FIBRONECTIN BASED SCAFFOLD DOMAIN PROTEINS THAT BIND PCSK9

SEQUENCE LISTING

[0001] The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. Said ASCII copy, created on April 13, 2011, is named 11594 PCT.ST25.txt and is 1,382 KB in size.

FIELD OF THE INVENTION

[0002] The present invention relates to fibronectin based scaffold domain proteins that bind proprotein convertase subtilisin kexin type 9 (PCSK9). The invention also relates to the use of the innovative proteins in therapeutic applications to treat atherosclerosis, hypercholesterolemia and other cholesterol related diseases. The invention further relates to cells comprising such proteins, polynucleotides encoding such proteins or fragments thereof, and to vectors comprising the polynucleotides encoding the innovative proteins.

INTRODUCTION

[0003] Atherosclerosis is a disease of the arteries responsible for coronary heart disease (CHD) that underlies most deaths in industrialized countries (Lusis (2000)). Several risk factors for CHD have now been well established: dyslipidemias, hypertension, diabetes, smoking, poor diet, inactivity and stress. The most clinically relevant and common dyslipidemias are characterized by an increase in low density lipoprotein and very low density lipoproteins (LDL and VLDL) with hypercholesterolemia in the absence or presence of hypertriglyceridemia (Fredrickson et al. (1967)). An isolated elevation of LDL cholesterol is one of the most common risk factors for CHD. PCSK9 (also referred to as HCHOLA3, NARC-1, or FH3) is a protease belonging to the proteinase K subfamily of the secretory subtilase family (Naureckiene et al., *Arch. Biochem. Biophy.*, 420:55-57 (2003)). PCSK9 has been shown to be a key regulator of cholesterol homeostasis and circulating low density lipoprotein levels. Circulating PCSK9 protein controls LDL metabolism by directly binding to the LDL receptor and promoting its degradation in hepatocytes. PCSK9-mediated down-

regulation of LDL receptor protein and activity leads to reduced clearance of LDL from the circulation and higher LDL levels. Several mutant forms of PCSK9 are known, including S127R, N157K, F216L, R218S, and D374Y, with S127R, F216L, and D374Y being linked to autosomal dominant hypercholesterolemia (ADH). It is believed that wild-type PCSK9 increases the turnover rate of the LDL receptor causing lower LDL clearance (Maxwell et al., *Proc. Natl. Acad. Sci.*, 102(6):2069-2074 (2005); Benjannet et al. and Lalanne et al.), while PCSK9 loss of function mutations result in increased levels of low density lipoprotein receptor (LDLR), increased clearance of circulating LDL, and a corresponding decrease in plasma cholesterol levels (Rashid et al., *Proc. Natl. Acad. Sci.*, 102(15):5374-5379 (2005)). As such, PCSK9 is a potential target for the treatment of atherosclerosis, hypercholesterolemia and other cholesterol related diseases.

[0004] Fibronectin based scaffolds are a family of proteins capable of evolving to bind any compound of interest. These proteins, which generally make use of a scaffold derived from a fibronectin type III (Fn3) or Fn3-1ike domain, function in a manner characteristic of natural or engineered antibodies (that is, polyclonal, monoclonal, or single-chain antibodies) and, in addition, possess structural advantages. Specifically, the structure of these antibody mimics has been designed for optimal folding, stability, and solubility, even under conditions that normally lead to the loss of structure and function in antibodies. An example of fibronectin-based scaffold proteins is Adnectins (Adnexus, a Bristol-Myers Squibb R&D Company).

[0005] Fibronectin type III (Fn3) domains comprise, in order from N-terminus to C-terminus, a beta or beta-like strand, A; a loop, AB; a beta or beta-like strand, B; a loop, BC; a beta or beta-like strand C; a loop CD; a beta or beta-like strand D; a loop DE; a beta or beta-like strand, E; a loop, EF; a beta or beta-like strand F; a loop FG; and a beta or beta-like strand G. Any or all of loops AB, BC, CD, DE, EF and FG may participate in target binding. The BC, DE, and FG loops are both structurally and functionally analogous to the complementarity determining regions (CDRs) from immunoglobulins. U.S. Patent No. 7,115,396 describes Fn3 domain proteins wherein alterations to the BC, DE, and FG loops result in high affinity TNFα binders. U.S. Publication No. 2007/0148126 describes Fn3 domain proteins wherein alterations to the BC, DE, and FG loops result in high affinity VEGFR2 binders.

[0006] It would be advantageous to obtain improved fibronectin domain scaffold proteins that bind PCSK9 for the therapeutic treatment of atherosclerosis, hypercholesterolemia and other cholesterol related diseases.

SUMMARY OF THE INVENTION

[0007] The application provides Adnectins against human PCSK9. One aspect of the invention provides for polypeptides comprising Fn3 domain in which one or more of the solvent accessible loops has been randomized or mutated. In some embodiments, the Fn3 domain is an Fn3 domain derived from the wild-type tenth module of the human fibronectin type III domain (^{10}Fn3). In some embodiments, the ^{10}Fn3 polypeptide of the invention is at least 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, or 90% identical to the human ^{10}Fn3 domain.

[0008] In some embodiments, one or more loops selected from BC, DE, and FG may be extended or shortened in length relative to the corresponding human fibronectin loop.

[0009] In some embodiments, the polypeptides of the invention comprise a tenth fibronectin type III (^{10}Fn3) domain, wherein the ^{10}Fn3 domain comprises a loop, AB; a loop, BC; a loop, CD; a loop, DE; a loop EF; and a loop FG; and has at least one loop selected from loop BC, DE, and FG with an altered amino acid sequence relative to the sequence of the corresponding loop of the human ^{10}Fn3 domain.

[0010] In some embodiments, the polypeptide of the invention comprises an Fn3 domain that comprises an amino acid sequence at least 80, 85, 90, 95, 98, 99 or 100% identical to the non-loop regions.

[0011] In some embodiments, the BC loop of the protein of the invention comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 2-17, 106-135, and 301-303. In certain embodiments, the BC loop of the protein of the invention comprises the shaded portion of any one of SEQ ID NOs: 2-17, 106-135, and 301-303 as shown in Table 3. For example, in one embodiment, a BC loop comprises the sequence PPPSHGYG (residues 3-10 of SEQ ID NO: 2), DAPAHAYG (residues 3-10 of SEQ ID NO: 5), EPFSRLPGGGE (residues 3-13 of SEQ ID NO: 106), or DAPADGGYG (residues 3-11 of SEQ ID NO: 107).

[0012] In some embodiments, the DE loop of the protein of the invention comprises an amino acid sequence selected from the group consisting of SEQ ID NOs:18-27 and

136-141. In certain embodiments, the DE loop of the protein of the invention comprises the shaded portion of any one of SEQ ID NOs: 18-27 and 136-141 as shown in Table 3. For example, in one embodiment, a DE loop comprises the sequence PGKG (residues 2-5 of SEQ ID NO: 18), VGVG (residues 2-5 SEQ ID NO: 27), or VSKS (residues 2-5 of SEQ ID NO: 137).

[0013] In some embodiments, the FG loop of the protein of the invention comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 28-38 and 142-172. In certain embodiments, the DE loop of the protein of the invention comprises the shaded portion of any one of SEQ ID NOs: 28-38 and 142-172 as shown in Table 3. For example, in one embodiment, a FG loop comprises the sequence EYPYKHSGYYHR (residues 1-12 in SEQ ID NO: 28), EYPYDYSGYYHR (residues 1-12 in SEQ ID NO: 142), or EFDFVGAGYYHR (residues 1-12 in SEQ ID NO: 167).

[0014] In some embodiments, the ^{10}Fn3 domain may begin and/or end with amino acid substitutions, insertions or deletions.

[0015] In some embodiments, the protein of the invention comprises one loop sequence from the BC loop sequences shown in SEQ ID NOs: 2-17, 106-135, and 301-303; one DE loop sequence shown in SEQ ID NOs:18-27 and 136-141; and one FG loop sequence shown in SEQ ID NOs:28-38 and 142-172. In certain embodiments, the protein of the invention comprises one BC loop sequence comprising the shaded portion of any one of SEQ ID NOs: 2-17, 106-135, and 301-303 as shown in Table 3; one DE loop sequence comprising the shaded portion of any one of SEQ ID NOs: 18-27 and 136-141 as shown in Table 3; and one FG loop sequence comprising the shaded portion of any one of SEQ ID NOs: 28-38 and 142-172 as shown in Table 3.

[0016] In some embodiments, the protein of the invention comprises a BC, DE and FG loop amino acid sequence at least 70, 75, 80, 85, 90, 95, 98, 99 or 100% identical to of any one of SEQ ID NOS:2-38, 106-172, and 301-303. In certain embodiments, the protein of the invention comprises a BC, DE and FG loop amino acid sequence at least 70, 75, 80, 85, 90, 95, 98, 99 or 100% identical to any of the shaded portions of the BC, DE, and FG loops as shown in Table 3, as described above.

[0017] In some embodiments, the anti-PCSK9 Adnectin comprises the amino acid sequence of any one of SEQ ID NOS:39-76, 173-290, and 304-309.

[0018] In some embodiments, the anti-PCSK9 Adnectin comprises the Fn3 domain amino acid sequence from position 3-96 of any one of SEQ ID NOS:39-76, 173-290, and 304-309.

[0019] In one aspect, the present disclosure provides an anti-PCSK9 Adnectin comprising a BC loop having the sequence $SW(X_1)_ZX_2G$ (SEQ ID NO: 323) where X_1 is any amino acid, Z is a number from 6-9, and X_2 is Y or H.

[0020] In one aspect, the present disclosure provides an anti-PCSK9 Adnectin comprising a DE loop having the sequence $PX_1X_1X_1X_3T$, (SEQ ID NO: 324) where X_1 is any amino acid and X_3 is G or S.

[0021] In one aspect, the present disclosure provides an anti-PCSK9 Adnectin comprising an FG loop having the sequence $EX_4X_1X_5X_1X_1X_6GYX_4HRP$ (SEQ ID NO: 325), where X_1 is any amino acid; X_4 is Y or F; X_5 is Y, F, or W; and X_6 is S or A. In certain embodiments, X_4 and X_5 are aromatic residues, each independently selected from Y, F, W, or H.

[0022] In one aspect, the present disclosure provides an anti-PCSK9 Adnectin comprising a BC loop having the sequence $SW(X_1)_ZX_2G$ (SEQ ID NO: 323), a DE loop having the sequence $PX_1X_1X_1X_3T$ (SEQ ID NO: 324), and an FG loop having the sequence $EX_4X_1X_5X_1X_1X_6GYX_4HRP$ (SEQ ID NO: 325) as defined herein.

[0023] In one aspect, the present disclosure provides an anti-PCSK9 Adnectin comprising a BC loop having the sequence SWEPFSRLPGGGE (SEQ ID NO: 106), a DE loop having the sequence $PX_1X_1X_1X_3T$ (SEQ ID NO: 324), and an FG loop having the sequence $EX_4X_1X_5X_1X_1X_6GYX_4HRP$ (SEQ ID NO: 325) as defined herein.

[0024] In one aspect, the present disclosure provides an anti-PCSK9 Adnectin comprising a BC loop having the sequence $(X_1)_ZX_2G$ (SEQ ID NO: 449) where X_1 is any amino acid, Z is a number from 6-9, and X_2 is Y or H.

[0025] In one aspect, the present disclosure provides an anti-PCSK9 Adnectin comprising a DE loop having the sequence $X_1X_1X_1X_3$, (SEQ ID NO: 450) where X_1 is any amino acid and X_3 is G or S.

[0026] In one aspect, the present disclosure provides an anti-PCSK9 Adnectin comprising an FG loop having the sequence $EX_4X_1X_5X_1X_1X_6GYX_4HR$ (SEQ ID NO: 451), where X_1 is any amino acid; X_4 is Y or F; X_5 is Y, F, or W; and X_6 is S or A. In

certain embodiments, X_4 and X_5 are aromatic residues each independently selected from Y, F, W, or H.

[0027] In one aspect, the present disclosure provides an anti-PCSK9 Adnectin comprising a BC loop having the sequence $(X_1)_ZX_2G$ (SEQ ID NO: 449), a DE loop having the sequence $X_1X_1X_1X_3$ (SEQ ID NO: 450), and an FG loop having the sequence $EX_4X_1X_5X_1X_1X_6GYX_4HR$ (SEQ ID NO: 451) as defined herein.

[0028] In some embodiments, there is at least one amino acid deletion from the N-terminus of the PCSK9 Adnectin.

[0029] In some embodiments, there is at least one amino acid deletion, insertion or substitution from the C-terminus of the PCSK9 Adnectin.

[0030] In some embodiments, a linker is added to the C-terminus of the PCSK9 Adnectin.

[0031] In some embodiments, the PCSK9 Adnectin can be conjugated to a non-^{10}Fn3 moiety such as Human Serum Albumin (HSA) as described in PCT Publication Nos. WO 2009/133208 and WO 2009/083804.

[0032] In some embodiments, the PCSK9 Adnectin may have mutations in the AB, CD and EF loop amino acid sequences as described in PCT Publication Nos. WO 2009/133208 and WO 2009/083804.

[0033] In one aspect, the anti-PCSK9 Adnectin further comprises a pharmacokinetic (PK) moiety. In one embodiment, the PK moiety comprises polyethylene glycol (PEG). In certain embodiments, the PK moiety comprises an Fc region. In some embodiments, the PK comprises one or more serum albumin-binding Adnectins. Exemplary anti-PCSK9 Adnectin-Fc fusions proteins are shown in Table 1. Exemplary anti-PCSK9-serum albumin binding Adnectin comprise SEQ ID NO: 618 or 619.

[0034] In certain embodiments, an anti-PCSK9 Adnectin having a PK moiety comprises the sequence as set forth in SEQ ID NO: 322.

[0035] In another aspect, the anti-PCSK9 Adnectin does not comprise any PK moiety (*i.e.*, a "naked" anti-PCSK9 Adnectin). In certain embodiments, the naked anti-PCSK9 Adnectin may be administered at a frequency that can sufficiently achieve the desired therapeutic effect. In another embodiment, the naked anti-PCSK9 Adnectin can be administered using an extended release formulation (*e.g.*, subcutaneous formulation). In some embodiments, the extended release formulation increases the length of the

absorption phase, or extends that pharmacodynamic effect, or both. Simply to illustrate, an extended release formulation comprises a propylene glycol/PBS solution.

[0036] In one aspect, the application provides an anti-PCSK9 Adnectin useful in the treatment of atherosclerosis, hypercholesterolemia and other cholesterol related diseases.

[0037] In one aspect, the present invention provides a fusion polypeptide comprising a fibronectin type III tenth (^{10}Fn3) domain that binds to serum albumin and an anti-PCSK9 Adnectin, wherein the serum albumin binding ^{10}Fn3 domain binds to serum albumin, *e.g.*, HSA, with a Kd of 1 uM or less. In certain embodiments, the ^{10}Fn3 domain that binds to serum albumin comprises an amino acid sequence at least 70% identical to SEQ ID NO: 330. In one embodiment, the ^{10}Fn3 domain that binds to serum albumin comprises a BC loop having the amino acid sequence set forth in SEQ ID NO: 331, a DE loop having the amino acid sequence set forth in SEQ ID NO: 332, and an FG loop having the amino acid sequence set forth in SEQ ID NO:333. In another embodiment, the ^{10}Fn3 domain that binds to serum albumin comprises one or more of a BC loop having the amino acid sequence set forth in SEQ ID NO: 331, a DE loop having the amino acid sequence set forth in SEQ ID NO: 332, and an FG loop having the amino acid sequence set forth in SEQ ID NO: 333.

[0038] In one embodiment, the serum albumin binding ^{10}Fn3 domain of the fusion polypeptide also binds to one or more of rhesus serum albumin (RhSA), cynomolgous monkey serum albumin (CySA), or murine serum albumin (MuSA). In other embodiments, the ^{10}Fn3 domain that binds to serum albumin does not cross-react with one or more of RhSA, CySA or MuSA.

[0039] In certain embodiments, the serum albumin binding ^{10}Fn3 domain of the fusion polypeptide binds to HSA with a Kd of 1 uM or less. In some embodiments, the serum albumin binding ^{10}Fn3 domain binds to HSA with a Kd of 500 nM or less. In other embodiments, the serum albumin binding ^{10}Fn3 domain binds to HSA with a Kd of at least 200 nM, 100 nM, 50 nM, 20 nM, 10 nM, or 5 nM.

[0040] In other embodiments, the serum albumin binding ^{10}Fn3 domain of the fusion polypeptide binds to domain I or II of HSA. In one embodiment, the serum albumin binding ^{10}Fn3 domain binds to both domains I and II of HSA. In some embodiments, the serum albumin binding ^{10}Fn3 domain binds to HSA at a pH range of 5.5 to 7.4. In other embodiments, the serum albumin binding ^{10}Fn3 domain binds to HSA with a Kd of 200

nM or less at pH 5.5. In another embodiment, the serum albumin binding ^{10}Fn3 domain binds to HSA with a Kd of at least 500 nM, 200 nM, 100 nM, 50 nM, 20 nM, 10 nM, or 5 nM at a pH range of 5.5 to 7.4. In one embodiment, the serum albumin binding ^{10}Fn3 domain binds to HSA with a Kd of at least 500 nM, 200 nM, 100 nM, 50 nM, 20 nM, 10 nM, or 5 nM at pH 5.5.

[0041] In some embodiments, the serum half-life of the fusion polypeptide in the presence of serum albumin is at least 5-fold greater than the serum half-life of the fusion polypeptide in the absence of serum albumin. In certain embodiments, the serum half-life of the fusion polypeptide in the presence of serum albumin is at least 2-fold, 5-fold, 7-fold, 10-fold, 12-fold, 15-fold, 20-fold, 22-fold, 25-fold, 27-fold, or 30-fold greater than the serum half-life of the fusion polypeptide in the absence of serum albumin. In some embodiments, the serum albumin is any one of HSA, RhSA, CySA, or MuSA.

[0042] In certain embodiments, the serum half-life of the fusion polypeptide in the presence of serum albumin is at least 20 hours. In certain embodiments, the serum half-life of the fusion polypeptide in the presence of serum albumin is at least 10 hours, 12 hours, 15 hours, 20 hours, 25 hours, 30 hours, 40 hours, 50 hours, 75 hours, 90 hours, 100 hours, 110 hours, 120 hours, 130 hours, 150 hours, 170 hours, or 200 hours. In some embodiments, the half-life of the fusion polypeptide is observed in a primate (*e.g.*, human or monkey) or a mouse.

[0043] In any of the foregoing aspects and embodiments, the ^{10}Fn3 domain that binds serum albumin comprises a sequence selected from SEQ ID NO: 334, 338, 342, 346, and 348-370.

BRIEF DESCRIPTION OF THE FIGURES

[0044] Figure 1 shows an alignment of exemplary anti-PCSK9 Adnectin amino acid sequences. The BC, DE and FG loop amino acid sequences are identified by underlining, italics/underlining or bold/underlining, respectively.

[0045] Figure 2 is a schematic depicting the PCSK9: Epidermal Growth Factor precursor homology domain (EGFA domain) fluorescence resonance energy transfer (FRET) assay which was used to measure potency of PCSK9:LDLR inhibiting PCSK9 Adnectins as described in Example 2.

[0046] Figure 3 shows the curve generated from a FRET assay which was used to measure the inhibition of human PCSK9:EGFA by PCSK9 Adnectin clones 1459D05, 1784F03, 1813E02, 1922G04 and 1923B02 (panel A) and clones 1459D05, 2012A04, 2011H05 and 2013E01 (panel B) as described in Example 2.

[0047] Figure 4 shows the curve generated from a FRET assay which was used to measure the inhibition of human PCSK9:ATI000972 interaction by PCSK9 Adnectin clones 1459D05, 1784F03, 1813E02, 1922G04 and 1923B02 (panel A) and clones 2011H05, 2012A04 and 2013E01 (panel B) as described in Example 2.

[0048] Figure 5 shows the activity of the PCSK9 Adnectin clones 1459D05, 1784F03, 1813E02, 1922G04 and 1923B02 (panel A) and clones 2011H05, 2012A04 and 2013E01 (panel B) in the direct binding human PCSK9 FRET assay as described in Example 2.

[0049] Figure 6 shows the inhibition of PCSK9 activity in HepG2 cells assayed by the DiI-LDL uptake method as described in Example 2.

[0050] Figure 7 shows the inhibition of PCSK9-induced LDLR depletion from HepG2 cell surface by PCSK9 Adnectin clones 1459D05, 1784F03, 2012A04, and 2011H05 (panel A) and Clone ID 2011H05, 2012A04 and 2013E01 (panel B) as described in Example 2. The EC_{50} (nM) of 1784F03, 2012A04, 2011H05, and 2013E01 are 15.98, 7.78, 8.85, and 12.41, respectively; the percentage of PCSK9 inhibition at 75 nM of PCSK9 Adnectin clones 1459D05, 1784F03, 2012A04, 2011H05, and 2013E01 are 66.8, 150.2, 190.1, 177.4, and 152.2, respectively.

[0051] Figure 8 shows the *in vivo* effect of PCSK9 Adnectin ATI000959 (100 mg/kg) on plasma cholesterol (panel A) and plasma unbound hPCSK9 (panel B) in hPCSK9 overexpressing transgenic mice as described in Example 3. ATI000959 contains a 40 kDa branched NOF PEG.

[0052] Figure 9 shows the *in vivo* effect of the PCSK9 Adnectin ATI001114 (10 or 60 mg/kg) on plasma cholesterol levels (panel A) and on plasma unbound hPCSK9 levels (panel B) in hPCSK9 overexpressing transgenic mice as described in Example 3.

[0053] Figure 10 shows the *in vivo* effect of the PCSK9 Adnectins ATI000959 (panel A) or ATI001114 (panel B) administered at 5 mg/kg intraperitoneal (i.p.), single dose, on unbound plasma hPCSK9 in normal expresser hPCSK9 transgenic mice (mean +/- SD) as described in Example 3.

[0054] Figure 11 shows the dose-dependent effect of the PCSK9 Adnectin ATI001114 on unbound hPCSK9 in normal expresser hPCSK9 transgenic mice as described in Example 3.

[0055] Figure 12 shows the effect of single dose of the PCSK9 Adnectin ATI001114 (5 mg/kg i.v.) on LDL-C lowering in cynomolgus monkeys (mean +/- SEM, n = 3) as described in Example 3.

[0056] Figure 13. ITC determination of PCSK9 Adnectin affinity and stoichiometry of binding to hPCSK9. PCSK9 Adnectins bind hPCSK9 with 1:1 stoichiometry. The left panel shows data for PCSK9 Adnectin ATI001081; the right panel shows data for PCSK9 Adnectin ATI001174.

[0057] Figure 14. Inhibition of PCSK9:EGFA FRET assay (left panel) and PCSK9:ATI-972 FRET assay (right panel) by PCSK9 Adnectins.

[0058] Figure 15. Inhibition of PCSK9-induced LDLR depletion from HepG2 cell surface by anti-PCSK9 Adnectins.

[0059] Figure 16. Inhibition of PCSK9-AF647 cell entry in HepG2 cells.

[0060] Figure 17. Plasma unbound hPCSK9 levels in transgenic mice treated with PRD460 (dosed i.p.).

[0061] Figure 18. Effect of PRD460 (15 mg/kg i.v.) on LDL-C and free PCSK9 in cyno monkeys (mean +/- SEM, n=3).

[0062] Figure 19. Effect of ATI-1081 (also referred to as ATI001081) on unbound PCSK9 levels in cynomolgus monkeys.

[0063] Figure 20. Effect of ATI-1081 on LDL-C levels in cynomolgus monkeys.

[0064] Figure 21. Effect of ATI-1081 in PBS vehicle in transgenic mice. The figure illustrates level of unbound plasma hPCSK9 in transgenic mice.

[0065] Figure 22. Effect of ATI-1081 dosed subcutaneously in PG vehicle in transgenic mice. The figure illustrates level of unbound hPCSK9 in transgenic mice.

[0066] Figure 23. *In vivo* HSA half-life in mice. HSA was injected into nude mice at 20 mg/kg (panel A) or 50 mg/kg (panel B).

[0067] Figure 24. Half-life determination of SABA 1.1 (panel A), SABA2.1 (panel B), SABA3.1 (panel C), and SABA4.1 (panel D) in mice.

[0068] Figure 25. Graph showing summary of half-life enhancement in mice of SABA1-4 when co-injected with HSA.

[0069] Figure 26. Half-life determination for SABA1.1 (panel A) and SABA5.1 (panel B) in cynomolgous monkey.

[0070] Figure 27. SABA1.2 binding to albumins from human, mouse and rat by direct binding ELISA assay.

[0071] Figure 28. Determination of SABA1.1 and HSA stoichiometry. SABA1.1 and HSA bind with a stoichiometry of 1:1.

[0072] Figure 29. BIACORE® analysis of SABA1.2 binding to recombinant domain fragments of HSA.

[0073] Figure 30. Pharmacokinetic profile for SABA1.2 in cynomolgus monkeys dosed at 1 mpk and 10 mpk.

[0074] Figure 31. Pharmacokinetic profile for SABA1.2 in monkeys dosed intravenously or subcutaneously at 1 mpk.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0075] By a "polypeptide" is meant any sequence of two or more amino acids, regardless of length, post-translation modification, or function. "Polypeptide," "peptide," and "protein" are used interchangeably herein. Polypeptides can include natural amino acids and non-natural amino acids such as those described in U.S. Patent No. 6,559,126, incorporated herein by reference. Polypeptides can also be modified in any of a variety of standard chemical ways (*e.g.*, an amino acid can be modified with a protecting group; the carboxy-terminal amino acid can be made into a terminal amide group; the amino-terminal residue can be modified with groups to, *e.g.*, enhance lipophilicity; or the polypeptide can be chemically glycosylated or otherwise modified to increase stability or *in vivo* half-life). Polypeptide modifications can include the attachment of another structure such as a cyclic compound or other molecule to the polypeptide and can also include polypeptides that contain one or more amino acids in an altered configuration (*i.e.*, R or S; or, L or D). The peptides of the invention are proteins derived from the tenth type III domain of fibronectin that have been modified to bind specifically to PCSK9 and are referred to herein as, "anti-PCSK9 Adnectin" or "PCSK9 Adnectin".

[0076] The term "PK" is an acronym for "pharmacokinetic" and encompasses properties of a compound including, by way of example, absorption, distribution,

metabolism, and elimination by a subject. A "PK modulation protein" or "PK moiety" refers to any protein, peptide, or moiety that affects the pharmacokinetic properties of a biologically active molecule when fused to or administered together with the biologically active molecule. Examples of a PK modulation protein or PK moiety include PEG, human serum albumin (HSA) binders (as disclosed in U.S. Publication Nos. 2005/0287153 and 2007/0003549, PCT Publication Nos. WO 2009/083804 and WO 2009/133208, and SABA molecules as described herein), human serum albumin, Fc or Fc fragments and variants thereof, and sugars (*e.g.*, sialic acid).

[0077] "Percent (%) amino acid sequence identity" herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in a selected sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN, ALIGN-2 or Megalign (DNASTAR®) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full-length of the sequences being compared.

[0078] An "isolated" polypeptide is one that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to greater than 95% by weight of polypeptide as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing condition using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes the polypeptide in situ within recombinant cells since at least one component of the polypeptide's natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

[0079] The notations "mpk", "mg/kg", or "mg per kg" refer to milligrams per kilogram. All notations are used interchangeably throughout the present disclosure.

[0080] The "half-life" of an amino acid sequence or compound can generally be defined as the time taken for the serum concentration of the polypeptide to be reduced by 50%, *in vivo*, for example due to degradation of the sequence or compound and/or clearance or sequestration of the sequence or compound by natural mechanisms. The half-life can be determined in any manner known per se, such as by pharmacokinetic analysis. Suitable techniques will be clear to the person skilled in the art, and may for example generally involve the steps of suitably administering to the primate a suitable dose of the amino acid sequence or compound of the invention; collecting blood samples or other samples from said primate at regular intervals; determining the level or concentration of the amino acid sequence or compound of the invention in said blood sample; and calculating, from (a plot of) the data thus obtained, the time until the level or concentration of the amino acid sequence or compound of the invention has been reduced by 50% compared to the initial level upon dosing. Reference is, for example, made to the standard handbooks, such as Kenneth, A. et al., *Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists* and in Peters et al., *Pharmacokinete Analysis: A Practical Approach* (1996). Reference is also made to Gibaldi, M. et al., *Pharmacokinetics*, 2nd Rev. Edition, Marcel Dekker (1982).

[0081] Half-life can be expressed using parameters such as the $t_{1/2}$-alpha, $t_{1/2}$-beta, HL_Lambda_z, and the area under the curve (AUC). In the present specification, an "increase in half-life" refers to an increase in any one of these parameters, any two of these parameters, any three of these parameters or all four of these parameters. An "increase in half-life" in particular refers to an increase in the $t_{1/2}$-beta and/or HL_Lambda_z, either with or without an increase in the $t_{1/2}$-alpha and/or the AUC or both.

Overview

[0082] This application provides Adnectins against human PCSK9. In order to identify PCSK9 specific antagonists, PCSK9 was presented to large synthetic libraries of Adnectins. Adnectins that bound to PCSK9 were screened for PCSK9 binding, for biophysical properties, and for PCSK9 inhibitory activity. The anti-PCSK9 Adnectins

were mutated and subjected to further selective pressure by lowering the target concentration and selecting for anti-PCSK9 Adnectins with slow off-rates. From this optimization process, a family of Adnectins was identified as PCSK9 specific inhibitors with favorable biochemical and biophysical properties.

Fibronectin Based Scaffolds

[0083] One aspect of the application provides for polypeptides comprising Fn3 domain in which one or more of the solvent accessible loops has been randomized or mutated. In some embodiments, the Fn3 domain is an Fn3 domain derived from the wild-type tenth module of the human fibronectin type III domain (^{10}Fn3): VSDVPRDLEVVAATPTSLLISWDAPAVTVRYYRITYGETGGNSPVQEFTVPGSKS TATISGLKPGVDYTITVYAVTGRGDSPASSKPISINYRT (SEQ ID NO: 1). In the ^{10}Fn3 sequence, the BC, DE and FG loops are underlined.

[0084] As described herein, non-ligand binding sequences of ^{10}Fn3, *i.e.*, the "^{10}Fn3 scaffold", may be altered provided that the ^{10}Fn3 retains ligand binding function and/or structural stability. A variety of mutant ^{10}Fn3 scaffolds have been reported. In one aspect, one or more of Asp 7, Glu 9, and Asp 23 is replaced by another amino acid, such as, for example, a non-negatively charged amino acid residue (*e.g.*, Asn, Lys, etc.). These mutations have been reported to have the effect of promoting greater stability of the mutant ^{10}Fn3 at neutral pH as compared to the wild-type form (See, PCT Publication No. WO 02/04523). A variety of additional alterations in the ^{10}Fn3 scaffold that are either beneficial or neutral have been disclosed. See, for example, Batori et al., *Protein Eng.*, 15(12):1015-1020 (Dec. 2002); Koide et al., *Biochemistry*, 40(34):10326-10333 (Aug. 28, 2001).

[0085] Both variant and wild-type ^{10}Fn3 proteins are characterized by the same structure, namely seven beta-strand domain sequences designated A through G and six loop regions (AB loop, BC loop, CD loop, DE loop, EF loop, and FG loop) which connect the seven beta-strand domain sequences. The beta strands positioned closest to the N- and C-termini may adopt a beta-like conformation in solution. In SEQ ID NO:1, the AB loop corresponds to residues 15-16, the BC loop corresponds to residues 21-30, the CD loop corresponds to residues 39-45, the DE loop corresponds to residues 51-56,

the EF loop corresponds to residues 60-66, and the FG loop corresponds to residues 76-87 (Xu et al., *Chemistry & Biology*, 9:933-942 (2002)).

[0086] In some embodiments, the ^{10}Fn3 polypeptide may be at least 40%, 50%, 60%, 65%, 70%, 75%, 80%, 85%, or 90% identical to the human ^{10}Fn3 domain, shown in SEQ ID NO:1. Much of the variability will generally occur in one or more of the loops. Each of the beta or beta-like strands of a ^{10}Fn3 polypeptide may consist essentially of an amino acid sequence that is at least 80%, 85%, 90%, 95% or 100% identical to the sequence of a corresponding beta or beta-like strand of SEQ ID NO:1, provided that such variation does not disrupt the stability of the polypeptide in physiological conditions.

[0087] In some embodiments, the disclosure provides polypeptides comprising a tenth fibronectin type III (^{10}Fn3) domain, wherein the ^{10}Fn3 domain comprises a loop, AB; a loop, BC; a loop, CD; a loop, DE; a loop EF; and a loop FG; and has at least one loop selected from loop BC, DE, and FG with an altered amino acid sequence relative to the sequence of the corresponding loop of the human ^{10}Fn3 domain. In some embodiments, the BC and FG loops are altered, and in some embodiments, the BC, DE, and FG loops are altered, *i.e.*, the Fn3 domains comprise non-naturally occurring loops. In some embodiments, the AB, CD and/or the EF loops are altered. By "altered" is meant one or more amino acid sequence alterations relative to a template sequence (corresponding human fibronectin domain) and includes amino acid additions, deletions, and substitutions. Altering an amino acid sequence may be accomplished through intentional, blind, or spontaneous sequence variation, generally of a nucleic acid coding sequence, and may occur by any technique, for example, PCR, error-prone PCR, or chemical DNA synthesis.

[0088] In some embodiments, one or more loops selected from BC, DE, and FG may be extended or shortened in length relative to the corresponding human fibronectin loop. In some embodiments, the length of the loop may be extended by 2-25 amino acids. In some embodiments, the length of the loop may be decreased by 1-11 amino acids. To optimize antigen binding, therefore, the length of a loop of ^{10}Fn3 may be altered in length as well as in sequence to obtain the greatest possible flexibility and affinity in antigen binding.

[0089] In some embodiments, the polypeptide comprises a Fn3 domain that comprises an amino acid sequence at least 80, 85, 90, 95, 98, 99 or 100% identical to the

non-loop regions of SEQ ID NO:1, wherein at least one loop selected from BC, DE, and FG is altered. In some embodiments, the altered BC loop has up to 10 amino acid substitutions, up to 4 amino acid deletions, up to 10 amino acid insertions, or a combination thereof. In some embodiments, the altered DE loop has up to 6 amino acid substitutions, up to 4 amino acid deletions, up to 13 amino acid insertions or a combination thereof. In some embodiments, the FG loop has up to 12 amino acid substitutions, up to 11 amino acid deletions, up to 25 amino acid insertions or a combination thereof.

[0090] As described above, amino acid residues corresponding to residues 21-30, 51-56, and 76-87 of SEQ ID NO: 1 define the BC, DE, and FG loops, respectively. However, it should be understood that not every residue within the loop region needs to be modified in order to achieve a ^{10}Fn3 binder having strong affinity for a desired target (*e.g.*, PCSK9).

[0091] For example, residues 21 (S) and 22 (W) of the BC loop as shown in SEQ ID NO: 1 do not need to be modified for binding PCSK9. That is, ^{10}Fn3 domains with high affinity binding to PCSK9 may be obtained by modifying only residues 23-30 of loop BC as shown in SEQ ID NO: 1. This is demonstrated in the BC loops exemplified in Table 3, which indicates that only the residues spanning the shaded positions were altered. Therefore, in some embodiments, a BC loop according to this designation comprises the shaded portion of any one of SEQ ID NOs: 2-17, 106-135, and 301-303 as shown in Table 3. For example, in one embodiment, a BC loop may comprise the sequence PPPSHGYG (residues 3-10 of SEQ ID NO: 2), DAPAHAYG (residues 3-10 of SEQ ID NO: 5), EPFSRLPGGGE (residues 3-13 of SEQ ID NO: 106), or DAPADGGYG (residues 3-11 of SEQ ID NO: 107).

[0092] Similarly, positions 51 (P) and 56 (T) of loop DE as shown in SEQ ID NO: 1 do not need to be modified for binding PCSK9. That is, ^{10}Fn3 domains with high affinity binding to PCSK9 may be obtained by modifying only residues 52-55 of loop DE as shown in SEQ ID NO: 1. This is demonstrated in the DE loops exemplified in Table 3, which indicates that only the residues spanning the shaded positions were altered. Therefore, in some embodiments, a DE loop according to this designation comprises the shaded portion of any one of SEQ ID NOs: 18-27 and 136-141, as shown in Table 3. For example, in one embodiment, a DE loop may comprise the sequence PGKG (residues 2-5

of SEQ ID NO: 18), VGVG (residues 2-5 SEQ ID NO: 27), or VSKS (residues 2-5 of SEQ ID NO: 137).

[0093] Likewise, position 87 (P) of the FG loop as shown in SEQ ID NO: 1 does not need to be modified for binding PCSK9. That is, ^{10}Fn3 domains with high affinity binding to PCSK9 may be obtained by modifying only residues 76-86 of the FG loop as shown in SEQ ID NO: 1. This is demonstrated in the FG loops exemplified in Table 3, which indicates that only the residues spanning the shaded positions were altered. Therefore, in some embodiments, an FG loop according to this designation comprises the shaded portion of any one of SEQ ID NOs: 28-38 and 142-172, as shown in Table 3. For example, in one embodiment, an FG loop may comprise the sequence EYPYKHSGYYHR (residues 1-12 in SEQ ID NO: 28), EYPYDYSGYYHR (residues 1-12 in SEQ ID NO: 142), or EFDFVGAGYYHR (residues 1-12 in SEQ ID NO: 167).

[0094] In some embodiments, the present application demonstrates that the BC, DE, and FG loop regions can be generally described according to consensus sequences. For example, the BC loop can be generally defined by the consensus sequence $SW(X_1)_ZX_2G$ (SEQ ID NO: 323) where X_1 is any amino acid, Z is a number from 6-9, and X_2 is Y or H. This consensus sequence is exemplified by BC loops shown in Table 3 except for the BC loop defined by SEQ ID NO: 106. In other embodiments, Z is a number selected from 2-5. In certain embodiments, Z is a number selected from 10-15. In some embodiments, X_2 is any aromatic residue (i.e., Y, F, W, or H).

[0095] In another embodiment, the DE loop can be generally defined by the consensus sequence $PX_1X_1X_1X_3T$, (SEQ ID NO: 324) where X_1 is any amino acid and X_3 is G or S. This consensus is exemplified by the DE loops shown in Table 3.

[0096] In another embodiment, the FG loop can be generally defined by the consensus sequence $EX_4X_1X_5X_1X_1X_6GYX_4HRP$ (SEQ ID NO: 325), where X_1 is any amino acid; X_4 is Y or F; X_5 is Y, F, or W; and X_6 is S or A. In certain embodiments, X_4 and X_5 are aromatic residues, each independently selected from Y, F, W, or H. This consensus is exemplified by the FG loops shown in Table 3.

[0097] Accordingly, in certain embodiments, the present disclosure provides a PCSK9 binding Adnectin comprising a BC loop having the sequence $SW(X_1)_ZX_2G$ (SEQ ID NO: 323), a DE loop having the sequence $PX_1X_1X_1X_3T$ (SEQ ID NO: 324), and an

FG loop having the sequence $EX_4X_1X_5X_1X_1X_6GYX_4HRP$ (SEQ ID NO: 325), as defined above.

[0098] In another embodiment, the present disclosure provides a PCSK9 binding Adnectin comprising a BC loop having the sequence SWEPFSRLPGGGE (SEQ ID NO: 106), a DE loop having the sequence $PX_1X_1X_1X_3T$ (SEQ ID NO: 324), and an FG loop having the sequence $EX_4X_1X_5X_1X_1X_6GYX_4HRP$ (SEQ ID NO: 325), as defined above.

[0099] In certain embodiments, a BC loop can be generally defined by the consensus sequence $(X_1)_ZX_2G$ (SEQ ID NO: 449) where X_1 is any amino acid, Z is a number from 6-9, and X_2 is Y or H. This consensus sequence is exemplified by BC loops shown in Table 3 except for the BC loop defined by SEQ ID NO: 106. In other embodiments, Z is a number selected from 2-5. In certain embodiments, Z is a number selected from 10-15. In some embodiments, X_2 is any aromatic residue (i.e., Y, F, W, or H).

[00100] In certain embodiments, the DE loop can be generally defined by the consensus sequence $X_1X_1X_1X_3$, (SEQ ID NO: 450) where X_1 is any amino acid and X_3 is G or S. This consensus is demonstrated by the DE loops shown in Table 3.

[00101] In certain embodiments, the FG loop can be generally defined by the consensus sequence $EX_4X_1X_5X_1X_1X_6GYX_4HR$ (SEQ ID NO: 451), where X_1 is any amino acid; X_4 is Y or F; X_5 is Y, F, or W; and X_6 is S or A. In some embodiments, X_4 and X_5 are aromatic residues, each independently selected from Y, F, W, or H. This consensus is exemplified by the FG loops shown in Table 3.

[00102] Accordingly, in one embodiment, the present disclosure provides a PCSK9 binding Adnectin having a BC loop comprising the sequence $(X_1)_ZX_2G$ (SEQ ID NO: 449), a DE loop comprising the sequence $X_1X_1X_1X_3$ (SEQ ID NO: 450), and an FG loop comprising the sequence $EX_4X_1X_5X_1X_1X_6GYX_4HR$ (SEQ ID NO: 451), as defined above.

[00103] In certain embodiments, antibody-like proteins based on the ^{10}Fn3 scaffold can be defined generally by the following sequence:

$EVVAAT(X)_aSLLI(X)_xYYRITYGE(X)_bQEFTV(X)_yATI(X)_cDYTITVYAV(X)_zISINYR$T (SEQ ID NO:328)

[00104] In SEQ ID NO:328, the AB loop is represented by X_a, the CD loop is represented by X_b, the EF loop is represented by X_c, the BC loop is represented by X_x, the DE loop is represented by X_y, and the FG loop is represented by X_z. X represents any amino acid and the subscript following the X represents an integer of the number of amino acids. In particular, *a* may be anywhere from 1-15, 2-15, 1-10, 2-10, 1-8, 2-8, 1-5, 2-5, 1-4, 2-4, 1-3, 2-3, or 1-2 amino acids; and *b, c, x, y* and *z* may each independently be anywhere from 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7, or 6-7 amino acids. In preferred embodiments, *a* is 2 amino acids, *b* is 7 amino acids, *c* is 7 amino acids, *x* is 9 amino acids, *y* is 6 amino acids, and *z* is 12 amino acids. The sequences of the beta strands may have anywhere from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0 to 1 substitutions, deletions or additions across all 7 scaffold regions relative to the corresponding amino acids shown in SEQ ID NO: 1. In an exemplary embodiment, the sequences of the beta strands may have anywhere from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0 to 1 conservative substitutions across all 7 scaffold regions relative to the corresponding amino acids shown in SEQ ID NO: 1. In certain embodiments, the core amino acid residues are fixed and any substitutions, conservative substitutions, deletions or additions occur at residues other than the core amino acid residues.

[00105] In exemplary embodiments, the BC, DE, and FG loops as represented by $(X)_x$, $(X)_y$, and $(X)_z$, respectively, are replaced with polypeptides comprising the BC, DE and FG loop sequences from any of the PCSK9 binders shown in Table 3, or the shaded portions thereof, or the consensus sequences 323-325 or 449-451.

[00106] In certain embodiments, Antibody-like proteins based on the ^{10}Fn3 scaffold can be defined generally by the sequence:

EVVAATPTSLLI$(X)_x$YYRITYGETGGNSPVQEFTV$(X)_y$ATISGLKPGVDYTITVYAV $(X)_z$ISINYRT (SEQ ID NO:329)

[00107] In SEQ ID NO:329, the BC loop is represented by X_x, the DE loop is represented by X_y, and the FG loop is represented by X_z. X represents any amino acid and the subscript following the X represents an integer of the number of amino acids. In

particular, x, y and z may each independently be anywhere from 2-20, 2-15, 2-10, 2-8, 5-20, 5-15, 5-10, 5-8, 6-20, 6-15, 6-10, 6-8, 2-7, 5-7, or 6-7 amino acids. In preferred embodiments, x is 9 amino acids, y is 6 amino acids, and z is 12 amino acids. The sequences of the beta strands may have anywhere from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0 to 1 substitutions, deletions or additions across all 7 scaffold regions relative to the corresponding amino acids shown in SEQ ID NO: 1. In an exemplary embodiment, the sequences of the beta strands may have anywhere from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0 to 1 conservative substitutions across all 7 scaffold regions relative to the corresponding amino acids shown in SEQ ID NO: 1. In certain embodiments, the core amino acid residues are fixed and any substitutions, conservative substitutions, deletions or additions occur at residues other than the core amino acid residues. In exemplary embodiments, the BC, DE, and FG loops as represented by $(X)_x$, $(X)_y$, and $(X)_z$, respectively, are replaced with polypeptides comprising the BC, DE and FG loop sequences from any of the PCSK9 binders shown in Table 3, or the shaded portions thereof, or the consensus sequences 323-325 or 449-451.

[00108] In certain embodiments, an anti-PCSK9 Adnectin described herein may comprise the sequence as set forth in SEQ ID NO: 328 or 329, wherein the BC, DE, and FG loops as represented by $(X)_x$, $(X)_y$, and $(X)_z$, respectively, are replaced with a respective set of specified BC, DE, and FG loops from any of the clones in Table 3, or sequences at least 75%, 80%, 85%, 90%, 95%, 97%, 98%, or 99% identical to the BC, DE or FG loop sequences of the clones listed in Table 3. In exemplary embodiments, an anti-PCSK9 Adnectin as described herein is defined by SEQ ID NO: 329 and has a respective set of BC, DE and FG loop sequences from any of the clones listed in Table 3. For example, clone 1459D05 in Table 3 comprises BC, DE, and FG loops as set forth in SEQ ID NOs: 2, 18, and 28, respectively. Therefore, an anti-PCSK9 Adnectin based on these loops may comprise SEQ ID NO: 328 or 329, wherein $(X)_x$ comprises SEQ ID NO: 2, $(X)_y$ comprises SEQ ID NO: 18, and $(X)_z$ comprises SEQ ID NO: 28. Similar constructs are contemplated utilizing the set of BC, DE and FG loops from the other clones in Table 3, or the consensus sequences 323-325 or 449-451. The scaffold regions of such anti-PCSK9 Adnectin may comprise anywhere from 0 to 20, from 0 to 15, from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0

to 1 substitutions, conservative substitutions, deletions or additions relative to the scaffold amino acids residues of SEQ ID NO: 1. Such scaffold modifications may be made, so long as the anti-PCSK9 Adnectin is capable of binding PCSK9 with a desired K_D.

[00109] In some embodiments, the BC loop of the protein of the invention comprises an amino acid sequence selected from the group consisting of SWPPPSHGYG (SEQ ID NO: 2), SWRPPIHAYG (SEQ ID NO: 3), SWDAPIHAYG (SEQ ID NO:4), SWDAPAHAYG (SEQ ID NO:5) and SWDAPAVTYG (SEQ ID NO:6), SWSPPANGYG (SEQ ID NO:7), SWTPPPKGYG (SEQ ID NO:8), SWRPPSHAYG (SEQ ID NO:9), SWDPPSHAYG (SEQ ID NO:10), SWEPPSHAYG (SEQ ID NO:11), SWSPPSHAYG (SEQ ID NO:12), SWRPPSNGHG (SEQ ID NO:13), SWVPPSDDYG (SEQ ID NO:14), SWVPSSHAYG (SEQ ID NO:15), SWDPSSHAYG (SEQ ID NO:16), and SWEPSSHAYG (SEQ ID NO:17). In further embodiments, the BC loop of the protein of the invention comprises an amino acid sequence selected from SEQ ID NOs: 106-135 and 301-303. In other embodiments, the BC loop of the protein of the invention comprises the shaded portion of any one of SEQ ID NOs: 2-17, 106-135, and 301-303 as shown in Table 3. For example, in one embodiment, a BC loop comprises the sequence PPPSHGYG (residues 3-10 of SEQ ID NO: 2), DAPAHAYG (residues 3-10 of SEQ ID NO: 5), EPFSRLPGGGE (residues 3-13 of SEQ ID NO: 106), or DAPADGGYG (residues 3-11 of SEQ ID NO: 107).

[00110] In some embodiments, the DE loop of the protein of the invention comprises an amino acid sequence selected from the group consisting of PPGKGT (SEQ ID NO:18), PIVEGT (SEQ ID NO:19), PGSEGT (SEQ ID NO:20), PGSKGT (SEQ ID NO:21), PGSKST (SEQ ID NO:22), PVGRGT (SEQ ID NO:23), PVGEGT (SEQ ID NO:24), PIGKGT (SEQ ID NO:25), PVNEGT (SEQ ID NO:26), and PVGVGT (SEQ ID NO:27). In further embodiments, the DE loop of the protein of the invention comprises an amino acid sequence selected from SEQ ID NOs: 136-141. In other embodiments, the DE loop of the protein of the invention comprises the shaded portion of any one of SEQ ID NOs: 18-27 and 136-141 as shown in Table 3. For example, in one embodiment, a DE loop comprises the sequence PGKG (residues 2-5 of SEQ ID NO: 18), VGVG (residues 2-5 SEQ ID NO: 27), or VSKS (residues 2-5 of SEQ ID NO: 137).

[00111] In some embodiments, the FG loop of the protein of the invention comprises an amino acid sequence selected from the group consisting of EYPYKHSGYYHRP (SEQ

ID NO:28), EYTFKHSGYYHRP (SEQ ID NO:29), EYTYKGSGYYHRP (SEQ ID NO:30), EYTYNGAGYYHRP (SEQ ID NO:31), EYTYIGAGYYHRP (SEQ ID NO:32), EYTYEGAGYYHRP (SEQ ID NO:33), EYAYNGAGYYHRP (SEQ ID NO:34), EYPWKGSGYYHRP (SEQ ID NO:35), EFPFKWSGYYHRP (SEQ ID NO:36), EFPWPHAGYYHRP (SEQ ID NO:37) and EYAFEGAGYYHRP (SEQ ID NO:38). In further embodiments, the FG loop of the protein of the invention comprises an amino acid sequence selected from SEQ ID NOs: 142-172. In other embodiments, the FG loop of the protein of the invention comprises the shaded portion of any one of SEQ ID NOs: 28-38 and 142-172 as shown in Table 3. For example, in one embodiment, an FG loop comprises the sequence EYPYKHSGYYHR (residues 1-12 in SEQ ID NO: 28), EYPYDYSGYYHR (residues 1-12 in SEQ ID NO: 142), or EFDFVGAGYYHR (residues 1-12 in SEQ ID NO: 167).

[00112] In some embodiments, the protein of the invention comprises one BC loop sequence selected from the BC loop sequences having SEQ ID NOs: 2-17, 106-135, and 301-303, or the shaded portion of any one of SEQ ID NOS: 2-17, 106-135, and 301-303, as shown in Table 3; one DE loop sequence selected from the DE loop sequences having SEQ ID NOs:18-27 and 136-141, or the shaded portion of any one of SEQ ID NOS:18-27 and 136-141 as shown in Table 3; and one FG loop sequence selected from the FG loop sequences having SEQ ID NOS: 28-38 and 142-172, or the shaded portion of any one of SEQ ID NOS: 28-38 and 142-172 as shown in Table 3. In some embodiments, the protein of the invention comprises a BC, DE and FG loop amino acid sequence at least 70, 75, 80, 85, 90, 95, 98, 99 or 100% identical to of any one of SEQ ID NOS: 2-38, 106-172, 301-303. In other embodiments, the protein of the invention comprises a BC, DE and FG loop amino acid sequence at least 70, 75, 80, 85, 90, 95, 98, 99 or 100% identical to the shaded portion of any one of SEQ ID NOS: 2-38, 106-172, 301-303 as shown in Table 3.

[00113] In some embodiments, the anti-PCSK9 Adnectin comprises the amino acid sequence of any one of SEQ ID NOS: 39-76, 173-290, and 304-309. In some embodiments, the anti-PCSK9 Adnectin comprises the Fn3 domain amino acid sequence from position 3-96 of any one of SEQ ID NOS: 39-76, 173-290, and 304-309. In some embodiments, the anti- PCSK9 Adnectin comprises an amino acid sequence at least 70,

75, 80, 85, 90, 95, 98, 99 or 100% identical to any one of SEQ ID NOS:39-76, 173-290, and 304-309.

[00114] Fibronectin naturally binds certain types of integrins through its integrin-binding motif, "arginine-glycine~aspartic acid" (RGD). In some embodiments, the polypeptide comprises a ^{10}Fn3 domain that lacks the (RGD) integrin binding motif. The integrin binding domain may be removed by altering the RGD sequence by amino acid substitution, deletion or insertion.

[00115] In certain embodiments, the anti-PCSK9 Adnectin molecules of the present invention may be modified to comprise an N-terminal extension sequence and/or a C-terminal extension. For example, an MG sequence may be placed at the N-terminus of the ^{10}Fn3 defined by SEQ ID NO: 1. The M will usually be cleaved off, leaving a G at the N-terminus. Alternatively, the first 10 amino acids of the anti-PCSK9 Adnectins shown in Table 4 may be replaced with an alternative N-terminal sequence, referred to herein as N-terminal extensions, as shown in Table 6 (*i.e.*, SEQ ID NOs: 371-379). In addition, an M, G or MG may also be placed N-terminal to any of the N-terminal extensions having SEQ ID NOs: 371-379. The anti-PCSK9 Adnectins described herein may also comprise alternative C-terminal tail sequences, referred to herein as C-terminal extension sequences. For example, the anti-PCSK9 Adnectin sequences shown in Table 4 may be truncated at the threonine corresponding to T94 of SEQ ID NO: 1 (*i.e.*, truncated after the INYRT (SEQ ID NO: 636) portion of the sequence). Such truncated version may be used as therapeutic molecules in the truncated form, or alternative C-terminal extensions may be added after the threonine residue. Exemplary C-terminal extension sequences are shown in Table 6 as SEQ ID NOs: 380-395. Exemplary anti-PCSK9 Adnectins comprising C-terminal extension sequences are shown in Table 4. For example, SEQ ID NO: 49 (clone 1813E02) comprises the naturally occurring C-terminal extension EIDKPSQ (SEQ ID NO: 380) followed by a His6 tag (SEQ ID NO: 637). However, it should be understood that the His6 tag is completely optional.

[00116] In certain embodiments, the C-terminal extension sequences (also called "tails"), comprise E and D residues, and may be between 8 and 50, 10 and 30, 10 and 20, 5 and 10, and 2 and 4 amino acids in length. In some embodiments, tail sequences include ED-based linkers in which the sequence comprises tandem repeats of ED. In exemplary embodiments, the tail sequence comprises 2-10, 2-7, 2-5, 3-10, 3-7, 3-5, 3, 4

or 5 ED repeats. In certain embodiments, the ED-based tail sequences may also include additional amino acid residues, such as, for example: EI (SEQ ID NO: 385), EID, ES, EC, EGS, and EGC. Such sequences are based, in part, on known Adnectin tail sequences, such as EIDKPSQ (SEQ ID NO: 380), in which residues D and K have been removed. In exemplary embodiments, the ED-based tail comprises an E, I or EI (SEQ ID NO: 385) residues before the ED repeats.

[00117] In other embodiments, the N- or C-terminal sequences may be combined with other known linker sequences (*e.g.*, SEQ ID NO: 396-419 in Table 6) as necessary when designing an anti-PCSK9 Adnectin fusion molecule. Exemplary anti-PCSK9 Adnectin comprising linker sequences are shown in Table 4 (*e.g.*, SEQ ID NOs: 53, 55, and 57). In some embodiments, sequences may be placed at the C-terminus of the ^{10}Fn3 domain to facilitate attachment of a pharmacokinetic moiety. For example, a cysteine containing linker such as GSGC (SEQ ID NO:77) may be added to the C-terminus to facilitate site directed PEGylation on the cysteine residue.

Pharmacokinetic Moieties

[00118] In one aspect, the application provides for anti-PCSK9 Adnectins further comprising a pharmacokinetic (PK) moiety. Improved pharmacokinetics may be assessed according to the perceived therapeutic need. Often it is desirable to increase bioavailability and/or increase the time between doses, possibly by increasing the time that a protein remains available in the serum after dosing. In some instances, it is desirable to improve the continuity of the serum concentration of the protein over time (*e.g.*, decrease the difference in serum concentration of the protein shortly after administration and shortly before the next administration). The anti-PCSK9 Adnectin may be attached to a moiety that reduces the clearance rate of the polypeptide in a mammal (*e.g.*, mouse, rat, or human) by greater than three-fold relative to the unmodified anti-PCSK9 Adnectin. Other measures of improved pharmacokinetics may include serum half-life, which is often divided into an alpha phase and a beta phase. Either or both phases may be improved significantly by addition of an appropriate moiety.

[00119] Moieties that tend to slow clearance of a protein from the blood, herein referred to as "PK moieties", include polyoxyalkylene moieties, *e.g.*, polyethylene glycol, sugars (*e.g.*, sialic acid), and well-tolerated protein moieties (*e.g.*, Fc and fragments and

variants thereof, transferrin, or serum albumin). The anti-PCSK9 Adnectin may be fused to albumin or a fragment (portion) or variant of albumin as described in U.S. Publication No. 2007/0048282. In some embodiments, the PCSK9 Adnectin may be fused to one or more serum albumin binding Adnectin, as described herein.

[00120] In some embodiments, the PK moiety is a serum albumin binding protein such as those described in U.S. Publication Nos. 2007/0178082 and 2007/0269422.

[00121] In some embodiments, the PK moiety is a serum immunoglobulin binding protein such as those described in U.S. Publication No. 2007/0178082

[00122] In some embodiments, the anti-PCSK9 Adnectin comprises polyethylene glycol (PEG). One or more PEG molecules may be attached at different positions on the protein, and such attachment may be achieved by reaction with amines, thiols or other suitable reactive groups. The amine moiety may be, for example, a primary amine found at the N-terminus of a polypeptide or an amine group present in an amino acid, such as lysine or arginine. In some embodiments, the PEG moiety is attached at a position on the polypeptide selected from the group consisting of: a) the N-terminus; b) between the N-terminus and the most N-terminal beta strand or beta-like strand; c) a loop positioned on a face of the polypeptide opposite the target-binding site; d) between the C-terminus and the most C-terminal beta strand or beta-like strand; and e) at the C-terminus.

[00123] Pegylation may be achieved by site-directed pegylation, wherein a suitable reactive group is introduced into the protein to create a site where pegylation preferentially occurs. In some embodiments, the protein is modified to introduce a cysteine residue at a desired position, permitting site directed pegylation on the cysteine. PEG may vary widely in molecular weight and may be branched or linear. In one embodiment the PEG has two branches. In another embodiment the PEG has four branches.

[00124] In some embodiments, the anti-PCSK9 Adnectin is fused to an immunoglobulin Fc domain, or a fragment or variant thereof. In an exemplary embodiment, the Fc domain is derived from an IgG1 subclass, however, other subclasses (*e.g.*, IgG2, IgG3, and IgG4) may also be used. Shown below is the sequence of a human IgG1 immunoglobulin Fc domain, and the relative position of each region within the Fc domain are indicated based on the EU numbering format:

*ASTKGPSVFPLAPSSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQS SGLYSLSSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSC*DKTHTCPPCPAPELL GGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVL DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 315)

The core hinge sequence is underlined, and the CH1 region is italicized; the CH2 and CH3 regions are in regular text. It should be understood that the C-terminal lysine is optional.

[00125] The fusion may be formed by attaching an anti-PCSK9 Adnectin to either end of the Fc molecule, *i.e.*, Fc-anti-PCSK9 Adnectin or anti-PCSK9 Adnectin-Fc arrangements. In certain embodiments, the Fc and anti-PCSK9 Adnectin are fused via a linker. Exemplary linker sequences include AGGGGSG (SEQ ID NO: 310), GSGSGSGSGSGS (SEQ ID NO: 311), QPDEPGGS (SEQ ID NO: 312), ELQLEESAAEAQDGELD (SEQ ID NO: 313), TVAAPS (SEQ ID NO: 314), KAGGGGSG (SEQ ID NO: 620), KGSGSGSGSGSGS (SEQ ID NO: 621), KQPDEPGGS (SEQ ID NO: 622), KELQLEESAAEAQDGELD (SEQ ID NO: 623), KTVAAPS (SEQ ID NO: 624), KAGGGGSGG (SEQ ID NO: 625), KGSGSGSGSGSGSG (SEQ ID NO: 626), KQPDEPGGSG (SEQ ID NO: 627), KELQLEESAAEAQDGELDG (SEQ ID NO: 628), KTVAAPSG (SEQ ID NO: 629) AGGGGSGG (SEQ ID NO: 630), GSGSGSGSGSGSG (SEQ ID NO: 631), QPDEPGGSG (SEQ ID NO: 632), ELQLEESAAEAQDGELDG (SEQ ID NO: 633), and TVAAPSG (SEQ ID NO: 634).

[00126] In some embodiments, the Fc region used in the anti-PCSK9 Adnectin fusion comprises the hinge region of an Fc molecule. As used herein, the "hinge" region comprises the core hinge residues spanning positions 104-119 of SEQ ID NO: 315 (DKTHTCPPCPAPELLG; SEQ ID NO: 316) of IgG1, which corresponds to positions 221-236 according to EU numbering. In certain embodiments, the anti-PCSK9 Adnectin-Fc fusion adopts a multimeric structure (*e.g.*, dimer) owing, in part, to the cysteine

residues at positions 109 and 112 of SEQ ID NO: 315 (EU numbering 226 and 229, respectively) within the hinge region. In other embodiments, the hinge region as used herein, may further include residues derived from the CH1 and CH2 regions that flank the core hinge sequence, as shown in SEQ ID NO: 315.

[00127] In some embodiments, the hinge sequence, may include substitutions that confer desirable pharmacokinetic, biophysical, and/or biological properties. Some exemplary hinge sequences include EPKSSDKTHTCPPCPAPELLGGPS (SEQ ID NO: 317; core hinge region underlined), EPKSSDKTHTCPPCPAPELLGGSS (SEQ ID NO: 318; core hinge region underlined), EPKSSGSTHTCPPCPAPELLGGSS (SEQ ID NO: 319; core hinge region underlined), DKTHTCPPCPAPELLGGPS (SEQ ID NO: 320; core hinge region underlined), and DKTHTCPPCPAPELLGGSS (SEQ ID NO: 321, core hinge region underlined). In one embodiment, the residue P at position 122 (EU numbering 238) of SEQ ID NO: 315 has been replaced with S to ablate Fc effector function; this replacement is exemplified in hinges having any one of SEQ ID NOs: 318, 319, and 321. In another embodiment, the residues DK at positions 104-105 of SEQ ID NO: 315 (EU numbering 221-222) have been replaced with GS to remove a potential clip site; this replacement is exemplified in SEQ ID NO: 319. In another embodiment, the C at position 103 of SEQ ID NO: 315 (EU numbering 220) has been replaced with S to prevent improper cystine bond formation in the absence of a light chain; this replacement is exemplified in SEQ ID NOs: 317-319.

[00128] In certain embodiments, an antiPCSK9 Adnectin – Fc fusion may have the following configurations: 1) anti-PCSK9 Adnectin-hinge-Fc or 2) hinge-Fc-anti-PCSK9 Adnectin. Therefore, any anti-PCSK9 Adnectin of the present invention can be fused to an Fc region comprising a hinge sequence according to these configurations. In some embodiments, a linker may be used to join the anti-PCSK9 Adnectin to the hinge-Fc moiety, for example, an exemplary fusion protein may have the configuration hinge-anti-PCSK9 Adnectin-linker-Fc. Additionally, depending on the system in which the fusion polypeptide is produced, a leader sequence may placed at the N-terminus of the fusion polypeptide. For example, if the fusion is produced in a mammalian system, a leader sequence such as METDTLLLWVLLLWVPGSTG (SEQ ID NO: 326) may be added to the N-terminus of the fusion molecule. If the fusion is produced in *E. coli*, the fusion sequence will be preceded by a methionine.

[00129] The following sequence exemplifies an anti-PCSK9 Adnectin-hinge-Fc construct produced in a mammalian system:

METDTLLLWVLLLWVPGSTG*GVSDVPRDLEVVAATPTSLLISWVPPSDDYGYYRIT YGETGGNSPVQEFTVPIGKGTATISGLKPGVDYTITVYAVEFPWPHAGYYHRPISINYRT EI*EPKSSGSTHTCPPCPAPELLGGSSVFLFPPKPKDTLMISRTPEVTCVVVDVSHED PEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCK VSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIA VEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEAL HNHYTQKSLSLSPGK (SEQ ID NO: 322). Here, the Fc domain comprises the human IgG1 CH2 and CH3 regions as follows:

VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPRE EQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQ VYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDG SFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK (SEQ ID NO: 448) and the hinge sequence of SEQ ID NO:319. In SEQ ID NO: 322, the leader sequence is in bold, the anti-PCSK9 Adnectin sequence is in italics, and the hinge region is underlined. It should be understood that the lysine at the end of SEQ ID NO: 322 is optional. The efficacy of the polypeptide fusion as set forth in SEQ ID NO: 322 (also described herein as PRD460) is demonstrated in Example 4.

[00130] Exemplary PCSK9 Adnectin-Fc fusions are shown in Table 1. All sequences may begin with a methionine or a mammalian leader sequence (*e.g.*, SEQ ID NO: 326).

Table 1

Exemplary Anti-PCSK9 Adnectin-Fc Fusion Proteins

SEQ ID	Clone or Name	Description	Sequence
PCSK9 Adnectin-X_1-Fc C-Terminal Fusions			
452	1459D05–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is	GVSDVPRDLEVVAATPTSLLISWPPPSHG YGYYRITYGETGGNSPVQEFTVPPGKGTA TISGLKPGVDYTITVYAVEYPYKHSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN

SEQ ID	Clone or Name	Description	Sequence
		selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
453	1784F03–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWRPPIHA YGYYRITYGETGGNSPVQEFTVPIVEGTA TISGLKPGVDYTITVYAVEYTFKHSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
454	1784F03-m1–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPIHA YGYYRITYGETGGNSPVQEFTVPGSEGTA TISGLKPGVDYTITVYAVEYTFKHSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
455	1784F03-m2–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is	GVSDVPRDLEVVAATPTSLLISWDAPAHA YGYYRITYGETGGNSPVQEFTVPGSKGTA TISGLKPGVDYTITVYAVEYTFKHSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH

SEQ ID	Clone or Name	Description	Sequence
		selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
456	1784F03-m3–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAVT YGYYRITYGETGGNSPVQEFTVPGSKSTA TISGLKPGVDYTITVYAVEYTFKHSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
457	1813E02–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWSPPANG YGYYRITYGETGGNSPVQEFTVPVGRGTA TISGLKPGVDYTITVYAVEYTYKGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
458	1923B02–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK	GVSDVPRDLEVVAATPTSLLISWTPPPKG YGYYRITYGETGGNSPVQEFTVPVGEGTA TISGLKPGVDYTITVYAVEYTYNGAGYYH RPISINYRT-X_1-X_2-

SEQ ID	Clone or Name	Description	Sequence
		(SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK
459	1923B02(N82I)–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWTPPPKG YGYYRITYGETGGNSPVQEFTVPVGEGTA TISGLKPGVDYTITVYAVEYTYIGAGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
460	1923B02(N82E) –Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWTPPPKG YGYYRITYGETGGNSPVQEFTVPVGEGTA TISGLKPGVDYTITVYAVEYTYEGAGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
461	1923B02(T80A) –Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID	GVSDVPRDLEVVAATPTSLLISWTPPPKG YGYYRITYGETGGNSPVQEFTVPVGEGTA TISGLKPGVDYTITVYAVEYAYNGAGYYH

SEQ ID	Clone or Name	Description	Sequence
		NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	RPISINYRT-X_1-X_2-VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
462	1922G04–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWRPPSHAYGYYRITYGETGGNSPVQEFTVPIGKGTATISGLKPGVDYTITVYAVEYPWKGSGYYHRPISINYRT-X_1-X_2-VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
463	1922G04(R25D)–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDPPSHAYGYYRITYGETGGNSPVQEFTVPIGKGTATISGLKPGVDYTITVYAVEYPWKGSGYYHRPISINYRT-X_1-X_2-VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG
464	1922G04(R25E)–Fc fusion	X1 is optional and when present can be selected from	GVSDVPRDLEVVAATPTSLLISWEPPSHAYGYYRITYGETGGNSPVQEFTVPIGKGTA

SEQ ID	Clone or Name	Description	Sequence
		E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	TISGLKPGVDYTITVYAVEYPWKGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
465	1922G04(R25S) –Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWSPPSHA YGYYRITYGETGGNSPVQEFTVPIGKGTA TISGLKPGVDYTITVYAVEYPWKGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
466	2012A04–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWRPPSNG HGYYRITYGETGGNSPVQEFTVPVNEGTA TISGLKPGVDYTITVYAVEFPFKWSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
467	2013E01–Fc	X1 is optional and when	GVSDVPRDLEVVAATPTSLLISWVPPSDD

SEQ ID	Clone or Name	Description	Sequence
	fusion	present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	YGYYRITYGETGGNSPVQEFTVPIGKGTA TISGLKPGVDYTITVYAVEFPWPHAGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
468	2011H05–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWVPSSHA YGYYRITYGETGGNSPVQEFTVPVGVGTA TISGLKPGVDYTITVYAVEYAFEGAGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
469	2011H05(V23D)–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDPSSHA YGYYRITYGETGGNSPVQEFTVPVGVGTA TISGLKPGVDYTITVYAVEYAFEGAGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG

SEQ ID	Clone or Name	Description	Sequence
470	2011H05(V23E) –Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWEPSSHA YGYYRITYGETGGNSPVQEFTVPVGVGTA TISGLKPGVDYTITVYAVEYAFEGAGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
471	2381B02–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWEPFSRL PGGGEYYRITYGETGGNSPLQQFTVPGSK GTATISGLKPGVDYTITVYAVEYPYDYSG YYHRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
472	2381B04–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWEPFSRL PGGGEYYRITYGETGGNSPLQQFTVPGSK GTATISGLKPGVDYTITVYAVEYPYEHSG YYHRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS

SEQ ID	Clone or Name	Description	Sequence
			LSPG
473	2381B06–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWEPFSRL PGGGEYYRITYGETGGNSPLQQFTVPGSK GTATISGLKPGVDYTITVYAVEYPYPHSG YYHRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
474	2381B08–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPADG GYGYYRITYGETGGNSPVQEFTVPSSKGT ATISGLKPGVDYTITVYAVEYTFPGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
475	2381D02–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWEPFSRL PGGGEYYRITYGETGGNSPLQQFTVPGSK GTATISGLKPGVDYTITVYAVEYPYDHSG YYHRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD

SEQ ID	Clone or Name	Description	Sequence
			KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
476	2381D04–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWEPFSRL PGGGEYYRITYGETGGNSPLQQFTVPGSK GTATISGLKPGVDYTITVYAVEFPYDHSG YYHRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
477	2381F11–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPADG GYGYYRITYGETGGNSPVQEFTVPVSKST ATISGLKPGVDYTITVYAVEYTFPGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
478	2381G03–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWEPFSRL PGGGEYYRITYGETGGNSPLQQFTVPGSK GTATISGLKPGVDYTITVYAVEFPYAHSG YYHRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN

SEQ ID	Clone or Name	Description	Sequence
			GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
479	2381G09–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAGD GYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEFTFPGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
480	2381H03–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWEPFSRL PGGGEYYRITYGETGGNSPLQQFTVPGSK GTATISGLKPGVDYTITVYAVEYPYAHSG YFHRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
481	2382A01–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally	GVSDVPRDLEVVAATPTSLLISWAAPAGG GYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEYDFPGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR

SEQ ID	Clone or Name	Description	Sequence
		include a C-terminal K	DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
482	2382B10–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPADA YGYYRITYGETGGNSPVQEFTVPSSKGTA TISGLKPGVDYTITVYAVEYDFPGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
483	2382B09–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPADA YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFDYPGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
484	2382C05–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-	GVSDVPRDLEVVAATPTSLLISWDAPADG AYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEYSFPGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK

SEQ ID	Clone or Name	Description	Sequence
		321; the Fc may optionally include a C-terminal K	ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
485	2382C09–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAEG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFDFPGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
486	2382D03–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPADE AYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEFDFPGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
487	2382D05–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge	GVSDVPRDLEVVAATPTSLLISWDAPADG GYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEFDFPGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN

SEQ ID	Clone or Name	Description	Sequence
		sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
488	2382D08–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPADG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFPFPGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
489	2382D09–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAEG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFDFPGAGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
490	2382F02–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is	GVSDVPRDLEVVAATPTSLLISWDAPAGG GYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEFDFPGSGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH

SEQ ID	Clone or Name	Description	Sequence
		selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
491	2382F03–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAAD AYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEFNFPGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
492	2382F05–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAEA GKHYGYYRITYGETGGNSPVQEFTVPVSK GTATISGLKPGVDYTITVYAVEFDFPGAG YYHRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
493	2382F08–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK	GVSDVPRDLEVVAATPTSLLISWDAPAEA YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFTYPGSGYYH RPISINYRT-X_1-X_2-

SEQ ID	Clone or Name	Description	Sequence
		(SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
494	2382F09–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAAA YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEYDFPGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
495	2382G04–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAGG GYGYYRITYGETGGNSPVQEFTVPSSKGT ATISGLKPGVDYTITVYAVEFDFPGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
496	2382H10–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID	GVSDVPRDLEVVAATPTSLLISWDAPAGG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFDFPGSGYYH

SEQ ID	Clone or Name	Description	Sequence
		NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
497	2382H11–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPADG YGYYRITYGETGGNSPVQEFTVPVFKGTA TISGLKPGVDYTITVYAVEFDYPGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
498	2382H04–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAAG GYGYYRITYGETGGNSPVQEFTVPSSKGT ATISGLKPGVDYTITVYAVEYDFPGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
499	2382H07–Fc fusion	X1 is optional and when present can be selected from	GVSDVPRDLEVVAATPTSLLISWDAPADA YGYYRITYGETGGNSPVQEFTVPGSKGTA

SEQ ID	Clone or Name	Description	Sequence
		E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	TISGLKPGVDYTITVYAVEFDFPGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
500	2382H09–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAAA YGYYRITYGETGGNSPVQEFTVPSSKGTA TISGLKPGVDYTITVYAVEFDFPGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
501	2451A02–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAAG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFPFPGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
502	2451B05–Fc	X1 is optional and when	GVSDVPRDLEVVAATPTSLLISWDAPAGG

SEQ ID	Clone or Name	Description	Sequence
	fusion	present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	YGYYRITYGETGGNSPVQEFTVPSSKGTA TISGLKPGVDYTITVYAVEFDYPGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
503	2451B06–Fc fusion (equivalent to 2382D05)	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPADG GYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEFDFPGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
504	2451C06–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAGA ASYGYYRITYGETGGNSPVQEFTVPVSKG TATISGLKPGVDYTITVYAVEFPFPGAGY YHRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG

SEQ ID	Clone or Name	Description	Sequence
505	2451D05–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAGA YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFDFPGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
506	2451F03–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDPPAEG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFNFPGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
507	2451G01–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAGG YGYYRITYGETGGNSPVQEFTVPSSKGTA TISGLKPGVDYTITVYAVEFDFPGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS

SEQ ID	Clone or Name	Description	Sequence
			LSPG
508	2451H07–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GITDVPRDLEVVAATPTSLLISWNPPDVN YGYYRITYGETGGNSPLQEFTVPVSKGTA TISGLKPGVDYTITVYAVEYPYAHAGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
509	2382E03–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAGD GYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEFDFPGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
510	2382E04–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAGG GYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEFTFPGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD

SEQ ID	Clone or Name	Description	Sequence
			KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
511	2382E05–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAEG GYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEFDFPGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
512	2382E09–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAEA YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEYDFPGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
513	2381A04–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWEPFSRL PGGGEYYRITYGETGGNSPLQQFTVPGSK GTATISGLKPGVDYTITVYAVEYPYPFSG YYHRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN

SEQ ID	Clone or Name	Description	Sequence
			GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
514	2381A08–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPADG GYGYYRITYGETGGNSPVQEFTVPGSKGT ATISGLKPGVDYTITVYAVEYDFPGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
515	2381B10–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAGG GYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEYNFIGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
516	2381C08–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally	GVSDVPRDLEVVAATPTSLLISWDAPADG AYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEFPYPFAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR

SEQ ID	Clone or Name	Description	Sequence
		include a C-terminal K	DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
517	2381G06–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWSEKLDG KARRGYYRITYGETGGNSPVQQFTVPGSK GTATISGLKPGVDYTITVYAVEFPYDHSG YYHRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
518	2381H01–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWSPRDST GLVRRGYYRITYGETGGNSPVQQFTVPGS KGTATISGLKPGVDYTITVYAVEYPYDHS GYYHRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
519	2381H06–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-	GVSDVPRDLEVVAATPTSLLISWGDVRTN EARQGYYRITYGETGGNSPLQGFTVPGSK GTATISGLKPGVDYTITVYAVEYTYEHSG YYHRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK

SEQ ID	Clone or Name	Description	Sequence
		321; the Fc may optionally include a C-terminal K	ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
520	2381H09–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAGG GYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEFDFVGAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
521	2382B11–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAAA YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEYDFAGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
522	2382B08–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge	GVSDVPRDLEVVAATPTSLLISWDAPADA YGYYRITYGETGGNSPVQEFTVPSSKGTA TISGLKPGVDYTITVYAVEFAFPGAGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN

SEQ ID	Clone or Name	Description	Sequence
		sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
523	2382C11–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAGG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEYDFAGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
524	2382G03–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAEA EAYGYYRITYGETGGNSPVQEFTVPVSKG TATISGLKPGVDYTITVYAVEYVFPGAGY YHRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
525	2382H03–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is	GVSDVPRDLEVVAATPTSLLISWDAPAEG AYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEYPYPFAGYY HRPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH

SEQ ID	Clone or Name	Description	Sequence
		selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
526	2451A10–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVTDVPRDMEVVAATPTSLLISWQPPAVT YGYYRITYGETGGNSTLQQFTVPVYKGTA TISGLKPGVDYTITVYAVEYPYDHSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
527	2451B02–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAAA YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFDYPGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
528	2451C11–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK	GIVDVPRDLEVVAATPTSLLISWDPPAGA YGYYRITYGETGGNSPKQQFTVPGYKGTA TISGLKPGVDYTITVYAVEYPYDHSGYYH RPISINYRT-X_1-X_2-

SEQ ID	Clone or Name	Description	Sequence
		(SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPGK
529	2451H01–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPAAG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEYDFPGSGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
530	2011B11–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWAPPSDA YGYYRITYGETGGNSPVQEFTVPIGKGTA TISGLKPGVDYTITVYAVEYPYSHAGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
531	2971A03–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID	GVSDVPRDLEVVAATPTSLLISWDPPSDD YGYYRITYGETGGNSPVQEFTVPIGKGTA TISGLKPGVDYTITVYAVEFPWPHAGYYH

SEQ ID	Clone or Name	Description	Sequence
		NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
532	2971A09–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPADD YGYYRITYGETGGNSPVQEFTVPIGKGTA TISGLKPGVDYTITVYAVEFPWPHAGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
533	2971E02–Fc fusion	X1 is optional and when present can be selected from E, EI, EID, EIDK (SEQ ID NO: 384), EIE, and EIEK (SEQ ID NO: 635); X2 is selected from hinge sequences SEQ ID NOs: 317-321; the Fc may optionally include a C-terminal K	GVSDVPRDLEVVAATPTSLLISWDAPSDD YGYYRITYGETGGNSPVQEFTVPIGKGTA TISGLKPGVDYTITVYAVEFPWPHAGYYH RPISINYRT-X_1-X_2- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG
X_1-Fc-X_2-PCSK9 Adnectin N-Terminal Fusions			
534	Fc-1459D05	X1 is selected from hinge	X_1-

SEQ ID	Clone or Name	Description	Sequence
	fusion	sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWPPPSHGY GYYRITYGETGGNSPVQEFTVPPGKGTAT ISGLKPGVDYTITVYAVEYPYKHSGYYHR PISINYRT-X_3
535	Fc-1784F03 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWRPPIHAY GYYRITYGETGGNSPVQEFTVPIVEGTAT ISGLKPGVDYTITVYAVEYTFKHSGYYHR PISINYRT-X_3
536	Fc-1784F03-m1 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPIHAY

SEQ ID	Clone or Name	Description	Sequence
			GYYRITYGETGGNSPVQEFTVPGSEGTAT ISGLKPGVDYTITVYAVEYTFKHSGYYHR PISINYRT-X_3
537	Fc-1784F03-m2 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAHAY GYYRITYGETGGNSPVQEFTVPGSKGTAT ISGLKPGVDYTITVYAVEYTFKHSGYYHR PISINYRT-X_3
538	Fc-1784F03-m3 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAVTY GYYRITYGETGGNSPVQEFTVPGSKSTAT ISGLKPGVDYTITVYAVEYTFKHSGYYHR PISINYRT-X_3
539	Fc-1813E02 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN

SEQ ID	Clone or Name	Description	Sequence
		present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWSPPANGY GYYRITYGETGGNSPVQEFTVPVGRGTAT ISGLKPGVDYTITVYAVEYTYKGSGYYHR PISINYRT-X_3
540	Fc-1923B02 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWTPPPKGY GYYRITYGETGGNSPVQEFTVPVGEGTAT ISGLKPGVDYTITVYAVEYTYNGAGYYHR PISINYRT-X_3
541	Fc-1923B02(N82I) fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWTPPPKGY GYYRITYGETGGNSPVQEFTVPVGEGTAT ISGLKPGVDYTITVYAVEYTYIGAGYYHR PISINYRT-X_3
542	Fc-1923B02(N82	X1 is selected from hinge sequences SEQ ID NOs: 317-	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH

SEQ ID	Clone or Name	Description	Sequence
	E) fusion	321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWTPPPKGY GYYRITYGETGGNSPVQEFTVPVGEGTAT ISGLKPGVDYTITVYAVEYTYEGAGYYHR PISINYRT-X_3
543	Fc-1923B02(T80A) fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWTPPPKGY GYYRITYGETGGNSPVQEFTVPVGEGTAT ISGLKPGVDYTITVYAVEYAYNGAGYYHR PISINYRT-X_3
544	Fc-1922G04 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWRPPSHAY GYYRITYGETGGNSPVQEFTVPIGKGTAT

SEQ ID	Clone or Name	Description	Sequence
			ISGLKPGVDYTITVYAVEYPWKGSGYYHR PISINYRT-X_3
545	Fc-1922G04(R25D) fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2-VSDVPRDLEVVAATPTSLLISWDPPSHAY GYYRITYGETGGNSPVQEFTVPIGKGTAT ISGLKPGVDYTITVYAVEYPWKGSGYYHR PISINYRT-X_3
546	Fc-1922G04(R25E) fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2-VSDVPRDLEVVAATPTSLLISWEPPSHAY GYYRITYGETGGNSPVQEFTVPIGKGTAT ISGLKPGVDYTITVYAVEYPWKGSGYYHR PISINYRT-X_3
547	Fc-1922G04(R25S) fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD

SEQ ID	Clone or Name	Description	Sequence
		tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWSPPSHAY GYYRITYGETGGNSPVQEFTVPIGKGTAT ISGLKPGVDYTITVYAVEYPWKGSGYYHR PISINYRT-X_3
548	Fc-2012A04 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWRPPSNGH GYYRITYGETGGNSPVQEFTVPVNEGTAT ISGLKPGVDYTITVYAVEFPFKWSGYYHR PISINYRT-X_3
549	Fc-2013E01 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWVPPSDDY GYYRITYGETGGNSPVQEFTVPIGKGTAT ISGLKPGVDYTITVYAVEFPWPHAGYYHR PISINYRT-X_3
550	Fc-2011H05 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN

SEQ ID	Clone or Name	Description	Sequence
		linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWVPSSHAY GYYRITYGETGGNSPVQEFTVPVGVGTAT ISGLKPGVDYTITVYAVEYAFEGAGYYHR PISINYRT-X_3
551	Fc-2011H05(V23D) fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDPSSHAY GYYRITYGETGGNSPVQEFTVPVGVGTAT ISGLKPGVDYTITVYAVEYAFEGAGYYHR PISINYRT-X_3
552	Fc-2011H05(V23E) fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWEPSSHAY GYYRITYGETGGNSPVQEFTVPVGVGTAT ISGLKPGVDYTITVYAVEYAFEGAGYYHR

SEQ ID	Clone or Name	Description	Sequence
			PISINYRT-X_3
553	Fc-2381B02 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWEPFSRLP GGGEYYRITYGETGGNSPLQQFTVPGSKG TATISGLKPGVDYTITVYAVEYPYDYSGY YHRPISINYRT-X_3
554	Fc-2381B04 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWEPFSRLP GGGEYYRITYGETGGNSPLQQFTVPGSKG TATISGLKPGVDYTITVYAVEYPYEHSGY YHRPISINYRT-X_3
555	Fc-2381B06 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS

SEQ ID	Clone or Name	Description	Sequence
		SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	LSPG-X_2-VSDVPRDLEVVAATPTSLLISWEPFSRLPGGGEYYRITYGETGGNSPLQQFTVPGSKGTATISGLKPGVDYTITVYAVEYPYPHSGYYHRPISINYRT-X_3
556	Fc-2381B08 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG-X_2-VSDVPRDLEVVAATPTSLLISWDAPADGGYGYYRITYGETGGNSPVQEFTVPSSKGTATISGLKPGVDYTITVYAVEYTFPGAGYYHRPISINYRT-X_3
557	Fc-2381D02 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG-X_2-VSDVPRDLEVVAATPTSLLISWEPFSRLPGGGEYYRITYGETGGNSPLQQFTVPGSKGTATISGLKPGVDYTITVYAVEYPYDHSGYYHRPISINYRT-X_3
558	Fc-2381D04 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNK

SEQ ID	Clone or Name	Description	Sequence
		NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWEPFSRLP GGGEYYRITYGETGGNSPLQQFTVPGSKG TATISGLKPGVDYTITVYAVEFPYDHSGY YHRPISINYRT-X_3
559	Fc-2381F11 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPADGG YGYYRITYGETGGNSPVQEFTVPVSKSTA TISGLKPGVDYTITVYAVEYTFPGAGYYH RPISINYRT-X_3
560	Fc-2381G03 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWEPFSRLP GGGEYYRITYGETGGNSPLQQFTVPGSKG TATISGLKPGVDYTITVYAVEFPYAHSGY YHRPISINYRT-X_3

SEQ ID	Clone or Name	Description	Sequence
561	Fc-2381G09 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG-X_2-VSDVPRDLEVVAATPTSLLISWDAPAGDGYGYYRITYGETGGNSPVQEFTVPVSKGTATISGLKPGVDYTITVYAVEFTFPGAGYYHRPISINYRT-X_3
562	Fc-2381H03 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG-X_2-VSDVPRDLEVVAATPTSLLISWEPFSRLPGGGEYYRITYGETGGNSPLQQFTVPGSKGTATISGLKPGVDYTITVYAVEYPYAHSGYFHRPISINYRT-X_3
563	Fc-2382A01 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPG-X_2-

SEQ ID	Clone or Name	Description	Sequence
		EIEK (SEQ ID NO: 635)	VSDVPRDLEVVAATPTSLLISWAAPAGGG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEYDFPGAGYYH RPISINYRT-X_3
564	Fc-2382B10 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2-VSDVPRDLEVVAATPTSLLISWDAPADAY GYYRITYGETGGNSPVQEFTVPSSKGTAT ISGLKPGVDYTITVYAVEYDFPGSGYYHR PISINYRT-X_3
565	Fc-2382B09 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2-VSDVPRDLEVVAATPTSLLISWDAPADAY GYYRITYGETGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEFDYPGSGYYHR PISINYRT-X_3
566	Fc-2382C05 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634;	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR

SEQ ID	Clone or Name	Description	Sequence
		X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPADGA YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEYSFPGAGYYH RPISINYRT-X_3
567	Fc-2382C09 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAEGY GYYRITYGETGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEFDFPGSGYYHR PISINYRT-X_3
568	Fc-2382D03 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPADEA YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFDFPGAGYYH RPISINYRT-X_3
569	Fc-2382D05	X1 is selected from hinge	X_1-

SEQ ID	Clone or Name	Description	Sequence
	fusion	sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPADGG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFDFPGAGYYH RPISINYRT-X_3
570	Fc-2382D08 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPADGY GYYRITYGETGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEFPFPGSGYYHR PISINYRT-X_3
571	Fc-2382D09 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAEGY

SEQ ID	Clone or Name	Description	Sequence
			GYYRITYGETGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEFDFPGAGYYHR PISINYRT-X_3
572	Fc-2382F02 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAGGG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFDFPGSGYYH RPISINYRT-X_3
573	Fc-2382F03 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAADA YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFNFPGAGYYH RPISINYRT-X_3
574	Fc-2382F05 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN

SEQ ID	Clone or Name	Description	Sequence
		present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAEAG KHYGYYRITYGETGGNSPVQEFTVPVSKG TATISGLKPGVDYTITVYAVEFDFPGAGY YHRPISINYRT-X_3
575	Fc-2382F08 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAEAY GYYRITYGETGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEFTYPGSGYYHR PISINYRT-X_3
576	Fc-2382F09 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAAAY GYYRITYGETGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEYDFPGSGYYHR PISINYRT-X_3
577	Fc-2382G04 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH

SEQ ID	Clone or Name	Description	Sequence
		321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAGGG YGYYRITYGETGGNSPVQEFTVPSSKGTA TISGLKPGVDYTITVYAVEFDFPGAGYYH RPISINYRT-X_3
578	Fc-2382H10 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAGGY GYYRITYGETGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEFDFPGSGYYHR PISINYRT-X_3
579	Fc-2382H11 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPADGY GYYRITYGETGGNSPVQEFTVPVFKGTAT

SEQ ID	Clone or Name	Description	Sequence
			ISGLKPGVDYTITVYAVEFDYPGSGYYHR PISINYRT-X_3
580	Fc-2382H04 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2-VSDVPRDLEVVAATPTSLLISWDAPAAGG YGYYRITYGETGGNSPVQEFTVPSSKGTA TISGLKPGVDYTITVYAVEYDFPGAGYYH RPISINYRT-X_3
581	Fc-2382H07 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2-VSDVPRDLEVVAATPTSLLISWDAPADAY GYYRITYGETGGNSPVQEFTVPGSKGTAT ISGLKPGVDYTITVYAVEFDFPGSGYYHR PISINYRT-X_3
582	Fc-2382H09 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD

SEQ ID	Clone or Name	Description	Sequence
		tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAAAY GYYRITYGETGGNSPVQEFTVPSSKGTAT ISGLKPGVDYTITVYAVEFDFPGSGYYHR PISINYRT-X_3
583	Fc-2451A02 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAAGY GYYRITYGETGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEFPFPGSGYYHR PISINYRT-X_3
584	Fc-2451B05 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAGGY GYYRITYGETGGNSPVQEFTVPSSKGTAT ISGLKPGVDYTITVYAVEFDYPGSGYYHR PISINYRT-X_3
585	Fc-2451B06 fusion (equivalent to	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN

SEQ ID	Clone or Name	Description	Sequence
	2382D05)	linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPADGG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFDFPGAGYYH RPISINYRT-X_3
586	Fc-2451C06 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAGAA SYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEFPFPGAGYY HRPISINYRT-X_3
587	Fc-2451D05 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAGAY GYYRITYGETGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEFDFPGSGYYHR

SEQ ID	Clone or Name	Description	Sequence
			PISINYRT-X_3
588	Fc-2451F03 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDPPAEGY GYYRITYGETGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEFNFPGSGYYHR PISINYRT-X_3
589	Fc-2451G01 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAGGY GYYRITYGETGGNSPVQEFTVPSSKGTAT ISGLKPGVDYTITVYAVEFDFPGSGYYHR PISINYRT-X_3
590	Fc-2451H07 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS

SEQ ID	Clone or Name	Description	Sequence
		SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	LSPG-X_2- ITDVPRDLEVVAATPTSLLISWNPPDVNY GYYRITYGETGGNSPLQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEYPYAHAGYYHR PISINYRT-X_3
591	Fc-2382E03 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAGDG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFDFPGAGYYH RPISINYRT-X_3
592	Fc-2382E04 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAGGG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFTFPGAGYYH RPISINYRT-X_3
593	Fc-2382E05 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK

SEQ ID	Clone or Name	Description	Sequence
		NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAEGG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFDFPGAGYYH RPISINYRT-X_3
594	Fc-2382E09 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAEAY GYYRITYGETGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEYDFPGSGYYHR PISINYRT-X_3
595	Fc-2381A04 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWEPFSRLP GGGEYYRITYGETGGNSPLQQFTVPGSKG TATISGLKPGVDYTITVYAVEYPYPFSGY YHRPISINYRT-X_3

SEQ ID	Clone or Name	Description	Sequence
596	Fc-2381A08 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2-VSDVPRDLEVVAATPTSLLISWDAPADGG YGYYRITYGETGGNSPVQEFTVPGSKGTA TISGLKPGVDYTITVYAVEYDFPGAGYYH RPISINYRT-X_3
597	Fc-2381B10 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2-VSDVPRDLEVVAATPTSLLISWDAPAGGG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEYNFIGAGYYH RPISINYRT-X_3
598	Fc-2381C08 Fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2-

SEQ ID	Clone or Name	Description	Sequence
		EIEK (SEQ ID NO: 635)	VSDVPRDLEVVAATPTSLLISWDAPADGA YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFPYPFAGYYH RPISINYRT-X_3
599	Fc-2381G06 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2-VSDVPRDLEVVAATPTSLLISWSEKLDGK ARRGYYRITYGETGGNSPVQQFTVPGSKG TATISGLKPGVDYTITVYAVEFPYDHSGY YHRPISINYRT-X_3
600	Fc-2381H01 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2-VSDVPRDLEVVAATPTSLLISWSPRDSTG LVRRGYYRITYGETGGNSPVQQFTVPGSK GTATISGLKPGVDYTITVYAVEYPYDHSG YYHRPISINYRT-X_3
601	Fc-2381H06 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634;	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR

SEQ ID	Clone or Name	Description	Sequence
		X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWGDVRTNE ARQGYYRITYGETGGNSPLQGFTVPGSKG TATISGLKPGVDYTITVYAVEYTYEHSGY YHRPISINYRT-X_3
602	Fc-2381H09 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAGGG YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEFDFVGAGYYH RPISINYRT-X_3
603	Fc-2382B11 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAAAY GYYRITYGETGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEYDFAGSGYYHR PISINYRT-X_3
604	Fc-2382B08	X1 is selected from hinge	X_1-

SEQ ID	Clone or Name	Description	Sequence
	fusion	sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPADAY GYYRITYGETGGNSPVQEFTVPSSKGTAT ISGLKPGVDYTITVYAVEFAFPGAGYYHR PISINYRT-X_3
605	Fc-2382C11 Fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAGGY GYYRITYGETGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEYDFAGSGYYHR PISINYRT-X_3
606	Fc-2382G03 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAEAE

SEQ ID	Clone or Name	Description	Sequence
			AYGYYRITYGETGGNSPVQEFTVPVSKGT ATISGLKPGVDYTITVYAVEYVFPGAGYY HRPISINYRT-X_3
607	Fc-2382H03 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAEGA YGYYRITYGETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEYPYPFAGYYH RPISINYRT-X_3
608	Fc-2451A10 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VTDVPRDMEVVAATPTSLLISWQPPAVTY GYYRITYGETGGNSTLQQFTVPVYKGTAT ISGLKPGVDYTITVYAVEYPYDHSGYYHR PISINYRT-X_3
609	Fc-2451B02 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN

SEQ ID	Clone or Name	Description	Sequence
		present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAAAY GYYRITYGETGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEFDYPGSGYYHR PISINYRT-X_3
610	Fc-2451C11 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- IVDVPRDLEVVAATPTSLLISWDPPAGAY GYYRITYGETGGNSPKQQFTVPGYKGTAT ISGLKPGVDYTITVYAVEYPYDHSGYYHR PISINYRT-X_3
611	Fc-2451H01 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPAAGY GYYRITYGETGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEYDFPGSGYYHR PISINYRT-X_3
612	Fc-2011B11 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH

SEQ ID	Clone or Name	Description	Sequence
		321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWAPPSDAY GYYRITYGETGGNSPVQEFTVPIGKGTAT ISGLKPGVDYTITVYAVEYPYSHAGYYHR PISINYRT-X_3
613	Fc-2971A03 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDPPSDDY GYYRITYGETGGNSPVQEFTVPIGKGTAT ISGLKPGVDYTITVYAVEFPWPHAGYYHR PISINYRT-X_3
614	Fc-2971A09 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1- VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2- VSDVPRDLEVVAATPTSLLISWDAPADDY GYYRITYGETGGNSPVQEFTVPIGKGTAT

SEQ ID	Clone or Name	Description	Sequence
			ISGLKPGVDYTITVYAVEFPWPHAGYYHR PISINYRT-X_3
615	Fc-2971E02 fusion	X1 is selected from hinge sequences SEQ ID NOs: 317-321; X2 is selected from linker sequences SEQ ID NOs: 310-314 and 620-634; X3 is optional and when present can be a C-terminal tail sequence selected from SEQ ID NOs: 380-395 and EIEK (SEQ ID NO: 635)	X_1-VFLFPPKPKDTLMISRTPEVTCVVVDVSH EDPEVKFNWYVDGVEVHNAKTKPREEQYN STYRVVSVLTVLHQDWLNGKEYKCKVSNK ALPAPIEKTISKAKGQPREPQVYTLPPSR DELTKNQVSLTCLVKGFYPSDIAVEWESN GQPENNYKTTPPVLDSDGSFFLYSKLTVD KSRWQQGNVFSCSVMHEALHNHYTQKSLS LSPG-X_2-VSDVPRDLEVVAATPTSLLISWDAPSDDY GYYRITYGETGGNSPVQEFTVPIGKGTAT ISGLKPGVDYTITVYAVEFPWPHAGYYHR PISINYRT-X_3

[00131] In some embodiments, the anti-PCSK9 Adnectin comprises an Fn3 domain and a PK moiety. In some embodiments, the Fn3 domain is a ^{10}Fn3 domain. In some embodiments, the PK moiety increases the serum half-life of the polypeptide by more than 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 120, 150, 200, 400, 600, 800, 1000% or more relative to the Fn3 domain alone.

[00132] In some embodiments, the PK moiety is a polymeric sugar. In some embodiments, the PK moiety is a polyethylene glycol moiety. In some embodiments the PK moiety is a serum albumin binding protein. In some embodiments the PK moiety is human serum albumin. In some embodiments the PK moiety is a serum immunoglobulin binding protein. In some embodiments, the PK moiety is transferrin.

[00133] In some embodiments the PK moiety is another Adnectin specific for a serum protein, e.g., HSA. The present application provides specific serum albumin binding Adnectin molecules (or SABA), as described herein. In certain embodiments, a PCSK9 Adnectin fused to a SABA can be defined generally as follows: X_1-PCSK9 Adnectin core-X_2-X_3-X_4-SABA core-X_5 (SEQ ID NO: 618), or X_1-SABA core-X_2-X_3-X_4- PCSK9 Adnectin core-X_5 (SEQ ID NO: 619), wherein X_1 and X_4 represent optional N-terminal

extension sequences, X_2 and X_5 represent optional C-terminal extension sequences, and X_3 is a linker. In one embodiment, the Adnectins (either PCSK9 or serum albumin binding) of SEQ ID NOs: 618 and 619 comprise the "core" region of Adnectin, i.e., a PCSK9 Adnectin core sequence may be any one of the PCSK9 Adnectin sequences shown in Table 4, wherein the sequence begins at the amino acid residue corresponding to E8 of SEQ ID NO:1 and ends at the amino acid corresponding to residue T94 of SEQ ID NO:1; and a SABA core sequence may be selected from any of the SABA core sequences shown in Table 6.

[00134] In some embodiments, X_1 and X_4 are independently optional, and when present are independently selected from SEQ ID NOs: 371-379 listed in Table 6, and may optionally comprise an M, G or MG sequence at the N-terminus when such residues are not already present. For expression in a mammalian system, the fusion proteins may further comprise a leader sequence at the N-terminus, such as METDTLLLWVLLLWVPGSTG (SEQ ID NO: 326). In some embodiments, X_2 and X_5 are independently optional, and when present are independently selected from SEQ ID NOs: 380-395 listed in Table 6. In certain embodiments, X_3 is a linker sequence selected from SEQ ID NOs: 396-419 listed in Table 6. The sequences shown in Table 2 represent exemplary fusions of anti-PCSK9 Adnectin and SABA. It should be understood that any PCSK9 Adnectin and SABA sequence described in the present application may be incorporated into these configurations.

Table 2

Exemplary PCSK9 Adnectin – SABA Fusion Sequences

SEQ ID	Clone or Name	Description	Sequence
616	PCSK9 Adnectin-SABA fusion	PCSK9 Adnectin sequence is underlined; SABA sequence is in bold. PCSK9 Adnectin sequence is the core region derived from clone 2013E01; SABA sequence is derived from SABA 1 (SEQ ID NO: 330)	X_1-EVVAATPTSLLISWVPPSDDYGYYRITY GETGGNSPVQEFTVPIGKGTATISGLKP GVDYTITVYAVEFPWPHAGYYHRPISIN YRT-X_2-X_3-X_4-**EVVAATPTSLLISWHSYYEQNSYYRITY GETGGNSPVQEFTVPYSQTTATISGLKP GVDYTITVYAVYGSKYYYPISINYRT-**

SEQ ID	Clone or Name	Description	Sequence
			X_5
617	SABA-PCSK9 Adnectin fusion	SABA sequence is in bold; PCSK9 Adnectin sequence is underlined. SABA sequence is derived from SABA 1 (SEQ ID NO: 330); PCSK9 Adnectin sequence is the core region derived from clone 2013E01	X_1- **EVVAATPTSLLISWHSYYEQNSYYRITY** **GETGGNSPVQEFTVPYSQTTATISGLKP** **GVDYTITVYAVYGSKYYYPISINYRT-** X_2-X_3-X_4- EVVAATPTSLLISWVPPSDDYGYYRITY GETGGNSPVQEFTVPIGKGTATISGLKP GVDYTITVYAVEFPWPHAGYYHRPISIN YRT-X_5

Biophysical and Biochemical Characterization

[00135] The application provides Adnectin comprising a Fn3 domain that binds to PCSK9. Polypeptide binding to a target molecule may be assessed in terms of equilibrium constants (*e.g.*, dissociation, K_D) and in terms of kinetic constants (*e.g.*, on-rate constant, K_{on} and off-rate constant, k_{off}). An Adnectin will generally bind to a target molecule with a K_D of less than 500 nM, 100 nM, 10 nM, 1 nM, 500 pM, 200 pM, 100 pM, although higher K_D values may be tolerated where the K_{off} is sufficiently low or the K_{on}, is sufficiently high.

[00136] The SEQ ID NOS of the BC, DE and FG loops of the anti-PCSK9 Adnectins of the invention are presented in Table 3.

Table 3

Anti-PCSK9 Adnectin BC, DE and FG Loops

Clone ID	Affinity (K_D, nM)	PCSK9-EGFA FRET (EC_{50}, nM)	LDLR Depletion (% inhibition at 75nM, EC_{50} (nM))	BC Loop	SEQ ID NO	DE Loop	SEQ ID NO	FG loop	SEQ ID NO
1459D05	14.4† 1.58* 26^	4	66.8, >200	SWPPPSHGYG	2	PPGKGT	18	EYPYKHSGYYHRP	28
1784F03	3.8^	2	150.2, 26±13	SWRPPIHAYG	3	PIVEGT	19	EYTFKHSGYYHRP	29
1784F03-m1	nd	nd	nd, >2000	SWDAPIHAYG	4	PGSEGT	20	EYTFKHSGYYHRP	29
1784F03-m2	nd	nd	nd, >2000	SWDAPAHAYG	5	PGSKGT	21	EYTFKHSGYYHRP	29
1784F03-m3	nd	nd	nd, >2000	SWDAPAVTYG	6	PGSKST	22	EYTFKHSGYYHRP	29
1813E02	<2^	1.3	nd,16	SWSPPANGYG	7	PVGRGT	23	EYTYKGSGYYHRP	30
1923B02	0.173*	2.3	178.0, 23±7	SWTPPPKGYG	8	PVGEGT	24	EYTYNGAGYYHRP	31
1923B02(N82I)	nd	nd	nd, 14	SWTPPPKGYG	8	PVGEGT	24	EYTYIGAGYYHRP	32
1923B02(N82E)	nd	nd	nd, 28	SWTPPPKGYG	8	PVGEGT	24	EYTYEGAGYYHRP	33
1923B02(T80A)	nd	nd	nd, 42	SWTPPPKGYG	8	PVGEGT	24	EYAYNGAGYYHRP	34
1922G04	0.09*	1.2	105.1, 10±2	SWRPPSHAYG	9	PIGKGT	25	EYPWKGSGYYHRP	35
1922G04(R25D)	nd	2.5	nd, 29±8	SWDPPSHAYG	10	PIGKGT	25	EYPWKGSGYYHRP	35

Clone ID	Affinity (K_D, nM)	PCSK9-EGFA FRET (EC_{50}, nM)	LDLR Depletion (% inhibition at 75nM, EC_{50} (nM))	BC Loop	SEQ ID NO	DE Loop	SEQ ID NO	FG loop	SEQ ID NO
1922G04(R25E)	nd	3.5	nd, 29±18	SWEPPSHAYG	11	PIGKGT	25	EYPWKGSGYYHRP	35
1922G04(R25S)	nd	nd	nd, 21	SWSPPSHAYG	12	PIGKGT	25	EYPWKGSGYYHRP	35
2012A04	0.25*	2.1	144.5, 12±6	SWRPPSNGHG	13	PVNEGT	26	EPPFKWSGYYHRP	36
2013E01	1.51† 0.29*	1.6	165.5, 10±4	SWVPPSDDYG	14	PIGKGT	25	EPPWPHAGYYHRP	37
2011H05	0.08*	2.7	197.6, 12±5	SWVPSSHAYG	15	PVGVGT	27	EYAPEGAGYYHRP	38
2011H05(V23D)	nd	5.5	nd, 18±3	SWDPSSHAYG	16	PVGVGT	27	EYAPEGAGYYHRP	38
2011H05(V23E)	nd	7.4	nd, 12±3	SWEPSSHAYG	17	PVGVGT	27	EYAPEGAGYYHRP	38
2381B02(1)	3.29†	2.5	125.4, nd	SWEPFSRLPGGGE	106	PGSKGT	21	EYPYDYSGYYHRP	142
2381B04(1)	0.527†	2.4	121.6, nd	SWEPFSRLPGGGE	106	PGSKGT	21	EYPYEHSGYYHRP	143
2381B06(1)	nd	3.5	119.7, nd	SWEPFSRLPGGGE	106	PGSKGT	21	EYPYPHSGYYHRP	144
2381B08	4.11†	2.6	124.8, nd	SWDAPADGGYG	107	PSSKGT	136	EYTFPGAGYYHRP	145
2381D02(1)	nd	3.1	185.0, nd	SWEPFSRLPGGGE	106	PGSKGT	21	EYPYDHSGYYHRP	146
2381D04(1)	0.237†	2.9	119.2, nd	SWEPFSRLPGGGE	106	PGSKGT	21	EFPYDHSGYYHRP	147
2381F11	1.59†	4	110.2, nd	SWDAPADGGYG	107	PVSKST	137	EYTFPGAGYYHRP	145
2381G03(1)	nd	3.4	70.2, nd	SWEPFSRLPGGGE	106	PGSKGT	21	EFPYAHSGYYHRP	148

Clone ID	Affinity (K_D, nM)	PCSK9-EGFA FRET (EC_{50}, nM)	LDLR Depletion (% inhibition at 75nM, EC_{50} (nM))	BC Loop	SEQ ID NO	DE Loop	SEQ ID NO	FG loop	SEQ ID NO
2381G09	1.12†	3.1	133.0, nd	SWDAPAGDGYG	108	PVSKGT	138	EFTFPGAGYYHRP	149
2381H03(1)	nd	3.4	89.8, nd	SWEPFSRLPGGGE	106	PGSKGT	21	EYPYAHSGYFHRP	150
2382A01	nd	12.9	119.8, nd	SWAAPAGGGYG	109	PVSKGT	138	EYDFPGAGYYHRP	151
2382B10	2.35†	3	100.2, nd	SWDAPADAYG	110	PSSKGT	136	EYDFPGSGYYHRP	152
2382B09	0.656†	3.8	105.0, nd	SWDAPADAYG	110	PVSKGT	138	EFDYPGSGYYHRP	153
2382C05	2.49†	4	105.3, nd	SWDAPADGAYG	111	PVSKGT	138	EYSFPGAGYYHRP	154
2382C09	0.757†	3.5	121.7, nd	SWDAPAEGYG	112	PVSKGT	138	EFDFPGSGYYHRP	155
2382D03	1.53†	3.3	80.4, nd	SWDAPADEAYG	113	PVSKGT	138	EFDFPGAGYYHRP	156
2382D05	0.314†	2.6	140.5, nd	SWDAPADGGYG	107	PVSKGT	138	EFDFPGAGYYHRP	156
2382D08	nd	3.1	106.6, nd	SWDAPADGYG	114	PVSKGT	138	EFPFPGSGYYHRP	157
2382D09	0.304†	2.6	109.1, nd	SWDAPAEGYG	112	PVSKGT	138	EFDFPGAGYYHRP	156
2382F02	nd	2.6	-6.3, nd	SWDAPAGGGYG	115	PVSKGT	138	EFDFPGSGYYHRP	155
2382F03	nd	2.7	88.6, nd	SWDAPAADAYG	116	PVSKGT	138	EFNFPGAGYYHRP	158
2382F05	4.54†	2.4	72.2, nd	SWDAPAEAGKHYG	117	PVSKGT	138	EFDFPGAGYYHRP	156
2382F08	nd	2.5	105.0, nd	SWDAPAEAYG	118	PVSKGT	138	EFTYPGSGYYHRP	159
2382F09	nd	3.1	109.7, nd	SWDAPAAAYG	119	PVSKGT	138	EYDFPGSGYYHRP	152

Clone ID	Affinity (K_D, nM)	PCSK9-EGFA FRET (EC_{50}, nM)	LDLR Depletion (% inhibition at 75nM, EC_{50} (nM))	BC Loop	SEQ ID NO	DE Loop	SEQ ID NO	FG loop	SEQ ID NO
2382G04	1.11†	2.9	146.1, nd	SWDAPAGGGYG	115	PSSKGT	136	EFDFPGAGYYHRP	156
2382H10	1.40†	2.6	118.6, nd	SWDAPAGGYG	120	PVSKGT	138	EFDFPGSGYYHRP	155
2382H11	nd	2.9	117.2, nd	SWDAPADGYG	114	PVFKGT	139	EFDYPGSGYYHRP	153
2382H04	nd	3.2	68.2, nd	SWDAPAAGGYG	121	PSSKGT	136	EYDFPGAGYYHRP	151
2382H07	nd	2.7	86.2, nd	SWDAPADAYG	110	PGSKGT	21	EFDFPGSGYYHRP	155
2382H09	1.86†	0.9	101.2, nd	SWDAPAAAYG	119	PSSKGT	136	EFDFPGSGYYHRP	155
2451A02	nd	3.2	106.4, nd	SWDAPAAGYG	122	PVSKGT	138	EFPFPGSGYYHRP	157
2451B05	nd	6.3	91.7, nd	SWDAPAGGYG	120	PSSKGT	136	EFDYPGSGYYHRP	153
2451B06	nd	4.5	92.2, nd	SWDAPADGGYG	107	PVSKGT	138	EFDFPGAGYYHRP	156
2451C06	1.27†	1.2	89.4, nd	SWDAPAGAASYG	123	PVSKGT	138	EFPFPGAGYYHRP	160
2451D05	nd	2.8	115.0, nd	SWDAPAGAYG	124	PVSKGT	138	EFDFPGSGYYHRP	155
2451F03	nd	2.8	113.2, nd	SWDPPAEGYG	125	PVSKGT	138	EFNFPGSGYYHRP	161
2451G01	nd	3.8	90.8, nd	SWDAPAGGYG	120	PSSKGT	136	EFDFPGSGYYHRP	155
2451H07(2)	2.08†	0.2	88.8, nd	SWNPPDVNYG	126	PVSKGT	138	EYPYAHAGYYHRP	162
2382E03	2.94†	2.4	89.5, nd	SWDAPAGDGYG	108	PVSKGT	138	EFDFPGAGYYHRP	156
2382E04	nd	3	61.5, nd	SWDAPAGGGYG	115	PVSKGT	138	EFTFPGAGYYHRP	149

Clone ID	Affinity (K_D, nM)	PCSK9-EGFA FRET (EC_{50}, nM)	LDLR Depletion (% inhibition at 75nM, EC_{50} (nM))	BC Loop	SEQ ID NO	DE Loop	SEQ ID NO	FG loop	SEQ ID NO
2382E05	0.604†	2.8	103.5, nd	SWDAPAEGGYG	127	PVSKGT	138	EFDFPGAGYYHRP	156
2382E09	nd	6.2	97.2, nd	SWDAPAEAYG	118	PVSKGT	138	EYDFPGSGYYHRP	152
2381A04(1)	nd	3.3	100.1, nd	SWEPFSRLPGGGE	106	PGSKGT	21	EYPYPFSGYYHRP	163
2381A08	nd	3.6	91.4, nd	SWDAPADGGYG	107	PGSKGT	21	EYDFPGAGYYHRP	151
2381B10	nd	7.3	96.4, nd	SWDAPAGGGYG	115	PVSKGT	138	EYNFIGAGYYHRP	164
2381C08	nd	0.7	15.3, nd	SWDAPADGAYG	111	PVSKGT	138	EFPYPFAGYYHRP	165
2381G06(3)	nd	9	57.7, nd	SWSEKLDGKARRG	128	PGSKGT	21	EFPYDHSGYYHRP	147
2381H01(3)	nd	4	22.2, nd	SWSPRDSTGLVRRG	129	PGSKGT	21	EYPYDHSGYYHRP	146
2381H06(4)	nd	5	53.4, nd	SWGDVRTNEAROG	130	PGSKGT	21	EYTYEHSGYYHRP	166
2381H09	3.23†	3.4	94.4, nd	SWDAPAGGGYG	115	PVSKGT	138	EFDFVGAGYYHRP	167
2382B11	nd	2.9	88.8, nd	SWDAPAAAYG	119	PVSKGT	138	EYDFAGSGYYHRP	168
2382B08	nd	2.9	107.2, nd	SWDAPADAYG	110	PSSKGT	136	EFAFPGAGYYHRP	169
2382C11	nd	3.7	82.9, nd	SWDAPAGGYG	120	PVSKGT	138	EYDFAGSGYYHRP	168
2382G03	nd	2.7	77.8, nd	SWDAPAEAEAYG	131	PVSKGT	138	EYVFPGAGYYHRP	170
2382H03	0.677†	3.4	102.1, nd	SWDAPAEGAYG	132	PVSKGT	138	EYPYPFAGYYHRP	171
2451A10(5)	nd	10.9	53.7, nd	SWQPPAVTYG	133	PVYKGT	140	EYPYDHSGYYHRP	146

Clone ID	Affinity (K_D, nM)	PCSK9-EGFA FRET (EC_{50}, nM)	LDLR Depletion (% inhibition at 75nM, EC_{50} (nM))	BC Loop	SEQ ID NO	DE Loop	SEQ ID NO	FG loop	SEQ ID NO
2451B02	nd	5.3	71.4, nd	SWDAPAAAYG	119	PVSKGT	138	EFDYPGSGYYHRP	153
2451C11(6)	nd	9.7	70.3, nd	SWDPPAGAYG	134	PGYKGT	141	EYPYDHSGYYHRP	146
2451H01	nd	2.8	95.8, nd	SWDAPAAGYG	122	PVSKGT	138	EYDFPGSGYYHRP	152
2011B11	nd	1.7	144.5, nd	SWAPPSDAYG	135	PIGKGT	25	EYPYSHAGYYHRP	172
2971A03	0.806†	nd	120.1, nd	SWDPPSDDYG	301	PIGKGT	25	EFPWPHAGYYHRP	37
2971A09	2.79†	nd	132.3, nd	SWDAPADDYG	302	PIGKGT	25	EFPWPHAGYYHRP	37
2971E02	1.78†	nd	126.2, nd	SWDAPSDDYG	303	PIGKGT	25	EFPWPHAGYYHRP	37

† K_D determined using Octet Red at 37 °C; * K_D determined using ProteOn at 25 °C; ^ K_D determined using ITC at 37 °C; (1) In addition to mutations in the loops, these clones also have the mutations V45L and E47Q; (2) In addition to mutations in the loops, this clone also has the mutations V1I, S2T, and V45L; (3) In addition to mutations in the loops, these clones also have the mutation E47Q; (4) In addition to mutations in the loops, this clone also has the mutations V45L and E47G; (5) In addition to mutations in the loops, this clone also has the mutations S2T, L8M, P44T, V45L, and E47Q; (6) In addition to mutations in the loops, this clone also has the mutations V1I, S2V, V45K, and E47Q.

[00137] The SEQ ID NOS of the family of anti- PCSK9 Adnectin of the invention are presented in Table 4.

Table 4

Anti-PCSK9 Adnectin Family

Clone	Sequence	
	Amino Acid	Nucleic Acid
1459D05 also referred to as ATI000891 or ATI-891	MGVSDVPRDLEVVAATPTSLLI SWPPPSHGYGYYRITYGETGGN SPVQEFTVPPGKGTATISGLKP GVDYTITVYAVEYPYKHSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:39)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGCCGCCGCCGTCTCATGGTTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCGCCTGGTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTACAAACATTCTGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:40)
1784F03	MGVSDVPRDLEVVAATPTSLLI SWRPPIHAYGYYRITYGETGGN SPVQEFTVPIVEGTATISGLKP GVDYTITVYAVEYTFKHSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:41)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGAGGCCGCCGATTCATGCTTACGGGTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGTTGAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATATACATTTAAACATTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:42)

Clone	Sequence	
	Amino Acid	Nucleic Acid
1784F03-m1	MGVSDVPRDLEVVAATPTSLLI SWDAPIHAYGYYRITYGETGGN SPVQEFTVPGSEGTATISGLKP GVDYTITVYAVEYTFKHSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:43)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGATTCATGCTTACGGGTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTTCTGAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATATACATTTAAACATTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:44)
1784F03-m2	MGVSDVPRDLEVVAATPTSLLI SWDAPAHAYGYYRITYGETGGN SPVQEFTVPGSKGTATISGLKP GVDYTITVYAVEYTFKHSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:45)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTCATGCTTACGGGTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATATACATTTAAACATTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:46)
1784F03-m3	MGVSDVPRDLEVVAATPTSLLI SWDAPAVTYGYYRITYGETGGN SPVQEFTVPGSKSTATISGLKP GVDYTITVYAVEYTFKHSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:47)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGTTACTTACGGGTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTTCTAAATCTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATATACATTTAAACATTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:48)

Clone	Sequence	
	Amino Acid	Nucleic Acid
1813E02	MGVSDVPRDLEVVAATPTSLLI SWSPPANGYGYYRITYGETGGN SPVQEFTVPVGRGTATISGLKP GVDYTITVYAVEYTYKGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:49)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGTCCCCACCGGCTAACGGTTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTGGTAGAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAGTATACCTACAAAGGCTCTGGTT ACTACCATCGCCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:50)
1923B02	MGVSDVPRDLEVVAATPTSLLI SWTPPPKGYGYYRITYGETGGN SPVQEFTVPVGEGTATISGLKP GVDYTITVYAVEYTYNGAGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:51)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGACGCCTCCCCCTAAAGGGTATGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTGGTGAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACACGTACAACGGTGCCGGTT ACTACCACCGGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:52)
1923B02(N82I)	MGVSDVPRDLEVVAATPTSLLI SWTPPPKGYGYYRITYGETGGN SPVQEFTVPVGEGTATISGLKP GVDYTITVYAVEYTYIGAGYYH RPISINYRTGSGSHHHHHH (SEQ ID NO:53)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGACGCCTCCCCCTAAAGGGTATGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTGGTGAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACACGTACATTGGTGCCGGTT ACTACCACCGGCCAATTTCCATTAATTACCGCACAGGTAGCGGTTCCCACCATCACCACCATCA C (SEQ ID NO:54)

Clone	Sequence	
	Amino Acid	Nucleic Acid
1923B02(N82E)	MGVSDVPRDLEVVAATPTSLLI SWTPPPKGYGYYRITYGETGGN SPVQEFTVPVGEGTATISGLKP GVDYTITVYAVEYTYEGAGYYH RPISINYRTGSGSHHHHHH (SEQ ID NO:55)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGACGCCTCCCCCTAAAGGGTATGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTGGTGAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACACGTACGAAGGTGCCGGTT ACTACCACCGGCCAATTTCCATTAATTACCGCACAGGTAGCGGTTCCCACCATCACCACCATCA C (SEQ ID NO:56)
1923B02(T80A)	MGVSDVPRDLEVVAATPTSLLI SWTPPPKGYGYYRITYGETGGN SPVQEFTVPVGEGTATISGLKP GVDYTITVYAVEYAYNGAGYYH RPISINYRTGSGSHHHHHH (SEQ ID NO:57)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGACGCCTCCCCCTAAAGGGTATGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTGGTGAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACGCGTACAACGGTGCCGGTT ACTACCACCGGCCAATTTCCATTAATTACCGCACAGGTAGCGGTTCCCACCATCACCACCATCA C (SEQ ID NO:58)
1922G04 also referred to herein as ATI001057 or ATI-1057	MGVSDVPRDLEVVAATPTSLLI SWRPPSHAYGYYRITYGETGGN SPVQEFTVPIGKGTATISGLKP GVDYTITVYAVEYPWKGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:59)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGCGGCCGCCATCTCATGCTTATGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGGGAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTGGAAAGGTTCTGGTT ACTACCATCGGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:60)

Clone	Sequence	
	Amino Acid	Nucleic Acid
1922G04(R25D)	MGVSDVPRDLEVVAATPTSLLI SWDPPSHAYGYYRITYGETGGN SPVQEFTVPIGKGTATISGLKP GVDYTITVYAVEYPWKGSGYYH RPISINYRTGSGSHHHHHH (SEQ ID NO:61)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACCCGCCATCTCATGCTTATGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGGGAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTGGAAAGGTTCTGGTT ACTACCATCGGCCAATTTCCATTAATTACCGCACAGGTAGCGGTTCCCACCATCACCACCATCA C (SEQ ID NO:62)
1922G04(R25E)	MGVSDVPRDLEVVAATPTSLLI SWEPPSHAYGYYRITYGETGGN SPVQEFTVPIGKGTATISGLKP GVDYTITVYAVEYPWKGSGYYH RPISINYRTGSGSHHHHHH (SEQ ID NO:63)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGAACCGCCATCTCATGCTTATGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGGGAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTGGAAAGGTTCTGGTT ACTACCATCGGCCAATTTCCATTAATTACCGCACAGGTAGCGGTTCCCACCATCACCACCATCA C (SEQ ID NO:64)
1922G04(R25S)	MGVSDVPRDLEVVAATPTSLLI SWSPPSHAYGYYRITYGETGGN SPVQEFTVPIGKGTATISGLKP GVDYTITVYAVEYPWKGSGYYH RPISINYRTGSGSHHHHHH (SEQ ID NO:65)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGAGCCCGCCATCTCATGCTTATGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGGGAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTGGAAAGGTTCTGGTT ACTACCATCGGCCAATTTCCATTAATTACCGCACAGGTAGCGGTTCCCACCATCACCACCATCA C (SEQ ID NO:66)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2012A04	MGVSDVPRDLEVVAATPTSLLI SWRPPSNGHGYYRITYGETGGN SPVQEFTVPVNEGTATISGLKP GVDYTITVYAVEFPFKWSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:67)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGCGGCCCCCCTCTAATGGTCACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTAATGAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCCCCTTCAAGTGGTCGGGCT ACTACCATCGACCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:68)
2013E01 also referred to as ATI001081 or ATI-1081	MGVSDVPRDLEVVAATPTSLLI SWVPPSDDYGYYRITYGETGGN SPVQEFTVPIGKGTATISGLKP GVDYTITVYAVEFPWPHAGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:69)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGTCCCGCCTTCAGATGATTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGGTAAAGGAACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAGTTTCCGTGGCCACATGCTGGTT ACTATCATCGGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:70)
2011H05 also referred to as ATI001091 or ATI-1091	MGVSDVPRDLEVVAATPTSLLI SWVPSSHAYGYYRITYGETGGN SPVQEFTVPVGVGTATISGLKP GVDYTITVYAVEYAFEGAGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:71)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGTTCCGTCGTCTCATGCCTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTGGGGGTAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACGCTTTCGAAGGGGCTGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:72)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2011H05(V23D)	MGVSDVPRDLEVVAATPTSLLI SWDPSSHAYGYYRITYGETGGN SPVQEFTVPVGVGTATISGLKP GVDYTITVYAVEYAFEGAGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:73)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACCCGTCGTCTCATGCCTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTGGGGGTAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACGCTTTCGAAGGGGCTGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:74)
2011H05(V23E)	MGVSDVPRDLEVVAATPTSLLI SWEPSSHAYGYYRITYGETGGN SPVQEFTVPVGVGTATISGLKP GVDYTITVYAVEYAFEGAGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:75)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGAACCGTCGTCTCATGCCTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTGGGGGTAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACGCTTTCGAAGGGGCTGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:76)
2381B02	MGVSDVPRDLEVVAATPTSLLI SWEPFSRLPGGGEYYRITYGET GGNSPLQQFTVPGSKGTATISG LKPGVDYTITVYAVEYPYDYSG YYHRPISINYRTEIDKPSQHHH HHH (SEQ ID NO:173)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGAGCCGTTCAGCCGGTTGCCCGGGGGCGGCGAGTATTACCGGATCACTTACGGCGA AACAGGAGGCAATAGCCCTCTGCAGCAGTTCACTGTGCCTGGTTCTAAAGGTACAGCTACCATC AGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTACGACT ATTCTGGTTACTACCATCGCCCCATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCA GCACCATCACCACCACCAC (SEQ ID NO:174)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2381B04	MGVSDVPRDLEVVAATPTSLLI SWEPFSRLPGGGEYYRITYGET GGNSPLQQFTVPGSKGTATISG LKPGVDYTITVYAVEYPYEHSG YYHRPISINYRTEIDKPSQHHH HHH (SEQ ID NO:175)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGAGCCGTTCAGCCGGTTGCCCGGGGGCGGCGAGTATTACCGGATCACTTACGGCGA AACAGGAGGCAATAGCCCTCTGCAGCAGTTCACTGTGCCTGGTTCTAAAGGTACAGCTACCATC AGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTACGAGC ATTCTGGGTACTATCATCGTCCGATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCA GCACCATCACCACCACCAC (SEQ ID NO:176)
2381B06	MGVSDVPRDLEVVAATPTSLLI SWEPFSRLPGGGEYYRITYGET GGNSPLQQFTVPGSKGTATISG LKPGVDYTITVYAVEYPYPHSG YYHRPISINYRTEIDKPSQHHH HHH (SEQ ID NO:177)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGAGCCGTTCAGCCGGTTGCCCGGGGGCGGCGAGTATTACCGGATCACTTACGGCGA AACAGGAGGCAATAGCCCTCTGCAGCAGTTCACTGTGCCTGGTTCTAAAGGTACAGCTACCATC AGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTACCCGC ATTCTGGTTACTACCATCGACCGATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCA GCACCATCACCACCACCAC (SEQ ID NO:178)
2381B08	MGVSDVPRDLEVVAATPTSLLI SWDAPADGGYGYYRITYGETGG NSPVQEFTVPSSKGTATISGLK PGVDYTITVYAVEYTFPGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:179)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGATGGAGGGTACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTAGTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACACCTTCCCGGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:180)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2381D02	MGVSDVPRDLEVVAATPTSLLI SWEPFSRLPGGGEYYRITYGET GGNSPLQQFTVPGSKGTATISG LKPGVDYTITVYAVEYPYDHSG YYHRPISINYRTEIDKPSQHHH HHH (SEQ ID NO:181)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGAGCCGTTCAGCCGGTTGCCCGGGGGCGGCGAGTATTACCGGATCACTTACGGCGA AACAGGAGGCAATAGCCCTCTGCAGCAGTTCACTGTGCCTGGTTCTAAAGGTACAGCTACCATC AGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTACGACC ATTCTGGTTACTACCATCGTCCCATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCA GCACCATCACCACCACCAC (SEQ ID NO:182)
2381D04	MGVSDVPRDLEVVAATPTSLLI SWEPFSRLPGGGEYYRITYGET GGNSPLQQFTVPGSKGTATISG LKPGVDYTITVYAVEFPYDHSG YYHRPISINYRTEIDKPSQHHH HHH (SEQ ID NO:183)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGAGCCGTTCAGCCGGTTGCCCGGGGGCGGCGAGTATTACCGGATCACTTACGGCGA AACAGGAGGCAATAGCCCTCTGCAGCAGTTCACTGTGCCTGGTTCTAAAGGTACAGCTACCATC AGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCCCGTACGACC ATTCTGGTTACTACCATCGGCCCATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCA GCACCATCACCACCACCAC (SEQ ID NO:184)
2381F11	MGVSDVPRDLEVVAATPTSLLI SWDAPADGGYGYYRITYGETGG NSPVQEFTVPVSKSTATISGLK PGVDYTITVYAVEYTFPGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:185)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGACGGGGGGTACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAAGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACACCTTCCCCGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:186)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2381G03	MGVSDVPRDLEVVAATPTSLLI SWEPFSRLPGGGEYYRITYGET GGNSPLQQFTVPGSKGTATISG LKPGVDYTITVYAVEFPYAHSG YYHRPISINYRTEIDKPSQHHH HHH (SEQ ID NO:187)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGAGCCGTTCAGCCGGTTGCCCGGGGGCGGCGAGTATTACCGGATCACTTACGGCGA AACAGGAGGCAATAGCCCTCTGCAGCAGTTCACTGTGCCTGGTTCTAAAGGTACAGCTACCATC AGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCCCGTACGCGC ATTCTGGGTACTACCATCGTCCGATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCA GCACCATCACCACCACCAC (SEQ ID NO:188)
2381G09	MGVSDVPRDLEVVAATPTSLLI SWDAPAGDGYGYYRITYGETGG NSPVQEFTVPVSKGTATISGLK PGVDYTITVYAVEFTFPGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:189)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGGGGACGGTTACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCCGTTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCACCTTCCCGGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:190)
2381H03	MGVSDVPRDLEVVAATPTSLLI SWEPFSRLPGGGEYYRITYGET GGNSPLQQFTVPGSKGTATISG LKPGVDYTITVYAVEYPYAHSG YFHRPISINYRTEIDKPSQHHH HHH (SEQ ID NO:191)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGAGCCGTTCAGCCGGTTGCCCGGGGGCGGCGAGTATTACCGGATCACTTACGGCGA AACAGGAGGCAATAGCCCTCTGCAGCAGTTCACTGTGCCTGGTTCTAAAGGTACAGCTACCATC AGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTACGCGC ATTCTGGTTACTTCCATCGTCCGATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCA GCACCATCACCACCACCAC (SEQ ID NO:192)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2382A01	MGVSDVPRDLEVVAATPTSLLI SWAAPAGGGYGYYRITYGETGG NSPVQEFTVPVSKGTATISGLK PGVDYTITVYAVEYDFPGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:193)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGCCGCTCCGGCTGGTGGTGGCTACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACGACTTCCCGGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:194)
2382B10	MGVSDVPRDLEVVAATPTSLLI SWDAPADAYGYYRITYGETGGN SPVQEFTVPSSKGTATISGLKP GVDYTITVYAVEYDFPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:195)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TAAGCTGGGACGCTCCGGCTGACGCGTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTAGTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACGACTTCCCCGGCAGCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:196)
2382B09	MGVSDVPRDLEVVAATPTSLLI SWDAPADAYGYYRITYGETGGN SPVQEFTVPVSKGTATISGLKP GVDYTITVYAVEFDYPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:197)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGACGCGTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTACCCCGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:198)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2382C05	MGVSDVPRDLEVVAATPTSLLI SWDAPADGAYGYYRITYGETGG NSPVQEFTVPVSKGTATISGLK PGVDYTITVYAVEYSFPGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:199)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGATGGGGCATACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAGGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACTCCTTCCCCGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:200)
2382C09	MGVSDVPRDLEVVAATPTSLLI SWDAPAEGYGYYRITYGETGGN SPVQEFTVPVSKGTATISGLKP GVDYTITVYAVEFDFPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:201)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGAGGGTTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCCGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:202)
2382D03	MGVSDVPRDLEVVAATPTSLLI SWDAPADEAYGYYRITYGETGG NSPVQEFTVPVSKGTATISGLK PGVDYTITVYAVEFDFPGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:203)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGACGAGGCGTACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGTGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCCGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:204)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2382D05	MGVSDVPRDLEVVAATPTSLLI SWDAPADGYGYYRITYGETGG NSPVQEFTVPVSKGTATISGLK PGVDYTITVYAVEFDFPGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:205)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGATGGTGGTTACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCGGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:206)
2382D08	MGVSDVPRDLEVVAATPTSLLI SWDAPADGYGYYRITYGETGGN SPVQEFTVPVSKGTATISGLKP GVDYTITVYAVEFPFPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:207)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGATGGCTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCCCCTTCCCCGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:208)
2382D09	MGVSDVPRDLEVVAATPTSLLI SWDAPAEGYGYYRITYGETGGN SPVQEFTVPVSKGTATISGLKP GVDYTITVYAVEFDFPGAGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:209)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGAAGGGTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCCGGCGCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:210)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2382F02	MGVSDVPRDLEVVAATPTSLLI SWDAPAGGGYGYYRITYGETGG NSPVQEFTVPVSKGTATISGLK PGVDYTITVYAVEFDFPGSGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:211)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGGCGGGGGGTACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCGGGCTCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:212)
2382F03	MGVSDVPRDLEVVAATPTSLLI SWDAPAADAYGYYRITYGETGG NSPVQEFTVPVSKGTATISGLK PGVDYTITVYAVEFNFPGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:213)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGCCGATGCTTACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCAACTTCCCGGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:214)
2382F05	MGVSDVPRDLEVVAATPTSLLI SWDAPAEAGKHYGYYRITYGET GGNSPVQEFTVPVSKGTATISG LKPGVDYTITVYAVEFDFPGAG YYHRPISINYRTEIDKPSQHHH HHH (SEQ ID NO:215)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGAAGCAGGTAAGCACTACGGTTATTACCGCATCACTTACGGCGA AACAGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATC AGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCGG GCGCCGGTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCA GCACCATCACCACCACCAC (SEQ ID NO:216)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2382F08	MGVSDVPRDLEVVAATPTSLLI SWDAPAEAYGYYRITYGETGGN SPVQEFTVPVSKGTATISGLKP GVDYTITVYAVEFTYPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:217)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGAAGCATACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCACCTACCCCGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:218)
2382F09	MGVSDVPRDLEVVAATPTSLLI SWDAPAAAYGYYRITYGETGGN SPVQEFTVPVSKGTATISGLKP GVDYTITVYAVEYDFPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:219)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGCAGCCTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACGACTTCCCCGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:220)
2382G04	MGVSDVPRDLEVVAATPTSLLI SWDAPAGGGYGYYRITYGETGG NSPVQEFTVPSSKGTATISGLK PGVDYTITVYAVEFDFPGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:221)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGGTGGGGGATACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTAGTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCGGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:222)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2382H10	MGVSDVPRDLEVVAATPTSLLI SWDAPAGGYGYYRITYGETGGN SPVQEFTVPVSKGTATISGLKP GVDYTITVYAVEFDFPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:223)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGGGGGCTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCCGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:224)
2382H11	MGVSDVPRDLEVVAATPTSLLI SWDAPADGYGYYRITYGETGGN SPVQEFTVPVFKGTATISGLKP GVDYTITVYAVEFDYPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:225)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGATGGTTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTTTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTACCCCGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:226)
2382H04	MGVSDVPRDLEVVAATPTSLLI SWDAPAAGGYGYYRITYGETGG NSPVQEFTVPSSKGTATISGLK PGVDYTITVYAVEYDFPGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:227)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGCGGGGGGGTACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTAGTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTATATGCTGTCGAATACGACTTCCCCGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:228)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2382H07	MGVSDVPRDLEVVAATPTSLLI SWDAPADAYGYYRITYGETGGN SPVQEFTVPGSKGTATISGLKP GVDYTITVYAVEFDFPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:229)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGATGCTTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCAGTCCAGGAGTTCACTGTGCCTGGTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCCGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:230)
2382H09	MGVSDVPRDLEVVAATPTSLLI SWDAPAAAYGYYRITYGETGGN SPVQEFTVPSSKGTATISGLKP GVDYTITVYAVEFDFPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:231)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGCGGCTTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTAGTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCCGGCTCCGGTT ACTACCATCGCCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:232)
2451A02	MGVSDVPRDLEVVAATPTSLLI SWDAPAAGYGYYRITYGETGGN SPVQEFTVPVSKGTATISGLKP GVDYTITVYAVEFPFPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:233)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGCGGGTTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCCCCTTCCCCGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:234)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2451B05	MGVSDVPRDLEVVAATPTSLLI SWDAPAGGYGYYRITYGETGGN SPVQEFTVPSSKGTATISGLKP GVDYTITVYAVEFDYPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:235)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGGGGGATACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTAGTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTACCCCGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:236)
2451B06 (equivalent to 2382D05)	MGVSDVPRDLEVVAATPTSLLI SWDAPADGGYGYYRITYGETGG NSPVQEFTVPVSKGTATISGLK PGVDYTITVYAVEFDFPGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:205)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGATGGTGGTTACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCGGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:206)
2451C06	MGVSDVPRDLEVVAATPTSLLI SWDAPAGAASYGYYRITYGETG GNSPVQEFTVPVSKGTATISGL KPGVDYTITVYAVEFPFPGAGY YHRPISINYRTEIDKPSQHHHH HH (SEQ ID NO:237)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGGGGCAGCGTCCTACGGTTATTACCGCATCACTTACGGCGAAAC AGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGC GGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCCCCTTCCCCGGCG CCGGTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCA CCATCACCACCACCAC (SEQ ID NO:238)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2451D05	MGVSDVPRDLEVVAATPTSLLI SWDAPAGAYGYYRITYGETGGN SPVQEFTVPVSKGTATISGLKP GVDYTITVYAVEFDFPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:239)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGGCGCGTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCCGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:240)
2451F03	MGVSDVPRDLEVVAATPTSLLI SWDPPAEGYGYYRITYGETGGN SPVQEFTVPVSKGTATISGLKP GVDYTITVYAVEFNFPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:241)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACCCTCCGGCTGAAGGTTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCAACTTCCCCGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:242)
2451G01	MGVSDVPRDLEVVAATPTSLLI SWDAPAGGYGYYRITYGETGGN SPVQEFTVPSSKGTATISGLKP GVDYTITVYAVEFDFPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:243)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGGGGGCTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTAGTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCGGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:244)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2451H07	MGITDVPRDLEVVAATPTSLLI SWNPPDVNYGYYRITYGETGGN SPLQEFTVPVSKGTATISGLKP GVDYTITVYAVEYPYAHAGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:245)	ATGGGTATCACGGATGTGCCGCGAGACTTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGAACCCGCCGGATGTGAATTACGGTTATTATCGCATCACTTACGGGGAAACAGGAGG CAATAGCCCTTTGCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATATCCGTACGCGCACGCTGGTT ACTACCATCGTCCGATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:246)
2382E03	MGVSDVPRDLEVVAATPTSLLI SWDAPAGDGYGYYRITYGETGG NSPVQEFTVPVSKGTATISGLK PGVDYTITVYAVEFDFPGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:247)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGGGGACGGGTACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCCGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:248)
2382E04	MGVSDVPRDLEVVAATPTSLLI SWDAPAGGGYGYYRITYGETGG NSPVQEFTVPVSKGTATISGLK PGVDYTITVYAVEFTFPGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:249)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGGTGGTGGATACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCACCTTCCCGGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:250)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2382E05	MGVSDVPRDLEVVAATPTSLLI SWDAPAEGGYGYYRITYGETGG NSPVQEFTVPVSKGTATISGLK PGVDYTITVYAVEFDFPGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:251)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGAGGGCGGCTACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCCGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:252)
2382E09	MGVSDVPRDLEVVAATPTSLLI SWDAPAEAYGYYRITYGETGGN SPVQEFTVPVSKGTATISGLKP GVDYTITVYAVEYDFPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:253)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGAGGCTTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACGACTTCCCCGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:254)
2381A04	MGVSDVPRDLEVVAATPTSLLI SWEPFSRLPGGGEYYRITYGET GGNSPLQQFTVPGSKGTATISG LKPGVDYTITVYAVEYPYPFSG YYHRPISINYRTEIDKPSQHHH HHH (SEQ ID NO:255)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGAGCCGTTCAGCCGGTTGCCCGGGGGCGGCGAGTATTACCGGATCACTTACGGCGA AACAGGAGGCAATAGCCCTCTGCAGCAGTTCACTGTGCCTGGTTCTAAAGGTACAGCTACCATC AGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTACCCGT TTTCTGGTTACTACCATCGTCCCATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCA GCACCATCACCACCACCAC (SEQ ID NO:256)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2381A08	MGVSDVPRDLEVVAATPTSLLI SWDAPADGGYGYYRITYGETGG NSPVQEFTVPGSKGTATISGLK PGVDYTITVYAVEYDFPGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:257)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGACGGCGGGTACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGGTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACGACTTCCCGGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:258)
2381B10	MGVSDVPRDLEVVAATPTSLLI SWDAPAGGGYGYYRITYGETGG NSPVQEFTVPVSKGTATISGLK PGVDYTITVYAVEYNFIGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:259)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGGGGGTGGATACGGTTATTACCGSATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACAACTTCATCGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:260)
2381C08	MGVSDVPRDLEVVAATPTSLLI SWDAPADGAYGYYRITYGETGG NSPVQEFTVPVSKGTATISGLK PGVDYTITVYAVEFPYPFAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:261)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGACGGTGCCTACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCCCCTACCCCTTCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:262)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2381G06	MGVSDVPRDLEVVAATPTSLLI SWSEKLDGKARRGYYRITYGET GGNSPVQQFTVPGSKGTATISG LKPGVDYTITVYAVEFPYDHSG YYHRPISINYRTEIDKPSQHHH HHH (SEQ ID NO:263)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGTCGGAGAAGTTGGACGGGAAGGCGCGCCGCGGGTATTACCGCATCACATACGGCGA AACAGGAGGCAATAGCCCTGTCCAGCAGTTCACTGTGCCTGGTTCTAAAGGTACAGCTACCATC AGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCCCGTACGACC ATTCTGGTTACTACCATCGTCCCATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCA GCACCATCACCACCACCAC (SEQ ID NO:264)
2381H01	MGVSDVPRDLEVVAATPTSLLI SWSPRDSTGLVRRGYYRITYGE TGGNSPVQQFTVPGSKGTATIS GLKPGVDYTITVYAVEYPYDHS GYYHRPISINYRTEIDKPSQHH HHHH (SEQ ID NO:265)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGAGCCCGCGGGACTCCACCGGCTTGGTGAGGCGGGGGTATTACCGCATCACTTACGG CGAAACAGGAGGCAATAGCCCTGTTCAGCAGTTCACTGTGCCTGGTTCTAAAGGTACAGCTACC ATCAGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTACG ACCATTCTGGTTACTACCATCGGCCCATTTCCATTAATTACCGCACAGAAATTGACAAACCATC CCAGCACCATCACCACCACCAC (SEQ ID NO:266)
2381H06	MGVSDVPRDLEVVAATPTSLLI SWGDVRTNEARQGYYRITYGET GGNSPLQGFTVPGSKGTATISG LKPGVDYTITVYAVEYTYEHSG YYHRPISINYRTEIDKPSQHHH HHH (SEQ ID NO:267)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGGCGACGTCCGGACGAACGAGGCGCGGCAGGGCTATTACCGGATCACTTACGGCGA AACAGGAGGCAATAGCCCTCTCCAGGGGTTCACTGTGCCTGGTTCTAAAGGTACAGCTACCATC AGCGGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAGTATACGTACGAGC ATTCTGGTTACTACCATCGTCCGATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCA GCACCATCACCACCACCAC (SEQ ID NO:268)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2381H09	MGVSDVPRDLEVVAATPTSLLI SWDAPAGGGYGYYRITYGETGG NSPVQEFTVPVSKGTATISGLK PGVDYTITVYAVEFDFVGAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:269)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGGGGGGGGCTACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCGTCGGCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:270)
2382B11	MGVSDVPRDLEVVAATPTSLLI SWDAPAAAYGYYRITYGETGGN SPVQEFTVPVSKGTATISGLKP GVDYTITVYAVEYDFAGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:271)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGCGGCCTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACGACTTCGCGGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:272)
2382B08	MGVSDVPRDLEVVAATPTSLLI SWDAPADAYGYYRITYGETGGN SPVQEFTVPSSKGTATISGLKP GVDYTITVYAVEFAFPGAGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:273)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGACGCGTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTAGTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTATATGCTGTCGAATTCGCCTTCCCCGGCGCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:274)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2382C11	MGVSDVPRDLEVVAATPTSLLI SWDAPAGGYGYYRITYGETGGN SPVQEFTVPVSKGTATISGLKP GVDYTITVYAVEYDFAGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:275)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGGAGGTTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACGACTTCGCGGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:276)
2382G03	MGVSDVPRDLEVVAATPTSLLI SWDAPAEAEAYGYYRITYGETG GNSPVQEFTVPVSKGTATISGL KPGVDYTITVYAVEYVFPGAGY YHRPISINYRTEIDKPSQHHHH HH (SEQ ID NO:277)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGAAGCAGAAGCGTACGGTTATTACCGCATCACTTACGGCGAAAC AGGAGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGC GGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACGTCTTCCCCGGCG CCGGTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCA CCATCACCACCACCAC (SEQ ID NO:278)
2382H03	MGVSDVPRDLEVVAATPTSLLI SWDAPAEGAYGYYRITYGETGG NSPVQEFTVPVSKGTATISGLK PGVDYTITVYAVEYPYPFAGYY HRPISINYRTEIDKPSQHHHHH H (SEQ ID NO:279)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGAGGGCGCTTACGGTTATTACCGCATCACTTACGGCGAAACAGG AGGCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGC CTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCCTACCCCTTCGCCG GTTACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCA TCACCACCACCAC (SEQ ID NO:280)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2451A10	MGVTDVPRDMEVVAATPTSLLI SWQPPAVTYGYYRITYGETGGN STLQQFTVPVYKGTATISGLKP GVDYTITVYAVEYPYDHSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:281)	ATGGGTGTCACCGATGTGCCGCGCGACATGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGCAGCCGCCGGCTGTTACTTACGGTTATTATCGCATCACTTACGGCGAAACAGGAGG CAATAGCACTCTCCAGCAGTTCACTGTGCCTGTTTATAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTACGACCATTCTGGGT ACTACCATCGGCCGATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:282)
2451B02	MGVSDVPRDLEVVAATPTSLLI SWDAPAAAYGYYRITYGETGGN SPVQEFTVPVSKGTATISGLKP GVDYTITVYAVEFDYPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:283)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGCTGCTTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTACCCCGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:284)
2451C11	MGIVDVPRDLEVVAATPTSLLI SWDPPAGAYGYYRITYGETGGN SPKQQFTVPGYKGTATISGLKP GVDYTITVYAVEYPYDHSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:285)	ATGGGTATCGTGGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACCCGCCGGCTGGTGCTTACGGTTATTATCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCAAAGCAGCAGTTCACTGTGCCTGGTTATAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTACGACCATTCTGGTT ACTACCATCGGCCGATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:286)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2451H01	MGVSDVPRDLEVVAATPTSLLI SWDAPAAGYGYYRITYGETGGN SPVQEFTVPVSKGTATISGLKP GVDYTITVYAVEYDFPGSGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:287)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCTCCGGCTGCGGGGTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACGACTTCCCCGGCTCCGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:288)
2011B11	MGVSDVPRDLEVVAATPTSLLI SWAPPSDAYGYYRITYGETGGN SPVQEFTVPIGKGTATISGLKP GVDYTITVYAVEYPYSHAGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:289)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGCGCCGCCTTCTGATGCGTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGGTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTATTCACATGCTGGTT ACTACCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:290)
2971A03	MGVSDVPRDLEVVAATPTSLLI SWDPPSDDYGYYRITYGETGGN SPVQEFTVPIGKGTATISGLKP GVDYTITVYAVEFPWPHAGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:304)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACCCGCCTTCGGATGATTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGGTAAAGGAACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAGTTTCCGTGGCCACATGCTGGTT ACTATCATCGGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:305)

Clone	Sequence	
	Amino Acid	Nucleic Acid
2971A09	MGVSDVPRDLEVVAATPTSLLI SWDAPADDYGYYRITYGETGGN SPVQEFTVPIGKGTATISGLKP GVDYTITVYAVEFPWPHAGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:306)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCGCCTGCGGATGATTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGGTAAAGGAACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAGTTTCCGTGGCCACATGCTGGTT ACTATCATCGGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:307)
2971E02	MGVSDVPRDLEVVAATPTSLLI SWDAPSDDYGYYRITYGETGGN SPVQEFTVPIGKGTATISGLKP GVDYTITVYAVEFPWPHAGYYH RPISINYRTEIDKPSQHHHHHH (SEQ ID NO:308)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGA TCAGCTGGGACGCGCCTTCGGATGATTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGG CAATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGGTAAAGGAACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAGTTTCCGTGGCCACATGCTGGTT ACTATCATCGGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATCCCAGCACCATCA CCACCACCAC (SEQ ID NO:309)

[00138] The SEQ ID NOS of the family of the pegylated anti-PCSK9 Adnectins of the invention are presented in Table 5.

Table 5

Anti-PCSK9 Adnectin Family Cysteine Mutants to Enable Pegylation

*Note: Some proteins listed have not yet been pegylated but are enabled to be pegylated via the cysteine mutation. Proteins that have been pegylated are indicated by asterisk.

ATI# / Clone# [Description]	Sequence	
	AA	NT
ATI001170 [2013E01-non His tagged Cys mut]	MGVSDVPRDLEVVAATPTSL LISWVPPSDDYGYYRITYGE TGGNSPVQEFTVPIGKGTAT ISGLKPGVDYTITVYAVEFP WPHAGYYHRPISINYRTEID KPCQ (SEQ ID NO:78)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGGTCCCGCCTTCAGATGATTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGGCA ATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGGTAAAGGAACAGCTACCATCAGCGGCCTTAAA CCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAGTTTCCGTGGCCACATGCTGGTTACTA TCATCGGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATGCCAGTG (SEQ ID NO:79)
ATI001172 [2013E01-non His tagged Cys mut]	MGVSDVPRDLEVVAATPTSL LISWVPPSDDYGYYRITYGE TGGNSPVQEFTVPIGKGTAT ISGLKPGVDYTITVYAVEFP WPHAGYYHRPISINYRTEGS GC (SEQ ID NO:80)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGGTCCCGCCTTCAGATGATTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGGCA ATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGGTAAAGGAACAGCTACCATCAGCGGCCTTAAA CCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAGTTTCCGTGGCCACATGCTGGTTACTA TCATCGGCCAATTTCCATTAATTACCGAACAGAAGGTAGCGGTTGCTG (SEQ ID NO:81)
ATI001174* [2013E01-non His tagged Cys mut] also referred to as ATI-1174	MGVSDVPRDLEVVAATPTSL LISWVPPSDDYGYYRITYGE TGGNSPVQEFTVPIGKGTAT ISGLKPGVDYTITVYAVEFP WPHAGYYHRPISINYRTEIE KPCQ (SEQ ID NO:82)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGGTCCCGCCTTCAGATGATTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGGCA ATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGGTAAAGGAACAGCTACCATCAGCGGCCTTAAA CCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAGTTTCCGTGGCCACATGCTGGTTACTA TCATCGGCCAATTTCCATTAATTACCGCACAGAAATTGAGAAACCATGCCAGTG (SEQ ID NO:83)

ATI# / Clone# [Description]	Sequence	
	AA	NT
ATI001114* [2013E01cys mut] also referred to as ATI-1114	MGVSDVPRDLEVVAATPTSL LISWVPPSDDYGYYRITYGE TGGNSPVQEFTVPIGKGTAT ISGLKPGVDYTITVYAVEFP WPHAGYYHRPISINYRTGSG CHHHHHH (SEQ ID NO:84)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGGTCCCGCCTTCAGATGATTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGGCA ATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGGTAAAGGAACAGCTACCATCAGCGGCCTTAAA CCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAGTTTCCGTGGCCACATGCTGGTTACTA TCATCGGCCAATTTCCATTAATTACCGCACAGGTAGCGGTTGCCACCATCACCACCATCAC (SEQ ID NO:85)
ATI000959* [1459D05 cys mut]	MGVSDVPRDLEVVAATPTSL LISWPPPSHGYGYYRITYGE TGGNSPVQEFTVPPGKGTAT ISGLKPGVDYTITVYAVEYP YKHSGYYHRPISINYRTEID KPCQHHHHHH (SEQ ID NO:86)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGCCGCCGCCGTCTCATGGTTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGGCA ATAGCCCTGTCCAGGAGTTCACTGTGCCGCCTGGTAAAGGTACAGCTACCATCAGCGGCCTTAAA CCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTACAAACATTCTGGTTACTA CCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATGCCAGCACCATCACCACC ACCAC (SEQ ID NO:87)
ATI001063* [1784F03 Cys mut]	MGVSDVPRDLEVVAATPTSL LISWRPPIHAYGYYRITYGE TGGNSPVQEFTVPIVEGTAT ISGLKPGVDYTITVYAVEYT FKHSGYYHRPISINYRTEID KPCQHHHHHH (SEQ ID NO:88)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGAGGCCGCCGATTCATGCTTACGGGTATTACCGCATCACTTACGGCGAAACAGGAGGCA ATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGTTGAAGGTACAGCTACCATCAGCGGCCTTAAA CCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATATACATTTAAACATTCCGGTTACTA CCATCGTCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATGCCAGCACCATCACCACC ACCAC (SEQ ID NO:89)

ATI# / Clone# [Description]	Sequence	
	AA	NT
ATI001119* [2012A04 Cys mut]	MGVSDVPRDLEVVAATPTSL LISWRPPSNGHGYYRITYGE TGGNSPVQEFTVPVNEGTAT ISGLKPGVDYTITVYAVEFP FKWSGYYHRPISINYRTGSG CHHHHHH (SEQ ID NO:90)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGCGGCCCCCCTCTAATGGTCACGGTTATTACCGCATCACTTACGGCGAAACAGGAGGCA ATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTAATGAAGGTACAGCTACCATCAGCGGCCTTAAA CCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCCCCTTCAAGTGGTCGGGCTACTA CCATCGACCAATTTCCATTAATTACCGCACAGGTAGCGGTTGCCACCATCACCACCATCAC (SEQ ID NO:91)
ATI001117* [2011H05 Cys mut]	MGVSDVPRDLEVVAATPTSL LISWVPSSHAYGYYRITYGE TGGNSPVQEFTVPVGVGTAT ISGLKPGVDYTITVYAVEYA FEGAGYYHRPISINYRTGSG CHHHHHH (SEQ ID NO:92)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGGTTCCGTCGTCTCATGCCTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGGCA ATAGCCCTGTCCAGGAGTTCACTGTGCCTGTGGGGGTAGGTACAGCTACCATCAGCGGCCTTAAA CCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACGCTTTCGAAGGGGCTGGTTACTA CCATCGTCCAATTTCCATTAATTACCGCACAGGTAGCGGTTGCCACCATCACCACCATCAC (SEQ ID NO:93)
ATI001194* [2011H05(V23D) Cys mut]	MGVSDVPRDLEVVAATPTSL LISWDPSSHAYGYYRITYGE TGGNSPVQEFTVPVGVGTAT ISGLKPGVDYTITVYAVEYA FEGAGYYHRPISINYRTEGS GCHHHHHH (SEQ ID NO:94)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGGACCCGTCGTCTCATGCCTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGGCA ATAGCCCTGTCCAGGAGTTCACTGTGCCTGTGGGGGTAGGTACAGCTACCATCAGCGGCCTTAAA CCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACGCTTTCGAAGGGGCTGGTTACTA CCATCGTCCAATTTCCATTAATTACCGCACAGAAGGTAGCGGTTGCCACCATCACCACCATCAC (SEQ ID NO:95)

ATI# / Clone# [Description]	Sequence	
	AA	NT
2011H05 (V23E)-Cys mut	MGVSDVPRDLEVVAATPTSL LISWEPSSHAYGYYRITYGE TGGNSPVQEFTVPVGVGTAT ISGLKPGVDYTITVYAVEYA FEGAGYYHRPISINYRTEGS GCHHHHHH (SEQ ID NO:96)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGGAACCGTCGTCTCATGCCTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGGCA ATAGCCCTGTCCAGGAGTTCACTGTGCCTGTGGGGGTAGGTACAGCTACCATCAGCGGCCTTAAA CCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACGCTTTCGAAGGGGCTGGTTACTA CCATCGTCCAATTTCCATTAATTACCGCACAGAAGGTAGCGGTTGCCACCATCACCACCATCAC (SEQ ID NO:97)
ATI001112 [1923B02 Cys mut]	MGVSDVPRDLEVVAATPTSL LISWTPPPKGYGYYRITYGE TGGNSPVQEFTVPVGEGTAT ISGLKPGVDYTITVYAVEYT YNGAGYYHRPISINYRTGSG CHHHHHH (SEQ ID NO:98)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGACGCCTCCCCCTAAAGGGTATGGTTATTACCGCATCACTTACGGCGAAACAGGAGGCA ATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTGGTGAAGGTACAGCTACCATCAGCGGCCTTAAA CCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACACGTACAACGGTGCCGGTTACTA CCACCGGCCAATTTCCATTAATTACCGCACAGGTAGCGGTTGCCACCATCACCACCATCAC (SEQ ID NO:99)
ATI001110 [1922G04 Cys mut]	MGVSDVPRDLEVVAATPTSL LISWRPPSHAYGYYRITYGE TGGNSPVQEFTVPIGKGTAT ISGLKPGVDYTITVYAVEYP WKGSGYYHRPISINYRTGSG CHHHHHH (SEQ ID NO:100)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGCGGCCGCCATCTCATGCTTATGGTTATTACCGCATCACTTACGGCGAAACAGGAGGCA ATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGGGAAAGGTACAGCTACCATCAGCGGCCTTAAA CCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTGGAAAGGTTCTGGTTACTA CCATCGGCCAATTTCCATTAATTACCGCACAGGTAGCGGTTGCCACCATCACCACCATCAC (SEQ ID NO:101)

ATI# / Clone# [Description]	Sequence	
	AA	NT
ATI001128 [1922G04 Cys mut]	MGVSDVPRDLEVVAATPTSL LISWRPPSHAYGYYRITYGE TGGNSPVQEFTVPIGKGTAT ISGLKPGVDYTITVYAVEYP WKGSGYYHRPISINYRTEID KPCQHHHHHH (SEQ ID NO:102)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGCGGCCGCCATCTCATGCTTATGGTTATTACCGCATCACTTACGGCGAAACAGGAGGCA ATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGGGAAAGGTACAGCTACCATCAGCGGCCTTAAA CCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTGGAAAGGTTCTGGTTACTA CCATCGGCCAATTTCCATTAATTACCGCACAGAAATTGACAAACCATGCCAGCACCACCACCACC ACCAC (SEQ ID NO:103)
ATI001184 * [1922G04(R23E) Cys mut]	MGVSDVPRDLEVVAATPTSL LISWEPPSHAYGYYRITYGE TGGNSPVQEFTVPIGKGTAT ISGLKPGVDYTITVYAVEYP WKGSGYYHRPISINYRTEGS GCHHHHHH (SEQ ID NO:104)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGGAACCGCCATCTCATGCTTATGGTTATTACCGCATCACTTACGGCGAAACAGGAGGCA ATAGCCCTGTCCAGGAGTTCACTGTGCCTATTGGGAAAGGTACAGCTACCATCAGCGGCCTTAAA CCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATACCCGTGGAAAGGTTCTGGTTACTA CCATCGGCCAATTTCCATTAATTACCGCACAGAAGGTAGCGGTTGCCACCATCACCACCATCAC (SEQ ID NO:105)
2381D04-Cys	MGVSDVPRDLEVVAATPTSL LISWEPFSRLPGGGEYYRIT YGETGGNSPLQQFTVPGSKG TATISGLKPGVDYTITVYAV EFPYDHSGYYHRPISINYRT GSGCHHHHHH (SEQ ID NO:291)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGGAGCCGTTCAGCCGGTTGCCCGGGGGCGGCGAGTATTACCGGATCACTTACGGCGAAA CAGGAGGCAATAGCCCTCTGCAGCAGTTCACTGTGCCTGGTTCTAAAGGTACAGCTACCATCAGC GGCCTTAAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCCCGTACGACCATTC TGGTTACTACCATCGGCCCATTTCCATTAATTACCGCACAGGTAGCGGTTGCCACCATCACCACC ATCAC (SEQ ID NO:292)

ATI# / Clone# [Description]	Sequence	
	AA	NT
2382D09-Cys	MGVSDVPRDLEVVAATPTSL LISWDAPAEGYGYYRITYGE TGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEFD FPGAGYYHRPISINYRTGSG CHHHHHH (SEQ ID NO:293)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGGACGCTCCGGCTGAAGGGTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGGCA ATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTTAAA CCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCCGGCGCCGGTTACTA CCATCGTCCAATTTCCATTAATTACCGCACAGGTAGCGGTTGCCACCATCACCACCATCAC (SEQ ID NO:294)
2451B06-Cys	MGVSDVPRDLEVVAATPTSL LISWDAPADGGYGYYRITYG ETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEF DFPGAGYYHRPISINYRTGS GCHHHHHH (SEQ ID NO:295)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGGACGCTCCGGCTGATGGTGGTTACGGTTATTACCGCATCACTTACGGCGAAACAGGAG GCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCGGGCGCCGGTTA CTACCATCGTCCAATTTCCATTAATTACCGCACAGGTAGCGGTTGCCACCATCACCACCATCAC (SEQ ID NO:296)
2382E05-Cys	MGVSDVPRDLEVVAATPTSL LISWDAPAEGGYGYYRITYG ETGGNSPVQEFTVPVSKGTA TISGLKPGVDYTITVYAVEF DFPGAGYYHRPISINYRTGS GCHHHHHH (SEQ ID NO:297)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGGACGCTCCGGCTGAGGGCGGCTACGGTTATTACCGCATCACTTACGGCGAAACAGGAG GCAATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTT AAACCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTTCCCCGGCGCCGGTTA CTACCATCGTCCAATTTCCATTAATTACCGCACAGGTAGCGGTTGCCACCATCACCACCATCAC (SEQ ID NO:298)

ATI# / Clone# [Description]	Sequence	
	AA	NT
2382B09-Cys	MGVSDVPRDLEVVAATPTSL LISWDAPADAYGYYRITYGE TGGNSPVQEFTVPVSKGTAT ISGLKPGVDYTITVYAVEFD YPGSGYYHRPISINYRTGSG CHHHHHH (SEQ ID NO:299)	ATGGGAGTTTCTGATGTGCCGCGCGACCTGGAAGTGGTTGCTGCCACCCCCACCAGCCTGCTGAT CAGCTGGGACGCTCCGGCTGACGCGTACGGTTATTACCGCATCACTTACGGCGAAACAGGAGGCA ATAGCCCTGTCCAGGAGTTCACTGTGCCTGTTTCTAAAGGTACAGCTACCATCAGCGGCCTTAAA CCTGGCGTTGATTATACCATCACTGTGTATGCTGTCGAATTCGACTACCCCGGCTCCGGTTACTA CCATCGTCCAATTTCCATTAATTACCGCACAGGTAGCGGTTGCCACCATCACCACCATCAC (SEQ ID NO:300)

Nucleic Acid-Protein Fusion Technology

[00139] In one aspect, the application provides an Adnectin comprising fibronectin type III domains that binds PCSK9. One way to rapidly make and test Fn3 domains with specific binding properties is the nucleic acid-protein fusion technology of Adnexus, a Bristol-Myers Squibb R&D Company. This disclosure utilizes the *in vitro* expression and tagging technology, termed PROfusion, which exploits nucleic acid-protein fusions (RNA- and DNA- protein fusions) to identify novel polypeptides and amino acid motifs that are important for binding to proteins. Nucleic acid-protein fusion technology is a technology that covalently couples a protein to its encoding genetic information. For a detailed description of the RNA-protein fusion technology and fibronectin-based scaffold protein library screening methods see Szostak et al., U.S. Patent Nos. 6,258,558, 6,261,804, 6,214,553, 6,281,344, 6,207,446, 6,518,018 and 6,818,418; and Roberts et al., *Proc. Natl. Acad. Sci.*, 94:12297-12302 (1997), herein incorporated by reference.

Vectors and Polynucleotide Embodiments

[00140] Nucleic acids encoding any of the various proteins or polypeptides disclosed herein may be synthesized chemically. Codon usage may be selected so as to improve expression in a cell. Such codon usage will depend on the cell type selected. Specialized codon usage patterns have been developed for *E. coli* and other bacteria, as well as mammalian ceils, plant cells, yeast cells and insect cells. See for example: Mayfield et al., *Proc. Natl. Acad. Sci. USA*, 100(2):438-442 (Jan. 21, 2003); Sinclair et al., *Protein Expr. Purif.*, 26(I):96-105 (Oct. 2002); Connell, N.D., *Curr. Opin. Biotechnol.*, 12(5):446-449 (Oct. 2001); Makrides et al., *Microbiol. Rev.*, 60(3):512-538 (Sep. 1996); and Sharp et al., *Yeast*, 7(7):657-678 (Oct. 1991).

[00141] General techniques for nucleic acid manipulation are described for example in Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edition, Vols. 1-3, Cold Spring Harbor Laboratory Press (1989), or Ausubel, F. et al., *Current Protocols in Molecular Biology*, Green Publishing and Wiley-Interscience, New York (1987) and periodic updates, herein incorporated by reference. Generally, the DNA encoding the polypeptide is operably linked to suitable transcriptional or translational regulatory elements derived from mammalian, viral, or insect genes. Such regulatory elements

include a transcriptional promoter, an optional operator sequence to control transcription, a sequence encoding suitable mRNA ribosomal binding sites, and sequences that control the termination of transcription and translation. The ability to replicate in a host, usually conferred by an origin of replication, and a selection gene to facilitate recognition of transformants is additionally incorporated.

[00142] The proteins described herein may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which is preferably a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. The heterologous signal sequence selected preferably is one that is recognized and processed (*i.e.*, cleaved by a signal peptidase) by the host cell. An exemplary N-terminal leader sequence for production of polypeptides in a mammalian system is METDTLLLWVLLLWVPGSTG (SEQ ID NO: 326), which is removed by the host cell following expression.

[00143] For prokaryotic host cells that do not recognize and process a native signal sequence, the signal sequence is substituted by a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders.

[00144] For yeast secretion the native signal sequence may be substituted by, *e.g.*, the yeast invertase leader, a factor leader (including Saccharomyces and Kluyveromyces alpha-factor leaders), or acid phosphatase leader, the C. albicans glucoamylase leader, or the signal described in U.S. Patent No. 5,631,144. In mammalian cell expression, mammalian signal sequences as well as viral secretory leaders, for example, the herpes simplex gD signal, are available. The DNA for such precursor regions may be ligated in reading frame to DNA encoding the protein.

[00145] Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Generally, in cloning vectors this sequence is one that enables the vector to replicate independently of the host chromosomal DNA, and includes origins of replication or autonomously replicating sequences. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2 micron plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian

cells. Generally, the origin of replication component is not needed for mammalian expression vectors (the SV40 origin may typically be used only because it contains the early promoter).

[00146] Expression and cloning vectors may contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, *e.g.*, ampicillin, neomycin, methotrexate, or tracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, *e.g.*, the gene encoding D-alanine racemase for Bacilli.

[00147] Expression and cloning vectors usually contain a promoter that is recognized by the host organism and is operably linked to the nucleic acid encoding the protein of the invention, *e.g.*, a fibronectin-based scaffold protein. Promoters suitable for use with prokaryotic hosts include the phoA promoter, beta-lactamase and lactose promoter systems, alkaline phosphatase, a tryptophan (trp) promoter system, and hybrid promoters such as the tan promoter. However, other known bacterial promoters are suitable. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding the protein of the invention. Promoter sequences are known for eukaryotes. Virtually all eukaryotic genes have an AT-rich region located approximately 25 to 30 bases upstream from the site where transcription is initiated. Another sequence found 70 to 80 bases upstream from the start of transcription of many genes is a CNCAAT region where N may be any nucleotide. At the 3′ end of most eukaryotic genes is an AATAAA sequence that may be the signal for addition of the poly A tall to the 3′ end of the coding sequence. All of these sequences are suitably inserted into eukaryotic expression vectors.

[00148] Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase or other glycolytic enzymes, such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

[00149] Transcription from vectors in mammalian host cells can be controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus, adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and most preferably Simian Virus

40 (SV40), from heterologous mammalian promoters, *e.g.*, the actin promoter or an immunoglobulin promoter, from heat-shock promoters, provided such promoters are compatible with the host cell systems.

[00150] Transcription of a DNA encoding proteins of the invention by higher eukaryotes is often increased by inserting an enhancer sequence into the vector. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, α-fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. See also Yaniv, *Nature*, 297:17-18 (1982) on enhancing elements for activation of eukaryotic promoters. The enhancer may be spliced into the vector at a position 5′ or 3′ to the peptide-encoding sequence, but is preferably located at a site 5′ from the promoter.

[00151] Expression vectors used in eukaryotic host cells (*e.g.*, yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5′ and, occasionally 3′, untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of mRNA encoding the protein of the invention. One useful transcription termination component is the bovine growth hormone polyadenylation region. See WO 94/11026 and the expression vector disclosed therein.

[00152] The recombinant DNA can also include any type of protein tag sequence that may be useful for purifying the protein. Examples of protein tags include but are not limited to a histidine tag, a FLAG tag, a myc tag, an HA tag, or a GST tag. Appropriate cloning and expression vectors for use with bacterial, fungal, yeast, and mammalian cellular hosts can be found in *Cloning Vectors: A Laboratory Manual*, (Elsevier, New York (1985)), the relevant disclosure of which is hereby incorporated by reference.

[00153] The expression construct is introduced into the host cell using a method appropriate to the host cell, as will be apparent to one of skill in the art. A variety of methods for introducing nucleic acids into host cells are known in the art, including, but not limited to, electroporation; transfection employing calcium chloride, rubidium

chloride, calcium phosphate, DEAE-dextran, or other substances; microprojectile bombardment; lipofection; and infection (where the vector is an infectious agent).

[00154] Suitable host cells include prokaryotes, yeast, mammalian cells, or bacterial cells. Suitable bacteria include gram negative or gram positive organisms, for example, *E. coli* or *Bacillus spp*. Yeast, preferably from the *Saccharomyces* species, such as *S. cerevisiae*, may also be used for production of polypeptides. Various mammalian or insect cell culture systems can also be employed to express recombinant proteins. Baculovirus systems for production of heterologous proteins in insect cells are reviewed by Luckow et al. (*Bio/Technology*, 6:47 (1988)). Examples of suitable mammalian host cell lines include endothelial cells, COS-7 monkey kidney cells, CV-1, L cells, C127, 3T3, Chinese hamster ovary (CHO), human embryonic kidney ceils, HeLa, 293, 293T, and BHK cell lines. Purified polypeptides are prepared by culturing suitable host/vector systems to express the recombinant proteins. For many applications, the small size of many of the polypeptides disclosed herein would make expression in *E. coli* as the preferred method for expression. The protein is then purified from culture media or cell extracts.

Protein Production

[00155] Host cells are transformed with the herein-described expression or cloning vectors for protein production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. In the examples shown here, the host cells used for high-throughput protein production (HTPP) and mid-scale production was the HMS174-bacterial strain. The host cells used to produce the proteins of this invention may be cultured in a variety of media. Commercially available media such as Ham's F10 (Sigma), Minimal Essential Medium ((MEM), (Sigma)), RPMI-1640 (Sigma), and Dulbecco's Modified Eagle's Medium ((DMEM), Sigma)) are suitable for culturing the host cells. In addition, may of the media described in Ham et al., *Meth. Enzymol.*, 58:44 (1979), Barites et al., *Anal. Biochem.*, 102:255 (1980), U.S. Patent Nos. 4,767,704, 4,657,866, 4,927,762, 4,560,655, 5,122,469, 6,048,728, 5,672,502, or U.S. Patent No. RE 30,985 may be used as culture media for the host cells. Any of these media may be supplemented as necessary with hormones and/or other growth factors (such as insulin,

transferrin, or epidermal growth factor), salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides (such as adenosine and thymidine), antibiotics (such as Gentamycin drug), trace elements (defined as inorganic compounds usually present at final concentrations in the micromolar range), and glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art. The culture conditions, such as temperature, pH, and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

[00156] Proteins disclosed herein can also be produced using cell-translation systems. For such purposes the nucleic acids encoding the polypeptide must be modified to allow *in vitro* transcription to produce mRNA and to allow cell-free translation of the mRNA in the particular cell-free system being utilized (eukaryotic such as a mammalian or yeast cell-free translation system or prokaryotic such as a bacterial ceil-free translation system.

[00157] Proteins of the invention can also be produced by chemical synthesis (*e.g.*, by the methods described in *Solid Phase Peptide Synthesis*, 2nd Edition, The Pierce Chemical Co., Rockford, IL (1984)). Modifications to the protein can also be produced by chemical synthesis.

[00158] The proteins of the present invention can be purified by isolation/purification methods for proteins generally known in the field of protein chemistry. Non-limiting examples include extraction, recrystallization, salting out (*e.g.*, with ammonium sulfate or sodium sulfate), centrifugation, dialysis, ultrafiltration, adsorption chromatography, ion exchange chromatography, hydrophobic chromatography, normal phase chromatography, reversed-phase chromatography, get filtration, gel permeation chromatography, affinity chromatography, electrophoresis, countercurrant distribution or any combinations of these. After purification, polypeptides may be exchanged into different buffers and/or concentrated by any of a variety of methods known to the art, including, but not limited to, filtration and dialysis.

[00159] The purified polypeptide is preferably at least 85% pure, or preferably at least 95% pure, and most preferably at least 98% pure. Regardless of the exact numerical value of the purity, the polypeptide is sufficiently pure for use as a pharmaceutical product.

[00160] A platform manufacturing process was used to prepare anti-PCSK9 Adnectin. The anti-PCSK9 Adnectin is produced in *Escherichia coli* (*E. coli*). *E. coli* BLR (DE3) cells were transformed with expression vector (pET9d/ATI001173) which produces the protein in a soluble form intracellularly. The recombinant strain is grown in stirred tank fermentors. At the end of fermentation the cells are collected, lysed, and clarified in preparation for purification. ATI001173 is a non-his tagged version of ATI001114. The purified anti-PCSK9 Adnectin is conjugated to a 40 kDa branched methoxyPEG using a maleimide linker. The conjugated material is subsequently repurified to remove free PEG, free anti-PCSK9 Adnectin and product related impurities. Quality control testing is performed on the bulk drug substance.

Therapeutic *In Vivo* Uses

[00161] In one aspect, the application provides anti-PCSK9 Adnectin useful in the treatment of atherosclerosis, hypercholesterolemia and other cholesterol related diseases. The application also provides methods for administering anti-PCSK9 Adnectin to a subject. In some embodiments, the subject is a human. In some embodiments, the anti-PCSK9 Adnectin are pharmaceutically acceptable to a mammal, in particular a human. A "pharmaceutically acceptable" polypeptide refers to a polypeptide that is administered to an animal without significant adverse medical consequences, such as essentially endotoxin free, or very low endotoxin levels.

Formulation and Administration

[00162] The application further provides pharmaceutically acceptable compositions comprising the anti-PCSK9 Adnectin or fusion proteins thereof described herein, wherein the composition is essentially endotoxin free. Therapeutic formulations comprising anti-PCSK9 Adnectin or fusions thereof are prepared for storage by mixing the described polypeptide having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Osol, A., *Remington's Pharmaceutical Sciences*, 16th Edition (1980)), in the form of aqueous solutions, lyophilized or other dried formulations. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as

octadecyidimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (*e.g.*, Zn-protein complexes); and/or non-ionic surfactants such as Tween, PLURONIC® or polyethylene glycol (PEG).

[00163] The formulations herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

[00164] The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

[00165] The skilled artisan will understand that the dosage of each therapeutic agent will be dependent on the identity of the agent.

[00166] For therapeutic applications, the anti-PCSK9 Adnectin or a fusion protein comprising an anti-PCSK9 Adnectin is administered to a subject, in a pharmaceutically acceptable dosage form. They can be administered intravenously as a bolus or by continuous infusion over a period of time, or by subcutaneous routes. Suitable pharmaceutically acceptable carriers, diluents, and excipients are well known and can be determined by those of skill in the art as the clinical situation warrants. Examples of suitable carriers, diluents and/or excipients include: (1) Dulbecco's phosphate buffered saline, (2) 0.9% saline (0.9% w/v NaC1), and (3) 5% (w/v) dextrose.

[00167] The method of the present invention can be practiced *in vitro*, *in vivo*, or ex vivo.

[00168] Administration of anti-PCSK9 Adnectin or a fusion thereof, and one or more additional therapeutic agents, whether co-administered or administered sequentially, may occur as described above for therapeutic applications. Suitable pharmaceutically

acceptable carriers, diluents, and excipients for co-administration will be understood by the skilled artisan to depend on the identity of the particular therapeutic agent being administered.

[00169] When present in an aqueous dosage form, rather than being lyophilized, the protein typically will be formulated at a concentration of about 0.1 mg/ml to 100 mg/ml, although wide variation outside of these ranges is permitted. For the treatment of disease, the appropriate dosage of anti-PCSK9 Adnectin or a fusion thereof will depend on the type of disease to be treated, the severity and course of the disease, whether the protein is administered for preventive or therapeutic purposes, the course of previous therapy, the patient's clinical history and response to the protein, and the discretion of the attending physician. The protein is suitably administered to the patient at one time or over a series of treatments.

Fusions of Serum Albumin Binding Adnectin (SABA)

[00170] In certain aspects, the application provides fusion proteins comprising anti-PCSK9 Adnectin fused to a ^{10}Fn3 domains that binds to human serum albumin (a Serum Albumin Binding Adnectin (^{10}Fn3 domain) or SABA). Such fusion proteins have extended serum half lives in the presence of albumin relative to the anti-PCSK9 Adnectin alone (*e.g.*, not conjugated to a PK moiety).

[00171] ^{10}Fn3 domains are cleared rapidly from circulation via renal filtration and degradation due to their small size of ~10 kDa ($t_{1/2}$ = 15–45 minutes in mice; 1-3 hours in monkeys). Fusion of a ^{10}Fn3 domain, such as an anti-PCSK9 Adnectin, to a second polypeptide comprising a ^{10}Fn3 domain that binds specifically to serum albumin, *e.g.*, human serum albumin (HSA), may be used to prolong the $t_{1/2}$ of the anti-PCSK9 Adnectin.

[00172] In certain embodiments, the serum half-life of the anti-PCSK9 Adnectin fused to the SABA is increased relative to the serum half-life of the anti-PCSK9 Adnectin when not conjugated to the SABA. In certain embodiments, the serum half-life of the SABA fusion is at least 20, 40, 60, 80, 100, 120, 150, 180, 200, 400, 600, 800, 1000, 1200, 1500, 1800, 1900, 2000, 2500, or 3000% longer relative to the serum half-life of the anti-PCSK9 Adnectin when not fused to the SABA. In other embodiments, the serum half-life of the SABA fusion is at least 1.5-fold, 2-fold, 2.5-fold, 3-fold, 3.5 fold, 4-fold, 4.5-fold,

5-fold, 6-fold, 7-fold, 8-fold, 10-fold, 12-fold, 13-fold, 15-fold, 17-fold, 20-fold, 22-fold, 25-fold, 27-fold, 30-fold, 35-fold, 40-fold, or 50-fold greater than the serum half-life of the anti-PCSK9 Adnectin when not fused to the SABA. In some embodiments, the serum half-life of the SABA fusion is at least 10 hours, 15 hours, 20 hours, 25 hours, 30 hours, 35 hours, 40 hours, 50 hours, 60 hours, 70 hours, 80 hours, 90 hours, 100 hours, 110 hours, 120 hours, 130 hours, 135 hours, 140 hours, 150 hours, 160 hours, or 200 hours.

[00173] In certain embodiments, the serum albumin binding portion of the SABA fusion protein binds to HSA with a K_D of less than 3 uM, 2.5 uM, 2 uM, 1.5 uM, 1 uM, 500 nM, 100 nM, 50 nM, 10 nM, 1 nM, 500 pM, 100 pM. 100 pM, 50 pM or 10 pM. In certain embodiments, the serum albumin binding portion of the SABA fusion proteins bind to HSA with a K_D of less than 3 uM, 2.5 uM, 2 uM, 1.5 uM, 1 uM, 500 nM, 100 nM, 50 nM, 10 nM, 1 nM, 500 pM, 100 pM. 100 pM, 50 pM or 10 pM at a pH range of 5.5 to 7.4 at 25 °C or 37 °C. In some embodiments, the serum albumin binding portion of the SABA fusion proteins bind more tightly to HSA at a pH less than 7.4 as compared to binding at pH 7.4.

[00174] Accordingly, the SABA fusion molecules described herein are useful for increasing the half-life of anti-PCSK9 Adnectin by creating a fusion between anti-PCSK9 Adnectin and the SABA. Such fusion molecules may be used to treat conditions which respond to the biological activity of PCSK9. The present invention contemplates the use of the SABA fusion molecules in diseases caused by the dysregulation of PCSK9.

[00175] The fusion may be formed by attaching anti-PCSK9 Adnectin to either end of the SABA molecule, *i.e.*, SABA-anti-PCSK9 Adnectin or anti-PCSK9 Adnectin-SABA arrangements.

[00176] HSA has a serum concentration of 600 μM and a $t_{1/2}$ of 19 days in humans. The extended $t_{1/2}$ of HSA has been attributed, in part, to its recycling via the neonatal Fc receptor (FcRn). HSA binds FcRn in a pH-dependent manner after endosomal uptake into endothelial cells; this interaction recycles HSA back into the bloodstream, thereby shunting it away from lysosomal degradation. FcRn is widely expressed and the recycling pathway is thought to be constitutive. In the majority of cell types, most FcRn resides in the intracellular sorting endosome. HSA is readily internalized by a nonspecific mechanism of fluid-phase pinocytosis and rescued from degradation in the lysosome by FcRn. At the acidic pH found in the endosome, HSA's affinity for FcRn

increases (5μM at pH 6.0). Once bound to FcRn, HSA is shunted away from the lysosomal degradation pathway, transcytosed to and released at the cell surface.

[00177] In certain embodiments, the serum albumin binding portion of the SABA fusion proteins described herein may also bind serum albumin from one or more of monkey, rat, or mouse. In certain embodiments, the HSA binding portion of the SABA fusion proteins described herein bind to rhesus serum albumin (RhSA) or cynomolgous monkey serum albumin (CySA) with a K_D of less than 3 uM, 2.5 uM, 2 uM, 1.5 uM, 1 uM, 500 nM, 100 nM, 50 nM, 10 nM, 1 nM, 500 pM or 100 pM.

[00178] In certain embodiments, the serum albumin binding portion of the SABA fusion proteins described herein bind to domain I and/or domain II of HSA. In one embodiment, the HSA binding portion of the SABA fusion proteins described herein do not bind to domain III of HSA.

[00179] In certain embodiments, the serum albumin binding portion of the SABA fusion proteins comprises a sequence having at least 40%, 50%, 60%, 70%, 75%, 80% or 85% identity to the wild-type ^{10}Fn3 domain (SEQ ID NO: 1). In one embodiment, at least one of the BC, DE, or FG loops is modified relative to the wild-type ^{10}Fn3 domain. In another embodiment, at least two of the BC, DE, or FG loops are modified relative to the wild-type ^{10}Fn3 domain. In another embodiment, all three of the BC, DE, and FG loops are modified relative to the wild-type ^{10}Fn3 domain. In other embodiments, a SABA comprises a sequence having at least 40%, 50%, 60%, 70%, 75%, 80%, 85%, 90%, or 95% identity to any one of the 26 core SABA sequences shown in Table 6 (*i.e.*, SEQ ID NO: 334, 338, 342, 346, and 348-370) or any one of the extended SABA sequences shown in Table 6 (*i.e.*, SEQ ID NO: 420-447, minus the 6xHIS tag).

[00180] In certain embodiments, the serum binding Adnectins based on the ^{10}Fn3 scaffold can be defined generally by the following sequence:

EVVAAT$(X)_a$SLLI$(X)_x$YYRITYGE$(X)_b$QEFTV$(X)_y$ATI$(X)_c$DYTITVYAV$(X)_z$ISINYRT (SEQ ID NO:328)

[00181] In certain embodiments, the serum binding Adnectins based on the ^{10}Fn3 scaffold can be defined generally by the sequence:

EVVAATPTSLLI$(X)_x$YYRITYGETGGNSPVQEFTV$(X)_y$ATISGLKPGVDYTITVYAV $(X)_z$ISINYRT (SEQ ID NO:329)

[00182] As described herein for anti-PCSK9 Adnectins, SEQ ID NOs: 328 and 329 can be defined and applied to SABA molecules in the same way. In exemplary embodiments, the BC, DE, and FG loops as represented by $(X)_x$, $(X)_y$, and $(X)_z$, respectively, are replaced with polypeptides comprising the BC, DE and FG loop sequences from any of the HSA binders shown in Table 6 below (i.e., SEQ ID NOs: 330, 334, 338, 342, 346, and 348-370 in Table 6). In certain embodiments, the BC, DE, or FG loop sequences shown in Table 6 may contain one or more additional residues flanking the N- and/or C-termini. In particular, the BC loop may contain an SW at the N-terminus of the BC loop sequences shown in Table 6 when replacing $(X)_x$ in SEQ ID NO: 328. Similarly, the DE loop may contain a P preceding loop DE and the residue T following loop DE when replacing $(X)_y$ in SEQ ID NO: 328. The FG loop may contain a P following the FG loop when replacing $(X)_z$ in SEQ ID NO: 328. For example, SEQ ID NO: 330 indicates that the BC, DE, and FG loops comprise HSYYEQNS (SEQ ID NO: 638), YSQT (SEQ ID NO: 639), and YGSKYYY (SEQ ID NO: 640), respectively. However, when replacing $(X)_x$, $(X)_y$, and $(X)_z$ in SEQ ID NO: 328, i.e., the BC, DE and FG loops, the $(X)_x$ sequence may be SWHSYYEQNS (SEQ ID NO: 641), the $(X)_y$ sequence may be PYSQTT (SEQ ID NO: 642), and the $(X)_z$ sequence may be YGSKYYYP (SEQ ID NO: 643).

[00183] In certain embodiments, a SABA for use in a fusion as described herein may comprise the sequence as set forth in SEQ ID NO: 328 or 329, wherein the BC, DE, and FG loops as represented by $(X)_x$, $(X)_y$, and $(X)_z$, respectively, are replaced with a respective set of specified BC, DE, and FG loops from any of the 26 core SABA sequences (i.e., SEQ ID NOs: 330, 334, 338, 342, 346, and 348-370 in Table 6), or sequences at least 75%, 80%, 85%, 90%, 95%, 97%, 98%, or 99% identical to the BC, DE and FG loop sequences of the 26 core SABA sequences. In exemplary embodiments, a SABA as described herein is defined by SEQ ID NO: 329 and has a set of BC, DE and FG loop sequences from any of the 26 core SABA sequences (i.e., SEQ ID NOs: 330, 334, 338, 342, 346, and 348-370 in Table 6), optionally with the N- and/or C-terminal additions to the loop sequences as described above. For example, SABA1 has the core

sequence set forth in SEQ ID NO: 330 and comprises BC, DE, and FG loops as set forth in SEQ ID NO: 331-333, respectively. Therefore, a SABA based on the SABA1 core may comprise SEQ ID NO: 328 or 329, wherein $(X)_x$ comprises SEQ ID NO: 331, $(X)_y$ comprises SEQ ID NO: 332, and $(X)_z$ comprises SEQ ID NO: 333. In some embodiments, the sequences that replace $(X)_x$, $(X)_y$, and $(X)_z$ comprise additional residue(s) on either or both ends of the loops as described above. Similar constructs are contemplated utilizing the set of BC, DE and FG loops from the other SABA core sequences. The scaffold regions of such SABA may comprise anywhere from 0 to 20, from 0 to 15, from 0 to 10, from 0 to 8, from 0 to 6, from 0 to 5, from 0 to 4, from 0 to 3, from 0 to 2, or from 0 to 1 substitutions, conservative substitutions, deletions or additions relative to the scaffold amino acids residues of SEQ ID NO: 1. Such scaffold modifications may be made, so long as the SABA is capable of binding serum albumin, e.g., HSA, with a desired K_D.

[00184] In certain embodiments, a SABA (*e.g.*, a SABA core sequence or a sequence based thereon as described above) may be modified to comprise an N-terminal extension sequence and/or a C-terminal extension sequence. Exemplary extension sequences are shown in Table 6. For example, SEQ ID NO: 420 designated as SABA1.1 comprises the core SABA 1 sequence (SEQ ID NO: 330) with an N-terminal sequence MGVSDVPRDLE (SEQ ID NO: 371, designated as AdNT1), and a C-terminal sequence EIDKPSQ (SEQ ID NO: 380, designated as AdCT1). SABA1.1 further comprises a His6 tag at the C-terminus, however, it should be understood that the His6 tag is completely optional and may be placed anywhere within the N- or C-terminal extension sequences, or may be absent from the sequence all together. Further, any of the exemplary N- or C-terminal extension sequences provided in Table 6 (SEQ ID NO: 371-395), and any variants thereof, can be used to modify any given SABA core sequence provided in Table 6.

[00185] In certain embodiments, the C-terminal extension sequences (also called "tails"), comprise E and D residues, and may be between 8 and 50, 10 and 30, 10 and 20, 5 and 10, and 2 and 4 amino acids in length. In some embodiments, tail sequences include ED-based linkers in which the sequence comprises tandem repeats of ED. In exemplary embodiments, the tail sequence comprises 2-10, 2-7, 2-5, 3-10, 3-7, 3-5, 3, 4 or 5 ED repeats. In certain embodiments, the ED-based tail sequences may also include

additional amino acid residues, such as, for example: EI, EID, ES, EC, EGS, and EGC. Such sequences are based, in part, on known Adnectin tail sequences, such as EIDKPSQ (SEQ ID NO: 380), in which residues D and K have been removed. In exemplary embodiments, the ED-based tail comprises an E, I or EI residues before the ED repeats.

[00186] In other embodiments, the tail sequences may be combined with other known linker sequences (*e.g.*, SEQ ID NO: 396-419 in Table 6) as necessary when designing a SABA fusion molecule.

Conjugation/Linkers

[00187] SABA fusions may be covalently or non-covalently linked. In some embodiments, a serum albumin binding ^{10}Fn3 may be directly or indirectly linked to an anti-PCSK9 Adnectin via a polypeptide linker. Suitable linkers for joining Fn3 domains are those which allow the separate domains to fold independently of each other forming a three dimensional structure that permits high affinity binding to a target molecule.

[00188] The disclosure provides a number of suitable linkers that meet these requirements, including glycine-serine based linkers, glycine-proline based linkers, as well as the linker having the amino acid sequence PSTSTST (SEQ ID NO: 416). The Examples described herein demonstrate that Fn3 domains joined via polypeptide linkers retain their target binding function. In some embodiments, the linker is a glycine-serine based linker. These linkers comprise glycine and serine residues and may be between 8 and 50, 10 and 30, and 10 and 20 amino acids in length. Examples include linkers having an amino acid sequence $(GS)_7$ (SEQ ID NO: 403), $G(GS)_6$ (SEQ ID NO: 398), and $G(GS)_7G$ (SEQ ID NO: 400). Other linkers contain glutamic acid, and include, for example, $(GSE)_5$ (SEQ ID NO: 405) and GGSE GGSE (SEQ ID NO: 409). Other exemplary glycine-serine linkers include $(GS)_4$ (SEQ ID NO: 402), $(GGGGS)_7$ (SEQ ID NO: 411), $(GGGGS)_5$ (SEQ ID NO: 412), and $(GGGGS)_3G$ (SEQ ID NO: 413). In some embodiments, the linker is a glycine-proline based linker. These linkers comprise glycine and proline residues and may be between 3 and 30, 10 and 30, and 3 and 20 amino acids in length. Examples include linkers having an amino acid sequence $(GP)_3G$ (SEQ ID NO: 414), $(GP)_5G$ (SEQ ID NO: 415), and GPG. In other embodiments, the linker may be a proline-alanine based linker having between 3 and 30, 10 and 30, and 3 and 20 amino acids in length. Examples of proline alanine based linkers include, for example,

$(PA)_3$ (SEQ ID NO: 417), $(PA)_6$ (SEQ ID NO: 418) and $(PA)_9$ (SEQ ID NO: 419). It is contemplated, that the optimal linker length and amino acid composition may be determined by routine experimentation in view of the teachings provided herein. In some embodiments, an anti-PCSK9 Adnectin is linked to a SABA via a polypeptide linker having a protease site that is cleavable by a protease in the blood or target tissue. Such embodiments can be used to release an anti-PCSK9 Adnectin for better delivery or therapeutic properties or more efficient production.

[00189] Additional linkers or spacers, may be introduced at the C-terminus of a Fn3 domain between the Fn3 domain and the polypeptide linker. Additional linkers or spacers may be introduced at the N-terminus of a Fn3 domain between the Fn3 domain and the polypeptide linker.

[00190] In some embodiments, an anti-PCSK9 Adnectin may be directly or indirectly linked to a SABA via a polymeric linker. Polymeric linkers can be used to optimally vary the distance between each component of the fusion to create a protein fusion with one or more of the following characteristics: 1) reduced or increased steric hindrance of binding of one or more protein domains when binding to a protein of interest, 2) increased protein stability or solubility, 3) decreased protein aggregation, and 4) increased overall avidity or affinity of the protein.

[00191] In some embodiments, an anti-PCSK9 Adnectin is linked to a SABA via a biocompatible polymer such as a polymeric sugar. The polymeric sugar can include an enzymatic cleavage site that is cleavable by an enzyme in the blood or target tissue. Such embodiments can be used to release an anti-PCSK9 Adnectin for better delivery or therapeutic properties or more efficient production.

Summary of Sequences

[00192] Many of the sequences referenced in "Fusions of Serum Albumin Binding Adnectin (SABA)" and "Conjugation/Linkers" sections above are summarized in Table 6 below. Unless otherwise specified, all N-terminal extensions are indicated with a single underline, all C-terminal tails/extensions are indicated with a double underline, and linker sequences are boxed. Loop regions BC, DE and FG are shaded for each core SABA sequence. As described further above, the modification sequences (*e.g.*, N or C terminal extensions and linkers) can also be used to modify anti-PCSK9 Adnectin molecules.

Table 6

Summary of Exemplary Sequences

SEQ ID	Sequence Name	Description	Sequence
Exemplary Serum Albumin-Binding Adnectins (SABA)			
327	^{10}Fn3WT core	WT core human ^{10}Fn3 domain	EVVAATPTSLLISWDAPAVTVRYYRITYGET GGNSPVQEFTVPGSKSTATISGLKPGVDYTI TVYAVTGRGDSPASSKPISINYRT
328	^{10}Fn3v6	Generic ^{10}Fn3 having 6 variable loops	EVVAAT(X)$_a$SLLI(X)$_x$YYRITYGE(X)$_b$QE FTV(X)$_y$ATI(X)$_c$DYTITVYAV(X)$_z$ISINY RT
329	^{10}Fn3v3	Generic ^{10}Fn3 having 3 variable loops	EVVAATPTSLLI(X)$_x$YYRITYGETGGNSPV QEFTV(X)$_y$ATISGLKPGVDYTITVYAV(X)$_z$ ISINYRT
330	SABA1	Core 1 Adnectin	EVVAATPTSLLISWHSYYEQNSYYRITYGET GGNSPVQEFTVPYSQTTATISGLKPGVDYTI TVYAVYGSKYYYPISINYRT
331	SABA1BC	Core 1 BC Loop	HSYYEQNS
332	SABA1DE	Core 1 DE Loop	YSQT
333	SABA1FG	Core 1 FG Loop	YGSKYYY
334	SABA2	Core 2 Adnectin	EVVAATPTSLLISWPKYDKTGHYYRITYGET GGNSPVQEFTVPTRQTTATISGLKPGVDYTI TVYAVSKDDYYPHEHRPISINYRT
335	SABA2BC	Core 2 BC Loop	PKYDKTGH
336	SABA2DE	Core 2 DE Loop	TRQT
337	SABA2FG	Core 2 FG Loop	SKDDYYPHEHR
338	SABA3	Core 3 Adnectin	EVVAATPTSLLISWSNDGPGLSYYRITYGET GGNSPVQEFTVPSSQTTATISGLKPGVDYTI TVYAVSYYTKKAYSAGPISINYRT
339	SABA3BC	Core 3 BC Loop	SNDGPGLS
340	SABA3DE	Core 3 DE Loop	SSQT
341	SABA3FG	Core 3 FG Loop	SYYTKKAYSAG

SEQ ID	Sequence Name	Description	Sequence
342	SABA4	Core 4 Adnectin; contains a scaffold mutation (bolded); scaffold-perfect version is SABA5	E**M**VAATPTSLLISWEDDSYYSRYYRITYGET GGNSPVQEFTVPSDLYTATISGLKPGVDYTI TVYAVTYDVTDLIMHEPISINYRT
343	SABA4BC	Core 4 BC Loop	EDDSYYSR
344	SABA4DE	Core 4 DE Loop	SDLY
345	SABA4FG	Core 4 FG Loop	YDVTDLIMHE
346	SABA5	Core 5 Adnectin; see description for SABA4; corrected residue is bolded	E**V**VAATPTSLLISWEDDSYYSRYYRITYGET GGNSPVQEFTVPSDLYTATISGLKPGVDYTI TVYAVTYDVTDLIMHEPISINYRT
347	SABA5BC	Core 5 BC Loop	EDDSYYSR
348	SABA5DE	Core 5 DE Loop	SDLY
349	SABA5FG	Core 5 FG Loop	YDVTDLIMHE
350	SABA6	Core 6 Adnectin	EVVAATPTSLLISWYMDEYDVRYYRITYGET GGNSPVQEFTVPNYYNTATISGLKPGVDYTI TVYAVTRIKANNYMYGPISINYRT
351	SABA7	Core 7 Adnectin	EVVAATPTSLLISWNHLEHVARYYRITYGET GGNSPVQEFTVPEYPTTATISGLKPGVDYTI TVYAVTITMLKYPTQSPISINYRT
352	SABA8	Core 8 Adnectin	EVVAATPTSLLISWGHYRRSGHYYRITYGET GGNSPVQEFTVDPSSYTATISGLKPGVDYTI TVYAVSKDDYYPHEHRPISINYRT
353	SABA9	Core 9 Adnectin	EVVAATPTSLLISWDASHYERRYYRITYGET GGNSPVQEFTVPRYHHTATISGLKPGVDYTI TVYAVTQAQEHYQPPISINYRT
354	SABA10	Core 10 Adnectin	EVVAATPTSLLISWNSYYHSADYYRITYGET GGNSPVQEFTVPYPPTTATISGLKPGVDYTI TVYAVYSAKSYYPISINYRT
355	SABA11	Core 11 Adnectin	EVVAATPTSLLISWSKYSKHGHYYRITYGET GGNSPVQEFTVPSGNATATISGLKPGVDYTI TVYAVEDTNDYPHTHRPISINYRT

SEQ ID	Sequence Name	Description	Sequence
356	SABA12	Core 12 Adnectin	EVVAATPTSLLISWHGEPDQTRYYRITYGET GGNSPVQEFTVPPYRRTATISGLKPGVDYTI TVYAVTSGYTGHYQPISINYRT
357	SABA13	Core 13 Adnectin	EVVAATPTSLLISWSKYSKHGHYYRITYGET GGNSPVQEFTVDPSSYTATISGLKPGVDYTI TVYAVSKDDYYPHEHRPISINYRT
358	SABA14	Core 14 Adnectin	EVVAATPTSLLISWYEPYTPIHYYRITYGET GGNSPVQEFTVPGYYGTATISGLKPGVDYTI TVYAVYGYYQYTPISINYRT
359	SABA15	Core 15 Adnectin	EVVAATPTSLLISWSKYSKHGHYYRITYGET GGNSPVQEFTVPSGNATATISGLKPGVDYTI TVYAVSDDNKYYHQHRPISINYRT
360	SABA16	Core 16 Adnectin	EVVAATPTSLLISWGHYRRSGHYYRITYGET GGNSPVQEFTVDPSSYTATISGLKPGVDYTI TVYAVSKDDYYPHEHRPISINYRT
361	SABA17	Core 17 Adnectin	EVVAATPTSLLISWSKYSKHGHYYRITYGET GGNSPVQEFTVPSGNATATISGLKPGVDYTI TVYAVEDTNDYPHTHRPISINYRT
362	SABA18	Core 18 Adnectin	EVVAATPTSLLISWYEPGASVYYYRITYGET GGNSPVQEFTVPSYYHTATISGLKPGVDYTI TVYAVYGYYEYEPISINYRT
363	SABA19	Core 19 Adnectin	EVVAATPTSLLISWQSYYAHSDYYRITYGET GGNSPVQEFTVPYPPQTATISGLKPGVDYTI TVYAVYAGSSYYPISINYRT
364	SABA20	Core 20 Adnectin	EVVAATPTSLLISWGHYRRSGHYYRITYGET GGNSPVQEFTVDPSSYTATISGLKPGVDYTI TVYAVSKDDYYPHEHRPISINYRT
365	SABA21	Core 21 Adnectin	EVVAATPTSLLISWPEPGTPVYYYRITYGET GGNSPVQEFTVPAYYGTATISGLKPGVDYTI TVYAVYGYYDYSPISINYRT
366	SABA22	Core 22 Adnectin	EVVAATPTSLLISWYRYEKTQHYYRITYGET GGNSPVQEFTVPPESGTATISGLKPGVDYTI TVYAVYAGYEYPHTHRPISINYRT

SEQ ID	Sequence Name	Description	Sequence
367	SABA23	Core 23 Adnectin	EVVAATPTSLLISWVKSEEYYRYYRITYGET GGNSPVQEFTVPYYVHTATISGLKPGVDYTI TVYAVTEYYYAGAVVSVPISINYRT
368	SABA24	Core 24 Adnectin	EVVAATPTSLLISWYDPYTYGSYYRITYGET GGNSPVQEFTVGPYTTTATISGLKPGVDYTI TVYAVSYYYSTQPISINYRT
369	SABA25	Core 25 Adnectin	EVVAATPTSLLISWSNDGPGLSYYRITYGET GGNSPVQEFTVPSSQTTATISGLKPGVDYTI TVYAVSYYTKKAYSAGPISINYRT
370	SABA26	Core 26 Adnectin	EVVAATPTSLLISWPDPYYKPDYYRITYGET GGNSPVQEFTVPRDYTTATISGLKPGVDYTI TVYAVYSYYGYYPISINYRT
Exemplary Adnectin N-Terminal Extension Sequences			
371	AdNT1	Exemplary leader	MGVSDVPRDL
372	AdNT2	Exemplary leader	GVSDVPRDL
373	AdNT3	Exemplary leader	VSDVPRDL
374	AdNT4	Exemplary leader	SDVPRDL
375	AdNT5	Exemplary leader	DVPRDL
376	AdNT6	Exemplary leader	VPRDL
377	AdNT7	Exemplary leader	PRDL
378	AdNT8	Exemplary leader	RDL
379	AdNT9	Exemplary leader	DL
Exemplary Adnectin C-Terminal Extension Sequences			
380	AdCT1	Exemplary tail	EIDKPSQ
381	AdCT2	Exemplary tail	EIDKPS
382	AdCT3	Exemplary tail	EIDKPC
383	AdCT4	Exemplary tail	EIDKP
384	AdCT5	Exemplary tail	EIDK
385	AdCT6	Exemplary tail	EI
386	AdCT7	Exemplary tail	EIEKPSQ
387	AdCT8	Exemplary tail	EIDKPSQLE
388	AdCT9	Exemplary tail	EIEDEDEDEDED
389	AdCT10	Exemplary tail	EIEKPSQEDEDEDEDED

SEQ ID	Sequence Name	Description	Sequence
390	AdCT11	Exemplary tail	EGSGS
391	AdCT12	Exemplary tail	EIDKPCQ
392	AdCT13	Exemplary tail	EIEKPCQ
393	AdCT14	Exemplary tail	GSGC
394	AdCT15	Exemplary tail	EGSGC
395	AdCT16	Exemplary tail	EIDKPCQLE
396	L1	$G(GS)_2$	GGSGS
397	L2	$G(GS)_4$	GGSGSGSGS
398	L3	$G(GS)_6$	GGSGSGSGSGSGS
399	L4	$G(GS)_7$	GGSGSGSGSGSGSGS
400	L5	$G(GS)_7G$	GGSGSGSGSGSGSGSG
401	L6	GSGS	GSGS
402	L7	$(GS)_4$	GSGSGSGS
403	L7	$(GS)_7$	GSGSGSGSGSGSGS
404	L9	GS(A)9GS	GSAAAAAAAAAGS
405	L10	$(GSE)_5$	GSEGSEGSEGSEGSE
406	L11	$(PAS)_5$	PASPASPASPASPAS
407	L12	$(GSP)_5$	GSPGSPGSPGSPGSP
408	L13	$GS(TVAAPS)_2$	GSTVAAPSTVAAPS
409	L14	$(GGSE)_2$	GGSEGGSE
410	L15	$(ST)_3G$	STSTSTG
411	L16	$(GGGGS)_7$	GGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGGSGGGS
412	L17	$(GGGGS)_5$	GGGGSGGGGSGGGGSGGGGSGGGGSGGGGS
413	L18	$(GGGGS)_3G$	GGGGSGGGGSGGGGSG
414	L19	$(GP)_3G$	GPGPGPG
415	L20	$(GP)_5G$	GPGPGPGPGPG
416	L21	$P(ST)_3$	PSTSTST
417	L22	$(PA)_3$	PAPAPA
418	L23	$(PA)_6$	PAPAPAPAPAPA
419	L24	$(PA)_9$	PAPAPAPAPAPAPAPAPA
Exemplary Extensions to Adnectin Core Sequences			

SEQ ID	Sequence Name	Description	Sequence
420	SABA1.1	Adnectin core 1 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWHSYYEQN SYYRITYGETGGNSPVQEFTVPYSQTTATIS GLKPGVDYTITVYAVYGSKYYYPISINYRTE IDKPSQHHHHHH
421	SABA1.2	Adnectin core 1 sequence having AdNT1 and AdCT8 terminal sequences	MGVSDVPRDLEVVAATPTSLLISWHSYYEQN SYYRITYGETGGNSPVQEFTVPYSQTTATIS GLKPGVDYTITVYAVYGSKYYYPISINYRTE IEDEDEDEDED
422	SABA1.3	Adnectin core 1 sequence having AdNT1 and AdCT9 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWHSYYEQN SYYRITYGETGGNSPVQEFTVPYSQTTATIS GLKPGVDYTITVYAVYGSKYYYPISINYRTE IEDEDEDEDEDHHHHHH
423	SABA2.1	Adnectin core 2 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWPKYDKTG HYYRITYGETGGNSPVQEFTVPTRQTTATIS GLKPGVDYTITVYAVSKDDYYPHEHRPISIN YRTEIDKPSQHHHHHH
424	SABA3.1	Adnectin core 3 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWSNDGPGL SYYRITYGETGGNSPVQEFTVPSSQTTATIS GLKPGVDYTITVYAVSYYTKKAYSAGPISIN YRTEIDKPSQHHHHHH
425	SABA4.1	Adnectin core 4 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEMVAATPTSLLISWEDDSYYS RYYRITYGETGGNSPVQEFTVPSDLYTATIS GLKPGVDYTITVYAVTYDVTDLIMHEPISIN YRTEIDKPSQHHHHHH
426	SABA5.1	Adnectin core 5 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWEDDSYYS RYYRITYGETGGNSPVQEFTVPSDLYTATIS GLKPGVDYTITVYAVTYDVTDLIMHEPISIN YRTEIDKPSQHHHHHH
427	SABA6.1	Adnectin core 6 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWYMDEYDV RYYRITYGETGGNSPVQEFTVPNYYNTATIS GLKPGVDYTITVYAVTRIKANNYMYGPISIN YRTEIDKPSQHHHHHH

SEQ ID	Sequence Name	Description	Sequence
428	SABA7.1	Adnectin core 7 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWNHLEHVA RYYRITYGETGGNSPVQEFTVPEYPTTATIS GLKPGVDYTITVYAVTITMLKYPTQSPISIN YRTEIDKPSQHHHHHH
429	SABA8.1	Adnectin core 8 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWGHYRRSG HYYRITYGETGGNSPVQEFTVDPSSYTATIS GLKPGVDYTITVYAVSKDDYYPHEHRPISIN YRTEIDKPSQHHHHHH
430	SABA9.1	Adnectin core 9 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWDASHYER RYYRITYGETGGNSPVQEFTVPRYHHTATIS GLKPGVDYTITVYAVTQAQEHYQPPISINYR TEIDKPSQHHHHHH
431	SABA10.1	Adnectin core 10 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWNSYYHSA DYYRITYGETGGNSPVQEFTVPYPPTTATIS GLKPGVDYTITVYAVYSAKSYYPISINYRTE IDKPSQHHHHHH
432	SABA11.1	Adnectin core 11 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWSKYSKHG HYYRITYGETGGNSPVQEFTVPSGNATATIS GLKPGVDYTITVYAVEDTNDYPHTHRPISIN YRTEIDKPSQHHHHHH
433	SABA12.1	Adnectin core 12 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWHGEPDQT RYYRITYGETGGNSPVQEFTVPPYRRTATIS GLKPGVDYTITVYAVTSGYTGHYQPISINYR TEIDKPSQHHHHHH
434	SABA13.1	Adnectin core 13 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWSKYSKHG HYYRITYGETGGNSPVQEFTVDPSSYTATIS GLKPGVDYTITVYAVSKDDYYPHEHRPISIN YRTEIDKPSQHHHHHH
435	SABA14.1	Adnectin core 14 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWYEPYTPI HYYRITYGETGGNSPVQEFTVPGYYGTATIS GLKPGVDYTITVYAVYGYYQYTPISINYRTE IDKPSQHHHHHH

SEQ ID	Sequence Name	Description	Sequence
436	SABA15.1	Adnectin core 15 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWSKYSKHG HYYRITYGETGGNSPVQEFTVPSGNATATIS GLKPGVDYTITVYAVSDDNKYYHQHRPISIN YRTEIDKPSQHHHHHH
437	SABA16.1	Adnectin core 16 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWGHYRRSG HYYRITYGETGGNSPVQEFTVDPSSYTATIS GLKPGVDYTITVYAVSKDDYYPHEHRPISIN YRTEIDKPSQHHHHHH
438	SABA17.1	Adnectin core 17 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWSKYSKHG HYYRITYGETGGNSPVQEFTVPSGNATATIS GLKPGVDYTITVYAVEDTNDYPHTHRPISIN YRTEIDKPSQHHHHHH
439	SABA18.1	Adnectin core 18 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWYEPGASV YYYRITYGETGGNSPVQEFTVPSYYHTATIS GLKPGVDYTITVYAVYGYYEYEPISINYRTE IDKPSQHHHHHH
440	SABA19.1	Adnectin core 19 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWQSYYAHS DYYRITYGETGGNSPVQEFTVPYPPQTATIS GLKPGVDYTITVYAVYAGSSYYPISINYRTE IDKPSQHHHHHH
441	SABA20.1	Adnectin core 20 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWGHYRRSG HYYRITYGETGGNSPVQEFTVDPSSYTATIS GLKPGVDYTITVYAVSKDDYYPHEHRPISIN YRTEIDKPSQHHHHHH
442	SABA21.1	Adnectin core 21 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWPEPGTPV YYYRITYGETGGNSPVQEFTVPAYYGTATIS GLKPGVDYTITVYAVYGYYDYSPISINYRTE IDKPSQHHHHHH
443	SABA22.1	Adnectin core 22 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWYRYEKTQ HYYRITYGETGGNSPVQEFTVPPESGTATIS GLKPGVDYTITVYAVYAGYEYPHTHRPISIN YRTEIDKPSQHHHHHH

SEQ ID	Sequence Name	Description	Sequence
444	SABA23.1	Adnectin core 23 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWVKSEEYY RYYRITYGETGGNSPVQEFTVPYYVHTATIS GLKPGVDYTITVYAVTEYYYAGAVVSVPISI NYRTEIDKPSQHHHHHH
445	SABA24.1	Adnectin core 24 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWYDPYTYG SYYRITYGETGGNSPVQEFTVGPYTTTATIS GLKPGVDYTITVYAVSYYYSTQPISINYRTE IDKPSQHHHHHH
446	SABA25.1	Adnectin core 25 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWSNDGPGL SYYRITYGETGGNSPVQEFTVPSSQTTATIS GLKPGVDYTITVYAVSYYTKKAYSAGPISIN YRTEIDKPSQHHHHHH
447	SABA26.1	Adnectin core 26 sequence having AdNT1 and AdCT1 terminal sequences with His6 tag	MGVSDVPRDLEVVAATPTSLLISWPDPYYKP DYYRITYGETGGNSPVQEFTVPRDYTTATIS GLKPGVDYTITVYAVYSYYGYYPISINYRTE IDKPSQHHHHHH

EXAMPLES

Example 1

Material and Methods Used Herein

High Throughput Protein Production (HTPP)

[00193] Selected binders cloned into pET9d vector and transformed into *E. coli* HMS174 cells were inoculated in 5 ml LB medium containing 50μg/mL kanamycin in a 24-well format and grown at 37 °C overnight. Fresh 5 ml LB medium (50μg/mL kanamycin) cultures were prepared for inducible expression by aspiration 200 μl from the overnight culture and dispensing it into the appropriate well. The cultures were grown at 37 °C until A_{600} 0.6-0.9. After induction with 1mM isopropyl-β-thiogalactoside (IPTG) the culture was expressed for 6 hours at 30 °C and harvested by centrifugation for 10 minutes at 2750 g at 4 °C.

[00194] Cell pellets (in 24-well format) were lysed by resuspension in 450µl of Lysis buffer (50mM NaH_2PO_4, 0.5 M NaCl, 1x Complete Protease Inhibitor Cocktail-EDTA free (Roche), 1mM PMSF, 10mM CHAPS, 40mM Imidazole, 1 mg/ml lysozyme, 30µg/ml DNAse, 2µg/ml aprotonin, pH 8.0) and shaken at room temperature for 1-3 hours. Lysates were clarified and re-racked into a 96-well format by transfer into a 96-well Whatman GF/D UNIFILTER® fitted with a 96-well, 1.2 ml catch plate and filtered by positive pressure. The clarified lysates were transferred to a 96-well Ni-Chelating Plate that had been equilibrated with equilibration buffer (50mM NaH_2PO_4, 0.5 M NaCl, 40mM Imidazole, pH 8.0) and was incubated for 5 min. Unbound material was removed by vacuum. The resin was washed 2 x 0.3 ml/well with Wash buffer #1 (50mM NaH_2PO_4, 0.5 M NaCl, 5 mM CHAPS, 40mM Imidazole, pH 8.0) with each wash removed by vacuum. Prior to elution each well was washed with 50µl Elution buffer (PBS + 20mM EDTA), incubated for 5 min and this wash was discarded by vacuum. Protein was eluted by applying an additional 100µl of Elution buffer to each well. After a 30 minute incubation at room temperature the plate(s) were centrifuged for 5 minutes at 200 g and eluted protein is collected in 96-well catch plates containing 5µl of 0.5M $MgCl_2$ added to the bottom of elution catch plate prior to elution. Eluted protein was quantified using a BCA assay with SGE as the protein standard.

Midscale Expression and Purification of Insoluble Fibronectin-Based Scaffold Protein Binders

[00195] For expression of insoluble clones, the clone(s), followed by the HIS_6tag, are cloned into a pET9d (EMD Bioscience, San Diego, CA) vector and are expressed in *E. coli* HMS174 cells. Twenty ml of an inoculum culture (generated from a single plated colony) is used to inoculate 1 liter of LB medium containing 50µg/ml carbenicillin and 34 µg/ml chloromphenicol. The culture is grown at 37 °C until A_{600} 0.6-1.0. After induction with 1mM isopropyl-β-thiogalactoside (IPTG) the culture is grown for 4 hours at 30 °C and is harvested by centrifugation for 30 minutes at ≥10,000 g at 4 °C. Cell pellets are frozen at -80 °C. The cell pellet is resuspended in 25 ml of lysis buffer (20mM NaH_2PO_4, 0.5 M NaCl, 1x Complete Protease Inhibitor Cocktail-EDTA free (Roche), 1mM PMSF, pH 7.4) using an ULTRA-TURRAX® homogenizer (IKA works) on ice. Cell lysis is achieved by high pressure homongenization (≥18,000 psi) using a Model M-110S

MICROFLUIDIZER® (Microfluidics). The insoluble fraction is separated by centrifugation for 30 minutes at 23,300 g at 4 °C. The insoluble pellet recovered from centrifugation of the lysate is washed with 20mM sodiumphosphate/500mM NaCl, pH7.4. The pellet is resolubilized in 6.0M guanidine hydrochloride in 20mM sodium phosphate/500M NaCl pH 7.4 with sonication followed by incubation at 37 degrees for 1-2 hours. The resolubilized pellet is filtered to 0.45 μm and loaded onto a Histrap column equilibrated with the 20mM sodium phosphate/500M NaCl/6.0M guanidine pH 7.4 buffer. After loading, the column is washed for an additional 25 CV with the same buffer. Bound protein is eluted with 50mM Imidazole in 20mM sodium phosphate/500mM NaCl/6.0M guan-HCl pH7.4. The purified protein is refolded by dialysis against 50mM sodium acetate/150mM NaCl pH 4.5.

Midscale Expression and Purification of Soluble Fibronectin-Base Scaffold Protein Binders

[00196] For expression of soluble clones, the clone(s), followed by the HIS_6tag, were cloned into a pET9d (EMD Bioscience, San Diego, CA) vector and were expressed in *E. coli* HMS174 cells. Twenty ml of an inoculum culture (generated from a single plated colony) was used to inoculate 1 liter of LB medium containing 50μg/ml carbenicillin and 34 μg/ml chloromphenicol. The culture was grown at 37 °C until A_{600} 0.6-1.0. After induction with 1mM isopropyl-β-thiogalactoside (IPTG), the culture was grown for 4 hours at 30 °C and was harvested by centrifugation for 30 minutes at ≥10,000 g at 4 °C. Cell pellets were frozen at -80 °C. The cell pellet was resuspended in 25 ml of lysis buffer (20mM NaH_2PO_4, 0.5 M NaCl, 1x Complete Protease Inhibitor Cocktail-EDTA free (Roche), 1mM PMSF, pH 7.4) using an ULTRA-TURRAX® homogenizer (IKA works) on ice. Cell lysis was achieved by high pressure homongenization (≥18,000 psi) using a Model M-110S MICROFLUIDIZER® (Microfluidics). The soluble fraction was separated by centrifugation for 30 minutes at 23,300 g at 4 °C. The supernatant was clarified via 0.45 μm filter. The clarified lysate was loaded onto a Histrap column (GE) pre-equilibrated with the 20mM sodium phosphate/500M NaCl pH 7.4. The column was then washed with 25 column volumes of the same buffer, followed by 20 column volumes of 20mM sodium phosphate/500M NaCl/ 25mM Imidazole, pH 7.4 and then 35 column volumes of 20mM sodium phosphate/500M NaCl/40mM Imidazole, pH 7.4.

Protein was eluted with 15 column volumes of 20mM sodium phosphate/500M NaCl/500mM Imidazole, pH 7.4, fractions were pooled based on absorbance at A_{280} and were dialyzed against 1x PBS, 50mM Tris, 150mM NaCl. pH 8.5 or 50mM NaOAc; 150mM NaCl; pH4.5. Any precipitate was removed by filtering at 0.22μm.

Example 2

In Vitro Nonclinical Pharmacology

K_D by SPR

[00197] The binding characteristics were characterized by Surface Plasmon Resonance (SPR). Human PCSK9 and Cynomolgus PCSK9 were immobilized on separate channels on one dimension of a ProteOn XPR (Bio-Rad) chip surfaces and exposed to 6 different concentrations of 2013E01 in the other dimension of the same SPR chip surface. This allowed kinetic determination in the absence of regeneration. Duplicate chips were used for kinetic determinations of the Human and Cynomolgus PCSK9 at 25 °C. Evaluation of the kinetic parameters was performed using the Langmuir interaction model and constant parameter fitting with the ProteOn Manager software.

[00198] Under these conditions, anti-PCSK9 Adnectins bound to human PCSK9 with dissociation constants (K_D) ranging from 80 pM to 1.6 nM and to the cyno PCSK9 with dissociation constants (K_D) ranging from 8 nM to 24 nM (Table 7). Association rates were approximately 10^5 $M^{-1}s^{-1}$, coupled with dissociations that were typically 10^{-3}- 10^{-5} s^{-1}. For some Adnectins, the off-rates from human PCSK9 were slow (on the order of 10^{-5} s^{1}), which is close to the limit of detection for SPR technologies so it is possible that these dissociation constant measurements from human PCSK9 are under-estimates.

Table 7

SPR-Determined Kinetic Parameters for Anti-PCSK9 Adnectins Against Directly Immobilized Human and Cyno PCSK9

Clone ID	PCSK9 Species	k_{on} (M^{-1} s^{-1})	k_{off} (s^{-1})	K_D (nM)
1459D05	human	1.13E+05	1.80E-04	1.58 ± 0.176
2013E01	human	7.03 ± 0.1 E+05	2.42 ± 0.3 E-05	0.292 ± 0.008
2013E01	cyno	2.19 E+05	1.77 E-03	8.1

Clone ID	PCSK9 Species	k_{on} (M^{-1} s^{-1})	k_{off} (s^{-1})	K_D (nM)
1922G04	human	5.41E+05	5.08E-05	0.094 ± 0.009
1922G04	cyno	4.65E+05	7.00E-03	15.03
2011H05	human	1.18E+05	9.76E-06	0.079 ± 0.038
2011H05	cyno	1.90E+05	4.40E-03	23.1
2012A04	human	2.59E+05	6.47E-05	0.251 ± 0.011
2012A04	cyno	1.95E+05	4.75E-03	24.32

K_D by BLI

[00199] The binding characteristics of Adnectins and human PCSK9 were also determined by Bio-Layer Interferometry (BLI). Biotinylated human PCSK9 was immobilized onto superstreptavidin sensor tips which were subsequently immersed into wells containing diluted Adnectin for the duration of the association phase. Tips were then immersed into a buffer-only well for observation of Adnectin dissociation. Experiments were performed in a temperature controlled environment at either 25 or 37 °C, and the oscillation speed was set at 1500 rpm.

[00200] Binding interaction analysis was performed using proprietary software from Fortebio (Fortebio Data Analysis Software version 6.3.0.36). Global fits were performed for all samples, using a 1:1 binding model. The nature of these global fits constrained all values of concentration to a single pair of association and dissociation rates that were themselves constrained to each other. Affinities (K_D), association and dissociation rates were averaged over the various loading levels used in the analysis. Under these conditions, Adnectins bound human PCSK9 with affinities ranging from 200pM to 7.5nM, as shown in Table 8 below. Association rates ranged from 10^4 - 10^5 $M^{-1}s^{-1}$, and coupled with dissociations that were typically 10^{-3}- 10^{-5} s^{-1}.

Table 8

BLI-Determined Kinetic Parameters for PCSK9 Adnectins Against Human PCSK9

Clone ID or ATI#	k_{on} (M^{-1} s^{-1})	k_{off} (s^{-1})	K_D (nM)
2381D04	2.66E+05 ± 6.4 E+04	6.90E-05 ± 6.9 E-05	0.237 ± 0.08

Clone ID or ATI#	k_{on} (M^{-1} s^{-1})	k_{off} (s^{-1})	K_D (nM)
2382D09	5.33E+05	1.64E-04	0.304
2382D05	5.05E+05 ± 2.0E+05	1.57E-04 ± 4.2E-05	0.314 ± 0.06
2381B04	3.09E+05 ± 2.1E+04	1.60E-04 ± 1.6E-04	0.527 ± 0.11
2382E05	4.36E+05 ± 1.6E+05	2.50E-04 ± 1.1E-05	0.604 ± 0.21
2382B09	4.51E+05 ± 4.7E+04	2.91E-04 ± 4.0E-05	0.656 ± 0.02
2382H03	4.71E+05 ± 1.4E+05	5.57E-04 ± 2.3E-04	0.677 ± 0.02
2382C09	3.49E+05	2.33E-04	0.757
2971A03	5.74E+05	4.20E-04	0.806
2382G04	4.19E+05	4.64E-04	1.11
2381G09	2.71E+05	2.91E-04	1.12
2451C06	3.47E+05 ± 5.4E+04	4.35E-04 ± 5.4E+04	1.27 ± 0.14
2382H10	2.88E+05	3.82E-04	1.40
2013E01	5.46E+05	8.37E-04	1.51
2382D03	3.54E+05	6.63E-04	1.53
2381F11	3.23E+05	5.22E-04	1.59
2971E02	3.55E+05	5.55E-04	1.78
2382H09	2.51E+05	4.83E-04	1.86
2451H07	4.48E+05	9.40E-04	2.08
2382B10	3.94E+05	9.77E-04	2.35
2382C05	3.68E+05	8.79E-04	2.49
2971A09	3.99E+05	1.05E-03	2.79
2382E03	2.20E+05	5.96E-04	2.94
2381H09	1.36E+05	4.60E-04	3.23
2381B02	2.65E+05	8.31E-04	3.29
2381B08	2.13E+05	9.40E-04	4.11
2382F05	2.44E+05	1.09E-03	4.54
1459D05	1.49E+05 ± 2.5E+04	2.02E-03 ± 2.0E-03	14.4 ± 0.2
ATI 1091	2.863E+05	8.201E-05	0.293
ATI001117	1.451E+05	5.074E-05	0.554
ATI001057	5.325E+05	1.403E-04	0.255

Clone ID or ATI#	k_{on} (M^{-1} s^{-1})	k_{off} (s^{-1})	K_D (nM)
ATI001119	8.190E+04	4.450E-04	5.296
ATI001168[1]	5.829E+05	3.335E-04	0.586
ATI001175[2]	6.558E+05	3.522E-04	0.543
ATI 1081	8.29E+05 ± 8.1E+05	3.49E-04 ± 3E-04	0.479 ± 0.11
ATI891	1.08E+05	4.03E-04	3.56
ATI1114	8.072E+04	3.952E-04	4.876
ATI1174	1.265E+05	9.012E-04	7.397

[1] ATI001168 is a deimmunized version of 1922G04 having an R23E substitution.

[2] ATI001175 is a deimmunized version of 1922G04 having an R23D substitution.

Solution Phase Affinity

KinExA

[00201] The solution affinities of ATI001081 and ATI001174 for human PCSK9 were measured using a Kinetic Exclusion Assay (KinExA). The relative unbound Adnectin concentrations were measured by capture on a hPCSK9 solid matrix followed by detection with a fluorescently labeled antibody that recognizes the Adnectin scaffold. Due to technical limitations, the lowest concentration of Adnectins that could be tested was 1 nM. The global K_D analyses estimate a K_D = 70 pM (28-127pM within a 95% confidence interval) for ATI001081 and a K_D = 223 pM for ATI001174 (range of 54-585pM within 95% confidence interval).

Table 9

Solution Phase Affinity Measurements for PCSK9 Adnectins

	ATI001081	ATI001174
K_D	69.5 pM	223 pM
95% confidence interval:		
Kd high	127 pM	585 pM
Kd low	28 pM	54 pM

ITC

[00202] The thermodynamics and stoichiometry of binding of Adnectins ATI001174 and ATI001081 to human PCSK9 were characterized by isothermal titration calorimetry (ITC). Solution phase binding was measured in 25 mM HEPES, pH 7.41, 150 mM NaCl at 37 °C. An average unimolecular binding constant of 1.3 ± 0.2 nM was observed for ATI001174 and 1.4 ± 0.4 nM for ATI001081. Detailed thermodynamic analyses are shown in Table 10 and Figure 13. The difference in observed enthalpies (-3.3 kcal/mol) for the two Adnectins suggests that ATI001174 incurs an order of magnitude reduction in its affinity for PCSK9 due to PEGylation that is at least partially offset by the corresponding difference in entropy (-10.4 cal/mol·K).

Table 10

Adnectin	Stoichiometry (N)	K_A (M^{-1})	K_D (nM)	ΔH (kcal/mol)	ΔS (cal/mol °C)
ATI001081	0.926	7.1E8 ± 2.1E8	1.4 ± 0.4 (±30%)	-26.6 ± 0.2	-45.4
ATI001174*	0.857	7.5E8 ± 1.5E8	1.3 ± 0.2	-29.9 ± 0.1	-55.8

* Average of 3 experiments

Fluorescence Resonance Energy Transfer (FRET) Assay

[00203] Three FRET based assays were developed to determine the binding affinity and potency of PCSK9-binding Adnectins, adapted from the general method described previously by Maio et al. (See, Miao, B. et al., *Meth. Enzymol.*, 357:180-188 (2002)). The PCSK9:EGFA FRET assay (Figures 2 and 3) measured the inhibition of PCSK9 binding to the low density lipoprotein receptor (LDLR) epidermal growth factor precursor homology domain (EGFA domain), using recombinant human PCSK9 expressed in baculovirus and a synthetic 40-mer EGFA peptide (biotinylated). EGFA has been shown to represent the key interacting domain of LDLR with PCSK9 (Kwon, H.J. et al., *Proc. Natl. Acad. Sci. USA*, 105(6):1820-1825 (2008)). This assay used a PCSK9 C-terminal domain binding mAb (mAb 4H5) labeled with Eu-chelate to provide FRET

interaction with biotinylated EGFA through the streptavidin/ allophycocyanin fluorophore complex.

[00204] Two other related, PCSK9-dependent FRET assays were also constructed. In one of these assays, competitive displacement by Adnectins of biotinylated Adnectins - ATI000972 or ATI001125 is quantified (ATI000972 results shown in Figure 4). ATI000972 is a biotinylated version of 1459D05 and ATI001125 is a biotinylated version of ATI001081. In another assay, direct binding of an Adnectin (his-tagged) to PCSK9 is assayed using anti-his6 antibody (Figure 5). In each of the FRET assays, human PCSK9 concentration was either 1 or 5 nM. In some cases cynomolgus monkey PCSK9 replaced hPCSK9. Table 11 summarizes the overall data from these three FRET assays.

Table 11

Summary of Adnectin Testing Data for 3 FRET Assays Using Human PCSK9 and 1 Assay for Cyno PCSK9

Clone ID	hPCSK9: EGFA IC50 (nM)	hPCSK9: ATI000972 IC50 (nM)	hPCSK9: ATI001125 IC50 (nM)	Direct binding hPCSK9 EC50 (nM)	cPCSK9:EGFA IC50 (nM)
1459D05	4.0	14	nd	3.9	2300
1784F03	2	1.9	nd	1.6	106
1813E02	1.3	2.4	nd	2.3	118
1923B02	2.3	3.2	nd	3.2	53.5
1922G04	1.2	2.0	nd	2.5	26.6
2012A04	2.1	1.2	nd	1.4	70.3
2011H05	2.7	1.4	nd	2.0	17.2
2013E01	1.6	1.8	nd	0.90	12.5
1922G04 (R25D)	2.5	nd	nd	nd	48.1
1922G04 (R25E)	3.5	nd	nd	nd	58.5
2382E03	2.4	nd	0.5	3.7	10.8
2382E05	2.8	nd	0.4	3.8	12.6
2381B08	2.6	nd	1	4.1	27.1
2381B02	2.5	nd	0.5	8.4	9.8

Clone ID	hPCSK9: EGFA IC50 (nM)	hPCSK9: ATI00097 2 IC50 (nM)	hPCSK9: ATI00112 5 IC50 (nM)	Direct binding hPCSK9 EC50 (nM)	cPCSK9:EGFA IC50 (nM)
2381B04	2.4	nd	0.5	4.2	17.3
2451H07	0.2	nd	0.2	13.2	27.1
2381D04	2.9	nd	0.5	3.7	12
2381F11	4	nd	0.8	< 1	26.5
2381G09	3.1	nd	1.1	4.5	25.2
2381H09	3.4	nd	0.5	4.1	20.2
2382B09	3.8	nd	0.6	4.0	37.2
2382B10	3	nd	0.5	3.1	18.1
2382C05	4	nd	0.9	3.4	27.2
2382C09	3.5	nd	0.6	2.9	23.9
2382D03	3.3	nd	0.6	3.3	11.8
2382D09	2.6	nd	0.4	3.7	13.9
2382F05	2.4	nd	0.9	3.8	14.6
2382G04	2.9	nd	0.5	3.6	20.1
2382H03	3.4	nd	0.3	3.8	19.8
2382H09	0.9	nd	0.3	3.6	17.9
2382H10	2.6	nd	0.4	4.6	18.2
2382D02	4.5	nd	0.5	5.3	57.8
2451C06	1.2	nd	0.4	5.5	24.7

Cell-Based Inhibition of PCSK9 Activity by PCSK9 Adnectins

DiI-LDL Uptake Assay

[00205] Cell culture methods were developed to assay the ability of Adnectins to inhibit PCSK9 activity on the LDLR. An effective means of measuring cellular LDLR activity is through an assay for uptake of labeled LDL, as shown by Lagace, T.A. et al. (*J. Clin. Invest.*, 116(11):2995-3005 (2006)). The work further adapted a method for LDLR functional activity using fluorescent-labeled LDL (DiI-LDL) uptake adapted from a method originally shown by Teupser et al. (*Biochim. Biophys. Acta*, 1303(3):193-198

(1996)). Cells were first preincubated with recombinant human PCSK9 protein (10 ug/mL, 135 nM) in the presence and absence of Adnectins as shown. After 2 hours, the remaining LDLR activity was assayed by incubation with DiI-LDL (5 ug) for 2 hours followed by an assessment of accumulated DiI-LDL inside the cells using high content fluorescent micrscopy and image analysis (Cellomics). Figure 6 shows the effect of several Adnectins to inhibit PCSK9 activity and restore LDLR functional activity in HepG2 cells. In this assay, the Adnectins inhibited PCSK9 and restored DiI-LDL uptake with the following EC_{50} values: 1459D05, EC_{50} = 190 nM; 1784F03, 210 nM; 2012A04, 130 nM; 2013E01, 160 nM.

LDLR Depletion Assay

[00206] HepG2 cells were grown in complete media, Eagle's Minimum Essential Medium (EMEM, ATCC®) with 10% FBS (Hyclone), and split twice a week with Trypsin 0.25% (Invitrogen). To induce upregulation of the LDL receptor, cells were incubated overnight in LPDS media [RPMI (ATCC) with 5% lipoprotein deficient serum (Intracel), 100nM superstatin (BMS) and 50uM Sodium Mevalonate (Sigma)]. The following day, cells were trypsinized briefly with Trypsin 0.05% (Invitrogen) and resuspended at 2 X10^6 cells per ml then aliquoted at 100ul per well in a V-bottom 96 well plate. In the meantime, Adnectins were pre-incubated with PCSK9 in LPDS media for an hour at 37°C. After an hour, cells were centrifuged and resuspended in 100ul of Adnectin/PCSK9 mix and incubated overnight at 37°C. The following day cells were labeled with an antibody for LDL receptor (BAF 2148 from R&D), followed by a phycoerythrin (PE)-streptavidin conjugated secondary antibody (BD554061from BD Pharmingen) and analyzed by FACS on the FACS CantoII (BD).

[00207] 10nM of PCSK9 was pre-incubated for an hour with increasing concentration of Adnectin candidates before being added to HepG2 cells. After overnight incubation LDLR level were measured by FACS and the percentage of inhibition of PCSK9-induced LDLR depletion was graphed and EC50 determined using PRISM. 1459D05 appears to be the least potent candidate among those tested and did not reach the maximum inhibition whereas the other clones reach 150-200% maximum inhibition of PCSK9 (Figure 7). A summary of the PCSK9 Adnectin *in vitro* pharmacology data is shown below in Table 12.

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Table 12

Clone ID	% monomer (SEC-HPLC)	Tm (°C, DSC)	KD hPCSK9 (37°C, Octet Red) (nM)	K_D hPCSK9 (25 °C, ProteOn) (nM)	Cyno cross-reactivity		PCSK9: GFA FRET (EC_{50}, nM)	LDLR Depletion	
					K_D cPCSK9 (25 °C, ProteOn) (nM)	Cyno PCSK9: EGFA FRET (EC_{50}, nM)		% inhibition at 75nM	EC_{50} (nM)
1459D05	≥95	63	14.4	1.58	>1000	>1000	5.8	66.8	>200
1813E02	≥95	70	nd	nd	nd	118.5	2.7	nd	16
1784F03	≥95	65	nd	nd	nd	106.5	2.01	150.2	26±13
1923B02	≥95	73	nd	0.17	nd	53.5	2.3	178	23±7
1922G04	100	83	nd	0.09	15.0	26.6	1.2	105.1	10±2
2013E01	100	81	nd	0.29	8.1	12.5	1.6	165.5	10±4
2012A04	100	84	nd	0.25	24.3	70.3	2.1	144.5	12±6
2011H05	100	76	nd	0.08	23.1	17.2	2.7	197.6	12±5
2382D05	97	86	0.314	nd	nd	57.8	2.6	140.5	nd
2382E03	96	83	2.94	nd	nd	10.8	2.4	89.5	nd
2382E05	95	84	0.604	nd	nd	12.6	2.8	103.5	nd
2381B02	96	68	3.29	nd	nd	9.8	2.5	125.4	nd
2381B04	98	77	0.527	nd	nd	17.3	2.4	121.6	nd
2381B08	97	78	4.11	nd	nd	27.1	2.6	124.8	nd

Clone ID	% monomer (SEC-HPLC)	Tm (°C, DSC)	KD hPCSK9 (37°C, Octet Red) (nM)	K_D hPCSK9 (25 °C, ProteOn) (nM)	Cyno cross-reactivity		PCSK9: GFA FRET (EC_{50}, nM)	LDLR Depletion	
					K_D cPCSK9 (25 °C, ProteOn) (nM)	Cyno PCSK9: EGFA FRET (EC_{50}, nM)		% inhibition at 75nM	EC_{50} (nM)
2381D04	98	70	0.237	nd	nd	12	2.9	119.2	nd
2381F11	95	79	1.59	nd	nd	26.5	4	110.2	nd
2381G09	96	78	1.12	nd	nd	25.2	3.1	133.0	nd
2381H09	77	63	3.23	nd	nd	20.2	3.4	94.4	nd
2382B09	99	88	0.656	nd	nd	37.2	3.8	105.0	nd
2382B10	99	82	2.35	nd	nd	18.1	3	100.2	nd
2382C05	97	85	2.49	nd	nd	27.2	4	105.3	nd
2382C09	96	85	0.757	nd	nd	23.9	3.5	121.7	nd
2382D03	97	84	1.53	nd	nd	11.8	3.3	80.4	nd
2382D09	93	84	0.304	nd	nd	13.9	2.6	109.1	nd
2382F05	99	83	4.54	nd	nd	14.6	2.4	72.2	nd
2382G04	95	81	1.11	nd	nd	20.1	2.9	146.1	nd
2382H03	96	85	0.677	nd	nd	19.8	3.4	102.1	nd
2382H09	95	81	1.86	nd	nd	17.9	0.9	101.2	nd
2382H10	97	87	1.40	nd	nd	18.2	2.6	118.6	nd

Clone ID	% monomer (SEC-HPLC)	Tm (°C, DSC)	KD hPCSK9 (37°C, Octet Red) (nM)	K_D hPCSK9 (25 °C, ProteOn) (nM)	Cyno cross-reactivity		PCSK9: GFA FRET (EC_{50}, nM)	LDLR Depletion	
					K_D cPCSK9 (25 °C, ProteOn) (nM)	Cyno PCSK9: EGFA FRET (EC_{50}, nM)		% inhibition at 75nM	EC_{50} (nM)
2451B06	nd	nd	nd	nd	nd	57.8	4.5	92.2	nd
2451C06	96	87	1.27	nd	nd	24.7	1.2	89.4	nd
2451H07	97	87	2.08	nd	nd	27.1	0.2	88.8	nd

Example 3

In Vivo Pharmacodynamic Effects of PCSK9 Adnectins

Human PCSK9 Transgenic Mouse Models

[00208] PCSK9 Adnectins exhibited pharmacodynamic effects *in vivo* in two different human transgenic mouse models. One mouse model overexpresses human PCSK9 levels markedly and exhibits hypercholesterolemia as a result (Lagace, T.A. et al., J. Clin. Invest., 116(11):2995-3005 (2006)). The other mouse model is a genomic hPCSK9 transgenic (BAC-transgenic) which is regulated in liver similarly to mouse PCSK9 and which expresses near human-normal levels of hPCSK9 in plasma. For these studies, ELISA assays using species-specific, site-specific labeled antibodies and Adnectins were developed to measure plasma unbound human PCSK9 levels (*i.e.*, hPCSK9 not complexed with the administered Adnectin) as an index of target engagement.

[00209] Single doses of PCSK9 Adnectins in PEGylated form were injected intraperitoneally into the overexpresser hPCSK9 transgenic mouse model at the doses shown in Figures 8-9. PBS or dialysate samples were also injected as controls. Adnectin 1459D05-PEG (100 mg/kg intraperitoneal) treatment rapidly decreased plasma total cholesterol (Figure 8A) and LDL-C (not shown) to >35% below baseline in 4 hr. Cholesterol levels in Adnectin treated mice remained below control levels throughout the 48 hr test period. This was accompanied by a sharp decrease in circulating levels of unbound hPCSK9 in the Adnectin treated transgenic mice (Figure 8B). Western blots of liver taken at 6 hours in parallel studies showed that LDLR protein levels were increased ~2-fold in Adnectin-treated mice (not shown). In further studies in this transgenic mouse model, ATI001114 was administered at 10 or 60 mg/kg. A marked, dose-dependent, rapid lowering of plasma cholesterol was seen, concomitant with a dose-related reduction in unbound hPCSK9 levels (Figure 9). These studies represent *in vivo* proof-of-concept for PCSK9 Adnectins as effective cholesterol lowering agents in a hypercholesterolemic human transgenic PCSK9 mouse model.

[00210] *In vivo* studies were conducted in the normal expresser hPCSK9 transgenic mouse model. Injection of single doses of 1459D05-PEG or ATI001114 (5 mg/kg) resulted in rapid and strong decreases in unbound hPCSK9 levels in plasma (Figure 10). This pharmacodynamic effect on unbound hPCSK9 was more pronounced following ATI001114 compared to1459D05-PEG, with greater magnitude and duration of effect

observed for the higher affinity/potency Adnectin. A further study of dose dependency revealed that that the 50% inhibitory dose (ED50) was less than 0.1 mg/kg for ATI001114 at time points from 3 to 48 hours post-dose, as seen in Figure 11. These findings in a normal expresser transgenic mouse model show that PCSK9 inhibitory Adnectins exhibit marked, affinity-dependent and dose-dependent effects on pharmacodynamic endpoints which are correlated with LDLR regulation and LDL cholesterol lowering.

Cynomolgus Monkeys

[00211] A pharmacodynamic study was conducted in normal lean cynomolgus monkeys. Adnectin ATI001114 was administered to cynos intravenously at 5 mg/kg, and plasma samples were collected at time intervals for LDL-C assay and pharmacokinetic assessment. A single dose of ATI001114 rapidly lowered plasma LDL-C levels to >50% vs. baseline (or vs. PBS control group) within 48 hours (Figure 12). The duration of effect on LDL-C continued for more than a week with eventual return to baseline by 3 wk. This effect was observed with both two-branched and four-branched 40kDa PEGylated forms of the anti-PCSK9 Adnectin (ATI001114 and ATI001211, respectively). ATI001211 is ATI001081 with a 40 kDa 4-branched NOF PEG moiety. Total cholesterol showed a similar pattern but no effect on HDL or other metabolic parameter was observed (not shown). Pharmacokinetic analysis revealed that the plasma half-life was approximately 80-120 hrs, consistent with the pharmacodynamics of LDL lowering in the cynos. These findings indicate that a PCSK9 Adnectin is efficacious and fast-acting with rapid, robust, specific effects on LDL-C lowering in cynomolgus monkey model.

Example 4

In Vitro and *In Vivo* Pharmacological Evaluation of the PCSK9 Adnectin-Fc Fusion Protein, PRD460

Production of PRD460

[00212] A vector encoding PRD460 was transfected into HEK-293 6E cells using polyethylenimine (PEI). The cells were grown at 37 °C for 5 days with 80% humidification and 5% CO_2. The cells were then pelleted, the supernatant was passed

through a 0.22 um filter and then loaded onto to a ProteinA column. The column was washed with PBS and the protein was eluted with 20mM Gylcine, 150 mM NaCl pH 2.8. The eluted protein was concentrated and passed over a superdex200 column in 50mM MES, 100 mM NaCl pH 5.8.

[00213]

PRD460 K_D by SPR

[00214] The binding characteristics were characterized by Surface Plasmon Resonance (SPR). Anti-human antibody was immobilized on a BIACORE® chip, and PRD460 (sequence as set forth in SEQ ID NO: 322) was captured on the chip surface. Varying concentrations of hPCSK9 were placed into the flow solution using $MgCl_2$ (3 M) for chip regeneration between cycles. For comparison, ATI-1081 was captured on an anti-His antibody immobilized on a BIACORE® chip. Duplicate experiments for PRD460 were performed on different days. Kinetic determinations were performed at 25 °C. Evaluation of the kinetic parameters was performed using the 1:1 Binding algorithm on the BIACORE® Evaluation software.

[00215] Under these conditions, ATI-1081 bound to human PCSK9 with a dissociation constant (K_D) of 6.7 nM at 25 °C and PRD460 bound to human PCSK9 with a dissociation constant (K_D) of 3.29 +/- 0.55 nM at 25 °C (Table 13). The off-rate determinations using this assay format may be artificially limited by the off-rate of the captured ligand from the immobilized capture antibody, thus the assay format using direct immobilization of PCSK9 is a more accurate reflection of dissociation constant (K_D) for ATI-1081.

Table 13

Kinetic Parameters for PRD460 and ATI-1081

Against Captured Human PCSK9

	ka (1/Ms)	kd (1/s)	KD (nM)
PRD460	3.75 +/- 0.7 E+04	1.21 +/- 0.05 E-04	3.29 +/- 0.55
ATI-1081	3.65E+04	2.45E-04	6.7

PCSK9 Binding FRET Assays

[00216] Two fluorescence resonance energy transfer (FRET) based assays were used to determine the competitive binding potency of PRD460 and other Adnectins to hPCSK9. The PCSK9:EGFA FRET assay measures the binding of PCSK9 to the LDLR, using a soluble epidermal growth factor precursor homology domain-A (EGFA) peptide and recombinant human PCSK9. The PCSK9:ATI972 FRET assay measures competitive displacement by Adnectins of the biotinylated Adnectin, ATI-972, from PCSK9.

[00217] In the PCSK9:EGFA FRET assay (at 5 nM PCSK9), PRD460 completely and potently displaced EGFA from the PCSK9 binding site with EC50 = 0.7 nM (Fig. 1, left panel). PRD460 was more potent in this assay than either ATI-1174 (EC50 = 1.9 nM) or ATI-1081 (EC50 = 3.7 nM) (Fig. 14). The greater apparent potency of PRD460 in this assay may be explained by bivalent (2:1) binding of Adnectin PRD460 to PCSK9 (theoretically) compared to monovalent (1:1) binding by ATI-1081 and ATI-1174.

[00218] Using the PCSK9:ATI-972 FRET assay (at 5 nM human PCSK9), PRD460 inhibited with EC50 = 0.3 nM, compared to 0.8 nM for ATI-1114 and 2.8 nm for ATI-1081 (Fig. 15). These findings indicate that PRD460 potently displaced the biotinylated Adnectin ATI-972 from its binding site on PCSK9. The higher potency of PRD460 relative to ATI-1081 and ATI-1174 is consistent with bivalent binding by PRD460.

Inhibition of PCSK9-induced LDLR Depletion in HepG2 Cells

[00219] Human PCSK9 promotes the depletion of LDLR from the surface of HepG2 cells. Pre-incubation of PCSK9 with PCSK9 Adnectins inhibits PCSK9 binding to LDLR and prevents the depletion of LDLR from the cell surface. This assay was used to measure the potency of ATI-1081, ATI-1174 and PRD460 to inhibit PCSK9 induced depletion of LDLR from the cell surface.

[00220] A dilution series of PCSK9 Adnectins were pre-incubated with 10 nM human PCSK9 for 1 hr at 37 degrees, the pre-incubated mixture was added to HepG2 cells, and the cells were incubated for 24 hours. Following this incubation, the level of LDLR on HepG2 cells was measured using FACS analysis. The percentage of inhibition of PCSK9-induced LDLR depletion was calculated and graphed (Fig. 15). In this assay ATI-1081, ATI-1174, and PRD460 inhibited PCSK9 with comparable EC50's (9nM, 8nM and 6nM respectively) although a leftward-shift of the response curve was consistently observed for PRD460. These EC50's represent the limit of the assay.

PCSK9 Cell Entry Assay in HepG2 Cells

[00221] PCSK9 binding to the LDLR on the surface of hepatocytes results in co-internalization of the LDLR-PCSK9 complex during LDLR endocytosis, leading to enhanced degradation of the LDLR. A cell-based assay was developed to measure LDLR-dependent cellular entry of fluorescent PCSK9. Human PCSK9 was covalently labeled using the fluorophore ALEXA FLUOR®-647(AF647). PCSK9-AF647 was incubated with HepG2 cells with or without PCSK9-Adnectins and the intracellular fluorescence was quantified by high content fluorescent microscopy and image analysis (Cellomics). Dependence of PCSK9-AF647 cell entry on LDLR endocytosis was established in preliminary experiments. HepG2 cells were incubated with 10 nM PCSK9-AF647 and varying levels of Adnectins for 4 hrs at 37 degrees. In this assay, potent inhibition of PCSK9-AF647 intracellular fluorescence was observed for PRD460 (EC50 = 6 nM) as well as for ATI-1174 (EC50 = 10 nM) (Fig. 16). These findings indicate that Adnectin PRD460 and ATI-1174 effectively blocked the binding of PCSK9 to cell surface LDLR in a human hepatic-derived cell line in culture, thereby reducing the internalization of PCSK9-AF647 during LDLR endocytosis.

In Vivo Transgenic Mouse Study

[00222] *In vivo* studies were conducted in the normal expresser hPCSK9 transgenic mouse model. Binding of Adnectins to PCSK9 in the plasma is predicted to result in a decrease in the measured amount of unbound (free) circulating PCSK9. The decrease in unbound PCSK9 is the initial pharmacodynamic event which results in inhibition of the PCSK9-LDLR interaction and in LDL cholesterol lowering. Administration of single doses of PRD460 (i.p. doses from 0.6 to 18 mg/kg) to the transgenic mice resulted in rapid, strong decreases in plasma unbound hPCSK9 levels (Fig. 17). Dose-dependent decreases in unbound PCSK9 were observed with ED50 <0.6 mg/kg at the 3 hr time point. These findings in the normal expresser human PCSK9 transgenic mouse model show that PRD460 binds strongly and potently to circulating hPCSK9 *in vivo*.

In Vivo Pharmacodynamics in Cynomolgus Monkeys

[00223] The pharmacodynamic effects of PCSK9 Adnectin PRD460 were evaluated in normal lean cynomolgus monkeys. PRD460 was administered to monkeys by i.v. dosing at 15 mg/kg, and plasma samples were collected at time intervals over 4 wks for the assay of LDL-C and free PCSK9 levels. A single dose of PRD460 rapidly lowered plasma LDL-C levels in the monkeys, reaching an average maximum effect of 42% of baseline LDL-C (58% reduction; n = 3 monkeys) by day 3 after dosing (Fig. 18). LDL-C levels were reduced by 50% or more for a week at this dose, remaining significantly below baseline for 3 wks and returning to baseline by 4 wks. Total cholesterol showed a similar pattern but no effect on HDL was observed (not shown). Treatment with PRD460 caused an immediate drop to near zero (below the lower limit of quantitation) in the unbound, free form of plasma PCSK9 (Fig. 18). The free PCSK9 levels remained near the lower limits of detection for several days then gradually returned to baseline levels by the end of 4 wks, consistent with a cause/effect relationship with plasma LDL-C. The data indicate that plasma LDL lowering mirrored the drop in free PCSK9 levels, consistent with PCSK9 inhibition regulating LDLR function following treatment with PRD460 *in vivo*. Pharmacokinetic analysis revealed that the plasma half-life of Adnectin PRD460 was approximately 70 hrs in this cynomolgus monkey study. These findings indicate that a PCSK9 Adnectin-Fc fusion protein is highly efficacious and fast-acting with robust, specific, and long-lasting effects on LDL-C lowering in the cynomolgus monkey model.

In Vivo Pharmacological Evaluation of the Unmodified PCSK9 Adnectin, ATI-1081

[00224] In addition to modified Adnectins containing a PK moiety (*e.g.*, PEGylated and Fc-fusion Adnectins), an unmodified ("naked") PCSK9 Adnectin can also be administered. Strategies for unmodified PCSK9 Adnectin treatment include more frequent dosing to accommodate the shorter PK half-life, or using an extended release subcutaneous formulation to increase the length of the absorption phase and extend the pharmacodynamic effect. Many such formulations can be envisioned including, as a simple example, propylene glycol/PBS solutions to delay the rate of absorption and increase the time of exposure to the Adnectin in the circulation.

[00225] The unmodified Adnectin ATI-1081 was administered to cynomolgus monkeys i.v. at 10 mg/kg in PBS vehicle. ATI-1114 (PEGylated version of the same Adnectin) was also administered at 1 mg/kg in PBS as a comparator. ATI-1081 elicited a

rapid, transient inhibition of unbound circulating PCSK9 levels. Within 30 minutes the extent of initial inhibition approached 100% (below the limits of quantitation) before returning to baseline several hours later (Figure 19). Concurrently, a trend to lower LDL-C levels was observed over the first 24 hrs in the ATI-1081 treated monkeys (Fig. 20).

[00226] The unmodified Adnectin ATI-1081 was also administered to the normal expresser hPCSK9 transgenic mice in a simple extended release subcutaneous formulation using 50:50 propylene glycol:PBS vehicle (PG vehicle) compared to PBS vehicle. This formulation is expected to modestly delay the rate of Adnectin absorption and increase the exposure time to ATI-1081 in the circulation, thus improving the pharmacodynamic response. Administration (intraperitoneal) of ATI-1081 at 1 mg/kg in PBS vehicle resulted in ~50% lowering of unbound plasma PCSK9 at 3 hr, compared to >85% lowering for ATI-1114 at 0.3 mg/kg (Fig. 21). In a second experiment in the transgenic mice, ATI-1081 administered by subcutaneous injection in PG vehicle resulted in nearly equivalent decreases in unbound LDL compared to ATI-1174, with an improved duration of effect over the first 6 hrs of the study (Fig. 22). These findings indicate that the unmodified PCSK9 Adnectin ATI-1081 when administered subcutaneously in a simple extended release vehicle bound to the target human PCSK9 *in vivo* and elicited the initial pharmacodynamic response. The time dependency of the response was consistent with extended release prolonging the duration of effect for the unmodified PCSK9 Adnectin.

Example 5
Serum Albumin-Binding Adnectins (SABA)

Example 5A. Screening and Selection of Candidate Serum Albumin-Binding Adnectin Overview

[00227] A selection technique known as PROfusion (see *e.g.*, Roberts et al., *Proc. Natl. Acad. Sci. USA*, 94(23):12297-12302 (1997) and WO 2008/066752) was applied to a DNA library with variable regions designed into the BC, DE and FG loops of ^{10}Fn3. A random library of greater than 10^{13} molecules was created from this design, and selection pressure was applied against a biotinylated form of HSA to isolate candidate serum albumin-binding Adnectin (SABA) with desirable binding properties.

High Throughput Protein Production (HTTP) Process

[00228] The various HSA binding Adnectins were purified using a high throughput protein production process (HTPP). Selected binders were cloned into pET9d vector containing a HIS6 tag and transformed into *E. coli* BL21(DE3)pLysS cells. Transformed cells were inoculated in 5 ml LB medium containing 50 µg/mL Kanamycin in a 24-well format and grown at 37 °C overnight. Fresh 5 ml LB medium (50 µg/mL Kanamycin) cultures were prepared for inducible expression by aspirating 200 µl from the overnight culture and dispensing it into the appropriate well. The cultures were grown at 37 °C until A_{600} 0.6-0.9. After induction with 1 mM isopropyl-β-thiogalactoside (IPTG), the culture was grown for another 4 hours at 30 °C and harvested by centrifugation for 10 minutes at 3220 x g at 4 °C. Cell Pellets were frozen at -80 °C.

[00229] Cell pellets (in 24-well format) were lysed by resuspension in 450 µl of Lysis buffer (50 mM NaH_2PO_4, 0.5 M NaCl, 1x Complete Protease Inhibitor Cocktail-EDTA free (Roche), 1 mM PMSF, 10 mM CHAPS, 40 mM Imidazole, 1 mg/ml lysozyme, 30 ug/ml DNAse, 2 ug/ml aprotonin, pH 8.0) and shaken at room temperature for 1 hour. Lysates were clarified and re-racked into a 96-well format by transfer into a 96-well Whatman GF/D UNIFILTER® fitted with a 96-well, 650 µl catch plate and centrifuged for 5 minutes at 200 x g. The clarified lysates were transferred to a 96-well Ni-Chelating Plate that had been equilibrated with equilibration buffer (50 mM NaH_2PO_4, 0.5 M NaCl,10 mM CHAPS, 40 mM Imidazole, pH 8.0) and incubated for 5 min. Unbound material was removed. The resin was washed 2 x 0.3 ml/well with Wash buffer #1 (50 mM NaH_2PO_4, 0.5 M NaCl, 5 mM CHAPS, 40 mM Imidazole, pH 8.0). Next the resin was washed with 3 x 0.3 ml/well with PBS. Prior to elution each well was washed with 50 µl Elution buffer (PBS + 20 mM EDTA), incubated for 5 min and this wash discarded by vacuum. Protein was eluted by applying an additional 100 ul of Elution buffer to each well. After 30 minute incubation at room temperature the plate(s) were centrifuged for 5 minutes at 200 x g and eluted protein collected in 96-well catch plates containing 5 µl of 0.5M $MgCl_2$ affixed to the bottom of the Ni-plates. Eluted protein was quantified using a BCA Protein assay with SGE (control Adnectin) as the protein standard. The SGE Adnectin is a wild-type ^{10}Fn3 domain (SEQ ID NO: 1) in which integrin binding domain (amino acids RGD at positions 78-80) have been replaced with SGE.

HSA, RhSA and MuSA Direct Binding ELISA

[00230] For assaying direct binders to HSA, MaxiSorp plates (Nunc International, Rochester, NY) were coated with 10 ug/mL HSA (Sigma, St. Louis, MO) in PBS at 4 °C overnight followed by blocking in casein block buffer (Thermo Scientific, Rockford, IL) for 1-3 hours at room temperature. For single-point screening assays, purified HTPP Adnectin were diluted 1:20 in casein block buffer and allowed to bind to HSA in each well for 1 hour at room temperature. For dose response assays, concentrations ranging from 0.1 nM up to 1 μM were used. After washing in PBST to remove unbound Adnectins, anti-His mAb-HRP conjugate (R&D Systems, MN) diluted 1:2500 in casein block buffer was added to the bound His-tagged Adnectin for 1 hour at room temperature. Excess conjugate was removed by washing with PBST and bound Adnectins detected using TMB detection reagents (BD Biosciences) according to the manufacturer's instructions.

Aggregation Measurement by Analytical Size Exclusion Chromatography

[00231] Size exclusion chromatography (SEC) was performed on the SABAs resulting from the HTPP. SEC of HTPP derived material was performed using a SUPERDEX® 200 5/150 or SUPERDEX® 75 5/150 column (GE Healthcare) on an Agilent 1100 or 1200 HPLC system with UV detection at A_{214} nm and A_{280} nm and with fluorescence detection (excitation = 280 nm, emission = 350 nm). A buffer of 100 mM sodium sulfate, 100 mM sodium phosphate, 150 mM sodium chloride, pH 6.8 at appropriate flow rate of the SEC column employed. Gel filtration standards (Bio-Rad Laboratories, Hercules, CA) were used for molecular weight calibration.

[00232] The results of the SEC on the HTPP purified SABAs were shown to be predominantly monomeric and eluted in the approximate range of 10 kDa vs. globular Gel Filtration standards (BioRad).

Identification of Candidate Serum Albumin-Binding Adnectin (SABA)

[00233] As a result of the screening for HSA/RhSA/MuSA binding and biophysical criteria, four unique serum albumin-binding Adnectins (SABA) were identified and chosen to have their half-lives evaluated in mice. In order to carry out *in vitro* and *in vivo*

characterization, midscales were undertaken for the four SABAs. Table 6 provides the sequences of twenty-six unique SABA core sequences identified from PROfusion, designated as SABA 1-26. SABA4 had a scaffold mutation that was fixed prior to midscaling. The scaffold-perfect version of SABA4 is SABA5. SABA4 and SABA5 have identical sequences in the BC, DE, and FG loops.

Example 5B. Production and Formulation of Candidate SABAs

Midscale Protein Production of SABAs

[00234] The selected SABAs described in Example 5A, followed by the His_6 tag, were cloned into a pET 9d vector and expressed in *E. coli* BL21(DE3)pLysS cells (see Table 6 for each His-tagged SABA sequence designated SABA1.1, SABA2.1, SABA3.1, and SABA5.1). 20 ml of an inoculum culture (generated from a single plated colony) was used to inoculate 1 liter of LB medium containing 50 µg/mL Kanamycin. The culture was grown at 37 °C until A_{600} 0.6-1.0. After induction with 1 mM isopropyl-β-thiogalactoside (IPTG) the culture was grown for another 4 hours at 30 °C and harvested by centrifugation for 30 minutes at ≥10,000 x g at 4 °C. Cell Pellets were frozen at -80 °C. The cell pellet was resuspended in 25 mL of lysis buffer (20 mM NaH_2PO_4, 0.5 M NaCl, 1x Complete Protease Inhibitor Cocktail-EDTA free (Roche), pH 7.4) using an ULTRA-TURRAX® homogenizer (IKA works) on ice. Cell lysis was achieved by high pressure homogenization (≥18,000 psi) using a Model M-110S MICROFLUIDIZER® (Microfluidics). The soluble fraction was separated by centrifugation for 30 minutes at 23,300 x g at 4 °C. The supernatant was clarified via 0.45 µm filter. The clarified lysate was loaded onto a HISTRAP® column (GE) pre-equilibrated with 20 mM NaH_2PO_4, 0.5 M NaCl, pH 7.4. The column was then washed with 25 column volumes of 20 mM NaH_2PO_4, 0.5 M NaCl, pH 7.4, followed by 20 column volumes of 20 mM NaH_2PO_4, 0.5 M NaCl, 25mM imidazole pH 7.4, and then 35 column volumes of 20 mM NaH_2PO_4, 0.5 M NaCl, 40 mM imidazole pH 7.4. Protein was eluted with 15 column volumes of 20 mM NaH_2PO_4, 0.5 M NaCl, 500 mM imidazole pH 7.4, fractions pooled based on absorbance at A_{280} and dialyzed against 1x PBS, 50 mM Tris, 150 mM NaCl pH 8.5 or 50 mM NaOAc; 150 mM NaCl; pH 4.5. Any precipitate was removed by filtering at 0.22 µm .

[00235] Midscale expression and purification yielded highly pure and active Adnectins that were expressed in a soluble form and purified from the soluble fraction of the bacterial cytosol. SEC analysis on a SUPERDEX® 200 or SUPERDEX® 75 10/30GL in a mobile phase of 100 mM $NaPO_4$, 100 mM $NaSO_4$, 150 mM NaCl, pH 6.8 (GE Healthcare) demonstrated predominantly monomeric Adnectins.

Formulation of SABA1.2

[00236] One specific SABA, SABA1.2 (SEQ ID NO: 411), was chosen for a preliminary formulation screen. SABA1.2 comprises an $(ED)_5$ extension on the "core 1" sequence of ^{10}Fn3 (see SEQ ID NO: 421 in Table 6). For SABA1.2, a stable formulation of 10 mM succinic acid, 8% sorbitol, 5% glycine at pH 6.0 and at a product concentration of 5 mg/mL was identified. In this formulation the protein melting temperature was 75 °C as determined by Differential Scanning Calorimetry (DSC) using a protein concentration of 1.25 mg/mL. The formulation provided satisfactory physical and chemical stability at 4 °C and 25 °C, with an initial aggregate level at 1.2%. After one month of stability, the level of aggregation was very low (1.6% at 4 °C and 3.8% at 25 °C). The protein was also stable in this formulation after five cycles of freeze-thaw as transitioned from -80 °C and -20 °C to ambient temperature. In addition, in this formulation SABA1.2 was soluble to at least 20 mg/mL protein concentration at 4 °C and ambient temperature with no precipitation or increase in aggregation.

Example 5C. Biophysical Characterization of Candidate SABAs

Size Exclusion Chromatography

[00237] Standard size exclusion chromatography (SEC) was performed on the candidate SABAs resulting from the midscale process. SEC of midscaled material was performed using a SUPERDEX® 200 10/30 or on a SUPERDEX® 75 10/30 column (GE Healthcare) on an Agilent 1100 or 1200 HPLC system with UV detection at A_{214} nm and A_{280} nm and with fluorescence detection (excitation = 280 nm, emission = 350 nm). A buffer of 100 mM sodium sulfate, 100 mM sodium phosphate, 150 mM sodium chloride, pH 6.8 at appropriate flow rate of the SEC column employed. Gel filtration standards (Bio-Rad Laboratories, Hercules, CA) were used for molecular weight calibration.

[00238] The results of the SEC on the midscaled purified SABAs showed predominantly monomeric Adnectin and elution in the approximate range of 10 kDa vs. globular Gel Filtration standards (BioRad) as showed.

Thermostability

[00239] Differential Scanning Calorimetry (DSC) analyses of the midscaled SABAs were performed to determine their respective T_m's. A 1 mg/ml solution was scanned in a N-DSC II calorimeter (Calorimetry Sciences Corp) by ramping the temperature from 5 °C to 95 °C at a rate of 1 degree per minute under 3 atm pressure. The data was analyzed vs. a control run of the appropriate buffer using a best fit using Orgin Software (OrginLab Corp). The results of the SEC and DSC analyses are summarized in Table 14.

Table 14

Summary of SEC and DSC Analyses on Candidate SABAs

Clone	SEC		DSC (Tm)
	Monomer (%)	Dimer (%)	
SABA1.1	92.3	7.7	63.9 °C
SABA5.1	88	12	70.1 °C
SABA2.1	91	9	58.5 °C/78.2 °C
SABA3.1	99	BLD	65.2 °C

Example 5D. Characterization of Candidate SABA1 Binding to Serum Albumin

[00240] The kinetics of selected SABA clones purified from HTPP and/or midscaled material described in Examples 5A and 5B were determined by capturing the respective serum albumin (HSA/RhSA/MuSA) on the surface of a Biasensor CM5 chip and flowing a concentration series of SABAs over both the reference flow cell and the captured albumins. In addition, binding to albumin was carried out under various pH conditions ranging from pH 5.5 to pH 7.4. HSA-binding Adnectins SABA2.1, SABA3.1, SABA4.1, and SABA1.1 cross reacted with RhSA but did not cross react with MuSA. SABA2 and SABA4 binding is pH sensitive whereas clone SABA3 demonstrated pH resistance

binding to HSA down to pH 6.0. SABA1.1 fits biochemical criteria for pH resistance and affinity/kinetics down to pH 5.5.

[00241] Domain mapping was determined by BIACORE®. Selected SABA clones purified from HTPP and/or midscaled material were determined by capturing HSA or a construct consisting of just HSA-domain I & II or HSA-domain III on the surface of a Biasensor CM5 chip and flowing a concentration series of the SABAs over both the reference flow cell and the captured albumins. Clones SABA2 & SABA1 bound to HSA and the HSA-domain I-II construct but not the HSA-domain III construct. Clones SABA3 & SABA4 bound to HSA but not to either the HSA-domain I-II or HSA-domain III constructs. The results are summarized in Table 15.

Table 15

Binding Affinity and Kinetics of Candidate SABAs (SABA1.1, 2.1, 3.1 and 4.1)

Adnectin	Target	K_D (nM)	K_{off} (s^{-1})	Resistant to pH 7.4→5.5?	Epitope on HSA
SABA2	HSA	33.8 +/- 20.5 (n=6)	1.71E-04	---	Domain I-II
	RhSA	63.6	4.42E-04		
SABA3	HSA	863	6.82E-02	+++ (down to pH 6.0)	Neither domain I-II nor III (interfacial?)
	RhSA	431	3.37E-02		
SABA4	HSA	412 +/- 8 (n=4)	7.82E-04	--	Neither domain I-II nor III (interfacial?)
	RhSA	>1000	3.83E-03		
SABA1	HSA	47.2 +/- 18.2 (n=9)	4.57E-04	+++	Domain I-II
	RhSA	778 +/- 313 (n=4)	5.45E-03		

Example 5E. Examination of the *in vivo* $t_{1/2}$ of candidate SABAs

[00242] The half-life of HSA in mice was determined to allow for evaluation of HSA-binding Adnectins in mice as the HSA-binding Adnectins do not cross react with MuSA. HSA was injected into the tail vein of approximately 6 week old Ncr nude female mice at a 20 mg/kg (Figure 23A) and 50 mg/kg dose (Figure 23B), and the concentration of HSA

in blood samples taken at intervals post-injection was determined by ELISA. The $t_{1/2}$ of HSA injected into mice at 20 mg/kg and 50 mg/kg were determined to be ~24 hrs and ~20 hrs, respectively.

Half-Life Determination of SABA1-4 in Mice

[00243] One liter *E. coli* growth of HSA binding clones SABA1.1, SABA2.1, SABA3.1, and SABA4.1 were prepared, purified and endotoxin removed. Each SABA variant was injected into the tail vein of mice, and the concentration in blood samples taken at intervals post-injection was determined by ELISA.

[00244] The pharmacokinetic profiles of each SABA were compared in the presence or absence of HSA in approximately 6 week old Ncr nude female mice. The mice that were co-injected with HSA had the HSA premixed with each SABA (HSA in a 3-4 molar excess) because the binding clone was selective for HSA and RhSA and did not bind the mouse serum albumin. The half-life of SABA1.1 (clone 1318H04) in mice plasma was 0.56 hours whereas the half-life of SABA1.1 co-injected with HSA was 5.6 hours, a ~10-fold increase in half life (Figure 24A). The half-life of SABA2.1 in mice plasma was 0.24 hours whereas the half-life of SABA2.1 co-injected with HSA was 2.8 hours, a ~12-fold increase in half life (Figure 24B). The half-life of SABA3.1 (clone 1245H07) in mice plasma was 0.28 hours whereas the half-life of SABA3.1 co-injected with HSA was 0.53 hours, a ~2-fold increase in half life (Figure 24C). The half-life of SABA4.1 in mice plasma was 0.66 hours whereas the half-life of SABA4 co-injected with HSA was 4.6 hours, a ~7-fold increase in half life (Figure 24D). A summary of the present example is shown in Figure 25. Table 16 summarizes similar data for SABA1.1, SABA2.1, SABA3.1, and SABA5.1; comparison is made to half life in cyno, where available.

Table 16

CLONE	PK (T1/2)		Comments
	Mice	Cyno	
SABA1.1	5.6 hrs	96-137 hrs	T1/2 = 96-137 hrs
SABA5.1	4.6 hrs	12 hrs	Poor binding affinity for RhSA. 2-fold decrease in KD observed at pH<6.0

SABA2.1	2.8 hrs	NA	Loss of binding at pH <6.5
SABA3.1	32 min	NA	Poor T1/2 observed in mice

Half-Life Determination of SABA1.1 and SABA5.1 in Cynomolgous Monkeys

[00245] A three week single dose proof of concept study of SABA1.1 (Figure 26A) and SABA5.1 (Figure 26B) was conducted in cynomolgus monkeys to assess pharmacokinetics at a 1 mg per kg (mpk) dose IV in 2 cynomolgus monkeys. The pharmacokinetics were evaluated using a quantitative ELISA-based assay that was developed to detect the Adnectin in plasma samples. SABA1.1 has a half-life in the range of 96-137 hours (Figure 26A and Table 17A). SABA5.1 has a half-life of approximately 12 hours and was only measureable in the ELISA up to 120 hours (Figure 26B). Table 17A summarizes data for SABA1.1; Table 17B summarizes data for SABA5.1.

Table 17A

SABA1.1

Monkey	t1/2 (hrs)	Cmax (µg/mL)	AUCall (hr*µg/mL)	Cl_obs (mL/hr/kg)	Vz_obs (mL/kg)
#1	95.8	9.03	673.7	1.45	200.8
#2	136.6	7.24	625.1	1.60	315.2

Table 17B

SABA5.1

	HL_Lambda_z (hr)	Cmax (µg/mL)	AUCall (hr*µg/mL)	Cl_obs (mL/hr/kg)	Vz_obs (mL/kg)
N	2	2	2	2	2
Mean	12.186	17.358	246.882	4.089	72.507
SD	1.451	3.08	36.245	0.596	19.045
Min	11.16	15.18	221.25	3.67	59.04
Max	13.21	19.54	272.51	4.51	85.97
CV%	11.9	17.7	14.7	14.6	26.3

Example 5F. Characterization of SABA1 Binding to Serum Albumin

SABA1.1 and 1.2 Binds to HSA and RhSA

[00246] SABA1.2, a "core 1" ^{10}Fn3 comprising an $(ED)_5$ extension (SEQ ID NO: 421 in Table 6) bound to human serum albumin (HSA) at neutral pH and 25 °C with an average association rate constant (ka) of 8.21E+03 $M^{-1}s^{-1}$, and an average dissociation rate constant (kd) of 4.43E-04 s^{-1}, for a calculated average K_d of 55.3 nM (Table 18). For rhesus serum albumin (RhSA), the measured average association rate constant was 6.6E+03 $M^{-1}s^{-1}$, and the dissociation rate constant was 3.78E-03 s^{-1}, giving a calculated average K_d of 580 nM. No measurable interaction between SABA1.2 and mouse or rat serum albumin could be observed up to 1 μM (Table 18 and Figure 27). At 37 °C, the ka and kd increased between 2 to 5-fold, leading to a ~2-fold increase in affinity for HSA and 1/2 the affinity for RhSA (Table 18).

Table 18

Kinetic parameters for SABA1.2 binding to albumins, in HBS-P buffer.

Albumin	Temp (°C)	ka (1/Ms)	kd (1/s)	KD (nM)
Human	25	8.21 ± 1.19 E+03	4.43 ± 0.65 E-04	55.3 ± 13.7
Rhesus		6.60 ± 1.18 E+03	3.78 ± 0.45 E-03	580 ± 62.6
Mouse		no observable binding		
Human	37	3.38E+04	8.15E-04	24.1
Rhesus		1.89E+04	1.85E-02	977.4
Mouse		no observable binding		

[00247] Additionally, a calorimetric titration was performed to determine the stoichiometry between SABA1 and HSA. For this study, SABA1.1, a "core 1" ^{10}Fn3 comprising a His6 extension (SEQ ID NO: 420 in Table 6), was used. HSA (10 μl per injection of 115 μM protein solution) was injected into the calorimetric cell containing SABA1.1 at a concentration of 8.1 μM. The experiment was performed at 37 °C in PBS buffer pH 7.4. Figure 28 shows that SABA1.1 binds to HSA with 1:1 stoichiometry.

SABA1.2 Binds Potently to HSA at Low pH

[00248] The long half-life of albumins (e.g., $t_{1/2}$ of HSA is 19 days) is due in large part to the fact that they are recycled from an endocytic pathway by binding to the neonatal Fc receptor, FcRn, under the low pH conditions that exist inside the endosome. As shown in Table 19 SABA1.2 potently bound HSA at the endosomal pH of 5.5, suggesting that the $t_{1/2}$ of SABA1, once bound to HSA, would also benefit from the FcRn recycling mechanism.

Table 19

Comparison of Albumin Binding Kinetics at pH 7.4 and 5.5, in MES Buffer

albumin	pH	ka (1/Ms)	kd (1/s)	KD (nM)
Human	7.4	9.26E+03	3.88E-04	41.9
	5.5	9.44E+03	2.70E-04	28.6
Rhesus	7.4	6.16E+03	2.95E-03	479
	5.5	7.57E+03	2.72E-03	359

SABA1.2 Binds to Domains I and II of HSA, but not Domain III

[00249] The binding site SABA1.2 on albumin was mapped to the N-terminal domains I or II using recombinant HSA fragments and has no detectable binding to domain III (Figure 29). Because domain III is the domain of HSA that primarily interacts with FcRn, it is less likely that SABA1.2 would compete for HSA binding to FcRn, again increasing the possibility of fully leveraging the recycling mechanism for enhanced half-life.

Example 5G. *In Vivo* Pharmacology of SABA1.2

[00250] A four week single dose pre-toxicology study of SABA1.2 was conducted in cynomolgus monkeys to assess pharmacokinetics and immunogenicity at two different dose levels. The pharmacokinetics and immunogenicity were also evaluated in a three-week, single-dose pre-toxicology study that included both intravenous and subcutaneous administration arms. Additionally, the pharmacokinetics of SABA1.2 was evaluated in two separate, single dose pre-toxicology studies in cynomolgus monkeys using a

quantitative ELISA-based assay that was developed to detect SABA1.2 in plasma samples.

[00251] SABA1.2 was administered to monkeys at 1 mpk and 10 mpk IV. Non-compartmental analyses using WINNONLIN® software were performed to evaluate pharmacokinetic parameters. As shown in Figure 30 and the parameters described below, SABA1.2 exhibited dose-dependent pharmacokinetics in this study as determined by area under the concentration-time curve (AUC) evaluation. The clearance (CL) for SABA1.2 at 10 mpk was 0.15 ml/hr/kg, the beta phase half-life ($t_{1/2}$) was 143 hours, the volume of distribution (Vz) was 30 mL/kg, and total drug exposure (AUCall) was 5,609,457 hr*nmol/L (Table 20). The clearance (CL) for SABA1.2 at 1 mpk was 0.4 ml/hr/kg, the half-life ($t_{1/2}$) was 124 hours, the volume of distribution (Vz) was 72 mL/kg, and total drug exposure (AUCall) was 214,636 hr*nmol/L (Table 20).

[00252] After SC or IV administration of SABA1.2, the beta-phase pharmacokinetic profiles were similar (Figure 31). The clearance (CL) for SABA1.2 at 1 mpk IV was 0.22 ml/hr/kg, the beta phase half-life ($t_{1/2}$) was 125 hours, the volume of distribution (Vz) was 40 mL/kg, and total drug exposure (AUCall) was 357,993 hr*nmol/L (Table 20). The clearance (CL) for SABA1.2 at 1 mpk SC was 0.32 ml/hr/kg, the beta phase half-life ($t_{1/2}$) was 134 hours, the volume of distribution (Vz) was 62 mL/kg, and total drug exposure (AUCall) was 251,339 hr*nmol/L (Table 20). The SC relative bioavailability (F) compared to IV was 0.7.

Table 20

Pharmacokinetic Parameters for SABA1.2 in Monkeys

Study #	1		2	
Dose (mg/kg)	1	10	1	1
Route of administration	i.v.	i.v.	i.v.	s.c.
N	3	3	1	2
CL (mL/hr/kg)	0.4	0.15	0.22	0.32
Vz (mL/kg)	72	30	40	62
AUCall (hr*nmol/L)	214,636	5,609,457	357,993	251,339

Study #	1		2	
beta $T_{1/2}$ (h)	124	143	125	134
Bioavailability (F)	n/a	n/a	n/a	0.7

Claims:

1. An isolated polypeptide comprising a fibronectin type III tenth (^{10}Fn3) domain wherein the ^{10}Fn3 has a BC, DE and FG loop, and wherein the BC loop comprises SEQ ID NO:14, the DE comprises SEQ ID NO:25 and the FG loop comprises SEQ ID NO:37, and wherein the polypeptide binds proprotein convertase subtilisin kexin type (PCSK9).

2. The isolated polypeptide of claim 1, wherein the polypeptide binds PCSK9 with a K_D of less than 500 nM.

3. The isolated polypeptide of claim 1, further comprising one or more pharmacokinetic (PK) moieties selected from the group consisting of polyethylene glycol, sialic acid, Fc, Fc fragment, transferring, serum albumin, a serum albumin binding protein, and a serum immunoglobulin binding protein.

4. A pharmaceutically acceptable composition comprising the polypeptide of claim 1.

5. An isolated polypeptide comprising a ^{10}Fn3 domain wherein the isolated polypeptide comprises SEQ ID NO:82, and wherein the isolated polypeptide binds PCSK9.

6. The isolated polypeptide of claim 5, wherein the polypeptide binds PCSK9 with a K_D of less than 500 nM.

7. The isolated polypeptide of claim 5, further comprising one or more pharmacokinetic (PK) moieties selected from the group consisting of polyethylene glycol, sialic acid, Fc, Fc fragment, transferring, serum albumin, a serum albumin binding protein, and a serum immunoglobulin binding protein.

8. A pharmaceutically acceptable composition comprising the polypeptide of claim 5.