kg.

[0250] In some embodiments, the frequency of dosing will take into account the pharmacokinetic parameters of a neutralizing PCSK9 variant and/or any additional therapeutic agents in the formulation used. In some embodiments, a clinician will administer the composition until a dosage is reached that achieves the desired effect. In some embodiments, the composition can therefore be administered as a single dose, as two or more doses (which may or may not contain the same amount of the desired molecule) over time, or as a continuous infusion via an implantation device or catheter. Further refinement of the appropriate dosage is routinely made by those of ordinary skill in the art and is within the ambit of tasks routinely performed by them. In some embodiments, appropriate dosages can be ascertained through use of appropriate dose-response data. In some embodiments, the amount and frequency of administration can take into account the desired cholesterol level (serum and/or total) to be obtained and the subject's present cholesterol level, LDL level, and/or LDLR levels, all of which can be obtained by methods that are well known to those of skill in the art.

[0251] In some embodiments, the route of administration of the pharmaceutical composition is in accord with known methods, *e.g.* orally, through injection by intravenous, intraperitoneal, intracerebral (intra-parenchymal), intracerebroventricular, intramuscular, subcutaneously, intra-ocular, intraarterial, intraportal, or intralesional routes; by sustained release systems or by implantation devices. In some embodiments, the compositions can be administered by bolus injection or continuously by infusion, or by implantation device. In some embodiments, the composition is configured for administration via any of these routes.

[0252] In some embodiments, the composition can be administered locally via implantation of a membrane, sponge or another appropriate material onto which the desired molecule has been absorbed or encapsulated. In some embodiments, where an implantation device is used, the device can be implanted into any suitable tissue or organ, and delivery of the desired molecule can be via diffusion, timed-release bolus, or continuous administration.

[0253] In some embodiments, it can be desirable to use a pharmaceutical composition comprising a neutralizing PCSK9 variant, with or without at least one additional therapeutic agent, in an *ex vivo* manner. In such instances, cells, tissues and/or organs that have been removed from the patient are exposed to a pharmaceutical composition comprising a neutralizing PCSK9 variant, with or without at least one additional therapeutic agent, after which the cells, tissues and/or organs are subsequently implanted back into the patient.

[0254] In some embodiments, a neutralizing PCSK9 variant and/or any additional therapeutic agents can be delivered by implanting certain cells that have been genetically engineered, using methods such as those described herein, to express and secrete the polypeptides. In some embodiments, such cells can be animal or human cells, and can be autologous, heterologous, or xenogeneic. In some embodiments, the cells can be immortalized. In some embodiments, in order to decrease the chance of an immunological response, the cells can be encapsulated to avoid infiltration of surrounding tissues. In some embodiments, the encapsulation materials are typically biocompatible, semi-permeable polymeric enclosures or membranes that allow the release of the protein product(s) but prevent the destruction of the cells by the patient's immune system or by other detrimental factors from the surrounding tissues.

[0255] Based on the ability of a neutralizing PCSK9 variant to significantly neutralize PCSK9 activity (as demonstrated in the Examples below), these neutralizing PCSK9 variants will have therapeutic effects in treating and preventing symptoms and conditions resulting from PCSK9-mediated activity, such as hypercholesterolemia.

EXAMPLES

[0256] The following examples, including the experiments conducted and results achieved, are provided for illustrative purposes only and are not to be construed as limiting the present invention.

EXAMPLE 1

Demonstration of a Neutralizing PCSK9 variant binding to the LDL receptor - LDLR
Competition assay

[0257] This example is directed to the ability of a neutralizing PCSK9 variant to compete with full length PCSK9 for binding to LDLR.

[0258] Clear, 96 well plates (Nunc) were coated overnight with 2 micrograms/ml of goat anti-LDL receptor antibody (R&D Systems) diluted in buffer A (100 mM sodium cacodylate, pH 7.4). Plates were washed thoroughly with buffer A and then blocked for 2 hours with buffer B (1% milk in buffer A). After washing, plates were incubated for 1.5 hours with 2.0 ug/ml of LDL receptor (R&D Systems) diluted in buffer C (buffer B supplemented with 10 mM CaCl₂). Concurrent with this incubation, 100 ng/ml of biotinylated wild-type human PCSK9 (hPCSK9), diluted in buffer C, was incubated with various concentrations of non-biotinylated competitor proteins (e.g. 31-447 of PCSK9 (SEQ ID NO: 3), full length PCSK9, and the V-domain of PCSK9, residues 450-692) also diluted in buffer C, or buffer C alone (control). The LDL receptor containing plates were washed. The biotinylated PCSK9/competitor protein mixture was transferred to the plates and incubated for 1 hour at room temperature. Binding of the biotinylated PCSK9 to the LDL receptor was detected by incubation with streptavidin-HRP (Biosource) at 500 ng/ml in buffer C followed by TMB substrate (KPL). The absorbance at 650 nm was measured.

[0259] The results are presented in FIG. 2. Both the neutralizing PCSK9 variant (amino acids 31-447 of SEQ ID NO: 3), and the full length PCSK9 (fl PCSK9), competed against biotin-labeled full length PCSK9 for binding to the immobilized LDLR. The V-domain protein did not. This data demonstrates that no more than amino acids 31-447 (of SEQ ID NO: 3) are required for binding to the LDLR.

EXAMPLE 2

Effect of a Neutralizing PCSK9 variant on Cell LDL uptake

[0260] The example is directed to the ability of one neutralizing PCSK9 variant to impact LDL uptake. HepG2 cells were seeded in 96-well plates (Costar) at a concentration of 5x10⁵ cells per well in DMEM medium (Mediatech, Inc) supplemented with 10% fetal bovine serum (FBS) and incubated overnight at 37°C (5% CO₂). The next day, cells were washed twice

with PBS. A serial 1:2 dilution of wild-type PCSK9 or the neutralizing PCSK9 variant (31-447 of SEQ ID NO: 3) was made, ranging from 1.6 ug/ml to 50ug/ml, and was added to cells. Following the addition of 6ug/ml of BODIPY-LDL (Invitrogen) and incubation for 3 hours at 37°C (5% CO2), the cells were washed thoroughly with PBS. Lastly, the cellular associated fluorescence signal was detected by Safire (TECAN) at 480~520nm (excitation) and 520~600nm (emission).

[0261] The results are presented in FIGs. 3A and 3B which represent two separate experiments of identical design performed on different dates. As can be observed in the figures, full length PCSK9 (having a H8 histidine purification tag) blocked the uptake of labeled LDL into the cultured cells as evidenced by the decrease in fluorescence from the cells with increasing PCSK9 levels added to the culture medium. In contrast, the neutralizing PCSK9 variant allows for the cells to take up LDL.

EXAMPLE 3

Western Blot Analysis of the Cellular Effects of a Neutralizing PCSK9 Variant

[0262] This example is directed to the cellular effects of the presence of a neutralizing PCSK9 variant.

[0263] HepG2 cells in 6 well plates were grown to confluence at 37°C in DMEM medium with 10% fetal bovine serum (FBS). Some cells were pretreated for 30 minutes with 100 uM chloroquine to inhibit acidification of endosomes. Cells were then treated with either vehicle (PBS, less than 50 ul), full length PCSK9 (50 ug/ml, 0.65 uM), or neutralizing PCSK9 variant (31-447 of SEQ ID NO: 3) (30 micrograms/ml, 0.65 uM) in 750 ul of DMEM with 1% FBS for 4 hours at 37°C. Cells were washed three times with PBS and whole cell lysate was prepared using lysis buffer (125 mM Tris, 2 mM CaCl2, 1% triton X-100, pH 8.5). Fifty ug of cell supernatant protein was resolved by SDS PAGE and LDLR levels determined using rabbit anti-human LDLR polyclonal antibody (RDI-PRO61099, Fitzgerald Industries International Inc.). Recombinant PCSK9 associated with the cells was detected by anti-human PCSK9 monoclonal antibody that detects the ~ 14 kDa prodomain of PCSK9. HRP-conjugated secondary antibodies (Santa Cruz Biotechnology Inc.) and ECL (GE Healthcare) were used for detecting signal. (Veh=vehicle (PBS), FL=full length, PC9=PCSK9).

[0264] The results are shown in FIG. 4. As can be seen in the figure, the neutralizing PCSK9 variant (31-447 of SEQ ID NO: 3) associated with cells but did not cause degradation of LDLR, unlike full length PCSK9.

[0265] As will be appreciated by one of skill in the art, the data from the above Examples indicate that while a neutralizing PCSK9 variant (*e.g.*, 31-447 of SEQ ID NO: 3) can bind to the LDLR it does not prevent LDL binding and LDL uptake by cells and does not cause LDLR degradation. In addition, the neutralizing PCSK9 variant (31-447 of SEQ ID NO: 3) allows LDLR recycling, preserving the normal function of the LDLR.

[0266] Given the present results, it is apparent that neutralizing PCSK9 variants can bind to the LDLR at the cell surface preventing the interaction of full length (wild-type) PCSK9 with the LDLR. Because the neutralizing PCSK9 variant preserves normal LDLR function it acts as a therapeutic protecting the LDLR from the effects of endogenous full length PCSK9.

EXAMPLE 4

Uses of a Neutralizing PCSK9 Variant for the Treatment of Cholesterol Related Disorders

[0267] A human patient exhibiting a Cholesterol Related Disorder (in which a reduction in cholesterol (such as serum cholesterol) can be beneficial) is administered a therapeutically effective amount of a neutralizing PCSK9 variant. At periodic times during the treatment, the patient is monitored to determine whether a symptom of the disorder has subsided. Following treatment, it is found that patients undergoing treatment with the neutralizing PCSK9 variant have reduced serum cholesterol levels, in comparison to patients that are not treated.

EXAMPLE 5

Uses of a Neutralizing PCSK9 Variant for the Treatment of Hypercholesterolemia

[0268] A human patient exhibiting symptoms of hypercholesterolemia is administered a therapeutically effective amount of a neutralizing PCSK9 variant. At periodic times during the treatment, the human patient is monitored to determine whether the serum cholesterol level (either as total cholesterol or more specifically LDL cholesterol) has declined. Following treatment, it is found that the patient receiving the treatment with a neutralizing

PCSK9 variant has reduced serum cholesterol levels in comparison to arthritis patients not receiving the treatment.

EXAMPLE 6

Uses of a Neutralizing PCSK9 Variant for the Prevention of Coronary Heart Disease and/or Recurrent Cardiovascular Events

[0269] A human patient at risk of developing coronary heart disease is identified. The patient is administered a therapeutically effective amount of a neutralizing PCSK9 variant, either alone, concurrently or sequentially with a statin, *e.g.*, simvastatin. At periodic times during the treatment, the human patient is monitored to determine whether the patient's total serum cholesterol level changes. Throughout the preventative treatment, it is found that the patient receiving the treatment with the neutralizing PCSK9 variant has reduced serum cholesterol thereby reducing their risk to coronary heart diseases or recurrent cardiovascular events in comparison to patients not receiving the treatment.

EXAMPLE 7

Use of a Neutralizing PCSK9 Variant for the Prevention of Hypercholesterolemia

[0270] A human patient exhibiting a risk of developing hypercholesterolemia is identified via family history analysis and/or lifestyle, and/or current cholesterol levels. The subject is regularly administered (*e.g.*, one time weekly) a therapeutically effective amount of a neutralizing PCSK9 variant. At periodic times during the treatment, the patient is monitored to determine whether serum cholesterol levels have decreased. Following treatment, it is found that subjects undergoing preventative treatment with a neutralizing PCSK9 variant have lowered serum cholesterol levels, in comparison to subjects that are not treated.

EXAMPLE 8

Mouse Model for PCSK9

[0271] The present example describes how to generate a mouse model for testing various neutralizing PCSK9 variants. To generate mice which over-expressed human PCSK9, three week old WT C57Bl/6 mice were injected via tail vein administration with various concentrations of adenoassociated virus (AAV), recombinantly modified to express human

PCSK9, to determine the correct titer which would provide a measurable increase of LDL-cholesterol in the mice. Using this particular virus which expressed human PCSK9, it was determined that 4.5×10^{12} pfu of virus would result in an LDL-cholesterol level of approximately 40mg/dL in circulating blood (normal levels of LDL in a WT mice are approximately 10mg/dL). The human PCSK9 levels in these animals were found to be approximately 13ug/mL. A colony of mice was generated using this injection criteria.

[0272] One week after injection, mice were assessed for LDL-cholesterol levels.

EXAMPLE 9

[0273] The mice from Example 8 can be used to test various neutralizing PCSK9 variants to determine how effective they are and which variants work *in vivo*.

[0274] A neutralizing PCSK9 variant can be administered, via tail vein injection, in a single bolus injection, or by AAV induced over-expression. Subgroups of animals (n=6-7) can then be euthanized at 24 and 48 hours after neutralizing PCSK9 variant administration. LDL levels can then be examined and optionally compared with various controls (*e.g.*, wild-type PCSK9, a water or unrelated protein injection, and the pro/cat domain). Completive PCSK9 variants that result in mice with lower serum LDL levels will be variants that can be effective in lowering serum LDL levels.

EXAMPLE 10

The LDLR EGFa Domain Binds to the Catalytic Domain of PCSK9

[0275] The present example presents the solved crystal structure of PCSK9 Pro/Cat (31-454) bound to the LDLR EGFa domain (293-334) at 2.9 Å resolution (the conditions for which are described in the below Examples).

[0276] A representation of the structure of PCSK9 bound to EGFa is shown in FIG. 5. The crystal structure (and its depiction in FIG. 5) reveals that the EGFa domain of LDLR binds to the catalytic domain of PCSK9. In addition, the interaction of PCSK9 and EGFa appears to occur across a surface of PCSK9 that is between residues D374 and S153 in the structure depicted in FIG. 5.

[0277] Specific core PCSK9 amino acid residues of the interaction interface with the LDLR EGFa domain were defined as PCSK9 residues that are within 5 Å of the EGFa domain.

The core residues are as follows: S153, I154, P155, R194, D238, A239, I369, S372, D374, C375, T377, C378, F379, V380, and S381.

[0278] Boundary PCSK9 amino acid residues of the interaction interface with the LDLR EGFa domain were defined as PCSK9 residues that are 5-8 Å from the EGFa domain. The boundary residues are as follows: W156, N157, L158, E159, H193, E195, H229, R237, G240, K243, D367, I368, G370, A371, S373, S376, and Q382. Residues that are underlined are nearly or completely buried within PCSK9.

[0279] As will be appreciated by one of skill in the art, the results from this example demonstrate where PCSK9 and EGFa interact. Thus, neutralizing PCSK9 variants that interact with or block any of these residues can be useful to inhibit the interaction between native PCSK9 and the EGFa domain of LDLR (and/or LDLR generally). In some embodiments, neutralizing PCSK9 variants that, when bound to PCSK9, interact with or block any of the above residues or are within 15-8, 8-8, 8-5, or 5 angstroms of the above residues are contemplated to provide useful inhibition of PCSK9 binding to LDLR.

EXAMPLE 11

Structural Interaction of LDLR and PCSK9

[0280] A model of full length PCSK9 protein bound to a full length representation of the LDLR was made using the PCSK9 Pro/Cat 31-454/EGFa complex structure. The structure of full length PCSK9 (Piper, D.E. et al. The crystal structure of PCSK9: a regulator of plasma LDL-cholesterol. *Structure* 15, 545-52 (2007)) was overlaid onto the PCSK9 Pro/Cat 31-454 from the complex and the structure of the LDLR in its low pH conformation (Rudenko, G. et al. Structure of the LDL receptor extracellular domain at endosomal pH. *Science* 298, 2353-8 (2002)) was overlaid onto the EGFa domain from the complex. Depictions of the model are shown in FIGs. 6 and 7. The EGFa domain from the PCSK9 Pro/Cat 31-454 / EGFa complex is enclosed within the box. The figures show regions of the LDLR outside of the immediate EGFa binding domain that lie in close proximity to PCSK9.

EXAMPLE 12

Expression and Purification of Protein Samples

[0281] The present example describes some methods by which the various embodiments of the PCSK9 proteins/variants were made and purified (including the LDLR EGFa domain). PCSK9 proteins/variants (e.g., PSCK9 31-692 N533A, PCSK9 449TEV and PCSK9 Pro/Cat 31-454) were expressed in baculovirus infected Hi-5 insect cells with an N-terminal honeybee melittin signal peptide followed by a His₆ tag. The PCSK9 proteins were purified by nickel affinity chromatography, ion exchange chromatography and size exclusion chromatography. The melittin-His₆ tag was removed during purification by cleavage with TEV protease. The construct PCSK9 449TEV was used to generate PCSK9 Pro/Cat (31-449 and V domain (450-692) samples. This construct had a TEV protease cleavage site inserted between PCSK9 residues 449 and 450.

[0282] The LDLR EGFa domain (293-334) was expressed as a GST fusion protein in *E. coli*. The EGFa domain was purified by ion exchange chromatography, glutathione sepharose affinity chromatography and size exclusion chromatography. The GST protein was removed during the purification by cleavage with PreScission protease.

EXAMPLE 13

Complex Formation and Crystallization

[0283] The present example describes how complexes and crystals used in the above structure examination Examples were made.

[0284] The PCSK9 31-454 / EGFa complex was made by mixing a 1.2 molar excess of EGFa domain with PCSK9 31-454. The PCSK9 31-454 / EGFa domain complex crystallized in 0.2 M potassium formate, 20% PEG 3350.

EXAMPLE 14

Data Collection and Structure Determination

[0285] The present example describes how the datasets were collected and the structures determined for the above structure examination Examples.

[0286] The PCSK9 31-454 / EGFa dataset was collected at the Berkeley Advanced Light Source beamline 5.0.2. All datasets were processed with denzo/scalepack or HKL2000 (Otwinowski, Z., Borek, D., Majewski, W. & Minor, W. Multiparametric scaling of diffraction intensities. *Acta Crystallogr A* 59, 228-34 (2003)).

[0287] PCSK9 / EGFa domain crystals grew in the space group P6₅22 with unit cell dimensions a=b=70.6, c=321.8 Å and diffract to 2.9 Å resolution. The PCSK9 / EGFa domain structure was solved by molecular replacement with the program MOLREP using the PCSK9 Pro/Cat as the starting search model. Analysis of the electron density maps showed clear electron density for the EGFa domain. The LDLR EGFa domain was fit by hand and the model was improved with multiple rounds of model building with Quanta and refinement with cnx.

[0288] Core interaction interface amino acids were determined as being all amino acid residues with at least one atom less than or equal to 5 Å from the PCSK9 partner protein. 5 Å was chosen as the core region cutoff distance to allow for atoms within a van der Waals radius plus a possible water-mediated hydrogen bond. Boundary interaction interface amino acids were determined as all amino acid residues with at least one atom less than or equal to 8 Å from the PCSK9 partner protein but not included in the core interaction list. Less than or equal to 8 Å was chosen as the boundary region cutoff distance to allow for the length of an extended arginine amino acid. Amino acids that met these distance criteria were calculated with the program PyMOL. (DeLano, W.L. The PyMOL Molecular Graphics System. (Palo Alto, 2002)).

[0289] The coordinates for the crystal structures discussed in the above Examples are presented in Table 35.2 of U.S. Prov. Pat. App. No. 61/010630, filed Jan. 9, 2008, the entirety of which is incorporated by reference. Neutralizing PCSK9 variants that interact with the relevant areas or residues of the structure of PCSK9 (including those areas or residues within 15, 15-8, 8, 8-5, 5, or fewer angstroms from where EGFa interacts with PCSK9) depicted in the figures and/or their corresponding positions on the structures from the coordinates are also contemplated.

EXAMPLE 15

Additional Neutralizing PCSK9 Variants

[0290] This example describes the ability of the D374Y point mutation in a neutralizing PCSK9 variant (amino acids 31-447 of SEQ ID NO: 3) to alter cell LDL uptake (FIG. 8) and compete with full length PCSK9 for binding to the LDLR (FIG. 9).

[0291] The protocol followed was generally similar to that outlined above regarding LDL uptake in the presence of the neutralizing PCSK9 variant (amino acids 31-447 of SEQ ID NO: 3), except that full length D374Y PCSK9, a neutralizing PCSK9 variant (amino acids 31-

447 of SEQ ID NO: 3) having the D374Y point mutation, and a full length wild-type hPCSK9 were used. The results are shown in FIG. 8.

[0292] In addition to the above experiment, LDLR was also captured in an ELISA plate via an LDLR antibody (2 ug/ml). Following this, biotin-WT_PCSK9 (100 ng/ml) and various concentrations of unbiotinylated full length D374Y PCSK9, V domain (V domain), and D374Y Pro/Cat (31-447) were added to the plate. Bound biotin-PCSK9 was detected by streptavidin-HRP. The results are presented in FIG. 9 and demonstrate the ability of the D374Y Pro/Cat domain and the D374Y full length PCSK9 to compete with the full length WT PCSK9 for binding to the LDLR.

[0293] As can be seen in the results displayed in FIGs. 8 and 9, neutralizing PCSK9 variants will also work to increase the amount of LDL uptake with respect to uptake that occurs in the presence of other forms of PCSK9.

Incorporation by Reference

[0294] All references cited herein, including patents, patent applications, papers, text books, and the like, and the references cited therein, to the extent that they are not already, are hereby incorporated herein by reference in their entirety. To the extent that any of the definitions or terms provided in the references incorporated by reference differ from the terms and discussion provided herein, the present terms and definitions control.

Equivalents

[0295] The foregoing written specification is considered to be sufficient to enable one skilled in the art to practice the invention. The foregoing description and examples detail certain embodiments of the invention. It will be appreciated, however, that no matter how detailed the foregoing may appear in text, the invention may be practiced in many ways.

CLAIMS

1. An isolated neutralizing PCSK9 variant comprising:
 - (a) a Pro/Cat domain, or fragment thereof; and
 - (b) an inactive V domain,
wherein the Pro/Cat domain or the fragment thereof
 - i) lacks amino acids 1-60 of SEQ ID NO: 3; or
 - ii) lacks amino acids 1-30 of SEQ ID NO: 3; and
wherein the neutralizing PCSK9 variant lacks at least 14 C-terminal amino acids of SEQ ID NO: 3, preferably the PCSK9 variant lacks the protein sequence defined from amino acids 453 to 692 of SEQ ID NO: 3.
2. An isolated nucleic acid molecule encoding the neutralizing PCSK9 variant according to Claim 1, preferably operably linked to a control sequence.
3. A vector comprising a nucleic acid molecule according to Claim 2.
4. A host cell comprising the nucleic acid molecule according to Claim 2 or the vector according to Claim 3.
5. The isolated neutralizing PCSK9 variant of claim 1, wherein said isolated neutralizing PCSK9 variant has no V domain.
6. The isolated neutralizing PCSK9 variant of Claim 1 or Claim 5, further comprising an antibody, or fragment thereof, conjugated to the neutralizing PCSK9 variant, wherein the antibody or fragment thereof preferably comprises an Fc domain of an antibody or optionally the fragment of the antibody consists of an Fc domain of an antibody.
7. A pharmaceutical composition comprising at least one neutralizing PCSK9 variant according to any one of Claims 1, 5 or 6, and a pharmaceutically acceptable excipient, optionally further comprising an additional active agent, preferably selected from the group consisting of a radioisotope, radionuclide, a toxin, or a therapeutic and a chemotherapeutic group.
8. A method for treating or preventing a condition associated with elevated serum cholesterol in a patient, comprising administering to a patient in thereof an effective amount of

at least one neutralizing PCSK9 variant according to any one of Claims 1, 5 or 6, wherein the condition preferably is hypercholesterolemia.

9. A method of inhibiting binding of PCSK9 to LDLR in a patient comprising administering an effective amount of a neutralizing PCSK9 variant according to any one of Claims 1, 5 or 6.

10. A method for treating or preventing a condition associated with elevated serum cholesterol in a subject, said method comprising administering to a subject in need thereof an effective amount of at least one neutralizing PCSK9 variant according to any one of Claims 1, 5 or 6 simultaneously or sequentially with an agent that elevates the availability of low density lipoprotein receptor (LDLR) protein,

wherein the agent that elevates the availability of LDLR protein optionally comprises a statin, preferably selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, or a combination thereof.

11. A method of lowering serum cholesterol in a subject, said method comprising administering to a subject an effective amount of at least one isolated neutralizing PCSK9 variant according to any one of Claims 1, 5 or 6, preferably simultaneously or sequentially with an agent that elevates the availability of low density lipoprotein receptor (LDLR) protein.

12. Use of a neutralizing PCSK9 variant of Claim 1, 5 or 6 in the manufacture of a medicament for the treatment of hypercholesterolemia.

13. Use of a neutralizing PCSK9 variant of Claim 1, 5 or 6 in the manufacture of a medicament for inhibiting binding of PCSK9 to LDLR.

14. Use of a neutralizing PCSK9 variant of Claim 1, 5 or 6 in the manufacture of a medicament for treating a condition associated with elevated serum cholesterol in a subject, wherein said medicament is adapted for simultaneous or sequential administration with an agent that elevates the availability of low density lipoprotein receptor (LDLR) protein,

wherein the agent that elevates the availability of LDLR protein optionally comprises a statin, preferably selected from the group consisting of atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin, or a combination thereof.

15. Use of a neutralizing PCSK9 variant of Claim 1, 5 or 6 in the manufacture of a medicament for lowering serum cholesterol in a subject, wherein said medicament is adapted for simultaneous or sequential administration with an agent that elevates the availability of low density lipoprotein receptor (LDLR) protein.

16. The neutralizing PCSK9 variant of Claim 1, 5 or 6 when used as a medicament.

17. The neutralizing PCSK9 variant of Claim 1, 5 or 6 when used in treating hypercholesterolemia.

18. A pharmaceutical composition comprising at least one neutralizing PCSK9 variant according to any of the Claims, 5, 6, 16 or 17, wherein the neutralizing PCSK9 variant is present in an amount effective for the treatment of a cholesterol related disorder.

19. The pharmaceutical composition of Claim 18, wherein the effective amount comprises:

- (i) an amount effective for lowering the level of LDL in a human; and/or
- (ii) an amount that elevates the availability of low density lipoprotein receptor (LDLR) protein in a human, wherein the elevation is preferably at least 5%, at least 20%, at least 50%, at least 100%, or at least 300%.

20. The pharmaceutical composition of Claim 19, wherein the human is a 100 kg male or a 50 kg male.

21. A pharmaceutical composition comprising:

- (a) a Pro/Cat domain, or fragment thereof;
- (b) an inactive V domain; and
- (c) a pharmaceutically acceptable carrier or diluent,

wherein the Pro/Cat domain, or the fragment thereof

- (i) lacks amino acids 1-60 of SEQ ID NO: 3; or
- (ii) lacks amino acids 1-30 of SEQ ID NO: 3; and

wherein the neutralizing PCSK9 variant lacks at least 14 C-terminal amino acids of SEQ ID NO: 3, preferably the PCSK9 variant lacks the protein sequence defined from amino acids 453 to 692 of SEQ ID NO: 3.

22. A pharmaceutical composition comprising a Pro/Cat domain, or fragment thereof, and an inactive V domain, wherein the Pro/Cat domain is present in an amount sufficient for the treatment of a cholesterol related disorder,

wherein the Pro/Cat domain:

- (i) comprises the amino acid sequence of the Pro/Cat domain in SEQ ID NO: 9 or 30; or
- (ii) consists of the amino acid sequence of the Pro/Cat domain in SEQ ID NO: 9 or 30; or
- (iii) consists essentially of the amino acid sequence of the Pro/Cat domain in SEQ ID NO: 9 or 30; or
- (iv) comprises the Cat domain of at least one of the amino acids sequences of SEQ ID NOs: 9, 11, 13, 15 or 3.

23. An isolated neutralizing PCSK9 variant according of Claim 1; an isolated nucleic acid molecule of Claim 2; a vector of Claim 3; a host cell of Claim 4; a pharmaceutical composition of any one of Claims 7, 18, 21 or 22; a method of any one of Claims 8 to 11; or use of any one of Claims 12 to 15, substantially as herein described with reference to any one or more of the examples but excluding comparative examples.

QEDEDGDYEELVLALRSEEDGLAEAPEHGTATFHRCAKDPWRLPGTYVVVLKEETHLSQS
ERTARRLQAQAARRGYLTKILHVFHGLLPGFLVKMSGDLLELALKLPHVDYIEEDSSVFAQ
SIPWNLERITPPRYRADEYQPPDGGSLVEVYLLDTSIQSDHREIEGRVMVTDFENVPEEDG
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QLVQPVGPLVLLPLAGGYSRVLNAAACQRLARAGVVLVTAAGNFRDDACLYSPASAPEVIT
VGATNAQDQPVTLGLTNFGRCVDLFAPGEDIIGASSDCSTCFVSQSGTSQAAAHVAGIA
AMMLSAEPELTIAELRQRLIHFSAKDVINEAWFPEDQRVLTPNLVAALPPSTHGAGWQLFC
RTVWSAHSGPTRMATAIARCAPDEELLCSSFSRSGKRRGERMEAQGGKLVCRAHNAFGGE
GVYAIARCCLLPQANC SVHTAPP AEASMGTRVHCHQQGHVLTGCSSHWEVEDLGTHKPPVL
RPRGQPNCVGHREASIHASCCHAPGLECKVKEHGIPAPQGQVTVACEEGWTLTGCSALPG
TSHVLGAYAVDNTCVRSRDVSTGSTSEEAVTAVAICCRSRHLAQASQELQ

SEQ ID NO:1

FIG. 1A

| | |
|--|-------------------------------|
| Query : atgggcacccgtcagctccaggcggtcctggtggccgctgccactgctgct SEQ ID NO:2 | 10 20 30 40 50 |
| Frame1 : M G T V S S R R S W W P L P L L L SEQ ID NO:3 | ----- ----- ----- ----- ----- |
| Query : gctgctgctgctgctcctgggtcccgcggcgcccgtgcg caggaggacg | 60 70 80 90 100 |
| Frame1 : L L L L L G P A G A R A Q E D E | ----- ----- ----- ----- ----- |
| Query : aggacggcgactacgaggagctggtgctagcctgcgtccgaggagac | 110 120 130 140 150 |
| Frame1 : D G D Y E E L V L A L R S E E D | ----- ----- ----- ----- ----- |
| Query : ggcctggccgaagcacccgagcacgaaaccacagccacccatccaccgctg | 50 160 170 180 190 200 |
| Frame1 : G L A E A P E H G T T A T F H R C | ----- ----- ----- ----- ----- |
| Query : cgc当地aggatccgtggagggtgcctggcacctacgtgggtgtgctgaagg | 210 220 230 240 250 |
| Frame1 : A K D P W R L P G T Y V V V L K E | ----- ----- ----- ----- ----- |
| Query : aggagaccccaccttcgcagtcagagcgcactgcccgcgcctgcaggcc | 50 260 270 280 290 300 |
| Frame1 : E T H L S Q S E R T A R R L Q A | ----- ----- ----- ----- ----- |
| Query : caggctgccccccgggatcacccatccaagatcctgcacatgtctccatgg | 310 320 330 340 350 |
| Frame1 : Q A A R R G Y L T K I L H V F H G | ----- ----- ----- ----- ----- |
| Query : ccttcttcctggcttcctggtaagatgagtggtggcacctgctggagctgg | 50 360 370 380 390 400 |
| Frame1 : L L P G F L V K M S G D L L E L A | ----- ----- ----- ----- ----- |
| Query : ccttgaagttgccccatgtcgactacatcgaggaggactcctctgtcttt | 410 420 430 440 450 |
| Frame1 : L K L P H V D Y I E E D S S V F | ----- ----- ----- ----- ----- |
| Query : gcccagagcatcccggtggAACCTGGAGCGGGATTACCCCTCCGCGGTACCG | 50 460 470 480 490 500 |
| Frame1 : A Q S I P W N L E R I T P P R Y R | ----- ----- ----- ----- ----- |
| Query : ggcggatgaataccagccccccgacggaggcagcctgggtggaggtgtatc | 510 520 530 540 550 |
| Frame1 : A D E Y Q P P D G G S L V E V Y L | ----- ----- ----- ----- ----- |

FIG. 1B₁

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| | |
|--------------------------|---|
| Query : | tcctagacaccagcatacagagtgaccaccggaaatcgagggcagggtc |
| Frame1 : | L D T S I Q S D H R E I E G R V |
| 50 560 570 580 590 600 | |
| Query : | atggtcaccgacttcgagaatgtgcccggaggacgggaccggcttcca |
| Frame1 : | M V T D F E N V P E E D G T R F H |
| 610 620 630 640 650 | |
| Query : | cagacaggccagcaagtgtgacagtcatggcacccacctggcagggtgg |
| Frame1 : | R Q A S K C D S H G T H L A G V V |
| 50 660 670 680 690 700 | |
| Query : | tcagcgccggatgccggcgatggcaagggtgccagcatgcgcagcctg |
| Frame1 : | S G R D A G V A K G A S M R S L |
| 710 720 730 740 750 | |
| Query : | cgcgtgctcaactgccaagggaaggggcacggtagcggcacccctcatagg |
| Frame1 : | R V L N C Q G K G T V S G T L I G |
| 50 760 770 780 790 800 | |
| Query : | cctggagttattcgaaaaagccagctggccagcctgtggccactgg |
| Frame1 : | L E F I R K S Q L V Q P V G P L V |
| 810 820 830 840 850 | |
| Query : | tggtgctgctgcccctggcggtgggtacagccgcgtcctcaacgcccgc |
| Frame1 : | V L L P L A G G Y S R V L N A A |
| 50 860 870 880 890 900 | |
| Query : | tgcctggcgccctggcgagggtgggtcggtcaccgcgtggccaa |
| Frame1 : | C Q R L A R A G V V L V T A A G N |
| 910 920 930 940 950 | |
| Query : | tttccgggacgtgcctgcctactccccagcctcagctcccgggtca |
| Frame1 : | F R D D A C L Y S P A S A P E V I |
| 50 960 970 980 990 1000 | |
| Query : | tcacagttggggccaccaatgcccaggaccgcgtgaccctggggact |
| Frame1 : | T V G A T N A Q D Q P V T L G T |
| 1010 1020 1030 1040 1050 | |
| Query : | ttggggaccaacttggccgtgtgtggacctttgccccagggagga |
| Frame1 : | L G T N F G R C V D L F A P G E D |

FIG. 1B₂

FIG. 1B₃

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| | | | | | | | | | | | | | | | | | |
|-------------------------------|--|------|------|------|------|--------------|---|---|---|--------------|---|---|---|---|---|---|---|
| 650 | 1660 | 1670 | 1680 | 1690 | 1700 | | | | | | | | | | | | |
| ----- ----- ----- ----- ----- | | | | | | | | | | | | | | | | | |
| Query : | cactgccaccaacagggccacgtcctcacaggctgcagctcccactggga | | | | | | | | | | | | | | | | |
| Frame1 : | H | C | H | Q | Q | G | H | V | L | T | G | C | S | S | H | W | E |
| 700 | 1710 | 1720 | 1730 | 1740 | 1750 | | | | | | | | | | | | |
| ----- ----- ----- ----- ----- | | | | | | | | | | | | | | | | | |
| Query : | ggggaggacccttggcacccacaagccgcctgtgctgaggccacgaggc | | | | | | | | | | | | | | | | |
| Frame1 : | V | E | D | L | G | T | H | K | P | P | V | L | R | P | R | G | Q |
| 750 | 1760 | 1770 | 1780 | 1790 | 1800 | | | | | | | | | | | | |
| ----- ----- ----- ----- ----- | | | | | | | | | | | | | | | | | |
| Query : | agcccaaccagtgcgtgggccacagggaggccagcatccacgcttcctgc | | | | | | | | | | | | | | | | |
| Frame1 : | P | N | Q | C | V | G | H | R | E | A | S | I | H | A | S | C | |
| 800 | 1810 | 1820 | 1830 | 1840 | 1850 | | | | | | | | | | | | |
| ----- ----- ----- ----- ----- | | | | | | | | | | | | | | | | | |
| Query : | tgccatccccaggctcggaaatgcaaagtcaaggagcatggaaatccggc | | | | | | | | | | | | | | | | |
| Frame1 : | C | H | A | P | G | L | E | C | K | V | K | E | H | G | I | P | A |
| 850 | 1860 | 1870 | 1880 | 1890 | 1900 | | | | | | | | | | | | |
| ----- ----- ----- ----- ----- | | | | | | | | | | | | | | | | | |
| Query : | ccctcaggggcaggtgaccgtggcctgcgaggaggctggaccctgactg | | | | | | | | | | | | | | | | |
| Frame1 : | P | Q | G | Q | V | T | V | A | C | E | E | G | W | T | L | T | G |
| 900 | 1910 | 1920 | 1930 | 1940 | 1950 | | | | | | | | | | | | |
| ----- ----- ----- ----- ----- | | | | | | | | | | | | | | | | | |
| Query : | gctgcagccctccctgggacctcccacgtcctggggcctacggcgta | | | | | | | | | | | | | | | | |
| Frame1 : | C | S | A | L | P | G | T | S | H | V | L | G | A | Y | A | V | |
| 950 | 1960 | 1970 | 1980 | 1990 | 2000 | | | | | | | | | | | | |
| ----- ----- ----- ----- ----- | | | | | | | | | | | | | | | | | |
| Query : | gacaacacgtgttagtcaggagccggacgtcagcactacaggcagcac | | | | | | | | | | | | | | | | |
| Frame1 : | D | N | T | C | V | V | R | S | R | D | V | S | T | T | G | S | T |
| 2010 | 2020 | 2030 | 2040 | 2050 | 2060 | | | | | | | | | | | | |
| ----- ----- ----- ----- ----- | | | | | | | | | | | | | | | | | |
| Query : | cagcgaagaggccgtgacagccgttgcacatctgctgccggagccggacc | | | | | | | | | | | | | | | | |
| Frame1 : | S | E | E | A | V | T | A | V | A | I | C | C | R | S | R | H | L |
| 50 | 2070 | 2080 | 2090 | 2100 | 2060 | | | | | | | | | | | | |
| ----- ----- ----- ----- ----- | | | | | | | | | | | | | | | | | |
| Query : | tggcgcaggccctccctggagactccag | | | | | SEQ ID NO: 2 | | | | | | | | | | | |
| Frame1 : | A | Q | A | S | Q | E | L | Q | | SEQ ID NO: 3 | | | | | | | |

FIG. 1B₄

| | | | | | |
|-----|------------|-------|-------|--|-----|
| 1 | rat | PCSK9 | (1) | MGIRCSTWLRWPLS-----PQLLILLLCPTGSRAQDEDGDYEEIMLALPS | 50 |
| | cyno | PCSK9 | (1) | MGTVSRSRSMWPLP----LPLLLLLLGPAAGARAQEDDGYEEELVIALRS | |
| | human | PCSK9 | (1) | MRTRGPAWPMPLP----LILMLGPAAGAQARDSEGDHEGLAFAFP | |
| | guinea pig | PCSK9 | (1) | MGTSCSARPWLLS----PLLLLLLRYMGAQAQDEDAEYEEIMLTLQS | |
| | hamster | PCSK9 | (1) | MGTHCSAWLRWPLPLLPPLLILCPTGAGAQDEGDGYEEIMLALPS | |
| | mouse | PCSK9 | (1) | MGT CSARSMWPL | |
| | Consensus | | (1) | PLILLILLLPAGAAAQDEGDGYEEIMLALPS | |
| 51 | rat | PCSK9 | (47) | QEDSLVDEASHV----ATATFRRCSKEAWRLPGLTYYYYVLLMEETQRLQVEQT | 100 |
| | cyno | PCSK9 | (48) | EEDGLADAPEHG----ATATEHRCAKDPWRLPGLTYYYYVLLKEETHRSQSERT | |
| | human | PCSK9 | (48) | EEDGLAEEAPEHG----TATATEHRCAKDPWRLPGLTYYYYVLLKEETHLSQSERT | |
| | guinea pig | PCSK9 | (46) | EEDGPAEAAPHPV----TAPFHRCSKDAWRLPGLTYLVVLKEGTHRQQTKEQT | |
| | hamster | PCSK9 | (47) | QDDGLADETDEAPQGATAAFHRCPEEAWRVPGTYTVMIAEAQWVHIEQT | |
| | mouse | PCSK9 | (51) | QEDGLADEAAHV----ATATFRRCSKEAWRLPGLTYYYYVLLMEETQRLQIEQT | |
| | Consensus | | (51) | QEDGLADEAAHV ATATFHRCSKDAWRLPGLTYYYYVLLKEETQRLQSEQT | |
| 101 | rat | PCSK9 | (94) | AHRLQTAARRGGYIKVLLHVFYDLFPGLVVKMSSDLGLALKLPHVVEYIE | 150 |
| | cyno | PCSK9 | (95) | ARRLQAQAAARRGGYLTKLHVFFHLLLPGLFVLVMSGDLLEALKLPHVVDIE | |
| | human | PCSK9 | (95) | ARRLQAQAAARRGGYLTKLHVFFHGLLPGFVLVMSGDLLEALKLPHVVDIE | |
| | guinea pig | PCSK9 | (93) | AHRLQAKAARRGGYTTVLLHVFFHLLVPGFLVVRMSGDLLDMALRLPFLVQYIE | |
| | hamster | PCSK9 | (97) | MHRLQTOAARRGGYIKIQUIFYDFLPAFVVKMSSDLDDALKLPHVVKYIE | |
| | mouse | PCSK9 | (98) | AHRLQTRAARRGGYIKVLLHIFYDLFPGLVVKMSSDLGLALKLPHVVEYIE | |
| | Consensus | | (101) | AHRLQTOAARRGGYVTKLHVFFHDLLPGLFVLVMSSDLDDALKLPHVVDIE | |
| 151 | rat | PCSK9 | (144) | EDSLVFAQSIPWNLERIIPAWQQTEDSS-----PDGSSSQVEVYLLDTSIQ | 200 |
| | cyno | PCSK9 | (145) | EDSSVFAQSIPWNLERITPARYRADEYQP-----PKGGSSLVEVYLLDTSIQ | |
| | human | PCSK9 | (145) | EDSSVFAQSIPWNLERITPARYRADEYQP-----PDGGSSLVEVYLLDTSIQ | |
| | guinea pig | PCSK9 | (143) | EDSSVFAQSIPWNLERIPVRHOAKEYSAP-----SHPVTVYLLDTSIQ | |
| | hamster | PCSK9 | (147) | EDSLVFAQSIPWNLERIDRIPAGRQAOEYSSSRKVPSGSQQVEVYLLDTSIQ | |
| | mouse | PCSK9 | (148) | EDSFVFAQSIPWNLERIIPAWHQTEDRS-----PDGSSSQVEVYLLDTSIQ | |
| | Consensus | | (151) | EDSSVFAQSIPWNLERIIPARHQADEYSS PDGSSSQVEVYLLDTSIQ | |
| 201 | rat | PCSK9 | (190) | SGHREIEGRVTITDFNSVPEEDGTRFHRQASKCDSHGTHLAGVSGRDAG | 250 |
| | cyno | PCSK9 | (191) | SDHREIEGRVMVTDFESVPEEDGTRFHRQASKCDSHGTHLAGVSGRDAG | |
| | human | PCSK9 | (191) | SDHREIEGRVMVTDEENVPEEDGTRFHRQASKCDSHGTHLAGVSGRDAG | |
| | guinea pig | PCSK9 | (187) | SGHREIQGRITVTDFFESVPEQEDGTRFHRQASKCDSHGTHLAGVSGRDAG | |
| | hamster | PCSK9 | (197) | SDHREIEGRVTVTDFNSVPEEDGTRFHRQASKCDSHGTHLAGVSGRDAG | |
| | mouse | PCSK9 | (194) | GAHREIEGRVTITDFNSVPEEDGTRFHRQASKCDSHGTHLAGVSGRDAG | |
| | Consensus | | (201) | SDHREIEGRVTVTDFNSVPEEDGTRFHRQASKCDSHGTHLAGVSGRDAG | |

FIG. 1C

| | | | | | |
|-----|------------|-------|-------|---|-----|
| 251 | rat | PCSK9 | (240) | VAKGTSLLHSLRVLN CQGKGT VSGT LIGLEFIRKS QQLI QPS GPLV VVLLPLA | 300 |
| | cyno | PCSK9 | (241) | VAKGAGLRLSLRVLN CQGKGT VSGT LIGLEFIRKS QQLI QPS GPLV VVLLPLA | |
| | human | PCSK9 | (241) | VAKGASMRSLLRVLN CQGKGT VSGT LIGLEFIRKS QQLI QPS GPLV VVLLPLA | |
| | guinea pig | PCSK9 | (237) | VAKGAGLRLSLRVLN CQGKGT VSGT LIGLEFIRKS QQLI QPS GPLV VVLLPLA | |
| | hamster | PCSK9 | (247) | VAKGTLLHGLRLRVLN CQGKGT VSGT LIGLEFIRKS QQLI QPS GPLV VVLLPLA | |
| | mouse | PCSK9 | (244) | VAKGTSLLHSLRVLN CQGKGT VSGT LIGLEFIRKS QQLI QPS GPLV VVLLPLA | |
| | Consensus | | (251) | VAKGTSLLRSLRVLN CQGKGT VSGT LIGLEFIRKS QQLI QPS GPLV VVLLPLA | |
| 301 | | | | GGYSRILNTACQRLARTGVV LVAAGGNFRDDACLYSPASAPEVITVGATN | 350 |
| | rat | PCSK9 | (290) | GGYSR VNAACQRLARTGVV LVAAGGNFRDDACLYSPASAPEVITVGATN | |
| | cyno | PCSK9 | (291) | GGYSR VLNAA CQRLARTGVV LVAAGGNFRDDACLYSPASAPEVITVGATN | |
| | human | PCSK9 | (291) | GGYSR VLNAA CQRLARTGVV LVAAGGNFRDDACLYSPASAPEVITVGATN | |
| | guinea pig | PCSK9 | (287) | GGYSR VLNAA CQRLARTGVV LVAAGGNFRDDACLYSPASAPEVITVGATN | |
| | hamster | PCSK9 | (297) | GRYSR VLNATACQH LARTGVV LVAAGGNFRDDACLYSPASAPEVITVGATD | |
| | mouse | PCSK9 | (294) | GGYSR VLNAA CQRLARTGVV LVAAGGNFRDDACLYSPASAPEVITVGATN | |
| | Consensus | | (301) | GGYSR VLNAA CQRLARTGVV LVAAGGNFRDDACLYSPASAPEVITVGATN | |
| 351 | | | | GGYSR VLNAA CQRLARTGVV LVAAGGNFRDDACLYSPASAPEVITVGATN | 400 |
| | rat | PCSK9 | (340) | AQDQPV TLGT LGT NFGRCV DLFAPGKDI GASSDC STCYS QSGT SQAAA | |
| | cyno | PCSK9 | (341) | AQDQPV TLGT LGT NFGRCV DLFAPGEDI GASSDC STCFV SRS GT SQAAA | |
| | human | PCSK9 | (341) | AQDQPV TLGT LGT NFGRCV DLFAPGEDI GASSDC STCFV SRS GT SQAAA | |
| | guinea pig | PCSK9 | (337) | AQDQPV TLGT LGT NFGRCV DLFAPGEDI GASSDC STCFV SRS GT SQAAA | |
| | hamster | PCSK9 | (347) | VQDQPV TLGT LGT NFGRCV DLFAPGKDI GASSDC STCFMS QSGT SQAAA | |
| | mouse | PCSK9 | (344) | AQDQPV TLGT LGT NFGRCV DLFAPGKDI GASSDC STCFMS QSGT SQAAA | |
| | Consensus | | (351) | AQDQPV TLGT LGT NFGRCV DLFAPGKDI GASSDC STCFMS QSGT SQAAA | |
| 401 | | | | HVAGIVAMMLN RDPALT LLAELR QRLI LFST KDV INMAWF PE DQRV LTPNR | 450 |
| | rat | PCSK9 | (390) | HVAGIAA MMLS AEP LT LLAELR QRLI HFSAKD VINE AWF PE DQRV LTPNL | |
| | cyno | PCSK9 | (391) | HVAGIAA MMLS AEP LT LLAELR QRLI HFSAKD VINE AWF PE DQRV LTPNL | |
| | human | PCSK9 | (391) | HVAGIAA MMLS AEP LT LLAELR QRLI HFSAKD VINE AWF PE DQRV LTPNL | |
| | guinea pig | PCSK9 | (387) | HVAGIVTMM LTAQPKL T LLAELW QRLI HFAKDV INMAWF PE DQRV LTPNL | |
| | hamster | PCSK9 | (397) | HVAGIVAMMLT LPEPLT LELR QRLI HFST KDA INMAWF PE DQRV LTPNL | |
| | mouse | PCSK9 | (394) | HVAGIVARMLS REPT LT LLAELR QRLI HFST KDV INMAWF PE DQRV LTPNL | |
| | Consensus | | (401) | HVAGIVAMMLS AEP LT LLAELR QRLI HFST KDV INMAWF PE DQRV LTPNL | |
| 451 | | | | VATLPPSTQETGGQ LICRTVWSAHSGPTRTATATARC APEEE LLS CSSFS | 500 |
| | rat | PCSK9 | (440) | VAA LPPSTH RAGW QLFC RTVWSAHSGPTRMATAVARCA QDE ELLS CSSFS | |
| | cyno | PCSK9 | (441) | VAA LPPSTHAGW QLFC RTVWSAHSGPTRMATAVARCA QDE ELLS CSSFS | |
| | human | PCSK9 | (441) | VATLPPSTHAGW QLFC RTVWSAHSGPTRMATAVARCA QDE ELLS CSSFS | |
| | guinea pig | PCSK9 | (437) | VATLPPSTRAGG RLLICRTVWSAHSGPTRMATAVARCA QDE ELLS CSSFS | |
| | hamster | PCSK9 | (447) | VATLPPSTHGTGGQLICRTVWSAHSGPTRMATAVARCA QDE ELLS CSSFS | |
| | mouse | PCSK9 | (444) | VATLPPSTHGTGGQLICRTVWSAHSGPTRMATAVARCA QDE ELLS CSSFS | |
| | Consensus | | (451) | VATLPPSTHGTGGQLICRTVWSAHSGPTRMATAVARCA QDE ELLS CSSFS | |

FIG. 1D

| | | | | |
|-----|------------|-------|-------|--|
| 550 | rat | PCSK9 | (490) | RSGRRRGDR1EAIGGQQVCKALNAAFEGEGYAYAVRCCILLPRVNCSTHNTP |
| | cyno | PCSK9 | (491) | RSGKRRGER1EAQGGKRVCRAHNAFEGEGYAYIARCCILLPQVNCVHTAP |
| | human | PCSK9 | (491) | RSGKRRGERMEAQGGKLVCRAHNAFEGEGYAYIARCCILLPQANCSVHTAP |
| | guinea pig | PCSK9 | (487) | RSGKRRGER1EVLRGRRVVCVAYNAFGGKVHAVARCCILLPRANCSLHTAP |
| | hamster | PCSK9 | (497) | RSGRRRGDR1EAIGGQQVCKALNAAFEGEGYAYAVRCCILLPRANCSTHNTP |
| | mouse | PCSK9 | (494) | RSGKRRRGDW1EAIGGQQVCKALNAAFEGEGYAYAVRCCILLPRANCSTHNTP |
| | Conensus | | (501) | RSGKRRRGDR1EAIGGQQVCKALNAAFEGEGYAYAVRCCILLPRANCSTHNTP |
| 551 | rat | PCSK9 | (540) | AARAGPOTPVICHQOKDHVLTGCSEHWEVENLRAOOOPLLRSRHOQGOCVG |
| | cyno | PCSK9 | (541) | PAGASMGTTRVICHQQGHVLTGCSSSHWEVEDLGTHKPPVLRPRGQPNQCVG |
| | human | PCSK9 | (541) | PAEASMGTTRVICHQQGHVLTGCSSSHWEVEDLGTHKPPVLRPRGQPNQCVG |
| | guinea pig | PCSK9 | (537) | -ARAGMEEPRVICHQHRKBDQVLTGCSSAWEAEDFRARGWMLRP-GGQSPQCVG |
| | hamster | PCSK9 | (547) | AARTSLETHAHCQOKDHVLTGCSSLHWVEGIGVQPLAVLRSRHQPGQCTG |
| | mouse | PCSK9 | (544) | AARAGLETHVICHQOKDHVLTGCSEHWEVEDLSVRQPALRSRQPGQCVG |
| | Conensus | | (551) | AARASMETRVICHQOKDHVLTGCSSHWEVEDLG_K_PVLRSRQPGQCVG |
| 601 | rat | PCSK9 | (590) | HQEASVHASCHAPGLECKIKEHGIGAQPQEVTVACEAGWTLTGCNVLPG |
| | cyno | PCSK9 | (591) | HREASIHASCCHAPGLECKVREHGIPAPQEQVIVACEDGWTLTGCALPG |
| | human | PCSK9 | (591) | HREASITHASCCHAPGLECKVKEHGIPAPQEQVTVACEEGWTLTGCALPG |
| | guinea pig | PCSK9 | (585) | HSKASVHASCCSAPGLECRIEHGVPWPAEQVTVACEAGWTLTGCSTLPG |
| | hamster | PCSK9 | (597) | HREASVHASCHAPGLECKIKEHGIGSPAEQVTVACEAGWTLTGCNVLPG |
| | mouse | PCSK9 | (594) | HQAASVYASCHAPGLECKIKEHGIGSPSEQVTVACEAGWTLTGCNVLPG |
| | Conensus | | (601) | HREASVHASCHAPGLECKIKEHGIGPQAEQVTVACEAGWTLTGCNVLPG |
| 651 | rat | PCSK9 | (640) | ASLPLGAYSVDNVICVARTDAGRADTSEEATVAAATCCRSRPSAKASWV |
| | cyno | PCSK9 | (641) | TSHVLGAYAVDNTCVVRSRDVSTTGSTSEEAVAAICCRRSLHVQASQE |
| | human | PCSK9 | (641) | TSHVLGAYAVDNTCVVRSRDVSTTGSTSEEAVAAICCRRSLHVQASQE |
| | guinea pig | PCSK9 | (635) | ASSVLTGTYAVDNTMCVVRSRDVKAIDRTRGEEATVAAICCRRSQASEQASQE |
| | hamster | PCSK9 | (647) | AFITLGAYAVDNTCVARSRVDTAGRTGEEATVAAICCRRNRPSSAKASWV |
| | mouse | PCSK9 | (644) | ASLTLGAYAVDNTLCVAVRHDATARADRTSGEATVAAICCRRSRPSAKASWV |
| | Conensus | | (651) | ASLVLGAYAVDNTCVVRSRDVSTAGRTSEEATVAAICCRRSRPSAQASWV |
| 701 | rat | PCSK9 | (690) | HOH-----HHHHHHH- |
| | cyno | PCSK9 | (691) | LQGKPIPNNPLGLDSTHHHHHH- |
| | human | PCSK9 | (691) | LQG-----PHHHHHHHH- |
| | guinea pig | PCSK9 | (685) | RQH-----HHHHH---- |
| | hamster | PCSK9 | (697) | HQH-----HHHHH---- |
| | mouse | PCSK9 | (694) | QGP-----HHHHHHH |
| | Conensus | | (701) | QH-----HHHHHHH |
| 723 | rat | PCSK9 | (8) | 8 |
| | cyno | PCSK9 | (7) | 7 |
| | human | PCSK9 | (24) | 24 |
| | guinea pig | PCSK9 | (4) | 4 |
| | hamster | PCSK9 | (5) | 5 |
| | mouse | PCSK9 | (6) | 6 |
| | Conensus | | (9) | 9 |
| 777 | rat | PCSK9 | (7) | 7 |
| | cyno | PCSK9 | (24) | 24 |
| | human | PCSK9 | (4) | 4 |
| | guinea pig | PCSK9 | (5) | 5 |
| | hamster | PCSK9 | (6) | 6 |
| | mouse | PCSK9 | (9) | 9 |
| | Conensus | | (9) | 9 |
| 888 | rat | PCSK9 | (7) | 7 |
| | cyno | PCSK9 | (24) | 24 |
| | human | PCSK9 | (4) | 4 |
| | guinea pig | PCSK9 | (5) | 5 |
| | hamster | PCSK9 | (6) | 6 |
| | mouse | PCSK9 | (9) | 9 |
| | Conensus | | (9) | 9 |
| 999 | rat | PCSK9 | (7) | 7 |
| | cyno | PCSK9 | (24) | 24 |
| | human | PCSK9 | (4) | 4 |
| | guinea pig | PCSK9 | (5) | 5 |
| | hamster | PCSK9 | (6) | 6 |
| | mouse | PCSK9 | (9) | 9 |
| | Conensus | | (9) | 9 |

FIG. 1E

| | | | |
|-------|-----|---|-----|
| Query | 1 | SIPWNLERITPPRYRADEYQPPDGGSILVEVYLLDTSIQSDHREIEGRVMVTDFENVPEED | 60 |
| Sbjct | 368 | SIPWNLDRLVLAPESRSEYYSPPNKGDQEVEVYLLDTSLQSGHREIEGKVTVADEFEDVPDED | 427 |
| Query | 61 | GTRFHROASKCDSHGTHLAGVVSSGRDAGVAKGASMRSLRVLNQGKGTVSGTLLIGLEFIR | 120 |
| Sbjct | 428 | G +FH QASKC+ SHGTH+AGV+SGRDAGVA+ A+RS+RVLNQGKGTVSGT GLEFIR | 487 |
| Query | 121 | KSQLVQPVGPLVVLPLAGGYSRVLNAACQRLARAGVVLVTAAGNFRDDACLYSPASAPE | 180 |
| Sbjct | 488 | ++QLVQP PL+VLLP AGG+SR LNAAC+ L R+G ++ AAGN+RDDAC YSPAS PE | 547 |
| Query | 181 | RTQLVQPVSPLVLLPFAGGHSRTLNAAACRLLVRSGAIAVIAAGNYRDDACSYSPASEPE | 240 |
| Sbjct | 548 | VITVGATNAQDQPVTLGTLGTCVLDLFAPGEDIIGASSDCSTCFVSQSGTSQAAAHV | 607 |
| Query | 241 | VITVGATNAQDQP LG LGTNGRCVLDLFAPGEDIIGASSDC TCF SQSGTSQAAAHV | 10 |
| Sbjct | 608 | VITVGATNAQDQPAALGALGTNGRCVLDLFAPGEDIIGASSDCGTCFTSQSGTSQAAAHV | 11 |
| | | AGIAAMMLSAEPELTIAELRQRLIHFSAKDVTINEAWFPEDQRVLTPNLVAALP | 12 |
| | | AGIA+M+L+AEP LT+ ELRQRLIHFS K+ INEAWFPEDQR+LTPNLVA LP | 13 |
| | | AGIASMLNAEPESLTVPELQRQLIHFSVKNAINEAWFPEDQRLLTPNLVARLP | 14 |
| | | SEQ ID | |
| | | NO: | |

FIG. 1F

| | | | |
|---------|-----|--|-----------|
| Query | 1 | SIPWNLERITPPRYRADEYQPPDGGSILVEVYLLDTSIQSDHREIEGRVMVTDFENVPEED S+PWNL+RI P + A ++ PP+ G VEVYLLDTSIQS+HREIEG+V VTDF+NVPEED | 60 |
| Subject | 144 | SVPWNLDRIVPAQOMASQFSPNTGDSVEVYLLDTSIQSNHREIEGKVFVTDQNVPEED | 203 |
| Query | 61 | GTRFHROASKCDSHGTHLAGVVSSGRDAGVAKGASMRSLLRVLNCGKGTVSGTLLIGLEFIR GTRFHROASKC+SHGTH+AGVV+GRDAGVAKG +RSLRVLNCGKGTVSG+L GLEFIR | 120 |
| Subject | 204 | GTRFHROASKCESHGTHMAGVVNGRDAVGVNVRSLRVLNCGKGTVSGSLTGLEFIR | 263 |
| Query | 121 | KSQLVQPVGPLVVLLPLAGGYSRVLNAACQRLARAGVVLVTAAGNFRDDACLYSPASAPE K+ + QP PL+V++P GGYSR+LNAA + L GV+++ AAGN+DDACLYSPAS PE | 180 |
| Subject | 264 | KTLIEQPYNPLIVIIPFVGGYSRILNAASRALVNTGVITIAAGNYKDDACLYSPASEPE | 323 |
| Query | 181 | VITVGATNAQDQPVTLGTLGNTFGRCVDLFAPGEDIIGASSDCSTCFVSQSGTSQAAAHV VIT+GATN QDQP T+G LGTN+G C+DLFAPG+DIIGASSDCSTCF S+SGTSQAAAHV | 240 |
| Subject | 324 | VITIGATNYQDQPATMGVLTNYGNCLDLFAPGDDIIIGASSDCSTCFTSKSGTSQAAAHV | 383 |
| Query | 241 | AGIAAMMLSAEPELTIAELRQLRIHFSAKDVINEAWFPEDQRVLTPNLVAALP AGIAAM+L+ +P+L++ELRQLRI FS K VINE WFPEDQR+TPN VA LP | 293 10 13 |
| Subject | 384 | AGIAAMILNDKPDLSVSELRQLIQFSTKKVINEVWFPEDQRLLITPNRVAGLP | 436 14 |
| | | SEQ ID | |

NO:

FIG. 1G

| | | | |
|---------|-----|--|---------|
| Query | 3 | PWNLERITPPRYRADYEYQPPDGGSILVEVYLLDTSIQSDHREIEGRVMVTDFFENVPEEDGT | 62 |
| Subject | 84 | PW+L R+ PR R P G+ VEVYL+D S+ S HRE+ GRV+VTDF +VP + PWSLRLP RPRGRR-----PGDGAAVEVYLMGDGVLSLSSHRELGGRVLVTDHFHSVPVGEAG | 137 |
| Query | 63 | RFHRQASKCDSHGTHLAGVVSGRDAGVAKGASMRSILRVLNQGKGTIVSGTLLIGLEFIRKS | 122 |
| Subject | 138 | HR+AS+C HGTH+A VV G D GVA GA + +RVL+C+GKGTVSG L G+E+IR + G-HREASRCKGHGTHVAAVVMGSDTGVAPGARVNLYRVLDRGKGTIVSGALAGVEYIRAA | 196 |
| Query | 123 | QLVQPVGPLVVLPILAGGYSRVLNAACQRLLARAGVVLVTAAGNFRDDACLYSPASAPE-- | 180 |
| Subject | 197 | P G VVLLP G +SR LNAAC+ L G V+V AAGN+RDDACLYSPAS PE LRAHPPGAAVVLLPFTGAFSRSLLNAACRDLVNTGAVVVVAAGNYRDDACLYSPASEPEVC | 256 |
| Query | 181 | ----- | ----- |
| Subject | 257 | VITVGATNAQDQPVTLGTLGTNFGRCVDLFA TITVGA N+ DQ V+ G GTN GRCVD+FA TGGSARSHTHTHTHLLQAVLVCVQVITVGAVNSADQLVSQGPGBTNVGRCVDFVA | 211 316 |
| Query | 212 | PGEDIIIGASSDCSTCFVQSQSGTSQAAAHHVAGIAAMMLSAEPELTAAELRQRLIHFSAKDV | 271 |
| Subject | 317 | PG DI+ ASSDC TCF S SGTSQAAAAG+AA+LS+ P LT ++ Q L+ +S PGGDIVSASSDCDTCFASGSGTSQAAAHHAGMAAVLSSSSPSLTPVQVLTLLRYS---- | 372 |
| Query | 272 | INEAWFPEDQRVLTPNLVAALPP 294 17 | |
| Subject | 373 | ++ + +TP+LVAALPP 15 VSLPSVSGRGRGLVTPSLVAALPP 395 16 SEQ ID NO: | |

FIG. 1H

FIG. 11 Sequence of Human and Mouse LDLR

Sequence of Human and Mouse LDLR

FIG. 1J Sequence of Human and Mouse LDLR

| Section 7 | | | | | | | | | | | |
|--------------------|-------|---|------------|------------------------------------|---------------------------|--------------------|--------|----------|---------------------|------------|------------|
| (439) hLDLR P01130 | 439 | 439 | 450 | C | β-Propeller 2 | | | 470 | 480 | 490 | 500 |
| mLDLR NP_034830 | (438) | SNRIYWSQLSORMICSTQIDRAHGVSSSYDTV | ISRD | QAPPGLAVIDWIH | HSNIYWTDSVLGTV | SVA | DTKGV | KRKT | | | 511 |
| Consensus | (439) | SNRIYWSQLSORMICSTQIDRAHGVSSSYDTV | ISRD | QAPPGLAVIDWIH | HSNIYWTDSVLGTV | SVA | DTKGV | KRKT | | | |
| Section 8 | | | | | | | | | | | |
| (512) hLDLR P01130 | 512 | 512 | 520 | 530 | 540 | 550 | 560 | 570 | 580 | 584 | |
| mLDLR NP_034830 | (511) | LFRENGSKPRAIVVDPVHGFMYWTDWGTPAKIKGGGLNGVDIY | Y | SLVTTENIQWPNGITLDL | ISL | SGR | LYW | VDS | KLH | | |
| Consensus | (511) | LFQEA | GSR | PRAIVVDPVHGFMYWTDWGTPAKIKGGGLNGVDI | Y | SLVTTENIQWPNGITLDL | ISL | SGR | LYW | VDS | KLH |
| Section 9 | | | | | | | | | | | |
| (585) hLDLR P01130 | 585 | 590 | 600 | 610 | 620 | 630 | 640 | 650 | 657 | | |
| mLDLR NP_034830 | (584) | SISSIDVNGGNRKTILEDEKRLAHPFSLAYEDK | V | WTD | LINEAIF | SDVNLI | AEN | LLSPE | DMV | L | FH |
| Consensus | (585) | SISSIDVNGGNRKTILEDEKRLAHPFSLAYEDK | V | WTD | LINEAIF | SDVNLI | AEN | LLSPE | DMV | L | FH |
| Section 10 | | | | | | | | | | | |
| (658) hLDLR P01130 | 658 | C | 670 | C | 680 | C | 690 | C | 700 | 710 | 720 |
| mLDLR NP_034830 | (657) | NTTQPRGVNWCERTTLS | -NGGCQY | YLCLPAPQINPHSPKFT | TCACPDGMLI | ARD | DMR | RSCL | TEA | AAA | V |
| Consensus | (657) | NTTQPRGVNWCERTTLS | -NGGCQY | YLCLPAPQINPHSPKFT | TCACPDGMLI | ARD | DMR | RSCL | TEA | AAA | V |
| Section 11 | | | | | | | | | | | |
| (731) hLDLR P01130 | 731 | 740 | 750 | 760 | 770 | 780 | 790 | 800 | 803 | | |
| mLDLR NP_034830 | (729) | TKYSSSTAVR-TQHITTRPV | PDT | SRILPGATPGL | Y | IV | TM | SHQ | ALGDV | AGR | NEKKPSSVRA |
| Consensus | (730) | TKYSSSTAVR-TQHITTRPV | PDT | SRILPGATPGL | Y | IV | TM | SHQ | ALGDV | AGR | NEKKPSSVRA |
| Section 12 | | | | | | | | | | | |
| (804) hLDLR P01130 | 804 | TM | 810 | 820 | Endocytosis signal | | | 840 | 850 | 865 | |
| mLDLR NP_034830 | (801) | FLCLGVFTLW | KNWRLKN | --INSINF | DNFVY | QKTTED | V | HICHNQDG | SYPSRQMVSLEDDVA | SEQ ID NO: | |
| Consensus | (803) | FLCLGVFTLW | KNWRLKN | --INSINF | DNFVY | QKTTED | V | HICRSQDG | YPSRQMVSLEDDVA | 18 | |
| | | LLVLGAVL | LLWKNWRLKN | ITINSINF | DNFVY | QKTTED | V | HICRSQDG | YPSRQMVSLEDDVA | 20 | |
| | | LL | LG | LLWKNWRLKN | INSINF | DNFVY | QKTTED | ELHIC | QDGYSYPSRQMVSLEDDVA | 21 | |

FIG. 1K Sequence of Human and Cyno LDLR

| | Section 1 | | | | | |
|---------------------|--|-------------|-----|-----|-----|-----|
| (1) | 1 | 10 | 20 | 30 | 40 | 50 |
| hLDLR 20080009918 | MGPWGWLRLRWTIVALLAAGTAGTAVGDRCERNEFQCCQDGKCI SYKWCDSAEQCDGSDESQETCLSVTCKSGD | | | | | 72 |
| cynLDLR 20080068365 | MEPWGWLRLRWTIVALLAEEAVGDRCERNEFQCEDGKCI SYKWCDSAEQCDGSDESQETCLSVTCKSGD | | | | | |
| Consensus (1) | M PWGWLRLRWTIVALLAEEAVGDRCERNEFQCCQDGSDESQETCLSVTCKSGD | | | | | |
| | Section 2 | | | | | |
| (73) | 73 | 80 | 90 | 100 | 110 | 120 |
| hLDLR 20080009918 | FSCGGRVNRCIPQFWRCGDQVDCDNGSDEQGCPPKTSQDEFRCHDGKCI SRQFVCDSDRDCLDGSDEASCP | | | | | 144 |
| cynLDLR 20080068365 | FSCGGRVNRCIPQFWRCGDGEVDCDENGSDEQDCCPPKTSQDEFRCHDGKCI TYRQFVCDSDRDCLDGSDEASCP | | | | | |
| Consensus (73) | FSCGGRVNRCIPQFWRCGDGVDCDENGSDEQ CPPKTSQDEFRCHDGKCI RQFVCDSDRDCLDGSDEASCP | | | | | |
| | Section 3 | | | | | |
| (145) | 145 | 150 | 160 | 170 | 180 | 190 |
| hLDLR 20080009918 | VLTCGPASFQCNSSSTCIPQLWACNDPDCEDGSDEWQRCRGLYVFQGDSSPCSAFFHCLSGECIHSSWR | | | | | 216 |
| cynLDLR 20080068365 | VLTCGPASFQCNSSSTCIPQLWACNDPDCEDGSDEWQHQCGQGLLEVPKRDSSPCSAFFHCQSGECIHSGWR | | | | | |
| Consensus (145) | VLTCGPASFQCNSSSTCIPQLWACNDPDCEDGSDEWQPCSDGCGLLEVPKRDSSPCSAFFHC DSSPCSAFEFH | C GL V | | | | |
| | Section 4 | | | | | |
| (217) | 217 | 230 | 240 | 250 | 260 | 270 |
| hLDLR 20080009918 | DGGPDCKDKSDEEENCAVATCRPDEFQCSDGNCIHGSRQCDREYDCKDMSDEVGC | V | | | | 288 |
| cynLDLR 20080068365 | DGGPDCKDKSDEEENCPVATCRPDEFQCSDGTCIHGSRQCDREYDCKDMSDEVGC | V | | | | |
| Consensus (217) | DGGPDCKDKSDEEENCPVATCRPDEFQCSDGCGLLEVPKRDSSPCSAFFHC INVTLC | EGPNFKCHSGE | | | | |
| | Section 5 | | | | | |
| (289) | 289 | 300 | 310 | 320 | 330 | 340 |
| hLDLR 20080009918 | CITLDKVCNMARDCRDWSDEPIKECGTNECILDNNNGCSHICNDLKI | GYEC | | | | 360 |
| cynLDLR 20080068365 | CISLDKVCNMARDCRDWSDEPIKECGTNECILDNNNGCSHICNDLKI | GYEC | | | | |
| Consensus (289) | CISLDKVCNMARDCRDWSDEPIKECGTNECILDNNNGCSHICNDLKI | GYEC | | | | |
| | Section 6 | | | | | |
| (361) | 361 | 370 | 380 | 390 | 400 | 410 |
| hLDLR 20080009918 | PDTCSQLCVNLEGGYKCQCEEFGQLDPHTKACKAVGSIAYLFFTNRHEVKMTLDRESEYTSLLIPNLRNVAL | | | | | 432 |
| cynLDLR 20080068365 | PDTCSQLCVNLEGSYKCQCEEFGQLDPHTKACKAVGSIAYLIFTNRHEVKMTLDRESEYTSLLIPNLRNVAL | | | | | |
| Consensus (361) | PDTCSQLCVNLEG YKCQCEEFGQLDPHTKACKAVGSIAYL FTRHEVKMTLDRESEYTSLLIPNLRNVAL | | | | | |

Sequence of Human and Cyno LDLR

SUBSTITUTE SHEET (RULE 26)

Cavia porcellus PCSK9

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Arg | Thr | Arg | Gly | Pro | Ala | Pro | Ala | Trp | Trp | Pro | Met | Leu | Leu | Leu |
| 1 | | | | 5 | | | | | 10 | | | 15 | | | |
| Leu | Met | Leu | Gly | Pro | Ala | Pro | Ala | Gly | Ala | Gln | Ala | Arg | Asp | Ser | Glu |
| | | | | | | | | 20 | | 25 | | | 30 | | |
| Asp | Gly | Asp | His | Glu | Gly | Leu | Ala | Phe | Ala | Phe | Pro | Pro | Glu | Glu | Asp |
| | | | | | | 35 | | 40 | | | 45 | | | | |
| Gly | Pro | Ala | Glu | Ala | Ala | Pro | His | Val | Pro | Thr | Ala | Pro | Phe | His | Arg |
| | | | | | | 50 | | 55 | | 60 | | | | | |
| Cys | Ser | Lys | Asp | Ala | Trp | Arg | Leu | Pro | Gly | Thr | Tyr | Leu | Val | Val | Leu |
| | | | | | | 65 | | 70 | | 75 | | | 80 | | |
| Lys | Glu | Gly | Thr | His | Arg | Gly | Gln | Thr | Lys | His | Thr | Ala | His | Arg | Leu |
| | | | | | | 85 | | 90 | | | 95 | | | | |
| Gln | Ala | Lys | Ala | Ala | Arg | Arg | Gly | Tyr | Val | Thr | Thr | Val | Leu | His | Leu |
| | | | | | | 100 | | 105 | | | 110 | | | | |
| Phe | His | His | Leu | Val | Pro | Gly | Phe | Leu | Val | Arg | Met | Ser | Gly | Asp | Leu |
| | | | | | | 115 | | 120 | | | 125 | | | | |
| Leu | Asp | Met | Ala | Leu | Arg | Leu | Pro | Leu | Val | Gln | Tyr | Ile | Glu | Glu | Asp |
| | | | | | | 130 | | 135 | | | 140 | | | | |
| Ser | Ser | Val | Phe | Ala | Gln | Ser | Val | Pro | Trp | Asn | Leu | Glu | Arg | Ile | Leu |
| | | | | | | 145 | | 150 | | | 155 | | | 160 | |
| Pro | Val | Arg | His | Gln | Ala | Lys | Glu | Tyr | Ser | Ala | Pro | Ser | His | Pro | Val |
| | | | | | | 165 | | 170 | | | 175 | | | | |
| Thr | Val | Tyr | Leu | Leu | Asp | Thr | Ser | Ile | Gln | Ser | Gly | His | Arg | Glu | Ile |
| | | | | | | 180 | | 185 | | | 190 | | | | |
| Gln | Gly | Arg | Ile | Thr | Val | Thr | Asp | Phe | Glu | Ser | Val | Pro | Gln | Glu | Asp |
| | | | | | | 195 | | 200 | | | 205 | | | | |
| Gly | Thr | Arg | Phe | His | Arg | Gln | Ala | Ser | Lys | Cys | Asp | Ser | His | Gly | Thr |
| | | | | | | 210 | | 215 | | | 220 | | | | |
| His | Leu | Ala | Gly | Val | Val | Ser | Gly | Arg | Asp | Ala | Gly | Val | Ala | Lys | Gly |
| | | | | | | 225 | | 230 | | | 235 | | | 240 | |
| Ala | Gly | Leu | Arg | Ser | Leu | Arg | Val | Leu | Asn | Cys | Gln | Gly | Arg | Gly | Thr |
| | | | | | | 245 | | 250 | | | 255 | | | | |
| Val | Ser | Ser | Thr | Leu | Arg | Gly | Leu | Glu | Phe | Ile | Arg | Lys | Ser | Gln | Leu |
| | | | | | | 260 | | 265 | | | 270 | | | | |
| Ala | Gln | Pro | Val | Glu | Pro | Leu | Val | Val | Leu | Leu | Pro | Leu | Ala | Gly | Gly |
| | | | | | | 275 | | 280 | | | 285 | | | | |
| Tyr | Ser | Arg | Thr | Leu | Asn | Ala | Ala | Cys | His | Leu | Leu | Ala | Arg | Ala | Gly |
| | | | | | | 290 | | 295 | | | 300 | | | | |
| Val | Val | Leu | Val | Ala | Ala | Ala | Gly | Asn | Phe | Arg | Asp | Asp | Ala | Cys | Leu |
| | | | | | | 305 | | 310 | | | 315 | | | 320 | |
| Tyr | Ser | Pro | Ala | Ser | Ala | Pro | Glu | Val | Ile | Thr | Val | Gly | Ala | Thr | Asn |
| | | | | | | 325 | | 330 | | | 335 | | | | |
| Ala | Gln | Asp | Gln | Pro | Val | Thr | Leu | Gly | Thr | Leu | Gly | Thr | Asn | Phe | Gly |
| | | | | | | 340 | | 345 | | | 350 | | | | |
| Arg | Cys | Val | Asp | Leu | Phe | Ala | Pro | Gly | Glu | Asp | Ile | Ile | Gly | Ala | Ser |
| | | | | | | 355 | | 360 | | | 365 | | | | |
| Ser | Asp | Cys | Ser | Thr | Cys | Phe | Val | Ser | Arg | Ser | Gly | Thr | Ser | Gln | Ala |
| | | | | | | 370 | | 375 | | | 380 | | | | |

FIG 1M₁

Ala Ala His Val Ala Gly Ile Val Thr Met Met Leu Thr Ala Gln Pro
 385 390 395 400
 Lys Leu Thr Leu Ala Glu Leu Trp Gln Arg Leu Ile His Phe Ala Ala
 405 410 415
 Lys Asp Val Ile Asn Glu Ala Trp Phe Pro Glu Asp Gln Arg Val Leu
 420 425 430
 Thr Pro Asn Leu Val Ala Thr Leu Pro Pro Ser Thr Arg Gly Ala Gly
 435 440 445
 Gly Arg Leu Leu Cys Arg Thr Val Trp Ser Ala Arg Ser Gly Pro Arg
 450 455 460
 His Thr Ala Thr Ala Leu Ala His Cys Thr Pro Gly Glu Glu Leu Leu
 465 470 475 480
 Ser Cys Ser Ser Phe Ser Arg Ser Gly Lys Arg Lys Gly Glu Arg Ile
 485 490 495
 Glu Val Leu Arg Gly Arg Arg Val Cys Val Ala Tyr Asn Ala Phe Gly
 500 505 510
 Gly Lys Gly Val His Ala Val Ala Arg Cys Cys Leu Leu Pro Arg Ala
 515 520 525
 Asn Cys Ser Leu His Thr Ala Pro Ala Arg Ala Gly Met Glu Pro Arg
 530 535 540
 Val His Cys His Arg Lys Asp Gln Val Leu Thr Gly Cys Ser Ala His
 545 550 555 560
 Trp Glu Ala Glu Asp Phe Arg Ala Arg Gly Trp Pro Met Leu Arg Pro
 565 570 575
 Gly Gly Pro Ser Gln Cys Val Gly His Ser Lys Ala Ser Val His Ala
 580 585 590
 Ser Cys Cys Ser Ala Pro Gly Leu Glu Cys Arg Ile Arg Glu His Gly
 595 600 605
 Val Pro Trp Pro Ala Glu Gln Val Thr Val Ala Cys Glu Asp Gly Trp
 610 615 620
 Thr Leu Thr Gly Cys Ser Thr Leu Pro Gly Ala Ser Ser Val Leu Gly
 625 630 635 640
 Thr Tyr Ala Val Asp Asp Met Cys Val Val Arg Ser Arg Asp Val Lys
 645 650 655
 Ala Leu Asp Arg Thr Arg Gly Glu Ala Leu Ala Ala Ile Ala Ile Cys
 660 665 670
 Cys Arg Ser Gln Ala Ser Glu Gln Ala Ser Pro Glu Arg Gln
 675 680 685

SEQ ID NO: 25

FIG 1M₂

SUBSTITUTE SHEET (RULE 26)

Mesocricetus auratus PCSK9

Met Gly Thr Ser Cys Ser Ala Arg Pro Arg Trp Leu Leu Ser Pro Leu
 1 5 10 15
 Leu Leu Leu Leu Leu Leu Arg Tyr Met Gly Ala Ser Ala Gln Asp
 20 25 30
 Glu Asp Ala Glu Tyr Glu Glu Leu Met Leu Thr Leu Gln Ser Gln Asp
 35 40 45
 Asp Gly Leu Ala Asp Glu Thr Asp Glu Ala Pro Gln Gly Ala Thr Ala
 50 55 60
 Ala Phe His Arg Cys Pro Glu Glu Ala Trp Arg Val Pro Gly Thr Tyr
 65 70 75 80
 Ile Val Met Leu Ala Glu Glu Ala Gln Trp Val His Ile Glu Gln Thr
 85 90 95
 Met His Arg Leu Gln Thr Gln Ala Ala Arg Arg Gly Tyr Val Ile Lys
 100 105 110
 Ile Gln His Ile Phe Tyr Asp Phe Leu Pro Ala Phe Val Val Lys Met
 115 120 125
 Ser Ser Asp Leu Leu Asp Leu Ala Leu Lys Leu Pro His Val Lys Tyr
 130 135 140
 Ile Glu Glu Asp Ser Leu Val Phe Ala Gln Ser Ile Pro Trp Asn Leu
 145 150 155 160
 Asp Arg Ile Ile Pro Ala Gly Arg Gln Ala Gln Glu Tyr Ser Ser Ser
 165 170 175
 Arg Lys Val Pro Ser Gly Ser Gly Gln Val Glu Val Tyr Leu Leu Asp
 180 185 190
 Thr Ser Ile Gln Ser Asp His Arg Glu Ile Glu Gly Arg Val Thr Val
 195 200 205
 Thr Asp Phe Asn Ser Val Pro Glu Glu Asp Gly Thr Arg Phe His Arg
 210 215 220
 Gln Ala Ser Lys Cys Asp Ser His Gly Thr His Leu Ala Gly Val Val
 225 230 235 240
 Ser Gly Arg Asp Ala Gly Val Ala Lys Gly Thr Ile Leu His Gly Leu
 245 250 255
 Arg Val Leu Asn Cys Gln Gly Lys Gly Ile Val Ser Gly Ile Leu Thr
 260 265 270
 Gly Leu Glu Phe Ile Trp Lys Ser Gln Leu Met Gln Pro Ser Gly Pro
 275 280 285
 Gln Val Val Leu Leu Pro Leu Ala Gly Arg Tyr Ser Arg Val Leu Asn
 290 295 300
 Thr Ala Cys Gln His Leu Ala Arg Thr Gly Val Val Leu Val Ala Ala
 305 310 315 320
 Ala Gly Asn Phe Arg Asp Asp Ala Cys Leu Tyr Ser Pro Ala Ser Ala
 325 330 335
 Pro Glu Val Ile Thr Val Gly Ala Thr Asp Val Gln Asp Gln Pro Val
 340 345 350
 Thr Leu Gly Thr Leu Gly Thr Asn Phe Gly Arg Cys Val Asp Leu Phe
 355 360 365
 Ala Pro Gly Lys Asp Ile Ile Gly Ala Ser Ser Asp Cys Ser Ala Cys
 370 375 380
 Phe Met Ser Gln Ser Gly Thr Ser Gln Ala Ala Ala His Val Ala Gly
 385 390 395 400

FIG 1N₁

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Val | Ala | Met | Met | Leu | Thr | Leu | Glu | Pro | Glu | Leu | Thr | Leu | Thr | Glu |
| | | | | 405 | | | | | 410 | | | | 415 | | |
| Leu | Arg | Gln | Arg | Leu | Ile | His | Phe | Ser | Thr | Lys | Asp | Ala | Ile | Asn | Met |
| | | | | 420 | | | | 425 | | | | 430 | | | |
| Ala | Trp | Phe | Pro | Glu | Asp | Gln | Arg | Val | Leu | Thr | Pro | Asn | Leu | Val | Ala |
| | | | | | 435 | | | 440 | | | 445 | | | | |
| Thr | Leu | Pro | Pro | Ser | Thr | His | Gly | Thr | Gly | Gly | Gln | Leu | Leu | Cys | Arg |
| | | | | | 450 | | 455 | | | | 460 | | | | |
| Thr | Val | Trp | Ser | Ala | His | Ser | Gly | Pro | Thr | Arg | Ala | Ala | Thr | Ala | Thr |
| 465 | | | | | 470 | | | | 475 | | | | 480 | | |
| Ala | Arg | Cys | Ala | Pro | Gly | Glu | Glu | Leu | Leu | Ser | Cys | Ser | Ser | Phe | Ser |
| | | | | | 485 | | | | 490 | | | | 495 | | |
| Arg | Ser | Gly | Arg | Arg | Arg | Gly | Asp | Arg | Ile | Glu | Ala | Ala | Gly | Thr | Gln |
| | | | | | 500 | | | 505 | | | | 510 | | | |
| Gln | Val | Cys | Lys | Ala | Leu | Asn | Ala | Phe | Gly | Gly | Glu | Gly | Val | Tyr | Ala |
| | | | | | 515 | | 520 | | | | 525 | | | | |
| Val | Ala | Arg | Cys | Cys | Leu | Leu | Pro | Arg | Ala | Asn | Cys | Ser | Ile | His | Thr |
| | | | | | | 530 | | 535 | | | 540 | | | | |
| Thr | Pro | Ala | Ala | Arg | Thr | Ser | Leu | Glu | Thr | His | Ala | His | Cys | His | Gln |
| 545 | | | | | | 550 | | | 555 | | | | 560 | | |
| Lys | Asp | His | Val | Leu | Thr | Gly | Cys | Ser | Leu | His | Trp | Glu | Val | Glu | Gly |
| | | | | | | 565 | | | 570 | | | | 575 | | |
| Ile | Gly | Val | Gln | Pro | Leu | Ala | Val | Leu | Arg | Ser | Arg | His | Gln | Pro | Gly |
| | | | | | | 580 | | 585 | | | | 590 | | | |
| Gln | Cys | Thr | Gly | His | Arg | Glu | Ala | Ser | Val | His | Ala | Ser | Cys | Cys | His |
| | | | | | 595 | | 600 | | | | 605 | | | | |
| Ala | Pro | Gly | Leu | Glu | Cys | Lys | Ile | Lys | Glu | His | Gly | Ile | Ser | Gly | Pro |
| | | | | | | 610 | | 615 | | | 620 | | | | |
| Ala | Glu | Gln | Val | Thr | Val | Ala | Cys | Glu | Ala | Gly | Trp | Thr | Leu | Thr | Gly |
| | | | | | | 625 | | 630 | | | 635 | | | 640 | |
| Cys | Asn | Val | Leu | Pro | Gly | Ala | Phe | Ile | Thr | Leu | Gly | Ala | Tyr | Ala | Val |
| | | | | | | 645 | | | 650 | | | 655 | | | |
| Asp | Asn | Thr | Cys | Val | Ala | Arg | Ser | Arg | Val | Thr | Asp | Thr | Ala | Gly | Arg |
| | | | | | | 660 | | 665 | | | | 670 | | | |
| Thr | Gly | Glu | Glu | Ala | Thr | Val | Ala | Ala | Ile | Cys | Cys | Arg | Asn | Arg | |
| | | | | | | 675 | | 680 | | | | 685 | | | |
| Pro | Ser | Ala | Lys | Ala | Ser | Trp | Val | His | Gln | | | | | | |
| | | | | | | 690 | | 695 | | | | | | | |

SEQ ID NO: 26

FIG 1N₂

SUBSTITUTE SHEET (RULE 26)

Mus musculus PCSK9

Met Gly Thr His Cys Ser Ala Trp Leu Arg Trp Pro Leu Leu Pro Leu
 1 5 10 15
 Leu Pro Pro Leu Leu Leu Leu Leu Leu Leu Cys Pro Thr Gly Ala
 20 25 30
 Gly Ala Gln Asp Glu Asp Gly Asp Tyr Glu Glu Leu Met Leu Ala Leu
 35 40 45
 Pro Ser Gln Glu Asp Gly Leu Ala Asp Glu Ala Ala His Val Ala Thr
 50 55 60
 Ala Thr Phe Arg Arg Cys Ser Lys Glu Ala Trp Arg Leu Pro Gly Thr
 65 70 75 80
 Tyr Ile Val Val Leu Met Glu Glu Thr Gln Arg Leu Gln Ile Glu Gln
 85 90 95
 Thr Ala His Arg Leu Gln Thr Arg Ala Ala Arg Arg Gly Tyr Val Ile
 100 105 110
 Lys Val Leu His Ile Phe Tyr Asp Leu Phe Pro Gly Phe Leu Val Lys
 115 120 125
 Met Ser Ser Asp Leu Leu Gly Leu Ala Leu Lys Leu Pro His Val Glu
 130 135 140
 Tyr Ile Glu Glu Asp Ser Phe Val Phe Ala Gln Ser Ile Pro Trp Asn
 145 150 155 160
 Leu Arg Ile Ile Pro Ala Trp His Gln Thr Glu Glu Asp Arg Ser Pro
 165 170 175
 Asp Gly Ser Ser Gln Val Glu Val Tyr Leu Leu Asp Thr Ser Ile Gln
 180 185 190
 Gly Ala His Arg Glu Ile Glu Gly Arg Val Thr Ile Thr Asp Phe Asn
 195 200 205
 Ser Val Pro Glu Glu Asp Gly Thr Arg Phe His Arg Gln Ala Ser Lys
 210 215 220
 Cys Asp Ser His Gly Thr His Leu Ala Gly Val Val Ser Gly Arg Asp
 225 230 235 240
 Ala Gly Val Ala Lys Gly Thr Ser Leu His Ser Leu Arg Val Leu Asn
 245 250 255
 Cys Gln Gly Lys Gly Thr Val Ser Gly Thr Leu Ile Gly Leu Glu Phe
 260 265 270
 Ile Arg Lys Ser Gln Leu Ile Gln Pro Ser Pro Leu Val Val Leu Pro
 275 280 285
 Leu Ala Gly Gly Tyr Ser Arg Ile Leu Asn Ala Ala Cys Arg His Leu
 290 295 300
 Ala Arg Thr Gly Val Val Leu Val Ala Ala Ala Gly Asn Phe Arg Asp
 305 310 315 320
 Asp Ala Cys Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val Ile Thr Val
 325 330 335
 Gly Ala Thr Asn Ala Gln Asp Gln Pro Val Thr Leu Gly Thr Leu Gly
 340 345 350
 Thr Asn Phe Gly Arg Cys Val Asp Leu Phe Ala Pro Gly Lys Asp Ile
 355 360 365
 Ile Gly Ala Ser Ser Asp Cys Ser Thr Cys Phe Met Ser Gln Ser Gly
 370 375 380
 Thr Ser Gln Ala Ala Ala His Val Ala Gly Ile Val Ala Arg Met Leu
 385 390 395 400

FIG 1O₁

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Arg | Glu | Pro | Thr | Leu | Thr | Leu | Ala | Leu | Arg | Gln | Arg | Ile | His | Phe |
| | | | | 405 | | | | | 410 | | | | 415 | | |
| Ser | Thr | Lys | Asp | Val | Ile | Asn | Met | Ala | Trp | Phe | Pro | Glu | Asp | Gln | Gln |
| | | | | 420 | | | | | 425 | | | | 430 | | |
| Val | Leu | Thr | Pro | Asn | Leu | Val | Ala | Thr | Leu | Pro | Pro | Ser | Thr | His | Glu |
| | | | | 435 | | | | 440 | | | | 445 | | | |
| Thr | Gly | Gly | Gln | Leu | Leu | Cys | Arg | Thr | Val | Trp | Ser | Ala | His | Ser | Gly |
| | | | | 450 | | 455 | | | | | 460 | | | | |
| Pro | Thr | Arg | Thr | Ala | Thr | Ala | Thr | Ala | Arg | Cys | Ala | Pro | Glu | Glu | Glu |
| | | | | 465 | | 470 | | | 475 | | | | 480 | | |
| Leu | Leu | Ser | Cys | Ser | Ser | Phe | Ser | Arg | Ser | Gly | Arg | Arg | Arg | Gly | Asp |
| | | | | | 485 | | | | 490 | | | | 495 | | |
| Arg | Ile | Glu | Ala | Ile | Gly | Gly | Gln | Gln | Val | Cys | Lys | Ala | Leu | Asn | Ala |
| | | | | | 500 | | | 505 | | | | | 510 | | |
| Phe | Gly | Gly | Glu | Gly | Val | Tyr | Ala | Val | Ala | Arg | Cys | Cys | Leu | Val | Pro |
| | | | | | 515 | | 520 | | | 525 | | | | | |
| His | Ala | Asn | Cys | Ser | Ile | His | Asn | Pro | Ala | Ala | Gly | Leu | Glu | Thr | |
| | | | | | 530 | | 535 | | | 540 | | | | | |
| His | Val | His | Cys | His | Gln | Lys | Asp | His | Val | Leu | Thr | Gly | Cys | Ser | Phe |
| | | | | | 545 | | 550 | | | 555 | | | | 560 | |
| His | Trp | Glu | Val | Glu | Asp | Leu | Ser | Val | Arg | Arg | Gln | Pro | Ala | Leu | Arg |
| | | | | | | 565 | | | 570 | | | | 575 | | |
| Ser | Arg | Arg | Gln | Pro | Gly | Gln | Cys | Val | Gly | His | Gln | Ala | Ala | Ser | Val |
| | | | | | | 580 | | | 585 | | | | 590 | | |
| Tyr | Ala | Ser | Cys | Cys | His | Ala | Pro | Gly | Leu | Glu | Cys | Lys | Ile | Lys | Glu |
| | | | | | | 595 | | | 600 | | | 605 | | | |
| His | Gly | Ile | Ser | Gly | Ser | Ser | Glu | Gln | Val | Thr | Val | Ala | Cys | Glu | Ala |
| | | | | | | 610 | | 615 | | | 620 | | | | |
| Gly | Trp | Thr | Leu | Thr | Gly | Cys | Asn | Val | Leu | Pro | Gly | Ala | Ser | Leu | Thr |
| | | | | | | 625 | | 630 | | | 635 | | | 640 | |
| Leu | Gly | Ala | Tyr | Ser | Val | Asp | Asn | Leu | Cys | Val | Ala | Arg | Val | His | Asp |
| | | | | | | | 645 | | | 650 | | | 655 | | |
| Thr | Ala | Arg | Ala | Asp | Arg | Thr | Gly | Glu | Thr | Val | Ala | Ala | Ile | Cys | |
| | | | | | | | 660 | | | 665 | | | 670 | | |
| Cys | Arg | Ser | Arg | Pro | Ser | Ala | Lys | Ala | Ser | Trp | Val | Gln | | | |
| | | | | | | 675 | | | 680 | | | 685 | | | |

SEQ ID NO: 27

FIG 1O₂

SUBSTITUTE SHEET (RULE 26)

Macaca fascicularis PCSK9

Met Gly Thr Val Ser Ser Arg Arg Ser Trp Trp Pro Leu Pro Leu Pro
 1 5 10 15
 Leu Leu Leu Leu Leu Leu Gly Pro Ala Gly Ala Arg Ala Gln Glu
 20 25 30
 Asp Glu Asp Gly Asp Tyr Glu Glu Leu Val Leu Ala Leu Arg Ser Glu
 35 40 45
 Glu Asp Gly Leu Ala Asp Ala Pro Glu His Gly Ala Thr Ala Thr Phe
 50 55 60
 His Arg Cys Ala Lys Asp Pro Trp Arg Leu Pro Gly Thr Tyr Val Val
 65 70 75 80
 Val Leu Lys Glu Glu Thr His Arg Ser Gln Ser Glu Arg Thr Ala Arg
 85 90 95
 Arg Leu Gln Ala Gln Ala Ala Arg Arg Gly Tyr Leu Thr Lys Ile Leu
 100 105 110
 His Val Phe His His Leu Leu Pro Gly Phe Leu Val Lys Met Ser Gly
 115 120 125
 Asp Leu Leu Glu Leu Ala Leu Lys Leu Pro His Val Asp Tyr Ile Glu
 130 135 140
 Glu Asp Ser Ser Val Phe Ala Gln Ser Ile Pro Trp Asn Glu Arg Ile
 145 150 155 160
 Thr Pro Ala Arg Tyr Arg Ala Asp Glu Tyr Gln Pro Pro Lys Gly Gly
 165 170 175
 Ser Leu Val Glu Val Tyr Leu Leu Asp Thr Ser Ile Gln Ser Asp His
 180 185 190
 Arg Glu Ile Glu Gly Arg Val Met Val Thr Asp Phe Glu Ser Val Pro
 195 200 205
 Glu Glu Asp Gly Thr Arg Phe His Arg Gln Ala Ser Lys Cys Asp Ser
 210 215 220
 His Gly Thr His Leu Ala Gly Val Val Ser Gly Arg Asp Ala Gly Val
 225 230 235 240
 Ala Lys Gly Ala Gly Leu Arg Ser Leu Arg Val Leu Asn Cys Gln Gly
 245 250 255
 Lys Gly Thr Val Ser Gly Thr Leu Ile Gly Leu Glu Phe Ile Arg Lys
 260 265 270
 Ser Gln Leu Val Gln Pro Val Pro Leu Val Val Leu Pro Leu Ala Gly
 275 280 285
 Gly Tyr Ser Arg Val Phe Asn Ala Ala Cys Gln Arg Leu Ala Arg Ala
 290 295 300
 Gly Val Val Leu Val Thr Ala Ala Gly Asn Phe Arg Asp Asp Ala Cys
 305 310 315 320
 Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val Ile Thr Val Gly Ala Thr
 325 330 335
 Asn Ala Gln Asp Gln Pro Val Thr Leu Gly Thr Leu Gly Thr Asn Phe
 340 345 350
 Gly Arg Cys Val Asp Leu Phe Ala Pro Gly Glu Asp Ile Ile Gly Ala
 355 360 365
 Ser Ser Asp Cys Ser Thr Cys Phe Val Ser Arg Ser Gly Thr Ser Gln
 370 375 380
 Ala Ala Ala His Val Ala Gly Ile Ala Ala Met Met Leu Ser Ala Glu
 385 390 395 400

FIG 1P₁

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Glu | Leu | Thr | Leu | Ala | Leu | Arg | Gln | Leu | Ile | His | Phe | Ser | Ala | Lys |
| | | | | 405 | | | | | 410 | | | | | 415 | |
| Asp | Val | Ile | Asn | Glu | Ala | Trp | Phe | Pro | Glu | Asp | Gln | Arg | Val | Leu | Thr |
| | | | | 420 | | | | 425 | | | | | 430 | | |
| Pro | Asn | Leu | Val | Ala | Ala | Leu | Pro | Pro | Ser | Thr | His | Arg | Ala | Gly | Trp |
| | | | | 435 | | | 440 | | | | 445 | | | | |
| Gln | Leu | Phe | Cys | Arg | Thr | Val | Trp | Ser | Ala | His | Ser | Gly | Pro | Thr | Arg |
| | | | | 450 | | 455 | | | | 460 | | | | | |
| Met | Ala | Thr | Ala | Val | Ala | Arg | Cys | Ala | Gln | Asp | Glu | Glu | Leu | Leu | Ser |
| | | | | 465 | | 470 | | | 475 | | | | | 480 | |
| Cys | Ser | Ser | Phe | Ser | Arg | Ser | Gly | Lys | Arg | Arg | Gly | Glu | Arg | Ile | Glu |
| | | | | 485 | | | 490 | | | | 495 | | | | |
| Ala | Gln | Gly | Gly | Lys | Arg | Val | Cys | Arg | Ala | His | Asn | Ala | Phe | Gly | Gly |
| | | | | 500 | | | 505 | | | | | 510 | | | |
| Glu | Gly | Val | Tyr | Ala | Ile | Ala | Arg | Cys | Cys | Leu | Leu | Pro | Gln | Val | Asn |
| | | | | 515 | | 520 | | | | | 525 | | | | |
| Cys | Ser | Val | His | Thr | Pro | Pro | Gly | Ala | Ser | Met | Gly | Thr | Arg | Val | His |
| | | | | 530 | | 535 | | | | 540 | | | | | |
| Cys | His | Gln | Gln | Gly | His | Val | Leu | Thr | Gly | Cys | Ser | Ser | His | Trp | Glu |
| | | | | 545 | | 550 | | | 555 | | | | | 560 | |
| Val | Glu | Asp | Leu | Gly | Thr | His | Lys | Pro | Pro | Val | Leu | Arg | Pro | Arg | Gly |
| | | | | 565 | | | 570 | | | | | 575 | | | |
| Gln | Pro | Asn | Gln | Cys | Val | Gly | His | Arg | Glu | Ala | Ser | Ile | His | Ala | Ser |
| | | | | 580 | | | 585 | | | | 590 | | | | |
| Cys | Cys | His | Ala | Pro | Gly | Leu | Glu | Cys | Lys | Val | Arg | Glu | His | Gly | Ile |
| | | | | 595 | | 600 | | | | 605 | | | | | |
| Pro | Ala | Pro | Gln | Glu | Gln | Val | Ile | Val | Ala | Cys | Glu | Asp | Gly | Trp | Thr |
| | | | | 610 | | 615 | | | | 620 | | | | | |
| Leu | Thr | Gly | Cys | Ser | Ala | Leu | Pro | Gly | Thr | Ser | His | Val | Leu | Gly | Ala |
| | | | | 625 | | 630 | | | 635 | | | | | 640 | |
| Tyr | Ala | Val | Asp | Asn | Thr | Cys | Val | Val | Arg | Ser | Arg | Asp | Val | Ser | Thr |
| | | | | 645 | | | 650 | | | | 655 | | | | |
| Thr | Gly | Ser | Thr | Glu | Ala | Val | Ala | Val | Ala | Ile | Cys | Cys | Arg | Ser | |
| | | | | 660 | | | 665 | | | | 670 | | | | |
| Arg | His | Leu | Val | Gln | Ala | Ser | Gln | Glu | Leu | Gln | | | | | |
| | | | | 675 | | | 680 | | | | | | | | |

SEQ ID NO: 28

FIG 1P₂

Rattus norvegicus PCSK9

Met Gly Ile Arg Cys Ser Thr Trp Leu Arg Trp Pro Leu Ser Pro Gln
 1 5 10 15
 Leu Leu Leu Leu Leu Leu Cys Pro Thr Gly Ser Arg Ala Gln Asp
 20 25 30
 Glu Asp Gly Asp Tyr Glu Glu Leu Met Leu Ala Leu Pro Ser Gln Glu
 35 40 45
 Asp Ser Leu Val Asp Glu Ala Ser His Val Ala Thr Ala Thr Phe Arg
 50 55 60
 Arg Cys Ser Lys Glu Ala Trp Arg Leu Pro Gly Thr Tyr Val Val Val
 65 70 75 80
 Leu Met Glu Glu Thr Gln Arg Leu Gln Val Glu Gln Thr Ala His Arg
 85 90 95
 Leu Gln Thr Trp Ala Ala Arg Arg Gly Tyr Val Ile Lys Val Leu His
 100 105 110
 Val Phe Tyr Asp Leu Phe Pro Gly Phe Leu Val Lys Met Ser Ser Asp
 115 120 125
 Leu Leu Gly Leu Ala Leu Lys Leu Pro His Val Glu Tyr Ile Glu Glu
 130 135 140
 Asp Ser Leu Val Phe Ala Gln Ser Ile Pro Trp Asn Leu Glu Arg Ile
 145 150 155 160
 Ile Pro Ala Trp Gln Gln Thr Glu Glu Asp Ser Ser Pro Asp Gly Ser
 165 170 175
 Ser Gln Val Glu Val Tyr Leu Leu Asp Thr Ser Ile Gln Ser Gly His
 180 185 190
 Arg Glu Ile Glu Gly Arg Val Thr Ile Thr Asp Phe Asn Ser Val Pro
 195 200 205
 Glu Glu Asp Gly Thr Arg Phe His Arg Gln Ala Ser Lys Cys Asp Ser
 210 215 220
 His Gly Thr His Leu Ala Gly Val Val Ser Gly Arg Asp Ala Gly Val
 225 230 235 240
 Ala Lys Gly Thr Ser Leu His Ser Leu Arg Val Leu Asn Cys Gln Gly
 245 250 255
 Lys Gly Thr Val Ser Gly Thr Leu Ile Gly Leu Glu Phe Ile Arg Lys
 260 265 270
 Ser Gln Leu Ile Gln Pro Ser Gly Pro Leu Val Val Leu Leu Pro Leu
 275 280 285
 Ala Gly Gly Tyr Ser Arg Ile Leu Asn Thr Ala Cys Gln Arg Leu Ala
 290 295 300
 Arg Thr Gly Val Val Leu Val Ala Ala Ala Gly Asn Phe Arg Asp Asp
 305 310 315 320
 Ala Cys Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val Ile Thr Val Gly
 325 330 335
 Ala Thr Asn Ala Gln Asp Gln Pro Val Thr Leu Gly Thr Leu Gly Thr
 340 345 350
 Asn Phe Gly Arg Cys Val Asp Leu Phe Ala Pro Gly Lys Asp Ile Ile
 355 360 365
 Gly Ala Ser Ser Asp Cys Ser Thr Cys Tyr Met Ser Gln Ser Gly Thr
 370 375 380
 Ser Gln Ala Ala Ala His Val Ala Gly Ile Val Ala Met Met Leu Asn
 385 390 395 400

FIG 1Q₁

SEQ ID NO: 29

FIG 1Q₂

Consensus sequence of PCSK9

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gly | Thr | Xaa | Cys | Ser | Ala | Arg | Ser | Trp | Trp | Pro | Leu | Xaa | Xaa | Xaa |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Xaa | Xaa | Pro | Leu | Pro | Ala | Gly | Ala | Ala |
| | | | | | | | | | | | | | 20 | 25 | 30 |
| Ala | Ala | Gln | Asp | Glu | Asp | Gly | Asp | Tyr | Glu | Glu | Leu | Met | Leu | Ala | Leu |
| | | | | | | | | 35 | 40 | | | | 45 | | |
| Pro | Ser | Gln | Glu | Asp | Gly | Leu | Ala | Asp | Glu | Ala | Glu | His | Val | Xaa | Xaa |
| | | | | | | 50 | 55 | | 60 | | | | | | |
| Xaa | Ala | Thr | Ala | Thr | Phe | His | Arg | Cys | Ser | Lys | Asp | Ala | Trp | Arg | Leu |
| | | | | | | 65 | 70 | | 75 | | | | | 80 | |
| Pro | Gly | Thr | Tyr | Val | Val | Val | Leu | Lys | Glu | Glu | Thr | Gln | Arg | Leu | Gln |
| | | | | | | 85 | | 90 | | | | | 95 | | |
| Ser | Glu | Gln | Thr | Ala | His | Arg | Leu | Gln | Thr | Gln | Ala | Ala | Arg | Arg | Gly |
| | | | | | | 100 | | 105 | | | | | 110 | | |
| Tyr | Val | Thr | Lys | Ile | Leu | His | Val | Phe | His | Asp | Leu | Leu | Pro | Gly | Phe |
| | | | | | | 115 | | 120 | | | | | 125 | | |
| Leu | Val | Lys | Met | Ser | Ser | Asp | Leu | Leu | Asp | Leu | Ala | Leu | Lys | Leu | Pro |
| | | | | | | 130 | | 135 | | | | 140 | | | |
| His | Val | Asp | Tyr | Ile | Glu | Glu | Asp | Ser | Ser | Val | Phe | Ala | Gln | Ser | Ile |
| | | | | | | 145 | | 150 | | | | 155 | | | 160 |
| Pro | Trp | Asn | Leu | Glu | Arg | Ile | Ile | Pro | Ala | Arg | His | Gln | Ala | Asp | Glu |
| | | | | | | 165 | | | 170 | | | | 175 | | |
| Tyr | Ser | Ser | Xaa | Xaa | Xaa | Xaa | Pro | Asp | Gly | Ser | Ser | Gln | Val | Glu | Val |
| | | | | | | 180 | | | 185 | | | | 190 | | |
| Tyr | Leu | Leu | Asp | Thr | Ser | Ile | Gln | Ser | Asp | His | Arg | Glu | Ile | Glu | Gly |
| | | | | | | 195 | | 200 | | | | 205 | | | |
| Arg | Val | Thr | Val | Thr | Asp | Phe | Asn | Ser | Val | Pro | Glu | Glu | Asp | Gly | Thr |
| | | | | | | 210 | | 215 | | | | 220 | | | |
| Arg | Phe | His | Arg | Gln | Ala | Ser | Lys | Cys | Asp | Ser | His | Gly | Thr | His | Leu |
| | | | | | | 225 | | 230 | | | | 235 | | | 240 |
| Ala | Gly | Val | Val | Ser | Gly | Arg | Asp | Ala | Gly | Val | Ala | Lys | Gly | Thr | Ser |
| | | | | | | 245 | | | 250 | | | | 255 | | |
| Leu | Arg | Ser | Leu | Arg | Val | Leu | Asn | Cys | Gln | Gly | Lys | Gly | Thr | Val | Ser |
| | | | | | | 260 | | 265 | | | | | 270 | | |
| Gly | Thr | Leu | Ile | Gly | Leu | Glu | Phe | Ile | Arg | Lys | Ser | Gln | Leu | Ile | Gln |
| | | | | | | 275 | | 280 | | | | | 285 | | |
| Pro | Val | Gly | Pro | Leu | Val | Val | Leu | Leu | Pro | Leu | Ala | Gly | Gly | Tyr | Ser |
| | | | | | | 290 | | 295 | | | | 300 | | | |
| Arg | Val | Leu | Asn | Ala | Ala | Cys | Gln | Arg | Leu | Ala | Arg | Thr | Gly | Val | Val |
| | | | | | | 305 | | 310 | | | | 315 | | | 320 |
| Leu | Val | Ala | Ala | Ala | Gly | Asn | Phe | Arg | Asp | Asp | Ala | Cys | Leu | Tyr | Ser |
| | | | | | | 325 | | | 330 | | | | 335 | | |
| Pro | Ala | Ser | Ala | Pro | Glu | Val | Ile | Thr | Val | Gly | Ala | Thr | Asn | Ala | Gln |
| | | | | | | 340 | | 345 | | | | | 350 | | |
| Asp | Gln | Pro | Val | Thr | Leu | Gly | Thr | Leu | Gly | Thr | Asn | Phe | Gly | Arg | Cys |
| | | | | | | 355 | | 360 | | | | | 365 | | |
| Val | Asp | Leu | Phe | Ala | Pro | Gly | Lys | Asp | Ile | Ile | Gly | Ala | Ser | Ser | Asp |
| | | | | | | 370 | | 375 | | | | 380 | | | |
| Cys | Ser | Thr | Cys | Phe | Met | Ser | Gln | Ser | Gly | Thr | Ser | Gln | Ala | Ala | Ala |
| | | | | | | 385 | | 390 | | | | 395 | | | 400 |

FIG 1R₁

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Val | Ala | Gly | Ile | Val | Ala | Met | Met | Leu | Ser | Ala | Glu | Pro | Glu | Leu |
| | | | | | | | 405 | | | 410 | | | | | 415 |
| Thr | Leu | Ala | Glu | Leu | Arg | Gln | Arg | Leu | Ile | His | Phe | Ser | Thr | Lys | Asp |
| | | | | | | | 420 | | 425 | | | | | | 430 |
| Val | Ile | Asn | Met | Ala | Trp | Phe | Pro | Glu | Asp | Gln | Arg | Val | Leu | Thr | Pro |
| | | | | | | | 435 | | 440 | | | | | | 445 |
| Asn | Leu | Val | Ala | Thr | Leu | Pro | Pro | Ser | Thr | His | Gly | Thr | Gly | Gly | Gln |
| | | | | | | | 450 | | 455 | | | | | | 460 |
| Leu | Leu | Cys | Arg | Thr | Val | Trp | Ser | Ala | His | Ser | Gly | Pro | Thr | Arg | Thr |
| | | | | | | | 465 | | 470 | | 475 | | | | 480 |
| Ala | Thr | Ala | Thr | Ala | Arg | Cys | Ala | Pro | Asp | Glu | Glu | Leu | Leu | Ser | Cys |
| | | | | | | | 485 | | | 490 | | | | | 495 |
| Ser | Ser | Phe | Ser | Arg | Ser | Gly | Lys | Arg | Arg | Gly | Asp | Arg | Ile | Glu | Ala |
| | | | | | | | 500 | | 505 | | | | | | 510 |
| Ile | Gly | Gly | Gln | Gln | Val | Cys | Lys | Ala | Leu | Asn | Ala | Phe | Gly | Gly | Glu |
| | | | | | | | 515 | | 520 | | | | | | 525 |
| Gly | Val | Tyr | Ala | Val | Ala | Arg | Cys | Cys | Leu | Leu | Pro | Arg | Ala | Asn | Cys |
| | | | | | | | 530 | | 535 | | | | | | 540 |
| Ser | Ile | His | Thr | Thr | Pro | Ala | Ala | Arg | Ala | Ser | Met | Glu | Thr | Arg | Val |
| | | | | | | | 545 | | 550 | | 555 | | | | 560 |
| His | Cys | His | Gln | Lys | Asp | His | Val | Leu | Thr | Gly | Cys | Ser | Ser | His | Trp |
| | | | | | | | 565 | | | 570 | | | | | 575 |
| Glu | Val | Glu | Asp | Leu | Gly | Xaa | Xaa | Lys | Xaa | Pro | Val | Leu | Arg | Ser | Arg |
| | | | | | | | 580 | | 585 | | | | | | 590 |
| Gly | Gln | Pro | Gly | Gln | Cys | Val | Gly | His | Arg | Glu | Ala | Ser | Val | His | Ala |
| | | | | | | | 595 | | 600 | | | | | | 605 |
| Ser | Cys | Cys | His | Ala | Pro | Gly | Leu | Glu | Cys | Lys | Ile | Lys | Glu | His | Gly |
| | | | | | | | 610 | | 615 | | | | | | 620 |
| Ile | Pro | Gly | Pro | Ala | Glu | Gln | Val | Thr | Val | Ala | Cys | Glu | Ala | Gly | Trp |
| | | | | | | | 625 | | 630 | | 635 | | | | 640 |
| Thr | Leu | Thr | Gly | Cys | Ser | Val | Leu | Pro | Gly | Ala | Ser | Leu | Val | Leu | Gly |
| | | | | | | | 645 | | | 650 | | | | | 655 |
| Ala | Tyr | Ala | Val | Asp | Asn | Thr | Cys | Val | Val | Arg | Ser | Arg | Asp | Val | Ser |
| | | | | | | | 660 | | 665 | | | | | | 670 |
| Thr | Ala | Gly | Arg | Thr | Ser | Glu | Glu | Ala | Thr | Val | Ala | Ala | Ala | Ile | Cys |
| | | | | | | | 675 | | 680 | | | | | | 685 |
| Cys | Arg | Ser | Arg | Pro | Ser | Ala | Gln | Ala | Ser | Trp | Val | Xaa | Gln | | |
| | | | | | | | 690 | | 695 | | | | | | 700 |

SEQ ID NO: 30

Xaa = Any Amino Acid or No Amino Acid

FIG 1R₂

SUBSTITUTE SHEET (RULE 26)

Homo sapiens PCSK9

Met Gly Thr Val Ser Ser Arg Arg Ser Trp Trp Pro Leu Pro Leu Leu
 1 5 10 15
 Leu Leu Leu Leu Leu Leu Gly Pro Ala Gly Ala Arg Ala Gln Glu
 20 25 30
 Asp Glu Asp Gly Asp Tyr Glu Glu Leu Val Leu Ala Leu Arg Ser Glu
 35 40 45
 Glu Asp Gly Leu Ala Glu Ala Pro Glu His Gly Thr Thr Ala Thr Phe
 50 55 60
 His Arg Cys Ala Lys Asp Pro Trp Arg Leu Pro Gly Thr Tyr Val Val
 65 70 75 80
 Val Leu Lys Glu Glu Thr His Leu Ser Gln Ser Glu Arg Thr Ala Arg
 85 90 95
 Arg Leu Gln Ala Gln Ala Ala Arg Arg Gly Tyr Leu Thr Lys Ile Leu
 100 105 110
 His Val Phe His Leu Leu Pro Gly Phe Leu Val Lys Met Ser Gly Asp
 115 120 125
 Leu Leu Glu Leu Ala Leu Lys Leu Pro His Val Asp Tyr Ile Glu Glu
 130 135 140
 Asp Ser Ser Val Phe Ala Gln Ser Ile Pro Trp Asn Leu Glu Arg Ile
 145 150 155 160
 Thr Pro Pro Arg Tyr Arg Ala Asp Glu Tyr Gln Pro Pro Asp Gly Gly
 165 170 175
 Ser Leu Val Glu Val Tyr Leu Leu Asp Thr Ser Ile Gln Ser Asp His
 180 185 190
 Arg Glu Ile Glu Gly Arg Val Met Val Thr Asp Phe Glu Asn Val Pro
 195 200 205
 Glu Glu Asp Gly Thr Arg Phe His Arg Gln Ala Ser Lys Cys Asp Ser
 210 215 220
 His Gly Thr His Leu Ala Gly Val Val Ser Gly Arg Asp Ala Gly Val
 225 230 235 240
 Ala Lys Gly Ala Ser Met Arg Ser Leu Arg Val Leu Asn Cys Gln Gly
 245 250 255
 Lys Gly Thr Val Ser Gly Thr Leu Ile Gly Leu Glu Phe Ile Arg Lys
 260 265 270
 Ser Gln Leu Val Gln Pro Val Pro Leu Val Val Leu Leu Pro Leu Ala
 275 280 285
 Gly Gly Tyr Ser Arg Val Leu Asn Ala Ala Cys Gln Arg Leu Ala Arg
 290 295 300
 Ala Gly Val Val Leu Val Thr Ala Ala Gly Asn Phe Arg Asp Asp Ala
 305 310 315 320
 Cys Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val Ile Thr Val Gly Ala
 325 330 335
 Thr Asn Ala Gln Asp Gln Pro Val Thr Leu Gly Thr Leu Gly Thr Asn
 340 345 350
 Phe Gly Arg Cys Val Asp Leu Phe Ala Pro Gly Glu Asp Ile Ile Gly
 355 360 365
 Ala Ser Ser Asp Cys Ser Thr Cys Phe Val Ser Gln Ser Gly Thr Ser
 370 375 380
 Gln Ala Ala Ala His Val Ala Gly Ile Ala Ala Met Met Leu Ser Ala
 385 390 395 400

FIG 1S₁

SEQ ID NO: 31

FIG 1S₂

30 / 38

LDLR Competition Assay

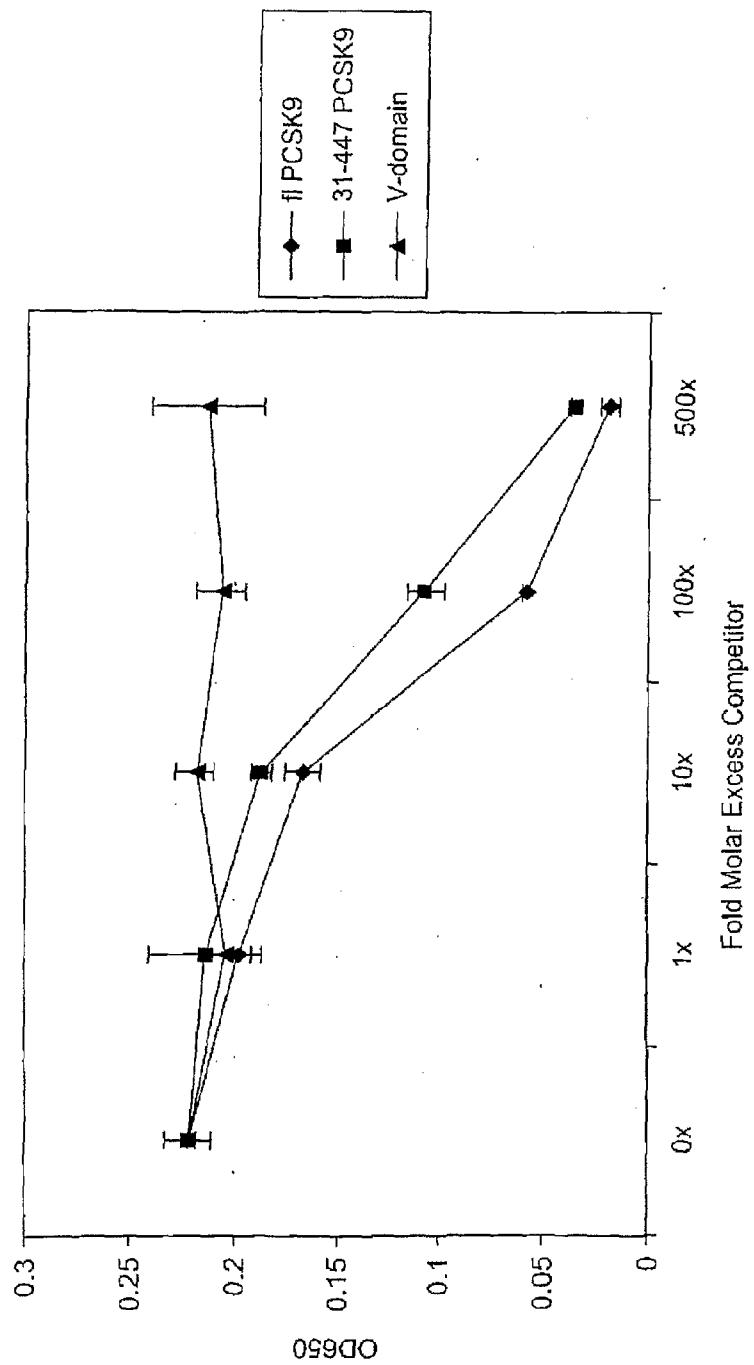


FIG. 2

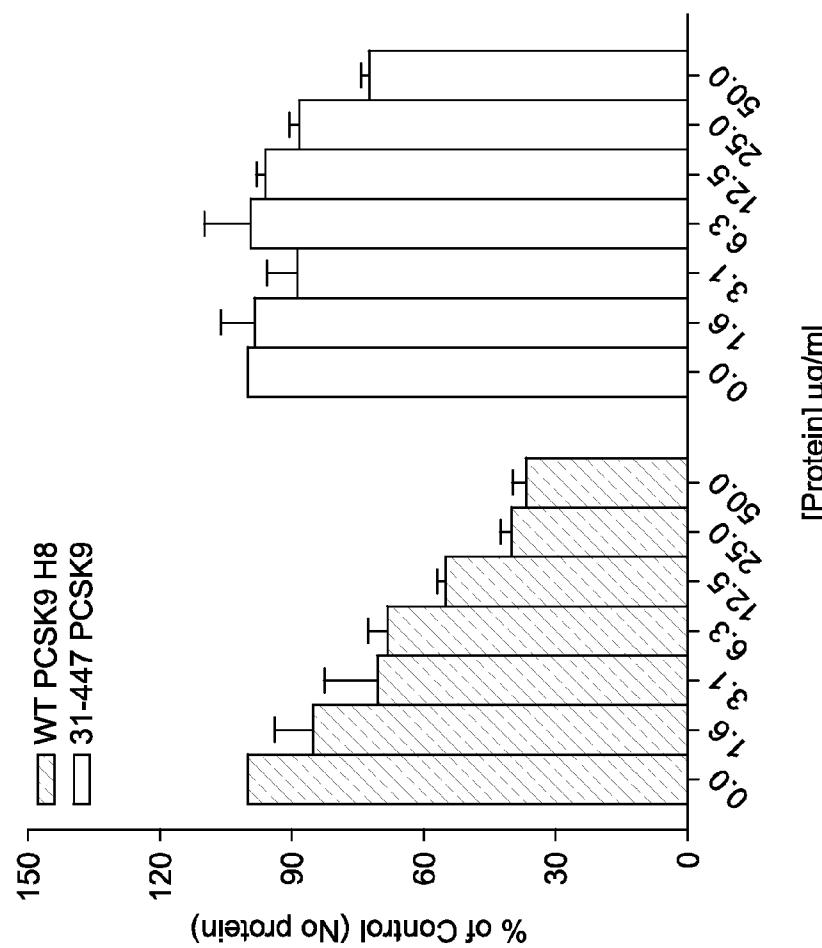


FIG. 3A

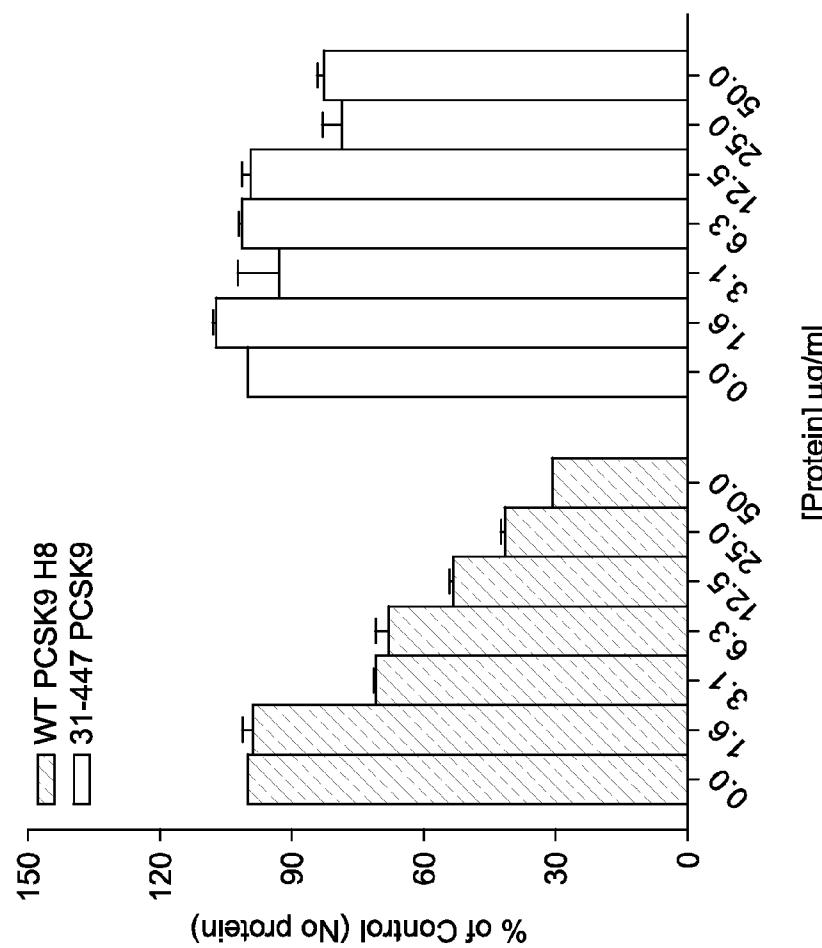


FIG. 3B

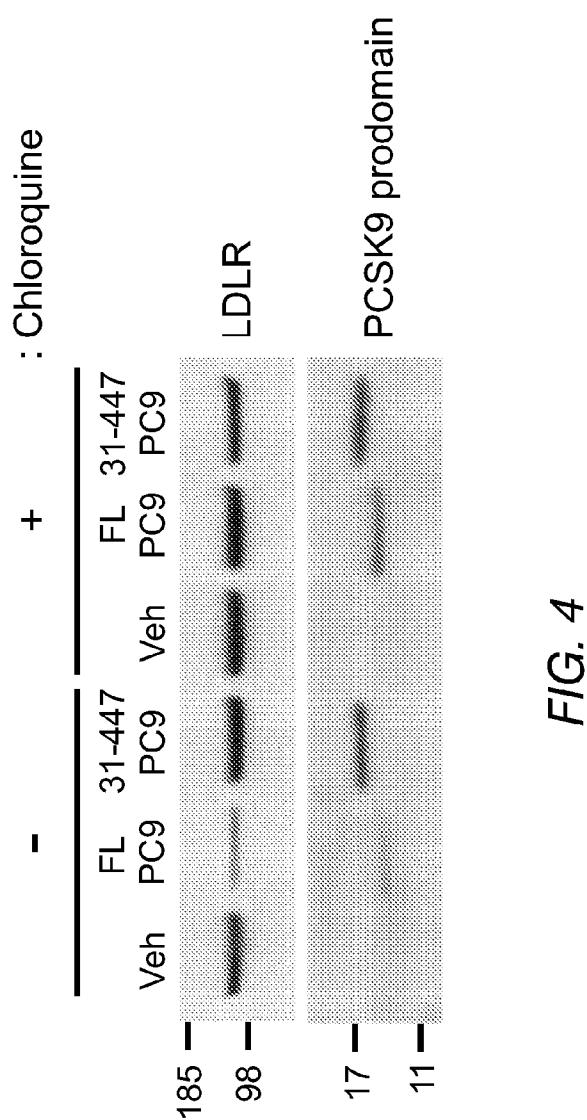


FIG. 4

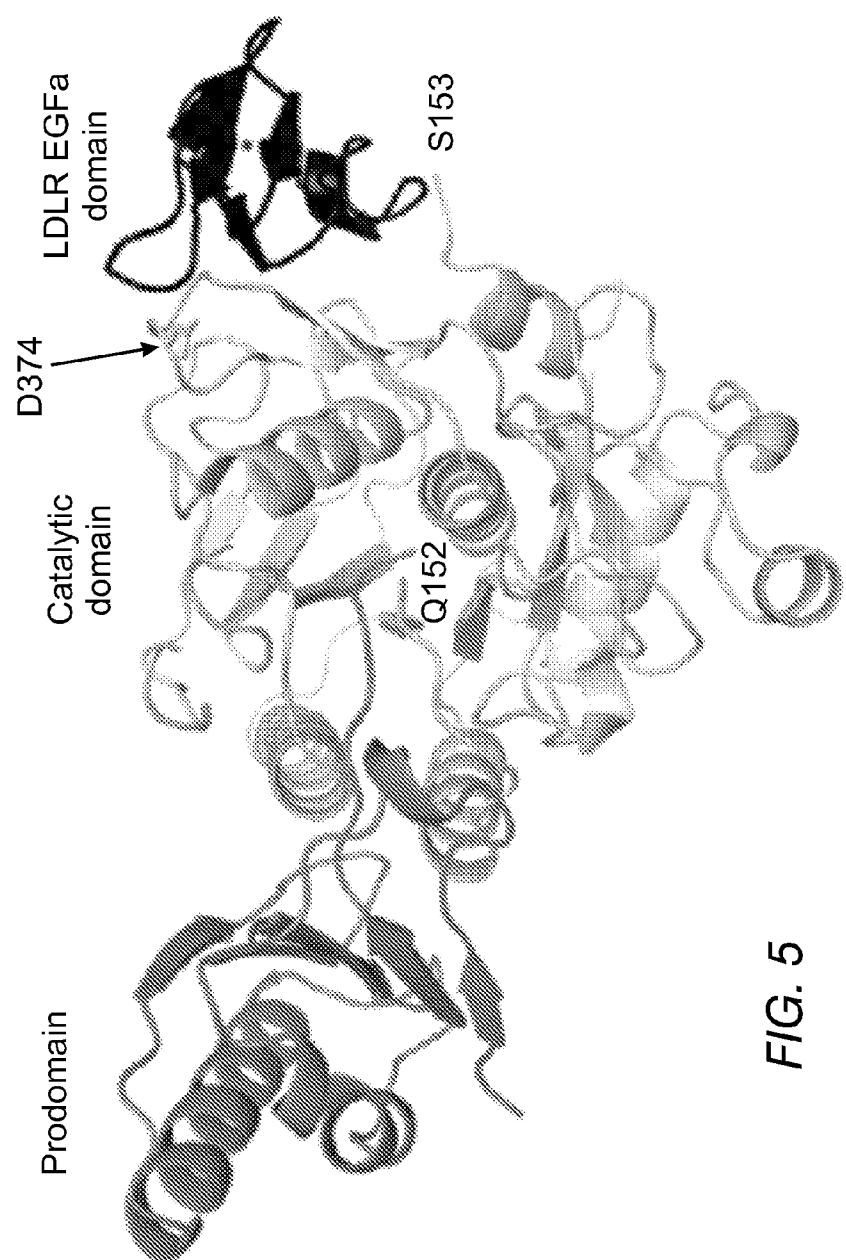
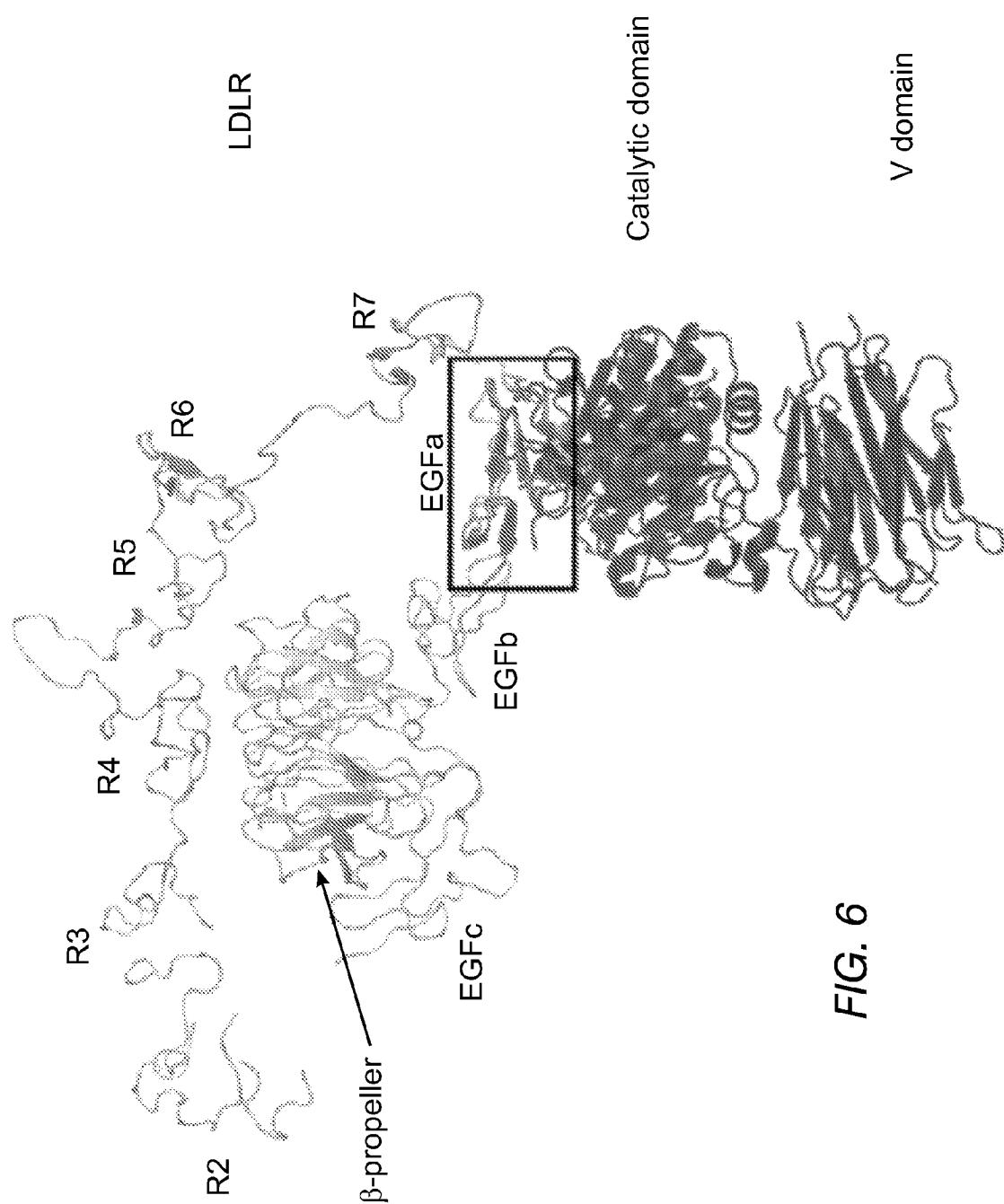


FIG. 5



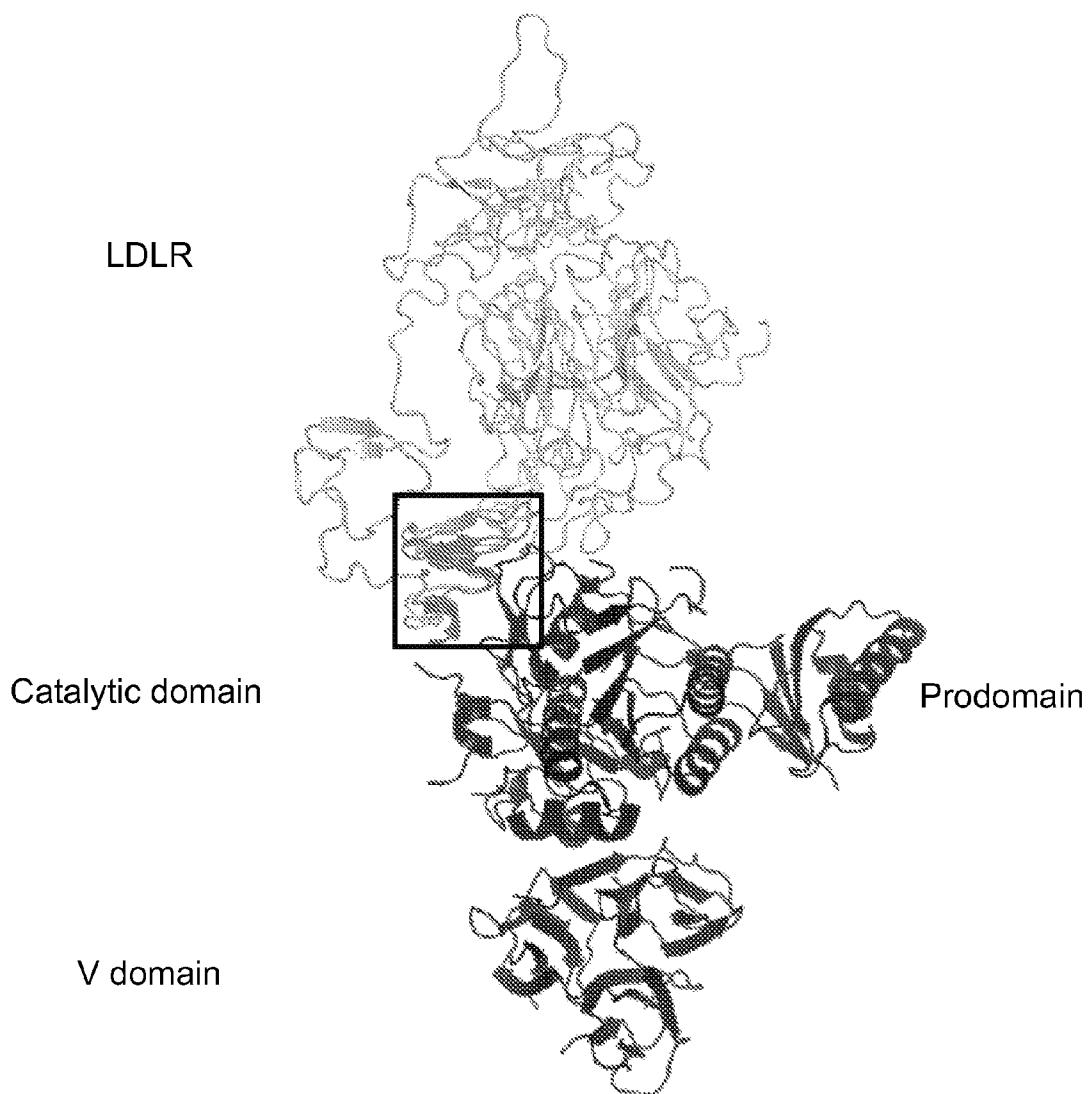


FIG. 7

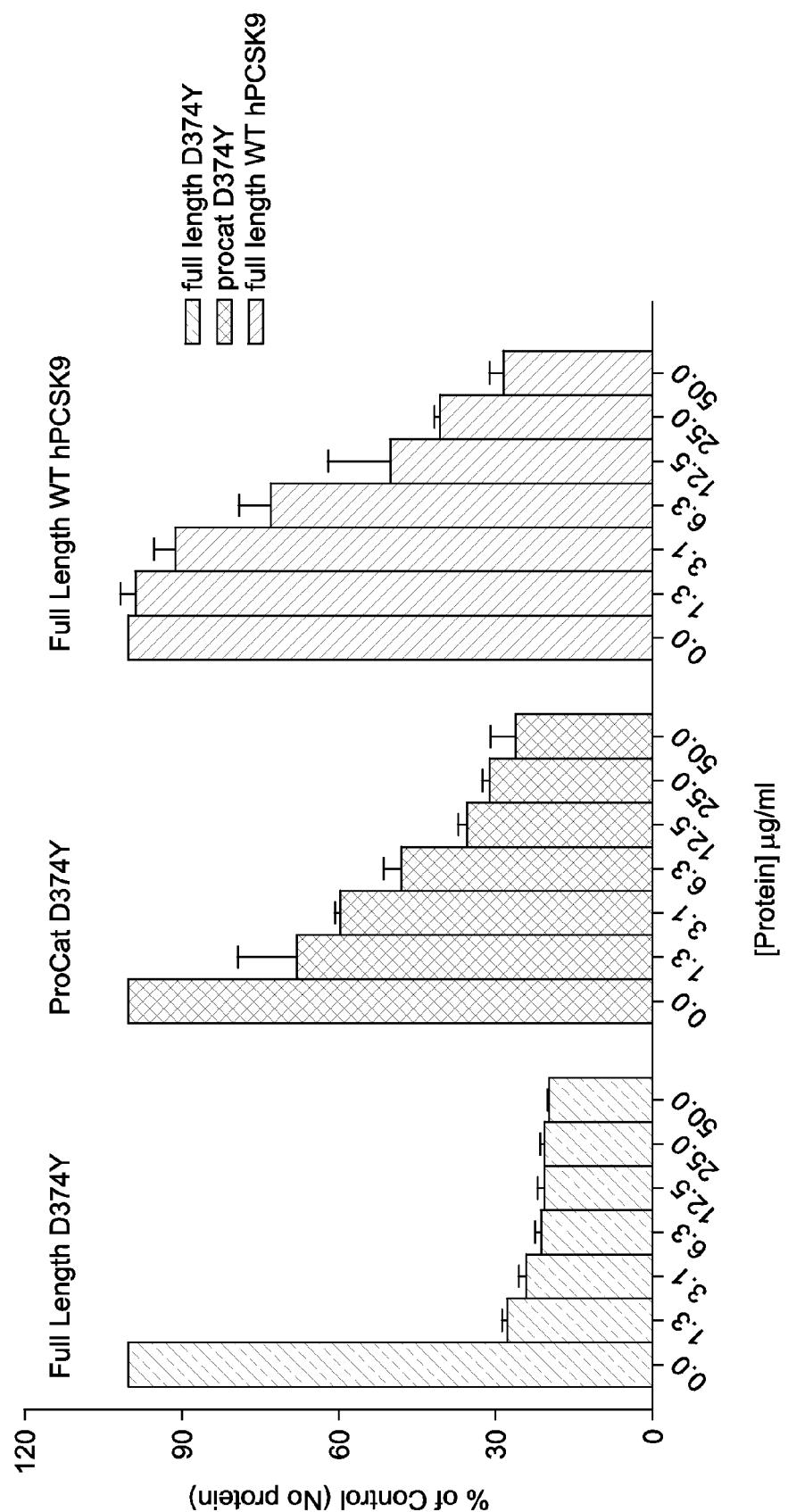


FIG. 8

LDLR Competition Assay

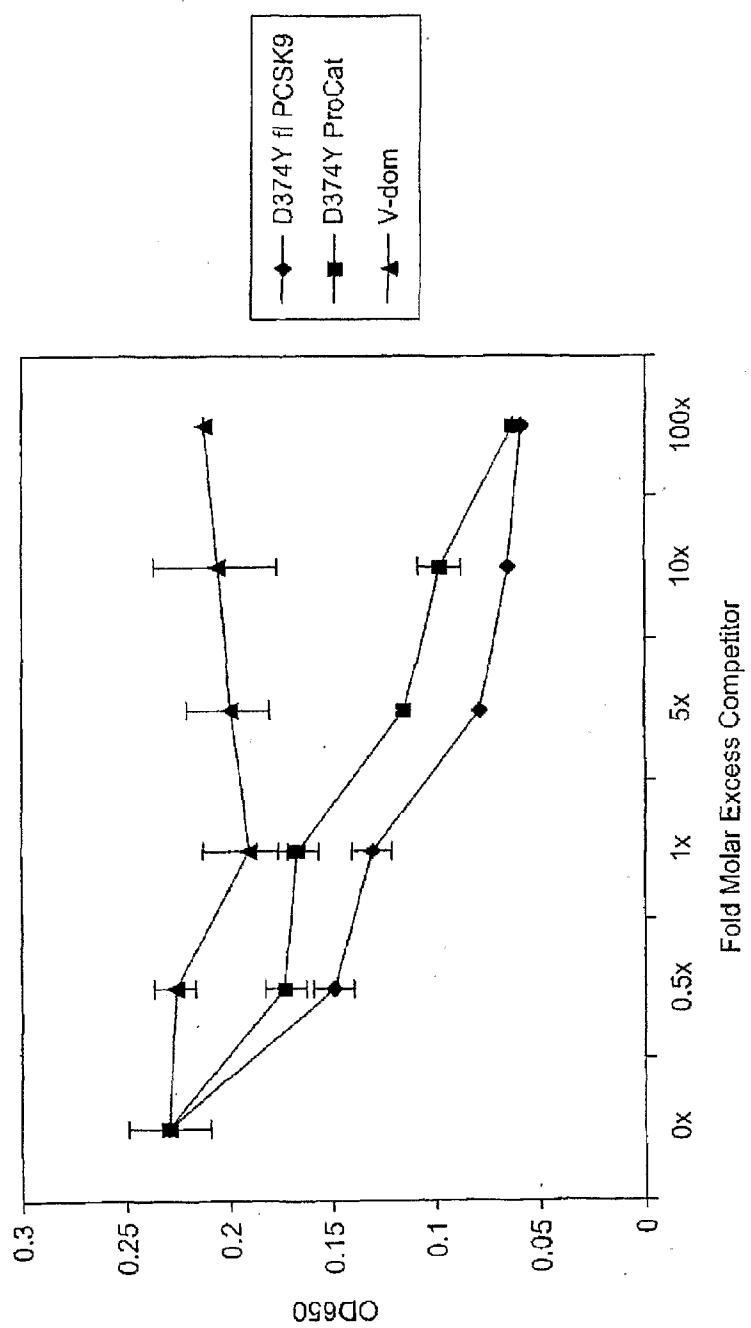


FIG. 9

SEQUENCE_LI STI NG_APMOL_005VPC

SEQUENCE LI STI NG

<110> Jackson, Simon Mark
Piper, Derek E.

<120> NEUTRALIZING PROPROTEIN CONVERTASE
SUBTILISIN KEXIN TYPE 9 (PCSK9) VARIANTS AND USES THEREOF

<130> APMOL. 005VPC

<150> 61/125304
<151> 2008-04-23

<160> 31

<170> Fast SEQ for Windows Version 4.0

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<213> Homo sapiens

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20 25 30
T h r P h e H i s A r g C y s A l a L y s A s p P r o T r p A r g L e u P r o G y T h r T y r
35 40 45
V a l V a l V a l L e u L y s G u G u T h r H i s L e u S e r G n S e r G u A r g T h r
50 55 60
A l a A r g A r g L e u G n A l a G n A l a A l a A r g A r g G y T y r L e u T h r L y s
65 70 75 80
I l e L e u H i s V a l P h e H i s G y L e u L e u P r o G y P h e L e u V a l L y s M e t
85 90 95
S e r G y A s p L e u L e u G u L e u A l a L e u L y s L e u P r o H i s V a l A s p T y r
100 105 110
I l e G u G u A s p S e r S e r V a l P h e A l a G n S e r I l e P r o T r p A s n L e u
115 120 125
G u A r g I l e T h r P r o P r o A r g T y r A r g A l a A s p G u T y r G n P r o P r o
130 135 140
A s p G y G y S e r L e u V a l G u V a l T y r L e u L e u A s p T h r S e r I l e G n
145 150 155 160
S e r A s p H i s A r g G u I l e G u G y A r g V a l M e t V a l T h r A s p P h e G u
165 170 175
A s n V a l P r o G u G u A s p G y T h r A r g P h e H i s A r g G n A l a S e r L y s
180 185 190
C y s A s p S e r H i s G y T h r H i s L e u A l a G y V a l V a l S e r G y A r g A s p
195 200 205
A l a G y V a l A l a L y s G y A l a S e r M e t A r g S e r L e u A r g V a l L e u A s n
210 215 220
C y s G n G y L y s G y T h r V a l S e r G y T h r L e u I l e G y L e u G u P h e
225 230 235 240
I l e A r g L y s S e r G n L e u V a l G n P r o V a l G y P r o L e u V a l V a l L e u
245 250 255
L e u P r o L e u A l a G y G y T y r S e r A r g V a l L e u A s n A l a A l a C y s G n
260 265 270
A r g L e u A l a A r g A l a G y V a l V a l L e u V a l T h r A l a A l a G y A s n P h e
275 280 285
A r g A s p A s p A l a C y s L e u T y r S e r P r o A l a S e r A l a P r o G u V a l I l e
290 295 300
T h r V a l G y A l a T h r A s n A l a G n A s p G n P r o V a l T h r L e u G y T h r
305 310 315 320
L e u G y T h r A s n P h e G y A r g C y s V a l A s p L e u P h e A l a P r o G y G u
325 330 335

SEQUENCE_LI STI NG_APMOL_005VPC

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 370 375 380
 Leu Ile His Phe Ser Ala Lys Asp Val Ile Asn Gln Ala Trp Phe Pro
 385 390 395 400
 Glu Asp Gln Arg Val Leu Thr Pro Asn Leu Val Ala Ala Leu Pro Pro
 405 410 415
 Ser Thr His Gly Ala Gly Trp Gln Leu Phe Cys Arg Thr Val Trp Ser
 420 425 430
 Ala His Ser Gly Pro Thr Arg Met Ala Thr Ala Ile Ala Arg Cys Ala
 435 440 445
 Pro Asp Glu Glu Leu Leu Ser Cys Ser Ser Phe Ser Arg Ser Gly Lys
 450 455 460
 Arg Arg Gly Glu Arg Met Glu Ala Gln Gly Gly Lys Leu Val Cys Arg
 465 470 475 480
 Ala His Asn Ala Phe Gly Gly Glu Gly Val Tyr Ala Ile Ala Arg Cys
 485 490 495
 Cys Leu Leu Pro Gln Ala Asn Cys Ser Val His Thr Ala Pro Pro Ala
 500 505 510
 Glu Ala Ser Met Gly Thr Arg Val His Cys His Gln Gln Gly His Val
 515 520 525
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 530 535 540
 Lys Pro Pro Val Leu Arg Pro Arg Gly Gln Pro Asn Gln Cys Val Gly
 545 550 555 560
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 Glu Cys Lys Val Lys Glu His Gly Ile Pro Ala Pro Gln Gly Gln Val
 580 585 590
 Thr Val Ala Cys Glu Glu Gly Trp Thr Leu Thr Gly Cys Ser Ala Leu
 595 600 605
 Pro Gly Thr Ser His Val Leu Gly Ala Tyr Ala Val Asp Asn Thr Cys
 610 615 620
 Val Val Arg Ser Arg Asp Val Ser Thr Thr Gly Ser Thr Ser Glu Glu
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<211> 2076

<212> DNA

<213> Homo sapiens

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 ct ggt gct ag cct t gcgt c cgaggaggac ggcct ggccg aagcacccga gcacgaaacc 180
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 gt gct gaagg aggagaccca cct ct cgcag t cagagcgc a ct gcccggcc cct gcaggcc 300
 caggct gccc gcccgggat a cct caccaag at cct gcat g t ct t ccat gg cct t ct t cct 360
 ggct t cct gg t gaagat gag t ggggacct g ct ggagct gg cct t gaagt t gccccat gt c 420
 gact acat cg aggaggact c ct ct gt ct t t gcccagagca t cccgt ggaa cct ggagcgg 480
 at t acccct c cgcggt accg ggcggat gaa t accagcccc ccgacggagg cagcct ggt g 540
 gaggt gt at c t cct agacac cagcat acag a gt gaccacc gggaaat cga gggcagggt c 600
 at ggt caccg act t cgagaa t gt gcccggag gaggacggga cccgct t cca cagacaggcc 660
 agcaagt gt g acagt cat gg caccacct g gcagggt gg t cagcggccg ggt gcccgc 720
 gt ggccaaagg gt gcccagcat ggcgagcct g cgcgt gct ca act gccaagg gaagggcacg 780
 gt t agcggca ccct cat agg cct ggagt t t at t cggaaaa gccagct ggt ccagcct gt g 840
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 gat gcccact gcc t ct act cccc agcct cagct cccgaggta t cacagt t gg gcccaccaat 1020
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SEQUENCE_LI STI NG_APMOL_005VPC

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 t ct gccgagc cggagct cac cct ggccgag t t gaggcaga gact gat cca ct t ct ct gcc 1260
 aaagat gt ca t caat gaggc ct ggt t ccct gaggaccagc ggtt act gac ccccaacct g 1320
 gt gcccggcc t gccccccag caccat ggg gcaggat t ggc agct gt t t t g caggact gt g 1380
 t ggt cagcac act cggggcc t acacggat g gccacagcca t cgccccgt g cgccccagat 1440
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 t acggcat t g ccaggt gct g cct gct accc caggccaaact gcagcgt cca cacagct cca 1620
 ccagct gagg ccagcat ggg gaccgt gt c cact gccacc aacaggccca cgt cct caca 1680
 ggct gcagct cccact gggg ggt ggaggac ct t ggcaccc acaagccgccc t gt gct gagg 1740
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 t gccat gccc caggt ct gga at gcaaagt c aaggagcat g gaat cccggc ccct cagggg 1860
 caggt gaccg t ggcct gcca ggagggct gg accct gact g gct gcagcgc cct ccct ggg 1920
 acct cccacg t cct gggggc ct acggcgt a gacaacacgt gt gt agt tag gagccgggac 1980
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<210> 3

<211> 692

<212> PRT

<213> Homo sapiens

<400> 3

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| Met | G | y | Thr | Val | Ser | Ser | Arg | Arg | Ser | Trp | Trp | Pro | Leu | Pro | Leu | Leu | | | | | | |
| 1 | | | | 5 | | | | | 10 | | | | 15 | | | | | | | | | |
| Leu | G | y | Pro | Ala | Ala | G | y | Ala | Arg | Ala | G | n | G | u | | |
| | | | | | | | 20 | | 25 | | | 30 | | | | | | | | | | |
| Asp | G | u | Asp | G | y | Asp | Tyr | G | u | G | u | Leu | Val | Leu | Ala | Leu | Arg | Ser | G | u | | |
| | 35 | | | | | 40 | | | | | | | 45 | | | | | | | | | |
| G | u | Asp | G | y | Leu | Ala | G | u | Ala | Pro | G | u | His | G | y | Thr | Thr | Ala | Thr | Phe | | |
| | 50 | | | | | | 55 | | | | | | 60 | | | | | | | | | |
| His | Arg | Cys | Ala | Ala | Lys | Asp | Pro | Trp | Arg | Leu | Pro | G | y | Thr | Tyr | Val | Val | | | | | |
| | 65 | | | | | 70 | | | | | 75 | | | | | | 80 | | | | | |
| Val | Leu | Lys | G | u | G | u | Thr | His | Leu | Ser | G | n | Ser | G | u | Arg | Thr | Ala | Arg | | | |
| | | | | | | | 85 | | | 90 | | | | | | 95 | | | | | | |
| Arg | Leu | G | n | Ala | G | n | Ala | Ala | Arg | Arg | G | y | Tyr | Leu | Thr | Lys | Ile | Leu | | | | |
| | 100 | | | | | | | 105 | | | 105 | | | | | 110 | | | | | | |
| His | Val | Phe | His | G | y | Leu | Leu | Pro | G | y | Phe | Leu | Val | Lys | M | et | Ser | G | y | | | |
| | 115 | | | | | | 120 | | | | | | 125 | | | | | | | | | |
| Asp | Leu | Leu | G | u | Leu | Ala | Leu | Lys | Leu | Pro | His | V | al | A | s | P | T | Y | Ile | G | u | |
| | 130 | | | | | | 135 | | | | | 140 | | | | | | | | | | |
| G | u | Asp | Ser | Ser | Val | Phe | Ala | G | n | Ser | Ile | Pro | T | r | A | s | N | Leu | G | u | Arg | |
| | 145 | | | | | 150 | | | | | 155 | | | | | | 160 | | | | | |
| Ile | Thr | Pro | Pro | Arg | Tyr | Arg | Ala | Asp | G | u | Tyr | G | n | P | ro | A | s | P | G | y | | |
| | | | | | | | 165 | | | 170 | | | | | | 175 | | | | | | |
| G | y | Ser | Leu | Val | G | u | Val | Tyr | Leu | Leu | Asp | Thr | Ser | Ile | G | n | Ser | A | s | P | | |
| | 180 | | | | | | 185 | | | | | | 190 | | | | | | | | | |
| His | Arg | G | u | Ile | G | u | G | y | Arg | Val | M | et | Val | Thr | A | s | P | he | G | u | Asn | Val |
| | 195 | | | | | | 200 | | | | | | 205 | | | | | | | | | |
| Pro | G | u | G | u | Asp | G | u | Thr | Arg | Phe | His | Arg | G | n | Ala | Ser | Lys | C | ys | A | s | |
| | 210 | | | | | | 215 | | | | | | 220 | | | | | | | | | |
| Ser | His | G | y | Thr | His | Leu | Ala | G | y | Val | Val | Ser | G | y | Arg | A | s | Ala | G | y | | |
| | 225 | | | | | 230 | | | | | | 235 | | | | | 240 | | | | | |
| Val | Ala | Lys | G | y | Ala | Ser | Met | Arg | Ser | Leu | Arg | Val | Leu | Asn | C | ys | G | n | | | | |
| | | | | | | 245 | | | | 250 | | | | | 255 | | | | | | | |
| G | y | Lys | G | y | Thr | Val | Ser | G | y | Thr | Leu | Ile | G | y | Leu | G | u | Phe | Ile | Arg | | |
| | 260 | | | | | | 265 | | | | | | 270 | | | | | | | | | |
| Lys | Ser | G | n | Leu | Val | G | n | Pro | Val | G | y | Pro | Leu | Val | Val | Leu | Leu | Pro | | | | |
| | 275 | | | | | | 280 | | | | | | 285 | | | | | | | | | |
| Leu | Ala | G | y | G | y | Tyr | Ser | Arg | Val | Leu | Asn | Ala | Ala | C | ys | G | n | Arg | Leu | | | |
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| Ala | Arg | Ala | G | y | Val | Val | Leu | Val | Thr | Ala | Ala | G | y | Asn | Phe | Arg | A | s | P | | | |
| | 305 | | | | | 310 | | | | | | 315 | | | | | 320 | | | | | |
| Asp | Ala | Oys | Leu | Tyr | Ser | Pro | Ala | Ser | Ala | Pro | G | u | Val | Ile | Thr | Val | | | | | | |
| | | | | | 325 | | | | | | 330 | | | | | 335 | | | | | | |
| G | y | Ala | Thr | Asn | Ala | G | n | Asp | G | n | Pro | Val | Thr | Leu | G | y | Thr | Leu | G | y | | |
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 370 375 380
 Thr Ser Gln Ala Ala Ala His Val Ala Gly Ile Ala Ala Met Met Leu
 385 390 395 400
 Ser Ala Glu Pro Glu Leu Thr Leu Ala Glu Leu Arg Gln Arg Leu Ile
 405 410 415
 His Phe Ser Ala Lys Asp Val Ile Asn Glu Ala Trp Phe Pro Glu Asp
 420 425 430
 Gln Arg Val Leu Thr Pro Asn Leu Val Ala Ala Leu Pro Pro Ser Thr
 435 440 445
 His Gly Ala Gly Trp Gln Leu Phe Cys Arg Thr Val Trp Ser Ala His
 450 455 460
 Ser Gly Pro Thr Arg Met Ala Thr Ala Ile Ala Arg Cys Ala Pro Asp
 465 470 475 480
 Glu Glu Leu Leu Ser Cys Ser Ser Phe Ser Arg Ser Gly Lys Arg Arg
 485 490 495
 Gly Glu Arg Met Glu Ala Gln Gly Gly Lys Leu Val Cys Arg Ala His
 500 505 510
 Asn Ala Phe Gly Gly Glu Val Tyr Ala Ile Ala Arg Cys Cys Leu
 515 520 525
 Leu Pro Gln Ala Asn Cys Ser Val His Thr Ala Pro Pro Ala Glu Ala
 530 535 540
 Ser Met Gly Thr Arg Val His Cys His Gln Gln Gly His Val Leu Thr
 545 550 555 560
 Gly Cys Ser Ser His Trp Glu Val Glu Asp Leu Gly Thr His Lys Pro
 565 570 575
 Pro Val Leu Arg Pro Arg Gly Gln Pro Asn Gln Cys Val Gly His Arg
 580 585 590
 Glu Ala Ser Ile His Ala Ser Cys Cys His Ala Pro Gly Leu Glu Cys
 595 600 605
 Lys Val Lys Glu His Gly Ile Pro Ala Pro Gln Gly Gln Val Thr Val
 610 615 620
 Ala Cys Glu Glu Gly Trp Thr Leu Thr Gly Cys Ser Ala Leu Pro Gly
 625 630 635 640
 Thr Ser His Val Leu Gly Ala Tyr Ala Val Asp Asn Thr Cys Val Val
 645 650 655
 Arg Ser Arg Asp Val Ser Thr Thr Gly Ser Thr Ser Glu Glu Ala Val
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 Gln Glu Leu Gln
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 <212> PRT
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<400> 4

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 35 40 45
 Gly Pro Ala Glu Ala Ala Pro His Val Pro Thr Ala Pro Phe His Arg
 50 55 60
 Cys Ser Lys Asp Ala Trp Arg Leu Pro Gly Thr Tyr Leu Val Val Leu
 65 70 75 80
 Lys Glu Gly Thr His Arg Gly Gln Thr Lys His Thr Ala His Arg Leu
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 Gln Ala Lys Ala Ala Arg Arg Gly Tyr Val Thr Thr Val Leu His Leu
 100 105 110
 Phe His His Leu Val Pro Gly Phe Leu Val Arg Met Ser Gly Asp Leu
 115 120 125

SEQUENCE_LI STI NG_APMOL_005VPC

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 Ser Ser Val Phe Ala Glu Ser Val Pro Trp Asn Leu Glu Arg Ile Leu
 145 150 155 160
 Pro Val Arg His Glu Ala Lys Glu Tyr Ser Ala Pro Ser His Pro Val
 165 170 175
 Thr Val Tyr Leu Leu Asp Thr Ser Ile Glu Ser Gly His Arg Glu Ile
 180 185 190
 Glu Gly Arg Ile Thr Val Thr Asp Phe Glu Ser Val Pro Glu Glu Asp
 195 200 205
 Gly Thr Arg Phe His Arg Glu Ala Ser Lys Cys Asp Ser His Gly Thr
 210 215 220
 His Leu Ala Gly Val Val Ser Gly Arg Asp Ala Gly Val Ala Lys Gly
 225 230 235 240
 Ala Gly Leu Arg Ser Leu Arg Val Leu Asn Cys Glu Gly Arg Gly Thr
 245 250 255
 Val Ser Ser Thr Leu Arg Gly Leu Glu Phe Ile Arg Lys Ser Glu Leu
 260 265 270
 Ala Glu Pro Val Glu Pro Leu Val Val Leu Leu Pro Leu Ala Gly Gly
 275 280 285
 Tyr Ser Arg Thr Leu Asn Ala Ala Cys His Leu Leu Ala Arg Ala Gly
 290 295 300
 Val Val Leu Val Ala Ala Gly Asn Phe Arg Asp Asp Ala Cys Leu
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 Tyr Ser Pro Ala Ser Ala Pro Glu Val Ile Thr Val Gly Ala Thr Asn
 325 330 335
 Ala Glu Asp Glu Pro Val Thr Leu Gly Thr Leu Gly Thr Asn Phe Gly
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 Arg Cys Val Asp Leu Phe Ala Pro Gly Glu Asp Ile Ile Gly Ala Ser
 355 360 365
 Ser Asp Cys Ser Thr Cys Phe Val Ser Arg Ser Gly Thr Ser Glu Ala
 370 375 380
 Ala Ala His Val Ala Gly Ile Val Thr Met Met Leu Thr Ala Glu Pro
 385 390 395 400
 Lys Leu Thr Leu Ala Glu Leu Trp Glu Arg Leu Ile His Phe Ala Ala
 405 410 415
 Lys Asp Val Ile Asn Glu Ala Trp Phe Pro Glu Asp Glu Arg Val Leu
 420 425 430
 Thr Pro Asn Leu Val Ala Thr Leu Pro Pro Ser Thr Arg Gly Ala Gly
 435 440 445
 Gly Arg Leu Leu Cys Arg Thr Val Trp Ser Ala Arg Ser Gly Pro Arg
 450 455 460
 His Thr Ala Thr Ala Leu Ala His Cys Thr Pro Glu Glu Leu Leu
 465 470 475 480
 Ser Cys Ser Ser Phe Ser Arg Ser Gly Lys Arg Lys Gly Glu Arg Ile
 485 490 495
 Glu Val Leu Arg Gly Arg Arg Val Cys Val Ala Tyr Asn Ala Phe Gly
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 Gly Lys Gly Val His Ala Val Ala Arg Cys Cys Leu Leu Pro Arg Ala
 515 520 525
 Asn Cys Ser Leu His Thr Ala Pro Ala Arg Ala Gly Met Glu Pro Arg
 530 535 540
 Val His Cys His Arg Lys Asp Glu Val Leu Thr Gly Cys Ser Ala His
 545 550 555 560
 Trp Glu Ala Glu Asp Phe Arg Ala Arg Gly Trp Pro Met Leu Arg Pro
 565 570 575
 Gly Gly Pro Ser Glu Cys Val Gly His Ser Lys Ala Ser Val His Ala
 580 585 590
 Ser Cys Cys Ser Ala Pro Gly Leu Glu Cys Arg Ile Arg Glu His Gly
 595 600 605
 Val Pro Trp Pro Ala Glu Glu Val Thr Val Ala Cys Glu Asp Gly Trp
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 Thr Leu Thr Gly Cys Ser Thr Leu Pro Gly Ala Ser Ser Val Leu Gly
 625 630 635 640
 Thr Tyr Ala Val Asp Asp Met Cys Val Val Arg Ser Arg Asp Val Lys
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 Ala Leu Asp Arg Thr Arg Gly Glu Ala Leu Ala Ile Ala Ile Cys
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SEQUENCE_LI STI NG_APMOL_005VPC
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 675 680 685
 His His His His
 690

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 35 40 45
 Asp Gly Leu Ala Asp Glu Thr Asp Glu Ala Pro Gln Gly Ala Thr Ala
 50 55 60
 Ala Phe His Arg Cys Pro Glu Glu Ala Trp Arg Val Pro Gly Thr Tyr
 65 70 75 80
 Ile Val Met Leu Ala Glu Gu Ala Gln Trp Val His Ile Glu Gln Thr
 85 90 95
 Met His Arg Leu Gln Thr Gln Ala Ala Arg Arg Gly Tyr Val Ile Lys
 100 105 110
 Ile Gln His Ile Phe Tyr Asp Phe Leu Pro Ala Phe Val Val Lys Met
 115 120 125
 Ser Ser Asp Leu Leu Asp Leu Ala Leu Lys Leu Pro His Val Lys Tyr
 130 135 140
 Ile Glu Gu Asp Ser Leu Val Phe Ala Gln Ser Ile Pro Trp Asn Leu
 145 150 155 160
 Asp Arg Ile Ile Pro Ala Gly Arg Gln Ala Gln Glu Tyr Ser Ser Ser
 165 170 175
 Arg Lys Val Pro Ser Gly Ser Gly Gln Val Glu Val Tyr Leu Leu Asp
 180 185 190
 Thr Ser Ile Gln Ser Asp His Arg Gln Ile Glu Gly Arg Val Thr Val
 195 200 205
 Thr Asp Phe Asn Ser Val Pro Glu Glu Asp Gly Thr Arg Phe His Arg
 210 215 220
 Gln Ala Ser Lys Cys Asp Ser His Gly Thr His Leu Ala Gln Val Val
 225 230 235 240
 Ser Gly Arg Asp Ala Gly Val Ala Lys Gly Thr Ile Leu His Gly Leu
 245 250 255
 Arg Val Leu Asn Cys Gln Gly Lys Gly Ile Val Ser Gly Ile Leu Thr
 260 265 270
 Gly Leu Glu Phe Ile Trp Lys Ser Gln Leu Met Gln Pro Ser Gly Pro
 275 280 285
 Gln Val Val Leu Leu Pro Leu Ala Gly Arg Tyr Ser Arg Val Leu Asn
 290 295 300
 Thr Ala Cys Gln His Leu Ala Arg Thr Gly Val Val Leu Val Ala Ala
 305 310 315 320
 Ala Gly Asn Phe Arg Asp Asp Ala Cys Leu Tyr Ser Pro Ala Ser Ala
 325 330 335
 Pro Glu Val Ile Thr Val Gly Ala Thr Asp Val Gln Asp Gln Pro Val
 340 345 350
 Thr Leu Gly Thr Leu Gly Thr Asn Phe Gly Arg Cys Val Asp Leu Phe
 355 360 365
 Ala Pro Gly Lys Asp Ile Ile Gly Ala Ser Ser Asp Cys Ser Ala Cys
 370 375 380
 Phe Met Ser Gln Ser Gly Thr Ser Gln Ala Ala Ala His Val Ala Gly
 385 390 395 400
 Ile Val Ala Met Met Leu Thr Leu Glu Pro Glu Leu Thr Leu Thr Glu
 405 410 415
 Leu Arg Gln Arg Leu Ile His Phe Ser Thr Lys Asp Ala Ile Asn Met
 420 425 430
 Ala Trp Phe Pro Glu Asp Gln Arg Val Leu Thr Pro Asn Leu Val Ala
 435 440 445

SEQUENCE_LI STI NG_APMOL_005VPC

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Leu | Pro | Pro | Ser | Thr | His | Gly | Thr | Gly | Gly | Gln | Leu | Leu | Cys | Arg |
| 450 | | | | | | 455 | | | 460 | | | | | | |
| Thr | Val | Trp | Ser | Ala | His | Ser | Gly | Pro | Thr | Arg | Ala | Ala | Thr | Ala | Thr |
| 465 | | | | | | 470 | | | 475 | | | | | | 480 |
| Ala | Arg | Cys | Ala | Pro | Gly | Gu | Gu | Leu | Leu | Ser | Cys | Ser | Ser | Phe | Ser |
| | | | | | 485 | | | 490 | | | 495 | | | | |
| Arg | Ser | Gly | Arg | Arg | Arg | Gly | Asp | Arg | Ile | Glu | Ala | Ala | Gly | Thr | Gln |
| | | | | | 500 | | | 505 | | | 510 | | | | |
| Gln | Val | Cys | Lys | Ala | Leu | Asn | Ala | Phe | Gly | Gly | Gu | Gly | Val | Tyr | Ala |
| | | | | | 515 | | | 520 | | | 525 | | | | |
| Val | Ala | Arg | Cys | Cys | Leu | Leu | Pro | Arg | Ala | Asn | Cys | Ser | Ile | His | Thr |
| | | | | | 530 | | | 535 | | | 540 | | | | |
| Thr | Pro | Ala | Ala | Arg | Thr | Ser | Leu | Glu | Thr | His | Ala | His | Cys | His | Gln |
| | | | | | 545 | | | 550 | | | 555 | | | | 560 |
| Lys | Asp | His | Val | Leu | Thr | Gly | Cys | Ser | Leu | His | Trp | Glu | Val | Glu | Gly |
| | | | | | 565 | | | 570 | | | 575 | | | | |
| Ile | Gly | Val | Gln | Pro | Leu | Ala | Val | Leu | Arg | Ser | Arg | His | Gln | Pro | Gly |
| | | | 580 | | | | 585 | | | 590 | | | | | |
| Gln | Cys | Thr | Gly | His | Arg | Glu | Ala | Ser | Val | His | Ala | Ser | Cys | Cys | His |
| | | | | | 595 | | | 600 | | | 605 | | | | |
| Ala | Pro | Gly | Leu | Glu | Cys | Lys | Ile | Lys | Glu | His | Gly | Ile | Ser | Gly | Pro |
| | | | | | 610 | | | 615 | | | 620 | | | | |
| Ala | Glu | Gln | Val | Thr | Val | Ala | Cys | Glu | Ala | Gly | Trp | Thr | Leu | Thr | Gly |
| | | | | | 625 | | | 630 | | | 635 | | | | 640 |
| Cys | Asn | Val | Leu | Pro | Gly | Ala | Phe | Ile | Thr | Leu | Gly | Ala | Tyr | Ala | Val |
| | | | | | 645 | | | 650 | | | 655 | | | | |
| Asp | Asn | Thr | Cys | Val | Ala | Arg | Ser | Arg | Val | Thr | Asp | Thr | Ala | Gly | Arg |
| | | | | | 660 | | | 665 | | | 670 | | | | |
| Thr | Gly | Gl | Gu | Ala | Thr | Val | Ala | Ala | Ala | Ile | Cys | Oys | Arg | Asn | Arg |
| | | | | | 675 | | | 680 | | | 685 | | | | |
| Pro | Ser | Ala | Lys | Ala | Ser | Trp | Val | His | Gln | His | His | His | His | His | His |
| | | | | | 690 | | | 695 | | | 700 | | | | |

<210> 6

<211> 695

<212> PRT

<213> Mus musculus

<400> 6

| | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gly | Thr | His | Cys | Ser | Ala | Trp | Leu | Arg | Trp | Pro | Leu | Leu | Pro | Leu | |
| 1 | | | | 5 | | | | 10 | | 15 | | | | | | |
| Leu | Pro | Pro | Leu | Cys | Pro | Thr | Gly | Ala | | |
| | | | | | | | | | | 20 | | 25 | 30 | | | |
| Gly | Ala | Gln | Asp | Glu | Asp | Gly | Asp | Tyr | Glu | Glu | Leu | Met | Leu | Ala | Leu | |
| | | | | | | | | 35 | 40 | | 45 | | | | | |
| Pro | Ser | Gln | Gl | Asp | Gly | Leu | Ala | Asp | Glu | Ala | Ala | Ala | His | Val | Ala | Thr |
| | | | | | | | | 50 | 55 | | 60 | | | | | |
| Ala | Thr | Phe | Arg | Arg | Cys | Ser | Lys | Glu | Ala | Trp | Arg | Leu | Pro | Gly | Thr | |
| | | | | | 65 | | | 70 | | | 75 | | | | 80 | |
| Tyr | Ile | Val | Val | Leu | Met | Glu | Glu | Thr | Gln | Arg | Leu | Gln | Ile | Glu | Gln | |
| | | | | | | | | | 85 | 90 | | 95 | | | | |
| Thr | Ala | His | Arg | Leu | Gln | Thr | Arg | Ala | Ala | Arg | Arg | Gly | Tyr | Val | Ile | |
| | | | | | 100 | | | | 105 | | 110 | | | | | |
| Lys | Val | Leu | His | Ile | Phe | Tyr | Asp | Leu | Phe | Pro | Gly | Phe | Leu | Val | Lys | |
| | | | | | 115 | | | 120 | | | 125 | | | | | |
| Met | Ser | Ser | Asp | Leu | Leu | Gly | Leu | Ala | Leu | Lys | Leu | Pro | His | Val | Glu | |
| | | | | | 130 | | | 135 | | | 140 | | | | | |
| Tyr | Ile | Glu | Gl | Asp | Ser | Phe | Val | Phe | Ala | Gln | Ser | Ile | Pro | Trp | Asn | |
| | | | | | 145 | | | 150 | | | 155 | | | | 160 | |
| Leu | Arg | Ile | Ile | Pro | Ala | Trp | His | Gln | Thr | Glu | Glu | Asp | Arg | Ser | Pro | |
| | | | | | | | | | 165 | | 170 | | | | 175 | |
| Asp | Gly | Ser | Ser | Gln | Val | Glu | Val | Tyr | Leu | Leu | Asp | Thr | Ser | Ile | Gln | |
| | | | | | 180 | | | 185 | | | 190 | | | | | |
| Gly | Ala | His | Arg | Gl | Ile | Gu | Gly | Arg | Val | Thr | Ile | Thr | Asp | Phe | Asn | |
| | | | | | 195 | | | 200 | | | 205 | | | | | |
| Ser | Val | Pro | Glu | Gu | Gu | Asp | Gly | Thr | Arg | Phe | His | Arg | Gln | Ala | Ser | Lys |
| | | | | | 210 | | | 215 | | | 220 | | | | | |

SEQUENCE_LI STI NG_APMOL_005VPC

Cys Asp Ser His Gly Thr His Leu Ala Gly Val Val Ser Gly Arg Asp
 225 230 235 240
 Ala Gly Val Ala Lys Gly Thr Ser Leu His Ser Leu Arg Val Leu Asn
 245 250 255
 Cys Gln Gly Lys Gly Thr Val Ser Gly Thr Leu Ile Gly Leu Glu Phe
 260 265 270 275
 Ile Arg Lys Ser Gln Leu Ile Gln Pro Ser Pro Leu Val Val Leu Pro
 275 280 285
 Leu Ala Gly Gly Tyr Ser Arg Ile Leu Asn Ala Ala Cys Arg His Leu
 290 295 300
 Ala Arg Thr Gly Val Val Leu Val Ala Ala Ala Gly Asn Phe Arg Asp
 305 310 315 320
 Asp Ala Cys Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val Ile Thr Val
 325 330 335
 Gly Ala Thr Asn Ala Gln Asp Gln Pro Val Thr Leu Gly Thr Leu Gly
 340 345 350
 Thr Asn Phe Gly Arg Cys Val Asp Leu Phe Ala Pro Gly Lys Asp Ile
 355 360 365
 Ile Gly Ala Ser Ser Asp Cys Ser Thr Cys Phe Met Ser Gln Ser Gly
 370 375 380
 Thr Ser Gln Ala Ala Ala His Val Ala Gly Ile Val Ala Arg Met Leu
 385 390 395 400
 Ser Arg Glu Pro Thr Leu Thr Leu Ala Leu Arg Gln Arg Ile His Phe
 405 410 415
 Ser Thr Lys Asp Val Ile Asn Met Ala Trp Phe Pro Glu Asp Gln Gln
 420 425 430
 Val Leu Thr Pro Asn Leu Val Ala Thr Leu Pro Pro Ser Thr His Glu
 435 440 445
 Thr Gly Gly Gln Leu Leu Cys Arg Thr Val Trp Ser Ala His Ser Gly
 450 455 460
 Pro Thr Arg Thr Ala Thr Ala Thr Ala Arg Cys Ala Pro Glu Glu Glu
 465 470 475 480
 Leu Leu Ser Cys Ser Ser Phe Ser Arg Ser Gly Arg Arg Arg Gly Asp
 485 490 495
 Arg Ile Glu Ala Ile Gly Gly Gln Gln Val Cys Lys Ala Leu Asn Ala
 500 505 510
 Phe Gly Gly Glu Gly Val Tyr Ala Val Ala Arg Cys Cys Leu Val Pro
 515 520 525
 His Ala Asn Cys Ser Ile His Asn Pro Ala Ala Ala Gly Leu Glu Thr
 530 535 540
 His Val His Cys His Gln Lys Asp His Val Leu Thr Gly Cys Ser Phe
 545 550 555 560
 His Trp Glu Val Glu Asp Leu Ser Val Arg Arg Gln Pro Ala Leu Arg
 565 570 575
 Ser Arg Arg Gln Pro Gly Gln Cys Val Gly His Gln Ala Ala Ser Val
 580 585 590
 Tyr Ala Ser Cys Cys His Ala Pro Gly Leu Glu Cys Lys Ile Lys Glu
 595 600 605
 His Gly Ile Ser Gly Ser Ser Glu Gln Val Thr Val Ala Cys Glu Ala
 610 615 620
 Gly Trp Thr Leu Thr Gly Cys Asn Val Leu Pro Gly Ala Ser Leu Thr
 625 630 635 640
 Leu Gly Ala Tyr Ser Val Asp Asn Leu Cys Val Ala Arg Val His Asp
 645 650 655
 Thr Ala Arg Ala Asp Arg Thr Gly Glu Thr Val Ala Ala Ala Ile Cys
 660 665 670
 Cys Arg Ser Arg Pro Ser Ala Lys Ala Ser Trp Val Gln Gly Pro His
 675 680 685
 His His His His His His
 690 695

<210> 7
 <211> 703
 <212> PRT
 <213> Macaca fascicularis

<400> 7

SEQUENCE_LI STI NG_APMOL_005VPC

Met G y Thr Val Ser Ser Arg Arg Ser Trp Trp Pro Leu Pro Leu Pro
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 Leu Leu Leu Leu Leu Leu G y Pro Ala G y Ala Arg Ala G n G u
 20 25 30
 Asp G u Asp G y Asp Tyr G u G u Leu Val Leu Ala Leu Arg Ser G u
 35 40 45
 G u Asp G y Leu Ala Asp Ala Pro G u His G y Ala Thr Ala Thr Phe
 50 55 60
 His Arg Cys Ala Lys Asp Pro Trp Arg Leu Pro G y Thr Tyr Val Val
 65 70 75 80
 Val Leu Lys G u G u Thr His Arg Ser G n Ser G u Arg Thr Ala Arg
 85 90 95
 Arg Leu G n Ala G n Ala Arg Arg G y Tyr Leu Thr Lys Ile Leu
 100 105 110
 His Val Phe His His Leu Leu Pro G y Phe Leu Val Lys Met Ser G y
 115 120 125
 Asp Leu Leu G u Leu Ala Leu Lys Leu Pro His Val Asp Tyr Ile G u
 130 135 140
 G u Asp Ser Ser Val Phe Ala G n Ser Ile Pro Trp Asn G u Arg Ile
 145 150 155 160
 Thr Pro Ala Arg Tyr Arg Ala Asp G u Tyr G n Pro Pro Lys G y G y
 165 170 175
 Ser Leu Val G u Val Tyr Leu Leu Asp Thr Ser Ile G n Ser Asp His
 180 185 190
 Arg G u Ile G u G y Arg Val Met Val Thr Asp Phe G u Ser Val Pro
 195 200 205
 G u G u Asp G y Thr Arg Phe His Arg G n Ala Ser Lys Cys Asp Ser
 210 215 220
 His G y Thr His Leu Ala G y Val Val Ser G y Arg Asp Ala G y Val
 225 230 235 240
 Ala Lys G y Ala G y Leu Arg Ser Leu Arg Val Leu Asn Cys G n G y
 245 250 255
 Lys G y Thr Val Ser G y Thr Leu Ile G y Leu G u Phe Ile Arg Lys
 260 265 270 275
 Ser G n Leu Val G n Pro Val Pro Leu Val Val Leu Pro Leu Ala G y
 280 285
 G y Tyr Ser Arg Val Phe Asn Ala Ala Cys G n Arg Leu Ala Arg Ala
 290 295 300
 G y Val Val Leu Val Thr Ala Ala G y Asn Phe Arg Asp Asp Ala Cys
 305 310 315 320
 Leu Tyr Ser Pro Ala Ser Ala Pro G u Val Ile Thr Val G y Ala Thr
 325 330 335
 Asn Ala G n Asp G n Pro Val Thr Leu G y Thr Leu G y Thr Asn Phe
 340 345 350
 G y Arg Cys Val Asp Leu Phe Ala Pro G y G u Asp Ile Ile G y Ala
 355 360 365
 Ser Ser Asp Cys Ser Thr Cys Phe Val Ser Arg Ser G y Thr Ser G n
 370 375 380 385
 Ala Ala Ala His Val Ala G y Ile Ala Ala Met Met Leu Ser Ala G u
 390 395 400
 Pro G u Leu Thr Leu Ala Leu Arg G n Leu Ile His Phe Ser Ala Lys
 405 410 415
 Asp Val Ile Asn G u Ala Trp Phe Pro G u Asp G n Arg Val Leu Thr
 420 425 430
 Pro Asn Leu Val Ala Ala Leu Pro Pro Ser Thr His Arg Ala G y Trp
 435 440 445
 G n Leu Phe Cys Arg Thr Val Trp Ser Ala His Ser G y Pro Thr Arg
 450 455 460
 Met Ala Thr Ala Val Ala Arg Cys Ala G n Asp G u G u Leu Leu Ser
 465 470 475 480
 Cys Ser Ser Phe Ser Arg Ser G y Lys Arg Arg G y G u Arg Ile G u
 485 490 495
 Ala G n G y G y Lys Arg Val Cys Arg Ala His Asn Ala Phe G y G y
 500 505 510
 G u G y Val Tyr Ala Ile Ala Arg Cys Cys Leu Leu Pro G n Val Asn
 515 520 525
 Cys Ser Val His Thr Pro Pro G y Ala Ser Met G y Thr Arg Val His
 530 535 540

SEQUENCE_LI STI NG_APMOL_005VPC

| | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | His | Gln | Gln | Gly | His | Val | Leu | Thr | Gly | Cys | Ser | Ser | His | Trp | Gl | |
| 545 | | | | 550 | | | | | 555 | | | | | | 560 | |
| Val | Gl | u | Asp | Leu | Gly | Thr | His | Lys | Pro | Pro | Val | Leu | Arg | Pro | Arg | Gly |
| | | | | 565 | | | | | 570 | | | | | | 575 | |
| Gln | Pro | Asn | Gln | Cys | Val | Gly | His | Arg | Glu | Ala | Ser | Ile | His | Ala | Ser | |
| | | | | 580 | | | | 585 | | | | | | | 590 | |
| Cys | Cys | His | Ala | Pro | Gly | Leu | Glu | Cys | Lys | Val | Arg | Glu | His | Gly | Ile | |
| | | | | 595 | | | | 600 | | | | | | | 605 | |
| Pro | Ala | Pro | Gln | Glu | Gln | Val | Ile | Val | Ala | Cys | Glu | Asp | Gly | Trp | Thr | |
| | | | | 610 | | | 615 | | | | | | | | 620 | |
| Leu | Thr | Gly | Cys | Ser | Ala | Leu | Pro | Gly | Thr | Ser | His | Val | Leu | Gly | Ala | |
| 625 | | | | 630 | | | | | 635 | | | | | | 640 | |
| Tyr | Ala | Val | Asp | Asn | Thr | Cys | Val | Val | Arg | Ser | Arg | Asp | Val | Ser | Thr | |
| | | | | 645 | | | | | 650 | | | | | | 655 | |
| Thr | Gly | Ser | Thr | Glu | Ala | Val | Ala | Ala | Val | Ala | Ile | Cys | Cys | Arg | Ser | |
| | | | | 660 | | | | 665 | | | | | | | 670 | |
| Arg | His | Leu | Val | Gln | Ala | Ser | Gln | Glu | Leu | Gln | Gly | Lys | Pro | Ile | Pro | |
| | | | | 675 | | | 680 | | | | | | | | 685 | |
| Asn | Pro | Leu | Leu | Gly | Leu | Asp | Ser | Thr | His | His | His | His | His | His | | |
| | | | | | | 695 | | | | | | | | | 700 | |

<210> 8
<211> 699
<212> PRT
<213> Rat t us nor vegi cus

<400> 8

| | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Met | Gly | Ile | Arg | Cys | Ser | Thr | Trp | Leu | Arg | Trp | Pro | Leu | Ser | Pro | Gln | |
| 1 | | | | 5 | | | | | 10 | | | | | | 15 | |
| Leu | Leu | Leu | Leu | Leu | Leu | Cys | Pro | Thr | Gly | Ser | Arg | Ala | Gln | Asp | | |
| | | | | | | 20 | | 25 | | | | | | 30 | | |
| Glu | Asp | Gly | Asp | Tyr | Glu | Glu | Leu | Met | Leu | Ala | Leu | Pro | Ser | Gln | Glu | |
| | | | | | | 35 | | 40 | | | | | | 45 | | |
| Asp | Ser | Leu | Val | Asp | Glu | Ala | Ser | His | Val | Ala | Thr | Ala | Thr | Phe | Arg | |
| | | | | | | 50 | | 55 | | | | | | 60 | | |
| Arg | Cys | Ser | Lys | Glu | Ala | Trp | Arg | Leu | Pro | Gly | Thr | Tyr | Val | Val | Val | |
| | | | | | | 65 | | 70 | | | | | | 80 | | |
| Leu | Met | Glu | Glu | Thr | Gln | Arg | Leu | Gln | Val | Glu | Gln | Thr | Ala | His | Arg | |
| | | | | | | 85 | | 90 | | | | | | 95 | | |
| Leu | Gln | Thr | Trp | Ala | Ala | Arg | Arg | Gly | Tyr | Val | Ile | Lys | Val | Leu | His | |
| | | | | | | 100 | | 105 | | | | | | 110 | | |
| Val | Phe | Tyr | Asp | Leu | Phe | Pro | Gly | Phe | Leu | Val | Lys | Met | Ser | Ser | Asp | |
| | | | | | | 115 | | 120 | | | | | | 125 | | |
| Leu | Leu | Gly | Leu | Ala | Leu | Lys | Leu | Pro | His | Val | Glu | Tyr | Ile | Glu | Glu | |
| | | | | | | 130 | | 135 | | | | | | 140 | | |
| Asp | Ser | Leu | Val | Phe | Ala | Gln | Ser | Ile | Pro | Trp | Asn | Leu | Glu | Arg | Ile | |
| | | | | | | 145 | | 150 | | | | | | 160 | | |
| Ile | Pro | Ala | Trp | Gln | Gln | Thr | Glu | Glu | Asp | Ser | Ser | Pro | Asp | Gly | Ser | |
| | | | | | | 165 | | 170 | | | | | | 175 | | |
| Ser | Gln | Val | Glu | Val | Tyr | Leu | Leu | Asp | Thr | Ser | Ile | Gln | Ser | Gly | His | |
| | | | | | | 180 | | 185 | | | | | | 190 | | |
| Arg | Glu | Ile | Glu | Gly | Arg | Val | Thr | Ile | Thr | Asp | Phe | Asn | Ser | Val | Pro | |
| | | | | | | 195 | | 200 | | | | | | 205 | | |
| Glu | Glu | Asp | Gly | Thr | Arg | Phe | His | Arg | Gln | Ala | Ser | Lys | Cys | Asp | Ser | |
| | | | | | | 210 | | 215 | | | | | | 220 | | |
| His | Gly | Thr | His | Leu | Ala | Gly | Val | Val | Ser | Gly | Arg | Asp | Ala | Gly | Val | |
| | | | | | | 225 | | 230 | | | | | | 235 | | |
| Ala | Lys | Gly | Thr | Ser | Leu | His | Ser | Leu | Arg | Val | Leu | Asn | Cys | Gln | Gly | |
| | | | | | | 245 | | 250 | | | | | | 255 | | |
| Lys | Gly | Thr | Val | Ser | Gly | Thr | Leu | Ile | Gly | Leu | Glu | Phe | Ile | Arg | Lys | |
| | | | | | | 260 | | 265 | | | | | | 270 | | |
| Ser | Gln | Leu | Ile | Gln | Pro | Ser | Gly | Pro | Leu | Val | Val | Leu | Leu | Pro | Leu | |
| | | | | | | 275 | | 280 | | | | | | 285 | | |
| Ala | Gly | Gly | Tyr | Ser | Arg | Ile | Leu | Asn | Thr | Ala | Cys | Gln | Arg | Leu | Ala | |
| | | | | | | 290 | | 295 | | | | | | 300 | | |
| Arg | Thr | Gly | Val | Val | Leu | Val | Ala | Ala | Ala | Gly | Asn | Phe | Arg | Asp | Asp | |
| | | | | | | 305 | | 310 | | | | | | 315 | | |

SEQUENCE_LI STI NG_APMOL_005VPC

| | | | | | | | | | | | | | | | |
|------|------|------|------|------|------|-----|------|------|-----|------|------|------|------|------|------|
| Ala | Cys | Leu | Tyr | Ser | Pro | Ala | Ser | Ala | Pro | Gl u | Val | Ile | Thr | Val | Gly |
| | | | | 325 | | | | | 330 | | | | | 335 | |
| Ala | Thr | Asn | Ala | Gln | Asp | Gln | Pro | Val | Thr | Leu | Gly | Thr | Leu | Gly | Thr |
| | | | | 340 | | | | 345 | | | | | 350 | | |
| Asn | Phe | Gly | Arg | Cys | Val | Asp | Leu | Phe | Ala | Pro | Gly | Lys | Asp | Ile | Ile |
| | | | | 355 | | | 360 | | | | 365 | | | | |
| Gly | Ala | Ser | Ser | Asp | Cys | Ser | Thr | Cys | Tyr | Met | Ser | Gln | Ser | Gly | Thr |
| | | | | 370 | | | 375 | | | | 380 | | | | |
| Ser | Gln | Ala | Ala | Ala | His | Val | Ala | Gly | Ile | Val | Ala | Met | Met | Leu | Asn |
| | | | | 385 | | | 390 | | | | 395 | | | | 400 |
| Arg | Asp | Pro | Ala | Leu | Thr | Leu | Ala | Gl u | Leu | Arg | Gln | Arg | Leu | Ile | Leu |
| | | | | 405 | | | | 410 | | | | | 415 | | |
| Phe | Ser | Thr | Lys | Asp | Val | Ile | Asn | Met | Ala | Trp | Phe | Pro | Gl u | Asp | Gln |
| | | | | 420 | | | | 425 | | | | | 430 | | |
| Arg | Val | Leu | Thr | Pro | Asn | Arg | Val | Ala | Thr | Leu | Pro | Pro | Ser | Thr | Gln |
| | | | | 435 | | | 440 | | | | 445 | | | | |
| Gl u | Thr | Gly | Gly | Gln | Leu | Leu | Cys | Arg | Thr | Val | Trp | Ser | Ala | His | Ser |
| | | | | 450 | | | 455 | | | | 460 | | | | |
| Gly | Pro | Thr | Arg | Thr | Ala | Thr | Ala | Arg | Cys | Ala | Pro | Gl u | Gl u | | |
| | | | | 465 | | | 470 | | | | 475 | | | | 480 |
| Gl u | Leu | Leu | Ser | Cys | Ser | Ser | Phe | Ser | Arg | Ser | Gly | Arg | Arg | Gly | |
| | | | | 485 | | | | 490 | | | | | 495 | | |
| Asp | Arg | Ile | Gl u | Ala | Ile | Gly | Gly | Gln | Gln | Val | Cys | Lys | Ala | Leu | Asn |
| | | | | 500 | | | | 505 | | | | | 510 | | |
| Ala | Phe | Gly | Gly | Gl u | Gly | Val | Tyr | Ala | Val | Ala | Arg | Cys | Cys | Leu | Leu |
| | | | | 515 | | | 520 | | | | | 525 | | | |
| Pro | Arg | Val | Asn | Cys | Ser | Ile | His | Asn | Thr | Pro | Ala | Ala | Arg | Ala | Gly |
| | | | | 530 | | | 535 | | | | 540 | | | | |
| Pro | Gln | Thr | Pro | Val | His | Cys | His | Gln | Lys | Asp | His | Val | Leu | Thr | Gly |
| | | | | 545 | | | 550 | | | | 555 | | | | 560 |
| Cys | Ser | Phe | His | Trp | Gl u | Val | Gl u | Asn | Leu | Arg | Ala | Gln | Gln | Pro | |
| | | | | 565 | | | | 570 | | | | | 575 | | |
| Leu | Leu | Arg | Ser | Arg | His | Gln | Pro | Gly | Gln | Oys | Val | Gly | His | Gln | Gl u |
| | | | | 580 | | | | 585 | | | | | 590 | | |
| Ala | Ser | Val | His | Ala | Ser | Cys | Cys | His | Ala | Pro | Gl u | Leu | Gl u | Cys | Lys |
| | | | | 595 | | | | 600 | | | | | 605 | | |
| Ile | Lys | Gl u | His | Gly | Ile | Ala | Gly | Pro | Ala | Gl u | Gln | Val | Thr | Val | Ala |
| | | | | 610 | | | | 615 | | | | | 620 | | |
| Cys | Gl u | Ala | Gly | Trp | Thr | Leu | Thr | Gly | Cys | Asn | Val | Leu | Pro | Gl y | Ala |
| | | | | 625 | | | 630 | | | | 635 | | | | 640 |
| Ser | Leu | Pro | Leu | Gl y | Ala | Tyr | Ser | Val | Asp | Asn | Val | Cys | Val | Ala | Arg |
| | | | | 645 | | | | 650 | | | | | 655 | | |
| Ile | Arg | Asp | Ala | Gl y | Arg | Ala | Asp | Arg | Thr | Ser | Gl u | Gl u | Ala | Thr | Val |
| | | | | 660 | | | | 665 | | | | | 670 | | |
| Ala | Ala | Ala | Ile | Cys | Cys | Arg | Ser | Arg | Pro | Ser | Ala | Lys | Ala | Ser | Trp |
| | | | | 675 | | | | 680 | | | | | 685 | | |
| Val | His | Gln | His | His | His | His | His | His | His | | | | | | |
| | | | | 690 | | | 695 | | | | | | | | |

<210> 9

<211> 722

<212> PRT

<213> Artificial Sequence

<220>

<223> Consensus sequence

<220>

<221> VARI ANT

<222> 4, 14, 15, 16, 17, 18, 63, 64, 65, 180, 181, 182, 183, 583, 584, 586, 701, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714

<223> Xaa = Any Amino Acid or No Amino Acid

<400> 9

| | | | | | | | | | | | | | | | |
|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gl y | Thr | Xaa | Cys | Ser | Ala | Arg | Ser | Trp | Trp | Pro | Leu | Xaa | Xaa | Xaa |
| 1 | | | | 5 | | | | | 10 | | | | 15 | | |

SEQUENCE_LI STI NG_APMOL_005VPC

Xaa Xaa Pro Leu Leu Leu Leu Leu Leu Leu Pro Ala Gly Ala Ala
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 Ala Ala Gln Asp Glu Asp Gly Asp Tyr Glu Glu Leu Met Leu Ala Leu
 35 40 45
 Pro Ser Gln Glu Asp Gly Leu Ala Asp Glu Ala Glu His Val Xaa Xaa
 50 55 60
 Xaa Ala Thr Ala Thr Phe His Arg Cys Ser Lys Asp Ala Trp Arg Leu
 65 70 75 80
 Pro Gly Thr Tyr Val Val Val Leu Lys Glu Glu Thr Glu Arg Leu Gln
 85 90 95
 Ser Gln Gln Thr Ala His Arg Leu Gln Thr Gln Ala Ala Arg Arg Gly
 100 105 110
 Tyr Val Thr Lys Ile Leu His Val Phe His Asp Leu Leu Pro Gly Phe
 115 120 125
 Leu Val Lys Met Ser Ser Asp Leu Leu Asp Leu Ala Leu Lys Leu Pro
 130 135 140
 His Val Asp Tyr Ile Glu Gu Asp Ser Ser Val Phe Ala Gln Ser Ile
 145 150 155 160
 Pro Trp Asn Leu Glu Arg Ile Ile Pro Ala Arg His Gln Ala Asp Gln
 165 170 175
 Tyr Ser Ser Xaa Xaa Xaa Xaa Pro Asp Gly Ser Ser Gln Val Glu Val
 180 185 190
 Tyr Leu Leu Asp Thr Ser Ile Gln Ser Asp His Arg Glu Ile Glu Gly
 195 200 205
 Arg Val Thr Val Thr Asp Phe Asn Ser Val Pro Glu Glu Asp Gly Thr
 210 215 220
 Arg Phe His Arg Gln Ala Ser Lys Cys Asp Ser His Gly Thr His Leu
 225 230 235 240
 Ala Gly Val Val Ser Gly Arg Asp Ala Gly Val Ala Lys Gly Thr Ser
 245 250 255
 Leu Arg Ser Leu Arg Val Leu Asn Cys Gln Gly Lys Gly Thr Val Ser
 260 265 270
 Gly Thr Leu Ile Gly Leu Glu Phe Ile Arg Lys Ser Gln Leu Ile Gln
 275 280 285
 Pro Val Gln Pro Leu Val Val Leu Leu Pro Leu Ala Gln Gln Tyr Ser
 290 295 300
 Arg Val Leu Asn Ala Ala Cys Gln Arg Leu Ala Arg Thr Gly Val Val
 305 310 315 320
 Leu Val Ala Ala Ala Gly Asn Phe Arg Asp Asp Ala Cys Leu Tyr Ser
 325 330 335
 Pro Ala Ser Ala Pro Glu Val Ile Thr Val Gly Ala Thr Asn Ala Gln
 340 345 350
 Asp Gln Pro Val Thr Leu Gly Thr Leu Gly Thr Asn Phe Gly Arg Gln
 355 360 365
 Val Asp Leu Phe Ala Pro Gln Lys Asp Ile Ile Gly Ala Ser Ser Asp
 370 375 380
 Cys Ser Thr Cys Phe Met Ser Gln Ser Gly Thr Ser Gln Ala Ala Ala
 385 390 395 400
 His Val Ala Gly Ile Val Ala Met Met Leu Ser Ala Glu Pro Glu Leu
 405 410 415
 Thr Leu Ala Glu Leu Arg Gln Arg Leu Ile His Phe Ser Thr Lys Asp
 420 425 430
 Val Ile Asn Met Ala Trp Phe Pro Glu Asp Gln Arg Val Leu Thr Pro
 435 440 445
 Asn Leu Val Ala Thr Leu Pro Pro Ser Thr His Gly Thr Gly Gln
 450 455 460
 Leu Leu Cys Arg Thr Val Trp Ser Ala His Ser Gly Pro Thr Arg Thr
 465 470 475 480
 Ala Thr Ala Thr Ala Arg Cys Ala Pro Asp Glu Glu Leu Leu Ser Cys
 485 490 495
 Ser Ser Phe Ser Arg Ser Gly Lys Arg Arg Gly Asp Arg Ile Glu Ala
 500 505 510
 Ile Gly Gly Gln Gln Val Cys Lys Ala Leu Asn Ala Phe Gly Gly Glu
 515 520 525
 Gly Val Tyr Ala Val Ala Arg Cys Cys Leu Leu Pro Arg Ala Asn Cys
 530 535 540
 Ser Ile His Thr Thr Pro Ala Ala Arg Ala Ser Met Glu Thr Arg Val
 545 550 555 560

SEQUENCE_LI STI NG_APMOL_005VPC

| | | | | | | | | | | | | | | | |
|------|-----|------|-----|-----|------|------|------|------|-----|------|-----|------|------|-----|-----|
| His | Cys | His | Gln | Lys | Asp | His | Val | Leu | Thr | Gly | Cys | Ser | Ser | His | Trp |
| | | | | 565 | | | | 570 | | | | | | | 575 |
| Gl u | Val | Gl u | Asp | Leu | Gly | Xaa | Xaa | Lys | Xaa | Pro | Val | Leu | Arg | Ser | Arg |
| | | | | 580 | | | | 585 | | | | | | | 590 |
| Gly | Gln | Pro | Gly | Gln | Oys | Val | Gly | His | Arg | Gl u | Ala | Ser | Val | His | Ala |
| | | | | 595 | | | 600 | | | | | | | | 605 |
| Ser | Cys | Cys | His | Ala | Pro | Gly | Leu | Gl u | Cys | Lys | Ile | Lys | Gl u | His | Gly |
| | | | | 610 | | | 615 | | | | 620 | | | | |
| Ile | Pro | Gly | Pro | Ala | Gl u | Gln | Val | Thr | Val | Ala | Cys | Gl u | Ala | Gly | Trp |
| | | | | 625 | | | 630 | | | | 635 | | | | 640 |
| Thr | Leu | Thr | Gly | Cys | Ser | Val | Leu | Pro | Gly | Ala | Ser | Leu | Val | Leu | Gly |
| | | | | 645 | | | | 650 | | | | | | | 655 |
| Ala | Tyr | Ala | Val | Asp | Asn | Thr | Cys | Val | Val | Arg | Ser | Arg | Asp | Val | Ser |
| | | | | 660 | | | | 665 | | | | | | | 670 |
| Thr | Ala | Gly | Arg | Thr | Ser | Gl u | Gl u | Ala | Thr | Val | Ala | Ala | Ala | Ile | Oys |
| | | | | 675 | | | 680 | | | | | | | | 685 |
| Cys | Arg | Ser | Arg | Pro | Ser | Ala | Gln | Ala | Ser | Trp | Val | Xaa | Gln | Xaa | Xaa |
| | | | | 690 | | | 695 | | | | 700 | | | | |
| Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | His | His | His | His | His | His | |
| | | | | | | | | | 710 | | 715 | | | | 720 |
| His | His | | | | | | | | | | | | | | |

<210> 10
 <211> 293
 <212> PRT
 <213> Homo sapiens

<400> 10
 Ser Ile Pro Trp Asn Leu Gl u Arg Ile Thr Pro Pro Arg Tyr Arg Al a
 1 5 10 15
 Asp Gl u Tyr Gln Pro Pro Asp Gly Gly Ser Leu Val Gl u Val Tyr Leu
 20 25 30
 Leu Asp Thr Ser Ile Gln Ser Asp His Arg Gl u Ile Gl u Gly Arg Val
 35 40 45
 Met Val Thr Asp Phe Gl u Asn Val Pro Gl u Gl u Asp Gly Thr Arg Phe
 50 55 60
 His Arg Gln Al a Ser Lys Cys Asp Ser His Gly Thr His Leu Al a Gl y
 65 70 75 80
 Val Val Ser Gl y Arg Asp Al a Gl y Val Al a Lys Gl y Al a Ser Met Arg
 85 90 95
 Ser Leu Arg Val Leu Asn Cys Gln Gl y Lys Gl y Thr Val Ser Gl y Thr
 100 105 110
 Leu Ile Gl y Leu Gl u Phe Ile Arg Lys Ser Gln Leu Val Gl n Pro Val
 115 120 125
 Gl y Pro Leu Val Val Leu Pro Leu Al a Gl y Gl y Tyr Ser Arg Val
 130 135 140
 Leu Asn Al a Al a Cys Gln Arg Leu Al a Arg Al a Gl y Val Val Leu Val
 145 150 155 160
 Thr Al a Al a Gl y Asn Phe Arg Asp Asp Al a Cys Leu Tyr Ser Pro Al a
 165 170 175
 Ser Al a Pro Gl u Val Ile Thr Val Gl y Al a Thr Asn Al a Gln Asp Gl n
 180 185 190
 Pro Val Thr Leu Gl y Thr Leu Gl y Thr Asn Phe Gl y Arg Cys Val Asp
 195 200 205
 Leu Phe Al a Pro Gl y Gl u Asp Ile Ile Gl y Al a Ser Ser Asp Cys Ser
 210 215 220
 Thr Cys Phe Val Ser Gln Ser Gl y Thr Ser Gln Al a Al a Al a His Val
 225 230 235 240
 Al a Gl y Ile Al a Al a Met Met Leu Ser Al a Gl u Pro Gl u Leu Thr Leu
 245 250 255
 Al a Gl u Leu Arg Gln Arg Leu Ile His Phe Ser Al a Lys Asp Val Ile
 260 265 270
 Asn Gl u Al a Trp Phe Pro Gl u Asp Gln Arg Val Leu Thr Pro Asn Leu
 275 280 285
 Val Al a Al a Leu Pro
 290

SEQUENCE_LI STI NG_APMOL_005VPC

<210> 11
<211> 293
<212> PRT
<213> Artificial Sequence

<220>
<223> Consensus sequence

<220>
<221> VARI ANT
<222> 7, 10, 11, 12, 13, 14, 16, 17, 20, 23, 24, 26, 27, 37, 40,
47, 49, 51, 55, 58, 62, 63, 66, 72, 78, 82, 91, 92, 94,
95, 98, 113, 114, 121, 122, 128, 129, 132, 137, 141, 144,
150, 151, 153, 155, 157, 158, 159, 160, 161, 166, 172, 178
<223> Xaa = Any Amino Acid or No Amino Acid

<220>
<221> VARI ANT
<222> 194, 195, 198, 224, 228, 245, 247, 249, 253, 256, 257, 268,
270, 271, 283, 291
<223> Xaa = Any Amino Acid or No Amino Acid

<400> 11
Ser Ile Pro Trp Asn Leu Xaa Arg Ile Xaa Xaa Xaa Xaa Arg Xaa
1 5 10 15
Xaa Gu Tyr Xaa Pro Pro Xaa Xaa Gly Xaa Xaa Val Glu Val Tyr Leu
20 25 30
Leu Asp Thr Ser Xaa Gln Ser Xaa His Arg Glu Ile Glu Gly Xaa Val
35 40 45
Xaa Val Xaa Asp Phe Glu Xaa Val Pro Xaa Glu Asp Gly Xaa Xaa Phe
50 55 60
His Xaa Gln Ala Ser Lys Cys Xaa Ser His Gly Thr His Xaa Ala Gly
65 70 75 80
Val Xaa Ser Gly Arg Asp Ala Gly Val Ala Xaa Xaa Ala Xaa Xaa Arg
85 90 95
Ser Xaa Arg Val Leu Asn Cys Gln Gly Lys Gly Thr Val Ser Gly Thr
100 105 110
Xaa Xaa Gly Leu Glu Phe Ile Arg Xaa Xaa Gln Leu Val Gln Pro Xaa
115 120 125
Xaa Pro Leu Xaa Val Leu Leu Pro Xaa Ala Gly Gly Xaa Ser Arg Xaa
130 135 140
Leu Asn Ala Ala Cys Xaa Xaa Leu Xaa Arg Xaa Gly Xaa Xaa Xaa Xaa
145 150 155 160
Xaa Ala Ala Gly Asn Xaa Arg Asp Asp Ala Cys Xaa Tyr Ser Pro Ala
165 170 175
Ser Xaa Pro Glu Val Ile Thr Val Gly Ala Thr Asn Ala Gln Asp Gln
180 185 190
Pro Xaa Xaa Leu Gly Xaa Leu Gly Thr Asn Phe Gly Arg Cys Val Asp
195 200 205
Leu Phe Ala Pro Gly Glu Asp Ile Ile Gly Ala Ser Ser Asp Cys Xaa
210 215 220
Thr Cys Phe Xaa Ser Gln Ser Gly Thr Ser Gln Ala Ala Ala His Val
225 230 235 240
Ala Gly Ile Ala Xaa Met Xaa Leu Xaa Ala Glu Pro Xaa Leu Thr Xaa
245 250 255
Xaa Glu Leu Arg Gln Arg Leu Ile His Phe Ser Xaa Lys Xaa Xaa Ile
260 265 270
Asn Glu Ala Trp Phe Pro Glu Asp Gln Arg Xaa Leu Thr Pro Asn Leu
275 280 285
Val Ala Xaa Leu Pro
290

<210> 12
<211> 293
<212> PRT

SEQUENCE_LI STI NG_APMOL_005VPC

<213> M_nodel phi s domestic

<400> 12

Ser Ile Pro Trp Asn Leu Asp Arg Ile Val Leu Ala Pro Ser Arg Ser
 1 5 10 15
 Glu Glu Tyr Ser Pro Pro Asn Lys Gly Asp Glu Val Glu Val Tyr Leu
 20 25 30
 Leu Asp Thr Ser Leu Glu Ser Gly His Arg Glu Ile Glu Gly Lys Val
 35 40 45
 Thr Val Ala Asp Phe Glu Asp Val Pro Asp Glu Asp Gly Ala Glu Phe
 50 55 60
 His Ser Glu Ala Ser Lys Cys Glu Ser His Gly Thr His Val Ala Gly
 65 70 75 80
 Val Leu Ser Gly Arg Asp Ala Gly Val Ala Arg Ala Ala Val Arg
 85 90 95
 Ser Val Arg Val Leu Asn Cys Glu Gly Lys Gly Thr Val Ser Gly Thr
 100 105 110
 Ala Arg Gly Leu Glu Phe Ile Arg Arg Thr Glu Leu Val Glu Pro Tyr
 115 120 125
 Ser Pro Leu Ile Val Leu Leu Pro Phe Ala Gly Gly His Ser Arg Thr
 130 135 140
 Leu Asn Ala Ala Cys Arg Leu Leu Val Arg Ser Gly Ala Ala Val Ile
 145 150 155 160
 Ala Ala Ala Gly Asn Tyr Arg Asp Asp Ala Cys Ser Tyr Ser Pro Ala
 165 170 175
 Ser Glu Pro Glu Val Ile Thr Val Gly Ala Thr Asn Ala Glu Asp Glu
 180 185 190
 Pro Ala Ala Leu Gly Ala Leu Gly Thr Asn Phe Gly Arg Cys Val Asp
 195 200 205
 Leu Phe Ala Pro Gly Glu Asp Ile Ile Gly Ala Ser Ser Asp Cys Gly
 210 215 220
 Thr Cys Phe Thr Ser Glu Ser Gly Thr Ser Glu Ala Ala Ala His Val
 225 230 235 240
 Ala Gly Ile Ala Ser Met Leu Leu Asn Ala Glu Pro Ser Leu Thr Val
 245 250 255
 Pro Glu Leu Arg Glu Arg Leu Ile His Phe Ser Val Lys Asn Ala Ile
 260 265 270
 Asn Glu Ala Trp Phe Pro Glu Asp Glu Arg Leu Leu Thr Pro Asn Leu
 275 280 285
 Val Ala Arg Leu Pro
 290

<210> 13

<211> 293

<212> PRT

<213> Artificial Sequence

<220>

<223> Consensus sequence

<220>

<221> VARI ANT

<222> 2, 7, 10, 12, 13, 14, 15, 17, 18, 19, 20, 23, 24, 26, 27,
 40, 47, 49, 54, 72, 78, 83, 93, 94, 95, 112, 114, 122, 123,
 124, 125, 128, 129, 132, 134, 135, 137, 138, 144, 149, 150,
 151, 153, 154, 155, 158, 159, 160, 161, 166, 167, 178

<223> Xaa = Any Ami no Acid or No Ami no Acid

<220>

<221> VARI ANT

<222> 184, 189, 194, 196, 198, 203, 205, 207, 214, 228, 230, 247,
 249, 250, 251, 253, 255, 256, 257, 265, 268, 270, 275, 283,
 284, 288, 291

<223> Xaa = Any Ami no Acid or No Ami no Acid

<400> 13

Ser Xaa Pro Trp Asn Leu Xaa Arg Ile Xaa Pro Xaa Xaa Xaa Ala

SEQUENCE_LI STI NG_APMOL_005VPC

| | | | | | | | | | | | | | | | | | | | |
|-----|------|-----|------|------|-----|-----|------|-----|-----|------|------|-----|------|-----|------|-----|-----|-----|-----|
| 1 | Xaa | Xaa | Xaa | Xaa | 5 | Pro | Pro | Xaa | Xaa | Gly | 10 | Xaa | Xaa | Val | Gl u | Val | 15 | Tyr | Leu |
| | | | | | 20 | | | | | 25 | | | | | | 30 | | | |
| Leu | Asp | Thr | Ser | Ile | 35 | Gln | Ser | Xaa | His | Arg | Gl u | Ile | Gl u | Gly | Xaa | Val | | | |
| | | | | | 40 | | | | | 45 | | | | | | 45 | | | |
| Xaa | Val | Thr | Asp | Phe | 50 | Xaa | Asn | Val | Pro | Gl u | Gl u | Asp | Gly | Thr | Arg | Phe | | | |
| | | | | | 55 | | | | | 60 | | | | | | 60 | | | |
| His | Arg | Gln | Ala | Ser | 65 | Lys | Cys | Xaa | Ser | His | Gly | Thr | His | Xaa | Ala | Gly | | | |
| | | | | | 70 | | | | | 75 | | | | | | 80 | | | |
| Val | Val | Xaa | Gly | Arg | 85 | Asp | Ala | Gly | Val | Ala | Lys | Gly | Xaa | Xaa | Xaa | Arg | | | |
| | | | | | 90 | | | | | 95 | | | | | | 95 | | | |
| Ser | Leu | Arg | Val | Leu | 100 | Asn | Cys | Gln | Gly | Lys | Gly | Thr | Val | Ser | Gly | Xaa | | | |
| | | | | | 105 | | | | | 110 | | | | | | 110 | | | |
| Leu | Xaa | Gly | Leu | Gl u | 115 | Phe | Ile | Arg | Lys | Xaa | Xaa | Xaa | Xaa | Gln | Pro | Xaa | | | |
| | | | | | 120 | | | | | 125 | | | | | | 125 | | | |
| Xaa | Pro | Leu | Xaa | Val | 130 | Xaa | Xaa | Pro | Xaa | Xaa | Gly | Gly | Tyr | Ser | Arg | Xaa | | | |
| | | | | | 135 | | | | | 140 | | | | | | 140 | | | |
| Leu | Asn | Ala | Ala | Xaa | 145 | Xaa | Xaa | Leu | Xaa | Xaa | Xaa | Gly | Val | Xaa | Xaa | Xaa | | | |
| | | | | | 150 | | | | | 155 | | | | | | 160 | | | |
| Xaa | Ala | Ala | Gly | Asn | 165 | Xaa | Xaa | Asp | Asp | Ala | Cys | Leu | Tyr | Ser | Pro | Ala | | | |
| | | | | | 170 | | | | | 175 | | | | | | 175 | | | |
| Ser | Xaa | Pro | Gl u | Val | 180 | Ile | Thr | Xaa | Gly | Ala | Thr | Asn | Xaa | Gln | Asp | Gln | | | |
| | | | | | 185 | | | | | 190 | | | | | | 190 | | | |
| Pro | Xaa | Thr | Xaa | Gly | 195 | Xaa | Leu | Gly | Thr | Asn | Xaa | Gly | Xaa | Cys | Xaa | Asp | | | |
| | | | | | 200 | | | | | 205 | | | | | | 205 | | | |
| Leu | Phe | Ala | Pro | Gly | 210 | Xaa | Asp | Ile | Ile | Gly | Ala | Ser | Ser | Asp | Cys | Ser | | | |
| | | | | | 215 | | | | | 220 | | | | | | 220 | | | |
| Thr | Cys | Phe | Xaa | Ser | 225 | Xaa | Ser | Gly | Thr | Ser | Gln | Ala | Ala | Ala | Ala | His | Val | | |
| | | | | | 230 | | | | | 235 | | | | | | 240 | | | |
| Ala | Gly | Ile | Ala | Ala | 245 | Ala | Met | Xaa | Leu | Xaa | Xaa | Xaa | Pro | Xaa | Leu | Xaa | Xaa | | |
| | | | | | 250 | | | | | 255 | | | | | | 255 | | | |
| Xaa | Gl u | Leu | Arg | Gln | 260 | Arg | Leu | Ile | Xaa | Phe | Ser | Xaa | Lys | Xaa | Val | Ile | | | |
| | | | | | 265 | | | | | 270 | | | | | | 270 | | | |
| Asn | Gl u | Xaa | Trp | Phe | 275 | Pro | Gl u | Asp | Gln | Arg | Xaa | Xaa | Thr | Pro | Asn | Xaa | | | |
| | | | | | 280 | | | | | 285 | | | | | | 285 | | | |
| Val | Ala | Xaa | Leu | Pro | 290 | | | | | | | | | | | | | | |

<210> 14

<211> 293

<212> PRT

<213> Xenopus laevis

<400> 14

| | | | | | | | | | | | | | | | | | | |
|-----|------|-----|------|------|-----|-----|-----|------|-----|------|------|------|------|-----|-----|-----|--|--|
| 1 | Ser | Val | Pro | Trp | Asn | Leu | Asp | Arg | Ile | Val | Pro | Ala | Gln | Gln | Met | Ala | | |
| | | | | | 5 | | | | | 10 | | | | | 15 | | | |
| Ser | Gln | Phe | Ser | Pro | Pro | Asn | Thr | Gly | Asp | Ser | Val | Gl u | Val | Tyr | Leu | | | |
| | | | | | 20 | | | | | 25 | | | | | 30 | | | |
| Leu | Asp | Thr | Ser | Ile | 35 | Gln | Ser | Asn | His | Arg | Gl u | Ile | Gl u | Gly | Lys | Val | | |
| | | | | | 40 | | | | | 45 | | | | | 45 | | | |
| Phe | Val | Thr | Asp | Phe | 50 | Gln | Asn | Val | Pro | Gl u | Gl u | Asp | Gly | Thr | Arg | Phe | | |
| | | | | | 55 | | | | | 60 | | | | | 60 | | | |
| His | Arg | Gln | Ala | Ser | 65 | Lys | Cys | Gl u | Ser | His | Gly | Thr | His | Met | Ala | Gly | | |
| | | | | | 70 | | | | | 75 | | | | | 80 | | | |
| Val | Val | Asn | Gly | Arg | 85 | Asp | Ala | Gly | Val | Ala | Lys | Gly | Val | Asn | Val | Arg | | |
| | | | | | 90 | | | | | 95 | | | | | | 95 | | |
| Ser | Leu | Arg | Val | Leu | 100 | Asn | Cys | Gln | Gly | Lys | Gly | Thr | Val | Ser | Gly | Ser | | |
| | | | | | 105 | | | | | 110 | | | | | | 110 | | |
| Leu | Thr | Gly | Leu | Gl u | 115 | Phe | Ile | Arg | Lys | Thr | Leu | Ile | Gl u | Gln | Pro | Tyr | | |
| | | | | | 120 | | | | | 125 | | | | | | 125 | | |
| Asn | Pro | Leu | Ile | Val | 130 | Ile | Ile | Pro | Phe | Val | Gly | Gly | Tyr | Ser | Arg | Ile | | |
| | | | | | 135 | | | | | 140 | | | | | | 140 | | |
| Leu | Asn | Ala | Ala | Ser | 145 | Arg | Ala | Leu | Val | Asn | Thr | Gly | Val | Ile | Ile | Ile | | |
| | | | | | 150 | | | | | 155 | | | | | | 160 | | |
| Ala | Ala | Ala | Gly | Asn | 165 | Tyr | Lys | Asp | Asp | Ala | Cys | Leu | Tyr | Ser | Pro | Ala | | |
| | | | | | 170 | | | | | 175 | | | | | | 175 | | |
| Ser | Gl u | Pro | Gl u | Val | 175 | Ile | Thr | Ile | Gly | Ala | Thr | Asn | Tyr | Gln | Asp | Gln | | |

SEQUENCE_LI STI NG_APMOL_005VPC

| | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Ala | Thr | 180 | Met | Gly | Val | Leu | Gly | Thr | Asn | Tyr | Gly | Asn | Cys | Ile | Asp |
| 195 | | | | | 200 | | | | | | | 205 | | | | |
| Leu | Phe | Ala | Pro | Gly | Asp | Asp | Ile | Ile | Gly | Ala | Ser | Ser | Asp | Cys | Ser | |
| 210 | | | | | 215 | | | | | | 220 | | | | | |
| Thr | Cys | Phe | Thr | Ser | Lys | Ser | Gly | Thr | Ser | Gln | Ala | Ala | Ala | Ala | His | Val |
| 225 | | | | | 230 | | | | | 235 | | | | | 240 | |
| Ala | Gly | Ile | Ala | Ala | Met | Ile | Leu | Asn | Asp | Lys | Pro | Asp | Leu | Ser | Val | |
| | | | | | 245 | | | | 250 | | | | | 255 | | |
| Ser | Glu | Leu | Arg | Gln | Arg | Leu | Ile | Gln | Phe | Ser | Thr | Lys | Lys | Val | Ile | |
| | | | | | 260 | | | | 265 | | | 270 | | | | |
| Asn | Glu | Val | Trp | Phe | Pro | Glu | Asp | Gln | Arg | Leu | Ile | Thr | Pro | Asn | Arg | |
| | | | | | 275 | | | | 280 | | | 285 | | | | |
| Val | Ala | Gly | Leu | Pro | | | | | | | | | | | | |
| | | | | | 290 | | | | | | | | | | | |

<210> 15

<211> 323

<212> PRT

<213> Artificial Sequence

<220>

<223> Consensus sequence

<220>

<221> VARI ANT

<222> 3, 6, 12, 18, 21, 26, 30, 35, 38, 41, 44, 50, 61, 62, 66, 68, 78, 80, 83, 92, 100, 104, 110, 131, 135, 145, 152, 173, 176, 177, 180, 184, 185, 188, 189, 191, 192, 193, 194, 195, 198

<223> Xaa = Any Amino Acid or No Amino Acid

<400> 15

| | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Pro | Trp | Xaa | Leu | Xaa | Arg | Xaa | Xaa | Xaa | Pro | Arg | Xaa | Arg | Xaa | Xaa | Xaa | Xaa | |
| 1 | | | | 5 | | | | 10 | | | | | | 15 | | | |
| Xaa | Xaa | Xaa | Pro | Xaa | Xaa | Gly | Xaa | Xaa | Val | Glu | Val | Tyr | Leu | Xaa | Asp | | |
| | | | | | | 20 | | | 25 | | | | | 30 | | | |
| Xaa | Ser | Xaa | Xaa | Ser | Xaa | His | Arg | Glu | Xaa | Xaa | Gly | Arg | Val | Xaa | Val | | |
| | | | | | | 35 | | | 40 | | | 45 | | | | | |
| Thr | Asp | Phe | Xaa | Xaa | Val | Pro | Xaa | His | Arg | | |
| | | | | | 50 | | | 55 | | | 60 | | | | | | |
| Xaa | Ala | Ser | Xaa | Cys | Xaa | Xaa | His | Gly | Thr | His | Xaa | Ala | Xaa | Val | Val | | |
| | | | | | 65 | | | 70 | | | 75 | | | 80 | | | |
| Xaa | Gly | Xaa | Asp | Xaa | Gly | Val | Ala | Xaa | Gly | Ala | Xaa | Xaa | Xaa | Xaa | Xaa | | |
| | | | | | 85 | | | 90 | | | 95 | | | | | | |
| Arg | Val | Leu | Xaa | Cys | Xaa | Gly | Lys | Gly | Thr | Val | Ser | Gly | Xaa | Leu | Xaa | | |
| | | | | | 100 | | | 105 | | | 110 | | | | | | |
| Gly | Xaa | Glu | Xaa | Ile | Arg | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Pro | Xaa | Gly | Xaa | | |
| | | | | | 115 | | | 120 | | | 125 | | | | | | |
| Xaa | Val | Val | Leu | Leu | Pro | Xaa | Xaa | Gly | Xaa | Xaa | Ser | Arg | Xaa | Leu | Asn | | |
| | | | | | 130 | | | 135 | | | 140 | | | | | | |
| Ala | Ala | Cys | Xaa | Xaa | Leu | Xaa | Xaa | Xaa | Gly | Xaa | Val | Xaa | Val | Xaa | Ala | | |
| | | | | | 145 | | | 150 | | | 155 | | | | 160 | | |
| Ala | Gly | Asn | Xaa | Arg | Asp | Asp | Ala | Cys | Leu | Tyr | Ser | Pro | Ala | Ser | Xaa | | |
| | | | | | 165 | | | 170 | | | 175 | | | | | | |
| Pro | Glu | Xaa | | |
| | | | | | 180 | | | 185 | | | 190 | | | | | | |
| Xaa | | |
| | | | | | 195 | | | 200 | | | 205 | | | | | | |
| Xaa | Val | Ile | Thr | Val | Gly | Ala | Xaa | Asn | Xaa | Xaa | Asp | Gln | Xaa | Val | Xaa | | |
| | | | | | 210 | | | 215 | | | 220 | | | | | | |
| Xaa | Gly | Xaa | Xaa | Gly | Thr | Asn | Xaa | Gly | Arg | Cys | Val | Asp | Xaa | Phe | Ala | | |
| | | | | | 225 | | | 230 | | | 235 | | | 240 | | | |
| Pro | Gly | Xaa | Asp | Ile | Xaa | Xaa | Ala | Ser | Ser | Asp | Cys | Xaa | Thr | Cys | Phe | | |
| | | | | | 245 | | | 250 | | | 255 | | | | | | |
| Xaa | Ser | Xaa | Ser | Gly | Thr | Ser | Gln | Ala | Ala | Ala | Ala | His | Xaa | Ala | Gly | Xaa | |
| | | | | | 260 | | | 265 | | | 270 | | | | | | |

SEQUENCE_LI STI NG_APMOL_005VPC

| | | | | | | | | | | | | | | | |
|------|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|
| Al a | Al a | Xaa | Xaa | Leu | Ser | Xaa | Xaa | Pro | Xaa | Leu | Thr | Xaa | Xaa | Xaa | Xaa |
| | | 275 | | | | 280 | | | | | | 285 | | | |
| Xaa | G n | Xaa | Xaa | Leu | Xaa | Xaa | Xaa | Ser | Xaa |
| | 290 | | | | 295 | | | | | | | 300 | | | |
| Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | Thr | Pro | Xaa | Leu | Val | Al a |
| | 305 | | | | 310 | | | | | | 315 | | | | 320 |
| Leu | Pro | Pro | | | | | | | | | | | | | |

<210> 16
<211> 312
<212> PRT
<213> Tetraodon ni grovi ridis

<400> 16

| | | | | | | | | | | | | | | | |
|------|------|------|------|------|------|------|------|------|------|------|-------|------|-------|------|------|
| Pro | Trp | Ser | Leu | Arg | Arg | Leu | Pro | Arg | Pro | Arg | G y | Arg | Pro | G y | Asp |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| G y | Al a | Al a | Val | G u | Val | Tyr | Leu | Met | Asp | G y | Ser | Val | Leu | Ser | Ser |
| | | | | 20 | | | | 25 | | | | | 30 | | |
| His | Arg | G lu | Leu | G y | G y | Arg | Val | Leu | Val | Thr | Asp | Phe | Hi s | Ser | Val |
| | | | | 35 | | | 40 | | | | | 45 | | | |
| Pro | Val | G y | G lu | Al a | G y | G y | His | Arg | G lu | Al a | Ser | Arg | Cys | Lys | G y |
| | | | | 50 | | | 55 | | | | | 60 | | | |
| His | G y | Thr | Hi s | Val | Al a | Al a | Val | Val | Met | G y | Ser | Asp | Thr | G y | Val |
| | 65 | | | 70 | | | | | | 75 | | | | 80 | |
| Al a | Pro | G y | Al a | Arg | Val | Asn | Leu | Val | Arg | Val | Leu | Asp | Cys | Arg | G y |
| | | | | 85 | | | | 90 | | | | | 95 | | |
| Lys | G y | Thr | Val | Ser | G y | Al a | Leu | Al a | G y | Val | G u | Tyr | I I e | Arg | Al a |
| | | | | 100 | | | | 105 | | | | | 110 | | |
| Al a | Leu | Arg | Al a | Hi s | Pro | Pro | G y | Al a | Al a | Val | Val | Leu | Leu | Pro | Phe |
| | | | | 115 | | | 120 | | | | | 125 | | | |
| Thr | G y | Al a | Phe | Ser | Arg | Ser | Leu | Asn | Al a | Al a | Cys | Arg | Asp | Leu | Val |
| | 130 | | | | 135 | | | | | | 140 | | | | |
| Asn | Thr | G y | Al a | Val | Val | Val | Al a | Al a | Al a | G y | Asn | Tyr | Arg | Asp | Asp |
| | 145 | | | | 150 | | | | | | 155 | | | | 160 |
| Al a | Cys | Leu | Tyr | Ser | Pro | Al a | Ser | G u | Pro | G u | Val | Cys | Thr | G y | G y |
| | | | | 165 | | | | 170 | | | | | 175 | | |
| Ser | Al a | Arg | Ser | Hi s | Thr | Hi s | Thr | Hi s | Leu |
| | | | | 180 | | | 185 | | | | | 190 | | | |
| Leu | G n | Al a | Val | Leu | Cys | Val | Cys | Val | G n | Val | I I e | Thr | Val | G y | Al a |
| | | | | 195 | | | 200 | | | | | 205 | | | |
| Val | Asn | Ser | Al a | Asp | G n | Leu | Val | Ser | G n | G y | Pro | G y | G y | Thr | Asn |
| | 210 | | | | 215 | | | | | | 220 | | | | |
| Val | G y | Arg | Cys | Val | Asp | Val | Phe | Al a | Pro | G y | G y | Asp | I I e | Val | Ser |
| | 225 | | | | 230 | | | | | | 235 | | | | 240 |
| Al a | Ser | Ser | Asp | Cys | Asp | Thr | Cys | Phe | Al a | Ser | G y | Ser | G y | Thr | Ser |
| | | | | 245 | | | | 250 | | | | | 255 | | |
| G n | Al a | Al a | Al a | Hi s | Al a | Al a | G y | Met | Al a | Al a | Val | Leu | Leu | Ser | Ser |
| | | | | 260 | | | | 265 | | | | | 270 | | |
| Ser | Pro | Ser | Leu | Thr | Pro | Val | G n | Val | Leu | G n | Thr | Leu | Leu | Arg | Tyr |
| | | | | 275 | | | | 280 | | | | | 285 | | |
| Ser | Val | Ser | Leu | Pro | Ser | Val | Ser | G y | Arg | Arg | G y | Leu | Val | Thr | Pro |
| | | | | | 295 | | | | | | 300 | | | | |
| Ser | Leu | Val | Al a | Al a | Leu | Pro | Pro | | | | | | | | |
| | | | | | 310 | | | | | | | | | | |

<210> 17
<211> 292
<212> PRT
<213> Homo sapiens

<400> 17

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-------|-----|-----|-----|-----|-----|-----|------|-----|-----|
| Pro | Trp | Asn | Leu | G u | Arg | I I e | Thr | Pro | Pro | Arg | Tyr | Arg | Al a | Asp | G u |
| 1 | | | | 5 | | | | 10 | | | | | 15 | | |
| Tyr | G n | Pro | Pro | Asp | G y | G y | Ser | Leu | Val | G u | Val | Tyr | Leu | Leu | Asp |
| | | | | 20 | | | | 25 | | | | | 30 | | |

SEQUENCE_LI STI NG_APMOL_005VPC

| | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Ser | Ile | Gln | Ser | Asp | His | Arg | Glu | Ile | Glu | Gly | Arg | Val | Met | Val | |
| 35 | | | | | | 40 | | | | | | 45 | | | | |
| Thr | Asp | Phe | Glu | Asn | Val | Pro | Glu | Glu | Asp | Gly | Thr | Arg | Phe | His | Arg | |
| 50 | | | | | | 55 | | | | | 60 | | | | | |
| Gln | Ala | Ser | Lys | Cys | Asp | Ser | His | Gly | Thr | His | Leu | Ala | Gly | Val | Val | |
| 65 | | | | | | 70 | | | | 75 | | | | 80 | | |
| Ser | Gly | Arg | Asp | Ala | Gly | Val | Ala | Lys | Gly | Ala | Ser | Met | Arg | Ser | Leu | |
| | | | | | | 85 | | | 90 | | | 95 | | | | |
| Arg | Val | Leu | Asn | Cys | Gln | Gly | Lys | Gly | Thr | Val | Ser | Gly | Thr | Leu | Ile | |
| | | | | | | 100 | | | 105 | | | 110 | | | | |
| Gly | Leu | Glu | Phe | Ile | Arg | Lys | Ser | Gln | Leu | Val | Gln | Pro | Val | Gly | Pro | |
| | | | | | | 115 | | | 120 | | | 125 | | | | |
| Leu | Val | Val | Leu | Leu | Pro | Leu | Ala | Gly | Gly | Tyr | Ser | Arg | Val | Leu | Asn | |
| | | | | | | 130 | | | 135 | | | 140 | | | | |
| Ala | Ala | Cys | Gln | Arg | Leu | Ala | Arg | Ala | Gly | Val | Val | Leu | Val | Thr | Ala | |
| | | | | | | 145 | | | 150 | | | 155 | | | 160 | |
| Ala | Gly | Asn | Phe | Arg | Asp | Asp | Ala | Cys | Leu | Tyr | Ser | Pro | Ala | Ser | Ala | |
| | | | | | | 165 | | | 170 | | | 175 | | | | |
| Pro | Glu | Val | Ile | Thr | Val | Gly | Ala | Thr | Asn | Ala | Gln | Asp | Gln | Pro | Val | |
| | | | | | | 180 | | | 185 | | | 190 | | | | |
| Thr | Leu | Gly | Thr | Leu | Gly | Thr | Asn | Phe | Gly | Arg | Cys | Val | Asp | Leu | Phe | |
| | | | | | | 195 | | | 200 | | | 205 | | | | |
| Ala | Pro | Gly | Glu | Asp | Ile | Ile | Gly | Ala | Ser | Ser | Asp | Cys | Ser | Thr | Cys | |
| | | | | | | 210 | | | 215 | | | 220 | | | | |
| Phe | Val | Ser | Gln | Ser | Gly | Thr | Ser | Gln | Ala | Ala | Ala | Ala | His | Val | Ala | Gly |
| | | | | | | 225 | | | 230 | | | 235 | | | 240 | |
| Ile | Ala | Ala | Ala | Met | Met | Leu | Ser | Ala | Glu | Pro | Glu | Leu | Thr | Leu | Ala | Glu |
| | | | | | | 245 | | | 250 | | | 255 | | | | |
| Leu | Arg | Gln | Arg | Leu | Ile | His | Phe | Ser | Ala | Lys | Asp | Val | Ile | Asn | Glu | |
| | | | | | | 260 | | | 265 | | | 270 | | | | |
| Ala | Trp | Phe | Pro | Glu | Asp | Gln | Arg | Val | Leu | Thr | Pro | Asn | Leu | Val | Ala | |
| | | | | | | 275 | | | 280 | | | 285 | | | | |
| Ala | Leu | Pro | Pro | | | | | | | | | | | | | |
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<210> 18

<211> 860

<212> PRT

<213> Homo sapiens

<400> 18

| | | | | | | | | | | | | | | | |
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| Met | Gly | Pro | Trp | Gly | Trp | Lys | Leu | Arg | Trp | Thr | Val | Ala | Leu | Leu | Leu |
| 1 | | | | 5 | | | | | 10 | | | | 15 | | |
| Ala | Ala | Ala | Gly | Thr | Ala | Val | Gly | Asp | Arg | Cys | Glu | Arg | Asn | Glu | Phe |
| | | | | | | 20 | | | 25 | | | 30 | | | |
| Gln | Cys | Gln | Asp | Gly | Lys | Cys | Ile | Ser | Tyr | Lys | Trp | Val | Cys | Asp | Gly |
| | | | | | | 35 | | | 40 | | | 45 | | | |
| Ser | Ala | Glu | Cys | Gln | Asp | Gly | Ser | Asp | Glu | Ser | Gln | Glu | Thr | Cys | Leu |
| | | | | | | 50 | | | 55 | | | 60 | | | |
| Ser | Val | Thr | Cys | Lys | Ser | Gly | Asp | Phe | Ser | Cys | Gly | Gly | Arg | Val | Asn |
| | | | | | | 65 | | | 70 | | | 75 | | | 80 |
| Arg | Cys | Ile | Pro | Gln | Phe | Trp | Arg | Cys | Asp | Gly | Gln | Val | Asp | Cys | Asp |
| | | | | | | 85 | | | 90 | | | 95 | | | |
| Asn | Gly | Ser | Asp | Glu | Gln | Gly | Cys | Pro | Pro | Lys | Thr | Cys | Ser | Gln | Asp |
| | | | | | | 100 | | | 105 | | | 110 | | | |
| Glu | Phe | Arg | Cys | His | Asp | Gly | Lys | Cys | Ile | Ser | Arg | Gln | Phe | Val | Cys |
| | | | | | | 115 | | | 120 | | | 125 | | | |
| Asp | Ser | Asp | Arg | Asp | Cys | Leu | Asp | Gly | Ser | Asp | Glu | Ala | Ser | Cys | Pro |
| | | | | | | 130 | | | 135 | | | 140 | | | |
| Val | Leu | Thr | Cys | Gly | Pro | Ala | Ser | Phe | Gln | Cys | Asn | Ser | Ser | Thr | Cys |
| | | | | | | 145 | | | 150 | | | 155 | | | 160 |
| Ile | Pro | Gln | Leu | Trp | Ala | Cys | Asp | Asn | Asp | Pro | Asp | Cys | Glu | Asp | Gly |
| | | | | | | 165 | | | 170 | | | 175 | | | |
| Ser | Asp | Glu | Trp | Pro | Gln | Arg | Cys | Arg | Gly | Leu | Tyr | Val | Phe | Gln | Gly |
| | | | | | | 180 | | | 185 | | | 190 | | | |
| Asp | Ser | Ser | Pro | Cys | Ser | Ala | Phe | Glu | Phe | His | Cys | Leu | Ser | Gly | Glu |
| | | | | | | 195 | | | 200 | | | 205 | | | |

SEQUENCE_LI STI NG_APMOL_005VPC

Cys Ile His Ser Ser Trp Arg Cys Asp Gly Gly Pro Asp Cys Lys Asp
 210 215 220
 Lys Ser Asp Glu Glu Asn Cys Ala Val Ala Thr Cys Arg Pro Asp Glu
 225 230 235 240
 Phe Gln Cys Ser Asp Gly Asn Cys Ile His Gly Ser Arg Gln Cys Asp
 245 250 255
 Arg Glu Tyr Asp Cys Lys Asp Met Ser Asp Glu Val Gly Cys Val Asn
 260 265 270
 Val Thr Leu Cys Glu Gly Pro Asn Lys Phe Lys Cys His Ser Gly Glu
 275 280 285
 Cys Ile Thr Leu Asp Lys Val Cys Asn Met Ala Arg Asp Cys Arg Asp
 290 295 300
 Trp Ser Asp Glu Pro Ile Lys Glu Cys Gly Thr Asn Glu Cys Leu Asp
 305 310 315 320
 Asn Asn Gly Gly Cys Ser His Val Cys Asn Asp Leu Lys Ile Gly Tyr
 325 330 335
 Glu Oys Leu Cys Pro Asp Gly Phe Gln Leu Val Ala Gln Arg Arg Cys
 340 345 350
 Glu Asp Ile Asp Glu Cys Gln Asp Pro Asp Thr Cys Ser Gln Leu Cys
 355 360 365
 Val Asn Leu Glu Gly Gly Tyr Lys Cys Gln Cys Glu Glu Gly Phe Gln
 370 375 380
 Leu Asp Pro His Thr Lys Ala Cys Lys Ala Val Gly Ser Ile Ala Tyr
 385 390 395 400
 Leu Phe Phe Thr Asn Arg His Glu Val Arg Lys Met Thr Leu Asp Arg
 405 410 415
 Ser Gln Tyr Thr Ser Leu Ile Pro Asn Leu Arg Asn Val Val Ala Leu
 420 425 430 430
 Asp Thr Glu Val Ala Ser Asn Arg Ile Tyr Trp Ser Asp Leu Ser Gln
 435 440 445
 Arg Met Ile Cys Ser Thr Gln Leu Asp Arg Ala His Gly Val Ser Ser
 450 455 460
 Tyr Asp Thr Val Ile Ser Arg Asp Ile Gln Ala Pro Asp Gly Leu Ala
 465 470 475 480
 Val Asp Trp Ile His Ser Asn Ile Tyr Trp Thr Asp Ser Val Leu Gly
 485 490 495
 Thr Val Ser Val Ala Asp Thr Lys Gly Val Lys Arg Lys Thr Leu Phe
 500 505 510
 Arg Glu Asn Gly Ser Lys Pro Arg Ala Ile Val Val Asp Pro Val His
 515 520 525
 Gly Phe Met Tyr Trp Thr Asp Trp Gly Thr Pro Ala Lys Ile Lys Lys
 530 535 540
 Gly Gly Leu Asn Gln Val Asp Ile Tyr Ser Leu Val Thr Gln Asn Ile
 545 550 555 560
 Gln Trp Pro Asn Gln Ile Thr Leu Asp Leu Leu Ser Gly Arg Leu Tyr
 565 570 575
 Trp Val Asp Ser Lys Leu His Ser Ile Ser Ser Ile Asp Val Asn Gly
 580 585 590
 Gly Asn Arg Lys Thr Ile Leu Glu Asp Glu Lys Arg Leu Ala His Pro
 595 600 605
 Phe Ser Leu Ala Val Phe Glu Asp Lys Val Phe Trp Thr Asp Ile Ile
 610 615 620
 Asn Glu Ala Ile Phe Ser Ala Asn Arg Leu Thr Gly Ser Asp Val Asn
 625 630 635 640
 Leu Leu Ala Glu Asn Leu Leu Ser Pro Glu Asp Met Val Leu Phe His
 645 650 655
 Asn Leu Thr Gln Pro Arg Gly Val Asn Trp Cys Glu Arg Thr Thr Leu
 660 665 670
 Ser Asn Gly Cys Gln Tyr Leu Cys Leu Pro Ala Pro Gln Ile Asn
 675 680 685
 Pro His Ser Pro Lys Phe Thr Cys Ala Cys Pro Asp Gly Met Leu Leu
 690 695 700
 Ala Arg Asp Met Arg Ser Cys Leu Thr Glu Ala Glu Ala Ala Val Ala
 705 710 715 720
 Thr Gln Glu Thr Ser Thr Val Arg Leu Lys Val Ser Ser Thr Ala Val
 725 730 735
 Arg Thr Gln His Thr Thr Arg Pro Val Pro Asp Thr Ser Arg Leu
 740 745 750

| SEQUENCE_LI STI NG_APMOL_005VPC | | | | | | | | | | | | | | | | | | |
|---------------------------------|-----|------|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|--|--|--|
| Pro | Gly | Ala | Thr | Pro | Gly | Leu | Thr | Thr | Val | Glu | Ile | Val | Thr | Met | Ser | | | |
| | | 755 | | | | | 760 | | | | | 765 | | | | | | |
| His | Gln | Ala | Leu | Gly | Asp | Val | Ala | Gly | Arg | Gly | Asn | Glu | Lys | Lys | Pro | | | |
| | | 770 | | | | 775 | | | | | 780 | | | | | | | |
| Ser | Ser | Val | Arg | Ala | Leu | Ser | Ile | Val | Leu | Pro | Ile | Val | Leu | Leu | Val | | | |
| | | 785 | | | 790 | | | | | 795 | | | | | 800 | | | |
| Phe | Leu | Cys | Leu | Gly | Val | Phe | Leu | Leu | Trp | Lys | Asn | Trp | Arg | Leu | Lys | | | |
| | | | | 805 | | | | | 810 | | | | | 815 | | | | |
| Asn | Ile | Asn | Ser | Ile | Asn | Phe | Asp | Asn | Pro | Val | Tyr | Gln | Lys | Thr | Thr | | | |
| | | | 820 | | | | | 825 | | | | | 830 | | | | | |
| Gl u | Asp | Gl u | Val | His | Ile | Cys | His | Asn | Gln | Asp | Gly | Tyr | Ser | Tyr | Pro | | | |
| | | 835 | | | | 840 | | | | | 845 | | | | | | | |
| Ser | Arg | Gln | Met | Val | Ser | Leu | Gl u | Asp | Asp | Val | Ala | | | | | | | |
| | | 850 | | | 855 | | | | | | 860 | | | | | | | |

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<212> PRT
<213> *Macaca fascicularis*

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 Glu Cys Glu Asp Gly Lys Cys Ile Ser Tyr Lys Trp Val Cys Asp Gly
 40 45 50
 Thr Ala Glu Cys Glu Asp Gly Ser Asp Glu Ser Glu Glu Thr Cys Leu
 55 60 65
 Ser Val Thr Cys Lys Ser Gly Asp Phe Ser Cys Gly Gly Arg Val Asn
 70 75 80
 Arg Cys Ile Pro Glu Phe Trp Arg Cys Asp Gly Gu Val Asp Cys Glu
 85 90 95
 Asn Gly Ser Asp Glu Glu Asp Cys Pro Pro Lys Thr Cys Ser Glu Asp
 100 105 110
 Glu Phe Arg Cys His Asp Gly Lys Cys Ile Tyr Arg Glu Phe Val Cys
 115 120 125
 Asp Ser Asp Arg Asp Cys Leu Asp Gly Ser Asp Glu Ala Ser Cys Pro
 130 135 140
 Val Leu Thr Cys Gly Pro Ala Ser Phe Glu Cys Asn Ser Ser Thr Cys
 145 150 155 160
 Ile Pro Glu Leu Trp Ala Cys Asp Asn Asp Pro Asp Cys Glu Asp Gly
 165 170 175
 Ser Asp Glu Trp Pro Glu His Cys Glu Gly Leu Glu Val Pro Lys Arg
 180 185 190
 Asp Ser Ser Pro Cys Ser Ala Phe Glu Phe His Cys Glu Ser Gly Glu
 195 200 205
 Cys Ile His Ser Gly Trp Arg Cys Asp Gly Gly Pro Asp Cys Lys Asp
 210 215 220
 Lys Ser Asp Glu Glu Asn Cys Pro Val Ala Thr Cys Arg Pro Asp Glu
 225 230 235 240
 Phe Glu Cys Ser Asp Gly Thr Cys Ile His Glu Ser Arg Glu Cys Asp
 245 250 255
 Arg Glu Tyr Asp Cys Lys Asp Met Ser Asp Glu Val Glu Cys Ile Asn
 260 265 270
 Val Thr Leu Cys Glu Gly Pro Asn Lys Phe Lys Cys His Ser Gly Glu
 275 280 285
 Cys Ile Ser Leu Asp Lys Val Cys Asn Met Ala Arg Asp Cys Arg Asp
 290 295 300
 Trp Ser Asp Glu Pro Ile Lys Glu Cys Gly Thr Asn Glu Cys Leu Asp
 305 310 315 320
 Asn Asn Gly Gly Cys Ser His Ile Cys Asn Asp Leu Lys Ile Gly Tyr
 325 330 335
 Glu Cys Leu Cys Pro Asp Gly Phe Glu Val Ala Glu Arg Arg Cys
 340 345 350
 Glu Asp Ile Asp Glu Cys Glu Asp Pro Asp Thr Cys Ser Glu Leu Cys
 355 360 365

SEQUENCE_LI STI NG_APML_005VPC

| | | | | | | | | | | | | | | | |
|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| Val | Asn | Leu | Gl u | G y | Ser | Tyr | Lys | Cys | G n | Cys | Gl u | Gl u | G y | Phe | G n |
| 370 | | | | | | 375 | | | | 380 | | | | | |
| Leu | Asp | Pro | His | Thr | Lys | Al a | Cys | Lys | Al a | Val | G y | Ser | Ile | Al a | Tyr |
| 385 | | | | | | 390 | | | | 395 | | | | | 400 |
| Leu | Ile | Phe | Thr | Asn | Arg | His | Gl u | Val | Arg | Lys | Met | Thr | Leu | Asp | Arg |
| | | | | | | 405 | | | | 410 | | | | | 415 |
| Ser | Gl u | Tyr | Thr | Ser | Leu | Ile | Pro | Asn | Leu | Arg | Asn | Val | Val | Al a | Leu |
| | | | | | | 420 | | | | 425 | | | | | 430 |
| Asp | Thr | Gl u | Val | Al a | Ser | Asn | Arg | Ile | Tyr | Trp | Ser | Asp | Leu | Ser | G n |
| | | | | | | 435 | | | | 440 | | | | | 445 |
| Arg | Met | Ile | Tyr | Ser | Thr | G n | Leu | Asp | Arg | Al a | His | Ser | Val | Ser | Ser |
| | | | | | | 450 | | | | 455 | | | | | 460 |
| Tyr | Asp | Thr | Val | Ile | Ser | Arg | Asp | Leu | G n | Al a | Pro | Asp | G y | Leu | Al a |
| | | | | | | 465 | | | | 470 | | | | | 480 |
| Val | Asp | Trp | Ile | His | Ser | Asn | Ile | Tyr | Trp | Thr | Asp | Ser | Val | Leu | G y |
| | | | | | | 485 | | | | 490 | | | | | 495 |
| Thr | Val | Ser | Val | Al a | Asp | Thr | Lys | Gl y | Val | Lys | Arg | Lys | Thr | Leu | Phe |
| | | | | | | 500 | | | | 505 | | | | | 510 |
| Arg | Gl u | Asn | G y | Ser | Lys | Pro | Arg | Al a | Ile | Val | Val | Asp | Pro | Val | His |
| | | | | | | 515 | | | | 520 | | | | | 525 |
| Gl y | Phe | Met | Tyr | Trp | Thr | Asp | Trp | Gl y | Thr | Pro | Al a | Lys | Ile | Lys | Lys |
| | | | | | | 530 | | | | 535 | | | | | 540 |
| Gl y | Gl y | Leu | Asn | Gl y | Val | Asp | Ile | Tyr | Ser | Leu | Val | Thr | Gl u | Asn | Ile |
| | | | | | | 545 | | | | 550 | | | | | 560 |
| Gl u | Trp | Pro | Asn | Gl y | Ile | Thr | Leu | Asp | Phe | Pro | Ser | Gl y | Arg | Leu | Tyr |
| | | | | | | 565 | | | | 570 | | | | | 575 |
| Trp | Val | Asp | Ser | Lys | Leu | His | Ser | Ile | Ser | Ser | Ile | Asp | Val | Asn | G y |
| | | | | | | 580 | | | | 585 | | | | | 590 |
| Gl y | Asn | Arg | Lys | Thr | Val | Leu | Gl u | Asp | Gl u | Gl u | Arg | Leu | Al a | His | Pro |
| | | | | | | 595 | | | | 600 | | | | | 605 |
| Phe | Ser | Leu | Al a | Ile | Phe | Gl u | Asp | Lys | Val | Phe | Trp | Thr | Asp | Ile | Ile |
| | | | | | | 610 | | | | 615 | | | | | 620 |
| Asn | Gl u | Al a | Ile | Phe | Ser | Al a | Asn | Arg | Leu | Thr | Gl y | Ser | Asp | Ile | Asn |
| | | | | | | 625 | | | | 630 | | | | | 640 |
| Leu | Leu | Al a | Gl u | Asn | Leu | Leu | Ser | Pro | Gl u | Asp | Met | Val | Leu | Phe | His |
| | | | | | | 645 | | | | 650 | | | | | 655 |
| Asn | Leu | Thr | G n | Pro | Arg | Gl y | Val | Asn | Trp | Cys | Gl u | Arg | Thr | Thr | Leu |
| | | | | | | 660 | | | | 665 | | | | | 670 |
| Ser | Asn | Gl y | Gl y | Cys | G n | Tyr | Leu | Cys | Leu | Pro | Al a | Pro | G n | Ile | Asn |
| | | | | | | 675 | | | | 680 | | | | | 685 |
| Pro | G n | Ser | Pro | Lys | Phe | Thr | Cys | Thr | Cys | Pro | Asp | Gl y | Met | Leu | Leu |
| | | | | | | 690 | | | | 695 | | | | | 700 |
| Al a | Lys | Asp | Met | Arg | Ser | Cys | Leu | Thr | Gl u | Al a | Gl u | Al a | Al a | Val | Al a |
| | | | | | | 705 | | | | 710 | | | | | 720 |
| Thr | G n | Gl u | Thr | Ser | Thr | Val | Arg | Leu | Met | Val | Ser | Ser | Lys | Al a | Val |
| | | | | | | 725 | | | | 730 | | | | | 735 |
| Al a | Thr | G n | His | Thr | Thr | Arg | Pro | Val | Pro | Asn | Thr | Ser | G n | Leu | |
| | | | | | | 740 | | | | 745 | | | | | 750 |
| Pro | Gl y | Al a | Thr | Pro | Gl y | Leu | Thr | Thr | Al a | Gl u | Thr | Val | Thr | Met | Ser |
| | | | | | | 755 | | | | 760 | | | | | 765 |
| His | G n | Al a | Leu | Gl y | Asp | Val | Al a | Gl y | Arg | Gl y | Asn | Gl u | Lys | Lys | Pro |
| | | | | | | 770 | | | | 775 | | | | | 780 |
| Lys | Ser | Val | G y | Al a | Leu | Ser | Ile | Val | Leu | Pro | Thr | Val | Leu | Leu | Val |
| | | | | | | 785 | | | | 790 | | | | | 800 |
| Phe | Leu | Cys | Leu | G y | Al a | Phe | Leu | Leu | Trp | Lys | Asn | Trp | Arg | Leu | Lys |
| | | | | | | 805 | | | | 810 | | | | | 815 |
| Ser | Ile | Asn | Ser | Ile | Asn | Phe | Asp | Asn | Pro | Val | Tyr | G n | Lys | Thr | Thr |
| | | | | | | 820 | | | | 825 | | | | | 830 |
| Gl u | Asp | Gl u | Val | His | Ile | Cys | Arg | Asn | G n | Asp | Gl y | Tyr | Ser | Tyr | Pro |
| | | | | | | 835 | | | | 840 | | | | | 845 |
| Ser | Arg | G n | Met | Val | Ser | Leu | Gl u | Asp | Asp | Val | Al a | | | | |
| | | | | | | 850 | | | | 855 | | | | | 860 |

<210> 20

<211> 862

<212> PRT

<213> Mus musculus

SEQUENCE_LI STI NG_APMOL_005VPC

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 35 40 45
 Ser Pro Glu Cys Pro Asp Gly Ser Asp Glu Ser Pro Glu Thr Cys Met
 50 55 60
 Ser Val Thr Cys Glu Ser Asn Glu Phe Ser Cys Gly Gly Arg Val Ser
 65 70 75 80
 Arg Cys Ile Pro Asp Ser Trp Arg Cys Asp Gly Glu Val Asp Cys Glu
 85 90 95
 Asn Asp Ser Asp Glu Glu Gly Cys Pro Pro Lys Thr Cys Ser Glu Asp
 100 105 110
 Asp Phe Arg Cys Glu Asp Gly Lys Cys Ile Ser Pro Glu Phe Val Cys
 115 120 125
 Asp Gly Asp Arg Asp Cys Leu Asp Gly Ser Asp Glu Ala His Cys Glu
 130 135 140
 Ala Thr Thr Cys Gly Pro Ala His Phe Arg Cys Asn Ser Ser Ile Cys
 145 150 155 160
 Ile Pro Ser Leu Trp Ala Cys Asp Gly Asp Val Asp Cys Val Asp Gly
 165 170 175
 Ser Asp Glu Trp Pro Glu Asn Cys Glu Gly Arg Asp Thr Ala Ser Lys
 180 185 190
 Gly Val Ser Ser Pro Cys Ser Ser Leu Glu Phe His Cys Gly Ser Ser
 195 200 205
 Glu Cys Ile His Arg Ser Trp Val Cys Asp Gly Glu Ala Asp Cys Lys
 210 215 220
 Asp Lys Ser Asp Glu Glu His Cys Ala Val Ala Thr Cys Arg Pro Asp
 225 230 235 240
 Glu Phe Glu Cys Ala Asp Gly Ser Cys Ile His Gly Ser Arg Glu Cys
 245 250 255
 Asp Arg Glu His Asp Cys Lys Asp Met Ser Asp Glu Leu Gly Cys Val
 260 265 270
 Asn Val Thr Glu Cys Asp Gly Pro Asn Lys Phe Lys Cys His Ser Gly
 275 280 285
 Glu Cys Ile Ser Leu Asp Lys Val Cys Asp Ser Ala Arg Asp Cys Glu
 290 295 300
 Asp Trp Ser Asp Glu Pro Ile Lys Glu Cys Lys Thr Asn Glu Cys Leu
 305 310 315 320
 Asp Asn Asn Gly Gly Cys Ser His Ile Cys Lys Asp Leu Lys Ile Gly
 325 330 335
 Ser Glu Cys Leu Cys Pro Ser Gly Phe Arg Leu Val Asp Leu His Arg
 340 345 350
 Cys Glu Asp Ile Asp Glu Cys Glu Pro Asp Thr Cys Ser Glu Leu
 355 360 365
 Cys Val Asn Leu Glu Gly Ser Tyr Lys Cys Glu Cys Glu Ala Gly Phe
 370 375 380
 His Met Asp Pro His Thr Arg Val Cys Lys Ala Val Glu Ser Ile Gly
 385 390 395 400
 Tyr Leu Leu Phe Thr Asn Arg His Glu Val Arg Lys Met Thr Leu Asp
 405 410 415
 Arg Ser Glu Tyr Thr Ser Leu Leu Pro Asn Leu Lys Asn Val Val Ala
 420 425 430
 Leu Asp Thr Glu Val Thr Asn Asn Arg Ile Tyr Trp Ser Asp Leu Ser
 435 440 445
 Glu Lys Ile Tyr Ser Ala Leu Met Asp Glu Ala Pro Asn Leu Ser
 450 455 460
 Tyr Asp Thr Ile Ile Ser Glu Asp Leu His Ala Pro Asp Gly Leu Ala
 465 470 475 480
 Val Asp Trp Ile His Arg Asn Ile Tyr Trp Thr Asp Ser Val Pro Gly
 485 490 495
 Ser Val Ser Val Ala Asp Thr Lys Glu Val Lys Arg Arg Thr Leu Phe
 500 505 510
 Glu Ala Gly Ser Arg Pro Arg Ala Ile Val Val Asp Pro Val His
 515 520 525

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G y Phe Met Tyr Trp Thr Asp Trp G y Thr Pro Ala Lys Ile Lys Lys
 530 535 540
 G y G y Leu Asn G y Val Asp Ile His Ser Leu Val Thr Glu Asn Ile
 545 550 555 560
 G n Trp Pro Asn G y Ile Thr Leu Asp Leu Ser Ser G y Arg Leu Tyr
 565 570 575
 Trp Val Asp Ser Lys Leu His Ser Ile Ser Ser Ile Asp Val Asn G y
 580 585 590
 G y Asn Arg Lys Thr Ile Leu Glu Asp Glu Asn Arg Leu Ala His Pro
 595 600 605
 Phe Ser Leu Ala Ile Tyr Glu Asp Lys Val Tyr Trp Thr Asp Val Ile
 610 615 620
 Asn Glu Ala Ile Phe Ser Ala Asn Arg Leu Thr G y Ser Asp Val Asn
 625 630 635 640
 Leu Val Ala Glu Asn Leu Leu Ser Pro Glu Asp Ile Val Leu Phe His
 645 650 655
 Lys Val Thr G n Pro Arg G y Val Asn Trp Cys Glu Thr Thr Ala Leu
 660 665 670
 Leu Pro Asn G y G y Cys G n Tyr Leu Cys Leu Pro Ala Pro G n Ile
 675 680 685
 G y Pro His Ser Pro Lys Phe Thr Cys Ala Cys Pro Asp G y Met Leu
 690 695 700
 Leu Ala Lys Asp Met Arg Ser Cys Leu Thr Glu Val Asp Thr Val Leu
 705 710 715 720
 Thr Thr G n G y Thr Ser Ala Val Arg Pro Val Val Thr Ala Ser Ala
 725 730 735
 Thr Arg Pro Pro Lys His Ser Glu Asp Leu Ser Ala Pro Ser Thr Pro
 740 745 750
 Arg G n Pro Val Asp Thr Pro G y Leu Ser Thr Val Ala Ser Val Thr
 755 760 765
 Val Ser His G n Val G n G y Asp Met Ala G y Arg G y Asn Glu Glu
 770 775 780
 G n Pro His G y Met Arg Phe Leu Ser Ile Phe Phe Pro Ile Ala Leu
 785 790 795 800
 Val Ala Leu Leu Val Leu G y Ala Val Leu Leu Trp Arg Asn Trp Arg
 805 810 815
 Leu Lys Asn Ile Asn Ser Ile Asn Phe Asp Asn Pro Val Tyr G n Lys
 820 825 830
 Thr Thr G u Asp G u Leu His Ile Cys Arg Ser G n Asp G y Tyr Thr
 835 840 845
 Tyr Pro Ser Arg G n Met Val Ser Leu Glu Asp Asp Val Ala
 850 855 860

<210> 21

<211> 865

<212> PRT

<213> Artificial Sequence

<220>

<223> Consensus Sequence

<220>

<221> VARI ANT

<222> 2, 3, 4, 5, 6, 7, 8, 11, 21, 24, 26, 27, 28, 35, 42, 50,
 53, 60, 61, 69, 71, 72, 80, 85, 86, 98, 117, 124, 130, 142,
 145, 146, 152, 154, 156, 159, 163, 169, 171, 174, 178, 183,
 185, 187, 188, 189, 190, 191, 192, 194, 201, 206, 208

<223> Xaa = Any Ami no Acid or No Ami no Acid

<220>

<221> VARI ANT

<222> 213, 216, 220, 221, 231, 248, 276, 298, 299, 304, 315, 331,
 337, 343, 346, 349, 350, 351, 375, 379, 381, 382, 385, 392,
 403, 438, 439, 451, 453, 455, 456, 459, 461, 462, 465, 472,
 475, 487, 496, 514, 516, 572, 604, 658, 670, 672, 674

<223> Xaa = Any Ami no Acid or No Ami no Acid

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<220>

<221> VARI ANT

<222> 675, 690, 717, 719, 720, 722, 725, 728, 731, 732, 738, 740, 741, 742, 745, 746, 747, 748, 749, 751, 753, 755, 757, 758, 766, 767, 774, 775, 785, 786, 788, 789, 792, 796, 797, 800, 803, 804, 806, 809, 810, 821, 822, 845, 846

<223> Xaa = Any Ami no Acid or No Ami no Acid

<400> 21

| | | | | | | | | | | | | | | | | |
|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|-----|
| Met | Xaa | Arg | Trp | Xaa | Ile | Ala | Leu | Leu | Leu | |
| 1 | | | | | | | | | | 5 | | | 10 | | 15 | |
| Ala | Ala | Ala | Ala | Gly | Xaa | Ala | Val | Xaa | Asp | Xaa | Xaa | Xaa | Arg | Asn | Gl u | Phe |
| | | | | 20 | | | | | 25 | | | | | 30 | | |
| Gl n | Oys | Xaa | Asp | Gly | Lys | Oys | Ile | Ala | Xaa | Lys | Trp | Val | Oys | Asp | Gly | |
| | | | | 35 | | | 40 | | | | | | 45 | | | |
| Ser | Xaa | Gl u | Cys | Xaa | Asp | Gly | Ser | Asp | Gl u | Ser | Xaa | Xaa | Thr | Cys | Leu | |
| | | | | 50 | | | 55 | | | | | | 60 | | | |
| Ser | Val | Thr | Cys | Xaa | Ser | Xaa | Xaa | Phe | Ser | Oys | Gly | Gly | Arg | Val | Xaa | |
| | | | | 65 | | | 70 | | | | 75 | | | 80 | | |
| Arg | Oys | Ile | Pro | Xaa | Xaa | Trp | Arg | Oys | Asp | Gly | Gl n | Val | Asp | Cys | Asp | |
| | | | | 85 | | | 90 | | | | | | 95 | | | |
| Asn | Xaa | Ser | Asp | Gl u | Gl n | Gly | Oys | Pro | Pro | Lys | Thr | Cys | Ser | Gl n | Asp | |
| | | | | 100 | | | 105 | | | | | | 110 | | | |
| Asp | Phe | Arg | Oys | Xaa | Asp | Gly | Lys | Oys | Ile | Ser | Xaa | Gl n | Phe | Val | Oys | |
| | | | | 115 | | | 120 | | | | | | 125 | | | |
| Asp | Xaa | Asp | Arg | Asp | Oys | Leu | Asp | Gly | Ser | Asp | Gl u | Al a | Xaa | Cys | Pro | |
| | | | | 130 | | | 135 | | | | | | 140 | | | |
| Xaa | Xaa | Thr | Cys | Gly | Pro | Al a | Xaa | Phe | Xaa | Oys | Xaa | Ser | Ser | Xaa | Oys | |
| | | | | 145 | | | 150 | | | | | | 155 | | | 160 |
| Ile | Pro | Xaa | Leu | Trp | Al a | Cys | Asp | Xaa | Asp | Xaa | Asp | Cys | Xaa | Asp | Gly | |
| | | | | 165 | | | 170 | | | | | | 175 | | | |
| Ser | Xaa | Gl u | Trp | Pro | Gl n | Xaa | Oys | Xaa | Al a | Xaa | Xaa | Xaa | Xaa | Xaa | Xaa | |
| | | | | 180 | | | 185 | | | | | | 190 | | | |
| Gly | Xaa | Ser | Ser | Pro | Oys | Ser | Al a | Xaa | Gl u | Phe | His | Cys | Xaa | Ser | Xaa | |
| | | | | 195 | | | 200 | | | | | | 205 | | | |
| Gl u | Oys | Ile | His | Xaa | Ser | Trp | Xaa | Cys | Asp | Gly | Xaa | Xaa | Asp | Cys | Lys | |
| | | | | 210 | | | 215 | | | | | | 220 | | | |
| Asp | Lys | Ser | Asp | Gl u | Gl u | Xaa | Cys | Al a | Val | Al a | Thr | Cys | Arg | Pro | Asp | |
| | | | | 225 | | | 230 | | | | | | 235 | | | 240 |
| Gl u | Phe | Gl n | Cys | Al a | Asp | Gly | Xaa | Cys | Ile | His | Gly | Ser | Arg | Gl n | Cys | |
| | | | | 245 | | | 250 | | | | | | 255 | | | |
| Asp | Arg | Gl u | His | Asp | Oys | Lys | Asp | Met | Ser | Asp | Gl u | Leu | Gly | Cys | Val | |
| | | | | 260 | | | 265 | | | | | | 270 | | | |
| Asn | Val | Thr | Xaa | Cys | Asp | Gly | Pro | Asn | Lys | Phe | Lys | Oys | His | Ser | Gly | |
| | | | | 275 | | | 280 | | | | | | 285 | | | |
| Gl u | Oys | Ile | Ser | Leu | Asp | Lys | Val | Oys | Xaa | Xaa | Al a | Arg | Asp | Cys | Xaa | |
| | | | | 290 | | | 295 | | | | | | 300 | | | |
| Asp | Trp | Ser | Asp | Gl u | Pro | Ile | Lys | Gl u | Cys | Xaa | Thr | Asn | Gl u | Cys | Leu | |
| | | | | 305 | | | 310 | | | | | | 315 | | | 320 |
| Asp | Asn | Asn | Gly | Gly | Cys | Ser | His | Ile | Cys | Xaa | Asp | Leu | Lys | Ile | Gly | |
| | | | | 325 | | | 330 | | | | | | 335 | | | |
| Xaa | Gl u | Oys | Leu | Cys | Pro | Xaa | Gly | Phe | Xaa | Leu | Val | Xaa | Xaa | Xaa | Arg | |
| | | | | 340 | | | 345 | | | | | | 350 | | | |
| Oys | Gl u | Asp | Ile | Asp | Gl u | Oys | Gl n | Asp | Pro | Asp | Thr | Oys | Ser | Gl n | Leu | |
| | | | | 355 | | | 360 | | | | | | 365 | | | |
| Cys | Val | Asn | Leu | Gl u | Gly | Xaa | Tyr | Lys | Oys | Xaa | Cys | Xaa | Xaa | Gly | Phe | |
| | | | | 370 | | | 375 | | | | | | 380 | | | |
| Xaa | Leu | Asp | Pro | His | Thr | Lys | Xaa | Cys | Lys | Al a | Val | Gly | Ser | Ile | Al a | |
| | | | | 385 | | | 390 | | | | | | 395 | | | 400 |
| Tyr | Leu | Xaa | Phe | Thr | Asn | Arg | His | Gl u | Val | Arg | Lys | Met | Thr | Leu | Asp | |
| | | | | 405 | | | 410 | | | | | | 415 | | | |
| Arg | Ser | Gl u | Tyr | Thr | Ser | Leu | Ile | Pro | Asn | Leu | Lys | Asn | Val | Val | Al a | |
| | | | | 420 | | | 425 | | | | | | 430 | | | |
| Leu | Asp | Thr | Gl u | Val | Xaa | Xaa | Asn | Arg | Ile | Tyr | Trp | Ser | Asp | Leu | Ser | |
| | | | | 435 | | | 440 | | | | | | 445 | | | |
| Gl n | Lys | Xaa | Ile | Xaa | Ser | Xaa | Xaa | Leu | Asp | Xaa | Al a | Xaa | Xaa | Leu | Ser | |
| | | | | 450 | | | 455 | | | | | | 460 | | | |
| Xaa | Tyr | Asp | Thr | Ile | Ile | Ser | Xaa | Asp | Ile | Xaa | Al a | Pro | Asp | Gly | Leu | |

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| | | | | | | | | | | | | | | | | | | |
|-----|------|-----|------|------|------|-----|------|-----|------|-----|------|-----|-----|-----|------|-----|------|-----|
| 465 | Al a | Val | Asp | Trp | Ile | 470 | His | Xaa | Asn | Ile | Tyr | 475 | Trp | Thr | Asp | Ser | Val | 480 |
| | | | | | | 485 | | | | | 490 | | | | | | 495 | |
| | Gly | Ser | Val | Ser | Val | 500 | Al a | Asp | Thr | Lys | Gly | 505 | Val | Lys | Arg | Lys | Thr | Leu |
| | Phe | Xaa | Glu | Xaa | Gly | 515 | Ser | Lys | Pro | Arg | Al a | 520 | Ile | Val | Val | Asp | Pro | Val |
| | His | Gly | Phe | Met | Tyr | 530 | Trp | Thr | Asp | Trp | Gly | 535 | Thr | Pro | Al a | Lys | Ile | Lys |
| | Lys | Gly | Gly | Leu | Asn | 545 | Gly | Val | Asp | Ile | His | 550 | Ser | Leu | Val | Thr | Glu | Asn |
| | Ile | Gly | Trp | Pro | Asn | 555 | Gly | Ile | Thr | Leu | Asp | 560 | Leu | Xaa | Ser | Gly | Arg | Leu |
| | Tyr | Trp | Val | Asp | Ser | 565 | | | | Leu | 565 | | | | | | 575 | |
| | Gly | Gly | Asn | Arg | Lys | 580 | Thr | Ile | Leu | His | 585 | Ser | Ser | Ile | Asp | Val | Asn | |
| | | | | | | 595 | | | | | 600 | | | | | | 590 | |
| | Pro | Phe | Ser | Leu | Al a | 610 | Ile | Phe | Glu | Asp | 615 | Lys | Val | Phe | Trp | Thr | Asp | Ile |
| | Ile | Asn | Glu | Al a | Ile | 620 | Phe | Ser | Al a | Asn | 625 | 630 | 635 | Trp | Thr | | | |
| | Asn | Leu | Leu | Al a | Glu | 645 | Asn | Leu | Leu | Ser | 645 | 650 | 655 | | | | | 640 |
| | His | Xaa | Leu | Thr | Gly | 660 | Pro | Arg | Gly | Val | 660 | 665 | 670 | Asn | Trp | Cys | Glu | Xaa |
| | Leu | Xaa | Xaa | Asn | Gly | 675 | Gly | Cys | Gly | Tyr | 675 | 680 | 685 | | | | | Thr |
| | Ile | Xaa | Pro | His | Ser | 690 | Pro | Lys | Phe | Thr | 690 | 695 | 700 | Cys | Al a | Cys | Pro | Asp |
| | Leu | Leu | Al a | Lys | Asp | 705 | Met | Arg | Ser | Cys | 705 | 710 | 715 | Leu | Thr | Glu | Xaa | Asp |
| | Leu | Xaa | Thr | Gly | Xaa | 725 | Thr | Ser | Xaa | Val | 725 | 730 | 735 | Xaa | Xaa | Val | Al a | Ser |
| | Al a | Xaa | Arg | Xaa | Xaa | 740 | Xaa | His | Ser | Xaa | 740 | 745 | 750 | Xaa | Xaa | Xaa | Pro | Xaa |
| | Xaa | Arg | Xaa | Pro | Xaa | 755 | Xaa | Xaa | Thr | Pro | 755 | 760 | 765 | Gly | Leu | Ser | Thr | Val |
| | Thr | Met | Ser | His | Gly | 770 | Xaa | Xaa | Xaa | Gly | 770 | 775 | 780 | Arg | Gly | Asn | Glu | |
| | Xaa | Xaa | Pro | Xaa | Xaa | 785 | Met | Arg | Xaa | Leu | 785 | 790 | 795 | Ile | Xaa | Xaa | Pro | Ile |
| | Leu | Leu | Xaa | Xaa | Leu | 805 | Xaa | Leu | Gly | Xaa | 805 | 810 | 815 | Xaa | Xaa | Asn | Trp | Trp |
| | Arg | Leu | Lys | Asn | Xaa | 820 | Xaa | Xaa | Ile | Asn | 820 | 825 | 830 | Ile | Asn | Phe | Asp | Asn |
| | Tyr | Gly | Lys | Thr | Thr | 835 | Glu | Asp | Gly | Leu | 835 | 840 | 845 | His | Ile | Cys | Xaa | Xaa |
| | Gly | Tyr | Ser | Tyr | Pro | 850 | Arg | Gly | Met | Val | 850 | 855 | 860 | Gly | Asp | Asp | Asp | Val |
| | Al a | | | | | 865 | | | | | | | | | | | | |

<210> 22

<211> 860

<212> PRT

<213> Artificial Sequence

<220>

<223> Consensus Sequence

<220>

<221> VARI ANT

<222> 2, 14, 20, 21, 35, 92, 103, 123, 183, 185, 188, 190, 191, 192, 205, 213, 232, 247, 374, 402, 452, 461, 561, 570, 571, 603, 690, 697, 730, 734, 737, 748, 751, 762, 764, 785, 788, 796, 806, 817, 840

<223> Xaa = Any Amino Acid or No Amino Acid

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<400> 22

| | | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|--|
| Met | Xaa | Pro | Trp | Gly | Trp | Lys | Leu | Arg | Trp | Thr | Val | Ala | Xaa | Leu | Leu | | | | | |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | | | | | | |
| Ala | Ala | Ala | Xaa | Xaa | Ala | Val | Gly | Asp | Arg | Oys | Gl | Arg | Asn | Gl | Phe | | | | | |
| | | | | | | | 20 | | 25 | | | | | 30 | | | | | | |
| Gl | n | Oys | Xaa | Asp | Gly | Lys | Cys | Ile | Ser | Tyr | Lys | Trp | Val | Cys | Asp | Gly | | | | |
| | | | | | | | 35 | | 40 | | | | 45 | | | | | | | |
| Ser | Ala | Gl | u | Cys | Gl | n | Asp | Gly | Ser | Asp | Gl | u | Ser | Gl | u | Thr | Cys | Leu | | |
| | | | | | | | 50 | | 55 | | | | 60 | | | | | | | |
| Ser | Val | Thr | Cys | Lys | Ser | Gly | Asp | Phe | Ser | Cys | Gly | Gly | Arg | Val | Asn | | | | | |
| | | | | | | | 65 | | 70 | | | 75 | | | | 80 | | | | |
| Arg | Cys | Ile | Pro | Gl | n | Phe | Trp | Arg | Oys | Asp | Gly | Xaa | Val | Asp | Oys | Asp | | | | |
| | | | | | | | 85 | | 90 | | | | | 95 | | | | | | |
| Asn | Gly | Ser | Asp | Gl | u | Gl | n | Xaa | Cys | Pro | Pro | Lys | Thr | Cys | Ser | Gl | n | Asp | | |
| | | | | | | | 100 | | 105 | | | | | 110 | | | | | | |
| Gl | u | Phe | Arg | Cys | His | Asp | Gly | Lys | Cys | Ile | Xaa | Arg | Gl | n | Phe | Val | Oys | | | |
| | | | | | | | 115 | | 120 | | | | 125 | | | | | | | |
| Asp | Ser | Asp | Arg | Asp | Oys | Leu | Asp | Gly | Ser | Asp | Gl | u | Ala | Ser | Cys | Pro | | | | |
| | | | | | | | 130 | | 135 | | | 140 | | | | | | | | |
| Val | Leu | Thr | Cys | Gly | Pro | Ala | Ser | Phe | Gl | n | Cys | Asn | Ser | Ser | Thr | Oys | | | | |
| | | | | | | | 145 | | 150 | | | 155 | | | | | 160 | | | |
| Ile | Pro | Gl | n | Leu | Trp | Ala | Oys | Asp | Asn | Asp | Pro | Asp | Cys | Gl | u | Asp | Gly | | | |
| | | | | | | | 165 | | 170 | | | | | 175 | | | | | | |
| Ser | Asp | Gl | u | Trp | Pro | Gl | n | Xaa | Cys | Xaa | Gly | Leu | Xaa | Val | Xaa | Xaa | Xaa | | | |
| | | | | | | | 180 | | 185 | | | | | 190 | | | | | | |
| Asp | Ser | Ser | Pro | Oys | Ser | Ala | Phe | Gl | u | Phe | His | Cys | Xaa | Ser | Gly | Gly | | | | |
| | | | | | | | 195 | | 200 | | | | 205 | | | | | | | |
| Oys | Ile | His | Ser | Xaa | Trp | Arg | Cys | Asp | Gly | Gly | Pro | Asp | Cys | Lys | Asp | | | | | |
| | | | | | | | 210 | | 215 | | | 220 | | | | | | | | |
| Lys | Ser | Asp | Gl | u | Gl | u | Asn | Cys | Xaa | Val | Ala | Thr | Oys | Arg | Pro | Asp | Gl | u | | |
| | | | | | | | 225 | | 230 | | | 235 | | | | | 240 | | | |
| Phe | Gl | n | Oys | Ser | Asp | Gly | Xaa | Cys | Ile | His | Gly | Ser | Arg | Gl | n | Oys | Asp | | | |
| | | | | | | | 245 | | 250 | | | | | 255 | | | | | | |
| Arg | Gl | u | Tyr | Asp | Cys | Lys | Asp | Met | Ser | Asp | Gl | u | Val | Gly | Cys | Ile | Asn | | | |
| | | | | | | | 260 | | 265 | | | | | 270 | | | | | | |
| Val | Thr | Leu | Cys | Gl | u | Gly | Pro | Asn | Lys | Phe | Lys | Cys | His | Ser | Gly | Gly | | | | |
| | | | | | | | 275 | | 280 | | | | 285 | | | | | | | |
| Cys | Ile | Ser | Leu | Asp | Lys | Val | Cys | Asn | Met | Ala | Arg | Asp | Oys | Arg | Asp | | | | | |
| | | | | | | | 290 | | 295 | | | 300 | | | | | | | | |
| Trp | Ser | Asp | Gl | u | Pro | Ile | Lys | Gl | u | Oys | Gly | Thr | Asn | Gl | u | Oys | Leu | Asp | | |
| | | | | | | | 305 | | 310 | | | 315 | | | | | 320 | | | |
| Asn | Asn | Gl | u | Gly | Cys | Ser | His | Ile | Oys | Asn | Asp | Leu | Lys | Ile | Gly | Tyr | | | | |
| | | | | | | | 325 | | 330 | | | | | 335 | | | | | | |
| Gl | u | Oys | Leu | Cys | Pro | Asp | Gly | Phe | Gl | n | Leu | Val | Ala | Gl | n | Arg | Arg | Oys | | |
| | | | | | | | 340 | | 345 | | | | | 350 | | | | | | |
| Gl | u | Asp | Ile | Asp | Gl | u | Cys | Gl | n | Asp | Pro | Asp | Thr | Cys | Ser | Gl | n | Leu | Oys | |
| | | | | | | | 355 | | 360 | | | | | 365 | | | | | | |
| Val | Asn | Leu | Gl | u | Gly | Xaa | Tyr | Lys | Cys | Gl | n | Oys | Gl | u | Gl | Gly | Phe | Gl | n | |
| | | | | | | | 370 | | 375 | | | | 380 | | | | | | | |
| Leu | Asp | Pro | His | Thr | Lys | Ala | Oys | Lys | Ala | Val | Gly | Ser | Ile | Ala | Tyr | | | | | |
| | | | | | | | 385 | | 390 | | | 395 | | | | | 400 | | | |
| Leu | Xaa | Phe | Thr | Asn | Arg | His | Gl | u | Val | Arg | Lys | Met | Thr | Leu | Asp | Arg | | | | |
| | | | | | | | 405 | | 410 | | | | | 415 | | | | | | |
| Ser | Gl | u | Tyr | Thr | Ser | Leu | Ile | Pro | Asn | Leu | Arg | Asn | Val | Val | Ala | Ile | Leu | | | |
| | | | | | | | 420 | | 425 | | | | | 430 | | | | | | |
| Asp | Thr | Gl | u | Val | Ala | Ser | Asn | Arg | Ile | Tyr | Trp | Ser | Asp | Leu | Ser | Gl | n | | | |
| | | | | | | | 435 | | 440 | | | | 445 | | | | | | | |
| Arg | Met | Ile | Xaa | Ser | Thr | Gl | n | Leu | Asp | Arg | Ala | His | Xaa | Val | Ser | Ser | Ser | | | |
| | | | | | | | 450 | | 455 | | | | 460 | | | | | | | |
| Tyr | Asp | Thr | Val | Ile | Ser | Arg | Asp | Ile | Gl | n | Ala | Pro | Asp | Gly | Leu | Ala | | | | |
| | | | | | | | 465 | | 470 | | | | 475 | | | | | 480 | | |
| Val | Asp | Trp | Ile | His | Ser | Asn | Ile | Tyr | Trp | Thr | Asp | Ser | Val | Leu | Gly | | | | | |
| | | | | | | | 485 | | 490 | | | | | 495 | | | | | | |
| Thr | Val | Ser | Val | Ala | Asp | Thr | Lys | Gly | Val | Lys | Arg | Lys | Thr | Leu | Phe | | | | | |
| | | | | | | | 500 | | 505 | | | | | 510 | | | | | | |
| Arg | Gl | u | Asn | Gly | Ser | Lys | Pro | Arg | Ala | Ile | Val | Val | Asp | Pro | Val | His | | | | |
| | | | | | | | 515 | | 520 | | | | 525 | | | | | | | |

SEQUENCE_LI STI NG_APMOL_005VPC

| | | | | | | | | | | | | | | | |
|------|-----|------|------|------|-----|------|------|-----|-----|------|------|------|------|------|------|
| G y | Phe | Met | Tyr | Trp | Thr | Asp | Trp | G y | Thr | Pro | Al a | Lys | Ile | Lys | Lys |
| 530 | | | | | | 535 | | | | | 540 | | | | |
| G y | G y | Leu | Asn | G y | Val | Asp | Ile | Tyr | Ser | Leu | Val | Thr | G u | Asn | Ile |
| 545 | | | | | 550 | | | | | 555 | | | | 560 | |
| Xaa | Trp | Pro | Asn | G y | Ile | Thr | Leu | Asp | Xaa | Xaa | Ser | G y | Arg | Leu | Tyr |
| | | | | 565 | | | | | 570 | | | | 575 | | |
| Trp | Val | Asp | Ser | Lys | Leu | His | Ser | Ile | Ser | Ser | Ile | Asp | Val | Asn | G y |
| | | | | 580 | | | | 585 | | | | | 590 | | |
| G y | Asn | Arg | Lys | Thr | Ile | Leu | G u | Asp | G u | Xaa | Arg | Leu | Al a | His | Pro |
| | | | | 595 | | | 600 | | | | | 605 | | | |
| Phe | Ser | Leu | Al a | Ile | Phe | G u | Asp | Lys | Val | Phe | Trp | Thr | Asp | Ile | Ile |
| | | | | | 615 | | | | | 620 | | | | | |
| Asn | G u | Al a | Ile | Phe | Ser | Al a | Asn | Arg | Leu | Thr | G y | Ser | Asp | Ile | Asn |
| | | | | | 630 | | | | | 635 | | | | 640 | |
| Leu | Leu | Al a | G u | Asn | Leu | Leu | Ser | Pro | G u | Asp | Met | Val | Leu | Phe | His |
| | | | | | 645 | | | | 650 | | | | | 655 | |
| Asn | Leu | Thr | G n | Pro | Arg | G y | Val | Asn | Trp | Cys | G u | Arg | Thr | Thr | Leu |
| | | | 660 | | | 665 | | | | | | 670 | | | |
| Ser | Asn | G y | G y | Cys | G n | Tyr | Leu | Cys | Leu | Pro | Al a | Pro | G n | Ile | Asn |
| | | 675 | | | | 680 | | | | | | 685 | | | |
| Pro | Xaa | Ser | Pro | Lys | Phe | Thr | Cys | Xaa | Cys | Pro | Asp | G y | Met | Leu | Leu |
| | | | | | 695 | | | | | 700 | | | | | |
| Al a | Lys | Asp | Met | Arg | Ser | Oys | Leu | Thr | G u | Al a | G u | Al a | Al a | Val | Al a |
| | | | | | 710 | | | | | 715 | | | | | 720 |
| Thr | G n | G u | Thr | Ser | Thr | Val | Arg | Leu | Xaa | Val | Ser | Ser | Xaa | Al a | Val |
| | | | | | 725 | | | | 730 | | | | | 735 | |
| Xaa | Thr | G n | His | Thr | Thr | Arg | Pro | Val | Pro | Xaa | Thr | Ser | Xaa | Leu | |
| | | | 740 | | | 745 | | | | | | 750 | | | |
| Pro | G y | Al a | Thr | Pro | G y | Leu | Thr | Thr | Xaa | G u | Xaa | Val | Thr | Met | Ser |
| | | 755 | | | | 760 | | | | | | 765 | | | |
| His | G n | Al a | Leu | G y | Asp | Val | Al a | G y | Arg | G y | Asn | G u | Lys | Lys | Pro |
| | | 770 | | | | 775 | | | | | 780 | | | | |
| Xaa | Ser | Val | Xaa | Al a | Leu | Ser | Ile | Val | Leu | Pro | Xaa | Val | Leu | Leu | Val |
| | | | | | 790 | | | | | 795 | | | | 800 | |
| Phe | Leu | Cys | Leu | G y | Xaa | Phe | Leu | Leu | Trp | Lys | Asn | Trp | Arg | Leu | Lys |
| | | | | | 805 | | | | 810 | | | | 815 | | |
| Xaa | Ile | Asn | Ser | Ile | Asn | Phe | Asp | Asn | Pro | Val | Tyr | G n | Lys | Thr | Thr |
| | | | | | 820 | | | 825 | | | | 830 | | | |
| G u | Asp | G u | Val | His | Ile | Cys | Xaa | Asn | G n | Asp | G y | Tyr | Ser | Tyr | Pro |
| | | | 835 | | | 840 | | | | | 845 | | | | |
| Ser | Arg | G n | Met | Val | Ser | Leu | G u | Asp | Asp | Val | Al a | | | | |
| | | 850 | | | 855 | | | | | 860 | | | | | |

<210> 23
 <211> 672
 <212> PRT
 <213> Homo sapiens

<400> 23
 G n G u Asp G u Asp G y Asp Tyr G u G u Leu Val Leu Al a Leu Arg
 1 5 10 15
 Ser G u G u Asp G y Leu Al a G u Al a Pro G u His G y Thr Thr Al a
 20 25 30
 Thr Phe His Arg Cys Al a Lys Asp Pro Trp Arg Leu Pro G y Thr Tyr
 35 40 45
 Val Val Val Leu Lys G u G u Thr His Leu Ser G n Ser G u Arg Thr
 50 55 60
 Al a Arg Arg Leu G n Al a G n Al a Al a Arg Arg G y Tyr Leu Thr Lys
 65 70 75 80
 Ile Leu His Val Phe His G y Leu Leu Pro G y Phe Leu Val Lys Met
 85 90 95
 Ser G y Asp Leu Leu G u Leu Al a Leu Lys Leu Pro His Val Asp Tyr
 100 105 110
 Ile G u G u Asp Ser Ser Val Phe Al a G n Ser Ile Pro Trp Asn Leu
 115 120 125
 G u Arg Ile Thr Pro Pro Arg Tyr Arg Al a Asp G u Tyr G n Pro Pro
 130 135 140

SEQUENCE_LI STI NG_APMDL_005VPC

Asp G y G y Ser Leu Val G u Val Tyr Leu Leu Asp Thr Ser Ile G n
 145 150 155 160
 Ser Asp His Arg Glu Ile G u G y Arg Val Met Val Thr Asp Phe G u
 165 170 175
 Asn Val Pro G u G u Asp G y Thr Arg Phe His Arg G n Al a Ser Lys
 180 185 190 195
 Cys Asp Ser His G y Thr His Leu Al a G y Val Val Ser G y Arg Asp
 200 205
 Al a G y Val Al a Lys G y Al a Ser Met Arg Ser Leu Arg Val Leu Asn
 210 215 220
 Cys G n G y Lys G y Thr Val Ser G y Thr Leu Ile G y Leu G u Phe
 225 230 235 240
 Ile Arg Lys Ser G n Leu Val G n Pro Val G y Pro Leu Val Val Leu
 245 250 255
 Leu Pro Leu Al a G y G y Tyr Ser Arg Val Leu Asn Al a Al a Cys G n
 260 265 270
 Arg Leu Al a Arg Al a G y Val Val Leu Val Thr Al a Al a G y Asn Phe
 275 280 285
 Arg Asp Asp Al a Cys Leu Tyr Ser Pro Al a Ser Al a Pro G u Val Ile
 290 295 300
 Thr Val G y Al a Thr Asn Al a G n Asp G n Pro Val Thr Leu G y Thr
 305 310 315 320
 Leu G y Thr Asn Phe G y Arg Cys Val Asp Leu Phe Al a Pro G y G u
 325 330 335
 Asp Ile Ile G y Al a Ser Ser Asp Cys Ser Thr Cys Phe Val Ser G n
 340 345 350
 Ser G y Thr Ser G n Al a Al a Al a His Val Al a G y Ile Al a Al a Met
 355 360 365
 Met Leu Ser Al a G u Pro G u Leu Thr Leu Al a G u Leu Arg G n Arg
 370 375 380
 Leu Ile His Phe Ser Al a Lys Asp Val Ile Asn G u Al a Trp Phe Pro
 385 390 395 400
 G u Asp G n Arg Val Leu Thr Pro Asn Leu Val Al a Al a Leu Pro Pro
 405 410 415
 Ser Thr His G y Al a G y Trp G n Leu Phe Cys Arg Thr Val Trp Ser
 420 425 430
 Al a His Ser G y Pro Thr Arg Met Al a Thr Al a Ile Al a Arg Cys Al a
 435 440 445
 Pro Asp G u G u Leu Leu Ser Cys Ser Ser Phe Ser Arg Ser G y Lys
 450 455 460
 Arg Arg G y G u Arg Met G u Al a G n G y G y Lys Leu Val Cys Arg
 465 470 475 480
 Al a His Asn Al a Phe G y G y G u G y Val Tyr Al a Ile Al a Arg Oys
 485 490 495
 Cys Leu Leu Pro G n Al a Asn Cys Ser Val His Thr Al a Pro Pro Al a
 500 505 510
 G u Al a Ser Met G y Thr Arg Val His Cys His G n G n G y His Val
 515 520 525
 Leu Thr G y Cys Ser Ser His Trp G u Val G u Asp Leu G y Thr His
 530 535 540
 Lys Pro Pro Val Leu Arg Pro Arg G y G n Pro Asn G n Cys Val G y
 545 550 555 560
 His Arg G u Al a Ser Ile His Al a Ser Cys Oys His Al a Pro G y Leu
 565 570 575
 G u Oys Lys Val Lys G u His G y Ile Pro Al a Pro G n G y G n Val
 580 585 590
 Thr Val Al a Cys G u G u G y Trp Thr Leu Thr G y Cys Ser Al a Leu
 595 600 605
 Pro G y Thr Ser His Val Leu G y Al a Tyr Al a Val Asp Asn Thr Cys
 610 615 620
 Val Val Arg Ser Arg Asp Val Ser Thr Thr G y Ser Thr Ser G u G u
 625 630 635 640
 Al a Val Thr Al a Val Al a Ile Cys Cys Arg Ser Arg His Leu Al a G n
 645 650 655
 Al a Ser G n G u Leu G n G y Pro His His His His His His His His
 660 665 670

SEQUENCE_LI STI NG_APMOL_005VPC

<210> 24
 <211> 699
 <212> PRT
 <213> Homo sapiens

<400> 24
 Met G y Thr Val Ser Ser Arg Arg Ser Trp Trp Pro Leu Pro Leu Leu
 1 5 10 15
 Leu Leu Leu Leu Leu Leu G y Pro Ala G y Ala Arg Ala G n G u
 20 25 30
 Asp G u Asp G y Asp Tyr G u G u Leu Val Leu Ala Leu Arg Ser G u
 35 40 45
 G u Asp G y Leu Ala G u Ala Pro G u His G y Thr Thr Ala Thr Phe
 50 55 60
 His Arg Cys Ala Lys Asp Pro Trp Arg Leu Pro G y Thr Tyr Val Val
 65 70 75 80
 Val Leu Lys G u G u Thr His Leu Ser G n Ser G u Arg Thr Ala Arg
 85 90 95
 Arg Leu G n Ala G n Ala Ala Arg Arg G y Tyr Leu Thr Lys Ile Leu
 100 105 110
 His Val Phe His Leu Leu Pro G y Phe Leu Val Lys Met Ser G y Asp
 115 120 125
 Leu Leu G u Leu Ala Leu Lys Leu Pro His Val Asp Tyr Ile G u G u
 130 135 140
 Asp Ser Ser Val Phe Ala G n Ser Ile Pro Trp Asn Leu G u Arg Ile
 145 150 155 160
 Thr Pro Pro Arg Tyr Arg Ala Asp G u Tyr G n Pro Pro Asp G y G y
 165 170 175
 Ser Leu Val G u Val Tyr Leu Leu Asp Thr Ser Ile G n Ser Asp His
 180 185 190
 Arg G u Ile G u G y Arg Val Met Val Thr Asp Phe G u Asn Val Pro
 195 200 205
 G u G u Asp G y Thr Arg Phe His Arg G n Ala Ser Lys Cys Asp Ser
 210 215 220
 His G y Thr His Leu Ala G y Val Val Ser G y Arg Asp Ala G y Val
 225 230 235 240
 Ala Lys G y Ala Ser Met Arg Ser Leu Arg Val Leu Asn Cys G n G y
 245 250 255
 Lys G y Thr Val Ser G y Thr Leu Ile G y Leu G u Phe Ile Arg Lys
 260 265 270
 Ser G n Leu Val G n Pro Val Pro Leu Val Val Leu Leu Pro Leu Ala
 275 280 285
 G y G y Tyr Ser Arg Val Leu Asn Ala Ala Qys G n Arg Leu Ala Arg
 290 295 300
 Ala G y Val Val Leu Val Thr Ala Ala G y Asn Phe Arg Asp Asp Ala
 305 310 315 320
 Cys Leu Tyr Ser Pro Ala Ser Ala Pro G u Val Ile Thr Val G y Ala
 325 330 335
 Thr Asn Ala G n Asp G n Pro Val Thr Leu G y Thr Leu G y Thr Asn
 340 345 350
 Phe G y Arg Qys Val Asp Leu Phe Ala Pro G y G u Asp Ile Ile G y
 355 360 365
 Ala Ser Ser Asp Cys Ser Thr Cys Phe Val Ser G n Ser G y Thr Ser
 370 375 380
 G n Ala Ala Ala His Val Ala G y Ile Ala Ala Met Met Leu Ser Ala
 385 390 395 400
 G u Pro G u Leu Thr Leu Ala G u Leu Arg G n Leu Ile His Phe Ser
 405 410 415
 Ala Lys Asp Val Ile Asn G u Ala Trp Phe Pro G u Asp G n Arg Val
 420 425 430
 Leu Thr Pro Asn Leu Val Ala Ala Leu Pro Pro Ser Thr His G y Ala
 435 440 445
 G y Trp G n Leu Phe Qys Arg Thr Val Trp Ser Ala His Ser G y Pro
 450 455 460
 Thr Arg Met Ala Thr Ala Ile Ala Arg Cys Ala Pro Asp G u G u Leu
 465 470 475 480
 Leu Ser Cys Ser Ser Phe Ser Arg Ser G y Lys Arg Arg G y G u Arg
 485 490 495

SEQUENCE_LI STI NG_APMOL_005VPC

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gu | Ala | Gn | Gy | Gy | Lys | Leu | Val | Cys | Arg | Ala | His | Asn | Ala | Phe |
| | | | 500 | | | | | 505 | | | | | 510 | | |
| Gy | Gy | Gu | Gy | Val | Tyr | Ala | Ile | Ala | Arg | Cys | Cys | Leu | Leu | Pro | Gn |
| | | | 515 | | | | 520 | | | | | 525 | | | |
| Ala | Asn | Cys | Ser | Val | His | Thr | Ala | Pro | Pro | Ala | Gu | Ala | Ser | Met | Gy |
| | | | 530 | | | 535 | | | | | 540 | | | | |
| Thr | Arg | Val | His | Cys | His | Gn | Gn | Gy | His | Val | Leu | Thr | Gy | Cys | Ser |
| | | | 545 | | | 550 | | | | 555 | | | | 560 | |
| Ser | His | Trp | Glu | Val | Glu | Asp | Leu | Gy | Thr | His | Lys | Pro | Pro | Val | Leu |
| | | | 565 | | | | 570 | | | | | 575 | | | |
| Arg | Pro | Arg | Gly | Gn | Pro | Asn | Gn | Cys | Val | Gy | His | Arg | Gu | Ala | Ser |
| | | | 580 | | | | 585 | | | | | 590 | | | |
| Ile | His | Ala | Ser | Cys | Cys | His | Ala | Pro | Gy | Leu | Gu | Cys | Lys | Val | Lys |
| | | | 595 | | | 600 | | | | | 605 | | | | |
| Gu | His | Gy | Ile | Pro | Ala | Pro | Gn | Gn | Val | Thr | Val | Ala | Cys | Gu | |
| | | | 610 | | | 615 | | | | 620 | | | | | |
| Gu | Gy | Trp | Thr | Leu | Thr | Gy | Cys | Ser | Ala | Leu | Pro | Gy | Thr | Ser | His |
| | | | 625 | | | 630 | | | | 635 | | | | 640 | |
| Val | Leu | Gy | Ala | Tyr | Ala | Val | Asp | Asn | Thr | Cys | Val | Val | Arg | Ser | Arg |
| | | | 645 | | | | 650 | | | | | 655 | | | |
| Asp | Val | Ser | Thr | Thr | Gy | Ser | Thr | Ser | Gu | Gu | Ala | Val | Thr | Ala | Val |
| | | | 660 | | | 665 | | | | | 670 | | | | |
| Ala | Ile | Cys | Arg | Ser | Arg | His | Leu | Ala | Gn | Ala | Ser | Gn | Gu | Leu | |
| | | | 675 | | | 680 | | | | | 685 | | | | |
| Gn | Gy | Pro | His | | | | |
| | | | 690 | | | 695 | | | | | | | | | |

<210> 25

<211> 686

<212> PRT

<213> Cavia porcellus

<400> 25

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Arg | Thr | Arg | Gy | Pro | Ala | Pro | Ala | Trp | Trp | Pro | Met | Leu | Leu | Leu |
| 1 | | | | 5 | | | | | 10 | | | | 15 | | |
| Leu | Met | Leu | Gy | Pro | Ala | Pro | Ala | Gy | Ala | Gn | Ala | Arg | Asp | Ser | Gu |
| | | | | 20 | | | | 25 | | | | | 30 | | |
| Asp | Gy | Asp | His | Gu | Gy | Leu | Ala | Phe | Ala | Phe | Pro | Pro | Gu | Gu | Asp |
| | | | | 35 | | | 40 | | | | | 45 | | | |
| Gy | Pro | Ala | Gu | Ala | Ala | Pro | His | Val | Pro | Thr | Ala | Pro | Phe | His | Arg |
| | | | 50 | | | 55 | | | | 60 | | | | | |
| Qys | Ser | Lys | Asp | Ala | Trp | Arg | Leu | Pro | Gy | Thr | Tyr | Leu | Val | Val | Leu |
| | | | 65 | | | 70 | | | | 75 | | | 80 | | |
| Lys | Gu | Gy | Thr | His | Arg | Gy | Gn | Thr | Lys | His | Thr | Ala | His | Arg | Leu |
| | | | 85 | | | | 90 | | | | | 95 | | | |
| Gn | Ala | Lys | Ala | Ala | Arg | Arg | Gy | Tyr | Val | Thr | Thr | Val | Leu | His | Leu |
| | | | 100 | | | | 105 | | | | | 110 | | | |
| Phe | His | His | Leu | Val | Pro | Gy | Phe | Leu | Val | Arg | Met | Ser | Gy | Asp | Leu |
| | | | 115 | | | | 120 | | | | | 125 | | | |
| Leu | Asp | Met | Ala | Leu | Arg | Leu | Pro | Leu | Val | Gn | Tyr | Ile | Gu | Gu | Asp |
| | | | 130 | | | 135 | | | | | 140 | | | | |
| Ser | Ser | Val | Phe | Ala | Gn | Ser | Val | Pro | Trp | Asn | Leu | Gu | Arg | Ile | Leu |
| | | | 145 | | | 150 | | | | 155 | | | 160 | | |
| Pro | Val | Arg | His | Gn | Ala | Lys | Glu | Tyr | Ser | Ala | Pro | Ser | His | Pro | Val |
| | | | 165 | | | | 170 | | | | | 175 | | | |
| Thr | Val | Tyr | Leu | Leu | Asp | Thr | Ser | Ile | Gn | Ser | Gy | His | Arg | Gu | Ile |
| | | | 180 | | | | 185 | | | | | 190 | | | |
| Gn | Gy | Arg | Ile | Thr | Val | Thr | Asp | Phe | Glu | Ser | Val | Pro | Gn | Gu | Asp |
| | | | 195 | | | | 200 | | | | | 205 | | | |
| Gy | Thr | Arg | Phe | His | Arg | Gn | Ala | Ser | Lys | Oys | Asp | Ser | His | Gy | Thr |
| | | | 210 | | | | 215 | | | | | 220 | | | |
| His | Leu | Ala | Gy | Val | Val | Ser | Gy | Arg | Asp | Ala | Gy | Val | Ala | Lys | Gy |
| | | | 225 | | | 230 | | | | | 235 | | | 240 | |
| Ala | Gy | Leu | Arg | Ser | Leu | Arg | Val | Leu | Asn | Oys | Gn | Gy | Arg | Gy | Thr |
| | | | 245 | | | | 250 | | | | | 255 | | | |
| Val | Ser | Ser | Thr | Leu | Arg | Gy | Leu | Glu | Phe | Ile | Arg | Lys | Ser | Gn | Leu |
| | | | 260 | | | | 265 | | | | | 270 | | | |

SEQUENCE_LI STI NG_APMOL_005VPC

Al a G n Pro Val Glu Pro Leu Val Val Leu Leu Pro Leu Al a G y G y
 275 280 285
 Tyr Ser Arg Thr Leu Asn Al a Al a Cys His Leu Leu Al a Arg Al a G y
 290 295 300
 Val Val Leu Val Al a Al a Al a G y Asn Phe Arg Asp Asp Al a Cys Leu
 305 310 315 320
 Tyr Ser Pro Al a Ser Al a Pro Glu Val Ile Thr Val G y Al a Thr Asn
 325 330 335
 Al a G n Asp G n Pro Val Thr Leu G y Thr Leu G y Thr Asn Phe G y
 340 345 350
 Arg Cys Val Asp Leu Phe Al a Pro G y Glu Asp Ile Ile G y Al a Ser
 355 360 365
 Ser Asp Cys Ser Thr Cys Phe Val Ser Arg Ser G y Thr Ser G n Al a
 370 375 380
 Al a Al a His Val Al a G y Ile Val Thr Met Met Leu Thr Al a G n Pro
 385 390 395 400
 Lys Leu Thr Leu Al a G u Leu Trp G n Arg Leu Ile His Phe Al a Al a
 405 410 415
 Lys Asp Val Ile Asn Glu Al a Trp Phe Pro Glu Asp G n Arg Val Leu
 420 425 430
 Thr Pro Asn Leu Val Al a Thr Leu Pro Pro Ser Thr Arg G y Al a G y
 435 440 445
 G y Arg Leu Leu Cys Arg Thr Val Trp Ser Al a Arg Ser G y Pro Arg
 450 455 460
 His Thr Al a Thr Al a Leu Al a His Cys Thr Pro G y Glu Glu Leu Leu
 465 470 475 480
 Ser Cys Ser Ser Phe Ser Arg Ser G y Lys Arg Lys G y Glu Arg Ile
 485 490 495
 Glu Val Leu Arg G y Arg Arg Val Oys Val Al a Tyr Asn Al a Phe G y
 500 505 510
 G y Lys G y Val His Al a Val Al a Arg Oys Cys Leu Leu Pro Arg Al a
 515 520 525
 Asn Cys Ser Leu His Thr Al a Pro Al a Arg Al a G y Met Glu Pro Arg
 530 535 540
 Val His Cys His Arg Lys Asp G n Val Leu Thr G y Cys Ser Al a His
 545 550 555 560
 Trp G u Al a G u Asp Phe Arg Al a Arg G y Trp Pro Met Leu Arg Pro
 565 570 575
 G y G y Pro Ser G n Cys Val G y His Ser Lys Al a Ser Val His Al a
 580 585 590
 Ser Cys Cys Ser Al a Pro G y Leu G u Oys Arg Ile Arg G u His G y
 595 600 605
 Val Pro Trp Pro Al a G u G n Val Thr Val Al a Cys G u Asp G y Trp
 610 615 620
 Thr Leu Thr G y Cys Ser Thr Leu Pro G y Al a Ser Ser Val Leu G y
 625 630 635 640
 Thr Tyr Al a Val Asp Asp Met Cys Val Val Arg Ser Arg Asp Val Lys
 645 650 655
 Al a Leu Asp Arg Thr Arg G y G u Al a Leu Al a Al a Ile Al a Ile Cys
 660 665 670
 Cys Arg Ser G n Al a Ser G u G n Al a Ser Pro G u Arg G n
 675 680 685

<210> 26

<211> 698

<212> PRT

<213> Mesocricetus auratus

<400> 26

Met G y Thr Ser Cys Ser Al a Arg Pro Arg Trp Leu Leu Ser Pro Leu
 1 5 10 15
 Leu Leu Leu Leu Leu Leu Arg Tyr Met G y Al a Ser Al a G n Asp
 20 25 30
 G u Asp Al a G u Tyr G u G u Leu Met Leu Thr Leu G n Ser G n Asp
 35 40 45
 Asp G y Leu Al a Asp G u Thr Asp G u Al a Pro G n G y Al a Thr Al a
 50 55 60

SEQUENCE_LI STI NG_APMOL_005VPC

Ala Phe His Arg Cys Pro Gu Glu Ala Trp Arg Val Pro Gly Thr Tyr
 65 70 75 80
 Ile Val Met Leu Ala Glu Gu Ala Gln Trp Val His Ile Glu Gln Thr
 85 90 95
 Met His Arg Leu Gln Thr Gln Ala Ala Arg Arg Gly Tyr Val Ile Lys
 100 105 110 115
 Ile Gln His Ile Phe Tyr Asp Phe Leu Pro Ala Phe Val Val Lys Met
 120 125
 Ser Ser Asp Leu Leu Asp Leu Ala Leu Lys Leu Pro His Val Lys Tyr
 130 135 140
 Ile Gu Glu Asp Ser Leu Val Phe Ala Gln Ser Ile Pro Trp Asn Leu
 145 150 155 160
 Asp Arg Ile Ile Pro Ala Gly Arg Gln Ala Gln Gu Tyr Ser Ser Ser
 165 170 175
 Arg Lys Val Pro Ser Gly Ser Gly Gln Val Glu Val Tyr Leu Leu Asp
 180 185 190
 Thr Ser Ile Gln Ser Asp His Arg Gln Ile Glu Gly Arg Val Thr Val
 195 200 205
 Thr Asp Phe Asn Ser Val Pro Glu Glu Asp Gly Thr Arg Phe His Arg
 210 215 220
 Gln Ala Ser Lys Cys Asp Ser His Gly Thr His Leu Ala Gly Val Val
 225 230 235 240
 Ser Gly Arg Asp Ala Gly Val Ala Lys Gly Thr Ile Leu His Gly Leu
 245 250 255
 Arg Val Leu Asn Cys Gln Gly Lys Gly Ile Val Ser Gly Ile Leu Thr
 260 265 270
 Gly Leu Glu Phe Ile Trp Lys Ser Gln Leu Met Gln Pro Ser Gly Pro
 275 280 285
 Gln Val Val Leu Leu Pro Leu Ala Gly Arg Tyr Ser Arg Val Leu Asn
 290 295 300
 Thr Ala Cys Gln His Leu Ala Arg Thr Gly Val Val Leu Val Ala Ala
 305 310 315 320
 Ala Gly Asn Phe Arg Asp Asp Ala Cys Leu Tyr Ser Pro Ala Ser Ala
 325 330 335
 Pro Glu Val Ile Thr Val Gly Ala Thr Asp Val Gln Asp Gln Pro Val
 340 345 350
 Thr Leu Gly Thr Leu Gly Thr Asn Phe Gly Arg Cys Val Asp Leu Phe
 355 360 365
 Ala Pro Gly Lys Asp Ile Ile Gly Ala Ser Ser Asp Cys Ser Ala Cys
 370 375 380
 Phe Met Ser Gln Ser Gly Thr Ser Gln Ala Ala Ala His Val Ala Gly
 385 390 395 400
 Ile Val Ala Met Met Leu Thr Leu Glu Pro Glu Leu Thr Leu Thr Glu
 405 410 415
 Leu Arg Gln Arg Leu Ile His Phe Ser Thr Lys Asp Ala Ile Asn Met
 420 425 430
 Ala Trp Phe Pro Glu Asp Gln Arg Val Leu Thr Pro Asn Leu Val Ala
 435 440 445
 Thr Leu Pro Pro Ser Thr His Gly Thr Gly Gln Leu Leu Cys Arg
 450 455 460
 Thr Val Trp Ser Ala His Ser Gly Pro Thr Arg Ala Ala Thr Ala Thr
 465 470 475 480
 Ala Arg Cys Ala Pro Gly Gu Glu Leu Leu Ser Cys Ser Ser Phe Ser
 485 490 495
 Arg Ser Gly Arg Arg Arg Gly Asp Arg Ile Glu Ala Ala Gly Thr Gln
 500 505 510
 Gln Val Cys Lys Ala Leu Asn Ala Phe Gly Gly Gu Gly Val Tyr Ala
 515 520 525
 Val Ala Arg Cys Cys Leu Leu Pro Arg Ala Asn Cys Ser Ile His Thr
 530 535 540
 Thr Pro Ala Ala Arg Thr Ser Leu Glu Thr His Ala His Cys His Gln
 545 550 555 560
 Lys Asp His Val Leu Thr Gly Cys Ser Leu His Trp Glu Val Glu Gly
 565 570 575
 Ile Gly Val Gln Pro Leu Ala Val Leu Arg Ser Arg His Gln Pro Gly
 580 585 590
 Gln Cys Thr Gly His Arg Gu Ala Ser Val His Ala Ser 600 605
 595

SEQUENCE_LI STI NG_APMOL_005VPC

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Pro | Gly | Leu | Glu | Cys | Lys | Ile | Lys | Glu | His | Gly | Ile | Ser | Gly | Pro |
| 610 | | | | | | 615 | | | | | 620 | | | | |
| Ala | Glu | Gln | Val | Thr | Val | Ala | Cys | Glu | Ala | Gly | Trp | Thr | Leu | Thr | Gly |
| 625 | | | | | | 630 | | | | | 635 | | | | 640 |
| Cys | Asn | Val | Leu | Pro | Gly | Ala | Phe | Ile | Thr | Leu | Gly | Ala | Tyr | Ala | Val |
| | | | | | | 645 | | | | | 650 | | | | 655 |
| Asp | Asn | Thr | Cys | Val | Ala | Arg | Ser | Arg | Val | Thr | Asp | Thr | Ala | Gly | Arg |
| | | | | | | 660 | | | | | 665 | | | | 670 |
| Thr | Gly | Glu | Gl | Ala | Thr | Val | Ala | Ala | Ala | Ile | Cys | Cys | Arg | Asn | Arg |
| | | | | | | 675 | | | | | 680 | | | | 685 |
| Pro | Ser | Ala | Lys | Ala | Ser | Trp | Val | His | Gln | | | | | | |
| | | | | | | 690 | | | | | 695 | | | | |

<210> 27
<211> 685
<212> PRT
<213> Mus musculus

<400> 27

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Gly | Thr | His | Cys | Ser | Ala | Trp | Leu | Arg | Trp | Pro | Leu | Leu | Pro | Leu |
| 1 | | | | 5 | | | | | 10 | | | | | | 15 |
| Leu | Pro | Pro | Leu | Cys | Pro | Thr | Gly | Ala | |
| | | | | | | | | | | 25 | | 30 | | | |
| Gly | Ala | Gln | Asp | Glu | Asp | Gly | Asp | Tyr | Glu | Glu | Leu | Met | Leu | Ala | Leu |
| | | | | | | | | | | | 45 | | | | |
| Pro | Ser | Gln | Glu | Asp | Gly | Leu | Ala | Asp | Glu | Ala | Ala | Ala | His | Val | Ala |
| | | | | | | 50 | | | | | 60 | | | | |
| Ala | Thr | Phe | Arg | Arg | Cys | Ser | Lys | Glu | Ala | Trp | Arg | Leu | Pro | Gly | Thr |
| | | | | | | 65 | | | | | 75 | | | | 80 |
| Tyr | Ile | Val | Val | Leu | Met | Glu | Glu | Thr | Gln | Arg | Leu | Gln | Ile | Glu | Gln |
| | | | | | | 85 | | | | | 90 | | | | 95 |
| Thr | Ala | His | Arg | Leu | Gln | Thr | Arg | Ala | Ala | Arg | Arg | Gly | Tyr | Val | Ile |
| | | | | | | 100 | | | | | 105 | | | | 110 |
| Lys | Val | Leu | His | Ile | Phe | Tyr | Asp | Leu | Phe | Pro | Gly | Phe | Leu | Val | Lys |
| | | | | | | 115 | | | | | 120 | | | | 125 |
| Met | Ser | Ser | Asp | Leu | Leu | Gly | Leu | Ala | Leu | Lys | Leu | Pro | His | Val | Glu |
| | | | | | | 130 | | | | | 135 | | | | 140 |
| Tyr | Ile | Glu | Glu | Asp | Ser | Phe | Val | Phe | Ala | Gln | Ser | Ile | Pro | Trp | Asn |
| | | | | | | 145 | | | | | 150 | | | | 160 |
| Leu | Arg | Ile | Ile | Pro | Ala | Trp | His | Gln | Thr | Glu | Glu | Asp | Arg | Ser | Pro |
| | | | | | | 165 | | | | | 170 | | | | 175 |
| Asp | Gly | Ser | Ser | Gln | Val | Glu | Val | Tyr | Leu | Leu | Asp | Thr | Ser | Ile | Gln |
| | | | | | | 180 | | | | | 185 | | | | 190 |
| Gly | Ala | His | Arg | Glu | Ile | Glu | Gly | Arg | Val | Thr | Ile | Thr | Asp | Phe | Asn |
| | | | | | | 195 | | | | | 200 | | | | 205 |
| Ser | Val | Pro | Glu | Glu | Asp | Gly | Thr | Arg | Phe | His | Arg | Gln | Ala | Ser | Lys |
| | | | | | | 210 | | | | | 215 | | | | 220 |
| Cys | Asp | Ser | His | Gly | Thr | His | Leu | Ala | Gly | Val | Val | Ser | Gly | Arg | Asp |
| | | | | | | 225 | | | | | 230 | | | | 240 |
| Ala | Gly | Val | Ala | Lys | Gly | Thr | Ser | Leu | His | Ser | Leu | Arg | Val | Leu | Asn |
| | | | | | | 245 | | | | | 250 | | | | 255 |
| Cys | Gln | Gly | Lys | Gly | Thr | Val | Ser | Gly | Thr | Leu | Ile | Gly | Leu | Glu | Phe |
| | | | | | | 260 | | | | | 265 | | | | 270 |
| Ile | Arg | Lys | Ser | Gln | Leu | Ile | Gln | Pro | Ser | Pro | Leu | Val | Val | Val | Leu |
| | | | | | | 275 | | | | | 280 | | | | 285 |
| Leu | Ala | Gly | Gly | Tyr | Ser | Arg | Ile | Leu | Asn | Ala | Ala | Cys | Arg | His | Leu |
| | | | | | | 290 | | | | | 295 | | | | 300 |
| Ala | Arg | Thr | Gly | Val | Val | Leu | Val | Ala | Ala | Ala | Gly | Asn | Phe | Arg | Asp |
| | | | | | | 305 | | | | | 310 | | | | 320 |
| Asp | Ala | Cys | Leu | Tyr | Ser | Pro | Ala | Ser | Ala | Pro | Glu | Val | Ile | Thr | Val |
| | | | | | | 325 | | | | | 330 | | | | 335 |
| Gly | Ala | Thr | Asn | Ala | Gln | Asp | Gln | Pro | Val | Thr | Leu | Gly | Thr | Leu | Gly |
| | | | | | | 340 | | | | | 345 | | | | 350 |
| Thr | Asn | Phe | Gly | Arg | Qys | Val | Asp | Leu | Phe | Ala | Pro | Gly | Lys | Asp | Ile |
| | | | | | | 355 | | | | | 360 | | | | 365 |
| Ile | Gly | Ala | Ser | Ser | Asp | Cys | Ser | Thr | Cys | Phe | Met | Ser | Gln | Ser | Gly |
| | | | | | | 370 | | | | | 375 | | | | 380 |

SEQUENCE_LI STI NG_APMOL_005VPC

Thr Ser Gln Ala Ala Ala His Val Ala Gly Ile Val Ala Arg Met Leu
 385 390 395 400
 Ser Arg Glu Pro Thr Leu Thr Leu Ala Leu Arg Gln Arg Ile His Phe
 405 410 415
 Ser Thr Lys Asp Val Ile Asn Met Ala Trp Phe Pro Glu Asp Gln Gln
 420 425 430
 Val Leu Thr Pro Asn Leu Val Ala Thr Leu Pro Pro Ser Thr His Glu
 435 440 445
 Thr Gly Gly Gln Leu Leu Cys Arg Thr Val Trp Ser Ala His Ser Gly
 450 455 460
 Pro Thr Arg Thr Ala Thr Ala Thr Ala Arg Cys Ala Pro Glu Glu
 465 470 475 480
 Leu Leu Ser Cys Ser Phe Ser Arg Ser Gly Arg Arg Arg Gly Asp
 485 490 495
 Arg Ile Glu Ala Ile Gly Gly Gln Gln Val Cys Lys Ala Leu Asn Ala
 500 505 510
 Phe Gly Gly Glu Gly Val Tyr Ala Val Ala Arg Cys Cys Leu Val Pro
 515 520 525
 His Ala Asn Cys Ser Ile His Asn Pro Ala Ala Ala Gly Leu Glu Thr
 530 535 540
 His Val His Cys His Gln Lys Asp His Val Leu Thr Gly Cys Ser Phe
 545 550 555 560
 His Trp Glu Val Glu Asp Leu Ser Val Arg Arg Gln Pro Ala Leu Arg
 565 570 575
 Ser Arg Arg Gln Pro Gly Gln Cys Val Gly His Gln Ala Ala Ser Val
 580 585 590
 Tyr Ala Ser Cys Cys His Ala Pro Gly Leu Glu Cys Lys Ile Lys Glu
 595 600 605
 His Gly Ile Ser Gly Ser Ser Glu Gln Val Thr Val Ala Cys Glu Ala
 610 615 620
 Gly Trp Thr Leu Thr Gly Cys Asn Val Leu Pro Gly Ala Ser Leu Thr
 625 630 635 640
 Leu Gly Ala Tyr Ser Val Asp Asn Leu Cys Val Ala Arg Val His Asp
 645 650 655
 Thr Ala Arg Ala Asp Arg Thr Gly Glu Thr Val Ala Ala Ala Ile Cys
 660 665 670
 Cys Arg Ser Arg Pro Ser Ala Lys Ala Ser Trp Val Gln
 675 680 685

<210> 28

<211> 683

<212> PRT

<213> Macaca fascicularis

<400> 28

Met Gly Thr Val Ser Ser Arg Arg Ser Trp Trp Pro Leu Pro Leu Pro
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 20 25 30
 Asp Glu Asp Gly Asp Tyr Gu Glu Leu Val Leu Ala Leu Arg Ser Glu
 35 40 45
 Glu Asp Gly Leu Ala Asp Ala Pro Glu His Gly Ala Thr Ala Thr Phe
 50 55 60
 His Arg Cys Ala Lys Asp Pro Trp Arg Leu Pro Gly Thr Tyr Val Val
 65 70 75 80
 Val Leu Lys Glu Glu Thr His Arg Ser Gln Ser Glu Arg Thr Ala Arg
 85 90 95
 Arg Leu Gln Ala Gln Ala Ala Arg Arg Gly Tyr Leu Thr Lys Ile Leu
 100 105 110
 His Val Phe His His Leu Leu Pro Gly Phe Leu Val Lys Met Ser Gly
 115 120 125
 Asp Leu Leu Glu Leu Ala Leu Lys Leu Pro His Val Asp Tyr Ile Glu
 130 135 140
 Glu Asp Ser Ser Val Phe Ala Gln Ser Ile Pro Trp Asn Glu Arg Ile
 145 150 155 160
 Thr Pro Ala Arg Tyr Arg Ala Asp Glu Tyr Gln Pro Pro Lys Gly Gly
 165 170 175

SEQUENCE_LI STI NG_APML_005VPC

| | | | | | | | | | | | | | | | |
|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|------|
| Ser | Leu | Val | Gl u | Val | Tyr | Leu | Leu | Asp | Thr | Ser | Ile | Gl n | Ser | Asp | Hi s |
| | | | 180 | | | | | 185 | | | | 190 | | | |
| Arg | Gl u | Ile | Gl u | Gl y | Arg | Val | Met | Val | Thr | Asp | Phe | Gl u | Ser | Val | Pro |
| | 195 | | | | | 200 | | | | | 205 | | | | |
| Gl u | Gl u | Asp | Gl y | Thr | Arg | Phe | Hi s | Arg | Gl n | Al a | Ser | Lys | Cys | Asp | Ser |
| | 210 | | | | 215 | | | | 220 | | | | | | |
| Hi s | Gl y | Thr | Hi s | Leu | Al a | Gl y | Val | Val | Ser | Gl y | Arg | Asp | Al a | Gl y | Val |
| | 225 | | | 230 | | | | | 235 | | | | 240 | | |
| Al a | Lys | Gl y | Al a | Gl y | Leu | Arg | Ser | Leu | Arg | Val | Leu | Asn | Cys | Gl n | Gl y |
| | | | | 245 | | | | 250 | | | | 255 | | | |
| Lys | Gl y | Thr | Val | Ser | Gl y | Thr | Leu | Ile | Gl y | Leu | Gl u | Phe | Ile | Arg | Lys |
| | | | 260 | | | | 265 | | | | 270 | | | | |
| Ser | Gl n | Leu | Val | Gl n | Pro | Val | Pro | Leu | Val | Val | Leu | Pro | Leu | Al a | Gl y |
| | | | | 275 | | | 280 | | | | 285 | | | | |
| Gl y | Tyr | Ser | Arg | Val | Phe | Asn | Al a | Al a | Cys | Gl n | Arg | Leu | Al a | Arg | Al a |
| | 290 | | | | 295 | | | | 300 | | | | | | |
| Gl y | Val | Val | Leu | Val | Thr | Al a | Al a | Gl y | Asn | Phe | Arg | Asp | Asp | Al a | Cys |
| | 305 | | | | 310 | | | | 315 | | | | 320 | | |
| Leu | Tyr | Ser | Pro | Al a | Ser | Al a | Pro | Gl u | Val | Ile | Thr | Val | Gl y | Al a | Thr |
| | | | 325 | | | | 330 | | | | 335 | | | | |
| Asn | Al a | Gl n | Asp | Gl n | Pro | Val | Thr | Leu | Gl y | Thr | Leu | Gl y | Thr | Asn | Phe |
| | | | 340 | | | | 345 | | | | 350 | | | | |
| Gl y | Arg | Cys | Val | Asp | Leu | Phe | Al a | Pro | Gl y | Gl u | Asp | Ile | Ile | Gl y | Al a |
| | | | 355 | | | 360 | | | | 365 | | | | | |
| Ser | Ser | Asp | Cys | Ser | Thr | Cys | Phe | Val | Ser | Arg | Ser | Gl y | Thr | Ser | Gl n |
| | | | | | 375 | | | | 380 | | | | | | |
| Al a | Al a | Al a | Hi s | Val | Al a | Gl y | Ile | Al a | Al a | Met | Met | Leu | Ser | Al a | Gl u |
| | | | | 385 | | 390 | | | 395 | | | | 400 | | |
| Pro | Gl u | Leu | Thr | Leu | Al a | Leu | Arg | Gl n | Leu | Ile | His | Phe | Ser | Al a | Lys |
| | | | 405 | | | | 410 | | | | 415 | | | | |
| Asp | Val | Ile | Asn | Gl u | Al a | Trp | Phe | Pro | Gl u | Asp | Gl n | Arg | Val | Leu | Thr |
| | | | 420 | | | | 425 | | | | 430 | | | | |
| Pro | Asn | Leu | Val | Al a | Al a | Leu | Pro | Pro | Ser | Thr | His | Arg | Al a | Gl y | Trp |
| | | | 435 | | | | 440 | | | | 445 | | | | |
| Gl n | Leu | Phe | Cys | Arg | Thr | Val | Trp | Ser | Al a | Hi s | Ser | Gl y | Pro | Thr | Arg |
| | | | 450 | | | 455 | | | | 460 | | | | | |
| Met | Al a | Thr | Al a | Val | Al a | Arg | Cys | Al a | Gl n | Asp | Gl u | Gl u | Leu | Leu | Ser |
| | | | 465 | | | 470 | | | | 475 | | | | 480 | |
| Cys | Ser | Ser | Phe | Ser | Arg | Ser | Gl y | Lys | Arg | Arg | Gl y | Gl u | Arg | Ile | Gl u |
| | | | | 485 | | | | 490 | | | | 495 | | | |
| Al a | Gl n | Gl y | Gl y | Lys | Arg | Val | Cys | Arg | Al a | Hi s | Asn | Al a | Phe | Gl y | Gl y |
| | | | | 500 | | | 505 | | | | 510 | | | | |
| Gl u | Gl y | Val | Tyr | Al a | Ile | Al a | Arg | Oys | Cys | Leu | Leu | Pro | Gl n | Val | Asn |
| | | | 515 | | | 520 | | | | 525 | | | | | |
| Cys | Ser | Val | Hi s | Thr | Pro | Pro | Gl y | Al a | Ser | Met | Gl y | Thr | Arg | Val | Hi s |
| | | | 530 | | | 535 | | | | 540 | | | | | |
| Cys | Hi s | Gl n | Gl n | Gl y | Hi s | Val | Leu | Thr | Gl y | Cys | Ser | Ser | Hi s | Trp | Gl u |
| | | | 545 | | | 550 | | | | 555 | | | | 560 | |
| Val | Gl u | Asp | Leu | Gl y | Thr | Hi s | Lys | Pro | Pro | Val | Leu | Arg | Pro | Arg | Gl y |
| | | | | 565 | | | 570 | | | | 575 | | | | |
| Gl n | Pro | Asn | Gl n | Cys | Val | Gl y | Hi s | Arg | Gl u | Al a | Ser | Ile | His | Al a | Ser |
| | | | | 580 | | | 585 | | | | 590 | | | | |
| Cys | Cys | Hi s | Al a | Pro | Gl y | Leu | Gl u | Cys | Lys | Val | Arg | Gl u | Hi s | Gl y | Ile |
| | | | 595 | | | 600 | | | | 605 | | | | | |
| Pro | Al a | Pro | Gl n | Gl u | Gl n | Val | Ile | Val | Al a | Cys | Gl u | Asp | Gl y | Trp | Thr |
| | | | 610 | | | 615 | | | | 620 | | | | | |
| Leu | Thr | Gl y | Cys | Ser | Al a | Leu | Pro | Gl y | Thr | Ser | Hi s | Val | Leu | Gl y | Al a |
| | | | 625 | | | 630 | | | | 635 | | | | 640 | |
| Tyr | Al a | Val | Asp | Asn | Thr | Cys | Val | Val | Arg | Ser | Arg | Asp | Val | Ser | Thr |
| | | | 645 | | | | | 650 | | | | 655 | | | |
| Thr | Gl y | Ser | Thr | Gl u | Al a | Val | Al a | Al a | Val | Al a | Ile | Cys | Cys | Arg | Ser |
| | | | 660 | | | | 665 | | | | 670 | | | | |
| Arg | Hi s | Leu | Val | Gl n | Al a | Ser | Gl n | Gl u | Leu | Gl n | | | | | |
| | 675 | | | | | 680 | | | | | | | | | |

SEQUENCE_LI STI NG_APMOL_005VPC

<212> PRT

<213> Rattus norvegicus

<400> 29

Met Gly Ile Arg Cys Ser Thr Trp Leu Arg Trp Pro Leu Ser Pro Glu
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 20 25 30
 Glu Asp Gly Asp Tyr Glu Glu Leu Met Leu Ala Leu Pro Ser Glu Glu
 35 40 45
 Asp Ser Leu Val Asp Glu Ala Ser His Val Ala Thr Ala Thr Phe Arg
 50 55 60
 Arg Cys Ser Lys Glu Ala Trp Arg Leu Pro Gly Thr Tyr Val Val Val
 65 70 75 80
 Leu Met Glu Glu Thr Glu Arg Leu Glu Val Glu Glu Thr Ala His Arg
 85 90 95
 Leu Glu Thr Trp Ala Ala Arg Arg Gly Tyr Val Ile Lys Val Leu His
 100 105 110
 Val Phe Tyr Asp Leu Phe Pro Gly Phe Leu Val Lys Met Ser Ser Asp
 115 120 125
 Leu Leu Glu Leu Ala Leu Lys Leu Pro His Val Glu Tyr Ile Glu Glu
 130 135 140
 Asp Ser Leu Val Phe Ala Glu Ser Ile Pro Trp Asn Leu Glu Arg Ile
 145 150 155 160
 Ile Pro Ala Trp Glu Glu Thr Glu Glu Asp Ser Ser Pro Asp Gly Ser
 165 170 175
 Ser Glu Val Glu Val Tyr Leu Leu Asp Thr Ser Ile Glu Ser Gly His
 180 185 190
 Arg Glu Ile Glu Gly Arg Val Thr Ile Thr Asp Phe Asn Ser Val Pro
 195 200 205
 Glu Glu Asp Gly Thr Arg Phe His Arg Glu Ala Ser Lys Cys Asp Ser
 210 215 220
 His Glu Thr His Leu Ala Glu Val Val Ser Glu Arg Asp Ala Glu Val
 225 230 235 240
 Ala Lys Glu Thr Ser Leu His Ser Leu Arg Val Leu Asn Cys Glu Glu
 245 250 255
 Lys Glu Thr Val Ser Glu Thr Leu Ile Glu Leu Glu Phe Ile Arg Lys
 260 265 270
 Ser Glu Leu Ile Glu Pro Ser Glu Pro Leu Val Val Leu Leu Pro Leu
 275 280 285
 Ala Glu Glu Tyr Ser Arg Ile Leu Asn Thr Ala Cys Glu Arg Leu Ala
 290 295 300
 Arg Thr Glu Val Val Leu Val Ala Ala Ala Glu Asn Phe Arg Asp Asp
 305 310 315 320
 Ala Oys Leu Tyr Ser Pro Ala Ser Ala Pro Glu Val Ile Thr Val Glu
 325 330 335
 Ala Thr Asn Ala Glu Asp Glu Pro Val Thr Leu Glu Thr Leu Glu Thr
 340 345 350
 Asn Phe Glu Arg Cys Val Asp Leu Phe Ala Pro Glu Lys Asp Ile Ile
 355 360 365
 Glu Ala Ser Ser Asp Cys Ser Thr Cys Tyr Met Ser Glu Ser Glu Thr
 370 375 380
 Ser Glu Ala Ala Ala His Val Ala Glu Ile Val Ala Met Met Leu Asn
 385 390 395 400
 Arg Asp Pro Ala Leu Thr Leu Ala Glu Leu Arg Glu Arg Leu Ile Leu
 405 410 415
 Phe Ser Thr Lys Asp Val Ile Asn Met Ala Trp Phe Pro Glu Asp Glu
 420 425 430
 Arg Val Leu Thr Pro Asn Arg Val Ala Thr Leu Pro Pro Ser Thr Glu
 435 440 445
 Glu Thr Glu Glu Glu Leu Leu Cys Arg Thr Val Trp Ser Ala His Ser
 450 455 460
 Gly Pro Thr Arg Thr Ala Thr Ala Arg Cys Ala Pro Glu Glu
 465 470 475 480
 Glu Leu Leu Ser Cys Ser Ser Phe Ser Arg Ser Glu Arg Arg Arg Glu
 485 490 495
 Asp Arg Ile Glu Ala Ile Glu Glu Glu Val Cys Lys Ala Leu Asn
 500 505 510

SEQUENCE_LI STI NG_APMOL_005VPC

Ala Phe Gly Gly Glu Gly Val Tyr Ala Val Ala Arg Cys Cys Leu Leu
 515 520 525
 Pro Arg Val Asn Cys Ser Ile His Asn Thr Pro Ala Ala Arg Ala Gly
 530 535 540
 Pro Gln Thr Pro Val His Cys His Gln Lys Asp His Val Leu Thr Gly
 545 550 555 560
 Cys Ser Phe His Trp Glu Val Glu Asn Leu Arg Ala Gln Gln Gln Pro
 565 570 575
 Leu Leu Arg Ser Arg His Gln Pro Gly Gln Cys Val Gly His Gln Glu
 580 585 590
 Ala Ser Val His Ala Ser Cys Cys His Ala Pro Gly Leu Glu Cys Lys
 595 600 605
 Ile Lys Glu His Gly Ile Ala Gly Pro Ala Glu Gln Val Thr Val Ala
 610 615 620
 Cys Glu Ala Gly Trp Thr Leu Thr Gly Cys Asn Val Leu Pro Gly Ala
 625 630 635 640
 Ser Leu Pro Leu Gly Ala Tyr Ser Val Asp Asn Val Cys Val Ala Arg
 645 650 655
 Ile Arg Asp Ala Gly Arg Ala Asp Arg Thr Ser Glu Glu Ala Thr Val
 660 665 670
 Ala Ala Ala Ile Cys Cys Arg Ser Arg Pro Ser Ala Lys Ala Ser Trp
 675 680 685
 Val His Gln
 690

<210> 30

<211> 702

<212> PRT

<213> Artificial Sequence

<220>

<223> Consensus sequence

<220>

<221> VARI ANT

<222> 4, 14, 15, 16, 17, 18, 63, 64, 65, 180, 181, 182, 183, 583, 584, 586, 701

<223> Xaa = Any Amino Acid or No Amino Acid

<400> 30

Met Gly Thr Xaa Cys Ser Ala Arg Ser Trp Trp Pro Leu Xaa Xaa Xaa
 1 5 10 15
 Xaa Xaa Pro Leu Leu Leu Leu Leu Leu Pro Ala Gly Ala Ala
 20 25 30
 Ala Ala Gln Asp Glu Asp Gly Asp Tyr Glu Glu Leu Met Leu Ala Leu
 35 40 45
 Pro Ser Gln Glu Asp Gly Leu Ala Asp Glu Ala Glu His Val Xaa Xaa
 50 55 60
 Xaa Ala Thr Ala Thr Phe His Arg Cys Ser Lys Asp Ala Trp Arg Leu
 65 70 75 80
 Pro Gly Thr Tyr Val Val Val Leu Lys Glu Glu Thr Gln Arg Leu Gln
 85 90 95
 Ser Glu Gln Thr Ala His Arg Leu Gln Thr Gln Ala Ala Arg Arg Gly
 100 105 110
 Tyr Val Thr Lys Ile Leu His Val Phe His Asp Leu Leu Pro Gly Phe
 115 120 125
 Leu Val Lys Met Ser Ser Asp Leu Leu Asp Leu Ala Leu Lys Leu Pro
 130 135 140
 His Val Asp Tyr Ile Glu Glu Asp Ser Ser Val Phe Ala Gln Ser Ile
 145 150 155 160
 Pro Trp Asn Leu Glu Arg Ile Ile Pro Ala Arg His Gln Ala Asp Glu
 165 170 175
 Tyr Ser Ser Xaa Xaa Xaa Xaa Pro Asp Gly Ser Ser Glu Val Glu Val
 180 185 190
 Tyr Leu Leu Asp Thr Ser Ile Gln Ser Asp His Arg Glu Ile Glu Gly
 195 200 205
 Arg Val Thr Val Thr Asp Phe Asn Ser Val Pro Glu Glu Asp Gly Thr

SEQUENCE_LI STI NG_APMDL_005VPC

| | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| 210 | Arg | Phe | His | Arg | Gln | Ala | 215 | Ser | Lys | Cys | Asp | Ser | 220 | His | Gly | Thr | His | Leu |
| 225 | | | | | | | 230 | | | | | 235 | | | | | 240 | |
| | Ala | Gly | Val | Val | Ser | Gly | | Arg | Asp | Ala | Gly | Val | Ala | Lys | Gly | Thr | Ser | |
| | | | | | 245 | | | | | | 250 | | | | | 255 | | |
| | Leu | Arg | Ser | Leu | Arg | Val | Leu | Asn | Cys | Gln | Gly | Lys | Gly | Thr | Val | Ser | | |
| | | | | | 260 | | | | 265 | | | | | 270 | | | | |
| | Gly | Thr | Leu | Ile | Gly | Leu | Glu | Phe | Ile | Arg | Lys | Ser | Gln | Leu | Ile | Gln | | |
| | | | | | 275 | | | 280 | | | | | 285 | | | | | |
| | Pro | Val | Gly | Pro | Leu | Val | Val | Leu | Leu | Pro | Leu | Ala | Gly | Gly | Tyr | Ser | | |
| | | | | | 290 | | | 295 | | | | 300 | | | | | | |
| | Arg | Val | Leu | Asn | Ala | Ala | Cys | Gln | Arg | Leu | Ala | Arg | Thr | Gly | Val | Val | | |
| | | | | | 305 | | | 310 | | | | 315 | | | | 320 | | |
| | Leu | Val | Ala | Ala | Ala | Gly | Asn | Phe | Arg | Asp | Asp | Ala | Cys | Leu | Tyr | Ser | | |
| | | | | | 325 | | | 330 | | | | | | 335 | | | | |
| | Pro | Ala | Ser | Ala | Pro | Glu | Val | Ile | Thr | Val | Gly | Ala | Thr | Asn | Ala | Gln | | |
| | | | | | 340 | | | 345 | | | | | 350 | | | | | |
| | Asp | Gln | Pro | Val | Thr | Leu | Gly | Thr | Leu | Gly | Thr | Asn | Phe | Gly | Arg | Cys | | |
| | | | | | 355 | | | 360 | | | | 365 | | | | | | |
| | Val | Asp | Leu | Phe | Ala | Pro | Gly | Lys | Asp | Ile | Ile | Gly | Ala | Ser | Ser | Asp | | |
| | | | | | 370 | | | 375 | | | | 380 | | | | | | |
| | Cys | Ser | Thr | Cys | Phe | Met | Ser | Gln | Ser | Gly | Thr | Ser | Gln | Ala | Ala | Ala | | |
| | | | | | 385 | | | 390 | | | | 395 | | | | 400 | | |
| | His | Val | Ala | Gly | Ile | Val | Ala | Met | Met | Leu | Ser | Ala | Glu | Pro | Glu | Leu | | |
| | | | | | 405 | | | 410 | | | | 415 | | | | | | |
| | Thr | Leu | Ala | Glu | Leu | Arg | Gln | Arg | Leu | Ile | His | Phe | Ser | Thr | Lys | Asp | | |
| | | | | | 420 | | | 425 | | | | 430 | | | | | | |
| | Val | Ile | Asn | Met | Ala | Trp | Phe | Pro | Glu | Asp | Gln | Arg | Val | Leu | Thr | Pro | | |
| | | | | | 435 | | | 440 | | | | 445 | | | | | | |
| | Asn | Leu | Val | Ala | Thr | Leu | Pro | Pro | Ser | Thr | His | Gly | Thr | Gly | Gly | Gln | | |
| | | | | | 450 | | | 455 | | | | 460 | | | | | | |
| | Leu | Leu | Cys | Arg | Thr | Val | Trp | Ser | Ala | His | Ser | Gly | Pro | Thr | Arg | Thr | | |
| | | | | | 465 | | | 470 | | | | 475 | | | | 480 | | |
| | Ala | Thr | Ala | Thr | Ala | Arg | Cys | Ala | Pro | Asp | Glu | Glu | Leu | Leu | Ser | Oys | | |
| | | | | | 485 | | | 490 | | | | | | 495 | | | | |
| | Ser | Ser | Phe | Ser | Arg | Ser | Gly | Lys | Arg | Arg | Gly | Asp | Arg | Ile | Glu | Ala | | |
| | | | | | 500 | | | 505 | | | | | 510 | | | | | |
| | Ile | Gly | Gly | Gln | Gln | Val | Cys | Lys | Ala | Leu | Asn | Ala | Phe | Gly | Gly | Glu | | |
| | | | | | 515 | | | 520 | | | | 525 | | | | | | |
| | Gly | Val | Tyr | Ala | Val | Ala | Arg | Cys | Cys | Leu | Leu | Pro | Arg | Ala | Asn | Cys | | |
| | | | | | 530 | | | 535 | | | | 540 | | | | | | |
| | Ser | Ile | His | Thr | Thr | Pro | Ala | Ala | Arg | Ala | Ser | Met | Glu | Thr | Arg | Val | | |
| | | | | | 545 | | | 550 | | | | 555 | | | | 560 | | |
| | His | Cys | His | Gln | Lys | Asp | His | Val | Leu | Thr | Gly | Cys | Ser | Ser | His | Trp | | |
| | | | | | 565 | | | 570 | | | | | | 575 | | | | |
| | Glu | Val | Glu | Asp | Leu | Gly | Xaa | Xaa | Lys | Xaa | Pro | Val | Leu | Arg | Ser | Arg | | |
| | | | | | 580 | | | 585 | | | | | 590 | | | | | |
| | Gly | Gln | Pro | Gly | Gln | Cys | Val | Gly | His | Arg | Glu | Ala | Ser | Val | His | Ala | | |
| | | | | | 595 | | | 600 | | | | 605 | | | | | | |
| | Ser | Cys | Cys | His | Ala | Pro | Gly | Leu | Glu | Cys | Lys | Ile | Lys | Glu | His | Gly | | |
| | | | | | 610 | | | 615 | | | | 620 | | | | | | |
| | Ile | Pro | Gly | Pro | Ala | Glu | Gln | Val | Thr | Val | Ala | Cys | Glu | Ala | Gly | Trp | | |
| | | | | | 625 | | | 630 | | | | 635 | | | | 640 | | |
| | Thr | Leu | Thr | Gly | Cys | Ser | Val | Leu | Pro | Gly | Ala | Ser | Leu | Val | Leu | Gly | | |
| | | | | | 645 | | | 650 | | | | | 655 | | | | | |
| | Ala | Tyr | Ala | Val | Asp | Asn | Thr | Cys | Val | Val | Arg | Ser | Arg | Asp | Val | Ser | | |
| | | | | | 660 | | | 665 | | | | | 670 | | | | | |
| | Thr | Ala | Gly | Arg | Thr | Ser | Glu | Glu | Ala | Thr | Val | Ala | Ala | Ala | Ile | Cys | | |
| | | | | | 675 | | | 680 | | | | | 685 | | | | | |
| | Oys | Arg | Ser | Arg | Pro | Ser | Ala | Gln | Ala | Ser | Trp | Val | Xaa | Gln | | | | |
| | | | | | 690 | | | 695 | | | | 700 | | | | | | |

<210> 31

<211> 689

<212> PRT

<213> Homo sapiens

SEQUENCE_LI STI NG_APMOL_005VPC

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 Leu Leu Leu Leu Leu Leu G y Pro Ala G y Ala Arg Ala G n G u
 20 25 30
 Asp G u Asp G y Asp Tyr G u G u Leu Val Leu Ala Leu Arg Ser G u
 35 40 45
 G u Asp G y Leu Ala G u Ala Pro G u His G y Thr Thr Ala Thr Phe
 50 55 60
 His Arg Cys Ala Lys Asp Pro Trp Arg Leu Pro G y Thr Tyr Val Val
 65 70 75 80
 Val Leu Lys G u G u Thr His Leu Ser G n Ser G u Arg Thr Ala Arg
 85 90 95
 Arg Leu G n Ala G n Ala Arg Arg G y Tyr Leu Thr Lys Ile Leu
 100 105 110
 His Val Phe His Leu Leu Pro G y Phe Leu Val Lys Met Ser G y Asp
 115 120 125
 Leu Leu G u Leu Ala Leu Lys Leu Pro His Val Asp Tyr Ile G u G u
 130 135 140
 Asp Ser Ser Val Phe Ala G n Ser Ile Pro Trp Asn Leu G u Arg Ile
 145 150 155 160
 Thr Pro Pro Arg Tyr Arg Ala Asp G u Tyr G n Pro Pro Asp G y G y
 165 170 175
 Ser Leu Val G u Val Tyr Leu Leu Asp Thr Ser Ile G n Ser Asp His
 180 185 190
 Arg G u Ile G u G y Arg Val Met Val Thr Asp Phe G u Asn Val Pro
 195 200 205
 G u G u Asp G y Thr Arg Phe His Arg G n Ala Ser Lys Cys Asp Ser
 210 215 220
 His G y Thr His Leu Ala G y Val Val Ser G y Arg Asp Ala G y Val
 225 230 235 240
 Ala Lys G y Ala Ser Met Arg Ser Leu Arg Val Leu Asn Cys G n G y
 245 250 255
 Lys G y Thr Val Ser G y Thr Leu Ile G y Leu G u Phe Ile Arg Lys
 260 265 270 275
 Ser G n Leu Val G n Pro Val Pro Leu Val Val Leu Leu Pro Leu Ala
 280 285
 G y G y Tyr Ser Arg Val Leu Asn Ala Ala Cys G n Arg Leu Ala Arg
 290 295 300
 Ala G y Val Val Leu Val Thr Ala Ala G y Asn Phe Arg Asp Asp Ala
 305 310 315 320
 Cys Leu Tyr Ser Pro Ala Ser Ala Pro G u Val Ile Thr Val G y Ala
 325 330 335
 Thr Asn Ala G n Asp G n Pro Val Thr Leu G y Thr Leu G y Thr Asn
 340 345 350
 Phe G y Arg Cys Val Asp Leu Phe Ala Pro G y G u Asp Ile Ile G y
 355 360 365
 Ala Ser Ser Asp Cys Ser Thr Cys Phe Val Ser G n Ser G y Thr Ser
 370 375 380
 G n Ala Ala Ala His Val Ala G y Ile Ala Ala Met Met Leu Ser Ala
 385 390 395 400
 G u Pro G u Leu Thr Leu Ala G u Leu Arg G n Leu Ile His Phe Ser
 405 410 415
 Ala Lys Asp Val Ile Asn G u Ala Trp Phe Pro G u Asp G n Arg Val
 420 425 430
 Leu Thr Pro Asn Leu Val Ala Ala Leu Pro Pro Ser Thr His G y Ala
 435 440 445
 G y Trp G n Leu Phe Cys Arg Thr Val Trp Ser Ala His Ser G y Pro
 450 455 460 465
 Thr Arg Met Ala Thr Ala Ile Ala Arg Cys Ala Pro Asp G u G u Leu
 470 475 480
 Leu Ser Cys Ser Ser Phe Ser Arg Ser G y Lys Arg Arg G y G u Arg
 485 490 495
 Met G u Ala G n G y G y Lys Leu Val Cys Arg Ala His Asn Ala Phe
 500 505 510
 G y G y G u G y Val Tyr Ala Ile Ala Arg Cys Cys Leu Leu Pro G n
 515 520 525
 Ala Asn Cys Ser Val His Thr Ala Pro Pro Ala G u Ala Ser Met G y

SEQUENCE_LISTTING_APMOL_005VPC

| | | | |
|---|-----------------------------|-----------------------------|-----|
| 530 | 535 | 540 | |
| Thr Arg Val His Cys His | Gln Gln Gly | His Val Leu Thr Gly Cys Ser | |
| 545 | 550 | 555 | |
| Ser His Trp Glu Val Glu Asp Leu Gly | Thr His Lys Pro Pro Val Leu | | |
| 565 | 570 | 575 | |
| Arg Pro Arg Gly Gln Pro Asn Gln Cys Val Gly His Arg Glu Ala Ser | | | |
| 580 | 585 | 590 | |
| Ile His Ala Ser Cys Oys His Ala Pro Gly Leu Glu Cys Lys Val Lys | | | |
| 595 | 600 | 605 | |
| Gl u His Gly Ile Pro Ala Pro Gln Glu Gln Val Thr Val Ala Cys Gl u | | | |
| 610 | 615 | 620 | |
| Gl u Gly Trp Thr Leu Thr Gly Cys Ser Ala Leu Pro Gl y Thr Ser His | | | |
| 625 | 630 | 635 | 640 |
| Val Leu Gly Ala Tyr Ala Val Asp Asn Thr Oys Val Val Arg Ser Arg | | | |
| 645 | 650 | 655 | 660 |
| Asp Val Ser Thr Thr Gly Ser Thr Ser Gl u Gl u Ala Val Thr Ala Val | | | |
| 660 | 665 | 670 | 675 |
| Ala Ile Cys Cys Arg Ser Arg His Leu Ala Gln Ala Ser Gl n Gu Leu | | | |
| 675 | 680 | 685 | 690 |
| Gln | | | |